(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 April 2020 (16.04.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/077236 A1

(51) International Patent Classification:
C12N 15/10 (2006.01)

(21) International Application Number:
PCT/US20 19/055894

(22) International Filing Date:
11 October 2019 (11.10.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/745,259	12 October 2018 (12. 10.2018)	US
62/813,634	04 March 2019 (04.03.2019)	US
62/829,402	04 April 2019 (04.04.2019)	US
62/887,339	15 August 2019 (15.08.2019)	US
62/890,971	23 August 2019 (23.08.2019)	US

(71) Applicants: **THE BROAD INSTITUTE, INC.** [US/US]; 415 Main Street, Cambridge, Massachusetts 02142 (US). **MASSACHUSETTS INSTITUTE OF TECHNOLOGY** [US/US]; 77 Massachusetts Avenue, Cambridge, Massachusetts 02139 (US). **THE GENERAL HOSPITAL CORPORATION** [US/US]; 55 Fruit Street, Boston, Massachusetts 021 14 (US).

(72) Inventors; and

(71) Applicants: **DROKHLYANSKY, Eugene** [US/US]; c/o 415 Main Street, Cambridge, Massachusetts 02142 (US). **ASHENBERG, Orr** [US/US]; c/o 415 Main Street, Cambridge, Massachusetts 02142 (US).

(72) Inventors: **REGEV, Aviv;** c/o **415** Main Street, Cambridge, Massachusetts **02142** (US). **MCCABE, Cristin;** c/o **415** Main Street, Cambridge, Massachusetts **02142** (US). **MELNIKOV, Alexandre;** c/o **415** Main Street, Cambridge, Massachusetts **02142** (US). **ROZENBLATT-ROSEN, Orit;** c/o **415** Main Street, Cambridge, Massachusetts **02142** (US). **SMILLIE, Christopher;** c/o 77 Massachusetts Avenue, Cambridge, Massachusetts **02139** (US). **XAVIER, Ramnik J.;** c/o **415** Main Street, Cambridge, Massachusetts **02142** (US). **ERASLAN, Gokcen;** c/o **415** Main Street, Cambridge, Massachusetts **02142** (US). **CHUNG, Hattie;** c/o **415** Main Street, Cambridge, MA **02142** (US).

(54) **Title:** METHOD FOR EXTRACTING NUCLEI OR WHOLE CELLS FROM FORMALIN-FIXED PARAFFIN-EMBEDDED TISSUES

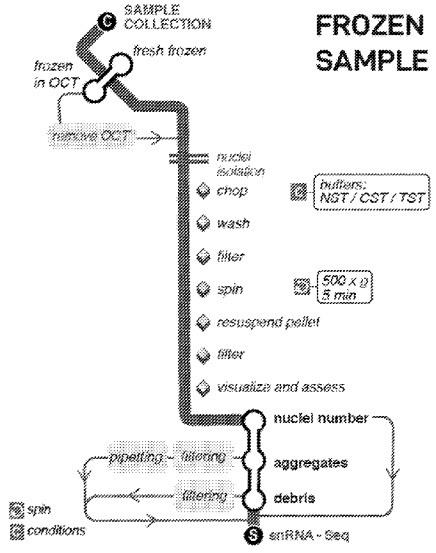


FIG. 54A

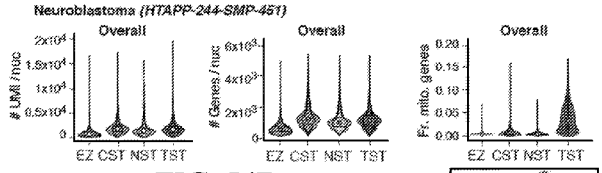


FIG. 54B

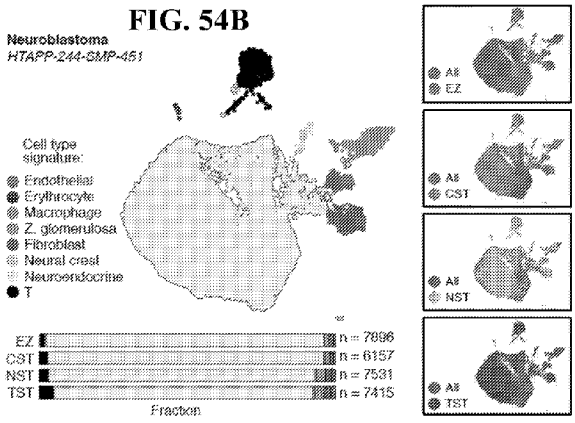


FIG. 54C FIG. 54D

(57) **Abstract:** The subject matter disclosed herein is generally directed to isolating single cells and nuclei from tissue samples for use in the analysis of single cells from archived biological samples. The subject matter disclosed herein is directed to isolating single cells and nuclei from formalin-fixed paraffin-embedded (FFPE) tissues. The subject matter disclosed herein is also directed to isolating single nuclei that preserve ribosomes or ribosomes and rough ER from frozen tissues. The subject matter disclosed herein is also directed to therapeutic targets, diagnostic targets and methods of screening for modulating agents.

WO 2020/077236 A1

[Continued on nextpage]

(74) Agent: REY, Gertrud U. et al. ; Johnson, Marcou & Isaacs, LLC, P.O. Box 691, Hoschton, Georgia 30548 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)* : AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)* : ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

METHOD FOR EXTRACTING NUCLEI OR WHOLE CELLS FROM FORMALIN-FIXED PARAFFIN-EMBEDDED TISSUES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/745,259, filed October 12, 2018; U.S. Provisional Application No. 62/813,634, filed March 4, 2019; U.S. Provisional Application No. 62/829,402, filed April 4, 2019; U.S. Provisional Application No. 62/887,339, filed August 15, 2019; and U.S. Provisional Application No. 62/890,971, filed August 23, 2019. The entire contents of the above-identified applications are hereby fully incorporated herein by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with government support under Grant No.(s) DK043351, DK1 14784 and DK1 17263 awarded by the National Institutes of Health. The government has certain rights in the invention.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[0003] The contents of the electronic sequence listing (BROD_3900_ST25.txt"; Size is 5,073 bytes and it was created on October 11, 2019) is herein incorporated by reference in its entirety.

TECHNICAL FIELD

[0004] The subject matter disclosed herein is generally directed to methods of single nuclei sequencing. The subject matter disclosed herein is also directed to isolating single cells and nuclei from frozen and formalin-fixed paraffin-embedded (FFPE) tissues for use in the analysis of single cells from archived biological samples. The subject matter disclosed herein is also directed to therapeutic targets, diagnostic targets and methods of screening for modulating agents.

BACKGROUND

[0005] Single cell methods (e.g., single cell RNA-Seq) has greatly extended our understanding of heterogeneous tissues, including the CNS (A. Zeisel *et al.*, Brain structure. Cell types in the

mouse cortex and hippocampus revealed by single-cell RNA-seq. *Science* 347, 1138-1 142 (2015); S. Darmanis *et al.*, A survey of human brain transcriptome diversity at the single cell level. *Proc Natl Acad Sci USA* 112, 7285-7290 (2015); J. Shin *et al.*, Single-Cell RNA-Seq with Waterfall Reveals Molecular Cascades underlying Adult Neurogenesis. *Cell Stem Cell* 17, 360-372 (2015); B. Tasic *et al.*, Adult mouse cortical cell taxonomy revealed by single cell transcriptomics. *Nat Neurosci* 19, 335-346 (2016); D. Usoskin *et al.*, Unbiased classification of sensory neuron types by large-scale single-cell RNA sequencing. *Nat Neurosci* 18, 145-153 (2015); E. R. Thomsen *et al.*, Fixed single-cell transcriptomic characterization of human radial glial diversity. *Nat Methods* 13, 87-93 (2016)), and is reshaping the concept of cell type and state. Formalin-fixed paraffin-embedded (FFPE) tissues are available for archival tissues, provide for easy storage and shipping, are available for rare diseases, and have well documented pathology. However, analyzing single cells from FFPE tissues has been challenging. For example, FFPE samples may have damaged cellular structures, low input and degraded/fragmented RNA, and the samples are cross linked. Thus, there is a need for improved devices and methods to allow for understanding heterogeneous tissues and cell populations present in FFPE samples.

[0006] Despite its central role in intestinal function and health, our understanding of the ENS is limited due to longstanding technical challenges; most of our knowledge to date is based on immunohistochemistry with a limited number of known markers. Because the ENS is dispersed among other cell types within the intestine (*e.g.*, myocytes and fibroblasts), enteric neurons are rare in any sample. Moreover, they are exceptionally challenging to isolate and study with genomic tools. Finally, most work on the ENS to date has been performed in rodent models with relatively few human studies *(13).* Single cell methods currently are not able to be used to analyze tissues from the ENS. Thus, there is a need for improved devices and methods to allow for understanding heterogeneous tissues and cell populations, such as the ENS. Moreover, treatment of diseases associated with the ENS are needed and require new biomarkers, methods of screening and therapeutic targets.

SUMMARY

[0007] In certain example embodiments, the present invention provides for methods of isolating nuclei or whole cells from tissue samples (e.g., frozen or FFPE). In further example

embodiments, the invention provides for a method of single cell sequencing comprising: extracting nuclei from a tissue sample under conditions that preserve the nuclear membranes, ribosomes and/or rough endoplasmic reticulum (ER); sorting single nuclei into separate reaction vessels; extracting RNA from the single nuclei; generating a cDNA library; and sequencing the library, whereby gene expression data from single cells is obtained. In further example embodiments, the invention provides for a method of single cell sequencing comprising: extracting whole cells from a tissue sample under conditions that preserve the cell membranes; sorting single cells into separate reaction vessels; extracting RNA from the single cells; generating a cDNA library; and sequencing the library, whereby gene expression data from single cells is obtained. In some embodiments, the reaction vessels may be single cell droplets.

[0008] In one aspect, the present invention provides for a method of recovering nuclei or whole cells from a formalin-fixed paraffin-embedded (FFPE) tissue comprising: dissolving paraffin from a FFPE tissue sample in a solvent, preferably the solvent is selected from the group consisting of xylene and mineral oil, wherein the tissue is dissolved at a temperature between 4C to 90C, preferably room temperature (20 to 25C) for recovering whole cells and 90C for recovering nuclei; rehydrating the tissue using a gradient of ethanol from 100% to 0% ethanol (EtOH); transferring the rehydrated tissue to a volume of a first buffer comprising a buffering agent, a detergent and an ionic strength between lOOmM and 200mM, optionally the first buffer comprises protease inhibitors or proteases and/or BSA; chopping or dounce homogenizing the tissue in the buffer; and removing debris by filtering and/or FACS sorting.

[0009] In certain embodiments, the method further comprises isolating nuclei or cell types by FACS sorting.

[0010] In certain embodiments, dissolving paraffin from a FFPE tissue sample, comprises incubating at least one time in xylene, at room temperature (RT), for about 10 minutes each, and wherein xylene is removed at each change. In certain embodiments, the method further comprises washing the tissue at least two times with xylene for about 10 min each, wherein the washes are performed at room temperature (RT), 90C, or at least one time at room temperature (RT) and at least one time at 90C, wherein xylene is removed at each change.

[0011] In certain embodiments, dissolving paraffin from a FFPE tissue sample, comprises incubating at least twice in about 5 ml xylene per 30-100 mg FFPE tissue sample, at room

temperature, for about 10 minutes each, wherein xylene is removed at each change. In certain embodiments, the method further comprises washing the tissue with xylene at 37C for about 10 min. In certain embodiments, the method further comprises cutting the tissue into two or more pieces and washing at least one piece of the tissue with xylene at 37C for about 10 min.

[0012] In certain embodiments, dissolving paraffin from a FFPE tissue sample, comprises incubating at least three times in xylene, at room temperature, for about 10 minutes each, and wherein xylene is removed at each change. In certain embodiments, the method further comprises washing the tissue three additional times with xylene for about 10 min each, wherein the first wash is at room temperature and the second and third washes are at 90C, and wherein xylene is removed at each change.

[0013] In certain embodiments, rehydrating the tissue comprises a step gradient of ethanol (EtOH) and the tissue is incubated between 1 to 10 minutes at each step. In certain embodiments, the step gradient comprises incubating the tissue for about 2 minutes each in successive washes of 95%, 75%, and 50% ethanol (EtOH).

[0014] In certain embodiments, after rehydrating the tissue the method further comprises placing the tissue samples on ice or on a device capable of maintaining the tissue between 4 and 10C, wherein all subsequent steps are performed at a temperature between 4 and 10C.

[0015] In certain embodiments, after the step of dissolving paraffin from the tissue or rehydrating the tissue the method further comprises dividing the tissue, preferably in half.

[0016] In certain embodiments, the first buffer comprises a detergent selected from the group consisting of NP40, CHAPS and Tween-20. In certain embodiments, the NP40 concentration is about 0.2%. In certain embodiments, the Tween-20 concentration is about 0.03%. In certain embodiments, the CHAPS concentration is about 0.49%. In certain embodiments, the first buffer is selected from the group consisting of CST, TST, NST and NSTnPo.

[0017] In certain embodiments, after the step of chopping or dounce homogenizing the method further comprises centrifuging, preferably, the sample is centrifuged at about 500g for about 5 min, and resuspending the sample in a second buffer comprising a buffering agent and an ionic strength between lOOmM and 200mM, optionally the second buffer comprises protease inhibitors. In certain embodiments, the second buffer is ST, optionally comprising protease inhibitors.

[0018] In certain embodiments, the sample is filtered through a 40 uM filter. In certain embodiments, the method further comprises washing the filtered sample in the first buffer. In certain embodiments, the method further comprises filtering the sample through a 30 uM filter.

[0019] In certain embodiments, after the step of chopping or dounce homogenizing the method further comprises adding an additional 2 volumes of the first buffer (3 volumes total) and filtering the sample through a 40 uM filter. In certain embodiments, the method further comprises adding an additional three volumes of the first buffer (6 volumes total), centrifuging, preferably, the sample is centrifuged at about 500g for about 5 min, and resuspending the sample in a second buffer comprising a buffering agent and an ionic strength between lOOmM and 200mM, optionally the second buffer comprises protease inhibitors. In certain embodiments, the second buffer is ST, optionally comprising protease inhibitors.

[0020] In certain embodiments, the method further comprises reversing cross-linking in the tissue sample before or during any step of the method. In certain embodiments, reversing cross-linking comprises proteinase digestion. In certain embodiments, the proteinase is proteinase K or a cold-active protease.

[0021] In certain embodiments, the method further comprises adding a reagent that stabilizes RNA to the tissue sample before or during any step of the method.

[0022] In certain embodiments, the method further comprises lysing recovered cells or nuclei and performing reverse transcription. In certain embodiments, the reverse transcription is performed in individual reaction vessels. In certain embodiments, the reaction vessels are wells, chambers, or droplets.

[0023] In certain embodiments, the method further comprises performing single cell, single nucleus or bulk RNA-seq, DNA-seq, ATAC-seq, or ChIP on the recovered nuclei or whole cells.

[0024] In certain embodiments, the method further comprises staining the recovered cells or nuclei. In certain embodiments, the stain comprises ruby stain.

[0025] In certain embodiments, single cells or nuclei are enriched by FACS or magnetic-activated cell sorting (MACS). The nuclei or cells of any method described herein may further be detectable by a fluorescent signal, whereby individual nuclei or cells may be further sorted. The single nuclei or cells may be immunostained with an antibody with specific affinity for an intranuclear protein or cell surface protein. The antibody may be specific for NeuN. The nuclei

may be stained with a nuclear stain. The nuclear stain may comprise DAPI, Ruby red, trypan blue, Hoechst or propidium iodine. In certain embodiments, nuclei can be labeled with ruby dye (Thermo Fisher Scientific, Vybrant DyeCycle Ruby Stain, #V-10309) added to the resuspension buffer at a concentration of 1:800.

[0026] In certain embodiments, the tissue sample is obtained from a subject suffering from a disease. In certain embodiments, the disease is cancer, a neurological disease, autoimmune disease, infection, or metabolic disease. The heterogeneous population of cells may be derived from a section of a tissue or a tumor from a subject. The section may be obtained by microdissection. The tissue may be nervous tissue. The nervous tissue maybe isolated from the brain, spinal cord or retina.

[0027] In another aspect, the present invention provides for a method of recovering nuclei and attached ribosomes from a tissue sample comprising: chopping the tissue sample at between 0-4 °C in a nuclear extraction buffer comprising Tris buffer, a detergent and salts; and filtering the sample through a filter between 30-50 uM, preferably 40 uM, and optionally washing the filter with fresh nuclear extraction buffer, wherein the nuclei are present in the supernatant passed through the filter. In certain embodiments, the nuclear extraction buffer comprises 10-20 mM Tris, about 0.49% CHAPS, a salt concentration having an ionic strength of l00-250mM, and about 0.01% BSA, whereby nuclei are recovered that have a preserved nuclear envelope and ribosomes. In certain embodiments, the nuclear extraction buffer is buffer CST. In certain embodiments, the nuclear extraction buffer comprises 10-20 mM Tris, about 0.03% Tween-20, a salt concentration having an ionic strength of l00-250mM, and about 0.01% BSA, whereby nuclei are recovered that have a preserved nuclear envelope, rough ER and ribosomes. In certain embodiments, the nuclear extraction buffer is buffer TST. In certain embodiments, the salts comprise 146 mM NaCl, lmM $CaCl_2$, and 2lmM $MgCl_2$. In certain embodiments, chopping comprises chopping with scissors for 1-10 minutes.

[0028] In certain embodiments, nuclei from specific cell types are genetically modified to express a detectable label on the nuclear membrane and the method further comprises enriching nuclei from the specific cell types using the detectable label. In certain embodiments, the method further comprises staining the recovered nuclei. In certain embodiments, the stain comprises ruby stain. In certain embodiments, the nuclei are sorted into discrete volumes by FACS.

[0029] In certain embodiments, the method further comprises pelleting the nuclei and resuspending the nuclei in a second buffer consisting of Tris buffer and salts. In certain embodiments, the second buffer is buffer ST.

[0030] In certain embodiments, the method further comprises generating a single nuclei barcoded library for the recovered nuclei, wherein the nucleic acid from each nuclei is labeled with a barcode sequence comprising a cell of origin barcode, optionally the barcode sequence includes a cell of origin barcode and a unique molecular identifier (UMI). In certain embodiments, RNA and/or DNA is labeled with the barcode sequence. In certain embodiments, the library is an RNA-seq, DNA-seq, and/or ATAC-seq library. In certain embodiments, the method further comprises sequencing the library.

[0031] In certain embodiments, the tissue sample is fresh frozen. In certain embodiments, the tissue sample comprises cells originating from the central nervous system (CNS) or enteric nervous system (ENS). In certain embodiments, the tissue sample is obtained from the gut or the brain. In certain embodiments, the tissue sample is obtained from a subject suffering from a disease. In certain embodiments, the tissue sample is treated with a reagent that stabilizes RNA.

[0032] In certain embodiments, the discrete volumes are droplets, wells in a plate, or microfluidic chambers.

[0033] In another aspect, the present invention provides for a method of treating a disease selected from the group consisting of Hirschsprung's disease (HSCR), inflammatory bowel disease (IBD), autism spectrum disorder (ASD), Parkinson's disease (PD) and schizophrenia in a subject in need thereof comprising administering one or more agents capable of modulating the function or activity of: one or more neurons selected from the group consisting of PEMN1, PEMN2, PIMN1, PIMN2, PIMN3, PIMN4, PIMN5, PIN1, PIN2, PSN and PSVN; or one or more cells functionally interacting with the one or more neurons. In certain embodiments, the one or more cells functionally interacting with the one or more neurons are selected from the group consisting of T cells, dendritic cells (DC), B cells, fibroblasts and adipocytes.

[0034] In another aspect, the present invention provides for a method of modulating appetite and energy metabolism in a subject in need thereof comprising administering one or more agents capable of modulating the function or activity of: one or more neurons selected from the group

consisting of PIMN4 and PIMN5; or one or more adipose cells functionally interacting with the one or more neurons.

[0035] In certain embodiments, the one or more neurons are characterized by expression of one or more markers according to Table 14 or Table 21. In certain embodiments, the one or more agents modulate the expression, activity or function of one or more genes according to Table 14 or Table 21. In certain embodiments, the one or more agents modulate the expression, activity or function of one or more genes selected from the group consisting of: NPY, CGRP, Glutamate, GABA, LEP, VIP, PACAP, Nitric oxide, NOS1, FGF1, PDGF, SLIT2, SLIT3, IL15, IL7, IL12A, PENK, CHAT and TPH2; or NPYR1, CALCRL, GRM8, GABRE, LEPR, VIPR2, GRIA4, GUCY1A3, FGFR1, PDGFRB, ROBOl, ROB02, IL15R, IL7R, IL12RB1, OPRM1, CHRNE and HTR3A. In certain embodiments, the one or more agents modulate the expression, activity or function of one or more genes selected from the group consisting of: NPY and CGRP; or NPYR1 and CALCRL. In certain embodiments, the one or more agents modulate the expression, activity or function of one or more core transcriptional programs according to Table 23. In certain embodiments, the one or more agents modulate the expression, activity or function of one or more genes of the one or more core transcriptional programs.

[0036] In certain embodiments, the one or more agents comprise an antibody, small molecule, small molecule degrader, genetic modifying agent, nucleic acid agent, antibody-like protein scaffold, aptamer, protein, or any combination thereof. In certain embodiments, the genetic modifying agent comprises a CRISPR system, RNAi system, a zinc finger nuclease system, a TALE, or a meganuclease. In certain embodiments, the CRISPR system comprises Cas9, Casl2, or Casl4. In certain embodiments, the CRISPR system comprises a dCas fused or otherwise linked to a nucleotide deaminase. In certain embodiments, the nucleotide deaminase is a cytidine deaminase or an adenosine deaminase. In certain embodiments, the dCas is a dCas9, dCasl2, dCasl3, or dCasl4. In certain embodiments, the nucleic acid agent or genetic modifying agent is administered with a vector. In certain embodiments, the nucleic acid agent or genetic modifying agent is under the control of a promoter specific to a marker gene for the one or more neurons according to Table 14 or Table 21. In certain embodiments, the nucleic acid agent is a nucleotide sequence encoding the one or more genes (e.g., an overexpression vector, a sequence encoding a cDNA of a gene).

[0037] In certain embodiments, the one or more agents are administered to the gut.

[0038] In another aspect, the present invention provides for a method of detecting one or more cells of the enteric nervous system (ENS) comprising detecting one or more markers according to Table 14-17 or Table 20-22. In certain embodiments, detecting the one or more markers comprises immunohistochemistry.

[0039] In another aspect, the present invention provides for a method of screening for agents capable of modulating expression of a transcription program according to Table 23 comprising: administering an agent to a population of cells comprising neurons selected from the group consisting of PEMN1, PEMN2, PIMN1, PIMN2, PIMN3, PIMN4, PIMN5, PIN1, PIN2, PSN and PSVN; and detecting expression of one or more genes in the transcriptional program. In certain embodiments, detecting expression comprises RT-PCR, RNA-seq, single cell RNA-seq, fluorescently labeled probes, or an immunoassay. In certain embodiments, the neurons express one or more reporter genes under control of a promoter specific to the one or more genes in the transcriptional program and detecting comprises detecting the reporter gene.

[0040] In another aspect, the present invention provides for a method of identifying gene expression in single cells comprising providing sequencing reads from a single nuclei sequencing library and counting sequencing reads mapping to introns and exons. In certain embodiments, the method further comprises filtering the single nuclei. In certain embodiments, nuclei doublets are removed by filtering. In certain embodiments, nuclei containing ambient RNA or ambient RNA alone is removed by filtering.

[0041] These and other aspects, objects, features, and advantages of the example embodiments will become apparent to those having ordinary skill in the art upon consideration of the following detailed description of illustrated example embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0042] An understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention may be utilized, and the accompanying drawings of which:

[0043] **FIG. 1** - Schematic of variables of extracting nuclei from a FFPE tissue block and preparing cDNA.

[0044] **FIG.** 2 - Image of nuclei and FACS plot using douncing in the FFPE extraction protocol.

[0045] **FIG.** 3 - Image of nuclei and FACS plot using chopping in the FFPE extraction protocol.

[0046] **FIG.** 4 - Image of nuclei and FACS plot using 90C extraction and proteinase K in the FFPE extraction protocol.

[0047] **FIG.** 5 - Image of nuclei and FACS plot using 90C extraction and no proteinase K in the FFPE extraction protocol.

[0048] **FIG.** 6 - Image of nuclei and FACS plot using room temperature extraction and proteinase K in the FFPE extraction protocol.

[0049] **FIG.** 7 - Image of nuclei and FACS plot using room temperature extraction and no proteinase K in the FFPE extraction protocol.

[0050] **FIG. 8** - Image of nuclei obtained from B16 PDX (patient derived xenograft) using 90C extraction in the FFPE extraction protocol.

[0051] **FIG.** 9 - Image of cells obtained from B16 PDX (patient derived xenograft) using room temperature extraction in the FFPE extraction protocol.

[0052] **FIG.** 10 - Image of nuclei obtained from d4mra (patient derived xenograft) using 90C extraction in the FFPE extraction protocol.

[0053] **FIG.** 11 - Image of cells obtained from d4mra (patient derived xenograft) using room temperature extraction in the FFPE extraction protocol.

[0054] **FIG.** 12 - Images of nuclei and cells obtained using the FFPE extraction protocol.

[0055] **FIG.** 13 - Bioanalyzer electropherograms showing RNA quality (left) and cDNA traces after amplification (right).

[0056] **FIG.** 14 - Image of nuclei used for RNA extraction and electropherograms showing cDNA traces with and without heat steps.

[0057] **FIG.** 15 - Bioanalyzer electropherogram showing cDNA traces from bulk sorted nuclei.

[0058] **FIG.** 16 - Bioanalyzer electropherograms from the samples in Table 5. (xylene sample in row5, oil sample in row 5, and frozen sample in row 8).

[0059] **FIG.** 17 - Bioanalyzer electropherograms from the samples extracted with TCL, 5000 nuclei and Xylene RNA control.

[0060] **FIG. 18** - Bioanalyzer electropherograms from a FFPE sample treated at 55C for 15 minutes using TCL lysis buffer and oil isolation.

[0061] **FIG. 19** - Bioanalyzer electropherograms from xylene extracted total RNA.

[0062] **FIG. 20 - RAISIN RNA-seq captures RNA from intact nuclei and associated ribosomes. (A)** Study overview. **(B)** Neuron nuclei enrichment with reporter mice. Representative histology (left) and FACS (right) of ENS nuclei labelling. Histology and FACS images for all models are in **fig. 24A-C. (C-E)** optimization of RAISIN and INNER Cell RNA-seq. **(C)** Cellular composition of each extraction. Ternary plot showing the proportion of nuclei expressing neuron, glia or neither signature (triangle edges) from each extraction type (dots). Purple, green: published protocols *(16, 17).* Blue, red: top performing protocols. *(n* = 5,236 GFP+ sorted nuclei across all protocols). **(D)** RAISIN and INNER Cell RNA-seq isolate nuclei with attached ribosomes and rough ER. Ultra-thin section transmission electron microscopy (TEM) of nuclei extractions from published methods (top) *(16, 17)* and with RAISIN (bottom left) and INNER Cell (bottom right) methods. **(E)** Higher exorrintron ratios in RAISIN and INNER Cell methods. Exomintron ratio *(y* axis, log2(ratio)) following snRNA-seq from each preparations in (D). All comparisons significant (Wilcoxon test, p-value < 10^{-10}); boxplots: 25%, 50%, and 75% quantiles; error bars: standard deviation (SD). **(F)** RAISIN RNA-seq is compatible with droplet-based RNA-seq. A t-distributed stochastic neighbor embedding (t-SNE) of RAISIN RNA-seq profiles from mouse colon of 10,889 unsorted RAISINs profiled by droplet-based scRNA-seq and colored by cell type.

[0063] **FIG. 21 - Mouse ENS atlas reveals 24 neuron subsets that vary with circadian phase and colon location. (A-B)** Mouse neuron reference map. **(A)** 24 neuron subsets profiled by RAISIN RNA-seq. t-SNE of 2,447 neuron RAISIN RNA-Seq profiles from mouse colon colored by major putative neuron classes based on *post hoc* annotation **(SOM). (B)** Neuron subsets vary by anatomical location and mouse line. Neuron subsets (columns) arranged by transcriptional similarity (dendrogram, top) and annotated with the proportion of cells isolated from each transgenic model (green pie chart) or colon segment (red/blue pie chart). Dot plot shows for select neurotransmitters and neuropeptides (rows), the fraction of cells in each subset (dot size) expressing the synthetic enzyme (top) or respective receptors (bottom) (genes for synthesis and

receptors in **table 18),** and the mean expression level in expressing cells in the subset (dot color). **(C,D)** Mouse ENS gene expression is affected by circadian rhythm. Distribution of neuron gene expression levels (*y* axis, $\log_2$(TP10K+l)) of select genes (x axis) that are upregulated at morning (red) or evening (blue) time points in all neurons (C) or at the morning time point in PSNls and PSN2s (D). **(E)** Changes in ENS expression along colon length. Mean expression across all neuron subsets (color bar) of significantly DE genes (columns) across colon regions (rows), arranged by location of peak expression from proximal to distal. **(F)** Revisions to the peristaltic model. Left: current model of the peristaltic circuit (adapted from *13).* Right: additions to this model derived from the ENS atlas. **(G)** The mechanosensitive ion channel Piezol is expressed in PIMNs and PEMNs. Distribution of gene expression levels (*y* axis, log2(TPlOK+l)) across neuron subsets (x axis) for genes in peristaltic model: Htr4 (top), Piezol (middle) and Piezo2 (bottom). **(H,I)** Validation of gene expression *in situ.* Representative images of smFISH for Caleb and Nmu (G) or Nog and Grp (H), both with Tubb3 immunostaining. Merged channels on right. Inset: example neuron expressing all three markers.

[0064] FIG. 22 - Atlas of the human colon muscularis propria reveals 11 neuron subsets with roles in immunity and disease. (A) Census of the human muscularis propria. t-SNE of 134,835 RAISIN RNA-seq profiles from the muscularis propria of cancer-proximal macroscopically normal colon resections from 10 human donors, colored by cell type, annotated *post hoc.* **(B)** Enteric neuron census. t-SNE of 83 1RAISIN RNA-seq profiles from enteric neurons, colored by subset, annotated *post hoc.* **(C)** Correspondence of human and mouse enteric neurons. Percent (dot size and color) of neurons from each human subset (rows) that matched each mouse neuron subset (column) according to the classifier **(SOM). (D)** Transcriptional signatures conserved between mouse and human neuron subsets. The fraction of expressing cells (dot size) and mean expression level in expressing cells (dot color) of selected genes (columns) identified as conserved for each neuron class (rows) between mouse (top) and human (bottom); full list available in **table 23. (E-G)** Characterization of ICCs in the colon **(E)** ICC gene signature. Fraction of expressing cells (dot size) and mean expression level in expressing cells (dot color) of selected ICC marker genes (columns) across human cell subsets (rows). **(F)** ICCs and not myocytes express receptors for nitric oxide. Distribution of expression levels (x axis, log2(TPlOK+l)) of acetylcholine (left) and nitric oxide (right) receptors across cell subsets (*y* axis). **(G)** *In situ*

expression of key ICC markers in the human colon. **(H)** Proposed peristaltic circuitry. **(I-J)** Inferred cell-cell interactions networks for human cells in the mucosa and muscularis propria. **(I)** Statistically significant interactions. Nodes: cell subsets, annotated by type (color) and colon location (bold: muscularis). Edges connect pairs of cell subsets with a significant excess of cognate receptor-ligand pairs expressed ($p < 0.05$) relative to a null model **(SOM). (J)** Select receptor-ligand interactions between neurons and adipocytes, fibroblasts, and immune cell subsets. **(K,L)** Representative *in situ* validations of IL-7 expression in NOS1+ neurons (K) and IL-12 expression in CHAT+ neurons (L).

[0065] FIG. 23 - Human enteric neurons express disease risk genes for primary enteroneuropathies, IBD, and CNS disorders with concomitant gut dysmotility. Mean expression (scaled log2(TPlOK+l)) across cell subsets (rows) of putative risk genes (columns) implicated by GWAS for Hirschsprung's disease (HRSC), inflammatory bowel disease (IBD), autism spectrum disorders (ASD), and Parkinson's disease (PD) **(SOM),** which were identified as cell-specific in either **(A)** the colon mucosa, or **(B)** the colon muscularis propria.

[0066] FIG. 24 - Mouse models for snRNA-seq optimization. (A-C) Labeling of nuclei in the mouse colon using different Cre-driver lines and conditional nuclear sfGFP (INTACT allele) **(A3),** or regulatory region driving expression of nuclear mCherry **(C).** Representative images show cross-section of mouse colon with muscularis propria (bottom) and mucosa (top) (left). FACS plots (right) show enriched populations. **(D)** snRNA-seq of GFP^+ nuclei from SoxlO-Cre;INTACT animals. Fraction (*y* axis) of identified cell-types (x axis) in samples obtained from the brain (grey) and colon (black) using two previously published snRNA-seq methods *(16, 17).*

[0067] FIG. 25 - Buffer optimization for snRNA-seq. (A) Decision tree for selection of best buffers. **(B)** RAISIN RNA-seq has optimal combination of ENS proportions and neuron quality scores. ENS signature score (*y* axis, mean and standard error of the mean (SEM); log2(TPlOK+l); **SOM)** and number of detected genes per nucleus (x axis, mean and SEM) for each of 36 total conditions. Dot size: percent neurons captured. Select nuclei extractions are marked in color (legend). **(C-E)** Quality scores across all tested parameters. Quality metrics (columns, x axes) for (C) a range of concentrations (*y* axes) across detergents, (D) mechanical extraction procedures, and (E) buffers.

[0068] FIG. 26 - Extracted nuclei across different protocols. Representative phase contrast images of nuclei isolated using extractions with different detergents or extraction kits (grey, **SOM)** and buffers (blue), with varying detergent concentrations and additives (marked on image). All extractions were performed with the 'chop' method **(SOM)** unless otherwise indicated.

[0069] FIG. 27 - Reproducibility and validations for the mouse ENS atlas. (A, B) Reproducible cell subset distributions across transgenic mouse lines and individual mice. t-SNE of RAISIN RNA-seq profiles of 2,447 neurons **(A)** and 2,734 glia **(B)** colored by cell subset (left), mouse model (middle), or donor mouse (right). **(C)** Neuron composition in colon. Percent of all cells in the colon that are neurons (*y* axis) as estimated by FACS (transgene expressing nuclei us. unlabeled nuclei) and *post-hoc* adjustment using RAISIN RNA-seq data. **(D)** $Chat^{+}Nosl^{+}$ neurons. Representative images of Chat and Nosl expression in neurons. **(E)** $Nog^{+}Grp^{+}$ neurons. Representative images of neurons that co-express Nog and Grp, showing they are not derived from the SoxlO-Cre lineage (GFP).

[0070] FIG. 28 - Representative *in situ* validations confirming the co-expression of marker genes for excitatory motor and sensory neurons. Grey-scale *in situ* validation showing co-expression of DAPI (blue) along with either **(A)** Piezo **1** (green), Chat (red) and Tubb3 (white); inset: $Piezol^{+}Chat^{+}Tubb3^{+}$ PEMN; **(B)** Htr4 (green), Chat (red), and Tubb3 (white); inset: $Htr4^{+}Chat^{+}Tubb3^{+}$ PEMN; **(C)** Htr4 (green), both forms of CGRP (red), and Tubb3 (white); top inset: $Calca^{+}Nosl^{+}Tubb3^{+}$ PSN; bottom inset: $Caleb^{+}Nosl^{+}Tubb3^{+}$ PSN; **(D)** Cck (green), Piezo2 (red), and Tubb3 (white); yellow inset: $Cck^{+}Piezo2^{+}Tubb3^{+}$ PSN in muscularis propria; red inset: $Cck^{+}Piezo2^{+}Tubb3^{+}$ PSN in lamina propria; or (E) Caleb (green), Chat (red), and Sst (white); inset: $Calcb^{+}Chat^{+}Sst^{+}$ PSN.

[0071] FIG. 29 - Expression profiles reveal key functions of mouse enteric neuron subsets. Fraction of expressing cells (dot size) and the mean levels in expressing (non-zero) cells (dot color) of select markers. **(A)** Major neurotransmitters and neuropeptides (left) and other genes (right) (columns), across neuron subsets (rows). **(B)** unique markers (columns) across neuron subsets (rows).

[0072] FIG. 30 - Reproducible cell subset distributions across ten human donors. (A-F) Shared and donor-specific cell subsets in the human cell census. t-SNE of 134,835 RAISIN RNA-seq profiles (A,D), 831 neurons (B,E), or 6,878 glia from cancer-proximal colon resections

collected from ten human donors, colored by cell subset (A-C) or patient identifier (D-F). **(G-J)** Removal of oxidative phosphorylation (OXPHOS) signal in human neurons improved clustering by cell subset rather than cell state. t-SNE of human enteric neurons after removal of PC1 (G, identical to C) and before removal of PC1 (H-J) colored by cell subset, PC1 score (I), or OXPHOS expression score (J).

[0073] **FIG.** 31 - **Expression profiles reveal key functions of human enteric neuron subsets.** Fraction of expressing cells (dot size) and the mean expression levels in expressing (non-zero) cells (dot color) of **(A)** major neurotransmitters and neuropeptides and **(B)** other genes (columns) across human neuron subsets (rows). Due to low levels of CHAT expression, Applicants used the acetylcholine transporter, SLC5A7, as a marker of cholinergic neurons.

[0074] FIG. 32 - Human enteric neurons express disease risk genes for autism, Parkinson's disease, schizophrenia, and IBD. Mean expression (scaled log2(TPlOK+l)) across cell subsets (rows) of putative risk genes (columns) implicated by GWAS for autism, Parkinson's disease, schizophrenia, and IBD.

[0075] **FIG.** 33 - Examples of multiple tissues and multiple individuals for analysis by single-cell genomics.

[0076] **FIG.** 34 - Single nuclei RNA-seq analysis pipeline.

[0077] **FIG.** 35 - Violin plots showing the number of genes detected per nuclei from two preparations of nuclei counting reads mapping to exons only or exons and introns.

[0078] **FIG.** 36 - Graph showing the number of nuclei passing quality control from two preparations of nuclei counting reads mapping to exons only or exons and introns.

[0079] **FIG.** 37 - Violin plots showing the number of genes detected per nuclei for nuclei subsets identified. The data was filtered using thresholds for single cell RNA-seq.

[0080] **FIG.** 38 - Violin plots showing the number of genes detected per nuclei for nuclei subsets identified. The data was filtered using thresholds for single cell RNA-seq. Plot showing expression of TRAC in the nuclei subsets.

[0081] **FIG.** 39 - Illustration of applying filters to remove data obtained from droplets containing a barcoded bead and doublets (two cells).

[0082] **FIG.** 40 - Illustration of applying filters to remove data obtained from droplets containing ambient RNA.

[0083] **FIG. 41** - Example of clustering lung cell subsets from a tissue sample.

[0084] **FIG.** 42 - Violin plots showing the number of genes detected per nuclei for four preparations from the same individual tissue.

[0085] **FIG. 43** - Violin plots showing the number of genes detected per nuclei for tissue samples from three individuals using the same nuclei preparation.

[0086] **FIG.** 44 - Violin plots showing the proportion of reads mapping to mitochondrial genes from nuclei isolated from lung and heart tissues.

[0087] **FIG.** 45 - tSNE plots combining single nuclei RNA-seq preparations from 12 samples. Left panel shows clusters identified. Right panel shows cells from each individual. Illustrates tSNE clusters cells by individuals without using batch correction.

[0088] **FIG.** 46 - tSNE plots combining single nuclei RNA-seq preparations from 12 samples. Left panel shows clusters identified. Right panel shows cells from each individual. Illustrates tSNE clusters cells by cell type when using batch correction (see, e.g., LIGER: Josh Welch, Evan Macosko (BRAIN BICCN project), *bioRxiv).*

[0089] **FIG.** 47 - tSNE plots for each sample after combining single nuclei RNA-seq preparations from the 12 samples. Each preparation shows similar clusters.

[0090] **FIG.** 48 - Heat map showing differential gene expression between the nuclei subsets.

[0091] **FIG.** 49 - tSNE of the single nuclei RNA-seq from the 12 lung samples showing clustering of the major subsets of parenchymal, stromal, and immune cells in lung tissue.

[0092] **FIG.** 50 - tSNE of the Genotype-Tissue Expression (GTEx) project tissues after using improved single nuclei RNA-seq methods.

[0093] **FIG. 51** - Schematic showing detection of quantitative trait loci (QTLs) using the improved single nuclei RNA-seq pipeline and multiple individuals.

[0094] **FIG. 52** - tSNE representing nuclei from three individuals that was pooled together (top). tSNE showing demultiplexing of the nuclei (bottom).

[0095] **FIG. 53A-53L - scRNA-Seq toolbox for fresh tumor samples.** (53A, 53B) Study Overview. (53A) sc/snRNA-Seq workflow, experimental and computational pipelines, and protocol selection criteria. (53B) Tumor types in the study. Right column: recommended protocols for fresh (black/cells) or frozen (blue/nuclei) tumor samples. (53C) Flow chart for collection and processing of fresh tumor samples. (53D-53G) Comparison of three dissociation protocols applied

to one NSCLC sample. (53D) Protocol performance varies across cell types. Top and middle: Distribution of number of reads/cell, number of UMI/cell, number of genes/cell, and fraction of mitochondrial reads (*y* axes) in each protocol (x axis) across the entire dataset, Bottom: Distribution of number of genes/cell (*y* axis) only in epithelial cells (left) or in B cells (right). (53E) Protocols vary in number of empty drops. UMAP embedding of single cell profiles (dots) for each protocol, colored by assignment as cell (grey) or empty drop (black). Horizontal bars: fraction of assigned cells (grey) and empty drops (black). (53F, 53G) Protocols vary in diversity of cell types captured. (53F) Top: UMAP embedding of single cell profiles (dots) from all three protocols, colored by assigned cell subset signature. Bottom: Proportion of cells in each subset in each of the three protocols, and in an analysis using CD45 depletion; *n* indicates the number of recovered cells passing QC. (53G) UMAP embedding as in (53F) colored by protocol. (53H-53L) Protocol comparison across tumor types. (53H) Cell type composition. Proportion of cells assigned to each cell subset signature (color) for each sample. R : Resection; B : Biopsy; A : Ascites; BD: Blood draw; O-PDX: Orthotopic patient-derived xenograft. (53I-53L) QC metrics. The median number of UMIs/cell, median number of genes/cell, median fraction of gene expression/cell from mitochondrial genes, and fraction of empty drops (x axes) for each sample in (53H) (*y* axis).

[0096] FIG. 54A-54J - snRNA-Seq toolbox for frozen tumor samples. (54A) Flow chart for collection and processing of frozen tumor samples. (54B-54D) Comparison of four nucleus isolation protocols in one neuroblastoma sample. (54B) Variation in protocol performance. Distribution of number of UMI/nucleus, number of genes/nucleus, and fraction of mitochondrial reads (*y* axes) in each protocol (x axis) across all nuclei in the dataset. (54C, 54D) Protocols vary in diversity of cell types captured. (54C) Top: UMAP embedding of single nucleus profiles (dots) from all four protocols, colored by assigned cell subset signature. Bottom: Proportion of cells from each subset in each of the four protocols. (54D) UMAP embedding as in (54C) colored by protocol. (54E-54H) Protocol comparison across tumor types. (54E) Cell-type composition. Proportion of cells assigned with each cell subset signature (color) for each sample. R : Resection; B : Biopsy; A : Ascites; BD: Blood draw; O-PDX: Orthotopic patient-derived xenograft. (54F-54H) QC metrics. Median number of UMI/nucleus, median number of genes/nucleus, and median fraction of gene expression/nucleus from mitochondrial genes for each sample in (54E). (54I-54J) scRNA-seq and snRNA-seq comparison in neuroblastoma. (541) Compositional differences between scRNA-Seq

and snRNA-Seq of the same sample. UMAP embedding of scRNA-seq and snRNA-Seq profiles of the same sample combined by CCA (Butler et al. *Nature biotechnology* 36:41 1-420 (2018)). (Methods) showing profiles (dots) from either scRNA-seq (left) or snRNA-Seq (right), colored by assigned cell type signatures. Bottom: Proportion of cells in each subset in the two protocols. (54J) Agreement in scRNA-seq and snRNA-seq intrinsic profiles. UMAP embedding as in (541) showing both scRNA-seq and snRNA-Seq profiles, colored by assigned cell type signatures (top, colored as in (541)) or by protocol (bottom).

[0097] **FIG.** 55 - **Overview of processed samples.** Samples processed in this study are listed by tumor type (rows), along with their ID, tissue source (fresh or frozen, and OCT embedding), processing protocols tested, the recommended protocol, and the Figure showing the sample's analysis.

[0098] **FIG. 56A-560 - ScRNA-Seq protocol comparison for one NSCLC sample.** (45A) Sample processing and QC overview. For each protocol, shown are the number of cells passing QC, and the number of sequencing reads and sequencing saturation across all cells. The remaining metrics are reported for those cells passing QC: the median number of reads per cell, median number of UMIs per cell, median number of genes per cell, median fraction of UMIs mapping to mitochondrial genes, median fraction of duplicated UMIs per cell, fraction of cell barcodes called as empty droplets, and fraction of cell barcodes called as doublets. (56B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis) across the three protocols (colored bars). (56C-56D) Overall and cell types specific QCs. Distribution of the number of reads per cell, number of UMIs per cell, number of genes per cell, fraction of UMIs mapping to mitochondrial genes in each cell, and fraction of duplicated UMIs per cell (*y* axes) in each of the three protocols (x axis), for all cells passing QC (56C) and for cells passing QC from each cell type (56D, rows; if a protocol has no cells of that type, it is not shown). (56E, 56F) Relation of empty droplets and doublets to cell types. UMAP embedding of single cell (grey), "empty droplet" (red, top), and doublet (red, bottom) profiles for each protocol. (56G-56I) Cell type assignment. UMAP embedding of single cell profiles from each protocol colored by assigned cell type signature. (56J-56L) Inferred CNA profiles. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single cells (rows). Top: reference cells not expected to contain CNA in this cancer type.

Bottom: cells tested for CNA relative to the reference cells. Color bar: assigned cell type signature for each cell. (56M-560) Ambient RNA estimates. SoupX (Young et al. *BioRxiv* 303727 (2018)). estimates of the fraction of RNA in each cell type derived from ambient RNA contamination (*y* axis), with cell types ordered by their mean number of UMIs/cell (x axis). Red line: global average of contamination fraction; Green line: LOWESS smoothed estimate of the contamination fraction within each cell type, along with the associated confidence interval.

[0099] FIG. 57A-57H - ScRNA-Seq protocol comparison for NSCLC following read down-sampling. Shown are analyses for NSCLC14 (as in Fig. 56), but after the total number of sequencing reads within each sample was down-sampled to match the protocol with the fewest total sequencing reads. (57A) Sample processing and QC overview. For each protocol, shown are the number of cells passing QC. The remaining metrics are reported for those cells passing QC: median number of UMIs per cell, median number of genes per cell, median fraction of UMIs mapping to mitochondrial genes in each cell, fraction of cell barcodes called as empty droplets, and fraction of cell barcodes called as doublets. (57B, 57C) Overall and cell types specific QCs. Distribution of the number of UMIs per cell, number of genes per cell, and fraction of gene expression per cell from mitochondrial genes (*y* axes) in each of the three protocols (x axis), for all cells passing QC (57B) and for cells from each cell type (57C, rows; if a protocol has no cells of that type, it is not shown). (57D, 57E) Relation of empty droplets and doublets to cell types. UMAP embedding and fraction (horizontal bar) of single cell (grey), "empty droplet" (red, left), and doublet (red, right) profiles for each protocol (57F-57H) Cell type assignment. UMAP embedding of single cell profiles from each protocol colored by assigned cell type signature.

[00100] FIG. 58A-58I - Depletion protocol enriches for malignant cells in freshly processed NSCLC. Cells were processed using the PDEC protocol or the PDEC protocol combined with depletion of $CD45^+$ cells. (58A) Sample processing and QC overview. For each protocol, shown are the number of cells passing QC, and the number of sequencing reads and sequencing saturation across all cells. The remaining metrics are reported for those cells passing QC: median number of reads per cell, median number of UMIs per cell, median number of genes per cell, median fraction of UMIs mapping to mitochondrial genes in each cell, fraction of cell barcodes called as empty droplets, and fraction of cell barcodes called as doublets. (58B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic

regions (x axis) in each of the two protocols (colored bars). (58C) Overall QCs. Distribution of the number of reads per cell, number of UMIs per cell, number of genes per cell, and fraction of UMIs mapping to mitochondrial genes in each cell (*y* axes) in each of the three protocols (x axis) for all cells passing QC. (58D, 58E) Relation of empty droplets and doublets to cell types. UMAP embedding and fraction (horizontal bar) of single cell (grey), "empty droplet" (red, left) and doublet (red, right) profiles for each protocol. (58F-58G) Cell type assignment. UMAP embedding of single cell profiles from each protocol colored by assigned cell type signature. (58H-58I) Inferred CNA profiles for cells from each protocol. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single cells (rows). Top: reference cells not expected to contain CNA in this cancer type. Bottom: cells tested for CNA relative to the reference cells. Color bar: assigned cell type signature for each cell.

[00101] FIG. 59A-59I - Application of $CD45^+$ cell depletion protocol for processing ascites from ovarian cancer. (59A) Sample processing and QC overview. Shown are the number of cells passing QC, and the number of sequencing reads and sequencing saturation across all cells. The remaining metrics are reported for those cells passing QC: median number of reads per cell, median number of UMIs per cell, median number of genes per cell, median fraction of UMIs mapping to mitochondrial genes in each cell, fraction of cell barcodes called as empty droplets, and fraction of cell barcodes called as doublets. (59B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (59C) Overall QCs. Distribution of the number of reads per cell, number of UMIs per cell, number of genes per cell, and fraction of UMIs mapping to mitochondrial genes in each cell (*y* axes) for all cells passing QC. (59D, 59E) Relation of empty droplets and doublets to cell types. UMAP embedding and fraction (horizontal bar) of single cell (grey), "empty droplet" (red, left) and doublet (red, right) profiles. (59F) Cell type assignment. UMAP embedding of single cell profiles colored by assigned cell type signature. (59G, 59H) Flow-cytometry comparison of single cells isolated (59G) without or (59H) with depletion of $CD45^+$ cells. Cells were gated by FSC and SSC (first column), doublets removed using FSC-A and FSC-H (second column), live cells identified using 7AAD (third column), and the distribution of immune and non-immune cells quantified using a CD45 antibody (fourth column). (591) Inferred CNA profiles for cells. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across

the single cells (rows). Top: reference cells not expected to contain CNA in this cancer type. Bottom: cells tested for CNA relative to the reference cells. Color bar: assigned cell type signature for each cell.

[00102] FIG. 60A-60G - Protocol for lymph node resection of metastatic breast cancer. (60A) Sample processing and QC overview. Shown are the number of cells passing QC, and the number of sequencing reads and sequencing saturation across all cells. The remaining metrics are reported for those cells passing QC: median number of reads per cell, median number of UMIs per cell, median number of genes per cell, median fraction of UMIs mapping to mitochondrial genes in each cell, fraction of cell barcodes called as empty droplets, and fraction of cell barcodes called as doublets. (60B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (60C) Overall QCs. Distribution of the number of reads per cell, number of UMIs per cell, number of genes per cell, and fraction of UMIs mapping to mitochondrial genes in each cell (*y* axes) for all cells passing QC. (60D, 60E) Relation of empty droplets and doublets to cell types. UMAP embedding and fraction (horizontal bar) of single cell (grey), "empty droplet" (red, left) and doublet (red, right) profiles. (60F) Cell type assignment. UMAP embedding of single cell profiles colored by assigned cell type signature. (60G) Inferred CNA profiles for cells. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single cells (rows). Top: reference cells not expected to contain CNA in this cancer type. Bottom: cells tested for CNA relative to the reference cells. Color bar: assigned cell type signature for each cell.

[00103] FIG. 61A-61G - Protocol for lymph node biopsy of metastatic breast cancer. (61A) Sample processing and QC overview. Shown are the number of cells passing QC, and the number of sequencing reads and sequencing saturation across all cells. The remaining metrics are reported for those cells passing QC: median number of reads per cell, median number of UMIs per cell, median number of genes per cell, median fraction of fraction of UMIs mapping to mitochondrial genes in each cell, fraction of cell barcodes called as empty droplets, and fraction of cell barcodes called as doublets. (61B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (61C) Overall QCs. Distribution of the number of reads per cell, number of UMIs per cell, number of genes per cell, and fraction of UMIs mapping to mitochondrial genes in each cell (*y* axes) for all cells passing

QC. (61D, 61E) Relation of empty droplets and doublets to cell types. UMAP embedding and fraction (horizontal bar) of single cell (grey), "empty droplet" (red, left) and doublet (red, right) profiles. (61F) Cell type assignment. UMAP embedding of single cell profiles colored by assigned cell type signature. (61G) Inferred CNA profiles for cells. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single cells (rows). Top: reference cells not expected to contain CNA in this cancer type. Bottom: cells tested for CNA relative to the reference cells. Color bar: assigned cell type signature for each cell.

[00104] FIG. 62A-62G - Protocol for liver biopsy of metastatic breast cancer. (62A) Sample processing and QC overview. Shown are the number of cells passing QC, and the number of sequencing reads and sequencing saturation across all cells. The remaining metrics are reported for those cells passing QC: median number of reads per cell, median number of UMIs per cell, median number of genes per cell, median fraction of UMIs mapping to mitochondrial genes in each cell, fraction of cell barcodes called as empty droplets, and fraction of cell barcodes called as doublets. (62B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (62C) Overall QCs. Distribution of the number of reads per cell, number of UMIs per cell, number of genes per cell, and fraction of UMIs mapping to mitochondrial genes in each cell (*y* axes) for all cells passing QC. (62D, 62E) Relation of empty droplets and doublets to cell types. UMAP embedding and fraction (horizontal bar) of single cell (grey), "empty droplet" (red, left) and doublet (red, right) profiles. (62F) Cell type assignment. UMAP embedding of single cell profiles colored by assigned cell type signature. (62G) Inferred CNA profiles for cells. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single cells (rows). Top: reference cells not expected to contain CNA in this cancer type. Bottom: cells tested for CNA relative to the reference cells. Color bar: assigned cell type signature for each cell.

[00105] FIG. 63A-63G - Protocol for liver biopsy of metastatic breast cancer. (63A) Sample processing and QC overview. Shown are the number of cells passing QC, and the number of sequencing reads and sequencing saturation across all cells. The remaining metrics are reported for those cells passing QC: median number of reads per cell, median number of UMIs per cell, median number of genes per cell, median fraction of UMIs mapping to mitochondrial genes in each cell, fraction of cell barcodes called as empty droplets, and fraction of cell barcodes called as

doublets. (63B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the transcriptome and intergenic regions (x axis). (63C) Overall QCs. Distribution of the number of reads per cell, number of UMIs per cell, number of genes per cell, and fraction of UMIs mapping to mitochondrial genes in each cell (*y* axes) for all cells passing QC. (63D, 63E) Relation of empty droplets and doublets to cell types. UMAP embedding and fraction (horizontal bar) of single cell (grey), "empty droplet" (red, left) and doublet (red, right) profiles. (63F) Cell type assignment. UMAP embedding of single cell profiles colored by assigned cell type signature. (63G) Inferred CNA profiles for cells. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single cells (rows). Top: reference cells not expected to contain CNA in this cancer type. Bottom: cells tested for CNA relative to the reference cells. Color bar: assigned cell type signature for each cell.

[00106] FIG. 64A-64G - Protocol for pre-treatment biopsy of neuroblastoma. (64A) Sample processing and QC overview. Shown are the number of cells passing QC, and the number of sequencing reads and sequencing saturation across all cells. The remaining metrics are reported for those cells passing QC: median number of reads per cell, median number of UMIs per cell, median number of genes per cell, median fraction of UMIs mapping to mitochondrial genes in each cell, fraction of cell barcodes called as empty droplets, and fraction of cell barcodes called as doublets. (64B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (64C) Overall QCs. Distribution of the number of reads per cell, number of UMIs per cell, number of genes per cell, and fraction of UMIs mapping to mitochondrial genes in each cell (*y* axes) for all cells passing QC. (64D, 64E) Relation of empty droplets and doublets to cell types. UMAP embedding and fraction (horizontal bar) of single cell (grey), "empty droplet" (red, left) and doublet (red, right) profiles. (64F) Cell type assignment. UMAP embedding of single cell profiles colored by assigned cell type signature. (64G) Inferred CNA profiles for cells. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single cells (rows). Top: reference cells not expected to contain CNA in this cancer type. Bottom: cells tested for CNA relative to the reference cells. Color bar: assigned cell type signature for each cell.

[00107] FIG. 65A-65G - Protocol for post-treatment resection of neuroblastoma. (65A) Sample processing and QC overview. Shown are the number of cells passing QC, and the number

of sequencing reads and sequencing saturation across all cells. The remaining metrics are reported for those cells passing QC: median number of reads per cell, median number of UMIs per cell, median number of genes per cell, median fraction of UMIs mapping to mitochondrial genes in each cell, fraction of cell barcodes called as empty droplets, and fraction of cell barcodes called as doublets. (65B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (65C) Overall QCs. Distribution of the number of reads per cell, number of UMIs per cell, number of genes per cell, and fraction of UMIs mapping to mitochondrial genes in each cell (*y* axes) for all cells passing QC. (65D, 65E) Relation of empty droplets and doublets to cell types. UMAP embedding and fraction (horizontal bar) of single cell (grey), "empty droplet" (red, left) and doublet (red, right) profiles. (65F) Cell type assignment. UMAP embedding of single cell profiles colored by assigned cell type signature. (65G) Inferred CNA profiles for cells. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single cells (rows). Top: reference cells not expected to contain CNA in this cancer type. Bottom: cells tested for CNA relative to the reference cells. Color bar: assigned cell type signature for each cell.

[00108] FIG. 66A-66F - Protocol for O-PDX of neuroblastoma. (66A) Sample processing and QC overview. Shown are the number of cells passing QC, and the number of sequencing reads and sequencing saturation across all cells. The remaining metrics are reported for those cells passing QC: median number of reads per cell, median number of UMIs per cell, median number of genes per cell, median fraction of UMIs mapping to mitochondrial genes in each cell, fraction of cell barcodes called as empty droplets, and fraction of cell barcodes called as doublets. (66B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (66C) Overall QCs. Distribution of the number of reads per cell, number of UMIs per cell, number of genes per cell, and fraction of UMIs mapping to mitochondrial genes in each cell (*y* axes) for all cells passing QC. (66D, 66E) Relation of empty droplets and doublets to cell types. UMAP embedding and fraction (horizontal bar) of single cell (grey), "empty droplet" (red, left) and doublet (red, right) profiles. (66F) Cell type assignment. UMAP embedding of single cell profiles colored by assigned cell type signature.

[00109] FIG. 67A-67G - Protocol for resection of neuroblastoma. (67A) Sample processing and QC overview. Shown are the number of cells passing QC, and the number of sequencing reads

and sequencing saturation across all cells. The remaining metrics are reported for those cells passing QC: median number of reads per cell, median number of UMIs per cell, median number of genes per cell, median fraction of UMIs mapping to mitochondrial genes in each cell, fraction of cell barcodes called as empty droplets, and fraction of cell barcodes called as doublets. (67B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (67C) Overall QCs. Distribution of the number of reads per cell, number of UMIs per cell, number of genes per cell, and fraction of UMIs mapping to mitochondrial genes in each cell (*y* axes) for all cells passing QC. (67D, 67E) Relation of empty droplets and doublets to cell types. UMAP embedding and fraction (horizontal bar) of single cell (grey), "empty droplet" (red, left) and doublet (red, right) profiles. (67F) Cell type assignment. UMAP embedding of single cell profiles colored by assigned cell type signature. (67G) Inferred CNA profiles for cells. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single cells (rows). Top: reference cells not expected to contain CNA in this cancer type. Bottom: cells tested for CNA relative to the reference cells. Color bar: assigned cell type signature for each cell.

[00110] FIG. 68A-68G - Protocol for resection of glioma. (68A) Sample processing and QC overview. Shown are the number of cells passing QC, and the number of sequencing reads and sequencing saturation across all cells. The remaining metrics are reported for those cells passing QC: median number of reads per cell, median number of UMIs per cell, median number of genes per cell, median fraction of UMIs mapping to mitochondrial genes in each cell, fraction of cell barcodes called as empty droplets, and fraction of cell barcodes called as doublets. (68B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (68C) Overall QCs. Distribution of the number of reads per cell, number of UMIs per cell, number of genes per cell, and fraction of UMIs mapping to mitochondrial genes in each cell (*y* axes) for all cells passing QC. (68D, 68E) Relation of empty droplets and doublets to cell types. UMAP embedding and fraction (horizontal bar) of single cell (grey), "empty droplet" (red, left) and doublet (red, right) profiles. (68F) Cell type assignment. UMAP embedding of single cell profiles colored by assigned cell type signature. (68G) Inferred CNA profiles for cells. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single cells (rows). Top: reference cells not expected

to contain CNA in this cancer type. Bottom: cells tested for CNA relative to the reference cells. Color bar: assigned cell type signature for each cell.

[00111] FIG. 69A-69G - Protocol for resection of ovarian cancer. (69A) Sample processing and QC overview. Shown are the number of cells passing QC, and the number of sequencing reads and sequencing saturation across all cells. The remaining metrics are reported for those cells passing QC: median number of reads per cell, median number of UMIs per cell, median number of genes per cell, median fraction of UMIs mapping to mitochondrial genes in each cell, fraction of cell barcodes called as empty droplets, and fraction of cell barcodes called as doublets. (69B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (69C) Overall QCs. Distribution of the number of reads per cell, number of UMIs per cell, number of genes per cell, and fraction of UMIs mapping to mitochondrial genes in each cell (*y* axes) for all cells passing QC. (69D, 69E) Relation of empty droplets and doublets to cell types. UMAP embedding and fraction (horizontal bar) of single cell (grey), "empty droplet" (red, left) and doublet (red, right) profiles. (69F) Cell type assignment. UMAP embedding of single cell profiles colored by assigned cell type signature. (69G) Inferred CNA profiles for cells. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single cells (rows). Top: reference cells not expected to contain CNA in this cancer type. Bottom: cells tested for CNA relative to the reference cells. Color bar: assigned cell type signature for each cell.

[00112] FIG. 70A-70G - Protocol for cryopreserved sample of CLL. (70A) Sample processing and QC overview. Shown are the number of cells passing QC, and the number of sequencing reads and sequencing saturation across all cells. The remaining metrics are reported for those cells passing QC: median number of reads per cell, median number of UMIs per cell, median number of genes per cell, median fraction of UMIs mapping to mitochondrial genes in each cell, fraction of cell barcodes called as empty droplets, and fraction of cell barcodes called as doublets. (70B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (70C) Overall QCs. Distribution of the number of reads per cell, number of UMIs per cell, number of genes per cell, and fraction of UMIs mapping to mitochondrial genes in each cell (*y* axes) for all cells passing QC. (70D, 70E) Relation of empty droplets and doublets to cell types. UMAP embedding and fraction (horizontal

bar) of single cell (grey), “empty droplet” (red, left) and doublet (red, right) profiles. (70F) Cell type assignment. UMAP embedding of single cell profiles colored by assigned cell type signature. (70G) Inferred CNA profiles for cells. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single cells (rows). Top: reference cells not expected to contain CNA in this cancer type. Bottom: cells tested for CNA relative to the reference cells. Color bar: assigned cell type signature for each cell.

[00113] FIG. 71A-71M - SnRNA-Seq protocol comparison for one neuroblastoma sample. (71A) Sample processing and QC overview. For each protocol, shown are the number of nuclei passing QC, and the number of sequencing reads and sequencing saturation across all nuclei. The remaining metrics are reported for those nuclei passing QC: the median number of reads per nucleus, median number of UMIs per nucleus, median number of genes per nucleus, median fraction of UMIs mapping to mitochondrial genes in each nucleus, median fraction of duplicated UMIs per nucleus, and fraction of nucleus barcodes called as doublets. (71B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis) across the four protocols (colored bars). (71C-71D) Overall and cell types specific QCs. Distribution of the number of reads per nucleus, number of UMIs per nucleus, number of genes per nucleus, fraction of UMIs mapping to mitochondrial genes in each nucleus, and fraction of duplicated UMIs per nucleus (*y* axes) in each of the four protocols (x axis), for all nuclei passing QC (71C) and for nuclei from each cell type (71D, rows; if a protocol has no cells of that type, it is not shown). (71E) Relation of doublets to cell types. UMAP embedding and fraction (horizontal bar) of single nucleus (grey) and doublet (red) profiles for each protocol. (71F-711) Cell type assignment. UMAP embedding of single nucleus profiles from each protocol colored by assigned cell type signature. (71J-71M) Inferred CNA profiles. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single nuclei (rows). Top: reference nuclei not expected to contain CNA in this cancer type. Bottom: nuclei tested for CNA relative to the reference nuclei. Color bar: assigned cell type signature for each nucleus.

[00114] FIG. 72A-72H - SnRNA-Seq protocol comparison for neuroblastoma following read down-sampling. Shown are analyses for NB HTAPP-244-SMP-451 (as in Fig. 71), but after the total number of sequencing reads within each sample was down-sampled to match the protocol

with the fewest total sequencing reads. (72A) Sample processing and QC overview. For each protocol, shown are the number of nuclei passing QC. The remaining metrics are reported for those nuclei passing QC: median number of UMIs per nucleus, median number of genes per nucleus, median fraction of UMIs mapping to mitochondrial genes in each nucleus, and fraction of nucleus barcodes called as doublets. (72B, 72C) Overall and cell types specific QCs. Distribution of the number of UMIs per nucleus, number of genes per nucleus, and fraction of UMIs mapping to mitochondrial genes in each nucleus (*y* axes) in each of the four protocols (x axis), for all nuclei passing QC (72B) and for nuclei from each cell type (72C, rows; if a protocol has no cells of that type, it is not shown). (72D) Relation of doublets to cell types. UMAP embedding and fraction (horizontal bar) of single nucleus (grey) and doublet (red) profiles for each protocol. (72E-72H) Cell type assignment. UMAP embedding of single nucleus profiles from each protocol colored by assigned cell type signature.

[00115] FIG. 73A-73H - Protocol comparison for resection of a breast cancer metastasis from the brain. (73A) Sample processing and QC overview. For each protocol, shown are the number of nuclei passing QC, and the number of sequencing reads and sequencing saturation across all nuclei. The remaining metrics are reported for those nuclei passing QC: median number of reads per nucleus, median number of UMIs per nucleus, median number of genes per nucleus, median fraction of UMIs mapping to mitochondrial genes in each nucleus, and fraction of nucleus barcodes called as doublets. (73B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (73C) Overall QCs. Distribution of the number of reads per nucleus, number of UMIs per nucleus, number of genes per nucleus, and fraction of UMIs mapping to mitochondrial genes in each nucleus (*y* axes) for all nuclei passing QC. (73D) Relation of doublets to cell types. UMAP embedding and fraction (horizontal bar) of single nucleus (grey) and doublet (red) profiles for each protocol. (73E-73F) Cell type assignment. UMAP embedding of single nucleus profiles from each protocol colored by assigned cell type signature. (73G-73H) Inferred CNA profiles for nuclei. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single nuclei (rows). Top: reference nuclei not expected to contain CNA in this cancer type. Bottom: nuclei tested for CNA relative to the reference nuclei. Color bar: assigned cell type signature for each nucleus.

[00116] FIG. 74A-74H - Protocol comparison for resection of metastatic breast cancer from the brain. (74A) Sample processing and QC overview. For each protocol, shown are the number of nuclei passing QC, and the number of sequencing reads and sequencing saturation across all nuclei. The remaining metrics are reported for those nuclei passing QC: median number of reads per nucleus, median number of UMIs per nucleus, median number of genes per nucleus, median fraction of UMIs mapping to mitochondrial genes in each nucleus, and fraction of nucleus barcodes called as doublets. (74B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (74C) Overall QCs. Distribution of the number of reads per nucleus, number of UMIs per nucleus, number of genes per nucleus, and fraction of UMIs mapping to mitochondrial genes in each nucleus (*y* axes) for all nuclei passing QC. (74D) Relation of doublets to cell types. UMAP embedding and fraction (horizontal bar) of single nucleus (grey) and doublet (red) profiles for each protocol. (74E-74F) Cell type assignment. UMAP embedding of single nucleus profiles from each protocol colored by assigned cell type signature. (74G-74H) Inferred CNA profiles for nuclei. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single nuclei (rows). Top: reference nuclei not expected to contain CNA in this cancer type. Bottom: nuclei tested for CNA relative to the reference nuclei. Color bar: assigned cell type signature for each nucleus.

[00117] FIG. 75A-75H - Protocol comparison for biopsy of metastatic breast cancer from the liver. (75A) Sample processing and QC overview. For each protocol, shown are the number of nuclei passing QC, and the number of sequencing reads and sequencing saturation across all nuclei. The remaining metrics are reported for those nuclei passing QC: median number of reads per nucleus, median number of UMIs per nucleus, median number of genes per nucleus, median fraction of UMIs mapping to mitochondrial genes in each nucleus, and fraction of nucleus barcodes called as doublets. (75B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (75C) Overall QCs. Distribution of the number of reads per nucleus, number of UMIs per nucleus, number of genes per nucleus, and fraction of UMIs mapping to mitochondrial genes in each nucleus (*y* axes) for all nuclei passing QC. (75D) Relation of doublets to cell types. UMAP embedding and fraction (horizontal bar) of single nucleus (grey) and doublet (red) profiles for each protocol. (75E-75F)

Cell type assignment. UMAP embedding of single nucleus profiles from each protocol colored by assigned cell type signature. (75G-75H) Inferred CNA profiles for nuclei. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single nuclei (rows). Top: reference nuclei not expected to contain CNA in this cancer type. Bottom: nuclei tested for CNA relative to the reference nuclei. Color bar: assigned cell type signature for each nucleus.

[00118] FIG. 76A-76J - Protocol comparison for resection of ovarian cancer. (76A) Sample processing and QC overview. For each protocol, shown are the number of nuclei passing QC, and the number of sequencing reads and sequencing saturation across all nuclei. The remaining metrics are reported for those nuclei passing QC: median number of reads per nucleus, median number of UMIs per nucleus, median number of genes per nucleus, median fraction of UMIs mapping to mitochondrial genes in each nucleus, and fraction of nucleus barcodes called as doublets. (76B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (76C) Overall QCs. Distribution of the number of reads per nucleus, number of UMIs per nucleus, number of genes per nucleus, and fraction of UMIs mapping to mitochondrial genes in each nucleus (*y* axes) for all nuclei passing QC. (76D) Relation of doublets to cell types. UMAP embedding and fraction (horizontal bar) of single nucleus (grey) and doublet (red) profiles for each protocol. (76E-76G) Cell type assignment. UMAP embedding of single nucleus profiles from each protocol colored by assigned cell type signature. (76H-76J) Inferred CNA profiles for nuclei. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single nuclei (rows). Top: reference nuclei not expected to contain CNA in this cancer type. Bottom: nuclei tested for CNA relative to the reference nuclei. Color bar: assigned cell type signature for each nucleus.

[00119] FIG. 77A-77H - Protocol comparison for resection of sarcoma. (77A) Sample processing and QC overview. For each protocol, shown are the number of nuclei passing QC, and the number of sequencing reads and sequencing saturation across all nuclei. The remaining metrics are reported for those nuclei passing QC: median number of reads per nucleus, median number of UMIs per nucleus, median number of genes per nucleus, median fraction of UMIs mapping to mitochondrial genes, and fraction of nucleus barcodes called as doublets. (77B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome,

and intergenic regions (x axis). (77C) Overall QCs. Distribution of the number of reads per nucleus, number of UMIs per nucleus, number of genes per nucleus, and fraction of UMIs mapping to mitochondrial genes in each nucleus (*y* axes) for all nuclei passing QC. (77D) Relation of doublets to cell types. UMAP embedding and fraction (horizontal bar) of single nucleus (grey) and doublet (red) profiles for each protocol. (77E-77F) Cell type assignment. UMAP embedding of single nucleus profiles from each protocol colored by assigned cell type signature. (77G-77H) Inferred CNA profiles for nuclei. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single nuclei (rows). Top: reference nuclei not expected to contain CNA in this cancer type. Bottom: nuclei tested for CNA relative to the reference nuclei. Color bar: assigned cell type signature for each nucleus.

[00120] FIG. 78A-78F - **Protocol for resection of glioma.** (78A) Sample processing and QC overview. Shown are the number of nuclei passing QC, and the number of sequencing reads and sequencing saturation across all nuclei. The remaining metrics are reported for those nuclei passing QC: median number of reads per nucleus, median number of UMIs per nucleus, median number of genes per nucleus, median fraction of UMIs mapping to mitochondrial genes in each nucleus, and fraction of nucleus barcodes called as doublets. (78B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (78C) Overall QCs. Distribution of the number of reads per nucleus, number of UMIs per nucleus, number of genes per nucleus, and fraction of UMIs mapping to mitochondrial genes in each nucleus (*y* axes) for all nuclei passing QC. (78D) Relation of doublets to cell types. UMAP embedding and fraction (horizontal bar) of single nucleus (grey) and doublet (red) profiles. (78E) Cell type assignment. UMAP embedding of single nucleus profiles colored by assigned cell type signature. (78F) Inferred CNA profiles for nuclei. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single nuclei (rows). Top: reference nuclei not expected to contain CNA in this cancer type. Bottom: nuclei tested for CNA relative to the reference nuclei. Color bar: assigned cell type signature for each nucleus.

[00121] FIG. 79A-79E - **Protocol for O-PDX of neuroblastoma.** (79A) Sample processing and QC overview. Shown are the number of nuclei passing QC, and the number of sequencing reads and sequencing saturation across all nuclei. The remaining metrics are reported for those nuclei passing QC: median number of reads per nucleus, median number of UMIs per nucleus,

median number of genes per nucleus, median fraction of UMIs mapping to mitochondrial genes in each nucleus, and fraction of nucleus barcodes called as doublets. (79B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (79C) Overall QCs. Distribution of the number of reads per nucleus, number of UMIs per nucleus, number of genes per nucleus, and fraction of UMIs mapping to mitochondrial genes in each nucleus (*y* axes) for all nuclei passing QC. (79D) Relation of doublets to cell types. UMAP embedding and fraction (horizontal bar) of single nucleus (grey) and doublet (red) profiles. (79E) Cell type assignment. UMAP embedding of single nucleus profiles colored by assigned cell type signature.

[00122] FIG. 80A-80F - Protocol for resection of neuroblastoma. (80A) Sample processing and QC overview. Shown are the number of nuclei passing QC, and the number of sequencing reads and sequencing saturation across all nuclei. The remaining metrics are reported for those nuclei passing QC: median number of reads per nucleus, median number of UMIs per nucleus, median number of genes per nucleus, median fraction of UMIs mapping to mitochondrial genes in each nucleus, and fraction of nucleus barcodes called as doublets. (80B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (80C) Overall QCs. Distribution of the number of reads per nucleus, number of UMIs per nucleus, number of genes per nucleus, and fraction of UMIs mapping to mitochondrial genes in each nucleus (*y* axes) for all nuclei passing QC. (80D) Relation of doublets to cell types. UMAP embedding and fraction (horizontal bar) of single nucleus (grey) and doublet (red) profiles for each protocol. (80E) Cell type assignment. UMAP embedding of single nucleus profiles from each protocol colored by assigned cell type signature. (80F) Inferred CNA profiles for nuclei. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single nuclei (rows). Top: reference nuclei not expected to contain CNA in this cancer type. Bottom: nuclei tested for CNA relative to the reference nuclei. Color bar: assigned cell type signature for each nucleus.

[00123] FIG. 81A-81F - Protocol for resection of sarcoma. (81A) Sample processing and QC overview. Shown are the number of nuclei passing QC, the number of sequencing reads, and sequencing saturation across all nuclei. The remaining metrics are reported for those nuclei passing QC: median number of reads per nucleus, median number of UMIs per nucleus, median number

of genes per nucleus, median fraction of UMIs mapping to mitochondrial genes in each nucleus, and fraction of nucleus barcodes called as doublets. (81B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (81C) Overall QCs. Distribution of the number of reads per nucleus, number of UMIs per nucleus, number of genes per nucleus, and fraction of UMIs mapping to mitochondrial genes in each nucleus (*y* axes) for all nuclei passing QC. (81D) Relation of doublets to cell types. UMAP embedding and fraction (horizontal bar) of single nucleus (grey) and doublet (red) profiles. (81E) Cell type assignment. UMAP embedding of single nucleus profiles colored by assigned cell type signature. (81F) Inferred CNA profiles for nuclei. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single nuclei (rows). Top: reference nuclei not expected to contain CNA in this cancer type. Bottom: nuclei tested for CNA relative to the reference nuclei. Color bar: assigned cell type signature for each nucleus.

[00124] FIG. 82A-82F - Protocol for resection of melanoma. (82A) Sample processing and QC overview. Shown are the number of nuclei passing QC, the number of sequencing reads, and sequencing saturation across all nuclei. The remaining metrics are reported for those nuclei passing QC: median number of reads per nucleus, median number of UMIs per nucleus, median number of genes per nucleus, median fraction of UMIs mapping to mitochondrial genes in each nucleus, and fraction of nucleus barcodes called as doublets. (82B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (82C) Overall QCs. Distribution of the number of reads per nucleus, number of UMIs per nucleus, number of genes per nucleus, and fraction of UMIs mapping to mitochondrial genes in each nucleus (*y* axes) for all nuclei passing QC. (82D) Relation of doublets to cell types. UMAP embedding and fraction (horizontal bar) of single nucleus (grey) and doublet (red) profiles. (82E) Cell type assignment. UMAP embedding of single nucleus profiles colored by assigned cell type signature. (82F) Inferred CNA profiles for nuclei. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single nuclei (rows). Top: reference nuclei not expected to contain CNA in this cancer type. Bottom: nuclei tested for CNA relative to the reference nuclei. Color bar: assigned cell type signature for each nucleus.

[00125] FIG. 83A-83F - Protocol for resection of melanoma. (83A) Sample processing and QC overview. Shown are the number of nuclei passing QC, the number of sequencing reads, and

sequencing saturation across all nuclei. The remaining metrics are reported for those nuclei passing QC: median number of reads per nucleus, median number of UMIs per nucleus, median number of genes per nucleus, median fraction of UMIs mapping to mitochondrial genes in each nucleus, and fraction of nucleus barcodes called as doublets. (83B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (83C) Overall QCs. Distribution of the number of reads per nucleus, number of UMIs per nucleus, number of genes per nucleus, and fraction of UMIs mapping to mitochondrial genes in each nucleus (*y* axes) for all nuclei passing QC. (83D) Relation of doublets to cell types. UMAP embedding and fraction (horizontal bar) of single nucleus (grey) and doublet (red) profiles. (83E) Cell type assignment. UMAP embedding of single nucleus profiles colored by assigned cell type signature. (83F) Inferred CNA profiles for nuclei. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single nuclei (rows). Top: reference nuclei not expected to contain CNA in this cancer type. Bottom: nuclei tested for CNA relative to the reference nuclei. Color bar: assigned cell type signature for each nucleus.

[00126] FIG. 84A-84F - Protocol for cryopreserved sample of CLL. (84A) Sample processing and QC overview. Shown are the number of nuclei passing QC, the number of sequencing reads, and sequencing saturation across all nuclei. The remaining metrics are reported for those nuclei passing QC: median number of reads per nucleus, median number of UMIs per nucleus, median number of genes per nucleus, median fraction of UMIs mapping to mitochondrial genes in each nucleus, and fraction of nucleus barcodes called as doublets. (84B) Read mapping QCs. The percent of bases in the sequencing reads (*y* axis) mapping to the genome, transcriptome, and intergenic regions (x axis). (84C) Overall QCs. Distribution of the number of reads per nucleus, number of UMIs per nucleus, number of genes per nucleus, and fraction of UMIs mapping to mitochondrial genes in each nucleus (*y* axes) for all nuclei passing QC. (84D) Relation of doublets to cell types. UMAP embedding and fraction (horizontal bar) of single nucleus (grey) and doublet (red) profiles. (84E) Cell type assignment. UMAP embedding of single nucleus profiles colored by assigned cell type signature. (84F) Inferred CNA profiles for nuclei. Chromosomal amplification (red) and deletion (blue) inferred in each chromosomal position (columns) across the single nuclei (rows). Top: reference nuclei not expected to contain CNA in this cancer type.

Bottom: nuclei tested for CNA relative to the reference nuclei. Color bar: assigned cell type signature for each nucleus.

[00127] FIG. 85A, 85B - Protocol comparison of V2 and V3 chemistry from lOx Genomics on a resection of sarcoma. (85A) Sample processing and QC overview. For each protocol, shown are the number of nuclei passing QC, after the total number of sequencing reads from the V3 protocol data was down-sampled to match the number of reads in the V2 data. The remaining metrics are reported for those nuclei passing QC: median number of UMIs per nucleus, median number of genes per nucleus, median fraction of UMIs mapping to mitochondrial genes in each nucleus, and fraction of nucleus barcodes called as doublets. (85B) Overall QCs. Distribution of number of UMIs per nucleus, number of genes per nucleus, and fraction of UMIs mapping to mitochondrial genes in each nucleus (*y* axes) for all nuclei passing QC.

[00128] FIG. 86A-86C - Comparison of scRNA-Seq and snRNA-Seq from a single blood draw sample of CLL (CLL1). (86A-86C) UMAP embedding of single cell and single nucleus profiles after batch correction by CCA (Methods) colored by either assigned cell type signature (86A; fractions in horizontal bar), cluster assignment (86B) or data type (c, cells or nuclei; horizontal bar: cluster assignment).

[00129] FIG. 87A-87C - Comparison of scRNA-Seq and snRNA-Seq from a single metastatic breast cancer sample (HTAPP-963-SMP-4741). (87A-87C) UMAP embedding of single cell and single nucleus profiles after batch correction by CCA (Methods) colored by either assigned cell type signature (87A; fractions in horizontal bar), cluster assignment (87B) or data type (87C, cells or nuclei; horizontal bar: cluster assignment).

[00130] FIG. 88A-88C - Comparison of scRNA-Seq and snRNA-Seq from a single neuroblastoma sample (HTAPP-656-SMP-3481). (88A-88C) UMAP embedding of single cell and single nucleus profiles after batch correction by CCA (Methods) colored by either assigned cell type signature (88A; fractions in horizontal bar), cluster assignment (88B) or data type (88C, cells or nuclei; horizontal bar: cluster assignment).

[00131] FIG. 89A-89C - Comparison of scRNA-Seq and snRNA-Seq from a single O-PDX neuroblastoma sample. (89A-89C) UMAP embedding of single cell and single nucleus profiles after batch correction by CCA (Methods) colored by either assigned cell type signature (89A;

fractions in horizontal bar), cluster assignment (89B) or data type (89C, cells or nuclei; horizontal bar: cluster assignment).

[00132] FIG. 90 - Validation of the SoxlO-Cre driver. Triple-transgenic mice harboring *SoxlO-Cre; INTACT;* conditional *tdTomato* alleles were used to evaluate concordance of genetically labeled cells and TUBB3 immunofluorescence.

[00133] FIG. 91A-91C - High quality neuron and glia transcriptomes. Mean expression levels (log2(TPlOK+l)) of hallmark genes (x axis) across cell subsets (y axis) for major cell classes (91 A), neuron subsets (91B), or glia subsets (91C). Cell subsets were profiled using either Smart-Seq2 (SS2) or droplet-based methods.

[00134] FIG. 92A-92F - Detection of Tph2 expression in the brain, but not colon. (92A) Schematic of coronal brain section. Raphe nuclei contain serotonergic (Tph2+) neurons and served as a positive control. The pontine reticular nucleus does not contain Tph2—expressing neurons and served as a negative control. (92B, 92C) Representative images of smFISH for Tph2 in the mouse brain (92B) and colon (92C) of SoxlO-Cre; INTACT (GFP) mice (n = 2 animals; 12 colon sections). (92D, 92E) Representative images of smFISH for Tph2 in the mouse brain (92B) and colon (92C) of wild-type C57BL/6J mice. (n = 2 animals; 12 colon sections). (92F) Analysis of bulk RNA-seq data from several tissues of C57BL/6 mice (Sollner et al. 2017). RNA expression of Tphl and Tph2 from the brain, colon and small intestine. RNA expression independently analyzed in three mice per tissue is indicated 1-3.

[00135] FIG. 93 - An overview of cloud-based analysis. The flow chart and table show that the pipeline for cloud based analysis after data processing is efficient and quick - it allows one analyze about a million cells within 2 hours as compared to runs that take days. It is also shareable and reproducible.

[00136] FIGs. 94A-94B - Fresh tissue test case for non-small cell lung carcinoma (NSCLC). (94A) Technical QCs for three different cell dissociation protocols. While the QCs look similar, each protocol results in a different proportion of cell types. (95B) Cell type diversity achieved from each protocol. NSCLC samples from all three cell dissociation protocols are embedded. Similar numbers of cells were recovered across protocols, but different cell type proportions.

[00137] FIG. 95 - Cell type-specific QCs for three different dissociation protocols. The C4 protocol has the greatest number of genes detected per cell overall. The LE protocol has the greatest number of genes detected per cell in epithelial cells. The PDEC protocol has the greatest number of genes detected per cell in B cells.

[00138] FIG. 96 - The fresh tumor toolbox was used successfully across six tumor types. Five types of fresh tumors were processed: non-small cell lung carcinoma (NSCLC), metastatic breast cancer (MBC), ovarian cancer, glioblastoma (GBM), and neuroblastoma, as well as a cryopreserved non-solid, chronic lymphocytic leukemia (CLL).

[00139] FIG. 97 - QC assessment across all cells in a sample and per cell type for tumors processed in Figure 96. QCs and cell proportions were measured for all of them. A recommended protocol was chosen for each tumor type.

[00140] FIG. 98 - Workflow of single nucleus RNA-seq from frozen tissue.

[00141] FIG. 99 - snRNA-seq toolbox for processing frozen tissue. The best approach was testing four different nucleus isolation buffers, three of which were very similar to each other apart from the detergent and the original buffer EZ.

[00142] FIG. 100 - The frozen tumor toolbox was used successfully across 7 tumor types.

[00143] FIG. 101 - snRNA -seq of pre-malignant breast ductal carcinoma in situ (DCIS). Analysis revealed pretty good QCs and Applicants were able to detect several cell types - including two clusters of epithelial cells, immune cells, endothelial cells, and fibroblasts.

[00144] FIG. 102 - Detection of specific breast cancer markers.

[00145] FIG. 103 - Optimization strategy for snRNA-seq of FFPE samples.

[00146] FIG. 104 - Workflow for snRNA-seq of FFPE samples.

[00147] FIG. 105 - Single-nucleus RNA-seq was tested on FFPE samples. Shown are (105A) human lung cancer and (105B) mouse brain tissue in FFPE block. The samples were prepared fresh and processed quickly.

[00148] FIG. 106 - Summary of optimization steps for processing FFPE tissue. Two different library construction (LC) methods were used: SCRB-Seq and Smart-seq2.

[00149] FIG. 107 - Optimization of methods for WTA and library construction (LC).

[00150] FIG. 108A-108B - QCs for SMART-Seq2 and SCRB-Seq. In 108B, Applicants used mineral oil for analysis of number of genes only.

[00151] FIG. 109 - Correlation across treatment, library prep and number of nuclei. As expected, the correlation goes down with the numbers of nuclei tested - since mouse cortex is a complex tissue with many cell types. Correlation across preps 100>10>1.

[00152] FIG. 110 - Profiling nuclei from mouse brain FFPE reveals expression of cortex genes. There were 65 single nuclei in total. No clear clusters were detected after accounting for batch/library type. Differential expression of known mouse cortex cell type markers was detected.

[00153] FIGs. 111A-111B - Nuclei profiled from mouse brain FFPE are predicted to map to mouse cortex cell types. The prediction accuracy was 0.69.

[00154] The figures herein are for illustrative purposes only and are not necessarily drawn to scale.

DETAILED DESCRIPTION OF THE EXAMPLE EMBODIMENTS

General Definitions

[00155] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure pertains. Definitions of common terms and techniques in molecular biology may be found in Molecular Cloning: A Laboratory Manual, 2nd edition (1989) (Sambrook, Fritsch, and Maniatis); Molecular Cloning: A Laboratory Manual, 4th edition (2012) (Green and Sambrook); Current Protocols in Molecular Biology (1987) (F.M. Ausubel et al. eds.); the series Methods in Enzymology (Academic Press, Inc.): PCR2: A Practical Approach (1995) (M.J. MacPherson, B.D. Hames, and G.R. Taylor eds.): Antibodies, A Laboratory Manual (1988) (Harlow and Lane, eds.): Antibodies A Laboratory Manual, 2nd edition 2013 (E.A. Greenfield ed.); Animal Cell Culture (1987) (R.I. Freshney, ed.); Benjamin Lewin, Genes IX, published by Jones and Bartlet, 2008 (ISBN 0763752223); Kendrew *et al.* (eds.), The Encyclopedia of Molecular Biology, published by Blackwell Science Ltd., 1994 (ISBN 0632021829); Robert A. Meyers (ed.), Molecular Biology and Biotechnology: a Comprehensive Desk Reference, published by VCH Publishers, Inc., 1995 (ISBN 9780471 185710); Singleton e/a/., Dictionary of Microbiology and Molecular Biology 2nd ed., J. Wiley & Sons (New York, N.Y. 1994), March, Advanced Organic Chemistry Reactions, Mechanisms and Structure 4th ed., John Wiley & Sons (New York, N.Y. 1992); and Marten H. Hofker and Jan van Deursen, Transgenic Mouse Methods and Protocols, 2nd edition (201 1) .

[00156] As used herein, the singular forms “a”, “an”, and “the” include both singular and plural referents unless the context clearly dictates otherwise.

[00157] The term “optional” or “optionally” means that the subsequent described event, circumstance or substituent may or may not occur, and that the description includes instances where the event or circumstance occurs and instances where it does not.

[00158] The recitation of numerical ranges by endpoints includes all numbers and fractions subsumed within the respective ranges, as well as the recited endpoints.

[00159] The terms “about” or “approximately” as used herein when referring to a measurable value such as a parameter, an amount, a temporal duration, and the like, are meant to encompass variations of and from the specified value, such as variations of +/-l0% or less, *+1-5%* or less, +/-1% or less, and +/-0.l% or less of and from the specified value, insofar such variations are appropriate to perform in the disclosed invention. It is to be understood that the value to which the modifier “about” or “approximately” refers is itself also specifically, and preferably, disclosed.

[00160] As used herein, a “biological sample” may contain whole cells and/or live cells and/or cell debris. The biological sample may contain (or be derived from) a “bodily fluid”. The present invention encompasses embodiments wherein the bodily fluid is selected from amniotic fluid, aqueous humour, vitreous humour, bile, blood serum, breast milk, cerebrospinal fluid, cerumen (earwax), chyle, chyme, endolymph, perilymph, exudates, feces, female ejaculate, gastric acid, gastric juice, lymph, mucus (including nasal drainage and phlegm), pericardial fluid, peritoneal fluid, pleural fluid, pus, rheum, saliva, sebum (skin oil), semen, sputum, synovial fluid, sweat, tears, urine, vaginal secretion, vomit and mixtures of one or more thereof. Biological samples include cell cultures, bodily fluids, cell cultures from bodily fluids. Bodily fluids may be obtained from a mammal organism, for example by puncture, or other collecting or sampling procedures.

[00161] The terms “subject,” “individual,” and “patient” are used interchangeably herein to refer to a vertebrate, preferably a mammal, more preferably a human. Mammals include, but are not limited to, murines, simians, humans, farm animals, sport animals, and pets. Tissues, cells and their progeny of a biological entity obtained in vivo or cultured in vitro are also encompassed.

[00162] Various embodiments are described hereinafter. It should be noted that the specific embodiments are not intended as an exhaustive description or as a limitation to the broader aspects discussed herein. One aspect described in conjunction with a particular embodiment is not

necessarily limited to that embodiment and can be practiced with any other embodiment(s). Reference throughout this specification to “one embodiment”, “an embodiment,” “an example embodiment,” means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, appearances of the phrases “in one embodiment,” “in an embodiment,” or “an example embodiment” in various places throughout this specification are not necessarily all referring to the same embodiment, but may. Furthermore, the particular features, structures or characteristics may be combined in any suitable manner, as would be apparent to a person skilled in the art from this disclosure, in one or more embodiments. Furthermore, while some embodiments described herein include some but not other features included in other embodiments, combinations of features of different embodiments are meant to be within the scope of the invention. For example, in the appended claims, any of the claimed embodiments can be used in any combination.

[00163] Reference is made to US provisional application 62/734,988, filed September 21, 2018 and PCT/US20 18/060860, filed November 13, 2018.

[00164] All publications, published patent documents, and patent applications cited herein are hereby incorporated by reference to the same extent as though each individual publication, published patent document, or patent application was specifically and individually indicated as being incorporated by reference.

OVERVIEW

[00165] Embodiments disclosed herein provide for methods of analyzing single cells from archived tissue samples or tissue samples that cannot be immediately processed (e.g., FFPE or frozen tissue). Embodiments disclosed herein also provide for methods of analyzing rare or difficult to isolate cells (e.g., neurons). Tissue processing directly for single cell or single nuclei genomics advantageously provides for the ability to analyze archival samples, longitudinal samples, samples that are shipped worldwide, samples from rare diseases, and/or samples that have well documented pathology.

[00166] It is an objective of the present invention to use single cell methods on FFPE tissue samples. Single nuclei or whole cells can be isolated from FFPE tissue samples for use in analyzing single cells in archived samples or samples that cannot be immediately processed. In certain embodiments, pre-malignant lesions or tissues from cancer patients are analyzed. In certain

embodiments, the methods can be used to generate an atlas of pre-cancer and cancer tissues. Most tissues are small and preserved as FFPE and present many challenges. FFPE may damage the cell and nuclear membranes, damages the RNA and cross-links nucleotides and the FFPE protocol varies (e.g. fixation time, storage). Applicants have previously performed single nucleus RNA-seq from frozen tissue. Applicants provide methods of isolating whole cells and nuclei from FFPE tissues that can be used in single cell methods.

[00167] It is an objective of the present invention to use single cell methods on nuclei isolated from tissue samples containing rare or difficult to isolate cells. Embodiments disclosed herein provide for methods of isolating nuclei, including ribosomes or ribosomes and rough ER, from tissue samples for use in analyzing single cells, preferably, in frozen samples or samples that cannot be immediately processed. As the largest branch of the autonomic nervous system, the enteric nervous system (ENS) controls the entire gastrointestinal (GI) tract tract, but remains incompletely characterized. However, its sparsity and location within the structurally resilient GI wall has precluded the application of modern single cell genomics approaches. Here, Applicants developed RAISIN RNA-seq, which enables the capture of ribosome bound mRNA along with intact single nuclei, and use it to profile the adult mouse and human colon to generate a reference map of the ENS at a single cell level, profiling 2,447 mouse and 831 human enteric neurons This map reveals an extraordinary diversity of neuron subtypes across intestinal locations, ages, and the circadian rhythm, with conserved transcriptional programs between human and mouse. The methods provided for novel insight into ENS function that was not possible using previous methods. Applicants further highlight possible revisions to the current model of peristalsis and molecular mechanisms that may allow enteric neurons to orchestrate tissue homeostasis, including immune regulation and stem cell maintenance. Lastly, Applicants show that human enteric neurons specifically express risk genes for neuropathic, inflammatory, and extra-intestinal diseases with concomitant gut dysmotility.

[00168] It is another objective of the present invention to use novel therapeutic targets, diagnostic targets and methods of screening for modulating agents based on the characterization of the ENS described further herein. The study described herein provides a roadmap to understanding the ENS in health and disease. The GWAS disease risk genes are now shown to be expressed in neurons. Therefore, diseases can be treated by targeting the neurons specifically.

Specific therapeutic targets include markers for each neuron, transcriptional core programs, or neurotransmitter and receptor pairs. The neurons are also shown to affect immune cells. Therefore, the diseases originally not connected to immunity can be treated with anti-immune therapy (e.g., targeting IL-7, IL-12, IL-15).

[00169] It is another objective of the present method to provide nuclei specific methods of analysis for single nuclei sequencing. Applicants show improved recovery of genes and cells by counting both exons and introns and using nuclei specific filtering and batch correction.

METHODS OF RECOVERING NUCLEI OR WHOLE CELLS FROM FFPE TISSUE

[00170] In certain embodiments the invention provides methods for recovering nuclei or whole cells from a formalin-fixed paraffin-embedded (FFPE) tissue comprising dissolving paraffin from a FFPE tissue sample in a solvent, preferably a solvent selected from the group consisting of xylene and mineral oil. The tissue may be dissolved at a temperature between 4C to 90C, preferably room temperature (20 to 25C) for recovering whole cells and 90C for recovering nuclei. The tissue may be rehydrated using a gradient of ethanol from 100% to 0% ethanol (EtOH). The rehydrated tissue may be transferred to a volume of a first buffer comprising a buffering agent, a detergent and an ionic strength between lOOmM and 200mM. Optionally the first buffer comprises protease inhibitors or proteases and/or BSA. The tissue may then be chopped or dounce homogenized in the buffer and the debris may be removed by filtering and/or FACS sorting.

Tissue Samples

[00171] The tissue sample for use with the present invention may be obtained from the brain. The tissue sample may be obtained from the gut. In certain embodiments, brain and gut cells are difficult to analyze by single cell RNA sequencing due to cell morphology. In certain embodiments, single nuclei sequencing can overcome difficulty in analyzing rare cells in the gut and brain due to cell morphology. In certain embodiments, the present invention provides for genetic targeting of rare cells in a complex tissue.

[00172] In certain embodiments, the tissue sample may be obtained from the heart, lung, prostate, skeletal muscle, esophagus, skin, breast, prostate, pancreas, or colon.

[00173] In certain embodiments, the tissue sample is obtained from a subject suffering from a disease. Since samples may be frozen and analyzed by single nuclei sequencing, samples from

many diseased patients may be analyzed at once. The samples do not need to be analyzed immediately after removal from a subject. Diseased samples may be compared to healthy samples and differentially genes may be detected. In certain embodiments, the disease is autism spectrum disorder. Other diseases may include, but are not limited to, cancer (e.g., brain cancer) and irritable bowel disease (IBD). In certain embodiments, the disease can be any disease described herein (see, e.g., Examples).

[00174] Previous methods (e.g., including commercial methods) for isolating nuclei contain lysis buffers incapable of preserving a portion of the outer nuclear envelope and ribosomes, outer nuclear envelope, rough endoplasmic reticulum (RER) with ribosomes, or outer nuclear envelope, RER, and mitochondria. Before the present invention it was not appreciated that gene expression of single cells may be improved by isolating nuclei that include a portion of the outer nuclear envelope, and/or attached ribosomes, and/or rough endoplasmic reticulum (RER). In certain embodiments, the ribosomes and/or RER is a site of RNA translation and includes fully spliced mRNA. Preserving a portion of the RER improves RNA recovery and single cell expression profiling.

[00175] In certain embodiments, single nuclei comprising ribosomes and/or RER are isolated using lysis buffers comprising detergent and salt. In certain embodiments, the ionic strength of the buffer is between 100 and 200mM. As used herein the term "ionic strength" of a solution refers to the measure of electrolyte concentration and is calculated by:

$$\mu = \frac{1}{2}\sum c_i z_i^2$$

where c is the molarity of a particular ion and z is the charge on the ion.

[00176] In certain embodiments, the ionic strength of the lysis solution can be obtained with salts, such as, but not limited to NaCl, KC1, and (NH4)2S04. For example, the buffer can comprise 100-200 mM NaCl or KC1 (i.e., ionic strength 100-200 mM). In one embodiment, the salt comprises NaCl and the concentration is l46mM.

[00177] In certain embodiments, the buffer comprises CaCl2. The CaCl2 may be about lmM. In certain embodiments, the buffer comprises MgCl2. The MgCl2 may be about 2lmM.

[00178] In certain embodiments, the buffer comprises a detergent concentration that preserves a portion of the outer nuclear envelope and/or ribosomes, and/or rough endoplasmic reticulum

(RER). The detergent may be an ionic, zwitterionic or nonionic detergent. The detergent concentration may be a concentration that is sufficient to lyse cells, but not strong enough to fully dissociate the outer nuclear membrane and RER or detach ribosomes. In certain embodiments, the detergent is selected from the group consisting of NP40, CHAPS and Tween-29. Detergent concentrations may be selected based on the critical micelle concentration (CMC) for each detergent (Table 1). The concentration may be varied above and below the CMC. In certain embodiments, the detergent concentration in the lysis buffer of the present invention comprises about 0.2% NP40, about 0.49% CHAPS, or about 0.03% Tween-20. The critical micelle concentration (CMC) is defined as the concentration of surfactants above which micelles form and all additional surfactants added to the system go to micelles. Before reaching the CMC, the surface tension changes strongly with the concentration of the surfactant. After reaching the CMC, the surface tension remains relatively constant or changes with a lower slope.

[00179] The isolated nuclei comprising a preserved portion of the outer membrane and RER and/or ribosomes may be further analyzed by single nuclei sequencing, droplet single nuclei sequencing or Div-seq as described in international application number PCT/US2016/059239 published as WO/2017/164936. In certain embodiments, single nuclei are sorted into separate wells of a plate. In certain embodiments, single nuclei are sorted into individual droplets. The droplets may contain beads for barcoding the nucleic acids present in the single nuclei. The plates may include barcodes in each well. Thus, barcodes specific to the nuclei (i.e., cell) of origin may be used to determine gene expression in single cells.

Table 1.

	MW (Da)	CMC	gram per 1mL	% w/v CMC
Nonidet P-40/IGEPAL CA-630	~603	0.08 mM(sigma); 0.05-0.3 mM (anatrace)	0.00048	0.048%
Tween-20	1228	0.049 mM	0.00006	0.006%
Digitonin	70000	<0.5 mM	0.035	3.5%
CHAPS	614.9	8 to 10 mM	0.00492	0.49%

[00180] Exemplary nuclei purification protocols may be used with a lysis buffer of the present invention (Table 2).

Table 2.

Composition	Buffer	Buffer concentration	Detergent	Detergent concentration (%)	Salt and concentration	Additives and concentration
1	Tris	10 mM	NP40	0.2	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	
2	Tris	10 mM	CHAPS	0.49	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	
3	Tris	10 mM	Tween-20	0.03	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	
4	Tricine	20 mM	NP40	0.2	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	0.15 mM spermine and 0.5 mM spermidine

[00181] One of skill in the art will recognize that methods and systems of the invention are not limited to any particular type of sample or tissue type, and methods and systems of the invention may be used with any type of organic, inorganic, or biological molecule (see, e.g, US Patent Publication No. 20120122714). In particular embodiments the sample may include nucleic acid target molecules. Nucleic acid molecules may be synthetic or derived from naturally occurring sources. In one embodiment, nucleic acid molecules may be isolated from a biological sample containing a variety of other components, such as proteins, lipids and non-template nucleic acids. Nucleic acid target molecules may be obtained from any cellular material, obtained from an animal, plant, bacterium, fungus, or any other cellular organism. In certain embodiments, the nucleic acid target molecules may be obtained from a single cell. Biological samples for use in the present invention may include viral particles or preparations. Nucleic acid target molecules may be obtained directly from an organism or from a biological sample obtained from an organism, e.g., from blood, urine, cerebrospinal fluid, seminal fluid, saliva, sputum, stool and tissue. Any tissue or body fluid specimen may be used as a source for nucleic acid for use in the invention. Nucleic acid target molecules may also be isolated from cultured cells, such as a primary cell culture or a cell line. The cells or tissues from which target nucleic acids are obtained may be infected with a virus or other intracellular pathogen. A sample may also be total RNA extracted

from a biological specimen, a cDNA library, viral, or genomic DNA. Tissues may be freshly dissected, frozen tissue, or fixed tissue. In specific embodiments, the tissues are frozen in clear tubes.

[00182] Nucleic acid obtained from biological samples typically may be fragmented to produce suitable fragments for analysis. Target nucleic acids may be fragmented or sheared to desired length, using a variety of mechanical, chemical and/or enzymatic methods. DNA may be randomly sheared via sonication, e.g. Covaris method, brief exposure to a DNase, or using a mixture of one or more restriction enzymes, or a transposase or nicking enzyme. RNA may be fragmented by brief exposure to an RNase, heat plus magnesium, or by shearing. The RNA may be converted to cDNA. If fragmentation is employed, the RNA may be converted to cDNA before or after fragmentation. In one embodiment, nucleic acid from a biological sample is fragmented by sonication. In another embodiment, nucleic acid is fragmented by a hydroshear instrument. Generally, individual nucleic acid target molecules may be from about 40 bases to about 40 kb. Nucleic acid molecules may be single-stranded, double-stranded, or double-stranded with single-stranded regions (for example, stem- and loop-structures).

[00183] A biological sample as described herein may be homogenized or fractionated in the presence of a detergent or surfactant. The concentration of the detergent in the buffer may be about 0.05% to about 10.0%. The concentration of the detergent may be up to an amount where the detergent remains soluble in the solution. In one embodiment, the concentration of the detergent is between 0.1% to about 2%. The detergent, particularly a mild one that is nondenaturing, may act to solubilize the sample. Detergents may be ionic or nonionic. Examples of nonionic detergents include triton, such as the Triton™ X series (Triton™ X-100 t-Oct-C6H4—(OCH2—CH2)xOH, x=9-l0, Triton™ X-100R, Triton™ X-1 14 x=7-8), octyl glucoside, polyoxyethylene(9)dodecyl ether, digitonin, IGEPAL™ CA630 octylphenyl polyethylene glycol, n-octyl-beta-D-glucopyranoside (betaOG), n-dodecyl-beta, Tween™. 20 polyethylene glycol sorbitan monolaurate, Tween™ 80 polyethylene glycol sorbitan monooleate, polidocanol, n-dodecyl beta-D-maltoside (DDM), NEMO nonylphenyl polyethylene glycol, C12E8 (octaethylene glycol n-dodecyl monoether), hexaethyleneglycol mono-n-tetradecyl ether (C14E06), octyl-beta-thioglucopyranoside (octyl thioglucoside, OTG), Emulgen, and polyoxyethylene 10 lauryl ether (C12E10). Examples of ionic detergents (anionic or cationic) include deoxycholate, sodium

dodecyl sulfate (SDS), N-lauroylsarcosine, and cetyltrimethylammoniumbromide (CTAB). A zwitterionic reagent may also be used in the purification schemes of the present invention, such as Chaps, zwitterion 3-14, and 3-[(3-cholamidopropyl)dimethylammonio]-l-propanesulf-onate. It is contemplated also that urea may be added with or without another detergent or surfactant.

[00184] In some embodiments, the paraffin from a FFPE tissue sample may be dissolved in any suitable solvent known in the art. Such solvents include, but are not necessarily limited to, xylene, toluene, mineral oil, and vegetable oil. In specific embodiments, the solvent is xylene. In specific embodiments, the solvent is mineral oil.

[00185] In some embodiments, the tissue may be dissolved at a temperature ranging from 4°C to 90°C, such as at 4°C, 5°C, 6°C, 7°C, 8°C, 9°C, l0°C, l l°C, l2°C, l3°C, l4°C, l5°C, l6°C, l7°C, l8°C, l9°C, 20°C, 2l°C, 22°C, 23°C, 24°C, 25°C, 26°C, 27°C, 28°C, 29°C, 30°C, 3l°C, 32°C, 33°C, 34°C, 35°C, 36°C, 37°C, 38°C, 39°C, 40°C, 4l°C, 42°C, 43°C, 44°C, 45°C, 46°C, 47°C, 48°C, 49°C, 50°C, 5l°C, 52°C, 53°C, 54°C, 55°C, 56°C, 57°C, 58°C, 59°C, 60°C, 6l°C, 62°C, 63°C, 64°C, 65°C, 66°C, 67°C, 68°C, 69°C, 70°C, 7l°C, 72°C, 73°C, 74°C, 75°C, 76°C, 77°C, 78°C, 79°C, 80°C, 8l°C, 82°C, 83°C, 84°C, 85°C, 86°C, 87°C, 88°C, 89°C, or 90°C.

[00186] In specific embodiments, the tissue may be dissolved at room temperature for the purpose of recovering whole cells, such as at a temperature ranging between 20°C and 25°C.

[00187] In specific embodiments, the tissue may be dissolved at 90°C for the purpose of recovering nuclei.

[00188] In specific embodiments, dissolving paraffin from a FFPE tissue sample comprises incubating at least one time in xylene, at room temperature (RT), for about 10 minutes each, wherein xylene is removed at each change.

[00189] In specific embodiments, the tissue may be washed at least two times with xylene for about 10 min each. The washes may be performed at room temperature (RT), 90C, or at least one time at room temperature (RT) and at least one time at 90C, wherein xylene is removed at each change.

[00190] In specific embodiments, dissolving paraffin from a FFPE tissue sample comprises incubating at least twice in about 5 ml xylene per 30-100 mg FFPE tissue sample, at room

temperature, for about 10 minutes each, wherein xylene is removed at each change. As such, the tissue may be washed with xylene at 37C for about 10 min.

[00191] The method may further comprise cutting the tissue into two or more pieces and washing at least one piece of the tissue with xylene at 37C for about 10 min.

[00192] In some embodiments, dissolving paraffin from a FFPE tissue sample comprises incubating the sample at least three times in xylene, at room temperature, for about 10 minutes each, and wherein xylene is removed at each change.

[00193] The method may further comprise washing the tissue three additional times with xylene for about 10 min each, wherein the first wash is at room temperature and the second and third washes are at 90C, and wherein xylene is removed at each change.

[00194] In some embodiments, after the step of dissolving paraffin from the tissue or rehydrating the tissue the method further comprises dividing the tissue, preferably in half.

[00195] The tissue may be rehydrated using a step gradient of ethanol in concentrations ranging from l00°C to 0°C ethanol (EtOH). The tissue may be incubated between 1 to 10 minutes at each step. For example, the step gradient may comprise incubating the tissue for about two minutes each in successive washes of 95% ethanol, 75% ethanol, and 50% ethanol, or any other suitable method known in the art. In some embodiments, after the tissue is rehydrated, the method may further comprise placing the tissue samples on ice or on a device capable of maintaining the tissue between 4 and 10C, wherein all subsequent steps are performed at a temperature between 4 and 10C.

[00196] Rehydrated tissue may be transferred to a volume of a first buffer comprising a buffering agent, a detergent and an ionic strength between lOOmM and 200mM. Optionally the first buffer comprises protease inhibitors or proteases and/or BSA.

[00197] In some embodiments, the first buffer comprises a detergent selected from the group consisting of NP40, CHAPS and Tween-20. In some embodiments, the NP40 concentration may be about 0.2%. In some embodiments, the Tween-20 concentration may be about 0.03%. In some embodiments, the CHAPS concentration may be about 0.49%. In some embodiments, the first buffer may be selected from the group consisting of CST, TST, NST and NSTnPo.

[00198] The tissue may be chopped or dounce homogenized in the buffer. Non-limiting examples of chopping include cutting with scissors, chopping with a scalpel or any blade known

in the art. Chopping may be manual. Chopping may use any device known in the art capable of chopping. Any method for dounce homogenizing known in the art may be used. An exemplary method for dounce homogenization is described in the examples.

[00199] In some embodiments, after the step of chopping or dounce homogenizing the method may further comprise centrifuging. Preferably, the sample is centrifuged at about 500g for about 5 min, and the sample is then resuspended in a second buffer comprising a buffering agent and an ionic strength between lOOmM and 200mM. Optionally the second buffer comprises protease inhibitors. In some embodiments, the second buffer is ST, optionally comprising protease inhibitors.

[00200] Debris may be removed by methods including, but not necessarily limited to, filtering and/or FACS sorting. In some embodiments, the sample is filtered through a 40 uM filter. In some embodiments, the sample is filtered through a 30 uM filter. In some embodiments, the method may further comprise washing the filtered sample in the first buffer.

[00201] In some embodiments, after the step of chopping or dounce homogenizing the method may further comprise adding an additional 2 volumes of the first buffer (3 volumes total) and filtering the sample through a 40 uM filter.

[00202] In some embodiments, the method may further comprise adding an additional three volumes of the first buffer (6 volumes total). The sample is then centrifuged. Preferably, the sample is centrifuged at about 500g for about 5 min, and the sample is then resuspended in a second buffer comprising a buffering agent and an ionic strength between lOOmM and 200mM. Optionally, the second buffer comprises protease inhibitors. In some embodiments, the second buffer is ST, optionally comprising protease inhibitors.

[00203] In some embodiments, the method may further comprise isolating nuclei or cell types by FACS sorting.

[00204] In some embodiments, the method may further comprise reversing cross-linking in the tissue sample before or during any step of the method. In some embodiments, reversing cross-linking may comprise proteinase digestion. In some embodiments, the proteinase is proteinase K or a cold-active protease.

[00205] In some embodiments, the method may further comprise adding a reagent that stabilizes RNA to the tissue sample before or during any step of the method.

[00206] In some embodiments, the method may further comprise lysing recovered cells or nuclei and performing reverse transcription, as described in more detail further below.

[00207] In specific embodiments, the reverse transcription is performed in individual reaction vessels.

[00208] The individual reaction vessel may be an individual discrete volume. An "individual discrete volume" is a discrete volume or discrete space, such as a container, receptacle, or other defined volume or space that can be defined by properties that prevent and/or inhibit migration of nucleic acids and reagents necessary to carry out the methods disclosed herein, for example a volume or space defined by physical properties such as walls, for example the walls of a well, tube, or a surface of a droplet, which may be impermeable or semipermeable, or as defined by other means such as chemical, diffusion rate limited, electro-magnetic, or light illumination, or any combination thereof. By "diffusion rate limited" (for example diffusion defined volumes) is meant spaces that are only accessible to certain molecules or reactions because diffusion constraints effectively defining a space or volume as would be the case for two parallel laminar streams where diffusion will limit the migration of a target molecule from one stream to the other. By "chemical" defined volume or space is meant spaces where only certain target molecules can exist because of their chemical or molecular properties, such as size, where for example gel beads may exclude certain species from entering the beads but not others, such as by surface charge, matrix size or other physical property of the bead that can allow selection of species that may enter the interior of the bead. By "electro-magnetically" defined volume or space is meant spaces where the electro-magnetic properties of the target molecules or their supports such as charge or magnetic properties can be used to define certain regions in a space such as capturing magnetic particles within a magnetic field or directly on magnets. By "optically" defined volume is meant any region of space that may be defined by illuminating it with visible, ultraviolet, infrared, or other wavelengths of light such that only target molecules within the defined space or volume may be labeled. One advantage to the used of non-walled, or semipermeable is that some reagents, such as buffers, chemical activators, or other agents maybe passed in our through the discrete volume, while other material, such as target molecules, maybe maintained in the discrete volume or space. Typically, a discrete volume will include a fluid medium, (for example, an aqueous solution, an oil, a buffer, and/or a media capable of supporting cell growth) suitable for labeling of the target molecule with

the indexable nucleic acid identifier under conditions that permit labeling. Exemplary discrete volumes or spaces useful in the disclosed methods include droplets (for example, microfluidic droplets and/or emulsion droplets), hydrogel beads or other polymer structures (for example poly-ethylene glycol di-acrylate beads or agarose beads), tissue slides (for example, fixed formalin paraffin embedded tissue slides with particular regions, volumes, or spaces defined by chemical, optical, or physical means), microscope slides with regions defined by depositing reagents in ordered arrays or random patterns, tubes (such as, centrifuge tubes, microcentrifuge tubes, test tubes, cuvettes, conical tubes, and the like), bottles (such as glass bottles, plastic bottles, ceramic bottles, Erlenmeyer flasks, scintillation vials and the like), wells (such as wells in a plate), plates, pipettes, or pipette tips among others. In certain example embodiments, the individual discrete volumes are the wells of a microplate. In certain example embodiments, the microplate is a 96 well, a 384 well, or a 1536 well microplate.

[00209] In specific embodiments, the individual reaction vessels may be wells, chambers, or droplets.

Single cell and single nuclei sequencing

[00210] In some embodiments, the method may further comprise performing single cell, single nucleus or bulk RNA-seq, DNA-seq, ATAC-seq, or ChIP on the recovered nuclei or whole cells.

[00211] In certain embodiments, the single nuclei and cells according to the present invention are used to generate a single nuclei or single cell sequencing library. The sequencing library may be generated according to any methods known in the art. Non-limiting examples are provided herein.

[00212] In certain embodiments, the invention involves single cell RNA sequencing (see, e.g., Kalisky, T., Blainey, P. & Quake, S. R. Genomic Analysis at the Single-Cell Level. Annual review of genetics 45, 431-445, (201 1); Kalisky, T. & Quake, S. R. Single-cell genomics. Nature Methods 8, 311-314 (201 1); Islam, S. et al. Characterization of the single-cell transcriptional landscape by highly multiplex RNA-seq. Genome Research, (201 1); Tang, F. et al. RNA-Seq analysis to capture the transcriptome landscape of a single cell. Nature Protocols 5, 516-535, (2010); Tang, F. et al. mRNA-Seq whole-transcriptome analysis of a single cell. Nature Methods 6, 377-382, (2009); Ramskold, D. et al. Full-length mRNA-Seq from single-cell levels of RNA and individual circulating tumor cells. Nature Biotechnology 30, 777-782, (2012); and Hashimshony, T., Wagner,

F., Sher, N. & Yanai, I. CEL-Seq: Single-Cell RNA-Seq by Multiplexed Linear Amplification. Cell Reports, Cell Reports, Volume 2, Issue 3, p666-673, 2012).

[00213] In certain embodiments, the invention involves plate based single cell RNA sequencing (see, e.g., Picelli, S. et al., 2014, "Full-length RNA-seq from single cells using Smart-seq2" Nature protocols 9, 171-181, doi:l0.l038/nprot.20l4.006).

[00214] In certain embodiments, the invention involves high-throughput single-cell RNA-seq. In this regard reference is made to Macosko et al., 2015, "Highly Parallel Genome-wide Expression Profiling of Individual Cells ETsing Nanoliter Droplets" Cell 161, 1202-1214; International patent application number PCT/US20 15/049 178, published as W02016/040476 on March 17, 2016; Klein et al., 2015, "Droplet Barcoding for Single-Cell Transcriptomics Applied to Embryonic Stem Cells" Cell 161, 1187-1201; International patent application number PCT/US20 16/027734, published as WO2016168584A1 on October 20, 2016; Zheng, et al., 2016, "Haplotyping germline and cancer genomes with high-throughput linked-read sequencing" Nature Biotechnology 34, 303-31 1; Zheng, et al., 2017, "Massively parallel digital transcriptional profiling of single cells" Nat. Commun. 8, 14049 doi: l0.l038/ncommsl4049; International patent publication number WO2014210353A2; Zilionis, et al., 2017, "Single-cell barcoding and sequencing using droplet microfluidics" Nat Protoc. Jan;l2(l):44-73; Cao et al., 2017, "Comprehensive single cell transcriptional profiling of a multicellular organism by combinatorial indexing" bioRxiv preprint first posted online Feb. 2, 2017, doi: dx.doi.org/l0.H0l/l04844; Rosenberg et al., 2017, "Scaling single cell transcriptomics through split pool barcoding" bioRxiv preprint first posted online Feb. 2, 2017, doi: dx.doi.org/l0.H0l/l05l63; Vitak, et al., "Sequencing thousands of single-cell genomes with combinatorial indexing" Nature Methods, l4(3):302-308, 2017; Cao, et al., Comprehensive single-cell transcriptional profiling of a multicellular organism. Science, 357(6352):66l-667, 2017; and Gierahn et al., "Seq-Well: portable, low-cost RNA sequencing of single cells at high throughput" Nature Methods 14, 395-398 (2017), all the contents and disclosure of each of which are herein incorporated by reference in their entirety.

[00215] In certain embodiments, the invention involves single nucleus RNA sequencing. In this regard reference is made to Swiech et al., 2014, "In vivo interrogation of gene function in the mammalian brain using CRISPR-Cas9" Nature Biotechnology Vol. 33, pp. 102-106; Habib et al.,

2016, “Div-Seq: Single-nucleus RNA-Seq reveals dynamics of rare adult newborn neurons” Science, Vol. 353, Issue 6302, pp. 925-928; Habib et al., 2017, “Massively parallel single-nucleus RNA-seq with DroNc-seq” Nat Methods. 2017 Oct;l4(lO):955-958; and International patent application number PCT/US2016/059239, published as WO2017164936 on September 28, 2017, which are herein incorporated by reference in their entirety.

[00216] In certain embodiments, the invention involves the Assay for Transposase Accessible Chromatin using sequencing (ATAC-seq) as described (see, e.g., Buenrostro, et al., Transposition of native chromatin for fast and sensitive epigenomic profiling of open chromatin, DNA-binding proteins and nucleosome position. Nature methods 2013; 10 (12): 1213-1218; Buenrostro et al., Single-cell chromatin accessibility reveals principles of regulatory variation. Nature 523, 486-490 (2015); Cusanovich, D. A., Daza, R., Adey, A., Pliner, H., Christiansen, L., Gunderson, K. L., Steemers, F. J., Trapnell, C. & Shendure, J. Multiplex single-cell profiling of chromatin accessibility by combinatorial cellular indexing. Science. 2015 May 22;348(6237):9l0-4. doi: l0.H26/science.aabl60l. Epub 2015 May 7; US20160208323A1; US20160060691A1; and WO2017156336A1).

[00217] In certain embodiments, single cell expression profiling comprises single nucleus RNA sequencing. Single nucleus RNA sequencing advantageously provides for expression profiling of rare or hard to isolate cells. Additionally, single nucleus RNA sequencing may be used on fixed or frozen tissues. The ability of single nucleus sequencing to be performed on frozen tissues allows for the analysis of archived samples isolated from diseased tissues. RNA recovery from previous single nuclei sequencing methods is robust enough for measuring single cell gene expression, however, increased RNA recovery can allow increase gene reads per single cell. Applicants have unexpectedly determined that single nuclei comprising a portion of the rough endoplasmic reticulum (RER) can be isolated and the resulting nuclei provides for improved RNA recovery and single cell expression profiling. In some embodiments, the methods provide for isolation of single nuclei with partially intact outer membrane containing RER. In some embodiments, the methods allow for isolation of single nuclei with partially intact outer membrane and partially intact RER with ribosomes. In some embodiments, the methods allow for isolation of single nuclei with partially intact outer membrane, RER and mitochondria.

[00218] In certain embodiments, the present invention provides for a method of single cell sequencing comprising: extracting nuclei from a population of cells under conditions that preserve a portion of the outer nuclear envelope and/or rough endoplasmic reticulum (RER); sorting single nuclei into separate reaction vessels (discrete volumes); extracting RNA from the single nuclei; generating a cDNA library; and sequencing the library, whereby gene expression data from single cells is obtained. As used herein, the term "discrete volume" refers to any reaction volume, vessel, chamber, or the like capable of separating one object from another (e.g., single cell, single nuclei, single bead. Non-limiting examples of discrete volumes include droplets (e.g., emulsion droplets), wells in a plate, or microfluidic chambers.

[00219] In certain embodiments, extracting nuclei under conditions that preserve a portion of the outer nuclear envelope and rough endoplasmic reticulum (RER) comprises chopping, homogenizing or grinding the population of cells in a lysis buffer comprising: a detergent selected from the group consisting of NP40, CHAPS and Tween-20; and an ionic strength between lOOmM and 200mM. The NP40 concentration may be about 0.2%. The Tween-20 concentration may be about 0.03%. The CHAPS concentration may be about 0.49%. In some embodiments, polyamines may be included. Non-limiting examples of chopping include cutting with scissors, chopping with a scalpel or any blade known in the art. Chopping may be manual. Chopping may use any device known in the art capable of chopping.

[00220] In certain embodiments, the population of cells may be treated with a reagent that stabilizes RNA. The reagent that stabilizes RNA may be a reagent that comprises the properties of RNAlaterTM.

[00221] In certain embodiments, the separate reaction vessels may be microwells in a plate, as described elsewhere herein. In certain embodiments, the separate reaction vessels may be microfluidic droplets.

[00222] Applicants developed microfluidic devices and protocols that allow Drop-seq analysis of thousands of isolated nuclei (Dronc-Seq) (see, e.g., Habib et al., 2016, "Div-Seq: Single-nucleus RNA-Seq reveals dynamics of rare adult newborn neurons" Science, Vol. 353, Issue 6302, pp. 925-928; Habib et al., 2017, "Massively parallel single-nucleus RNA-seq with DroNc-seq" Nat Methods. 2017 Oct;l4(lO):955-958; and International patent application number PCT/US2016/059239). Furthermore, Applicants have recently made important progress with

reverse emulsion devices used for other nuclei-based molecular biology applications, such as a droplet version of single-cell ATAC-Seq. The methods can be applied to single nuclei extracted from tissue samples (e.g., FFPE and frozen tissues). To develop Dronc-Seq Applicants combined the nuclei preparation protocol of Nuc-Seq, a new device compatible with nuclei separation, and Drop-Seq reagents (barcoded beads, molecular biology protocols, lysis buffers) for the in-drop and subsequent phases of the protocol. Briefly, as in Nuc-Seq, Applicants used the published (Sweich et al., 2015) protocols for high quality generation of nuclei suspensions from mouse hippocampus. Unlike Nuc-Seq, where Applicants next sort single nuclei using FACS, in Dronc-Seq Applicants use a microfluidics device, following on the design principles of Drop-Seq, but optimized for the size and properties of nuclei. The nuclei are lysed in drops, and their mRNA captured on the Drop-Seq beads. Notably, given the smaller quantity of mRNA in nuclei, ensuring efficient capture is key. A complementary modality (Klein et al., 2015) has higher capture but lower throughput than Drop-Seq. Finally, Applicants test for cross-contamination due to 'sticky' RNA from the lysed cytoplasms or leakage from nuclei using the cross-species controls developed for Drop-Seq (Macosko et al., 2015). Nuclei can also be sorted through FACS prior to Drop-Seq encapsulation. Applicants can also use pore-blocking polymers called poloxamers, such as F-68 and F-127 (Sengupta et al.,20l5). Applicants can use Dronc-Seq in the hippocampal biological system and compare to the available of Nuc-Seq benchmarking data. Applicants can also generate Nuc-Seq and Dronc-Seq data from the retina, demonstrating its generality.

[00223] In some embodiments, the method may further comprise staining the recovered cells or nuclei using any suitable staining methods known in the art. In specific embodiments, the stain comprises ruby stain.

METHODS OF RECOVERING NUCLEI AND ATTACHED RIBOSOMES FROM A TISSUE SAMPLE

[00224] In some embodiments, the invention provides for methods of recovering nuclei and attached ribosomes from a tissue sample comprising chopping the tissue sample at between 0-4 °C in a nuclear extraction buffer comprising Tris buffer, a detergent and salts; and filtering the sample through a filter between 30-50 uM, preferably 40 uM, and optionally washing the filter with fresh

nuclear extraction buffer, wherein the nuclei are present in the supernatant passed through the filter.

[00225] As described elsewhere herein, the buffer may comprise a detergent concentration that preserves a portion of the outer nuclear envelope and/or ribosomes, and/or rough endoplasmic reticulum (RER). The detergent may be an ionic, zwitterionic or nonionic detergent. The detergent concentration may be a concentration that is sufficient to lyse cells, but not strong enough to fully dissociate the outer nuclear membrane and RER or detach ribosomes. In certain embodiments, the detergent is selected from the group consisting of NP40, CHAPS and Tween-29. Detergent concentrations may be selected based on the critical micelle concentration (CMC) for each detergent (Table 1). The concentration may be varied above and below the CMC. In certain embodiments, the detergent concentration in the lysis buffer of the present invention comprises about 0.2% NP40, about 0.49% CHAPS, or about 0.03% Tween-20. The critical micelle concentration (CMC) is defined as the concentration of surfactants above which micelles form and all additional surfactants added to the system go to micelles. Before reaching the CMC, the surface tension changes strongly with the concentration of the surfactant. After reaching the CMC, the surface tension remains relatively constant or changes with a lower slope.

[00226] In some embodiments, the nuclear extraction buffer comprises 10-20 mM Tris, about 0.49% CHAPS, a salt concentration having an ionic strength of l00-250mM, and about 0.01% BSA, whereby nuclei are recovered that have a preserved nuclear envelope and ribosomes.

[00227] In some embodiments, the nuclear extraction buffer is buffer CST.

[00228] In some embodiments, the nuclear extraction buffer comprises 10-20 mM Tris, about 0.03% Tween-20, a salt concentration having an ionic strength of l00-250mM, and about 0.01% BSA, whereby nuclei are recovered that have a preserved nuclear envelope, rough ER and ribosomes.

[00229] In some embodiments, the nuclear extraction buffer is buffer TST.

[00230] In some embodiments, the salts comprise 146 mM NaCl, lmM CaCl2, and 2lmM MgCl2.

[00231] As described elsewhere herein, chopping may comprise chopping with scissors for 1-10 minutes.

[00232] In some embodiments, nuclei from specific cell types are genetically modified to express a detectable label on the nuclear membrane and the method further comprises enriching nuclei from the specific cell types using the detectable label.

[00233] In some embodiments, the method may further comprise staining the recovered nuclei. In some embodiments, the stain comprises ruby stain.

[00234] In some embodiments, the nuclei may be sorted into discrete volumes by FACS, as described elsewhere herein.

[00235] In some embodiments, the method may further comprise pelleting the nuclei and resuspending the nuclei in a second buffer consisting of Tris buffer and salts. In some embodiments, the second buffer is buffer ST.

[00236] In some embodiments, the method may further comprise generating a single nucleus barcoded library for the recovered nuclei, wherein the nucleic acid from each nucleus is labeled with a barcode sequence comprising a cell of origin barcode, optionally the barcode sequence includes a cell of origin barcode and a unique molecular identifier (UMI).

[00237] The term “unique molecular identifiers” (UMI) as used herein refers to a sequencing linker or a subtype of nucleic acid barcode used in a method that uses molecular tags to detect and quantify unique amplified products. A UMI is used to distinguish effects through a single clone from multiple clones. The term “clone” as used herein may refer to a single transcript (e.g., mRNA) or target nucleic acid to be sequenced. Each clone amplified will have a different random UMI that will indicate that the amplified product originated from that clone. The UMI may also be used to determine the number of transcripts that gave rise to an amplified product, or in the case of target barcodes, the number of binding events. In preferred embodiments, the amplification is by PCR or multiple displacement amplification (MDA).

[00238] In certain embodiments, reverse transcription (RT) is used to label RNA from single cells or single nuclei with a cell of origin barcode, preferably, a cell of origin barcode and unique molecular identifier (UMI). The barcode may be included on a barcoded RT primer. The primer may also include a capture sequence (e.g., poly T sequence). Thus, the present invention may include barcoding.

[00239] The term “barcode” as used herein refers to a short sequence of nucleotides (for example, DNA or RNA) that is used as an identifier for an associated molecule, such as a target

molecule and/or target nucleic acid, or as an identifier of the source of an associated molecule, such as a cell-of-origin or individual transcript. A barcode may also refer to any unique, non-naturally occurring, nucleic acid sequence that may be used to identify the originating source of a nucleic acid fragment. Although it is not necessary to understand the mechanism of an invention, it is believed that the barcode sequence provides a high-quality individual read of a barcode associated with a single cell, single nuclei, a viral vector, labeling ligand (e.g., antibody or aptamer), protein, shRNA, sgRNA or cDNA such that multiple species can be sequenced together. Exemplary barcodes may be sequences including but not limited to, TTGAGCCT, AGTTGCTT, CCAGTTAG, ACCAACTG, GTATAACA or CAGGAGCC.

[00240] Barcoding may be performed based on any of the compositions or methods disclosed in patent publication WO 2014047561 Al, Compositions and methods for labeling of agents, incorporated herein in its entirety. In certain embodiments barcoding uses an error correcting scheme (T. K. Moon, Error Correction Coding: Mathematical Methods and Algorithms (Wiley, New York, ed. 1, 2005)). Not being bound by a theory, amplified sequences from single cells can be sequenced together and resolved based on the barcode associated with each cell or nuclei.

[00241] The invention provides a mixture comprising a plurality of nucleotide- or oligonucleotide- adorned beads, wherein said beads comprises: a linker; an identical sequence for use as a sequencing priming site; a uniform or near-uniform nucleotide or oligonucleotide sequence; a ETnique Molecular Identifier (ΕΓΜΙ) which differs for each priming site; an oligonucleotide redundant sequence for capturing polyadenylated mRNAs and priming reverse transcription; and optionally at least one additional oligonucleotide sequences, which provide substrates for downstream molecular-biological reactions; wherein the uniform or near-uniform nucleotide or oligonucleotide sequence is the same across all the priming sites on any one bead, but varies among the oligonucleotides on an individual bead.

[00242] In some embodiments, RNA and/or DNA is labeled with the barcode sequence.

[00243] In some embodiments, the library is an RNA-seq, DNA-seq, and/or ATAC-seq library, as described elsewhere herein.

[00244] In some embodiments, the method may further comprise sequencing the library.

[00245] In some embodiments, the tissue sample is fresh frozen.

Nuclei purification protocol from frozen tissue

[00246] In certain embodiments, nuclei extracted from FFPE tissues is compared to nuclei extracted from frozen tissue. Nuclei purification protocol (see., e.g., Swiech L, et al., Nat Biotechnol. 2015 Jan;33(l): 102-6. doi: l0.l038/nbt.3055. Epub 2014 Oct 19). The protocol may be modified by using the lysis buffer as described above. In certain embodiments, the procedure may be used for frozen/fixed tissue.

1. **Dounce** homogenize tissue in **2ml** of ice-cold lysis buffer (25 times with a, 25 times with b), transfer to a 15 ml tube.

1. Rinse homogenizer with **2ml** of ice-cold lysis buffer to get final 4 ml, and collect in the same tube.

2. Mix well and set on ice for 5 minutes.

3. Collect the nuclei by centrifugation at 500 x g for 5 minutes at 4 °C. Carefully aspirate the clear supernatant from each tube and set the nuclei pellet on ice. Note: The supernatant contains cytoplasmic components and can be saved for later analysis or use.

4. Resuspend. Add 1 ml cold lysis buffer and mix by pipetting gently with a lml tip to completely suspend nuclei pellet. Add the remaining 3 ml of lysis buffer, mix well and set on ice for 5 minutes.

5. Collect washed nuclei by centrifugation as in step 3. Carefully aspirate the clear supernatant and set the nuclei pellet on ice.

6. Optional: Wash. Resuspend in 4ml **0.01% PBS BSA or Resuspension buffer (RB*).** Collect washed nuclei by centrifugation as in step 3.

7. Resuspend with ~500pl **Resuspension buffer (RB*) or 0.01 %PBS BSA + RNAse inhibitor** carefully by slow vortex & pipette lOx with a lml tip, then transfer to tubes (for FACS, filter through a membrane to get better purity.

8. Counterstain nuclei with **Ruby Dye 1:500-1:1000** (check for clumps in the microscope before sorting).

Table 3. Resuspension buffer- based on the original nuclei resuspension buffer from Swiech *et al.* 2015:

	Stocks	**For 10 ml**
340 mM Sucrose	1 M	3.4 ml
2 mM MgCl2	1 M	10 ul
25 mM KCl	2M	125 ul

65 mM glycerophosphate	1M	650ul
5% glycerol	100%	500 ul

[00247] In certain embodiments, nuclei extracted according to any method described herein may be isolated by sucrose gradient centrifugation as described (Swiech L, et al. Nat Biotechnol. 2015 Jan;33(l): 102-6).

[00248] In some embodiments, the tissue sample comprises cells originating from the central nervous system (CNS) or enteric nervous system (ENS). In some embodiments, the tissue sample is obtained from the gut or the brain. In some embodiments, the tissue sample is obtained from a subject suffering from a disease.

[00249] In some embodiments, the tissue sample is treated with a reagent that stabilizes RNA.

[00250] In some embodiments, the discrete volumes may be droplets, wells in a plate, or microfluidic chambers, as described elsewhere herein.

METHODS OF TREATING DISEASES

[00251] The invention also provides a method of treating a disease selected from the group consisting of Hirschsprung's disease (HSCR), inflammatory bowel disease (IBD), autism spectrum disorder (ASD), Parkinson's disease (PD) and schizophrenia in a subject in need thereof. The method comprises administering one or more agents capable of modulating the function or activity of one or more neurons selected from the group consisting of PEMN1, PEMN2, PIMN1, PIMN2, PIMN3, PIMN4, PIMN5, PIN1, PIN2, PSN and PSVN, or one or more cells functionally interacting with the one or more neurons.

[00252] As used herein, "treatment" or "treating," or "palliating" or "ameliorating" are used interchangeably. These terms refer to an approach for obtaining beneficial or desired results including but not limited to a therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant any therapeutically relevant improvement in or effect on one or more diseases, conditions, or symptoms under treatment. For prophylactic benefit, the compositions may be administered to a subject at risk of developing a particular disease, condition, or symptom, or to a subject reporting one or more of the physiological symptoms of a disease, even though the disease, condition, or symptom may not have yet been manifested. As used herein "treating" includes

ameliorating, curing, preventing it from becoming worse, slowing the rate of progression, or preventing the disorder from re-occurring (i.e., to prevent a relapse).

[00253] The term "effective amount" or "therapeutically effective amount" refers to the amount of an agent that is sufficient to effect beneficial or desired results. The therapeutically effective amount may vary depending upon one or more of: the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will provide an image for detection by any one of the imaging methods described herein. The specific dose may vary depending on one or more of: the particular agent chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to be imaged, and the physical delivery system in which it is carried.

Modulating Agents

[00254] In certain embodiments, the present invention provides for one or more therapeutic agents against combinations of targets identified. Targeting the identified genes or cells may provide for enhanced or otherwise previously unknown activity in the treatment of disease. In certain embodiments, an agent against one of the targets may already be known or used clinically. In certain embodiments, a combination therapy may require less of the agent as compared to the current standard of care and provide for less toxicity and improved treatment. In certain embodiments, the agents are used to modulate cell types. For example, the agents may be used to modulate cells for adoptive cell transfer. In certain embodiments, the one or more agents comprises a small molecule inhibitor, small molecule degrader (e.g., PROTAC), genetic modifying agent, antibody, antibody fragment, antibody-like protein scaffold, aptamer, protein, or any combination thereof.

[00255] The terms "therapeutic agent", "therapeutic capable agent" or "treatment agent" are used interchangeably and refer to a molecule or compound that confers some beneficial effect upon administration to a subject. The beneficial effect includes enablement of diagnostic determinations; amelioration of a disease, symptom, disorder, or pathological condition; reducing or preventing the onset of a disease, symptom, disorder or condition; and generally counteracting a disease, symptom, disorder or pathological condition.

[00256] In certain embodiments, the one or more agents is a small molecule. The term "small molecule" refers to compounds, preferably organic compounds, with a size comparable to those organic molecules generally used in pharmaceuticals. The term excludes biological macromolecules (e.g., proteins, peptides, nucleic acids, etc.). Preferred small organic molecules range in size up to about 5000 Da, e.g., up to about 4000, preferably up to 3000 Da, more preferably up to 2000 Da, even more preferably up to about 1000 Da, e.g., up to about 900, 800, 700, 600 or up to about 500 Da. In certain embodiments, the small molecule may act as an antagonist or agonist (e.g., blocking an enzyme active site or activating a receptor by binding to a ligand binding site).

[00257] One type of small molecule applicable to the present invention is a degrader molecule. Proteolysis Targeting Chimera (PROTAC) technology is a rapidly emerging alternative therapeutic strategy with the potential to address many of the challenges currently faced in modern drug development programs. PROTAC technology employs small molecules that recruit target proteins for ubiquitination and removal by the proteasome (see, e.g., Zhou et al., Discovery of a Small-Molecule Degrader of Bromodomain and Extra- Terminal (BET) Proteins with Picomolar Cellular Potencies and Capable of Achieving Tumor Regression. J. Med. Chem. 2018, 61, 462-481; Bondeson and Crews, Targeted Protein Degradation by Small Molecules, Annu Rev Pharmacol Toxicol. 2017 Jan 6; 57: 107-123; and Lai et al., Modular PROTAC Design for the Degradation of Oncogenic BCR-ABL Angew Chem Int Ed Engl. 2016 Jan 11; 55(2): 807-810).

[00258] In certain embodiments, the one or more modulating agents may be a genetic modifying agent. The genetic modifying agent may comprise a CRISPR system, a zinc finger nuclease system, a TALEN, a meganuclease or RNAi system.

CRISPR Systems

[00259] In general, a CRISPR-Cas or CRISPR system as used in herein and in documents, such as WO 2014/093622 (PCT/US20 13/074667), refers collectively to transcripts and other elements involved in the expression of or directing the activity of CRISPR-associated ("Cas") genes, including sequences encoding a Cas gene, a tracr (trans-activating CRISPR) sequence (e.g. tracrRNA or an active partial tracrRNA), a tracr-mate sequence (encompassing a "direct repeat" and a tracrRNA-processed partial direct repeat in the context of an endogenous CRISPR system), a guide sequence (also referred to as a "spacer" in the context of an endogenous CRISPR system), or "RNA(s)" as that term is herein used (e.g., RNA(s) to guide Cas, such as Cas9, e.g. CRISPR

RNA and transactivating (tracr) RNA or a single guide RNA (sgRNA) (chimeric RNA)) or other sequences and transcripts from a CRISPR locus. In general, a CRISPR system is characterized by elements that promote the formation of a CRISPR complex at the site of a target sequence (also referred to as a protospacer in the context of an endogenous CRISPR system). See, e.g, Shmakov et al. (2015) "Discovery and Functional Characterization of Diverse Class 2 CRISPR-Cas Systems", Molecular Cell, DOI: dx.doi.org/l0.l0l6/j.molcel. 2015. 10.008.

[00260] In certain embodiments, a protospacer adjacent motif (PAM) or PAM-like motif directs binding of the effector protein complex as disclosed herein to the target locus of interest. In some embodiments, the PAM may be a 5' PAM (i.e., located upstream of the 5' end of the protospacer). In other embodiments, the PAM may be a 3' PAM (i.e., located downstream of the 5' end of the protospacer). The term "PAM" may be used interchangeably with the term "PFS" or "protospacer flanking site" or "protospacer flanking sequence".

[00261] In a preferred embodiment, the CRISPR effector protein may recognize a 3' PAM. In certain embodiments, the CRISPR effector protein may recognize a 3' PAM which is 5'H , wherein H is A, C or U.

[00262] In the context of formation of a CRISPR complex, "target sequence" refers to a sequence to which a guide sequence is designed to have complementarity, where hybridization between a target sequence and a guide sequence promotes the formation of a CRISPR complex. A target sequence may comprise RNA polynucleotides. The term "target RNA" refers to a RNA polynucleotide being or comprising the target sequence. In other words, the target RNA may be a RNA polynucleotide or a part of a RNA polynucleotide to which a part of the gRNA, i.e. the guide sequence, is designed to have complementarity and to which the effector function mediated by the complex comprising CRISPR effector protein and a gRNA is to be directed. In some embodiments, a target sequence is located in the nucleus or cytoplasm of a cell.

[00263] In certain example embodiments, the CRISPR effector protein may be delivered using a nucleic acid molecule encoding the CRISPR effector protein. The nucleic acid molecule encoding a CRISPR effector protein, may advantageously be a codon optimized CRISPR effector protein. An example of a codon optimized sequence, is in this instance a sequence optimized for expression in eukaryote, e.g., humans (i.e. being optimized for expression in humans), or for another eukaryote, animal or mammal as herein discussed; see, e.g., SaCas9 human codon

optimized sequence in WO 2014/093622 (PCT/US20 13/074667). Whilst this is preferred, it will be appreciated that other examples are possible and codon optimization for a host species other than human, or for codon optimization for specific organs is known. In some embodiments, an enzyme coding sequence encoding a CRISPR effector protein is a codon optimized for expression in particular cells, such as eukaryotic cells. The eukaryotic cells may be those of or derived from a particular organism, such as a plant or a mammal, including but not limited to human, or non-human eukaryote or animal or mammal as herein discussed, e.g., mouse, rat, rabbit, dog, livestock, or non-human mammal or primate. In some embodiments, processes for modifying the germ line genetic identity of human beings and/or processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes, may be excluded. In general, codon optimization refers to a process of modifying a nucleic acid sequence for enhanced expression in the host cells of interest by replacing at least one codon (e.g. about or more than about 1, 2, 3, 4, 5, 10, 15, 20, 25, 50, or more codons) of the native sequence with codons that are more frequently or most frequently used in the genes of that host cell while maintaining the native amino acid sequence. Various species exhibit particular bias for certain codons of a particular amino acid. Codon bias (differences in codon usage between organisms) often correlates with the efficiency of translation of messenger RNA (mRNA), which is in turn believed to be dependent on, among other things, the properties of the codons being translated and the availability of particular transfer RNA (tRNA) molecules. The predominance of selected tRNAs in a cell is generally a reflection of the codons used most frequently in peptide synthesis. Accordingly, genes can be tailored for optimal gene expression in a given organism based on codon optimization. Codon usage tables are readily available, for example, at the "Codon Usage Database" available at kazusa.orjp/codon/ and these tables can be adapted in a number of ways. See Nakamura, Y., et al. "Codon usage tabulated from the international DNA sequence databases: status for the year 2000" Nucl. Acids Res. 28:292 (2000). Computer algorithms for codon optimizing a particular sequence for expression in a particular host cell are also available, such as Gene Forge (Aptagen; Jacobus, PA), are also available. In some embodiments, one or more codons (e.g. 1, 2, 3, 4, 5, 10, 15, 20, 25, 50, or more, or all codons) in a sequence encoding a Cas correspond to the most frequently used codon for a particular amino acid.

[00264] In certain embodiments, the methods as described herein may comprise providing a Cas transgenic cell in which one or more nucleic acids encoding one or more guide RNAs are provided or introduced operably connected in the cell with a regulatory element comprising a promoter of one or more gene of interest. As used herein, the term "Cas transgenic cell" refers to a cell, such as a eukaryotic cell, in which a Cas gene has been genomically integrated. The nature, type, or origin of the cell are not particularly limiting according to the present invention. Also the way the Cas transgene is introduced in the cell may vary and can be any method as is known in the art. In certain embodiments, the Cas transgenic cell is obtained by introducing the Cas transgene in an isolated cell. In certain other embodiments, the Cas transgenic cell is obtained by isolating cells from a Cas transgenic organism. By means of example, and without limitation, the Cas transgenic cell as referred to herein may be derived from a Cas transgenic eukaryote, such as a Cas knock-in eukaryote. Reference is made to WO 2014/093622 (PCT/US13/74667), incorporated herein by reference. Methods of US Patent Publication Nos. 20120017290 and 201 10265198 assigned to Sangamo BioSciences, Inc. directed to targeting the Rosa locus may be modified to utilize the CRISPR Cas system of the present invention. Methods of US Patent Publication No. 20130236946 assigned to Cellectis directed to targeting the Rosa locus may also be modified to utilize the CRISPR Cas system of the present invention. By means of further example reference is made to Platt et. al. (Cell; 159(2):440-455 (2014)), describing a Cas9 knock-in mouse, which is incorporated herein by reference. The Cas transgene can further comprise a Lox-Stop-polyA-Lox(LSL) cassette thereby rendering Cas expression inducible by Cre recombinase. Alternatively, the Cas transgenic cell may be obtained by introducing the Cas transgene in an isolated cell. Delivery systems for transgenes are well known in the art. By means of example, the Cas transgene may be delivered in for instance eukaryotic cell by means of vector (e.g., AAV, adenovirus, lentivirus) and/or particle and/or nanoparticle delivery, as also described herein elsewhere.

[00265] It will be understood by the skilled person that the cell, such as the Cas transgenic cell, as referred to herein may comprise further genomic alterations besides having an integrated Cas gene or the mutations arising from the sequence specific action of Cas when complexed with RNA capable of guiding Cas to a target locus.

[00266] In certain aspects the invention involves vectors, e.g. for delivering or introducing in a cell Cas and/or RNA capable of guiding Cas to a target locus (i.e. guide RNA), but also for propagating these components (e.g. in prokaryotic cells). A used herein, a "vector" is a tool that allows or facilitates the transfer of an entity from one environment to another. It is a replicon, such as a plasmid, phage, or cosmid, into which another DNA segment may be inserted so as to bring about the replication of the inserted segment. Generally, a vector is capable of replication when associated with the proper control elements. In general, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. Vectors include, but are not limited to, nucleic acid molecules that are single-stranded, double-stranded, or partially double-stranded; nucleic acid molecules that comprise one or more free ends, no free ends (e.g. circular); nucleic acid molecules that comprise DNA, RNA, or both; and other varieties of polynucleotides known in the art. One type of vector is a "plasmid," which refers to a circular double stranded DNA loop into which additional DNA segments can be inserted, such as by standard molecular cloning techniques. Another type of vector is a viral vector, wherein virally-derived DNA or RNA sequences are present in the vector for packaging into a virus (e.g. retroviruses, replication defective retroviruses, adenoviruses, replication defective adenoviruses, and adeno-associated viruses (AAVs)). Viral vectors also include polynucleotides carried by a virus for transfection into a host cell. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g. bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively-linked. Such vectors are referred to herein as "expression vectors." Common expression vectors of utility in recombinant DNA techniques are often in the form of plasmids.

[00267] Recombinant expression vectors can comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory elements, which may be selected on the basis of the host cells to be used for expression, that is operatively-linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean

that the nucleotide sequence of interest is linked to the regulatory element(s) in a manner that allows for expression of the nucleotide sequence (e.g. in an in vitro transcription/translation system or in a host cell when the vector is introduced into the host cell). With regards to recombination and cloning methods, mention is made of U.S. patent application 10/815,730, published September 2, 2004 as US 2004-0171 156 Al, the contents of which are herein incorporated by reference in their entirety. Thus, the embodiments disclosed herein may also comprise transgenic cells comprising the CRISPR effector system. In certain example embodiments, the transgenic cell may function as an individual discrete volume. In other words samples comprising a masking construct may be delivered to a cell, for example in a suitable delivery vesicle and if the target is present in the delivery vesicle the CRISPR effector is activated and a detectable signal generated.

[00268] The vector(s) can include the regulatory element(s), e.g., promoter(s). The vector(s) can comprise Cas encoding sequences, and/or a single, but possibly also can comprise at least 3 or 8 or 16 or 32 or 48 or 50 guide RNA(s) (e.g., sgRNAs) encoding sequences, such as 1-2, 1-3, 1-4 1-5, 3-6, 3-7, 3-8, 3-9, 3-10, 3-8, 3-16, 3-30, 3-32, 3-48, 3-50 RNA(s) (e.g., sgRNAs). In a single vector there can be a promoter for each RNA (e.g., sgRNA), advantageously when there are up to about 16 RNA(s); and, when a single vector provides for more than 16 RNA(s), one or more promoter(s) can drive expression of more than one of the RNA(s), e.g., when there are 32 RNA(s), each promoter can drive expression of two RNA(s), and when there are 48 RNA(s), each promoter can drive expression of three RNA(s). By simple arithmetic and well established cloning protocols and the teachings in this disclosure one skilled in the art can readily practice the invention as to the RNA(s) for a suitable exemplary vector such as AAV, and a suitable promoter such as the U6 promoter. For example, the packaging limit of AAV is ~4.7 kb. The length of a single U6-gRNA (plus restriction sites for cloning) is 361 bp. Therefore, the skilled person can readily fit about 12-16, e.g., 13 U6-gRNA cassettes in a single vector. This can be assembled by any suitable means, such as a golden gate strategy used for TALE assembly (genome-engineering.org/taleffectors/). The skilled person can also use a tandem guide strategy to increase the number of U6-gRNAs by approximately 1.5 times, e.g., to increase from 12-16, e.g., 13 to approximately 18-24, e.g., about 19 U6-gRNAs. Therefore, one skilled in the art can readily reach approximately 18-24, e.g., about 19 promoter-RNAs, e.g., U6-gRNAs in a single vector, e.g., an AAV vector. A further means for increasing the number of promoters and RNAs in a vector is to use a single promoter (e.g., U6) to

express an array of RNAs separated by cleavable sequences. And an even further means for increasing the number of promoter-RNAs in a vector, is to express an array of promoter-RNAs separated by cleavable sequences in the intron of a coding sequence or gene; and, in this instance it is advantageous to use a polymerase II promoter, which can have increased expression and enable the transcription of long RNA in a tissue specific manner. (see, e.g., nar.oxfordjournals.org/content/34/7/e53.short and nature.com/mt/journal/vl6/n9/abs/mt2008l44a.html). In an advantageous embodiment, AAV may package U6 tandem gRNA targeting up to about 50 genes. Accordingly, from the knowledge in the art and the teachings in this disclosure the skilled person can readily make and use vector(s), e.g., a single vector, expressing multiple RNAs or guides under the control or operatively or functionally linked to one or more promoters—especially as to the numbers of RNAs or guides discussed herein, without any undue experimentation.

[00269] The guide RNA(s) encoding sequences and/or Cas encoding sequences, can be functionally or operatively linked to regulatory element(s) and hence the regulatory element(s) drive expression. The promoter(s) can be constitutive promoter(s) and/or conditional promoter(s) and/or inducible promoter(s) and/or tissue specific promoter(s). The promoter can be selected from the group consisting of RNA polymerases, pol I, pol II, pol III, T7, U6, Hl, retroviral Rous sarcoma virus (RSV) LTR promoter, the cytomegalovirus (CMV) promoter, the SV40 promoter, the dihydrofolate reductase promoter, the β-actin promoter, the phosphoglycerol kinase (PGK) promoter, and the EFla promoter. An advantageous promoter is the promoter is U6.

[00270] Additional effectors for use according to the invention can be identified by their proximity to casl genes, for example, though not limited to, within the region 20 kb from the start of the casl gene and 20 kb from the end of the casl gene. In certain embodiments, the effector protein comprises at least one HEPN domain and at least 500 amino acids, and wherein the C2c2 effector protein is naturally present in a prokaryotic genome within 20 kb upstream or downstream of a Cas gene or a CRISPR array. Non-limiting examples of Cas proteins include Casl, CaslB, Cas2, Cas3, Cas4, Cas5, Cas6, Cas7, Cas8, Cas9 (also known as Csnl and Csxl2), CaslO, Csyl, Csy2, Csy3, Csel, Cse2, Cscl, Csc2, Csa5, Csn2, Csm2, Csm3, Csm4, Csm5, Csm6, Cmrl, Cmr3, Cmr4, Cmr5, Cmr6, Csbl, Csb2, Csb3, Csxl7, Csxl4, CsxlO, Csxl6, CsaX, Csx3, Csxl, Csxl5, Csfl, Csf2, Csf3, Csf4, homologues thereof, or modified versions thereof. In certain example

embodiments, the C2c2 effector protein is naturally present in a prokaryotic genome within 20kb upstream or downstream of a Cas 1 gene. The terms “orthologue” (also referred to as “ortholog” herein) and “homologue” (also referred to as “homolog” herein) are well known in the art. By means of further guidance, a “homologue” of a protein as used herein is a protein of the same species which performs the same or a similar function as the protein it is a homologue of. Homologous proteins may but need not be structurally related, or are only partially structurally related. An “orthologue” of a protein as used herein is a protein of a different species which performs the same or a similar function as the protein it is an orthologue of. Orthologous proteins may but need not be structurally related, or are only partially structurally related.

Guide Molecules

[00271] The methods described herein may be used to screen inhibition of CRISPR systems employing different types of guide molecules. As used herein, the term “guide sequence” and “guide molecule” in the context of a CRISPR-Cas system, comprises any polynucleotide sequence having sufficient complementarity with a target nucleic acid sequence to hybridize with the target nucleic acid sequence and direct sequence-specific binding of a nucleic acid-targeting complex to the target nucleic acid sequence. The guide sequences made using the methods disclosed herein may be a full-length guide sequence, a truncated guide sequence, a full-length sgRNA sequence, a truncated sgRNA sequence, or an E+F sgRNA sequence. In some embodiments, the degree of complementarity of the guide sequence to a given target sequence, when optimally aligned using a suitable alignment algorithm, is about or more than about 50%, 60%, 75%, 80%, 85%, 90%, 95%, 97.5%, 99%, or more. In certain example embodiments, the guide molecule comprises a guide sequence that may be designed to have at least one mismatch with the target sequence, such that a RNA duplex formed between the guide sequence and the target sequence. Accordingly, the degree of complementarity is preferably less than 99%. For instance, where the guide sequence consists of 24 nucleotides, the degree of complementarity is more particularly about 96% or less. In particular embodiments, the guide sequence is designed to have a stretch of two or more adjacent mismatching nucleotides, such that the degree of complementarity over the entire guide sequence is further reduced. For instance, where the guide sequence consists of 24 nucleotides, the degree of complementarity is more particularly about 96% or less, more particularly, about 92% or less, more particularly about 88% or less, more particularly about 84% or less, more particularly about

80% or less, more particularly about 76% or less, more particularly about 72% or less, depending on whether the stretch of two or more mismatching nucleotides encompasses 2, 3, 4, 5, 6 or 7 nucleotides, etc. In some embodiments, aside from the stretch of one or more mismatching nucleotides, the degree of complementarity, when optimally aligned using a suitable alignment algorithm, is about or more than about 50%, 60%, 75%, 80%, 85%, 90%, 95%, 97.5%, 99%, or more. Optimal alignment may be determined with the use of any suitable algorithm for aligning sequences, non-limiting example of which include the Smith-Waterman algorithm, the Needleman-Wunsch algorithm, algorithms based on the Burrows-Wheeler Transform (e.g., the Burrows Wheeler Aligner), ClustalW, Clustal X, BLAT, Novoalign (Novocraft Technologies; available at www.novocraft.com), ELAND (Illumina, San Diego, CA), SOAP (available at soap.genomics.org.cn), and Maq (available at maq.sourceforge.net). The ability of a guide sequence (within a nucleic acid-targeting guide RNA) to direct sequence-specific binding of a nucleic acid -targeting complex to a target nucleic acid sequence may be assessed by any suitable assay. For example, the components of a nucleic acid-targeting CRISPR system sufficient to form a nucleic acid-targeting complex, including the guide sequence to be tested, may be provided to a host cell having the corresponding target nucleic acid sequence, such as by transfection with vectors encoding the components of the nucleic acid-targeting complex, followed by an assessment of preferential targeting (e.g., cleavage) within the target nucleic acid sequence, such as by Surveyor assay as described herein. Similarly, cleavage of a target nucleic acid sequence (or a sequence in the vicinity thereof) may be evaluated in a test tube by providing the target nucleic acid sequence, components of a nucleic acid-targeting complex, including the guide sequence to be tested and a control guide sequence different from the test guide sequence, and comparing binding or rate of cleavage at or in the vicinity of the target sequence between the test and control guide sequence reactions. Other assays are possible, and will occur to those skilled in the art. A guide sequence, and hence a nucleic acid-targeting guide RNA may be selected to target any target nucleic acid sequence.

[00272] In certain embodiments, the guide sequence or spacer length of the guide molecules is from 15 to 50 nt. In certain embodiments, the spacer length of the guide RNA is at least 15 nucleotides. In certain embodiments, the spacer length is from 15 to 17 nt, e.g., 15, 16, or 17 nt, from 17 to 20 nt, e.g., 17, 18, 19, or 20 nt, from 20 to 24 nt, e.g., 20, 21, 22, 23, or 24 nt, from 23

to 25 nt, e.g., 23, 24, or 25 nt, from 24 to 27 nt, e.g., 24, 25, 26, or 27 nt, from 27-30 nt, e.g., 27, 28, 29, or 30 nt, from 30-35 nt, e.g., 30, 31, 32, 33, 34, or 35 nt, or 35 nt or longer. In certain example embodiment, the guide sequence is 15, 16, 17,18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 40, 41, 42, 43, 44, 45, 46, 47 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80., 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 nt.

[00273] In some embodiments, the guide sequence is an RNA sequence of between 10 to 50 nt in length, but more particularly of about 20-30 nt advantageously about 20 nt, 23-25 nt or 24 nt. The guide sequence is selected so as to ensure that it hybridizes to the target sequence. This is described more in detail below. Selection can encompass further steps which increase efficacy and specificity.

[00274] In some embodiments, the guide sequence has a canonical length (e.g., about 15-30 nt) is used to hybridize with the target RNA or DNA. In some embodiments, a guide molecule is longer than the canonical length (e.g., >30 nt) is used to hybridize with the target RNA or DNA, such that a region of the guide sequence hybridizes with a region of the RNA or DNA strand outside of the Cas-guide target complex. This can be of interest where additional modifications, such deamination of nucleotides is of interest. In alternative embodiments, it is of interest to maintain the limitation of the canonical guide sequence length.

[00275] In some embodiments, the sequence of the guide molecule (direct repeat and/or spacer) is selected to reduce the degree secondary structure within the guide molecule. In some embodiments, about or less than about 75%, 50%, 40%, 30%, 25%, 20%, 15%, 10%, 5%, 1%, or fewer of the nucleotides of the nucleic acid-targeting guide RNA participate in self-complementary base pairing when optimally folded. Optimal folding may be determined by any suitable polynucleotide folding algorithm. Some programs are based on calculating the minimal Gibbs free energy. An example of one such algorithm is rnFold, as described by Zuker and Stiegler (Nucleic Acids Res. 9 (1981), 133-148). Another example folding algorithm is the online Webserver RNAfold, developed at Institute for Theoretical Chemistry at the University of Vienna, using the centroid structure prediction algorithm (see e.g., A.R. Gruber et al., 2008, Cell 106(1): 23-24; and PA Carr and GM Church, 2009, Nature Biotechnology 27(12): 1151-62).

[00276] In some embodiments, it is of interest to reduce the susceptibility of the guide molecule to RNA cleavage, such as to cleavage by Casl3. Accordingly, in particular embodiments, the guide molecule is adjusted to avoid cleavage by Casl3 or other RNA-cleaving enzymes.

[00277] In certain embodiments, the guide molecule comprises non-naturally occurring nucleic acids and/or non-naturally occurring nucleotides and/or nucleotide analogs, and/or chemically modifications. Preferably, these non-naturally occurring nucleic acids and non-naturally occurring nucleotides are located outside the guide sequence. Non-naturally occurring nucleic acids can include, for example, mixtures of naturally and non-naturally occurring nucleotides. Non-naturally occurring nucleotides and/or nucleotide analogs may be modified at the ribose, phosphate, and/or base moiety. In an embodiment of the invention, a guide nucleic acid comprises ribonucleotides and non-ribonucleotides. In one such embodiment, a guide comprises one or more ribonucleotides and one or more deoxyribonucleotides. In an embodiment of the invention, the guide comprises one or more non-naturally occurring nucleotide or nucleotide analog such as a nucleotide with phosphorothioate linkage, a locked nucleic acid (LNA) nucleotides comprising a methylene bridge between the 2' and 4' carbons of the ribose ring, or bridged nucleic acids (BNA). Other examples of modified nucleotides include 2'-0-methyl analogs, 2'-deoxy analogs, or 2'-fluoro analogs. Further examples of modified bases include, but are not limited to, 2-aminopurine, 5-bromo-uridine, pseudouridine, inosine, 7-methylguanosine. Examples of guide RNA chemical modifications include, without limitation, incorporation of 2'-0-methyl (M), 2'-0-methyl 3'phosphorothioate (MS), S-constrained ethyl(cEt), or 2'-0-methyl 3'thioPACE (MSP) at one or more terminal nucleotides. Such chemically modified guides can comprise increased stability and increased activity as compared to unmodified guides, though on-target vs. off-target specificity is not predictable. (See, Hendel, 2015, Nat Biotechnol. 33(9):985-9, doi: l0.l038/nbt.3290, published online 29 June 2015 Ragdarm et al., 0215, PNAS, E71 10-E71 11; Allerson et al., J. Med. Chem. 2005, 48:901-904; Bramsen et al., Front. Genet., 2012, 3:154; Deng et al., PNAS, 2015, 112:1 1870-1 1875; Sharma et al., MedChemComm., 2014, 5:1454-1471; Hendel et ak, Nat. Biotechnol. (2015) 33(9): 985-989; Li et ak, Nature Biomedical Engineering, 2017, 1, 0066 D01:l0.l038/s4l55l-0l7-0066). In some embodiments, the 5' and/or 3' end of a guide RNA is modified by a variety of functional moieties including fluorescent dyes, polyethylene glycol, cholesterol, proteins, or detection tags. (See Kelly et ak, 2016, J. Biotech. 233:74-83). In certain

embodiments, a guide comprises ribonucleotides in a region that binds to a target RNA and one or more deoxyribonucleotides and/or nucleotide analogs in a region that binds to Casl3. In an embodiment of the invention, deoxyribonucleotides and/or nucleotide analogs are incorporated in engineered guide structures, such as, without limitation, stem-loop regions, and the seed region. For Casl3 guide, in certain embodiments, the modification is not in the 5'-handle of the stem-loop regions. Chemical modification in the 5'-handle of the stem-loop region of a guide may abolish its function (see Li, et al., Nature Biomedical Engineering, 2017, 1:0066). In certain embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, or 75 nucleotides of a guide is chemically modified. In some embodiments, 3-5 nucleotides at either the 3' or the 5' end of a guide is chemically modified. In some embodiments, only minor modifications are introduced in the seed region, such as 2'-F modifications. In some embodiments, 2'-F modification is introduced at the 3' end of a guide. In certain embodiments, three to five nucleotides at the 5' and/or the 3' end of the guide are chemically modified with 2'-0-methyl (M), 2'-0-methyl 3' phosphorothioate (MS), S-constrained ethyl(cEt), or 2'-0-methyl 3' thioPACE (MSP). Such modification can enhance genome editing efficiency (see Hendel et al., Nat. Biotechnol. (2015) 33(9): 985-989). In certain embodiments, all of the phosphodiester bonds of a guide are substituted with phosphorothioates (PS) for enhancing levels of gene disruption. In certain embodiments, more than five nucleotides at the 5' and/or the 3' end of the guide are chemically modified with 2'-0-Me, 2'-F or S-constrained ethyl(cEt). Such chemically modified guide can mediate enhanced levels of gene disruption (see Ragdarm et al., 0215, PNAS, E71 10-E71 11). In an embodiment of the invention, a guide is modified to comprise a chemical moiety at its 3' and/or 5' end. Such moieties include, but are not limited to amine, azide, alkyne, thio, dibenzocyclooctyne (DBCO), or Rhodamine. In certain embodiment, the chemical moiety is conjugated to the guide by a linker, such as an alkyl chain. In certain embodiments, the chemical moiety of the modified guide can be used to attach the guide to another molecule, such as DNA, RNA, protein, or nanoparticles. Such chemically modified guide can be used to identify or enrich cells generically edited by a CRISPR system (see Lee et al., eLife, 2017, 6:e253l2, DOI: 10.7554).

[00278] In some embodiments, the modification to the guide is a chemical modification, an insertion, a deletion or a split. In some embodiments, the chemical modification includes, but is

not limited to, incorporation of 2'-0-methyl (M) analogs, 2'-deoxy analogs, 2-thiouridine analogs, N6-methyladenosine analogs, 2'-fluoro analogs, 2-aminopurine, 5-bromo-uridine, pseudouridine (Ψ), Nl-methylpseudouridine (me^), 5-methoxyuridine(5moU), inosine, 7-methylguanosine, *2'*-O-methyl 3'phosphorothioate (MS), S-constrained ethyl(cEt), phosphorothioate (PS), or 2'-0-methyl 3'thioPACE (MSP). In some embodiments, the guide comprises one or more of phosphorothioate modifications. In certain embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 25 nucleotides of the guide are chemically modified. In certain embodiments, one or more nucleotides in the seed region are chemically modified. In certain embodiments, one or more nucleotides in the 3'-terminus are chemically modified. In certain embodiments, none of the nucleotides in the 5'-handle is chemically modified. In some embodiments, the chemical modification in the seed region is a minor modification, such as incorporation of a 2'-fluoro analog. In a specific embodiment, one nucleotide of the seed region is replaced with a 2'-fluoro analog. In some embodiments, 5 to 10 nucleotides in the 3'-terminus are chemically modified. Such chemical modifications at the 3'-terminus of the Casl3 CrRNA may improve Casl3 activity. In a specific embodiment, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 nucleotides in the 3'-terminus are replaced with 2'-fluoro analogues. In a specific embodiment, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 nucleotides in the 3'-terminus are replaced with 2'- O-methyl (M) analogs.

[00279] In some embodiments, the loop of the 5'-handle of the guide is modified. In some embodiments, the loop of the 5'-handle of the guide is modified to have a deletion, an insertion, a split, or chemical modifications. In certain embodiments, the modified loop comprises 3, 4, or 5 nucleotides. In certain embodiments, the loop comprises the sequence of E⌈CUU, E⌈UUU, E⌈AE⌈U, or UGUU.

[00280] In some embodiments, the guide molecule forms a stemloop with a separate non-covalently linked sequence, which can be DNA or RNA. In particular embodiments, the sequences forming the guide are first synthesized using the standard phosphoramidite synthetic protocol (Herdewijn, P., ed., Methods in Molecular Biology Col 288, Oligonucleotide Synthesis: Methods and Applications, Humana Press, New Jersey (2012)). In some embodiments, these sequences can be functionalized to contain an appropriate functional group for ligation using the standard protocol known in the art (Hermanson, G. T., Bioconjugate Techniques, Academic Press (2013)). Examples of functional groups include, but are not limited to, hydroxyl, amine, carboxylic acid,

carboxylic acid halide, carboxylic acid active ester, aldehyde, carbonyl, chlorocarbonyl, imidazolylcarbonyl, hydrozide, semicarbazide, thio semicarbazide, thiol, maleimide, haloalkyl, sulfonyl, ally, propargyl, diene, alkyne, and azide. Once this sequence is functionalized, a covalent chemical bond or linkage can be formed between this sequence and the direct repeat sequence. Examples of chemical bonds include, but are not limited to, those based on carbamates, ethers, esters, amides, imines, amidines, aminotrizines, hydrozone, disulfides, thioethers, thioesters, phosphorothioates, phosphorodithioates, sulfonamides, sulfonates, fulfones, sulfoxides, ureas, thioureas, hydrazide, oxime, triazole, photolabile linkages, C-C bond forming groups such as Diels-Alder cyclo-addition pairs or ring-closing metathesis pairs, and Michael reaction pairs.

[00281] In some embodiments, these stem-loop forming sequences can be chemically synthesized. In some embodiments, the chemical synthesis uses automated, solid-phase oligonucleotide synthesis machines with 2'-acetoxyethyl orthoester (2'-ACE) (Scaringe et al., J. Am. Chem. Soc. (1998) 120: 11820-1 1821; Scaringe, Methods Enzymol. (2000) 317: 3-18) or 2'-thionocarbamate (2'-TC) chemistry (Dellinger et al., J. Am. Chem. Soc. (201 1) 133: 11540-1 1546; Hendel et al., Nat. Biotechnol. (2015) 33:985-989).

[00282] In certain embodiments, the guide molecule comprises (1) a guide sequence capable of hybridizing to a target locus and (2) a tracr mate or direct repeat sequence whereby the direct repeat sequence is located upstream (i.e., 5') from the guide sequence. In a particular embodiment the seed sequence (i.e. the sequence essential critical for recognition and/or hybridization to the sequence at the target locus) of the guide sequence is approximately within the first 10 nucleotides of the guide sequence.

[00283] In a particular embodiment the guide molecule comprises a guide sequence linked to a direct repeat sequence, wherein the direct repeat sequence comprises one or more stem loops or optimized secondary structures. In particular embodiments, the direct repeat has a minimum length of 16 nts and a single stem loop. In further embodiments the direct repeat has a length longer than 16 nts, preferably more than 17 nts, and has more than one stem loops or optimized secondary structures. In particular embodiments the guide molecule comprises or consists of the guide sequence linked to all or part of the natural direct repeat sequence. A typical Type V or Type VI CRISPR-cas guide molecule comprises (in 3' to 5' direction or in 5' to 3' direction): a guide sequence a first complimentary stretch (the "repeat"), a loop (which is typically 4 or 5 nucleotides

long), a second complimentary stretch (the "anti-repeat" being complimentary to the repeat), and a poly A (often poly U in RNA) tail (terminator). In certain embodiments, the direct repeat sequence retains its natural architecture and forms a single stem loop. In particular embodiments, certain aspects of the guide architecture can be modified, for example by addition, subtraction, or substitution of features, whereas certain other aspects of guide architecture are maintained. Preferred locations for engineered guide molecule modifications, including but not limited to insertions, deletions, and substitutions include guide termini and regions of the guide molecule that are exposed when complexed with the CRISPR-Cas protein and/or target, for example the stemloop of the direct repeat sequence.

[00284] In particular embodiments, the stem comprises at least about 4bp comprising complementary X and Y sequences, although stems of more, e.g., 5, 6, 7, 8, 9, 10, 11 or 12 or fewer, e.g., 3, 2, base pairs are also contemplated. Thus, for example X2-10 and Y2-10 (wherein X and Y represent any complementary set of nucleotides) may be contemplated. In one aspect, the stem made of the X and Y nucleotides, together with the loop will form a complete hairpin in the overall secondary structure; and, this may be advantageous and the amount of base pairs can be any amount that forms a complete hairpin. In one aspect, any complementary X:Y basepairing sequence (e.g., as to length) is tolerated, so long as the secondary structure of the entire guide molecule is preserved. In one aspect, the loop that connects the stem made of X:Y basepairs can be any sequence of the same length (e.g., 4 or 5 nucleotides) or longer that does not interrupt the overall secondary structure of the guide molecule. In one aspect, the stemloop can further comprise, e.g. an MS2 aptamer. In one aspect, the stem comprises about 5-7bp comprising complementary X and Y sequences, although stems of more or fewer basepairs are also contemplated. In one aspect, non-Watson Crick basepairing is contemplated, where such pairing otherwise generally preserves the architecture of the stemloop at that position.

[00285] In particular embodiments the natural hairpin or stemloop structure of the guide molecule is extended or replaced by an extended stemloop. It has been demonstrated that extension of the stem can enhance the assembly of the guide molecule with the CRISPR-Cas protein (Chen et al. Cell. (2013); 155(7): 1479-1491). In particular embodiments the stem of the stemloop is extended by at least 1, 2, 3, 4, 5 or more complementary basepairs (i.e. corresponding to the

addition of 2,4, 6, 8, 10 or more nucleotides in the guide molecule). In particular embodiments these are located at the end of the stem, adjacent to the loop of the stemloop.

[00286] In particular embodiments, the susceptibility of the guide molecule to RNAses or to decreased expression can be reduced by slight modifications of the sequence of the guide molecule which do not affect its function. For instance, in particular embodiments, premature termination of transcription, such as premature transcription of U6 Pol-III, can be removed by modifying a putative Pol-III terminator (4 consecutive U's) in the guide molecules sequence. Where such sequence modification is required in the stemloop of the guide molecule, it is preferably ensured by a basepair flip.

[00287] In a particular embodiment, the direct repeat may be modified to comprise one or more protein-binding RNA aptamers. In a particular embodiment, one or more aptamers may be included such as part of optimized secondary structure. Such aptamers may be capable of binding a bacteriophage coat protein as detailed further herein.

[00288] In some embodiments, the guide molecule forms a duplex with a target RNA comprising at least one target cytosine residue to be edited. Upon hybridization of the guide RNA molecule to the target RNA, the cytidine deaminase binds to the single strand RNA in the duplex made accessible by the mismatch in the guide sequence and catalyzes deamination of one or more target cytosine residues comprised within the stretch of mismatching nucleotides.

[00289] A guide sequence, and hence a nucleic acid-targeting guide RNA may be selected to target any target nucleic acid sequence. The target sequence may be mRNA.

[00290] In certain embodiments, the target sequence should be associated with a PAM (protospacer adjacent motif) or PFS (protospacer flanking sequence or site); that is, a short sequence recognized by the CRISPR complex. Depending on the nature of the CRISPR-Cas protein, the target sequence should be selected such that its complementary sequence in the DNA duplex (also referred to herein as the non-target sequence) is upstream or downstream of the PAM. In the embodiments of the present invention where the CRISPR-Cas protein is a Casl3 protein, the complementary sequence of the target sequence is downstream or 3' of the PAM or upstream or 5' of the PAM. The precise sequence and length requirements for the PAM differ depending on the Casl3 protein used, but PAMs are typically 2-5 base pair sequences adjacent the protospacer (that is, the target sequence). Examples of the natural PAM sequences for different Casl3

orthologues are provided herein below and the skilled person will be able to identify further PAM sequences for use with a given Casl3 protein.

[00291] Further, engineering of the PAM Interacting (PI) domain may allow programing of PAM specificity, improve target site recognition fidelity, and increase the versatility of the CRISPR-Cas protein, for example as described for Cas9 in Kleinstiver BP et al. Engineered CRISPR-Cas9 nucleases with altered PAM specificities. Nature. 2015 Jul 23;523(756l):48l-5. doi: 10. l038/naturel4592. As further detailed herein, the skilled person will understand that Casl3 proteins may be modified analogously.

[00292] In particular embodiment, the guide is an escorted guide. By "escorted" is meant that the CRISPR-Cas system or complex or guide is delivered to a selected time or place within a cell, so that activity of the CRISPR-Cas system or complex or guide is spatially or temporally controlled. For example, the activity and destination of the 3 CRISPR-Cas system or complex or guide may be controlled by an escort RNA aptamer sequence that has binding affinity for an aptamer ligand, such as a cell surface protein or other localized cellular component. Alternatively, the escort aptamer may for example be responsive to an aptamer effector on or in the cell, such as a transient effector, such as an external energy source that is applied to the cell at a particular time.

[00293] The escorted CRISPR-Cas systems or complexes have a guide molecule with a functional structure designed to improve guide molecule structure, architecture, stability, genetic expression, or any combination thereof. Such a structure can include an aptamer.

[00294] Aptamers are biomolecules that can be designed or selected to bind tightly to other ligands, for example using a technique called systematic evolution of ligands by exponential enrichment (SELEX; Tuerk C, Gold L: "Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase." Science 1990, 249:505-510). Nucleic acid aptamers can for example be selected from pools of random-sequence oligonucleotides, with high binding affinities and specificities for a wide range of biomedically relevant targets, suggesting a wide range of therapeutic utilities for aptamers (Keefe, Anthony D., Supriya Pai, and Andrew Ellington. "Aptamers as therapeutics." Nature Reviews Drug Discovery 9.7 (2010): 537-550). These characteristics also suggest a wide range of uses for aptamers as drug delivery vehicles (Levy-Nissenbaum, Etgar, et al. "Nanotechnology and aptamers: applications in drug delivery." Trends in biotechnology 26.8 (2008): 442-449; and, Hicke BJ, Stephens AW.

“Escort aptamers: a delivery service for diagnosis and therapy.” J Clin Invest 2000, 106:923-928.). Aptamers may also be constructed that function as molecular switches, responding to a que by changing properties, such as RNA aptamers that bind fluorophores to mimic the activity of green fluorescent protein (Paige, Jeremy S., Karen Y. Wu, and Sarnie R. Jaffrey. "RNA mimics of green fluorescent protein." Science 333.6042 (201 1): 642-646). It has also been suggested that aptamers may be used as components of targeted siRNA therapeutic delivery systems, for example targeting cell surface proteins (Zhou, Jiehua, and John J. Rossi. "Aptamer-targeted cell-specific RNA interference." Silence 1.1 (2010): 4).

[00295] Accordingly, in particular embodiments, the guide molecule is modified, e.g., by one or more aptamer(s) designed to improve guide molecule delivery, including delivery across the cellular membrane, to intracellular compartments, or into the nucleus. Such a structure can include, either in addition to the one or more aptamer(s) or without such one or more aptamer(s), moiety(ies) so as to render the guide molecule deliverable, inducible or responsive to a selected effector. The invention accordingly comprehends an guide molecule that responds to normal or pathological physiological conditions, including without limitation pH, hypoxia, 0 2 concentration, temperature, protein concentration, enzymatic concentration, lipid structure, light exposure, mechanical disruption (e.g. ultrasound waves), magnetic fields, electric fields, or electromagnetic radiation.

[00296] Light responsiveness of an inducible system may be achieved via the activation and binding of cryptochrome-2 and CIB1. Blue light stimulation induces an activating conformational change in cryptochrome-2, resulting in recruitment of its binding partner CIB1. This binding is fast and reversible, achieving saturation in <15 sec following pulsed stimulation and returning to baseline <15 min after the end of stimulation. These rapid binding kinetics result in a system temporally bound only by the speed of transcription/translation and transcript/protein degradation, rather than uptake and clearance of inducing agents. Crytochrome-2 activation is also highly sensitive, allowing for the use of low light intensity stimulation and mitigating the risks of phototoxicity. Further, in a context such as the intact mammalian brain, variable light intensity may be used to control the size of a stimulated region, allowing for greater precision than vector delivery alone may offer.

[00297] The invention contemplates energy sources such as electromagnetic radiation, sound energy or thermal energy to induce the guide. Advantageously, the electromagnetic radiation is a component of visible light. In a preferred embodiment, the light is a blue light with a wavelength of about 450 to about 495 nm. In an especially preferred embodiment, the wavelength is about 488 nm. In another preferred embodiment, the light stimulation is via pulses. The light power may range from about 0-9 mW/cm2. In a preferred embodiment, a stimulation paradigm of as low as 0.25 sec every 15 sec should result in maximal activation.

[00298] The chemical or energy sensitive guide may undergo a conformational change upon induction by the binding of a chemical source or by the energy allowing it act as a guide and have the Casl3 CRISPR-Cas system or complex function. The invention can involve applying the chemical source or energy so as to have the guide function and the Casl3 CRISPR-Cas system or complex function; and optionally further determining that the expression of the genomic locus is altered.

[00299] There are several different designs of this chemical inducible system: 1. ABI-PYL based system inducible by Abscisic Acid (ABA) (see, e.g., stke.sciencemag.org/cgi/content/abstract/sigtrans;4/l64/rs2), 2. FKBP-FRB based system inducible by rapamycin (or related chemicals based on rapamycin) (see, e.g., www.nature.com/nmeth/journal/v2/n6/full/nmeth763.html), 3. GID1-GAI based system inducible by Gibberellin (GA) (see, e.g., www.nature.com/nchembio/journal/v8/n5/full/nchembio.922.html).

[00300] A chemical inducible system can be an estrogen receptor (ER) based system inducible by 4-hydroxytamoxifen (40HT) (see, e.g., www.pnas.org/content/l04/3/l027. abstract). A mutated ligand-binding domain of the estrogen receptor called ERT2 translocates into the nucleus of cells upon binding of 4-hydroxytamoxifen. In further embodiments of the invention any naturally occurring or engineered derivative of any nuclear receptor, thyroid hormone receptor, retinoic acid receptor, estrogen receptor, estrogen-related receptor, glucocorticoid receptor, progesterone receptor, androgen receptor may be used in inducible systems analogous to the ER based inducible system.

[00301] Another inducible system is based on the design using Transient receptor potential (TRP) ion channel based system inducible by energy, heat or radio-wave (see, e.g.,

www.sciencemag.org/content/336/608l/604). These TRP family proteins respond to different stimuli, including light and heat. When this protein is activated by light or heat, the ion channel will open and allow the entering of ions such as calcium into the plasma membrane. This influx of ions will bind to intracellular ion interacting partners linked to a polypeptide including the guide and the other components of the Casl3 CRISPR-Cas complex or system, and the binding will induce the change of sub-cellular localization of the polypeptide, leading to the entire polypeptide entering the nucleus of cells. Once inside the nucleus, the guide protein and the other components of the Casl3 CRISPR-Cas complex will be active and modulating target gene expression in cells.

[00302] While light activation may be an advantageous embodiment, sometimes it may be disadvantageous especially for in vivo applications in which the light may not penetrate the skin or other organs. In this instance, other methods of energy activation are contemplated, in particular, electric field energy and/or ultrasound which have a similar effect.

[00303] Electric field energy is preferably administered substantially as described in the art, using one or more electric pulses of from about 1 Volt/cm to about 10 kVolts/cm under in vivo conditions. Instead of or in addition to the pulses, the electric field may be delivered in a continuous manner. The electric pulse may be applied for between 1 μs and 500 milliseconds, preferably between 1 ps and 100 milliseconds. The electric field may be applied continuously or in a pulsed manner for 5 about minutes.

[00304] As used herein, 'electric field energy' is the electrical energy to which a cell is exposed. Preferably the electric field has a strength of from about 1 Volt/cm to about 10 kVolts/cm or more under in vivo conditions (see WO97/49450).

[00305] As used herein, the term "electric field" includes one or more pulses at variable capacitance and voltage and including exponential and/or square wave and/or modulated wave and/or modulated square wave forms. References to electric fields and electricity should be taken to include reference the presence of an electric potential difference in the environment of a cell. Such an environment may be set up by way of static electricity, alternating current (AC), direct current (DC), etc., as known in the art. The electric field may be uniform, non-uniform or otherwise, and may vary in strength and/or direction in a time dependent manner.

[00306] Single or multiple applications of electric field, as well as single or multiple applications of ultrasound are also possible, in any order and in any combination. The ultrasound

and/or the electric field may be delivered as single or multiple continuous applications, or as pulses (pulsatile delivery).

[00307] Electroporation has been used in both in vitro and in vivo procedures to introduce foreign material into living cells. With in vitro applications, a sample of live cells is first mixed with the agent of interest and placed between electrodes such as parallel plates. Then, the electrodes apply an electrical field to the cell/implant mixture. Examples of systems that perform in vitro electroporation include the Electro Cell Manipulator ECM600 product, and the Electro Square Porator T820, both made by the BTX Division of Genetronics, Inc (see ET.S. Pat. No 5,869,326).

[00308] The known electroporation techniques (both in vitro and in vivo) function by applying a brief high voltage pulse to electrodes positioned around the treatment region. The electric field generated between the electrodes causes the cell membranes to temporarily become porous, whereupon molecules of the agent of interest enter the cells. In known electroporation applications, this electric field comprises a single square wave pulse on the order of 1000 V/cm, of about 100 mu duration. Such a pulse may be generated, for example, in known applications of the Electro Square Porator T820.

[00309] Preferably, the electric field has a strength of from about 1 V/cm to about 10 kV/cm under in vitro conditions. Thus, the electric field may have a strength of 1 V/cm, 2 V/cm, 3 V/cm, 4 V/cm, 5 V/cm, 6 V/cm, 7 V/cm, 8 V/cm, 9 V/cm, 10 V/cm, 20 V/cm, 50 V/cm, 100 V/cm, 200 V/cm, 300 V/cm, 400 V/cm, 500 V/cm, 600 V/cm, 700 V/cm, 800 V/cm, 900 V/cm, 1 kV/cm, 2 kV/cm, 5 kV/cm, 10 kV/cm, 20 kV/cm, 50 kV/cm or more. More preferably from about 0.5 kV/cm to about 4.0 kV/cm under in vitro conditions. Preferably the electric field has a strength of from about 1 V/cm to about 10 kV/cm under in vivo conditions. However, the electric field strengths may be lowered where the number of pulses delivered to the target site are increased. Thus, pulsatile delivery of electric fields at lower field strengths is envisaged.

[00310] Preferably the application of the electric field is in the form of multiple pulses such as double pulses of the same strength and capacitance or sequential pulses of varying strength and/or capacitance. As used herein, the term “pulse” includes one or more electric pulses at variable capacitance and voltage and including exponential and/or square wave and/or modulated wave/square wave forms.

[00311] Preferably the electric pulse is delivered as a waveform selected from an exponential wave form, a square wave form, a modulated wave form and a modulated square wave form.

[00312] A preferred embodiment employs direct current at low voltage. Thus, Applicants disclose the use of an electric field which is applied to the cell, tissue or tissue mass at a field strength of between lV/cm and 20V/cm, for a period of 100 milliseconds or more, preferably 15 minutes or more.

[00313] Ultrasound is advantageously administered at a power level of from about 0.05 W/cm2 to about 100 W/cm2. Diagnostic or therapeutic ultrasound may be used, or combinations thereof.

[00314] As used herein, the term “ultrasound” refers to a form of energy which consists of mechanical vibrations the frequencies of which are so high they are above the range of human hearing. Lower frequency limit of the ultrasonic spectrum may generally be taken as about 20 kHz. Most diagnostic applications of ultrasound employ frequencies in the range 1 and 15 MHz' (From Ultrasonics in Clinical Diagnosis, P. N. T. Wells, ed., 2nd. Edition, Publ. Churchill Livingstone [Edinburgh, London & NY, 1977]).

[00315] Ultrasound has been used in both diagnostic and therapeutic applications. When used as a diagnostic tool ("diagnostic ultrasound"), ultrasound is typically used in an energy density range of up to about 100 mW/cm2 (FDA recommendation), although energy densities of up to 750 mW/cm2 have been used. In physiotherapy, ultrasound is typically used as an energy source in a range up to about 3 to 4 W/cm2 (WHO recommendation). In other therapeutic applications, higher intensities of ultrasound may be employed, for example, HIFU at 100 W/cm up to 1 kW/cm2 (or even higher) for short periods of time. The term "ultrasound" as used in this specification is intended to encompass diagnostic, therapeutic and focused ultrasound.

[00316] Focused ultrasound (FUS) allows thermal energy to be delivered without an invasive probe (see Morocz et al 1998 Journal of Magnetic Resonance Imaging Vol.8, No. 1, pp. 136-142. Another form of focused ultrasound is high intensity focused ultrasound (HIFU) which is reviewed by Moussatov et al in Ultrasonics (1998) Vol.36, No.8, pp. 893-900 and TranHuuHue et al in Acustica (1997) Vol.83, No. 6, pp. 1103-1 106.

[00317] Preferably, a combination of diagnostic ultrasound and a therapeutic ultrasound is employed. This combination is not intended to be limiting, however, and the skilled reader will

appreciate that any variety of combinations of ultrasound may be used. Additionally, the energy density, frequency of ultrasound, and period of exposure may be varied.

[00318] Preferably the exposure to an ultrasound energy source is at a power density of from about 0.05 to about 100 Wcm-2. Even more preferably, the exposure to an ultrasound energy source is at a power density of from about 1 to about 15 Wcm-2.

[00319] Preferably the exposure to an ultrasound energy source is at a frequency of from about 0.015 to about 10.0 MHz. More preferably the exposure to an ultrasound energy source is at a frequency of from about 0.02 to about 5.0 MHz or about 6.0 MHz. Most preferably, the ultrasound is applied at a frequency of 3 MHz.

[00320] Preferably the exposure is for periods of from about 10 milliseconds to about 60 minutes. Preferably the exposure is for periods of from about 1 second to about 5 minutes. More preferably, the ultrasound is applied for about 2 minutes. Depending on the particular target cell to be disrupted, however, the exposure may be for a longer duration, for example, for 15 minutes.

[00321] Advantageously, the target tissue is exposed to an ultrasound energy source at an acoustic power density of from about 0.05 Wcm-2 to about 10 Wcm-2 with a frequency ranging from about 0.015 to about 10 MHz (see WO 98/52609). However, alternatives are also possible, for example, exposure to an ultrasound energy source at an acoustic power density of above 100 Wcm-2, but for reduced periods of time, for example, 1000 Wcm-2 for periods in the millisecond range or less.

[00322] Preferably the application of the ultrasound is in the form of multiple pulses; thus, both continuous wave and pulsed wave (pulsatile delivery of ultrasound) may be employed in any combination. For example, continuous wave ultrasound may be applied, followed by pulsed wave ultrasound, or vice versa. This may be repeated any number of times, in any order and combination. The pulsed wave ultrasound may be applied against a background of continuous wave ultrasound, and any number of pulses may be used in any number of groups.

[00323] Preferably, the ultrasound may comprise pulsed wave ultrasound. In a highly preferred embodiment, the ultrasound is applied at a power density of 0.7 Wcm-2 or 1.25 Wcm-2 as a continuous wave. Higher power densities may be employed if pulsed wave ultrasound is used.

[00324] Use of ultrasound is advantageous as, like light, it may be focused accurately on a target. Moreover, ultrasound is advantageous as it may be focused more deeply into tissues unlike

light. It is therefore better suited to whole-tissue penetration (such as but not limited to a lobe of the liver) or whole organ (such as but not limited to the entire liver or an entire muscle, such as the heart) therapy. Another important advantage is that ultrasound is a non-invasive stimulus which is used in a wide variety of diagnostic and therapeutic applications. By way of example, ultrasound is well known in medical imaging techniques and, additionally, in orthopedic therapy. Furthermore, instruments suitable for the application of ultrasound to a subject vertebrate are widely available and their use is well known in the art.

[00325] In particular embodiments, the guide molecule is modified by a secondary structure to increase the specificity of the CRISPR-Cas system and the secondary structure can protect against exonuclease activity and allow for 5' additions to the guide sequence also referred to herein as a protected guide molecule.

[00326] In one aspect, the invention provides for hybridizing a "protector RNA" to a sequence of the guide molecule, wherein the "protector RNA" is an RNA strand complementary to the 3' end of the guide molecule to thereby generate a partially double-stranded guide RNA. In an embodiment of the invention, protecting mismatched bases (i.e. the bases of the guide molecule which do not form part of the guide sequence) with a perfectly complementary protector sequence decreases the likelihood of target RNA binding to the mismatched basepairs at the 3' end. In particular embodiments of the invention, additional sequences comprising an extended length may also be present within the guide molecule such that the guide comprises a protector sequence within the guide molecule. This "protector sequence" ensures that the guide molecule comprises a "protected sequence" in addition to an "exposed sequence" (comprising the part of the guide sequence hybridizing to the target sequence). In particular embodiments, the guide molecule is modified by the presence of the protector guide to comprise a secondary structure such as a hairpin. Advantageously there are three or four to thirty or more, e.g., about 10 or more, contiguous base pairs having complementarity to the protected sequence, the guide sequence or both. It is advantageous that the protected portion does not impede thermodynamics of the CRISPR-Cas system interacting with its target. By providing such an extension including a partially double stranded guide molecule, the guide molecule is considered protected and results in improved specific binding of the CRISPR-Cas complex, while maintaining specific activity.

[00327] In particular embodiments, use is made of a truncated guide (tru-guide), i.e. a guide molecule which comprises a guide sequence which is truncated in length with respect to the canonical guide sequence length. As described by Nowak et al. (Nucleic Acids Res (2016) 44 (20): 9555-9564), such guides may allow catalytically active CRISPR-Cas enzyme to bind its target without cleaving the target RNA. In particular embodiments, a truncated guide is used which allows the binding of the target but retains only nickase activity of the CRISPR-Cas enzyme.

CRISPR RNA-Targeting Effector Proteins

[00328] In one example embodiment, the CRISPR system effector protein is an RNA-targeting effector protein. In certain embodiments, the CRISPR system effector protein is a Type VI CRISPR system targeting RNA (e.g., Casl3a, Casl3b, Casl3c or Casl3d). Example RNA-targeting effector proteins include Casl3b and C2c2 (now known as Casl3a). It will be understood that the term "C2c2" herein is used interchangeably with "Casl3a". "C2c2" is now referred to as "Casl3a", and the terms are used interchangeably herein unless indicated otherwise. As used herein, the term "Casl3" refers to any Type VI CRISPR system targeting RNA (e.g., Casl3a, Casl3b, Casl3c or Casl3d). When the CRISPR protein is a C2c2 protein, a tracrRNA is not required. C2c2 has been described in Abudayyeh et al. (2016) "C2c2 is a single-component programmable RNA-guided RNA-targeting CRISPR effector"; Science; DOI: l0.H26/science.aaf5573; and Shmakov et al. (2015) "Discovery and Functional Characterization of Diverse Class 2 CRISPR-Cas Systems", Molecular Cell, DOI: dx.doi.org/l0.l0l6/j.molcel. 2015. 10.008; which are incorporated herein in their entirety by reference. Casl3b has been described in Smargon et al. (2017) "Casl3b Is a Type VI-B CRISPR-Associated RNA-Guided RNases Differentially Regulated by Accessory Proteins Csx27 and Csx28," Molecular Cell. 65, 1-13; dx.doi.org/l0.l0l6/j.molcel. 2016. 12.023., which is incorporated herein in its entirety by reference.

[00329] In some embodiments, one or more elements of a nucleic acid-targeting system is derived from a particular organism comprising an endogenous CRISPR RNA-targeting system. In certain example embodiments, the effector protein CRISPR RNA-targeting system comprises at least one HEPN domain, including but not limited to the HEPN domains described herein, HEPN domains known in the art, and domains recognized to be HEPN domains by comparison to consensus sequence motifs. Several such domains are provided herein. In one non-limiting

example, a consensus sequence can be derived from the sequences of C2c2 or Casl3b orthologs provided herein. In certain example embodiments, the effector protein comprises a single HEPN domain. In certain other example embodiments, the effector protein comprises two HEPN domains.

[00330] In one example embodiment, the effector protein comprise one or more HEPN domains comprising a RxxxxH motif sequence. The RxxxxH motif sequence can be, without limitation, from a HEPN domain described herein or a HEPN domain known in the art. RxxxxH motif sequences further include motif sequences created by combining portions of two or more HEPN domains. As noted, consensus sequences can be derived from the sequences of the orthologs disclosed in ET.S. Provisional Patent Application 62/432,240 entitled "Novel CRISPR Enzymes and Systems," ET.S. Provisional Patent Application 62/471,710 entitled "Novel Type VI CRISPR Orthologs and Systems" filed on March 15, 2017, and U.S. Provisional Patent Application entitled "Novel Type VI CRISPR Orthologs and Systems," labeled as attorney docket number 47627-05-2133 and filed on April 12, 2017.

[00331] In certain other example embodiments, the CRISPR system effector protein is a C2c2 nuclease (also referred to as Casl3a). The activity of C2c2 may depend on the presence of two HEPN domains. These have been shown to be RNase domains, i.e. nuclease (in particular an endonuclease) cutting RNA. C2c2 HEPN may also target DNA, or potentially DNA and/or RNA. On the basis that the HEPN domains of C2c2 are at least capable of binding to and, in their wild-type form, cutting RNA, then it is preferred that the C2c2 effector protein has RNase function. Regarding C2c2 CRISPR systems, reference is made to U.S. Provisional 62/351,662 filed on June 17, 2016 and U.S. Provisional 62/376,377 filed on August 17, 2016. Reference is also made to U.S. Provisional 62/351,803 filed on June 17, 2016. Reference is also made to U.S. Provisional entitled "Novel Crispr Enzymes and Systems" filed December 8, 2016 bearing Broad Institute No. 10035. PA4 and Attorney Docket No. 47627.03.2133. Reference is further made to East-Seletsky et al. "Two distinct RNase activities of CRISPR-C2c2 enable guide-RNA processing and RNA detection" Nature doi: 10/1 038/nature 19802 and Abudayyeh et al. "C2c2 is a single-component programmable RNA-guided RNA targeting CRISPR effector" bioRxiv doi: 10. 1101/054742.

[00332] In certain embodiments, the C2c2 effector protein is from an organism of a genus selected from the group consisting of: Leptotrichia, Listeria, Corynebacter, Sutterella, Legionella,

Treponema, Filifactor, Eubacterium, Streptococcus, Lactobacillus, Mycoplasma, Bacteroides, Flaviivola, Flavobacterium, Sphaerochaeta, Azospirillum, Gluconacetobacter, Neisseria, Roseburia, Parvibaculum, Staphylococcus, Nitratifractor, Mycoplasma, Campylobacter, and Lachnospira, or the C2c2 effector protein is an organism selected from the group consisting of: Leptotrichia shahii, Leptotrichia. wadei, Listeria seeligeri, Clostridium aminophilum, Carnobacterium gallinarum, Paludibacter propionicigenes, Listeria weihenstephanensis, or the C2c2 effector protein is a L. wadei F0279 or L. wadei F0279 (Lw2) C2C2 effector protein. In another embodiment, the one or more guide RNAs are designed to detect a single nucleotide polymorphism, splice variant of a transcript, or a frameshift mutation in a target RNA or DNA.

[00333] In certain example embodiments, the RNA-targeting effector protein is a Type VI-B effector protein, such as Casl3b and Group 29 or Group 30 proteins. In certain example embodiments, the RNA-targeting effector protein comprises one or more HEPN domains. In certain example embodiments, the RNA-targeting effector protein comprises a C-terminal HEPN domain, aN-terminal HEPN domain, or both. Regarding example Type VI-B effector proteins that may be used in the context of this invention, reference is made to US Application No. 15/33 1,792 entitled "Novel CRISPR Enzymes and Systems" and filed October 21, 2016, International Patent Application No. PCT/US2016/058302 entitled "Novel CRISPR Enzymes and Systems", and filed October 21, 2016, and Smargon et al. "Casl3b is a Type VI-B CRISPR-associated RNA-Guided RNase differentially regulated by accessory proteins Csx27 and Csx28" Molecular Cell, 65, 1-13 (2017); dx.doi.org/l0.l0l6/j.molcel. 2016. 12.023, and U.S. Provisional Application No. to be assigned, entitled "Novel Casl3b Orthologues CRISPR Enzymes and System" filed March 15, 2017. In particular embodiments, the Casl3b enzyme is derived from Bergeyella zoohelcum.

[00334] In certain example embodiments, the RNA-targeting effector protein is a Casl3c effector protein as disclosed in U.S. Provisional Patent Application No. 62/525,165 filed June 26, 2017, and PCT Application No. US 2017/047193 filed August 16, 2017.

[00335] In some embodiments, one or more elements of a nucleic acid-targeting system is derived from a particular organism comprising an endogenous CRISPR RNA-targeting system. In certain embodiments, the CRISPR RNA-targeting system is found in Eubacterium and Ruminococcus. In certain embodiments, the effector protein comprises targeted and collateral ssRNA cleavage activity. In certain embodiments, the effector protein comprises dual HEPN

domains. In certain embodiments, the effector protein lacks a counterpart to the Helical- 1 domain of Casl3a. In certain embodiments, the effector protein is smaller than previously characterized class 2 CRISPR effectors, with a median size of 928 aa. This median size is 190 aa (17%) less than that of Casl3c, more than 200 aa (18%) less than that of Casl3b, and more than 300 aa ***(26%)*** less than that of Casl3a. In certain embodiments, the effector protein has no requirement for a flanking sequence (e.g., PFS, PAM).

[00336] In certain embodiments, the effector protein locus structures include a WYL domain containing accessory protein (so denoted after three amino acids that were conserved in the originally identified group of these domains; see, e.g., WYL domain IPR026881). In certain embodiments, the WYL domain accessory protein comprises at least one helix-turn-helix (HTH) or ribbon-helix-helix (RHH) DNA-binding domain. In certain embodiments, the WYL domain containing accessory protein increases both the targeted and the collateral ssRNA cleavage activity of the RNA-targeting effector protein. In certain embodiments, the WYL domain containing accessory protein comprises an N-terminal RHH domain, as well as a pattern of primarily hydrophobic conserved residues, including an invariant tyrosine-leucine doublet corresponding to the original WYL motif. In certain embodiments, the WYL domain containing accessory protein is WYL1. WYL1 is a single WYL-domain protein associated primarily with Ruminococcus.

[00337] In other example embodiments, the Type VI RNA-targeting Cas enzyme is Casl3d. In certain embodiments, Casl3d is Eubacterium siraeum DSM 15702 (EsCasl3d) or Ruminococcus sp. N15.MGS-57 (RspCasl3d) (see, e.g., Yan et al., Casl3d Is a Compact RNA-Targeting Type VI CRISPR Effector Positively Modulated by a WYL-Domain-Containing Accessory Protein, Molecular Cell (2018), doi.org/l0.l0l6/j.molcel.20l8.02.028). RspCasl3d and EsCasl3d have no flanking sequence requirements (e.g., PFS, PAM).

Casl3 RNA Editing

[00338] In one aspect, the invention provides a method of modifying or editing a target transcript in a eukaryotic cell. In some embodiments, the method comprises allowing a CRISPR-Cas effector module complex to bind to the target polynucleotide to effect RNA base editing, wherein the CRISPR-Cas effector module complex comprises a Cas effector module complexed with a guide sequence hybridized to a target sequence within said target polynucleotide, wherein said guide sequence is linked to a direct repeat sequence. In some embodiments, the Cas effector

module comprises a catalytically inactive CRISPR-Cas protein. In some embodiments, the guide sequence is designed to introduce one or more mismatches to the RNA/RNA duplex formed between the target sequence and the guide sequence. In particular embodiments, the mismatch is an A-C mismatch. In some embodiments, the Cas effector may associate with one or more functional domains (e.g. via fusion protein or suitable linkers). In some embodiments, the effector domain comprises one or more cytidine or adenosine deaminases that mediate endogenous editing of via hydrolytic deamination. In particular embodiments, the effector domain comprises the adenosine deaminase acting on RNA (ADAR) family of enzymes. In particular embodiments, the adenosine deaminase protein or catalytic domain thereof capable of deaminating adenosine or cytidine in RNA or is an RNA specific adenosine deaminase and/or is a bacterial, human, cephalopod, or Drosophila adenosine deaminase protein or catalytic domain thereof, preferably TadA, more preferably ADAR, optionally huADAR, optionally (hu)ADARl or (hu)ADAR2, preferably huADAR2 or catalytic domain thereof.

[00339] The present application relates to modifying a target RNA sequence of interest (see, e.g, Cox et al., Science. 2017 Nov 24;358(6366): 1019-1027). Using RNA-targeting rather than DNA targeting offers several advantages relevant for therapeutic development. First, there are substantial safety benefits to targeting RNA: there will be fewer off-target events because the available sequence space in the transcriptome is significantly smaller than the genome, and if an off-target event does occur, it will be transient and less likely to induce negative side effects. Second, RNA-targeting therapeutics will be more efficient because they are cell-type independent and not have to enter the nucleus, making them easier to deliver.

[00340] A further aspect of the invention relates to the method and composition as envisaged herein for use in prophylactic or therapeutic treatment, preferably wherein said target locus of interest is within a human or animal and to methods of modifying an Adenine or Cytidine in a target RNA sequence of interest, comprising delivering to said target RNA, the composition as described herein. In particular embodiments, the CRISPR system and the adenosine deaminase, or catalytic domain thereof, are delivered as one or more polynucleotide molecules, as a ribonucleoprotein complex, optionally via particles, vesicles, or one or more viral vectors. In particular embodiments, the invention thus comprises compositions for use in therapy. This

implies that the methods can be performed in vivo, ex vivo or in vitro. In particular embodiments, when the target is a human or animal target, the method is carried out ex vivo or in vitro.

[00341] A further aspect of the invention relates to the method as envisaged herein for use in prophylactic or therapeutic treatment, preferably wherein said target of interest is within a human or animal and to methods of modifying an Adenine or Cytidine in a target RNA sequence of interest, comprising delivering to said target RNA, the composition as described herein. In particular embodiments, the CRISPR system and the adenosine deaminase, or catalytic domain thereof, are delivered as one or more polynucleotide molecules, as a ribonucleoprotein complex, optionally via particles, vesicles, or one or more viral vectors.

[00342] In one aspect, the invention provides a method of generating a eukaryotic cell comprising a modified or edited gene. In some embodiments, the method comprises (a) introducing one or more vectors into a eukaryotic cell, wherein the one or more vectors drive expression of one or more of: Cas effector module, and a guide sequence linked to a direct repeat sequence, wherein the Cas effector module associate one or more effector domains that mediate base editing, and (b) allowing a CRISPR-Cas effector module complex to bind to a target polynucleotide to effect base editing of the target polynucleotide within said disease gene, wherein the CRISPR-Cas effector module complex comprises a Cas effector module complexed with the guide sequence that is hybridized to the target sequence within the target polynucleotide, wherein the guide sequence may be designed to introduce one or more mismatches between the RNA/RNA duplex formed between the guide sequence and the target sequence. In particular embodiments, the mismatch is an A-C mismatch. In some embodiments, the Cas effector may associate with one or more functional domains (e.g. via fusion protein or suitable linkers). In some embodiments, the effector domain comprises one or more cytidine or adenosine deaminases that mediate endogenous editing of via hydrolytic deamination. In particular embodiments, the effector domain comprises the adenosine deaminase acting on RNA (ADAR) family of enzymes. In particular embodiments, the adenosine deaminase protein or catalytic domain thereof capable of deaminating adenosine or cytidine in RNA or is an RNA specific adenosine deaminase and/or is a bacterial, human, cephalopod, or Drosophila adenosine deaminase protein or catalytic domain thereof, preferably TadA, more preferably ADAR, optionally huADAR, optionally (hu)ADARl or (hu)ADAR2, preferably huADAR2 or catalytic domain thereof.

[00343] The present invention may also use a Casl2 CRISPR enzyme. Casl2 enzymes include Casl2a (Cpfl), Casl2b (C2cl), and Casl2c (C2c3), described further herein.

[00344] A further aspect relates to an isolated cell obtained or obtainable from the methods described herein comprising the composition described herein or progeny of said modified cell, preferably wherein said cell comprises a hypoxanthine or a guanine in replace of said Adenine in said target RNA of interest compared to a corresponding cell not subjected to the method. In particular embodiments, the cell is a eukaryotic cell, preferably a human or non-human animal cell, optionally a therapeutic T cell or an antibody-producing B-cell.

[00345] In some embodiments, the modified cell is a therapeutic T cell, such as a T cell suitable for adoptive cell transfer therapies (e.g., CAR-T therapies). The modification may result in one or more desirable traits in the therapeutic T cell, as described further herein.

[00346] The invention further relates to a method for cell therapy, comprising administering to a patient in need thereof the modified cell described herein, wherein the presence of the modified cell remedies a disease in the patient.

[00347] The present invention may be further illustrated and extended based on aspects of CRISPR-Cas development and use as set forth in the following articles and particularly as relates to delivery of a CRISPR protein complex and uses of an RNA guided endonuclease in cells and organisms:

- Multiplex genome engineering using CRISPR-Cas systems. Cong, L., Ran, F.A., Cox, D., Lin, S., Barretto, R., Habib, N., Hsu, P.D., Wu, X., Jiang, W., Marraffmi, L.A., & Zhang, F. Science Feb 15;339(6121):819-23 (2013);
- RNA-guided editing of bacterial genomes using CRISPR-Cas systems. Jiang W., Bikard D., Cox D., Zhang F, Marraffmi LA. Nat Biotechnol Mar;3l(3):233-9 (2013);
- One-Step Generation of Mice Carrying Mutations in Multiple Genes by CRISPR-Cas-Mediated Genome Engineering. Wang H , Yang H., Shivalila CS., Dawlaty MM., Cheng AW., Zhang F., Jaenisch R. Cell May 9;153(4):910-8 (2013);
- Optical control of mammalian endogenous transcription and epigenetic states. Konermann S, Brigham MD, Trevino AE, Hsu PD, Heidenreich M, Cong L, Platt RJ, Scott DA, Church GM, Zhang F. Nature. Aug 22;500(7463):472-6. doi: 10. 103 8/Nature 12466. Epub 2013 Aug 23 (2013);

- Double Nicking by RNA-Guided CRISPR Cas9 for Enhanced Genome Editing Specificity. Ran, FA., Hsu, PD., Lin, CY., Gootenberg, JS., Konermann, S., Trevino, AE., Scott, DA., Inoue, A., Matoba, S., Zhang, Y., & Zhang, F. Cell Aug 28. pii: S0092-8674(l3)0l0l5-5 (20 13-A);
- DNA targeting specificity of RNA-guided Cas9 nucleases. Hsu, P., Scott, D., Weinstein, J., Ran, FA., Konermann, S., Agarwala, V., Li, Y., Fine, E., Wu, X., Shalem, O., Cradick, TJ., Marraffmi, LA., Bao, G., & Zhang, F. Nat Biotechnol doi:l0.l038/nbt.2647 (2013);
- Genome engineering using the CRISPR-Cas9 system. Ran, FA., Hsu, PD., Wright, J., Agarwala, V., Scott, DA., Zhang, F. Nature Protocols Nov;8(l l):228l-308 (2013-B);
- Genome-Scale CRISPR-Cas9 Knockout Screening in Human Cells. Shalem, O., Sanjana, NE., Hartenian, E., Shi, X., Scott, DA., Mikkelson, T., Heckl, D., Ebert, BL., Root, DE., Doench, JG., Zhang, F. Science Dec 12. (2013);
- Crystal structure of cas9 in complex with guide RNA and target DNA. Nishimasu, H., Ran, FA., Hsu, PD., Konermann, S., Shehata, SI., Dohmae, N., Ishitani, R., Zhang, F., Nureki, O. Cell Feb 27, l56(5):935-49 (2014);
- Genome-wide binding of the CRISPR endonuclease Cas9 in mammalian cells. Wu X., Scott DA., Kriz AJ., Chiu AC., Hsu PD., Dadon DB., Cheng AW., Trevino AE., Konermann S., Chen S., Jaenisch R., Zhang F., Sharp PA. Nat Biotechnol. Apr 20. doi: l0.l038/nbt.2889 (2014);
- CRISPR-Cas9 Knockin Mice for Genome Editing and Cancer Modeling. Platt RJ, Chen S, Zhou Y, Yim MJ, Swiech L, Kempton HR, Dahlman JE, Parnas O, Eisenhaure TM, Jovanovic M, Graham DB, Jhunjhunwala S, Heidenreich M, Xavier RJ, Langer R, Anderson DG, Hacohen N, Regev A, Feng G, Sharp PA, Zhang F. Cell 159(2): 440-455 DOI: 10. l0l6/j. cell.2014.09.014(2014);
- Development and Applications of CRISPR-Cas9 for Genome Engineering, Hsu PD, Lander ES, Zhang F., Cell. Jun 5;l57(6):l262-78 (2014).
- Genetic screens in human cells using the CRISPR-Cas9 system, Wang T, Wei JJ, Sabatini DM, Lander ES., Science. January 3; 343(6166): 80-84. doi:10.1126/science. 1246981 (2014);

- Rational design of highly active sgRNAs for CRISPR-Cas9-mediated gene inactivation, Doench JG, Hartenian E, Graham DB, Tothova Z, Hegde M, Smith I, Sullender M, Ebert BL, Xavier RJ, Root DE., (published online 3 September 2014) Nat Biotechnol. Dec;32(l2): 1262-7 (2014);
- *In vivo* interrogation of gene function in the mammalian brain using CRISPR-Cas9, Swiech L, Heidenreich M, Banerjee A, Habib N, Li Y, Trombetta J, Sur M, Zhang F., (published online 19 October 2014) Nat Biotechnol. Jan;33(l): 102-6 (2015);
- Genome-scale transcriptional activation by an engineered CRISPR-Cas9 complex, Konermann S, Brigham MD, Trevino AE, Joung J, Abudayyeh OO, Barcena C, Hsu PD, Habib N, Gootenberg JS, Nishimasu H, Nureki O, Zhang F., Nature. Jan 29;5 17(7536): 583-8 (2015).
- A split-Cas9 architecture for inducible genome editing and transcription modulation, Zetsche B, Volz SE, Zhang F., (published online 02 February 2015) Nat Biotechnol. Feb;33(2): 139-42 (2015);
- Genome-wide CRISPR Screen in a Mouse Model of Tumor Growth and Metastasis, Chen S, Sanjana NE, Zheng K, Shalem O, Lee K, Shi X, Scott DA, Song J, Pan JQ, Weissleder R, Lee H, Zhang F, Sharp PA. Cell 160, 1246-1260, March 12, 2015 (multiplex screen in mouse), and
- In *vivo* genome editing using *Staphylococcus aureus* Cas9, Ran FA, Cong L, Yan WX, Scott DA, Gootenberg JS, Kriz AJ, Zetsche B, Shalem O, Wu X, Makarova KS, Koonin EV, Sharp PA, Zhang F., (published online 0 1 April 2015), Nature. Apr 9;520(7546):l86-9 1 (2015).
- Shalem et al., "High-throughput functional genomics using CRISPR-Cas9," Nature Reviews Genetics 16, 299-31 1 (May 2015).
- Xu et al., "Sequence determinants of improved CRISPR sgRNA design," Genome Research 25, 1147-1 157 (August 2015).
- Parnas et ak, "A Genome-wide CRISPR Screen in Primary Immune Cells to Dissect Regulatory Networks," Cell 162, 675-686 (July 30, 2015).
- Ramanan et ak, CRISPR-Cas9 cleavage of viral DNA efficiently suppresses hepatitis B virus," Scientific Reports 5:10833. doi: !0.l038/srepl0833 (June 2, 2015)

- Nishimasu et al., Crystal Structure of Staphylococcus aureus Cas9," Cell 162, 1113-1 126 (Aug. 27, 2015)
- BCL1 1A enhancer dissection by Cas9-mediated in situ saturating mutagenesis, Canver et al., Nature 527(7577): 192-7 (Nov. 12, 2015) doi: l0.l038/naturel552l. Epub 2015 Sep 16.
- *Cpfl Is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System*, Zetsche et al., Cell 163, 759-71 (Sep 25, 2015).
- *Discovery and Functional Characterization of Diverse Class 2 CRISPR-Cas Systems*, Shmakov et al., Molecular Cell, 60(3), 385-397 doi: 10. l0l6/j.molcel. 2015. 10.008 Epub October 22, 2015.
- *Rationally engineered Cas9 nucleases with improved specificity*, Slaymaker et al., Science 2016 Jan 1 351(6268): 84-88 doi: l0.H26/science.aad5227. Epub 2015 Dec 1.
- Gao *et al*, "Engineered Cpfl Enzymes with Altered PAM Specificities," bioRxiv 09161 1; doi: http://dx.doi.org/l0.H0l/09l6l l (Dec. 4, 2016).
- Cox et al., "RNA editing with CRISPR-Cas 13," Science. 2017 Nov 24;358(6366):1019-1027. doi: l0.H26/science.aaq0l80. Epub 2017 Oct 25.
- Gaudelli et al. "Programmable base editing of A-T to G-C in genomic DNA without DNA cleavage" Nature 464(551); 464-471 (2017).

each of which is incorporated herein by reference, may be considered in the practice of the instant invention, and discussed briefly below:

- Cong *et al.* engineered type II CRISPR-Cas systems for use in eukaryotic cells based on both *Streptococcus thermophilus* Cas9 and also *Streptococcus pyogenes* Cas9 and demonstrated that Cas9 nucleases can be directed by short RNAs to induce precise cleavage of DNA in human and mouse cells. Their study further showed that Cas9 as converted into a nicking enzyme can be used to facilitate homology-directed repair in eukaryotic cells with minimal mutagenic activity. Additionally, their study demonstrated that multiple guide sequences can be encoded into a single CRISPR array to enable simultaneous editing of several at endogenous genomic loci sites within the mammalian genome, demonstrating easy programmability and wide applicability of the RNA-guided nuclease technology. This ability to use RNA to program sequence specific DNA cleavage in cells defined a new

class of genome engineering tools. These studies further showed that other CRISPR loci are likely to be transplantable into mammalian cells and can also mediate mammalian genome cleavage. Importantly, it can be envisaged that several aspects of the CRISPR-Cas system can be further improved to increase its efficiency and versatility.

- Jiang *et al.* used the clustered, regularly interspaced, short palindromic repeats (CRISPR)-associated Cas9 endonuclease complexed with dual-RNAs to introduce precise mutations in the genomes of *Streptococcus pneumoniae* and *Escherichia coli.* The approach relied on dual-RNA:Cas9-directed cleavage at the targeted genomic site to kill unmutated cells and circumvents the need for selectable markers or counter-selection systems. The study reported reprogramming dual-RNA:Cas9 specificity by changing the sequence of short CRISPR RNA (crRNA) to make single- and multinucleotide changes carried on editing templates. The study showed that simultaneous use of two crRNAs enabled multiplex mutagenesis. Furthermore, when the approach was used in combination with recombineering, in *S. pneumoniae* , nearly 100% of cells that were recovered using the described approach contained the desired mutation, and in *E. coli,* 65% that were recovered contained the mutation.
- Wang *et al.* (2013) used the CRISPR-Cas system for the one-step generation of mice carrying mutations in multiple genes which were traditionally generated in multiple steps by sequential recombination in embryonic stem cells and/or time-consuming intercrossing of mice with a single mutation. The CRISPR-Cas system will greatly accelerate the *in vivo* study of functionally redundant genes and of epistatic gene interactions.
- Konermann *et al.* (2013) addressed the need in the art for versatile and robust technologies that enable optical and chemical modulation of DNA-binding domains based CRISPR Cas9 enzyme and also Transcriptional Activator Like Effectors
- Ran *et al.* (2013-A) described an approach that combined a Cas9 nickase mutant with paired guide RNAs to introduce targeted double-strand breaks. This addresses the issue of the Cas9 nuclease from the microbial CRISPR-Cas system being targeted to specific genomic loci by a guide sequence, which can tolerate certain mismatches to the DNA target and thereby promote undesired off-target mutagenesis. Because individual nicks in the genome are repaired with high fidelity, simultaneous nicking *via* appropriately offset guide

RNAs is required for double-stranded breaks and extends the number of specifically recognized bases for target cleavage. The authors demonstrated that using paired nicking can reduce off-target activity by 50- to 1,500-fold in cell lines and to facilitate gene knockout in mouse zygotes without sacrificing on-target cleavage efficiency. This versatile strategy enables a wide variety of genome editing applications that require high specificity.

- Hsu *el al.* (2013) characterized SpCas9 targeting specificity in human cells to inform the selection of target sites and avoid off-target effects. The study evaluated >700 guide RNA variants and SpCas9-induced indel mutation levels at >100 predicted genomic off-target loci in 293T and 293FT cells. The authors that SpCas9 tolerates mismatches between guide RNA and target DNA at different positions in a sequence-dependent manner, sensitive to the number, position and distribution of mismatches. The authors further showed that SpCas9-mediated cleavage is unaffected by DNA methylation and that the dosage of SpCas9 and guide RNA can be titrated to minimize off-target modification. Additionally, to facilitate mammalian genome engineering applications, the authors reported providing a web-based software tool to guide the selection and validation of target sequences as well as off-target analyses.
- Ran *el al.* (2013-B) described a set of tools for Cas9-mediated genome editing *via* non-homologous end joining (NHEJ) or homology-directed repair (HDR) in mammalian cells, as well as generation of modified cell lines for downstream functional studies. To minimize off-target cleavage, the authors further described a double-nicking strategy using the Cas9 nickase mutant with paired guide RNAs. The protocol provided by the authors experimentally derived guidelines for the selection of target sites, evaluation of cleavage efficiency and analysis of off-target activity. The studies showed that beginning with target design, gene modifications can be achieved within as little as 1-2 weeks, and modified clonal cell lines can be derived within 2-3 weeks.
- Shalem *el al.* described a new way to interrogate gene function on a genome-wide scale. Their studies showed that delivery of a genome-scale CRISPR-Cas9 knockout (GeCKO) library targeted 18,080 genes with 64,751 unique guide sequences enabled both negative and positive selection screening in human cells. First, the authors showed use of the GeCKO library to identify genes essential for cell viability in cancer and pluripotent stem

cells. Next, in a melanoma model, the authors screened for genes whose loss is involved in resistance to vemurafenib, a therapeutic that inhibits mutant protein kinase BRAE Their studies showed that the highest-ranking candidates included previously validated genes NF1 and MED12 as well as novel hits NF2, CUL3, TADA2B, and TADA1. The authors observed a high level of consistency between independent guide RNAs targeting the same gene and a high rate of hit confirmation, and thus demonstrated the promise of genome-scale screening with Cas9.

- Nishimasu *et al.* reported the crystal structure of *Streptococcuspyogenes* Cas9 in complex with sgRNA and its target DNA at 2.5 A° resolution. The structure revealed a bilobed architecture composed of target recognition and nuclease lobes, accommodating the sgRNA:DNA heteroduplex in a positively charged groove at their interface. Whereas the recognition lobe is essential for binding sgRNA and DNA, the nuclease lobe contains the HNH and RuvC nuclease domains, which are properly positioned for cleavage of the complementary and non-complementary strands of the target DNA, respectively. The nuclease lobe also contains a carboxyl-terminal domain responsible for the interaction with the protospacer adjacent motif (PAM). This high-resolution structure and accompanying functional analyses have revealed the molecular mechanism of RNA-guided DNA targeting by Cas9, thus paving the way for the rational design of new, versatile genome-editing technologies.
- Wu *et al.* mapped genome-wide binding sites of a catalytically inactive Cas9 (dCas9) from *Streptococcus pyogenes* loaded with single guide RNAs (sgRNAs) in mouse embryonic stem cells (mESCs). The authors showed that each of the four sgRNAs tested targets dCas9 to between tens and thousands of genomic sites, frequently characterized by a 5-nucleotide seed region in the sgRNA and an NGG protospacer adjacent motif (PAM). Chromatin inaccessibility decreases dCas9 binding to other sites with matching seed sequences; thus 70% of off-target sites are associated with genes. The authors showed that targeted sequencing of 295 dCas9 binding sites in mESCs transfected with catalytically active Cas9 identified only one site mutated above background levels. The authors proposed a two-state model for Cas9 binding and cleavage, in which a seed match triggers binding but extensive pairing with target DNA is required for cleavage.

- Platt *et al.* established a Cre-dependent Cas9 knockin mouse. The authors demonstrated *in vivo* as well as *ex vivo* genome editing using adeno-associated virus (AAV)-, lentivirus-, or particle-mediated delivery of guide RNA in neurons, immune cells, and endothelial cells.
- Hsu *et al.* (2014) is a review article that discusses generally CRISPR-Cas9 history from yogurt to genome editing, including genetic screening of cells.
- Wang *et al.* (2014) relates to a pooled, loss-of-function genetic screening approach suitable for both positive and negative selection that uses a genome-scale lentiviral single guide RNA (sgRNA) library.
- Doench *et al.* created a pool of sgRNAs, tiling across all possible target sites of a panel of six endogenous mouse and three endogenous human genes and quantitatively assessed their ability to produce null alleles of their target gene by antibody staining and flow cytometry. The authors showed that optimization of the PAM improved activity and also provided an on-line tool for designing sgRNAs.
- Swiech *et al.* demonstrate that AAV-mediated SpCas9 genome editing can enable reverse genetic studies of gene function in the brain.
- Konermann *et al.* (2015) discusses the ability to attach multiple effector domains, e.g., transcriptional activator, functional and epigenomic regulators at appropriate positions on the guide such as stem or tetraloop with and without linkers.
- Zetsche *et al.* demonstrates that the Cas9 enzyme can be split into two and hence the assembly of Cas9 for activation can be controlled.
- Chen *et al.* relates to multiplex screening by demonstrating that a genome-wide *in vivo* CRISPR-Cas9 screen in mice reveals genes regulating lung metastasis.
- Ran *et al.* (2015) relates to SaCas9 and its ability to edit genomes and demonstrates that one cannot extrapolate from biochemical assays.
- Shalem *et al.* (2015) described ways in which catalytically inactive Cas9 (dCas9) fusions are used to synthetically repress (CRISPRi) or activate (CRISPRa) expression, showing advances using Cas9 for genome-scale screens, including arrayed and pooled screens, knockout approaches that inactivate genomic loci and strategies that modulate transcriptional activity.

- Xu *et al.* (2015) assessed the DNA sequence features that contribute to single guide RNA (sgRNA) efficiency in CRISPR-based screens. The authors explored efficiency of CRISPR-Cas9 knockout and nucleotide preference at the cleavage site. The authors also found that the sequence preference for CRISPRi/a is substantially different from that for CRISPR-Cas9 knockout.
- Parnas *et al.* (2015) introduced genome-wide pooled CRISPR-Cas9 libraries into dendritic cells (DCs) to identify genes that control the induction of tumor necrosis factor (Tnf) by bacterial lipopolysaccharide (LPS). Known regulators of Tlr4 signaling and previously unknown candidates were identified and classified into three functional modules with distinct effects on the canonical responses to LPS.
- Ramanan *et al* (20 15) demonstrated cleavage of viral episomal DNA (cccDNA) in infected cells. The HBV genome exists in the nuclei of infected hepatocytes as a 3.2kb double-stranded episomal DNA species called covalently closed circular DNA (cccDNA), which is a key component in the HBV life cycle whose replication is not inhibited by current therapies. The authors showed that sgRNAs specifically targeting highly conserved regions of HBV robustly suppresses viral replication and depleted cccDNA.
- Nishimasu *et al.* (2015) reported the crystal structures of SaCas9 in complex with a single guide RNA (sgRNA) and its double-stranded DNA targets, containing the 5'-TTGAAT-3' PAM and the 5'-TTGGGT-3' PAM. A structural comparison of SaCas9 with SpCas9 highlighted both structural conservation and divergence, explaining their distinct PAM specificities and orthologous sgRNA recognition.
- Canver *et al.* (2015) demonstrated a CRISPR-Cas9-based functional investigation of non-coding genomic elements. The authors developed pooled CRISPR-Cas9 guide RNA libraries to perform *in situ* saturating mutagenesis of the human and mouse BCL1 1A enhancers which revealed critical features of the enhancers.
- Zetsche et al. (2015) reported characterization of Cpfl, a class 2 CRISPR nuclease from Francisella novicida U 112 having features distinct from Cas9. Cpfl is a single RNA-guided endonuclease lacking tracrRNA, utilizes a T-rich protospacer-adjacent motif, and cleaves DNA via a staggered DNA double-stranded break.

- Shmakov et al. (2015) reported three distinct Class 2 CRISPR-Cas systems. Two system CRISPR enzymes (C2cl and C2c3) contain RuvC-like endonuclease domains distantly related to Cpfl. Unlike Cpfl, C2cl depends on both crRNA and tracrRNA for DNA cleavage. The third enzyme (C2c2) contains two predicted HEPN RNase domains and is tracrRNA independent.
- Slaymaker et al (2016) reported the use of structure-guided protein engineering to improve the specificity of Streptococcus pyogenes Cas9 (SpCas9). The authors developed "enhanced specificity" SpCas9 (eSpCas9) variants which maintained robust on-target cleavage with reduced off-target effects.
- Cox et al., (2017) reported the use of catalytically inactive Casl3 (dCasl3) to direct adenosine-to-inosine deaminase activity by ADAR2 (adenosine deaminase acting on RNA type 2) to transcripts in mammalian cells. The system, referred to as RNA Editing for Programmable A to I Replacement (REPAIR), has no strict sequence constraints and can be used to edit full-length transcripts. The authors further engineered the system to create a high-specificity variant and minimized the system to facilitate viral delivery.

[00348] The methods and tools provided herein are may be designed for use with or Casl3, a type II nuclease that does not make use of tracrRNA. Orthologs of Casl3 have been identified in different bacterial species as described herein. Further type II nucleases with similar properties can be identified using methods described in the art (Shmakov et al. 2015, 60:385-397; Abudayyeh et al. 2016, Science, 5;353(6299)). In particular embodiments, such methods for identifying novel CRISPR effector proteins may comprise the steps of selecting sequences from the database encoding a seed which identifies the presence of a CRISPR Cas locus, identifying loci located within 10 kb of the seed comprising Open Reading Frames (ORFs) in the selected sequences, selecting therefrom loci comprising ORFs of which only a single ORF encodes a novel CRISPR effector having greater than 700 amino acids and no more than 90% homology to a known CRISPR effector. In particular embodiments, the seed is a protein that is common to the CRISPR-Cas system, such as Casl. In further embodiments, the CRISPR array is used as a seed to identify new effector proteins.

[00349] Also, "Dimeric CRISPR RNA-guided Fokl nucleases for highly specific genome editing", Shengdar Q. Tsai, Nicolas Wyvekens, Cyd Khayter, Jennifer A. Foden, Vishal Thapar,

Deepak Reyon, Mathew J. Goodwin, Martin J. Aryee, J. Keith Joung Nature Biotechnology 32(6): 569-77 (2014), relates to dimeric RNA-guided Fokl Nucleases that recognize extended sequences and can edit endogenous genes with high efficiencies in human cells.

[00350] Also, Harrington et al. "Programmed DNA destruction by miniature CRISPR-Casl4 enzymes" Science 2018 doi:l0/H26/science.aav4293, relates to Casl4.

[00351] With respect to general information on CRISPR/Cas Systems, components thereof, and delivery of such components, including methods, materials, delivery vehicles, vectors, particles, and making and using thereof, including as to amounts and formulations, as well as CRISPR-Cas-expressing eukaryotic cells, CRISPR-Cas expressing eukaryotes, such as a mouse, reference is made to: US Patents Nos. 8,999,641, 8,993,233, 8,697,359, 8,771,945, 8,795,965, 8,865,406, 8,871,445, 8,889,356, 8,889,418, 8,895,308, 8,906,616, 8,932,814, and 8,945,839; US Patent Publications US 2014-0310830 (US App. Ser. No. 14/105,031), US 2014-0287938 Al (U.S. App. Ser. No. 14/213,991), US 2014-0273234 Al (U.S. App. Ser. No. 14/293,674), US2014-0273232 Al (U.S. App. Ser. No. 14/290,575), US 2014-0273231 (U.S. App. Ser. No. 14/259,420), US 2014-0256046 Al (U.S. App. Ser. No. 14/226,274), US 2014-0248702 Al (U.S. App. Ser. No. 14/258,458), US 2014-0242700 Al (U.S. App. Ser. No. 14/222,930), US 2014-0242699 Al (U.S. App. Ser. No. 14/183,512), US 2014-0242664 Al (U.S. App. Ser. No. 14/104,990), US 2014-0234972 Al (U.S. App. Ser. No. 14/183,471), US 2014-0227787 Al (U.S. App. Ser. No. 14/256,912), US 2014-0189896 Al (U.S. App. Ser. No. 14/105,035), US 2014-0186958 (U.S. App. Ser. No. 14/105,017), US 2014-0186919 Al (U.S. App. Ser. No. 14/104,977), US 2014-0186843 Al (U.S. App. Ser. No. 14/104,900), US 2014-0179770 Al (U.S. App. Ser. No. 14/104,837) and US 2014-0179006 Al (U.S. App. Ser. No. 14/183,486), US 2014-0170753 (US App Ser No 14/183,429); US 2015-0184139 (U.S. App. Ser. No. 14/324,960); 14/054,414 European Patent Applications EP 2 771 468 (EP13818570.7), EP 2 764 103 (EP13824232.6), and EP 2 784 162 (EP 14 170383. 5); and PCT Patent Publications WO20 14/093 661 (PCT/US20 13/074743), WO20 14/093694 (PCT/US20 13/074790), WO2014/093595 (PCT/US20 13/074611), WO20 14/093718 (PCT/US20 13/074825), WO20 14/093 709 (PCT/US20 13/074812), WO20 14/093 622 (PCT/US20 13/074667), WO2014/093635 (PCT/US20 13/074691), WO2014/093655 (PCT/US20 13/074736), WO2014/093712 (PCT/US20 13/074819), WO20 14/093 701 (PCT/US20 13/074800), WO20 14/0 18423

(PCT/US2013/051418), WO20 14/204723 (PCT/US20 14/04 1790), WO20 14/204724
(PCT/US20 14/04 1800), WO20 14/204725 (PCT/US20 14/04 1803), WO20 14/204726
(PCT/US20 14/04 1804), WO20 14/204727 (PCT/US20 14/04 1806), WO20 14/204728
(PCT/US20 14/04 1808), WO20 14/204729 (PCT/US20 14/04 1809), WO20 15/0893 5 1
(PCT/US20 14/069897), WO20 15/0893 54 (PCT/US20 14/069902), WO2015/089364
(PCT/US20 14/069925), WO20 15/089427 (PCT/US20 14/070068), WO20 15/089462
(PCT/US20 14/070 127), WO20 15/0894 19 (PCT/US20 14/070057), WO20 15/089465
(PCT/US2014/070135), WO20 15/089486 (PCT/US20 14/070 175), W02015/058052
(PCT/US20 14/06 1077), WO20 15/070083 (PCT/US20 14/064663), WO20 15/0893 54
(PCT/US20 14/069902), WO20 15/0893 5 1 (PCT/US20 14/069897), WO2015/089364
(PCT/US20 14/069925), WO20 15/089427 (PCT/US20 14/070068), WO20 15/089473
(PCT/US20 14/070 152), WO20 15/089486 (PCT/US20 14/070 175), WO20 16/049258
(PCT/US20 15/05 1830), WO20 16/094867 (PCT/US20 15/0653 85), WO20 16/094872
(PCT/US20 15/065393), WO20 16/094874 (PCT/US20 15/065396), WO20 16/1 06244
(PCT/US20 15/067 177).

[00352] Mention is also made of US application 62/180,709, l7-Jun-l5, PROTECTED GUIDE RNAS (PGRNAS); US application 62/091,455, filed, 12-Dec- 14, PROTECTED GUIDE RNAS (PGRNAS); US application 62/096,708, 24-Dec-l4, PROTECTED GUIDE RNAS (PGRNAS); US applications 62/091,462, !2-Dec-l4, 62/096,324, 23-Dec-l4, 62/180,681, !7-Jun-20l5, and 62/237,496, 5-Oct-20l5, DEAD GUIDES FOR CRISPR TRANSCRIPTION FACTORS; US application 62/091,456, l2-Dec-l4 and 62/180,692, l7-Jun-20l5, ESCORTED AND FUNCTIONALIZED GUIDES FOR CRISPR-CAS SYSTEMS; US application 62/091,461, 12-Dec-l4, DELIVERY, USE AND THERAPEUTIC APPLICATIONS OF THE CRISPR-CAS SYSTEMS AND COMPOSITIONS FOR GENOME EDITING AS TO HEMATOPOETIC STEM CELLS (HSCs); US application 62/094,903, l9-Dec-l4, UNBIASED IDENTIFICATION OF DOUBLE-STRAND BREAKS AND GENOMIC REARRANGEMENT BY GENOME-WISE INSERT CAPTURE SEQUENCING; US application 62/096,761, 24-Dec-l4, ENGINEERING OF SYSTEMS, METHODS AND OPTIMIZED ENZYME AND GUIDE SCAFFOLDS FOR SEQUENCE MANIPULATION; US application 62/098,059, 30-Dec-l4, 62/181,641, l8-Jun-20l5, and 62/181,667, l8-Jun-20l5, RNA-TARGETING SYSTEM; US

application 62/096,656, 24-Dec-l4 and 62/181,151, l7-Jun-20l5, CRISPR HAVING OR ASSOCIATED WITH DESTABILIZATION DOMAINS; US application 62/096,697, 24-Dec-14, CRISPR HAVING OR ASSOCIATED WITH AAV; US application 62/098,158, 30-Dec-l4, ENGINEERED CRISPR COMPLEX INSERTIONAL TARGETING SYSTEMS; US application 62/151,052, 22-Apr-l5, CELLULAR TARGETING FOR EXTRACELLULAR EXOSOMAL REPORTING; US application 62/054,490, 24-Sep-l4, DELIVERY, USE AND THERAPEUTIC APPLICATIONS OF THE CRISPR-CAS SYSTEMS AND COMPOSITIONS FOR TARGETING DISORDERS AND DISEASES USING PARTICLE DELIVERY COMPONENTS; US application 61/939,154, 12-F EB-14, SYSTEMS, METHODS AND COMPOSITIONS FOR SEQUENCE MANIPULATION WITH OPTIMIZED FUNCTIONAL CRISPR-CAS SYSTEMS; US application 62/055,484, 25-Sep-l4, SYSTEMS, METHODS AND COMPOSITIONS FOR SEQUENCE MANIPULATION WITH OPTIMIZED FUNCTIONAL CRISPR-CAS SYSTEMS; US application 62/087,537, 4-Dec-l4, SYSTEMS, METHODS AND COMPOSITIONS FOR SEQUENCE MANIPULATION WITH OPTIMIZED FUNCTIONAL CRISPR-CAS SYSTEMS; US application 62/054,651, 24-Sep-l4, DELIVERY, USE AND THERAPEUTIC APPLICATIONS OF THE CRISPR-CAS SYSTEMS AND COMPOSITIONS FOR MODELING COMPETITION OF MULTIPLE CANCER MUTATIONS IN VIVO; US application 62/067,886, 23-Oct-l4, DELIVERY, USE AND THERAPEUTIC APPLICATIONS OF THE CRISPR-CAS SYSTEMS AND COMPOSITIONS FOR MODELING COMPETITION OF MULTIPLE CANCER MUTATIONS IN VIVO; US applications 62/054,675, 24-Sep-l4 and 62/181,002, l7-Jun-20l5, DELIVERY, USE AND THERAPEUTIC APPLICATIONS OF THE CRISPR-CAS SYSTEMS AND COMPOSITIONS IN NEURONAL CELLS/TISSUES; US application 62/054,528, 24-Sep-l4, DELIVERY, USE AND THERAPEUTIC APPLICATIONS OF THE CRISPR-CAS SYSTEMS AND COMPOSITIONS IN IMMUNE DISEASES OR DISORDERS; US application 62/055,454, 25-Sep-l4, DELIVERY, USE AND THERAPEUTIC APPLICATIONS OF THE CRISPR-CAS SYSTEMS AND COMPOSITIONS FOR TARGETING DISORDERS AND DISEASES USING CELL PENETRATION PEPTIDES (CPP); US application 62/055,460, 25-Sep-l4, MULTIFUNCTIONAL-CRISPR COMPLEXES AND/OR OPTIMIZED ENZYME LINKED FUNCTIONAL-CRISPR COMPLEXES; US application 62/087,475, 4-Dec-l4 and 62/181,690, l8-Jun-20l5, FUNCTIONAL SCREENING

WITH OPTIMIZED FUNCTIONAL CRISPR-CAS SYSTEMS; US application 62/055,487, 25-Sep-l4, FUNCTIONAL SCREENING WITH OPTIMIZED FUNCTIONAL CRISPR-CAS SYSTEMS; US application 62/087,546, 4-Dec-l4 and 62/181,687, l8-Jun-20l5, MULTIFUNCTIONAL CRISPR COMPLEXES AND/OR OPTIMIZED ENZYME LINKED FUNCTIONAL-CRISPR COMPLEXES; and US application 62/098,285, 30-Dec-l4, CRISPR MEDIATED IN VIVO MODELING AND GENETIC SCREENING OF TUMOR GROWTH AND METASTASIS.

[00353] Mention is made of US applications 62/181,659, l8-Jun-20l5 and 62/207,318, l9-Aug-2015, ENGINEERING AND OPTIMIZATION OF SYSTEMS, METHODS, ENZYME AND GUIDE SCAFFOLDS OF CAS9 ORTHOLOGS AND VARIANTS FOR SEQUENCE MANIPULATION. Mention is made of US applications 62/181,663, l8-Jun-20l5 and 62/245,264, 22-Oct-20l5, NOVEL CRISPR ENZYMES AND SYSTEMS, US applications 62/181,675, l8-Jun-20l5, 62/285,349, 22-Oct-20l5, 62/296,522, l7-Feb-20l6, and 62/320,231, 8-Apr-20l6, NOVEL CRISPR ENZYMES AND SYSTEMS, US application 62/232,067, 24-Sep-2015, US Application 14/975,085, l8-Dec-20l5, European application No. 16150428.7, US application 62/205,733, l6-Aug-20l5, US application 62/201,542, 5-Aug-20l5, US application 62/193,507, l6-Jul-20l5, and US application 62/181,739, l8-Jun-20l5, each entitled NOVEL CRISPR ENZYMES AND SYSTEMS and of US application 62/245,270, 22-Oct-20l5, NOVEL CRISPR ENZYMES AND SYSTEMS. Mention is also made of US application 61/939,256, 12-Feb-20l4, and WO 2015/089473 (PCT/US20 14/070 152), l2-Dec-20l4, each entitled ENGINEERING OF SYSTEMS, METHODS AND OPTIMIZED GUIDE COMPOSITIONS WITH NEW ARCHITECTURES FOR SEQUENCE MANIPULATION. Mention is also made of PCT/US20 15/045504, l5-Aug-20l5, US application 62/180,699, l7-Jun-20l5, and US application 62/038,358, l7-Aug-20l4, each entitled GENOME EDITING USING CAS9 NICKASES.

[00354] Each of these patents, patent publications, and applications, and all documents cited therein or during their prosecution ("appln cited documents") and all documents cited or referenced in the appln cited documents, together with any instructions, descriptions, product specifications, and product sheets for any products mentioned therein or in any document therein and incorporated by reference herein, are hereby incorporated herein by reference, and may be employed in the

practice of the invention. All documents (e.g., these patents, patent publications and applications and the appln cited documents) are incorporated herein by reference to the same extent as if each individual document was specifically and individually indicated to be incorporated by reference.

[00355] In particular embodiments, pre-complexed guide RNA and CRISPR effector protein, (optionally, adenosine deaminase fused to a CRISPR protein or an adaptor) are delivered as a ribonucleoprotein (RNP). RNPs have the advantage that they lead to rapid editing effects even more so than the RNA method because this process avoids the need for transcription. An important advantage is that both RNP delivery is transient, reducing off-target effects and toxicity issues. Efficient genome editing in different cell types has been observed by Kim et al. (2014, Genome Res. 24(6): 1012-9), Paix et al. (2015, Genetics 204(l):47-54), Chu et al. (2016, BMC Biotechnol. 16:4), and Wang et al. (2013, Cell. 9;153(4):910-8).

[00356] In particular embodiments, the ribonucleoprotein is delivered by way of a polypeptide-based shuttle agent as described in WO2016161516. WO2016161516 describes efficient transduction of polypeptide cargos using synthetic peptides comprising an endosome leakage domain (ELD) operably linked to a cell penetrating domain (CPD), to a histidine-rich domain and a CPD. Similarly, these polypeptides can be used for the delivery of CRISPR-effector based RNPs in eukaryotic cells.

Tale Systems

[00357] As disclosed herein editing can be made by way of the transcription activator-like effector nucleases (TALENs) system. Transcription activator-like effectors (TALEs) can be engineered to bind practically any desired DNA sequence. Exemplary methods of genome editing using the TALEN system can be found for example in Cermak T. Doyle EL. Christian M. Wang L. Zhang Y. Schmidt C, et al. Efficient design and assembly of custom TALEN and other TAL effector-based constructs for DNA targeting. Nucleic Acids Res. 201 l;39:e82; Zhang F. Cong L. Lodato S. Kosuri S. Church GM. Arlotta P Efficient construction of sequence-specific TAL effectors for modulating mammalian transcription. Nat Biotechnol. 201 1;29:149-153 and US Patent Nos. 8,450,471, 8,440,431 and 8,440,432, all of which are specifically incorporated by reference.

[00358] In advantageous embodiments of the invention, the methods provided herein use isolated, non-naturally occurring, recombinant or engineered DNA binding proteins that comprise

TALE monomers as a part of their organizational structure that enable the targeting of nucleic acid sequences with improved efficiency and expanded specificity.

[00359] Naturally occurring TALEs or "wild type TALEs" are nucleic acid binding proteins secreted by numerous species of proteobacteria. TALE polypeptides contain a nucleic acid binding domain composed of tandem repeats of highly conserved monomer polypeptides that are predominantly 33, 34 or 35 amino acids in length and that differ from each other mainly in amino acid positions 12 and 13. In advantageous embodiments the nucleic acid is DNA. As used herein, the term "polypeptide monomers", or "TALE monomers" will be used to refer to the highly conserved repetitive polypeptide sequences within the TALE nucleic acid binding domain and the term "repeat variable di-residues" or "RVD" will be used to refer to the highly variable amino acids at positions 12 and 13 of the polypeptide monomers. As provided throughout the disclosure, the amino acid residues of the RVD are depicted using the IUPAC single letter code for amino acids. A general representation of a TALE monomer which is comprised within the DNA binding domain is Xl-l 1-(X 12X 13)-X 14-33 or 34 or 35, where the subscript indicates the amino acid position and X represents any amino acid. X12X13 indicate the RVDs. In some polypeptide monomers, the variable amino acid at position 13 is missing or absent and in such polypeptide monomers, the RVD consists of a single amino acid. In such cases the RVD may be alternatively represented as X*, where X represents X12 and (*) indicates that X13 is absent. The DNA binding domain comprises several repeats of TALE monomers and this may be represented as (Xl-l 1-(X 12X 13)-X 14-33 or 34 or 35)z, where in an advantageous embodiment, z is at least 5 to 40. In a further advantageous embodiment, z is at least 10 to 26.

[00360] The TALE monomers have a nucleotide binding affinity that is determined by the identity of the amino acids in its RVD. For example, polypeptide monomers with an RVD of NI preferentially bind to adenine (A), polypeptide monomers with an RVD of NG preferentially bind to thymine (T), polypeptide monomers with an RVD of HD preferentially bind to cytosine (C) and polypeptide monomers with an RVD of NN preferentially bind to both adenine (A) and guanine (G). In yet another embodiment of the invention, polypeptide monomers with an RVD of IG preferentially bind to T. Thus, the number and order of the polypeptide monomer repeats in the nucleic acid binding domain of a TALE determines its nucleic acid target specificity. In still further embodiments of the invention, polypeptide monomers with an RVD of N S recognize all four base

pairs and may bind to A, T, G or C. The structure and function of TALEs is further described in, for example, Moscou et al., Science 326:1501 (2009); Boch et al., Science 326:1509-1512 (2009); and Zhang et al., Nature Biotechnology 29:149-153 (2011), each of which is incorporated by reference in its entirety.

[00361] The TALE polypeptides used in methods of the invention are isolated, non-naturally occurring, recombinant or engineered nucleic acid-binding proteins that have nucleic acid or DNA binding regions containing polypeptide monomer repeats that are designed to target specific nucleic acid sequences.

[00362] As described herein, polypeptide monomers having an RVD of HN or NH preferentially bind to guanine and thereby allow the generation of TALE polypeptides with high binding specificity for guanine containing target nucleic acid sequences. In a preferred embodiment of the invention, polypeptide monomers having RVDs RN, NN, NK, SN, NH, KN, HN, NQ, HH, RG, KH, RH and SS preferentially bind to guanine. In a much more advantageous embodiment of the invention, polypeptide monomers having RVDs RN, NK, NQ, HH, KH, RH, SS and SN preferentially bind to guanine and thereby allow the generation of TALE polypeptides with high binding specificity for guanine containing target nucleic acid sequences. In an even more advantageous embodiment of the invention, polypeptide monomers having RVDs HH, KH, NH, NK, NQ, RH, RN and SS preferentially bind to guanine and thereby allow the generation of TALE polypeptides with high binding specificity for guanine containing target nucleic acid sequences. In a further advantageous embodiment, the RVDs that have high binding specificity for guanine are RN, NH RH and KH. Furthermore, polypeptide monomers having an RVD of NV preferentially bind to adenine and guanine. In more preferred embodiments of the invention, polypeptide monomers having RVDs of H*, HA, KA, N*, NA, NC, NS, RA, and S* bind to adenine, guanine, cytosine and thymine with comparable affinity.

[00363] The predetermined N-terminal to C-terminal order of the one or more polypeptide monomers of the nucleic acid or DNA binding domain determines the corresponding predetermined target nucleic acid sequence to which the TALE polypeptides will bind. As used herein the polypeptide monomers and at least one or more half polypeptide monomers are "specifically ordered to target" the genomic locus or gene of interest. In plant genomes, the natural TALE-binding sites always begin with a thymine (T), which may be specified by a cryptic signal

within the non-repetitive N-terminus of the TALE polypeptide; in some cases this region may be referred to as repeat 0. In animal genomes, TALE binding sites do not necessarily have to begin with a thymine (T) and TALE polypeptides may target DNA sequences that begin with T, A, G or C. The tandem repeat of TALE monomers always ends with a half-length repeat or a stretch of sequence that may share identity with only the first 20 amino acids of a repetitive full length TALE monomer and this half repeat may be referred to as a half-monomer (FIG. 8), which is included in the term "TALE monomer". Therefore, it follows that the length of the nucleic acid or DNA being targeted is equal to the number of full polypeptide monomers plus two.

[00364] As described in Zhang et al., Nature Biotechnology 29:149-153 (2011), TALE polypeptide binding efficiency may be increased by including amino acid sequences from the "capping regions" that are directly N-terminal or C-terminal of the DNA binding region of naturally occurring TALEs into the engineered TALEs at positions N-terminal or C-terminal of the engineered TALE DNA binding region. Thus, in certain embodiments, the TALE polypeptides described herein further comprise an N-terminal capping region and/or a C-terminal capping region.

[00365] An exemplary amino acid sequence of a N-terminal capping region is:

M D P I R S R T P S P A R E L L S G P Q P D G V Q P T A D R G V S P

P A G G P L D G L P A R R T M S R T R L P S P P A P S P A F S A D S

F S D L L R Q F D P S L F N T S L F D S L P P F G A H H T E AAT G

E W D E V Q S G L R AAD A P P P T M R VAV TAA R P P R A K P A

P R R R A A Q P S D A S P A A Q V D L R T L G Y S Q Q Q Q E K I K P

K V R S T V A Q H H E A L V G H G F T H A H I V A L S Q H P A A L G

T VAVKY Q D M I A A L P E A T H E A I V G V G K Q W S G A R A L

E A L L T V A G E L R G P P L Q L D T G Q L L K I A K R G G V T A V

E A V H A W R N A L T G A P L N (SEQ. I.D. No. 1)

An exemplary amino acid sequence of a C-terminal capping region is:

R P A L E S I V A Q L S R P D P A L AAL T N D H L VAL A C L G

G R P A L D AVK K G L P H A P A L I K R T N R R I P E R T S H R

V A D H A Q V V R V L G F F Q C H S H P A Q A F D D A M T Q F G M

S R H G L L Q L F R R V G V T E L E A R S G T L P P A S Q R W D R

I L Q A S G M K R A K P S P T S T Q T P D Q A S L H A F A D S L E

R D L D A P S P M H E G D Q T R A S (SEQ. I.D. No. 2)

[00366] As used herein the predetermined "N-terminus" to "C terminus" orientation of the N-terminal capping region, the DNA binding domain comprising the repeat TALE monomers and the C-terminal capping region provide structural basis for the organization of different domains in the d-TALEs or polypeptides of the invention.

[00367] The entire N-terminal and/or C-terminal capping regions are not necessary to enhance the binding activity of the DNA binding region. Therefore, in certain embodiments, fragments of the N-terminal and/or C-terminal capping regions are included in the TALE polypeptides described herein.

[00368] In certain embodiments, the TALE polypeptides described herein contain a N-terminal capping region fragment that included at least 10, 20, 30, 40, 50, 54, 60, 70, 80, 87, 90, 94, 100, 102, 110, 117, 120, 130, 140, 147, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260 or 270 amino acids of an N-terminal capping region. In certain embodiments, the N-terminal capping region fragment amino acids are of the C-terminus (the DNA-binding region proximal end) of an N-terminal capping region. As described in Zhang et al., Nature Biotechnology 29: 149-153 (201 1), N-terminal capping region fragments that include the C-terminal 240 amino acids enhance binding activity equal to the full length capping region, while fragments that include the C-terminal 147 amino acids retain greater than 80% of the efficacy of the full length capping region, and fragments that include the C-terminal 117 amino acids retain greater than 50% of the activity of the full-length capping region.

[00369] In some embodiments, the TALE polypeptides described herein contain a C-terminal capping region fragment that included at least 6, 10, 20, 30, 37, 40, 50, 60, 68, 70, 80, 90, 100, 110, 120, 127, 130, 140, 150, 155, 160, 170, 180 amino acids of a C-terminal capping region. In certain embodiments, the C-terminal capping region fragment amino acids are of the N-terminus (the DNA-binding region proximal end) of a C-terminal capping region. As described in Zhang et al., Nature Biotechnology 29:149-153 (201 1), C-terminal capping region fragments that include

the C-terminal 68 amino acids enhance binding activity equal to the full length capping region, while fragments that include the C-terminal 20 amino acids retain greater than 50% of the efficacy of the full length capping region.

[00370] In certain embodiments, the capping regions of the TALE polypeptides described herein do not need to have identical sequences to the capping region sequences provided herein. Thus, in some embodiments, the capping region of the TALE polypeptides described herein have sequences that are at least 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical or share identity to the capping region amino acid sequences provided herein. Sequence identity is related to sequence homology. Homology comparisons may be conducted by eye, or more usually, with the aid of readily available sequence comparison programs. These commercially available computer programs may calculate percent (%) homology between two or more sequences and may also calculate the sequence identity shared by two or more amino acid or nucleic acid sequences. In some preferred embodiments, the capping region of the TALE polypeptides described herein have sequences that are at least 95% identical or share identity to the capping region amino acid sequences provided herein.

[00371] Sequence homologies may be generated by any of a number of computer programs known in the art, which include but are not limited to BLAST or FASTA. Suitable computer program for carrying out alignments like the GCG Wisconsin Bestfit package may also be used. Once the software has produced an optimal alignment, it is possible to calculate % homology, preferably % sequence identity. The software typically does this as part of the sequence comparison and generates a numerical result.

[00372] In advantageous embodiments described herein, the TALE polypeptides of the invention include a nucleic acid binding domain linked to the one or more effector domains. The terms “effector domain” or “regulatory and functional domain” refer to a polypeptide sequence that has an activity other than binding to the nucleic acid sequence recognized by the nucleic acid binding domain. By combining a nucleic acid binding domain with one or more effector domains, the polypeptides of the invention may be used to target the one or more functions or activities mediated by the effector domain to a particular target DNA sequence to which the nucleic acid binding domain specifically binds.

[00373] In some embodiments of the TALE polypeptides described herein, the activity mediated by the effector domain is a biological activity. For example, in some embodiments the effector domain is a transcriptional inhibitor (i.e., a repressor domain), such as an mSin interaction domain (SID). SID4X domain or a Kriippel-associated box (KRAB) or fragments of the KRAB domain. In some embodiments the effector domain is an enhancer of transcription (i.e. an activation domain), such as the VP 16, VP64 or p65 activation domain. In some embodiments, the nucleic acid binding is linked, for example, with an effector domain that includes but is not limited to a transposase, integrase, recombinase, resolvase, invertase, protease, DNA methyltransferase, DNA demethylase, histone acetylase, histone deacetylase, nuclease, transcriptional repressor, transcriptional activator, transcription factor recruiting, protein nuclear-localization signal or cellular uptake signal.

[00374] In some embodiments, the effector domain is a protein domain which exhibits activities which include but are not limited to transposase activity, integrase activity, recombinase activity, resolvase activity, invertase activity, protease activity, DNA methyltransferase activity, DNA demethylase activity, histone acetylase activity, histone deacetylase activity, nuclease activity, nuclear-localization signaling activity, transcriptional repressor activity, transcriptional activator activity, transcription factor recruiting activity, or cellular uptake signaling activity. Other preferred embodiments of the invention may include any combination the activities described herein.

ZN-Finger Nucleases

[00375] Other preferred tools for genome editing for use in the context of this invention include zinc finger systems. One type of programmable DNA-binding domain is provided by artificial zinc-finger (ZF) technology, which involves arrays of ZF modules to target new DNA-binding sites in the genome. Each finger module in a ZF array targets three DNA bases. A customized array of individual zinc finger domains is assembled into a ZF protein (ZFP).

[00376] ZFPs can comprise a functional domain. The first synthetic zinc finger nucleases (ZFNs) were developed by fusing a ZF protein to the catalytic domain of the Type IIS restriction enzyme Fokl. (Kim, Y. G. et al., 1994, Chimeric restriction endonuclease, Proc. Natl. Acad. Sci. U.S.A. 91, 883-887; Kim, Y. G. et al., 1996, Hybrid restriction enzymes: zinc finger fusions to Fok I cleavage domain. Proc. Natl. Acad. Sci. U.S.A. 93, 1156-1 160). Increased cleavage

specificity can be attained with decreased off target activity by use of paired ZFN heterodimers, each targeting different nucleotide sequences separated by a short spacer. (Doyon, Y. et al., 201 1, Enhancing zinc-finger-nuclease activity with improved obligate heterodimeric architectures. Nat. Methods 8, 74-79). ZFPs can also be designed as transcription activators and repressors and have been used to target many genes in a wide variety of organisms. Exemplary methods of genome editing using ZFNs can be found for example in ET.S. Patent Nos. 6,534,261, 6,607,882, 6,746,838, 6,794,136, 6,824,978, 6,866,997, 6,933,113, 6,979,539, 7,013,219, 7,030,215, 7,220,719, 7,241,573, 7,241,574, 7,585,849, 7,595,376, 6,903,185, and 6,479,626, all of which are specifically incorporated by reference.

Meganucleases

[00377] As disclosed herein editing can be made by way of meganucleases, which are endodeoxyribonucleases characterized by a large recognition site (double-stranded DNA sequences of 12 to 40 base pairs). Exemplary method for using meganucleases can be found in ETS Patent Nos: 8,163,514; 8,133,697; 8,021,867; 8,119,361; 8,1 19,381; 8,124,369; and 8,129,134, which are specifically incorporated by reference.

RNAi

[00378] In certain embodiments, the genetic modifying agent is RNAi (e.g., shRNA). As used herein, “gene silencing” or “gene silenced” in reference to an activity of an RNAi molecule, for example a siRNA or miRNA refers to a decrease in the mRNA level in a cell for a target gene by at least about 5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 99%, about 100% of the mRNA level found in the cell without the presence of the miRNA or RNA interference molecule. In one preferred embodiment, the mRNA levels are decreased by at least about 70%, about 80%, about 90%, about 95%, about 99%, about 100%.

[00379] As used herein, the term “RNAi” refers to any type of interfering RNA, including but not limited to, siRNAi, shRNAi, endogenous microRNA and artificial microRNA. For instance, it includes sequences previously identified as siRNA, regardless of the mechanism of down-stream processing of the RNA (i.e. although siRNAs are believed to have a specific method of in vivo processing resulting in the cleavage of mRNA, such sequences can be incorporated into the vectors in the context of the flanking sequences described herein). The term “RNAi” can include both gene

silencing RNAi molecules, and also RNAi effector molecules which activate the expression of a gene.

[00380] As used herein, a "siRNA" refers to a nucleic acid that forms a double stranded RNA, which double stranded RNA has the ability to reduce or inhibit expression of a gene or target gene when the siRNA is present or expressed in the same cell as the target gene. The double stranded RNA siRNA can be formed by the complementary strands. In one embodiment, a siRNA refers to a nucleic acid that can form a double stranded siRNA. The sequence of the siRNA can correspond to the full-length target gene, or a subsequence thereof. Typically, the siRNA is at least about 15-50 nucleotides in length (e.g., each complementary sequence of the double stranded siRNA is about 15-50 nucleotides in length, and the double stranded siRNA is about 15-50 base pairs in length, preferably about 19-30 base nucleotides, preferably about 20-25 nucleotides in length, e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length).

[00381] As used herein "shRNA" or "small hairpin RNA" (also called stem loop) is a type of siRNA. In one embodiment, these shRNAs are composed of a short, e.g. about 19 to about 25 nucleotide, antisense strand, followed by a nucleotide loop of about 5 to about 9 nucleotides, and the analogous sense strand. Alternatively, the sense strand can precede the nucleotide loop structure and the antisense strand can follow.

[00382] The terms "microRNA" or "miRNA" are used interchangeably herein are endogenous RNAs, some of which are known to regulate the expression of protein-coding genes at the posttranscriphonal level. Endogenous microRNAs are small RNAs naturally present in the genome that are capable of modulating the productive utilization of mRNA. The term artificial microRNA includes any type of RNA sequence, other than endogenous microRNA, which is capable of modulating the productive utilization of mRNA. MicroRNA sequences have been described in publications such as Lim, et al., Genes & Development, 17, p. 991 - 1008 (2003), Lim et al Science 299, 1540 (2003), Lee and Ambros Science, 294, 862 (2001), Lau et al., Science 294, 858-861 (2001), Lagos-Quintana et al, Current Biology, 12, 735-739 (2002), Lagos Quintana et al, Science 294, 853- 857 (2001), and Lagos-Quintana et al, RNA, 9, 175- 179 (2003), which are incorporated by reference. Multiple microRNAs can also be incorporated into a precursor molecule. Furthermore, miRNA-like stem-loops can be expressed in cells as a vehicle to deliver artificial

miRNAs and short interfering RNAs (siRNAs) for the purpose of modulating the expression of endogenous genes through the miRNA and or RNAi pathways.

[00383] As used herein, “double stranded RNA” or “dsRNA” refers to RNA molecules that are comprised of two strands. Double-stranded molecules include those comprised of a single RNA molecule that doubles back on itself to form a two-stranded structure. For example, the stem loop structure of the progenitor molecules from which the single-stranded miRNA is derived, called the pre-miRNA (Bartel et al. 2004. Cell 1 16:281 -297), comprises a dsRNA molecule.

Antibodies

[00384] In certain embodiments, the one or more agents is an antibody. The term "antibody" is used interchangeably with the term "immunoglobulin" herein, and includes intact antibodies, fragments of antibodies, e.g., Fab, F(ab')2 fragments, and intact antibodies and fragments that have been mutated either in their constant and/or variable region (e.g., mutations to produce chimeric, partially humanized, or fully humanized antibodies, as well as to produce antibodies with a desired trait, e.g., enhanced binding and/or reduced FcR binding). The term "fragment" refers to a part or portion of an antibody or antibody chain comprising fewer amino acid residues than an intact or complete antibody or antibody chain. Fragments can be obtained via chemical or enzymatic treatment of an intact or complete antibody or antibody chain. Fragments can also be obtained by recombinant means. Exemplary fragments include Fab, Fab', F(ab')2, Fabc, Fd, dAb, VHH and scFv and/or Fv fragments.

[00385] As used herein, a preparation of antibody protein having less than about 50% of non-antibody protein (also referred to herein as a "contaminating protein"), or of chemical precursors, is considered to be "substantially free." 40%, 30%, 20%, 10% and more preferably 5% (by dry weight), of non-antibody protein, or of chemical precursors is considered to be substantially free. When the antibody protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture medium represents less than about 30%, preferably less than about 20%, more preferably less than about 10%, and most preferably less than about 5% of the volume or mass of the protein preparation.

[00386] The term "antigen-binding fragment" refers to a polypeptide fragment of an immunoglobulin or antibody that binds antigen or competes with intact antibody (i.e., with the intact antibody from which they were derived) for antigen binding (i.e., specific binding). As such

these antibodies or fragments thereof are included in the scope of the invention, provided that the antibody or fragment binds specifically to a target molecule.

[00387] It is intended that the term "antibody" encompass any Ig class or any Ig subclass (e.g. the IgGl, IgG2, IgG3, and IgG4 subclasses of IgG) obtained from any source (e.g., humans and non-human primates, and in rodents, lagomorphs, caprines, bovines, equines, ovines, etc.).

[00388] The term "Ig class" or "immunoglobulin class", as used herein, refers to the five classes of immunoglobulin that have been identified in humans and higher mammals, IgG, IgM, IgA, IgD, and IgE. The term "Ig subclass" refers to the two subclasses of IgM (H and L), three subclasses of IgA (IgAl, IgA2, and secretory IgA), and four subclasses of IgG (IgGl, IgG2, IgG3, and IgG4) that have been identified in humans and higher mammals. The antibodies can exist in monomeric or polymeric form; for example, lgM antibodies exist in pentameric form, and IgA antibodies exist in monomeric, dimeric or multimeric form.

[00389] The term "IgG subclass" refers to the four subclasses of immunoglobulin class IgG - IgGl, IgG2, IgG3, and IgG4 that have been identified in humans and higher mammals by the heavy chains of the immunoglobulins, VI - γ4, respectively. The term "single-chain immunoglobulin" or "single-chain antibody" (used interchangeably herein) refers to a protein having a two-polypeptide chain structure consisting of a heavy and a light chain, said chains being stabilized, for example, by interchain peptide linkers, which has the ability to specifically bind antigen. The term "domain" refers to a globular region of a heavy or light chain polypeptide comprising peptide loops (e.g., comprising 3 to 4 peptide loops) stabilized, for example, by β pleated sheet and/or intrachain disulfide bond. Domains are further referred to herein as "constant" or "variable", based on the relative lack of sequence variation within the domains of various class members in the case of a "constant" domain, or the significant variation within the domains of various class members in the case of a "variable" domain. Antibody or polypeptide "domains" are often referred to interchangeably in the art as antibody or polypeptide "regions". The "constant" domains of an antibody light chain are referred to interchangeably as "light chain constant regions", "light chain constant domains", "CL" regions or "CL" domains. The "constant" domains of an antibody heavy chain are referred to interchangeably as "heavy chain constant regions", "heavy chain constant domains", "CH" regions or "CH" domains). The "variable" domains of an antibody light chain are referred to interchangeably as "light chain variable regions", "light chain variable domains", "VL"

regions or "VL" domains). The "variable" domains of an antibody heavy chain are referred to interchangeably as "heavy chain constant regions", "heavy chain constant domains", "VH" regions or "VH" domains).

[00390] The term "region" can also refer to a part or portion of an antibody chain or antibody chain domain (e.g., a part or portion of a heavy or light chain or a part or portion of a constant or variable domain, as defined herein), as well as more discrete parts or portions of said chains or domains. For example, light and heavy chains or light and heavy chain variable domains include "complementarity determining regions" or "CDRs" interspersed among "framework regions" or "FRs", as defined herein.

[00391] The term "conformation" refers to the tertiary structure of a protein or polypeptide (e.g., an antibody, antibody chain, domain or region thereof). For example, the phrase "light (or heavy) chain conformation" refers to the tertiary structure of a light (or heavy) chain variable region, and the phrase "antibody conformation" or "antibody fragment conformation" refers to the tertiary structure of an antibody or fragment thereof.

[00392] The term “antibody-like protein scaffolds” or “engineered protein scaffolds” broadly encompasses proteinaceous non-immunoglobulin specific-binding agents, typically obtained by combinatorial engineering (such as site-directed random mutagenesis in combination with phage display or other molecular selection techniques). Usually, such scaffolds are derived from robust and small soluble monomeric proteins (such as Kunitz inhibitors or lipocalins) or from a stably folded extra-membrane domain of a cell surface receptor (such as protein A, fibronectin or the ankyrin repeat).

[00393] Such scaffolds have been extensively reviewed in Binz et al. (Engineering novel binding proteins from nonimmunoglobulin domains. Nat Biotechnol 2005, 23:1257-1268), Gebauer and Skerra (Engineered protein scaffolds as next-generation antibody therapeutics. Curr Opin Chem Biol. 2009, 13:245-55), Gill and Damle (Biopharmaceutical drug discovery using novel protein scaffolds. Curr Opin Biotechnol 2006, 17:653-658), Skerra (Engineered protein scaffolds for molecular recognition. J Mol Recognit 2000, 13:167-187), and Skerra (Alternative non-antibody scaffolds for molecular recognition. Curr Opin Biotechnol 2007, 18:295-304), and include without limitation affibodies, based on the Z-domain of staphylococcal protein A, a three-helix bundle of 58 residues providing an interface on two of its alpha-helices (Nygren, Alternative

binding proteins: Affibody binding proteins developed from a small three-helix bundle scaffold. FEBS J 2008, 275:2668-2676); engineered Kunitz domains based on a small (ca. 58 residues) and robust, disulphide-crosslinked serine protease inhibitor, typically of human origin (e.g. LACI-D1), which can be engineered for different protease specificities (Nixon and Wood, Engineered protein inhibitors of proteases. Curr Opin Drug Discov Dev 2006, 9:261-268); monobodies or adnectins based on the lOth extracellular domain of human fibronectin III (l0Fn3), which adopts an Ig-like beta-sandwich fold (94 residues) with 2-3 exposed loops, but lacks the central disulphide bridge (Koide and Koide, Monobodies: antibody mimics based on the scaffold of the fibronectin type III domain. Methods Mol Biol 2007, 352:95-109); anticalins derived from the lipocalins, a diverse family of eight-stranded beta-barrel proteins (ca. 180 residues) that naturally form binding sites for small ligands by means of four structurally variable loops at the open end, which are abundant in humans, insects, and many other organisms (Skerra, Alternative binding proteins: Anticalins — harnessing the structural plasticity of the lipocalin ligand pocket to engineer novel binding activities. FEBS J 2008, 275:2677-2683); DARPins, designed ankyrin repeat domains (166 residues), which provide a rigid interface arising from typically three repeated beta-turns (Stumpp et al., DARPins: a new generation of protein therapeutics. Drug Discov Today 2008, 13:695-701); avimers (multimerized LDLR-A module) (Silverman et al., Multivalent avimer proteins evolved by exon shuffling of a family of human receptor domains. Nat Biotechnol 2005, 23:1556-1561); and cysteine-rich knottin peptides (Kolmar, Alternative binding proteins: biological activity and therapeutic potential of cystine-knot miniproteins. FEBS J 2008, 275:2684-2690).

[00394] "Specific binding" of an antibody means that the antibody exhibits appreciable affinity for a particular antigen or epitope and, generally, does not exhibit significant cross reactivity. "Appreciable" binding includes binding with an affinity of at least 25 μM. Antibodies with affinities greater than 1 x 107 M-l (or a dissociation coefficient of IμM or less or a dissociation coefficient of lnm or less) typically bind with correspondingly greater specificity. Values intermediate of those set forth herein are also intended to be within the scope of the present invention and antibodies of the invention bind with a range of affinities, for example, 100ηM or less, 75nM or less, 50nM or less, 25nM or less, for example 10ηM or less, 5nM or less, lnM or less, or in embodiments 500pM or less, lOOpM or less, 50pM or less or 25pM or less. An antibody that "does not exhibit significant crossreactivity" is one that will not appreciably bind to an entity

other than its target (e.g., a different epitope or a different molecule). For example, an antibody that specifically binds to a target molecule will appreciably bind the target molecule but will not significantly react with non-target molecules or peptides. An antibody specific for a particular epitope will, for example, not significantly crossreact with remote epitopes on the same protein or peptide. Specific binding can be determined according to any art-recognized means for determining such binding. Preferably, specific binding is determined according to Scatchard analysis and/or competitive binding assays.

[00395] As used herein, the term "affinity" refers to the strength of the binding of a single antigen-combining site with an antigenic determinant. Affinity depends on the closeness of stereochemical fit between antibody combining sites and antigen determinants, on the size of the area of contact between them, on the distribution of charged and hydrophobic groups, etc. Antibody affinity can be measured by equilibrium dialysis or by the kinetic BIACORE™ method. The dissociation constant, Kd, and the association constant, Ka, are quantitative measures of affinity.

[00396] As used herein, the term "monoclonal antibody" refers to an antibody derived from a clonal population of antibody-producing cells (e.g., B lymphocytes or B cells) which is homogeneous in structure and antigen specificity. The term "polyclonal antibody" refers to a plurality of antibodies originating from different clonal populations of antibody-producing cells which are heterogeneous in their structure and epitope specificity but which recognize a common antigen. Monoclonal and polyclonal antibodies may exist within bodily fluids, as crude preparations, or may be purified, as described herein.

[00397] The term "binding portion" of an antibody (or "antibody portion") includes one or more complete domains, e.g., a pair of complete domains, as well as fragments of an antibody that retain the ability to specifically bind to a target molecule. It has been shown that the binding function of an antibody can be performed by fragments of a full-length antibody. Binding fragments are produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact immunoglobulins. Binding fragments include Fab, Fab', F(ab')2, Fabc, Fd, dAb, Fv, single chains, single-chain antibodies, e.g., scFv, and single domain antibodies.

[00398] "Humanized" forms of non-human (e.g., murine) antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. For the most part,

humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity. In some instances, FR residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin.

[00399] Examples of portions of antibodies or epitope-binding proteins encompassed by the present definition include: (i) the Fab fragment, having VL, CL, VH and CH1 domains; (ii) the Fab' fragment, which is a Fab fragment having one or more cysteine residues at the C-terminus of the CH1 domain; (iii) the Fd fragment having VH and CH1 domains; (iv) the Fd' fragment having VH and CH1 domains and one or more cysteine residues at the C-terminus of the CHI domain; (v) the Fv fragment having the VL and VH domains of a single arm of an antibody; (vi) the dAb fragment (Ward et al., 341 Nature 544 (1989)) which consists of a VH domain or a VL domain that binds antigen; (vii) isolated CDR regions or isolated CDR regions presented in a functional framework; (viii) F(ab')2 fragments which are bivalent fragments including two Fab' fragments linked by a disulphide bridge at the hinge region; (ix) single chain antibody molecules (e.g., single chain Fv; scFv) (Bird et al., 242 Science 423 (1988); and Huston et al., 85 PNAS 5879 (1988)); (x) "diabodies" with two antigen binding sites, comprising a heavy chain variable domain (VH) connected to a light chain variable domain (VL) in the same polypeptide chain (see, e.g., EP 404,097; WO 93/1 1161; Hollinger et al., 90 PNAS 6444 (1993)); (xi) "linear antibodies" comprising a pair of tandem Fd segments (VH-Chl-VH-Chl) which, together with complementary light chain polypeptides, form a pair of antigen binding regions (Zapata et al., Protein Eng. 8(10): 1057-62 (1995); and U.S. Patent No. 5,641,870).

[00400] As used herein, a "blocking" antibody or an antibody "antagonist" is one which inhibits or reduces biological activity of the antigen(s) it binds. In certain embodiments, the blocking antibodies or antagonist antibodies or portions thereof described herein completely inhibit the biological activity of the antigen(s).

[00401] Antibodies may act as agonists or antagonists of the recognized polypeptides. For example, the present invention includes antibodies which disrupt receptor/ligand interactions either partially or fully. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or of one of its down-stream substrates by immunoprecipitation followed by western blot analysis. In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

[00402] The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex. Likewise, encompassed by the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides disclosed herein. The antibody agonists and antagonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Pat. No. 5,81 1,097; Deng et al., Blood 92(6): 1981-1988 (1998); Chen et ah, Cancer Res. 58(l6):3668-3678 (1998); Harrop et al., J. Immunol. 161(4): 1786-1794 (1998); Zhu et ak, Cancer Res. 58(l5):3209-32l4 (1998); Yoon et ak, J. Immunol. 160(7):3 170-3 179 (1998); Prat et ak, J. Cell. Sci. Ill (Pt2):237-247 (1998); Pitard et ak, J. Immunol. Methods 205(2): 177-190

(1997); Liautard et al., Cytokine 9(4):233-24l (1997); Carlson et al., J. Biol. Chem. 272(17): 11295-1 1301 (1997); Taryman et al., Neuron l4(4):755-762 (1995); Muller et al., Structure 6(9): 1153-1 167 (1998); Bartunek et al., Cytokine 8(1): 14-20 (1996).

[00403] The antibodies as defined for the present invention include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

[00404] Simple binding assays can be used to screen for or detect agents that bind to a target protein, or disrupt the interaction between proteins (e.g., a receptor and a ligand). Because certain targets of the present invention are transmembrane proteins, assays that use the soluble forms of these proteins rather than full-length protein can be used, in some embodiments. Soluble forms include, for example, those lacking the transmembrane domain and/or those comprising the IgV domain or fragments thereof which retain their ability to bind their cognate binding partners. Further, agents that inhibit or enhance protein interactions for use in the compositions and methods described herein, can include recombinant peptido-mimetics.

[00405] Detection methods useful in screening assays include antibody-based methods, detection of a reporter moiety, detection of cytokines as described herein, and detection of a gene signature as described herein.

[00406] Another variation of assays to determine binding of a receptor protein to a ligand protein is through the use of affinity biosensor methods. Such methods may be based on the piezoelectric effect, electrochemistry, or optical methods, such as ellipsometry, optical wave guidance, and surface plasmon resonance (SPR).

Aptamers

[00407] In certain embodiments, the one or more agents is an aptamer. Nucleic acid aptamers are nucleic acid species that have been engineered through repeated rounds of in vitro selection or equivalently, SELEX (systematic evolution of ligands by exponential enrichment) to bind to various molecular targets such as small molecules, proteins, nucleic acids, cells, tissues and organisms. Nucleic acid aptamers have specific binding affinity to molecules through interactions other than classic Watson-Crick base pairing. Aptamers are useful in biotechnological and therapeutic applications as they offer molecular recognition properties similar to antibodies. In addition to their discriminate recognition, aptamers offer advantages over antibodies as they can be engineered completely in a test tube, are readily produced by chemical synthesis, possess desirable storage properties, and elicit little or no immunogenicity in therapeutic applications. In certain embodiments, RNA aptamers may be expressed from a DNA construct. In other embodiments, a nucleic acid aptamer may be linked to another polynucleotide sequence. The polynucleotide sequence may be a double stranded DNA polynucleotide sequence. The aptamer may be covalently linked to one strand of the polynucleotide sequence. The aptamer may be ligated to the polynucleotide sequence. The polynucleotide sequence may be configured, such that the polynucleotide sequence may be linked to a solid support or ligated to another polynucleotide sequence.

[00408] Aptamers, like peptides generated by phage display or monoclonal antibodies ("mAbs"), are capable of specifically binding to selected targets and modulating the target's activity, e.g., through binding, aptamers may block their target's ability to function. A typical aptamer is 10-15 kDa in size (30-45 nucleotides), binds its target with sub-nanomolar affinity, and discriminates against closely related targets (e.g., aptamers will typically not bind other proteins from the same gene family). Structural studies have shown that aptamers are capable of using the same types of binding interactions (e.g., hydrogen bonding, electrostatic complementarity, hydrophobic contacts, steric exclusion) that drives affinity and specificity in antibody-antigen complexes.

[00409] Aptamers have a number of desirable characteristics for use in research and as therapeutics and diagnostics including high specificity and affinity, biological efficacy, and excellent pharmacokinetic properties. In addition, they offer specific competitive advantages over antibodies and other protein biologies. Aptamers are chemically synthesized and are readily scaled

as needed to meet production demand for research, diagnostic or therapeutic applications. Aptamers are chemically robust. They are intrinsically adapted to regain activity following exposure to factors such as heat and denaturants and can be stored for extended periods (>l yr) at room temperature as lyophilized powders. Not being bound by a theory, aptamers bound to a solid support or beads may be stored for extended periods.

[00410] Oligonucleotides in their phosphodiester form may be quickly degraded by intracellular and extracellular enzymes such as endonucleases and exonucleases. Aptamers can include modified nucleotides conferring improved characteristics on the ligand, such as improved in vivo stability or improved delivery characteristics. Examples of such modifications include chemical substitutions at the ribose and/or phosphate and/or base positions. SELEX identified nucleic acid ligands containing modified nucleotides are described, e.g., in ET.S. Pat. No. 5,660,985, which describes oligonucleotides containing nucleotide derivatives chemically modified at the 2' position of ribose, 5 position of pyrimidines, and 8 position of purines, ET.S. Pat. No. 5,756,703 which describes oligonucleotides containing various 2' -modified pyrimidines, and U.S. Pat. No. 5,580,737 which describes highly specific nucleic acid ligands containing one or more nucleotides modified with 2'-amino (2'-NH2), 2'-fluoro (2'-F), and/or 2'-0-methyl (2'-OMe) substituents. Modifications of aptamers may also include, modifications at exocyclic amines, substitution of 4-thiouridine, substitution of 5-bromo or 5-iodo-uracil; backbone modifications, phosphorothioate or allyl phosphate modifications, methylations, and unusual base-pairing combinations such as the isobases isocytidine and isoguanosine. Modifications can also include 3' and 5' modifications such as capping. As used herein, the term phosphorothioate encompasses one or more non-bridging oxygen atoms in a phosphodiester bond replaced by one or more sulfur atoms. In further embodiments, the oligonucleotides comprise modified sugar groups, for example, one or more of the hydroxyl groups is replaced with halogen, aliphatic groups, or functionalized as ethers or amines. In one embodiment, the 2'-position of the furanose residue is substituted by any of an O-methyl, O-alkyl, O-allyl, S-alkyl, S-allyl, or halo group. Methods of synthesis of 2'-modified sugars are described, e.g., in Sproat, et al., Nucl. Acid Res. 19:733-738 (1991); Cotten, et al, Nucl. Acid Res. 19:2629-2635 (1991); and Hobbs, et al, Biochemistry 12:5138-5145 (1973). Other modifications are known to one of ordinary skill in the art. In certain embodiments, aptamers include aptamers with improved off-rates as described in International Patent Publication No. WO

2009012418, "Method for generating aptamers with improved off-rates," incorporated herein by reference in its entirety. In certain embodiments aptamers are chosen from a library of aptamers. Such libraries include, but are not limited to those described in Rohloff et al., "Nucleic Acid Ligands With Protein-like Side Chains: Modified Aptamers and Their Use as Diagnostic and Therapeutic Agents," Molecular Therapy Nucleic Acids (2014) 3, e20l. Aptamers are also commercially available (see, e.g., SomaLogic, Inc., Boulder, Colorado). In certain embodiments, the present invention may utilize any aptamer containing any modification as described herein.

[00411] In some embodiments, the one or more cells functionally interacting with the one or more neurons are selected from the group consisting of T cells, dendritic cells (DC), B cells, fibroblasts and adipocytes.

METHODS OF MODULATING APPETITE AND ENERGY METABOLISM

[00412] In some embodiments, the invention also provides a method of modulating appetite and energy metabolism in a subject in need thereof comprising administering one or more agents capable of modulating the function or activity of one or more neurons selected from the group consisting of PIMN4 and PIMN5; or one or more adipose cells functionally interacting with the one or more neurons.

[00413] The term "modulate" broadly denotes a qualitative and/or quantitative alteration, change or variation in that which is being modulated. Where modulation can be assessed quantitatively - for example, where modulation comprises or consists of a change in a quantifiable variable such as a quantifiable property of a cell or where a quantifiable variable provides a suitable surrogate for the modulation - modulation specifically encompasses both increase (e.g., activation) or decrease (e.g., inhibition) in the measured variable. The term encompasses any extent of such modulation, e.g., any extent of such increase or decrease, and may more particularly refer to statistically significant increase or decrease in the measured variable. By means of example, modulation may encompass an increase in the value of the measured variable by at least about 10%, e.g., by at least about 20%, preferably by at least about 30%, e.g., by at least about 40%, more preferably by at least about 50%, e.g., by at least about 75%, even more preferably by at least about 100%, e.g., by at least about 150%, 200%, 250%, 300%, 400% or by at least about 500%, compared to a reference situation without said modulation; or modulation may encompass a

decrease or reduction in the value of the measured variable by at least about 10%, e.g., by at least about 20%, by at least about 30%, e.g., by at least about 40%, by at least about 50%, e.g., by at least about 60%, by at least about 70%, e.g., by at least about 80%, by at least about 90%, e.g., by at least about 95%, such as by at least about 96%, 97%, 98%, 99% or even by 100%, compared to a reference situation without said modulation. Preferably, modulation may be specific or selective, hence, one or more desired phenotypic aspects of an immune cell or immune cell population may be modulated without substantially altering other (unintended, undesired) phenotypic aspect(s).

[00414] The term "agent" broadly encompasses any condition, substance or agent capable of modulating one or more phenotypic aspects of a cell or cell population as disclosed herein. Such conditions, substances or agents may be of physical, chemical, biochemical and/or biological nature. The term "candidate agent" refers to any condition, substance or agent that is being examined for the ability to modulate one or more phenotypic aspects of a cell or cell population as disclosed herein in a method comprising applying the candidate agent to the cell or cell population (e.g., exposing the cell or cell population to the candidate agent or contacting the cell or cell population with the candidate agent) and observing whether the desired modulation takes place.

[00415] Agents may include any potential class of biologically active conditions, substances or agents, such as for instance antibodies, proteins, peptides, nucleic acids, oligonucleotides, small molecules, or combinations thereof, as described herein.

[00416] In some embodiments, the one or more neurons may be characterized by expression of one or more markers according to Table 14 or Table 21.

[00417] In some embodiments, the one or more agents modulate the expression, activity or function of one or more genes according to Table 14 or Table 21.

[00418] In some embodiments, the one or more agents may modulate the expression, activity or function of one or more genes selected from the group consisting of: NPY, CGRP, Glutamate, GABA, LEP, VIP, PACAP, Nitric oxide, NOS1, FGF1, PDGF, SLIT2, SLIT3, IL15, IL7, IL12A, PENK, CHAT and TPH2; or NPYR1, CALCRL, GRM8, GABRE, LEPR, VIPR2, GRIA4, GUCY1A3, FGFR1, PDGFRB, ROBOl, ROB02, IL15R, IL7R, IL12RB1, OPRM1, CHRNE and HTR3A.

[00419] In some embodiments, the one or more agents may modulate the expression, activity or function of one or more genes selected from the group consisting of NPY and CGRP; or NPYR1 and CALCRL.

[00420] In some embodiments, the one or more agents may modulate the expression, activity or function of one or more core transcriptional programs according to Table 23.

[00421] In some embodiments, the one or more agents may modulate the expression, activity or function of one or more genes of the one or more core transcriptional programs.

[00422] In some embodiments, the one or more agents are administered to the gut.

[00423] In some embodiments, the one or more agents may comprise an antibody, small molecule, small molecule degrader, genetic modifying agent, nucleic acid agent, antibody-like protein scaffold, aptamer, protein, or any combination thereof, as described elsewhere herein.

[00424] In some embodiments, the genetic modifying agent may comprise a CRISPR system, RNAi system, a zinc finger nuclease system, a TALE, or a meganuclease, as described above.

[00425] In specific embodiments, the CRISPR system comprises Cas9, Casl2, or Casl4.

[00426] In specific embodiments, the CRISPR system comprises a dCas fused or otherwise linked to a nucleotide deaminase. The nucleotide deaminase may be a cytidine deaminase or an adenosine deaminase. The dCas may be a dCas9, dCasl2, dCasl3, or dCasl4.

[00427] In some embodiments, the nucleic acid agent or genetic modifying agent may be administered with a vector.

[00428] In some embodiments, the nucleic acid agent or genetic modifying agent may be under the control of a promoter specific to a marker gene for the one or more neurons according to Table 14 or Table 21.

METHODS OF DETECTING CELLS OF THE ENTERIC NERVOUS SYSTEM (ENS)

[00429] In some embodiments, the invention provides a method of detecting one or more cells of the enteric nervous system (ENS) comprising detecting one or more markers according to Tables 14-17 or Tables 20-22.

Biomarkers

[00430] The invention provides biomarkers for the identification, diagnosis and manipulation of cell properties, for use in a variety of diagnostic and/or therapeutic indications. Biomarkers in

the context of the present invention encompasses, without limitation nucleic acids, together with their polymorphisms, mutations, variants, modifications, subunits, fragments, and other analytes or sample-derived measures.

[00431] Biomarkers are useful in methods of diagnosing, prognosing and/or staging an immune response in a subject by detecting a first level of expression, activity and/or function of one or more biomarker and comparing the detected level to a control of level wherein a difference in the detected level and the control level indicates that the presence of an immune response in the subject.

[00432] These biomarkers are useful in methods of identifying patient populations at risk or suffering from an immune response based on a detected level of expression, activity and/or function of one or more biomarkers. These biomarkers are also useful in monitoring subjects undergoing treatments and therapies for suitable or aberrant response(s) to determine efficaciousness of the treatment or therapy and for selecting or modifying therapies and treatments that would be efficacious in treating, delaying the progression of or otherwise ameliorating a symptom. The biomarkers provided herein are useful for selecting a group of patients at a specific state of a disease with accuracy that facilitates selection of treatments.

[00433] The present invention also may comprise a kit with a detection reagent that binds to one or more biomarkers.

[00434] In one embodiment, the signature genes, biomarkers, and/or cells may be detected or isolated by immunofluorescence, immunohistochemistry, fluorescence activated cell sorting (FACS), mass cytometry (CyTOF), RNA-seq, scRNA-seq (e.g., Drop-seq,, InDrop, 10X Genomics), single cell qPCR, MERFISH (multiplex (in situ) RNA FISH) and/or by in situ hybridization. Other methods including absorbance assays and colorimetric assays are known in the art and may be used herein. detection may comprise primers and/or probes or fluorescently bar-coded oligonucleotide probes for hybridization to RNA (see e.g., Geiss GK, et al., Direct multiplexed measurement of gene expression with color-coded probe pairs. Nat Biotechnol. 2008 Mar;26(3):3 17-25).

Gene Signatures

[00435] As used herein a “signature” may encompass any gene or genes, protein or proteins (e.g., gene products), or epigenetic element(s) whose expression profile or whose occurrence is

associated with a specific cell type, subtype, or cell state of a specific cell type or subtype within a population of cells (e.g., neurogenic cell). In certain embodiments, the signature is dependent on epigenetic modification of the genes or regulatory elements associated with the genes (e.g., methylation, ubiquitination). Thus, in certain embodiments, use of signature genes includes epigenetic modifications that may be detected or modulated. For ease of discussion, when discussing gene expression, any of gene or genes, protein or proteins, or epigenetic element(s) may be substituted. As used herein, the terms "signature", "expression profile", "transcription profile" or "expression program" may be used interchangeably. It is to be understood that also when referring to proteins (e.g. differentially expressed proteins), such may fall within the definition of "gene" signature. Levels of expression or activity may be compared between different cells in order to characterize or identify for instance signatures specific for cell (sub)populations. Increased or decreased expression or activity or prevalence of signature genes may be compared between different cells in order to characterize or identify for instance specific cell (sub)populations. The detection of a signature in single cells may be used to identify and quantitate for instance specific cell (sub)populations. A signature may include a gene or genes, protein or proteins, or epigenetic element(s) whose expression or occurrence is specific to a cell (sub)population, such that expression or occurrence is exclusive to the cell (sub)population. A gene signature as used herein, may thus refer to any set of up- and/or down-regulated genes that are representative of a cell type or subtype. A gene signature as used herein, may also refer to any set of up- and/or down-regulated genes between different cells or cell (sub)populations derived from a gene-expression profile. For example, a gene signature may comprise a list of genes differentially expressed in a distinction of interest.

[00436] The signature as defined herein (being it a gene signature, protein signature or other genetic or epigenetic signature) can be used to indicate the presence of a cell type, a subtype of the cell type, the state of the microenvironment of a population of cells, a particular cell type population or subpopulation, and/or the overall status of the entire cell (sub)population. Furthermore, the signature may be indicative of cells within a population of cells in vivo. The signature may also be used to suggest for instance particular therapies, or to follow up treatment, or to suggest ways to modulate immune systems. The signatures of the present invention may be discovered by analysis of expression profiles of single-cells within a population of cells from

isolated samples (e.g. nervous tissue), thus allowing the discovery of novel cell subtypes or cell states that were previously invisible or unrecognized, for example, adult newborn neurons. The presence of subtypes or cell states may be determined by subtype specific or cell state specific signatures. The presence of these specific cell (sub)types or cell states may be determined by applying the signature genes to bulk sequencing data in a sample. The signatures of the present invention may be microenvironment specific, such as their expression in a particular spatio-temporal context. In certain embodiments, signatures as discussed herein are specific to a particular developmental stage or pathological context. In certain embodiments, a combination of cell subtypes having a particular signature may indicate an outcome. The signatures may be used to deconvolute the network of cells present in a particular developmental stage or pathological condition. The presence of specific cells and cell subtypes may also be indicative of a particular developmental stage, a particular response to treatment, such as including increased or decreased susceptibility to treatment. The signature may indicate the presence of one particular cell type. In one embodiment, the novel signatures are used to detect multiple cell states or hierarchies that occur in subpopulations of cells that are linked to particular stages of development or particular pathological condition, or linked to a particular outcome or progression of the disease, or linked to a particular response to treatment of the disease (e.g. resistance to therapy).

[00437] The signature according to certain embodiments of the present invention may comprise or consist of one or more genes, proteins and/or epigenetic elements, such as for instance 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more. In certain embodiments, the signature may comprise or consist of two or more genes, proteins and/or epigenetic elements, such as for instance 2, 3, 4, 5, 6, 7, 8, 9, 10 or more. In certain embodiments, the signature may comprise or consist of three or more genes, proteins and/or epigenetic elements, such as for instance 3, 4, 5, 6, 7, 8, 9, 10 or more. In certain embodiments, the signature may comprise or consist of four or more genes, proteins and/or epigenetic elements, such as for instance 4, 5, 6, 7, 8, 9, 10 or more. In certain embodiments, the signature may comprise or consist of five or more genes, proteins and/or epigenetic elements, such as for instance 5, 6, 7, 8, 9, 10 or more. In certain embodiments, the signature may comprise or consist of six or more genes, proteins and/or epigenetic elements, such as for instance 6, 7, 8, 9, 10 or more. In certain embodiments, the signature may comprise or consist of seven or more genes, proteins and/or epigenetic elements, such as for instance 7, 8, 9, 10 or more. In certain

embodiments, the signature may comprise or consist of eight or more genes, proteins and/or epigenetic elements, such as for instance 8, 9, 10 or more. In certain embodiments, the signature may comprise or consist of nine or more genes, proteins and/or epigenetic elements, such as for instance 9, 10 or more. In certain embodiments, the signature may comprise or consist of ten or more genes, proteins and/or epigenetic elements, such as for instance 10, 11, 12, 13, 14, 15, or more. It is to be understood that a signature according to the invention may for instance also include genes or proteins as well as epigenetic elements combined.

[00438] In certain embodiments, a signature is characterized as being specific for a particular cell or cell (sub)population if it is upregulated or only present, detected or detectable in that particular cell or cell (sub)population, or alternatively is downregulated or only absent, or undetectable in that particular cell or cell (sub)population. In this context, a signature consists of one or more differentially expressed genes/proteins or differential epigenetic elements when comparing different cells or cell (sub)populations, including comparing different neurogenic cells, for example, neuronal stem cells, neuronal precursor cells, neuroblasts, immature neurons and newborn neurons, as well as comparing immune cells or immune cell (sub)populations with other immune cells or immune cell (sub)populations. It is to be understood that "differentially expressed" genes/proteins include genes/proteins which are up- or down-regulated as well as genes/proteins which are turned on or off. When referring to up-or down-regulation, in certain embodiments, such up- or down-regulation is preferably at least two-fold, such as two-fold, three-fold, four-fold, five-fold, or more, such as for instance at least ten-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, or more. Alternatively, or in addition, differential expression may be determined based on common statistical tests, as is known in the art.

[00439] As discussed herein, differentially expressed genes/proteins, or differential epigenetic elements may be differentially expressed on a single cell level, or may be differentially expressed on a cell population level. Preferably, the differentially expressed genes/ proteins or epigenetic elements as discussed herein, such as constituting the gene signatures as discussed herein, when as to the cell population level, refer to genes that are differentially expressed in all or substantially all cells of the population (such as at least 80%, preferably at least 90%, such as at least 95% of the individual cells). This allows one to define a particular subpopulation of cells. As referred to herein, a "subpopulation" of cells preferably refers to a particular subset of cells of a particular cell

type (e.g., proliferating) which can be distinguished or are uniquely identifiable and set apart from other cells of this cell type. The cell subpopulation may be phenotypically characterized, and is preferably characterized by the signature as discussed herein. A cell (sub)population as referred to herein may constitute a (sub)population of cells of a particular cell type characterized by a specific cell state.

[00440] When referring to induction, or alternatively reducing or suppression of a particular signature, preferable is meant induction or alternatively reduction or suppression (or upregulation or downregulation) of at least one gene/protein and/or epigenetic element of the signature, such as for instance at least two, at least three, at least four, at least five, at least six, or all genes/proteins and/or epigenetic elements of the signature.

[00441] Various aspects and embodiments of the invention may involve analyzing gene signatures, protein signatures, and/or other genetic or epigenetic signatures based on single cell analyses (e.g. single cell RNA sequencing) or alternatively based on cell population analyses, as is defined herein elsewhere.

[00442] The invention further relates to various uses of the gene signatures, protein signature, and/or other genetic or epigenetic signature as defined herein. Particular advantageous uses include methods for identifying agents capable of inducing or suppressing neurogenesis, particularly inducing or suppressing neurogenic cell(sub)populations based on the gene signatures, protein signature, and/or other genetic or epigenetic signature as defined herein. The invention further relates to agents capable of inducing or suppressing particular neurogenic cell (sub)populations based on the gene signatures, protein signature, and/or other genetic or epigenetic signature as defined herein, as well as their use for modulating, such as inducing or repressing, a particular gene signature, protein signature, and/or other genetic or epigenetic signature. In one embodiment, genes in one population of cells may be activated or suppressed in order to affect the cells of another population. In related aspects, modulating, such as inducing or repressing, a particular gene signature, protein signature, and/or other genetic or epigenetic signature may modulate neurogenesis, and/or neurogeneic cell subpopulation composition or distribution, or functionality.

[00443] The signature genes of the present invention were discovered by analysis of expression profiles of single-cells within a population of neurogenic cells, thus allowing the discovery of novel cell subtypes that were previously invisible or rare in a population of cells within the nervous

tissue. The presence of subtypes may be determined by subtype specific signature genes. The presence of these specific cell types may be determined by applying the signature genes to bulk sequencing data in a patient. Not being bound by a theory, many cells make up a microenvironment, whereby the cells communicate and affect each other in specific ways. As such, specific cell types within this microenvironment may express signature genes specific for this microenvironment. Not being bound by a theory the signature genes of the present invention may be microenvironment specific. The signature genes may indicate the presence of one particular cell type. In one embodiment, the expression may indicate the presence of proliferating cell types. Not being bound by a theory, a combination of cell subtypes in a subject may indicate an outcome.

[00444] As used herein the term "biological program" can be used interchangeably with "expression program" or "transcriptional program" and may refer to a set of genes that share a role in a biological function (e.g., an activation program, cell differentiation program, proliferation program). Biological programs can include a pattern of gene expression that result in a corresponding physiological event or phenotypic trait. Biological programs can include up to several hundred genes that are expressed in a spatially and temporally controlled fashion. Expression of individual genes can be shared between biological programs. Expression of individual genes can be shared among different single cell types; however, expression of a biological program may be cell type specific or temporally specific (e.g., the biological program is expressed in a cell type at a specific time). Expression of a biological program may be regulated by a master switch, such as a nuclear receptor or transcription factor.

[00445] All gene name symbols refer to the gene as commonly known in the art. The examples described herein that refer to the mouse gene names are to be understood to also encompasses human genes, as well as genes in any other organism (e.g., homologous, orthologous genes). The term, homolog, may apply to the relationship between genes separated by the event of speciation (e.g., ortholog). Orthologs are genes in different species that evolved from a common ancestral gene by speciation. Normally, orthologs retain the same function in the course of evolution. Gene symbols may be those referred to by the HUGO Gene Nomenclature Committee (HGNC) or National Center for Biotechnology Information (NCBI). Any reference to the gene symbol is a reference made to the entire gene or variants of the gene. The signature as described herein may encompass any of the genes described herein.

[00446] In specific embodiments, detecting the one or more markers comprises immunohistochemistry.

METHODS OF SCREENING

[00447] The invention also provides for methods of screening for agents capable of modulating expression of a transcription program according to Table 23. Such methods may comprise administering an agent to a population of cells comprising neurons selected from the group consisting of PEMN1, PEMN2, PIMN1, PIMN2, PIMN3, PIMN4, PIMN5, PIN1, PIN2, PSN and PSVN; and detecting expression of one or more genes in the transcriptional program.

Screening for modulating agents

[00448] A further aspect of the invention relates to a method for identifying an agent capable of modulating one or more phenotypic aspects of a cell or cell population as disclosed herein, comprising: a) applying a candidate agent to the cell or cell population; b) detecting modulation of one or more phenotypic aspects of the cell or cell population by the candidate agent, thereby identifying the agent.

[00449] The term "modulate" broadly denotes a qualitative and/or quantitative alteration, change or variation in that which is being modulated. Where modulation can be assessed quantitatively - for example, where modulation comprises or consists of a change in a quantifiable variable such as a quantifiable property of a cell or where a quantifiable variable provides a suitable surrogate for the modulation - modulation specifically encompasses both increase (e.g., activation) or decrease (e.g., inhibition) in the measured variable. The term encompasses any extent of such modulation, e.g., any extent of such increase or decrease, and may more particularly refer to statistically significant increase or decrease in the measured variable. By means of example, modulation may encompass an increase in the value of the measured variable by at least about 10%, e.g., by at least about 20%, preferably by at least about 30%, e.g., by at least about 40%, more preferably by at least about 50%, e.g., by at least about 75%, even more preferably by at least about 100%, e.g., by at least about 150%, 200%, 250%, 300%, 400% or by at least about 500%, compared to a reference situation without said modulation; or modulation may encompass a decrease or reduction in the value of the measured variable by at least about 10%, e.g., by at least about 20%, by at least about 30%, e.g., by at least about 40%, by at least about 50%, e.g., by at

least about 60%, by at least about 70%, e.g., by at least about 80%, by at least about 90%, e.g., by at least about 95%, such as by at least about 96%, 97%, 98%, 99% or even by 100%, compared to a reference situation without said modulation. Preferably, modulation may be specific or selective, hence, one or more desired phenotypic aspects of an immune cell or immune cell population may be modulated without substantially altering other (unintended, undesired) phenotypic aspect(s).

[00450] The term "agent" broadly encompasses any condition, substance or agent capable of modulating one or more phenotypic aspects of a cell or cell population as disclosed herein. Such conditions, substances or agents may be of physical, chemical, biochemical and/or biological nature. The term "candidate agent" refers to any condition, substance or agent that is being examined for the ability to modulate one or more phenotypic aspects of a cell or cell population as disclosed herein in a method comprising applying the candidate agent to the cell or cell population (e.g., exposing the cell or cell population to the candidate agent or contacting the cell or cell population with the candidate agent) and observing whether the desired modulation takes place.

[00451] Agents may include any potential class of biologically active conditions, substances or agents, such as for instance antibodies, proteins, peptides, nucleic acids, oligonucleotides, small molecules, or combinations thereof, as described herein.

[00452] In certain embodiments, the present invention provides for gene signature screening. The concept of signature screening was introduced by Stegmaier et al. (Gene expression-based high-throughput screening (GE-HTS) and application to leukemia differentiation. Nature Genet. 36, 257-263 (2004)), who realized that if a gene-expression signature was the proxy for a phenotype of interest, it could be used to find small molecules that effect that phenotype without knowledge of a validated drug target. The signatures of the present invention may be used to screen for drugs that reduce the signature in cells as described herein. The signature may be used for GE-HTS. In certain embodiments, pharmacological screens may be used to identify drugs that are selectively toxic to cells having a signature.

[00453] The Connectivity Map (cmap) is a collection of genome-wide transcriptional expression data from cultured human cells treated with bioactive small molecules and simple pattern-matching algorithms that together enable the discovery of functional connections between drugs, genes and diseases through the transitory feature of common gene-expression changes (see, Lamb et al., The Connectivity Map: ETsing Gene-Expression Signatures to Connect Small

Molecules, Genes, and Disease. Science 29 Sep 2006: Vol. 313, Issue 5795, pp. 1929-1935, DOI: 10. H26/science. 1132939; and Lamb, L, The Connectivity Map: a new tool for biomedical research. Nature Reviews Cancer January 2007: Vol. 7, pp. 54-60). In certain embodiments, Cmap can be used to screen for small molecules capable of modulating a signature of the present invention in silico.

[00454] In some embodiments, detecting expression comprises RT-PCR, RNA-seq, single cell RNA-seq, fluorescently labeled probes, or an immunoassay, as described elsewhere herein.

[00455] In some embodiments, the neurons express one or more reporter genes under control of a promoter specific to the one or more genes in the transcriptional program. In some embodiments, detecting comprises detecting the reporter gene.

METHODS OF IDENTIFYING GENE EXPRESSION IN SINGLE CELLS

[00456] The invention also provides a method of identifying gene expression in single cells comprising providing sequencing reads from a single nucleus sequencing library and counting sequencing reads mapping to introns and exons.

Microfluidics

[00457] In a preferred embodiment, single cell or single nuclei analysis is performed using microfluidics. Microfluidics involves micro-scale devices that handle small volumes of fluids. Because microfluidics may accurately and reproducibly control and dispense small fluid volumes, in particular volumes less than 1 μï, application of microfluidics provides significant cost-savings. The use of microfluidics technology reduces cycle times, shortens time-to-results, and increases throughput. Furthermore, incorporation of microfluidics technology enhances system integration and automation. Microfluidic reactions are generally conducted in microdroplets. The ability to conduct reactions in microdroplets depends on being able to merge different sample fluids and different microdroplets. See, e.g., US Patent Publication No. 20120219947 and PCT publication No.W020l4085802 Al.

[00458] Droplet microfluidics offers significant advantages for performing high-throughput screens and sensitive assays. Droplets allow sample volumes to be significantly reduced, leading to concomitant reductions in cost. Manipulation and measurement at kilohertz speeds enable up to 108 samples to be screened in a single day. Compartmentalization in droplets increases assay

sensitivity by increasing the effective concentration of rare species and decreasing the time required to reach detection thresholds. Droplet microfluidics combines these powerful features to enable currently inaccessible high-throughput screening applications, including single-cell and single-molecule assays. See, e.g., Guo et al., Lab Chip, 2012,12, 2146-2155.

[00459] The manipulation of fluids to form fluid streams of desired configuration, discontinuous fluid streams, droplets, particles, dispersions, etc., for purposes of fluid delivery, product manufacture, analysis, and the like, is a relatively well-studied art. Microfluidic systems have been described in a variety of contexts, typically in the context of miniaturized laboratory (e.g., clinical) analysis. Other uses have been described as well. For example, WO 2001/89788; WO 2006/040551 ; U.S. Patent Application Publication No. 2009/0005254; WO 2006/040554; U.S. Patent Application Publication No. 2007/0184489; WO 2004/002627; U.S. Patent No. 7,708,949; WO 2008/063227; U.S. Patent Application Publication No. 2008/0003142; WO 2004/091763; U.S. Patent Application Publication No. 2006/0163385; WO 2005/021 151 ; U.S. Patent Application Publication No. 2007/0003442; WO 2006/096571 ; U.S. Patent Application Publication No. 2009/0131543; WO 2007/089541; U.S. Patent Application Publication No. 2007/0195127; WO 2007/081385; U.S. Patent Application Publication No. 2010/0137163; WO 2007/133710; U.S. Patent Application Publication No. 2008/0014589; U.S. Patent Application Publication No. 2014/0256595; and WO 201 1/079176. In a preferred embodiment, single cell analysis is performed in droplets using methods according to WO 2014085802. Each of these patents and publications is herein incorporated by reference in their entireties for all purposes.

[00460] Single cells or nuclei may be sorted into separate vessels by dilution of the sample and physical movement, such as micromanipulation devices or pipetting. A computer controlled machine may control pipetting and separation.

[00461] Single cells or single nuclei of the present invention may be divided into single droplets using a microfluidic device. The single cells or nuclei in such droplets may be further labeled with a barcode. In this regard reference is made to Macosko et al., 2015, “Highly Parallel Genome-wide Expression Profiling of Individual Cells Using Nanoliter Droplets” Cell 161, 1202-1214 and Klein et al., 2015, “Droplet Barcoding for Single-Cell Transcriptomics Applied to Embryonic Stem Cells” Cell 161, 1187-1201 all the contents and disclosure of each of which are herein incorporated

by reference in their entirety. Not being bound by a theory, the volume size of an aliquot within a droplet may be as small as 1 fL

[00462] Single cells or single nuclei may be diluted into a physical multi-well plate or a plate free environment. The multi-well assay modules (e.g., plates) may have any number of wells and/or chambers of any size or shape, arranged in any pattern or configuration, and be composed of a variety of different materials. Preferred embodiments of the invention are multi-well assay plates that use industry standard multi-well plate formats for the number, size, shape and configuration of the plate and wells. Examples of standard formats include 96-, 384-, 1536- and 9600-well plates, with the wells configured in two-dimensional arrays. Other formats include single well, two well, six well and twenty-four well and 6144 well plates. Plate free environments of the present invention utilize a single polymerizable gel containing compartmentalized cells or single nuclei. In one embodiment, extraction of single cells or single nuclei may be by a mechanical punch. Single cells or single nuclei may be visualized in the gel before a punch.

[00463] In one embodiment, to ensure proper staining of intracellular and intranuclear proteins and nucleic acids single cells or nuclei are embedded in hydrogel droplets. Not being bound by a theory, the hydrogel mesh provides a physical framework, chemically incorporates biomolecules and is permeable to macromolecules such as antibodies (Chung et al., (2013). Structural and molecular interrogation of intact biological systems. Nature 497, 332-337). In one embodiment, to further improve permeability and staining efficiency, lipids are cleared (Chung et al., 2013). Not being bound by a theory, the clearance of the lipids and the porosity of the hydrogel allow for more efficient washing. This higher accuracy of measurement is important for the high multiplex measurements and computational inference of regulatory mechanisms.

[00464] In one embodiment, the nucleic acids of single cells or nuclei are crosslinked to prevent loss of nucleic acids. Not being bound by a theory, leakage of mRNA from nuclei may be prevented by crosslinking. Nucleic acids can be reverse cross-linked after separation of cells or nuclei into separate wells or droplets. The contents of individual wells or droplets may then be sequenced. In one embodiment, crosslinking may be reversed by incubating the cross-linked sample in high salt (approximately 200 mM NaCl) at 65°C for at least 4h.

[00465] The invention provides a nucleotide- or oligonucleotide-adorned bead wherein said bead comprises: a linker; an identical sequence for use as a sequencing priming site; a uniform or

near-uniform nucleotide or oligonucleotide sequence (e.g., each bead has a barcode sequence that is unique to each bead in a plurality of beads); a Unique Molecular Identifier which differs for each priming site; optionally an oligonucleotide redundant sequence for capturing polyadenylated mRNAs and priming reverse transcription; and optionally at least one other oligonucleotide barcode which provides an additional substrate for identification.

[00466] In an embodiment of the invention, the nucleotide or oligonucleotide sequences on the surface of the bead is a molecular barcode. In a further embodiment, the barcode ranges from 4 to 1000 nucleotides in length. In another embodiment, the oligonucleotide sequence for capturing polyadenylated mRNAs and priming reverse transcription is an oligo dT sequence.

[00467] In an embodiment of the invention, the linker is a non-cleavable, straight-chain polymer. In another embodiment, the linker is a chemically-cleavable, straight-chain polymer. In a further embodiment, the linker is a non-cleavable, optionally substituted hydrocarbon polymer. In another embodiment, the linker is a photolabile optionally substituted hydrocarbon polymer. In another embodiment, the linker is a polyethylene glycol. In an embodiment, the linker is a PEG-C3 to PEG-24.

[00468] In an embodiment of the invention, the nucleotide or oligonucleotide sequence on the surface of the bead is a molecular barcode. In a further embodiment, the barcode ranges from 4 to 1000 nucleotides in length. In another embodiment, the oligonucleotide sequence for capturing polyadenylated mRNAs and priming reverse transcription is an oligo dT sequence.

[00469] In an embodiment of the invention, the mixture comprises at least one oligonucleotide sequences, which provide for substrates for downstream molecular-biological reactions. In another embodiment, the downstream molecular biological reactions are for reverse transcription of mature mRNAs; capturing specific portions of the transcriptome, priming for DNA polymerases and/or similar enzymes; or priming throughout the transcriptome or genome. In an embodiment of the invention, the additional oligonucleotide sequence comprises an oligo-dT sequence. In another embodiment of the invention, the additional oligonucleotide sequence comprises a primer sequence. In an embodiment of the invention, the additional oligonucleotide sequence comprises an oligo-dT sequence and a primer sequence.

[00470] The invention provides an error-correcting barcode bead wherein said bead comprises: a linker; an identical sequence for use as a sequencing priming site; a uniform or near-uniform

nucleotide or oligonucleotide sequence which comprises at least a nucleotide base duplicate; a Unique Molecular Identifier which differs for each priming site; and an oligonucleotide redundant for capturing polyadenylated mRNAs and priming reverse transcription.

[00471] In an embodiment of the invention, the error-correcting barcode beads fail to hybridize to the mRNA thereby failing to undergo reverse transcription.

[00472] The invention also provides a kit which comprises a mixture of oligonucleotide bound beads and self-correcting barcode beads.

[00473] The invention provides a method for creating a single-cell sequencing library comprising: merging one uniquely barcoded RNA capture microbead with a single-cell or single nuclei in an emulsion droplet having a diameter from 50 pm to 210 pm; lysing the cell thereby capturing the RNA on the RNA capture microbead; breaking droplets and pooling beads in solution; performing a reverse transcription reaction to convert the cells' RNA to first strand cDNA that is covalently linked to the RNA capture microbead; or conversely reverse transcribing within droplets and thereafter breaking droplets and collecting cDNA-attached beads; preparing and sequencing a single composite RNA-Seq library, containing cell barcodes that record the cell-of-origin of each RNA, and molecular barcodes that distinguish among RNAs from the same cell..

[00474] In an embodiment the diameter of the emulsion droplet is between 50-210 pm. In a further embodiment, the method wherein the diameter of the mRNA capture microbeads is from 10 pm to 95 pm. In a further embodiment the diameter of the emulsion droplet is 90 pm.

[00475] The invention provides a method for preparing a plurality of beads with unique nucleic acid sequence comprising: performing polynucleotide synthesis on the surface of the plurality of beads in a pool-and-split process, such that in each cycle of synthesis the beads are split into a plurality of subsets wherein each subset is subjected to different chemical reactions; repeating the pool-and-split process from anywhere from 2 cycles to 200 cycles.

[00476] In an embodiment of the invention the polynucleotide synthesis is phosphoramidite synthesis. In another embodiment of the invention the polynucleotide synthesis is reverse direction phosphoramidite chemistry. In an embodiment of the invention, each subset is subjected to a different nucleotide. In another embodiment, each subset is subjected to a different canonical nucleotide. In an embodiment of the invention the method is repeated three, four, or twelve times.

[00477] In an embodiment the covalent bond is polyethylene glycol. In another embodiment the diameter of the mRNA capture microbeads is from 10 pm to 95 pm. In an embodiment, wherein the multiple steps is twelve steps.

[00478] In a further embodiment the method further comprises a method for preparing uniquely barcoded mRNA capture microbeads, which has a unique barcode and diameter suitable for microfluidic devices comprising: 1) performing reverse phosphoramidite synthesis on the surface of the bead in a pool-and-split fashion, such that in each cycle of synthesis the beads are split into four reactions with one of the four canonical nucleotides (T, C, G, or A); 2) repeating this process a large number of times, at least six, and optimally more than twelve, such that, in the latter, there are more than 16 million unique barcodes on the surface of each bead in the pool.

[00479] In an embodiment, the diameter of the mRNA capture microbeads is from 10 pm to 95 pm.

[00480] The invention provides a method for simultaneously preparing a plurality of nucleotide- or oligonucleotide-adorned beads wherein a uniform, near-uniform, or patterned nucleotide or oligonucleotide sequence is synthesized upon any individual bead while vast numbers of different nucleotide or oligonucleotide sequences are simultaneously synthesized on different beads, comprising: forming a mixture comprising a plurality of beads; separating the beads into subsets; extending the nucleotide or oligonucleotide sequence on the surface of the beads by adding an individual nucleotide via chemical synthesis; pooling the subsets of beads in (c) into a single common pool; repeating steps (b), (c) and (d) multiple times to produce a combinatorially a thousand or more nucleotide or oligonucleotide sequences; and collecting the nucleotide- or oligonucleotide-adorned beads.

[00481] In an embodiment of the invention, the nucleotide or oligonucleotide sequence on the surface of the bead is a molecular barcode. In a further embodiment, the pool-and-split synthesis steps occur every 2-10 cycles, rather than every cycle.

[00482] In an embodiment of the invention, the barcode contains built-in error correction. In another embodiment, the barcode ranges from 4 to 1000 nucleotides in length. In embodiment of the invention the polynucleotide synthesis is phosphoramidite synthesis. In a further embodiment, the polynucleotide synthesis is reverse direction phosphoramidite chemistry. In an embodiment of the invention each subset is subjected to a different nucleotide. In a further embodiment, one

or more subsets receive a cocktail of two nucleotides. In an embodiment, each subset is subjected to a different canonical nucleotide.

[00483] The method provided by the invention contemplates a variety of embodiments wherein the bead is a microbead, a nanoparticle, or a macrobead. Similarly, the invention contemplates that the oligonucleotide sequence is a dinucleotide or trinucleotide.

[00484] The invention provides a method for simultaneously preparing a thousand or more nucleotide- or oligonucleotide-adorned beads wherein a uniform or near-uniform nucleotide or oligonucleotide sequence is synthesized upon any individual bead while a plurality of different nucleotide or oligonucleotide sequences are simultaneously synthesized on different beads, comprising: forming a mixture comprising a plurality of beads; separating the beads into subsets; extending the nucleotide or oligonucleotide sequence on the surface of the beads by adding an individual nucleotide via chemical synthesis; pooling the subsets of beads in (c) into a single common pool; repeating steps (b), (c) and (d) multiple times to produce a combinatorically large number of nucleotide or oligonucleotide sequences; and collecting the nucleotide- or oligonucleotide-adorned beads; performing polynucleotide synthesis on the surface of the plurality of beads in a pool-and-split synthesis, such that in each cycle of synthesis the beads are split into a plurality of subsets wherein each subset is subjected to different chemical reactions; repeating the pool-and-split synthesis multiple times.

[00485] In an embodiment of the invention, the nucleotide or oligonucleotide sequence on the surface of the bead is a molecular barcode. In an embodiment, the pool-and-split synthesis steps occur every 2 to 10 cycles, rather than every cycle. In an embodiment, the generated barcode contains built-in error correction. In another embodiment, the barcode ranges from 4 to 1000 nucleotides in length. In embodiment of the invention the polynucleotide synthesis is phosphoramidite synthesis. In a further embodiment, the polynucleotide synthesis is reverse direction phosphoramidite chemistry. In an embodiment of the invention each subset is subjected to a different nucleotide. In a further embodiment, one or more subsets receive a cocktail of two nucleotides. In an embodiment, each subset is subjected to a different canonical nucleotide.

[00486] The method provided by the invention contemplates a variety of embodiments wherein the bead is a microbead, a nanoparticle, or a macrobead. Similarly, the invention contemplates that the oligonucleotide sequence is a dinucleotide or trinucleotide.

[00487] The invention further provides an apparatus for creating a composite single-cell sequencing library via a microfluidic system, comprising: an oil-surfactant inlet comprising a filter and two carrier fluid channels, wherein said carrier fluid channel further comprises a resistor; an inlet for an analyte comprising a filter and two carrier fluid channels, wherein said carrier fluid channel further comprises a resistor; an inlet for mRNA capture microbeads and lysis reagent comprising a carrier fluid channel; said carrier fluid channels have a carrier fluid flowing therein at an adjustable and predetermined flow rate; wherein each said carrier fluid channels merge at a junction; and said junction being connected to a constriction for droplet pinch-off followed by a mixer, which connects to an outlet for drops.

[00488] In an embodiment of the apparatus, the analyte comprises a chemical reagent, a genetically perturbed cell, a protein, a drug, an antibody, an enzyme, a nucleic acid, an organelle like the mitochondrion or nucleus, a cell or any combination thereof. In an embodiment of the apparatus the analyte is a cell. In a further embodiment, the analyte is a mammalian cell. In another embodiment, the analyte of the apparatus is complex tissue. In a further embodiment, the cell is a brain cell. In an embodiment of the invention, the cell is a retina cell. In another embodiment, the cell is a human bone marrow cell. In an embodiment, the cell is a host-pathogen cell. In an embodiment, the analyte is a nucleus from a cell.

[00489] In an embodiment of the apparatus the lysis reagent comprises an anionic surfactant such as sodium lauroyl sarcosinate, or a chaotropic salt such as guanidinium thiocyanate. In an embodiment of the apparatus the filter is consists of square PDMS posts; the filter on the cell channel consists of such posts with sides ranging between 125-135 pm with a separation of 70-100 mm between the posts. The filter on the oil-surfactant inlet comprises square posts of two sizes; one with sides ranging between 75-100 pm and a separation of 25-30 pm between them and the other with sides ranging between 40-50 pm and a separation of 10-15 pm. In an embodiment of the apparatus the resistor is serpentine having a length of 7000 - 9000 pm, width of 50 - 75 pm and depth of 100 - 150 mm. In an embodiment of the apparatus the channels have a length of 8000 - 12,000 pm for oil-surfactant inlet, 5000- 7000 for analyte (cell) inlet, and 900 - 1200 pm for the inlet for microbead and lysis agent. All channels have a width of 125 - 250 mm, and depth of 100 - 150 mm. In another embodiment, the width of the cell channel is 125-250 pm and the depth is 100-150 pm. In an embodiment of the apparatus the mixer has a length of 7000-9000 pm, and a

width of 110-140 μιη with 35-45° zig-zigs every 150 μm. In an embodiment, the width of the mixer is 125 μιη. In an embodiment of the apparatus the oil-surfactant is PEG Block Polymer, such as BIORAD™ QX200 Droplet Generation Oil. In an embodiment of the apparatus the carrier fluid is water-glycerol mixture.

[00490] A mixture comprising a plurality of microbeads adorned with combinations of the following elements: bead-specific oligonucleotide barcodes created by the methods provided; additional oligonucleotide barcode sequences which vary among the oligonucleotides on an individual bead and can therefore be used to differentiate or help identify those individual oligonucleotide molecules; additional oligonucleotide sequences that create substrates for downstream molecular-biological reactions, such as oligo-dT (for reverse transcription of mature mRNAs), specific sequences (for capturing specific portions of the transcriptome, or priming for DNA polymerases and similar enzymes), or random sequences (for priming throughout the transcriptome or genome). In an embodiment, the individual oligonucleotide molecules on the surface of any individual microbead contain all three of these elements, and the third element includes both oligo-dT and a primer sequence.

[00491] In another embodiment, a mixture comprising a plurality of microbeads, wherein said microbeads comprise the following elements: at least one bead-specific oligonucleotide barcode obtainable by the process outlined; at least one additional identifier oligonucleotide barcode sequence, which varies among the oligonucleotides on an individual bead, and thereby assisting in the identification and of the bead specific oligonucleotide molecules; optionally at least one additional oligonucleotide sequences, which provide substrates for downstream molecular-biological reactions. In another embodiment the mixture comprises at least one oligonucleotide sequences, which provide for substrates for downstream molecular-biological reactions. In a further embodiment the downstream molecular biological reactions are for reverse transcription of mature mRNAs; capturing specific portions of the transcriptome, priming for DNA polymerases and/or similar enzymes; or priming throughout the transcriptome or genome. In a further embodiment the mixture the additional oligonucleotide sequence comprising an oligo-dT sequence. In another embodiment the mixture further comprises the additional oligonucleotide sequence comprises a primer sequence. In another embodiment the mixture further comprises the additional oligonucleotide sequence comprising an oligo-dT sequence and a primer sequence.

[00492] Examples of the labeling substance which may be employed include labeling substances known to those skilled in the art, such as fluorescent dyes, enzymes, coenzymes, chemiluminescent substances, and radioactive substances. Specific examples include radioisotopes (e.g., 32P, 14C, 1251, 3H, and 1311), fluorescein, rhodamine, dansyl chloride, umbelliferone, luciferase, peroxidase, alkaline phosphatase, β-galactosidase, β-glucosidase, horseradish peroxidase, glucoamylase, lysozyme, saccharide oxidase, microperoxidase, biotin, and ruthenium. In the case where biotin is employed as a labeling substance, preferably, after addition of a biotin-labeled antibody, streptavidin bound to an enzyme (e.g., peroxidase) is further added.

[00493] Advantageously, the label is a fluorescent label. Examples of fluorescent labels include, but are not limited to, Atto dyes, 4-acetamido-4'-isothiocyanatostilbene-2,2'disulfonic acid; acridine and derivatives: acridine, acridine isothiocyanate; 5-(2'-aminoethyl)aminonaphthalene-l -sulfonic acid (EDANS); 4-amino-N-[3-vinylsulfonyl)phenyl]naphthalimide-3,5 disulfonate; N-(4-anilino-l-naphthyl)maleimide; anthranilamide; BODIPY; Brilliant Yellow; coumarin and derivatives; coumarin, 7-amino-4-methylcoumarin (AMC, Coumarin 120), 7-amino-4-trifluoromethylcouluarin (Coumaran 151); cyanine dyes; cyanosine; 4',6-diaminidino-2-phenylindole (DAPI); 5'5''-dibromopyrogallol-sulfonaphthalein (Bromopyrogallol Red); 7-diethylamino-3-(4'-isothiocyanatophenyl)-4-methylcoumarin; diethylenetriamine pentaacetate; 4,4'-diisothiocyanatodihydro-stilbene-2,2'-disulfonic acid; 4,4'-diisothiocyanatostilbene-2,2'-disulfonic acid; 5-[dimethylamino]naphthalene-l-sulfonyl chloride (DNS, dansylchloride); 4-dimethylaminophenylazophenyl-4'-isothiocyanate (DABITC); eosin and derivatives; eosin, eosin isothiocyanate, erythrosin and derivatives; erythrosin B, erythrosin, isothiocyanate; ethidium; fluorescein and derivatives; 5-carboxyfluorescein (FAM), 5-(4,6-dichlorotriazin-2-yl)aminofluorescein (DTAF), 2',7'-dimethoxy-4'5'-dichloro-6-carboxyfluorescein, fluorescein, fluorescein isothiocyanate, QFITC, (XRITC); fluorescamine; IR144; IR1446; Malachite Green isothiocyanate; 4-methylumbelliferoneortho cresolphthalein; nitrotyrosine; pararosaniline; Phenol Red; B-phycoerythrin; o-phthaldialdehyde; pyrene and derivatives: pyrene, pyrene butyrate, succinimidyl 1-pyrene; butyrate quantum dots; Reactive Red 4 (Cibacron.TM. Brilliant Red 3B-A) rhodamine and derivatives: 6-carboxy-X-rhodamine (ROX), 6-carboxyrhodamine (R6G), lissamine rhodamine B sulfonyl chloride rhodamine (Rhod), rhodamine B, rhodamine 123, rhodamine X

isothiocyanate, sulforhodamine B, sulforhodamine 101, sulfonyl chloride derivative of sulforhodamine 101 (Texas Red); N,N,N',N' tetramethyl-6-carboxyrhodamine (TAMRA); tetramethyl rhodamine; tetramethyl rhodamine isothiocyanate (TRITC); riboflavin; rosolic acid; terbium chelate derivatives; Cy3; Cy5; Cy5.5; Cy7; IRD 700; IRD 800; La Jolta Blue; phthalo cyanine; and naphthalo cyanine.

[00494] The fluorescent label may be a fluorescent protein, such as blue fluorescent protein, cyan fluorescent protein, green fluorescent protein, red fluorescent protein, yellow fluorescent protein or any photoconvertible protein. Colormetric labeling, bioluminescent labeling and/or chemiluminescent labeling may further accomplish labeling. Labeling further may include energy transfer between molecules in the hybridization complex by perturbation analysis, quenching, or electron transport between donor and acceptor molecules, the latter of which may be facilitated by double stranded match hybridization complexes. The fluorescent label may be a perylene or a terrylen. In the alternative, the fluorescent label may be a fluorescent bar code.

[00495] In an advantageous embodiment, the label may be light sensitive, wherein the label is light-activated and/or light cleaves the one or more linkers to release the molecular cargo. The light-activated molecular cargo may be a major light-harvesting complex (LHCII). In another embodiment, the fluorescent label may induce free radical formation.

[00496] In an advantageous embodiment, agents may be uniquely labeled in a dynamic manner (see, e.g., US provisional patent application serial no. 61/703,884 filed September 21, 2012). The unique labels are, at least in part, nucleic acid in nature, and may be generated by sequentially attaching two or more detectable oligonucleotide tags to each other and each unique label may be associated with a separate agent. A detectable oligonucleotide tag may be an oligonucleotide that may be detected by sequencing of its nucleotide sequence and/or by detecting non-nucleic acid detectable moieties to which it may be attached.

[00497] The oligonucleotide tags may be detectable by virtue of their nucleotide sequence, or by virtue of a non-nucleic acid detectable moiety that is attached to the oligonucleotide such as but not limited to a fluorophore, or by virtue of a combination of their nucleotide sequence and the nonnucleic acid detectable moiety.

[00498] In some embodiments, a detectable oligonucleotide tag may comprise one or more nonoligonucleotide detectable moieties. Examples of detectable moieties may include, but are not

limited to, fluorophores, microparticles including quantum dots (Empodocles, et al., Nature 399:126-130, 1999), gold nanoparticles (Reichert et al., Anal. Chem. 72:6025-6029, 2000), microbeads (Lacoste et al., Proc. Natl. Acad. Sci. USA 97(l7):946l-9466, 2000), biotin, DNP (dinitrophenyl), fucose, digoxigenin, haptens, and other detectable moieties known to those skilled in the art. In some embodiments, the detectable moieties may be quantum dots. Methods for detecting such moieties are described herein and/or are known in the art.

[00499] Thus, detectable oligonucleotide tags may be, but are not limited to, oligonucleotides which may comprise unique nucleotide sequences, oligonucleotides which may comprise detectable moieties, and oligonucleotides which may comprise both unique nucleotide sequences and detectable moieties.

[00500] A unique label may be produced by sequentially attaching two or more detectable oligonucleotide tags to each other. The detectable tags may be present or provided in a plurality of detectable tags. The same or a different plurality of tags may be used as the source of each detectable tag may be part of a unique label. In other words, a plurality of tags may be subdivided into subsets and single subsets may be used as the source for each tag.

[00501] In some embodiments, one or more other species may be associated with the tags. In particular, nucleic acids released by a lysed cell may be ligated to one or more tags. These may include, for example, chromosomal DNA, RNA transcripts, tRNA, mRNA, mitochondrial DNA, or the like. Such nucleic acids may be sequenced, in addition to sequencing the tags themselves, which may yield information about the nucleic acid profile of the cells, which can be associated with the tags, or the conditions that the corresponding droplet or cell was exposed to.

[00502] The invention described herein enables high throughput and high resolution delivery of reagents to individual emulsion droplets that may contain cells, organelles, nucleic acids, proteins, etc. through the use of monodisperse aqueous droplets that are generated by a microfluidic device as a water-in-oil emulsion. The droplets are carried in a flowing oil phase and stabilized by a surfactant. In one aspect single cells or single organellesor single molecules (proteins, RNA, DNA) are encapsulated into uniform droplets from an aqueous solution/dispersion. In a related aspect, multiple cells or multiple molecules may take the place of single cells or single molecules. The aqueous droplets of volume ranging from 1 pL to 10 nL work

as individual reactors. Disclosed embodiments provide thousands of single cells in droplets which can be processed and analyzed in a single run.

[00503] To utilize microdroplets for rapid large-scale chemical screening or complex biological library identification, different species of microdroplets, each containing the specific chemical compounds or biological probes cells or molecular barcodes of interest, have to be generated and combined at the preferred conditions, e.g., mixing ratio, concentration, and order of combination.

[00504] Each species of droplet is introduced at a confluence point in a main microfluidic channel from separate inlet microfluidic channels. Preferably, droplet volumes are chosen by design such that one species is larger than others and moves at a different speed, usually slower than the other species, in the carrier fluid, as disclosed in U.S. Publication No. US 2007/0195127 and International Publication No. WO 2007/089541, each of which are incorporated herein by reference in their entirety. The channel width and length is selected such that faster species of droplets catch up to the slowest species. Size constraints of the channel prevent the faster moving droplets from passing the slower moving droplets resulting in a train of droplets entering a merge zone. Multi-step chemical reactions, biochemical reactions, or assay detection chemistries often require a fixed reaction time before species of different type are added to a reaction. Multi-step reactions are achieved by repeating the process multiple times with a second, third or more confluence points each with a separate merge point. Highly efficient and precise reactions and analysis of reactions are achieved when the frequencies of droplets from the inlet channels are matched to an optimized ratio and the volumes of the species are matched to provide optimized reaction conditions in the combined droplets.

[00505] Fluidic droplets may be screened or sorted within a fluidic system of the invention by altering the flow of the liquid containing the droplets. For instance, in one set of embodiments, a fluidic droplet may be steered or sorted by directing the liquid surrounding the fluidic droplet into a first channel, a second channel, etc. In another set of embodiments, pressure within a fluidic system, for example, within different channels or within different portions of a channel, can be controlled to direct the flow of fluidic droplets. For example, a droplet can be directed toward a channel junction including multiple options for further direction of flow (e.g., directed toward a branch, or fork, in a channel defining optional downstream flow channels). Pressure within one or more of the optional downstream flow channels can be controlled to direct the droplet

selectively into one of the channels, and changes in pressure can be effected on the order of the time required for successive droplets to reach the junction, such that the downstream flow path of each successive droplet can be independently controlled. In one arrangement, the expansion and/or contraction of liquid reservoirs may be used to steer or sort a fluidic droplet into a channel, e.g., by causing directed movement of the liquid containing the fluidic droplet. In another embodiment, the expansion and/or contraction of the liquid reservoir may be combined with other flow-controlling devices and methods, e.g., as described herein. Non-limiting examples of devices able to cause the expansion and/or contraction of a liquid reservoir include pistons.

[00506] Key elements for using microfluidic channels to process droplets include: (1) producing droplet of the correct volume, (2) producing droplets at the correct frequency and (3) bringing together a first stream of sample droplets with a second stream of sample droplets in such a way that the frequency of the first stream of sample droplets matches the frequency of the second stream of sample droplets. Preferably, bringing together a stream of sample droplets with a stream of premade library droplets in such a way that the frequency of the library droplets matches the frequency of the sample droplets.

[00507] Methods for producing droplets of a uniform volume at a regular frequency are well known in the art. One method is to generate droplets using hydrodynamic focusing of a dispersed phase fluid and immiscible carrier fluid, such as disclosed in U.S. Publication No. US 2005/0172476 and International Publication No. WO 2004/002627. It is desirable for one of the species introduced at the confluence to be a pre-made library of droplets where the library contains a plurality of reaction conditions, e.g., a library may contain plurality of different compounds at a range of concentrations encapsulated as separate library elements for screening their effect on cells or enzymes, alternatively a library could be composed of a plurality of different primer pairs encapsulated as different library elements for targeted amplification of a collection of loci, alternatively a library could contain a plurality of different antibody species encapsulated as different library elements to perform a plurality of binding assays. The introduction of a library of reaction conditions onto a substrate is achieved by pushing a premade collection of library droplets out of a vial with a drive fluid. The drive fluid is a continuous fluid. The drive fluid may comprise the same substance as the carrier fluid (e.g., a fluorocarbon oil). For example, if a library consists of ten pico-liter droplets is driven into an inlet channel on a microfluidic substrate with a drive

fluid at a rate of 10,000 pico-liters per second, then nominally the frequency at which the droplets are expected to enter the confluence point is 1000 per second. However, in practice droplets pack with oil between them that slowly drains. Over time the carrier fluid drains from the library droplets and the number density of the droplets (number/mL) increases. Hence, a simple fixed rate of infusion for the drive fluid does not provide a uniform rate of introduction of the droplets into the microfluidic channel in the substrate. Moreover, library-to-library variations in the mean library droplet volume result in a shift in the frequency of droplet introduction at the confluence point. Thus, the lack of uniformity of droplets that results from sample variation and oil drainage provides another problem to be solved. For example if the nominal droplet volume is expected to be 10 pico-liters in the library, but varies from 9 to 11 pico-liters from library-to-library then a 10,000 pico-liter/second infusion rate will nominally produce a range in frequencies from 900 to 1,100 droplet per second. In short, sample to sample variation in the composition of dispersed phase for droplets made on chip, a tendency for the number density of library droplets to increase over time and library-to-library variations in mean droplet volume severely limit the extent to which frequencies of droplets may be reliably matched at a confluence by simply using fixed infusion rates. In addition, these limitations also have an impact on the extent to which volumes may be reproducibly combined. Combined with typical variations in pump flow rate precision and variations in channel dimensions, systems are severely limited without a means to compensate on a run-to-run basis. The foregoing facts not only illustrate a problem to be solved, but also demonstrate a need for a method of instantaneous regulation of microfluidic control over microdroplets within a microfluidic channel.

[00508] Combinations of surfactant(s) and oils must be developed to facilitate generation, storage, and manipulation of droplets to maintain the unique chemical/biochemical/biological environment within each droplet of a diverse library. Therefore, the surfactant and oil combination must (1) stabilize droplets against uncontrolled coalescence during the drop forming process and subsequent collection and storage, (2) minimize transport of any droplet contents to the oil phase and/or between droplets, and (3) maintain chemical and biological inertness with contents of each droplet (e.g., no adsorption or reaction of encapsulated contents at the oil-water interface, and no adverse effects on biological or chemical constituents in the droplets). In addition to the requirements on the droplet library function and stability, the surfactant-in-oil solution must be

coupled with the fluid physics and materials associated with the platform. Specifically, the oil solution must not swell, dissolve, or degrade the materials used to construct the microfluidic chip, and the physical properties of the oil (e.g., viscosity, boiling point, etc.) must be suited for the flow and operating conditions of the platform.

[00509] Droplets formed in oil without surfactant are not stable to permit coalescence, so surfactants must be dissolved in the oil that is used as the continuous phase for the emulsion library. Surfactant molecules are amphiphilic—part of the molecule is oil soluble, and part of the molecule is water soluble. When a water-oil interface is formed at the nozzle of a microfluidic chip for example in the inlet module described herein, surfactant molecules that are dissolved in the oil phase adsorb to the interface. The hydrophilic portion of the molecule resides inside the droplet and the fluorophilic portion of the molecule decorates the exterior of the droplet. The surface tension of a droplet is reduced when the interface is populated with surfactant, so the stability of an emulsion is improved. In addition to stabilizing the droplets against coalescence, the surfactant should be inert to the contents of each droplet and the surfactant should not promote transport of encapsulated components to the oil or other droplets.

[00510] A droplet library may be made up of a number of library elements that are pooled together in a single collection (see, e.g., US Patent Publication No. 2010002241). Libraries may vary in complexity from a single library element to 1015 library elements or more. Each library element may be one or more given components at a fixed concentration. The element may be, but is not limited to, cells, organelles, virus, bacteria, yeast, beads, amino acids, proteins, polypeptides, nucleic acids, polynucleotides or small molecule chemical compounds. The element may contain an identifier such as a label. The terms "droplet library" or "droplet libraries" are also referred to herein as an "emulsion library" or "emulsion libraries." These terms are used interchangeably throughout the specification.

[00511] A cell library element may include, but is not limited to, hybridomas, B-cells, primary cells, cultured cell lines, cancer cells, stem cells, cells obtained from tissue (e.g., brain, gut or gastrointestinal, retinal or human bone marrow), peripheral blood mononuclear cell, or any other cell type. Cellular library elements are prepared by encapsulating a number of cells from one to hundreds of thousands in individual droplets. The number of cells encapsulated is usually given by Poisson statistics from the number density of cells and volume of the droplet. However, in some

cases the number deviates from Poisson statistics as described in Edd et al., "Controlled encapsulation of single-cells into monodisperse picolitre drops." Lab Chip, 8(8): 1262-1264, 2008. The discrete nature of cells allows for libraries to be prepared in mass with a plurality of cellular variants all present in a single starting media and then that media is broken up into individual droplet capsules that contain at most one cell. These individual droplets capsules are then combined or pooled to form a library consisting of unique library elements. Cell division subsequent to, or in some embodiments following, encapsulation produces a clonal library element.

[00512] A variety of analytes may be contemplated for use with the foregoing Drop-Sequencing methods. Examples of cells which are contemplated are mammalian cells, however the invention contemplates a method for profiling host-pathogen cells. To characterize the expression of host-pathogen interactions it is important to grow the host and pathogen in the same cell without multiple opportunities of pathogen infection.

[00513] A bead based library element may contain one or more beads, of a given type and may also contain other reagents, such as antibodies, enzymes or other proteins. In the case where all library elements contain different types of beads, but the same surrounding media, the library elements may all be prepared from a single starting fluid or have a variety of starting fluids. In the case of cellular libraries prepared in mass from a collection of variants, such as genomically modified, yeast or bacteria cells, the library elements will be prepared from a variety of starting fluids.

[00514] Often it is desirable to have exactly one cell or nuclei per droplet with only a few droplets containing more than one cell or nuclei when starting with a plurality of cells or yeast or bacteria, engineered to produce variants on a protein. In some cases, variations from Poisson statistics may be achieved to provide an enhanced loading of droplets such that there are more droplets with exactly one cell per droplet and few exceptions of empty droplets or droplets containing more than one cell.

[00515] Examples of droplet libraries are collections of droplets that have different contents, ranging from beads, cells, nuclei, small molecules, DNA, primers, antibodies. Smaller droplets may be in the order of femtoliter (fL) volume drops, which are especially contemplated with the droplet dispensors. The volume may range from about 5 to about 600 fL. The larger droplets range

in size from roughly 0.5 micron to 500 micron in diameter, which corresponds to about 1 pico liter to 1 nano liter. However, droplets may be as small as 5 microns and as large as 500 microns. Preferably, the droplets are at less than 100 microns, about 1 micron to about 100 microns in diameter. The most preferred size is about 20 to 40 microns in diameter (10 to 100 picoliters). The preferred properties examined of droplet libraries include osmotic pressure balance, uniform size, and size ranges.

[00516] The droplets comprised within the emulsion libraries of the present invention may be contained within an immiscible oil which may comprise at least one fluorosurfactant. In some embodiments, the fluorosurfactant comprised within immiscible fluorocarbon oil is a block copolymer consisting of one or more perfluorinated polyether (PFPE) blocks and one or more polyethylene glycol (PEG) blocks. In other embodiments, the fluorosurfactant is a triblock copolymer consisting of a PEG center block covalently bound to two PFPE blocks by amide linking groups. The presence of the fluorosurfactant (similar to uniform size of the droplets in the library) is critical to maintain the stability and integrity of the droplets and is also essential for the subsequent use of the droplets within the library for the various biological and chemical assays described herein. Fluids (e.g., aqueous fluids, immiscible oils, etc.) and other surfactants that may be utilized in the droplet libraries of the present invention are described in greater detail herein.

[00517] The present invention provides an emulsion library which may comprise a plurality of aqueous droplets within an immiscible oil (e.g., fluorocarbon oil) which may comprise at least one fluorosurfactant, wherein each droplet is uniform in size and may comprise the same aqueous fluid and may comprise a different library element. The present invention also provides a method for forming the emulsion library which may comprise providing a single aqueous fluid which may comprise different library elements, encapsulating each library element into an aqueous droplet within an immiscible fluorocarbon oil which may comprise at least one fluorosurfactant, wherein each droplet is uniform in size and may comprise the same aqueous fluid and may comprise a different library element, and pooling the aqueous droplets within an immiscible fluorocarbon oil which may comprise at least one fluorosurfactant, thereby forming an emulsion library.

[00518] For example, in one type of emulsion library, all different types of elements (e.g., cells or beads), may be pooled in a single source contained in the same medium. After the initial pooling, the cells or beads are then encapsulated in droplets to generate a library of droplets wherein each

droplet with a different type of bead or cell is a different library element. The dilution of the initial solution enables the encapsulation process. In some embodiments, the droplets formed will either contain a single cell or bead or will not contain anything, i.e., be empty. In other embodiments, the droplets formed will contain multiple copies of a library element. The cells or beads being encapsulated are generally variants on the same type of cell or bead. In one example, the cells may comprise cancer cells of a tissue biopsy, and each cell type is encapsulated to be screened for genomic data or against different drug therapies. Another example is that 101 1 or 1015 different type of bacteria; each having a different plasmid spliced therein, are encapsulated. One example is a bacterial library where each library element grows into a clonal population that secretes a variant on an enzyme.

[00519] In another example, the emulsion library may comprise a plurality of aqueous droplets within an immiscible fluorocarbon oil, wherein a single molecule may be encapsulated, such that there is a single molecule contained within a droplet for every 20-60 droplets produced (e.g., 20, 25, 30, 35, 40, 45, 50, 55, 60 droplets, or any integer in between). Single molecules may be encapsulated by diluting the solution containing the molecules to such a low concentration that the encapsulation of single molecules is enabled. In one specific example, a LacZ plasmid DNA was encapsulated at a concentration of 20 fM after two hours of incubation such that there was about one gene in 40 droplets, where 10 pm droplets were made at 10 kHz per second. Formation of these libraries rely on limiting dilutions.

[00520] The present invention also provides an emulsion library which may comprise at least a first aqueous droplet and at least a second aqueous droplet within a fluorocarbon oil which may comprise at least one fluorosurfactant, wherein the at least first and the at least second droplets are uniform in size and comprise a different aqueous fluid and a different library element. The present invention also provides a method for forming the emulsion library which may comprise providing at least a first aqueous fluid which may comprise at least a first library of elements, providing at least a second aqueous fluid which may comprise at least a second library of elements, encapsulating each element of said at least first library into at least a first aqueous droplet within an immiscible fluorocarbon oil which may comprise at least one fluorosurfactant, encapsulating each element of said at least second library into at least a second aqueous droplet within an immiscible fluorocarbon oil which may comprise at least one fluorosurfactant, wherein the at least

first and the at least second droplets are uniform in size and comprise a different aqueous fluid and a different library element, and pooling the at least first aqueous droplet and the at least second aqueous droplet within an immiscible fluorocarbon oil which may comprise at least one fluorosurfactant thereby forming an emulsion library.

[00521] Lysis or homogenization solutions may further contain other agents, such as reducing agents. Examples of such reducing agents include dithiothreitol (DTT), β-mercaptoethanol, DTE, GSH, cysteine, cysteamine, tricarboxyethyl phosphine (TCEP), or salts of sulfurous acid.

[00522] Size selection of the nucleic acids may be performed to remove very short fragments or very long fragments. The nucleic acid fragments may be partitioned into fractions which may comprise a desired number of fragments using any suitable method known in the art. Suitable methods to limit the fragment size in each fragment are known in the art. In various embodiments of the invention, the fragment size is limited to between about 10 and about 100 Kb or longer.

[00523] In another embodiment, the sample includes individual target proteins, protein complexes, proteins with translational modifications, and protein/nucleic acid complexes. Protein targets include peptides, and also include enzymes, hormones, structural components such as viral capsid proteins, and antibodies. Protein targets may be synthetic or derived from naturally-occurring sources. In one embodiment of the invention protein targets are isolated from biological samples containing a variety of other components including lipids, non-template nucleic acids, and nucleic acids. In certain embodiments, protein targets may be obtained from an animal, bacterium, fungus, cellular organism, and single cells. Protein targets may be obtained directly from an organism or from a biological sample obtained from the organism, including bodily fluids such as blood, urine, cerebrospinal fluid, seminal fluid, saliva, sputum, stool and tissue. Protein targets may also be obtained from cell and tissue lysates and biochemical fractions. An individual protein is an isolated polypeptide chain. A protein complex includes two or polypeptide chains. Samples may include proteins with post translational modifications including but not limited to phosphorylation, methionine oxidation, deamidation, glycosylation, ubiquitination, carbamylation, S-carboxymethylation, acetylation, and methylation. Protein/nucleic acid complexes include cross-linked or stable protein-nucleic acid complexes.

[00524] Extraction or isolation of individual proteins, protein complexes, proteins with translational modifications, and protein/nucleic acid complexes is performed using methods known in the art.

[00525] Methods of the invention involve forming sample droplets. The droplets are aqueous droplets that are surrounded by an immiscible carrier fluid. Methods of forming such droplets are shown for example in Link et al. (U.S. patent application numbers 2008/0014589, 2008/0003142, and 2010/0137163), Stone et al. (U.S. Pat. No. 7,708,949 and U.S. patent application number 2010/0172803), Anderson et al. (U.S. Pat. No. 7,041,481 and which reissued as RE4l,780) and European publication number EP2047910 to Raindance Technologies Inc. The content of each of which is incorporated by reference herein in its entirety.

[00526] The sample fluid may typically comprise an aqueous buffer solution, such as ultrapure water (e.g., 18 mega-ohm resistivity, obtained, for example by column chromatography), 10 mM Tris HC1 and 1 mM EDTA (TE) buffer, phosphate buffer saline (PBS) or acetate buffer. Any liquid or buffer that is physiologically compatible with nucleic acid molecules can be used. The carrier fluid may include one that is immiscible with the sample fluid. The carrier fluid can be a non-polar solvent, decane (e.g., tetradecane or hexadecane), fluorocarbon oil, silicone oil, an inert oil such as hydrocarbon, or another oil (for example, mineral oil).

[00527] In certain embodiments, the carrier fluid may contain one or more additives, such as agents which reduce surface tensions (surfactants). Surfactants can include Tween, Span, fluorosurfactants, and other agents that are soluble in oil relative to water. In some applications, performance is improved by adding a second surfactant to the sample fluid. Surfactants can aid in controlling or optimizing droplet size, flow and uniformity, for example by reducing the shear force needed to extrude or inject droplets into an intersecting channel. This can affect droplet volume and periodicity, or the rate or frequency at which droplets break off into an intersecting channel. Furthermore, the surfactant can serve to stabilize aqueous emulsions in fluorinated oils from coalescing.

[00528] In certain embodiments, the droplets may be surrounded by a surfactant which stabilizes the droplets by reducing the surface tension at the aqueous oil interface. Preferred surfactants that may be added to the carrier fluid include, but are not limited to, surfactants such as sorbitan-based carboxylic acid esters (e.g., the "Span" surfactants, Fluka Chemika), including

sorbitan monolaurate (Span 20), sorbitan monopalmitate (Span 40), sorbitan monostearate (Span 60) and sorbitan monooleate (Span 80), and perfluorinated polyethers (e.g., DuPont Krytox 157 FSL, FSM, and/or FSH). Other non-limiting examples of non-ionic surfactants which may be used include polyoxyethylenated alkylphenols (for example, nonyl-, ρ-dodecyl-, and dinonylphenols), polyoxyethylenated straight chain alcohols, polyoxyethylenated polyoxypropylene glycols, polyoxyethylenated mercaptans, long chain carboxylic acid esters (for example, glyceryl and polyglyceryl esters of natural fatty acids, propylene glycol, sorbitol, polyoxyethylenated sorbitol esters, polyoxyethylene glycol esters, etc.) and alkanolamines (e.g., diethanolamine-fatty acid condensates and isopropanolamine-fatty acid condensates).

[00529] In certain embodiments, the carrier fluid may be caused to flow through the outlet channel so that the surfactant in the carrier fluid coats the channel walls. In one embodiment, the fluorosurfactant can be prepared by reacting the perfluorinated polyether DuPont Krytox 157 FSL, FSM, or FSH with aqueous ammonium hydroxide in a volatile fluorinated solvent. The solvent and residual water and ammonia can be removed with a rotary evaporator. The surfactant can then be dissolved (e.g., 2.5 wt %) in a fluorinated oil (e.g., Fluorinert (3M)), which then serves as the carrier fluid.

[00530] Activation of sample fluid reservoirs to produce regent droplets is now described. The disclosed invention is based on the concept of dynamic reagent delivery (e.g., combinatorial barcoding) via an on demand capability. The on demand feature may be provided by one of a variety of technical capabilities for releasing delivery droplets to a primary droplet, as described herein.

[00531] An aspect in developing this device will be to determine the flow rates, channel lengths, and channel geometries. Once these design specifications are established, droplets containing random or specified reagent combinations can be generated on demand and merged with the "reaction chamber" droplets containing the samples/cells/substrates of interest.

[00532] By incorporating a plurality of unique tags into the additional droplets and joining the tags to a solid support designed to be specific to the primary droplet, the conditions that the primary droplet is exposed to may be encoded and recorded. For example, nucleic acid tags can be sequentially ligated to create a sequence reflecting conditions and order of same. Alternatively, the tags can be added independently appended to solid support. Non-limiting examples of a

dynamic labeling system that may be used to bioninformatically record information can be found at US Provisional Patent Application entitled “Compositions and Methods for Unique Labeling of Agents” filed September 21, 2012 and November 29, 2012. In this way, two or more droplets may be exposed to a variety of different conditions, where each time a droplet is exposed to a condition, a nucleic acid encoding the condition is added to the droplet each ligated together or to a unique solid support associated with the droplet such that, even if the droplets with different histories are later combined, the conditions of each of the droplets are remain available through the different nucleic acids. Non-limiting examples of methods to evaluate response to exposure to a plurality of conditions can be found at US Provisional Patent Application entitled “Systems and Methods for Droplet Tagging” filed September 21, 2012.

[00533] Applications of the disclosed device may include use for the dynamic generation of molecular barcodes (e.g., DNA oligonucleotides, fluorophores, etc.) either independent from or in concert with the controlled delivery of various compounds of interest (drugs, small molecules, siRNA, CRISPR guide RNAs, reagents, etc.). For example, unique molecular barcodes can be created in one array of nozzles while individual compounds or combinations of compounds can be generated by another nozzle array. Barcodes/compounds of interest can then be merged with cell-containing droplets. An electronic record in the form of a computer log file is kept to associate the barcode delivered with the downstream reagent(s) delivered. This methodology makes it possible to efficiently screen a large population of cells for applications such as single-cell drug screening, controlled perturbation of regulatory pathways, etc. The device and techniques of the disclosed invention facilitate efforts to perform studies that require data resolution at the single cell (or single molecule) level and in a cost effective manner. Disclosed embodiments provide a high throughput and high resolution delivery of reagents to individual emulsion droplets that may contain cells, nucleic acids, proteins, etc. through the use of monodisperse aqueous droplets that are generated one by one in a microfluidic chip as a water-in-oil emulsion. Hence, the invention proves advantageous over prior art systems by being able to dynamically track individual cells and droplet treatments/combinations during life cycle experiments. Additional advantages of the disclosed invention provides an ability to create a library of emulsion droplets on demand with the further capability of manipulating the droplets through the disclosed process(es). Disclosed embodiments may, thereby, provide dynamic tracking of the droplets and create a history of

droplet deployment and application in a single cell based environment. In certain example embodiments, the methods disclosed herein may be used to conduct pooled CRISPR screening such as that disclosed in Datlinger et al. bioRXiv dx.doi.org/l0. 1101/083774.

[00534] Droplet generation and deployment is produced via a dynamic indexing strategy and in a controlled fashion in accordance with disclosed embodiments of the present invention. Disclosed embodiments of the microfluidic device described herein provides the capability of microdroplets that be processed, analyzed and sorted at a highly efficient rate of several thousand droplets per second, providing a powerful platform which allows rapid screening of millions of distinct compounds, biological probes, proteins or cells either in cellular models of biological mechanisms of disease, or in biochemical, or pharmacological assays.

[00535] A plurality of biological assays as well as biological synthesis are contemplated for the present invention.

[00536] In an advantageous embodiment, polymerase chain reactions (PCR) are contemplated (see, e.g., US Patent Publication No. 20120219947). Methods of the invention may be used for merging sample fluids for conducting any type of chemical reaction or any type of biological assay. In certain embodiments, methods of the invention are used for merging sample fluids for conducting an amplification reaction in a droplet. Amplification refers to production of additional copies of a nucleic acid sequence and is generally carried out using polymerase chain reaction or other technologies well known in the art (e.g., Dieffenbach and Dveksler, PCR Primer, a Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y. [1995]). The amplification reaction may be any amplification reaction known in the art that amplifies nucleic acid molecules, such as polymerase chain reaction, nested polymerase chain reaction, polymerase chain reaction-single strand conformation polymorphism, ligase chain reaction (Barany F. (1991) PNAS 88:189-193; Barany F. (1991) PCR Methods and Applications 1:5-16), ligase detection reaction (Barany F. (1991) PNAS 88:189-193), strand displacement amplification and restriction fragments length polymorphism, transcription based amplification system, nucleic acid sequence-based amplification, rolling circle amplification, and hyper-branched rolling circle amplification.

[00537] In certain embodiments, the amplification reaction is the polymerase chain reaction. Polymerase chain reaction (PCR) refers to methods by K. B. Mullis (U.S. Pat. Nos. 4,683,195 and 4,683,202, hereby incorporated by reference) for increasing concentration of a segment of a target

sequence in a mixture of genomic DNA without cloning or purification. The process for amplifying the target sequence includes introducing an excess of oligonucleotide primers to a DNA mixture containing a desired target sequence, followed by a precise sequence of thermal cycling in the presence of a DNA polymerase. The primers are complementary to their respective strands of the double stranded target sequence.

[00538] To effect amplification, primers are annealed to their complementary sequence within the target molecule. Following annealing, the primers are extended with a polymerase so as to form a new pair of complementary strands. The steps of denaturation, primer annealing and polymerase extension may be repeated many times (i.e., denaturation, annealing and extension constitute one cycle; there may be numerous cycles) to obtain a high concentration of an amplified segment of a desired target sequence. The length of the amplified segment of the desired target sequence is determined by relative positions of the primers with respect to each other, and therefore, this length is a controllable parameter.

[00539] Methods for performing PCR in droplets are shown for example in Link et al. (U.S. Patent application numbers 2008/0014589, 2008/0003142, and 2010/0137163), Anderson et al. (U.S. Pat. No. 7,041,481 and which reissued as RE4l,780) and European publication number EP2047910 to Raindance Technologies Inc. The content of each of which is incorporated by reference herein in its entirety.

[00540] The first sample fluid contains nucleic acid templates. Droplets of the first sample fluid are formed as described above. Those droplets will include the nucleic acid templates. In certain embodiments, the droplets will include only a single nucleic acid template, and thus digital PCR may be conducted. The second sample fluid contains reagents for the PCR reaction. Such reagents generally include Taq polymerase, deoxynucleotides of type A, C, G and T, magnesium chloride, and forward and reverse primers, all suspended within an aqueous buffer. The second fluid also includes detectably labeled probes for detection of the amplified target nucleic acid, the details of which are discussed below. This type of partitioning of the reagents between the two sample fluids is not the only possibility. In certain embodiments, the first sample fluid will include some or all of the reagents necessary for the PCR whereas the second sample fluid will contain the balance of the reagents necessary for the PCR together with the detection probes.

[00541] Primers may be prepared by a variety of methods including but not limited to cloning of appropriate sequences and direct chemical synthesis using methods well known in the art (Narang et al., Methods Enzymol., 68:90 (1979); Brown et al., Methods Enzymol., 68:109 (1979)). Primers may also be obtained from commercial sources such as Operon Technologies, Amersham Pharmacia Biotech, Sigma, and Life Technologies. The primers may have an identical melting temperature. The lengths of the primers may be extended or shortened at the 5' end or the 3' end to produce primers with desired melting temperatures. Also, the annealing position of each primer pair may be designed such that the sequence and, length of the primer pairs yield the desired melting temperature. The simplest equation for determining the melting temperature of primers smaller than 25 base pairs is the Wallace Rule (Td=2(A+T)+4(G+C)). Computer programs may also be used to design primers, including but not limited to Array Designer Software (Arrayit Inc.), Oligonucleotide Probe Sequence Design Software for Genetic Analysis (Olympus Optical Co.), NetPrimer, and DNAsis from Hitachi Software Engineering. The TM (melting or annealing temperature) of each primer is calculated using software programs such as Oligo Design, available from Invitrogen Corp.

[00542] A droplet containing the nucleic acid is then caused to merge with the PCR reagents in the second fluid according to methods of the invention described above, producing a droplet that includes Taq polymerase, deoxynucleotides of type A, C, G and T, magnesium chloride, forward and reverse primers, detectably labeled probes, and the target nucleic acid.

[00543] Once mixed droplets have been produced, the droplets are thermal cycled, resulting in amplification of the target nucleic acid in each droplet. In certain embodiments, the droplets are flowed through a channel in a serpentine path between heating and cooling lines to amplify the nucleic acid in the droplet. The width and depth of the channel may be adjusted to set the residence time at each temperature, which may be controlled to anywhere between less than a second and minutes.

[00544] In certain embodiments, the three temperature zones are used for the amplification reaction. The three temperature zones are controlled to result in denaturation of double stranded nucleic acid (high temperature zone), annealing of primers (low temperature zones), and amplification of single stranded nucleic acid to produce double stranded nucleic acids (intermediate temperature zones). The temperatures within these zones fall within ranges well

known in the art for conducting PCR reactions. See for example, Sambrook et al. (Molecular Cloning, A Laboratory Manual, 3rd edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 2001).

[00545] In certain embodiments, the three temperature zones are controlled to have temperatures as follows: 95°C (TH), 55°C (TL), 72°C (TM). The prepared sample droplets flow through the channel at a controlled rate. The sample droplets first pass the initial denaturation zone (TH) before thermal cycling. The initial preheat is an extended zone to ensure that nucleic acids within the sample droplet have denatured successfully before thermal cycling. The requirement for a preheat zone and the length of denaturation time required is dependent on the chemistry being used in the reaction. The samples pass into the high temperature zone, of approximately 95° C., where the sample is first separated into single stranded DNA in a process called denaturation. The sample then flows to the low temperature, of approximately 55° C., where the hybridization process takes place, during which the primers anneal to the complementary sequences of the sample. Finally, as the sample flows through the third medium temperature, of approximately 72°C, the polymerase process occurs when the primers are extended along the single strand of DNA with a thermostable enzyme.

[00546] The nucleic acids undergo the same thermal cycling and chemical reaction as the droplets pass through each thermal cycle as they flow through the channel. The total number of cycles in the device is easily altered by an extension of thermal zones. The sample undergoes the same thermal cycling and chemical reaction as it passes through N amplification cycles of the complete thermal device.

[00547] In other embodiments, the temperature zones are controlled to achieve two individual temperature zones for a PCR reaction. In certain embodiments, the two temperature zones are controlled to have temperatures as follows: 95°C (TH) and 60°C (TL). The sample droplet optionally flows through an initial preheat zone before entering thermal cycling. The preheat zone may be important for some chemistry for activation and also to ensure that double stranded nucleic acid in the droplets is fully denatured before the thermal cycling reaction begins. In an exemplary embodiment, the preheat dwell length results in approximately 10 minutes preheat of the droplets at the higher temperature.

[00548] The sample droplet continues into the high temperature zone, of approximately 95°C, where the sample is first separated into single stranded DNA in a process called denaturation. The sample then flows through the device to the low temperature zone, of approximately 60° C., where the hybridization process takes place, during which the primers anneal to the complementary sequences of the sample. Finally, the polymerase process occurs when the primers are extended along the single strand of DNA with a thermostable enzyme. The sample undergoes the same thermal cycling and chemical reaction as it passes through each thermal cycle of the complete device. The total number of cycles in the device is easily altered by an extension of block length and tubing.

[00549] After amplification, droplets may be flowed to a detection module for detection of amplification products. The droplets may be individually analyzed and detected using any methods known in the art, such as detecting for the presence or amount of a reporter. Generally, the detection module is in communication with one or more detection apparatuses. The detection apparatuses may be optical or electrical detectors or combinations thereof. Examples of suitable detection apparatuses include optical waveguides, microscopes, diodes, light stimulating devices, (e.g., lasers), photo multiplier tubes, and processors (e.g., computers and software), and combinations thereof, which cooperate to detect a signal representative of a characteristic, marker, or reporter, and to determine and direct the measurement or the sorting action at a sorting module. Further description of detection modules and methods of detecting amplification products in droplets are shown in Link et al. (U.S. patent application numbers 2008/0014589, 2008/0003142, and 2010/0137163) and European publication number EP2047910 to Raindance Technologies Inc.

[00550] In another embodiment, examples of assays are ELISA assays (see, e.g., US Patent Publication No. 20100022414). The present invention provides another emulsion library which may comprise a plurality of aqueous droplets within an immiscible fluorocarbon oil which may comprise at least one fluorosurfactant, wherein each droplet is uniform in size and may comprise at least a first antibody, and a single element linked to at least a second antibody, wherein said first and second antibodies are different. In one example, each library element may comprise a different bead, wherein each bead is attached to a number of antibodies and the bead is encapsulated within a droplet that contains a different antibody in solution. These antibodies may then be allowed to form "ELISA sandwiches," which may be washed and prepared for a ELISA assay. Further, these

contents of the droplets may be altered to be specific for the antibody contained therein to maximize the results of the assay.

[00551] In another embodiment, single-cell assays are also contemplated as part of the present invention (see, e.g., Ryan et al., Biomicrofluidics 5, 021501 (201 1) for an overview of applications of microfluidics to assay individual cells). A single-cell assay may be contemplated as an experiment that quantifies a function or property of an individual cell when the interactions of that cell with its environment may be controlled precisely or may be isolated from the function or property under examination. The research and development of single-cell assays is largely predicated on the notion that genetic variation causes disease and that small subpopulations of cells represent the origin of the disease. Methods of assaying compounds secreted from cells, subcellular components, cell-cell or cell-drug interactions as well as methods of patterning individual cells are also contemplated within the present invention

[00552] In other embodiments, chemical prototyping and synthetic chemical reactions are also contemplated within the methods of the invention.

[00553] In certain embodiments, nucleic acids are labeled with a nucleoside analogue. The nucleoside analogue may be any nucleoside analogue known in the art or developed after the filing of the present invention that is incorporated into replicated DNA and can be detectable by a label. The label may be incorporated into the nucleoside analogue or may include a labeling step after incorporation into DNA with a detectable label. In preferred embodiments, the label is a fluorescent label. In certain embodiments, the nucleoside analogue may be EdU (5-ethynyl-2'-deoxyuridine) or BrdU (5-bromo-2'-deoxyuridine).

[00554] In one embodiment of the invention, the method comprises obtaining at least one section from one or more tissue samples. Any suitable tissue sample can be used in the methods described herein. For example, the tissue can be epithelium, muscle, organ tissue, nerve tissue, tumor tissue, and combinations thereof. Samples of tissue can be obtained by any standard means (e.g., biopsy, core puncture, dissection, and the like, as will be appreciated by a person of skill in the art). At least one section may be labeled with a histological stain, to produce a histologically stained section. As used in the invention described herein, histological stains can be any standard stain as appreciated in the art, including but not limited to, alcian blue, Fuchsin, haematoxylin and eosin (H&E), Masson trichrome, toluidine blue, Wrighf s/Giemsa stain, and combinations thereof.

As will be appreciated by a person of skill in the art, traditional histological stains are not fluorescent. At least one other section may be labeled with at least one fluorescently labeled reagent to produce a fluorescently labeled section. As used in the invention described herein, the panel of fluorescently labeled reagents comprises a number of reagents, such as fluorescently labeled antibodies, fluorescently labeled peptides, fluorescently labeled polypeptides, fluorescently labeled aptamers, fluorescently labeled oligonucleotides (e.g. nucleic acid probes, DNA, RNA, cDNA, PNA, and the like), fluorescently labeled chemicals and fluorescent chemicals (e.g., Hoechst 33342, propidium iodide, Draq-5, Nile Red, fluorescently labeled phalloidin), and combinations thereof. Each fluorescently labeled reagent is specific for at least one biomarker. As used herein, a "biomarker" is a molecule which provides a measure of cellular and/or tissue function. For example, and without limitation, a biomarker can be the measure of receptor expression levels, (e.g., estrogen receptor expression levels, Her2/neu expression); transcription factor activation; location or amount or activity of a protein, polynucleotide, organelle, and the like; the phosphorylation status of a protein, etc. In one embodiment, a biomarker is a nucleic acid (e.g., DNA, RNA, including micro RNAs, snRNAs, mRNA, rRNA, etc.), a receptor, a cell membrane antigen, an intracellular antigen, and extracellular antigen, a signaling molecule, a protein, and the like. In one embodiment of the invention, a panel of fluorescently labeled reagents detects at least about four different biomarkers. In another embodiment of the invention, a panel of fluorescently labeled reagents detects at least about four to about six, to about ten, to about twelve different biomarkers or more. In a further embodiment, each fluorescently labeled reagent has different fluorescent properties, which are sufficient to distinguish the different fluorescently labeled reagents in the panel.

[00555] A single biomarker can provide a read-out of more than one feature. For example, Hoechst dye detects DNA, which is an example of a biomarker. A number of features can be identified by the Hoechst dye in the tissue sample such as nucleus size, cell cycle stage, number of nuclei, presence of apoptotic nuclei, etc. In one embodiment of the invention, the imaging procedures are automated.

[00556] In one embodiment of the invention, the one or more tissue samples are isolated from one or more animals. For example, in one embodiment, the one or more animals are one or more rodents, preferably a mouse. The tissue may be isolated from a human subject. In certain

embodiments tissues are isolated post mortem. In a particular embodiment, one or more tissue samples are isolated from an animal at one or more time points.

[00557] Methods of dissecting tissues from any organism are well known in the art. One method that may be utilized according to the present invention may be microdissection. Laser Capture Microdissection (LCM) enables separation of clusters of cells or even individual cells of interest from a background of millions of other cells. The collected cells can be directly visualized to verify their identity and purity. LCM is used to select small clusters of cells of interest from frozen sections of tissue by embedding them in a transfer film, e.g., a thermoplastic polymer. An example of a suitable thermoplastic polymer is ethylene vinyl acetate (EVA). The general methods of LCM are well known. See, e.g., U.S. Pat. Nos. 5,985,085; 5,859,699; and 5,843,657; as well as Suarez-Quian et al., "Laser Capture Microdissection of Single Cells from Complex Tissues," BioTechniques, Vol. 26, pages 328- 335 (1999); Simone et al., "Laser-capture microdissection: opening the microscopic frontier to molecular analysis," TIG, Vol. 14, pages 272-276 (1998); and Bonner et al., "Laser Capture Microdissection: Molecular Analysis of Tissue," Science, Vol. 278, pages 1481-1483 (1997).

[00558] LCM is a process by which cells and portions of biological tissue samples are acquired directly from tissue sections mounted on glass slides or other solid surfaces. Once the cells or tissue portions of interest (tissue targets) are located in the sample, a laser is focused over the tissue targets. When the laser is fired, the thin-film located directly above the tissue targets melts, flows down and adheres to the tissue targets. The tissue targets are now stabilized and ready for molecular analysis.

[00559] The present may also be performed on tissue samples isolated from transgenic animals, such as mice. In certain embodiments, the animals may express a transgene. The transgene may be expressed in a specific cell type (e.g., a neuron). Expression of the transgene may produce a marker that can be used to enrich for single cells or nuclei of a specific cell type. In certain embodiments, the animal may express a genome editing system such as described in “In vivo interrogation of gene function in the mammalian brain using CRISPR-Cas9” Swiech L., et al., Nat Biotechnol Oct 19. (2014). The animal may be xenograft. Xenotransplantation of tumor cells into immunocompromised mice is a research technique frequently used in pre-clinical oncology

research. The tissue may express a transgene for isolating tissue specifically from a tumor. The tissue may be labeled with a nucleoside analogue in order to isolate cells of a developmental stage.

[00560] In some embodiments, the method further comprises filtering the single nuclei, as described elsewhere herein. In some embodiments, nuclei doublets are removed by filtering.

[00561] In some embodiments, nuclei containing ambient RNA or ambient RNA alone are removed by filtering.

[00562] The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

EXAMPLES

Example 1 - Performing Single Cell Genomics in FFPE Tissue

Summary of Results

[00563] Extracting single nuclei or cells from FFPE samples requires many variables, including temperature, chemical, buffers, and mechanical variables (Fig. 1). cDNA may be obtained from single nuclei by sorting the nuclei into plates or droplets (Fig. 1). Applicants varied extraction methods and were able to isolate nuclei and whole cells from FFPE. Nuclei and whole cells can subsequently be used for transcriptome analysis; RNA extraction, cDNA generation, WTA amplification (whole transcriptome amplification), library construction, sequencing, and cell type identification. Nuclei and whole cells can subsequently be used for chromatic analysis using single cell/nucleus ATAC-seq, single cell/nucleus ChIP, or bulk (pooled) nuclei analysis using these methods. Single cells/nuclei can subsequently be used for single cell/nucleus DNA sequencing (e.g. cancer mutations in single cells). Single cells and nuclei can be stained by antibodies and FACS sorted following isolation from FFPE to isolate specific single cells or to get single-cell type population profiling for transcriptomes, DNA sequences (e.g. mutations in cancer), or epigenomic analysis. Applicants are developing low-RNA input transcriptome generation. This has been done down to 33 pg. Applicants can perform RNA analysis from bulk FFPE extracted nuclei. Applicants have obtained WTA from 5000 pooled nuclei as assessed by a bioanalyzer. Determinants of RNA quality from FFPE samples has been described previously (see, e.g., von Ahlfen et al., 2007, Determinants of RNA Quality from FFPE Samples. PLoS ONE 2(12): el26l).

Tissue extraction and nuclei isolation method 1:

- Cut excess paraffin from tissue (FFPE brain) and split into 30-100 mg pieces
- Dissolve paraffin at room temperature with two x 10-minute changes of xylene (5 mL each)
- Perform 1 wash at 37C for 10 min
- Cut tissue into smaller pieces, take 1 piece/tube and repeat 37 C wash.
- The tissue was then rehydrated with 100 µl of 95%, 75%, and 50% ethanol (EtOH) for 2 minutes each
- The tissue was either chopped in CST or TST for 10 min or dounce homogenized. (these are buffers from the Raisin-seq filing).
- Tissue was filtered through 40 uM filter
- Tissue was washed in ST and filtered again in 30 uM filter
- Images taken and FACS test with Ruby stain

[00564] Results are shown using dounce homogenization (Fig. 2) and chopping (Fig. 3).

Tissue extraction and nuclei isolation method 2:

- Cut tissue (FFPE brain) out of paraffin
- Dissolve paraffin:
    - Room temperature with three 10-minute changes of xylene (1 mL each) in the microcentrifuge tube
    - Room temperature for 10 min and then 2 x 90C, 10 min washes
- For each change, remove xylene
- The tissue was then rehydrated with 100 µl of 95%, 75%, and 50% ethanol (EtOH) for 2 minutes each.
- Split each tissue in ½ and re-suspend in NST
- Dounce and either add PK (proteinase K) or proceed to spin without PK.
- For PK, add PK to ST and proceed
- Enzymatic digestion was then performed by adding 100 µl of freshly prepared proteinase K solution. **Stock at 800 U/ml, use at 1:50 so for 1 mL add 20 uL and incubate at RT for 10 minutes.**
- Spin down and re-suspend in ST
- Ruby stain, sort and also analyze by microscope

[00565] Results of method 2 are shown in Figs. 4-7.

Tissue extraction and nuclei isolation method 3:

[00566] Nuclei and whole cells are isolated depending on temperature (e.g., 90C steps for nuclei and room temperature steps for cells).

- Add protease inhibitors to CST and ST buffers prior to starting
- Cut tissue out of paraffin (B16 and D4M.3A FFPE tumor tissue; melanoma PDX)
- Dissolve paraffin in lml xylene at RT for 10 min
- Divide tissue in halThalf. Tissue will get two additional 10 min washes in lml xylene: either at room temperature or at 90C.
- Rehydrate tissue with lmL of 95%, 75%, and 50% ethanol (EtOH) for 2 minutes each.
- All subsequent steps on ice.
- Place tissue into lmL of CST and chop for lOmin
- Bring to 2 mL with CST
- Filter in large 40 uM filter
- Add 3 mL of ST
- Spin down at 500g for 5min and re-suspend in 500uL ST
- Examine under microscope

[00567] Results of method 3 are shown in Figs. 8-1 1.

[00568] Applicants have tested several protocols for nuclei extraction (Fig. 12). These are examples of what the nuclei suspensions look like with filtering alone for debris removal. The mouse brain nuclei image was from an experiment that tested use of heat and/or proteinase K on deparaffmization using NST buffer. The Melanoma Nuclei and cells image was taken from an experiment omitting heat from the deparaffmization step, and chopping in CST buffer. The Mouse Lung nuclei image was from an experiment that tested using Mineral Oil and heat deparaffmization, and douncing or chopping. These are representative images showing that the methods yield nuclei. Additional images of nuclei and cell extraction are also shown.

Example 2 - FFPE RNA extraction and Whole Transcriptome Amplification (WTA)

[00569] Applicants performed RNA extraction of FFPE tissue using FormaPure RNA extraction kit. This kit uses mineral oil for deparaffmization. Applicants also modified the

beginning of this protocol to use Xylene for deparaffmization. The RNA quality was low in the Xylene and oil experiments compared to the control (Fig. 13). The control was frozen tissue extracted using Qiagen RNeasy kit with DNA eliminator columns. The FormaPure FFPE RNA extraction kit most similarly follows the SMART-Seq2 protocol in that it also uses SPRI beads for total nucleotide extraction. There is an option to elute with a DNAse I digestion and rebind the RNA to the SPRI beads. Applicants did not perform that step as it is not used for the SS2 protocol. RNA was quantified by Qubit RiboGreen HS RNA kit, which only binds to RNA and not double-stranded DNA. Applicants analyzed cDNA production with the low input RNA extraction from FFPE. Applicants observed high quality cDNA traces from FFPE bulk extractions (Fig. 13). Low input yields could be improved with added PCR cycles. Applicants extracted RNA from 5000 nuclei and tested cDNA from RNA extracted from bulk sorted FFPE nuclei with and without heat (Fig. 14). Applicants observed high quality cDNA under both conditions.

[00570] Applicants extracted RNA from FFPE of mouse brain tissue using this kit: FormaPure RNA cat. no. C19683AB with the following modifications to the manufacturer protocol

Deparaffinization by Xylene

- Cut a tiny section of tissue from the FFPE block.
- in l.5mL tubes, dissolve paraffin in Xylene:
  - Room Temp. for lOmins and then 2 x 90C, lmL each wash
  - For each change, remove xylene
- Rehydrate with lmL of 90% Ethanol, then 75%, then 50% for 2 mins each at room temp.
- Rinse with ice cold ST buffer to remove last traces of ethanol.
- Proceed to FormaPure protocol step: 3 Tissue Digestion
- Note: will not observe a phase separation
  - Skip step 4 - no need to remove lower phase to a new tube.
  - Make careful observations of how well the tissue is dissolved. (can include a homogenization step)
- Proceed to step 5 with no other modifications to the protocol

Deparaffinization by FormaPure method (mineral oil)

- Transfer 3 lOum thick sections of tissue to a l.5mL tube and add 450ul of Mineral Oil.

- Note: FFPE blocks are not prepared properly to use a microtome. The tissue can be minced prior to adding to mineral oil.

- Follow FormaPure protocol and make careful observations of how well paraffin is dissolved and tissue is lysed.

[00571] SS2 of bulk sorted nuclei without modifications does not yield any measurable amount of cDNA. Adding a Proteinase K heat step to help reverse cross linking of sorted and lysed nuclei works well (Fig. 15) (5,000 nuclei are sorted into 5ul of TCL+l%BME lysis buffer -Final volumes are around l5-l7ul. Removed l5ul to a new plate for SS2). cDNA traces are still of high quality with large fragment sizes. (5000 nuclei and 14 cycles of PCR). Applicants can perform library construction and sequencing. Applicants also tested including after the Proteinase K digestion, an extra heat step which acts to reverse cross link RNA and also to inactivate the Proteinase K. These samples need SPRI cleaning and this extra heat step does seem to cause some degradation - although yields may be slightly increased.

[00572] Following the sNuc-Seq SMART-Seq2 protocol with a range of input concentrations of RNA Applicants added lul of RNA to 4ul of the Mix 1 and proceeded from step 22.

[00573] Input RNA concentrations across 12 wells in rows (Table 4):

Table 4.

Using 1ul added to 4ul of Mix 1	
ng/ul	*pg/ul*
0.5000	*500.0*
0.2500	*250.0*
0.1250	*125.0*
0.0625	*62.5*
0.0313	*31.3*

0.0156	*15.6*
0.0078	*7.8*
0.0039	*3.9*
0.0020	*2.0*
0.0010	*1.0*
0.0005	*0.5*
0.0000	*0*

Table 5. Qubit Results:

Well	*pg input*	*Xylene Row B*	*Mineral Oil Row C*	*Frozen (high RIN control) Row D*
1	*500.0*	*4.53*	*7.64*	*37.8*
2	*250.0*	*4.15*	*5.02*	*23.2*
3	*125.0*	*2.92*	*3.03*	*10.4*
4	*62.5*	*1.98*	*2.14*	*8.14*
5	*31.3*	*1.49*	*1.70*	*2.76*
6	*15.6*	*0.969*	*0.965*	*1.13*
7	*7.8*	*1.25*	*0.841*	*0.861*
8	*3.9*	*1.48*	*0.934*	*0.802*

9	*2.0*	*0.761*	*0.811*	*0.530*
10	*1.0*	*1.04*	*1.06*	*0.642*
11	*0.5*	*1.38*	*1.20*	*1.07*
12	*0*	*1.20*	*0.710*	*0.756*

[00574] Highlighted wells were also run on BioAnalyzer High Sensitivity Chip (Fig. 16).

WTA preparation from FFPE extracted nuclei:

Xylene Deparaffmization:

1. Using a 1.5mm punch biopsy tool to section tissue from FFPE blocks
2. Add lmL xylene to tissue in eppendorf tubes - in fume hood.
3. Incubate 1 Omin atRT, and then 2 x 90C, lmL each wash. For each change, remove xylene, and wrap caps with parafilm
4. Rehydrate tissue with lmL of 95%, 75% and 50% ethanol for 2 mins each at room temp.
5. All subsequent steps on ice, move quickly
6. Place tissue in lmL of CST for chop in a well of 6w plate, chop for 10 mins.
7. Add lmL of CST and filter
8. Raise volume to 5mL with ST buffer - 5mL final volume
9. Centrifuge at 500g for 5mins (lower brake speed to 5)
10. Remove supernatant, and resuspend pellet in desired volume of ST buffer plus 0.04% BSA
11. examine under microscope, and count with cellometer.

Mineral Oil Deparaffmization

1. Add 450ul of mineral oil to tissue in eppendorf tubes, incubate at 80C for 15 mins.
2. Remove mineral oil and Rehydrate with lmL of 95%, 75% and 50% ethanol for 2 mins each at room temp.
3. Continue from step 4 above.

[00575] Add Ruby to each sample and sort with the SONY sorter (FACS).

Prepare Lysis Plates for Sorting

[00576] 6 Plates each of TCL + BME, and 4 Plates of TritonX-lOO using Eppendorf twin.tec PCR Plate 96, skirted, colorless

[00577] Make 750ul of each lysis buffer:

[00578] TCL buffer - add lOul per mL for 1% solution

Table 6.

Reagent	*1 rnx*	*750ul*	*Final Conc*	
TritonX-100 (10%)	*0.08*	*15*	*0.2%*	
Trehalose (1M)	*3.6*	*697.5*	*0.93*	*M*
RNase Inhibitor (40U/ul)	*0.2*	*37.5*	*2U/ul*	

[00579] a. Aliquot 85ul to 8 wells of strip tube and use a multichannel to pipet 5ul of TCL+ 1% BME to each well of columns 1 and 2 of 6 plates

[00580] b. Aliquot 85ul to 8 wells of a strip tube and use a multichannel to pipet 4ul of TritonX-lOO lysis buffer to each well of columns 1 and 2 of 6 plates

[00581] Seal plates and place one ice. Prior to sorting, spin them down.

SS2 of bulk samples:

[00582] ETsing one sample of bulk - A1 in TCL + 1% BME. Add wells of RNA at lng and 5ng total input, and use 14 cycles of amplification for cDNA Amp. Also include an no template control (NTC) for 4 wells total. Take total RNA with R⌈N 8 or better, dilute to lng/ul and 0.2ng/ul for the lng and 5ng input positive controls.

[00583] 5,000 nuclei (measured volume to be around l5-l7ul); added 34ul of SPRI

- 5ng RIN 9 -lOul of each (5ul of TCL buffer, plus the 5ul of RNA controls)
- lng RIN 9
- 5ng Xylene RNA
- NTC

[00584] Applicants used 34ul of SPRI for all of these and proceeded with the protocol eluting in 4ul of Mix 1. Applicants observed that the nuclei did not amplify as the RNA controls did (Fig. 17). Applicants hypothesized that cross-linking was not fully reversed.

Test using Proteinase K

[00585] Prior to SPRI nucleotide purification from lysate, pick a bulk lysate from the TCL and the Triton X-100 lysis buffers, and include lng RNAs as controls- degraded xylene extracted RNA, and RIN9 and NTC. Take l5ul of the bulk sorted nuclei - (the volume from the sorter significantly raises the volume of the sample). all of it.

[00586] Make a Proteinase K dilution and add lul to each sample:

NEB P8107S 800U/mL = 20mg/mL = 20ug/ul = 0.8U/ul

Use lul and dilute into 49ul of water

Set Thermal Cycler to 60C for 60 mins and on for 55C for l5mins

Samples for 60C for 60 mins

A - 5K nuclei - TX lysis buf - mineral oil isolation (take l5ul)

B - 5K nuclei - TCL lysis buf - mineral oil isolation (take l5ul)

C - lng RIN 9 positive control

D - lng Xylene extracted total RNA (RIN 2)

E - NTC

F - 5K nuclei - TX lysis buf - xylene isolation

Samples for 55C for l5mins

A - 5K nuclei - TX lysis buf - mineral oil isolation

B - 5K nuclei - TCL lysis buf - mineral oil isolation

C - lng RIN 9 positive control

D - lng Xylene extracted total RNA (RIN 2)

E - NTC

[00587] Applicants used maxima RT enzyme and 14 cycles of PCR.

[00588] Applicants observed that the TX lysis buffer does not work as the nuclei probably did not lyse. The 55 for l5min plate obtained good WTA from the bulk nuclei in TCL buffer (Fig. 18). The 55 for l5min plate obtained good WTA from the Xylene extracted total RNA (Fig. 19).

Example 3 - FFPE Materials and Methods

[00589] TCL lysis buffer (Qiagen, #1031576) was used as described herein. Single nucleus RNA was first purified using RNAClean XP beads (Beckman Coulter, Agencourt RNA-Clean XP, #A63987) at 2.2X beads to sample volume ratio. Single nucleus derived cDNA libraries can be generated following a modified Smart-seq2 method. Reverse transcription (RT) can be performed with Maxima RNase-minus RT (Thermo Fisher Scientific, Maxima Reverse Transcriptase, #EP0752), 2µ1 5x Maxima RT buffer, 2µ1 Betaine (Sigma Aldrich, 5M, #B0300), 0.9µ1 MgCl2 (Sigma Aldrich, lOOmM, #M 1028), Iµï TSO primer (10 pm), 0.25pl RNase inhibitor (40U/pl). Samples can then be amplified with KAPA HiFi HotStart ReadyMix (KAPA Biosystems, #KK2602). PCR product can be purified using AMPure XP (Beckman Coulter, Agencourt AMPure XP, #A63880) and eluted in TE buffer (Thermo Fisher Scientific, #AM9849). Purified cDNA libraries can be analyzed on Agilent 2100 Bioanalyzer (Agilent, Agilent High Sensitivity DNA Kit, #5067-4626) and quantified using picogreen (Thermo Fisher Scientific, Quant-iT PicoGreen dsDNA Assay Kit, #P 11496) on a plate reader (Biotek, Synergy H4, wavelength at 485nm, 528nm with 20nm bandwidth). Sequencing libraries can be prepared using Nextera XT kit (Illumina, #FC-l3 1-1024) as described previously. Chopping can use sharp dissection scissors for 10 min. 40 micron nylon cell strainer (Falcon 352340) may be used.

[00590] Pieces of tissue should be small; less than 30, 40, 50, 60, 70, 80, 90, 100 or 200 mg, or less than about 1 cm3, or half an almond. If tissue is limited, one can go as low as 10, 15, 20 or 25 mg for a single preparation.

[00591] In certain embodiments, buffers were used to extract nuclei by chopping tissue with scissors for 10 minutes in the respective buffer. In certain embodiments, extracted nuclei or cells were filtered through a 40 micron filter, and washed once. Compositions of buffers used are shown in Table 7 and Table 8. Reagents used to make buffers were procured from VWR, Sigma, and other vendors. Alternative buffer component concentrations that deviate from the buffers below may be used. In certain embodiments, tricine may improve small molecule diffusion. Regarding buffering agents (e.g., Tris, Tricine, HEPES, PIPES) if a tissue is neutral pH then the buffer concentration may be close to zero (e.g. 1 mM). Regarding detergents, Applicants tested down to 0.0012 for tween-20. In certain embodiments, the concentration for detergents is between 0.001 or 0.0005 %. In certain embodiments, detergent concentration is up to 1-2%. Regarding salts, the

buffer may be adjusted down to 10 mM for NaCl, 0.1 mM for CaCl2, and 1 mM for MgCl2. Regarding polyamines, the buffer may be adjusted down to 0.1 mM for both spermidine and spermine.

Table 7. Compositions of Buffers

Buffer	**Buffer Concen-tration**	**Detergent**	**Detergent Concentration (%)**	**Salt and Concentration**	**Additives and Concentration**
Tris	10 mM	NP40	0.2	146 mM NaCl, 1mM $CaCl_2$, 21mM $MgCl_2$	
Tris	10 mM	CHAPS	0.49	146 mM NaCl, 1mM $CaCl_2$, 21mM $MgCl_2$	
Tris	10 mM	Tween-20	0.03	146 mM NaCl, 1mM $CaCl_2$, 21mM $MgCl_2$	
Tricine	20 mM	NP40	0.2	146 mM NaCl, 1mM $CaCl_2$, 21mM $MgCl_2$	0.15 mM spermine and 0.5 mM spermidine

Table 8. Compositions of Buffers.

Composition	**Buffer**	**Buffer conc.**	**Detergent**	**Detergent concentration (%)**	**Salt conc.**	**Additives concentration**
ST	Tris	10 mM			146 mM NaCl, 1mM CaCl2, 21mM MgCl2	
CST	Tris	10 mM	CHAPS	0.49	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	0.01% BSA

TST	Tris	10 mM	Tween-20	0.03	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	0.01% BSA
NSTnPo	Tricine	20 mM	NP40	0.2	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	0.15 mM spermine 0.5 mM spermidine 0.01% BSA
NST	Tris	10 mM	NP40	0.2	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	0.01% BSA

Example 4 - **sNucER-seq**

[00592] Previously, Applicants developed single nucleus RNA sequencing (sNuc-seq) as a method to profile the expression of single cells. The outer membrane of the nucleus is continuous with the rough endoplasmic reticulum (RER). The RER is a site of RNA translation. Preserving a portion of it with the nucleus would improve RNA recovery and single cell expression profiling. Applicants conducted a screen to improve sNuc-seq. The compositions of nuclei isolation solutions that worked best preserve a portion of the nuclear outer membrane/RER along with ribosomes as determined by electron microscopy. This method is referred to as single nucleus and rough endoplasmic reticulum (sNucER)-seq.

[00593] *Screen summary.* Applicants focused on the enteric nervous system, which represents a rare cell population in a complex tissue. Applicants used a double transgenic mouse which labels enteric nervous system nuclei with GFP and allows for FACS following nuclei isolation. Selected nuclei were processed using smart-seq2 and sequenced.

[00594] *Detergents·*. Applicants conducted a screen to optimize single nucleus RNA profiling of cells from tissues. Applicants tested a range of detergents that have previously been reported for nuclei extraction (Tween-20, Nonidet P-40/IGEPAL CA-630, Digitonin), and not reported

(CHAPS). Applicants also compared a commercial nuclei extraction reagent (Nuclei EZ lysis buffer, SIGMA).

[00595] Based on the published literature it was not clear which concentrations of detergents would be optimal for nuclei extraction for sNuc-seq. Additionally, there was no data on CHAPS. Applicants chose to include CHAPS to increase detergent diversity. Tween-20, and Nonidet P-40/IGEPAL CA-630 are both non-ionic detergents. CHAPS is a zwitterionic detergent; as a note, CHAPS performed the best, and it is likely other zwitterionic detergents could do equally well.

[00596] Applicants chose the detergent concentrations based on the critical micelle concentration (CMC) for each detergent. Applicants then varied it either above or below the CMC.

[00597] *Buffers*: As part of the screen, Applicants also tested different buffers that have been used in the literature (Tris, Tricine, and HEPES). Although Tris performed the best, it is likely that the buffer choice is less critical than the detergents.

[00598] *Salts*: Applicants chose fixed salts concertation for the tests, although Applicants did try hypotonic solutions. The salts concentration was based on cellular concentrations of salts and what has been previously reported. Applicants used 146 mM NaCl, lmM CaCl2, and 2lmM MgCl2. The NaCl concertation can likely be varied up to 300 mM, or completely eliminated, and replaced with another salt such as KC1 (as has been done in various biochemistry preparations as needed). Similar, CaCl2 can likely be replaced with other calcium containing salts and concentrations can be increased to 20 mM or more. The same is true for varying MgCl2 or adding in other salts.

[00599] *Results*: From the screen Applicants identified four compositions that worked the best for isolating enteric nervous system nuclei (appropriate cell types detected, high gene representation of expected cell types, most genes per cell, least background) (see, Table 2).

[00600] Applicants performed a further comparison among these four and compositions 2 and 3 (Table 2) performed the best. Applicants examined these nuclei preparations with electron microscopy and found that they preserved a portion of the outer nuclear envelope/RER with the nuclei. As a comparison, Applicants tested the commercial Nuclei EZ lysis buffer from Sigma, which did not preserve the nuclear envelope. Applicants are in the process of performing EM on preparations from the other 2 buffers.

[00601] CST with 0.49% CHAPS was the top extraction solution with the highest ENS score and lowest contamination. The nuclei have a nuclear membrane (not double membrane in all places), the membrane contiguous with RER and has ribosomes, and mitochondrial contamination was reduced.

[00602] Applicants found that the CST buffer has a lower intron/exon ratio compared to nuclei-only preps with EZ lysis reagent supporting more spliced RNA. The Intron/Exon ratio for each were as follows: CST = 1.27904; EZ frozen = 1.642955; and EZ chop = 2.081659.

[00603] Additionally, Applicants confirmed that droplet based, DroNcER-seq works and that the isolated nuclei are compatible with the Chromium lOx single cell system. Additionally, Applicants are testing whether sNucER-seq works with other cell types and tissues. Preliminary data suggest the method is compatible with epithelial cells, brain cells, most cell types tested (immune, epithelial, vasculature, lyphatics, muscle, adipose, neuron, glia, muscle) and the lOx system.

Example 5 - The enteric nervous system of the human and mouse colon at a single-cell resolution

[00604] The enteric nervous system (ENS) is an extensive network of neurons and glia along the gastrointestinal (GI) tract, which coordinates motility, digestion, nutrient absorption, and barrier defense (1). The human ENS rivals the spinal cord in complexity (2). The ENS is broadly partitioned into the myenteric (Auerbach's) plexus and submucosal (Meissner's) plexus (3); with anecdotally reported differences in anatomy and composition within ganglia, across intestinal regions, and among species (2). In addition, other factors were proposed to contribute to ENS diversity, including age (4), sex (5), circadian oscillations (6), and functional dysmotility disorders (7).

[00605] The ENS is implicated in abroad range of intra- and extra- intestinal disorders. Primary enteric neuropathies, including Hirschsprung's disease, chronic intestinal pseudo-obstruction, Waardenburg syndrome type IV, and MASH1 deficiency, directly affect enteric neurons, result in agangliosis and impaired GI transit (2) and are poorly understood (8). Moreover, studies of neuro-epithelial and neuro-immune interactions (1), such as neuronal activation of group 2 innate lymphoid cells (ILC2s) (9), suggest that ENS dysfunction can impact local inflammation, motivating ENS characterization in other diseases that affect the gut (10). Intriguingly, several

extra-intestinal disorders, including those affecting the central nervous system (CNS) (e.g., autism spectrum disorders (11) and Parkinson's disease (12)) are associated with early GI motility dysfunction. However, the pathophysiology of the ENS across these disorders, including affected cell types, is poorly understood.

[00606] Here, Applicants generated a reference map of the ENS at single cell resolution across age, gender, location, circadian phases, and species (Fig. 20A). Applicants first developed a new method, Ribosomes And Intact Single Nucleus ("RAISIN") RNA-seq, and applied it to generate a high quality single-cell census of the ENS in adult humans and mice, overcoming challenges in single-cell and single-nucleus RNA-seq (scRNA-Seq, snRNA-seq) (14-18) of the ENS. In the mouse, Applicants used genetic tools to directly enrich for and profile 2,447 enteric neurons using deep, full-length snRNA-Seq spanning four colon segments (proximal to distal) of three transgenic models (both sexes, multiple ages, two phases of the circadian rhythm). In humans, where enrichment was not possible, Applicants sequenced 163,741 single RAISINs (i.e. nuclei and attached ribosomes) from the muscularis propria of 10 individuals (men and women; 35-90 years old) and identified diverse cell types, among them 831 enteric neurons and 431 rare Interstitial Cells of Cajal (ICCs). Enteric neurons partitioned into 24 murine and 11 human subsets, which Applicants annotated with putative functions (e.g., motor, sensory, secretomotor) using known marker genes, and matched between the two species based on conserved transcriptional programs. Applicants mapped signaling interactions between human enteric neurons and other cell types in the colon, identifying possible neuro-immune, neuro-adipose, neuro-epithelial, neuro-muscular, and neuro-ICC regulatory pathways. Finally, Applicants show that enteric neurons express genes specifically associated with primary enteroneuropathies, inflammatory disorders of the gut, as well as with CNS disorders with early gut motility dysfunction, highlighting their potential roles in these disorders.

Example 6 - Systematic optimization of nuclei extraction conditions enables profiling of single ENS nuclei from the colon

[00607] Because neurons comprise less than 1% of all colon cells, Applicants first devised a strategy to enrich for the mouse ENS. Applicants used three mouse models: (1) Wntl-Cre2 (19) and (2) SoxlO-Cre (20) transgenic mice, which are established Cre-drivers that efficiently label the neural crest (21, 22), and (3) Uchl1-Histone2BmCherry:GFP-gpi mice, which specifically

labels neurons (23). For both Cre-driver mice, nuclei were tagged using the conditional INTACT (Isolation of Nuclei TAgged in specific Cell Types) allele (24). In all cases, Applicants extracted labeled nuclei, FACS-enriched them, and profiled them using SMART-Seq2 (17) (Fig. 20A,B, fig. 24A-C).

[00608] Previously published snRNA-seq protocols (16, 17) did not perform well on ENS nuclei from the colon, in contrast to their excellent performance on labelled nuclei from the brain (fig. 24D). In addition, the Wntl-Cre2 driver mostly labeled non-ENS cells within the colon (fig. 24B), and the SoxlO-Cre driver labelled both neurons and oligodendrocytes in the brain (fig. 24D), whereas Applicants anticipated recovering only brain oligodendrocytes (25). These limitations raised the need to develop new snRNA-seq approaches.

[00609] To develop snRNA-seq methods that are compatible with a broader range of tissues, including colon, Applicants performed an optimization with nuclei from adult SoxlO-Cre;INTACT mice, systematically varying the detergent (NP40, CHAPS, Tween, or Digitonin), detergent concentrations, buffer (HEPES, Tris, Tricine), mechanical extraction conditions (dounced, chopped, or ground tissue), and added modifiers (e.g. salts, polyamines) used in nuclei isolation (SOM), and compared to published protocols (16, 17) (fig. 25). Applicants profiled 5,236 nuclei isolated across 104 preparations spanning 36 extraction conditions (mean = 145 nuclei per condition) using SMART-Seq2 (Fig. 20A; fig. 25). Applicants scored conditions by (1) the recovery rate of neurons and glia relative to other cells (i.e. damaged or contaminating cells), (2) the number of genes detected per cell; and (3) an ENS signature score of known markers of enteric neurons and glia (Fig. 20C; fig. 25B-E and 26; SOM).

[00610] Detergent type, detergent concentration, buffer, and mechanical force each impacted quality metrics (fig. 25B-E and 26) and Applicants identified two conditions with high ENS recovery and low contamination rates (-20% neurons, 55% glia, 25% contamination across both conditions, Fig. 20C), which also yielded high-quality profiles enriched in the ENS signature score (fig. 25B-E). Applicants termed these preparations "CST" (0.49% CHAPS detergent, Salts, Tris buffer, and "chopped" tissue) and "TST" (0.03% Tween-20 detergent, Salts, Tris buffer, and "chopped" tissue). Both preparations yielded higher numbers of detected genes than published methods (mean = 2,486 for CST and 2,542 for TST vs. 1,502 for published protocols on average across all nuclei; $p < 10\text{-}10$ for both comparisons; Wilcoxon test).

[00611] For all three transgenic lines, Applicants validated nuclei labeling within TUBB3+ neurons and confirmed their ability to enrich for extracted labeled nuclei using FACS (Figure 24C). For the SoxlO-Cre driver, Applicants confirmed extensive neuron labeling by generating a triple transgenic animal harboring *SoxlO-Cre, INTACT*, and conditional *tdTomato* (Madisen et al., 2010) alleles, to label both the nuclei (i.e. INTACT) and cell bodies and their projections (i.e. tdTomato) of the ENS. There was excellent concordance between TUBB3 (neuron) immunostaining and reporter expression within the mouse colon (Figure 90; tdTomato+/TUBB3- cells represent glia). For the Wntl-Cre2 driver, Applicants observed labeled neuron nuclei, and also extensive signal in the colon mucosa (Figure 24C); Applicants validated that the Wntl-Cre2 driver also labeled colon epithelial cells by snRNA-seq. This off-target labeling may explain why a previous study using the Wntl-Cre driver to target the ENS removed the mucosa when profiling enteric neurons of early post-natal mice with scRNA-seq (Zeisel et al., 2018). Lastly, for the Uchll-H22B mCherry mice, Applicants observed labeling of enteric neurons but not of enterendocrine cells (the main neuroendocrine type in the intestine; Modlin et al., 2008), by histology (Figure 24C) and snRNA-seq.

Example 7 - Preservation of ribosomes or rough endoplasmic reticulum on the nuclear envelope allows for mature mRNA capture

[00612] To understand the basis for these performance differences among nuclei preparations, Applicants compared nuclei structure between CST, TST, and published preparations for snRNA-seq (16, 17), using ultrathin-section transmission electron microscopy (TEM) (SOM, Fig. 20D). As expected, the two published methods yielded isolated intact nuclei (Fig. 20D). In contrast, CST preserved not only the nuclear envelope, but also the ribosomes (26) on the outer nuclear membrane (Fig. 20D); Applicants thus termed this method RAISIN (Ribosomes And Intact Single Nucleus) RNA-seq. TST maintained both the rough ER and its attached ribosomes (26) on the outer nuclear membrane (Fig. 20D); Applicants thus termed this method, INNER Cell (INtact Nucleus and Endoplasmic Reticulum from a single Cell) RNA-seq. Consistent with the TEM results, both RAISIN-RNA-seq and INNER-Cell RNA-seq yielded higher exomintron ratios than the published methods (Fig. 20E; 41% and 64% increases, respectively), suggesting greater recovery of mRNA relative to pre-mRNA.

[00613] Of the two methods, Applicants opted to use RAISIN RNA-seq to profile the mouse and human ENS, because it captures more neurons and has fewer contaminants than INNER Cell RNA-seq (Fig. 20C; fig. 25B-E). To test whether RAISIN RNA-seq is compatible with massively parallel droplet-based scRNA-seq, Applicants also sequenced 10,889 unsorted RAISINs from the mouse colon (SOM). Applicants recovered most major cell types in the colon, including epithelial cells, myocytes, fibroblasts, endothelial cells, immune cells, mesothelial cells, neurons, and glia (Fig. 20F), without any apparent "doublet" clusters, indicating that RAISINs correspond to single nuclei rather than to cellular aggregates. Therefore, even though RAISIN RNA-seq captures RNA both inside and outside the nuclear envelope, it is compatible with droplet-based scRNA-seq and yields little observed contamination.

Example 8 - RAISIN RNA-seq survey of the ENS from adult mice identifies 24 neuron and 3 glia subsets

[00614] Applicants used RAISIN RNA-seq with SMART-Seq2 to profile 5,181 high-quality transcriptomes from the ENS of 24 adult mice, spanning a range of ages (11-52 weeks), both males and females, and two phases of the circadian rhythm (morning or evening), and dividing each colon specimen into four equally sized segments along the proximal-distal axis to capture differences in anatomical location (Fig. 20A). Applicants initially used Wntl-Cre2;INTACT and SoxlO-Cre;INTACT mice to label both neurons and glia, and Uchll-Histone2BmCherry:GFP-gpi mice to subsequently enrich for enteric neurons (fig. 24A-C); however, because the Wntl-Cre2 driver targeted mainly epithelial cells (fig. 24B), Applicants focused on the other transgenic mouse models.

[00615] Among the 5,181 transcriptomes, Applicants identified 2,447 neurons and 2,710 glia (mean 7,491 and 4,732 genes per RAISIN, respectively), which Applicants clustered into 24 neuron and 3 glia subsets (Fig. 2lA,B; fig. 27A,B, table 18), arranged into a hierarchy (Fig. 21B), and annotated post-hoc by known marker genes (Fig. 21B; SOM), many of which Applicants validated in situ (Fig. 2lG,H, 27D,E 28). Of the 2,447 neurons and 2,710 glia identified, there was an average of 7,491 and 4,732 genes detected per RAISIN, respectively, which partitioned into 24 and 3 subsets, respectively (Figs. 91A-91C; 21A, 27B). The clusters were enriched for markers of neuron and glia transcriptomes from scRNA-seq studies (Figs. 91A, 91B) (Haber et al., 2017; Lasrado et al., 2017), with no detectable epithelial or enteroendocrine contamination, except for 8

contaminating cells in the “Other 2” cluster (Fig. 91A-91C). Neurons and glia clustered primarily by cell subsets, rather than by mouse, intestinal region, or other known technical covariates (fig. 27A,B). Applicants estimate that enteric neurons comprise less than 1% of all nuclei in the murine colon after adjusting the numbers of FACS-sorted nuclei by the proportions of neurons identified in each mouse model (SOM) (fig. 27C).

[00616] Broadly, neurons partitioned into either cholinergic (Chat+) or nitrergic (Nosl+) subsets (Fig. 21B, Ach and NO producing, respectively). As exceptions, four subsets expressed both Chat and Nosl (defined as log2(TPlOK+l) > 0.5), which Applicants validated in situ (fig. 27D), and one subset expressed neither marker. Based on expression of known marker genes, Applicants defined putative neurons subsets (Fig. 2lA,B), including: (1) Chat+Tacl+ excitatory motor neurons (PEMNs; 6 subsets), and (2) Nosl+Vip+ inhibitory motor neurons (PIMNs; 7 subsets), which together coordinate muscle contraction and relaxation; (3) CGRP+ sensory neurons (PSNs; 4 subsets), which sense and respond to chemical and mechanical signals in the intestine; (4) interneurons (PINs; 3 subsets), which relay signals between neurons; and (5) Glp2r+ secretomotor and vasodilator neurons (PSVNs; 2 subsets), which trigger secretions and fluid movement in other cell types.

[00617] The only major marker that Applicants could not detect was the neuronal enzyme for serotonin synthesis, Tph2 (Gershon, 2009; Mawe and Hoffman, 2013). Applicants probed for Tph2 in situ in the colon as well as targeted brain regions, which served as positive (raphe nuclei) and negative (pontine reticular nucleus) controls (Fig. 92A-92E), but only observed Tph2 signal in the brain. Applicants considered the possibility that Tph2-expressing enteric neurons are rare (Costa et al., 1982, 1996), and examined published bulk RNA-seq data (Sollner et al., 2017), finding Tph2 expression in the brain, but not the colon (Fig. 92F). Lastly, an independent scRNA-seq study of the small intestine myenteric plexus did not yield serotonergic neurons (Zeisel et al., 2018). However, Applicants cannot exclude the possibility that Tph2 is expressed only under different physiological conditions, in other locations, or cannot be captured using current genomic and RNA-FISH tools. One possibility is that serotonergic neurons only populate the small intestines, as conditional Tphl knock-out mice crossed with a Villin-Cre driver, which lack serotonin production by the mucosa, have detectable serotonin in the duodenum and jejunum;

although these regions still had detectable Tphl mRNA in the conditional knock-out (Kim et al., 2018).

Example 9 - ENS composition and expression programs vary by region and with circadian oscillations

[00618] To systematically assess sources of variation in the ENS, Applicants leveraged the fact that the atlas comprises samples that vary by genetic background, age, sex, circadian time point, and anatomical location, to test how each factor impacts ENS composition (i.e. the relative proportions of neuron subsets) or gene expression within each neuron subset.

[00619] The transgenic background had profound effects on neuron composition (Fig. 21B; fig. 27A), suggesting distinct developmental origins for some neuron subsets. In particular, two subsets of putative sensory neurons (PSN1 and PSN2) were nearly absent from SoxlO-Cre mice (Fig. 21B), suggesting they may arise from distinct lineages (20, 27). ENS composition also varied significantly along the length of the colon within each of the SoxlO and ETchll lines, with distinct neuron subsets enriched in different regions (Fig. 21B). For example, PSN1 and PSN2 were enriched in the proximal colon ($P < 10\text{-}22$ and 10-6, respectively; Fisher's exact test), whereas distinct subsets of putative motor neurons (PMNs) were enriched in either the proximal or distal colon (Fig. 21B).

[00620] Applicants next used a regression framework to identify genes that were differentially expressed (DE) with respect to age, sex, circadian phase, and colon location, in a manner shared across neuron subsets (SOM). Overall, few DE genes were associated with age or sex (with the exception of genes on the X and Y chromosomes) (Table 18); however, the circadian clock and colon location had substantial impacts on gene expression of many neuron genes (table 18). For example, core clock regulators were among the most DE genes during morning (Arntl) and evening (Perl, Per2, Per3) (Fig. 21C). In the morning, there was also increased expression of cytoskeleton-associated genes (e.g., Tubb3, Prph, Tubb2a, Cfll), suggesting circadian regulation of structural remodeling (28), and genes involved in neuronal signaling (e.g., Scg2, Pcskln, and Slc7al l). In PSN1 and PSN2, Applicants also observed morning upregulation of genes involved in neuro-immune signaling (e.g., Caleb, Ill3ral) (Fig. 21C) (29,30). In the evening, several TFs were upregulated relative to morning, including Nrld2, Tef, Rfx2, and Dbp (Fig. 21C), many of which are known circadian regulators (31).

[00621] In addition, there were significant changes in gene expression across colon regions, after controlling for differences in ENS composition (which itself varies by location) (Fig. 21D). Most notably, neurons in the distal mouse colon had higher expression of several neurotransmitter receptors, including serotonin receptors (Htr3a, Htr3b), glutamate receptors (Gria3, Gridl), acetylcholine receptors (Chrna7, Chrml), and potassium and sodium channels (Kcnq5, Scn5a), suggesting electrophysiological differences along the ENS.

Example 10 - Motor neuron expression profiles suggest that mechanosensation drives the peristaltic reflex

[00622] The myenteric plexus is a major functional unit of the ENS, moving luminal contents along the intestine through coordinated muscle contraction and relaxation (13). The canonical model of the peristaltic reflex (Fig. 21E, left) (13) begins with the release of serotonin (5HT) by enterochromaffm cells, which acts on sensory neurons via the 5HT receptor 4 (HTR4). Interneurons then relay this signal to ascending and descending motor neurons, which elicit muscle contraction and relaxation, respectively (13). This model is based on associations between muscle contraction and serotonin release, but was recently challenged, because neither ablation of serotonin synthesis in enterochromaffm cells nor mucosa removal abrogate muscle contraction (32). Applicants therefore hypothesized that the molecular signatures of neuron subsets could help build and test models of peristalsis.

[00623] The transcriptional profiles of putative motor neurons suggest revisions to the peristaltic model, with a possible role for the mechanosensation of gut distention in driving peristaltic reflexes (Fig. 21F, right). First, nearly all putative motor neurons express the mechanosensitive ion channel, Piezol (Fig. 21G, PEMNs and PIMNs; confirmed in situ, fig. 28A), suggesting they have the capacity to directly sense distention. Mechanosensation in the GI tract is currently attributed to enterochromaffm cells, with speculation that some interneurons and intestinofugal neurons are also mechanosensitive (33). However, expression of Piezol in putative motor neurons, and the dispensability of mucosal serotonin for smooth muscle activity, raises the hypothesis that peristalsis is at least partially driven by distention, specifically via motor neuron depolarization through Piezol.

[00624] Moreover, although the peristaltic model posits that enterochromaffm cells act on sensory neurons via serotonin receptor 4 (Htr4) (Fig. 21F, left) (13), Htr4 is expressed by putative

excitatory motor neurons (PEMNs), and Applicants confirmed this in situ in Chat+ neurons of the myenteric plexus (fig. 28B). This suggests that serotonin may be able to act directly on motor neurons rather than only via sensory and interneuron intermediates.

Example 11 - Sensory neurons express key regulators of ILC responses and tissue homeostasis

[00625] Applicants identified four subsets of putative sensory neurons (PSNs) by expression of calcitonin gene-related peptide (CGRP), a marker of sensory neurons expressed in two forms (Calca, Caleb), which is involved in feeding, pain sensation, hormone secretion, and inflammation (34). While all four subsets express Caleb, only PSN3 expresses Calca at significant (but low) levels (fig. 29A), which Applicants confirmed in situ (fig. 28C). The CGRP receptor (Calcrl) and one of its three co-receptors (Rampl) are expressed in all neurons, except putative secretomotor neurons (fig. 29A).

[00626] Applicants inferred the likely target cells for each PSN subset based on the signaling molecules and receptors that they express (Fig. 21B, table 18, fig. 29A,B). For example, most sensory neuron subsets express receptors for glucagon (Gcgr), glucagon-like peptide 1 (Glplr), and galanin (Galr) (Fig. 21B; fig. 29A), peptides that are produced by enteroendocrine cells with roles in hunger and satiety (35). One subset, PSN3, co-expresses Cck and Vip (Fig. 21B), markers of intestinofugal neurons that innervate the prevertebral ganglia (36), thus supporting connections to the sympathetic nervous system. This subset also uniquely expresses brain-derived neurotrophic factor (Bdnf, Fig. 29B), which is elevated in patients with irritable bowel syndrome (IBS), where it is correlated to abdominal pain (37), and Piezo2 (Fig. 21G), a mechanosensitive ion channel, which may help detect and regulate smooth muscle tone (38) (confirmed in situ; fig. 28D). Another Calcb+ subset, PSN4, uniquely expresses somatostatin (Sst, Fig. 21B, fig. 29B) (validated in situ; fig. 28E), previously attributed to interneurons (13); the role of SST in the GI tract is poorly understood, but has been broadly linked to regulating most GI functions, including motility, secretion, absorption and the sensation of visceral pain (39). Localization of Sst expression to a single neuron subset now empowers dissection of its function in the ENS.

[00627] One sensory neuron subset, PSN1, uniquely expresses Noggin (Nog) and Neuromedin El (Nmu) (Fig. 21B), validated in situ (Fig. 2lH,I): both genes are known key regulators of epithelial stem cells (40) and immune cells (9), respectively. In particular, Noggin is a BMP

antagonist that is necessary for maintaining the intestinal stem cell niche, but whose cellular source is unknown. Noggin expression by sensory neurons raises the hypothesis that these neurons could help regulate the positioning or differentiation of intestinal stem cells. Furthermore, the neuropeptide NMU regulates type 2 cytokine responses via activation of innate lymphoid cells (ILCs) (9). Expression of its receptors, Nmurl andNmur2, on excitatory motor (PEMN1, PEMN2; fig. 29A) and sensory (PSN1, PSN2, PSN3; fig. 29B) neurons, respectively, suggests diverse neuronal targets of NMU, that may help orchestrate inflammation. PSN1 cells also express additional genes that may interact with ILCs, including Caleb, both subunits of the 11-13 receptor (Il4ra and IIUral, fig. 29A), and 11-7 (fig. 29B), a major regulator of ILC differentiation and survival (41). Lastly, both PSN1 and PSN2 cells express gastrin-releasing peptide (Grp, Fig. 21B), which in the lung is produced by neuroendocrine cells and contributes to the response to tissue injury (42).

Example 12 - Secretomotor neurons may integrate epithelial and immune signals

[00628] Secretomotor/vasodilator neurons (SVNs) integrate signals from the mucosa and sympathetic ganglia to regulate fluid movement between the body and the lumen. Applicants identified two subsets of putative secretomotor/vasodilator neurons (PSVNs) corresponding to non-cholinergic (PSVN1) and cholinergic (PSVN2) subtypes (43) (Fig. 2lA,B). Both subsets uniquely express receptors for GLP-2 (Glp2r) and secretin (Sctr), hormones released by enteroendocrine cells that stimulate blood flow (44) and epithelial secretions (45), respectively (Fig. 21B; fig. 29A). Most local reflexes regulating water and electrolyte balance likely act through non-cholinergic SVNs (43), and the data suggest that cholinergic SVNs may support tissue homeostasis. Specifically, the GM-CSF receptor (Csf2rb, Csf2rb2, fig. 29B) and Thymic Stromal Lymphopoietin (Tslp, fig. 29A) are expressed by PSVN2s, suggesting these neurons participate in GI immune responses (46, 47).

Example 13 - Profiling the human muscularis propria using RAISIN RNA-seq

[00629] Next, Applicants profiled human colon enteric neurons. Unlike genetic mouse models, Applicants could not enrich for nuclei from human enteric neurons, and thus opted to profile the muscularis propria (MP), which has a higher proportion of neurons than the submucosa or mucosa. Applicants isolated and profiled nuclei from cancer-adjacent normal colon segments from colorectal cancer resections from both genders (5 male, 5 female) and a range of ages (35 - 90)

(Tables 19-22). Based on the mouse data (fig. 27C), Applicants conservatively estimated a 0.5% capture rate for neuron nuclei, such that in order to capture 500 human neurons, Applicants would need to profile at least 100,000 unsorted nuclei.

[00630] Profiling 134,835 human RAISINs from the muscularis propria recovered transcriptomes from neurons, adipocytes, endothelial cells (lymphatic, vascular), fibroblasts, glia, immune cells (macrophages, mast cells, lymphoid cells), interstitial cells of Cajal (ICCs), myocytes, and pericytes (Fig. 22A), each annotated by expression of known marker genes (fig. 30A; Tables 19-22). Some subsets were enriched in specific patients (fig. 30A-F), which may be due to differences in sampled locations, variable cellular states or variation in the sampling of rare cells. Additionally, human RAISIN RNA-seq data contained more background contamination than either mouse RAISIN SMART-Seq2 or droplet data (data not shown), possibly due to delayed tissue freezing time following resection.

Example 14 - Human enteric neurons cluster into 11 subsets with distinct transcriptional programs

[00631] The 134,835 RAISINs include 831 human enteric neurons (0.6%), which clustered into 11 subsets (Fig. 22B) after correcting for putative differences in cell quality (fig. 30G-J; SOM). Notably, the neuron recovery rate in humans slightly exceeded Applicants original estimate, likely because the muscularis propria is enriched for neurons relative to the rest of the colon.

[00632] Although Applicants detect many hallmark neurotransmitters, CHAT was lowly expressed (fig. 31A), either due to actual low expression in human cells, reduced levels in the nucleus, or cancer-adjacent effects. Applicants do detect the SLC5A7 (fig. 31A), a transporter that mediates choline uptake into cholinergic neurons (48), which is co-expressed with Chat in mouse neurons. Applicants therefore used SLC5A7 as a surrogate marker for CHAT in human neurons. Interestingly, Applicants observed broad, albeit low, levels of expression of tryptophan hydroxylase 2 (TPH2; required for serotonin biosynthesis) across almost all human neuron subsets (fig. 31B), but not in mouse neurons (data not shown), suggesting differences in serotonergic signaling between the two species.

Example 15 - Human ENS contains sensory, motor, interneuron, and secretomotor/vasodilator subsets that share core transcriptional programs with mouse

[00633] Applicants used a classification-based approach (SOM) to map the 11 subsets of human neurons onto the 24 mouse subsets (Fig. 22C), leveraging the larger number of cells and deeper sequencing data in mouse to annotate the human cells. Applicants identified 2 PEMN subsets, 5 PIMN subsets, 1 PSN subset, 2 PIN subsets, and 2 PSVN subsets (Fig. 22B) and confirmed these annotations with known markers (fig. 3lA,B). Despite representing distinct regions of the colon (i.e. full colon vs. muscularis propria), both species contained similar neuron compositions, with excitatory and inhibitory motor neurons being the most abundant classes (Fig. 22C). However, sensory neurons were more abundant and more diverse in mouse. This may be due to removal of the human submucosa: humans contained only one sensory subset, whereas mice contained four (although Applicants cannot entirely rule out the possibility that the different number of profiled neurons may contribute to this difference as well). Furthermore, while the fraction of secretomotor/vasodilator neurons was similar across both species, the human muscularis propria lacked the cholinergic subtype, whereas mice contained both cholinergic and non-cholinergic subsets.

[00634] Applicants leveraged the human-mouse mapping to identify conserved (core) programs (Fig. 22D; Table 23; SOM) for each of five major neuron types. For example, the core transcriptional program for excitatory motor neurons (n = 75 genes) includes acetylcholine, various receptors (e.g., GFRA2, OPRK1, HTR4), solute transporters (e.g., SLC5A7), transcription factors (e.g., CASZ1), and COLQ, which tethers acetylcholinesterase within the neuromuscular junction (49) (Fig. 22D, fig. 31B, Table 23). In addition, human PEMNs uniquely express the mechanosensitive ion channel, PIEZ02 (fig. 31B), whereas mice express Piezol (Fig. 21G). Similarly, Applicants defined core transcriptional programs for inhibitory motor neurons (n = 89 genes; e.g., VIP, NOS1, CARTPT, GFRA1, OPRD1, ETV1), sensory neurons (n = 76 genes; e.g., CALCB, NMU, NOG, SST, VIPR2), interneurons (n = 57 genes; e.g., PENK, TAC1, ADRA2A), and secretomotor/vasodilator neurons (n = 46 genes; e.g., VIP, GAL, SCGN, CALB2) (Fig. 22D; Table 23).

Example 16 - Human Interstitial Cells of Cajal (ICCs) may underlie smooth muscle relaxation

[00635] Applicants' reference map of the human muscularis propria includes 431 $KIT^{+}ANOl^{+}$ ICCs **(Fig. 22A; fig. 30A),** which are regarded as pacemaker cells that rhythmically alter the excitability of smooth muscle tissue *(50, 51).* Two major models exist for ICC function *(50):* either (1) neurons signal directly to smooth muscle, with an indirect role for ICCs (e.g., to generate motor patterns), or (2) neurons signal to ICCs, which then relay signals to smooth muscle to coordinate peristalsis.

[00636] To distinguish between these possibilities, Applicants defined a gene signature for ICCs (Fig. 22E) and mapped known ligand-receptor pairs onto neurons, ICCs, and smooth muscle cells (SOM). Although motor activity requires both excitatory (i.e. cholinergic) and inhibitory (i.e. nitrergic) signals to elicit contraction and relaxation, respectively, smooth muscle cells only expressed the receptors for acetylcholine (Fig. 22F). In contrast, the receptor for nitric oxide were expressed by ICCs (Fig. 22F), which Applicants validated in situ (Fig. 22G). As a positive control, Applicants note that nitric oxide receptors are detected in pericytes **(Fig. 22F)** *(52).* These results suggest a revised model of smooth muscle function, where enteric neurons directly activate smooth muscle contraction, but elicit smooth muscle relaxation indirectly via ICCs **(Fig. 22H).** Consistent with this hypothesis, smooth muscle-specific knockout of the B1 subunit of the nitric oxide receptor only partially reduces relaxation, whereas its global knockout nearly abolishes relaxation (53).

Example 17 - Enteric neurons interact with diverse stromal and immune cells in the colon

[00637] To systematically examine interactions between the enteric nervous system and other cell types in the human colon, Applicants analyzed profiles from the 134,835 RAISINs from the muscularis propria (above) together with 115,517 single cells from the colon mucosa *(i.e.* epithelium and lamina propria) *(54).* In total, these data include a wide range of cell types in the human colon, including 16 epithelial subsets, 26 immune subsets (myeloid and lymphoid), 7 endothelial subsets, 9 fibroblast subsets, myocytes, ICCs, adipocytes, 2 glia subsets (muscularis propria and lamina propria), and 11 neuron subsets. Applicants mapped thousands of receptor-ligand pairs onto this dataset and identified pairs of cell subsets expressing a significantly greater number of cognate receptor-ligand pairs than is expected under a null model (Fig. 221; SOM).

[00638] Broadly, neurons were enriched for interactions with other cells from the muscularis propria rather than from the mucosa, suggesting the recovery of local interactions. This approach highlighted known interactions between excitatory motor neurons and smooth muscle (13), secretomotor/vasodilator neurons and both epithelial cells (i.e. tuft and enteroendocrine) and lymphatics (2), and glia and multiple subsets of neurons (Fig. 221).

[00639] More unexpectedly, Applicants found statistically enriched interactions between neurons and diverse stromal cells, most notably adipocytes and fibroblasts (Fig. 221,J), the two largest producers of neurotrophic growth factor (NGF) outside of the ENS in the data (Tables 19-22). Potential enteric neuron signaling to adipocytes spanned neuropeptides that regulate appetite and energy metabolism (CGRP/CALCRL, NPY/NPYR1) (55, ***56),*** and two neurotransmitters (glutamate/GRM8, GABA/GABRE) **(Fig. 22J).** Adipocytes reciprocally signal to neurons via the leptin pathway, with all neuron subsets expressing the leptin receptor (LEPR) **(Fig. 22J).** In addition, inferred neuron signaling to fibroblasts included neuropeptides (PACAP/VIP/VIPR2) **(Fig. 22J),** neurotransmitters (glutamate/GRIA4, nitric oxide/GUCYlA3), growth factors (FGF1/FGFR1, PDGF/PDGFRB), guidance cues (SLIT2/ROB01, SLIT3/R0B02), and IL15/IL15R **(Fig. 22J).**

[00640] Even if cell subsets are not enriched for interactions, they may still interact through a more limited, but functionally important, receptor-ligand repertoire. Given recent reports describing neuro-immune crosstalk (1), Applicants searched for specific examples of interactions between neurons and immune cells (Fig. 22J). Applicants identified potential neuron signaling to (1) T cells via IL7/IL7R, IL12A/IL12RB1 (neuronal expression validated in situ, Fig. 22K,L), and PENK/OPRM1, (2) dendritic cells via CHAT/CHRNE, and (3) B cells via TPH2/HTR3A (Fig. 22J). Both IL-7 and IL-12 have key roles in lymphocyte and ILC survival and Thl polarization (57), suggesting key pathways by which enteric neurons may regulate adaptive immunity. Finally, human PSNls express NMU, which activates ILC2s (9); however, Applicants did not detect expression of the NMU receptor gene in the ILCs.

Example 18 - Human enteric neurons express risk genes for enteric neuropathies, intestinal inflammatory disorders, and extra-intestinal disorders with GI dysmotility

[00641] To interrogate potential contributions of the ENS to human diseases, Applicants examined whether enteric neurons expressed any genes associated with diseases with varying

degrees of known ENS involvement. These ranged from Hirschsprung's disease (HSCR), a primary enteroneuropathy that directly affects the ENS to autism spectrum disorder (ASD) and to Parkinson's disease (PD), which are extra-intestinal CNS disorders that are associated with dysfunctions in gut motility that occur early in disease progression (58-60). In addition, because the ENS is thought to play a pivotal role in inflammation - for example, through the activation of ILCs (9) - Applicants also examined whether IBD-associated genes are expressed by enteric neurons.

[00642] Mapping a curated list of 185 disease-associated genes (SOM) onto cell subsets from the muscularis propria, lamina propria, and epithelium (above), Applicants identified many genes that were specifically enriched in enteric neurons (Fig. 23A). For example, even though it is a neurodevelopmental disorder, Applicants mapped most HSCR-associated genes onto adult enteric neurons, including RET, PHOX2B, GFRA1, ZEB2, and ECE1 (Fig. 23A). The two exceptions, EDN3 and EDNRB, mediate endothelin signaling in the embryonic neural crest (61). Although most IBD risk genes localize to epithelial and immune cells, a subset of genes were most highly expressed in neurons, including GRP, BTBD8, KSR1, NDFIP1, and REV3L (Fig. 23B). In particular, GRP products stimulate GI hormone release, muscle contraction, and epithelial cell proliferation (62). Another such gene, REV3L, is also perturbed in the craniofacial neurologic disorder Mobius syndrome (63). Indeed, increased expression of many neuropeptides (e.g., tachykinin and galanin) has been reported in IBD patients (64).

[00643] The risk genes for CNS diseases with concomitant GI dysfunction predominantly mapped to enteric neurons, with exceptions in ASD and PD (e.g., P2RX5 and IL1R2 in B cells and epithelial cells, respectively) (Fig. 23C). CNS disease risk genes that mapped specifically to enteric neurons include: (1) ANK2, DSCAM, and NRXN1 for ASD, and (2) DLG2, SCNA and SCN3A for PD (Fig. 23C). Expression of these risk genes specifically by enteric neurons, compared with a colon reference map, motivate further investigation of the role that enteric neurons play in the development and progression of dysmotility in intra- and extra- intestinal disorders. Applicants also show the disease risk genes for schizophrenia are expressed in neurons (FIG. 32).

Example 19 - Discussion

[00644] Here, Applicants constructed reference maps of the colon enteric nervous system of adult mice and humans at single cell resolution, revealing the broad capacity of neurons to orchestrate tissue homeostasis. Isolating individual enteric neurons from adult animals for transcriptional profiling has not been previously possible due to technical limitations, and recent efforts using whole-cell dissociations have been limited to embryonic or post-natal animals (21, 22). The development of RAISIN and INNER Cell RNA-seq, which preserve ribosome-attached RNA on intact nuclei, allowed Applicants to profile 2,447 mouse and 831 human enteric neurons, along with other diverse cell types from both species (e.g., epithelial, stromal, and immune cells). These methods can be applied to both fresh and frozen tissue specimens, opening the way to characterizing the ENS and a range of archived frozen tissue samples. Additionally, preservation of the ER on nuclei may allow for the enrichment of nuclei with antibodies targeting specific membrane proteins, which are synthesized in the ER.

[00645] Applicants identified all major classes of enteric neurons, spanning 24 mouse subsets and 11 human subsets, including motor, sensory, secretomotor/vasodilator and interneuron types. Mining their expression signatures allowed Applicants to infer signaling among neurons and between neurons and non-neuronal cells, such as adipocytes, ICCs, immune cells, and epithelial cells. Applicants show circadian regulation of the ENS, including core clock genes, motivating further investigation into temporal variation of ENS function, nutrient absorption, and metabolism (65). Applicants also show differences in neuron composition across the mouse colon (e.g., sensory neurons enriched in the proximal colon) suggesting that ENS function varies along the length of the GI tract. Comparison of mouse and human neurons allowed Applicants to derive core transcriptional signatures for subsets across species, highlighting biological processes that can be modeled in mouse; for example, sensory neurons in both species express Noggin a gene known to support the epithelial stem cell niche (40). Taken together, these data enable the generation of testable hypothesis and experimental dissection of ENS function.

[00646] Finally, given the extensive neuro-immune signaling Applicants observe in the mouse and human ENS, Applicants propose that neuronal dysfunction can lead to immune dysregulation, which can exacerbate inflammation and related pathologies. For example, several IBD risk genes are expressed in neurons, raising the need to further characterize the role of enteric neurons in

intestinal inflammation. Intriguingly, dozens of risk genes for early-life and late-onset CNS disorders with concomitant gut dysmotility are highly expressed by enteric neurons suggesting a mechanism for gut motility dysfunction in these diseases, and that profiling the much more accessible ENS may allow Applicants to study human disease biology. Furthermore, recent associations between the gut microbiota and extra-intestinal diseases, such as autoimmune disorders (reviewed in (66) and cancers and cancer therapies (reviewed in (67), suggest that immune modulation in the gut can have systemic effects. Proper immune function is thought to be necessary for CNS maintenance and repair, with immune dysregulation contributing to neurodegenerative disease (reviewed in (68). Thus, the ENS may be a central conduit linking the gut, the immune system and the brain, and neurological dysfunction in the gut may exacerbate diseases of the CNS.

Example 20 - ENS Materials and Methods

[00647] Human donors and tissue samples. All colon resection samples were obtained from colon cancer patients after informed consent at either the Dana Farber Cancer Institute, Boston (IRB 03-189; ORSP 3490) or Massachusetts General Hospital, Boston (IRB 02-240; ORSP 1702). Metadata for the samples are provided in Tables 19-22. Normal colon located proximal to tumor was placed into conical tubes containing Roswell Park Memorial Institute (RPMI) media supplemented with 2% human serum and placed on ice for transport to the Broad Institute, Boston. ETpon arrival, the muscularis propria was dissected from the remainder of the tissue (e.g., submucosa), divided into pieces (approximately 20-120 mg), which were placed into cryo-vials, frozen on dry-ice and stored at -80°C. When possible, a portion of the tissue was fixed overnight in 4% paraformaldehyde at 4°C for histology.

[00648] Mouse models. All animal work was performed under the guidelines of the Division of Comparative Medicine, in accordance with the Institutional Animal Care and ETse Committees (IACETC) relevant guidelines at the Broad Institute and MIT, and consistent with the Guide for Care and ETse of Laboratory Animals, National Research Council, 1996 (institutional animal welfare assurance no. A471 1-01), with protocol 0122-10-16. Mice were housed under specific-pathogen-free (SPF) conditions at the Broad Institute vivarium. The following strains were used:

Table 9.

Strain	Jackson Laboratory (Bar Harbor, ME) catalog number	Reference
C57BL/6J	000664	
B6;CBA-Tg(Sox10-cre)1Wdr/J	025807	(*102*)
129S4.Cg-E2f1Tg(Wnt1-cre)2Sor/J	022137	(*103*)
B6;129-Gt(ROSA)26Sortm5(CAG-Sun1/sfGFP)Nat/J	021039	(*69*)
Tg(Uchl1-HIST2H2BE/mCherry/EGFP*)FSout/J	016981	(*70*)

[00649] Tissue collection for snRNA-seq. For snRNA-seq optimization, tissue was collected from 11-14 week animals. For the ENS atlas, tissue was collected from 11-14 week old and 50-52 week old mice at either 7-8am or 7-8pm. Each colon was isolated and rinsed in ice cold PBS. Next, the colon was opened longitudinally and separated into four equally-sized sections, which were frozen in a 1.5 mL tube on dry ice. For brain collection, the brain was removed, quartered and frozen in a 1.5 mL tube on dry ice. Frozen tissue was stored at -80°C until subsequent tissue processing.

[00650] Tissue collection and preparation for RNA fluorescence in situ hybridization and immunohistochemistry. For RNA fluorescence in situ hybridization (RNA FISH) and Immunohistochemistry (IHC), isolated colon was cut into four sections of equal size and processed as described (71). Briefly, tissue was fixed in 4% paraformaldehyde overnight at 4°C. Then, tissue was sequentially passed through PBS containing 7.5%, 15% and 30% (w/v) sucrose at 4°C. Tissue was then embedded in O.C.T. (23-730-571, Fisher Scientific, Hampton, NH) and stored at -80°C. Tissue was cut at 25 micron thick sections onto Superfrost Plus microscope slides (22-037-246, Fisher Scientific) using a Leica CM1950 Cryostat (Leica Biosystems Inc., Buffalo Grove, IL).

[00651] Immunofluorescence (IF). Slides with tissue sections were washed three times in PBS for 10 minutes, blocked 1 hour in CAS-Block Histochemical Reagent (00-8120, Thermo Fisher Scientific), incubated with primary antibodies overnight at 4°C, washed three times in PBS for 10 minutes, and then incubated with secondary antibodies at for 1 hour at room temperature. Slides were then washed twice in PBS for 10 minutes and then for 10 minutes with a PBS containing DAPI (D9542, Sigma-Aldrich). Lastly, slides were mounted using Southern Biotech Fluoromount-G (010001, VWR) and sealed. Antibodies used for IF: Rabbit anti-Tubb3 (1:1000, AB 18207,

Abeam), Chicken anti-mCherry (1:1000, AB3 56481, EMD Millipore), and Alexa Fluor 488-, 594-, and 647-conjugated secondary antibodies (Life Technologies) were used.

[00652] Single-molecule fluorescence in situ hybridization (smFISH). RNAScope Multiplex Fluorescent Kit (Advanced Cell Diagnostics) was used per manufacturer's recommendations for fresh-frozen samples with the following alterations. All Wash Buffer times were increased to 5 minutes and, following final HRP-Block step, slides were washed for 10 minutes with PBS containing DAPI (Sigma-Aldrich) followed by mounting with Southern Biotech Fluoromount-G (VWR) and sealed. Probes used for smISH (Advanced Cell Diagnostics): Calca (417961), Caleb (42551 1), Cck (402271), Chat (40873 1-C2), Grp (317861-C2), Nmu (446831), Nog (467391), Nosl (43765 1-C3), Piezol (50051 1), Piezo2 (400191-C3), Sst (40463 1-C3), ANOl (349021-C2), CHAT (450671 and 450671-C2), GUCY1A3 (425831), IL7 (424251), IL12A (402061), KIT (606401-C3), and NOS1 (506551-C2) were used.

[00653] Combined smFISH and IF. smFISH was performed as described above, with the following changes. After the final HRP-Block step, tissue sections were incubated with primary antibodies overnight at 4°C, washed in TBST for 5 minutes, twice, and then incubated with secondary antibodies for 30 min at room temperature. Slides were then washed in TBST for 5 minutes, twice, followed by a 10 minutes wash with containing DAPI (Sigma-Aldrich) before mounting with Southern Biotech Fluoromount-G (VWR) and sealed.

[00654] Confocal microscopy and image analysis. Images were taken using a Nikon TI-E microscope with a Yokohama W l spinning disk, 405/488/561/640 lasers, and a Plan Apo 60X/1.4 objective. Images were visualized and overlaid using FIJI (72-75). The Bio-Formats plugin (76) was used to import all images.

[00655] **Nuclei Extractions.** The following nuclei extractions were performed from either mouse colon or brain and subsequently processed for profiling:

[00656] ***Dounce homogenization:*** Nuclei were extracted using either dounce homogenization followed by sucrose gradient centrifugation as described (77), or using the Nuclei EZ Prep (NUC101-1KT, Sigma-Aldrich) as described (78), with the following modifications. The tissues were dounce homogenized with a 7 mL Dounce Tissue Grinder (VWR 22877-280) (20 times pestle A, 20 times pestle B) and buffer volumes were increased to 5 mL for homogenization.

[00657] ***Tissue grinding:*** Fresh-Frozen tissues were crushed into a fine powder with a mortar and pestle (89038-144 and 89038-160, VWR) over a bath of liquid nitrogen. The powder was briefly resuspended in 2 mL of liquid nitrogen for transfer to a 50 mL conical tube, where liquid nitrogen was allowed to evaporate. The tissue powder was resuspended in 5 mL of Nuclei EZ Prep reagent (NUC101-1KT, Sigma-Aldrich) or NST (NP-40, Salts and Tris; see Tables 11 and 12) and transferred to a 7 mL Dounce Tissue Grinder. For the Nuclei EZ Prep kit, all subsequent steps were as described (78). For NST, the tissue was dounce homogenized with a 7 mL Dounce Tissue Grinder (VWR 22877-280) (20 times pestle A, 20 times pestle B), filtered through a 40 pm strainer (Falcon), and flow-through was spun at 500g for 5 minutes at 4°C. The pellet was resuspended in 0.5-3 mL of ST (Salts: 146 mM NaCl, 1 mM CaCl2, 2 1 mM MgCl2; Tris; see Tables 11 and 12).

[00658] ***Chopping extraction:*** Fresh-frozen tissues were disaggregated in 1 mL of custom nuclear extraction buffer (see Tables 11 and 12 for all combinations used) with mild chopping by Tungsten Carbide Straight 11.5 cm Fine Scissors (14558-1 1, Fine Science Tools, Foster City, CA) for 10 minutes on ice. Large debris were removed with a 40 pm strainer (Falcon). An additional 1 mL of buffer was used to wash the filter before proceeding to fluorescence-activated cell sorting (FACS). For droplet-based RNA-Seq, nuclei were isolated as described above, but with the addition of 3 ml of ST (Salts and Tris; Tables 11 and 12) to extracted nuclei. Nuclei were then pelleted at 500g for 5 mins at 4°C. Supernatant was discarded and the nuclei pellet was resuspended in 100-500 pL of ST buffer (Salts and Tris; Tables 11 and 12) before filtering through a 40 pm strainer-capped round bottom tube (Falcon).

[00659] **Fluorescence-activated cell sorting (FACS).** Prior to sorting, isolated nuclei and RAISINs were stained with Vybrant DyeCycle Ruby Stain (V-10309, Thermo Fisher Scientific). Sorting was performed on a MoFlo Astrios EQ Cell Sorter (Beckman Coulter) using 488nm (GFP, 513/26 filter) or 56lnm (mCherry 614/20 filter), and 640nm (Vybrant DyeCycle Ruby, 671/30 filter) lasers. Single nuclei were sorted into the wells of a 96-well PCR plate containing 5 pl of TCL buffer (1031576, Qiagen) with 1% β-mercaptoethanol. The 96 well plate was sealed tightly with a Microseal F and centrifuged at 800g for 3 minutes before being frozen on dry ice. Frozen plates were stored at -80°C until whole-transcriptome amplification, library construction, sequencing, and processing.

[00660] Whole-transcriptome amplification, library construction, sequencing, and processing. Libraries from isolated single nuclei and RAISINs were generated using SMART-seq2 as described (79), with the following modifications. RNA from individual wells was first purified with Agencourt RNAClean XP beads (A63987, Beckman Coulter) prior to oligo-dT primed reverse transcription with Maxima reverse transcriptase (EP0753, Thermo Fisher Scientific) and locked TSO oligonucleotide, which was followed by 21 cycles of PCR amplification using KAPA HiFi HotStart ReadyMix (NC0295239, KAPA Biosystems). cDNA was purified twice using Agencourt AMPure XP beads (A63881, Beckman Coulter) as described (79). The Nextera XT Library Prep kit (FC-131-1096, Illumina, San Diego, CA) with custom barcode adapters (sequences available upon request) was used for library preparation. Libraries from 384 wells (nuclei/RAISINs) with unique barcodes were combined and sequenced using a NextSeq 500 sequencer (FC-404-2005, Illumina).

[00661] Droplet-based RAISIN RNA-seq. Single RAISINs were processed through the GemCode Single Cell Platform using the GemCode Gel Bead kit (v2 chemistry), Chip and Library Kits (10X Genomics, Pleasanton, CA), following the manufacturer's protocol. RAISINs were resuspended in ST buffer (Salt and Tris; Tables 11 and 12). An input of 7,000 RAISINs was added to each channel of a chip. The RAISINs were then partitioned into Gel Beads in Emulsion (GEMs) in the GemCode instrument, where lysis and barcoded reverse transcription of RNA occurred, followed by amplification, shearing and 5' adaptor and sample index attachment. Libraries were sequenced on an Illumina NextSeq 500.

[00662] Transmission electron microscopy (TEM). Extracted nuclei and RAISINs were pelleted and fixed at 4°C overnight in 2.5% Glutaraldehyde and 2% Paraformaldehyde in 0.1 M sodium cacodylate buffer (pH 7.4). The pellet was then washed in 0.1M cacodylate buffer, and post-fixed with 1% Osmiumtetroxide (Os04) and 1.5% Potassiumferrocyanide (KFeCN6) for 1 hour. Next, the pellet was washed in water 3 times and incubated in 1% aqueous uranyl acetate for 1 hour followed by 2 washes in water and subsequent dehydration in grades of alcohol (10 minutes each; 50%, 70%, 90%, 100%, and 100%). The pellet was then put in propyleneoxide for 1 hour and infiltrated overnight in a 1:1 mixture of propyleneoxide and TAAB Epon (Marivac Canada Inc. St. Laurent, Canada). The following day the samples were embedded in TAAB Epon and polymerized at 60oC for 48 hours.

[00663] Ultrathin sections (about 60nm) were cut on a Reichert Ultracut-S microtome, picked up on to copper grids stained with lead citrate and examined in a JEOL 1200EX Transmission electron microscope and images were recorded with an AMT 2k CCD camera.

[00664] **Processing FASTQ reads into gene expression matrices.** For SMART-seq2, FASTQ files were demultiplexed and aligned to a reference transcriptome (see "Mouse and human reference transcriptomes"), and transcripts were quantified using RSEM, as previously described (80). For droplet-based scRNA-Seq, Cell Ranger v2.0 was used to demultiplex the FASTQ reads, align them to a reference transcriptome, and extract their "cell" and "ΕΓΜΙ" barcodes. The output of each pipeline is a digital gene expression (DGE) matrix for each sample, which records the number of transcripts or EIMIs for each gene that are associated with each cell barcode. DGE matrices were filtered to remove low quality cells, defined as cells with fewer than 500 detected genes. This cutoff was set to remove contaminating cells, while retaining neurons and glia, which typically have high numbers of detected genes. To account for differences in sequencing depth across cells, DGE counts were normalized by the total number of transcripts or EIMIs per cell and converted to transcripts-per-l 0,000 (henceforth "TP10K").

[00665] **Mouse and human reference transcriptomes.** For the optimization of nuclei extraction conditions, reads were aligned to the mm 10 reference transcriptome. However, for the mouse and human ENS atlases, Applicants augmented the reference transcriptomes with introns, thus allowing pre-mRNAs to be mapped along with mature mRNAs. Both the mm 10 and hgl9 reference transcriptomes were modified according to the instructions provided by the 10X Genomics website (support.lOxgenomics.com/single-cell-gene-expression/software/pipelines/latest/advanced/references). Briefly, Applicants converted the standard GTF files into pre-mRNA GTF files by changing all "transcript" feature tags to "exon" feature tags. Elsing these modified GTF files, Applicants then constructed Cell Ranger compatible references using the Cell Ranger "mkref ' command. These modified GTF files were used for both the Cell Ranger pipeline and for the SMART-seq2 data (i.e. mouse ENS atlas).

[00666] **Cell clustering overview.** To cluster single cells into distinct cell subsets, Applicants followed the general procedure Applicants have previously outlined in (81) with additional modifications. This workflow includes the following steps: the selection of variable genes, batch correction, dimensionality reduction by PCA, and clustering. In all cases, clustering was performed

twice: first, to separate neurons and glia from other cells, and then, to sub-cluster the neurons and glia to obtain high-resolution clusters within each group.

[00667] Partitioning cells into neuron, glia, and "other" compartments. Cells were partitioned into neuron, glia, and non-ENS compartments based on their expression of known marker genes (see "Gene signatures"). Signature scores were calculated as the mean log2(TPlOK+l) across all genes in the signature. Each cluster was assigned to the compartment of its maximal score and all cluster assignments were inspected to ensure the accurate segregation of cells. Neurons and glia were then assembled into two separate DGE matrices for further analysis.

[00668] Variable gene selection. To identify variable genes within a sample, Applicants first calculated the mean (μ) and the coefficient of variation (CV) of expression of each gene. Genes were then grouped into 20 equal-frequency bins (ventiles) according to their mean expression levels. LOESS regression was used to fit the relationship, log(CV) ~ log(p), and the 1,500 genes with the highest residuals were evenly sampled across these expression bins. To extend this approach to multiple samples, Applicants performed variable gene selection separately for each sample to prevent "batch" differences between samples from unduly impacting the variable gene set. A consensus list of 1,500 variable genes was then formed by selecting the genes with the greatest recovery rates across samples, with ties broken by random sampling. This consensus gene set was then pruned through the removal of all ribosomal, mitochondrial, immunoglobulin, and ELLA genes, which were found to induce unwanted batch effects in some samples in downstream clustering steps.

[00669] Batch correction. Applicants observed substantial variability between cells that had been obtained from different mice or different individuals, which likely reflects a combination of technical and biological differences. In some cases, these "batch effects" led to cells clustering first by mouse or individual, rather than by cell type or cell state. To control for these batch differences, Applicants ran ComBat (Johnson et al., 2007) with default parameters on the log2(TPlOK+l) expression matrix, allowing cells to be clustered by cell type or cell state. Importantly, these batch-corrected data were only used for the PCA and other steps relying on PCA (e.g. clustering, t-SNE visualization); all other analyses (e.g. differential expression analysis) were based on the original expression data. Note that Applicants tested two additional methods for batch correction - one based on Canonical Correlation Analysis (82) and another on a k-nearest

neighbors (k-NN) approach (79) - but did not obtain any enhancement in performance (data not shown).

[00670] Dimensionality reduction, graph clustering, and t-SNE visualization. Cells were clustered at two stages of the analysis: first, to initially partition the cells into neuron, glia, and "other" compartments, and second, to sub-cluster neurons and glia into different subsets. In all cases, Applicants ran low-rank PCA on the variable genes of the batch-corrected log2(TPlOK+l) expression matrix. Applicants then applied Phenograph (Levine et al., 2015) to the k-NN graph defined using the first n PCs and k nearest neighbors, which were separately estimated for each dataset. First, to estimate n, Applicants calculated the number of "significant" PCs using a permutation test. Because this test may underestimate the number of PCs, Applicants conservatively increased this number (i.e. to 15 or 30; see Table 10 below) to ensure that most of the variability in the dataset was captured. Next, to estimate k, Applicants considered a range of clustering solutions with varying values of k, and calculated the marker genes for each set of clusters. Applicants selected k based on inspection of the data. When clustering data from multiple cell types, Applicants tried to select k such that the major cell types (e.g. neurons, glia, and muscle) were split, without fragmenting them into several sub-clusters. When clustering neurons and glia, Applicants tried to select a k yielding the highest granularity clusters that were still biologically distinct, determined by close examination of the marker gene lists. Finally, the Barnes-Hut t-Distributed Stochastic Neighbor Embedding (t-SNE) algorithm was run on the selected PCs with perplexity = 20 and for 10,000 iterations to produce two-dimensional embeddings of the data for visualization.

Table 10.

Dataset	Cell type	# Sig PCs	Used PCs	*k*-NN
Optimization	All cells	13	1 to 15	250 (separates neurons and glia)
Mouse atlas	All cells	16	1 to 30	250 (separates neurons and glia)
Mouse atlas	Neurons	15	1 to 30	25
Mouse atlas	Glia	7	1 to 15	250

Mouse droplet	All cells	19	1 to 30	100 (separates major cell types)
Human atlas	All cells	20	2 to 30*	100 (separates major cell types)
Human atlas	Neurons	9	1 to 15	25
Human atlas	Glia	8	1 to 15	100

* See "Clustering of human neurons".

[00671] Clustering of human neurons. Initial clustering of the 831 human neurons revealed 15 subsets (fig. 30H). However, in several cases, Applicants noticed that a single neuron type had been split into two clusters based on the expression of oxidative phosphorylation genes, which were strongly enriched in PC1 (fig. 301,J). This could reflect differences in differentiating vs. mature neurons (79), cancer-proximal effects, or a rapid transcriptional response to tissue resection or handling. Applicants therefore re-clustered the cells based on the other PCs (i.e. PCs 2 to 30), yielding 11 final subsets of human neurons (fig. 30C,G).

[00672] Scoring nuclei extraction conditions. To identify optimal conditions for snRNA-seq of the ENS, Applicants performed nuclei extractions while systematically varying the detergent (CHAPS, Digitonin, EZ, NP40, Tween), buffer (HEPES, Tricine, Tris), mechanical extraction conditions (Dounce, Grind, Chop), and additional modifiers (e.g. polyamines, RNAse inhibitors) (Tables 11 and 12). In total, 104 different extraction conditions were examined. For each extraction, Applicants profiled single nuclei transcriptomes by SMART-Seq2 and clustered the resulting RNA into neurons, glia, and "other" (i.e. non-ENS or low quality) clusters (see "Cell clustering overview"). To compare extractions, Applicants calculated several quality metrics for each condition: (1) the proportion of recovered neurons, glia, and "other" cells, (2) the mean number of detected genes per cell, and (3) the mean ENS signature score (derived from markers of neurons and glia; see "Cell type signatures"). Conditions that yielded high-quality nuclei enriched in the ENS signature score were then identified.

[00673] Cell lineage dendrogram. As an auxiliary tool, cell subsets were organized on a dendrogram according to their transcriptional similarities (Fig. 21B, top). To construct this tree,

Applicants performed complete linkage clustering on the distance matrix corresponding to the mean transcriptional distances among all cell subsets, calculated using the variable genes from the log2(TPlOK+l) expression matrix. These calculations were performed using the “hclust” and “dist” functions in R with default parameters.

[00674] **Enteric neuron annotation and classification.** Applicants employed the following markers and considerations in annotating enteric neurons subsets post hoc.

Broad segmentation of the mouse ENS

[00675] Broadly, neurons segmented into two major divisions comprising either cholinergic or nitrergic subsets. This broad division was correlated with several other genes. For example, the glial cell line-derived neurotrophic factor (GDNF) family receptors a1 (Gfiral) and a2 (Gfra2) segregate Nosl and Chat expressing neurons, respectively. Gfral/2 are co-receptors for the GDNF receptor, Ret, which is necessary for ENS formation (83,84). Similar, Chat and Nosl expressing subsets also differentially expressed the transcription factors (TFs), Caszl and Etvl.

Annotating mouse excitatory motor neurons

[00676] Applicants annotated 6 subsets of putative excitatory motor neurons (PEMNs) based on co-expression of Chat and Tael (85) and position within the dendrogram on one subtree (Fig. 21B). Subsets of PEMNs express the endogenous opioid, enkephalin (Penk), which is found in motor neurons (85), and/or the myenteric motor neuron marker, calretinin (Calb2) (86).

Annotating mouse inhibitory motor neurons

[00677] Applicants annotated 7 subsets of putative inhibitory motor neurons (PIMNs), which have high Nosl and Vip co-expression (87,88), and occupy one subtree of the dendrogram (Fig. 21B). In total, 73% of Vip-positive neurons co-express Nosl, which is consistent with the previously reported estimate of 75% (87,88). In addition, PIMN 6 and 7 have significant expression of somatostatin receptor 2 (Sstr2), which plays an important role in cauded relaxation, as blocking Sstr2 nearly abolishes muscle relaxation (87).

Annotating mouse interneurons

[00678] Enteric interneurons (INs) relay sensory information and coordinate excitatory and inhibitory motor neuron activity, but their classification is unclear. Six potential subtypes have been previously reported: (1) descending INs that signal via Chat, 5HT and ATP, (2) descending Nosl+Vip+Grp+Chat- INs, (3) descending Vip+Chat+Nosl+ INs with ATP signaling, (4)

descending Chat+Sst+ INs, (5) descending Penk+ INs (responsive to Sst), and (6) ascending Chat+Penk+ INs with ATP signaling (87, 89-91).

[00679] Some of these subsets (3, 5, 6) are at least partly matched as discrete clusters in the data, whereas others (1, 2, 4) are not clearly observed in the atlas. PIMN7 is a potential candidate for the descending Vip+Chat+Nosl+ INs with ATP signaling (3 above), based on co-expression of Vip, Chat, Nosl, and various ATP transporters (e.g. SLC28al, Slc28a2, Slc28a3, Slc29al, Slc29a2, Slc29a3, Slc29a4; (85). PSN3 also express these genes, but their expression of Cck, Calca, and Caleb makes it unlikely they are interneurons. Three subsets of Chat+Penk+ putative INs (PIN1-3) may reflect either descending Penk+ INs (5 above; responsive to Sst), or ascending Chat+Penk+ INs with ATP signaling (6 above). Because all express combinations of Sst receptors, they may be descending INs. However, given the substantial number of additional receptors expressed by all of these PINs (for 5HT, VIP, GAL, GLP, prolactin, prostaglandin E2, EGF and BMP) or some of them (e.g., catecholamine synthetic enzymes), they may not be INs. Finally, there was little to no evidence for other IN subtypes: Applicants did not detect any serotonergic (5HT) neurons (1 above) in the sampling, consistent with previous observations (88); found no discernible cluster of Nosl+Vip+Grp+Chat- cells; and the only Chat+Sst+ neurons Applicants observed were the Calcb+ PSN4 subset, which Applicants interpret as a sensory neuron, not INs.

Annotating mouse secretomotor and vasodilator neurons

[00680] Applicants annotated two subsets of Glp2r+ putative secretomotor/vasodilator (PSVNs) in one subtree of the dendrogram (Fig. 21B), one Vip+ non-cholinergic subtype (PSVN1) and one Chat+ cholinergic subset (PSVN2). The PSVN2 subset expresses Gal, previously reported in neurons that innervate the epithelium and arterioles (92) and neuropeptide Y expressed in a secretomotor neurons (90). Also, some neurons in PSVN2 expresses glutamate decarboxylase 2 (Gad2), possibly forming cholinergic/GABAergic neurons.

Annotating human interneuron subtype 2

[00681] Human PIN2s express two specific markers of mouse sensory neurons, CALCB and GRP, suggesting they may be misannotated sensory neurons. Another possibility is that PIN2s correspond to multiple neuron subtypes, which cannot be resolved with the number of neurons Applicants profiled. Consistent with this possibility, PENK and CALCB expression are mutually exclusive within this subset (3 of 34 co-positive cells; expected = 7.24; Fisher test, $p < 0.001$).

[00682] **Differential expression analysis.** Differential expression (DE) tests were performed using MAST (Finak et al., 2015), which fits a hurdle model to the expression of each gene, consisting of logistic regression for the zero process (i.e. whether the gene is expressed) and linear regression for the continuous process (i.e. the expression level). For the mouse atlas, this regression model included terms to capture the effects of the cell subset, age, sex, colon location, circadian phase, transgenic model, and cell complexity. For the human atlas, this regression model only included terms for cell subset and cell complexity.

[00683] For the mouse atlas, Applicants used the regression formula, Yi ~ X + A + C + L + S + T + N, where Yi is the standardized log2(TPlOK+l) expression vector for gene i across cells, X is a variable reflecting cell subset membership (e.g. PSNs vs. non-PSNs), A is the age associated with each cell (adult vs. aged), C is the circadian phase for each cell (morning vs. evening), L is the location for each cell (segments 1-4), S is the sex for each cell (male vs. female), T is the transgenic model for each cell (SoxlO vs. Uchll), and N is the standardized number of genes for each cell (i.e. cell complexity). For the human atlas, Applicants used the regression formula, Yi ~ X + N, with X and N defined as above.

[00684] Additionally, two heuristics were used to increase the speed of the tests: Applicants required all tested genes to have a minimum fold change of 1.2 and to be expressed by at least 1% of the cells within the group of interest. In all cases, the discrete and continuous coefficients of the model were retrieved and p-values were calculated using the likelihood ratio test in MAST. Q-values were separately estimated for each cell subset comparison using the Benjamini-Hochberg correction. Unless otherwise indicated, all reported DE coefficients and q-values correspond to the discrete component of the model (i.e. the logistic regression).

[00685] **Acquisition and scoring of gene signatures.** Applicants compiled the following lists of marker genes for enteric neurons and glia from the literature (93). These gene signatures were then combined to construct an overall "ENS" signature score (Fig. 20C and fig. 25).

[00686] Neurons: Tubb3, Elavl4, Ret, Phox2b, Chrnb4, Eml5, Smpd3, Tagln3, Snap25, Gpr22, Gdaplll, Stmn3, Chrna3, Scg3, Syt4, Ncan, Crmpl, Adcyaplrl, Elavl3, Dlg2, Cacna2d.

[00687] Glia: Erbb3, SoxlO, Fabp7, Plpl, Gas7, Nidl, Qk, Sparc, Mest, Nfia, Wwtrl, Gpm6b, Rasa3, Flrtl, Itpripll, Itga4, Lama4, Postn, Ptprzl, Pdpn, Coll8al, Nrcam.

[00688] To prevent highly expressed genes from dominating a gene signature score, Applicants scaled each gene vector of the log2(TPlOK+l) expression matrix by its root mean squared expression across all cells (using the 'scale' function in R with center = FALSE). The signature score for each cell was then computed as the mean scaled expression across all genes in the signature.

[00689] **Estimation of false discovery rate.** Unless otherwise specified, false discovery rates were estimated with the Benjamini-Hochberg correction (94), using the "p.adjust" R function with the "fdr" method.

[00690] **Matching human and mouse subsets.** To map human neurons onto their mouse counterparts, Applicants first trained a Random Forest classifier to distinguish the each of 24 subsets of mouse neurons (i.e., PEMN, PIMN, PIN, PSN, PSVN) using the log2(TPlOK+l) expression matrix of the mouse variable genes that also had human orthologs (see "Variable gene selection"). The Random Forest model was built with the R "randomForest" package using default parameters with the following exception: to account for class imbalances, Applicants down-sampled each neuron class to the minimum class size while constructing each tree (implemented using the "sampsize" argument). In total, the "out of bag" estimate of the error rate (which estimates test rather than training error) was 8.8%, indicating that Applicants can accurately distinguish among major neuron classes. Next, to extend this model to humans, Applicants predicted the class for each human neuron using expression data for the human orthologs of the variable genes. All class assignments were then manually examined to ensure accurate predictions for all cells. Note that Applicants also tested an alternative approach using a variational autoencoder (VAE) (95), but did not observe a noticeable improvement in performance (data not shown).

[00691] **Identifying a core transcriptional program for major neuron classes.** To identify conserved transcriptional signatures for each of the 5 major neuron classes (i.e., PEMN, PIMN, PIN, PSN, PSVN), Applicants first mapped all mouse genes to their corresponding human orthologs (using only 1:1 orthologs), and combined both expression matrices according to these genes. Applicants next calculated DE orthologs within each major neuron class (see "Differential expression analysis"), then selected genes that were significantly DE in the combined dataset, the mouse dataset, and the human dataset (Table 6).

[00692] Using receptor-ligand pairs to infer cell-cell interactions. To identify cell-cell interactions, Applicants mapped the FANTOM5 database of literature-supported receptor-ligand interactions (96) onto the lists of cell subset markers. Following a recent approach (CellPhoneDB (97)), Applicants filtered this database to remove all integrins (defined using the HUGO "Integrin" gene group), which were involved in many non-specific cell-cell interactions. Applicants further required cell subset markers to be expressed in at least 5% of all cells within the subset. For all networks, Applicants quantified the interaction strength between two cell subsets as the number of unique receptors and ligands connecting them, resulting in an adjacency matrix summarizing all cell-cell interactions within the dataset. Statistical significance was then empirically assessed by permuting the receptors and ligands among all cell subsets, thus preserving the number of receptors and ligands encoded within each cell subset, and preserving the distribution of ligand-receptor connectivity (but possibly changing the connectivity between cell subsets, in those cases where one receptor has multiple ligands, or vice versa). After running 10,000 total permutations, p-values were computed as the number of times the edge strength in the permuted network was greater than or equal to the edge strength in the true network. To plot cell-cell interaction networks, Applicants applied the Fruchterman-Reingold layout algorithm to a network defined using the -logl0(p-value), using only the edges with p-value < 0.05. Although edge weights were used to generate the layout, they were removed from the final visualization for visual clarity (Fig. 221).

[00693] Defining disease risk genes. Applicants compiled lists of genes that have been implicated by human genetics or genome-wide association studies (GWAS) as contributing to risk for the following diseases: Hirschsprung's disease (HRSC), inflammatory bowel disease (IBD), autism spectrum disorders (ASDs), and Parkinson's disease (PD). Because GWAS or human genetics studies do not always pinpoint a causative risk gene, Applicants used the literature to identify sets of genes that are particularly likely to contribute to disease risk, including: 9 HRSC-associated genes (98), 106 IBD-associated genes (99), 28 ASD-associated genes (100), and 29 PD-associated genes (101).

Tables

[00694] Tables 11-12. Optimization of nuclei extractions for the enteric nervous system. Description and statistics for nuclei extractions, aggregated either by sample (Table 11) or condition (Table 12). Includes descriptions of the buffers, detergents, detergent concentrations,

salts, and modifiers profiled, along with various statistics, including exon:intron ratios, the number of genes per cell, and ENS compositions.

Table 11. Samples

Sample ID	Extraction solution	Tissue	Preparation	Buffer	Salt	Detergent	Detergent Concentration	Modifier
S1	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S2	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.05	N/A
S3	NST	Colon	chop	Tris	None	None	0	N/A
S4	NST	Colon	chop	Tricine	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S5	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	Polyamines
S6	NST	Colon	chop	Tricine	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	Polyamines
S7	NST	Colon	chop	Tricine	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S8	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S9	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.001	N/A
S10	DST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Digitonin	0.01	N/A
S11	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.006	N/A
S12	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	N/A
S13	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.03	N/A
S14	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	Sucrose
S15	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S16	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.025	N/A
S17	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.005	N/A
S18	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.003	N/A
S19	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	N/A
S20	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.00024	N/A
S21	DST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Digitonin	0.002	N/A
S22	DST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Digitonin	0.01	N/A
S23	DST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Digitonin	0.05	N/A
S24	CST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	CHAPS	0.49	N/A
S25	CST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	CHAPS	0.098	N/A
S26	CST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	CHAPS	0.0196	N/A

S27	TST	Brain	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	N/A
S28	NP40	Brain	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S29	Sigma-Aldrich EZ prep	Brain	dounce	EZ	N/A		N/A	N/A
S30	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	N/A
S31	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S32	Sigma-Aldrich EZ prep	Colon	grind	EZ		EZ	#N/A	N/A
S33	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	N/A
S34	TSH	Colon	chop	HEPES	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	N/A
S35	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	Protease inhibitor
S36	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	Translation inhibitor
S37	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	Cytoskeletal drug
S38	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	Rnase inhibitor
S39	NSH	Colon	chop	HEPES	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S40	DSH	Colon	chop	HEPES	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Digitonin	0.01	N/A
S41	DST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Digitonin	0.01	N/A
S42	NSH	Colon	chop	HEPES	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S43	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S44	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.01	N/A
S45	TSH	Colon	chop	HEPES	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	N/A
S46	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	N/A
S47	TSH	Colon	chop	HEPES	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.006	N/A
S48	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.006	N/A
S49	NSH	Colon	chop	HEPES	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.01	N/A
S50	TSH	Colon	chop	HEPES	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	N/A
S51	Sigma-Aldrich EZ prep	Colon	grind	EZ	N/A	EZ	#N/A	N/A
S52	Sigma-Aldrich EZ prep	Colon	grind	EZ	N/A	EZ	#N/A	N/A
S53	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.006	N/A
S54	CST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	CHAPS	0.49	N/A
S55	CST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	CHAPS	0.098	N/A
S56	CST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	CHAPS	0.0196	N/A

S57	CST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	CHAPS	0.49	N/A
S58	CST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	CHAPS	0.098	N/A
S59	CST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	CHAPS	0.0196	N/A
S60	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.006	N/A
S61	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.03	N/A
S62	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.03	N/A
S63	Sigma-Aldrich EZ prep	Colon	chop	EZ	N/A	EZ	N/A	N/A
S64	Sigma-Aldrich EZ prep	Colon	chop	EZ	N/A	EZ	N/A	N/A
S65	Sigma-Aldrich EZ prep	Colon	chop	EZ	N/A	EZ	N/A	N/A
S66	NST	Colon	grind	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S67	NST	Colon	grind	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S68	NSTn	Colon	chop	Tricine	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S69	NST	Colon	grind	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S70	NSTn	Colon	chop	Tricine	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	Polyamines
S71	NSTn	Colon	chop	Tricine	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S72	NSTn	Colon	chop	Tricine	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S73	NSTn	Colon	chop	Tricine	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	Polyamines
S74	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	Polyamines
S75	Sigma-Aldrich EZ prep	Colon	grind	EZ	N/A	EZ	N/A	N/A
S76	Sigma-Aldrich EZ prep	Colon	grind	EZ	N/A	EZ	N/A	N/A
S77	Sigma-Aldrich EZ prep	Colon	grind	EZ	N/A	EZ	N/A	N/A
S78	Sigma-Aldrich EZ prep	Colon	grind	EZ	N/A	EZ	N/A	N/A
S79	Sigma-Aldrich EZ prep	Brain	dounce	EZ	N/A	EZ	N/A	N/A
S80	NST	Brain	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S81	Sigma-Aldrich EZ prep	Colon	grind	EZ	N/A	EZ	N/A	N/A
S82	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S83	Sigma-Aldrich EZ prep	Colon	grind	EZ	N/A	EZ	N/A	N/A
S84	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S85	Sigma-Aldrich EZ prep	Brain	dounce	EZ	N/A	EZ	N/A	N/A
S86	NST	Brain	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A

S87	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S88	NSTn	Colon	chop	Tricine	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	Polyamines
S89	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.03	N/A
S90	CST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	CHAPS	0.49	N/A
S91	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S92	NSTn	Colon	chop	Tricine	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	Polyamines
S93	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.03	N/A
S94	CST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	CHAPS	0.49	N/A
S95	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.03	N/A
S96	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
S97	NSTn	Colon	chop	Tricine	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	Polyamines
S98	CST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	CHAPS	0.49	N/A
S99	NST	Brain	dounce	Tris	5 mM CaCl, 3 mM Mg(Ac)2	NP40	0.1	Sucrose, EDTA, PMSF, β-mercaptoethanol
S100	NST	Brain	dounce	Tris	5 mM CaCl, 3 mM Mg(Ac)2	NP40	0.1	Sucrose, EDTA, PMSF, β-mercaptoethanol
S101	NST	Colon	dounce	Tris	5 mM CaCl, 3 mM Mg(Ac)2	NP40	0.1	Sucrose, EDTA, PMSF, β-mercaptoethanol
S102	NST	Colon	dounce	Tris	5 mM CaCl, 3 mM Mg(Ac)2	NP40	0.1	Sucrose, EDTA, PMSF, β-mercaptoethanol
S103	Sigma-Aldrich EZ prep	Colon	dounce	EZ	N/A	EZ	N/A	N/A
S104	Sigma-Aldrich EZ prep	Colon	dounce	EZ	N/A	EZ	N/A	N/A

Sample ID	**GFP+ Sorted**	**%Exon (mean)**	**%Intron (mean)**	**%Intergenic (mean)**	**%Exon (SD)**	**%Intron (SD)**	**%Intergenic (SD)**	**Number of detected genes (mean)**
S1	Yes	22.21	49.22	28.55	3.01	3.38	2.65	2645.625
S2	Yes	28.59	52.87	18.52	3.36	3.65	0.89	2763.28125
S3	Yes	14.4	13.7	71.87	1.72	0.61	2.02	1119.78125
S4	Yes	11.68	18.95	69.35	2.03	1	1.77	877.5
S5	Yes	13.91	20.32	65.75	1.63	0.83	2.22	1512.451613
S6	Yes	29.8	44.55	25.63	1.44	1.9	2.25	2281.129032
S7	Yes	28.4	43.09	28.49	1.94	2.51	1.72	3326.1875
S8	Yes	18.7	43.09	38.18	1.33	1.8	1.93	2918
S9	Yes	24.04	30.97	44.97	2.38	2.23	3.52	1881.3125
S10	Yes	34.68	43.3	21.99	3.15	3.24	2.24	2438.645161
S11	Yes	30.14	44.75	25.09	2.46	2.94	2.25	2548.65625
S12	Yes	31.78	51.95	16.25	1.79	1.93	0.93	3005.4375
S13	Yes	37.21	35.71	27.06	2.07	2.63	1.9	1715
S14	Yes	27.31	54.1	18.57	2.41	3.31	1.47	2360
S15	Yes	30.67	38.43	30.89	2.29	2.97	1.8	2432.65625
S16	Yes	37	35.93	27.05	2.39	3.15	1.91	2405.1875
S17	Yes	36.05	38.79	25.15	3.01	3.82	1.83	2634.65625
S18	Yes	56.9	21.83	21.26	2.29	2.44	0.5	4703.53125
S19	Yes	56.18	26.55	17.26	2.64	2.94	0.42	4688.258065
S20	Yes	53.66	27.09	19.24	2.34	2.71	0.59	4571.53125
S21	Yes	23.38	21.85	54.76	2.78	1.37	2.29	1655.65625
S22	Yes	22.85	38.12	39.01	2.18	2.56	3.17	2107.53125

S23	Yes	17.38	15.09	67.51	3.07	1.05	3.1	1094.21875
S24	Yes	31	44.22	24.77	2.41	3.79	1.63	2403.75
S25	Yes	33.56	43.82	22.6	2.49	3	1.66	2443.6875
S26	Yes	33.47	36.61	29.91	2.91	3.31	2.4	1783.15625
S27	No	37.08	50.3	12.57	1.75	1.91	0.98	2463.375
S28	No	24	61.41	14.57	2.31	2.81	1.03	3008.09375
S29	No	28.29	55.55	16.13	1.95	2.41	2.08	3741.5
S30	No	32.53	43.75	23.7	1.93	3.17	2.51	2319.375
S31	No	33.03	40.8	26.16	2.81	3.71	3.11	1966.322581
S32	No	15.36	24.35	60.26	2.39	2.02	3.05	1691.90625
S33	Yes	32.53	44.73	22.72	1.96	3.06	2.08	2331.625
S34	Yes	27.05	50.42	22.51	1.85	2.87	2.57	2436.375
S35	Yes	27.96	52.74	19.29	0.95	2.61	2.33	2893.5
S36	Yes	37.66	24.95	37.38	2.14	1.72	2.35	1525.96875
S37	Yes	33.84	49.78	16.36	1.96	2.62	1.66	2783.90625
S38	Yes	33.6	49.77	16.62	1.68	2.31	1.5	2768.75
S39	Yes	28.47	50.31	21.21	2.51	4.02	3.19	1882.708333
S40	Yes	35.76	45.91	18.31	3.36	4.29	1.59	2179.586207
S41	Yes	31.76	45.95	22.27	3.24	3.84	1.91	2013.8
S42	Yes	32.38	46.81	20.79	3.19	4.09	1.54	1849.827586
S43	Yes	26.11	54.55	19.32	2.46	4.05	2.42	2290.37037
S44	Yes	33.48	44.98	21.52	2.96	3.51	2.34	2021.769231
S45	Yes	36.86	37.98	25.14	2.22	3.1	2.33	2113.5
S46	Yes	36.72	39.24	24.03	2.02	2.83	2.24	2379.645161
S47	Yes	40.22	42.88	16.89	2.67	3.01	1.86	2690.36
S48	Yes	36.99	38.49	24.51	2.05	3.05	2.72	2323.333333
S49	Yes	34.21	38.8	26.98	2.26	3.22	3.25	2070.714286
S50	Yes	34.25	39.19	26.55	2.28	3.32	2.09	1591.28
S51	Yes	26.79	28.05	45.13	2.52	1.49	2.76	1469.34375
S52	Yes	26.02	27.92	46.03	2.53	1.28	2.62	1271.59375
S53	Yes	35.53	48.2	16.25	1.77	2.5	1	3237.8125
S54	Yes	27.88	56.27	15.83	1.93	2.35	0.83	2907.4375
S55	Yes	30.97	50.99	18.02	1.76	2.71	2.27	2904.064516
S56	Yes	35.23	45.12	19.63	2.88	2.92	2.16	2066.9375
S57	Yes	35.38	45.25	19.34	3.11	3.64	1.83	2200.53125
S58	Yes	39.43	46.38	14.18	2.9	3.39	0.66	2724.40625
S59	Yes	40.92	42.7	16.37	3.05	3.23	1.3	2020.3125
S60	Yes	38.95	44.28	16.76	2.55	3.22	1.63	2701.21875
S61	Yes	33.71	48.2	18.06	2.76	3.66	2.28	2786.875
S62	Yes	39.35	42.48	18.15	2.55	2.69	1.36	2172.125
S63	Yes	20.77	42.13	37.08	1.22	2.22	3.19	3024.125
S64	Yes	21.71	46.17	32.1	2.08	3.12	3.56	2890.125
S65	Yes	24.58	43.76	31.64	2.09	1.7	2.87	3991.6875
S66	Yes	25.95	55.12	18.91	1.44	2.47	1.69	3034.28125
S67	Yes	28.61	56.55	14.82	1.88	2.29	0.85	3221
S68	Yes	24.25	56.78	18.96	1.59	2.1	1.27	2897.875
S69	Yes	29.39	53.74	16.85	2.4	3.04	1.46	3265.78125
S70	Yes	25.75	59.52	14.72	1.8	2.25	0.8	3713.875
S71	Yes	23.87	56.7	19.41	1.31	1.95	1.67	2693.71875
S72	Yes	26.62	54.25	19.11	1.76	2.62	1.49	3157.65625
S73	Yes	26.56	54.31	19.11	1.96	3.16	2.19	3158.59375
S74	Yes	25.51	53.14	21.32	2.36	3.01	2.3	3271.75
S75	Yes	15.99	24.84	59.08	1.7	0.85	1.52	1451.364583
S76	Yes	20.53	26.28	53.15	2.27	1	1.66	1340.3125
S77	Yes	21.29	29.59	49.07	1.44	0.71	1.34	982.46875
S78	Yes	21.85	28.46	49.62	1.66	0.73	1.46	857.59375
S79	Yes	23.46	38.71	37.82	1.04	1.3	1.5	1852.145833
S80	Yes	23.41	54.33	22.24	1.33	1.43	1.01	2627.877778
S81	Yes	20.39	40.46	39.13	1.21	1.32	1.59	2217.364583
S82	Yes	21.72	51.87	26.34	0.85	1.22	1.57	2745.864583

S83	Yes	13.31	18.52	68.15	1.54	0.94	1.5	938.7083333
S84	Yes	24.02	33.7	42.25	2.02	1.9	1.77	2147.565217
S85	Yes	26.67	58.28	15.03	1.2	1.2	0.54	3367.510417
S86	Yes	20.74	60.01	19.23	1.3	1.65	1.08	3558.75
S87	Yes	24.64	51.5	23.84	1.62	1.79	1.23	2301.6875
S88	Yes	25.9	53.52	20.55	1.61	1.97	1.23	2202.905263
S89	Yes	33.61	50.64	15.74	1.05	1.24	0.64	2864.333333
S90	Yes	29.75	47.92	22.3	1.53	1.91	1.42	2624.666667
S91	Yes	29.31	44.36	26.3	1.68	2.07	1.23	1912.197917
S92	Yes	26.43	43.98	29.56	1.23	1.84	1.55	2099.178947
S93	Yes	30.68	47.06	22.24	1.24	1.6	1.06	2216.9375
S94	Yes	31	43.77	25.21	1.37	1.83	1.08	2259.3125
S95	Yes	44.07	40.17	15.74	2.04	2.11	0.69	2087.989583
S96	Yes	34.83	41.73	23.43	2.11	2.74	0.84	1829.315789
S97	Yes	35.81	43.38	20.79	2.22	2.65	1.08	2062.78125
S98	Yes	33.3	43.76	22.92	1.79	2.43	1.11	2302.852632
S99	Yes	26.06	52.92	20.99	1.54	1.63	1.03	2472.6875
S100	Yes	26.06	52.92	20.99	1.54	1.63	1.03	2472.6875
S101	Yes	7.16	17.72	75.07	0.83	1.04	1.62	1393.115789
S102	Yes	7.16	17.72	75.07	0.83	1.04	1.62	1393.115789
S103	Yes	6.27	19.57	74.15	0.65	0.35	0.64	739.6282723
S104	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Sample ID	**Number of detected genes (SD)**	**ENS score (mean)**	**ENS score (SD)**	**%Contamination**	**%Glia**	**%Neuron**	**%Oligodendrocyte**	**Other notes**
S1	246.0692998	0.517487812	0.046710372	31.25	43.75	25	0	
S2	239.0918817	0.571013987	0.055967354	25	53.12	21.88	0	
S3	99.09030516	0.140582076	0.017994945	100	0	0	0	
S4	72.01593126	0.14157225	0.015252253	96.88	0	3.12	0	
S5	100.0461489	0.254010663	0.027300561	87.1	0	12.9	0	
S6	175.0803118	0.367383292	0.041975178	48.39	16.13	35.48	0	
S7	234.8703719	0.594395928	0.049252277	18.75	46.88	34.38	0	
S8	161.2109726	0.510735547	0.033370415	35.94	26.56	37.5	0	
S9	163.0430346	0.321009425	0.037783865	56.25	15.62	28.12	0	
S10	310.2750481	0.528793814	0.0818039	45.16	45.16	9.68	0	
S11	203.3450042	0.53162348	0.049800207	15.62	53.12	31.25	0	
S12	283.1151059	0.73283716	0.069021494	15.62	59.38	25	0	
S13	218.3253805	0.300466538	0.048395745	40.62	31.25	28.12	0	
S14	214.1698621	0.490194685	0.049812532	37.5	43.75	18.75	0	
S15	168.4015016	0.372111999	0.036967513	71.88	21.88	6.25	0	
S16	168.4543374	0.461930365	0.056740355	53.12	46.88	0	0	
S17	225.9403406	0.380320973	0.04857395	59.38	25	15.62	0	
S18	265.949482	0.38830923	0.03919231	96.88	0	3.12	0	

S19	286.9543554	0.558661729	0.056283988	83.87	12.9	3.23	0	
S20	322.5542308	0.466359257	0.04562064	84.38	9.38	6.25	0	
S21	135.1935635	0.292462761	0.030285883	50	28.12	21.88	0	
S22	143.7087387	0.547637604	0.04331021	25	68.75	6.25	0	
S23	99.48560982	0.165875827	0.023523719	100	0	0	0	
S24	269.939345	0.479135709	0.0507139	18.75	43.75	37.5	0	
S25	169.5745711	0.605212146	0.061010943	18.75	68.75	12.5	0	
S26	176.4810377	0.37780399	0.048632415	34.38	53.12	12.5	0	
S27	103.630574	0.63298758	0.034426981	3.12	0	96.88	0	
S28	240.7179925	0.401384304	0.040879496	28.12	3.12	68.75	0	
S29	366.155198	0.586737757	0.058422585	25	3.12	71.88	0	
S30	153.9019951	0.090131698	0.016136935	87.5	12.5	0	0	
S31	195.3795335	0.070591285	0.019138342	90.32	6.45	3.23	0	
S32	144.9514961	0.094854465	0.013770037	100	0	0	0	
S33	184.4068453	0.524922893	0.058846544	31.25	56.25	12.5	0	
S34	173.595474	0.65842355	0.05161194	15.62	68.75	15.62	0	
S35	186.6460446	0.739473309	0.067441152	15.62	71.88	12.5	0	
S36	119.1792453	0.127670371	0.032200529	78.12	18.75	3.12	0	
S37	169.3346703	0.353067338	0.069624828	53.12	40.62	6.25	0	
S38	160.2833492	0.245947409	0.059468452	68.75	28.12	3.12	0	
S39	242.5403782	0.401102789	0.061582641	37.5	54.17	8.33	0	
S40	250.4656575	0.612086704	0.078135069	27.59	58.62	13.79	0	
S41	185.5913841	0.558478448	0.05829107	20	70	10	0	
S42	224.9159507	0.36859913	0.053696715	48.28	34.48	17.24	0	
S43	235.4811111	0.514082318	0.061993498	25.93	51.85	22.22	0	
S44	176.5703025	0.390002047	0.06842437	34.62	65.38	0	0	
S45	142.857189	0.408512721	0.058249402	40	53.33	6.67	0	
S46	209.8923869	0.113515515	0.016334735	93.55	6.45	0	0	
S47	220.59499	0.122575989	0.043663634	88	12	0	0	
S48	180.160707	0.061303295	0.010546457	100	0	0	0	

S49	189.2795367	0.073396284	0.015456326	96.43	3.57	0	0	
S50	167.8122514	0.375565058	0.03970777	20	72	8	0	
S51	173.8214439	0.195239054	0.039474432	75	9.38	15.62	0	
S52	112.6758022	0.129755651	0.025574235	93.75	3.12	3.12	0	
S53	223.3577452	0.685834686	0.074344992	28.12	50	21.88	0	
S54	171.5970168	0.731453698	0.0600894	15.62	71.88	12.5	0	
S55	190.1828149	0.418916111	0.066578726	45.16	32.26	22.58	0	
S56	211.2054588	0.64183187	0.076435172	25	65.62	9.38	0	
S57	220.3067966	0.594686956	0.072331089	25	59.38	15.62	0	
S58	254.9191794	0.595443051	0.066785796	28.12	43.75	28.12	0	
S59	212.5849092	0.639461107	0.080444011	25	71.88	3.12	0	
S60	245.2738953	0.505838108	0.085442789	50	40.62	9.38	0	
S61	254.521217	0.617510985	0.072519785	25	43.75	31.25	0	
S62	207.7758405	0.571861747	0.065471268	15.62	75	9.38	0	
S63	160.770635	0.234494003	0.037413783	81.25	6.25	12.5	0	
S64	253.2868081	0.559062958	0.050066241	28.12	25	46.88	0	
S65	272.0860182	0.638246144	0.061210333	37.5	28.12	34.38	0	
S66	308.0100518	0.57944942	0.059375935	28.12	46.88	25	0	
S67	273.4773132	0.689994078	0.048788258	16.13	67.74	16.13	0	
S68	226.6177138	0.648766914	0.051087142	9.38	62.5	28.12	0	
S69	220.4961539	0.651748562	0.045368808	21.88	50	28.12	0	
S70	245.6461351	0.59576544	0.045132269	25	53.12	21.88	0	
S71	205.6223256	0.672005566	0.043062783	3.12	81.25	15.62	0	
S72	203.7467277	0.532447996	0.045073891	37.5	56.25	6.25	0	
S73	180.9742054	0.582683534	0.046995763	15.62	59.38	25	0	
S74	204.6925606	0.559512898	0.049220998	31.25	46.88	21.88	0	
S75	101.4126743	0.121399246	0.014331084	94.79	0	5.21	0	
S76	108.7523798	0.119536131	0.015173832	95.83	0	4.17	0	
S77	82.03261273	0.113124397	0.013307323	95.83	0	4.17	0	
S78	70.59721054	0.09311867	0.010695734	100	0	0	0	

S79	151.8801055	0.215888409	0.02399188	73.96	3.12	22.92	0	
S80	140.9983937	0.415160488	0.02312713	14.44	5.56	60	20	
S81	160.6604175	0.466902297	0.03003252 7	48.96	31.25	17.71	2.08	
S82	190.3147748	0.534450363	0.03082365 3	29.17	12.5	48.96	9.38	
S83	57.58330334	0.083048351	0.00805016 7	100	0	0	0	
S84	177.1615987	0.393485977	0.03226148 7	57.61	15.22	27.17	0	
S85	184.9098275	0.627958 91	0.02638861 4	9.38	0	52.08	38.54	
S86	195.6620408	0.462490187	0.02386389 2	15.62	4.17	75	5.21	
S87	140.1542581	0.563629855	0.03171140 1	27.08	48.96	23.96	0	
S88	121.5645424	0.511081234	0.02713958 1	24.21	55.79	20	0	
S89	102.1500387	0.653612274	0.04450395 9	31.25	50	18.75	0	
S90	133.2338217	0.729282333	0.03028370 6	11.46	60.42	28.12	0	
S91	126.4834576	0.416086467	0.02910744	41.67	44.79	13.54	0	
S92	114.4440116	0.423227011	0.02789546 5	33.68	47.37	18.95	0	
S93	96.78193953	0.522875462	0.03273510 8	27.08	57.29	15.62	0	
S94	126.8554428	0.543466412	0.03036977 4	22.92	60.42	16.67	0	
S95	128.5896417	0.668102621	0.04414961 5	26.04	62.5	11.46	0	
S96	134.4131313	0.346486871	0.03315 39	57.89	25.26	16.84	0	
S97	158.1346585	0.366243638	0.03452027 2	63.54	25	11.46	0	
S98	157.7946225	0.434185883	0.03737510 6	47.37	31.58	21.05	0	
S99	176.2946561	0.561490105	0.01963515 3	19.79	8.33	37.5	34.38	Gradient purification
S100	176.2946561	0.561490105	0.01963515 3	19.79	8.33	37.5	34.38	Gradient purification
S101	73.3041492	0.234474567	0.01184992 6	93.68	5.26	1.05	0	Gradient purification
S102	73.3041492	0.234474567	0.01184992 6	93.68	5.26	1.05	0	Gradient purification
S103	17.12959905	0.090708806	0.00560908 8	99.48	0	0.52	0	
S104	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

Table 12. Conditions

Condition	Extraction solution	Type	Preparation	Buffer	Salt	Detergent	Detergent Concentration	Modifier
1	NST	Brain	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A

2	NST	Brain	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	N/A
3	Sigma-Aldrich Nuclei EZ Prep	Brain	dounce	EZ	N/A	EZ	N/A	N/A
4	NST	Brain	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
5	Sigma-Aldrich Nuclei EZ Prep	Brain	dounce	EZ	N/A	EZ	N/A	N/A
6	NST	Brain	dounce	Tris	5 mM CaCl, 3 mM Mg(Ac)2	NP40	0.1	Sucrose, EDTA, PMSF, -mercaptoethanol
7	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
8	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	N/A
9	Sigma-Aldrich Nuclei EZ Prep	Colon	grind	EZ	N/A	EZ	N/A	N/A
10	Sigma-Aldrich Nuclei EZ Prep	Colon	chop	EZ	N/A	EZ	N/A	N/A
11	DSH	Colon	chop	HEPES	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Digitonin	0.01	N/A
12	NSH	Colon	chop	HEPES	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.01	N/A
13	NSH	Colon	chop	HEPES	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
14	TSH	Colon	chop	HEPES	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	N/A
15	TSH	Colon	chop	HEPES	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.006	N/A
16	NSTn	Colon	chop	Tricine	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
17	NSTn	Colon	chop	Tricine	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	Polyamines
18	CST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	CHAPS	0.0196	N/A
19	CST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	CHAPS	0.098	N/A
20	CST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	CHAPS	0.49	N/A
21	DST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Digitonin	0.002	N/A
22	DST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Digitonin	0.01	N/A
23	DST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Digitonin	0.05	N/A
24	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.001	N/A
25	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.005	N/A
26	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.01	N/A
27	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.025	N/A
28	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.05	N/A
29	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
30	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	Polyamines
31	NST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	Sucrose

32	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.00024	N/A
33	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	Cytoskeletal drug
34	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	N/A
35	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	Protease inhibitor
36	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	Rnase inhibitor
37	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.0012	Translation inhibitor
38	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.003	N/A
39	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.006	N/A
40	TST	Colon	chop	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	Tween	0.03	N/A
41	Tris only; Hypotonic	Colon	chop	Tris	None	None	0	N/A
42	Sigma-Aldrich Nuclei EZ Prep	Colon	dounce	EZ	N/A	EZ	N/A	N/A
43	Sigma-Aldrich Nuclei EZ Prep	Colon	grind	EZ	N/A	EZ	N/A	N/A
44	NST	Colon	grind	Tris	146 mM NaCl, 1mM CaCl2, 21mM MgCl2	NP40	0.2	N/A
45	NST	Colon	dounce	Tris	5 mM CaCl, 3 mM Mg(Ac)2	NP40	0.1	Sucrose, EDTA, PMSF, -mercaptoethanol
Condition	**GFP+ Sorted**	**%Exon (mean)**	**%Intron (mean)**	**%Intergenic (mean)**	**%Exon (SD)**	**%Intron (SD)**	**%Intergenic (SD)**	**Number of detected genes (mean)**
1	No	24	61.41	14.57	2.31	2.81	1.03	3008.09375
2	No	37.08	50.3	12.57	1.75	1.91	0.98	2463.375
3	No	28.29	55.55	16.13	1.95	2.41	2.08	3741.5
4	Yes	22.02	57.28	20.68	0.93	1.12	0.75	3108.327957
5	Yes	25.05	48.44	26.49	0.8	1.13	1.14	2609.828125
6	Yes	26.06	52.92	20.99	1.08	1.15	0.72	2472.6875
7	No	33.03	40.8	26.16	2.81	3.71	3.11	1966.322581
8	No	32.53	43.75	23.7	1.93	3.17	2.51	2319.375
9	No	15.36	24.35	60.26	2.39	2.02	3.05	1691.90625
10	Yes	22.35	44.02	33.61	1.07	1.39	1.86	3301.979167
11	Yes	35.76	45.91	18.31	3.36	4.29	1.59	2179.586207
12	Yes	34.21	38.8	26.98	2.26	3.22	3.25	2070.714286
13	Yes	30.61	48.39	20.98	2.08	2.87	1.65	1864.716981
14	Yes	32.5	42.9	24.58	1.29	1.86	1.38	2082.195402
15	Yes	40.22	42.88	16.89	2.67	3.01	1.86	2690.36
16	Yes	22.96	45.95	31.06	0.9	1.48	1.7	2590.5875
17	Yes	28.87	48.44	22.67	0.82	1.05	0.66	2355.272966
18	Yes	36.54	41.48	21.97	1.72	1.84	1.29	1956.802083
19	Yes	34.69	47.02	18.27	1.44	1.77	1.01	2688.473684
20	Yes	31.36	46.03	22.59	0.77	1.03	0.58	2422.997389
21	Yes	23.38	21.85	54.76	2.78	1.37	2.29	1655.65625
22	Yes	29.67	42.38	27.94	1.73	1.88	1.67	2187.666667
23	Yes	17.38	15.09	67.51	3.07	1.05	3.1	1094.21875
24	Yes	24.04	30.97	44.97	2.38	2.23	3.52	1881.3125
25	Ys	36.05	38.79	25.15	3.01	3.82	1.83	2634.65625
26	Yes	33.48	44.98	21.52	2.96	3.51	2.34	2021.769231
27	Yes	37	35.93	27.05	2.39	3.15	1.91	2405.1875
28	Yes	28.59	52.87	18.52	3.36	3.65	0.89	2763.28125
29	Yes	26	44.93	29.04	0.66	0.79	0.6	2302.530159
30	Yes	19.8	36.99	43.19	1.61	2.61	3.24	2406.063492

31	Yes	27.31	54.1	18.57	2.41	3.31	1.47	2360
32	Yes	53.66	27.09	19.24	2.34	2.71	0.59	4571.53125
33	Yes	33.84	49.78	16.36	1.96	2.62	1.66	2783.90625
34	Yes	39.19	40.74	20.06	1.37	1.58	0.85	3094.373016
35	Yes	27.96	52.74	19.29	0.95	2.61	2.33	2893.5
36	Yes	33.6	49.77	16.62	1.68	2.31	1.5	2768.75
37	Yes	37.66	24.95	37.38	2.14	1.72	2.35	1525.96875
38	Yes	56.9	21.83	21.26	2.29	2.44	0.5	4703.53125
39	Yes	35.34	44.15	20.49	1.15	1.48	1.03	2718.178862
40	Yes	36.28	45	18.7	0.78	0.88	0.48	2348.481771
41	Yes	14.4	13.7	71.87	1.72	0.61	2.02	1119.78125
42	Yes	6.27	19.57	74.15	0.65	0.35	0.64	739.6282723
43	Yes	19.68	28.08	52.19	0.65	0.44	0.68	1305.21875
44	Yes	27.98	55.12	16.88	1.12	1.5	0.81	3173.189474
45	Yes	7.16	17.72	75.07	0.59	0.74	1.14	1393.115789

Condition	Number of detected genes (SD)	ENS score (mean)	ENS score (SD)	%Contamination	%Glia	%Neuron	%Oligodendrocyte	Other notes
1	240.7179925	0.401384304	0.040879496	28.12	3.12	68.75	0	
2	103.630574	0.63298758	0.034426981	3.12	0	96.88	0	
3	366.155198	0.586737757	0.058422585	25	3.12	71.88	0	
4	126.2705059	0.439588719	0.016685561	15.05	4.84	67.74	12.37	
5	131.3222121	0.421923659	0.023207359	41.67	1.56	37.5	19.27	
6	124.3323857	0.561490105	0.013847756	19.79	8.33	37.5	34.38	Gradient purification
7	195.3795335	0.070591285	0.019138342	90.32	6.45	3.23	0	
8	153.9019951	0.090131698	0.016136935	87.5	12.5	0	0	
9	144.9514961	0.094854465	0.013770037	100	0	0	0	
10	142.7489853	0.477267702	0.033965434	48.96	19.79	31.25	0	
11	250.4656575	0.612086704	0.078135069	27.59	58.62	13.79	0	
12	189.2795367	0.073396284	0.015456326	96.43	3.57	0	0	
13	163.3765326	0.383317768	0.040176319	43.4	43.4	13.21	0	
14	99.86258915	0.490966226	0.032647268	25.29	64.37	10.34	0	
15	220.59499	0.122575989	0.043663634	88	12	0	0	
16	111.9460862	0.517837731	0.024375511	33.12	49.38	17.5	0	
17	69.25384424	0.45411528	0.015049033	37.8	42.78	19.42	0	
18	115.403659	0.553032322	0.041934142	28.12	63.54	8.33	0	
19	120.6675505	0.541130166	0.038049419	30.53	48.42	21.05	0	
20	69.05119207	0.577546689	0.017717045	25.33	52.74	21.93	0	
21	135.1935635	0.292462761	0.030285883	50	28.12	21.88	0	

22	129.303049	0.544853387	0.035944082	30.11	61.29	8.6	0	
23	99.48560982	0.165875827	0.023523719	100	0	0	0	
24	163.0430346	0.321009425	0.037783865	56.25	15.62	28.12	0	
25	225.9403406	0.380320973	0.04857395	59.38	25	15.62	0	
26	176.5703025	0.390002047	0.06842437	34.62	65.38	0	0	
27	168.4543374	0.461930365	0.056740355	53.12	46.88	0	0	
28	239.0918817	0.571013987	0.055967354	25	53.12	21.88	0	
29	59.37318779	0.459541993	0.0121788	42.06	30.48	26.03	1.43	
30	159.6915756	0.409186402	0.034190499	58.73	23.81	17.46	0	
31	214.1698621	0.490194685	0.049812532	37.5	43.75	18.75	0	
32	322.5542308	0.466359257	0.04562064	84.38	9.38	6.25	0	
33	169.3346703	0.353067338	0.069624828	53.12	40.62	6.25	0	
34	147.8431665	0.484808066	0.033634941	55.56	34.13	10.32	0	
35	186.6460446	0.739473309	0.067441152	15.62	71.88	12.5	0	
36	160.2833492	0.245947409	0.059468452	68.75	28.12	3.12	0	
37	119.1792453	0.127670371	0.032200529	78.12	18.75	3.12	0	
38	265.949482	0.38830923	0.039192231	96.88	0	3.12	0	
39	111.5573251	0.461794063	0.0377798	46.34	37.4	16.26	0	
40	60.56465103	0.585300862	0.020452456	27.86	54.95	17.19	0	
41	99.09030516	0.140582076	0.017994945	100	0	0	0	
42	17.12959905	0.090708806	0.005609088	99.48	0	0.52	0	
43	42.58852379	0.165819099	0.008309999	88.75	5.31	5.62	0.31	
44	154.3900503	0.639875283	0.029840916	22.11	54.74	23.16	0	
45	51.6965525	0.234474567	0.008356966	93.68	5.26	1.05	0	Gradient purification

[00695] Tables 13-17. Summary and marker genes for mouse ENS atlas. (Table 13) Description of each mouse and mouse sample profiled in this study, including model, age, sex, circadian phase, and colon location. Marker genes for mouse (Tables 14 and 15) neurons sequenced with SS2 (Table 14, markers; Table 15, Covariates), (Table 16) mouse glia sequenced with SS2, and (Table 17) all cells from the mouse colon profiled with droplet-based 10X sequencing.

Table 13.

Cre_driver	Sample_ID	Gender	Colon_order	Time_collected	~Age (weeks)
Sox10	Navin3_S24	F	All	#N/A	12
Sox10	Navin6_S54	M	All	#N/A	12
Sox10	Navin6_S57	M	All	#N/A	12
Sox10	Navin8_S90	M	All	#N/A	12
Sox10	Navin9_S94	F	All	2PM	12
Sox10	Navin10_S98	M	All	7AM	12
Sox10	ENS1A_1	F	1	7AM	12
Sox10	ENS1A_2	F	2	7AM	12
Sox10	ENS1A_3	F	3	7AM	12
Sox10	ENS1A_4	F	4	7AM	12
Sox10	ENS1B_1	F	1	7AM	12
Sox10	ENS1B_2	F	2	7AM	12
Sox10	ENS1B_3	F	3	7AM	12
Sox10	ENS1B_4	F	4	7AM	12
Sox10	ENS2_1	F	1	7PM	12
Sox10	ENS2_2	F	2	7PM	12
Sox10	ENS2_3	F	3	7PM	12
Sox10	ENS2_4	F	4	7PM	12
Sox10	ENS3_1	M	1	7AM	12
Sox10	ENS3_2	M	2	7AM	12
Sox10	ENS3_3	M	3	7AM	12
Sox10	ENS3_4	M	4	7AM	12
Sox10	ENS4_1	M	1	7PM	12
Sox10	ENS4_2	M	2	7PM	12
Sox10	ENS4_3	M	3	7PM	12
Sox10	ENS4_4	M	4	7PM	12
Sox10	ENS5_1	M	1	7AM	12
Sox10	ENS5_2	M	2	7AM	12
Sox10	ENS5_3	M	3	7AM	12
Sox10	ENS5_4	M	4	7AM	12
Sox10	ENS6_1	M	1	7PM	12
Sox10	ENS6_2	M	2	7PM	12
Sox10	ENS6_3	M	3	7PM	12
Sox10	ENS6_4	M	4	7PM	12
Sox10	ENS7_1	M	1	7PM	12
Sox10	ENS7_2	M	2	7PM	12
Sox10	ENS7_3	M	3	7PM	12
Sox10	ENS7_4	M	4	7PM	12
WNT1	ENS8_1	F	1	7AM	12
WNT1	ENS8_2	F	2	7AM	12
WNT1	ENS9_1	M	1	7PM	12
WNT1	ENS9_2	M	2	7PM	12
WNT1	ENS9_3	M	3	7PM	12
WNT1	ENS9_4	M	4	7PM	12
AGED	ENS10A_1	F	1	7PM	52
AGED	ENS10B_1	F	1	7PM	52
AGED	ENS10A_2	F	2	7PM	52
AGED	ENS10A_3	F	3	7PM	52
AGED	ENS10A_4	F	4	7PM	52
AGED	ENS10B_4	F	4	7PM	52
Uchl1	ENS11_1	M	1	7AM	12
Uchl1	ENS11_2	M	2	7AM	12
Uchl1	ENS11_3	M	4	7AM	12
Uchl1	ENS11_4	M	4	7AM	12
Sox10	ENS12_1	M	1	7AM	12
Sox10	ENS12_2	M	2	7AM	12
Sox10	ENS12_3	M	3	7AM	12

Sox10	ENS12_4	M	4	7AM	12
Uchl1	ENS14_1	M	1	7AM	12
Uchl1	ENS14_2	M	4	7AM	12
Sox10	ENS13_1	F	1	7AM	12
Sox10	ENS13_2	F	4	7AM	12
AGED	ENS15_1	M	1	7PM	52
AGED	ENS15_2	M	2	7PM	52
AGED	ENS15_3	M	3	7PM	52
AGED	ENS15_4	M	4	7PM	52
Uchl1	ENS16A_1	M	1	7PM	12
Uchl1	ENS16A_2	M	2	7PM	12
Uchl1	ENS16A_3	M	3	7PM	12
Uchl1	ENS16A_4	M	4	7PM	12
Uchl1	ENS16B_1	M	1	7PM	12
Uchl1	ENS16B_2	M	2	7PM	12
Uchl1	ENS16B_3	M	3	7PM	12
Uchl1	ENS16B_4	M	4	7PM	12
AGED	ENS17_1	M	1	7AM	52
AGED	ENS17_2	M	2	7AM	52
AGED	ENS17_3	M	3	7AM	52
AGED	ENS17_4	M	4	7AM	52
Uchl1	ENS18_1	F	1	7PM	12
Uchl1	ENS18_2	F	2	7PM	12
Uchl1	ENS18_3	F	3	7PM	12
Uchl1	ENS18_4	F	4	7PM	12
Uchl1	ENS19_1	F	1	7AM	11
Uchl1	ENS19_2	F	2	7AM	12
Uchl1	ENS19_3	F	2	7AM	11
Uchl1	ENS19_4	F	4	7AM	11

Table 14.

ident	gene	padjH
Other_1	Fam129a	4.17E-69
Other_1	Matn1	5.45E-48
Other_1	Atp1a2	1.28E-44
Other_1	Shroom4	5.83E-42
Other_1	Plxnb3	3.19E-41
Other_1	Tacr3	1.37E-33
Other_1	Rasl12	1.78E-33
Other_1	F13b	3.76E-33
Other_1	C4b	7.67E-33
Other_1	Serpinb9c	1.67E-32
Other_1	Wdr69	7.07E-31
Other_1	Bbox1	2.46E-30
Other_1	Tmprss5	7.97E-29
Other_1	5430428K19Rik	4.25E-27
Other_1	Foxp2	2.18E-25
Other_1	Wdr96	2.57E-25
Other_1	Mtrf1	7.31E-24
Other_1	Rad54b	1.90E-21
Other_1	Afap1l2	3.11E-21
Other_1	Abca8a	1.34E-20
Other_1	Rai14	2.19E-20
Other_1	Kank1	4.52E-20
Other_1	Sox5	5.77E-20
Other_1	Egfbp2	6.59E-20
Other_1	Musk	1.54E-19

ident	gene	padjH
PIMN_1	Cadps2	2.68E-56
PIMN_1	Dach2	3.09E-56
PIMN_1	Entpd3	2.76E-55
PIMN_1	Kcnab1	4.67E-55
PIMN_1	Rnf112	3.86E-54
PIMN_1	Thsd7b	2.08E-53
PIMN_1	Cacna1c	1.62E-52
PIMN_1	Ptprz1	2.77E-52
PIMN_1	Kcnh6	1.07E-51
PIMN_1	Slc35d3	4.59E-51
PIMN_1	Kcnq4	1.29E-49
PIMN_1	Synpo2	3.22E-49
PIMN_1	Sspo	2.16E-48
PIMN_1	Stard13	7.17E-48
PIMN_1	Dach1	1.04E-46
PIMN_1	Kcnj5	1.91E-46
PIMN_1	Sntb1	2.51E-46
PIMN_1	Ntrk3	2.65E-46
PIMN_1	Bves	1.48E-45
PIMN_1	Slc44a5	1.62E-45
PIMN_1	Kcnh8	4.03E-45
PIMN_1	Arhgap42	6.52E-45
PIMN_1	Atp2b1	7.25E-45
PIMN_1	Lrrk1	7.81E-45
PIMN_1	Kcnq3	1.57E-44

ident	gene	padjH
PIN_1	Rhox5	2.55E-02
PIN_1	Mageb3	2.90E-02
PIN_1	Gm11346	4.52E-02
PIN_2	Fut9	1.19E-67
PIN_2	Ptger2	7.58E-64
PIN_2	Penk	3.51E-59
PIN_2	Gm20754	3.53E-59
PIN_2	Tac1	4.57E-58
PIN_2	Nfatc1	1.54E-55
PIN_2	Egfr	1.79E-54
PIN_2	Lamc3	5.00E-49
PIN_2	Cd200	7.97E-48
PIN_2	Lingo2	1.51E-44
PIN_2	Pde4d	2.89E-44
PIN_2	Car8	1.17E-43
PIN_2	Ntrk2	1.99E-41
PIN_2	Ptprz1	6.25E-37
PIN_2	Col27a1	2.56E-36
PIN_2	Stac	2.60E-36
PIN_2	Rgs4	3.66E-35
PIN_2	Nsg1	4.91E-35
PIN_2	Pitpnc1	1.45E-33
PIN_2	Kctd16	1.90E-33
PIN_2	Slc10a4	1.54E-32
PIN_2	Psmd1	6.39E-32

Other_1	4930448C13Rik	5.99E-19
Other_1	Cdh19	1.39E-18
Other_1	Fzd6	1.20E-17
Other_1	Gm10863	1.55E-17
Other_1	Ccdc114	5.32E-16
Other_1	2810055G20Rik	7.07E-16
Other_1	Dapp1	2.69E-15
Other_1	Lhfp	3.60E-15
Other_1	H2-T10	3.68E-15
Other_1	Plac9a	7.76E-15
Other_1	Col18a1	1.55E-14
Other_1	Lpar1	3.73E-14
Other_1	Chi3l1	3.78E-14
Other_1	Icos	3.78E-14
Other_1	Sox13	5.72E-14
Other_1	Trabd2b	1.81E-13
Other_1	Col12a1	2.06E-13
Other_1	Ntng2	8.43E-13
Other_1	Agmo	1.30E-12
Other_1	Col11a1	5.68E-12
Other_1	9130409I23Rik	2.51E-11
Other_1	Loxl3	1.03E-10
Other_1	Kif27	1.84E-10
Other_1	2810025M15Rik	2.57E-10
Other_1	Gm10389	2.75E-10
Other_1	Upb1	2.78E-10
Other_1	Cyp39a1	1.58E-09
Other_1	Sox6	1.61E-09
Other_1	Nckap5	1.86E-09
Other_1	C1qtnf7	2.30E-09
Other_1	2610307P16Rik	2.51E-09
Other_1	Sall1	2.94E-09
Other_1	4930432M17Rik	3.79E-09
Other_1	Etl4	4.03E-09
Other_1	Dock5	7.00E-09
Other_1	Smoc1	8.22E-09
Other_1	Zcchc24	9.94E-09
Other_1	Wwtr1	1.03E-08
Other_1	Frzb	1.04E-08
Other_1	Il1rap	1.21E-08
Other_1	Hyal4	1.32E-08
Other_1	Baz1a	1.64E-08
Other_1	Prdm16	2.25E-08
Other_1	Gsn	2.56E-08
Other_1	Apoc3	4.72E-08
Other_1	Nod1	7.80E-08
Other_1	Pmepa1	1.09E-07
Other_1	Fam107a	1.28E-07
Other_1	Slc7a2	1.30E-07
Other_1	Dydc2	1.37E-07
Other_1	Sox10	1.45E-07
Other_1	Nhp2	1.74E-07
Other_1	Tgfb2	1.95E-07
Other_1	Plac9b	2.24E-07
Other_1	Oosp1	2.39E-07
Other_1	Npm3-ps1	2.95E-07
Other_1	Abca15	4.96E-07
Other_1	Apoe	5.11E-07
Other_1	Gm3143	6.47E-07
Other_1	Prodh	7.24E-07
PIMN_1	Kcnip4	3.24E-44
PIMN_1	Ablim2	6.46E-44
PIMN_1	Kcnj3	1.48E-43
PIMN_1	Ncald	1.89E-43
PIMN_1	Ppap2b	1.98E-43
PIMN_1	4930486F22Rik	6.37E-43
PIMN_1	Clvs1	9.46E-43
PIMN_1	Srcin1	1.77E-42
PIMN_1	Chd7	6.37E-42
PIMN_1	Plvap	8.64E-42
PIMN_1	Unc13c	1.02E-41
PIMN_1	Ass1	1.52E-41
PIMN_1	Dgkg	5.30E-41
PIMN_1	Slc4a4	7.73E-41
PIMN_1	Rnf182	1.39E-40
PIMN_1	Sipa1l1	4.39E-40
PIMN_1	Dmd	6.28E-40
PIMN_1	Rasa4	3.29E-39
PIMN_1	Tmod1	4.42E-39
PIMN_1	Cped1	5.39E-39
PIMN_1	Grid2	6.67E-39
PIMN_1	Il1rapl1	7.70E-39
PIMN_1	Plekha5	9.88E-39
PIMN_1	Akap13	1.24E-38
PIMN_1	Il20ra	2.60E-38
PIMN_1	Mfsd4	4.97E-38
PIMN_1	Fstl5	4.97E-38
PIMN_1	Sipa1l2	3.16E-37
PIMN_1	Arhgef10l	4.30E-37
PIMN_1	Samd5	4.67E-37
PIMN_1	A130077B15Rik	4.83E-37
PIMN_1	Creb5	5.57E-37
PIMN_1	Cox6c	6.48E-36
PIMN_1	Man1a	7.39E-36
PIMN_1	Padi2	5.03E-32
PIMN_1	Eln	1.20E-22
PIMN_1	Sept9	8.46E-21
PIMN_1	Chst9	1.85E-16
PIMN_1	Caskin2	3.62E-16
PIMN_1	Aim1l	4.13E-16
PIMN_1	Pcolce	1.98E-15
PIMN_1	Fndc1	3.64E-15
PIMN_1	Slco2a1	3.42E-12
PIMN_1	Grpr	5.17E-12
PIMN_1	Nnmt	7.65E-11
PIMN_1	Pon3	9.70E-11
PIMN_1	Fgfr4	3.22E-09
PIMN_1	Wisp2	2.57E-08
PIMN_1	Gpc4	7.49E-08
PIMN_1	Lsp1	1.31E-07
PIMN_1	Krt24	8.05E-07
PIMN_1	Edaradd	9.51E-07
PIMN_1	Gpr12	4.92E-06
PIMN_1	Rdh7	5.70E-06
PIMN_1	Rbm24	6.99E-06
PIMN_1	Lgi2	1.99E-05
PIMN_1	Kdr	3.00E-05
PIMN_1	Gm13031	3.33E-05
PIMN_1	Defb33	3.90E-05
PIMN_1	Olah	8.95E-05
PIN_2	Pde7b	3.25E-31
PIN_2	Unc5d	5.46E-31
PIN_2	4930509J09Rik	1.35E-30
PIN_2	Skap1	2.04E-30
PIN_2	Jph1	1.04E-29
PIN_2	Gm5868	2.00E-29
PIN_2	Kctd8	2.07E-28
PIN_2	Gucy2g	8.42E-28
PIN_2	Dlgap1	1.32E-27
PIN_2	Leprel1	1.60E-27
PIN_2	Abcc8	5.78E-27
PIN_2	Itgb8	6.60E-27
PIN_2	1810006J02Rik	1.10E-26
PIN_2	Kl	2.43E-26
PIN_2	Mgll	3.75E-25
PIN_2	Sstr1	4.19E-25
PIN_2	Galr1	5.26E-25
PIN_2	Ust	1.04E-24
PIN_2	Tmem132e	1.50E-24
PIN_2	Nhsl2	3.09E-24
PIN_2	Htr2b	3.97E-24
PIN_2	Dock10	3.97E-24
PIN_2	Fras1	4.19E-24
PIN_2	Thbs1	1.33E-22
PIN_2	Gpr64	1.51E-22
PIN_2	Slc12a2	2.56E-22
PIN_2	Thsd4	6.03E-22
PIN_2	Siglec15	7.36E-22
PIN_2	Whrn	1.59E-21
PIN_2	5530401A14Rik	1.95E-21
PIN_2	Fam19a5	2.77E-21
PIN_2	Dnaja1	8.38E-21
PIN_2	Proser2	1.37E-20
PIN_2	Pbx3	1.58E-20
PIN_2	Tmc3	2.95E-20
PIN_2	Rwdd3	4.12E-20
PIN_2	Hoxb5	6.02E-20
PIN_2	Psmd13	1.76E-19
PIN_2	Grm7	4.65E-19
PIN_2	Snx7	5.16E-19
PIN_2	Parva	5.60E-19
PIN_2	Cd109	1.10E-18
PIN_2	Gda	1.35E-18
PIN_2	2900055J20Rik	2.28E-18
PIN_2	Mbp	4.45E-18
PIN_2	Fibcd1	5.22E-18
PIN_2	Vmn2r28	5.22E-18
PIN_2	Fjx1	6.83E-18
PIN_2	Galnt9	1.10E-17
PIN_2	Prkg1	1.68E-17
PIN_2	Cntn5	1.80E-17
PIN_2	Bnc2	1.81E-17
PIN_2	Ldlrad3	9.12E-17
PIN_2	Scg3	1.39E-16
PIN_2	Gm19782	1.41E-16
PIN_2	Gm10440	1.45E-16
PIN_2	Epdr1	1.58E-16
PIN_2	L3mbtl4	2.92E-16
PIN_2	Cntn6	3.69E-16
PIN_2	Bicc1	5.46E-16

Other_1	Car12	1.00E-06
Other_1	Cmtm5	1.32E-06
Other_1	Rreb1	1.75E-06
Other_1	1700112E06Rik	2.41E-06
Other_1	Stard8	2.59E-06
Other_1	Ddx49	2.63E-06
Other_1	Acox2	2.63E-06
Other_1	Gli3	2.80E-06
Other_1	Kctd1	4.35E-06
Other_1	Gbp5	4.64E-06
Other_1	1700010I14Rik	5.81E-06
Other_1	Mrvi1	5.92E-06
Other_1	Megf10	6.01E-06
Other_1	AI661453	6.01E-06
Other_1	Mob3b	7.40E-06
Other_1	Kirrel	7.46E-06
Other_1	Bhmt	9.22E-06
Other_1	Ajap1	1.13E-05
Other_1	Olfml1	1.85E-05
Other_1	Ankle1	1.85E-05
Other_1	Cml3	2.93E-05
Other_1	Tmem254a	3.78E-05
Other_1	Slc35f2	3.95E-05
Other_1	Bcl2l12	4.13E-05
Other_1	Entpd2	5.55E-05
Other_1	Gcnt1	6.44E-05
Other_1	Sox2ot	7.47E-05
Other_1	Ikbke	8.38E-05
Other_1	1700047M11Rik	8.63E-05
Other_1	Megf6	1.48E-04
Other_1	Tbx18	2.01E-04
Other_1	Myh11	3.46E-04
Other_1	Myof	4.10E-04
Other_1	Gpr17	4.55E-04
Other_1	Ptgfrn	4.85E-04
Other_1	Efhd1	6.72E-04
Other_1	Myh6	7.64E-04
Other_1	Fendrr	9.37E-04
Other_1	Col6a3	9.57E-04
Other_1	Fhl4	1.47E-03
Other_1	Col9a2	1.90E-03
Other_1	Lcp2	2.13E-03
Other_1	Mapk15	2.47E-03
Other_1	Kcnj10	5.38E-03
Other_1	Car13	6.95E-03
Other_1	Cep72	7.24E-03
Other_1	4932435O22Rik	8.43E-03
Other_1	Tex36	1.01E-02
Other_1	Lims2	1.29E-02
Other_1	Rrad	1.70E-02
Other_1	S1pr3	1.80E-02
Other_1	Nfatc4	2.45E-02
Other_1	Evc	2.61E-02
Other_1	Arhgef19	4.94E-02
Other_2	Arhgef38	6.44E-117
Other_2	Agr2	4.04E-86
Other_2	Oit1	4.43E-83
Other_2	Cphx1	1.01E-81
Other_2	Shroom3	9.76E-69
Other_2	Sh2d1b2	5.63E-58
PIMN_1	Klra10	1.63E-04
PIMN_1	Gldc	1.72E-04
PIMN_1	Ces4a	1.88E-04
PIMN_1	Crh	1.96E-04
PIMN_1	Tnxb	4.71E-04
PIMN_1	Prl3b1	5.93E-04
PIMN_1	4933433H22Rik	6.27E-04
PIMN_1	Rdh19	6.28E-04
PIMN_1	Gm20751	1.05E-03
PIMN_1	Msl3l2	1.07E-03
PIMN_1	Dear1	1.58E-03
PIMN_1	Serpinb9b	1.77E-03
PIMN_1	Chrna1	1.84E-03
PIMN_1	Syt8	1.85E-03
PIMN_1	Gm6583	1.89E-03
PIMN_1	Cyp1b1	2.06E-03
PIMN_1	Dpys	2.71E-03
PIMN_1	Gm2042	2.88E-03
PIMN_1	Dntt	3.00E-03
PIMN_1	B930092H01Rik	3.71E-03
PIMN_1	Pglyrp2	3.88E-03
PIMN_1	Gimap5	4.06E-03
PIMN_1	Krt40	4.31E-03
PIMN_1	Gpr37	5.16E-03
PIMN_1	4930548H24Rik	5.36E-03
PIMN_1	Cmtm2b	5.43E-03
PIMN_1	Hgd	5.96E-03
PIMN_1	Cd207	6.54E-03
PIMN_1	Cryaa	6.67E-03
PIMN_1	Alpl	9.03E-03
PIMN_1	Cfd	9.66E-03
PIMN_1	Vmn2r45	1.05E-02
PIMN_1	Krt26	1.08E-02
PIMN_1	4930467K11Rik	1.12E-02
PIMN_1	Mfsd7a	1.12E-02
PIMN_1	Olfr119	1.19E-02
PIMN_1	Cd52	1.22E-02
PIMN_1	Gm21276	1.27E-02
PIMN_1	Gm13102	1.52E-02
PIMN_1	Car6	1.62E-02
PIMN_1	Fam26d	1.68E-02
PIMN_1	C730027H18Rik	1.93E-02
PIMN_1	Duxbl1	1.93E-02
PIMN_1	Tmem89	2.07E-02
PIMN_1	Samt2	2.20E-02
PIMN_1	4930509K18Rik	2.25E-02
PIMN_1	Olfr1030	2.38E-02
PIMN_1	Snora35	2.49E-02
PIMN_1	Fam71f1	2.86E-02
PIMN_1	Xlr	3.02E-02
PIMN_1	Asb10	3.24E-02
PIMN_1	Myh7	3.31E-02
PIMN_1	Psg17	3.35E-02
PIMN_1	Gm19424	3.47E-02
PIMN_1	9530053A07Rik	3.51E-02
PIMN_1	I730028E13Rik	3.58E-02
PIMN_1	Spdyb	3.83E-02
PIMN_1	1700054M17Rik	4.19E-02
PIMN_1	Pabpc2	4.31E-02
PIMN_1	E130018N17Rik	4.41E-02
PIN_2	Nhs	6.32E-16
PIN_2	Arhgap28	7.59E-16
PIN_2	Nrp2	7.90E-16
PIN_2	Ptk2b	1.07E-15
PIN_2	Atp2b4	1.21E-15
PIN_2	Prkcb	1.56E-15
PIN_2	Tagln3	2.15E-15
PIN_2	Kirrel3	3.48E-15
PIN_2	Arhgef3	3.64E-15
PIN_2	Tgfb1i1	5.72E-15
PIN_2	Slitrk4	7.27E-15
PIN_2	Sorbs2	1.21E-14
PIN_2	Asic2	1.49E-14
PIN_2	Txndc16	1.76E-14
PIN_2	Pfn2	2.68E-14
PIN_2	A730046J19Rik	3.37E-14
PIN_2	Fxyd7	3.62E-14
PIN_2	Il22ra1	7.93E-14
PIN_2	Itih3	8.03E-13
PIN_2	Slco4c1	5.94E-12
PIN_2	BC051537	1.58E-10
PIN_2	Trim71	2.71E-10
PIN_2	Ptgdr	2.61E-09
PIN_2	BC055402	3.03E-09
PIN_2	4833428L15Rik	3.83E-09
PIN_2	Bpifa3	4.03E-09
PIN_2	Gm13277	1.81E-08
PIN_2	Ripply3	5.41E-08
PIN_2	Tectb	3.00E-07
PIN_2	Lyzl6	7.20E-07
PIN_2	Ctxn3	8.56E-07
PIN_2	AA387883	1.07E-06
PIN_2	Zfp474	1.39E-06
PIN_2	C1ql2	1.41E-06
PIN_2	Vmn2r122	1.99E-06
PIN_2	Vmn2r94	3.85E-06
PIN_2	9830107B12Rik	5.67E-06
PIN_2	4930431P03Rik	6.73E-06
PIN_2	Spesp1	1.09E-05
PIN_2	Crabp2	1.48E-05
PIN_2	Slc30a2	1.79E-05
PIN_2	Btla	1.93E-05
PIN_2	AI607873	2.31E-05
PIN_2	Mag	2.68E-05
PIN_2	Gm4567	3.90E-05
PIN_2	Slco1a5	4.80E-05
PIN_2	Ramp2	6.89E-05
PIN_2	Fzd2	8.02E-05
PIN_2	Gm11240	1.38E-04
PIN_2	Ctcfl	1.39E-04
PIN_2	Klf17	1.48E-04
PIN_2	Hbb-b1	1.71E-04
PIN_2	Chi3l1	2.31E-04
PIN_2	Nostrin	2.40E-04
PIN_2	4930404H11Rik	2.55E-04
PIN_2	Gm17745	2.79E-04
PIN_2	Mog	3.97E-04
PIN_2	4930564D02Rik	4.34E-04
PIN_2	Krt74	4.37E-04
PIN_2	D16Ertd519e	4.40E-04

Other_2	Mecom	2.55E-55
Other_2	Gm14204	6.90E-55
Other_2	Gm10415	2.58E-49
Other_2	Gm7073	1.44E-46
Other_2	Slc12a8	4.50E-45
Other_2	Sprr2b	4.81E-44
Other_2	Tnfaip8	1.83E-41
Other_2	Galnt12	1.77E-36
Other_2	Rasef	3.64E-35
Other_2	Nipsnap3a	5.48E-31
Other_2	Atp8b1	6.22E-30
Other_2	Sytl2	9.47E-30
Other_2	Mctp2	9.54E-30
Other_2	Fam3b	7.05E-29
Other_2	Cdcp1	7.94E-29
Other_2	Eps8	1.49E-28
Other_2	Tff3	3.22E-28
Other_2	Muc2	2.06E-27
Other_2	Capn13	2.16E-27
Other_2	1700120E14Rik	2.09E-26
Other_2	Spink4	2.16E-26
Other_2	BC030870	1.78E-25
Other_2	Sprr2a1	7.41E-24
Other_2	D930020B18Rik	6.05E-23
Other_2	Tmem236	3.33E-22
Other_2	Ano9	2.17E-21
Other_2	Myo5b	2.89E-21
Other_2	Fcamr	5.37E-21
Other_2	Itgal	5.90E-21
Other_2	Slfn4	5.90E-21
Other_2	Nupr1	7.13E-21
Other_2	Hepacam2	1.45E-20
Other_2	1810007I06Rik	2.54E-20
Other_2	Sprr2a2	2.54E-20
Other_2	Fermt1	4.22E-20
Other_2	E230025N22Rik	4.93E-20
Other_2	Mroh4	7.84E-20
Other_2	Gm609	1.27E-19
Other_2	Myo5c	2.03E-19
Other_2	Zan	2.58E-19
Other_2	Gm10754	5.79E-19
Other_2	Slc15a1	6.44E-19
Other_2	Saa1	1.31E-18
Other_2	Mrgpra9	1.56E-18
Other_2	Blnk	1.60E-18
Other_2	Abcg5	2.86E-18
Other_2	Rbm47	3.97E-18
Other_2	Crxos1	4.13E-18
Other_2	Plac8	5.43E-18
Other_2	Ano7	1.92E-17
Other_2	Spink3	1.95E-17
Other_2	Myo3a	3.13E-17
Other_2	Frmd7	4.11E-17
Other_2	4921508A21Rik	4.33E-17
Other_2	4930511M11Rik	1.13E-16
Other_2	Spdef	2.28E-16
Other_2	Abo	2.76E-16
Other_2	Epcam	7.96E-16
Other_2	Rdh18-ps	1.23E-15
Other_2	Slc34a2	1.67E-15
PIMN_1	Lyg2	4.76E-02
PIMN_1	Xlr5b	4.88E-02
PIMN_2	Cmah	2.78E-43
PIMN_2	Col25a1	1.24E-32
PIMN_2	Pear1	1.12E-31
PIMN_2	Lhfp	1.12E-31
PIMN_2	Pde1a	1.31E-27
PIMN_2	Ano4	1.63E-27
PIMN_2	Rgs7	1.70E-27
PIMN_2	Dagla	9.50E-26
PIMN_2	Asic2	9.50E-26
PIMN_2	5530401A14Rik	1.45E-25
PIMN_2	Krt23	3.50E-25
PIMN_2	Ltk	3.51E-24
PIMN_2	Chst15	3.85E-24
PIMN_2	Mfsd4	2.17E-23
PIMN_2	Egfem1	5.57E-23
PIMN_2	Sgcd	1.14E-22
PIMN_2	Prkg2	1.29E-22
PIMN_2	Slc1a5	1.99E-22
PIMN_2	Cadps2	2.20E-22
PIMN_2	Zfp536	3.31E-22
PIMN_2	Plch2	4.08E-22
PIMN_2	Kcnh1	4.08E-22
PIMN_2	Cdk18	1.05E-21
PIMN_2	Nos1	1.33E-21
PIMN_2	Ngf	6.23E-20
PIMN_2	Ablim2	9.76E-20
PIMN_2	Itga8	1.41E-18
PIMN_2	Ryr2	1.43E-18
PIMN_2	Cyp2s1	1.53E-18
PIMN_2	Rarb	1.82E-18
PIMN_2	Asic4	2.02E-18
PIMN_2	Gm21949	2.55E-18
PIMN_2	Rnf144b	2.55E-18
PIMN_2	Slc35d3	3.02E-18
PIMN_2	Kirrel3	3.39E-18
PIMN_2	Gpc5	6.91E-18
PIMN_2	Gsg1l	6.96E-18
PIMN_2	Gfra1	1.24E-17
PIMN_2	Fat3	2.28E-17
PIMN_2	Asl	2.79E-17
PIMN_2	Pde1c	4.55E-17
PIMN_2	Creb5	6.87E-17
PIMN_2	Slc4a4	1.13E-16
PIMN_2	Syt7	1.80E-16
PIMN_2	Asap2	5.10E-16
PIMN_2	Ass1	7.93E-16
PIMN_2	Plcb1	1.34E-15
PIMN_2	Lrrc32	5.51E-15
PIMN_2	Lamb1	5.58E-15
PIMN_2	Prkd1	6.82E-15
PIMN_2	Plxnb1	9.39E-15
PIMN_2	Il20ra	9.46E-15
PIMN_2	Trpc4	1.00E-14
PIMN_2	Ebf1	1.24E-14
PIMN_2	Kcnj5	2.56E-14
PIMN_2	A730090N16Rik	4.13E-14
PIMN_2	Cpne7	5.26E-14
PIMN_2	Mical2	6.26E-14
PIN_2	1700108F19Rik	4.45E-04
PIN_2	Evc	4.46E-04
PIN_2	Cdh3	6.58E-04
PIN_2	LOC100504608	1.13E-03
PIN_2	Vmn2r67	1.24E-03
PIN_2	E030044B06Rik	1.31E-03
PIN_2	Duoxa1	1.33E-03
PIN_2	Cyp26a1	1.68E-03
PIN_2	Gm826	1.70E-03
PIN_2	Gm2762	2.33E-03
PIN_2	Aifm3	2.82E-03
PIN_2	Cxcr4	2.97E-03
PIN_2	Ankk1	3.36E-03
PIN_2	Trim75	5.30E-03
PIN_2	Ddit4l	5.85E-03
PIN_2	2310015B20Rik	7.10E-03
PIN_2	A330070K13Rik	7.30E-03
PIN_2	AI847159	7.53E-03
PIN_2	BC049635	7.79E-03
PIN_2	Hmox1	8.29E-03
PIN_2	Myh2	8.60E-03
PIN_2	2210409D07Rik	8.72E-03
PIN_2	Mrgprb1	1.10E-02
PIN_2	Ccl2	1.19E-02
PIN_2	1700054A03Rik	1.28E-02
PIN_2	Adam33	1.68E-02
PIN_2	Cxcl14	1.92E-02
PIN_2	Agtr2	2.77E-02
PIN_2	Gm13032	2.84E-02
PIN_2	Vmn1r3	3.28E-02
PIN_2	Clec1b	3.58E-02
PIN_2	Hmgn5	4.22E-02
PIN_3	Gna14	0.00E+00
PIN_3	Nxph2	0.00E+00
PIN_3	Klhl1	0.00E+00
PIN_3	Ano5	1.22E-204
PIN_3	Ntng1	2.56E-175
PIN_3	Zmat4	6.93E-164
PIN_3	Kif26b	2.16E-148
PIN_3	Tmeff2	1.01E-133
PIN_3	Csmd1	1.46E-124
PIN_3	Slc17a6	1.76E-116
PIN_3	Galnt18	3.57E-116
PIN_3	Trps1	3.57E-116
PIN_3	Dlc1	2.63E-115
PIN_3	Kcnh7	3.38E-96
PIN_3	Pcp4l1	1.52E-91
PIN_3	Zbbx	5.62E-87
PIN_3	Skap1	8.33E-87
PIN_3	Cntn5	1.68E-86
PIN_3	Serpini1	2.01E-84
PIN_3	Ddc	5.25E-80
PIN_3	Tenm4	7.47E-80
PIN_3	Flrt2	3.34E-76
PIN_3	Gng2	4.77E-74
PIN_3	Atp7a	8.93E-74
PIN_3	Sgcz	1.99E-73
PIN_3	Tnr	3.83E-73
PIN_3	Olfr78	2.76E-72
PIN_3	0610009B14Rik	4.48E-71

Other_2	4930515L19Rik	3.79E-15
Other_2	Ms4a8a	4.79E-15
Other_2	Lypd8	6.50E-15
Other_2	Atp2c2	8.54E-15
Other_2	Tmem45b	2.43E-14
Other_2	Capn8	2.79E-14
Other_2	Slc22a14	2.79E-14
Other_2	Mlph	6.98E-14
Other_2	Ano1	9.16E-14
Other_2	Atp2a3	9.83E-14
Other_2	Shroom2	1.55E-13
Other_2	Gpr128	2.41E-13
Other_2	Hgfac	2.72E-13
Other_2	Pld1	3.68E-13
Other_2	Ern2	4.18E-13
Other_2	Mob3b	5.18E-13
Other_2	Arhgap18	1.30E-12
Other_2	Gm5414	1.70E-12
Other_2	Cdh17	1.90E-12
Other_2	Esrp1	1.94E-12
Other_2	Sh2d4a	2.78E-12
Other_2	Cyp2d13	2.79E-12
Other_2	Bsph2	2.79E-12
Other_2	Serpina9	3.08E-12
Other_2	Zg16	3.27E-12
Other_2	Spink5	4.62E-12
Other_2	Rab11fip1	4.77E-12
Other_2	Glis3	6.24E-12
Other_2	Best2	1.34E-11
Other_2	Capn9	1.35E-11
Other_2	Cpm	1.64E-11
Other_2	Cmtm8	1.64E-11
Other_2	B3galt5	1.64E-11
Other_2	Muc13	2.83E-11
Other_2	Clec2d	2.84E-11
Other_2	Slc17a9	3.15E-11
Other_2	Slc26a9	3.69E-11
Other_2	Cyp2d34	5.36E-11
Other_2	9030619P08Rik	1.11E-10
Other_2	Kit	1.23E-10
Other_2	Gm19510	1.75E-10
Other_2	5830428M24Rik	1.35E-09
Other_2	6030408B16Rik	1.86E-09
Other_2	Gata6	2.55E-09
Other_2	Kcnv2	6.86E-09
Other_2	Hoxa11as	7.96E-09
Other_2	Cyp4f40	6.23E-08
Other_2	Hpd	1.06E-07
Other_2	Abcc2	1.65E-07
Other_2	Vmn1r63	2.35E-07
Other_2	Tmem82	3.95E-07
Other_2	Tmc8	1.94E-06
Other_2	Dsp	2.06E-06
Other_2	Noxa1	2.21E-06
Other_2	Trpv3	5.56E-06
Other_2	Entpd8	1.32E-05
Other_2	Krt12	1.40E-05
Other_2	Gm53	1.51E-05
Other_2	Cdh16	4.86E-05
Other_2	Hoxa11	1.04E-04
PIMN_2	Utrn	6.85E-14
PIMN_2	Cacna1c	7.68E-14
PIMN_2	Schip1	7.68E-14
PIMN_2	Vmn1r41	8.42E-14
PIMN_2	Rgs6	1.19E-13
PIMN_2	P2rx3	1.61E-13
PIMN_2	Kcnd3	1.86E-13
PIMN_2	Postn	2.13E-13
PIMN_2	Rab37	2.41E-13
PIMN_2	Map7	3.01E-13
PIMN_2	Tenm2	3.11E-13
PIMN_2	Plekha5	3.11E-13
PIMN_2	Kcnab1	8.28E-13
PIMN_2	Specc1	8.98E-13
PIMN_2	Iqgap2	1.36E-12
PIMN_2	Cers6	1.38E-12
PIMN_2	Sulf1	1.52E-12
PIMN_2	Ldb2	1.74E-12
PIMN_2	Syne1	1.77E-12
PIMN_2	Nxn	1.79E-12
PIMN_2	Evpl	1.97E-12
PIMN_2	Scml4	2.52E-12
PIMN_2	Etv1	2.92E-12
PIMN_2	Sybu	3.58E-12
PIMN_2	Gnb3	3.59E-12
PIMN_2	Sorcs2	3.79E-12
PIMN_2	F2rl2	4.63E-12
PIMN_2	Trpm3	5.00E-12
PIMN_2	Tnr	5.58E-12
PIMN_2	Entpd3	5.58E-12
PIMN_2	Vwf	7.19E-12
PIMN_2	Tyro3	7.80E-12
PIMN_2	Dppa3	8.06E-12
PIMN_2	Acacb	1.24E-11
PIMN_2	Rims3	1.36E-11
PIMN_2	Fbxw14	1.39E-11
PIMN_2	Tmc3	1.70E-11
PIMN_2	Grik3	2.03E-11
PIMN_2	Mlxip	2.60E-11
PIMN_2	Csgalnact1	3.16E-11
PIMN_2	Sh3pxd2a	3.57E-11
PIMN_2	Fscn3	4.21E-11
PIMN_2	Clec3b	4.57E-11
PIMN_2	Slc38a4	1.92E-10
PIMN_2	Htr1d	9.33E-09
PIMN_2	Pax2	1.16E-08
PIMN_2	Calr4	2.50E-08
PIMN_2	Lgr6	3.79E-08
PIMN_2	Il9r	1.10E-07
PIMN_2	Trim50	1.94E-07
PIMN_2	Otop3	2.38E-07
PIMN_2	Wdr86	3.82E-07
PIMN_2	Afp	6.58E-07
PIMN_2	Wnt7a	1.03E-06
PIMN_2	Cd4	1.12E-06
PIMN_2	Optc	1.83E-06
PIMN_2	Akr1c18	4.84E-06
PIMN_2	Otop2	4.89E-06
PIMN_2	Serpinb2	5.95E-06
PIMN_2	4930459L07Rik	7.75E-06
PIN_3	Spock3	2.91E-70
PIN_3	Eif3h	2.58E-69
PIN_3	Nefm	2.05E-67
PIN_3	Bmpr1b	2.98E-66
PIN_3	Penk	1.84E-62
PIN_3	Prkca	3.44E-62
PIN_3	Kcng1	1.42E-61
PIN_3	Sv2c	4.17E-61
PIN_3	Pbx3	1.47E-60
PIN_3	Nefl	1.56E-60
PIN_3	Ddah1	2.19E-59
PIN_3	Adcyap1	1.18E-57
PIN_3	Sez6l	1.30E-57
PIN_3	Lrrn3	2.25E-57
PIN_3	Arhgap28	2.84E-57
PIN_3	Spock1	2.57E-55
PIN_3	Mir466g	1.38E-54
PIN_3	Bcl2	2.09E-54
PIN_3	Nebl	3.30E-54
PIN_3	Cd24a	1.38E-53
PIN_3	Npy1r	1.44E-53
PIN_3	Stac	1.74E-52
PIN_3	Pcdh7	7.43E-52
PIN_3	Rasgrf1	6.57E-51
PIN_3	March1	8.38E-51
PIN_3	L3mbtl4	9.55E-51
PIN_3	Onecut2	2.03E-49
PIN_3	Osbpl6	4.24E-49
PIN_3	Fam107b	7.82E-49
PIN_3	Nox3	1.39E-48
PIN_3	Tmem44	6.71E-48
PIN_3	D930015E06Rik	1.68E-47
PIN_3	1700042O10Rik	2.18E-46
PIN_3	Fam5c	2.35E-46
PIN_3	Parva	3.22E-46
PIN_3	Sytl5	1.06E-45
PIN_3	Fam19a2	1.15E-45
PIN_3	Mndal	1.81E-45
PIN_3	Cdh18	2.35E-45
PIN_3	Mmp17	7.91E-45
PIN_3	Enox1	2.82E-43
PIN_3	Dbh	5.52E-43
PIN_3	Cpne8	1.27E-42
PIN_3	Ush1c	2.48E-41
PIN_3	9330175M20Rik	5.32E-41
PIN_3	Itm2a	4.78E-40
PIN_3	Mfap3l	5.58E-40
PIN_3	Meis1	9.25E-40
PIN_3	Cyb561	9.40E-40
PIN_3	Tanc2	4.38E-39
PIN_3	Mt3	7.53E-39
PIN_3	Tshr	9.11E-39
PIN_3	Rab27b	1.00E-38
PIN_3	Xpr1	1.28E-38
PIN_3	Htr4	1.79E-38
PIN_3	2610307P16Rik	1.86E-38
PIN_3	Epb4.1l4a	5.98E-38
PIN_3	2810471M01Rik	8.53E-37
PIN_3	Pde9a	1.38E-36
PIN_3	Zfhx3	4.36E-36

Other_2	Rasal1	1.90E-04
Other_2	Duox2	2.95E-04
Other_2	Naip6	2.99E-04
Other_2	Kif12	3.69E-04
Other_2	Gnrhr	4.75E-04
Other_2	Hopx	5.58E-04
Other_2	Ppp1r3b	6.67E-04
Other_2	Cyp2d12	6.92E-04
Other_2	Gm14812	7.32E-04
Other_2	Mrgprb1	9.48E-04
Other_2	Pla2g4d	1.16E-03
Other_2	Hes2	1.59E-03
Other_2	Cyp2d11	2.34E-03
Other_2	Slc23a3	2.61E-03
Other_2	Ccdc42	3.01E-03
Other_2	Shh	3.13E-03
Other_2	Slfn2	3.52E-03
Other_2	Unc5cl	3.84E-03
Other_2	Lrrc66	4.09E-03
Other_2	Mir192	5.77E-03
Other_2	Scnn1g	6.96E-03
Other_2	P2ry4	8.39E-03
Other_2	Pla2g2c	1.01E-02
Other_2	Slc34a1	1.03E-02
Other_2	AF067063	1.17E-02
Other_2	Retnla	2.05E-02
Other_2	Rbbp8nl	2.35E-02
Other_2	Hbegf	4.31E-02
Other_2	Tnfsf15	4.35E-02
Other_2	Gm9926	4.96E-02
PEMN_1	Cntn4	2.42E-140
PEMN_1	Fstl4	4.51E-105
PEMN_1	Car10	1.00E-103
PEMN_1	Zcchc16	6.71E-95
PEMN_1	Cntn5	1.95E-90
PEMN_1	Csmd3	3.57E-89
PEMN_1	Nxph1	3.55E-88
PEMN_1	Cacna2d3	1.30E-84
PEMN_1	Shc4	3.16E-82
PEMN_1	Dock10	4.59E-80
PEMN_1	Lama2	1.06E-78
PEMN_1	Unc5d	1.17E-68
PEMN_1	Ntrk2	5.06E-66
PEMN_1	Gda	1.57E-62
PEMN_1	Trpc5	1.57E-62
PEMN_1	Thsd4	1.69E-59
PEMN_1	Adamts12	9.02E-59
PEMN_1	Agtr1a	2.47E-57
PEMN_1	Lrp1b	1.30E-55
PEMN_1	Synpr	5.82E-49
PEMN_1	Adgb	2.32E-45
PEMN_1	Antxr2	4.93E-45
PEMN_1	Fgfr2	1.09E-41
PEMN_1	Pion	1.30E-40
PEMN_1	Tpd52l1	1.51E-40
PEMN_1	Tac1	7.75E-39
PEMN_1	5530401A14Rik	9.60E-38
PEMN_1	Ccdc60	6.16E-37
PEMN_1	Hgf	8.76E-36
PEMN_1	Crispld1	2.12E-35
PIMN_2	Vcam1	9.92E-06
PIMN_2	2310039L15Rik	1.41E-05
PIMN_2	Pecam1	1.55E-05
PIMN_2	Gm216	1.79E-05
PIMN_2	Gm10584	1.84E-05
PIMN_2	1700010D01Rik	3.94E-05
PIMN_2	4933402N22Rik	4.04E-05
PIMN_2	Ramp3	5.30E-05
PIMN_2	2610028E06Rik	5.81E-05
PIMN_2	Tgm6	1.38E-04
PIMN_2	Spink6	1.64E-04
PIMN_2	Gja8	2.09E-04
PIMN_2	Fsd2	2.66E-04
PIMN_2	Arhgap9	2.70E-04
PIMN_2	Trim71	3.36E-04
PIMN_2	4931429L15Rik	3.36E-04
PIMN_2	Rbbp8nl	5.42E-04
PIMN_2	Usp44	5.45E-04
PIMN_2	Opalin	6.98E-04
PIMN_2	Mmp27	7.06E-04
PIMN_2	1700066B17Rik	7.46E-04
PIMN_2	4930558J18Rik	1.32E-03
PIMN_2	Ttll2	1.70E-03
PIMN_2	Hspg2	2.21E-03
PIMN_2	Gm14461	2.70E-03
PIMN_2	1700120K04Rik	2.71E-03
PIMN_2	Ly9	2.82E-03
PIMN_2	5430416O09Rik	3.32E-03
PIMN_2	H60b	3.51E-03
PIMN_2	Rbp3	3.83E-03
PIMN_2	Gm11166	3.98E-03
PIMN_2	Apol11a	4.03E-03
PIMN_2	4933425L06Rik	4.42E-03
PIMN_2	Fbxo43	5.59E-03
PIMN_2	Hlx	5.85E-03
PIMN_2	Pvrl4	6.42E-03
PIMN_2	Ripk4	7.02E-03
PIMN_2	Necab3	7.77E-03
PIMN_2	Lrrc43	8.74E-03
PIMN_2	Gm10494	9.24E-03
PIMN_2	Apol11b	1.23E-02
PIMN_2	Gm9992	1.31E-02
PIMN_2	E230025N22Rik	1.44E-02
PIMN_2	Uts2d	1.46E-02
PIMN_2	0610039K10Rik	1.50E-02
PIMN_2	Gm10745	1.50E-02
PIMN_2	Krt80	1.67E-02
PIMN_2	Gli2	2.03E-02
PIMN_2	H19	2.10E-02
PIMN_2	C1rl	2.58E-02
PIMN_2	Dok2	2.60E-02
PIMN_2	Trpv1	2.79E-02
PIMN_2	Sall4	2.87E-02
PIMN_2	Smok2a	2.95E-02
PIMN_2	4930448F12Rik	3.16E-02
PIMN_2	9630013A20Rik	3.19E-02
PIMN_2	Ltb	3.26E-02
PIMN_2	Lrat	3.30E-02
PIMN_2	Epor	3.45E-02
PIMN_2	Wnt4	3.59E-02
PIN_3	Ifi203	6.22E-36
PIN_3	Unc5c	7.37E-36
PIN_3	Colq	8.64E-36
PIN_3	Apba1	8.97E-36
PIN_3	1600029O15Rik	4.03E-35
PIN_3	Pde4b	1.28E-34
PIN_3	Palm2	1.79E-34
PIN_3	Plcl1	2.96E-34
PIN_3	Lpar4	1.09E-33
PIN_3	AW549542	1.14E-33
PIN_3	Islr2	1.90E-33
PIN_3	Fam122b	1.21E-32
PIN_3	Gm16065	1.34E-25
PIN_3	Npy5r	5.23E-25
PIN_3	Runx1	7.56E-24
PIN_3	Sstr5	2.36E-21
PIN_3	A630033H20Rik	6.88E-18
PIN_3	Taar1	1.57E-15
PIN_3	4930556J02Rik	2.60E-14
PIN_3	Taar2	1.11E-13
PIN_3	Irf5	2.44E-13
PIN_3	Spp2	4.48E-13
PIN_3	Cd40	8.35E-13
PIN_3	Ankrd34c	1.32E-12
PIN_3	4930598F16Rik	4.37E-12
PIN_3	Cckar	4.69E-12
PIN_3	Olfr560	2.35E-11
PIN_3	Islr	8.90E-10
PIN_3	Rtp1	2.65E-09
PIN_3	Vnn1	2.11E-08
PIN_3	Tmprss13	4.90E-08
PIN_3	Odam	1.67E-07
PIN_3	Fbxw28	3.92E-07
PIN_3	Ccdc33	7.77E-07
PIN_3	Samd7	9.49E-07
PIN_3	Efcab8	9.89E-07
PIN_3	Myo1g	1.95E-06
PIN_3	Zp2	2.04E-06
PIN_3	Rhox3a	8.09E-06
PIN_3	Olfr5	8.74E-06
PIN_3	Pde4c	2.13E-05
PIN_3	Taar3	2.14E-05
PIN_3	Slc6a2	5.71E-05
PIN_3	Adra2b	5.74E-05
PIN_3	Acsm2	9.09E-05
PIN_3	Prss23	1.13E-04
PIN_3	1700027A15Rik	1.18E-04
PIN_3	Vrtn	1.57E-04
PIN_3	Olfr1383	2.00E-04
PIN_3	Hoxb1	3.87E-04
PIN_3	Prl2c2	4.79E-04
PIN_3	4930513O06Rik	5.29E-04
PIN_3	Prss40	5.44E-04
PIN_3	Taar4	8.69E-04
PIN_3	4930470P17Rik	9.21E-04
PIN_3	2810433D01Rik	1.48E-03
PIN_3	1700021N21Rik	1.85E-03
PIN_3	Cd5l	2.72E-03
PIN_3	A430089I19Rik	2.87E-03
PIN_3	Nr1h5	2.99E-03

PEMN_1	Prkg1	4.67E-35
PEMN_1	Kctd8	3.50E-34
PEMN_1	Elfn1	5.84E-34
PEMN_1	Stk32a	1.27E-32
PEMN_1	Colq	6.58E-32
PEMN_1	Spock3	1.13E-31
PEMN_1	2610316D01Rik	2.11E-31
PEMN_1	Erbb4	2.21E-31
PEMN_1	Pcdh10	3.54E-31
PEMN_1	Dlgap2	6.54E-31
PEMN_1	Tmem164	1.99E-30
PEMN_1	Prkcb	3.25E-30
PEMN_1	Olfm3	6.46E-30
PEMN_1	Sh3rf3	7.06E-30
PEMN_1	Slit1	7.35E-30
PEMN_1	Syt16	4.37E-29
PEMN_1	Pdlim3	5.78E-29
PEMN_1	Gria1	1.56E-28
PEMN_1	Lsamp	2.79E-28
PEMN_1	Oprk1	1.22E-27
PEMN_1	Gpc6	1.22E-27
PEMN_1	Mir669b	1.57E-27
PEMN_1	Cacna1e	2.98E-27
PEMN_1	Ralyl	6.24E-27
PEMN_1	Atp2b2	9.58E-27
PEMN_1	Dmd	1.21E-26
PEMN_1	Amigo2	2.18E-26
PEMN_1	Gulo	4.03E-26
PEMN_1	Calcrl	1.13E-25
PEMN_1	Fam19a5	1.22E-25
PEMN_1	Pgm5	3.72E-25
PEMN_1	Dach1	6.94E-25
PEMN_1	Grik2	7.85E-25
PEMN_1	Grip1	8.12E-25
PEMN_1	Pld5	9.31E-25
PEMN_1	Neto1	1.32E-24
PEMN_1	Nebl	1.84E-24
PEMN_1	Kcnc2	4.09E-24
PEMN_1	Ltbp4	6.53E-24
PEMN_1	D330022K07Rik	6.80E-24
PEMN_1	Frem1	9.78E-24
PEMN_1	Rxfp3	2.67E-23
PEMN_1	Tenm1	2.95E-23
PEMN_1	Asic2	3.44E-23
PEMN_1	Sorbs2	6.21E-23
PEMN_1	Cntn3	7.09E-23
PEMN_1	Ust	7.82E-23
PEMN_1	Efnb2	1.74E-22
PEMN_1	Epb4.1l5	1.74E-22
PEMN_1	Gas7	1.96E-22
PEMN_1	Cdh18	2.46E-22
PEMN_1	Casz1	2.65E-22
PEMN_1	Ogfrl1	3.32E-22
PEMN_1	Cnr1	7.66E-22
PEMN_1	Kcnd2	8.34E-22
PEMN_1	Pmp22	1.83E-21
PEMN_1	Meis1	1.97E-21
PEMN_1	Ets1	2.31E-21
PEMN_1	Ryr3	7.01E-21
PEMN_1	Pde1c	1.57E-20
PIMN_2	Akr1b7	3.84E-02
PIMN_2	4732456N10Rik	4.20E-02
PIMN_2	Hic1	4.89E-02
PIMN_3	Thsd7b	1.09E-123
PIMN_3	Opcml	2.14E-102
PIMN_3	Cdh12	4.36E-100
PIMN_3	Rgs6	2.62E-93
PIMN_3	Epha8	5.07E-88
PIMN_3	Thsd7a	6.67E-88
PIMN_3	Nos1	6.21E-86
PIMN_3	Vcan	9.44E-86
PIMN_3	Hmcn1	2.05E-83
PIMN_3	Dgkb	3.29E-80
PIMN_3	Kcnab1	1.71E-79
PIMN_3	Ntrk3	1.33E-78
PIMN_3	Susd4	7.76E-77
PIMN_3	Man1a	1.62E-76
PIMN_3	Gria3	8.49E-75
PIMN_3	Tenm3	1.55E-74
PIMN_3	Slc44a5	2.26E-71
PIMN_3	Bves	6.32E-71
PIMN_3	Gm2516	5.67E-70
PIMN_3	Hdac9	9.05E-70
PIMN_3	Mfsd4	1.84E-68
PIMN_3	Bglap	7.72E-66
PIMN_3	Kcnt2	8.27E-66
PIMN_3	Cadps2	4.74E-65
PIMN_3	Etv1	2.19E-63
PIMN_3	Slc35d3	2.94E-63
PIMN_3	Gfra1	2.94E-63
PIMN_3	Dnahc11	2.11E-60
PIMN_3	Airn	2.45E-60
PIMN_3	Fat1	2.81E-60
PIMN_3	Dok5	6.73E-59
PIMN_3	Chrna7	3.07E-58
PIMN_3	Unc13c	1.26E-57
PIMN_3	Lgr5	3.14E-57
PIMN_3	Alcam	1.86E-55
PIMN_3	Oprd1	1.32E-54
PIMN_3	Auts2	1.67E-54
PIMN_3	Ank2	1.73E-54
PIMN_3	Kcnj3	2.25E-54
PIMN_3	Cacnb2	1.22E-50
PIMN_3	Arid5b	2.25E-49
PIMN_3	Stard13	5.98E-49
PIMN_3	Rbfox3	2.92E-48
PIMN_3	Ppfia2	4.85E-48
PIMN_3	Vwa5b1	9.31E-48
PIMN_3	Plekha5	3.46E-47
PIMN_3	Epha5	4.50E-47
PIMN_3	Frmd4a	1.18E-46
PIMN_3	Epha6	5.66E-46
PIMN_3	Dpysl3	6.50E-46
PIMN_3	Ppap2b	7.12E-46
PIMN_3	Dcc	2.38E-45
PIMN_3	Arhgap15	3.50E-45
PIMN_3	Fgf14	5.63E-45
PIMN_3	Celf4	1.25E-44
PIMN_3	Wwc2	5.76E-44
PIMN_3	Enpp1	1.08E-43
PIN_3	Prrx1	3.11E-03
PIN_3	Krtap12-1	4.32E-03
PIN_3	Taar5	4.43E-03
PIN_3	Procr	6.09E-03
PIN_3	4930503O07Rik	6.68E-03
PIN_3	Prps1l1	7.47E-03
PIN_3	1500015L24Rik	8.41E-03
PIN_3	6530402F18Rik	9.58E-03
PIN_3	Gm10024	1.19E-02
PIN_3	Cldn24	1.19E-02
PIN_3	Serpina4-ps1	1.30E-02
PIN_3	Hoxa13	1.64E-02
PIN_3	Il17c	2.42E-02
PIN_3	Zcchc5	2.44E-02
PIN_3	Gm3285	2.98E-02
PIN_3	Unc5cl	3.60E-02
PIN_3	1700095B10Rik	3.66E-02
PIN_3	Mir137	4.04E-02
PIN_3	C430002E04Rik	4.84E-02
PIN_3	Ms4a15	4.87E-02
PSN_1	Ano2	5.87E-212
PSN_1	Cdh8	1.13E-193
PSN_1	Speer7-ps1	1.96E-157
PSN_1	Mgat4c	9.12E-133
PSN_1	Zfp804a	3.13E-123
PSN_1	Iqub	4.81E-117
PSN_1	Efr3a	2.72E-112
PSN_1	Dapk2	1.08E-110
PSN_1	Speer8-ps1	1.11E-108
PSN_1	Itgb6	9.47E-94
PSN_1	Dgkg	4.49E-89
PSN_1	Gpr149	1.62E-83
PSN_1	A330076C08Rik	1.28E-79
PSN_1	Ccbe1	1.71E-78
PSN_1	Robo2	7.01E-77
PSN_1	Nmu	1.69E-75
PSN_1	Rab27b	1.40E-74
PSN_1	Grin3a	2.36E-73
PSN_1	Arhgap6	1.87E-69
PSN_1	Clstn2	4.48E-69
PSN_1	Cux2	5.55E-69
PSN_1	Tcf7l2	1.07E-66
PSN_1	Cpne4	1.96E-60
PSN_1	Speer5-ps1	9.20E-57
PSN_1	Myl1	2.14E-54
PSN_1	Cbln2	3.81E-53
PSN_1	Ngfr	7.20E-53
PSN_1	Cdh6	9.77E-52
PSN_1	Layn	2.65E-49
PSN_1	Hpcal1	5.69E-49
PSN_1	Slc2a13	9.27E-49
PSN_1	Scn7a	4.95E-47
PSN_1	Pcdh9	1.05E-44
PSN_1	Speer4d	2.51E-44
PSN_1	Vgll3	1.04E-42
PSN_1	4930572O03Rik	1.62E-42
PSN_1	Hpca	2.14E-42
PSN_1	Pkib	2.11E-41
PSN_1	Hspb8	2.11E-41
PSN_1	Prkag2	1.37E-39

PEMN_1	Slc16a12	2.75E-20
PEMN_1	Reln	3.17E-20
PEMN_1	Hs6st1	5.23E-20
PEMN_1	Tox	5.33E-20
PEMN_1	Atrnl1	7.23E-20
PEMN_1	Parvb	1.93E-19
PEMN_1	Rimbp2	3.08E-19
PEMN_1	Sec14l5	4.08E-19
PEMN_1	Pcsk1	5.27E-19
PEMN_1	Epha6	9.23E-19
PEMN_1	Sertm1	1.32E-15
PEMN_1	Itgax	5.36E-15
PEMN_1	F730043M19Rik	3.79E-14
PEMN_1	Crhbp	1.63E-11
PEMN_1	Vmn2r101	2.44E-11
PEMN_1	Gpr55	1.42E-09
PEMN_1	Mpped1	1.45E-09
PEMN_1	Pate4	4.30E-09
PEMN_1	Rdh8	1.10E-08
PEMN_1	Nostrin	1.28E-08
PEMN_1	5430427O19Rik	1.64E-08
PEMN_1	Hapln4	5.31E-08
PEMN_1	4933400B14Rik	8.38E-08
PEMN_1	Serpinb3c	8.92E-08
PEMN_1	Col9a1	9.03E-08
PEMN_1	Bhlha15	1.39E-07
PEMN_1	Lrtm1	1.46E-07
PEMN_1	Gm1631	2.36E-07
PEMN_1	Ptcra	1.47E-06
PEMN_1	Gm5860	1.31E-05
PEMN_1	AA387883	1.32E-05
PEMN_1	Fgr	1.45E-05
PEMN_1	Spc25	1.97E-05
PEMN_1	Gm11186	2.02E-05
PEMN_1	Cyp2c37	3.07E-05
PEMN_1	BC051628	3.28E-05
PEMN_1	Mmp12	1.14E-04
PEMN_1	Prlhr	1.19E-04
PEMN_1	Gad1	1.33E-04
PEMN_1	Ptprv	1.51E-04
PEMN_1	Ccdc108	1.77E-04
PEMN_1	Cldn18	1.80E-04
PEMN_1	Upk1b	1.81E-04
PEMN_1	Ccna1	2.02E-04
PEMN_1	Ccdc113	2.34E-04
PEMN_1	Pvrl4	2.49E-04
PEMN_1	Ccdc154	3.21E-04
PEMN_1	Klf2	3.25E-04
PEMN_1	Itgb2l	3.35E-04
PEMN_1	Ppp1r1c	4.30E-04
PEMN_1	1700064J06Rik	4.78E-04
PEMN_1	Arhgap36	5.35E-04
PEMN_1	A230077H06Rik	5.50E-04
PEMN_1	Cd180	5.60E-04
PEMN_1	Myf6	1.00E-03
PEMN_1	Gjc3	1.49E-03
PEMN_1	1700006H21Rik	1.65E-03
PEMN_1	Lrrc10b	1.91E-03
PEMN_1	1700112H15Rik	1.97E-03
PEMN_1	A230001M10Rik	2.98E-03
PIMN_3	Kcnj5	2.71E-43
PIMN_3	Rarb	7.49E-43
PIMN_3	Bmp2k	1.24E-42
PIMN_3	Il20ra	1.45E-42
PIMN_3	Plch2	3.65E-42
PIMN_3	Fam155a	4.17E-42
PIMN_3	Syt2	5.48E-42
PIMN_3	Lpp	7.98E-42
PIMN_3	Igf2r	1.75E-41
PIMN_3	Slit3	2.21E-41
PIMN_3	Igsf21	3.27E-41
PIMN_3	Col5a2	2.45E-40
PIMN_3	A730090N16Rik	9.16E-40
PIMN_3	Tmem108	1.30E-39
PIMN_3	Ablim2	1.38E-39
PIMN_3	Pcdh15	3.25E-39
PIMN_3	Robo1	4.41E-39
PIMN_3	Wipi1	5.21E-39
PIMN_3	Cped1	6.87E-39
PIMN_3	Atp8a2	9.72E-39
PIMN_3	Abca1	1.04E-38
PIMN_3	Tcf7l1	2.69E-38
PIMN_3	Dusp15	3.37E-38
PIMN_3	Creb5	6.58E-38
PIMN_3	Gm5607	1.04E-37
PIMN_3	Pdlim5	2.42E-37
PIMN_3	Slc35f1	2.82E-37
PIMN_3	Gm11602	1.56E-36
PIMN_3	Sntb1	1.67E-36
PIMN_3	P2rx2	1.77E-36
PIMN_3	Clvs1	2.12E-36
PIMN_3	Pcdh9	2.91E-36
PIMN_3	Gm14391	4.53E-36
PIMN_3	Grb14	8.10E-36
PIMN_3	Synpo2	8.10E-36
PIMN_3	Tnr	2.83E-35
PIMN_3	Plekha7	3.86E-35
PIMN_3	Adamts5	1.51E-34
PIMN_3	Lama5	6.22E-34
PIMN_3	Cacna1d	1.51E-33
PIMN_3	Kcnq4	1.66E-33
PIMN_3	Gnal	1.77E-33
PIMN_3	Ccnjl	3.51E-33
PIMN_3	Bglap2	4.19E-33
PIMN_3	Mpz	8.28E-28
PIMN_3	Exph5	1.20E-25
PIMN_3	Ptch2	1.96E-25
PIMN_3	Mmd2	3.21E-24
PIMN_3	Grin2b	1.48E-22
PIMN_3	Cox8b	2.21E-20
PIMN_3	Apcdd1	4.83E-20
PIMN_3	3110039I08Rik	1.69E-18
PIMN_3	Gfpt2	9.69E-17
PIMN_3	Myo10	9.27E-16
PIMN_3	Rhbdf2	4.18E-15
PIMN_3	Ar	2.41E-11
PIMN_3	Sox8	9.05E-11
PIMN_3	Sox2ot	4.39E-09
PIMN_3	Npy	1.18E-08
PIMN_3	Eda2r	1.90E-06
PSN_1	Avil	3.91E-39
PSN_1	Gm9758	4.93E-39
PSN_1	Tmeff2	1.05E-38
PSN_1	Calcb	2.41E-38
PSN_1	Speer4e	3.27E-38
PSN_1	Tacr1	4.65E-38
PSN_1	Gm17019	1.39E-37
PSN_1	Apba2	1.88E-37
PSN_1	Agrn	3.03E-37
PSN_1	Rph3a	4.70E-37
PSN_1	Atoh8	2.49E-35
PSN_1	Il7	4.88E-35
PSN_1	Gcgr	7.46E-35
PSN_1	Snx31	7.46E-35
PSN_1	Nrxn3	1.99E-34
PSN_1	Tbx2	5.30E-34
PSN_1	Pak7	7.24E-34
PSN_1	Il13ra1	8.99E-34
PSN_1	Htr3a	3.61E-33
PSN_1	Dgki	1.56E-32
PSN_1	Galr1	5.14E-32
PSN_1	Ptprt	1.42E-31
PSN_1	Nos1ap	3.00E-31
PSN_1	Dclk3	7.74E-31
PSN_1	Dlx3	8.81E-31
PSN_1	Gm9199	1.29E-30
PSN_1	B3galt1	1.60E-30
PSN_1	Unc13c	2.90E-30
PSN_1	Capn5	3.98E-30
PSN_1	Ntrk3	6.86E-30
PSN_1	Pkia	3.09E-29
PSN_1	Smad6	8.97E-29
PSN_1	Grp	1.40E-28
PSN_1	Lhfpl2	2.87E-28
PSN_1	Gm12530	3.33E-28
PSN_1	Greb1	1.62E-27
PSN_1	Met	1.68E-27
PSN_1	Spock3	2.63E-27
PSN_1	1700007B14Rik	6.30E-27
PSN_1	Cachd1	2.96E-26
PSN_1	Slc12a7	4.27E-26
PSN_1	Dnaja1	5.85E-26
PSN_1	Gstm1	6.53E-26
PSN_1	Spag5	7.05E-26
PSN_1	Spsb1	7.45E-26
PSN_1	Psmd13	9.77E-26
PSN_1	Hspb1	4.93E-25
PSN_1	Cntnap3	5.97E-25
PSN_1	Pcgf1	2.95E-24
PSN_1	Syt15	4.72E-24
PSN_1	March1	7.70E-24
PSN_1	Amigo2	1.26E-23
PSN_1	Kcnb2	1.26E-23
PSN_1	Vmn2r-ps54	5.10E-23
PSN_1	Cysltr2	6.83E-23
PSN_1	Scube1	2.95E-22
PSN_1	Chst15	3.08E-22
PSN_1	Prrt2	3.97E-22
PSN_1	Asah2	4.18E-22
PSN_1	Susd2	4.22E-22

PEMN_1	BC125332	3.00E-03
PEMN_1	Bhmt	3.04E-03
PEMN_1	Shisa3	3.40E-03
PEMN_1	Capn9	3.65E-03
PEMN_1	Foxj1	3.93E-03
PEMN_1	Trpa1	5.65E-03
PEMN_1	4933425H06Rik	5.97E-03
PEMN_1	Asb17	7.04E-03
PEMN_1	Tarm1	7.85E-03
PEMN_1	Prss29	8.05E-03
PEMN_1	Gpr33	9.93E-03
PEMN_1	Cmtm2a	9.96E-03
PEMN_1	7630403G23Rik	1.13E-02
PEMN_1	Gpr52	1.26E-02
PEMN_1	Hs3st6	1.33E-02
PEMN_1	Ndufs5	1.34E-02
PEMN_1	Tmem154	1.36E-02
PEMN_1	Yipf7	1.49E-02
PEMN_1	Ribc2	1.52E-02
PEMN_1	H60c	1.88E-02
PEMN_1	Vmn2r70	1.98E-02
PEMN_1	Rhoh	2.07E-02
PEMN_1	1700025F24Rik	2.08E-02
PEMN_1	1110059M19Rik	2.60E-02
PEMN_1	Ttc24	2.90E-02
PEMN_1	Ecel1	3.07E-02
PEMN_1	P2ry13	3.21E-02
PEMN_1	Pinc	3.36E-02
PEMN_1	Fmo6	4.06E-02
PEMN_1	1700031A10Rik	4.37E-02
PEMN_1	Dcaf12l2	4.48E-02
PEMN_1	Tmem81	4.76E-02
PEMN_2	Pgm5	1.56E-45
PEMN_2	Plxdc2	4.99E-44
PEMN_2	Edil3	8.16E-42
PEMN_2	Pion	1.32E-35
PEMN_2	Kcns3	2.94E-35
PEMN_2	Lrp1b	2.43E-34
PEMN_2	Gda	1.41E-32
PEMN_2	Prom1	1.84E-32
PEMN_2	Extl1	4.61E-32
PEMN_2	Csmd3	6.31E-32
PEMN_2	Cntn3	1.05E-31
PEMN_2	Gria1	1.27E-28
PEMN_2	Rab3b	6.77E-28
PEMN_2	Nxph1	2.64E-27
PEMN_2	Plcl1	3.61E-27
PEMN_2	Abca5	9.35E-27
PEMN_2	Shc4	5.90E-26
PEMN_2	Sphkap	6.85E-26
PEMN_2	Vldlr	1.39E-25
PEMN_2	Synpr	2.99E-25
PEMN_2	Lrrc7	3.84E-25
PEMN_2	Tac1	1.35E-24
PEMN_2	Ccdc60	1.27E-23
PEMN_2	Agtr1a	1.75E-23
PEMN_2	Cntn5	3.06E-23
PEMN_2	Prkg1	1.75E-22
PEMN_2	Pdlim3	1.43E-21
PEMN_2	Pde1b	2.16E-21
PIMN_3	Gpr88	4.76E-06
PIMN_3	Klk1b1	1.04E-05
PIMN_3	Spn-ps	1.37E-05
PIMN_3	Runx3	1.88E-05
PIMN_3	Pipox	2.15E-05
PIMN_3	2310030G06Rik	4.03E-05
PIMN_3	Lmo2	5.40E-05
PIMN_3	Serpina3c	7.46E-05
PIMN_3	Fzd10	1.06E-04
PIMN_3	A930009A15Rik	1.09E-04
PIMN_3	1700085C21Rik	1.15E-04
PIMN_3	Ajap1	1.29E-04
PIMN_3	H1foo	1.63E-04
PIMN_3	Gm15091	1.71E-04
PIMN_3	Smyd1	1.72E-04
PIMN_3	Meox2	2.22E-04
PIMN_3	Gm20743	3.11E-04
PIMN_3	Ripk3	3.56E-04
PIMN_3	Foxo6	4.18E-04
PIMN_3	Serpina3i	4.88E-04
PIMN_3	Nr2f1	6.44E-04
PIMN_3	Ifi44l	9.46E-04
PIMN_3	Serpina3b	1.16E-03
PIMN_3	4930548J01Rik	1.36E-03
PIMN_3	2900002K06Rik	1.44E-03
PIMN_3	Xcl1	1.70E-03
PIMN_3	Cdca5	1.90E-03
PIMN_3	Slc25a48	2.92E-03
PIMN_3	Vmn2r69	2.94E-03
PIMN_3	2700046A07Rik	3.55E-03
PIMN_3	Htr5a	3.60E-03
PIMN_3	1700049E22Rik	3.65E-03
PIMN_3	Fam47e	3.65E-03
PIMN_3	Nlrp4f	3.66E-03
PIMN_3	2310034O05Rik	3.73E-03
PIMN_3	Cd8a	3.96E-03
PIMN_3	Foxs1	4.87E-03
PIMN_3	Prox1	5.02E-03
PIMN_3	Tuba8	7.51E-03
PIMN_3	Aadacl3	9.29E-03
PIMN_3	Lox	9.56E-03
PIMN_3	Lyg1	9.61E-03
PIMN_3	Ctf2	1.38E-02
PIMN_3	Gm5549	1.65E-02
PIMN_3	Qrfp	1.73E-02
PIMN_3	4930433I11Rik	1.75E-02
PIMN_3	1190002F15Rik	1.80E-02
PIMN_3	Gm7168	2.16E-02
PIMN_3	Tmem52	2.19E-02
PIMN_3	Kcnj4	2.22E-02
PIMN_3	Treml2	2.26E-02
PIMN_3	Gm4858	2.30E-02
PIMN_3	Pgc	2.49E-02
PIMN_3	Fabp6	2.70E-02
PIMN_3	Cdc20	2.95E-02
PIMN_3	9230110F15Rik	2.99E-02
PIMN_3	Gm11756	2.99E-02
PIMN_3	Hemgn	3.02E-02
PIMN_3	Psapl1	3.05E-02
PIMN_3	9130209A04Rik	3.13E-02
PSN_1	Aldh1l1	1.40E-21
PSN_1	Nog	1.11E-20
PSN_1	Serpinf1	7.36E-19
PSN_1	Gpr126	1.25E-18
PSN_1	Adamts14	4.08E-18
PSN_1	Mybph	8.05E-18
PSN_1	Cplx4	1.24E-17
PSN_1	Gm6756	2.69E-15
PSN_1	Gm8096	1.30E-14
PSN_1	Slc6a19	2.27E-14
PSN_1	Hey1	7.33E-14
PSN_1	Otof	5.81E-13
PSN_1	Pdlim2	5.33E-12
PSN_1	Serpina3n	2.92E-11
PSN_1	Gm2721	4.58E-11
PSN_1	Kcp	7.59E-11
PSN_1	Arsi	8.65E-11
PSN_1	Folh1	1.62E-10
PSN_1	Zfp819	1.99E-10
PSN_1	Cox6b2	2.11E-09
PSN_1	Cxcr7	4.43E-09
PSN_1	Fmod	5.11E-09
PSN_1	Gm16197	5.76E-09
PSN_1	Myh4	7.68E-09
PSN_1	Gstm6	9.74E-09
PSN_1	4930453H23Rik	1.64E-08
PSN_1	Tmem119	3.42E-08
PSN_1	E2f1	3.51E-08
PSN_1	Irs3	3.53E-08
PSN_1	Gng13	7.01E-08
PSN_1	Amelx	7.20E-08
PSN_1	Gbp2	1.06E-07
PSN_1	Psg26	1.58E-07
PSN_1	Foxa2	1.59E-07
PSN_1	Inhbb	9.31E-07
PSN_1	Sod3	9.38E-07
PSN_1	Mrap	1.05E-06
PSN_1	Trim47	1.82E-06
PSN_1	2700070H01Rik	3.46E-06
PSN_1	Ppm1n	4.06E-06
PSN_1	2410124H12Rik	4.62E-06
PSN_1	4930417O13Rik	4.03E-05
PSN_1	Gdf5	5.22E-05
PSN_1	Hrk	9.92E-05
PSN_1	1110032F04Rik	1.27E-04
PSN_1	Ccdc8	2.72E-04
PSN_1	Gja3	3.65E-04
PSN_1	Oas1e	1.20E-03
PSN_1	Chrdl2	3.69E-03
PSN_1	Klhl30	5.65E-03
PSN_1	AW011738	6.49E-03
PSN_1	Ppp3r2	2.02E-02
PSN_1	Iigp1	2.24E-02
PSN_1	Hist1h2bp	4.36E-02
PSN_2	Mgat4c	6.98E-268
PSN_2	A930011G23Rik	1.69E-247
PSN_2	Cdh9	6.92E-146
PSN_2	Agtr1b	1.37E-135
PSN_2	Speer4a	2.66E-106
PSN_2	Arhgap6	1.49E-89

PEMN_2	Crispld1	9.44E-21
PEMN_2	Lingo2	2.92E-20
PEMN_2	Dock10	5.93E-20
PEMN_2	Socs2	1.68E-19
PEMN_2	Cntnap5b	5.11E-19
PEMN_2	Gas7	1.18E-18
PEMN_2	Kcnc2	1.83E-18
PEMN_2	Arhgap28	5.03E-18
PEMN_2	Srgap1	9.68E-17
PEMN_2	Ism1	1.34E-16
PEMN_2	Lin7a	1.79E-16
PEMN_2	Rmst	2.12E-16
PEMN_2	Grem2	3.69E-16
PEMN_2	Colq	3.84E-16
PEMN_2	Kctd8	7.66E-16
PEMN_2	Lphn3	8.63E-16
PEMN_2	Fgfr2	1.07E-15
PEMN_2	Gpc6	1.25E-15
PEMN_2	Runx1t1	1.30E-15
PEMN_2	Olfm2	1.37E-15
PEMN_2	Fam19a5	1.82E-15
PEMN_2	Ryr2	1.83E-15
PEMN_2	Exoc3l4	2.46E-15
PEMN_2	Atp2b2	3.17E-15
PEMN_2	Ets1	3.17E-15
PEMN_2	A830018L16Rik	3.53E-15
PEMN_2	Dmd	3.53E-15
PEMN_2	Dach1	4.59E-15
PEMN_2	Unc5d	4.62E-15
PEMN_2	Prkcb	4.62E-15
PEMN_2	Il2	4.99E-15
PEMN_2	Calcrl	1.21E-14
PEMN_2	Lsamp	1.26E-14
PEMN_2	Ltbp4	3.55E-14
PEMN_2	Elavl2	7.97E-14
PEMN_2	Sh3rf3	1.32E-13
PEMN_2	Pld5	2.03E-13
PEMN_2	Tmem255a	2.07E-13
PEMN_2	Cnr1	2.71E-13
PEMN_2	Ptprm	2.71E-13
PEMN_2	Grik1	5.58E-13
PEMN_2	St8sia2	7.14E-13
PEMN_2	Casz1	1.10E-12
PEMN_2	Hgf	1.19E-12
PEMN_2	Grm7	1.28E-12
PEMN_2	Gch1	1.94E-12
PEMN_2	Htr1f	1.97E-12
PEMN_2	Stk32a	2.31E-12
PEMN_2	Nkain2	2.47E-12
PEMN_2	Gucy1a3	2.76E-12
PEMN_2	Pmp22	5.40E-12
PEMN_2	Spock1	5.69E-12
PEMN_2	Slc16a12	5.96E-12
PEMN_2	Necab2	6.92E-12
PEMN_2	Whrn	6.93E-12
PEMN_2	Nr1h4	7.65E-12
PEMN_2	Slc6a17	9.66E-12
PEMN_2	Camk4	1.04E-11
PEMN_2	Prmt8	1.09E-11
PEMN_2	Epb4.1l5	1.16E-11
PIMN_3	Cd3d	3.44E-02
PIMN_3	Spta1	3.58E-02
PIMN_3	Lef1	3.63E-02
PIMN_3	Cyp4a29-ps	3.65E-02
PIMN_3	Cdcp2	3.70E-02
PIMN_3	Mtl5	3.91E-02
PIMN_3	5430440P10Rik	4.03E-02
PIMN_3	Ctla4	4.15E-02
PIMN_3	Spin4	4.24E-02
PIMN_3	7420461P10Rik	4.46E-02
PIMN_3	Cga	4.97E-02
PIMN_4	Ltbp1	4.74E-104
PIMN_4	Cttnbp2	6.26E-96
PIMN_4	Thsd7a	1.29E-95
PIMN_4	Thsd7b	7.98E-94
PIMN_4	Vcan	3.49E-85
PIMN_4	Col7a1	2.48E-78
PIMN_4	Dcc	6.72E-74
PIMN_4	Vwa5b1	1.37E-71
PIMN_4	Opcml	3.88E-71
PIMN_4	Tenm3	3.12E-63
PIMN_4	Rgs6	4.56E-62
PIMN_4	Nos1	9.62E-61
PIMN_4	Ntrk3	3.47E-55
PIMN_4	Fat1	6.35E-53
PIMN_4	Gfra1	3.06E-52
PIMN_4	Unc13c	5.70E-52
PIMN_4	Kcnj3	2.09E-50
PIMN_4	Igf1r	3.05E-49
PIMN_4	Gm5607	2.48E-48
PIMN_4	Dok5	3.19E-47
PIMN_4	Etv1	2.57E-46
PIMN_4	Fgf14	2.73E-45
PIMN_4	Airn	6.25E-44
PIMN_4	Creb5	1.48E-43
PIMN_4	Cacnb2	1.48E-43
PIMN_4	Ptprg	6.80E-43
PIMN_4	Lpp	9.44E-42
PIMN_4	Kcnh8	1.11E-41
PIMN_4	Gm2516	1.62E-41
PIMN_4	Bves	5.24E-41
PIMN_4	Oprd1	6.15E-41
PIMN_4	Stab2	6.04E-40
PIMN_4	Slc44a5	9.32E-40
PIMN_4	Mboat2	4.23E-39
PIMN_4	Gabrb2	5.90E-39
PIMN_4	Dach1	6.05E-39
PIMN_4	Cacna1d	1.08E-38
PIMN_4	Syn3	1.30E-38
PIMN_4	Lama5	3.39E-38
PIMN_4	Epha8	5.93E-38
PIMN_4	Mfsd4	8.22E-37
PIMN_4	Col5a2	1.38E-36
PIMN_4	Kcnj5	1.80E-36
PIMN_4	Ppap2b	1.87E-36
PIMN_4	Timp3	2.18E-36
PIMN_4	Asap1	4.28E-36
PIMN_4	A530058N18Rik	9.41E-36
PIMN_4	Kcnab1	9.41E-36
PIMN_4	Man1a	1.46E-35
PSN_2	Gm10471	4.92E-83
PSN_2	Mir466g	3.36E-79
PSN_2	Gm10220	1.59E-78
PSN_2	Glra1	2.55E-75
PSN_2	Klhl1	1.51E-64
PSN_2	5031410I06Rik	1.03E-63
PSN_2	March1	7.48E-59
PSN_2	Galnt18	1.15E-53
PSN_2	Cdh8	1.21E-53
PSN_2	Serpine2	1.26E-53
PSN_2	Cacna2d3	1.06E-52
PSN_2	Vmn2r15	1.10E-52
PSN_2	Vwc2l	1.35E-50
PSN_2	9330175M20Rik	1.42E-47
PSN_2	Ano2	7.32E-47
PSN_2	2210039B01Rik	1.30E-45
PSN_2	Tmeff2	2.10E-43
PSN_2	Dgkg	2.17E-43
PSN_2	Nmur2	3.18E-43
PSN_2	Plcl1	1.11E-41
PSN_2	Sgcz	7.60E-40
PSN_2	Gm1604b	1.25E-38
PSN_2	Pcdh9	4.52E-38
PSN_2	Zbbx	7.17E-38
PSN_2	2610307P16Rik	2.27E-34
PSN_2	Galnt13	2.80E-34
PSN_2	Cblb	7.77E-34
PSN_2	Spock3	1.24E-33
PSN_2	Gm648	5.34E-33
PSN_2	1700013H16Rik	1.09E-31
PSN_2	Nek1	1.90E-31
PSN_2	Htr4	2.39E-31
PSN_2	Ctnna2	8.47E-31
PSN_2	Zfhx3	1.28E-30
PSN_2	Disp1	6.10E-30
PSN_2	Kif26b	1.09E-29
PSN_2	Clstn2	1.17E-29
PSN_2	Sdpr	9.03E-29
PSN_2	Mir1970	1.02E-27
PSN_2	Cntnap2	1.28E-27
PSN_2	Tcf7l2	1.93E-25
PSN_2	Pbx3	3.28E-25
PSN_2	Mapk4	4.62E-25
PSN_2	Kcnk2	9.36E-25
PSN_2	Car10	1.10E-24
PSN_2	Cachd1	1.98E-24
PSN_2	Htr1f	2.84E-24
PSN_2	Scgn	2.93E-24
PSN_2	Palld	1.00E-23
PSN_2	Pax4	2.04E-23
PSN_2	Syt9	1.51E-22
PSN_2	Dgki	4.46E-22
PSN_2	Apba1	4.59E-22
PSN_2	Sema5a	5.05E-22
PSN_2	Slc2a13	7.60E-22
PSN_2	Robo2	1.96E-21
PSN_2	Ccbe1	2.91E-21
PSN_2	Aff3	3.18E-21
PSN_2	Hs6st2	4.29E-21
PSN_2	Cadm2	8.60E-21

PEMN_2	Sertm1	1.44E-11
PEMN_2	Gm15179	1.67E-11
PEMN_2	Trpc7	1.86E-11
PEMN_2	Gabrg3	1.90E-11
PEMN_2	Slit1	1.96E-11
PEMN_2	Msrb3	2.52E-11
PEMN_2	Ralyl	2.54E-11
PEMN_2	Olfm1	2.86E-11
PEMN_2	Chst1	3.88E-11
PEMN_2	Diras2	5.82E-11
PEMN_2	Nyap2	5.84E-11
PEMN_2	Pcdh10	8.74E-11
PEMN_2	Corin	2.93E-10
PEMN_2	Tmem252	6.73E-10
PEMN_2	Gm15080	1.18E-09
PEMN_2	9830132P13Rik	1.21E-09
PEMN_2	Adra1d	1.30E-09
PEMN_2	Dbpht2	1.61E-09
PEMN_2	1700027H10Rik	1.07E-08
PEMN_2	Vmn2r105	1.93E-08
PEMN_2	Treml1	2.33E-08
PEMN_2	Nrsn2	4.30E-08
PEMN_2	Enc1	5.49E-08
PEMN_2	Trpm8	7.61E-08
PEMN_2	Prlhr	1.12E-07
PEMN_2	Lypd1	1.77E-07
PEMN_2	2010204K13Rik	2.02E-07
PEMN_2	Cel	2.06E-07
PEMN_2	Cst12	2.81E-07
PEMN_2	Gm11413	3.18E-07
PEMN_2	1700109G14Rik	5.03E-07
PEMN_2	Cpvl	3.50E-06
PEMN_2	Klhdc8a	4.14E-06
PEMN_2	Nox4	7.51E-06
PEMN_2	Mro	2.64E-05
PEMN_2	Adm	3.17E-05
PEMN_2	Olfr53	4.63E-05
PEMN_2	Emx2os	4.81E-05
PEMN_2	Rxfp3	5.04E-05
PEMN_2	Bmx	5.73E-05
PEMN_2	7420701I03Rik	7.05E-05
PEMN_2	Gm4340	7.54E-05
PEMN_2	Gata1	9.95E-05
PEMN_2	Zpld1	1.31E-04
PEMN_2	C1qtnf7	2.02E-04
PEMN_2	Alx1	2.12E-04
PEMN_2	Pdgfra	2.89E-04
PEMN_2	Aurkb	4.27E-04
PEMN_2	Psrc1	4.59E-04
PEMN_2	Hck	7.42E-04
PEMN_2	2310005A03Rik	7.89E-04
PEMN_2	Cenpm	9.08E-04
PEMN_2	Gabrd	9.53E-04
PEMN_2	Apitd1	1.04E-03
PEMN_2	Fam84b	1.05E-03
PEMN_2	Apobec2	1.72E-03
PEMN_2	Gdnf	2.31E-03
PEMN_2	C330022C24Rik	2.51E-03
PEMN_2	Tcl1b4	2.90E-03
PEMN_2	Gm14139	2.90E-03

PIMN_4	Slc35d3	4.20E-35
PIMN_4	Kcnt2	1.03E-34
PIMN_4	Tmem108	3.11E-34
PIMN_4	C1ql1	1.09E-33
PIMN_4	Ccnjl	3.51E-33
PIMN_4	Rnf144b	8.68E-33
PIMN_4	Ablim2	1.26E-32
PIMN_4	Arhgef26	5.91E-32
PIMN_4	Zfp536	1.66E-31
PIMN_4	Gulp1	1.85E-31
PIMN_4	Sntb1	2.96E-31
PIMN_4	Dnahc11	1.23E-30
PIMN_4	Clvs1	1.31E-30
PIMN_4	Rarb	1.79E-30
PIMN_4	Cacna1c	1.94E-30
PIMN_4	Ank2	2.19E-30
PIMN_4	Fbxo7	5.21E-30
PIMN_4	Tcf7l1	9.25E-30
PIMN_4	1700113H08Rik	1.24E-29
PIMN_4	Sox8	2.91E-29
PIMN_4	Caln1	3.46E-29
PIMN_4	Hmcn1	4.91E-29
PIMN_4	Entpd3	3.55E-28
PIMN_4	Igf2r	6.27E-28
PIMN_4	Srcin1	9.75E-28
PIMN_4	Gm14718	1.06E-27
PIMN_4	Sgk1	1.21E-27
PIMN_4	Ncald	1.36E-27
PIMN_4	Synpo2	3.44E-27
PIMN_4	Alcam	4.22E-27
PIMN_4	Kcnq4	5.56E-27
PIMN_4	Wipi1	7.51E-27
PIMN_4	Ptchd1	1.16E-26
PIMN_4	Auts2	1.84E-26
PIMN_4	Bmper	5.05E-26
PIMN_4	Cped1	5.58E-26
PIMN_4	Spsb4	8.03E-26
PIMN_4	Wwc2	4.02E-25
PIMN_4	Epha5	4.11E-25
PIMN_4	Afap1l1	5.18E-25
PIMN_4	Acpl2	6.32E-25
PIMN_4	Ass1	7.60E-25
PIMN_4	Dock9	1.67E-24
PIMN_4	Frmd4a	2.04E-24
PIMN_4	Sema3a	2.11E-24
PIMN_4	Popdc3	8.71E-24
PIMN_4	Robo1	2.96E-23
PIMN_4	Pde1c	5.46E-23
PIMN_4	Ppm1h	6.79E-23
PIMN_4	Oprm1	7.65E-23
PIMN_4	Fam155a	9.85E-23
PIMN_4	Efcc1	1.13E-22
PIMN_4	Nptx1	1.63E-20
PIMN_4	5930412G12Rik	4.61E-19
PIMN_4	Igdcc3	1.85E-17
PIMN_4	Sox2ot	6.40E-14
PIMN_4	Lmx1b	9.93E-13
PIMN_4	Lipf	6.31E-09
PIMN_4	Ptgds	2.28E-07
PIMN_4	E030019B06Rik	3.64E-07

PSN_2	Ddah1	3.58E-20
PSN_2	Cck	3.96E-20
PSN_2	Speer5-ps1	2.70E-19
PSN_2	Ephx2	5.49E-19
PSN_2	Gabrg3	5.51E-19
PSN_2	Bcl2	7.73E-19
PSN_2	Clca2	2.63E-18
PSN_2	Nrxn3	1.33E-17
PSN_2	4933416M07Rik	1.48E-17
PSN_2	Speer7-ps1	8.30E-17
PSN_2	Alk	8.76E-17
PSN_2	Epha3	9.02E-17
PSN_2	Rasgef1b	9.31E-17
PSN_2	Gm20754	9.31E-17
PSN_2	2410137M14Rik	1.81E-16
PSN_2	Serpini1	2.79E-16
PSN_2	Osbpl6	5.03E-16
PSN_2	Umod	8.62E-16
PSN_2	Vsnl1	1.08E-15
PSN_2	Il1rapl1	1.35E-15
PSN_2	Cd244	2.27E-15
PSN_2	Apba2	2.38E-15
PSN_2	Spert	2.38E-15
PSN_2	Dlc1	3.02E-15
PSN_2	B3galtl	3.36E-15
PSN_2	Tbx2	3.76E-15
PSN_2	Xkr4	4.96E-15
PSN_2	Stxbp2	7.18E-15
PSN_2	Ank	7.83E-15
PSN_2	Tshz3	8.02E-15
PSN_2	Rph3a	8.38E-15
PSN_2	Sntg1	1.24E-14
PSN_2	1700072O05Rik	2.23E-14
PSN_2	Pbx1	7.26E-14
PSN_2	Fgd2	1.95E-13
PSN_2	Oas2	2.61E-13
PSN_2	1500009C09Rik	2.61E-13
PSN_2	Rspo3	2.84E-13
PSN_2	Hormad2	5.28E-13
PSN_2	Gfral	8.11E-13
PSN_2	Vmn1r58	1.30E-12
PSN_2	Tekt5	1.04E-10
PSN_2	Ucn3	3.24E-10
PSN_2	Gpr132	7.27E-10
PSN_2	Enc1	1.12E-09
PSN_2	Gm4745	5.33E-09
PSN_2	Hist1h4m	5.70E-09
PSN_2	Fabp7	5.85E-09
PSN_2	Slc2a5	8.10E-09
PSN_2	Defb23	1.86E-08
PSN_2	Chrna2	2.11E-08
PSN_2	4933439K11Rik	2.30E-08
PSN_2	Slc6a13	2.93E-08
PSN_2	Klk1b3	6.91E-08
PSN_2	Lrtm1	1.13E-07
PSN_2	1700017G19Rik	1.29E-07
PSN_2	Pygo1	2.37E-07
PSN_2	Gstt4	3.77E-07
PSN_2	1700030M09Rik	3.84E-07
PSN_2	6430562O15Rik	4.16E-07

PEMN_2	Tsga8	3.37E-03
PEMN_2	Hs3st3a1	3.59E-03
PEMN_2	Fcrl1	4.28E-03
PEMN_2	Gm11762	4.68E-03
PEMN_2	F730043M19Rik	5.09E-03
PEMN_2	Krt76	6.59E-03
PEMN_2	Kel	7.85E-03
PEMN_2	Klri1	8.17E-03
PEMN_2	Wbp2nl	9.69E-03
PEMN_2	Rsg1	9.84E-03
PEMN_2	Rprm	9.90E-03
PEMN_2	Tec	1.03E-02
PEMN_2	3110070M22Rik	1.21E-02
PEMN_2	Gpr44	1.50E-02
PEMN_2	Gm4981	1.62E-02
PEMN_2	Il21	1.71E-02
PEMN_2	Wnt4	1.90E-02
PEMN_2	Wnt3a	1.99E-02
PEMN_2	Plac1	2.05E-02
PEMN_2	9230104L09Rik	2.41E-02
PEMN_2	Pnma1	2.55E-02
PEMN_2	Cd3e	2.70E-02
PEMN_2	Gm8298	2.72E-02
PEMN_2	Nmur1	2.72E-02
PEMN_2	Erg	3.05E-02
PEMN_2	Ip6k3	3.45E-02
PEMN_2	Aqp12	3.98E-02
PEMN_2	Vmn2r68	4.01E-02
PEMN_2	4933416M06Rik	4.30E-02
PEMN_2	A630095N17Rik	4.31E-02
PEMN_2	Alyref	4.36E-02
PEMN_2	AA387883	4.55E-02
PEMN_3	Mir669a-7	1.23E-120
PEMN_3	Mir669a-5	1.15E-82
PEMN_3	Mir669a-10	4.21E-80
PEMN_3	Mir669p-1	1.37E-63
PEMN_3	Mir669a-4	5.53E-63
PEMN_3	Mir669a-6	3.11E-61
PEMN_3	Mir669a-8	9.12E-59
PEMN_3	Mir669a-11	1.26E-55
PEMN_3	Mir669p-2	9.48E-37
PEMN_3	Defb9	4.31E-29
PEMN_3	Mir669a-12	6.71E-29
PEMN_3	Astl	1.05E-28
PEMN_3	Mir669a-9	1.95E-26
PEMN_3	Prss45	1.07E-25
PEMN_3	Ms4a6b	1.82E-19
PEMN_3	Galp	2.61E-19
PEMN_3	C5ar2	2.34E-17
PEMN_3	Siglec5	5.57E-16
PEMN_3	C330011F03Rik	2.00E-12
PEMN_3	Gm17821	1.00E-11
PEMN_3	Gm17830	1.73E-11
PEMN_3	Sult2a6	1.10E-10
PEMN_3	BC107364	6.26E-10
PEMN_3	AI504432	1.03E-08
PEMN_3	1700066J24Rik	1.66E-08
PEMN_3	Gm12603	2.10E-08
PEMN_3	1700057G04Rik	6.15E-08
PEMN_3	Ces2h	8.26E-08
PIMN_4	Ucn2	4.05E-07
PIMN_4	1700007F19Rik	8.60E-07
PIMN_4	Lpin3	1.72E-06
PIMN_4	Tm4sf5	8.11E-06
PIMN_4	Stfa1	8.53E-06
PIMN_4	Sox2	1.07E-05
PIMN_4	Gm10046	1.60E-05
PIMN_4	Fgf5	1.68E-05
PIMN_4	Magix	4.75E-05
PIMN_4	4930413E15Rik	6.73E-05
PIMN_4	Slc25a34	8.15E-05
PIMN_4	Nobox	8.61E-05
PIMN_4	Ldhal6b	1.11E-04
PIMN_4	Klk1b4	1.54E-04
PIMN_4	Slitrk6	1.67E-04
PIMN_4	Lta	1.74E-04
PIMN_4	4930545E07Rik	1.85E-04
PIMN_4	Klhl31	2.17E-04
PIMN_4	4933432G23Rik	2.73E-04
PIMN_4	Trim10	3.88E-04
PIMN_4	Gm3286	5.36E-04
PIMN_4	Krt28	5.95E-04
PIMN_4	Slc13a3	6.06E-04
PIMN_4	Hist2h3c1	6.47E-04
PIMN_4	Lmod3	9.68E-04
PIMN_4	Mir100	1.10E-03
PIMN_4	Lctl	1.44E-03
PIMN_4	Olfr970	2.40E-03
PIMN_4	Il3	3.40E-03
PIMN_4	Sct	4.29E-03
PIMN_4	Nid2	4.54E-03
PIMN_4	Vmn2r66	4.83E-03
PIMN_4	Defb7	5.85E-03
PIMN_4	Tyrp1	6.08E-03
PIMN_4	1700051A21Rik	6.09E-03
PIMN_4	4930425O10Rik	7.44E-03
PIMN_4	Gprc5c	9.28E-03
PIMN_4	Prss38	1.20E-02
PIMN_4	Tbx22	1.21E-02
PIMN_4	1700012B09Rik	1.25E-02
PIMN_4	Wfdc8	1.30E-02
PIMN_4	Gm10790	1.42E-02
PIMN_4	Trim42	1.57E-02
PIMN_4	Sash3	1.59E-02
PIMN_4	Wisp1	1.75E-02
PIMN_4	AU022751	1.76E-02
PIMN_4	Mug1	1.81E-02
PIMN_4	Prl2a1	1.85E-02
PIMN_4	Trim69	1.87E-02
PIMN_4	1700003G13Rik	1.89E-02
PIMN_4	Serpinb6d	2.01E-02
PIMN_4	Slc7a9	2.02E-02
PIMN_4	Gm16405	2.15E-02
PIMN_4	Defb6	2.20E-02
PIMN_4	Acsm4	2.21E-02
PIMN_4	Gm16430	2.29E-02
PIMN_4	Treml4	2.35E-02
PIMN_4	Prok1	2.81E-02
PIMN_4	Gm5166	2.85E-02
PIMN_4	Pira4	2.90E-02
PSN_2	Dkk2	5.22E-07
PSN_2	Otc	1.55E-06
PSN_2	Cpa3	2.98E-06
PSN_2	Dlx3	3.25E-06
PSN_2	Phf11a	8.23E-06
PSN_2	4933427I22Rik	3.22E-05
PSN_2	Camkv	3.49E-05
PSN_2	Fgf16	3.56E-05
PSN_2	Nat3	3.93E-05
PSN_2	Hrh1	4.44E-05
PSN_2	Clec2h	5.24E-05
PSN_2	Amelx	7.38E-05
PSN_2	Nfe2	1.11E-04
PSN_2	Gm14812	3.11E-04
PSN_2	AU023762	7.58E-04
PSN_2	Rnu12	1.38E-03
PSN_2	Mc4r	1.74E-03
PSN_2	Emilin2	2.03E-03
PSN_2	Kif7	2.15E-03
PSN_2	Psmb11	2.36E-03
PSN_2	Nr2e1	2.97E-03
PSN_2	4930474N09Rik	3.02E-03
PSN_2	5031434C07Rik	3.16E-03
PSN_2	Sall4	3.59E-03
PSN_2	Rp1l1	4.75E-03
PSN_2	Crisp3	4.99E-03
PSN_2	Gm1082	5.34E-03
PSN_2	1700013G23Rik	5.49E-03
PSN_2	Pabpc5	6.93E-03
PSN_2	1810019D21Rik	7.51E-03
PSN_2	Hist1h4k	8.01E-03
PSN_2	Slc35g3	8.55E-03
PSN_2	Lrrc17	9.58E-03
PSN_2	2610100L16Rik	1.49E-02
PSN_2	Ccnf	1.58E-02
PSN_2	Gm10789	1.78E-02
PSN_2	AI507597	1.97E-02
PSN_2	Nrarp	2.28E-02
PSN_2	Ephb3	2.77E-02
PSN_2	4930471C04Rik	2.82E-02
PSN_2	9130023H24Rik	3.56E-02
PSN_2	Rspo1	3.57E-02
PSN_2	Clec4d	4.62E-02
PSN_2	Krt16	4.95E-02
PSN_3	Piezo2	1.32E-168
PSN_3	Abca9	5.02E-166
PSN_3	Sema5a	8.19E-144
PSN_3	Mir466g	2.19E-117
PSN_3	Ror1	9.21E-117
PSN_3	Xcr1	5.07E-108
PSN_3	Gng2	1.03E-86
PSN_3	Sgcz	1.78E-84
PSN_3	Kif26b	3.50E-80
PSN_3	Kcnh7	5.07E-80
PSN_3	Sorbs2	1.17E-77
PSN_3	Syt10	2.02E-76
PSN_3	Ntng1	1.36E-69
PSN_3	Loxl3	9.55E-67
PSN_3	Nodal	2.60E-57
PSN_3	Gpr126	3.05E-57

PEMN_3	Slc6a18	2.94E-07
PEMN_3	Dppa4	3.64E-07
PEMN_3	Plekhs1	7.18E-07
PEMN_3	Ddx43	7.18E-07
PEMN_3	Pabpc6	8.98E-07
PEMN_3	Sh3d21	1.03E-06
PEMN_3	Gm8801	1.44E-06
PEMN_3	Piwil4	1.44E-06
PEMN_3	C5ar1	6.17E-06
PEMN_3	1700029F12Rik	7.03E-06
PEMN_3	Fam78a	1.69E-05
PEMN_3	Tada3	2.18E-05
PEMN_3	Traip	6.43E-05
PEMN_3	Awat2	6.96E-05
PEMN_3	Lipm	8.95E-05
PEMN_3	Vegfa	2.74E-04
PEMN_3	Gm13544	2.92E-04
PEMN_3	Pramel4	4.74E-04
PEMN_3	D5Ertd577e	4.97E-04
PEMN_3	Mrps7	6.01E-04
PEMN_3	8030443G20Rik	7.07E-04
PEMN_3	Rn4.5s	8.46E-04
PEMN_3	Opn5	8.69E-04
PEMN_3	Olfr1	8.81E-04
PEMN_3	Nmral1	1.08E-03
PEMN_3	9530080O11Rik	1.08E-03
PEMN_3	Il13ra2	1.08E-03
PEMN_3	Vsig2	1.17E-03
PEMN_3	2610318N02Rik	1.20E-03
PEMN_3	Gm20337	1.27E-03
PEMN_3	6030498E09Rik	1.37E-03
PEMN_3	2310034O05Rik	1.38E-03
PEMN_3	Gm8363	1.56E-03
PEMN_3	Adra1a	1.56E-03
PEMN_3	Kdm6b	3.44E-03
PEMN_3	Iqgap3	3.63E-03
PEMN_3	Sec1	4.02E-03
PEMN_3	Fcrl5	4.03E-03
PEMN_3	Slc9c1	4.03E-03
PEMN_3	Cspg4	4.52E-03
PEMN_3	Nxt2	4.54E-03
PEMN_3	Trim30a	4.55E-03
PEMN_3	4930564G21Rik	4.57E-03
PEMN_3	Pou2f2	4.96E-03
PEMN_3	Chrnb3	5.32E-03
PEMN_3	Btk	5.35E-03
PEMN_3	Ccr4	5.81E-03
PEMN_3	Gramd1c	6.66E-03
PEMN_3	Yipf7	7.24E-03
PEMN_3	Cyp2j5	7.57E-03
PEMN_3	Fat2	7.62E-03
PEMN_3	Gch1	8.05E-03
PEMN_3	Oscp1	8.16E-03
PEMN_3	Crisp2	8.62E-03
PEMN_3	Cxcr6	8.83E-03
PEMN_3	9330133O14Rik	1.01E-02
PEMN_3	Pbld1	1.01E-02
PEMN_3	Akip1	1.03E-02
PEMN_3	Gm5458	1.04E-02
PEMN_3	Lef1	1.04E-02

PIMN_4	Tgtp1	2.95E-02
PIMN_4	Prss51	3.00E-02
PIMN_4	1700018C11Rik	3.01E-02
PIMN_4	Krt27	3.02E-02
PIMN_4	Cdkn2a	3.03E-02
PIMN_4	Mir1929	3.32E-02
PIMN_4	Prss22	3.45E-02
PIMN_4	Cpb1	3.45E-02
PIMN_4	Ces1e	3.47E-02
PIMN_4	Tcl1b2	3.51E-02
PIMN_4	Wfdc15b	3.84E-02
PIMN_4	Xlr4c	3.93E-02
PIMN_4	1700001F09Rik	3.96E-02
PIMN_4	Ppp1r17	4.04E-02
PIMN_4	4930556C24Rik	4.08E-02
PIMN_4	Fbp1	4.35E-02
PIMN_4	Scarna13	4.36E-02
PIMN_4	Prl3c1	4.53E-02
PIMN_4	Selp	4.61E-02
PIMN_4	Ccl8	4.75E-02
PIMN_4	Trim30b	4.80E-02
PIMN_4	4930572O13Rik	4.87E-02
PIMN_5	Dgkb	1.87E-65
PIMN_5	Cmah	2.96E-59
PIMN_5	Rarb	3.31E-58
PIMN_5	Hmcn1	2.24E-56
PIMN_5	Sorcs3	3.34E-56
PIMN_5	Epha8	2.63E-51
PIMN_5	Gria3	1.11E-46
PIMN_5	Eya4	2.48E-44
PIMN_5	Dpp10	1.82E-43
PIMN_5	Gsg1l	4.95E-43
PIMN_5	Rgs6	7.08E-43
PIMN_5	Stra8	1.43E-41
PIMN_5	Cdh12	1.51E-41
PIMN_5	Dach2	8.14E-41
PIMN_5	Cyct	2.74E-39
PIMN_5	Cadps2	1.96E-38
PIMN_5	Plch2	5.02E-38
PIMN_5	Mfsd4	7.15E-37
PIMN_5	Nxn	5.16E-36
PIMN_5	Slc35d3	5.56E-35
PIMN_5	Nos1	8.41E-35
PIMN_5	Bves	2.36E-33
PIMN_5	Rgs7	3.52E-33
PIMN_5	Gfra1	4.06E-33
PIMN_5	Sorcs2	7.11E-32
PIMN_5	Col25a1	9.08E-32
PIMN_5	Rapgef3	1.76E-31
PIMN_5	Slc39a12	2.48E-31
PIMN_5	Igsf21	6.47E-31
PIMN_5	Alcam	7.92E-30
PIMN_5	Grb14	3.87E-27
PIMN_5	Gas6	2.49E-26
PIMN_5	Etv1	2.67E-26
PIMN_5	Tmc3	5.23E-26
PIMN_5	Fat3	9.62E-26
PIMN_5	Creb5	2.84E-25
PIMN_5	Pcdh9	4.31E-25
PIMN_5	Slc6a1	5.03E-25

PSN_3	Epb4.1l3	3.92E-56
PSN_3	9130019P16Rik	5.59E-50
PSN_3	Ano5	2.64E-49
PSN_3	D330022K07Rik	6.52E-49
PSN_3	Zfhx3	5.30E-47
PSN_3	Scgb2b2	4.53E-45
PSN_3	Bdnf	1.43E-44
PSN_3	Ppara	2.24E-44
PSN_3	Rfx6	5.15E-44
PSN_3	Rerg	9.69E-44
PSN_3	BC049352	1.59E-43
PSN_3	Trim36	1.47E-42
PSN_3	Skap1	2.21E-40
PSN_3	Pbx3	2.47E-39
PSN_3	Tenm4	3.72E-39
PSN_3	Grid1	7.63E-38
PSN_3	Palm2	2.30E-37
PSN_3	Atp7a	4.97E-37
PSN_3	Dapk1	8.51E-37
PSN_3	Mast4	1.56E-35
PSN_3	Spock1	2.94E-35
PSN_3	Rassf4	2.04E-33
PSN_3	Ush1c	2.30E-33
PSN_3	Galnt18	3.44E-33
PSN_3	Gmpr	6.38E-33
PSN_3	Fndc3b	1.01E-32
PSN_3	Abca8b	5.10E-32
PSN_3	Baiap3	5.46E-32
PSN_3	Tmeff2	8.83E-32
PSN_3	Ifi203	1.43E-31
PSN_3	Cck	5.30E-31
PSN_3	Chst8	5.41E-31
PSN_3	Akap2	1.54E-30
PSN_3	Lrriq4	6.55E-30
PSN_3	Cd24a	2.74E-29
PSN_3	Ddah1	3.35E-29
PSN_3	Rttn	1.51E-28
PSN_3	March1	1.51E-28
PSN_3	Calb1	2.67E-28
PSN_3	Gpc6	2.67E-28
PSN_3	Phlda1	4.35E-27
PSN_3	Myo18b	1.25E-26
PSN_3	Meis1	1.56E-26
PSN_3	Arhgap28	9.48E-26
PSN_3	Serpini1	9.69E-26
PSN_3	Cachd1	1.38E-25
PSN_3	Cpne8	4.27E-25
PSN_3	Calcb	8.04E-25
PSN_3	Esyt3	1.04E-24
PSN_3	AW549542	1.42E-24
PSN_3	Dlc1	1.70E-24
PSN_3	Slc7a3	2.35E-24
PSN_3	Slc17a6	2.35E-24
PSN_3	Apcdd1	8.70E-24
PSN_3	Ccdc85a	9.02E-24
PSN_3	Galnt14	3.14E-23
PSN_3	L3mbtl4	3.25E-23
PSN_3	Tanc2	3.26E-23
PSN_3	Gm5441	4.22E-23
PSN_3	Trps1	4.25E-23

PEMN_3	Tmem132b	1.11E-02
PEMN_3	Lsm3	1.21E-02
PEMN_3	Gm8267	1.21E-02
PEMN_3	Gm3258	1.32E-02
PEMN_3	Cpsf7	1.42E-02
PEMN_3	Zmym1	1.46E-02
PEMN_3	Slc25a41	1.48E-02
PEMN_3	1700120C14Rik	1.71E-02
PEMN_3	Nosip	1.77E-02
PEMN_3	Mir568	1.85E-02
PEMN_3	Zfp106	2.07E-02
PEMN_3	Cyld	2.07E-02
PEMN_3	Gprc6a	2.20E-02
PEMN_3	Usp17le	2.34E-02
PEMN_3	Sap30	2.34E-02
PEMN_3	Musk	2.47E-02
PEMN_3	Olfr536	2.64E-02
PEMN_3	Klhdc8a	2.64E-02
PEMN_3	Gm20187	3.12E-02
PEMN_3	Thpo	3.27E-02
PEMN_3	Cytl1	3.32E-02
PEMN_3	Jag1	3.49E-02
PEMN_3	Lrrc71	3.51E-02
PEMN_3	2010003O02Rik	3.61E-02
PEMN_3	Laptm5	3.61E-02
PEMN_3	Vmn2r98	4.02E-02
PEMN_3	Tmc2	4.32E-02
PEMN_3	Tnfrsf11a	4.32E-02
PEMN_3	Gm10058	4.36E-02
PEMN_3	Il1rl1	4.38E-02
PEMN_3	Cdc45	4.39E-02
PEMN_3	Gm20747	4.39E-02
PEMN_3	1700008J07Rik	4.49E-02
PEMN_3	Fsbp	4.49E-02
PEMN_3	Zfp607	4.49E-02
PEMN_3	Raet1d	4.70E-02
PEMN_3	Vmn2r44	4.71E-02
PEMN_3	Mira	4.75E-02
PEMN_3	Alox12	4.85E-02
PEMN_4	Tmem132c	7.91E-199
PEMN_4	Ptprt	3.10E-189
PEMN_4	Grik1	8.96E-152
PEMN_4	Fbxw24	7.83E-123
PEMN_4	Plcxd3	2.04E-117
PEMN_4	Fam5b	4.21E-115
PEMN_4	Cdc14a	5.51E-114
PEMN_4	Sdk2	1.62E-111
PEMN_4	Tcf7l2	1.53E-108
PEMN_4	Arhgap24	4.76E-105
PEMN_4	Bnc2	4.52E-104
PEMN_4	Galnt14	2.15E-99
PEMN_4	Alk	1.27E-98
PEMN_4	Caln1	1.98E-96
PEMN_4	Rbfox1	8.81E-95
PEMN_4	Satb1	6.50E-92
PEMN_4	Chat	1.43E-91
PEMN_4	Adamtsl1	3.60E-91
PEMN_4	Fam19a1	6.15E-91
PEMN_4	Fgfr2	2.74E-90
PEMN_4	Fbxw15	5.92E-90
PIMN_5	Vwa5b1	1.09E-24
PIMN_5	Zfp804a	2.81E-24
PIMN_5	Tmem196	4.82E-24
PIMN_5	Grik3	6.18E-24
PIMN_5	Pcdh15	6.18E-24
PIMN_5	Slc4a4	1.28E-23
PIMN_5	Tenm2	1.82E-23
PIMN_5	Rbfox3	2.30E-23
PIMN_5	Ablim2	1.20E-22
PIMN_5	Rnf144b	1.61E-22
PIMN_5	Prkd1	3.64E-22
PIMN_5	Il20ra	1.29E-21
PIMN_5	Egfem1	2.02E-21
PIMN_5	Plekha7	3.18E-21
PIMN_5	Cacnb2	3.97E-21
PIMN_5	Gpr98	7.99E-21
PIMN_5	Auts2	1.41E-20
PIMN_5	Mkx	1.70E-20
PIMN_5	Ltk	1.98E-20
PIMN_5	Slc44a5	2.14E-20
PIMN_5	Khdrbs2	2.30E-20
PIMN_5	Ryr2	2.53E-20
PIMN_5	Arhgap15	3.48E-20
PIMN_5	4930428E07Rik	5.74E-20
PIMN_5	Wwc2	6.31E-20
PIMN_5	Syt2	7.22E-20
PIMN_5	Rtn4rl1	1.15E-19
PIMN_5	Stxbp6	1.54E-19
PIMN_5	Dagla	2.34E-19
PIMN_5	Plekha5	3.17E-19
PIMN_5	Epha5	6.58E-19
PIMN_5	Cyp2s1	7.62E-19
PIMN_5	Gtsf1l	1.65E-18
PIMN_5	Kcnab1	2.42E-18
PIMN_5	Gm11602	4.46E-18
PIMN_5	Tspan18	4.64E-18
PIMN_5	Tmem255b	6.83E-18
PIMN_5	Ank2	6.88E-18
PIMN_5	Gpc5	9.27E-18
PIMN_5	Kcnt2	2.72E-17
PIMN_5	Tmem150c	3.40E-17
PIMN_5	Dock6	4.59E-17
PIMN_5	Ptch2	9.26E-17
PIMN_5	Kcnq4	9.70E-17
PIMN_5	Dgkg	9.96E-17
PIMN_5	Schip1	1.17E-16
PIMN_5	Fbn1	1.29E-16
PIMN_5	P2ry6	1.32E-16
PIMN_5	Cobll1	1.33E-16
PIMN_5	Wipi1	2.35E-16
PIMN_5	A530058N18Rik	3.67E-16
PIMN_5	Clmp	4.08E-16
PIMN_5	Grem2	5.89E-16
PIMN_5	Arid5b	5.89E-16
PIMN_5	Nbas	5.89E-16
PIMN_5	Ass1	6.34E-16
PIMN_5	Camk4	7.86E-16
PIMN_5	Bglap	1.79E-15
PIMN_5	Gucy1a2	2.30E-15
PIMN_5	C1ql1	2.60E-15
PSN_3	Tnr	8.65E-23
PSN_3	Prkca	2.05E-22
PSN_3	Nefm	2.41E-22
PSN_3	Nell1	2.48E-22
PSN_3	Nnat	4.72E-22
PSN_3	Kazn	1.03E-21
PSN_3	Chrm3	1.17E-21
PSN_3	Nefl	2.21E-21
PSN_3	Pcp4l1	2.59E-21
PSN_3	Jazf1	3.05E-21
PSN_3	Sez6l	8.53E-21
PSN_3	5830418P13Rik	1.10E-20
PSN_3	Eif3h	2.08E-20
PSN_3	Bcl2	2.60E-20
PSN_3	Limch1	1.08E-19
PSN_3	Rxrg	1.66E-19
PSN_3	Mndal	1.71E-19
PSN_3	Colq	2.24E-19
PSN_3	2810055G20Rik	2.92E-19
PSN_3	Bfsp2	3.54E-19
PSN_3	Abca8a	3.83E-19
PSN_3	Ltk	4.21E-19
PSN_3	Tshz3	4.21E-19
PSN_3	Tiam1	6.03E-19
PSN_3	Pdyn	7.15E-19
PSN_3	Bmpr1b	6.43E-18
PSN_3	Prr15	9.67E-18
PSN_3	Stra6	1.55E-17
PSN_3	Dok1	5.35E-16
PSN_3	Crhr2	1.08E-15
PSN_3	Skint1	3.90E-15
PSN_3	Il18r1	7.17E-15
PSN_3	Fbln1	7.64E-15
PSN_3	A330050F15Rik	9.84E-15
PSN_3	Slc38a11	1.31E-14
PSN_3	Gm13278	1.41E-14
PSN_3	Cacng5	2.58E-14
PSN_3	Npy5r	3.13E-13
PSN_3	Hmga2-ps1	3.27E-13
PSN_3	Bpifc	7.29E-13
PSN_3	Nckap1l	1.34E-12
PSN_3	Anxa1	2.43E-12
PSN_3	Gm5640	6.78E-12
PSN_3	Rem2	7.79E-12
PSN_3	Tas1r2	1.22E-11
PSN_3	Pcdh12	1.36E-11
PSN_3	Tmem211	2.28E-11
PSN_3	Zdhhc19	3.10E-10
PSN_3	Btnl9	4.70E-10
PSN_3	Gm14685	1.65E-09
PSN_3	Ifi204	2.04E-09
PSN_3	0610007N19Rik	1.17E-08
PSN_3	4930452G13Rik	2.09E-08
PSN_3	Slco1a4	3.98E-08
PSN_3	Mnda	5.20E-08
PSN_3	Cd300lb	6.35E-08
PSN_3	Ace2	3.05E-07
PSN_3	Cyp2g1	6.22E-07
PSN_3	Gprc6a	1.32E-06
PSN_3	Eras	1.49E-06

PEMN_4	Cacna1e	6.65E-90
PEMN_4	Oprk1	3.14E-81
PEMN_4	Pi15	3.99E-81
PEMN_4	Wbscr17	6.40E-81
PEMN_4	Kalrn	3.87E-80
PEMN_4	Tmem117	2.80E-76
PEMN_4	Ngef	4.99E-73
PEMN_4	Ccbe1	2.08E-71
PEMN_4	St6galnac3	1.98E-70
PEMN_4	Casz1	3.90E-69
PEMN_4	Slc35f4	1.33E-68
PEMN_4	Fam19a2	6.33E-67
PEMN_4	Enox1	4.81E-66
PEMN_4	Pbx1	1.33E-64
PEMN_4	Fam19a5	8.03E-64
PEMN_4	Gm2694	4.13E-63
PEMN_4	Dlgap2	4.96E-63
PEMN_4	Fhit	1.30E-62
PEMN_4	Pknox2	9.14E-62
PEMN_4	Bcar3	1.80E-61
PEMN_4	Gfra2	4.47E-61
PEMN_4	Prmt8	6.14E-59
PEMN_4	Pcdh7	7.14E-59
PEMN_4	Fam196b	1.08E-58
PEMN_4	Col6a1	1.95E-58
PEMN_4	Slc26a4	3.65E-58
PEMN_4	Chsy3	1.21E-57
PEMN_4	Syn2	3.91E-57
PEMN_4	Gpc6	1.06E-56
PEMN_4	Fbln5	6.90E-56
PEMN_4	Pde4b	3.14E-55
PEMN_4	Cd84	3.30E-54
PEMN_4	Sec16b	3.49E-54
PEMN_4	Nfia	1.76E-53
PEMN_4	Scube1	1.95E-53
PEMN_4	Fgd6	3.25E-52
PEMN_4	Dock2	4.17E-52
PEMN_4	Ly6e	1.72E-51
PEMN_4	Xylt1	1.82E-51
PEMN_4	1810041L15Rik	2.67E-51
PEMN_4	Plod2	2.67E-51
PEMN_4	Dmkn	5.72E-51
PEMN_4	Syt6	6.83E-51
PEMN_4	Piezo1	1.23E-50
PEMN_4	Chgb	3.17E-50
PEMN_4	Ptpn5	1.11E-49
PEMN_4	Ghr	1.11E-49
PEMN_4	Mdga1	2.52E-48
PEMN_4	Nfib	3.73E-48
PEMN_4	Psd3	5.98E-48
PEMN_4	Cpne8	3.47E-47
PEMN_4	Elmo1	4.38E-47
PEMN_4	Pld5	2.61E-46
PEMN_4	Cyb561	2.69E-46
PEMN_4	Zfp521	4.91E-46
PEMN_4	Ebf3	5.51E-46
PEMN_4	Rspo2	1.54E-45
PEMN_4	4933400C23Rik	2.44E-45
PEMN_4	Dpyd	2.60E-44
PEMN_4	Sulf2	1.68E-43
PIMN_5	Kcnq5	2.60E-15
PIMN_5	Ptprz1	3.47E-15
PIMN_5	Kcnk9	6.74E-15
PIMN_5	Rhox4f	9.70E-13
PIMN_5	Pbp2	1.64E-12
PIMN_5	Hcrtr1	8.31E-12
PIMN_5	Vmn2r52	9.27E-09
PIMN_5	Btnl6	1.05E-06
PIMN_5	Uox	1.75E-06
PIMN_5	Ttll8	5.25E-06
PIMN_5	C130079G13Rik	7.14E-06
PIMN_5	Wnt10a	1.23E-05
PIMN_5	Igf2bp1	1.57E-05
PIMN_5	Anxa10	1.61E-05
PIMN_5	Obox2	4.30E-05
PIMN_5	Gm14207	5.69E-05
PIMN_5	2610018G03Rik	9.63E-05
PIMN_5	Lrrc32	1.06E-04
PIMN_5	Bcl11a	1.16E-04
PIMN_5	Itgad	1.17E-04
PIMN_5	Kcnh3	1.36E-04
PIMN_5	Dmrtc1a	1.50E-04
PIMN_5	H2-Eb2	1.57E-04
PIMN_5	Fam159a	2.77E-04
PIMN_5	Dmp1	3.75E-04
PIMN_5	Ucn2	4.34E-04
PIMN_5	1700049E15Rik	4.96E-04
PIMN_5	5430416O09Rik	6.03E-04
PIMN_5	Arrdc5	6.17E-04
PIMN_5	Macc1	7.43E-04
PIMN_5	Srms	8.04E-04
PIMN_5	Cyp2a12	8.60E-04
PIMN_5	Krtap10-10	9.70E-04
PIMN_5	Cd96	1.05E-03
PIMN_5	Scn10a	1.37E-03
PIMN_5	4933400A11Rik	1.53E-03
PIMN_5	8430437L04Rik	1.57E-03
PIMN_5	Ndufs5	1.80E-03
PIMN_5	Gm216	2.42E-03
PIMN_5	Asic5	2.48E-03
PIMN_5	Tmem27	2.62E-03
PIMN_5	Zc3h12d	2.81E-03
PIMN_5	4933406K04Rik	2.89E-03
PIMN_5	Lrcol1	2.91E-03
PIMN_5	Gm19784	3.02E-03
PIMN_5	Gm16796	3.02E-03
PIMN_5	Fcgr4	3.55E-03
PIMN_5	Gm19434	3.81E-03
PIMN_5	Zbtb12	3.82E-03
PIMN_5	Cxcl5	4.17E-03
PIMN_5	Gm15114	4.55E-03
PIMN_5	Nrl	5.51E-03
PIMN_5	9530002B09Rik	6.01E-03
PIMN_5	Luzp4	6.42E-03
PIMN_5	4930564B18Rik	6.95E-03
PIMN_5	4933402J15Rik	7.37E-03
PIMN_5	4931431B13Rik	7.37E-03
PIMN_5	C86187	8.55E-03
PIMN_5	2410004I01Rik	8.83E-03
PIMN_5	Csn1s1	9.33E-03
PSN_3	Slc15a3	1.84E-06
PSN_3	Fam187b	4.69E-06
PSN_3	Gmnc	1.05E-05
PSN_3	Gm829	1.10E-05
PSN_3	Il10ra	1.41E-05
PSN_3	Olfr122	4.59E-05
PSN_3	Csn3	5.21E-05
PSN_3	Clec3a	1.08E-04
PSN_3	Gpr26	1.22E-04
PSN_3	Irs3	2.43E-04
PSN_3	Cdhr1	2.70E-04
PSN_3	Lrat	3.34E-04
PSN_3	Lrrc25	3.56E-04
PSN_3	C030007H22Rik	6.55E-04
PSN_3	Kcns1	8.61E-04
PSN_3	Cd3g	9.38E-04
PSN_3	Hephl1	1.34E-03
PSN_3	4930461G14Rik	1.34E-03
PSN_3	Chrna10	1.73E-03
PSN_3	4933407E24Rik	1.87E-03
PSN_3	Rbpjl	2.16E-03
PSN_3	Elf5	3.96E-03
PSN_3	Vsig8	4.80E-03
PSN_3	Ucp1	5.19E-03
PSN_3	Olfr1030	5.76E-03
PSN_3	Iltifb	6.10E-03
PSN_3	Fam43b	7.39E-03
PSN_3	Vmn1r45	8.02E-03
PSN_3	Ldlrad2	1.40E-02
PSN_3	Tm4sf19	1.85E-02
PSN_3	9330175E14Rik	2.06E-02
PSN_3	Cited1	2.44E-02
PSN_3	Thbs2	2.56E-02
PSN_3	D830015G02Rik	3.15E-02
PSN_3	G630090E17Rik	3.48E-02
PSN_3	Gm1653	3.61E-02
PSN_3	Olfr59	3.64E-02
PSN_3	Chrng	3.71E-02
PSN_3	Fat2	4.59E-02
PSN_4	Satb2	7.50E-224
PSN_4	9530026P05Rik	9.18E-167
PSN_4	Vipr2	3.87E-158
PSN_4	Sst	3.90E-147
PSN_4	Chsy3	4.78E-142
PSN_4	Fam19a2	2.84E-131
PSN_4	Myrip	6.21E-106
PSN_4	Slit3	1.01E-105
PSN_4	Oas1a	8.15E-104
PSN_4	Gfra2	1.16E-101
PSN_4	Adamts9	4.12E-101
PSN_4	Gm12216	8.90E-100
PSN_4	Ldb2	3.18E-98
PSN_4	Scube1	1.18E-92
PSN_4	Adamts20	1.65E-92
PSN_4	Elmo1	3.32E-92
PSN_4	2610017I09Rik	8.39E-92
PSN_4	Plxna4	1.05E-91
PSN_4	Rbm20	2.65E-91
PSN_4	Inpp4b	1.63E-87
PSN_4	Grp	4.40E-80

PEMN_4	Ppfibp1	1.75E-43
PEMN_4	Itgb5	4.39E-43
PEMN_4	Pdzrn4	8.06E-42
PEMN_4	Zbtb7c	8.97E-42
PEMN_4	Igsf3	2.79E-41
PEMN_4	Tshz2	5.07E-41
PEMN_4	Lrig3	1.14E-40
PEMN_4	Tox	4.45E-40
PEMN_4	Abcc8	7.29E-40
PEMN_4	1700123O21Rik	1.59E-39
PEMN_4	Peli2	2.58E-39
PEMN_4	Itga6	4.51E-39
PEMN_4	Sgpp2	1.51E-38
PEMN_4	Scg2	2.61E-38
PEMN_4	Cyyr1	1.21E-37
PEMN_4	Gpm6b	3.06E-37
PEMN_4	B3gat1	1.17E-36
PEMN_4	1700085B03Rik	3.96E-36
PEMN_4	Ppapdc1a	7.01E-36
PEMN_4	Cxcl12	2.71E-34
PEMN_4	Drd2	2.88E-34
PEMN_4	Sntg2	6.81E-32
PEMN_4	Kcns2	3.80E-28
PEMN_4	Dsc3	1.01E-26
PEMN_4	Cldn8	3.00E-25
PEMN_4	Fbxw16	2.35E-23
PEMN_4	Zfp185	2.88E-23
PEMN_4	Heg1	6.07E-23
PEMN_4	Itga4	9.57E-21
PEMN_4	Cacng3	3.61E-20
PEMN_4	Hsd3b6	1.25E-17
PEMN_4	Plekhd1	2.78E-17
PEMN_4	Cbln1	5.01E-17
PEMN_4	Ahsg	9.32E-17
PEMN_4	Mn1	3.22E-15
PEMN_4	Rgcc	8.72E-14
PEMN_4	Bpifb4	6.26E-13
PEMN_4	Ly6c1	8.21E-13
PEMN_4	Aldh3a1	3.80E-12
PEMN_4	Entpd2	6.52E-12
PEMN_4	Ces2g	7.64E-12
PEMN_4	Tnnt2	5.60E-11
PEMN_4	Sardh	7.15E-11
PEMN_4	4632428N05Rik	4.71E-10
PEMN_4	Gabra4	6.39E-10
PEMN_4	Fam83a	7.00E-10
PEMN_4	Crispld2	1.46E-09
PEMN_4	Krt79	3.13E-09
PEMN_4	Aldh1a7	4.68E-08
PEMN_4	Megf6	9.24E-08
PEMN_4	Chst5	1.40E-07
PEMN_4	C330008G21Rik	2.49E-07
PEMN_4	1700007K13Rik	3.42E-05
PEMN_4	Prdm12	3.42E-05
PEMN_4	Ndufa4l2	4.20E-05
PEMN_4	Ubxn10	5.53E-05
PEMN_4	Gm6455	9.45E-05
PEMN_4	Il7r	1.78E-04
PEMN_4	Psg25	2.23E-04
PEMN_4	Klra6	2.75E-04

PIMN_5	Lbp	9.94E-03
PIMN_5	Snord4a	1.13E-02
PIMN_5	Gpr142	1.30E-02
PIMN_5	Ms4a13	1.32E-02
PIMN_5	Hsh2d	1.35E-02
PIMN_5	Fpr1	1.61E-02
PIMN_5	Foxn4	1.64E-02
PIMN_5	Chia	1.73E-02
PIMN_5	Scarf2	1.84E-02
PIMN_5	Accsl	2.15E-02
PIMN_5	Kcne2	2.19E-02
PIMN_5	4933425B07Rik	2.35E-02
PIMN_5	Lgi3	2.67E-02
PIMN_5	Klk7	2.69E-02
PIMN_5	Was	2.76E-02
PIMN_5	Topaz1	2.86E-02
PIMN_5	Gm17751	2.88E-02
PIMN_5	Gm156	2.92E-02
PIMN_5	Mpo	3.01E-02
PIMN_5	Fam209	3.08E-02
PIMN_5	4933422H20Rik	3.12E-02
PIMN_5	Gm9920	3.24E-02
PIMN_5	Lrrc52	3.48E-02
PIMN_5	Fam71b	3.59E-02
PIMN_5	Il19	4.37E-02
PIMN_5	Tgm5	4.47E-02
PIMN_5	Myh3	4.47E-02
PIMN_5	Cd40lg	4.75E-02
PIMN_5	AB099516	4.84E-02
PIMN_6	Chga	2.33E-43
PIMN_6	Cygb	4.97E-42
PIMN_6	Bglap2	4.44E-36
PIMN_6	Bglap	4.44E-36
PIMN_6	C1ql1	7.87E-33
PIMN_6	Dkk3	1.16E-32
PIMN_6	Ctsb	5.73E-32
PIMN_6	Rprml	4.76E-31
PIMN_6	Cd80	4.66E-30
PIMN_6	Ccdc11	5.52E-30
PIMN_6	Ngb	2.68E-29
PIMN_6	Ngfr	1.71E-28
PIMN_6	Crabp1	7.82E-28
PIMN_6	Tmem176b	8.45E-28
PIMN_6	Gal	1.85E-27
PIMN_6	Gas6	4.66E-27
PIMN_6	Vip	7.12E-27
PIMN_6	Gsg1l	2.23E-26
PIMN_6	Tubb3	2.39E-26
PIMN_6	Qdpr	4.18E-26
PIMN_6	S100a16	2.09E-25
PIMN_6	Slc35d3	2.64E-25
PIMN_6	Defb40	3.04E-25
PIMN_6	Mfsd4	2.27E-24
PIMN_6	Slc22a8	3.41E-24
PIMN_6	Ptgir	9.90E-24
PIMN_6	Epha8	2.54E-23
PIMN_6	Plch2	2.54E-23
PIMN_6	Dgkb	4.52E-23
PIMN_6	S100a6	1.27E-22
PIMN_6	Aldoart1	2.32E-22

PSN_4	Smarca2	4.40E-80
PSN_4	Calcb	9.32E-80
PSN_4	Nrxn3	5.10E-73
PSN_4	Nell1	3.31E-72
PSN_4	Ccbe1	2.18E-71
PSN_4	Oas1g	4.43E-71
PSN_4	Vwc2	1.44E-70
PSN_4	Bcl2	2.99E-70
PSN_4	1810041L15Rik	1.94E-67
PSN_4	Sel1l3	2.05E-67
PSN_4	Oxtr	4.75E-67
PSN_4	Sema3c	9.92E-67
PSN_4	Kcnn3	5.06E-66
PSN_4	Arhgap24	1.28E-65
PSN_4	Scn11a	6.46E-65
PSN_4	St3gal6	1.54E-64
PSN_4	Tshz2	2.44E-64
PSN_4	Grm1	1.09E-63
PSN_4	Prrt2	1.48E-63
PSN_4	Dlgap2	7.64E-61
PSN_4	Colec12	8.92E-60
PSN_4	Wbscr17	5.40E-59
PSN_4	Rbfox1	5.94E-59
PSN_4	Dbc1	7.11E-59
PSN_4	Ptpn5	3.25E-57
PSN_4	Pknox2	4.58E-57
PSN_4	Itga6	4.02E-56
PSN_4	Pag1	1.43E-55
PSN_4	Piezo1	2.03E-55
PSN_4	Pcbp3	3.68E-55
PSN_4	Zbtb7c	4.09E-55
PSN_4	Insc	4.77E-55
PSN_4	Ppfibp2	6.05E-55
PSN_4	Frmd4b	6.77E-55
PSN_4	Lrrn2	7.04E-53
PSN_4	Ptprm	4.20E-51
PSN_4	Plod2	5.92E-50
PSN_4	Ptgs1	6.29E-50
PSN_4	Pcsk2	1.47E-49
PSN_4	Syn2	1.60E-49
PSN_4	Hnf4g	4.50E-49
PSN_4	Pdgfd	4.57E-49
PSN_4	Rgs9	4.69E-49
PSN_4	Gcgr	1.81E-48
PSN_4	Ssbp3	3.33E-48
PSN_4	St6galnac3	4.45E-48
PSN_4	Fbxw24	5.53E-48
PSN_4	Ptprk	1.07E-46
PSN_4	Dgki	6.37E-45
PSN_4	Col5a3	1.27E-44
PSN_4	Begain	5.89E-44
PSN_4	3110047P20Rik	8.61E-44
PSN_4	P2rx2	1.17E-43
PSN_4	Cachd1	1.29E-43
PSN_4	March4	2.31E-43
PSN_4	Tcf7l2	2.40E-43
PSN_4	Dmkn	5.17E-43
PSN_4	Chat	5.81E-43
PSN_4	Slc36a1	7.72E-43
PSN_4	Igsf3	8.67E-43

PEMN_4	Fetub	6.31E-04
PEMN_4	Ang3	7.43E-04
PEMN_4	Ang5	7.44E-04
PEMN_4	Klra19	8.59E-04
PEMN_4	Cplx3	1.05E-03
PEMN_4	Gm10787	1.75E-03
PEMN_4	Cyp27b1	2.64E-03
PEMN_4	Slc17a1	4.07E-03
PEMN_4	Mup19	4.37E-03
PEMN_4	Pla2g2f	4.42E-03
PEMN_4	4930529C04Rik	4.92E-03
PEMN_4	5430427M07Rik	5.03E-03
PEMN_4	Olfr283	5.06E-03
PEMN_4	Acap1	6.19E-03
PEMN_4	C130074G19Rik	6.53E-03
PEMN_4	Ctsq	8.02E-03
PEMN_4	1700023F02Rik	8.37E-03
PEMN_4	Comp	8.63E-03
PEMN_4	4930433N12Rik	1.06E-02
PEMN_4	Lefty2	1.22E-02
PEMN_4	Kif2c	1.71E-02
PEMN_4	Adam28	1.82E-02
PEMN_4	Slc22a26	1.88E-02
PEMN_4	Gsta2	1.94E-02
PEMN_4	1700003H04Rik	2.18E-02
PEMN_4	Gm5105	2.46E-02
PEMN_4	Myh8	2.53E-02
PEMN_4	Gm11190	2.95E-02
PEMN_4	Ccl21b	3.57E-02
PEMN_4	Chrna9	4.02E-02
PEMN_4	Odf3l1	4.16E-02
PEMN_4	Strc	4.19E-02
PEMN_4	BC018473	4.26E-02
PEMN_4	Gm13807	4.26E-02
PEMN_4	Sim2	4.33E-02
PEMN_4	Slc10a5	4.38E-02
PEMN_4	Gm5797	4.59E-02
PEMN_4	Sp6	4.65E-02
PEMN_5	Oprk1	1.40E-59
PEMN_5	Alk	2.34E-57
PEMN_5	Galntl6	2.39E-57
PEMN_5	Nkain2	8.20E-56
PEMN_5	Ptprt	4.60E-55
PEMN_5	Fgfr2	7.19E-53
PEMN_5	Prmt8	1.19E-51
PEMN_5	Grik1	1.04E-49
PEMN_5	Pde4b	9.32E-49
PEMN_5	Pld5	5.80E-47
PEMN_5	Sdk2	6.56E-47
PEMN_5	Adamtsl1	7.79E-46
PEMN_5	Plscr2	3.65E-44
PEMN_5	Bnc2	9.74E-44
PEMN_5	Satb1	1.40E-43
PEMN_5	Colq	1.40E-42
PEMN_5	Ubash3b	3.70E-42
PEMN_5	Tac1	1.40E-38
PEMN_5	Tmem163	2.38E-38
PEMN_5	Gucy1a3	5.02E-38
PEMN_5	Casz1	5.66E-37
PEMN_5	Gfra2	1.46E-36

PIMN_6	Aldoart2	2.86E-22
PIMN_6	Ppia	4.20E-22
PIMN_6	Vmn2r-ps54	4.65E-22
PIMN_6	Ass1	4.94E-22
PIMN_6	Hmcn1	5.20E-22
PIMN_6	Slc6a1	6.99E-22
PIMN_6	Cyp2s1	3.56E-21
PIMN_6	Adcy2	4.05E-21
PIMN_6	Ctsf	5.11E-21
PIMN_6	Slc7a11	5.71E-21
PIMN_6	Skint6	8.61E-21
PIMN_6	Skint10	2.02E-20
PIMN_6	Cmah	2.56E-20
PIMN_6	Bglap3	3.02E-20
PIMN_6	Kcnab2	3.48E-20
PIMN_6	Abhd3	5.36E-20
PIMN_6	Gm6682	5.36E-20
PIMN_6	Cdh12	5.40E-20
PIMN_6	Ckb	1.91E-19
PIMN_6	Gm12070	2.18E-19
PIMN_6	Tuba1a	4.39E-19
PIMN_6	Hcrtr1	5.23E-19
PIMN_6	Vat1	6.18E-19
PIMN_6	Cartpt	7.95E-19
PIMN_6	Dbh	9.80E-19
PIMN_6	Nsg2	1.01E-18
PIMN_6	Bves	1.21E-18
PIMN_6	Aldoa	1.88E-18
PIMN_6	Eya4	2.15E-18
PIMN_6	Gclm	2.15E-18
PIMN_6	Tuba1b	3.42E-18
PIMN_6	Tppp3	4.71E-18
PIMN_6	Camp	9.96E-18
PIMN_6	Nos1	9.96E-18
PIMN_6	Gria3	9.96E-18
PIMN_6	Sele	1.61E-17
PIMN_6	Abhd12b	2.68E-17
PIMN_6	Kcng4	3.23E-17
PIMN_6	Il20ra	3.23E-17
PIMN_6	Pcsk6	3.23E-17
PIMN_6	Atp6ap2	3.95E-17
PIMN_6	Rgs6	4.46E-17
PIMN_6	Adm	4.62E-17
PIMN_6	Phyhip	6.74E-17
PIMN_6	Cplx2	1.57E-16
PIMN_6	Nefl	2.51E-16
PIMN_6	Popdc3	3.30E-16
PIMN_6	Gfra1	3.32E-16
PIMN_6	Galnt7	7.59E-16
PIMN_6	Rab17	1.02E-15
PIMN_6	Igsf21	1.06E-15
PIMN_6	Grb14	1.12E-15
PIMN_6	Tubb5	1.64E-15
PIMN_6	Sorcs2	2.53E-15
PIMN_6	Tmem255b	2.57E-15
PIMN_6	Pcsk1n	4.23E-15
PIMN_6	Kctd12	4.74E-15
PIMN_6	Slc1a1	5.34E-15
PIMN_6	Oaz1	5.53E-15
PIMN_6	Kcnq4	7.22E-15

PSN_4	Kcnh1	8.67E-43
PSN_4	Dcc	9.35E-43
PSN_4	Zfp618	6.92E-42
PSN_4	Fbxw15	4.99E-41
PSN_4	Smoc2	4.99E-41
PSN_4	Tmcc3	1.07E-40
PSN_4	Pak3	2.84E-40
PSN_4	Dync1i1	5.67E-40
PSN_4	Oas1h	8.44E-40
PSN_4	Adcy1	1.32E-39
PSN_4	Bnc2	1.41E-39
PSN_4	Casz1	1.93E-39
PSN_4	Ddah1	2.75E-39
PSN_4	Galnt5	3.91E-39
PSN_4	Ptprt	3.97E-39
PSN_4	Syndig1	9.28E-39
PSN_4	Cdc14a	1.27E-38
PSN_4	Adam19	3.86E-38
PSN_4	Nrp2	4.58E-38
PSN_4	Lypd6b	8.08E-38
PSN_4	Atoh8	9.35E-38
PSN_4	Runx2	4.62E-34
PSN_4	9130024F11Rik	4.86E-33
PSN_4	Col24a1	5.10E-31
PSN_4	Crhr1	3.32E-29
PSN_4	Oas1d	6.64E-29
PSN_4	Rtp4	3.93E-25
PSN_4	Lmcd1	2.54E-24
PSN_4	Nmbr	8.24E-23
PSN_4	Olr1	2.21E-22
PSN_4	Sp100	3.97E-22
PSN_4	Cpne5	1.61E-21
PSN_4	Aldh1a2	2.38E-18
PSN_4	Robo3	2.06E-16
PSN_4	Palmd	8.78E-16
PSN_4	Pinlyp	2.29E-15
PSN_4	Cckbr	4.29E-13
PSN_4	Tlr4	8.37E-13
PSN_4	Sftpc	2.57E-11
PSN_4	Oas1e	5.04E-11
PSN_4	Tifab	4.07E-09
PSN_4	Th	1.65E-08
PSN_4	4930474M22Rik	5.86E-08
PSN_4	Chrna6	2.58E-07
PSN_4	Gm10536	5.32E-07
PSN_4	Ermn	3.03E-06
PSN_4	Il5	3.23E-06
PSN_4	Fzd6	4.28E-06
PSN_4	Olfr943	6.98E-06
PSN_4	Fbxw19	1.12E-05
PSN_4	Mx1	1.34E-05
PSN_4	Pitx3	1.79E-05
PSN_4	Clec7a	1.96E-05
PSN_4	Mettl7a3	5.89E-05
PSN_4	Tex15	7.89E-05
PSN_4	Zfp503	8.00E-05
PSN_4	Fam84a	3.07E-04
PSN_4	Glb1l2	5.50E-04
PSN_4	1700029P11Rik	6.24E-04
PSN_4	1700097N02Rik	8.15E-04

PEMN_5	Syt6	2.15E-35
PEMN_5	Rab3b	4.17E-35
PEMN_5	Pcdh7	5.37E-35
PEMN_5	Chat	1.33E-34
PEMN_5	St6galnac3	3.58E-34
PEMN_5	Arhgap24	5.06E-34
PEMN_5	Elfn1	7.60E-34
PEMN_5	Trpc7	8.58E-34
PEMN_5	Gm5535	1.29E-33
PEMN_5	Fam19a5	5.15E-33
PEMN_5	Unc5d	6.27E-33
PEMN_5	Dmkn	6.89E-33
PEMN_5	Plod2	9.61E-33
PEMN_5	Tpd52l1	1.81E-32
PEMN_5	Cntnap5b	2.15E-32
PEMN_5	Sulf2	3.76E-32
PEMN_5	Synpr	3.97E-32
PEMN_5	Ralyl	5.55E-32
PEMN_5	Fam19a1	6.66E-32
PEMN_5	1810041L15Rik	1.91E-31
PEMN_5	Sphkap	4.51E-31
PEMN_5	Prickle2	5.70E-31
PEMN_5	Cd44	1.49E-30
PEMN_5	Rbfox1	1.49E-30
PEMN_5	Plcxd3	2.35E-30
PEMN_5	Kctd8	2.39E-30
PEMN_5	Cdh13	8.59E-30
PEMN_5	Gm2694	1.48E-29
PEMN_5	Ddr2	1.50E-29
PEMN_5	Zbtb16	2.71E-29
PEMN_5	Lingo2	1.22E-28
PEMN_5	Ust	1.65E-28
PEMN_5	Epha7	2.01E-28
PEMN_5	Grm7	2.42E-28
PEMN_5	Zbtb7c	9.91E-28
PEMN_5	Tmem117	1.24E-27
PEMN_5	Slc5a7	2.28E-27
PEMN_5	Mdga1	9.45E-27
PEMN_5	Colec12	3.07E-26
PEMN_5	Calcrl	7.82E-26
PEMN_5	Bcar3	8.49E-26
PEMN_5	Abtb2	1.37E-25
PEMN_5	Kalrn	1.54E-25
PEMN_5	6330403A02Rik	1.68E-25
PEMN_5	Abcc8	2.23E-25
PEMN_5	Usp6nl	2.90E-25
PEMN_5	Prkcb	3.02E-25
PEMN_5	Unc5c	4.04E-25
PEMN_5	Vldlr	9.29E-25
PEMN_5	Gpc6	1.40E-24
PEMN_5	Gch1	1.40E-24
PEMN_5	Dpyd	2.67E-24
PEMN_5	Frmd4b	4.78E-24
PEMN_5	Itga6	5.11E-24
PEMN_5	Meis1	1.50E-23
PEMN_5	Lrp1b	1.63E-23
PEMN_5	Htr4	1.64E-23
PEMN_5	Stxbp5l	3.56E-23
PEMN_5	Tshz2	3.80E-23
PEMN_5	Ptprd	4.82E-23
PIMN_6	Cobll1	1.55E-14
PIMN_6	P2ry6	1.87E-14
PIMN_6	Asic4	1.92E-14
PIMN_6	Gm4907	2.20E-14
PIMN_6	Gm12504	2.47E-14
PIMN_6	Fxyd6	2.71E-14
PIMN_6	Map1b	2.71E-14
PIMN_6	Hspa2	3.16E-14
PIMN_6	Rarb	3.89E-14
PIMN_6	Scd1	6.99E-14
PIMN_6	Gm11747	5.50E-13
PIMN_6	C1qtnf1	1.76E-12
PIMN_6	Ugt1a2	5.31E-12
PIMN_6	Myoz3	1.12E-11
PIMN_6	Kcnv1	3.15E-11
PIMN_6	Sec14l3	8.57E-10
PIMN_6	Adra1d	2.77E-09
PIMN_6	Pcdh20	3.51E-09
PIMN_6	Nxph4	5.85E-09
PIMN_6	Aif1l	8.63E-09
PIMN_6	Defb48	9.39E-08
PIMN_6	Garem1	1.77E-07
PIMN_6	Fam162b	6.95E-07
PIMN_6	Lgi3	7.04E-07
PIMN_6	Gjb4	7.15E-07
PIMN_6	Cyp4a31	1.00E-06
PIMN_6	Frat1	3.11E-06
PIMN_6	Gata2	4.07E-06
PIMN_6	Gm14139	6.41E-06
PIMN_6	Omg	7.40E-06
PIMN_6	Dpep2	9.79E-06
PIMN_6	Stfa2l1	2.44E-05
PIMN_6	Sult5a1	3.15E-05
PIMN_6	Tmem89	3.84E-05
PIMN_6	Mc1r	1.31E-04
PIMN_6	Gpr88	1.31E-04
PIMN_6	Panx3	1.61E-04
PIMN_6	Fcer1a	1.61E-04
PIMN_6	Cd1d2	3.46E-04
PIMN_6	Agtrap	4.68E-04
PIMN_6	Blk	6.90E-04
PIMN_6	Avpr1b	1.08E-03
PIMN_6	Actn3	1.10E-03
PIMN_6	Adra2c	1.11E-03
PIMN_6	1700055N04Rik	1.26E-03
PIMN_6	Gm11648	1.68E-03
PIMN_6	Tlcd2	2.83E-03
PIMN_6	Gm53	2.99E-03
PIMN_6	Dpys	3.14E-03
PIMN_6	Cdh15	3.54E-03
PIMN_6	Nrk	3.84E-03
PIMN_6	Gpr182	4.26E-03
PIMN_6	Klhl34	4.86E-03
PIMN_6	Tcf21	5.55E-03
PIMN_6	Lgals2	5.98E-03
PIMN_6	Prl7d1	6.91E-03
PIMN_6	Pik3ap1	7.75E-03
PIMN_6	Gm5039	7.78E-03
PIMN_6	Pgk2	9.52E-03
PIMN_6	Arl4d	1.02E-02
PSN_4	Gm1965	1.24E-03
PSN_4	Gm15348	1.39E-03
PSN_4	Psg-ps1	2.16E-03
PSN_4	4933429O19Rik	2.31E-03
PSN_4	Ttpa	2.86E-03
PSN_4	Gm19990	3.04E-03
PSN_4	Spo11	3.05E-03
PSN_4	Olfr1082	3.23E-03
PSN_4	Acot3	3.41E-03
PSN_4	Dsg3	3.80E-03
PSN_4	Tmem8c	3.94E-03
PSN_4	A630012P03Rik	4.47E-03
PSN_4	Svs1	5.01E-03
PSN_4	Tgtp2	5.82E-03
PSN_4	Cxcr5	6.44E-03
PSN_4	Gm20556	6.58E-03
PSN_4	Rlbp1	6.84E-03
PSN_4	Olfr168	7.92E-03
PSN_4	Serpinb12	8.24E-03
PSN_4	Tex28	8.34E-03
PSN_4	Dio2	8.35E-03
PSN_4	Dmbx1	8.92E-03
PSN_4	Fam124b	1.06E-02
PSN_4	Gja1	1.62E-02
PSN_4	Krt71	1.71E-02
PSN_4	Apol7a	1.82E-02
PSN_4	Etd	2.01E-02
PSN_4	Atp6v1e2	2.29E-02
PSN_4	Ankrd7	2.48E-02
PSN_4	Lipn	2.78E-02
PSN_4	Padi3	3.39E-02
PSN_4	Snora64	3.59E-02
PSN_4	Gm4251	4.02E-02
PSN_4	Olfr166	4.09E-02
PSN_4	Nkx2-2	4.58E-02
PSN_4	Vmn2r49	4.88E-02
PSVN_1	Astn2	4.07E-179
PSVN_1	Cpne4	1.62E-155
PSVN_1	Adam12	5.19E-146
PSVN_1	Scgn	1.95E-128
PSVN_1	Moxd1	4.16E-126
PSVN_1	Vip	3.82E-90
PSVN_1	Rerg	7.66E-87
PSVN_1	Lama4	1.14E-86
PSVN_1	Tcerg1l	3.81E-80
PSVN_1	2410114N07Rik	2.29E-79
PSVN_1	Cpa6	6.36E-79
PSVN_1	Luzp2	1.18E-78
PSVN_1	Prex2	2.94E-76
PSVN_1	Tacr1	1.10E-75
PSVN_1	Slc6a12	1.93E-70
PSVN_1	Gpr149	1.39E-63
PSVN_1	P2rx2	1.25E-61
PSVN_1	4930402F11Rik	1.27E-55
PSVN_1	Cux2	2.67E-54
PSVN_1	Fst	9.32E-51
PSVN_1	Ptpre	1.08E-49
PSVN_1	Glp2r	1.15E-48
PSVN_1	Slc4a4	8.35E-48
PSVN_1	Kcnd2	8.73E-48

PEMN_5	Plscr4	9.52E-23
PEMN_5	Syn2	2.34E-22
PEMN_5	Ccdc60	4.55E-22
PEMN_5	Npy1r	7.12E-22
PEMN_5	Grip1	7.35E-22
PEMN_5	Ltbp4	9.97E-22
PEMN_5	Neat1	9.97E-22
PEMN_5	Lrrc7	1.08E-21
PEMN_5	Nyap2	1.08E-21
PEMN_5	Syt1	1.17E-21
PEMN_5	Ryr1	1.27E-21
PEMN_5	Col4a2	1.52E-21
PEMN_5	Nxph1	2.92E-21
PEMN_5	Fam117a	4.95E-21
PEMN_5	Tox	7.17E-21
PEMN_5	Slc26a4	1.05E-20
PEMN_5	Slit1	1.17E-20
PEMN_5	Slc6a17	1.78E-20
PEMN_5	Gm15881	4.79E-20
PEMN_5	BC030500	1.10E-19
PEMN_5	Adrb2	1.42E-18
PEMN_5	9530026F06Rik	6.31E-16
PEMN_5	Ffar3	5.40E-14
PEMN_5	Cnih3	4.98E-13
PEMN_5	Cldn8	6.27E-13
PEMN_5	Adamtsl2	3.83E-12
PEMN_5	Fam19a3	6.00E-11
PEMN_5	Rgcc	1.58E-10
PEMN_5	Hs3st4	3.01E-10
PEMN_5	Pthlh	1.68E-09
PEMN_5	Prl2c5	2.69E-09
PEMN_5	Gm10637	1.22E-08
PEMN_5	Gm4791	2.60E-08
PEMN_5	Adamts14	3.45E-08
PEMN_5	Tmem92	2.10E-07
PEMN_5	Vwa2	7.37E-07
PEMN_5	Pdcd1	9.79E-07
PEMN_5	4930539C22Rik	1.07E-06
PEMN_5	Sprr2d	1.58E-06
PEMN_5	1700029H14Rik	4.21E-05
PEMN_5	Defb1	4.26E-05
PEMN_5	Hsd17b13	7.82E-05
PEMN_5	BC030867	8.84E-05
PEMN_5	Ccdc153	8.93E-05
PEMN_5	Ccr4	1.17E-04
PEMN_5	Cyp4f18	1.25E-04
PEMN_5	Grasp	1.33E-04
PEMN_5	Acan	1.41E-04
PEMN_5	6030419C18Rik	1.42E-04
PEMN_5	Fli1	2.11E-04
PEMN_5	Tspan11	2.45E-04
PEMN_5	4930479D17Rik	2.52E-04
PEMN_5	Folr1	3.79E-04
PEMN_5	Fxyd2	3.99E-04
PEMN_5	Cyp3a59	5.04E-04
PEMN_5	Ifitm1	5.34E-04
PEMN_5	Tctex1d4	7.73E-04
PEMN_5	Cd209a	7.89E-04
PEMN_5	Gm5168	8.36E-04
PEMN_5	1700073E17Rik	9.36E-04
PIMN_6	Fsd2	1.10E-02
PIMN_6	Gm12409	1.24E-02
PIMN_6	Pldi	1.24E-02
PIMN_6	Cxcl13	1.59E-02
PIMN_6	4930500F04Rik	1.63E-02
PIMN_6	Foxr2	1.71E-02
PIMN_6	Mxd3	1.74E-02
PIMN_6	Klk13	1.83E-02
PIMN_6	Gm16548	1.94E-02
PIMN_6	Rgs2	2.37E-02
PIMN_6	Adam24	2.50E-02
PIMN_6	2610318N02Rik	2.53E-02
PIMN_6	Prf1	2.67E-02
PIMN_6	Derl3	2.73E-02
PIMN_6	Mblac1	2.88E-02
PIMN_6	4930471C04Rik	3.61E-02
PIMN_6	Scx	3.86E-02
PIMN_6	Stc2	3.87E-02
PIMN_6	Pcdhb2	3.88E-02
PIMN_6	Hyal1	4.15E-02
PIMN_7	Adarb2	2.61E-102
PIMN_7	Grik3	1.44E-43
PIMN_7	2610028E06Rik	4.01E-42
PIMN_7	Wfdc1	1.32E-36
PIMN_7	Cyp2a5	3.94E-33
PIMN_7	Sstr2	1.34E-31
PIMN_7	Pde1a	3.93E-29
PIMN_7	Vip	1.55E-26
PIMN_7	Ntng1	1.05E-25
PIMN_7	Lhfp	1.14E-23
PIMN_7	5530401A14Rik	1.52E-21
PIMN_7	Prkg2	3.64E-21
PIMN_7	Pdgfd	4.09E-21
PIMN_7	Pear1	9.88E-21
PIMN_7	Chrm3	1.36E-20
PIMN_7	Etl4	3.49E-20
PIMN_7	Ebf1	1.16E-19
PIMN_7	Plekhg1	2.22E-19
PIMN_7	Enthd1	1.21E-18
PIMN_7	Asic2	1.59E-17
PIMN_7	Tmem132d	1.21E-16
PIMN_7	Ccr5	5.38E-16
PIMN_7	Syt10	9.17E-16
PIMN_7	Creb5	1.41E-15
PIMN_7	A830018L16Rik	4.43E-15
PIMN_7	Cbln4	8.91E-15
PIMN_7	Asl	2.38E-14
PIMN_7	1700029J03Rik	2.38E-14
PIMN_7	Camk4	5.09E-14
PIMN_7	Chst15	5.60E-14
PIMN_7	Ldb2	6.34E-14
PIMN_7	Casr	1.10E-13
PIMN_7	Jazf1	1.68E-13
PIMN_7	Sparcl1	1.81E-13
PIMN_7	Ltk	1.92E-13
PIMN_7	Dnahc1	4.17E-13
PIMN_7	Prkd1	4.17E-13
PIMN_7	Sorcs2	9.23E-13
PIMN_7	Rxfp3	1.15E-12
PIMN_7	Pcdh19	1.16E-12
PSVN_1	Sctr	2.20E-45
PSVN_1	B230216N24Rik	2.23E-45
PSVN_1	Lmo7	4.89E-45
PSVN_1	Col4a2	9.66E-45
PSVN_1	Etl4	1.81E-44
PSVN_1	Dbh	4.64E-44
PSVN_1	Bai1	5.22E-44
PSVN_1	Tspan12	1.36E-43
PSVN_1	Spock3	2.19E-43
PSVN_1	Nav2	1.92E-41
PSVN_1	Arpp21	2.11E-41
PSVN_1	Kcnq5	5.15E-41
PSVN_1	Plxna4	2.14E-39
PSVN_1	Gpc5	2.17E-38
PSVN_1	Camk2a	2.99E-38
PSVN_1	Myo16	2.99E-38
PSVN_1	Ebf1	1.50E-36
PSVN_1	Pde8b	4.84E-36
PSVN_1	Kcnk13	3.70E-35
PSVN_1	Oas1g	4.92E-35
PSVN_1	Col4a1	6.42E-35
PSVN_1	Grin3a	6.62E-35
PSVN_1	Pxmp2	1.22E-34
PSVN_1	Bean1	1.56E-34
PSVN_1	Frmpd1	2.11E-34
PSVN_1	AW549542	4.01E-34
PSVN_1	Myrip	2.69E-33
PSVN_1	Phactr1	2.98E-33
PSVN_1	Igfbp7	3.35E-33
PSVN_1	Grhl3	6.86E-33
PSVN_1	Cyp2c66	1.82E-32
PSVN_1	Npr1	3.60E-32
PSVN_1	2610307P16Rik	4.67E-32
PSVN_1	Pcdha4-g	9.37E-32
PSVN_1	Slc22a23	1.02E-31
PSVN_1	1700120G07Rik	1.28E-31
PSVN_1	Prkd1	2.84E-31
PSVN_1	Wwtr1	3.07E-31
PSVN_1	Pappa	4.07E-31
PSVN_1	Calb2	4.33E-31
PSVN_1	Lrrc55	1.54E-30
PSVN_1	Sacs	3.71E-30
PSVN_1	Tmeff1	4.84E-30
PSVN_1	Cdh19	5.40E-29
PSVN_1	Mmd	1.88E-28
PSVN_1	Ankar	2.12E-27
PSVN_1	Gm11549	2.96E-27
PSVN_1	Ntng1	1.00E-26
PSVN_1	Nrp1	1.08E-26
PSVN_1	R3hdm1	1.46E-26
PSVN_1	Tmtc2	2.44E-26
PSVN_1	Acpl2	2.89E-26
PSVN_1	Vsig4	2.94E-26
PSVN_1	Orai2	4.26E-26
PSVN_1	Etv1	4.96E-26
PSVN_1	Ccdc60	1.07E-25
PSVN_1	Rtn4rl1	1.25E-25
PSVN_1	Agrn	1.29E-25
PSVN_1	Upk3b	4.23E-25
PSVN_1	Trim52	5.00E-25

PEMN_5	Gm20187	9.62E-04
PEMN_5	Myl10	1.07E-03
PEMN_5	4930567H12Rik	1.09E-03
PEMN_5	4930438E09Rik	1.21E-03
PEMN_5	Slc38a3	1.24E-03
PEMN_5	A530050N04Rik	1.30E-03
PEMN_5	Vmn2r106	1.36E-03
PEMN_5	Cst12	1.92E-03
PEMN_5	Ffar2	2.84E-03
PEMN_5	Slc51b	2.86E-03
PEMN_5	4933407G14Rik	3.09E-03
PEMN_5	Krt79	3.86E-03
PEMN_5	Pyhin1	4.17E-03
PEMN_5	Hist1h2an	4.33E-03
PEMN_5	Gzmf	4.81E-03
PEMN_5	Tmprss3	6.35E-03
PEMN_5	1700065J18Rik	6.88E-03
PEMN_5	Nxnl2	7.17E-03
PEMN_5	Gm4956	7.59E-03
PEMN_5	Pga5	8.53E-03
PEMN_5	Xlr5c	9.75E-03
PEMN_5	Gm9866	1.17E-02
PEMN_5	4930455B14Rik	1.21E-02
PEMN_5	Tfap2c	1.25E-02
PEMN_5	Lacc1	1.33E-02
PEMN_5	Samsn1	1.70E-02
PEMN_5	1700065D16Rik	1.86E-02
PEMN_5	Zbtb42	1.95E-02
PEMN_5	Ptafr	2.15E-02
PEMN_5	AI747448	2.24E-02
PEMN_5	Wnt8a	2.28E-02
PEMN_5	Cebpe	2.55E-02
PEMN_5	Olfr1157	2.62E-02
PEMN_5	Lrit3	2.65E-02
PEMN_5	Rtp2	2.66E-02
PEMN_5	Mir22	2.73E-02
PEMN_5	Serpinb8	2.73E-02
PEMN_5	Pgf	2.88E-02
PEMN_5	Ctrb1	3.00E-02
PEMN_5	4930487D11Rik	3.03E-02
PEMN_5	Ttc34	3.44E-02
PEMN_5	2310014L17Rik	3.52E-02
PEMN_5	3110045C21Rik	3.55E-02
PEMN_5	Bhmt2	4.12E-02
PEMN_5	4833412C05Rik	4.12E-02
PEMN_5	Pira2	4.43E-02
PEMN_5	Hsd3b1	4.47E-02
PEMN_5	Myoz1	4.48E-02
PEMN_5	Serpinb9g	4.78E-02
PEMN_6	Oprk1	3.46E-78
PEMN_6	Galntl6	1.75E-67
PEMN_6	Epha6	2.00E-56
PEMN_6	Lrp1b	3.65E-56
PEMN_6	Csmd3	5.09E-56
PEMN_6	Usp6nl	9.60E-55
PEMN_6	Cd44	1.59E-54
PEMN_6	Nxph1	1.43E-53
PEMN_6	Cdh18	4.47E-52
PEMN_6	Tac1	2.85E-49
PEMN_6	Grik1	5.16E-48
PIMN_7	Sema6a	1.86E-12
PIMN_7	Psg22	2.24E-12
PIMN_7	Kcng4	2.53E-12
PIMN_7	Rgs6	3.71E-12
PIMN_7	Krt23	3.75E-12
PIMN_7	Lamb1	5.09E-12
PIMN_7	Lama4	5.09E-12
PIMN_7	Trhde	6.66E-12
PIMN_7	Cmah	7.41E-12
PIMN_7	Adamts12	7.97E-12
PIMN_7	Frmpd1	1.19E-11
PIMN_7	Robo2	1.78E-11
PIMN_7	Gsg1l	2.11E-11
PIMN_7	Dkk3	2.33E-11
PIMN_7	Rarb	3.50E-11
PIMN_7	Matn4	5.06E-11
PIMN_7	Vat1l	6.41E-11
PIMN_7	Vmn2r-ps54	7.79E-11
PIMN_7	Fam159a	8.60E-11
PIMN_7	Gm20757	9.29E-11
PIMN_7	Kcnv1	1.72E-10
PIMN_7	Deptor	2.23E-10
PIMN_7	Evpl	2.27E-10
PIMN_7	Iqsec3	2.33E-10
PIMN_7	Nos1	3.81E-10
PIMN_7	Gm21949	3.90E-10
PIMN_7	Gnb3	5.71E-10
PIMN_7	Kirrel3	7.96E-10
PIMN_7	Tmc3	1.29E-09
PIMN_7	Adamts17	1.36E-09
PIMN_7	Ngf	2.41E-09
PIMN_7	Slc7a3	4.26E-09
PIMN_7	Nsg2	6.68E-09
PIMN_7	Stk32a	7.18E-09
PIMN_7	Mfsd4	7.80E-09
PIMN_7	Camp	8.86E-09
PIMN_7	Serpini1	1.33E-08
PIMN_7	Col25a1	1.63E-08
PIMN_7	BC080695	1.79E-08
PIMN_7	Cntnap5b	3.21E-08
PIMN_7	Ass1	3.53E-08
PIMN_7	Slc44a5	4.06E-08
PIMN_7	Dagla	4.31E-08
PIMN_7	Pde8b	4.32E-08
PIMN_7	Stom	4.80E-08
PIMN_7	Grid1	4.80E-08
PIMN_7	Chst11	6.35E-08
PIMN_7	Nav2	8.12E-08
PIMN_7	AW549542	1.07E-07
PIMN_7	Plch2	1.16E-07
PIMN_7	Crtac1	1.30E-07
PIMN_7	Kcnq5	1.49E-07
PIMN_7	Synm	1.67E-07
PIMN_7	Kctd1	1.73E-07
PIMN_7	Ngb	2.06E-07
PIMN_7	Ngfr	2.65E-07
PIMN_7	Prokr1	2.73E-07
PIMN_7	Postn	3.09E-07
PIMN_7	Dhrs3	3.30E-07
PIMN_7	Sh3pxd2a	4.30E-07
PSVN_1	Kcnj5	7.60E-25
PSVN_1	Rmst	1.07E-24
PSVN_1	Lphn3	1.53E-24
PSVN_1	Cdh6	1.89E-24
PSVN_1	Gm13399	1.98E-24
PSVN_1	Inf2	2.86E-24
PSVN_1	Npy2r	3.59E-24
PSVN_1	Fbn1	5.78E-24
PSVN_1	Ssbp2	8.40E-24
PSVN_1	Prune2	8.81E-24
PSVN_1	4932414N04Rik	1.59E-23
PSVN_1	Spag17	1.70E-23
PSVN_1	Emr1	2.19E-23
PSVN_1	Tmem44	4.01E-23
PSVN_1	Srrm4	4.43E-23
PSVN_1	Cntnap2	4.82E-23
PSVN_1	E430016F16Rik	1.73E-21
PSVN_1	Cbln4	7.18E-19
PSVN_1	Clec14a	1.00E-17
PSVN_1	Rhox2b	2.05E-16
PSVN_1	Tubal3	2.86E-11
PSVN_1	Tspan10	1.12E-10
PSVN_1	Bmp8a	9.67E-10
PSVN_1	Tdrd1	1.47E-09
PSVN_1	Gabre	2.04E-09
PSVN_1	Olfr1355	2.55E-09
PSVN_1	Gm4894	1.04E-08
PSVN_1	1700061F12Rik	8.79E-08
PSVN_1	Ssty2	1.06E-07
PSVN_1	1600025M17Rik	4.12E-07
PSVN_1	5430403N17Rik	4.41E-07
PSVN_1	4931440L10Rik	7.45E-07
PSVN_1	Slfn10-ps	1.17E-06
PSVN_1	Ugt2b1	1.46E-06
PSVN_1	Klrb1b	2.22E-06
PSVN_1	Gm15107	2.76E-06
PSVN_1	Htra4	2.92E-06
PSVN_1	Cdh5	3.53E-06
PSVN_1	Igfbp2	3.66E-06
PSVN_1	6330407A03Rik	5.45E-06
PSVN_1	Gm10057	1.01E-05
PSVN_1	Cdh22	1.18E-05
PSVN_1	Bpifb5	1.37E-05
PSVN_1	Twist2	2.02E-05
PSVN_1	Spic	2.45E-05
PSVN_1	4933406J08Rik	2.56E-05
PSVN_1	Akap3	3.61E-05
PSVN_1	Tie1	3.73E-05
PSVN_1	Gm41	4.54E-05
PSVN_1	2410003L11Rik	5.29E-05
PSVN_1	Wfdc6a	5.33E-05
PSVN_1	Gm10408	7.03E-05
PSVN_1	1190003K10Rik	9.39E-05
PSVN_1	Cts8-ps	9.40E-05
PSVN_1	Crx	1.01E-04
PSVN_1	Bst1	1.25E-04
PSVN_1	Edn3	1.33E-04
PSVN_1	Lpar3	1.35E-04
PSVN_1	Srd5a2	1.50E-04
PSVN_1	Gm20755	1.51E-04

PEMN_6	St6galnac3	2.75E-47
PEMN_6	Fgfr2	1.31E-46
PEMN_6	Hgf	1.90E-46
PEMN_6	Antxr2	2.41E-46
PEMN_6	Pld5	1.50E-45
PEMN_6	Tpd52l1	2.19E-45
PEMN_6	Car10	3.72E-44
PEMN_6	Agtr1a	4.13E-42
PEMN_6	Elfn1	7.48E-41
PEMN_6	Gda	4.80E-40
PEMN_6	Spock1	2.27E-39
PEMN_6	Col6a1	2.83E-39
PEMN_6	Mir669b	2.54E-38
PEMN_6	Gucy1a3	2.78E-38
PEMN_6	Kctd8	4.93E-38
PEMN_6	Alk	5.07E-37
PEMN_6	Rftn1	7.24E-37
PEMN_6	Rhox2a	7.67E-37
PEMN_6	Unc5d	2.65E-36
PEMN_6	Plscr2	3.06E-36
PEMN_6	Colec12	1.09E-35
PEMN_6	Col6a2	3.04E-35
PEMN_6	Lrrc7	3.73E-34
PEMN_6	Satb1	3.95E-34
PEMN_6	Dlgap2	1.12E-33
PEMN_6	Pi15	3.56E-33
PEMN_6	Bnc2	1.60E-32
PEMN_6	Ralyl	4.07E-32
PEMN_6	Colq	5.33E-32
PEMN_6	Fstl4	5.34E-32
PEMN_6	Ccdc60	5.78E-32
PEMN_6	Gfra2	8.50E-32
PEMN_6	Slit1	2.18E-31
PEMN_6	Prickle2	2.41E-31
PEMN_6	Gpc6	4.29E-31
PEMN_6	Bai3	4.74E-31
PEMN_6	Epha7	6.61E-30
PEMN_6	Meis1	7.11E-30
PEMN_6	Prkcb	1.65E-29
PEMN_6	Fam19a5	3.01E-29
PEMN_6	Fam5b	5.74E-29
PEMN_6	Htr4	6.84E-29
PEMN_6	Dnahc5	9.07E-29
PEMN_6	Rgs20	2.68E-28
PEMN_6	Cpne8	4.28E-28
PEMN_6	Sphkap	4.96E-28
PEMN_6	Ltbp4	5.23E-28
PEMN_6	Cntn3	5.23E-28
PEMN_6	2610316D01Rik	5.85E-28
PEMN_6	Slc5a7	1.15E-27
PEMN_6	Agbl4	1.18E-27
PEMN_6	Chat	5.80E-27
PEMN_6	Parvb	7.63E-27
PEMN_6	Ets1	1.84E-26
PEMN_6	Cntnap5b	2.47E-26
PEMN_6	Kcnma1	3.24E-26
PEMN_6	Ryr3	1.37E-25
PEMN_6	Hs3st4	3.17E-25
PEMN_6	Pcdh7	5.19E-25
PEMN_6	Fstl5	5.59E-25

PIMN_7	Igfbp5	5.11E-07
PIMN_7	Ptgir	6.82E-07
PIMN_7	Pdyn	8.57E-07
PIMN_7	Vwf	1.42E-06
PIMN_7	Allc	3.74E-06
PIMN_7	9430076C15Rik	4.53E-06
PIMN_7	Apoa2	6.46E-06
PIMN_7	Serpina3g	8.39E-06
PIMN_7	Clec1a	2.25E-05
PIMN_7	Gm20597	2.38E-05
PIMN_7	4930556M19Rik	3.08E-05
PIMN_7	Rbpjl	3.81E-05
PIMN_7	2810055G20Rik	7.24E-05
PIMN_7	Tekt3	7.31E-05
PIMN_7	Cd97	7.62E-05
PIMN_7	Nov	9.10E-05
PIMN_7	Serpinb3b	9.92E-05
PIMN_7	Calcoco2	1.22E-04
PIMN_7	CK137956	1.76E-04
PIMN_7	Atp6ap1l	2.06E-04
PIMN_7	Apol8	2.76E-04
PIMN_7	Prss35	3.42E-04
PIMN_7	Timeless	5.71E-04
PIMN_7	Neurl3	5.73E-04
PIMN_7	Omp	7.12E-04
PIMN_7	Gpr119	7.55E-04
PIMN_7	F10	1.12E-03
PIMN_7	Khdc1b	1.55E-03
PIMN_7	Gm12185	1.89E-03
PIMN_7	Kcnj9	1.96E-03
PIMN_7	Afm	1.98E-03
PIMN_7	Myrf	2.05E-03
PIMN_7	Kank4	2.30E-03
PIMN_7	Gpr150	3.89E-03
PIMN_7	Mroh4	4.96E-03
PIMN_7	Htr2a	5.36E-03
PIMN_7	Hmga2	6.11E-03
PIMN_7	Vmn2r106	6.11E-03
PIMN_7	Adra2c	7.66E-03
PIMN_7	Slc23a3	1.04E-02
PIMN_7	Smim18	1.05E-02
PIMN_7	Capza3	1.11E-02
PIMN_7	Hoxa11	1.17E-02
PIMN_7	A530046M15Rik	1.27E-02
PIMN_7	Gm10494	1.43E-02
PIMN_7	Plcg2	1.59E-02
PIMN_7	Clec9a	1.96E-02
PIMN_7	Retn	1.98E-02
PIMN_7	Gal3st1	2.03E-02
PIMN_7	Hepacam	2.76E-02
PIMN_7	Cd300e	3.20E-02
PIMN_7	Gm438	4.55E-02
PIN_1	Pde7b	0.00E+00
PIN_1	Camk1d	0.00E+00
PIN_1	Sema3e	1.67E-292
PIN_1	L3mbtl4	7.38E-285
PIN_1	Kctd16	1.45E-268
PIN_1	Eepd1	1.15E-187
PIN_1	Dock1	2.86E-161
PIN_1	Prr16	1.66E-149

PSVN_1	AW495222	2.00E-04
PSVN_1	4930480M12Rik	2.09E-04
PSVN_1	Fmo4	2.28E-04
PSVN_1	1700129C05Rik	3.17E-04
PSVN_1	Slc38a5	3.52E-04
PSVN_1	Vmn1r181	3.84E-04
PSVN_1	Siglec1	4.01E-04
PSVN_1	Olfr1167	4.13E-04
PSVN_1	Wfdc11	4.83E-04
PSVN_1	Gsdma2	6.78E-04
PSVN_1	Plin1	8.08E-04
PSVN_1	Ugt2a1	8.62E-04
PSVN_1	Ncf4	1.50E-03
PSVN_1	Rab19	1.57E-03
PSVN_1	Vmn1r132	1.58E-03
PSVN_1	Bin2	1.84E-03
PSVN_1	Ercc6l	1.88E-03
PSVN_1	Gm14781	1.89E-03
PSVN_1	E130006D01Rik	1.98E-03
PSVN_1	Ermap	2.04E-03
PSVN_1	4930547C10Rik	2.10E-03
PSVN_1	Gm20815	2.10E-03
PSVN_1	Pax3	2.32E-03
PSVN_1	Hist1h4c	2.41E-03
PSVN_1	Gm20917	2.42E-03
PSVN_1	Cst13	3.04E-03
PSVN_1	Gm7714	3.41E-03
PSVN_1	Tsga13	3.50E-03
PSVN_1	Smgc	4.12E-03
PSVN_1	Olfr869	5.65E-03
PSVN_1	Ticrr	5.72E-03
PSVN_1	Mslnl	6.19E-03
PSVN_1	Ankrd1	6.64E-03
PSVN_1	Serpinb7	6.66E-03
PSVN_1	Gm10413	8.97E-03
PSVN_1	Otop1	1.04E-02
PSVN_1	1190003J15Rik	1.16E-02
PSVN_1	Bpifa6	1.33E-02
PSVN_1	Slc6a7	1.55E-02
PSVN_1	Dusp27	1.71E-02
PSVN_1	Scnn1g	1.79E-02
PSVN_1	Cd8b1	1.88E-02
PSVN_1	Rhox3h	3.44E-02
PSVN_1	5430421F17Rik	4.40E-02
PSVN_1	Scn4b	4.86E-02
PSVN_2	Trhde	1.92E-285
PSVN_2	Col18a1	1.10E-160
PSVN_2	Mctp1	1.65E-151
PSVN_2	Gal	8.04E-141
PSVN_2	Myo1e	2.24E-96
PSVN_2	Ebf1	7.52E-92
PSVN_2	Greb1l	1.27E-91
PSVN_2	Cntn4	3.63E-85
PSVN_2	St18	3.45E-84
PSVN_2	AI593442	3.37E-83
PSVN_2	Cdh10	9.66E-81
PSVN_2	Mical2	2.25E-76
PSVN_2	Efemp1	2.36E-75
PSVN_2	Col19a1	3.75E-72
PSVN_2	Rmst	5.89E-72

PEMN_6	Tmem117	1.14E-24
PEMN_6	Slc16a12	1.22E-24
PEMN_6	Calcrl	1.69E-24
PEMN_6	Rbfox1	1.87E-24
PEMN_6	Ghr	2.02E-24
PEMN_6	Fam196b	2.26E-24
PEMN_6	Specc1	3.62E-24
PEMN_6	Casz1	6.72E-24
PEMN_6	Grip1	8.18E-24
PEMN_6	Nkain2	8.72E-24
PEMN_6	Pde4b	1.58E-23
PEMN_6	Col5a3	2.00E-23
PEMN_6	Lingo2	3.27E-23
PEMN_6	Pgm5	4.71E-23
PEMN_6	A830018L16Rik	4.73E-23
PEMN_6	Necab2	5.77E-23
PEMN_6	Cntnap2	9.64E-23
PEMN_6	Lemd1	1.18E-22
PEMN_6	Pdlim3	1.26E-22
PEMN_6	Tox	1.50E-22
PEMN_6	Slc6a17	1.68E-22
PEMN_6	Tmem163	2.60E-22
PEMN_6	Sntg2	4.50E-22
PEMN_6	Slc24a4	1.22E-21
PEMN_6	Dcbld2	1.27E-21
PEMN_6	Nrgn	2.80E-21
PEMN_6	Sdk2	2.80E-21
PEMN_6	Rfx3	3.02E-21
PEMN_6	Olfm3	3.95E-21
PEMN_6	Gm13034	2.10E-17
PEMN_6	4933407I05Rik	7.43E-14
PEMN_6	Mocs3	4.11E-11
PEMN_6	Arhgef39	5.12E-11
PEMN_6	6530411M01Rik	2.57E-10
PEMN_6	Card11	2.93E-09
PEMN_6	Apbb1ip	1.71E-08
PEMN_6	C030034L19Rik	1.41E-07
PEMN_6	Ghrh	2.08E-07
PEMN_6	Habp2	1.43E-06
PEMN_6	Il23a	2.50E-06
PEMN_6	Obp1a	4.13E-06
PEMN_6	Gm6936	4.16E-06
PEMN_6	8430422H06Rik	4.95E-06
PEMN_6	Cyp4f39	1.08E-05
PEMN_6	Dct	1.36E-05
PEMN_6	Ace2	1.55E-05
PEMN_6	Ace3	2.58E-05
PEMN_6	Galnt15	3.21E-05
PEMN_6	Grpr	4.35E-05
PEMN_6	Serpinf2	4.35E-05
PEMN_6	Btnl1	7.72E-05
PEMN_6	Esm1	9.57E-05
PEMN_6	Mogat1	1.14E-04
PEMN_6	Dsg1b	1.36E-04
PEMN_6	Ndnf	1.90E-04
PEMN_6	A830019L24Rik	2.09E-04
PEMN_6	Gm14858	2.19E-04
PEMN_6	Rfx8	3.63E-04
PEMN_6	4933405O20Rik	3.84E-04
PEMN_6	Sema7a	4.92E-04
PIN_1	Shisa6	2.82E-148
PIN_1	Mgll	5.52E-136
PIN_1	Sema5b	1.84E-135
PIN_1	Egflam	8.88E-134
PIN_1	Stac	1.60E-132
PIN_1	Dlgap1	6.65E-132
PIN_1	Nfatc1	3.40E-130
PIN_1	Met	3.92E-129
PIN_1	Lamc3	1.48E-124
PIN_1	Leprel1	3.35E-123
PIN_1	Fam189a1	8.51E-123
PIN_1	Slc24a2	6.21E-122
PIN_1	Nckap5	6.80E-121
PIN_1	Grm8	1.29E-117
PIN_1	Grm7	1.97E-115
PIN_1	Lingo2	9.45E-114
PIN_1	Fras1	5.71E-103
PIN_1	Mir466d	2.74E-100
PIN_1	Fut9	1.46E-99
PIN_1	Ntn1	1.33E-95
PIN_1	Col27a1	1.45E-95
PIN_1	Fibcd1	5.41E-95
PIN_1	Inpp4b	8.46E-95
PIN_1	Dapk1	1.60E-94
PIN_1	Egfr	6.15E-93
PIN_1	Khdrbs3	4.23E-91
PIN_1	Gm20754	7.91E-91
PIN_1	Wnk4	8.93E-89
PIN_1	2900055J20Rik	5.93E-87
PIN_1	Egfl6	7.30E-87
PIN_1	Cadm2	9.52E-84
PIN_1	Hcn1	2.54E-82
PIN_1	Grid1	1.75E-81
PIN_1	Flrt2	2.44E-81
PIN_1	Map2	9.18E-81
PIN_1	Pitpnc1	1.61E-79
PIN_1	Tac1	9.28E-77
PIN_1	Lmo7	9.28E-77
PIN_1	Gm1604b	1.09E-76
PIN_1	Galr1	7.54E-76
PIN_1	Pbx3	1.92E-75
PIN_1	Tmtc1	8.99E-74
PIN_1	Skap1	2.87E-73
PIN_1	Ror2	1.50E-71
PIN_1	Ppp3ca	1.65E-71
PIN_1	Col8a1	1.93E-70
PIN_1	Snx7	3.05E-70
PIN_1	Cldn11	9.35E-69
PIN_1	Shisa9	2.19E-68
PIN_1	Epb4.1l4a	2.10E-67
PIN_1	Pde4d	4.44E-67
PIN_1	Phactr1	8.97E-67
PIN_1	Prlr	9.36E-67
PIN_1	Gucy2g	7.98E-66
PIN_1	Chrm3	7.69E-63
PIN_1	Prkg1	1.75E-62
PIN_1	Nos1ap	1.95E-62
PIN_1	Pbx1	2.79E-62
PIN_1	Calcrl	1.51E-61
PIN_1	Pdia5	1.69E-61
PSVN_2	Myo16	7.52E-72
PSVN_2	Lphn2	1.42E-70
PSVN_2	Glp2r	4.58E-67
PSVN_2	Man1c1	1.42E-66
PSVN_2	Cpa6	1.95E-66
PSVN_2	Neurod6	9.01E-66
PSVN_2	Gad2	2.82E-63
PSVN_2	Gm8179	2.58E-61
PSVN_2	Plekhg3	9.29E-61
PSVN_2	Cntnap2	1.63E-58
PSVN_2	Tmc3	4.12E-58
PSVN_2	Prkd1	1.45E-56
PSVN_2	Fbn2	9.62E-56
PSVN_2	Kcnk13	1.28E-55
PSVN_2	Kcnd2	5.85E-54
PSVN_2	Egfem1	1.17E-53
PSVN_2	Gm1715	8.71E-53
PSVN_2	Fstl4	6.20E-51
PSVN_2	BC051070	7.60E-51
PSVN_2	Cacna1i	8.24E-50
PSVN_2	Ccser1	1.12E-49
PSVN_2	Rasgrf2	1.48E-49
PSVN_2	Col4a2	3.50E-48
PSVN_2	Trps1	7.09E-46
PSVN_2	Mpp4	6.29E-45
PSVN_2	Glyctk	1.28E-42
PSVN_2	2010016I18Rik	3.15E-42
PSVN_2	Zfp385b	1.43E-41
PSVN_2	Arpp21	1.69E-41
PSVN_2	Fgf12	3.51E-41
PSVN_2	Csf2rb2	5.07E-41
PSVN_2	Ccdc85a	8.27E-41
PSVN_2	Sdk1	4.20E-40
PSVN_2	Asb2	1.42E-39
PSVN_2	Etv1	1.23E-38
PSVN_2	Prkg2	8.16E-38
PSVN_2	Dnahc9	1.49E-37
PSVN_2	Eml6	5.60E-37
PSVN_2	Hs6st3	1.15E-36
PSVN_2	Asic2	2.61E-36
PSVN_2	Sctr	2.37E-35
PSVN_2	Als2	1.47E-34
PSVN_2	Trpm3	7.22E-34
PSVN_2	Kcnk10	1.01E-33
PSVN_2	Snca	7.15E-33
PSVN_2	Col26a1	9.60E-33
PSVN_2	Tll2	1.02E-32
PSVN_2	Slc18a2	1.51E-32
PSVN_2	Ece1	5.02E-32
PSVN_2	Fmn1	1.22E-31
PSVN_2	Rtn4rl1	1.60E-31
PSVN_2	Cdh11	3.63E-30
PSVN_2	Tll1	5.39E-29
PSVN_2	Camkk2	7.71E-29
PSVN_2	Mbnl1	9.73E-29
PSVN_2	Pid1	3.77E-28
PSVN_2	5530401A14Rik	3.83E-28
PSVN_2	Gfra1	3.83E-28
PSVN_2	Dhrs7c	4.98E-28
PSVN_2	Ltk	7.42E-28

PEMN_6	Oxgr1	5.51E-04
PEMN_6	1700034K08Rik	6.66E-04
PEMN_6	4933407L21Rik	7.46E-04
PEMN_6	Cpa4	7.46E-04
PEMN_6	BC055111	7.90E-04
PEMN_6	Gm14635	7.90E-04
PEMN_6	Nmur1	9.80E-04
PEMN_6	Akr1cl	1.09E-03
PEMN_6	BC090627	1.17E-03
PEMN_6	1700007K09Rik	1.67E-03
PEMN_6	Cyp2b10	1.92E-03
PEMN_6	Snai1	1.96E-03
PEMN_6	Tat	2.06E-03
PEMN_6	Grm2	2.28E-03
PEMN_6	Gm6260	2.58E-03
PEMN_6	Ctsm	2.71E-03
PEMN_6	4930438E09Rik	2.77E-03
PEMN_6	Htr5b	3.09E-03
PEMN_6	Dsg1a	3.52E-03
PEMN_6	Crisp1	3.95E-03
PEMN_6	Gimap3	5.82E-03
PEMN_6	Stc1	6.16E-03
PEMN_6	Tmco2	6.26E-03
PEMN_6	Gm11110	7.00E-03
PEMN_6	C86695	7.06E-03
PEMN_6	Batf	8.19E-03
PEMN_6	Tcl1b1	8.20E-03
PEMN_6	Gm5077	1.06E-02
PEMN_6	Prl2c1	1.07E-02
PEMN_6	Il21	1.38E-02
PEMN_6	Alx3	1.79E-02
PEMN_6	Peg10	1.94E-02
PEMN_6	Neu2	2.25E-02
PEMN_6	Mettl11b	2.38E-02
PEMN_6	Tnfrsf26	2.50E-02
PEMN_6	Kcnj10	2.58E-02
PEMN_6	Fgb	2.60E-02
PEMN_6	LOC171588	2.64E-02
PEMN_6	Gm3776	2.71E-02
PEMN_6	Gsdma	2.71E-02
PEMN_6	Ftcd	2.86E-02
PEMN_6	1700003F12Rik	2.89E-02
PEMN_6	5830403L16Rik	2.94E-02
PEMN_6	F2rl1	2.97E-02
PEMN_6	Usp51	3.16E-02
PEMN_6	Tlr5	3.20E-02
PEMN_6	Sec14l4	3.44E-02
PEMN_6	Hes3	3.57E-02
PEMN_6	Gm11186	3.97E-02
PEMN_6	H2-Ob	4.17E-02
PEMN_6	Nek2	4.57E-02
PEMN_6	Psg28	4.60E-02
PEMN_6	Susd3	4.85E-02
PEMN_6	Vax2os	4.93E-02
PIMN_1	Cdh20	9.96E-140
PIMN_1	Rgs22	2.59E-111
PIMN_1	Syn3	8.57E-105
PIMN_1	Nos1	5.17E-103
PIMN_1	Timp3	2.42E-96
PIMN_1	1700113H08Rik	8.42E-94
PIN_1	Fam126a	2.10E-61
PIN_1	Kctd8	4.82E-61
PIN_1	Zfhx3	3.62E-60
PIN_1	Cnksr2	5.61E-59
PIN_1	Fam196a	5.51E-58
PIN_1	4930509J09Rik	3.34E-57
PIN_1	Cask	4.98E-57
PIN_1	Enpp2	2.95E-55
PIN_1	Tenm4	1.89E-54
PIN_1	Tmc3	2.41E-54
PIN_1	Kirrel3	9.91E-54
PIN_1	Fam107b	8.82E-52
PIN_1	Sptb	4.98E-51
PIN_1	Stxbp5l	5.81E-51
PIN_1	Plcl1	1.61E-50
PIN_1	Fam19a5	3.85E-50
PIN_1	Boc	5.39E-50
PIN_1	Ptprz1	1.02E-49
PIN_1	Slitrk4	1.49E-49
PIN_1	Bicc1	5.21E-49
PIN_1	Nhs	4.00E-48
PIN_1	Mast4	1.91E-47
PIN_1	Kcnh5	7.11E-47
PIN_1	Sez6l	5.42E-46
PIN_1	Abcc8	1.44E-45
PIN_1	Dock2	2.06E-45
PIN_1	Atp1a3	2.14E-45
PIN_1	Crim1	9.39E-45
PIN_1	Fam196b	2.09E-44
PIN_1	Phactr2	4.27E-44
PIN_1	Ggta1	1.90E-43
PIN_1	Aff3	1.70E-42
PIN_1	Sparcl1	8.76E-42
PIN_1	Hsd11b1	3.98E-40
PIN_1	4930578E11Rik	6.85E-40
PIN_1	Mtnr1a	2.67E-32
PIN_1	Ramp2	1.70E-29
PIN_1	Gm12171	7.07E-28
PIN_1	Gcsam	2.80E-27
PIN_1	Bmp6	9.80E-27
PIN_1	2810011L19Rik	3.97E-26
PIN_1	Col5a1	9.66E-18
PIN_1	Kirrel2	3.34E-17
PIN_1	Sfrp2	4.22E-17
PIN_1	4933416E03Rik	5.83E-15
PIN_1	Pcdh8	1.66E-12
PIN_1	Cenph	1.47E-11
PIN_1	Sostdc1	1.55E-11
PIN_1	Gm17745	1.69E-11
PIN_1	6720468P15Rik	3.65E-11
PIN_1	Lrrc18	2.52E-10
PIN_1	Ces2b	3.78E-10
PIN_1	Zfp831	2.84E-09
PIN_1	4932435O22Rik	1.00E-08
PIN_1	Cd300a	2.37E-08
PIN_1	Ibsp	6.01E-08
PIN_1	Rbp7	7.29E-08
PIN_1	Gm826	1.09E-07
PIN_1	Tectb	1.14E-07
PIN_1	Gngt2	1.15E-07
PSVN_2	Agfg1	1.13E-27
PSVN_2	Stard5	1.35E-27
PSVN_2	Schip1	6.42E-27
PSVN_2	Mgat4a	6.80E-27
PSVN_2	Gabrb3	2.24E-26
PSVN_2	Map3k5	3.15E-26
PSVN_2	Csf2rb	5.64E-26
PSVN_2	Shisa6	1.75E-25
PSVN_2	Baalc	3.09E-25
PSVN_2	Nedd4l	6.12E-25
PSVN_2	3110047P20Rik	6.32E-25
PSVN_2	Frem1	1.08E-24
PSVN_2	Myt1l	1.27E-24
PSVN_2	Npas3	1.42E-24
PSVN_2	Nrip3	2.56E-24
PSVN_2	Cd209c	4.14E-24
PSVN_2	Smtnl2	4.51E-24
PSVN_2	Mrc2	4.59E-24
PSVN_2	Tmem232	7.10E-24
PSVN_2	Oxr1	8.35E-24
PSVN_2	Ttc39b	9.71E-24
PSVN_2	Scgn	1.17E-23
PSVN_2	Enox1	1.50E-23
PSVN_2	Kcnj5	1.78E-23
PSVN_2	March11	2.19E-23
PSVN_2	Trpv6	5.49E-21
PSVN_2	Abcc12	3.92E-20
PSVN_2	D430036J16Rik	2.14E-17
PSVN_2	Umodl1	9.76E-16
PSVN_2	Gm12159	1.58E-15
PSVN_2	Fam131c	9.58E-15
PSVN_2	Best3	2.84E-14
PSVN_2	Ms4a2	9.34E-13
PSVN_2	Tpbg	1.08E-12
PSVN_2	Htr1b	1.96E-12
PSVN_2	4933430N04Rik	6.73E-12
PSVN_2	Scimp	1.24E-11
PSVN_2	Fam159b	1.70E-11
PSVN_2	Gm13124	1.38E-10
PSVN_2	Psat1	1.05E-09
PSVN_2	Ascl3	2.43E-09
PSVN_2	Magel2	1.14E-08
PSVN_2	Vmn2r86	1.43E-08
PSVN_2	Gm3279	1.60E-08
PSVN_2	Il2rb	1.04E-07
PSVN_2	Inhba	1.15E-07
PSVN_2	Tex35	2.38E-07
PSVN_2	Grin2c	7.46E-07
PSVN_2	Epor	7.52E-07
PSVN_2	Tslp	8.18E-07
PSVN_2	Opalin	1.47E-06
PSVN_2	Spaca3	5.27E-06
PSVN_2	Gm1045	6.18E-06
PSVN_2	Ces2f	3.05E-05
PSVN_2	Micalcl	3.24E-05
PSVN_2	BB557941	3.52E-05
PSVN_2	Cuzd1	3.84E-05
PSVN_2	Col6a5	5.96E-05
PSVN_2	Pde6c	7.94E-05
PSVN_2	Onecut1	1.01E-04

PIMN_1	Fam65b	8.26E-93
PIMN_1	Adcy2	9.99E-90
PIMN_1	Aldh1a3	7.02E-89
PIMN_1	Htr2c	5.23E-88
PIMN_1	Pde1c	6.69E-87
PIMN_1	Alcam	3.24E-84
PIMN_1	Stxbp6	1.95E-80
PIMN_1	Fat3	1.54E-79
PIMN_1	Kirrel3	7.96E-79
PIMN_1	Stab2	8.53E-79
PIMN_1	Vwa5b1	2.79E-78
PIMN_1	Col5a2	1.23E-74
PIMN_1	Slco3a1	4.23E-74
PIMN_1	Cntnap5a	2.33E-73
PIMN_1	Fbxo7	3.80E-73
PIMN_1	Rora	4.71E-73
PIMN_1	Rnf144b	5.06E-72
PIMN_1	St18	5.20E-72
PIMN_1	Zfp536	8.90E-72
PIMN_1	Gfra1	5.11E-70
PIMN_1	Epha5	1.04E-69
PIMN_1	Oprd1	1.24E-69
PIMN_1	Slc35f1	7.07E-69
PIMN_1	Aebp1	8.86E-69
PIMN_1	Cacnb2	6.04E-67
PIMN_1	Plxnb1	1.48E-65
PIMN_1	Enpp1	1.32E-63
PIMN_1	Dgkb	1.32E-63
PIMN_1	Fam155a	2.04E-63
PIMN_1	Col25a1	2.71E-60
PIMN_1	Pde1a	9.57E-60
PIMN_1	Lrrc4c	1.06E-59
PIMN_1	Etv1	4.15E-59
PIMN_1	Cd1d1	6.07E-57
PIMN_1	Arhgap15	1.21E-56
PIN_1	Kng1	5.46E-07
PIN_1	Ntrk1	6.63E-07
PIN_1	9130015L21Rik	7.51E-07
PIN_1	Kcna3	1.36E-06
PIN_1	Ccl7	2.22E-06
PIN_1	Nphs1as	3.40E-06
PIN_1	4932411E22Rik	4.20E-06
PIN_1	Cxcr4	7.12E-06
PIN_1	Gm13119	2.92E-05
PIN_1	1700034G24Rik	3.00E-05
PIN_1	Lox	4.05E-05
PIN_1	Pla2g1b	7.44E-05
PIN_1	Hoxd8	7.96E-05
PIN_1	4930596D02Rik	1.09E-04
PIN_1	Ces1b	1.46E-04
PIN_1	Trem3	2.34E-04
PIN_1	Angptl4	2.67E-04
PIN_1	Hoxd1	3.32E-04
PIN_1	BC055402	4.15E-04
PIN_1	Prnd	6.82E-04
PIN_1	Bsx	7.95E-04
PIN_1	1700061I17Rik	1.05E-03
PIN_1	Nptx2	1.40E-03
PIN_1	4930500F04Rik	2.00E-03
PIN_1	Aadacl2	2.08E-03
PIN_1	Srpx2	3.87E-03
PIN_1	Gabrq	4.15E-03
PIN_1	Pla2g2d	6.63E-03
PIN_1	Fcgr2b	7.56E-03
PIN_1	Ptges	9.90E-03
PIN_1	Notum	1.21E-02
PIN_1	Ccl11	1.30E-02
PIN_1	Lin28a	1.32E-02
PIN_1	Lrrc52	2.24E-02
PIN_1	Slamf8	2.46E-02
PSVN_2	Ly6g6d	1.05E-04
PSVN_2	4930453L07Rik	1.57E-04
PSVN_2	Gm13944	2.62E-04
PSVN_2	Wnt3	3.03E-04
PSVN_2	Inmt	3.29E-04
PSVN_2	Cthrc1	4.56E-04
PSVN_2	Olfr691	6.08E-04
PSVN_2	4933402J07Rik	6.70E-04
PSVN_2	Olfr301	8.44E-04
PSVN_2	S100a9	1.34E-03
PSVN_2	Rgs9bp	1.39E-03
PSVN_2	4930524C18Rik	1.83E-03
PSVN_2	Pdlim4	2.52E-03
PSVN_2	Gm6537	3.57E-03
PSVN_2	Smok2a	6.58E-03
PSVN_2	Il12b	7.85E-03
PSVN_2	Tuba3a	8.51E-03
PSVN_2	Cecr6	8.86E-03
PSVN_2	Icam1	9.34E-03
PSVN_2	Fcrlb	9.40E-03
PSVN_2	2310001K24Rik	1.05E-02
PSVN_2	Kcnk7	1.22E-02
PSVN_2	F11	1.24E-02
PSVN_2	D730048I06Rik	1.99E-02
PSVN_2	Cacng1	2.07E-02
PSVN_2	Gm11756	2.11E-02
PSVN_2	AU022793	2.12E-02
PSVN_2	H1fnt	2.26E-02
PSVN_2	Hapln2	2.28E-02
PSVN_2	1700056E22Rik	2.31E-02
PSVN_2	Piwil1	2.45E-02
PSVN_2	Gm4814	2.55E-02
PSVN_2	Klra3	3.86E-02
PSVN_2	Nrl	4.49E-02
PSVN_2	Gm7538	4.68E-02

Table 15.

ident	gene	padjH
ageOld	Srsf2	6.07766E-16
ageOld	Car1	6.09443E-15
ageOld	Tmem181c-ps	7.91498E-14
ageOld	Spag5	3.67891E-09
ageOld	Fgf14	6.87261E-09
ageOld	Actb	1.23307E-08
ageOld	Mptx1	1.40342E-07
ageOld	Grid1	8.60015E-07
ageOld	Zg16	3.74902E-06
ageOld	Fth1	5.21996E-06
ageOld	Rps23	2.76709E-05
ageOld	Park2	4.3162E-05
ageOld	Klf8	6.86159E-05
ageOld	Fcrla	6.86159E-05
ageOld	1810065E05Rik	8.77811E-05
ageOld	Gm15319	9.52802E-05
ageOld	Ildr2	0.000267131
ageOld	Lgals1	0.000392336
ageOld	Cyp2c55	0.000426978
ageOld	Ly6h	0.000481607
genderF	Gm14525	1.23139E-07
genderF	Ovch2	2.1328E-07
genderF	Pla2g2a	7.97488E-07
genderF	Kcnk9	1.08163E-06
genderF	Pla2g5	2.53393E-05
genderF	Klk1b16	2.64395E-05
genderF	Aldh1a1	3.21958E-05
genderF	4930447C04Rik	3.51266E-05
genderF	Slpi	3.81138E-05
genderF	Ccdc88c	7.75044E-05
genderF	Hist1h2ba	9.77188E-05
genderF	Ces1c	0.000137196
genderF	Lpo	0.000153441
genderF	Spink6	0.000216662
genderF	Tspy-ps	0.000266299
genderF	Reg3g	0.000281366
genderF	Insrr	0.000540425
genderF	Ces2e	0.000634637
genderF	Adamdec1	0.000942276
genderF	Olfr631	0.001712112

ageOld	S100a6	0.000571241	genderF	Ces2a	0.0018362
ageOld	Gpr158	0.000571241	genderF	Tlr8	0.001926716
ageOld	AI317395	0.000695207	genderF	Slc38a3	0.00280639
ageOld	Katnbl1	0.000862634	genderF	S100g	0.003723584
ageOld	Frem3	0.000862634	genderF	Scel	0.003723584
ageOld	Kcnk12	0.000862634	genderF	Gsdmc2	0.004161108
ageOld	Lin7c	0.000862634	genderF	Gm20750	0.004557207
ageOld	Sycn	0.000993206	genderF	Srgn	0.00484209
ageOld	1500032L24Rik	0.001146544	genderF	Gm15760	0.005507258
ageOld	Tuba1c	0.001146743	genderF	Hsd3b5	0.006034702
ageOld	A730008H23Rik	0.001199386	genderF	1810006J02Rik	0.008906683
ageOld	Xrra1	0.001249032	genderF	Zdbf2	0.009214387
ageOld	Kcnd2	0.001249032	genderF	Mal	0.009362334
ageOld	Cox4i1	0.002001917	genderF	Gm10057	0.010474958
ageOld	Clca3	0.002209389	genderF	Gm14492	0.010913036
ageOld	Gm13247	0.002209389	genderF	Sh3bp2	0.012359271
ageOld	Rasl2-9	0.002209389	genderF	Wnt2	0.012780624
ageOld	Syt2	0.002454158	genderF	Tex40	0.013290824
ageOld	Glt1d1	0.002547402	genderF	Speer1-ps1	0.014137867
ageOld	A330023F24Rik	0.003040926	genderF	Pyroxd2	0.015638802
ageOld	Frmd4a	0.003472805	genderF	Prss30	0.016005394
ageOld	Man1c1	0.003555611	genderF	Hsd17b2	0.017135393
ageOld	Insm2	0.003555611	genderF	Tmprss5	0.017864893
ageOld	Apbb1	0.003555611	genderF	Gm4925	0.018934066
ageOld	Gm4832	0.003583683	genderF	Ces2c	0.019055403
ageOld	Lnx2	0.003921359	genderF	0610007N19Rik	0.019137519
ageOld	Prph	0.003921359	genderF	Defb39	0.021498302
ageOld	Degs1	0.003921359	genderF	E030044B06Rik	0.022176689
ageOld	Lrrk2	0.003944509	genderF	D5Ertd577e	0.024572843
ageOld	Mtmr14	0.004301636	genderF	Clec3b	0.025090447
ageOld	Csmd3	0.004769697	genderF	Phldb2	0.027315419
ageOld	Gm14525	0.004871094	genderF	Slc25a41	0.031031026
ageOld	Kif13b	0.004892722	genderF	Klk1b5	0.033619031
ageOld	Rgs9	0.005087452	genderF	Cyp2r1	0.034330497
ageOld	Gm6548	0.005087452	genderF	Gabrr1	0.034737168
ageOld	Kcnq3	0.005087452	genderF	BC064078	0.037994863
ageOld	Cst3	0.005087452	genderF	Astl	0.03831308
ageOld	Rpl14	0.005103391	genderF	Tmem170	0.039154133
ageOld	Agbl4	0.005343339	genderF	Tbata	0.039242099
ageOld	Dok6	0.005458881	genderF	Ikbke	0.039242099
ageOld	1810034E14Rik	0.005511478	genderF	Dpep1	0.039251396
ageOld	Gm13710	0.005511478	genderF	Pcdhb7	0.039437361
ageOld	BC147527	0.005511478	genderF	Mir5109	0.040626516
ageOld	DQ267100	0.005687892	genderF	Cd70	0.044843484
ageOld	Rps20	0.005725902	genderF	Lgi4	0.044892382
ageOld	Cdyl	0.006028623	genderF	Casq1	0.048056803
ageOld	Ubb	0.006028623	time7PM	Per3	5.19873E-62
ageOld	Gm15421	0.006028623	time7PM	Arntl	7.18728E-54
ageOld	Slc25a41	0.006140714	time7PM	Nr1d2	8.43445E-30
ageOld	1700030F04Rik	0.00671004	time7PM	Tef	3.2917E-20
ageOld	Coa3	0.006828839	time7PM	Per2	3.48865E-16
ageOld	Nop10	0.006901915	time7PM	Rgs4	1.87781E-12
ageOld	Gm6682	0.006916998	time7PM	Ppia	4.01694E-12
ageOld	E330020D12Rik	0.006980499	time7PM	Scg2	4.75066E-12
ageOld	Atp6v0b	0.006980499	time7PM	Ckb	5.66075E-12
ageOld	Tmem132c	0.006980499	time7PM	Pcsk1n	6.30192E-12
ageOld	Gadd45gip1	0.006980499	time7PM	Rpl3	1.05766E-11
ageOld	Galnt13	0.006980499	time7PM	Slc25a4	1.30729E-11
ageOld	Mdh2	0.007068543	time7PM	Rps20	1.44938E-11
ageOld	Grb10	0.007941134	time7PM	Rps3a1	1.87538E-11

ageOld	Fxyd1	0.007941134	time7PM	Tpt1	1.87538E-11
ageOld	Znrf3	0.007941134	time7PM	Olfm1	1.89635E-11
ageOld	B3gnt5	0.007941134	time7PM	Prph	4.57481E-11
ageOld	Ppia	0.007941134	time7PM	1500032L24Rik	5.12427E-11
ageOld	Pdzrn4	0.007941134	time7PM	Cst3	5.55487E-11
ageOld	Maml3	0.007941134	time7PM	Gm13498	5.55487E-11
ageOld	Serpine2	0.008006634	time7PM	Srsf2	5.66263E-11
ageOld	Rnasek	0.008063272	time7PM	Tubb2a	5.74992E-11
ageOld	Ntrk2	0.008172838	time7PM	Cfl1	5.74992E-11
ageOld	Lrrc32	0.008504862	time7PM	Map1lc3a	1.01946E-10
ageOld	Rpl4	0.008504862	time7PM	Cd80	2.10894E-10
ageOld	Hist3h2ba	0.008833056	time7PM	Chchd2	2.95065E-10
ageOld	Dapk1	0.009165737	time7PM	Nap1l5	3.01022E-10
ageOld	Zfp708	0.00923333	time7PM	Bex2	4.7105E-10
ageOld	Stk40	0.009585982	time7PM	Rps23	5.65576E-10
ageOld	H2afz	0.009807021	time7PM	Rplp2-ps1	6.27462E-10
ageOld	Nudc	0.009841722	time7PM	Cd81	1.10114E-09
ageOld	Slc25a5	0.010310706	time7PM	Rasl2-9	1.17794E-09
ageOld	Osmr	0.010338349	time7PM	Atp6v0c	1.24843E-09
ageOld	1700126H18Rik	0.010338349	time7PM	Oaz1	2.21838E-09
ageOld	Hsd3b5	0.010651553	time7PM	BC147527	3.94126E-09
ageOld	Hist1h2bb	0.011822191	time7PM	Reep5	4.68766E-09
ageOld	Sprr2a1	0.011864799	time7PM	Slc7a11	5.37567E-09
ageOld	Mkx	0.01197707	time7PM	Rpl7	5.37567E-09
ageOld	Cables1	0.013906124	time7PM	Slc1a1	5.91408E-09
ageOld	Rps27	0.01393806	time7PM	Plat	7.30632E-09
ageOld	Sprr2a2	0.01393806	time7PM	Hnrnpk	7.30632E-09
ageOld	Sox5	0.01393806	time7PM	Skint10	7.30632E-09
ageOld	Snw1	0.01393806	time7PM	Ndrg4	7.91227E-09
ageOld	Gm20750	0.014721298	time7PM	Itga9	8.05619E-09
ageOld	Nsun3	0.015015236	time7PM	Eef1a1	1.03687E-08
ageOld	A330040F15Rik	0.015161855	time7PM	Ngfrap1	1.09681E-08
ageOld	Fbln7	0.015161855	time7PM	Actg1	1.09681E-08
ageOld	Gm9758	0.015161855	time7PM	Eef2	1.09681E-08
ageOld	Praf2	0.015271991	time7PM	1700034F02Rik	1.09681E-08
ageOld	Slc12a5	0.015650837	time7PM	Srrm2	1.32471E-08
ageOld	Pfn1	0.01664306	time7PM	Zfp712	1.36428E-08
ageOld	Eras	0.018128683	time7PM	Chrna3	1.58211E-08
ageOld	Snora34	0.018179864	time7PM	Prdx2	1.80085E-08
ageOld	Eif3c	0.018179864	time7PM	Zfp708	2.17839E-08
ageOld	Fkrp	0.020587043	time7PM	1700016L04Rik	2.17839E-08
ageOld	Akr1c19	0.020587043	time7PM	Tuba1b	2.25733E-08
ageOld	Rnf128	0.021128227	time7PM	Aldoart1	2.34208E-08
ageOld	Lmx1b	0.02123735	time7PM	Vat1	2.41603E-08
ageOld	Nell2	0.02123735	time7PM	Ndn	2.44194E-08
ageOld	Ednrb	0.022763491	time7PM	Skint6	2.82101E-08
ageOld	Gm17019	0.024302519	time7PM	Magee1	2.93161E-08
ageOld	Wnt5b	0.025124717	time7PM	Aldoart2	2.99209E-08
ageOld	Rhox1	0.025753926	time7PM	Rnasek	3.08044E-08
ageOld	Emcn	0.026396683	time7PM	Cxx1c	3.2434E-08
ageOld	Sema3b	0.026532981	time7PM	Tubb3	3.73276E-08
ageOld	Il15ra	0.026690774	time7PM	Gm5148	3.78794E-08
ageOld	Gm853	0.026901659	time7PM	Rimklb	3.88177E-08
ageOld	Tff3	0.026901659	time7PM	Rpl31-ps12	3.94705E-08
ageOld	Hoxc4	0.026982377	time7PM	Rfx2	4.41387E-08
ageOld	Sdr42e1	0.027257207	time7PM	Dbp	4.74225E-08
ageOld	Zfp259	0.029003604	time7PM	Ywhaq	5.03044E-08
ageOld	Otog	0.029492315	time7PM	Ndufa2	6.65414E-08
ageOld	Gm4907	0.03012438	time7PM	Cox8a	6.65414E-08
ageOld	Lgals12	0.030489031	time7PM	Gm9079	7.43157E-08

ageOld	Slc8a3	0.031611422	time7PM	Cox4i1	8.92263E-08
ageOld	Kctd2	0.032259761	time7PM	Tnfsf4	9.74321E-08
ageOld	4833420G17Rik	0.032259761	time7PM	Vps13a	1.00194E-07
ageOld	Kcnk1	0.032907243	time7PM	Tspan3	1.00211E-07
ageOld	Nav2	0.03465402	time7PM	2210404O07Rik	1.04649E-07
ageOld	Tubb6	0.035965408	time7PM	Pla2g4c	1.04649E-07
ageOld	Ccdc152	0.036207742	time7PM	Gm129	1.05284E-07
ageOld	Tubb2a-ps2	0.036657963	time7PM	Banp	1.11336E-07
ageOld	Bckdha	0.036704894	time7PM	Chrnb4	1.15915E-07
ageOld	Cmtm3	0.040041837	time7PM	Slc25a39	1.17567E-07
ageOld	Yipf4	0.040041837	time7PM	Rpl14	1.18238E-07
ageOld	Dgat2	0.041204157	time7PM	Fau	1.18238E-07
ageOld	1700084F23Rik	0.043156316	time7PM	Emc10	1.30289E-07
ageOld	Gm101	0.044744139	time7PM	Pgam1	1.31912E-07
ageOld	Ampd1	0.044744139	time7PM	Ubb	1.53672E-07
ageOld	Tnfsf10	0.045051174	time7PM	Hist1h2bf	1.58901E-07
ageOld	Slc18a3	0.045478161	time7PM	Syt4	1.58901E-07
ageOld	Tmem79	0.045478161	time7PM	Gm12070	1.58901E-07
ageOld	Tubg1	0.046083911	time7PM	Flot1	1.60309E-07
ageOld	Atp5g1	0.047100837	time7PM	Gm11978	1.86443E-07
ageOld	Mill2	0.047682204	time7PM	Gm6548	2.07259E-07
ageOld	Zfp595	0.048095699	time7PM	Per1	2.20958E-07
ageOld	Alyref2	0.048476918	time7PM	Gm6682	2.20958E-07
ageOld	Csl	0.049020179	time7PM	H3f3b	2.20958E-07
ageOld	Rapsn	0.049033248	time7PM	Nedd8	2.35247E-07
ageOld	Serpinb9c	0.049033248	time7PM	Vamp2	2.60795E-07
ageOld	Gm766	0.049708376	time7PM	Lgals1	3.23817E-07
creUchl1	Gm13710	4.2735E-223	time7PM	B3gnt1	4.25683E-07
creUchl1	Slc15a2	5.1994E-130	time7PM	Hist1h2bb	8.41838E-07
creUchl1	Klk1b22	1.6295E-127	time7PM	4931408D14Rik	1.87191E-06
creUchl1	Pisd-ps3	1.2742E-112	time7PM	Hist1h2bm	3.25781E-06
creUchl1	Sft2d2	3.0183E-99	time7PM	Gm4980	3.49497E-06
creUchl1	Retnlb	3.01731E-97	time7PM	Tubb2a-ps2	3.91079E-06
creUchl1	Dlgap1	5.39245E-94	time7PM	Zbtb16	4.21897E-06
creUchl1	Ccrn4l	1.37044E-92	time7PM	2310047M10Rik	3.05115E-05
creUchl1	Ulk4	1.95177E-85	time7PM	Tnfsf18	4.48974E-05
creUchl1	Dpp10	8.96092E-85	time7PM	Olfr631	7.7947E-05
creUchl1	Gm3893	5.96367E-75	time7PM	Gm7977	0.000345879
creUchl1	Celf3	1.43761E-73	time7PM	Wfs1	0.000633638
creUchl1	Kcnh6	6.37973E-72	time7PM	Gm15941	0.000806771
creUchl1	Gm8909	6.49835E-72	time7PM	Uts2	0.001578899
creUchl1	H2-Q9	1.15933E-68	time7PM	Serpine2	0.001648971
creUchl1	H2-Q5	2.60328E-67	time7PM	Sstr2	0.00177418
creUchl1	Mill2	4.08829E-66	time7PM	Nrsn2	0.001803124
creUchl1	Rbm5	2.96937E-64	time7PM	Cdh19	0.00188134
creUchl1	Lrrfip1	7.17414E-63	time7PM	2010109I03Rik	0.002657443
creUchl1	Klk1b24	6.19282E-62	time7PM	Mep1a	0.002683042
creUchl1	Klk1b21	1.70466E-59	time7PM	Otoa	0.002739061
creUchl1	Ybx1	5.68308E-59	time7PM	Gm14525	0.002911147
creUchl1	Picalm	1.90543E-56	time7PM	Rec8	0.002977444
creUchl1	Srsf2	4.88531E-56	time7PM	Cck	0.002981295
creUchl1	H2-Q4	3.73991E-54	time7PM	Mrgpre	0.003366782
creUchl1	Muc2	8.22203E-53	time7PM	Tmem35	0.003592314
creUchl1	Csad	6.59049E-49	time7PM	1700003E16Rik	0.003602257
creUchl1	Park2	3.72467E-48	time7PM	Hspb1	0.003602257
creUchl1	Ccl27a	6.34247E-48	time7PM	Rps4y2	0.003900878
creUchl1	Agbl4	1.99264E-47	time7PM	Insm2	0.003900878
creUchl1	Spag5	9.10051E-47	time7PM	Mt3	0.005469945
creUchl1	4933409K07Rik	6.95104E-46	time7PM	Fjx1	0.006599597
creUchl1	Zfp69	1.34956E-45	time7PM	Hrh3	0.006712859

creUchl1	Phgr1	1.93335E-45
creUchl1	Cnksr2	5.44495E-43
creUchl1	Lypd8	9.90467E-43
creUchl1	H2-K2	1.98848E-40
creUchl1	Alcam	7.94138E-40
creUchl1	H2-Q1	1.92544E-39
creUchl1	Sidt1	1.92544E-39
creUchl1	Pla2g2a	5.47989E-39
creUchl1	Guca2a	1.18948E-38
creUchl1	BC117090	6.15387E-38
creUchl1	Rims1	6.15387E-38
creUchl1	Mdga2	2.51402E-37
creUchl1	Rftn1	1.88305E-36
creUchl1	Gal	1.52923E-35
creUchl1	Miip	1.95768E-35
creUchl1	Akap6	3.26377E-35
creUchl1	F2rl2	1.29829E-34
creUchl1	Col5a2	2.88333E-34
creUchl1	Hist1h2bb	3.12393E-34
creUchl1	A530054K11Rik	2.76122E-33
creUchl1	Parp3	8.41797E-33
creUchl1	Hist1h2bf	5.36091E-32
creUchl1	Cd163l1	7.19204E-32
creUchl1	Lgals4	9.38785E-32
creUchl1	Glt1d1	1.37936E-31
creUchl1	3110007F17Rik	2.17533E-31
creUchl1	Hspa8	3.75661E-31
creUchl1	Klk1b27	4.94029E-31
creUchl1	Gcnt4	5.6452E-31
creUchl1	Acaa1b	5.6771E-31
creUchl1	H2-M5	6.60765E-31
creUchl1	Hist1h2bm	1.63291E-30
creUchl1	H2-Bl	1.718E-30
creUchl1	Ptchd4	1.8279E-30
creUchl1	Map6	3.45255E-30
creUchl1	Lin7c	3.56589E-30
creUchl1	Ush1c	8.591E-30
creUchl1	Clvs2	1.16157E-29
creUchl1	Cnep1r1	2.85064E-29
creUchl1	Ceacam1	7.19479E-29
creUchl1	Cntn5	1.17301E-28
creUchl1	Sgcz	2.63549E-28
creUchl1	1700016L04Rik	3.07577E-28
creUchl1	H2-T24	8.04211E-28
creUchl1	Pcdh9	9.50962E-28
creUchl1	Lhfp	2.1352E-27
creUchl1	Zfp804a	3.77034E-27
creUchl1	Alad	4.2361E-27
creUchl1	Prdx6b	4.2361E-27
creUchl1	Rnf121	4.63125E-27
creUchl1	Gm10125	5.50223E-27
creUchl1	Nlrp5-ps	8.85582E-27
creUchl1	Ccdc85a	1.21731E-26
creUchl1	Dcc	3.93053E-26
creUchl1	B2m	5.38627E-26
creUchl1	2610035D17Rik	6.32541E-26
creUchl1	Gpc6	1.65307E-25
creUchl1	P2ry6	1.9365E-25
creUchl1	Gm13305	8.60062E-25
creUchl1	Magohb	1.13325E-24
time7PM	Adora1	0.006922857
time7PM	BC049762	0.008130523
time7PM	Slc26a3	0.008474715
time7PM	Klk1b3	0.008948655
time7PM	Vmn2r52	0.00993029
time7PM	Gbp11	0.010130941
time7PM	Kbtbd7	0.010702991
time7PM	Arsj	0.010809842
time7PM	Klk1b21	0.011493587
time7PM	Ngfr	0.011755879
time7PM	Ces1b	0.011982297
time7PM	Hsd3b5	0.012488186
time7PM	Gm20753	0.014226719
time7PM	Gm6588	0.014570697
time7PM	Ddc	0.015274067
time7PM	Ccdc88c	0.015592684
time7PM	Rad51ap2	0.015717409
time7PM	Klf15	0.015863914
time7PM	Gtsf1	0.015923358
time7PM	Ncrna00086	0.015954763
time7PM	Il13ra1	0.01646116
time7PM	Ikzf1	0.016590373
time7PM	Pttg1	0.016683837
time7PM	4930564C03Rik	0.019189435
time7PM	Sstr3	0.019420943
time7PM	Pgk2	0.019470565
time7PM	Klk1b22	0.020743647
time7PM	AI504432	0.021135189
time7PM	Reg3g	0.021654862
time7PM	Phxr4	0.022335477
time7PM	Dclk3	0.022525958
time7PM	Rasal3	0.022530636
time7PM	Cd177	0.023585934
time7PM	4930503O07Rik	0.023819512
time7PM	Adamts19	0.026662255
time7PM	AU019990	0.027841476
time7PM	Gm14015	0.029305401
time7PM	Grp	0.03018402
time7PM	Stk32b	0.030342447
time7PM	Hus1b	0.03182747
time7PM	Mad2l1	0.032326524
time7PM	Tex28	0.03299506
time7PM	Aldh1a1	0.033261856
time7PM	Calcb	0.033261856
time7PM	Birc5	0.034043722
time7PM	Kcna5	0.034096188
time7PM	Dll1	0.034237457
time7PM	4930598F16Rik	0.034667601
time7PM	1700009C05Rik	0.035480569
time7PM	Tal1	0.036554406
time7PM	Gabre	0.038750127
time7PM	Klk1b24	0.040016715
time7PM	Cidea	0.040482335
time7PM	Cml3	0.043405043
time7PM	Mr1	0.044196594
time7PM	Lrrc18	0.046015378
locationDistal	1810065E05Rik	5.0302E-71
locationDistal	Col5a3	1.79412E-20
locationDistal	Guca2a	9.79186E-26
locationDistal	Muc2	5.0291E-123

creUchl1	Ppfia2	1.15746E-24	locationDistal	Dmbt1	1.02141E-18
creUchl1	Eda	1.29817E-24	locationDistal	Hmgcs2	3.45357E-22
creUchl1	Slc25a5	1.64471E-24	locationDistal	Thy1	1.31805E-11
creUchl1	Hp1bp3	3.97608E-24	locationDistal	Ltk	0.000140038
creUchl1	Tpt1	4.25055E-24	locationDistal	Col27a1	2.42041E-09
creUchl1	Zfp933	5.78568E-24	locationDistal	5930412G12Rik	0.000215047
creUchl1	Lrfn5	6.1858E-24	locationDistal	Rapgef4	3.47654E-15
creUchl1	Hist2h2bb	2.80492E-23	locationDistal	Ceacam1	9.56246E-16
creUchl1	Klk1b11	3.36773E-23	locationDistal	4930443O20Rik	1.23225E-11
creUchl1	Aif1	4.46261E-21	locationDistal	Itpr1	3.84226E-09
creUchl1	Glp1r	1.42772E-18	locationDistal	Stxbp6	9.7137E-07
creUchl1	Slpi	3.73363E-17	locationDistal	Snca	4.1084E-10
creUchl1	Fbln7	1.4645E-16	locationDistal	Gcnt3	1.46163E-12
creUchl1	Ror2	5.30774E-14	locationDistal	Spock1	2.34254E-14
creUchl1	AA388235	8.08526E-13	locationDistal	2310067B10Rik	7.15354E-08
creUchl1	Aldh1a1	3.92692E-12	locationDistal	Gm5607	0.000261527
creUchl1	2210039B01Rik	9.15718E-12	locationDistal	Cyp2c55	1.19148E-13
creUchl1	Btnl4	3.72023E-10	locationDistal	Itga8	6.54859E-10
creUchl1	Lyz1	7.70189E-10	locationDistal	Car1	4.65878E-23
creUchl1	Gm853	1.99949E-09	locationDistal	Vat1l	3.45552E-14
creUchl1	Scrg1	1.20341E-08	locationDistal	Lin7a	4.8049E-09
creUchl1	Klk1b1	4.69649E-08	locationDistal	Reg3g	2.6867E-08
creUchl1	Trim43b	3.09257E-07	locationDistal	Trim9	8.2977E-06
creUchl1	Gm11194	3.58963E-07	locationDistal	Syt6	0.000142955
creUchl1	Dcdc2a	8.54491E-07	locationDistal	Cdr1	3.29476E-07
creUchl1	Beta-s	1.19204E-06	locationDistal	Pex5l	3.19064E-05
creUchl1	Abcc3	1.42355E-06	locationDistal	Cacna1h	1.54266E-05
creUchl1	Pyroxd2	3.3952E-06	locationDistal	Tnfsf4	0.002705121
creUchl1	Slc39a4	5.44387E-06	locationDistal	Retnlb	2.63419E-12
creUchl1	Hist1h2ba	1.31435E-05	locationDistal	Ptpro	4.21106E-06
creUchl1	Cd177	1.95339E-05	locationDistal	Ephb1	1.07692E-09
creUchl1	Npc1l1	4.44712E-05	locationDistal	Kcnh7	5.84873E-07
creUchl1	Gbp1	4.65027E-05	locationDistal	Drp2	3.44848E-05
creUchl1	Kif20b	5.97114E-05	locationDistal	Unc5d	6.68818E-08
creUchl1	Hal	6.00534E-05	locationDistal	2810032G03Rik	2.30157E-06
creUchl1	1700109F18Rik	8.16682E-05	locationDistal	Gmip	0.00012201
creUchl1	Prss41	8.38497E-05	locationDistal	Adcy1	0.001280619
creUchl1	4930402F11Rik	0.000294652	locationDistal	Tle1	0.000147795
creUchl1	Slc51a	0.000379863	locationDistal	Spred3	5.38764E-06
creUchl1	9130008F23Rik	0.000577028	locationDistal	Gpr176	1.46439E-05
creUchl1	Thpo	0.000690239	locationDistal	Usp35	0.000439112
creUchl1	1810019J16Rik	0.000717694	locationDistal	Kcnk3	2.79654E-05
creUchl1	Gpr139	0.000740082	locationDistal	Dzip1l	0.000251404
creUchl1	Il10ra	0.000914087	locationDistal	Kcnj6	1.39606E-06
creUchl1	Fcgr1	0.000974108	locationDistal	Fabp2	4.95157E-15
creUchl1	Spin4	0.001144009	locationDistal	Gm5424	0.001021026
creUchl1	Cd5	0.001217532	locationDistal	Lmx1b	2.21744E-06
creUchl1	Awat2	0.001632976	locationDistal	4833424O15Rik	1.69837E-06
creUchl1	Gja3	0.001687002	locationDistal	Gm21949	7.00341E-05
creUchl1	1700040N02Rik	0.001715414	locationDistal	Pparg	3.30454E-07
creUchl1	Rfx6	0.001759615	locationDistal	Slc9a9	0.000009044
creUchl1	Dgat2l6	0.001879127	locationDistal	Ncald	2.43406E-11
creUchl1	Dnajb13	0.00204671	locationDistal	Dlc1	2.53692E-07
creUchl1	Rhou	0.002096123	locationDistal	Pdia5	9.16607E-05
creUchl1	Sult6b1	0.002431541	locationDistal	4931430N09Rik	1.48831E-05
creUchl1	Slamf1	0.004178791	locationDistal	Pde1c	9.50749E-10
creUchl1	Gm6936	0.005040296	locationDistal	Nell1	8.59222E-08
creUchl1	Cd40	0.005835231	locationDistal	Wipf1	0.0008214
creUchl1	Ube2t	0.006097185	locationDistal	Ipw	6.46278E-07
creUchl1	Stag3	0.006245129	locationDistal	Clvs2	7.87803E-10

creUchl1	Lefty2	0.006485665
creUchl1	Mfge8	0.00652646
creUchl1	E330012B07Rik	0.007024439
creUchl1	Cd14	0.007254097
creUchl1	Eras	0.010898441
creUchl1	Khdc3	0.013260293
creUchl1	Cbs	0.014165671
creUchl1	Ldlrad2	0.017800706
creUchl1	Rhox2h	0.019220788
creUchl1	Vmn2r6	0.020214484
creUchl1	Tmem119	0.020600584
creUchl1	Sod3	0.022987632
creUchl1	Gm3716	0.023731509
creUchl1	Mtl5	0.028100377
creUchl1	Sigirr	0.030921788
creUchl1	Plg	0.032516554
creUchl1	Mir338	0.0325854
creUchl1	4930433I11Rik	0.033794892
creUchl1	Olfr287	0.035394182
creUchl1	Plekhg6	0.036120445
creUchl1	E030044B06Rik	0.037433981
creUchl1	Bin2	0.043606602
creUchl1	Tdrd1	0.045254704
creUchl1	Igsf23	0.046615514
creUchl1	1700034G24Rik	0.047071049
creUchl1	Tal1	0.04848236
creWNT1	Allc	2.46861E-13
creWNT1	B4galnt3	6.68121E-08
creWNT1	Cylc1	6.68121E-08
creWNT1	C730002L08Rik	2.58796E-07
creWNT1	Gm3696	3.21851E-06
creWNT1	Serpinb9c	3.79883E-06
creWNT1	Cd70	7.39893E-06
creWNT1	Car5a	2.21711E-05
creWNT1	Prss12	2.27632E-05
creWNT1	Vmn2r81	2.29544E-05
creWNT1	Ptprq	3.39912E-05
creWNT1	Rftn1	0.000114291
creWNT1	Mir669a-7	0.000374422
creWNT1	Fam78a	0.000498802
creWNT1	2210408I21Rik	0.000498802
creWNT1	Trpa1	0.000529901
creWNT1	4930567K20Rik	0.001270571
creWNT1	Cdk5rap2	0.001270571
creWNT1	1700120E14Rik	0.001745793
creWNT1	Megf6	0.001901194
creWNT1	1700001G17Rik	0.001978481
creWNT1	Mamdc2	0.002454858
creWNT1	Mir669h	0.002572548
creWNT1	Ppp1r36	0.002596876
creWNT1	Gm10409	0.002612369
creWNT1	Tbxa2r	0.003124112
creWNT1	Gm3500	0.00335704
creWNT1	Tbx21	0.00335704
creWNT1	E030003E18Rik	0.003967941
creWNT1	Mir337	0.004850625
creWNT1	Naip7	0.007546055
creWNT1	F830016B08Rik	0.009510925
creWNT1	Stard8	0.018514642
creWNT1	Il2ra	0.018514642

locationDistal	Aebp1	0.012043316
locationDistal	Epn1	1.51932E-05
locationDistal	Lrrc16b	0.000279829
locationDistal	Cacna1c	2.78953E-13
locationDistal	Atxn2l	6.23173E-11
locationDistal	Lmtk3	5.20768E-07
locationDistal	Car10	9.45705E-08
locationDistal	Speg	2.50992E-07
locationDistal	Cttnbp2	0.000172105
locationDistal	Vwa5b1	0.000031955
locationDistal	Map7d1	0.001682708
locationDistal	Sh3rf1	5.45096E-06
locationDistal	Mki67	0.000185017
locationDistal	Emp1	0.003479236
locationDistal	Hs6st1	0.010483316
locationDistal	Syne2	0.001677064
locationDistal	Bri3	0.001679786
locationDistal	Arhgap42	3.12067E-06
locationDistal	Epha7	2.08181E-05
locationDistal	Mtmr1	0.000911969
locationDistal	Dcc	0.000048386
locationDistal	Cnga3	0.008187081
locationDistal	Rtkn	0.000689193
locationDistal	Card10	0.031186874
locationDistal	Tgfb2	0.001181946
locationDistal	Slc30a10	0.041784807
locationDistal	Spns2	0.000572287
locationDistal	St3gal1	1.23051E-08
locationDistal	Il31ra	6.175E-12
locationDistal	Arhgap10	0.000361424
locationDistal	Fat3	5.46203E-05
locationDistal	Ttyh3	5.05248E-07
locationDistal	Hgf	0.020503301
locationDistal	Trim25	0.002030274
locationDistal	Tmem245	0.00294364
locationDistal	Cnnm1	2.86069E-05
locationDistal	Slc18a3	1.04564E-17
locationDistal	Hoxb13	7.45641E-17
locationDistal	Ffar3	3.7311E-17
locationDistal	Sycn	1.06115E-24
locationDistal	Adh1	1.6346E-32
locationDistal	Saa1	4.34575E-21
locationDistal	Car4	8.29501E-18
locationDistal	Pmepa1	2.56399E-18
locationDistal	Vstm4	2.78601E-15
locationDistal	Stmn1	1.65275E-18
locationDistal	Susd5	2.21536E-25
locationDistal	Nefl	5.55625E-16
locationDistal	Chgb	1.25167E-18
locationDistal	Ncam1	3.06112E-15
locationDistal	Skint10	9.10951E-22
locationDistal	Ddx5	2.3161E-24
locationDistal	Dpysl2	3.7311E-17
locationDistal	Gm12504	9.42966E-16
locationDistal	Hspa5	1.128E-15
locationDistal	Prkar1a	1.87598E-17
locationDistal	9330111N05Rik	3.42945E-17
locationDistal	Hnrnpa2b1	1.71251E-17
locationDistal	Calr	1.03054E-15
locationDistal	Map1b	1.00008E-23

creWNT1	Tinag	0.019084356
creWNT1	4930459L07Rik	0.019084356
creWNT1	Gm2027	0.019084356
creWNT1	Litaf	0.019084356
creWNT1	4930555G01Rik	0.027954627
creWNT1	Zdhhc11	0.027954627
creWNT1	BC048644	0.027954627
creWNT1	Fgf9	0.027972954
creWNT1	Mir669a-10	0.030214147
creWNT1	4930432K09Rik	0.035380602
creWNT1	Srsf2	0.036657657
creWNT1	Klhl14	0.038415208
creWNT1	Nrk	0.039080173
creWNT1	Loxhd1	0.039456866
creWNT1	1700046C09Rik	0.043023116
creWNT1	D7Ertd443e	0.043964887
creWNT1	Gnal	0.043964887
creWNT1	Gypc	0.044363418
creWNT1	Gm3383	0.046976444
creWNT1	Pole	0.046976444
genderF	Tsix	0
genderF	Xist	0
genderF	Uty	0
genderF	Gm20867	2.8816E-293
genderF	Gm20738	2.1971E-292
genderF	Gm20823	3.6653E-287
genderF	Eif2s3y	8.0506E-282
genderF	Gm20816	1.1202E-281
genderF	Gm20736	1.4483E-236
genderF	Klk1b22	1.6261E-158
genderF	Kdm5d	1.0299E-146
genderF	Gm13710	2.42887E-98
genderF	Pisd-ps3	5.28451E-90
genderF	Klk1b21	8.32343E-83
genderF	Srsf2	8.84863E-75
genderF	Klk1b24	1.24083E-70
genderF	Gm20871	7.9467E-69
genderF	Slc15a2	1.79311E-59
genderF	Sft2d2	6.26851E-55
genderF	Gm20854	1.05704E-36
genderF	Klk1b27	4.81131E-33
genderF	Sly	5.89545E-33
genderF	Tuba1c	1.29992E-32
genderF	Klk1b11	6.06754E-31
genderF	Ulk4	1.92696E-29
genderF	BC117090	4.44252E-26
genderF	Rbm5	7.22375E-25
genderF	Retnlb	1.4118E-24
genderF	Zfp69	1.86732E-24
genderF	Hnrnpc	2.7214E-24
genderF	Adamts13	7.43422E-23
genderF	Kdm6a	2.62243E-22
genderF	Ccrn4l	3.60768E-21
genderF	H2-Q5	5.39364E-21
genderF	Gm3893	5.39364E-21
genderF	H2-Q9	6.83468E-20
genderF	4932443I19Rik	8.84372E-19
genderF	4933409K07Rik	1.73157E-18
genderF	Car1	7.27138E-18
genderF	Fth1	1.33518E-17
locationDistal	Gm13498	1.12451E-22
locationDistal	Atp6v0c	1.14896E-24
locationDistal	Cfl1	2.86766E-15
locationDistal	Srsf5	4.00949E-17
locationDistal	Calm1	2.75276E-15
locationDistal	Actb	1.87352E-15
locationDistal	Pgam1	2.64348E-21
locationDistal	Calm2	1.15628E-16
locationDistal	Chrna3	1.73066E-15
locationDistal	Tagln2	1.12992E-15
locationDistal	Cd80	3.45357E-22
locationDistal	Prdx6b	6.09396E-77
locationDistal	Htr3b	6.86195E-19
locationDistal	Gm19782	1.68069E-25
locationDistal	Zfp708	6.32465E-22
locationDistal	Ckb	4.77236E-17
locationDistal	Gapdh	2.78564E-15
locationDistal	Hsp90ab1	4.49299E-16
locationDistal	Lypd8	9.12116E-27
locationDistal	Ngfr	1.90527E-16
locationDistal	Tppp3	2.97386E-15
locationDistal	Oaz1	4.0001E-13
locationDistal	Plekha7	7.59332E-08
locationDistal	Slc25a4	6.20713E-14
locationDistal	Ephx1	6.38082E-10
locationDistal	Dstn	2.53679E-11
locationDistal	Aldoart2	2.80512E-31
locationDistal	Fth1	1.50153E-07
locationDistal	Tmem176b	9.05029E-12
locationDistal	Moxd1	4.47882E-12
locationDistal	Ubb	1.84237E-21
locationDistal	Tmx2	1.39932E-14
locationDistal	Gas6	1.42101E-13
locationDistal	Psmd13	2.19629E-10
locationDistal	Tubb2a	3.08863E-13
locationDistal	Cd81	3.06112E-15
locationDistal	Ppia	4.71693E-14
locationDistal	Tubb5	2.16838E-16
locationDistal	Atp5b	4.0001E-13
locationDistal	Serinc1	4.71283E-11
locationDistal	Faim2	1.128E-15
locationDistal	Pdzd2	1.60902E-16
locationDistal	Skil	3.49607E-22
locationDistal	Tuba1a	2.33422E-27
locationDistal	Ngb	1.6377E-06
locationDistal	Ubc	1.43121E-17
locationDistal	Crip1	2.89977E-10
locationDistal	Pcsk1n	1.28637E-14
locationDistal	Fgf14	4.29965E-33
locationDistal	Cst3	5.23179E-17
locationDistal	H3f3b	2.50429E-17
locationDistal	Slc7a11	2.69319E-40
locationDistal	Sprr2a2	2.80341E-12
locationDistal	Hsp90b1	1.06719E-16
locationDistal	Dusp3	4.9835E-13
locationDistal	2610017I09Rik	6.38082E-10
locationDistal	1700016L04Rik	3.63201E-32
locationDistal	Aldoa	2.24053E-24
locationDistal	Aldoart1	2.65567E-32
locationDistal	Mid1	1.61409E-15

genderF	Gm8909	7.80276E-17
genderF	Rn45s	4.14997E-16
genderF	Dlgap1	4.86945E-16
genderF	H2-Q4	2.51145E-15
genderF	Gpsm1	4.29472E-15
genderF	Rftn1	1.13391E-14
genderF	Mill2	1.15631E-13
genderF	Celf3	2.11585E-13
genderF	Selenbp1	4.13667E-13
genderF	Fam163b	6.01723E-13
genderF	Gal	7.02594E-13
genderF	Guca2a	7.19575E-13
genderF	Picalm	2.17293E-12
genderF	H2-Q1	2.39041E-12
genderF	Phgr1	2.45709E-12
genderF	Bzrap1	2.45709E-12
genderF	Ybx1	6.46464E-12
genderF	Tmprss6	7.56943E-12
genderF	Klk1b3	9.61136E-12
genderF	Nlrp5-ps	9.86982E-12
genderF	Fras1	2.30727E-11
genderF	Selenbp2	3.86985E-11
genderF	Gpr19	4.73732E-11
genderF	Loxl2	6.10962E-11
genderF	Gm7120	1.0785E-10
genderF	Zg16	1.08286E-10
genderF	Rnf121	1.37718E-10
genderF	Fabp2	1.91674E-10
genderF	Klk1b1	6.03329E-10
genderF	H2-Bl	8.13666E-10
genderF	Kcnh6	1.11854E-09
genderF	Slc27a2	1.2876E-09
genderF	DQ267100	1.47828E-09
genderF	Prdx6b	2.01581E-09
genderF	B2m	2.04809E-09
genderF	Mgst1	7.7396E-09
genderF	Hist2h2bb	8.94628E-09
genderF	E030019B13Rik	9.33954E-09
genderF	Magohb	9.43109E-09
genderF	Miip	9.77397E-09
genderF	Mptx1	1.37867E-08
genderF	Poteg	1.37867E-08
genderF	Slc4a4	1.50896E-08
genderF	Ccdc3	1.52029E-08
genderF	3110007F17Rik	1.91748E-08
genderF	Cnksr2	3.11545E-08
genderF	Ptpro	3.35981E-08
genderF	Pirt	4.65243E-08
genderF	Prdx6	5.98586E-08
genderF	Sod2	5.98586E-08
genderF	Ndfip2	6.26697E-08
genderF	Cldn3	6.94496E-08
genderF	Pde6a	8.1929E-08
genderF	Csad	8.70955E-08
genderF	Kcnip1	8.95196E-08
genderF	H2-M5	9.10283E-08
genderF	9330111N05Rik	1.0249E-07
genderF	Agr2	1.09098E-07
genderF	Rps3a1	1.21709E-07

locationDistal	Vip	6.8116E-16
locationDistal	S100a6	8.84934E-21
locationDistal	Sprr2a1	1.49715E-12
locationDistal	Frmd5	5.84034E-20
locationDistal	Gm6548	6.73722E-27
locationDistal	Tmem255b	8.31669E-09
locationDistal	Eef1a1	5.71406E-24
locationDistal	Canx	8.24407E-12
locationDistal	Cd9	1.57612E-19
locationDistal	Slc35d3	0.002088855
locationDistal	Scn5a	4.17905E-10
locationDistal	6330403K07Rik	1.2319E-30
locationDistal	Gm12070	2.38431E-24
locationDistal	Kcnq5	6.25436E-35
locationDistal	Nell2	1.99749E-33
locationDistal	Slc1a1	2.8046E-22
locationDistal	Syt2	4.89713E-23
locationDistal	Vmn2r-ps54	4.69693E-48
locationDistal	Ctsb	1.49754E-23
locationDistal	Itm2b	2.15884E-19
locationDistal	Epha8	4.99284E-07
locationDistal	Actg1	8.16605E-11
locationDistal	Chrm1	1.49258E-10
locationDistal	Slc10a4	9.65963E-18
locationDistal	Scg2	1.654E-24
locationDistal	Gm6682	1.67156E-36
locationDistal	Gm1821	3.73976E-24
locationDistal	Ldlrad4	4.08505E-42
locationDistal	Tuba1b	4.15124E-25
locationDistal	Hspa8	3.27521E-31
locationDistal	Dkk3	3.06472E-54
locationDistal	Prdx6	9.51863E-60
locationDistal	Prnp	1.41056E-27
locationDistal	Rgs9	1.03541E-29
locationDistal	Bglap	5.83044E-19
locationDistal	Htr3a	5.25799E-52
locationDistal	Il22ra2	0.00270681
locationDistal	Hoxd13	0.003043785
locationDistal	Nobox	0.009799842
locationDistal	Fam115e	0.011774848
locationDistal	Tcf21	0.013858468
locationDistal	Btbd17	0.016327774
locationDistal	S100a5	0.023025186
locationDistal	Krt1	0.023421018
locationDistal	Hbb-b1	0.028663261
locationDistal	Agtr2	0.031135797
locationDistal	Olfr55	0.031811195
locationDistal	Slc34a1	0.035725695
locationDistal	Tas2r108	0.03627001
locationDistal	Eppin	0.036602586
locationDistal	Olfr1352	0.038091947
locationDistal	Otor	0.038669996
locationDistal	Sftpc	0.039119673
locationDistal	Mup16	0.043704727
locationDistal	H1fnt	0.044551941
locationDistal	Prnd	0.044868375
locationDistal	H19	0.046982862
locationDistal	Nts	0.047727188

Table 16.

ident	gene	padjH
Glia_1	Etl4	2.6493E-207
Glia_1	Agbl4	3.8197E-193
Glia_1	Hmcn1	1.3015E-167
Glia_1	Kank1	1.2357E-132
Glia_1	Lsamp	1.5045E-118
Glia_1	AW549542	4.7263E-112
Glia_1	Auts2	3.7028E-110
Glia_1	Cpe	5.8938E-105
Glia_1	Col9a2	6.80903E-98
Glia_1	Fam184b	1.16823E-90
Glia_1	Bcan	1.49796E-89
Glia_1	Cdc14a	4.35941E-87
Glia_1	Pxdn	4.47141E-86
Glia_1	Erc2	4.70356E-86
Glia_1	Mapk10	2.04324E-82
Glia_1	2810055G20Rik	2.04324E-82
Glia_1	Adarb2	4.7573E-81
Glia_1	Kif21a	6.2727E-81
Glia_1	Zfpm2	8.21426E-81
Glia_1	Foxp2	1.07084E-76
Glia_1	Bai3	2.19602E-75
Glia_1	Slc18a2	5.56287E-71
Glia_1	Grid1	3.23449E-69
Glia_1	Sfxn5	1.89025E-67
Glia_1	Pde3a	1.11362E-66
Glia_1	Trim9	9.4315E-66
Glia_1	Plxna4	4.29509E-60
Glia_1	Hmgcll1	4.08361E-59
Glia_1	Nrg3	9.07368E-57
Glia_1	Tspan18	6.07183E-54
Glia_1	Dkk3	6.19463E-54
Glia_1	Rgs9	1.28429E-52
Glia_1	Ncam2	1.68797E-52
Glia_1	Nckap5	7.11858E-52
Glia_1	Kctd1	4.4845E-51
Glia_1	Zfp423	2.36683E-49
Glia_1	Gpc6	2.48969E-49
Glia_1	Hecw2	4.83158E-49
Glia_1	Sorl1	2.11189E-47
Glia_1	Ccdc148	2.30674E-47
Glia_1	Tshz2	7.95663E-47
Glia_1	Airn	7.99303E-46
Glia_1	Fam5c	2.06954E-45
Glia_1	Enkur	6.1597E-45
Glia_1	Gpam	4.98277E-44
Glia_1	Col8a1	1.8472E-43
Glia_1	Rhbdl3	2.46025E-42
Glia_1	Cacng4	5.63167E-41
Glia_1	Ccdc164	9.78126E-41
Glia_1	Ext1	4.71115E-40
Glia_1	Rap1gap	9.38064E-40
Glia_1	Tacr3	2.18492E-39
Glia_1	Bzrap1	5.04049E-39
Glia_1	Pde4d	5.04049E-39
Glia_1	Armc2	9.68774E-39
Glia_1	Igfbp4	1.62816E-38

ident	gene	padjH
Glia_2	Adam12	2.59102E-10
Glia_2	Gm10863	3.82453E-10
Glia_2	Agap1	4.37285E-10
Glia_2	Synpo	4.97644E-10
Glia_2	Arhgap39	8.33233E-10
Glia_2	Aspa	9.03857E-10
Glia_2	Msrb3	1.48556E-09
Glia_2	2610203C20Rik	1.56141E-09
Glia_2	Arhgef37	1.57435E-09
Glia_2	Adamts12	1.62534E-09
Glia_2	Lypla2	2.27939E-09
Glia_2	Ivns1abp	2.47973E-09
Glia_2	Nox4	2.55493E-09
Glia_2	Fgl2	2.57842E-09
Glia_2	Lamb1	8.82846E-09
Glia_2	Cdc42ep3	9.95911E-08
Glia_2	Tnfrsf1b	1.54571E-07
Glia_2	Cmklr1	1.63653E-06
Glia_2	1700010K23Rik	1.72005E-06
Glia_2	Gbp10	1.56425E-05
Glia_2	Npc1l1	5.38733E-05
Glia_2	Mfap5	5.503E-05
Glia_2	Fam26e	0.000131791
Glia_2	Mad2l1bp	0.000228031
Glia_2	Cpn2	0.000394738
Glia_2	Rab37	0.000476322
Glia_2	Vmn2r84	0.000522186
Glia_2	Ssx9	0.000631415
Glia_2	A730085A09Rik	0.000874202
Glia_2	A930016O22Rik	0.000874202
Glia_2	Gm6249	0.000910352
Glia_2	Rfc4	0.001015805
Glia_2	4930448I18Rik	0.001044069
Glia_2	Gm20757	0.001047842
Glia_2	Hbegf	0.001194231
Glia_2	Gm9920	0.001657125
Glia_2	9430037G07Rik	0.002144316
Glia_2	Gpr153	0.002488871
Glia_2	Gm3279	0.002519058
Glia_2	Krtap1-3	0.002551787
Glia_2	Nkx2-2as	0.002582022
Glia_2	Colq	0.002867618
Glia_2	Irs3	0.003182844
Glia_2	Cdc6	0.004473539
Glia_2	Apol9a	0.004549637
Glia_2	Nlrp3	0.004676623
Glia_2	Mybpc3	0.004986801
Glia_2	Pde6c	0.00509867
Glia_2	Hist1h2bh	0.005429391
Glia_2	BC021891	0.005518423
Glia_2	1700085C21Rik	0.006436227
Glia_2	Arl4d	0.006514074
Glia_2	Xkr7	0.007148345
Glia_2	Arr3	0.008118789
Glia_2	Nodal	0.008473808
Glia_2	Rab27b	0.010415343

Glia_1	Cml3	2.99284E-38	Glia_2	Lrrn4cl	0.011769879
Glia_1	Msi2	1.89266E-37	Glia_2	Apol8	0.011827463
Glia_1	Sned1	8.29944E-37	Glia_2	Mbnl3	0.01218435
Glia_1	Sulf1	9.0677E-37	Glia_2	Apol7a	0.012969039
Glia_1	Tprkb	1.33089E-36	Glia_2	Gm10584	0.012985431
Glia_1	Apoe	2.83612E-36	Glia_2	5430440P10Rik	0.013325935
Glia_1	C230004F18Rik	6.50039E-36	Glia_2	Pde4c	0.013760433
Glia_1	Cadps	2.15901E-35	Glia_2	9130227L01Rik	0.014192439
Glia_1	Lrriq1	4.50061E-35	Glia_2	Selplg	0.01462793
Glia_1	Bai2	1.45354E-34	Glia_2	Six4	0.016210118
Glia_1	Arhgap42	1.78474E-34	Glia_2	Rnf43	0.016620049
Glia_1	Ulk4	7.88379E-34	Glia_2	Ninj2	0.016658095
Glia_1	Ctnna3	1.83837E-33	Glia_2	P2ry10	0.019260995
Glia_1	Ncdn	3.24943E-33	Glia_2	Wdhd1	0.020242493
Glia_1	Pitpnc1	4.37316E-33	Glia_2	Gm13305	0.020463333
Glia_1	Lrrc9	8.6402E-33	Glia_2	Gstm6	0.020684895
Glia_1	Igf2r	1.04023E-32	Glia_2	Mobp	0.023679115
Glia_1	Smoc1	1.52193E-32	Glia_2	Rltpr	0.024992858
Glia_1	Itga8	1.13278E-31	Glia_2	Slc26a5	0.025230391
Glia_1	Plcb1	1.4539E-31	Glia_2	Nov	0.026481593
Glia_1	Cpxm2	4.64102E-31	Glia_2	Il5ra	0.028377246
Glia_1	Alcam	5.56399E-31	Glia_2	Gm8221	0.028978374
Glia_1	Ntm	7.4704E-31	Glia_2	Sh2d1b2	0.03028365
Glia_1	Zfhx4	8.51794E-31	Glia_2	B930025P03Rik	0.03209964
Glia_1	Tes	1.1166E-30	Glia_2	Tubb1	0.03209964
Glia_1	Frzb	1.16382E-30	Glia_2	Krtap1-4	0.032183185
Glia_1	Cntfr	2.91649E-30	Glia_2	Cacng5	0.033593585
Glia_1	A330076C08Rik	3.23789E-30	Glia_2	Tmprss12	0.036709416
Glia_1	Ramp1	4.2952E-30	Glia_2	4833427F10Rik	0.041182614
Glia_1	Creg2	5.77247E-30	Glia_2	Gm4858	0.044157528
Glia_1	Greb1	2.25352E-29	Glia_2	Dbx2	0.046754332
Glia_1	Fmo1	6.81302E-29	Glia_2	Fam212a	0.048170734
Glia_1	Hey2	1.41074E-28	Glia_2	Selp	0.048888788
Glia_1	Col11a1	2.06893E-28	Glia_3	Ntng1	3.1402E-121
Glia_1	Mterfd2	1.1382E-27	Glia_3	Csmd1	3.35967E-75
Glia_1	Dlg2	1.78281E-27	Glia_3	Frmd4a	2.14247E-66
Glia_1	Mcc	1.87011E-27	Glia_3	Pappa	1.66678E-65
Glia_1	Fstl4	3.04287E-27	Glia_3	Matn2	1.31184E-63
Glia_1	Fbln5	4.57858E-27	Glia_3	Slc2a13	6.75121E-63
Glia_1	Ptgfrn	5.00395E-27	Glia_3	Col6a3	1.39796E-61
Glia_1	Gria4	5.50254E-27	Glia_3	Fndc1	6.27717E-61
Glia_1	Mapk15	5.71885E-27	Glia_3	Xylt1	1.96682E-60
Glia_1	Sox2ot	9.54627E-27	Glia_3	Rasgef1c	8.23307E-56
Glia_1	Ptprg	1.7758E-26	Glia_3	Cadm2	3.53989E-54
Glia_1	Sgsm1	4.54204E-23	Glia_3	Kcna1	8.66125E-54
Glia_1	Tekt1	1.01448E-22	Glia_3	Specc1	2.86975E-45
Glia_1	Ttc21a	5.27234E-22	Glia_3	Agap1	2.88939E-42
Glia_1	Lrp8	3.35532E-21	Glia_3	Scn7a	1.21085E-40
Glia_1	Kndc1	1.37146E-20	Glia_3	Aspa	7.70602E-39
Glia_1	Gm216	3.9437E-20	Glia_3	Celf2	2.66842E-37
Glia_1	Dnahc11	8.82409E-20	Glia_3	A330049N07Rik	6.91802E-37
Glia_1	Cthrc1	6.03368E-18	Glia_3	Nrp1	2.16648E-36
Glia_1	Ccdc108	1.62567E-16	Glia_3	Col5a3	1.15592E-35
Glia_1	Ntsr1	5.97769E-15	Glia_3	Epb4.1l4b	1.25556E-35
Glia_1	Omg	6.76777E-13	Glia_3	Adam19	7.75581E-35
Glia_1	Dnaaf3	1.27183E-12	Glia_3	Ephb2	3.31129E-34
Glia_1	Ccdc40	1.02017E-11	Glia_3	Prl3b1	5.05972E-34
Glia_1	Otor	2.46665E-11	Glia_3	Rcan2	2.84867E-33
Glia_1	Wdr69	5.37382E-11	Glia_3	Rxrg	8.80895E-33
Glia_1	Slc1a3	1.36148E-10	Glia_3	Mbp	8.80895E-33

Glia_1	Slc7a10	9.61106E-10	Glia_3	Ank3	9.0754E-32
Glia_1	Rgs7bp	9.92033E-10	Glia_3	Slc1a5	3.80479E-30
Glia_1	1500002O10Rik	1.29923E-09	Glia_3	Kcnh8	7.57345E-30
Glia_1	Fzd6	1.30968E-09	Glia_3	Kcna2	4.08618E-28
Glia_1	1700003M07Rik	3.54314E-09	Glia_3	Adamtsl1	4.29719E-28
Glia_1	Ccdc135	2.02305E-08	Glia_3	Prex2	2.62789E-27
Glia_1	Tecta	3.19405E-08	Glia_3	Antxr2	6.90021E-27
Glia_1	Tmem255b	3.69528E-08	Glia_3	Itih5	2.45432E-26
Glia_1	6430531B16Rik	6.39635E-08	Glia_3	Gfra3	2.55982E-26
Glia_1	Ddo	1.20134E-07	Glia_3	Nkd2	3.34741E-26
Glia_1	P2rx6	1.44631E-07	Glia_3	Apba2	1.27407E-25
Glia_1	Shisa7	3.20791E-07	Glia_3	Ajap1	1.3498E-25
Glia_1	Elmod1	2.38839E-06	Glia_3	Clvs1	7.5139E-25
Glia_1	Wdr16	5.07725E-06	Glia_3	Col20a1	1.09261E-24
Glia_1	1700001C19Rik	7.13366E-06	Glia_3	Sh3pxd2a	1.30115E-24
Glia_1	Efcab1	7.44406E-06	Glia_3	Efemp1	1.75294E-24
Glia_1	1110017D15Rik	1.09666E-05	Glia_3	Plxna2	2.7608E-24
Glia_1	Caps2	1.17523E-05	Glia_3	Prima1	3.10485E-24
Glia_1	4933436C20Rik	1.28628E-05	Glia_3	Kcnk13	1.41991E-23
Glia_1	Mlf1	1.7278E-05	Glia_3	Nav2	2.42242E-23
Glia_1	Meig1	2.42364E-05	Glia_3	Col1a1	4.93057E-23
Glia_1	Ppp2r2c	3.11918E-05	Glia_3	Prex1	8.43914E-23
Glia_1	Vipr2	4.13931E-05	Glia_3	Pde8a	9.45957E-23
Glia_1	Ptx4	7.26245E-05	Glia_3	Postn	1.23876E-22
Glia_1	Slc7a8	0.000126748	Glia_3	Abca8b	1.28381E-22
Glia_1	D130043K22Rik	0.000140838	Glia_3	Epb4.1l3	1.65371E-21
Glia_1	Tex26	0.000158839	Glia_3	Ppp1r12b	4.27773E-21
Glia_1	Aif1l	0.000210577	Glia_3	Malat1	1.09631E-20
Glia_1	Ankrd66	0.000228033	Glia_3	Vwa1	3.78833E-20
Glia_1	Slc7a4	0.000432775	Glia_3	1700047M11Rik	3.93514E-20
Glia_1	Ppp1r1a	0.000482375	Glia_3	Col28a1	4.51846E-20
Glia_1	C530044C16Rik	0.000646068	Glia_3	Mpp7	6.26336E-20
Glia_1	E030019B06Rik	0.000748804	Glia_3	Prnp	9.00764E-20
Glia_1	Ankrd45	0.001041986	Glia_3	Slc35f1	1.15646E-19
Glia_1	Rsph4a	0.001322708	Glia_3	Iqgap2	1.23305E-19
Glia_1	Ubxn10	0.001537994	Glia_3	Akap2	3.2087E-19
Glia_1	Iqca	0.00161044	Glia_3	Nrn1	3.47583E-19
Glia_1	Tnni3	0.001912103	Glia_3	Sox6	6.14016E-19
Glia_1	Lect1	0.00317526	Glia_3	Slc10a6	1.05524E-18
Glia_1	Oprk1	0.003362741	Glia_3	Insc	1.32324E-18
Glia_1	1700007K13Rik	0.004157784	Glia_3	Olfml2b	1.54827E-18
Glia_1	B4galnt4	0.004365071	Glia_3	Cpne8	1.9441E-18
Glia_1	Arhgap8	0.004767805	Glia_3	Hspg2	5.38489E-18
Glia_1	AU022754	0.004863659	Glia_3	Acsbg1	5.48077E-18
Glia_1	Bex4	0.008379063	Glia_3	Srgap1	9.00375E-18
Glia_1	Igsf1	0.010469209	Glia_3	Col14a1	1.06822E-16
Glia_1	Ssxb5	0.010867103	Glia_3	Neat1	1.16861E-16
Glia_1	Ssxb3	0.012876761	Glia_3	Prkcq	1.45074E-16
Glia_1	Olfr267	0.013190464	Glia_3	Adamts20	2.07065E-16
Glia_1	Cited1	0.013306834	Glia_3	Nid2	2.08242E-16
Glia_1	Ftsj2	0.014441779	Glia_3	Col1a2	2.10834E-16
Glia_1	Dmkn	0.015250648	Glia_3	Ppip5k2	5.34839E-16
Glia_1	F2rl1	0.01918841	Glia_3	Maml3	5.65913E-16
Glia_1	Kcnk3	0.020470418	Glia_3	Ctnnd1	9.44667E-16
Glia_1	Cml2	0.02234017	Glia_3	Gfra2	1.02206E-15
Glia_1	Ccdc24	0.026306226	Glia_3	Cldn14	1.45265E-15
Glia_1	Hs3st1	0.028130595	Glia_3	Stard13	1.75628E-15
Glia_1	Dok7	0.029724311	Glia_3	Ndst3	1.84069E-15
Glia_1	Angpt4	0.029925287	Glia_3	Prickle2	2.2777E-15
Glia_1	Sec1	0.030421564	Glia_3	Cspg4	2.84872E-15

Glia_1	Dmrtb1	0.030577875	Glia_3	Cables1	2.84872E-15
Glia_1	Prss35	0.030868418	Glia_3	Zeb2	5.31706E-15
Glia_1	E130018N17Rik	0.031438115	Glia_3	Lama2	6.0343E-15
Glia_1	E2f2	0.031806638	Glia_3	Itpr2	1.37038E-14
Glia_1	1700101E01Rik	0.032871926	Glia_3	Il1rap	2.4431E-14
Glia_1	4930429F24Rik	0.034754088	Glia_3	Cdk6	2.47593E-14
Glia_1	Cxcl14	0.037257002	Glia_3	Ablim1	2.55903E-14
Glia_1	Dll1	0.037594566	Glia_3	Sorcs2	2.55903E-14
Glia_1	Lmo1	0.042079618	Glia_3	Abca8a	4.32193E-14
Glia_1	Arl9	0.042404944	Glia_3	Adcy1	4.55758E-14
Glia_1	Lax1	0.044533461	Glia_3	Gas2l3	6.006E-14
Glia_1	9930014A18Rik	0.049042233	Glia_3	Lbh	9.24711E-14
Glia_2	Rgs6	2.9875E-108	Glia_3	Art3	9.45182E-14
Glia_2	Col28a1	3.24732E-80	Glia_3	Dcpp3	2.15644E-13
Glia_2	Cadm2	2.49772E-79	Glia_3	Lypd6	8.27271E-13
Glia_2	Nrxn1	9.08305E-77	Glia_3	Mlph	7.78696E-12
Glia_2	Xkr4	3.00526E-73	Glia_3	D730001G18Rik	9.14983E-12
Glia_2	Scn7a	2.95963E-66	Glia_3	Lgi1	2.82677E-11
Glia_2	Maml3	6.37856E-62	Glia_3	4932413F04Rik	4.65592E-11
Glia_2	Ptprm	7.36693E-54	Glia_3	Mpz	4.36451E-09
Glia_2	Insc	1.44019E-52	Glia_3	Rem1	5.12849E-09
Glia_2	Piezo2	1.7486E-50	Glia_3	Alx4	1.27083E-08
Glia_2	Ank3	2.03318E-49	Glia_3	Klk8	3.1261E-07
Glia_2	Nav2	2.41183E-42	Glia_3	Itga7	1.09984E-06
Glia_2	Ephb2	1.02252E-40	Glia_3	Klhl30	6.56023E-06
Glia_2	Rasgef1c	3.627E-40	Glia_3	Tnfaip8l1	1.46027E-05
Glia_2	Rimklb	3.07753E-39	Glia_3	Ankrd53	2.63537E-05
Glia_2	Prnp	3.91321E-38	Glia_3	Pygm	3.05924E-05
Glia_2	Chst15	3.72061E-36	Glia_3	Mb21d1	4.07807E-05
Glia_2	Col14a1	1.89348E-35	Glia_3	Trpc7	0.000134687
Glia_2	Col5a3	6.70987E-35	Glia_3	4933431G14Rik	0.000662086
Glia_2	Lcp2	1.61702E-32	Glia_3	Sema7a	0.000907929
Glia_2	Lama2	3.91981E-31	Glia_3	Dhrs9	0.000935153
Glia_2	Igsf21	1.34615E-29	Glia_3	Palmd	0.000963442
Glia_2	Il34	3.05248E-29	Glia_3	Ina	0.001456608
Glia_2	Abca8b	1.94271E-28	Glia_3	Neu2	0.001661338
Glia_2	Ajap1	2.97444E-28	Glia_3	Mtnr1a	0.001806038
Glia_2	Klhl29	6.34965E-27	Glia_3	Klk10	0.001864488
Glia_2	Grik2	1.76518E-26	Glia_3	Gcm2	0.002084779
Glia_2	Olfm2	2.22333E-26	Glia_3	Ces2b	0.00214981
Glia_2	Prex2	4.46867E-26	Glia_3	Slc22a14	0.002387257
Glia_2	Kcna1	9.30801E-26	Glia_3	Tdrd1	0.002500184
Glia_2	Tanc2	4.41436E-24	Glia_3	Gata5	0.003294594
Glia_2	Slc35f1	6.22357E-24	Glia_3	Gm20187	0.003363837
Glia_2	Clvs1	1.03869E-23	Glia_3	Adra1d	0.003775315
Glia_2	Kank4	2.19424E-23	Glia_3	Gm19510	0.003939477
Glia_2	Frmd4a	5.94549E-23	Glia_3	Smpdl3b	0.004356848
Glia_2	Gpnmb	8.07252E-23	Glia_3	Optc	0.004782232
Glia_2	Matn2	1.63663E-22	Glia_3	Gli1	0.005344248
Glia_2	Nkain2	1.64553E-21	Glia_3	Klk9	0.005508542
Glia_2	Sgcd	2.31678E-21	Glia_3	Ces2g	0.006395829
Glia_2	Deptor	2.56698E-21	Glia_3	Clec4d	0.006412059
Glia_2	Dock11	2.95713E-21	Glia_3	Zfp663	0.006460574
Glia_2	Lphn3	3.65057E-20	Glia_3	Il10	0.006817796
Glia_2	Arpc1b	4.64575E-20	Glia_3	Ltk	0.007065998
Glia_2	Kcnip1	8.01507E-20	Glia_3	Gm10415	0.007328322
Glia_2	Wbscr17	2.61792E-19	Glia_3	Htr3b	0.009697209
Glia_2	Sfrp5	5.57014E-19	Glia_3	Cyp4x1	0.0100129
Glia_2	Hspg2	9.20002E-18	Glia_3	Pnliprp2	0.010334957
Glia_2	Mmp17	1.08463E-16	Glia_3	4933433F19Rik	0.010539214

Glia_2	Kcnn2	2.29753E-16	Glia_3	Asb4	0.011150368
Glia_2	Abca8a	2.35532E-16	Glia_3	Gm13582	0.012941176
Glia_2	Slc22a23	2.9752E-16	Glia_3	Gm6121	0.013812083
Glia_2	Cspg4	2.66749E-15	Glia_3	Cacng2	0.014435786
Glia_2	Kcnk5	2.73549E-15	Glia_3	Pax4	0.014711407
Glia_2	Gfra2	3.36902E-15	Glia_3	Adra1b	0.014738884
Glia_2	Ncam1	5.75721E-15	Glia_3	Olfr389	0.015461699
Glia_2	Cryab	7.93853E-15	Glia_3	Cd3e	0.017181541
Glia_2	Kcna2	9.83328E-15	Glia_3	Psg19	0.017349299
Glia_2	Gas2l3	9.83328E-15	Glia_3	Chrna2	0.017619426
Glia_2	Fbln1	1.27659E-14	Glia_3	Btnl2	0.018860223
Glia_2	Pmp22	1.64665E-14	Glia_3	Cyp2b23	0.018875949
Glia_2	Col5a1	2.01238E-14	Glia_3	Aqp2	0.020225909
Glia_2	Il16	5.3736E-14	Glia_3	Idi2	0.021844847
Glia_2	Artn	6.24451E-14	Glia_3	E230025N22Rik	0.02402981
Glia_2	Adamts2	2.05954E-13	Glia_3	Gm13031	0.024452234
Glia_2	Ablim1	3.47608E-13	Glia_3	Tmprss7	0.025664004
Glia_2	Pex5l	3.57475E-13	Glia_3	4930423M02Rik	0.025664004
Glia_2	Lbp	8.59133E-13	Glia_3	Pou3f1	0.026193435
Glia_2	C4b	9.02476E-13	Glia_3	Fst	0.026801339
Glia_2	Epb4.1l4b	1.30533E-12	Glia_3	1700034K08Rik	0.027502267
Glia_2	Gli2	1.30533E-12	Glia_3	Zfp541	0.028121716
Glia_2	Prkca	1.72494E-12	Glia_3	F730043M19Rik	0.030445926
Glia_2	Nkd2	1.90045E-12	Glia_3	Fam105a	0.030530011
Glia_2	Sfrp1	2.23171E-12	Glia_3	4930461G14Rik	0.031513524
Glia_2	Gulp1	3.81131E-12	Glia_3	Serpinb9e	0.033724623
Glia_2	Ngf	3.93428E-12	Glia_3	Adamts15	0.035299242
Glia_2	Stard13	4.84026E-12	Glia_3	Osr1	0.037681426
Glia_2	Cdh19	7.54394E-12	Glia_3	Gm6792	0.03845916
Glia_2	Pnpla3	9.29113E-12	Glia_3	Klra4	0.038744889
Glia_2	L1cam	9.45143E-12	Glia_3	Grem2	0.039802663
Glia_2	Pdgfa	1.73064E-11	Glia_3	Cts3	0.039979328
Glia_2	Rnd3	3.67316E-11	Glia_3	Scara3	0.039979328
Glia_2	Gas7	3.99808E-11	Glia_3	Gm14483	0.040199595
Glia_2	Vgll3	4.01943E-11	Glia_3	D030025P21Rik	0.040949965
Glia_2	Art3	6.24539E-11	Glia_3	Tmem40	0.046945019
Glia_2	Nrp1	1.01557E-10	Glia_3	Ptk6	0.049311297
Glia_2	Mpp7	1.80742E-10			

Table 17.

ident	gene	padjH
Colonocytes	Cyp2c55	0.00E+00
Colonocytes	Slc26a3	3.04E-253
Colonocytes	Emp1	2.03E-182
Colonocytes	Ceacam20	3.04E-182
Colonocytes	Krt20	4.79E-177
Colonocytes	Mxd1	2.90E-171
Colonocytes	Lypd8	3.35E-170
Colonocytes	Slc9a3	3.12E-166
Colonocytes	Abcb1a	4.06E-160
Colonocytes	Atp2b1	2.16E-158
Colonocytes	Lmo7	8.86E-157
Colonocytes	Clec2h	7.11E-146
Colonocytes	Eps8	8.70E-146
Colonocytes	Erbb2ip	1.71E-143
Colonocytes	Lgals3	3.90E-141
Colonocytes	Muc3	4.88E-140
Colonocytes	Maoa	6.14E-140
Colonocytes	Mgat4c	1.17E-134
Colonocytes	Ptprh	2.32E-131
Colonocytes	Cyp3a13	1.78E-130
Colonocytes	Slc9a2	1.54E-128

ident	gene	padjH
Epithelial_Progenitors	Fam189a1	1.56E-13
Epithelial_Progenitors	AI838599	9.21E-13
Epithelial_Progenitors	Samd5	7.54E-12
Epithelial_Progenitors	Cbfa2t3	1.01E-11
Epithelial_Progenitors	Clca3a2	2.03E-11
Epithelial_Progenitors	Hiat1	4.29E-11
Epithelial_Progenitors	Gm26908	6.63E-11
Epithelial_Progenitors	Pck1	1.07E-10
Epithelial_Progenitors	Rnf32	1.12E-10
Epithelial_Progenitors	Mettl1	1.62E-10
Epithelial_Progenitors	Tpcn2	2.98E-10
Epithelial_Progenitors	C2cd4b	5.47E-10
Epithelial_Progenitors	A4gnt	2.98E-09
Epithelial_Progenitors	Meg3	3.97E-09
Epithelial_Progenitors	Gm13247	3.98E-09
Epithelial_Progenitors	Uck2	4.08E-09
Epithelial_Progenitors	Clca3b	5.14E-09
Epithelial_Progenitors	Pgm3	1.69E-08
Epithelial_Progenitors	Rhbdl3	1.71E-08
Epithelial_Progenitors	Gm12860	1.75E-08
Epithelial_Progenitors	Hopx	1.82E-08

ident	gene	padjH
Macrophage	AI607873	4.07E-20
Macrophage	Unc93b1	1.48E-19
Macrophage	Adcy7	1.77E-19
Macrophage	March1	2.17E-19
Macrophage	Dock2	2.50E-19
Macrophage	Mitf	3.29E-19
Macrophage	Sirpa	6.07E-19
Macrophage	Mctp1	1.01E-18
Macrophage	P2ry12	1.01E-18
Macrophage	Tgfbr1	1.25E-18
Macrophage	Myo5a	1.40E-18
Macrophage	Srgap2	2.59E-18
Macrophage	Abca9	2.79E-18
Macrophage	Adap2os	2.79E-18
Macrophage	Frmd4b	2.90E-18
Macrophage	Gm26522	3.81E-18
Macrophage	Cd300a	6.08E-18
Macrophage	Ms4a7	1.37E-17
Macrophage	Fli1	1.99E-17
Macrophage	Adap2	2.04E-17
Macrophage	Fcgr2b	2.51E-17

Colonocytes	Prom1	2.11E-125
Colonocytes	Eps8l2	2.31E-125
Colonocytes	Klf6	3.72E-125
Colonocytes	Hsd3b3	4.67E-125
Colonocytes	Clca4a	2.01E-124
Colonocytes	Prss30	4.51E-124
Colonocytes	Myh14	5.13E-124
Colonocytes	Slc8a1	6.63E-123
Colonocytes	Ceacam1	6.63E-123
Colonocytes	Stk25	1.28E-121
Colonocytes	Myo15b	4.10E-121
Colonocytes	Iqgap2	3.46E-116
Colonocytes	Coro2a	1.49E-115
Colonocytes	Guca2a	2.57E-113
Colonocytes	Ethe1	2.78E-113
Colonocytes	Slc13a2	4.49E-109
Colonocytes	Trpm6	3.24E-108
Colonocytes	Fa2h	5.67E-108
Colonocytes	2200002D01Rik	2.18E-105
Colonocytes	Pmp22	5.43E-105
Colonocytes	Slc25a20	2.74E-99
Colonocytes	Pls1	1.66E-98
Colonocytes	Phgr1	1.99E-98
Colonocytes	Ipmk	3.46E-98
Colonocytes	Sptssb	1.04E-97
Colonocytes	Nr3c2	2.36E-97
Colonocytes	Klf4	5.36E-96
Colonocytes	1810065E05Rik	3.26E-94
Colonocytes	Areg	1.17E-93
Colonocytes	Tcf7l2	2.72E-93
Colonocytes	St3gal4	5.90E-92
Colonocytes	Akap13	7.96E-92
Colonocytes	Nostrin	1.24E-91
Colonocytes	Sgk1	3.53E-91
Colonocytes	Dsg2	6.04E-90
Colonocytes	Chp1	1.25E-89
Colonocytes	Misp	3.31E-88
Colonocytes	March3	2.48E-86
Colonocytes	Gtpbp2	8.19E-86
Colonocytes	2010109I03Rik	1.54E-85
Colonocytes	Krt8	3.79E-85
Colonocytes	Plac8	1.83E-83
Colonocytes	Asap1	2.89E-83
Colonocytes	Errfi1	1.35E-81
Colonocytes	Nlrp9b	3.24E-81
Colonocytes	Selenbp1	1.36E-80
Colonocytes	Pcsk5	1.37E-80
Colonocytes	Car4	4.58E-80
Colonocytes	Ezr	5.89E-80
Colonocytes	Sema3c	6.22E-80
Colonocytes	Ms4a8a	2.76E-79
Colonocytes	Gda	2.97E-79
Colonocytes	Pla2g3	5.31E-79
Colonocytes	Usp53	1.49E-77
Colonocytes	Specc1l	2.84E-77
Colonocytes	Nudt4	4.14E-77
Colonocytes	Pparg	2.79E-76
Colonocytes	Higd1a	4.05E-75
Colonocytes	Atp10b	5.91E-75
Colonocytes	Abcg2	1.90E-73
Colonocytes	Myo1e	3.73E-73
Colonocytes	Actn4	4.55E-73
Colonocytes	Gprc5a	4.68E-73
Colonocytes	Rnasel	2.27E-72
Epithelial_Progenitors	Rab15	3.44E-08
Epithelial_Progenitors	Fam98a	3.76E-08
Epithelial_Progenitors	Slc16a7	4.41E-08
Epithelial_Progenitors	Mcoln2	1.25E-07
Epithelial_Progenitors	4933406C10Rik	4.06E-07
Epithelial_Progenitors	Slc39a8	5.57E-07
Epithelial_Progenitors	Pex5l	5.86E-07
Epithelial_Progenitors	Kif15	9.97E-07
Epithelial_Progenitors	Eepd1	1.03E-06
Epithelial_Progenitors	Ccdc125	1.17E-06
Epithelial_Progenitors	Pacsin1	1.51E-06
Epithelial_Progenitors	Gm14342	1.64E-06
Epithelial_Progenitors	Kcnh3	2.00E-06
Epithelial_Progenitors	Inpp1	2.40E-06
Epithelial_Progenitors	Creb3l4	2.89E-06
Epithelial_Progenitors	Lgals12	1.09E-05
Epithelial_Progenitors	9430060I03Rik	1.34E-05
Epithelial_Progenitors	Mmp28	1.68E-05
Epithelial_Progenitors	Gm43191	2.45E-05
Epithelial_Progenitors	Kif11	2.65E-05
Epithelial_Progenitors	Neil3	3.63E-05
Epithelial_Progenitors	Wdr76	3.96E-05
Epithelial_Progenitors	Pnmal2	4.18E-05
Epithelial_Progenitors	Palmd	4.72E-05
Epithelial_Progenitors	Acsl1	6.66E-05
Epithelial_Progenitors	Smoc2	6.71E-05
Epithelial_Progenitors	Abo	7.52E-05
Epithelial_Progenitors	Fut9	8.90E-05
Epithelial_Progenitors	Fbxo21	1.00E-04
Epithelial_Progenitors	Triqk	1.13E-04
Epithelial_Progenitors	D930020B18Rik	1.71E-04
Epithelial_Progenitors	Ttc39aos1	1.91E-04
Epithelial_Progenitors	Zwilch	3.75E-04
Epithelial_Progenitors	Plk2	4.10E-04
Epithelial_Progenitors	Gm15848	4.48E-04
Epithelial_Progenitors	Mastl	4.81E-04
Epithelial_Progenitors	Pik3c2g	5.12E-04
Epithelial_Progenitors	N6amt1	5.95E-04
Epithelial_Progenitors	Spc24	7.12E-04
Epithelial_Progenitors	Wdhd1	7.36E-04
Epithelial_Progenitors	Zfp612	1.29E-03
Epithelial_Progenitors	Agtr1b	1.74E-03
Epithelial_Progenitors	Isyna1	2.52E-03
Epithelial_Progenitors	1700013F07Rik	4.27E-03
Epithelial_Progenitors.1	Rpl41	1.86E-115
Epithelial_Progenitors.1	Rpl23	5.03E-93
Epithelial_Progenitors.1	Rplp1	1.96E-89
Epithelial_Progenitors.1	Gm10073	4.09E-87
Epithelial_Progenitors.1	Gm8730	4.20E-83
Epithelial_Progenitors.1	Rps3	4.65E-82
Epithelial_Progenitors.1	mt-Cytb	1.08E-79
Epithelial_Progenitors.1	Rps19	2.55E-79
Epithelial_Progenitors.1	Rps9	1.60E-77
Epithelial_Progenitors.1	Rps24	2.92E-77
Epithelial_Progenitors.1	Rpl37	3.68E-77
Epithelial_Progenitors.1	Rpl19	3.68E-77
Epithelial_Progenitors.1	Rps23	3.73E-77
Epithelial_Progenitors.1	Rpl9-ps6	4.29E-77
Epithelial_Progenitors.1	Rps14	3.67E-76
Epithelial_Progenitors.1	Rps18	3.67E-76
Epithelial_Progenitors.1	Rps8	3.67E-76
Epithelial_Progenitors.1	Rpl32	9.28E-76
Epithelial_Progenitors.1	Rps15	9.76E-76
Epithelial_Progenitors.1	Pigr	4.26E-75
Macrophage	Cybb	6.05E-17
Macrophage	Hpgds	7.91E-17
Macrophage	Runx1	2.60E-16
Macrophage	Lst1	2.65E-16
Macrophage	Tbxas1	2.82E-16
Macrophage	H2-Ab1	3.36E-16
Macrophage	Tmcc3	3.44E-16
Macrophage	Clec4a2	5.05E-16
Macrophage	Tgfbi	1.09E-15
Macrophage	Ubash3b	2.24E-15
Macrophage	Malat1	5.90E-15
Macrophage	Wdfy4	6.06E-15
Macrophage	Bank1	8.83E-15
Macrophage	Abca1	1.19E-14
Macrophage	Ccr5	1.21E-14
Macrophage	Epsti1	1.51E-14
Macrophage	Ptprj	2.60E-14
Macrophage	Fermt3	2.74E-14
Macrophage	Dock4	3.28E-14
Macrophage	Rreb1	8.35E-14
Macrophage	Hck	8.55E-14
Macrophage	Lilrb4a	9.73E-14
Macrophage	Tyrobp	5.45E-13
Macrophage	Ccr1	8.62E-13
Macrophage	C3ar1	3.35E-12
Macrophage	Dnase1l3	4.58E-12
Macrophage	Gpr141	6.83E-12
Macrophage	Havcr2	4.68E-11
Macrophage	Cmklr1	5.43E-11
Macrophage	Cd86	5.77E-11
Macrophage	Arrb2	6.84E-11
Macrophage	Ncf1	2.05E-10
Macrophage	Gm42747	2.47E-10
Macrophage	Lilra5	2.47E-10
Macrophage	H2-DMb1	4.22E-10
Macrophage	Cyth4	6.52E-10
Macrophage	AF251705	2.06E-09
Macrophage	Slc11a1	2.06E-09
Macrophage	2010013B24Rik	2.06E-09
Macrophage	Gpr34	2.16E-09
Macrophage	Ntpcr	2.20E-09
Macrophage	Amz1	2.32E-09
Macrophage	Msr1	7.48E-09
Macrophage	Itgax	1.65E-08
Macrophage	Hk3	1.65E-08
Macrophage	Adgrg5	1.65E-08
Macrophage	Ms4a6d	1.65E-08
Macrophage	Serpinb8	1.65E-08
Macrophage	Nxpe5	1.65E-08
Macrophage	Apol7c	1.65E-08
Macrophage	I830077J02Rik	2.03E-08
Macrophage	Il10ra	2.27E-08
Macrophage	Arhgap22	5.51E-08
Macrophage	Rasgrp4	7.78E-08
Macrophage	Slamf7	1.59E-07
Macrophage	Ccr2	1.59E-07
Macrophage	9530059O14Rik	8.01E-07
Macrophage	H2-DMa	9.35E-07
Macrophage	Clec4a3	1.16E-06
Macrophage	C130050O18Rik	1.16E-06
Macrophage	Mpeg1	1.16E-06
Macrophage	Pik3r6	1.17E-06
Macrophage	Ms4a14	1.22E-06
Macrophage	Ptafr	1.43E-06

Colonocytes	Aqp8	4.11E-72
Colonocytes	Car1	5.06E-72
Colonocytes	Cdkn1a	5.44E-72
Colonocytes	Cdhr5	1.23E-70
Colonocytes	Muc13	1.23E-70
Colonocytes	Mep1b	2.30E-70
Colonocytes	Xist	3.72E-70
Colonocytes	Ces2a	4.74E-70
Colonocytes	Ugdh	3.64E-69
Colonocytes	Rock2	1.57E-68
Colonocytes	Stk10	1.13E-67
Colonocytes	Cyp2d34	4.86E-67
Colonocytes	Apol10a	8.61E-67
Colonocytes	Prdx6	9.14E-67
Colonocytes	Slc13a1	2.35E-66
Colonocytes	Noct	1.60E-64
Colonocytes	4732465J04Rik	1.77E-64
Colonocytes	Sgk2	3.93E-64
Colonocytes	Lama3	6.28E-64
Colonocytes	Ccng2	1.17E-63
Colonocytes	Sdcbp2	4.30E-62
Colonocytes	Cpn1	4.42E-60
Colonocytes	Tmigd1	1.39E-59
Colonocytes	Aldh1a1	3.18E-52
Colonocytes	4930539E08Rik	1.43E-50
Colonocytes	Hbegf	2.24E-50
Colonocytes	Abca12	4.79E-48
Colonocytes	Gm3054	1.57E-45
Colonocytes	Gm15345	3.18E-44
Colonocytes	Cry1	2.59E-43
Colonocytes	Dhrs9	1.31E-42
Colonocytes	Cyp4f14	6.42E-42
Colonocytes	Rhod	3.13E-38
Colonocytes	Tmem140	5.09E-37
Colonocytes	Slc10a2	8.04E-37
Colonocytes	5430427M07Rik	1.15E-36
Colonocytes	Ttc22	4.25E-36
Colonocytes	Ppm1j	2.01E-34
Colonocytes	Fmo5	3.40E-34
Colonocytes	Lamb3	1.05E-33
Colonocytes	Mal	1.91E-33
Colonocytes	Tmem252	5.05E-32
Colonocytes	Dgat2	8.80E-31
Colonocytes	Anks4b	1.67E-30
Colonocytes	Dusp10	3.49E-30
Colonocytes	RP23-143J24.4	5.89E-30
Colonocytes	Hkdc1	7.51E-30
Colonocytes	Ptk6	1.83E-29
Colonocytes	Cidec	2.45E-29
Colonocytes	Igsf9	1.96E-28
Colonocytes	Ifit1bl1	2.60E-27
Colonocytes	Atf3	4.07E-27
Colonocytes	H2-Q1	5.42E-27
Colonocytes	Trim40	1.05E-25
Colonocytes	Sult2b1	1.28E-25
Colonocytes	Gm15998	4.99E-24
Colonocytes	Syt12	8.81E-24
Colonocytes	Chp2	1.49E-23
Colonocytes	3100003L05Rik	1.97E-23
Colonocytes	Trim15	4.75E-23
Colonocytes	Slc3a1	2.17E-22
Colonocytes	Plekhg6	6.26E-22
Colonocytes	Gm16233	7.02E-21
Colonocytes	Slc51b	2.40E-20
Colonocytes	Sh3tc1	8.35E-20
Colonocytes	Agbl2	2.06E-17
Colonocytes	Grin3a	3.32E-17
Colonocytes	Slc34a2	9.50E-17
Epithelial_Progenitors.1	Cox8a	5.16E-74
Epithelial_Progenitors.1	Eef1a1	4.33E-73
Epithelial_Progenitors.1	Rpl26	2.45E-72
Epithelial_Progenitors.1	Rpl13a	3.64E-72
Epithelial_Progenitors.1	mt-Nd4	6.24E-72
Epithelial_Progenitors.1	Wdr89	4.96E-71
Epithelial_Progenitors.1	Rps2	5.61E-71
Epithelial_Progenitors.1	Rpl21	1.29E-70
Epithelial_Progenitors.1	mt-Co2	1.29E-70
Epithelial_Progenitors.1	mt-Atp6	1.52E-70
Epithelial_Progenitors.1	Rpl8	8.16E-70
Epithelial_Progenitors.1	Rpl11	2.05E-69
Epithelial_Progenitors.1	Rpl18a	2.85E-69
Epithelial_Progenitors.1	Rpl35a	1.65E-68
Epithelial_Progenitors.1	mt-Nd1	2.55E-68
Epithelial_Progenitors.1	Rps16	4.06E-68
Epithelial_Progenitors.1	Rps4x	5.10E-67
Epithelial_Progenitors.1	mt-Co3	2.37E-66
Epithelial_Progenitors.1	Rpl37a	3.78E-66
Epithelial_Progenitors.1	Rps27a	5.37E-66
Epithelial_Progenitors.1	Rps20	5.73E-65
Epithelial_Progenitors.1	Rplp0	6.50E-65
Epithelial_Progenitors.1	Rpsa	8.50E-65
Epithelial_Progenitors.1	Rps5	1.87E-64
Epithelial_Progenitors.1	Gm10036	4.50E-64
Epithelial_Progenitors.1	Rpl10a	1.18E-63
Epithelial_Progenitors.1	Rpl7	2.92E-63
Epithelial_Progenitors.1	Uqcrh	5.51E-63
Epithelial_Progenitors.1	Rpl27a	2.89E-62
Epithelial_Progenitors.1	Rpl18	5.88E-62
Epithelial_Progenitors.1	Mt1	3.39E-61
Epithelial_Progenitors.1	Rpl28	4.94E-61
Epithelial_Progenitors.1	Rps6	7.59E-61
Epithelial_Progenitors.1	Rps11	1.24E-59
Epithelial_Progenitors.1	Scd2	7.56E-59
Epithelial_Progenitors.1	Rpl14	1.02E-58
Epithelial_Progenitors.1	Rpl4	1.08E-57
Epithelial_Progenitors.1	Rps29	3.22E-57
Epithelial_Progenitors.1	Gm9843	3.33E-57
Epithelial_Progenitors.1	Rps26	9.08E-57
Epithelial_Progenitors.1	Gpx2	1.64E-54
Epithelial_Progenitors.1	Rpl24	8.24E-54
Epithelial_Progenitors.1	Rpl13-ps3	9.49E-54
Epithelial_Progenitors.1	Rps17	1.25E-53
Epithelial_Progenitors.1	Cox6c	2.59E-53
Epithelial_Progenitors.1	Uqcr10	8.97E-53
Epithelial_Progenitors.1	Tecpr2	4.91E-52
Epithelial_Progenitors.1	mt-Co1	3.30E-51
Epithelial_Progenitors.1	Rps26-ps1	6.74E-51
Epithelial_Progenitors.1	Rpl36al	3.23E-50
Epithelial_Progenitors.1	Rpl29	6.33E-50
Epithelial_Progenitors.1	Rps10	1.18E-49
Epithelial_Progenitors.1	Cox6a1	6.43E-49
Epithelial_Progenitors.1	Rps27rt	9.46E-49
Epithelial_Progenitors.1	Rpl39	1.81E-48
Epithelial_Progenitors.1	Rpl6l	3.04E-48
Epithelial_Progenitors.1	Rps18-ps3	6.15E-48
Epithelial_Progenitors.1	Rps3a1	3.15E-47
Epithelial_Progenitors.1	Tpt1	3.84E-45
Epithelial_Progenitors.1	Rps25	1.97E-44
Epithelial_Progenitors.1	Ftl1	1.10E-43
Epithelial_Progenitors.1	Ddah1	2.39E-43
Epithelial_Progenitors.1	Rps21	5.06E-43
Epithelial_Progenitors.1	Rpl5	5.50E-42
Epithelial_Progenitors.1	Rpl27-ps3	6.68E-42
Epithelial_Progenitors.1	Ptma	7.74E-42
Epithelial_Progenitors.1	Ctla4	4.76E-41
Epithelial_Progenitors.1	Nrg1	3.98E-40
Macrophage	Cd80	3.13E-06
Macrophage	Asb2	3.60E-06
Macrophage	Csf2rb	5.78E-06
Macrophage	Gm30382	6.01E-06
Macrophage	Kmo	6.09E-06
Macrophage	Clec4n	6.19E-06
Macrophage	Trpm2	1.73E-05
Macrophage	Cd4	5.89E-05
Macrophage	Retnla	1.70E-04
Macrophage	Tg	2.01E-04
Macrophage	Rab3il1	2.19E-04
Macrophage	Kcnip3	2.47E-04
Macrophage	Slamf8	2.50E-04
Macrophage	Fmnl1	1.44E-03
Macrophage	Irf5	2.23E-03
Macrophage	Arl4c	2.75E-03
Mesothelial	Dcn	2.48E-108
Mesothelial	Gpm6a	1.19E-91
Mesothelial	C3	8.52E-90
Mesothelial	Cav1	4.47E-86
Mesothelial	Wdr17	4.60E-85
Mesothelial	Upk3b	3.99E-77
Mesothelial	Bnc2	5.99E-74
Mesothelial	Gas1	2.78E-73
Mesothelial	Cfh	2.27E-72
Mesothelial	Muc16	5.46E-67
Mesothelial	Rspo1	3.15E-62
Mesothelial	Efna5	6.59E-61
Mesothelial	Plxna4	2.77E-60
Mesothelial	Wt1	1.68E-59
Mesothelial	Upk1b	5.31E-58
Mesothelial	Bicd1	1.23E-55
Mesothelial	Aebp1	8.12E-55
Mesothelial	Fmo2	5.85E-54
Mesothelial	Dlc1	6.88E-53
Mesothelial	Ptrf	1.26E-52
Mesothelial	Tmtc1	6.21E-52
Mesothelial	Rarres2	3.55E-51
Mesothelial	Col3a1	4.15E-50
Mesothelial	Celf2	1.74E-49
Mesothelial	Igfbp6	1.84E-49
Mesothelial	Kcnab1	1.71E-47
Mesothelial	Lvrn	1.86E-47
Mesothelial	Eya4	2.41E-47
Mesothelial	Cdon	2.50E-47
Mesothelial	Slpi	5.66E-47
Mesothelial	Arhgap29	3.13E-46
Mesothelial	Vim	6.26E-45
Mesothelial	Msln	8.01E-45
Mesothelial	9530026P05Rik	1.31E-44
Mesothelial	Meg3	2.28E-44
Mesothelial	Ap4e1	4.94E-44
Mesothelial	Sparc	2.58E-43
Mesothelial	Meis1	9.43E-43
Mesothelial	Meis2	1.27E-42
Mesothelial	Zfpm2	1.78E-42
Mesothelial	Lrrn4	8.53E-42
Mesothelial	Wnt5a	1.76E-39
Mesothelial	Sulf1	1.93E-39
Mesothelial	Efemp1	2.66E-39
Mesothelial	Adamtsl1	6.95E-38
Mesothelial	Pcdh7	4.06E-37
Mesothelial	Sox6	2.50E-36
Mesothelial	Tmeff2	2.61E-36
Mesothelial	Tmem108	1.15E-34
Mesothelial	Slit3	2.44E-34
Mesothelial	Sdpr	2.64E-34
Mesothelial	Cdh11	3.34E-34

Colonocytes	Cxcl16	5.07E-16
Colonocytes	Bmp8b	2.09E-15
Colonocytes	C130074G19Rik	3.61E-15
Colonocytes	Sprr1a	7.30E-15
Colonocytes	Maff	2.31E-14
Colonocytes	Adamts18	2.84E-14
Colonocytes	Oasl1	3.40E-14
Colonocytes	Tat	4.38E-14
Colonocytes	Psg28	1.39E-13
Colonocytes	Akr1b7	1.59E-13
Colonocytes	E130012A19Rik	2.25E-13
Colonocytes	Aspa	2.25E-13
Colonocytes	Baat	4.58E-13
Colonocytes	Arg2	5.32E-13
Colonocytes	Rsad2	1.19E-12
Colonocytes	Ifit1bl2	6.99E-12
Colonocytes	2010005H15Rik	1.60E-11
Colonocytes	Gm10522	6.65E-11
Colonocytes	Slc30a10	2.66E-09
Colonocytes	Myom3	6.15E-09
Colonocytes.1	Prdx6	4.33E-223
Colonocytes.1	Lypd8	1.89E-199
Colonocytes.1	Tgm3	4.84E-179
Colonocytes.1	Car4	4.08E-166
Colonocytes.1	Slc26a3	5.20E-154
Colonocytes.1	Saa1	1.62E-153
Colonocytes.1	Ceacam20	3.54E-146
Colonocytes.1	Slc20a1	2.83E-142
Colonocytes.1	Sepp1	1.06E-138
Colonocytes.1	Muc3	1.24E-136
Colonocytes.1	Slc15a1	2.15E-129
Colonocytes.1	Fxyd4	4.27E-121
Colonocytes.1	Slc37a2	4.91E-118
Colonocytes.1	Sprr2a3	1.20E-117
Colonocytes.1	Aqp8	1.75E-116
Colonocytes.1	Atp12a	2.75E-116
Colonocytes.1	Tmem45b	3.13E-115
Colonocytes.1	Mxd1	6.43E-115
Colonocytes.1	Crip1	1.09E-109
Colonocytes.1	Trpm6	2.21E-109
Colonocytes.1	Plac8	6.62E-107
Colonocytes.1	Rdh16	1.87E-106
Colonocytes.1	Cyp2c55	5.20E-105
Colonocytes.1	Ggh	1.18E-101
Colonocytes.1	Clic5	9.32E-101
Colonocytes.1	2200002D01Rik	1.06E-100
Colonocytes.1	Slc26a2	6.04E-97
Colonocytes.1	Cyp2d34	1.24E-94
Colonocytes.1	Abcb1a	3.61E-94
Colonocytes.1	Tnni1	1.49E-93
Colonocytes.1	Ly6g	6.71E-91
Colonocytes.1	Gpr137b	9.44E-90
Colonocytes.1	Slc6a8	3.39E-87
Colonocytes.1	Phlpp2	7.14E-87
Colonocytes.1	AA467197	1.59E-86
Colonocytes.1	Slc40a1	2.11E-86
Colonocytes.1	Btg1	4.24E-86
Colonocytes.1	Mgat4a	2.84E-84
Colonocytes.1	Ifit1bl1	3.57E-84
Colonocytes.1	Sectm1b	4.20E-82
Colonocytes.1	Tm4sf20	4.20E-82
Colonocytes.1	Sult1b1	1.71E-81
Colonocytes.1	B4galt1	1.38E-80
Colonocytes.1	Pmp22	2.32E-80
Colonocytes.1	Slc9a2	2.62E-80
Colonocytes.1	Sycn	3.84E-79
Colonocytes.1	Nudt4	9.75E-79
Epithelial_Progenitors.1	Sycn	1.18E-39
Epithelial_Progenitors.1	Gm10263	2.01E-39
Epithelial_Progenitors.1	mt-Nd2	3.28E-39
Epithelial_Progenitors.1	Atp5e	4.45E-39
Epithelial_Progenitors.1	Rpl38	6.37E-39
Epithelial_Progenitors.1	Rps28	1.02E-38
Epithelial_Progenitors.1	Gnb2l1	1.49E-37
Epithelial_Progenitors.1	Sumf1	7.13E-37
Epithelial_Progenitors.1	Rpl17	8.97E-37
Epithelial_Progenitors.1	Rpl34	9.85E-37
Epithelial_Progenitors.1	Eef1g	5.38E-36
Epithelial_Progenitors.1	Eef1b2	1.73E-35
Epithelial_Progenitors.1	Gm9493	3.01E-35
Epithelial_Progenitors.1	Rps27l	4.31E-35
Epithelial_Progenitors.1	Uqcr11	1.90E-34
Epithelial_Progenitors.1	Slc5a8	2.44E-33
Epithelial_Progenitors.1	Atp5g1	2.51E-33
Epithelial_Progenitors.1	Atp5g2	5.27E-30
Epithelial_Progenitors.1	Wfdc2	4.18E-29
Epithelial_Progenitors.1	Mt2	8.75E-29
Epithelial_Progenitors.1	Hsp90ab1	9.95E-28
Epithelial_Progenitors.1	Rps12-ps3	4.23E-22
Epithelial_Progenitors.1	Anapc13	4.57E-19
Epithelial_Progenitors.1	Gm8186	6.05E-19
Epithelial_Progenitors.1	Hoxb13	2.85E-16
Epithelial_Progenitors.1	Lsm4	6.99E-15
Epithelial_Progenitors.1	2410015M20Rik	1.92E-14
Epithelial_Progenitors.1	Banf1	2.56E-14
Epithelial_Progenitors.1	Mgst1	3.75E-14
Epithelial_Progenitors.1	Spink4	6.36E-14
Epithelial_Progenitors.1	Mei4	1.12E-13
Epithelial_Progenitors.1	Gm15013	1.27E-11
Epithelial_Progenitors.1	Romo1	4.04E-11
Epithelial_Progenitors.1	Cyp2c68	5.31E-11
Epithelial_Progenitors.1	Gm11273	5.35E-11
Epithelial_Progenitors.1	Cfap46	5.65E-11
Epithelial_Progenitors.1	Rab25	8.98E-11
Epithelial_Progenitors.1	Nhp2	3.84E-10
Epithelial_Progenitors.1	Lsm5	4.08E-10
Epithelial_Progenitors.1	Impdh2	4.37E-10
Epithelial_Progenitors.1	Ndufa8	1.06E-09
Epithelial_Progenitors.1	Smim11	5.93E-09
Epithelial_Progenitors.1	Uba52	6.93E-09
Epithelial_Progenitors.1	Fut4	1.05E-08
Epithelial_Progenitors.1	Birc5	2.33E-08
Epithelial_Progenitors.1	Plbd1	1.16E-07
Epithelial_Progenitors.1	Unc119	1.31E-07
Epithelial_Progenitors.1	Ube2c	3.24E-07
Epithelial_Progenitors.1	Slc35b2	3.42E-07
Epithelial_Progenitors.1	Hmgn2	5.59E-07
Epithelial_Progenitors.1	Rpl27	1.03E-06
Epithelial_Progenitors.1	Cdca3	1.04E-06
Epithelial_Progenitors.1	Cebpzos	2.22E-06
Epithelial_Progenitors.1	Knstrn	4.65E-06
Epithelial_Progenitors.1	Ran	7.01E-06
Epithelial_Progenitors.1	Pdzk1ip1	8.00E-06
Epithelial_Progenitors.1	Tspan33	1.12E-05
Epithelial_Progenitors.1	Tmem192	2.90E-05
Epithelial_Progenitors.1	Yif1a	7.48E-05
Epithelial_Progenitors.1	Snrnp25	2.63E-04
Epithelial_Progenitors.1	Gm10053	5.20E-04
Epithelial_Progenitors.2	Hsd3b3	1.85E-121
Epithelial_Progenitors.2	Gsdmc2	2.52E-86
Epithelial_Progenitors.2	Dmbt1	9.47E-73
Epithelial_Progenitors.2	Gsdmc4	1.95E-71
Epithelial_Progenitors.2	Hao2	3.17E-70
Epithelial_Progenitors.2	Cftr	2.52E-67
Mesothelial	Spock2	5.46E-33
Mesothelial	Timp2	6.74E-33
Mesothelial	Oasl2	9.33E-33
Mesothelial	Runx1t1	1.39E-32
Mesothelial	Cdh3	5.93E-31
Mesothelial	Mpp6	8.77E-31
Mesothelial	Adam33	1.69E-30
Mesothelial	Tgm2	3.53E-30
Mesothelial	Col6a1	9.33E-30
Mesothelial	Gm20400	1.75E-29
Mesothelial	Dab2	2.77E-29
Mesothelial	Aldh1a2	2.84E-29
Mesothelial	Pde10a	6.95E-29
Mesothelial	Ar	1.09E-28
Mesothelial	Col4a5	3.71E-28
Mesothelial	Sema3e	8.97E-28
Mesothelial	Pkhd1l1	1.10E-27
Mesothelial	Cd200	2.26E-27
Mesothelial	Ptpn13	4.34E-27
Mesothelial	Dpp4	4.67E-27
Mesothelial	Zbtb16	5.04E-27
Mesothelial	Laptm4a	1.01E-26
Mesothelial	Bicc1	1.68E-26
Mesothelial	Tnfrsf11b	2.05E-26
Mesothelial	Rbbp8	2.05E-26
Mesothelial	Serpinh1	2.34E-26
Mesothelial	Sema3d	5.79E-26
Mesothelial	Il6st	6.85E-26
Mesothelial	Piezo2	7.46E-26
Mesothelial	Mmp16	1.20E-25
Mesothelial	Ano1	1.78E-25
Mesothelial	Gulp1	2.14E-25
Mesothelial	Zfhx4	2.28E-25
Mesothelial	Ildr2	2.70E-25
Mesothelial	Mast4	4.23E-25
Mesothelial	Col4a6	4.84E-25
Mesothelial	Arhgap28	5.20E-25
Mesothelial	Il1rapl1	8.88E-25
Mesothelial	Abcb1b	9.03E-25
Mesothelial	Tm4sf1	1.44E-24
Mesothelial	Wt1os	1.66E-24
Mesothelial	Ahnak	2.12E-24
Mesothelial	Cald1	3.41E-24
Mesothelial	Nbl1	4.09E-24
Mesothelial	Vwa3a	6.41E-24
Mesothelial	Rbpms	6.45E-24
Mesothelial	Adgrd1	1.11E-23
Mesothelial	Ccbe1	1.51E-23
Mesothelial	Nxph1	1.99E-20
Mesothelial	Cybrd1	3.90E-20
Mesothelial	Gpc3	6.67E-20
Mesothelial	C1s1	1.22E-19
Mesothelial	Gm15581	1.67E-18
Mesothelial	Myrf	2.83E-18
Mesothelial	Fam184a	4.35E-18
Mesothelial	Gm12381	1.31E-17
Mesothelial	Bcam	5.99E-16
Mesothelial	Stk26	1.34E-15
Mesothelial	Fam180a	2.40E-14
Mesothelial	Podn	3.86E-14
Mesothelial	Gm765	2.37E-13
Mesothelial	Clu	3.17E-13
Mesothelial	Npr1	3.58E-13
Mesothelial	Lrp2	1.19E-12
Mesothelial	Osr1	2.55E-12
Mesothelial	Krt14	2.55E-12
Mesothelial	A330015K06Rik	2.92E-12

Colonocytes.1	March3	7.99E-77
Colonocytes.1	Tspan1	8.80E-77
Colonocytes.1	Slco2a1	2.89E-76
Colonocytes.1	Endod1	2.89E-76
Colonocytes.1	Prss30	7.15E-76
Colonocytes.1	Myo15b	2.53E-75
Colonocytes.1	Tns4	9.42E-75
Colonocytes.1	Fth1	1.62E-74
Colonocytes.1	Fbxo32	2.08E-74
Colonocytes.1	Atp2b1	1.92E-73
Colonocytes.1	Nlrp9b	5.95E-73
Colonocytes.1	Nt5e	6.93E-73
Colonocytes.1	Atp1b1	3.20E-72
Colonocytes.1	Coro2a	1.47E-71
Colonocytes.1	Sprr2a2	6.53E-71
Colonocytes.1	2610528A11Rik	2.00E-70
Colonocytes.1	Cnnm4	6.84E-70
Colonocytes.1	St3gal4	9.77E-70
Colonocytes.1	Ipmk	4.63E-69
Colonocytes.1	Lama3	8.12E-69
Colonocytes.1	Ahnak	8.98E-69
Colonocytes.1	Max	1.20E-68
Colonocytes.1	Ctss	1.88E-68
Colonocytes.1	Ly6a	2.83E-68
Colonocytes.1	9530026P05Rik	4.21E-68
Colonocytes.1	Mep1a	4.72E-68
Colonocytes.1	Myl12b	5.18E-68
Colonocytes.1	Bmp2	8.43E-68
Colonocytes.1	Cs	1.11E-67
Colonocytes.1	Myh14	2.11E-67
Colonocytes.1	Krt20	3.83E-67
Colonocytes.1	Eif2s2	5.01E-66
Colonocytes.1	Themis3	9.17E-66
Colonocytes.1	Abat	2.49E-65
Colonocytes.1	Ifngr1	3.26E-65
Colonocytes.1	Misp	3.44E-65
Colonocytes.1	mt-Co1	5.57E-65
Colonocytes.1	Itm2b	9.06E-65
Colonocytes.1	Itih5	2.11E-64
Colonocytes.1	Slc25a20	3.39E-64
Colonocytes.1	Pdzk1ip1	4.76E-63
Colonocytes.1	Rhoc	7.42E-63
Colonocytes.1	S100a6	1.32E-62
Colonocytes.1	Ckmt1	1.83E-62
Colonocytes.1	Rhbdl2	3.01E-62
Colonocytes.1	Gm30613	3.16E-62
Colonocytes.1	Prr15l	4.47E-62
Colonocytes.1	Mcl1	6.59E-62
Colonocytes.1	Noct	2.53E-61
Colonocytes.1	Fhl1	4.07E-61
Colonocytes.1	mt-Atp6	4.74E-61
Colonocytes.1	Tmem37	1.76E-60
Colonocytes.1	Prss32	2.31E-60
Colonocytes.1	Unc119	4.09E-56
Colonocytes.1	Pmaip1	4.07E-55
Colonocytes.1	Gcnt1	9.48E-55
Colonocytes.1	Mt1	1.45E-54
Colonocytes.1	Lhfpl2	2.32E-51
Colonocytes.1	Pllp	3.26E-51
Colonocytes.1	Gpr137b-ps	2.31E-49
Colonocytes.1	Stom	3.20E-49
Colonocytes.1	Trpv3	1.59E-48
Colonocytes.1	2310079G19Rik	1.72E-48
Colonocytes.1	Tmem140	1.22E-46
Colonocytes.1	Apob	6.68E-45
Colonocytes.1	Rbp2	1.18E-43
Colonocytes.1	Otub1	2.25E-41
Colonocytes.1	A930011G23Rik	4.19E-39

Epithelial_Progenitors.2	Hnf4g	2.01E-65
Epithelial_Progenitors.2	Gm26917	5.05E-64
Epithelial_Progenitors.2	Sult1a1	1.23E-59
Epithelial_Progenitors.2	Hmgcs2	3.70E-58
Epithelial_Progenitors.2	Chd9	4.13E-58
Epithelial_Progenitors.2	Satb2	2.08E-55
Epithelial_Progenitors.2	Cyp2c55	4.48E-52
Epithelial_Progenitors.2	Apol10a	1.82E-48
Epithelial_Progenitors.2	Slc8a1	8.43E-46
Epithelial_Progenitors.2	Gsdmc3	1.40E-44
Epithelial_Progenitors.2	Slc5a8	7.50E-43
Epithelial_Progenitors.2	Fkbp5	9.49E-43
Epithelial_Progenitors.2	Dgkh	2.20E-42
Epithelial_Progenitors.2	Mecom	4.68E-42
Epithelial_Progenitors.2	Adk	1.16E-40
Epithelial_Progenitors.2	Aqp4	1.87E-40
Epithelial_Progenitors.2	Pcsk5	6.16E-40
Epithelial_Progenitors.2	Vwa8	2.91E-38
Epithelial_Progenitors.2	Pparg	2.91E-38
Epithelial_Progenitors.2	Immp2l	2.07E-32
Epithelial_Progenitors.2	Krt19	3.06E-32
Epithelial_Progenitors.2	Slc26a3	3.96E-32
Epithelial_Progenitors.2	Ptprd	1.32E-31
Epithelial_Progenitors.2	Ahcyl2	1.94E-30
Epithelial_Progenitors.2	Pof1b	4.25E-29
Epithelial_Progenitors.2	Trim2	5.45E-29
Epithelial_Progenitors.2	B4galnt2	6.81E-29
Epithelial_Progenitors.2	Coro2a	8.17E-29
Epithelial_Progenitors.2	Paqr5	8.18E-28
Epithelial_Progenitors.2	Papss2	9.48E-27
Epithelial_Progenitors.2	Mgat4c	2.45E-25
Epithelial_Progenitors.2	Ptprk	1.14E-24
Epithelial_Progenitors.2	Nr5a2	3.75E-24
Epithelial_Progenitors.2	Magi1	8.23E-24
Epithelial_Progenitors.2	Pdss2	8.43E-24
Epithelial_Progenitors.2	Nr1h4	1.42E-23
Epithelial_Progenitors.2	Hsd3b2	4.73E-23
Epithelial_Progenitors.2	Pde3a	1.85E-22
Epithelial_Progenitors.2	Plekha5	2.43E-22
Epithelial_Progenitors.2	Mboat1	2.50E-22
Epithelial_Progenitors.2	Fgd4	3.52E-22
Epithelial_Progenitors.2	Gipc2	3.73E-22
Epithelial_Progenitors.2	Maoa	1.46E-21
Epithelial_Progenitors.2	Acnat1	1.64E-21
Epithelial_Progenitors.2	Flnb	4.07E-21
Epithelial_Progenitors.2	Pla2g3	5.57E-21
Epithelial_Progenitors.2	Gm42418	5.92E-21
Epithelial_Progenitors.2	Car1	8.45E-21
Epithelial_Progenitors.2	Ugdh	8.86E-21
Epithelial_Progenitors.2	Clint1	1.21E-20
Epithelial_Progenitors.2	Plekha6	1.43E-20
Epithelial_Progenitors.2	Myo1d	1.50E-20
Epithelial_Progenitors.2	Htr4	1.61E-20
Epithelial_Progenitors.2	Nfe2l2	5.34E-20
Epithelial_Progenitors.2	Xist	1.48E-19
Epithelial_Progenitors.2	Selenbp1	3.10E-19
Epithelial_Progenitors.2	Sgpp2	7.17E-19
Epithelial_Progenitors.2	Id1	1.45E-18
Epithelial_Progenitors.2	Gpatch2	4.15E-18
Epithelial_Progenitors.2	Nbeal1	4.51E-18
Epithelial_Progenitors.2	Ildr1	4.64E-18
Epithelial_Progenitors.2	Dsc2	2.59E-17
Epithelial_Progenitors.2	Car2	2.82E-17
Epithelial_Progenitors.2	Tnfrsf11a	3.73E-17
Epithelial_Progenitors.2	Kitl	3.79E-17
Epithelial_Progenitors.2	Pard3b	4.18E-17
Epithelial_Progenitors.2	Vsig10	4.66E-17
Epithelial_Progenitors.2	Ppara	7.65E-17

Mesothelial	Medag	3.42E-11
Mesothelial	Basp1	7.62E-11
Mesothelial	Bnc1	2.62E-10
Mesothelial	Fmod	2.62E-10
Mesothelial	Stbd1	2.62E-10
Mesothelial	Smtnl2	3.09E-10
Mesothelial	Smim1	3.24E-10
Mesothelial	Rcn1	6.53E-10
Mesothelial	2600014E21Rik	1.41E-09
Mesothelial	Prss12	1.62E-09
Mesothelial	Zfp185	2.06E-09
Mesothelial	Tmem119	2.48E-09
Mesothelial	Lox	2.21E-08
Mesothelial	Tmem255a	2.24E-08
Mesothelial	Iigp1	2.43E-08
Mesothelial	Rpp25	1.81E-07
Mesothelial	Esam	2.08E-07
Mesothelial	Col4a3	2.29E-07
Mesothelial	Angptl4	2.52E-07
Mesothelial	Crb2	2.52E-07
Mesothelial	Lgals7	2.52E-07
Mesothelial	Sh3tc2	3.91E-07
Mesothelial	Thbd	4.86E-07
Mesothelial	Tgfb3	5.26E-07
Mesothelial	Gjb5	8.19E-07
Mesothelial	Vwc2	1.66E-06
Mesothelial	Serpinb6b	2.40E-06
Mesothelial	Sult5a1	4.89E-06
Mesothelial	Slc4a3	7.26E-06
Mesothelial	Nnmt	8.09E-06
Mesothelial	Gpr88	1.32E-05
Mesothelial	Galnt15	1.37E-05
Mesothelial	Steap4	2.67E-05
Mesothelial	Il18r1	5.47E-05
Mesothelial	Sspn	5.95E-05
Mesothelial	P2rx6	1.07E-04
Mesothelial	Gm4951	1.07E-04
Mesothelial	AW551984	2.16E-04
Mesothelial	Sox12	3.93E-04
Mesothelial	Lrrn4cl	3.94E-04
Mesothelial	Spon2	1.83E-03
Mesothelial	Miat	2.06E-03
Mesothelial	Gabre	3.05E-03
Muscle/ICCs	Myh11	6.96E-216
Muscle/ICCs	Cacnb2	2.71E-210
Muscle/ICCs	Dmd	3.97E-205
Muscle/ICCs	Prkg1	1.42E-201
Muscle/ICCs	Rbpms	1.42E-192
Muscle/ICCs	Cacna1c	3.39E-170
Muscle/ICCs	Sntg2	5.97E-170
Muscle/ICCs	Synpo2	3.80E-166
Muscle/ICCs	Slc24a3	4.47E-154
Muscle/ICCs	Cald1	5.50E-152
Muscle/ICCs	Kcnip4	3.71E-139
Muscle/ICCs	Meis2	2.14E-134
Muscle/ICCs	Actg2	6.39E-131
Muscle/ICCs	Svil	2.31E-130
Muscle/ICCs	Flna	1.85E-129
Muscle/ICCs	Acta2	4.19E-128
Muscle/ICCs	Foxp2	1.39E-124
Muscle/ICCs	Mir143hg	1.92E-124
Muscle/ICCs	Mylk	3.30E-123
Muscle/ICCs	Lpp	1.34E-122
Muscle/ICCs	Tpm1	3.61E-118
Muscle/ICCs	Gm26632	1.21E-111
Muscle/ICCs	Tagln	2.73E-110
Muscle/ICCs	Pdlim3	4.40E-108
Muscle/ICCs	Trps1	1.44E-107

Colonocytes.1	Upp1	8.72E-38
Colonocytes.1	Slc34a2	1.01E-35
Colonocytes.1	H2-Q1	1.99E-35
Colonocytes.1	Cyp2d12	2.83E-35
Colonocytes.1	Eno3	3.02E-33
Colonocytes.1	Edn1	6.17E-32
Colonocytes.1	Tnfaip3	5.90E-30
Colonocytes.1	Slc30a10	1.23E-29
Colonocytes.1	Cyp2d10	7.41E-28
Colonocytes.1	Slc30a1	1.89E-27
Colonocytes.1	Pla2g4f	6.22E-27
Colonocytes.1	Gm15998	2.52E-26
Colonocytes.1	4930552P12Rik	3.32E-26
Colonocytes.1	Hoxd11	2.67E-23
Colonocytes.1	Abcg8	1.16E-22
Colonocytes.1	2010003K11Rik	1.53E-22
Colonocytes.1	Gjb5	3.49E-21
Colonocytes.1	Gm31363	1.35E-20
Colonocytes.1	4833407H14Rik	1.68E-20
Colonocytes.1	D330045A20Rik	2.32E-20
Colonocytes.1	Slc46a1	1.88E-19
Colonocytes.1	Anxa8	1.28E-18
Colonocytes.1	Prdx6b	2.08E-18
Colonocytes.1	Abcg5	2.51E-18
Colonocytes.1	Hist1h4h	3.93E-18
Colonocytes.1	Asb11	2.41E-17
Colonocytes.1	Cyp2d9	2.94E-17
Colonocytes.1	2010005H15Rik	1.22E-16
Colonocytes.1	Xkr9	6.56E-16
Colonocytes.1	S100g	2.27E-15
Colonocytes.1	Gm13412	2.94E-15
Colonocytes.1	Hoxd13	1.17E-14
Colonocytes.1	Csta1	4.35E-14
Colonocytes.1	Zfp775	3.20E-13
Colonocytes.1	Trpv6	1.89E-12
Colonocytes.1	1700019G17Rik	2.65E-12
Colonocytes.1	Scnn1g	4.23E-12
Colonocytes.1	Plekhg6	4.26E-12
Colonocytes.1	Abcg1	8.93E-12
Colonocytes.1	BC025446	1.25E-11
Colonocytes.1	Slc16a3	1.60E-10
Colonocytes.1	Ifit1bl2	4.83E-10
Colonocytes.1	Gm12056	7.25E-10
Colonocytes.1	Gm11535	9.59E-10
Colonocytes.1	Ttc39c	1.96E-09
Colonocytes.1	Ceacam18	2.75E-09
Colonocytes.1	Saa2	3.09E-09
Colonocytes.2	mt-Co1	1.95E-188
Colonocytes.2	mt-Co3	7.32E-171
Colonocytes.2	Guca2a	1.39E-161
Colonocytes.2	mt-Atp6	6.92E-155
Colonocytes.2	mt-Co2	9.78E-152
Colonocytes.2	mt-Nd1	7.29E-130
Colonocytes.2	Phgr1	1.33E-125
Colonocytes.2	2200002D01Rik	4.24E-116
Colonocytes.2	Muc3	1.22E-115
Colonocytes.2	mt-Cytb	1.98E-111
Colonocytes.2	Cox8a	8.93E-104
Colonocytes.2	Cyp2c55	5.95E-103
Colonocytes.2	mt-Nd4	5.35E-96
Colonocytes.2	S100a6	4.16E-88
Colonocytes.2	Cox6a1	9.10E-84
Colonocytes.2	Fth1	1.18E-83
Colonocytes.2	Cox6c	3.06E-83
Colonocytes.2	Car1	9.22E-83
Epithelial_Progenitors.2	Ppargc1b	8.80E-17
Epithelial_Progenitors.2	Cyp2c65	1.29E-16
Epithelial_Progenitors.2	Sema5a	1.39E-16
Epithelial_Progenitors.2	Lgals3	3.52E-16
Epithelial_Progenitors.2	Ap3b1	3.93E-16
Epithelial_Progenitors.2	Plce1	3.94E-16
Epithelial_Progenitors.2	Lurap1l	4.74E-16
Epithelial_Progenitors.2	Lgals4	2.73E-15
Epithelial_Progenitors.2	Pycard	3.14E-15
Epithelial_Progenitors.2	Pbx1	3.21E-15
Epithelial_Progenitors.2	Nr3c2	3.34E-15
Epithelial_Progenitors.2	Slc4a4	5.54E-15
Epithelial_Progenitors.2	Akr1c19	8.28E-15
Epithelial_Progenitors.2	Ppp1r9a	1.45E-14
Epithelial_Progenitors.2	Ppard	2.28E-14
Epithelial_Progenitors.2	Sema3c	2.81E-14
Epithelial_Progenitors.2	Palld	3.22E-14
Epithelial_Progenitors.2	Samd12	3.92E-14
Epithelial_Progenitors.2	Ces1f	7.39E-14
Epithelial_Progenitors.2	Prkca	9.52E-14
Epithelial_Progenitors.2	Snx13	1.02E-13
Epithelial_Progenitors.2	Ank	1.27E-13
Epithelial_Progenitors.2	Zfp618	3.34E-13
Epithelial_Progenitors.2	Tex9	4.66E-13
Epithelial_Progenitors.2	Pigr	1.12E-12
Epithelial_Progenitors.2	Ccl28	1.21E-12
Epithelial_Progenitors.2	Fa2h	2.42E-12
Epithelial_Progenitors.2	Tubal3	1.31E-10
Epithelial_Progenitors.2	Pitpnm3	1.64E-10
Epithelial_Progenitors.2	Cldn8	2.67E-09
Epithelial_Progenitors.2	Pbld2	3.54E-09
Epithelial_Progenitors.2	Utp20	4.69E-09
Epithelial_Progenitors.2	9130008F23Rik	4.99E-09
Epithelial_Progenitors.2	Trabd2b	8.74E-09
Epithelial_Progenitors.2	Prelid2	1.00E-08
Epithelial_Progenitors.2	4430402I18Rik	2.03E-08
Epithelial_Progenitors.2	Slc22a18	5.33E-08
Epithelial_Progenitors.2	Prkg2	6.37E-08
Epithelial_Progenitors.2	Vstm5	2.06E-07
Epithelial_Progenitors.2	Spata17	3.29E-07
Epithelial_Progenitors.2	Trim16	3.32E-07
Epithelial_Progenitors.2	Cyp2c68	3.92E-07
Epithelial_Progenitors.2	Ugt2b5	4.30E-07
Epithelial_Progenitors.2	Gm10399	4.30E-07
Epithelial_Progenitors.2	Acsm3	4.32E-07
Epithelial_Progenitors.2	Tbc1d2	5.65E-07
Epithelial_Progenitors.2	E230001N04Rik	7.65E-07
Epithelial_Progenitors.2	Dnah8	1.06E-06
Epithelial_Progenitors.2	Nqo1	1.28E-06
Epithelial_Progenitors.2	Dgkg	1.37E-06
Epithelial_Progenitors.2	Cwh43	1.74E-06
Epithelial_Progenitors.2	Il18	2.16E-06
Epithelial_Progenitors.2	Slc16a9	2.56E-06
Epithelial_Progenitors.2	Sult1b1	3.73E-06
Epithelial_Progenitors.2	Lancl3	4.47E-06
Epithelial_Progenitors.2	Zfp697	6.14E-06
Epithelial_Progenitors.2	Aadac	7.08E-06
Epithelial_Progenitors.2	Hunk	7.24E-06
Epithelial_Progenitors.2	Cmbl	8.86E-06
Epithelial_Progenitors.2	Nceh1	4.17E-05
Epithelial_Progenitors.2	Rnf152	4.40E-05
Epithelial_Progenitors.2	Pgd	4.43E-05
Epithelial_Progenitors.2	Gm43824	4.49E-05
Epithelial_Progenitors.2	Smad6	8.40E-05
Epithelial_Progenitors.2	Slc39a5	1.00E-04
Muscle/ICCs	Sema3a	1.91E-107
Muscle/ICCs	Malat1	1.59E-103
Muscle/ICCs	Smtn	7.23E-100
Muscle/ICCs	Myl9	6.75E-99
Muscle/ICCs	Dlc1	6.91E-99
Muscle/ICCs	Pgm5	2.14E-98
Muscle/ICCs	Pcdh7	2.18E-95
Muscle/ICCs	Myl6	3.36E-93
Muscle/ICCs	Des	1.19E-92
Muscle/ICCs	Csrp1	2.64E-91
Muscle/ICCs	Ppm1e	4.07E-89
Muscle/ICCs	Enah	1.67E-88
Muscle/ICCs	Meis1	1.13E-86
Muscle/ICCs	Atp2b4	2.09E-85
Muscle/ICCs	Itga1	3.04E-83
Muscle/ICCs	Cacna2d1	3.50E-82
Muscle/ICCs	Adam33	2.64E-81
Muscle/ICCs	Hmcn2	1.20E-80
Muscle/ICCs	Sparcl1	1.64E-80
Muscle/ICCs	Sgcd	9.25E-80
Muscle/ICCs	Slc8a1	1.10E-79
Muscle/ICCs	Sorbs1	1.39E-77
Muscle/ICCs	Zfpm2	1.97E-77
Muscle/ICCs	Arhgap6	2.27E-77
Muscle/ICCs	Pde4b	4.38E-75
Muscle/ICCs	Cnn1	5.11E-75
Muscle/ICCs	Ppp1r12b	1.69E-74
Muscle/ICCs	Clmp	2.10E-74
Muscle/ICCs	Myocd	7.66E-74
Muscle/ICCs	Ryr2	9.62E-74
Muscle/ICCs	Pbx3	1.37E-73
Muscle/ICCs	Efna5	5.17E-73
Muscle/ICCs	Fnbp1	3.80E-70
Muscle/ICCs	Msrb3	1.13E-69
Muscle/ICCs	Tns1	3.87E-69
Muscle/ICCs	Epha7	4.02E-69
Muscle/ICCs	Ryr3	4.05E-69
Muscle/ICCs	Abcc9	1.25E-68
Muscle/ICCs	Kcnma1	5.95E-68
Muscle/ICCs	Lmod1	1.91E-66
Muscle/ICCs	Nexn	6.32E-66
Muscle/ICCs	Chrm2	1.48E-64
Muscle/ICCs	Ctnna3	2.02E-64
Muscle/ICCs	Col5a2	3.24E-64
Muscle/ICCs	Prickle1	5.16E-64
Muscle/ICCs	Kcnip1	6.33E-64
Muscle/ICCs	Bnc2	2.55E-63
Muscle/ICCs	Filip1	4.30E-63
Muscle/ICCs	Ckb	1.23E-62
Muscle/ICCs	Akap6	1.86E-62
Muscle/ICCs	Dtna	1.07E-61
Muscle/ICCs	Pdzrn3	1.31E-61
Muscle/ICCs	Pdlim7	1.89E-61
Muscle/ICCs	Tpm2	3.01E-61
Muscle/ICCs	Plcb1	8.98E-61
Muscle/ICCs	Rora	1.01E-59
Muscle/ICCs	Tnc	1.73E-59
Muscle/ICCs	Ppp1r12a	2.53E-58
Muscle/ICCs	Tgfbr3	5.35E-58
Muscle/ICCs	Samd4	1.09E-57
Muscle/ICCs	Antxrl	1.52E-56
Muscle/ICCs	Eml1	1.29E-55
Muscle/ICCs	Nxn	1.67E-55
Muscle/ICCs	Zbtb20	2.83E-55
Muscle/ICCs	Colec12	3.79E-55

Colonocytes.2	Crip1	6.84E-75
Colonocytes.2	Lgals3	1.54E-73
Colonocytes.2	1810065E05Rik	1.00E-72
Colonocytes.2	Fabp2	1.12E-71
Colonocytes.2	Rplp1	2.08E-70
Colonocytes.2	Tmsb4x	2.42E-70
Colonocytes.2	Emp1	3.75E-66
Colonocytes.2	Krt8	2.90E-65
Colonocytes.2	Cox7a2	5.20E-63
Colonocytes.2	Mgat4c	9.61E-63
Colonocytes.2	Gm10073	3.78E-62
Colonocytes.2	Cox6b1	4.80E-62
Colonocytes.2	Chchd10	2.84E-60
Colonocytes.2	Slc6a14	2.52E-59
Colonocytes.2	Plac8	5.58E-59
Colonocytes.2	Slc16a1	2.77E-58
Colonocytes.2	mt-Nd2	2.77E-58
Colonocytes.2	Atp1a1	4.21E-58
Colonocytes.2	Lypd8	6.01E-57
Colonocytes.2	Aqp4	6.94E-56
Colonocytes.2	Slc26a3	1.86E-55
Colonocytes.2	Calm1	4.23E-55
Colonocytes.2	mt-Nd5	4.76E-55
Colonocytes.2	Uqcrh	6.72E-55
Colonocytes.2	Uqcrq	7.34E-55
Colonocytes.2	Uqcr11	2.94E-54
Colonocytes.2	Atp1b1	1.72E-53
Colonocytes.2	Slc26a2	2.86E-53
Colonocytes.2	Bsg	1.11E-52
Colonocytes.2	Gm9843	2.43E-51
Colonocytes.2	Tmbim6	3.06E-51
Colonocytes.2	Ndufa6	4.18E-51
Colonocytes.2	Serf2	8.43E-50
Colonocytes.2	Ethe1	4.11E-49
Colonocytes.2	Atp5j2	4.82E-49
Colonocytes.2	Ftl1	1.11E-48
Colonocytes.2	Prdx6	3.29E-48
Colonocytes.2	Perp	4.22E-48
Colonocytes.2	Ndufa1	5.01E-48
Colonocytes.2	Endod1	3.95E-47
Colonocytes.2	Cdhr5	4.68E-47
Colonocytes.2	Cox5a	6.56E-47
Colonocytes.2	AA467197	7.59E-47
Colonocytes.2	Dmbt1	1.64E-46
Colonocytes.2	mt-Nd4l	1.75E-46
Colonocytes.2	Selenbp1	2.10E-46
Colonocytes.2	2010107E04Rik	4.66E-46
Colonocytes.2	Apol10a	1.39E-45
Colonocytes.2	Rfk	2.51E-45
Colonocytes.2	Cox7c	3.76E-45
Colonocytes.2	Uqcr10	6.31E-44
Colonocytes.2	Mkrn1	9.28E-44
Colonocytes.2	Abhd11os	4.35E-43
Colonocytes.2	Edf1	1.05E-42
Colonocytes.2	Cnnm4	4.52E-42
Colonocytes.2	Cycs	5.38E-42
Colonocytes.2	Mep1a	6.86E-42
Colonocytes.2	Krt19	1.05E-41
Colonocytes.2	Atp5j	1.14E-41
Colonocytes.2	Plec	1.31E-41
Colonocytes.2	S100a10	4.41E-41
Colonocytes.2	Cox5b	4.80E-41
Colonocytes.2	Ndufa2	5.23E-41
Colonocytes.2	Ndufb9	9.33E-41
Colonocytes.2	Cyp2c65	1.03E-40
Colonocytes.2	Atp5e	2.87E-40
Colonocytes.2	Tgoln1	3.20E-40
Colonocytes.2	Epcam	4.73E-40
Colonocytes.2	Cdh17	5.68E-40
Epithelial_Progenitors.2	Maob	1.16E-04
Epithelial_Progenitors.2	Tlr1	1.16E-04
Epithelial_Progenitors.2	Gpr160	1.38E-04
Epithelial_Progenitors.2	Glod5	4.05E-04
Epithelial_Progenitors.2	Cyp4f40	4.14E-04
Epithelial_Progenitors.2	Jag1	4.14E-04
Epithelial_Progenitors.2	Sh3rf2	8.56E-04
Epithelial_Progenitors.2	Sobp	1.25E-03
Epithelial_Progenitors.2	Rassf9	1.42E-03
Epithelial_Progenitors.2	Rgp1	1.53E-03
Epithelial_Progenitors.2	Fzd5	1.83E-03
Epithelial_Progenitors.2	Slc16a5	2.23E-03
Epithelial_Progenitors.2	Fahd1	2.99E-03
Epithelial_Progenitors.2	S100b	3.02E-03
Epithelial_Progenitors.2	Mypop	3.21E-03
Epithelial_Progenitors.2	Pm20d1	4.05E-03
Epithelial_Progenitors.2	E2f5	4.32E-03
Epithelial_Progenitors.2	Mst1r	4.56E-03
Epithelial_Progenitors.2	Arl14	4.98E-03
Epithelial_Progenitors.2	Ddx43	5.64E-03
Epithelial_Progenitors.2	Gm15884	6.31E-03
Epithelial_Progenitors.2	Adap1	7.97E-03
Epithelial_Progenitors.2	Gm12576	3.23E-02
Fibroblast	Celf2	2.95E-111
Fibroblast	Lama2	9.21E-111
Fibroblast	Pcdh7	2.34E-108
Fibroblast	Col3a1	2.98E-97
Fibroblast	Pid1	1.12E-91
Fibroblast	Sdk1	1.67E-86
Fibroblast	Dlc1	3.26E-84
Fibroblast	Tenm3	4.02E-82
Fibroblast	Zeb2	1.40E-76
Fibroblast	Robo2	3.67E-76
Fibroblast	Bmp5	1.77E-70
Fibroblast	Col5a2	2.09E-70
Fibroblast	Slit3	8.92E-66
Fibroblast	Tgfbr3	1.60E-64
Fibroblast	Gpc6	1.27E-59
Fibroblast	Adamdec1	3.41E-59
Fibroblast	Col1a2	2.45E-55
Fibroblast	Robo1	1.63E-53
Fibroblast	Sox5	4.81E-53
Fibroblast	Col6a3	4.13E-52
Fibroblast	Ghr	7.14E-52
Fibroblast	Rora	1.19E-50
Fibroblast	Bicc1	1.86E-50
Fibroblast	Dcn	1.67E-48
Fibroblast	Pdgfra	3.50E-47
Fibroblast	Malat1	9.73E-47
Fibroblast	Cped1	1.43E-45
Fibroblast	Rad51b	2.72E-45
Fibroblast	Negr1	9.63E-45
Fibroblast	Adgrl3	4.12E-44
Fibroblast	Tnc	4.04E-42
Fibroblast	Tshz2	1.33E-40
Fibroblast	Dnm3	1.99E-40
Fibroblast	Fndc1	9.05E-40
Fibroblast	Zbtb20	1.20E-39
Fibroblast	Efemp1	5.04E-39
Fibroblast	Abi3bp	1.03E-38
Fibroblast	Pde1a	2.31E-37
Fibroblast	Rbms3	2.36E-37
Fibroblast	Zbtb16	6.20E-37
Fibroblast	Postn	1.04E-36
Fibroblast	Magi2	1.68E-35
Fibroblast	Pappa	1.84E-35
Fibroblast	Ext1	3.09E-35
Fibroblast	Bmp4	1.29E-34
Fibroblast	Fbn1	1.74E-34
Muscle/ICCs	Cap2	4.50E-53
Muscle/ICCs	Kcnd3	9.63E-53
Muscle/ICCs	Fam129a	6.34E-52
Muscle/ICCs	Pdzrn4	9.83E-52
Muscle/ICCs	Mrvi1	1.92E-51
Muscle/ICCs	Itga5	1.59E-50
Muscle/ICCs	Magi2	5.25E-50
Muscle/ICCs	Ltbp1	1.05E-48
Muscle/ICCs	Dpp10	5.28E-47
Muscle/ICCs	Dmpk	8.80E-47
Muscle/ICCs	Satb1	4.09E-46
Muscle/ICCs	Wscd2	8.36E-42
Muscle/ICCs	Ppp1r14a	4.34E-41
Muscle/ICCs	Cnn2	6.67E-40
Muscle/ICCs	Gm10848	1.39E-39
Muscle/ICCs	Jph2	2.41E-39
Muscle/ICCs	Hspb1	1.21E-38
Muscle/ICCs	Pamr1	1.50E-34
Muscle/ICCs	Klhl23	1.53E-33
Muscle/ICCs	Grem2	8.70E-33
Muscle/ICCs	Rspo3	3.10E-32
Muscle/ICCs	A630023A22Rik	4.47E-32
Muscle/ICCs	Slc7a8	1.33E-31
Muscle/ICCs	C1qtnf7	2.11E-31
Muscle/ICCs	Mapk4	2.40E-30
Muscle/ICCs	Flnc	1.17E-28
Muscle/ICCs	Mcam	2.81E-28
Muscle/ICCs	Rgs5	8.47E-28
Muscle/ICCs	Frem2	1.41E-27
Muscle/ICCs	Tspan2	5.23E-27
Muscle/ICCs	Fgf10	9.11E-27
Muscle/ICCs	Ptn	6.40E-26
Muscle/ICCs	Cspg4	9.45E-26
Muscle/ICCs	Rgs1	1.16E-25
Muscle/ICCs	Gem	1.82E-24
Muscle/ICCs	Fendrr	4.06E-24
Muscle/ICCs	Atcayos	1.44E-23
Muscle/ICCs	Mab21l2	9.14E-22
Muscle/ICCs	Slc2a4	3.00E-21
Muscle/ICCs	Aoc3	1.89E-20
Muscle/ICCs	Tgfb1i1	2.32E-20
Muscle/ICCs	Gm13269	9.26E-20
Muscle/ICCs	Scube2	9.64E-20
Muscle/ICCs	Kcnj8	1.03E-19
Muscle/ICCs	Slc6a17	1.98E-19
Muscle/ICCs	Mettl24	1.55E-17
Muscle/ICCs	Kcnb1	2.15E-16
Muscle/ICCs	Pln	4.42E-15
Muscle/ICCs	Ctxn3	4.33E-14
Muscle/ICCs	Colec10	6.01E-14
Muscle/ICCs	Gm16141	1.53E-13
Muscle/ICCs	Kcnmb1	4.05E-13
Muscle/ICCs	Cyr61	7.09E-13
Muscle/ICCs	Igfbp2	1.15E-12
Muscle/ICCs	Olfml2b	1.20E-12
Muscle/ICCs	Actn2	1.65E-12
Muscle/ICCs	Nkd1	1.96E-12
Muscle/ICCs	Grem1	5.23E-12
Muscle/ICCs	Lrch2	5.81E-12
Muscle/ICCs	Adrb3	3.88E-11
Muscle/ICCs	Egflam	1.16E-10
Muscle/ICCs	Trnp1	1.92E-09
Muscle/ICCs	Il17d	3.67E-09
Muscle/ICCs	Cyp7b1	4.35E-09
Muscle/ICCs	Shisa4	2.84E-08
Muscle/ICCs	Dkk2	4.32E-08
Muscle/ICCs	A630012P03Rik	5.46E-08
Neuron	Syt1	1.08E-136
Neuron	Snap25	2.16E-136

Colonocytes.2	Minos1	5.94E-40
Colonocytes.2	Ceacam1	2.63E-39
Colonocytes.2	Krt20	4.49E-39
Colonocytes.2	Ahnak	2.84E-38
Colonocytes.2	Spint2	4.08E-38
Colonocytes.2	Psap	4.24E-38
Colonocytes.2	Gpx1	4.36E-38
Colonocytes.2	Tmsb10	4.87E-38
Colonocytes.2	Txn1	5.46E-38
Colonocytes.2	Mgst3	9.65E-38
Colonocytes.2	Cox7b	1.09E-37
Colonocytes.2	Itm2b	1.52E-37
Colonocytes.2	Tspan1	3.45E-37
Colonocytes.2	Ces2e	5.43E-35
Colonocytes.2	Entpd5	7.35E-34
Colonocytes.2	Slc35g1	3.66E-32
Colonocytes.2	Cwh43	7.28E-31
Colonocytes.2	Mall	4.17E-29
Colonocytes.2	Sptssb	5.20E-29
Colonocytes.2	Smim24	9.42E-29
Colonocytes.2	Plpp2	1.14E-27
Colonocytes.2	Fzd5	1.39E-27
Colonocytes.2	Ndufa8	1.52E-27
Colonocytes.2	Gm3336	9.80E-27
Colonocytes.2	Slc27a4	1.70E-26
Colonocytes.2	Prdx5	1.91E-26
Colonocytes.2	Lad1	6.16E-26
Colonocytes.2	Cox7a1	1.22E-25
Colonocytes.2	1810043H04Rik	1.32E-25
Colonocytes.2	Nlrp4e	5.08E-25
Colonocytes.2	Abcb6	5.63E-25
Colonocytes.2	Lipg	2.92E-21
Colonocytes.2	Slc9a3r1	2.96E-21
Colonocytes.2	Erbb2	7.09E-21
Colonocytes.2	Ermp1	1.93E-19
Colonocytes.2	Cyp4f14	4.35E-19
Colonocytes.2	Apob	7.24E-19
Colonocytes.2	H2-Q2	1.05E-18
Colonocytes.2	Fam83h	3.46E-18
Colonocytes.2	Gm5617	3.16E-17
Colonocytes.2	Ube2m	3.91E-17
Colonocytes.2	Prap1	1.18E-16
Colonocytes.2	Adra2a	1.04E-15
Colonocytes.2	Rab8a	3.37E-15
Colonocytes.2	Cyp2c69	4.20E-14
Colonocytes.2	Slc51b	6.72E-14
Colonocytes.2	Tmem252	1.68E-13
Colonocytes.2	Srxn1	2.87E-13
Colonocytes.2	S100g	6.70E-13
Colonocytes.2	Slc39a4	7.22E-13
Colonocytes.2	Tmigd1	3.34E-12
Colonocytes.2	Txnl4a	4.23E-12
Colonocytes.2	Akr1b8	5.62E-12
Colonocytes.2	Edn2	6.33E-12
Colonocytes.2	Slc51a	8.64E-12
Colonocytes.2	Aldob	1.39E-11
Colonocytes.2	Ankrd50	7.05E-11
Colonocytes.2	Cda	8.44E-11
Colonocytes.2	Slc22a19	1.05E-10
Colonocytes.2	Slc39a3	1.81E-10
Colonocytes.2	Slc30a1	3.43E-10
Colonocytes.2	Akr1c12	1.12E-09
Colonocytes.2	Ehd1	4.59E-09
Colonocytes.2	Gsta1	8.46E-09
Colonocytes.2	Rxra	2.77E-08
Colonocytes.2	Hkdc1	5.17E-08
Colonocytes.2	mt-Nd6	2.24E-07
Colonocytes.2	Mal	7.51E-07
Colonocytes.2	Ttll12	1.22E-06
Colonocytes.2	Gm44026	2.05E-06

Fibroblast	Bmp6	3.77E-34
Fibroblast	Arhgap6	3.86E-34
Fibroblast	Dpt	5.92E-34
Fibroblast	Fstl1	7.65E-34
Fibroblast	Pcdh9	1.27E-33
Fibroblast	Col1a1	3.43E-33
Fibroblast	Tcf4	4.30E-33
Fibroblast	Pdzrn3	1.50E-32
Fibroblast	Zfpm2	2.78E-32
Fibroblast	Chsy3	3.29E-32
Fibroblast	Fmnl2	3.40E-32
Fibroblast	Hmcn2	8.92E-32
Fibroblast	Prr16	1.27E-31
Fibroblast	Sparc	1.54E-31
Fibroblast	Arhgap10	4.01E-31
Fibroblast	Aspn	6.11E-31
Fibroblast	9530026P05Rik	9.51E-31
Fibroblast	Bnc2	1.24E-30
Fibroblast	Prickle1	1.95E-30
Fibroblast	Fbxl7	2.88E-30
Fibroblast	Igfbp7	3.48E-30
Fibroblast	Lamc1	4.59E-30
Fibroblast	Rhoj	9.29E-30
Fibroblast	Ebf1	1.51E-29
Fibroblast	Meis2	1.55E-29
Fibroblast	Gsn	4.64E-29
Fibroblast	Rbpms	5.71E-29
Fibroblast	Eln	1.02E-28
Fibroblast	Gli3	2.55E-28
Fibroblast	Nav1	5.31E-28
Fibroblast	Zeb1	7.36E-28
Fibroblast	Svep1	8.37E-28
Fibroblast	Col6a1	1.29E-27
Fibroblast	Lhfp	1.52E-27
Fibroblast	Ncam1	1.74E-27
Fibroblast	Serping1	1.77E-27
Fibroblast	Col6a2	2.04E-27
Fibroblast	Fbln1	3.36E-27
Fibroblast	Nckap5	1.03E-26
Fibroblast	Ddr2	4.55E-26
Fibroblast	Meg3	8.59E-26
Fibroblast	Rbms1	1.16E-25
Fibroblast	Gm26719	3.82E-25
Fibroblast	Vcan	5.59E-25
Fibroblast	Ldlrad4	9.33E-25
Fibroblast	Mast4	1.96E-24
Fibroblast	Abca8a	3.72E-24
Fibroblast	Meis1	9.19E-24
Fibroblast	Tcf21	2.30E-23
Fibroblast	Cald1	3.06E-23
Fibroblast	Lama4	3.45E-23
Fibroblast	Akt3	3.77E-23
Fibroblast	Prickle2	4.55E-23
Fibroblast	Arhgap28	1.34E-22
Fibroblast	Bgn	1.13E-21
Fibroblast	Ccdc80	2.64E-21
Fibroblast	Axl	2.92E-21
Fibroblast	Lamb1	2.23E-20
Fibroblast	Htra3	3.61E-19
Fibroblast	Serpinh1	9.76E-19
Fibroblast	Mmp2	1.41E-18
Fibroblast	Pla2r1	1.62E-18
Fibroblast	4930467D21Rik	1.95E-18
Fibroblast	Spon2	2.65E-18
Fibroblast	Fam198b	9.64E-17
Fibroblast	Tshz3	2.36E-16
Fibroblast	Lum	6.68E-16
Fibroblast	Clec3b	6.70E-16
Fibroblast	Scube1	1.03E-15
Fibroblast	Ptgs1	2.70E-15

Neuron	Snhg11	7.18E-136
Neuron	Elavl4	2.69E-130
Neuron	Ank2	2.11E-121
Neuron	Map1b	1.05E-120
Neuron	Rab3c	3.69E-120
Neuron	Fgf13	3.76E-119
Neuron	Slc7a14	5.37E-119
Neuron	Celf4	2.13E-117
Neuron	Ncam2	2.76E-114
Neuron	Kcnq3	5.28E-112
Neuron	Dpp6	1.99E-111
Neuron	Cntn1	2.21E-110
Neuron	Fam155a	5.59E-110
Neuron	Pcbp3	1.20E-108
Neuron	Mapk10	1.26E-107
Neuron	Rtn1	1.39E-103
Neuron	Prph	1.62E-102
Neuron	Nrg3	1.62E-102
Neuron	Ctnna2	4.56E-102
Neuron	Kcnc2	2.12E-101
Neuron	Cadm1	9.82E-101
Neuron	Rit2	1.68E-100
Neuron	Elavl3	3.01E-100
Neuron	Sgip1	4.63E-100
Neuron	Khdrbs2	2.48E-99
Neuron	Clvs1	6.47E-98
Neuron	Ncam1	3.88E-97
Neuron	Nrxn1	4.30E-97
Neuron	Fgf14	1.26E-96
Neuron	Ppfia2	5.48E-96
Neuron	Mdga2	3.03E-95
Neuron	Stmn2	1.09E-94
Neuron	Gabrb3	1.61E-94
Neuron	Pcdh15	2.92E-94
Neuron	Kcnip4	3.64E-94
Neuron	Gria4	4.20E-94
Neuron	Lrfn5	8.08E-94
Neuron	Kif5a	9.38E-94
Neuron	Spock2	1.05E-93
Neuron	Map2	4.06E-93
Neuron	Lrrtm4	9.41E-93
Neuron	Gria2	2.28E-92
Neuron	Enah	1.04E-91
Neuron	Nrg3os	2.03E-91
Neuron	Ptprn	2.92E-91
Neuron	Pclo	5.01E-91
Neuron	Cadps	1.32E-90
Neuron	Nav3	3.22E-90
Neuron	Kcnb2	1.05E-89
Neuron	Negr1	2.19E-89
Neuron	Akap6	5.81E-89
Neuron	Garnl3	6.56E-89
Neuron	Erc2	1.12E-87
Neuron	Kcnt2	1.39E-87
Neuron	Unc79	1.47E-87
Neuron	Myt1l	1.14E-86
Neuron	Cdh2	2.71E-86
Neuron	Fstl5	3.50E-86
Neuron	Grid2	5.07E-86
Neuron	Dgki	1.42E-85
Neuron	Dscam	3.83E-85
Neuron	Sntg1	3.04E-84
Neuron	Mapt	4.60E-84
Neuron	Nrxn2	6.12E-83
Neuron	Eml5	2.15E-82
Neuron	Fam163a	4.82E-82
Neuron	Stmn3	6.69E-82
Neuron	Pcsk1n	1.08E-81
Neuron	Chrna3	1.04E-80
Neuron	Snap91	1.04E-80

Colonocytes.2	Hsd17b13	2.27E-06
Colonocytes.2	Chp2	4.56E-06
Colonocytes.2	Vps4a	5.78E-06
Colonocytes.2	Fzd8	1.19E-05
Colonocytes.2	2010003K11Rik	3.31E-05
Colonocytes.2	Gm42562	2.80E-04
Colonocytes.2	Lsm14b	2.80E-04
Colonocytes.2	Cdc42ep2	2.85E-04
Colonocytes.2	Rbp2	3.14E-03
Endothelial	Mmrn1	6.76E-152
Endothelial	Reln	3.16E-148
Endothelial	Ccl21a	3.25E-125
Endothelial	Nxn	2.60E-117
Endothelial	Galnt18	1.05E-109
Endothelial	Ldb2	6.41E-108
Endothelial	Lyve1	2.93E-103
Endothelial	Prex2	2.22E-97
Endothelial	Ebf1	2.17E-94
Endothelial	Rbms1	3.54E-94
Endothelial	Timp3	5.88E-91
Endothelial	Cp	6.48E-87
Endothelial	Cldn5	1.45E-85
Endothelial	Pecam1	1.35E-79
Endothelial	Fmnl2	1.35E-79
Endothelial	Rhoj	2.25E-78
Endothelial	Abi3bp	1.21E-77
Endothelial	Pitpnc1	1.32E-76
Endothelial	Kank3	2.95E-76
Endothelial	Igfbp5	3.45E-74
Endothelial	Fgl2	3.20E-71
Endothelial	Sema6a	5.21E-71
Endothelial	Wdr17	7.84E-71
Endothelial	Ntn1	1.18E-69
Endothelial	Sptbn1	4.92E-69
Endothelial	Podxl	2.05E-67
Endothelial	Wipf3	1.97E-65
Endothelial	Elk3	7.59E-62
Endothelial	Pard6g	1.11E-61
Endothelial	Lama4	1.91E-61
Endothelial	Shank3	6.40E-61
Endothelial	Tshz2	1.17E-59
Endothelial	Sema3d	1.60E-58
Endothelial	Cyyr1	4.67E-58
Endothelial	Dlg1	4.67E-58
Endothelial	Flt4	1.49E-57
Endothelial	Emcn	3.49E-57
Endothelial	Thsd7a	2.49E-56
Endothelial	Dock9	1.03E-55
Endothelial	4930448N21Rik	2.05E-55
Endothelial	Utrn	2.95E-55
Endothelial	Ptprm	3.22E-54
Endothelial	Ece1	4.01E-53
Endothelial	Dock4	2.71E-52
Endothelial	Tspan9	7.97E-52
Endothelial	Piezo2	2.08E-51
Endothelial	Zfpm2	5.82E-51
Endothelial	Fgd5	9.17E-51
Endothelial	D5Ertd615e	4.61E-50
Endothelial	Sdpr	5.57E-50
Endothelial	9330175M20Rik	6.46E-50
Endothelial	Tll1	6.23E-49
Endothelial	Adgrg3	6.44E-49
Endothelial	Maf	7.24E-49
Endothelial	Etl4	9.60E-49
Endothelial	Malat1	2.60E-47
Endothelial	Calcrl	3.63E-47
Endothelial	Adgrl4	1.70E-46
Endothelial	Prox1	1.81E-46
Endothelial	Nfat5	1.96E-46
Endothelial	Cped1	3.37E-46
Fibroblast	Mfap5	8.75E-15
Fibroblast	Hgf	9.90E-15
Fibroblast	Dnm3os	1.27E-14
Fibroblast	Emid1	3.83E-14
Fibroblast	Cxcl12	5.76E-14
Fibroblast	Pi16	6.28E-14
Fibroblast	Bdkrb2	1.11E-13
Fibroblast	Fam20a	1.76E-13
Fibroblast	Tmem119	1.99E-13
Fibroblast	Gm42532	2.16E-13
Fibroblast	Mgp	2.16E-13
Fibroblast	Ednra	3.59E-13
Fibroblast	Mfap4	9.12E-13
Fibroblast	Gli2	1.06E-12
Fibroblast	Col15a1	1.19E-12
Fibroblast	Cygb	2.75E-12
Fibroblast	Col4a6	5.07E-12
Fibroblast	Nova1	5.09E-12
Fibroblast	Col24a1	1.06E-11
Fibroblast	Srpx2	9.65E-11
Fibroblast	Cilp	1.55E-10
Fibroblast	Ms4a4d	1.63E-10
Fibroblast	Ereg	1.98E-10
Fibroblast	Cml3	6.21E-09
Fibroblast	Pcolce	7.25E-09
Fibroblast	Ednrb	1.08E-08
Fibroblast	Olfml2b	4.37E-08
Fibroblast	Sfrp1	1.93E-07
Fibroblast	Jam2	2.36E-07
Fibroblast	Lama1	3.83E-07
Fibroblast	Naa11	4.26E-07
Fibroblast	Enpp2	4.31E-07
Fibroblast	Podn	4.33E-07
Fibroblast	Col5a3	6.36E-07
Fibroblast	Adamts5	8.81E-07
Fibroblast	C1qtnf7	1.40E-06
Fibroblast	Cyp7b1	1.64E-06
Fibroblast	Prkcdbp	2.99E-06
Fibroblast	Syt13	5.85E-06
Glia	Cdh19	9.31E-191
Glia	Nkain2	5.05E-184
Glia	Slc35f1	2.42E-180
Glia	Ncam1	4.01E-145
Glia	Ptprz1	2.38E-144
Glia	Grik2	1.52E-133
Glia	Ppp2r2b	6.24E-129
Glia	Kcnq5	5.36E-124
Glia	Dtna	1.04E-121
Glia	Lrrc4c	1.63E-110
Glia	Sorcs1	1.74E-107
Glia	Ank3	4.51E-105
Glia	Rora	5.26E-103
Glia	Col11a1	1.49E-102
Glia	Plce1	2.77E-102
Glia	Il1rapl1	4.82E-95
Glia	Sntb1	5.57E-93
Glia	Adam23	9.22E-90
Glia	Adgrl3	1.48E-89
Glia	Zeb2	1.83E-88
Glia	Sgip1	2.81E-87
Glia	Cdh2	8.15E-86
Glia	Plcb1	5.43E-81
Glia	Scn7a	8.03E-80
Glia	Col12a1	1.48E-79
Glia	Etl4	2.23E-79
Glia	Gfra1	2.36E-79
Glia	Tgfb2	5.69E-77
Glia	Csmd1	1.01E-75
Glia	Adam11	3.26E-74
Glia	Glp2r	4.42E-73
Neuron	Ndst4	3.20E-80
Neuron	Scg2	3.99E-80
Neuron	Frmd4a	7.91E-80
Neuron	Reep1	8.89E-80
Neuron	Unc80	1.01E-79
Neuron	Ctnnd2	1.67E-79
Neuron	Hmgn3	2.09E-79
Neuron	Syt11	3.94E-79
Neuron	Gabrg3	6.68E-78
Neuron	Nap1l5	1.15E-77
Neuron	Trpm3	1.28E-77
Neuron	Ret	1.35E-77
Neuron	Cacna2d1	1.96E-77
Neuron	Pcsk2	2.08E-77
Neuron	Dlg2	5.68E-77
Neuron	Ppp2r2b	6.81E-77
Neuron	Fhod3	8.09E-77
Neuron	Nsg2	8.13E-77
Neuron	Rbms3	4.66E-76
Neuron	Ahi1	6.16E-76
Neuron	Pirt	1.28E-75
Neuron	Kcnd2	1.42E-75
Neuron	Meg3	5.86E-75
Neuron	Lix1	6.30E-75
Neuron	Chrm2	2.12E-74
Neuron	Prkcb	2.49E-74
Neuron	Celf3	4.29E-74
Neuron	Scn3a	6.64E-74
Neuron	Ina	2.47E-60
Neuron	Hs3st2	1.45E-56
Neuron	Tmem179	8.08E-54
Neuron	Mapk8ip2	6.72E-52
Neuron	Doc2b	3.76E-49
Neuron	Gdap1	3.08E-48
Neuron	Gpr22	1.62E-45
Neuron	Rims3	1.62E-45
Neuron	P2rx2	1.27E-44
Neuron	Atp2b3	6.29E-42
Neuron	Vgf	1.64E-37
Neuron	Cend1	1.64E-37
Neuron	Golga7b	9.28E-36
Neuron	Ap3b2	9.28E-36
Neuron	Oprk1	6.95E-35
Neuron	Clip3	6.95E-35
Neuron	Dusp26	5.06E-34
Neuron	Tmem59l	5.06E-34
Neuron	Tpbgl	5.06E-34
Neuron	Gm11418	2.69E-32
Neuron	Slc10a4	2.69E-32
Neuron	Abcg4	1.99E-31
Neuron	Hpcal4	1.44E-30
Neuron	Pnmal1	1.44E-30
Neuron	Kcnc1	1.44E-30
Neuron	Elovl4	1.04E-29
Neuron	Ly6h	7.28E-29
Neuron	Slc35d3	5.17E-28
Neuron	Celsr3	5.17E-28
Neuron	Lhfpl4	3.63E-27
Neuron	Schip1	3.63E-27
Neuron	Rprml	2.54E-26
Neuron	Cnih2	2.54E-26
Neuron	Cartpt	1.76E-25
Neuron	Htr3a	1.76E-25
Neuron	Arhgdig	1.76E-25
Neuron	Necab2	1.76E-25
Neuron	Rnf112	1.76E-25
Neuron	Sprn	1.21E-24
Neuron	Sncb	5.64E-23
Neuron	Tro	5.64E-23
Neuron	Sycp2	5.64E-23

Endothelial	Gab2	4.41E-46
Endothelial	Hspa12b	8.92E-46
Endothelial	Cav1	2.05E-45
Endothelial	Prkg1	3.22E-43
Endothelial	Gm2163	3.92E-43
Endothelial	Tanc2	2.85E-42
Endothelial	Tns1	3.06E-42
Endothelial	Kalrn	8.19E-42
Endothelial	Meis2	9.32E-42
Endothelial	Dennd4a	1.97E-41
Endothelial	Ppp1r2	2.42E-41
Endothelial	Zfp521	3.09E-41
Endothelial	Hip1	4.51E-41
Endothelial	Adamtsl1	4.99E-41
Endothelial	Stxbp6	2.89E-40
Endothelial	Cdh5	1.44E-39
Endothelial	Arap3	1.81E-39
Endothelial	Gpm6a	3.78E-39
Endothelial	Arhgap31	1.37E-38
Endothelial	Tcf4	3.24E-38
Endothelial	Zbtb20	8.63E-38
Endothelial	Sncaip	1.16E-37
Endothelial	Arhgap29	2.61E-37
Endothelial	Prkch	3.29E-37
Endothelial	Grk5	5.49E-37
Endothelial	Tmtc1	1.68E-36
Endothelial	Prelp	5.42E-36
Endothelial	Tmsb4x	6.44E-36
Endothelial	Elmo1	2.28E-35
Endothelial	Dysf	3.84E-35
Endothelial	Ptprb	5.48E-35
Endothelial	Ltbp4	8.26E-35
Endothelial	Osmr	3.53E-34
Endothelial	Tgfbr2	3.92E-34
Endothelial	Arl15	2.60E-33
Endothelial	Ppfibp1	9.71E-33
Endothelial	Ackr3	1.94E-32
Endothelial	Syne1	2.33E-32
Endothelial	Ifitm3	2.72E-32
Endothelial	Trpc3	6.15E-32
Endothelial	Slco2b1	7.30E-31
Endothelial	Palm	1.87E-30
Endothelial	S1pr1	8.04E-30
Endothelial	Lbp	1.25E-29
Endothelial	Eng	7.13E-29
Endothelial	Flt1	9.71E-27
Endothelial	Gucy1b3	5.38E-26
Endothelial	Adgrf5	7.37E-26
Endothelial	Ramp2	2.93E-25
Endothelial	4930578C19Rik	4.98E-25
Endothelial	Nhsl2	5.93E-25
Endothelial	Ecscr	7.38E-25
Endothelial	Kdr	1.09E-24
Endothelial	Thsd1	1.28E-24
Endothelial	Tie1	2.13E-23
Endothelial	Pkhd1l1	2.13E-23
Endothelial	Ushbp1	6.36E-23
Endothelial	Ets1	2.88E-22
Endothelial	Stab1	6.10E-22
Endothelial	Lmo2	3.35E-20
Endothelial	Btnl9	4.22E-20
Endothelial	Parvb	7.19E-19
Endothelial	Cd300lg	1.36E-18
Endothelial	Tbx1	1.01E-17
Endothelial	Dtx1	2.42E-17
Endothelial	Sh3gl3	4.92E-17
Endothelial	Slc10a6	5.94E-16
Endothelial	Sema3f	6.89E-16
Endothelial	4833422C13Rik	1.67E-15

Glia	Dmd	4.13E-72
Glia	Sox5	2.44E-71
Glia	Ncam2	2.59E-70
Glia	Kif21a	3.60E-70
Glia	Sorbs1	1.69E-67
Glia	Pmepa1	1.83E-67
Glia	Hmcn1	1.83E-67
Glia	Chl1	4.51E-67
Glia	Qk	2.37E-64
Glia	Sox10	8.41E-64
Glia	Nrg3	1.24E-63
Glia	Dock10	1.44E-62
Glia	Dlgap1	1.72E-62
Glia	Lsamp	4.02E-62
Glia	Agmo	1.40E-60
Glia	Tmprss5	6.64E-59
Glia	Ctnna3	2.00E-58
Glia	Ltbp1	2.19E-58
Glia	Zfp536	3.40E-57
Glia	Igsf11	4.05E-56
Glia	Sparc	2.78E-55
Glia	Erc2	3.88E-54
Glia	Col18a1	5.37E-54
Glia	Art3	8.85E-54
Glia	Grb14	1.13E-53
Glia	Fign	1.41E-52
Glia	Zbtb20	1.89E-52
Glia	Pde7b	2.18E-52
Glia	Lpar1	2.18E-52
Glia	Sorbs2	4.10E-52
Glia	Ank2	9.14E-52
Glia	Ggta1	2.68E-51
Glia	Ldlrad4	6.70E-51
Glia	Gpcpd1	7.86E-51
Glia	Malat1	9.66E-51
Glia	Lrrtm3	1.21E-49
Glia	Sema3e	1.95E-48
Glia	Tbx3os1	2.55E-48
Glia	Sgcd	3.39E-48
Glia	P3h2	1.04E-47
Glia	Agbl4	1.22E-46
Glia	Apoe	3.14E-46
Glia	Klhl29	9.22E-46
Glia	Atp1a2	1.32E-45
Glia	Zfhx4	6.25E-45
Glia	Prkg1	1.69E-44
Glia	Gm10863	5.06E-43
Glia	Pdzd2	1.34E-42
Glia	Stk32a	2.06E-42
Glia	Fxyd1	4.68E-42
Glia	Dst	6.15E-42
Glia	Abca8a	1.02E-41
Glia	Lgi4	1.44E-41
Glia	Efna5	1.86E-41
Glia	Ablim2	3.69E-41
Glia	Tanc2	4.20E-41
Glia	Piezo2	5.91E-41
Glia	Adam12	6.33E-41
Glia	Gm38505	7.40E-41
Glia	Adarb2	1.64E-40
Glia	Plxdc2	3.30E-40
Glia	Celf2	7.79E-40
Glia	Zeb1	1.65E-39
Glia	Plxna4	4.91E-38
Glia	Fam184b	7.20E-38
Glia	Ldb2	3.07E-37
Glia	Limch1	2.43E-36
Glia	Edil3	4.73E-36
Glia	Gpam	1.22E-35

Neuron	Elmod1	3.85E-22
Neuron	Cdk5r2	3.85E-22
Neuron	Gm38112	2.60E-21
Neuron	Gm10419	2.60E-21
Neuron	Elavl2	1.75E-20
Neuron	Shc2	1.75E-20
Neuron	Tmc3	1.17E-19
Neuron	Lhfpl5	1.17E-19
Neuron	Rab9b	7.67E-19
Neuron	Frrs1l	7.67E-19
Neuron	Brsk2	7.67E-19
Neuron	Bglap	5.10E-18
Neuron	Rltpr	5.10E-18
Neuron	Mir124a-1hg	5.10E-18
Neuron	Rtn2	3.34E-17
Neuron	Gpr27	3.34E-17
Neuron	Srsf12	3.34E-17
Neuron	Oprl1	3.34E-17
Neuron	Tmem121	3.34E-17
Neuron	Nefh	3.34E-17
Neuron	Ttc9b	2.18E-16
Neuron	Kcnc4	2.18E-16
Neuron	Pcsk2os1	2.18E-16
Neuron	Fam131b	2.18E-16
Neuron	Sox11	1.43E-15
Neuron	Tram1l1	1.43E-15
Neuron	Ankrd45	1.43E-15
Neuron	Calcb	9.33E-15
Neuron	Dbh	9.33E-15
Neuron	Fbxw15	9.33E-15
Neuron	Mfap2	9.33E-15
Neuron	Epha8	9.33E-15
Neuron	Inha	9.33E-15
Neuron	Rasl10b	6.02E-14
Neuron	Adcy1	6.02E-14
Neuron	Slitrk5	6.02E-14
Neuron	RP23-291B1.2	3.87E-13
Neuron	Fibcd1	3.87E-13
Neuron	Diras1	3.87E-13
Neuron	Gm10605	2.50E-12
Neuron	Ephb6	2.50E-12
Neuron	Prokr1	2.50E-12
Neuron	Gpr61	2.50E-12
Neuron	Tmem145	2.50E-12
Neuron	Oxtr	1.60E-11
Neuron	Nudt11	1.60E-11
Neuron	Kcnv1	1.60E-11
Neuron	Grp	1.02E-10
Neuron	Islr2	1.02E-10
Neuron	Gm11342	1.02E-10
Neuron	Gm37640	1.02E-10
Neuron	Cngb1	1.02E-10
Neuron	Zkscan2	1.02E-10
Neuron	Kcnj5	6.51E-10
Neuron	Cbln2	4.08E-09
Neuron	Slc17a6	4.08E-09
Neuron	Zik1	4.08E-09
Neuron	Gm12130	4.08E-09
T_cells	Mir142hg	1.00E-153
T_cells	Arhgap15	5.67E-127
T_cells	Hmha1	9.54E-116
T_cells	Ebf1	2.66E-93
T_cells	Ptprc	5.64E-88
T_cells	Gm26740	3.29E-86
T_cells	Bank1	5.56E-82
T_cells	Gm43291	2.71E-81
T_cells	Ikzf3	5.21E-72
T_cells	Gimap6	5.89E-69
T_cells	Dock2	1.71E-66

Endothelial	Apba2	6.23E-15
Endothelial	Sept4	1.26E-14
Endothelial	Iigp1	2.11E-14
Endothelial	Ackr2	3.13E-14
Endothelial	Cyp4b1	5.77E-14
Endothelial	Scn1b	6.04E-14
Endothelial	4930578G10Rik	8.28E-14
Endothelial	Gprc5b	1.20E-13
Endothelial	Erg	2.87E-13
Endothelial	D830026I12Rik	3.53E-13
Endothelial	Lrg1	1.16E-12
Endothelial	Apold1	1.22E-12
Endothelial	Ly6c1	3.59E-12
Endothelial	Tal1	3.90E-12
Endothelial	Islr2	6.84E-12
Endothelial	Thbd	1.49E-11
Endothelial	Gpihbp1	4.40E-11
Endothelial	Clec1a	5.33E-11
Endothelial	Ecm2	9.67E-11
Endothelial	Arhgef15	4.77E-10
Endothelial	Slfn3	5.88E-10
Endothelial	Cd93	6.88E-10
Endothelial	She	9.89E-10
Endothelial	Fmnl3	2.50E-08
Endothelial	Plvap	6.80E-07
Enteroendocrine	Kcnb2	2.07E-89
Enteroendocrine	Chgb	5.11E-76
Enteroendocrine	Cadps	5.11E-76
Enteroendocrine	Rimbp2	1.18E-73
Enteroendocrine	Chga	3.34E-72
Enteroendocrine	Snap25	1.25E-69
Enteroendocrine	Scn3a	1.31E-66
Enteroendocrine	Rgs7	1.71E-61
Enteroendocrine	Slc38a11	3.57E-60
Enteroendocrine	Adcy2	4.94E-57
Enteroendocrine	Cacna2d1	5.09E-55
Enteroendocrine	Ctnna2	1.10E-54
Enteroendocrine	Cacna1a	2.67E-54
Enteroendocrine	Runx1t1	5.85E-54
Enteroendocrine	Ddc	5.85E-54
Enteroendocrine	1700042O10Rik	3.50E-53
Enteroendocrine	Cerkl	4.85E-51
Enteroendocrine	Nrxn1	4.69E-50
Enteroendocrine	Rfx6	8.58E-48
Enteroendocrine	Tph1	1.91E-44
Enteroendocrine	Ptprn2	4.21E-42
Enteroendocrine	Pyy	8.13E-42
Enteroendocrine	Cpe	1.64E-41
Enteroendocrine	Lmx1a	7.23E-41
Enteroendocrine	Gm609	3.05E-40
Enteroendocrine	Fam19a1	2.80E-38
Enteroendocrine	Vwa5b2	5.28E-38
Enteroendocrine	Map2	5.71E-38
Enteroendocrine	Rab3c	9.55E-37
Enteroendocrine	Pam	2.40E-36
Enteroendocrine	St18	9.47E-36
Enteroendocrine	Rfx3	7.40E-34
Enteroendocrine	Slc18a1	8.62E-34
Enteroendocrine	Pcsk1n	2.76E-33
Enteroendocrine	Fam105a	4.66E-33
Enteroendocrine	Gcg	6.45E-32
Enteroendocrine	Map1b	5.03E-31
Enteroendocrine	Pclo	4.64E-30
Enteroendocrine	Sct	5.19E-30
Enteroendocrine	Enox1	9.64E-30
Enteroendocrine	Rora	1.23E-29
Glia	Rerg	6.40E-34
Glia	Gpm6b	4.06E-33
Glia	Plp1	7.87E-33
Glia	Pxdn	3.60E-32
Glia	Shc4	2.10E-31
Glia	Hand2	7.95E-31
Glia	Fam19a5	8.13E-31
Glia	Astn1	6.42E-30
Glia	Abca8b	1.65E-29
Glia	Kcna1	4.26E-29
Glia	Armc2	5.27E-29
Glia	S1pr3	7.62E-27
Glia	Cd59a	1.12E-26
Glia	Gfap	8.52E-26
Glia	Gpr37l1	1.17E-25
Glia	Olfml2a	9.82E-25
Glia	Ctgf	1.07E-24
Glia	Mest	4.56E-24
Glia	Kcna6	5.82E-24
Glia	Gm11099	2.22E-22
Glia	Nme5	1.48E-20
Glia	Cmtm5	2.96E-19
Glia	Kcna2	1.65E-18
Glia	Ttyh1	1.96E-18
Glia	Gjc3	3.42E-18
Glia	C130071C03Rik	3.43E-18
Glia	Snca	7.80E-18
Glia	Islr	8.95E-18
Glia	Itgb8	1.47E-15
Glia	Lrrn2	2.00E-15
Glia	Gfra2	3.32E-15
Glia	Kcnip3	1.01E-14
Glia	Scrn1	1.28E-14
Glia	P4ha3	2.19E-14
Glia	Col9a2	4.27E-14
Glia	Pdgfb	5.44E-14
Glia	Plxnb3	3.20E-13
Glia	Frzb	5.61E-13
Glia	Lrriq1	6.28E-13
Glia	Hey2	9.19E-13
Glia	Sostdc1	6.03E-12
Glia	Slitrk6	6.03E-12
Glia	Kcnj10	7.57E-12
Glia	Drc1	1.03E-11
Glia	Srcin1	1.75E-11
Glia	Gm12688	1.97E-11
Glia	9630001P10Rik	2.90E-11
Glia	Stk33	3.61E-11
Glia	Gm11149	4.36E-11
Glia	Gm37679	5.26E-11
Glia	Olfml3	8.85E-11
Glia	A630012P03Rik	9.69E-11
Glia	Gm20726	1.60E-10
Glia	Fam107a	3.90E-10
Glia	Gm4477	8.31E-10
Glia	Iqub	4.00E-09
Glia	Sdc3	5.60E-09
Glia	Lrrc9	7.04E-09
Glia	Rsph10b	1.80E-08
Glia	Atp1b2	2.20E-08
Glia	E530001K10Rik	2.82E-08
Glia	Hoxc4	7.90E-08
Glia	Paqr6	8.95E-08
Glia	Crtac1	1.12E-07
Glia	Vstm4	1.15E-07
Glia	Cfap44	1.52E-07
T_cells	Dock10	6.41E-63
T_cells	Gm43603	2.18E-60
T_cells	Cd79a	1.87E-59
T_cells	Cd74	5.75E-59
T_cells	Mef2c	4.97E-56
T_cells	Mbnl1	1.10E-54
T_cells	Fam65b	6.08E-49
T_cells	Bach2	1.89E-46
T_cells	Man1a	1.89E-46
T_cells	Ccnd3	3.02E-45
T_cells	Ly6e	6.59E-45
T_cells	Lcp1	1.18E-44
T_cells	Ikzf1	3.77E-43
T_cells	Aff3	7.77E-41
T_cells	Rhoh	2.46E-40
T_cells	Inpp5d	7.10E-40
T_cells	Gimap4	7.00E-36
T_cells	Bcl2	1.24E-35
T_cells	Siglecg	1.12E-34
T_cells	Fli1	3.19E-34
T_cells	Kcnq5	3.41E-34
T_cells	Prkcb	7.51E-34
T_cells	Tspan32	1.09E-31
T_cells	Gm43388	5.33E-31
T_cells	St6galnac3	1.33E-30
T_cells	Apobec3	3.70E-30
T_cells	Cd79b	7.49E-30
T_cells	Itga4	2.62E-29
T_cells	Pax5	4.57E-29
T_cells	Cd52	3.98E-28
T_cells	H2-D1	5.82E-28
T_cells	Ptpn22	6.23E-28
T_cells	Ppp1r16b	8.44E-28
T_cells	Coro1a	9.27E-28
T_cells	Rabgap1l	6.37E-27
T_cells	Tbc1d10c	1.74E-26
T_cells	Foxp1	1.91E-26
T_cells	Stat4	1.95E-26
T_cells	Ralgps2	2.95E-26
T_cells	Ptprcap	1.57E-25
T_cells	Skap1	1.62E-25
T_cells	H2-Aa	1.68E-25
T_cells	Srgn	2.23E-24
T_cells	Gm17660	2.50E-24
T_cells	Lyn	4.88E-24
T_cells	Arhgap30	6.09E-24
T_cells	H2-Eb1	8.16E-24
T_cells	H2-Ab1	8.76E-24
T_cells	Laptm5	8.97E-24
T_cells	Tespa1	1.15E-23
T_cells	Inpp4b	1.15E-23
T_cells	Gm15987	2.11E-23
T_cells	Pou2f2	4.61E-23
T_cells	Sh3kbp1	5.66E-23
T_cells	Blk	7.22E-23
T_cells	Mndal	7.25E-23
T_cells	Wdfy4	2.19E-22
T_cells	Gm10552	2.64E-22
T_cells	Rbm39	2.89E-22
T_cells	Gm20388	3.70E-22
T_cells	Shisa5	9.19E-22
T_cells	Fermt3	1.47E-21
T_cells	Nedd9	1.87E-21
T_cells	Tmem163	2.04E-21
T_cells	Dock11	4.87E-21
T_cells	Ets1	1.71E-20

Enteroendocrine	Olfr78	2.73E-29
Enteroendocrine	Stxbp5l	3.28E-28
Enteroendocrine	Pde4d	5.07E-28
Enteroendocrine	Nkx2-2	1.87E-27
Enteroendocrine	Slc8a1	1.09E-26
Enteroendocrine	Insl5	5.97E-26
Enteroendocrine	Jazf1	1.13E-24
Enteroendocrine	Hmgn3	1.21E-23
Enteroendocrine	Etv1	7.28E-23
Enteroendocrine	Myt1	2.38E-22
Enteroendocrine	Otud7a	4.44E-22
Enteroendocrine	Kcnh7	6.08E-22
Enteroendocrine	Scg5	4.06E-21
Enteroendocrine	1810006J02Rik	5.70E-21
Enteroendocrine	Unc79	9.51E-21
Enteroendocrine	Pex5l	1.70E-20
Enteroendocrine	Ctnnd2	1.85E-20
Enteroendocrine	Fry	1.44E-19
Enteroendocrine	Isl1	1.99E-19
Enteroendocrine	Piezo2	2.15E-19
Enteroendocrine	Asic2	4.14E-19
Enteroendocrine	Ptprn	4.60E-19
Enteroendocrine	Celf3	8.34E-19
Enteroendocrine	Gfra3	1.34E-18
Enteroendocrine	Kcnmb2	8.80E-18
Enteroendocrine	Kcnh8	2.73E-17
Enteroendocrine	Ghr	3.34E-17
Enteroendocrine	Man1c1	3.82E-17
Enteroendocrine	Insm1	3.82E-17
Enteroendocrine	Zbtb20	5.18E-17
Enteroendocrine	Glis3	5.92E-17
Enteroendocrine	Cyp4x1	6.48E-17
Enteroendocrine	Ptprt	7.80E-17
Enteroendocrine	Negr1	1.90E-16
Enteroendocrine	Rims2	2.27E-16
Enteroendocrine	Pappa2	2.32E-16
Enteroendocrine	Dach1	2.54E-16
Enteroendocrine	Pax6	3.11E-16
Enteroendocrine	Syn2	5.82E-16
Enteroendocrine	Stk32a	5.83E-16
Enteroendocrine	Nbea	7.39E-16
Enteroendocrine	Nrg1	1.29E-15
Enteroendocrine	Wif1	1.59E-15
Enteroendocrine	Cacna1c	1.75E-15
Enteroendocrine	Pde11a	4.19E-15
Enteroendocrine	Gnao1	6.72E-15
Enteroendocrine	Astn2	9.59E-15
Enteroendocrine	Phldb2	2.12E-14
Enteroendocrine	Scg3	3.82E-14
Enteroendocrine	Rasal2	4.28E-14
Enteroendocrine	Rap1gap2	4.39E-14
Enteroendocrine	Nxph1	5.71E-14
Enteroendocrine	Itpr1	6.50E-14
Enteroendocrine	Resp18	7.37E-14
Enteroendocrine	Robo1	2.25E-13
Enteroendocrine	Cacnb2	3.12E-13
Enteroendocrine	Lin7a	3.63E-13
Enteroendocrine	Rundc3a	5.66E-13
Enteroendocrine	Lcorl	5.92E-13
Enteroendocrine	Peg3	1.04E-12
Enteroendocrine	Pax6os1	1.40E-12
Enteroendocrine	Gpr119	1.50E-12
Enteroendocrine	Cck	2.26E-11
Enteroendocrine	Lrrn3	2.26E-11
Enteroendocrine	Slc29a4	4.21E-11
Enteroendocrine	Nfasc	6.62E-11
Enteroendocrine	March4	2.69E-10
Enteroendocrine	Amigo2	3.24E-10
Enteroendocrine	Mreg	3.94E-10
Glia	Kcnj12	2.66E-07
Glia	Tub	1.38E-06
Goblet	Fcgbp	0.00E+00
Goblet	Zg16	1.62E-294
Goblet	Clca1	2.77E-272
Goblet	Fer1l6	3.18E-200
Goblet	Clec2h	2.10E-158
Goblet	Muc2	2.80E-148
Goblet	Bcas1	5.45E-143
Goblet	Sval1	1.19E-138
Goblet	Tff3	5.43E-134
Goblet	Sytl2	6.33E-125
Goblet	Rab27b	1.18E-108
Goblet	Rep15	4.88E-107
Goblet	Spink1	5.64E-106
Goblet	Scin	1.28E-98
Goblet	Hepacam2	1.52E-97
Goblet	Rab27a	1.61E-92
Goblet	Nr3c2	1.33E-85
Goblet	Myo5c	1.07E-76
Goblet	Hsd11b2	7.50E-75
Goblet	Lgals4	1.33E-71
Goblet	Kcnma1	1.45E-71
Goblet	Tnfaip8	1.06E-70
Goblet	Pla2g10os	1.59E-70
Goblet	Klf4	6.15E-68
Goblet	Inpp4b	3.60E-67
Goblet	Mcf2l	3.36E-66
Goblet	St6gal1	8.77E-64
Goblet	Srgap1	6.67E-62
Goblet	Gm12511	3.01E-59
Goblet	Mlph	7.21E-56
Goblet	Cyp2d34	2.46E-55
Goblet	Shroom3	1.08E-54
Goblet	Ptprn2	2.32E-54
Goblet	Nupr1	2.95E-54
Goblet	Slfn4	1.55E-53
Goblet	Ceacam1	4.01E-52
Goblet	Muc13	4.01E-52
Goblet	Lypd8	6.35E-52
Goblet	Il13ra1	6.54E-51
Goblet	Pde4d	6.69E-51
Goblet	AW112010	9.37E-51
Goblet	Neat1	1.78E-50
Goblet	Galnt7	8.53E-50
Goblet	Ms4a8a	1.45E-46
Goblet	Capn9	1.88E-46
Goblet	Krt8	2.73E-46
Goblet	9030622O22Rik	3.04E-46
Goblet	P2rx4	5.27E-46
Goblet	Ang4	6.97E-46
Goblet	Plcb1	9.43E-46
Goblet	2610035D17Rik	1.11E-43
Goblet	Plcl2	2.86E-43
Goblet	Atp2c2	3.87E-41
Goblet	Krt18	5.86E-41
Goblet	Bace2	9.35E-41
Goblet	Ptprr	6.66E-38
Goblet	Atp8a1	8.79E-38
Goblet	Agr2	3.12E-37
Goblet	Smim6	5.25E-37
Goblet	Slc4a7	2.39E-36
Goblet	Cpd	2.17E-35
Goblet	Trim25	8.09E-35
Goblet	Cdc42ep3	1.20E-34
Goblet	Ffar4	1.73E-34
Goblet	Clmn	2.05E-34
Goblet	Stxbp1	3.14E-34
Goblet	Anxa3	6.14E-34
T_cells	AU020206	2.91E-20
T_cells	Cd53	2.93E-20
T_cells	Ly86	3.67E-20
T_cells	Cd84	3.78E-20
T_cells	Serinc3	4.16E-20
T_cells	Btla	4.27E-20
T_cells	Sp100	4.42E-20
T_cells	Jchain	4.73E-20
T_cells	Acap1	1.55E-19
T_cells	Fchsd2	1.61E-19
T_cells	Slamf6	1.73E-19
T_cells	Rasgrp3	2.21E-19
T_cells	Lax1	2.60E-19
T_cells	Ankrd44	2.94E-19
T_cells	Fam49b	3.59E-19
T_cells	C130026I21Rik	4.39E-19
T_cells	Hivep2	6.48E-19
T_cells	Ly6d	6.60E-19
T_cells	Ltb	7.40E-19
T_cells	Cd48	7.47E-19
T_cells	Pik3cd	1.09E-18
T_cells	Cr2	1.40E-18
T_cells	Raet1e	3.46E-18
T_cells	Tnfrsf13b	5.84E-18
T_cells	Fcrl1	7.23E-18
T_cells	Cd37	7.92E-18
T_cells	Gpr132	6.84E-17
T_cells	Klrd1	8.09E-17
T_cells	Tnfrsf13c	3.07E-16
T_cells	Pou2af1	4.16E-16
T_cells	Dok3	8.98E-16
T_cells	Stap1	1.16E-15
T_cells	H2-DMb2	4.30E-15
T_cells	Rac2	4.84E-15
T_cells	Nrros	1.21E-14
T_cells	Cd72	2.02E-14
T_cells	Gimap3	5.38E-14
T_cells	Napsa	7.25E-14
T_cells	Clec2i	1.06E-13
T_cells	Selplg	1.72E-13
T_cells	Rasgrp1	1.97E-13
T_cells	Dusp2	2.54E-13
T_cells	Nxpe3	2.68E-13
T_cells	Rinl	6.25E-13
T_cells	Nckap1l	7.23E-13
T_cells	Cyfip2	1.43E-12
T_cells	Lck	1.93E-12
T_cells	AI662270	2.23E-12
T_cells	Ctsw	2.55E-12
T_cells	Ciita	4.99E-12
T_cells	Mirt1	1.11E-11
T_cells	Clnk	1.13E-11
T_cells	H2-Ob	1.27E-11
T_cells	Sp140	1.99E-11
T_cells	Cd22	2.38E-11
T_cells	Fcer2a	3.12E-11
T_cells	Ccr6	3.12E-11
T_cells	Gm16152	9.69E-11
T_cells	Myo1g	2.53E-10
T_cells	Mzb1	3.81E-10
T_cells	Runx3	9.65E-10
T_cells	Gm16158	1.17E-09
T_cells	H2-Q6	1.60E-09
T_cells	Arhgdib	2.20E-09
T_cells	Grap2	2.89E-09
T_cells	Derl3	3.82E-09
T_cells	Txk	9.35E-09
T_cells	Adrb2	1.73E-08
T_cells	Cd226	2.27E-08

Enteroendocrine	Unc13a	1.20E-09
Enteroendocrine	Slc6a19	1.21E-09
Enteroendocrine	Avpr1b	1.21E-09
Enteroendocrine	Galr1	2.47E-09
Enteroendocrine	Kcnk3	4.87E-09
Enteroendocrine	Iapp	8.92E-09
Enteroendocrine	Baiap3	1.76E-08
Enteroendocrine	Serpinf2	6.40E-08
Enteroendocrine	Scgn	6.40E-08
Enteroendocrine	Cryba2	6.40E-08
Enteroendocrine	Cxxc4	8.62E-08
Enteroendocrine	Gsdma	9.32E-08
Enteroendocrine	Ace2	9.87E-08
Enteroendocrine	Igsf21	1.08E-07
Enteroendocrine	Rcan2	1.14E-07
Enteroendocrine	Tm4sf4	1.38E-07
Enteroendocrine	Gipr	1.90E-07
Enteroendocrine	Fam20c	3.20E-07
Enteroendocrine	Gm15716	4.45E-07
Enteroendocrine	Miat	4.63E-07
Enteroendocrine	Slc26a4	5.53E-07
Enteroendocrine	Gdap1l1	6.82E-07
Enteroendocrine	Gm17276	2.27E-06
Enteroendocrine	Maats1	3.62E-06
Enteroendocrine	4931429I11Rik	3.79E-06
Enteroendocrine	Slc35d3	8.56E-06
Enteroendocrine	Unc5a	1.09E-05
Enteroendocrine	Dcx	1.42E-05
Enteroendocrine	Gck	2.04E-05
Enteroendocrine	Syndig1l	2.44E-05
Enteroendocrine	Sez6l2	6.45E-05
Enteroendocrine	AW551984	6.92E-05
Enteroendocrine	Dnaic1	1.04E-04
Enteroendocrine	Sst	1.16E-04
Enteroendocrine	Rimkla	1.58E-04
Enteroendocrine	Elavl2	3.38E-04
Enteroendocrine	Gm27162	7.60E-04
Epithelial_Progenitors	Gmds	3.61E-141
Epithelial_Progenitors	Ntan1	2.40E-78
Epithelial_Progenitors	5330417C22Rik	8.03E-78
Epithelial_Progenitors	Gfpt1	2.63E-75
Epithelial_Progenitors	Fut8	2.30E-73
Epithelial_Progenitors	Tox	1.55E-70
Epithelial_Progenitors	Pdxdc1	1.03E-67
Epithelial_Progenitors	Golph3l	4.55E-65
Epithelial_Progenitors	Airn	6.54E-65
Epithelial_Progenitors	9030622O22Rik	4.00E-64
Epithelial_Progenitors	Arhgef38	2.79E-63
Epithelial_Progenitors	Slc12a8	6.01E-63
Epithelial_Progenitors	Oit1	3.89E-58
Epithelial_Progenitors	Fam13a	7.30E-58
Epithelial_Progenitors	Mecom	1.45E-53
Epithelial_Progenitors	Slc35a3	2.51E-51
Epithelial_Progenitors	Galnt7	2.72E-49
Epithelial_Progenitors	Gne	2.72E-47
Epithelial_Progenitors	Creb3l1	4.10E-41
Epithelial_Progenitors	Sorbs2	4.65E-40
Epithelial_Progenitors	Mcc	4.65E-40
Epithelial_Progenitors	Slc12a2	9.96E-39
Epithelial_Progenitors	Klf5	7.87E-37
Epithelial_Progenitors	Naaladl2	1.92E-36
Epithelial_Progenitors	Gm26848	2.92E-36
Epithelial_Progenitors	Greb1l	6.02E-35
Epithelial_Progenitors	Sidt1	9.63E-35
Epithelial_Progenitors	Vps13b	9.76E-35
Epithelial_Progenitors	Rgs17	1.24E-34
Goblet	Fut8	1.79E-33
Goblet	Ccl6	2.32E-32
Goblet	S100a6	3.21E-32
Goblet	Gcnt3	3.25E-32
Goblet	Atoh1	3.54E-32
Goblet	Fmn1	3.54E-32
Goblet	Tcf7l2	4.18E-32
Goblet	Dennd1b	2.25E-31
Goblet	Ano7	2.62E-31
Goblet	Slc22a23	5.35E-31
Goblet	Iqgap2	2.83E-30
Goblet	Phgr1	1.06E-29
Goblet	Mctp2	1.80E-29
Goblet	Cdkn1a	4.28E-29
Goblet	Camk2n1	7.61E-29
Goblet	Txn1	2.82E-28
Goblet	Gna14	4.42E-28
Goblet	Grpr	5.15E-28
Goblet	Tfcp2l1	7.84E-28
Goblet	Lgals9	1.27E-27
Goblet	Pld1	2.32E-27
Goblet	Tmco3	2.93E-27
Goblet	Syt7	3.46E-27
Goblet	Baiap2l1	7.02E-27
Goblet	Atrnl1	8.91E-27
Goblet	Id3	1.07E-26
Goblet	Trp53inp1	1.95E-25
Goblet	Tsc22d1	2.49E-25
Goblet	Galnt10	3.38E-25
Goblet	Ghr	3.38E-25
Goblet	Gm1123	3.38E-25
Goblet	Qsox1	5.71E-25
Goblet	Dopey2	5.96E-25
Goblet	F3	4.28E-24
Goblet	Clic4	5.00E-24
Goblet	Mfsd7a	9.31E-24
Goblet	Mptx1	5.30E-23
Goblet	Rasa4	7.63E-22
Goblet	Ddx60	9.67E-22
Goblet	Muc4	1.93E-21
Goblet	Frmd3	2.37E-21
Goblet	Capn5	1.71E-20
Goblet	2210011C24Rik	4.73E-20
Goblet	Gde1	9.46E-20
Goblet	Entpd8	1.30E-19
Goblet	Pkhd1	2.10E-19
Goblet	Best2	6.95E-19
Goblet	Gm6086	1.28E-18
Goblet	Scnn1b	2.73E-18
Goblet	Fhl2	2.85E-18
Goblet	Cmtm8	8.91E-18
Goblet	Spats2l	1.48E-17
Goblet	Tpsg1	4.86E-17
Goblet	Samd8	1.24E-15
Goblet	Cldn4	4.50E-15
Goblet	Apobec1	7.24E-15
Goblet	Gnb5	9.59E-15
Goblet	Smim5	1.71E-14
Goblet	Sytl5	2.08E-14
Goblet	Fam117a	4.55E-13
Goblet	Tor3a	4.39E-12
Goblet	Rasd2	6.97E-12
Goblet	Rasd1	8.74E-12
Goblet	Sytl4	1.12E-11
Goblet	Zfp664	5.99E-11
Goblet	Cyp2d12	6.59E-11
T_cells	Ccl5	2.28E-08
T_cells	5031414D18Rik	2.93E-08
T_cells	H2-DMb1	3.38E-08
T_cells	Gm28053	8.83E-08
T_cells	Cd244	2.23E-07
Tuft	St18	4.65E-124
Tuft	Dclk1	1.03E-116
Tuft	Sh2d6	4.94E-107
Tuft	Rgs13	5.84E-93
Tuft	Nebl	1.82E-89
Tuft	Fyb	2.92E-70
Tuft	Dgki	1.02E-68
Tuft	Gnat3	2.02E-59
Tuft	Ccdc129	6.11E-56
Tuft	Pik3r5	3.24E-53
Tuft	Hck	4.27E-49
Tuft	Avil	9.92E-49
Tuft	Pstpip2	1.72E-48
Tuft	Plcg2	8.72E-47
Tuft	Dnah5	5.15E-46
Tuft	Matk	1.32E-44
Tuft	Lrmp	1.83E-44
Tuft	Chat	2.41E-43
Tuft	Inpp5d	6.69E-42
Tuft	Mast4	5.86E-39
Tuft	Strip2	2.47E-38
Tuft	Pde4d	4.39E-37
Tuft	Slc9a9	1.57E-36
Tuft	Runx1	3.73E-36
Tuft	Pou2f3	8.43E-36
Tuft	Adh1	1.40E-34
Tuft	Bmx	2.19E-34
Tuft	Trpm5	8.90E-33
Tuft	Chn2	3.90E-32
Tuft	Ltc4s	9.35E-32
Tuft	Pik3cg	2.69E-30
Tuft	Ppp3ca	5.73E-30
Tuft	Nav2	9.66E-30
Tuft	Sh2d7	1.27E-29
Tuft	Ptpn18	1.75E-29
Tuft	Cd24a	3.20E-29
Tuft	Gm21954	3.67E-28
Tuft	Il13ra1	8.86E-27
Tuft	Malrd1	1.25E-26
Tuft	Map2	4.59E-26
Tuft	Alox5	6.04E-26
Tuft	Myo1b	2.70E-25
Tuft	Fam19a1	1.42E-23
Tuft	1810046K07Rik	1.49E-23
Tuft	Ano6	6.00E-23
Tuft	Ptprc	2.26E-22
Tuft	Hpgds	1.33E-21
Tuft	Cd300lf	1.79E-21
Tuft	Spib	2.37E-21
Tuft	Abhd18	2.95E-21
Tuft	Pygl	1.35E-19
Tuft	A630010A05Rik	3.64E-19
Tuft	Lima1	4.43E-19
Tuft	Adgrb3	2.24E-18
Tuft	F930017D23Rik	2.41E-18
Tuft	Suco	2.41E-18
Tuft	Bub3	3.45E-18
Tuft	Rgs22	5.61E-18
Tuft	Vav1	7.02E-18
Tuft	Fam221a	7.23E-18
Tuft	Abhd2	7.46E-18

Epithelial_Progenitors	Spdef	6.75E-34
Epithelial_Progenitors	Myo3a	1.54E-33
Epithelial_Progenitors	Prkca	3.85E-33
Epithelial_Progenitors	Nupr1	1.74E-32
Epithelial_Progenitors	Ptprk	2.72E-32
Epithelial_Progenitors	Car8	5.18E-32
Epithelial_Progenitors	Gcc2	6.90E-32
Epithelial_Progenitors	Ehf	8.03E-32
Epithelial_Progenitors	Mia3	1.66E-31
Epithelial_Progenitors	Camk1d	3.50E-30
Epithelial_Progenitors	Tnfaip8	1.14E-29
Epithelial_Progenitors	Arhgef28	2.30E-29
Epithelial_Progenitors	Agr2	4.35E-29
Epithelial_Progenitors	Klf12	5.57E-29
Epithelial_Progenitors	Rapgef5	6.74E-29
Epithelial_Progenitors	Nfib	1.55E-27
Epithelial_Progenitors	Nfia	1.60E-27
Epithelial_Progenitors	Kcnma1	3.78E-27
Epithelial_Progenitors	Etv5	3.78E-27
Epithelial_Progenitors	Col8a1	3.78E-27
Epithelial_Progenitors	Galnt10	3.78E-27
Epithelial_Progenitors	Gm609	5.02E-27
Epithelial_Progenitors	Kank1	6.40E-27
Epithelial_Progenitors	St3gal6	9.50E-27
Epithelial_Progenitors	Ptprt	1.22E-26
Epithelial_Progenitors	Ephb2	2.09E-26
Epithelial_Progenitors	Satb2	2.33E-26
Epithelial_Progenitors	Pawr	4.28E-26
Epithelial_Progenitors	Chrm3	6.85E-26
Epithelial_Progenitors	Pla2g4a	1.97E-25
Epithelial_Progenitors	Tbc1d4	3.16E-25
Epithelial_Progenitors	Slc50a1	5.21E-25
Epithelial_Progenitors	Fut2	5.69E-25
Epithelial_Progenitors	St6galnac6	1.15E-24
Epithelial_Progenitors	Atp8b1	7.23E-24
Epithelial_Progenitors	Ern2	1.35E-23
Epithelial_Progenitors	Ica1	1.67E-23
Epithelial_Progenitors	0610040J01Rik	3.63E-23
Epithelial_Progenitors	Neat1	7.17E-23
Epithelial_Progenitors	Tc2n	9.21E-23
Epithelial_Progenitors	Pdia5	1.72E-22
Epithelial_Progenitors	Arhgap24	2.08E-22
Epithelial_Progenitors	Ptprn2	7.60E-22
Epithelial_Progenitors	Mettl23	1.49E-21
Epithelial_Progenitors	Cadps2	1.99E-21
Epithelial_Progenitors	Ralgapa2	3.07E-21
Epithelial_Progenitors	Slc1a5	4.45E-21
Epithelial_Progenitors	Tmem181a	4.87E-21
Epithelial_Progenitors	Tpd52	5.27E-21
Epithelial_Progenitors	Rsrp1	5.31E-21
Epithelial_Progenitors	Cdk6	8.30E-21
Epithelial_Progenitors	Galnt3	1.51E-20
Epithelial_Progenitors	Slc17a9	1.68E-20
Epithelial_Progenitors	Thrb	3.03E-20
Epithelial_Progenitors	Plcb4	4.04E-20
Epithelial_Progenitors	St3gal3	4.43E-20
Epithelial_Progenitors	Sybu	4.75E-20
Epithelial_Progenitors	Rbm39	7.85E-20
Epithelial_Progenitors	Mgat5	7.98E-20
Epithelial_Progenitors	C1galt1	8.14E-20
Epithelial_Progenitors	Pmm2	1.35E-19
Epithelial_Progenitors	Mctp1	1.36E-19
Epithelial_Progenitors	Vgll4	2.71E-19
Epithelial_Progenitors	Ppp2r3a	4.19E-19
Epithelial_Progenitors	Utrn	5.26E-19
Epithelial_Progenitors	Cftr	5.35E-19
Epithelial_Progenitors	Arid5b	6.17E-19
Epithelial_Progenitors	Chchd3	9.43E-19
Epithelial_Progenitors	Acer3	1.10E-18

Goblet	Gpr20	1.09E-10
Goblet	Gm9994	6.81E-10
Goblet	Bcas1os2	1.06E-08
Goblet	Tmc1	3.56E-08
Goblet	Ttc39aos1	9.56E-08
Goblet	Pla2g2c	1.02E-07
Goblet	Kcnf1	7.36E-07
Goblet	Slc23a3	7.83E-07
Goblet	Upk1a	3.72E-06
Goblet	Ubxn10	7.02E-06
Goblet	Gm28588	1.13E-05
Goblet	Dhrs9	1.25E-05
Goblet	Nlrp4e	1.65E-05
Goblet	Spire1	5.13E-05
Goblet	Slc2a10	7.55E-05
Goblet	Oasl1	1.59E-04
Goblet	Atp12a	2.72E-04
Goblet	Cacna2d2	3.49E-04
Goblet	Grin1	7.37E-04
Goblet	Sct	1.54E-03
Goblet	Gm15658	4.63E-03
Macrophage	Rbpj	9.28E-69
Macrophage	Zeb2	1.25E-62
Macrophage	Slc9a9	3.94E-62
Macrophage	Ms4a6c	7.02E-53
Macrophage	Arhgap15	6.77E-50
Macrophage	Mrc1	1.70E-48
Macrophage	F13a1	1.04E-46
Macrophage	Pid1	2.40E-46
Macrophage	F630028O10Rik	1.98E-45
Macrophage	Trps1	1.47E-44
Macrophage	Fyb	2.17E-43
Macrophage	Dab2	1.63E-40
Macrophage	Adgre1	3.19E-40
Macrophage	H2-Eb1	2.17E-36
Macrophage	Stab1	5.09E-36
Macrophage	Myo1f	1.68E-35
Macrophage	Ctsc	1.12E-34
Macrophage	Lyz2	8.00E-34
Macrophage	Cd74	2.50E-33
Macrophage	Pip4k2a	1.02E-31
Macrophage	Inpp5d	3.86E-31
Macrophage	Gm26740	2.74E-30
Macrophage	Hmha1	3.55E-30
Macrophage	C1qc	8.29E-30
Macrophage	Mir142hg	6.85E-29
Macrophage	Aoah	7.30E-29
Macrophage	Fam105a	1.37E-28
Macrophage	Ms4a6b	1.27E-27
Macrophage	Ptprc	2.81E-27
Macrophage	Abcg3	5.10E-27
Macrophage	Csf1r	5.19E-27
Macrophage	Dock10	5.59E-27
Macrophage	Lyn	1.42E-26
Macrophage	Spi1	8.79E-26
Macrophage	Ms4a4a	1.14E-25
Macrophage	Lcp1	3.84E-25
Macrophage	Ly86	3.85E-25
Macrophage	P2ry6	8.33E-25
Macrophage	C1qb	2.58E-24
Macrophage	Cd84	5.13E-24
Macrophage	Gab2	5.13E-24
Macrophage	Cd163	9.79E-24
Macrophage	Cd33	9.79E-24
Macrophage	Lair1	9.79E-24
Macrophage	Pla2g7	3.29E-23
Macrophage	Apobec1	3.98E-23
Macrophage	Mafb	9.40E-23
Macrophage	Klra2	3.67E-22

Tuft	Rabgap1l	2.76E-17
Tuft	Tmem116	4.38E-17
Tuft	Hmx2	5.73E-17
Tuft	Lyn	7.67E-17
Tuft	Ptprj	8.08E-17
Tuft	Gm609	4.06E-16
Tuft	1700112E06Rik	5.87E-16
Tuft	Siglecf	6.81E-15
Tuft	Ppp1r14c	7.34E-15
Tuft	Pnpla3	7.57E-15
Tuft	Bcl2l14	7.57E-15
Tuft	Ly6g6d	1.32E-14
Tuft	Mlip	1.75E-14
Tuft	Man2a1	1.79E-14
Tuft	Adcy2	2.47E-14
Tuft	Fryl	3.24E-14
Tuft	Zfhx3	3.02E-13
Tuft	Larp1b	4.15E-13
Tuft	Tmem245	6.70E-13
Tuft	Zbtb20	7.97E-13
Tuft	Hyal5	9.54E-13
Tuft	Ptgs1	1.09E-12
Tuft	Tanc2	1.23E-12
Tuft	Cacnb4	1.61E-12
Tuft	Txndc16	1.65E-12
Tuft	Oxr1	1.67E-12
Tuft	Itpr2	2.54E-12
Tuft	1700111E14Rik	2.62E-12
Tuft	Il17rb	5.79E-12
Tuft	Gnai1	6.11E-12
Tuft	Gpc6	1.34E-11
Tuft	Zdhhc17	3.27E-11
Tuft	Ahnak2	5.11E-11
Tuft	Man1a	5.46E-11
Tuft	Gm2245	8.26E-11
Tuft	Rac2	9.05E-11
Tuft	Espn	1.30E-10
Tuft	Tspan6	1.42E-10
Tuft	Tnik	1.50E-10
Tuft	Kctd12	2.27E-10
Tuft	Cdkn1c	2.28E-10
Tuft	Dmxl2	2.71E-10
Tuft	Ccnj	2.87E-10
Tuft	Snrnp25	4.10E-10
Tuft	Slco4a1	2.61E-09
Tuft	Gm42609	1.35E-08
Tuft	Ttll11	2.81E-08
Tuft	Cyp2j13	3.58E-08
Tuft	Ly6g6f	1.42E-07
Tuft	Trim38	2.20E-07
Tuft	Pea15a	7.26E-07
Tuft	Plcb2	1.40E-06
Tuft	Crisp3	2.60E-06
Tuft	Agt	3.32E-06
Tuft	Adcy5	1.11E-05
Tuft	Hap1	1.52E-05
Tuft	Kcnq4	1.86E-05
Tuft	Msi1	2.13E-05
Tuft	Gfi1b	2.81E-05
Tuft	Ffar3	2.81E-05
Tuft	Sptb	5.02E-05
Tuft	Gm4952	5.69E-05
Tuft	Adam22	1.05E-04
Tuft	Limd2	1.54E-04
Tuft	Nrg4	4.72E-04
Tuft	Srpx2	9.96E-04
Tuft	Alox5ap	1.22E-03
Tuft	Fcnaos	1.83E-03
Tuft	Ankrd33b	2.02E-03

Epithelial_Progenitors	Uhrf2	1.24E-18
Epithelial_Progenitors	Sgsm3	1.25E-18
Epithelial_Progenitors	Slc1a4	3.62E-18
Epithelial_Progenitors	Hes6	7.77E-18
Epithelial_Progenitors	Nxpe2	6.41E-17
Epithelial_Progenitors	Gm13832	7.57E-17
Epithelial_Progenitors	Lpcat2	9.70E-16
Epithelial_Progenitors	Bsn	1.21E-15
Epithelial_Progenitors	Dync1i1	3.33E-15
Epithelial_Progenitors	Kit	1.65E-14

Macrophage	H2-Aa	4.93E-22
Macrophage	Apoe	7.91E-22
Macrophage	Adam19	8.07E-22
Macrophage	Ikzf1	1.86E-21
Macrophage	C1qa	1.86E-21
Macrophage	Maf	1.86E-21
Macrophage	Fcer1g	5.10E-21
Macrophage	Mbnl1	1.83E-20
Macrophage	Cfh	2.19E-20
Macrophage	Pf4	3.63E-20

Tuft	Grin2b	5.03E-03
Tuft	Gm2447	1.33E-02
Tuft	Krt23	1.56E-02
Tuft	Kcnk3	1.56E-02
Tuft	Cabp1	2.62E-02
Tuft	Drd3	2.64E-02
Tuft	Dlgap3	3.16E-02
Tuft	Lzts3	4.16E-02
Tuft	Pkp1	4.35E-02

[00696] **Table 18. Genes comprising signatures in Figure 21B.** Gene(s) encoding either synthetic enzymes or respective receptors displayed in Figure 21B.

Name	Abbreviation	Type	Genes
Acetylcholine	Ach	Synthesis	Chat
Nitric oxide	NO	Synthesis	Nos1
Norepinephrine	Norepinephrine	Synthesis	Dbh
Calcb	Calcb	Synthesis	Calcb
Cartpt	Cartpt	Synthesis	Cartpt
Cholecystokinin	Cck	Synthesis	Cck
Dynorphin	Dynorphin	Synthesis	Pdyn
Enkephalin	Enkephalin	Synthesis	Penk
Galanin	Galanin	Synthesis	Gal
Gastrin releasing peptide	Grp	Synthesis	Grp
Neuromedin U	Nmu	Synthesis	Nmu
PACAP	PACAP	Synthesis	Adcyap1
Somatostatin	Sst	Synthesis	Sst
Tachykinin	Tachykinin	Synthesis	Tac1
Vasoactive intestinal peptide	Vip	Synthesis	Vip
Dynorphin	Dynorphin	Receptor	Oprd1, Oprk1, Oprm1
Enkephalin	Enkephalin	Receptor	Oprd1, Oprm1
Galanin	Galanin	Receptor	Galr1, Galr2
Glucagon	Glucagon	Receptor	Gcgr
Glucagon-like peptide-1	Glp1	Receptor	Glp1r
Glucagon-like peptide-2	Glp2	Receptor	Glp2r
Neuromedin U	Nmu	Receptor	Nmur1, Nmur2
Oxytocin	Oxytocin	Receptor	Oxtr
Secretin	Secretin	Receptor	Sctr
Tachykinin	Tachykinin	Receptor	Tacr1
Vasoactive intestinal peptide	Vip	Receptor	Vipr1, Vipr2, Adcyap1r1

[00697] Tables 19-22. Summary and marker genes for human ENS atlas. (Table 19) Description of each patient and sample profiled in this study, including age, sex, and colon location. Marker genes for all (Table 20) cells, (Table 21) neurons, and (Table 22) glia from the human muscularis propria profiled with droplet-based 10X sequencing.

Table 19.

Patient_ID	Sample_ID	Location_ID	Age	Gender

PID_405	ColFr0_Mye_1	N/A	78	F
PID_405	ColFr0_Muc_2	N/A	78	F
PID_405	ColFr0_Mye_3	N/A	78	F
PID_405	ColFr0_Mye_4	N/A	78	F
PID_405	ColFr0_Mye_5	N/A	78	F
PID_405	ColFr0_Mye_6	N/A	78	F
PID_405	ColFr0_Mye_3b	N/A	78	F
PID_405	ColFr0_Mye_4b	N/A	78	F
PID_405	ColFr0_Mye_5b	N/A	78	F
PID_405	ColFr0_Mye_6b	N/A	78	F
PID_413	ColFr0_Sub_1a	Right	59	F
PID_413	ColFr0_Sub_1b	Right	59	F
PID_405	ColFr0_Mye_7a1	N/A	78	F
PID_405	ColFr0_Mye_7a2	N/A	78	F
PID_405	ColFr0_Mye_7a3	N/A	78	F
PID_405	ColFr0_Mye_7a4	N/A	78	F
PID_405	ColFr0_Mye_7b1	N/A	78	F
PID_405	ColFr0_Mye_7b2	N/A	78	F
PID_405	ColFr0_Mye_7b3	N/A	78	F
PID_405	ColFr0_Mye_7b4	N/A	78	F
PID_03403	ColFr0_Mye_8a1	N/A	53	M
PID_03403	ColFr0_Mye_8a2	N/A	53	M
PID_03412	ColFr0_Mye_9	Left	42	M
PID_03412	ColFr0_Sub_2	Left	42	M
PID_03412	ColFr0_Mye_10a1	Left	42	M
PID_03412	ColFr0_Mye_10b1	Left	42	M
PID_03412	ColFr0_Sub_3a1	Left	42	M
PID_03412	ColFr0_Sub_3b1	Left	42	M
PID_03445	ColFr0_Mye_11	Right	90	M
PID_03445	ColFr0_Sub_4a1	Right	90	M
PID_03445	ColFr0_Sub_4a2	Right	90	M
PID_03452	ColFr0_Mye_12	Right	56	F
PID_03452	ColFr0_Sub_5	Right	56	F
PID_03403	ColFr0_Mye_13a1	N/A	53	M
PID_03403	ColFr0_Mye_13a2	N/A	53	M
PID_03403	ColFr0_Mye_13b1	N/A	53	M
PID_03403	ColFr0_Mye_13b2	N/A	53	M
PID_03412	ColFr0_Mye_14a1	Left	42	M
PID_03412	ColFr0_Mye_14a2	Left	42	M
PID_03409	ColFr0_Mye_15a1	Right	70	F
PID_03409	ColFr0_Mye_15a2	Right	70	F
PID_432	ColFr0_Mye_16a1	Cecum	72	F
PID_432	ColFr0_Mye_16a2	Cecum	72	F
PID_444	ColFr0_Mye_17a1	Right	60	M
PID_444	ColFr0_Mye_17a2	Right	60	M
PID_03494	ColFr0_Mye_18a1	Sigmoid	35	M
PID_03494	ColFr0_Mye_18a2	Sigmoid	35	M
PID_03494	ColFr0_Mye_18a3	Sigmoid	35	M
PID_03494	ColFr0_Mye_18a4	Sigmoid	35	M

Table 20.

ident	gene	padjH
ASMT+	PPP1R12B	4.75E-108
ASMT+	CACNA1C	3.26E-93
ASMT+	DMD	1.20E-85
ASMT+	PRUNE2	6.98E-82
ASMT+	CALD1	2.78E-79
ASMT+	NEAT1	2.78E-79
ASMT+	ATRNL1	3.14E-77

ident	gene	padjH
MPO+	RPS7	0.00E+00
MPO+	SLC25A6	0.00E+00
MPO+	RPS23	0.00E+00
MPO+	COX4I1	0.00E+00
MPO+	MT-ND2	0.00E+00
MPO+	RPL19	0.00E+00
MPO+	RPL7	0.00E+00

ident	gene	padjH
SPP1+	NAT8	1.21E-02
SPP1+	RP11-513O17.2	1.26E-02
SPP1+	TIMM21	1.29E-02
SPP1+	ARHGEF16	1.30E-02
SPP1+	GSTO2	1.46E-02
SPP1+	LINC00958	1.64E-02
SPP1+	MFAP3L	2.17E-02

ASMT+	SORBS1	8.81E-76
ASMT+	PRKG1	3.11E-68
ASMT+	KCNMA1	1.66E-67
ASMT+	LPP	1.12E-66
ASMT+	MYH11	1.07E-63
ASMT+	MEIS1	1.28E-61
ASMT+	SYNPO2	5.60E-60
ASMT+	RYR2	6.74E-55
ASMT+	LINC00578	5.53E-52
ASMT+	TPM1	1.26E-50
ASMT+	PCDH7	1.33E-49
ASMT+	ACTN1	9.99E-49
ASMT+	RBPMS	6.48E-48
ASMT+	BNC2	8.00E-46
ASMT+	COL6A2	3.27E-45
ASMT+	FOXP2	5.30E-45
ASMT+	FBXO32	2.03E-44
ASMT+	CACNA2D1	2.04E-42
ASMT+	COL4A2	6.07E-42
ASMT+	PDE4D	6.11E-42
ASMT+	SULF1	1.16E-40
ASMT+	PDZRN4	1.51E-40
ASMT+	MIR143HG	1.21E-38
ASMT+	TNC	3.35E-37
ASMT+	ITGA1	1.21E-35
ASMT+	ATP2B4	4.58E-34
ASMT+	RP11-123O10.4	1.05E-32
ASMT+	MYLK	2.78E-32
ASMT+	TMTC2	3.74E-32
ASMT+	MEIS2	6.93E-32
ASMT+	SLC8A1	1.08E-31
ASMT+	ADAMTS9-AS2	1.89E-31
ASMT+	COL4A1	2.60E-30
ASMT+	PDE3A	1.72E-29
ASMT+	PARD3	1.84E-29
ASMT+	CHRM3	1.22E-28
ASMT+	FN1	3.60E-28
ASMT+	MID1	4.18E-28
ASMT+	DIP2C	7.46E-27
ASMT+	PALLD	1.61E-26
ASMT+	PDLIM5	2.27E-26
ASMT+	CACNB2	3.50E-26
ASMT+	MIR145	6.20E-26
ASMT+	CDK8	6.61E-26
ASMT+	TTTY14	1.18E-25
ASMT+	TRIO	1.82E-25
ASMT+	CHRM2	1.99E-25
ASMT+	AC007392.3	4.46E-25
ASMT+	GPM6A	6.77E-25
ASMT+	LMOD1	8.21E-25
ASMT+	SOBP	4.30E-24
ASMT+	WLS	7.67E-24
ASMT+	TRPS1	1.49E-23
ASMT+	HDAC4	1.74E-23
ASMT+	PDLIM3	1.77E-23
ASMT+	COL6A1	1.07E-22
ASMT+	SMTN	1.07E-22
ASMT+	PDZRN3	7.13E-22
ASMT+	LRBA	1.54E-21
ASMT+	FENDRR	1.61E-21
ASMT+	PRKD1	2.70E-21
ASMT+	PGM5	3.03E-21
ASMT+	SPEG	4.72E-21
ASMT+	NBEA	4.87E-21
ASMT+	SLFNL1	1.16E-20
ASMT+	LRIG1	1.34E-20
ASMT+	CNTNAP3B	1.56E-20
ASMT+	EPHA7	3.50E-20
ASMT+	NAV2	1.05E-19
ASMT+	ARHGEF3	4.04E-19
ASMT+	ZNF248	4.72E-19
ASMT+	ASMT	9.68E-19
ASMT+	COL15A1	1.32E-18
MPO+	RPL35A	0.00E+00
MPO+	OAZ1	0.00E+00
MPO+	RPL4	0.00E+00
MPO+	RPS3A	0.00E+00
MPO+	RPS11	0.00E+00
MPO+	RPL18	0.00E+00
MPO+	RPS6	0.00E+00
MPO+	RPS14	0.00E+00
MPO+	RPS18	0.00E+00
MPO+	RPL36	0.00E+00
MPO+	RPS12	0.00E+00
MPO+	RPS27A	0.00E+00
MPO+	MT-CYB	0.00E+00
MPO+	RPL27	0.00E+00
MPO+	SERF2	0.00E+00
MPO+	TPT1	0.00E+00
MPO+	MT-ND1	0.00E+00
MPO+	RPL32	0.00E+00
MPO+	RPL11	0.00E+00
MPO+	RPL12	0.00E+00
MPO+	RPL23A	0.00E+00
MPO+	RPS20	0.00E+00
MPO+	CHCHD2	0.00E+00
MPO+	RPL6	0.00E+00
MPO+	ZNF90	0.00E+00
MPO+	RPL7A	0.00E+00
MPO+	RPS4X	0.00E+00
MPO+	RPS15A	0.00E+00
MPO+	RPS8	0.00E+00
MPO+	RPL3	0.00E+00
MPO+	RPS16	0.00E+00
MPO+	RPL30	0.00E+00
MPO+	RPL34	0.00E+00
MPO+	RPS24	0.00E+00
MPO+	RPS25	0.00E+00
MPO+	PPIA	0.00E+00
MPO+	RPS2	0.00E+00
MPO+	RPS19	0.00E+00
MPO+	RPS9	0.00E+00
MPO+	MT-ATP6	0.00E+00
MPO+	RPL13A	0.00E+00
MPO+	EEF1A1	0.00E+00
MPO+	MT-ND4	0.00E+00
MPO+	RPL10A	0.00E+00
MPO+	RPL31	0.00E+00
MPO+	RPLP2	0.00E+00
MPO+	PTMA	0.00E+00
MPO+	FTL	0.00E+00
MPO+	RPS3	0.00E+00
MPO+	RPL13	0.00E+00
MPO+	RPL27A	0.00E+00
MPO+	XPO5	0.00E+00
MPO+	APOO	0.00E+00
MPO+	BAIAP2L1	0.00E+00
MPO+	RPLP1	0.00E+00
MPO+	RPL41	0.00E+00
MPO+	TXNRD1	0.00E+00
MPO+	MT-CO2	0.00E+00
MPO+	AMBRA1	0.00E+00
MPO+	RPL10	0.00E+00
MPO+	MT-CO3	0.00E+00
MPO+	NBEAL1	0.00E+00
MPO+	MT-CO1	0.00E+00
MPO+	RPL5	0.00E+00
MPO+	RPL37	0.00E+00
MPO+	H2AFZ	0.00E+00
MPO+	LDHB	0.00E+00
MPO+	FAU	0.00E+00
MPO+	RPL24	0.00E+00
MPO+	RPL37A	0.00E+00
MPO+	FTH1	0.00E+00
MPO+	C1QBP	1.38E-278
MPO+	STMN1	5.28E-275
SPP1+	TM7SF2	2.18E-02
SPP1+	GSTA1	2.25E-02
SPP1+	SLC37A4	2.85E-02
SPP1+	TM2D2	3.21E-02
SPP1+	TMEM37	3.31E-02
SPP1+	RBM15B	3.65E-02
SPP1+	EGOT	4.10E-02
SPP1+	PPP1R26	4.53E-02
T cells	ARHGAP15	2.09E-129
T cells	PTPRC	1.44E-101
T cells	ANKRD44	3.72E-93
T cells	FAM65B	3.69E-77
T cells	CXCR4	2.40E-62
T cells	SKAP1	1.67E-59
T cells	CELF2	1.84E-58
T cells	CCND3	3.16E-58
T cells	IL7R	1.21E-54
T cells	RCSD1	5.76E-54
T cells	BTG1	1.82E-53
T cells	THEMIS	2.28E-53
T cells	ETS1	4.24E-51
T cells	BCL2	1.72E-49
T cells	PRKCB	4.15E-49
T cells	TNFAIP8	8.39E-49
T cells	RHOH	9.01E-49
T cells	RP11-347P5.1	9.06E-49
T cells	TXK	9.66E-49
T cells	TC2N	6.60E-48
T cells	MAML2	3.56E-47
T cells	TMC8	4.25E-46
T cells	CD96	1.67E-45
T cells	RP11-277P12.20	8.80E-42
T cells	STK17B	2.83E-41
T cells	BCL11B	6.26E-41
T cells	CDC42SE2	1.92E-39
T cells	IKZF1	4.34E-39
T cells	LEF1	1.46E-38
T cells	SSH2	3.05E-38
T cells	PARP8	1.15E-37
T cells	PDE7A	1.84E-37
T cells	SCML4	4.08E-37
T cells	CHST11	4.96E-37
T cells	KIAA0922	4.98E-37
T cells	BACH2	7.99E-37
T cells	CAMK4	3.40E-36
T cells	DOCK10	5.44E-36
T cells	PIP4K2A	1.79E-35
T cells	CD69	2.39E-35
T cells	RABGAP1L	8.25E-35
T cells	MS4A1	1.28E-34
T cells	CD247	1.51E-33
T cells	FYN	2.33E-33
T cells	FYB	4.23E-33
T cells	RP11-553K8.5	4.30E-33
T cells	DOCK8	4.61E-33
T cells	STK4	8.42E-33
T cells	CLEC2D	2.52E-32
T cells	CD53	5.48E-32
T cells	ITK	1.06E-31
T cells	ATM	2.05E-31
T cells	AC104820.2	2.95E-31
T cells	EVL	2.95E-31
T cells	LINC00861	6.89E-31
T cells	STAT4	1.71E-30
T cells	SEMA4D	3.70E-30
T cells	PRKCH	3.85E-30
T cells	TRAF3IP3	7.91E-30
T cells	PRKCQ	1.16E-29
T cells	HLA-B	5.20E-29
T cells	INPP4B	1.52E-28
T cells	PACS1	3.30E-27
T cells	CTB-4E7.1	9.07E-27
T cells	HLA-C	3.32E-26

ASMT+	SYNM	1.74E-18	MPO+	HMGA1	1.11E-265	T cells	SYTL3	3.55E-26
ASMT+	ABCC9	2.94E-18	MPO+	MRPL23	2.51E-264	T cells	KLF12	6.32E-26
ASMT+	MX1	4.82E-18	MPO+	RPL22L1	1.77E-211	T cells	MBNL1	6.32E-26
ASMT+	AP001347.6	6.13E-18	MPO+	GLRX5	3.21E-193	T cells	B2M	8.86E-26
ASMT+	LTBP1	7.38E-18	MPO+	LYL1	2.34E-182	T cells	HLA-A	1.17E-25
ASMT+	AKAP6	9.01E-18	MPO+	CKS2	1.06E-178	T cells	PIK3IP1	1.26E-25
ASMT+	CPXM2	1.17E-17	MPO+	HIST1H4C	7.52E-165	T cells	CARD11	3.54E-25
ASMT+	MBD5	1.76E-17	MPO+	NPM3	3.63E-159	T cells	TXNIP	5.02E-25
ASMT+	AC098617.1	2.50E-17	MPO+	TIMM10	1.50E-135	T cells	EMB	1.97E-24
ASMT+	BOC	2.57E-17	MPO+	COA4	5.78E-135	T cells	BANK1	2.48E-24
ASMT+	CNTNAP3	4.39E-17	MPO+	KIAA0125	2.86E-123	T cells	SH3KBP1	2.54E-24
ASMT+	TRPC4	6.60E-17	MPO+	MRPS12	2.13E-120	T cells	RUNX3	3.83E-24
ASMT+	MAGI2	7.48E-17	MPO+	PTRHD1	2.44E-120	T cells	PRKCQ-AS1	4.78E-24
ASMT+	GRIP1	8.82E-17	MPO+	CKS1B	2.95E-107	T cells	APBB1IP	7.71E-24
ASMT+	MACF1	1.25E-16	MPO+	AKR7A2	2.30E-105	T cells	GRAP2	1.02E-23
ASMT+	GJC1	2.00E-16	MPO+	HBD	2.75E-105	T cells	RASA2	5.99E-23
ASMT+	PBX3	2.06E-16	MPO+	ALKBH7	3.99E-100	T cells	ITGA4	1.51E-22
ASMT+	ROR2	2.15E-16	MPO+	C19orf77	1.23E-86	T cells	SMCHD1	2.02E-22
ASMT+	PHF21A	2.78E-16	MPO+	MARCKSL1	1.74E-86	T cells	CYTIP	2.03E-22
ASMT+	ADAMTSL3	2.78E-16	MPO+	ZWINT	2.16E-79	T cells	CD3D	2.91E-21
ASMT+	ST6GALNAC5	5.32E-16	MPO+	MKI67	3.55E-79	T cells	ANK3	3.03E-21
ASMT+	SOGA2	7.50E-16	MPO+	CDT1	9.14E-79	T cells	RUNX1	9.53E-21
ASMT+	IFI6	4.34E-15	MPO+	CDK2AP2	5.48E-78	T cells	PITPNC1	9.66E-21
ASMT+	EMILIN1	4.83E-15	MPO+	FAM212A	3.47E-76	T cells	SERINC5	1.17E-20
ASMT+	JPH2	1.29E-14	MPO+	ICAM3	1.06E-66	T cells	ADAM28	1.30E-20
ASMT+	NLGN4Y	1.08E-13	MPO+	TK1	1.76E-60	T cells	PYHIN1	2.21E-20
ASMT+	PLOD2	1.83E-13	MPO+	H2AFX	2.05E-58	T cells	MGAT5	2.58E-20
ASMT+	GNAO1	2.12E-13	MPO+	S1PR4	3.60E-58	T cells	CD3G	1.08E-19
ASMT+	HEPH	3.50E-13	MPO+	MPO	7.03E-57	T cells	FAIM3	1.28E-19
ASMT+	RAB23	3.50E-13	MPO+	RP11-354E11.2	2.15E-56	T cells	STK17A	1.28E-19
ASMT+	PPP4R1L	5.05E-13	MPO+	FAM26F	8.89E-54	T cells	IQGAP2	1.34E-19
ASMT+	STAT1	1.10E-12	MPO+	NRGN	4.83E-52	T cells	RP5-1022J11.2	2.07E-19
ASMT+	IFI44	1.55E-12	MPO+	KLF1	5.60E-52	T cells	SLFN12L	1.02E-18
ASMT+	HERC6	2.08E-12	MPO+	SMIM1	1.33E-50	T cells	RP11-624C23.1	1.02E-18
ASMT+	RSAD2	2.95E-12	MPO+	ALYREF	7.17E-50	T cells	OXNAD1	1.33E-18
ASMT+	CTC-228N24.2	3.30E-12	MPO+	CDKN2D	5.01E-49	T cells	SLA	1.83E-18
ASMT+	CDH11	8.47E-12	MPO+	PPBP	1.69E-48	T cells	CD37	4.59E-17
ASMT+	SPATS2L	1.09E-11	MPO+	TMEM60	1.92E-47	T cells	SIDT1	1.06E-16
ASMT+	NCS1	1.26E-11	MPO+	PF4	4.25E-47	T cells	AIM1	1.14E-16
ASMT+	EPSTI1	1.65E-11	MPO+	SMIM10	6.73E-46	T cells	ACAP1	1.29E-16
ASMT+	AC011043.1	2.06E-11	MPO+	STXBP2	8.40E-45	T cells	TBC1D10C	3.73E-16
ASMT+	ADCY5	2.17E-11	MPO+	EVA1B	1.90E-44	T cells	ZAP70	1.00E-15
ASMT+	ZFHX4	4.06E-11	MPO+	GP9	2.30E-43	T cells	SELL	1.07E-15
ASMT+	KLHL23	6.02E-11	MPO+	TMEM97	3.66E-40	T cells	ICOS	1.32E-15
ASMT+	HOXD10	8.78E-11	MPO+	EXOSC4	1.20E-39	T cells	ITGB2-AS1	4.30E-15
ASMT+	KCND3	2.54E-10	MPO+	NMB	2.64E-39	T cells	AMICA1	4.46E-15
ASMT+	RP11-834C11.3	2.83E-10	MPO+	C9orf40	1.09E-36	T cells	CCR7	6.30E-15
ASMT+	ISG15	3.76E-10	MPO+	CRYGD	1.94E-35	T cells	LINC00926	1.48E-14
ASMT+	NPTN	6.45E-10	MPO+	HBB	2.05E-35	T cells	RP11-456D7.1	2.53E-14
ASMT+	GPR125	1.04E-09	MPO+	CMTM5	3.32E-35	T cells	ARHGAP25	7.45E-14
ASMT+	FAXC	1.39E-09	MPO+	CTSG	2.36E-34	T cells	LTB	8.09E-14
ASMT+	PHKG1	7.06E-09	MPO+	RAC3	4.56E-34	T cells	KLRB1	1.09E-13
ASMT+	WNT9A	1.37E-08	MPO+	RGS18	2.70E-33	T cells	LCP1	1.09E-13
ASMT+	LINC00278	2.84E-08	MPO+	CCNB1	5.07E-33	T cells	CD2	1.14E-13
ASMT+	NFATC4	8.02E-08	MPO+	LINC01003	5.83E-32	T cells	SPOCK2	1.14E-13
ASMT+	KLHL42	8.43E-08	MPO+	GAPT	8.84E-32	T cells	SLAMF1	1.96E-13
ASMT+	SLC13A5	9.31E-08	MPO+	CA2	1.80E-28	T cells	TRABD2A	2.02E-13
ASMT+	AOC3	1.16E-07	MPO+	MCM2	5.23E-28	T cells	CD52	7.07E-13
ASMT+	CTD-2127H9.1	1.18E-07	MPO+	ENDOG	5.44E-28	T cells	GIMAP7	9.52E-13
ASMT+	RP11-81N13.1	2.37E-07	MPO+	DEFB1	4.01E-26	T cells	LCP2	1.45E-12
ASMT+	PTP4A3	2.48E-07	MPO+	SPP1	1.02E-25	T cells	TNFSF8	6.51E-12
ASMT+	SYDE2	5.84E-07	MPO+	PDZK1IP1	1.45E-25	T cells	KIAA1551	9.31E-12
ASMT+	AC078941.1	7.03E-07	MPO+	ICAM4	8.68E-25	T cells	AC092580.4	1.22E-11
ASMT+	ARHGEF17	7.26E-07	MPO+	HBQ1	1.04E-24	T cells	CD7	1.25E-11
ASMT+	KDM5D	1.12E-06	MPO+	EVI2B	2.59E-22	T cells	CD6	1.66E-11
ASMT+	BTC	2.19E-06	MPO+	LRRC8D	3.93E-22	T cells	GPRIN3	4.00E-10
ASMT+	KDM3A	2.64E-06	MPO+	FKBP1B	8.69E-22	T cells	TESPA1	4.49E-10
ASMT+	SNAP25	2.92E-06	MPO+	NAT8	8.98E-22	T cells	MIR155HG	9.44E-10
ASMT+	RP11-368L12.1	6.27E-06	MPO+	MT1F	3.41E-21	T cells	BLK	1.03E-09
ASMT+	EBF4	1.48E-05	MPO+	APOBEC3B	5.94E-21	T cells	SLAMF6	1.97E-09
ASMT+	IDS	1.67E-05	MPO+	MESP1	6.28E-21	T cells	MYBL1	3.27E-09
ASMT+	MASP1	2.02E-05	MPO+	SLC25A10	1.68E-20	T cells	BFSP2	6.81E-09
ASMT+	GMPR	4.48E-05	MPO+	AHSP	1.80E-20	T cells	FCRL1	7.56E-09

ASMT+	IFIT1	4.64E-05
ASMT+	PHLDA3	7.92E-05
ASMT+	MCM8	8.66E-05
ASMT+	CPEB2	1.21E-04
ASMT+	RP4-669L17.10	1.71E-04
ASMT+	SDC3	1.83E-04
ASMT+	FNDC1	1.88E-04
ASMT+	ZBTB1	2.07E-04
ASMT+	COL27A1	2.90E-04
ASMT+	OAS1	4.18E-04
ASMT+	CISD1	5.79E-04
ASMT+	RP11-497G19.1	7.32E-04
ASMT+	HOXD3	8.48E-04
ASMT+	TTTY15	1.06E-03
ASMT+	AC004053.1	1.10E-03
ASMT+	MEMO1	1.31E-03
ASMT+	FST	1.71E-03
ASMT+	NSUN2	1.91E-03
ASMT+	THBS4	2.29E-03
ASMT+	RP11-634B7.4	6.89E-03
Adipose	ACACB	0.00E+00
Adipose	PLIN1	2.00E-246
Adipose	AQP7	5.28E-209
Adipose	CIDEC	4.75E-193
Adipose	GHR	4.82E-187
Adipose	ANXA1	1.95E-180
Adipose	EBF1	3.31E-179
Adipose	PNPLA2	1.76E-174
Adipose	PPARG	6.21E-164
Adipose	CPM	1.90E-162
Adipose	PIRT	5.05E-158
Adipose	GPAM	8.83E-158
Adipose	NEAT1	6.05E-156
Adipose	TMEM132C	9.50E-155
Adipose	LPL	3.18E-154
Adipose	SLC7A6	3.18E-154
Adipose	FOXO1	8.98E-142
Adipose	GPD1	3.10E-139
Adipose	PDE3B	2.22E-137
Adipose	SLC7A6OS	2.58E-136
Adipose	ACSL1	7.97E-135
Adipose	ADIPOQ	5.05E-134
Adipose	CTA-360L10.1	7.92E-130
Adipose	GPC6	9.33E-130
Adipose	LIPE	9.50E-128
Adipose	PRKAR2B	9.25E-120
Adipose	AGPAT2	2.40E-114
Adipose	TXNIP	5.23E-112
Adipose	FGF1	3.88E-111
Adipose	TLN2	8.14E-111
Adipose	FKBP5	4.88E-110
Adipose	LIPE-AS1	2.16E-107
Adipose	CBLB	1.30E-105
Adipose	MGST1	5.69E-104
Adipose	RP11-779O18.3	1.35E-100
Adipose	FRMD4A	1.35E-100
Adipose	MLXIPL	7.52E-100
Adipose	ZNF318	1.00E-98
Adipose	RP11-295P9.3	2.43E-97
Adipose	ABHD5	1.01E-96
Adipose	MARC1	1.62E-94
Adipose	SLC1A3	5.36E-93
Adipose	SLC19A3	9.20E-93
Adipose	GYG2	1.15E-92
Adipose	HOOK2	1.41E-92
Adipose	PLIN4	6.83E-92
Adipose	VIM	8.45E-91
Adipose	KCNIP2-AS1	1.12E-90
Adipose	ADH1B	3.62E-90
Adipose	EMP1	1.12E-88
Adipose	FABP4	3.74E-88
Adipose	CD36	1.72E-87
Adipose	JUN	1.72E-87
MPO+	AVP	3.82E-20
MPO+	RNF113A	4.07E-19
MPO+	C11orf21	4.70E-19
MPO+	ZMYND19	2.25E-18
MPO+	CISH	5.57E-18
MPO+	AC004540.4	5.78E-18
MPO+	POMC	2.00E-17
MPO+	HPDL	4.40E-17
MPO+	MT1G	5.12E-17
MPO+	FXYD2	5.60E-17
MPO+	UGT2B7	6.26E-16
MPO+	CHST13	1.45E-14
MPO+	ALDOB	5.49E-14
MPO+	MT1H	6.69E-13
Mast cells	TPSAB1	0.00E+00
Mast cells	CD69	2.79E-177
Mast cells	KIT	9.34E-152
Mast cells	SRGN	5.37E-122
Mast cells	HPGDS	3.00E-119
Mast cells	NTM	6.55E-111
Mast cells	IL18R1	1.10E-110
Mast cells	PZP	3.64E-101
Mast cells	CPM	4.56E-94
Mast cells	SYTL3	2.96E-76
Mast cells	CPA3	4.88E-74
Mast cells	RGS13	5.03E-70
Mast cells	RP11-680B3.2	5.03E-70
Mast cells	ANXA1	5.95E-65
Mast cells	VWA5A	2.68E-63
Mast cells	RGS1	1.65E-62
Mast cells	HDC	2.95E-59
Mast cells	BATF	3.50E-57
Mast cells	TSC22D3	1.11E-54
Mast cells	GATA2	5.72E-53
Mast cells	SAMSN1	1.20E-51
Mast cells	AP003025.2	3.28E-46
Mast cells	RP13-726E6.1	1.11E-44
Mast cells	BMP2K	1.62E-44
Mast cells	SLCO2B1	2.22E-43
Mast cells	SLC24A3	2.00E-41
Mast cells	RP13-143G15.3	6.80E-41
Mast cells	C1orf186	9.17E-41
Mast cells	COX16	1.17E-40
Mast cells	GLOD5	6.98E-39
Mast cells	RHOH	9.34E-38
Mast cells	RP13-143G15.4	9.88E-38
Mast cells	RP11-779O18.3	5.83E-37
Mast cells	ZNF107	1.45E-36
Mast cells	CTD-3179P9.1	1.11E-35
Mast cells	CHN2	1.35E-34
Mast cells	LIF	6.61E-34
Mast cells	RGS2	8.52E-34
Mast cells	ARHGAP15	2.16E-33
Mast cells	DUSP1	2.85E-33
Mast cells	FER	2.26E-32
Mast cells	ARHGAP18	7.21E-32
Mast cells	SGK1	1.22E-30
Mast cells	RP11-217L21.1	6.82E-30
Mast cells	CUL2	7.59E-30
Mast cells	STX3	2.09E-28
Mast cells	HPGD	2.60E-28
Mast cells	TG	4.30E-28
Mast cells	FOSB	1.18E-26
Mast cells	PRKX-AS1	8.94E-26
Mast cells	SLC8A3	9.10E-26
Mast cells	ZEB2	3.32E-25
Mast cells	ELMO1-AS1	4.06E-25
Mast cells	ACER3	1.94E-24
Mast cells	SLC18A2	3.14E-24
Mast cells	ANKRD44	3.42E-24
Mast cells	FOS	1.09E-23
Mast cells	NFKBIA	1.56E-23
Mast cells	RAB11A	4.27E-23
T cells	TRAT1	1.65E-08
T cells	IRF8	1.65E-08
T cells	FAM196B	4.88E-08
T cells	BTN3A1	6.00E-08
T cells	LIMD2	3.62E-07
T cells	ISG20	1.83E-06
T cells	CD28	1.88E-05
VEGFC+	LDB2	5.22E-80
VEGFC+	MCTP1	2.35E-73
VEGFC+	TCF4	2.66E-70
VEGFC+	ARL15	5.74E-70
VEGFC+	MECOM	1.18E-69
VEGFC+	RALGAPA2	1.37E-62
VEGFC+	MAGI1	3.61E-58
VEGFC+	EPAS1	4.59E-58
VEGFC+	PTPRM	1.35E-56
VEGFC+	PITPNC1	6.01E-56
VEGFC+	ABLIM1	2.50E-55
VEGFC+	MAST4	5.49E-53
VEGFC+	PTPRB	1.82E-48
VEGFC+	VWF	4.39E-43
VEGFC+	PLEKHG1	5.99E-42
VEGFC+	SASH1	2.17E-41
VEGFC+	RASGRF2	1.77E-40
VEGFC+	TMTC1	3.95E-40
VEGFC+	PREX2	6.37E-40
VEGFC+	MYO1E	1.69E-39
VEGFC+	ABLIM3	3.55E-38
VEGFC+	ADAMTS9	8.00E-38
VEGFC+	TSHZ2	4.63E-37
VEGFC+	WWTR1	5.97E-37
VEGFC+	PRKCH	1.41E-36
VEGFC+	ELTD1	7.76E-36
VEGFC+	TACC1	1.28E-35
VEGFC+	RAPGEF5	2.17E-35
VEGFC+	DOCK9	8.33E-35
VEGFC+	MEF2C	1.39E-34
VEGFC+	VEGFC	1.79E-34
VEGFC+	PLCB4	4.34E-34
VEGFC+	NEDD9	4.46E-34
VEGFC+	NRP1	1.87E-33
VEGFC+	SEC14L1	2.05E-31
VEGFC+	EGFL7	3.63E-29
VEGFC+	EVA1C	7.87E-29
VEGFC+	ST6GALNAC3	8.85E-29
VEGFC+	TPO	1.52E-28
VEGFC+	RAPGEF1	4.98E-28
VEGFC+	RP3-510L9.1	5.06E-27
VEGFC+	NFIB	7.44E-27
VEGFC+	MKL2	8.36E-27
VEGFC+	ERG	2.25E-26
VEGFC+	IGFBP3	1.51E-25
VEGFC+	FLT1	1.74E-25
VEGFC+	CLDN5	3.53E-25
VEGFC+	ENPP2	9.08E-25
VEGFC+	SPRY1	2.02E-24
VEGFC+	ELMO1	3.55E-24
VEGFC+	XAF1	3.67E-24
VEGFC+	PKP4	3.72E-24
VEGFC+	UTRN	9.96E-24
VEGFC+	CD93	1.17E-23
VEGFC+	PALMD	1.27E-23
VEGFC+	MYH9	8.97E-23
VEGFC+	EMCN	1.09E-22
VEGFC+	AQP1	5.49E-22
VEGFC+	PPAP2A	1.45E-21
VEGFC+	ZNF385D	1.80E-21
VEGFC+	GNAQ	2.55E-21
VEGFC+	PPP1R16B	2.66E-21
VEGFC+	GALNT18	4.43E-21
VEGFC+	ANO2	1.92E-20
VEGFC+	CRIM1	3.32E-20
VEGFC+	CYYR1	6.44E-20

Adipose	SVEP1	4.99E-86
Adipose	ROCK2	5.97E-86
Adipose	MMP19	4.50E-85
Adipose	FOSB	1.52E-82
Adipose	TNFAIP8	2.33E-81
Adipose	DUSP1	3.93E-81
Adipose	ZFP36	9.58E-81
Adipose	RHOBTB3	1.95E-79
Adipose	HSPB7	2.43E-75
Adipose	ACVR1C	1.58E-74
Adipose	SAT1	5.48E-74
Adipose	GPX3	1.81E-72
Adipose	RP11-701P16.2	3.75E-71
Adipose	MT1X	4.70E-71
Adipose	SCD	9.11E-70
Adipose	PALMD	1.51E-69
Adipose	BCL2	1.80E-69
Adipose	PTPRG	2.86E-68
Adipose	COL4A1	1.00E-67
Adipose	RP11-124N14.3	1.58E-66
Adipose	RP11-353M9.1	2.28E-65
Adipose	ITSN1	2.83E-65
Adipose	PHLDB1	4.49E-65
Adipose	EPHA1-AS1	1.36E-64
Adipose	PLXNA4	1.43E-64
Adipose	SIK2	1.43E-64
Adipose	G0S2	3.17E-63
Adipose	RP11-64D24.2	1.77E-62
Adipose	SAA1	2.93E-62
Adipose	ANGPTL4	1.27E-61
Adipose	C6	1.54E-61
Adipose	LAMB1	5.30E-61
Adipose	RBMS3-AS3	1.24E-60
Adipose	RP11-286B14.1	1.59E-60
Adipose	C14orf180	7.34E-60
Adipose	COL4A2	9.20E-60
Adipose	LIMA1	7.28E-59
Adipose	RP11-444D3.1	2.65E-58
Adipose	RP11-665G4.1	8.59E-58
Adipose	ASPH	9.93E-58
Adipose	AP000304.12	2.82E-57
Adipose	FNDC3B	1.86E-56
Adipose	GPT	2.52E-56
Adipose	ACSS3	7.60E-56
Adipose	GBE1	1.78E-55
Adipose	PFKFB3	7.79E-55
Adipose	FASN	1.08E-54
Adipose	LGALS12	2.74E-54
Adipose	RASD1	5.65E-54
Adipose	FZD4	4.09E-53
Adipose	SLC7A10	1.19E-49
Adipose	CIDEA	1.42E-49
Adipose	HEPN1	1.77E-49
Adipose	APCDD1	1.04E-44
Adipose	COX14	2.59E-43
Adipose	PCK1	1.60E-41
Adipose	RP1-193H18.3	9.96E-40
Adipose	RGCC	2.29E-39
Adipose	CDO1	1.57E-38
Adipose	GABRE	8.99E-37
Adipose	NIPSNAP3B	1.70E-36
Adipose	KCNIP2	1.95E-36
Adipose	RP11-563P16.1	2.38E-35
Adipose	AKR1C2	1.13E-34
Adipose	GPC6-AS1	2.25E-32
Adipose	DGAT2	8.50E-31
Adipose	RP11-157I4.4	4.75E-30
Adipose	ZNF117	1.32E-27
Adipose	MT1M	6.34E-27
Adipose	RP11-111E14.1	1.03E-25
Adipose	RBP4	5.14E-24
Adipose	ADRA2A	4.26E-23
Adipose	TIMP4	4.48E-23

Mast cells	LINC00937	5.34E-23
Mast cells	CDK15	7.44E-23
Mast cells	RCSD1	8.69E-23
Mast cells	TNIK	2.57E-22
Mast cells	KIAA1549	2.58E-22
Mast cells	FTH1	2.61E-22
Mast cells	SLC2A3	2.84E-22
Mast cells	CTSG	1.95E-21
Mast cells	P2RX1	2.76E-21
Mast cells	XIST	6.14E-21
Mast cells	PAQR3	8.66E-21
Mast cells	CD44	1.03E-20
Mast cells	MIR24-2	1.91E-20
Mast cells	RP11-815J21.4	6.45E-20
Mast cells	VIM	3.19E-19
Mast cells	LMNA	5.06E-19
Mast cells	TESPA1	7.45E-18
Mast cells	DOCK10	1.11E-17
Mast cells	CPEB4	1.18E-17
Mast cells	AKAP13	2.18E-17
Mast cells	MAML3	2.84E-17
Mast cells	RP11-557H15.4	4.96E-17
Mast cells	MCTP2	5.86E-17
Mast cells	EIF2B5-AS1	7.34E-17
Mast cells	SLC38A11	7.34E-17
Mast cells	ALOX5	7.34E-17
Mast cells	PRKX	7.34E-17
Mast cells	MKRN3	1.02E-16
Mast cells	LAX1	2.14E-16
Mast cells	RP11-347P5.1	3.30E-16
Mast cells	PHF20	3.42E-16
Mast cells	H3F3B	1.18E-15
Mast cells	RAB27B	2.84E-15
Mast cells	TRAF3IP3	3.24E-15
Mast cells	RP11-768F21.1	3.61E-15
Mast cells	SAT1	7.73E-15
Mast cells	SKAP1	8.08E-15
Mast cells	AC009313.1	9.73E-15
Mast cells	IER2	1.23E-14
Mast cells	PARP4	1.54E-14
Mast cells	KCNE1	1.57E-14
Mast cells	GRAP2	1.69E-14
Mast cells	CSF1	3.39E-14
Mast cells	RENBP	3.54E-14
Mast cells	SYTL2	3.92E-14
Mast cells	LCP2	1.72E-13
Mast cells	AGPAT9	2.68E-13
Mast cells	MIR142	4.98E-13
Mast cells	TNFAIP3	6.51E-13
Mast cells	RP11-406A9.2	2.90E-12
Mast cells	CD37	4.17E-12
Mast cells	TMC8	9.98E-12
Mast cells	MLPH	5.26E-11
Mast cells	PIK3R6	7.39E-11
Mast cells	EMR2	7.90E-11
Mast cells	ARHGAP25	1.42E-10
Mast cells	MS4A4E	4.77E-10
Mast cells	ANKRD18B	5.48E-10
Mast cells	CTD-2197I11.1	8.26E-10
Mast cells	IKZF1	9.59E-10
Mast cells	CTD-2583P5.1	1.89E-09
Mast cells	RP11-456D7.1	2.08E-08
Mast cells	RP11-553K8.5	3.08E-08
Mast cells	RP11-440I14.2	1.17E-07
Mast cells	CD22	3.01E-07
Mast cells	NLRP9	1.06E-06
Mast cells	CTD-2562J17.2	1.31E-06
Mast cells	RP11-179A10.1	1.73E-06
Mast cells	RP5-1022J11.2	4.93E-06
Mast cells	GPR68	5.19E-06
Mast cells	BTK	1.59E-05
Mast cells	WNT8B	3.47E-05
Mast cells	CD84	5.75E-05

VEGFC+	CTTNBP2NL	6.64E-20
VEGFC+	GRB10	9.31E-20
VEGFC+	NDRG1	1.04E-19
VEGFC+	SYNE2	1.49E-19
VEGFC+	MTUS1	1.54E-19
VEGFC+	TGFBR2	2.16E-19
VEGFC+	IFI44L	2.77E-19
VEGFC+	PICALM	3.39E-19
VEGFC+	FLI1	9.86E-19
VEGFC+	SPARCL1	1.74E-18
VEGFC+	THSD7A	2.07E-18
VEGFC+	RAPGEF4	2.11E-18
VEGFC+	MPZL2	2.22E-18
VEGFC+	TM4SF1	3.08E-18
VEGFC+	DOCK4	4.86E-18
VEGFC+	CADPS2	5.68E-18
VEGFC+	DACH1	1.64E-17
VEGFC+	RBMS2	1.75E-17
VEGFC+	PDLIM1	2.31E-17
VEGFC+	ARHGAP29	2.51E-17
VEGFC+	IFI44	4.32E-17
VEGFC+	LIMCH1	5.34E-17
VEGFC+	EXOC6	9.62E-17
VEGFC+	SWAP70	9.84E-17
VEGFC+	ARHGAP31	1.01E-16
VEGFC+	CCNY	1.48E-16
VEGFC+	PPP3CA	1.66E-16
VEGFC+	PIK3R3	3.80E-16
VEGFC+	EPB41L4A	4.94E-16
VEGFC+	AL035610.2	5.86E-16
VEGFC+	PDE10A	1.13E-15
VEGFC+	DOCK1	1.26E-15
VEGFC+	PODXL	1.74E-15
VEGFC+	CXorf36	1.77E-15
VEGFC+	NEURL1B	2.06E-15
VEGFC+	RP11-435O5.2	3.51E-15
VEGFC+	SLC9C1	4.30E-15
VEGFC+	ACER2	5.38E-15
VEGFC+	C10orf10	1.39E-14
VEGFC+	AJ239322.3	1.45E-14
VEGFC+	ICAM2	4.01E-14
VEGFC+	BHLHE40	8.69E-14
VEGFC+	STC1	2.11E-13
VEGFC+	FKBP1A	2.74E-13
VEGFC+	CD59	5.51E-13
VEGFC+	SIPA1L2	8.59E-13
VEGFC+	RAMP3	3.57E-12
VEGFC+	CTC-484P3.3	1.12E-11
VEGFC+	RP11-834C11.3	2.62E-11
VEGFC+	SLC45A4	5.33E-11
VEGFC+	AC011526.1	6.19E-10
VEGFC+	SIK1	6.49E-10
VEGFC+	MEOX2	1.05E-09
VEGFC+	TEK	2.21E-09
VEGFC+	DLL4	2.38E-09
VEGFC+	NOTCH4	2.65E-09
VEGFC+	RP1-55C23.7	6.62E-09
VEGFC+	ADCY4	7.50E-09
VEGFC+	CLEC14A	1.05E-08
VEGFC+	AC010084.1	1.40E-08
VEGFC+	MMRN2	1.63E-08
VEGFC+	JAG1	4.71E-08
VEGFC+	S1PR1	2.43E-07
VEGFC+	BTNL9	2.43E-07
VEGFC+	SHANK3	2.64E-07
VEGFC+	CLEC1A	4.90E-07
VEGFC+	LRRC32	5.79E-07
VEGFC+	RP11-805F19.2	6.57E-07
VEGFC+	CD160	1.20E-06
VEGFC+	TSPAN7	1.44E-06
VEGFC+	EFNB2	5.34E-06
VEGFC+	IGF2	6.20E-06
VEGFC+	LINC00312	2.15E-05

Adipose	PSG8	7.03E-22
Adipose	RP11-286N3.2	1.02E-21
Adipose	PFKFB1	1.36E-21
Adipose	ID4	1.37E-21
Adipose	RP11-154B12.3	2.76E-21
Adipose	AZGP1	2.96E-21
Adipose	PSG4	1.60E-20
Adipose	FNDC4	7.36E-20
Adipose	RP11-161D15.3	1.52E-19
Adipose	CTB-43E15.3	3.98E-18
Adipose	SPATA9	6.43E-17
Adipose	MT1A	2.12E-15
Adipose	HEPACAM	2.55E-15
Adipose	AMOTL2	1.48E-14
Adipose	TM7SF2	1.92E-14
Adipose	VEGFA	6.80E-14
Adipose	MDFI	9.42E-14
Adipose	CTD-2363C16.1	5.89E-13
Adipose	KLHL31	4.65E-12
Adipose	RP11-16N2.1	1.75E-11
Adipose	RP11-295P9.8	2.51E-11
Adipose	CNTFR	7.29E-11
Adipose	ORMDL3	1.20E-10
Adipose	RP11-511B23.3	1.36E-10
Adipose	NPY1R	8.76E-10
Adipose	MOCS1	9.56E-10
Adipose	SPRY4	6.41E-09
Adipose	APOL4	8.79E-08
Epithelial	PHGR1	2.68E-238
Epithelial	FXYD3	2.68E-238
Epithelial	SLC26A3	2.56E-226
Epithelial	ELF3	4.55E-192
Epithelial	TSPAN1	5.93E-189
Epithelial	PIGR	2.79E-185
Epithelial	MS4A12	9.60E-179
Epithelial	LGALS4	5.97E-174
Epithelial	HHLA2	1.00E-165
Epithelial	SLC26A2	9.34E-162
Epithelial	LIPH	1.25E-155
Epithelial	CDHR5	8.42E-154
Epithelial	MUC12	5.27E-153
Epithelial	KRT19	2.29E-150
Epithelial	FABP1	2.74E-142
Epithelial	SYTL2	2.55E-136
Epithelial	SHROOM3	9.20E-132
Epithelial	NR3C2	1.39E-125
Epithelial	MYO1D	2.22E-124
Epithelial	RP11-665N17.4	2.79E-124
Epithelial	CEACAM1	1.46E-122
Epithelial	CEACAM7	1.75E-122
Epithelial	SATB2	2.76E-119
Epithelial	LGALS3	2.15E-116
Epithelial	PPARG	2.49E-116
Epithelial	KRT20	7.43E-115
Epithelial	GUCA2A	4.25E-114
Epithelial	TMEM45B	4.50E-112
Epithelial	TCF7L2	9.59E-107
Epithelial	BTNL8	3.51E-106
Epithelial	HSD11B2	3.11E-105
Epithelial	SLC17A4	9.97E-105
Epithelial	FRYL	2.61E-103
Epithelial	HNF4A	4.82E-102
Epithelial	PLAC8	1.91E-101
Epithelial	CDH17	2.70E-101
Epithelial	SDCBP2	1.89E-100
Epithelial	LLGL2	2.36E-100
Epithelial	SELENBP1	7.55E-99
Epithelial	AMN	2.24E-98
Epithelial	PIP5K1B	2.24E-97
Epithelial	TMPRSS2	4.07E-97
Epithelial	PCK1	5.11E-97
Epithelial	KLF5	1.19E-96
Epithelial	PRSS3	1.40E-96
Mast cells	AC007879.1	7.56E-05
Mast cells	GALNT3	1.12E-04
Mast cells	LINC01094	1.99E-04
Mast cells	MIIP	2.69E-04
Mast cells	FAM196B	2.96E-04
Mast cells	GAB3	3.41E-04
Mast cells	ITGAX	3.44E-04
Mast cells	LAIR1	8.78E-04
Mast cells	EIF2D	6.32E-03
Mast cells	ALOX5AP	1.25E-02
NKX2-3+	PIK3C2G	4.12E-234
NKX2-3+	NFIB	1.53E-211
NKX2-3+	RP11-499F3.2	2.40E-202
NKX2-3+	TTC6	1.73E-190
NKX2-3+	C8orf4	1.57E-187
NKX2-3+	HLA-B	9.67E-171
NKX2-3+	BMP5	2.12E-158
NKX2-3+	HLA-A	3.50E-138
NKX2-3+	TMC5	4.27E-137
NKX2-3+	PIGR	5.67E-134
NKX2-3+	HMGB3	6.02E-129
NKX2-3+	CXCL17	3.50E-128
NKX2-3+	LINC00669	2.86E-120
NKX2-3+	SDK1	1.87E-118
NKX2-3+	MIR205HG	7.76E-115
NKX2-3+	IDO1	2.03E-114
NKX2-3+	WFDC2	1.77E-111
NKX2-3+	SLC26A2	3.05E-106
NKX2-3+	CLIC6	7.58E-106
NKX2-3+	PDE5A	4.33E-103
NKX2-3+	BCL2	9.39E-103
NKX2-3+	PLEKHA7	1.51E-102
NKX2-3+	ELF3	1.14E-98
NKX2-3+	CDKN2A	1.15E-97
NKX2-3+	SOX4	7.17E-97
NKX2-3+	ALCAM	1.14E-96
NKX2-3+	RPS19	7.33E-95
NKX2-3+	CD99L2	1.48E-94
NKX2-3+	PLCZ1	3.45E-93
NKX2-3+	GPR98	6.80E-93
NKX2-3+	MDM4	6.78E-92
NKX2-3+	SNTB1	1.98E-91
NKX2-3+	EYA2	1.31E-88
NKX2-3+	DNAH14	1.87E-83
NKX2-3+	CTD-2034I4.1	1.60E-82
NKX2-3+	L3MBTL4	6.10E-82
NKX2-3+	SYCP2	1.05E-79
NKX2-3+	CA1	1.15E-79
NKX2-3+	NEBL	1.04E-76
NKX2-3+	PLEKHA5	2.81E-73
NKX2-3+	RP11-1084J3.4	5.71E-71
NKX2-3+	RP11-25H12.1	3.28E-69
NKX2-3+	KCNB2	5.22E-69
NKX2-3+	SEC11C	1.01E-68
NKX2-3+	FRMPD4	9.96E-68
NKX2-3+	RP11-337C18.8	1.73E-67
NKX2-3+	RP11-664H17.1	3.69E-67
NKX2-3+	FMO3	5.09E-67
NKX2-3+	ATP13A3	6.56E-67
NKX2-3+	RP11-69E11.4	2.42E-65
NKX2-3+	NKX2-1	2.49E-64
NKX2-3+	MLPH	2.00E-63
NKX2-3+	RP11-120J1.1	6.04E-63
NKX2-3+	GALNT1	1.56E-62
NKX2-3+	ALDH3A2	1.93E-62
NKX2-3+	CDH7	2.10E-62
NKX2-3+	RPLP2	5.76E-62
NKX2-3+	RNMT	1.67E-61
NKX2-3+	MECOM	5.89E-61
NKX2-3+	HLA-C	6.25E-61
NKX2-3+	VEGFA	1.49E-60
NKX2-3+	WDR49	4.83E-59
NKX2-3+	SOX2	5.81E-59
VEGFC+	RASA4B	5.00E-05
VEGFC+	MYCT1	6.06E-05
VEGFC+	GJA1	6.47E-05
VEGFC+	PHF10	9.40E-05
VEGFC+	TEX22	1.12E-04
VEGFC+	SERPINE1	1.59E-04
VEGFC+	TNFAIP1	3.23E-04
VEGFC+	TAOK2	4.46E-04
VEGFC+	DUSP5	4.51E-04
VEGFC+	SHROOM1	4.62E-04
VEGFC+	LINC00968	5.26E-04
VEGFC+	LMCD1	1.02E-03
VEGFC+	THBD	1.15E-03
VEGFC+	RP11-90K6.1	1.46E-03
VEGFC+	SLC10A6	1.63E-03
VEGFC+	RP11-420O16.1	2.05E-03
VEGFC+	MID2	3.95E-03
VEGFC+	GUCA1C	4.09E-02
Lymphatic endothelial	PKHD1L1	0.00E+00
Lymphatic endothelial	MMRN1	1.65E-229
Lymphatic endothelial	CCL21	3.71E-187
Lymphatic endothelial	AC007319.1	1.74E-184
Lymphatic endothelial	PPFIBP1	7.34E-184
Lymphatic endothelial	CD36	9.13E-174
Lymphatic endothelial	ST6GALNAC3	4.44E-156
Lymphatic endothelial	RELN	5.25E-156
Lymphatic endothelial	TFPI	2.85E-132
Lymphatic endothelial	TSHZ2	3.65E-129
Lymphatic endothelial	CTD-3179P9.1	1.81E-128
Lymphatic endothelial	KALRN	1.90E-124
Lymphatic endothelial	RP4-678D15.1	3.06E-113
Lymphatic endothelial	RP11-782C8.2	3.15E-112
Lymphatic endothelial	LYVE1	1.18E-110
Lymphatic endothelial	RHOJ	7.76E-106
Lymphatic endothelial	DOCK5	2.92E-105
Lymphatic endothelial	EFNA5	1.29E-102
Lymphatic endothelial	RP11-417J8.6	4.78E-101
Lymphatic endothelial	CTB-118N6.3	4.68E-96
Lymphatic endothelial	PTPRE	1.93E-90
Lymphatic endothelial	ARHGAP26	3.42E-87
Lymphatic endothelial	LDB2	1.04E-79
Lymphatic endothelial	MMP28	4.23E-78
Lymphatic endothelial	DLG1	6.24E-74
Lymphatic endothelial	STOX2	8.86E-73
Lymphatic endothelial	EMP1	1.54E-72
Lymphatic endothelial	SLC22A23	9.56E-72
Lymphatic endothelial	CTB-107G13.1	2.47E-71
Lymphatic endothelial	KANK3	6.39E-68
Lymphatic endothelial	PROX1	2.35E-64
Lymphatic endothelial	SASH1	3.47E-62
Lymphatic endothelial	MAGI1	1.74E-61
Lymphatic endothelial	C6orf141	4.73E-61
Lymphatic endothelial	KIAA1671	6.56E-60
Lymphatic endothelial	GPR97	2.27E-59
Lymphatic endothelial	VAV3	1.45E-58
Lymphatic endothelial	PPAP2A	4.81E-58
Lymphatic endothelial	TBX1	1.39E-56
Lymphatic endothelial	KLF6	2.28E-56
Lymphatic endothelial	TIMP3	2.30E-56
Lymphatic endothelial	STON2	3.10E-56
Lymphatic endothelial	TLL1	7.04E-54
Lymphatic endothelial	ZDHHC14	1.02E-52
Lymphatic endothelial	AC139100.3	4.29E-51
Lymphatic endothelial	CNKSR3	1.41E-48
Lymphatic endothelial	PARD6G	2.56E-48
Lymphatic endothelial	SPTBN1	5.73E-48
Lymphatic endothelial	PIEZO2	1.11E-47
Lymphatic endothelial	SNTG2	4.94E-46
Lymphatic endothelial	NHSL1	1.09E-45
Lymphatic endothelial	FRMD4B	1.54E-45
Lymphatic endothelial	RALGAPA2	3.16E-44
Lymphatic endothelial	PIK3C2G	1.77E-43
Lymphatic endothelial	NRG3	7.59E-42

Epithelial	GDA	7.30E-96
Epithelial	LINC00511	2.02E-94
Epithelial	EPCAM	1.48E-93
Epithelial	ATP1A1	2.12E-92
Epithelial	SGK2	4.97E-92
Epithelial	CEA	7.04E-92
Epithelial	MUC13	1.32E-91
Epithelial	TMPRSS4	1.47E-91
Epithelial	MT-CO1	2.42E-91
Epithelial	LINC00278	1.57E-90
Epithelial	PLS1	2.71E-90
Epithelial	BCAS1	3.91E-90
Epithelial	MYH14	1.25E-89
Epithelial	GCNT3	8.51E-89
Epithelial	TRIM31-AS1	9.19E-89
Epithelial	ABCC3	3.22E-87
Epithelial	TMIGD1	1.34E-86
Epithelial	GPA33	2.63E-86
Epithelial	MGLL	2.74E-86
Epithelial	MT-CO2	4.98E-86
Epithelial	CLCA4	1.63E-85
Epithelial	PIGZ	3.52E-84
Epithelial	EZR	4.66E-84
Epithelial	PAG1	2.43E-83
Epithelial	CA4	2.76E-83
Epithelial	MYO1E	2.90E-83
Epithelial	NEDD4L	2.99E-83
Epithelial	FAM3D	1.69E-81
Epithelial	DHRS9	2.81E-80
Epithelial	CLDN3	4.40E-80
Epithelial	AGR3	1.13E-79
Epithelial	TINAG	1.21E-79
Epithelial	ST14	1.10E-78
Epithelial	CA12	3.81E-78
Epithelial	RP11-747D18.1	4.74E-78
Epithelial	HDHD3	1.04E-77
Epithelial	GRAMD3	1.45E-77
Epithelial	NXPE1	1.78E-77
Epithelial	SLC4A4	6.02E-77
Epithelial	MT-CO3	5.80E-76
Epithelial	CXADR	1.06E-74
Epithelial	ITM2C	1.49E-74
Epithelial	PDE3A	1.31E-73
Epithelial	MXD1	7.57E-73
Epithelial	MAST2	8.24E-73
Epithelial	SLC44A4	3.04E-72
Epithelial	TFCP2L1	1.14E-71
Epithelial	RBM47	1.96E-71
Epithelial	KRT18	3.48E-71
Epithelial	ACSS2	3.67E-71
Epithelial	KRT8	2.57E-70
Epithelial	SCNN1B	7.73E-70
Epithelial	PRSS8	1.40E-69
Epithelial	PPARGC1A	6.97E-69
Epithelial	B3GALT5	2.92E-68
Epithelial	PDZD3	6.35E-67
Epithelial	AQP8	1.00E-66
Epithelial	EPS8L3	2.54E-66
Epithelial	TMEM54	3.86E-66
Epithelial	SERINC2	3.84E-64
Epithelial	CCDC64B	1.95E-59
Epithelial	RASSF7	4.58E-58
Epithelial	MTMR11	3.65E-57
Epithelial	TMEM171	6.61E-57
Epithelial	FAM132A	7.20E-57
Epithelial	VSIG2	2.98E-56
Epithelial	LYPD8	1.75E-54
Epithelial	TFF3	2.92E-53
Epithelial	CTD-2228K2.5	6.91E-53
Epithelial	TRIM31	8.16E-52
Epithelial	MALL	2.04E-50
Epithelial	RP11-396O20.2	6.09E-46
Epithelial	C19orf33	3.16E-45
NKX2-3+	SFTA3	5.81E-59
NKX2-3+	KCTD8	3.82E-58
NKX2-3+	CP	8.27E-57
NKX2-3+	WARS	1.36E-56
NKX2-3+	FMR1	1.41E-56
NKX2-3+	RP11-793A3.2	2.96E-56
NKX2-3+	KCNK1	3.36E-56
NKX2-3+	AL589743.1	1.17E-55
NKX2-3+	MDK	8.66E-55
NKX2-3+	RPL10	5.09E-54
NKX2-3+	CD74	6.64E-54
NKX2-3+	RP11-361I14.2	2.54E-53
NKX2-3+	AC159540.1	2.94E-53
NKX2-3+	SLC34A2	5.45E-53
NKX2-3+	CEACAM6	1.32E-52
NKX2-3+	RPS27	2.47E-52
NKX2-3+	RP11-638I2.8	4.26E-52
NKX2-3+	ABHD3	1.25E-51
NKX2-3+	SMCHD1	2.04E-51
NKX2-3+	IFI27	3.45E-51
NKX2-3+	GDE1	8.45E-51
NKX2-3+	RERGL	9.99E-51
NKX2-3+	FANCL	2.37E-50
NKX2-3+	RPLP1	2.48E-49
NKX2-3+	SMC4	5.82E-49
NKX2-3+	RPS23	6.16E-49
NKX2-3+	OOEP	9.82E-49
NKX2-3+	NUCKS1	1.16E-48
NKX2-3+	CDKAL1	3.79E-48
NKX2-3+	KLK12	6.25E-48
NKX2-3+	CHODL	6.70E-48
NKX2-3+	HES6	7.96E-48
NKX2-3+	GALNTL6	1.40E-47
NKX2-3+	RP11-191L9.4	1.43E-47
NKX2-3+	RPL38	2.45E-47
NKX2-3+	HLA-F	5.34E-47
NKX2-3+	TOX3	1.46E-46
NKX2-3+	CLDN3	6.73E-44
NKX2-3+	FOXA1	3.94E-42
NKX2-3+	RDH10	7.20E-42
NKX2-3+	EHF	1.96E-39
NKX2-3+	SLFN13	2.88E-37
NKX2-3+	FAM111B	6.36E-37
NKX2-3+	E2F1	3.46E-36
NKX2-3+	TFAP2A	3.15E-33
NKX2-3+	ASPM	3.16E-33
NKX2-3+	PNMA3	1.17E-32
NKX2-3+	PRAME	1.20E-32
NKX2-3+	SLITRK6	1.89E-32
NKX2-3+	SLPI	1.30E-30
NKX2-3+	KLK11	3.43E-30
NKX2-3+	TCP10L2	3.68E-30
NKX2-3+	CENPK	1.83E-28
NKX2-3+	ASCL1	7.16E-28
NKX2-3+	CRNDE	1.08E-27
NKX2-3+	PFKFB2	4.01E-26
NKX2-3+	KRT18	1.74E-24
NKX2-3+	AC116614.1	2.26E-24
NKX2-3+	SLC15A5	3.95E-24
NKX2-3+	AC011298.2	3.59E-23
NKX2-3+	KRT7	6.11E-23
NKX2-3+	PLEKHG4B	4.51E-22
NKX2-3+	RASD1	8.08E-22
NKX2-3+	FAM84B	8.93E-21
NKX2-3+	HTR1F	2.89E-20
NKX2-3+	GBP5	3.19E-20
NKX2-3+	HOOK1	4.00E-20
NKX2-3+	SIX1	5.17E-20
NKX2-3+	HOXB7	6.97E-20
NKX2-3+	CNKSR1	3.96E-19
NKX2-3+	CALML5	4.43E-19
NKX2-3+	RP11-357H14.17	7.32E-19
NKX2-3+	PAX9	9.20E-19
Lymphatic endothelial	LRRC1	8.12E-42
Lymphatic endothelial	CLDN5	1.00E-41
Lymphatic endothelial	TFF3	1.07E-41
Lymphatic endothelial	GRAPL	1.36E-40
Lymphatic endothelial	SEMA6A	2.52E-40
Lymphatic endothelial	ARHGAP29	9.09E-40
Lymphatic endothelial	PDE1A	3.70E-39
Lymphatic endothelial	LRCOL1	6.69E-39
Lymphatic endothelial	NR2F2-AS1	2.26E-37
Lymphatic endothelial	SAP30BP	9.46E-37
Lymphatic endothelial	RP11-435B5.3	3.04E-36
Lymphatic endothelial	RP3-523E19.2	1.06E-35
Lymphatic endothelial	NTN1	2.26E-35
Lymphatic endothelial	PLEKHG1	7.67E-35
Lymphatic endothelial	RP11-527H14.2	7.79E-35
Lymphatic endothelial	GNAT3	8.28E-35
Lymphatic endothelial	CALCRL	5.97E-34
Lymphatic endothelial	ECSCR	8.38E-34
Lymphatic endothelial	ASAP1	2.23E-33
Lymphatic endothelial	ARHGAP26-AS1	2.20E-32
Lymphatic endothelial	RASGRP3	6.64E-32
Lymphatic endothelial	EGFL7	3.80E-31
Lymphatic endothelial	ZFPM2	7.83E-31
Lymphatic endothelial	EPB41L2	2.24E-30
Lymphatic endothelial	IL7	3.22E-30
Lymphatic endothelial	FLT4	6.17E-30
Lymphatic endothelial	PLXDC2	6.94E-30
Lymphatic endothelial	SMAD1	1.10E-29
Lymphatic endothelial	ADD3	1.92E-29
Lymphatic endothelial	DOCK9	5.76E-29
Lymphatic endothelial	PRKCH	1.03E-28
Lymphatic endothelial	RPGR	5.02E-28
Lymphatic endothelial	CATSPERB	6.57E-28
Lymphatic endothelial	EFCAB4A	1.13E-27
Lymphatic endothelial	ZNF521	1.27E-27
Lymphatic endothelial	AC139100.2	2.43E-27
Lymphatic endothelial	DNAJC18	2.77E-27
Lymphatic endothelial	TANC2	3.18E-27
Lymphatic endothelial	APP	3.91E-27
Lymphatic endothelial	RP11-14N7.2	6.95E-27
Lymphatic endothelial	KLHL4	8.25E-27
Lymphatic endothelial	TSPAN5	9.04E-27
Lymphatic endothelial	PLD1	2.97E-26
Lymphatic endothelial	DPYSL3	7.58E-26
Lymphatic endothelial	STK32B	7.98E-26
Lymphatic endothelial	CYP8B1	1.32E-25
Lymphatic endothelial	RGS16	1.86E-25
Lymphatic endothelial	RP11-782C8.5	3.62E-24
Lymphatic endothelial	PROX1-AS1	4.95E-24
Lymphatic endothelial	SH3BGRL2	1.67E-21
Lymphatic endothelial	PANK2	3.62E-20
Lymphatic endothelial	SLC9C1	3.90E-20
Lymphatic endothelial	STC1	4.39E-20
Lymphatic endothelial	DPEP2	5.36E-20
Lymphatic endothelial	ARL4A	3.29E-19
Lymphatic endothelial	SNCG	6.64E-19
Lymphatic endothelial	LINC01117	9.46E-19
Lymphatic endothelial	RP11-435B5.5	1.96E-18
Lymphatic endothelial	KBTBD11	6.84E-18
Lymphatic endothelial	RP11-327I22.6	4.13E-17
Lymphatic endothelial	IGF1	1.31E-16
Lymphatic endothelial	ZNF554	1.37E-16
Lymphatic endothelial	PTPN3	1.39E-16
Lymphatic endothelial	CTD-2536I1.1	3.17E-16
Lymphatic endothelial	KDR	6.20E-16
Lymphatic endothelial	ART4	1.66E-15
Lymphatic endothelial	MAP4K2	2.62E-15
Lymphatic endothelial	TSTA3	6.35E-15
Lymphatic endothelial	PEAR1	4.30E-14
Lymphatic endothelial	RP11-776H12.1	4.92E-14
Lymphatic endothelial	SCN3B	7.62E-14
Lymphatic endothelial	EYA1	1.57E-13
Lymphatic endothelial	TAL1	7.50E-13

Epithelial	COL17A1	3.65E-44
Epithelial	ENTPD8	2.03E-41
Epithelial	GUCA2B	3.50E-41
Epithelial	MEP1A	6.29E-41
Epithelial	HMGCS2	1.31E-38
Epithelial	USH1C	3.21E-38
Epithelial	VIPR1	9.98E-38
Epithelial	FUT3	6.97E-37
Epithelial	DHRS11	1.02E-36
Epithelial	C10orf99	2.23E-36
Epithelial	NXPE4	1.73E-35
Epithelial	PRR15L	6.12E-34
Epithelial	TFF1	8.37E-34
Epithelial	GPT	5.88E-33
Epithelial	ARHGEF16	6.52E-33
Epithelial	ZG16	9.63E-32
Epithelial	CDKN2B	1.99E-31
Epithelial	MUC2	7.66E-31
Epithelial	RP11-357H14.17	6.65E-30
Epithelial	SMIM5	7.17E-30
Epithelial	RP5-1185I7.1	9.18E-30
Epithelial	PRR15	2.53E-27
Epithelial	ARL14	6.13E-25
Epithelial	RP11-59E19.1	1.01E-24
Epithelial	CHP2	2.78E-22
Epithelial	LGALS9C	4.22E-22
Epithelial	AC009133.14	2.65E-21
Epithelial	C12orf36	3.10E-20
Epithelial	AC024592.9	6.00E-20
Epithelial	APOBR	2.31E-19
Epithelial	RP11-567C2.1	5.56E-19
Epithelial	CLDN23	6.91E-19
Epithelial	DOK4	4.61E-18
Epithelial	RP11-465B22.8	5.73E-18
Epithelial	C11orf86	1.49E-17
Epithelial	C6orf222	1.30E-16
Epithelial	FAM110C	1.51E-16
Epithelial	TRIM15	2.17E-16
Epithelial	CLDN8	4.14E-16
Epithelial	FRMD1	4.37E-16
Epithelial	SLC6A19	3.11E-15
Epithelial	IL2RG	8.71E-15
Epithelial	MYO1A	1.94E-14
Epithelial	PRAP1	2.99E-14
Epithelial	MUC3A	7.24E-14
Epithelial	FGFR3	9.27E-14
Epithelial	HEPACAM2	1.75E-13
Fibroblast	LAMA2	1.87E-210
Fibroblast	DCN	4.37E-201
Fibroblast	ABCA6	7.85E-154
Fibroblast	PID1	4.25E-144
Fibroblast	RP4-678D15.1	1.44E-112
Fibroblast	GPC6	5.31E-105
Fibroblast	LINC00478	7.92E-103
Fibroblast	EBF1	1.04E-97
Fibroblast	FBN1	9.48E-94
Fibroblast	RP11-14N7.2	9.48E-94
Fibroblast	DLC1	6.92E-91
Fibroblast	TSHZ2	4.36E-89
Fibroblast	PLXDC2	5.19E-87
Fibroblast	MGP	1.39E-82
Fibroblast	SLIT2	3.53E-82
Fibroblast	DCLK1	3.53E-82
Fibroblast	RORA	2.54E-78
Fibroblast	RBMS3	1.55E-76
Fibroblast	MFAP5	1.51E-71
Fibroblast	MEG3	2.19E-70
Fibroblast	ABCA8	3.41E-63
Fibroblast	FBLN1	3.27E-58
Fibroblast	KAZN	4.47E-58
Fibroblast	RBMS3-AS3	3.71E-56
Fibroblast	AC005237.4	2.69E-55
Fibroblast	RP11-39M21.1	1.13E-54
NKX2-3+	ONECUT2	2.55E-16
NKX2-3+	RP11-328N19.1	7.72E-16
NKX2-3+	RP11-279F6.3	6.77E-15
NKX2-3+	FGL1	7.30E-15
NKX2-3+	RECQL4	1.06E-14
NKX2-3+	AC096670.3	1.28E-14
NKX2-3+	CNFN	1.31E-14
NKX2-3+	GEMIN4	7.60E-14
NKX2-3+	RP1	7.61E-14
NKX2-3+	TMEM30B	1.27E-13
NKX2-3+	MIOX	1.87E-13
NKX2-3+	COLCA1	4.45E-13
NKX2-3+	RP11-499F3.1	7.41E-13
NKX2-3+	RP11-96D1.11	1.93E-12
NKX2-3+	ZNF275	2.01E-12
NKX2-3+	RP11-683L23.1	3.44E-12
NKX2-3+	SLC6A20	4.23E-12
NKX2-3+	PLEKHG4	7.48E-12
NKX2-3+	GYLTL1B	1.35E-11
NKX2-3+	DLL1	2.48E-11
NKX2-3+	GBP4	6.70E-11
NKX2-3+	DUSP26	9.29E-11
NKX2-3+	SPINT1	1.97E-10
NKX2-3+	RAB17	2.28E-10
NKX2-3+	ZNF395	1.30E-09
NKX2-3+	BRPF3	1.59E-08
NKX2-3+	FANCB	6.66E-08
Neuron	MEG3	6.09E-160
Neuron	SYT1	5.80E-149
Neuron	UCHL1	1.59E-147
Neuron	PRPH	5.56E-130
Neuron	STMN2	5.42E-115
Neuron	MAP1B	2.69E-113
Neuron	CTNNA2	1.71E-110
Neuron	PCSK1N	6.16E-103
Neuron	KIF21A	1.91E-97
Neuron	ANK2	5.62E-94
Neuron	GAL	4.31E-90
Neuron	PARM1	1.95E-89
Neuron	THY1	5.21E-81
Neuron	VIP	2.29E-79
Neuron	MT-CO1	1.18E-78
Neuron	GAP43	1.26E-77
Neuron	MT-CO3	1.32E-76
Neuron	DSCAM	7.52E-76
Neuron	TMEM59L	2.54E-75
Neuron	PCDH9	1.20E-73
Neuron	TMEM108	2.17E-73
Neuron	MIR137HG	9.01E-73
Neuron	ELAVL4	2.20E-72
Neuron	SNAP25	5.29E-71
Neuron	SCG2	1.87E-70
Neuron	SNCG	3.64E-68
Neuron	UNC80	1.16E-64
Neuron	ALCAM	1.22E-64
Neuron	BAI3	1.46E-64
Neuron	PTPRN	4.55E-64
Neuron	KIF1A	1.39E-63
Neuron	GNG3	2.52E-63
Neuron	CHRNA3	5.49E-62
Neuron	MLLT11	5.49E-62
Neuron	RAB3B	5.74E-62
Neuron	AC016716.2	4.39E-60
Neuron	TAGLN3	8.26E-60
Neuron	CADM1	1.50E-59
Neuron	PCLO	7.79E-59
Neuron	HS6ST3	6.03E-58
Neuron	YWHAH	1.59E-57
Neuron	EML5	1.89E-57
Neuron	PLEKHA5	2.71E-57
Neuron	CNTNAP2	1.56E-56
Neuron	MT-CO2	1.82E-56
Neuron	NCAM2	1.95E-54
Lymphatic endothelial	ROBO4	2.02E-12
Lymphatic endothelial	RP11-423O2.5	1.11E-11
Lymphatic endothelial	DKK3	1.23E-11
Lymphatic endothelial	RP11-1070N10.4	1.44E-11
Lymphatic endothelial	CD200	1.13E-10
Lymphatic endothelial	CARD10	1.48E-10
Lymphatic endothelial	RP11-318M2.2	1.59E-10
Lymphatic endothelial	RHAG	3.41E-10
Lymphatic endothelial	RNF152	8.66E-10
Lymphatic endothelial	GJA1	8.85E-10
Lymphatic endothelial	C6orf123	1.59E-08
Lymphatic endothelial	C5orf64	2.85E-08
Lymphatic endothelial	CTA-221G9.11	3.54E-08
Lymphatic endothelial	RP4-640H8.2	4.15E-08
Lymphatic endothelial	RP11-728F11.4	5.79E-08
Lymphatic endothelial	AC010091.1	2.98E-07
Lymphatic endothelial	GRPEL2-AS1	7.68E-07
Lymphatic endothelial	LAYN	1.39E-06
Lymphatic endothelial	TNFAIP8L3	1.67E-06
Lymphatic endothelial	EFNA1	7.05E-06
Macrophages	RBPJ	4.86E-178
Macrophages	SRGN	2.09E-158
Macrophages	MS4A6A	2.76E-134
Macrophages	F13A1	1.07E-132
Macrophages	SAT1	8.03E-123
Macrophages	CD163	6.13E-114
Macrophages	RBM47	6.24E-104
Macrophages	LYVE1	1.26E-102
Macrophages	FRMD4B	1.42E-101
Macrophages	STK17B	2.09E-95
Macrophages	SRGAP2	2.77E-95
Macrophages	ZEB2	3.57E-94
Macrophages	RP11-347P5.1	1.38E-89
Macrophages	MAN1A1	4.97E-88
Macrophages	MSR1	3.48E-86
Macrophages	TBXAS1	7.73E-84
Macrophages	SLC9A9	4.03E-83
Macrophages	FGD2	6.09E-80
Macrophages	MAFB	1.18E-77
Macrophages	SYK	2.86E-74
Macrophages	CD74	1.43E-69
Macrophages	VSIG4	8.53E-69
Macrophages	LRRC16A	8.85E-68
Macrophages	CD14	1.76E-65
Macrophages	RP11-343N15.1	2.09E-64
Macrophages	MEF2C	2.31E-63
Macrophages	PTPRC	3.06E-62
Macrophages	CPM	4.09E-61
Macrophages	RP11-452H21.1	4.76E-57
Macrophages	TYMP	6.19E-57
Macrophages	CPVL	6.19E-57
Macrophages	FMN1	1.57E-56
Macrophages	STAB1	1.63E-56
Macrophages	TG	2.35E-56
Macrophages	FCGR2B	2.51E-56
Macrophages	SMAP2	1.46E-54
Macrophages	IQGAP2	5.41E-54
Macrophages	LILRB5	9.77E-54
Macrophages	DPYD	5.98E-53
Macrophages	MS4A4E	8.36E-52
Macrophages	ATG7	3.20E-51
Macrophages	ANXA1	3.43E-51
Macrophages	AMICA1	1.13E-50
Macrophages	MS4A4A	1.42E-50
Macrophages	SLCO2B1	4.02E-50
Macrophages	RCSD1	2.19E-49
Macrophages	ARHGAP18	2.76E-49
Macrophages	ATP8B4	6.55E-49
Macrophages	C5AR1	1.11E-47
Macrophages	PDGFC	4.99E-47
Macrophages	CD86	7.36E-47
Macrophages	CELF2	9.09E-47
Macrophages	RP11-701P16.2	1.26E-46

Fibroblast	ADH1B	2.56E-54
Fibroblast	DPT	1.67E-53
Fibroblast	C1orf21	3.11E-53
Fibroblast	COL5A2	8.10E-52
Fibroblast	CBLB	3.43E-51
Fibroblast	TNXB	6.39E-50
Fibroblast	UAP1	1.37E-48
Fibroblast	ACKR3	3.29E-48
Fibroblast	C7	1.09E-47
Fibroblast	LHFP	8.37E-47
Fibroblast	NEGR1	1.82E-46
Fibroblast	GFPT2	1.34E-43
Fibroblast	ABCA9	1.12E-41
Fibroblast	IGFBP6	2.20E-40
Fibroblast	NFIA	7.88E-40
Fibroblast	PLCB1	1.48E-37
Fibroblast	COL1A2	1.33E-36
Fibroblast	ADAMTS5	4.04E-36
Fibroblast	SH3PXD2B	4.08E-36
Fibroblast	LPAR1	1.18E-35
Fibroblast	COL3A1	2.44E-34
Fibroblast	ZBTB16	2.60E-34
Fibroblast	RERG	7.23E-34
Fibroblast	SVEP1	1.22E-32
Fibroblast	FABP6	2.00E-32
Fibroblast	KCNN3	2.23E-32
Fibroblast	GALNT15	7.53E-32
Fibroblast	BICC1	1.55E-31
Fibroblast	RHOBTB3	1.55E-31
Fibroblast	ADD3	1.29E-30
Fibroblast	CFD	5.92E-30
Fibroblast	AC007319.1	6.72E-30
Fibroblast	SDK1	2.76E-29
Fibroblast	STEAP2	6.07E-29
Fibroblast	LSP1	1.07E-28
Fibroblast	LAMB1	3.27E-28
Fibroblast	TSC22D3	6.61E-28
Fibroblast	NOX4	6.97E-28
Fibroblast	TGFBR3	9.37E-28
Fibroblast	PI16	1.69E-27
Fibroblast	FKBP5	1.96E-27
Fibroblast	SPON2	9.15E-27
Fibroblast	RP11-64D24.2	9.19E-27
Fibroblast	SCARA5	3.37E-26
Fibroblast	SLIT3	5.62E-26
Fibroblast	EXT1	1.20E-25
Fibroblast	MEDAG	1.33E-25
Fibroblast	MAML2	1.33E-25
Fibroblast	PRR16	1.80E-25
Fibroblast	FOXO3	3.65E-25
Fibroblast	LAMC1	5.12E-25
Fibroblast	SRPX2	8.17E-25
Fibroblast	FSTL1	2.21E-24
Fibroblast	EGR1	2.47E-24
Fibroblast	CILP	4.22E-24
Fibroblast	LUM	6.92E-24
Fibroblast	F3	1.27E-23
Fibroblast	LRRC16A	1.27E-23
Fibroblast	PLA2G2A	1.37E-23
Fibroblast	GSN	1.71E-23
Fibroblast	VCAN	2.98E-23
Fibroblast	MAPK10	7.96E-23
Fibroblast	AOX1	1.19E-22
Fibroblast	CCDC80	1.71E-22
Fibroblast	FAM65C	1.73E-22
Fibroblast	SCN7A	1.85E-22
Fibroblast	CREB5	1.90E-22
Fibroblast	PDGFRB	2.09E-22
Fibroblast	GPRC5A	4.05E-21
Fibroblast	RP11-597D13.9	4.73E-21
Fibroblast	PIK3R1	7.88E-21
Fibroblast	RP11-219B17.1	1.14E-20
Fibroblast	FMNL2	1.27E-20

Neuron	DKK3	3.95E-54
Neuron	MT-CYB	4.22E-54
Neuron	RALYL	8.84E-54
Neuron	L1CAM	1.20E-53
Neuron	BEX1	5.98E-53
Neuron	CEND1	2.88E-52
Neuron	CAMK4	2.60E-51
Neuron	CADPS	2.62E-51
Neuron	CARTPT	3.25E-51
Neuron	KIF5C	5.16E-51
Neuron	S100A6	7.32E-51
Neuron	SCN3A	4.22E-50
Neuron	FAIM2	4.80E-50
Neuron	NCAM1	6.12E-50
Neuron	KIF5A	8.67E-50
Neuron	STMN4	9.97E-50
Neuron	ARHGAP26	9.97E-50
Neuron	RTN1	1.51E-49
Neuron	NRSN1	7.21E-49
Neuron	RET	3.96E-48
Neuron	CADM3	5.56E-48
Neuron	MEG8	5.76E-48
Neuron	CACNA1B	5.82E-48
Neuron	TUBB2B	3.72E-47
Neuron	FHOD3	9.13E-47
Neuron	SYP	9.34E-47
Neuron	SCN9A	1.03E-46
Neuron	CDH2	1.03E-46
Neuron	SYT4	2.26E-46
Neuron	JAKMIP1	2.46E-45
Neuron	PTPRR	3.99E-45
Neuron	MT-ATP6	3.99E-45
Neuron	CTC-548K16.1	1.23E-44
Neuron	PCBP3	2.29E-44
Neuron	MAP2	2.98E-44
Neuron	TPPP3	3.29E-44
Neuron	LGALS1	3.38E-44
Neuron	DPYSL2	1.12E-43
Neuron	TUBA1B	1.72E-43
Neuron	ENTPD3	1.99E-43
Neuron	SPOCK2	5.33E-43
Neuron	CALM1	1.14E-42
Neuron	NCOA7	1.29E-42
Neuron	DCBLD2	3.95E-42
Neuron	ATP1B1	1.15E-41
Neuron	SGIP1	1.95E-41
Neuron	NOS1	2.13E-41
Neuron	FGF13	3.36E-41
Neuron	LPHN3	3.54E-41
Neuron	MIAT	3.91E-41
Neuron	ADAMTS19	4.86E-41
Neuron	KIAA1244	6.08E-41
Neuron	MAP1A	1.27E-40
Neuron	IFI27L2	1.28E-40
Neuron	CELF3	1.62E-40
Neuron	BEX2	2.84E-39
Neuron	TTC9B	2.06E-37
Neuron	RUNDC3A	6.72E-37
Neuron	AC008067.2	2.36E-36
Neuron	PDIA2	2.08E-35
Neuron	CALY	6.17E-35
Neuron	MAPK8IP2	8.52E-35
Neuron	SULT4A1	8.96E-33
Neuron	SYNGR3	1.52E-32
Neuron	CHGA	9.44E-31
Neuron	PHOX2B	1.98E-30
Neuron	TLX2	2.63E-30
Neuron	ADCYAP1	2.36E-28
Neuron	ODAM	7.09E-28
Neuron	BEX5	1.57E-26
Neuron	SYT5	1.71E-26
Neuron	PNMA2	4.88E-26
Neuron	GPR22	8.44E-25

Macrophages	PIK3R5	1.90E-46
Macrophages	NAMPT	3.78E-46
Macrophages	TFRC	4.28E-43
Macrophages	CLEC7A	6.58E-43
Macrophages	CTSB	9.96E-43
Macrophages	HCLS1	1.12E-42
Macrophages	SIGLEC1	6.21E-42
Macrophages	SLC11A1	1.15E-41
Macrophages	PLXDC2	3.97E-41
Macrophages	P2RY14	1.26E-40
Macrophages	RNF149	1.61E-40
Macrophages	DUSP1	1.63E-40
Macrophages	TSC22D3	3.02E-40
Macrophages	LGMN	8.29E-40
Macrophages	RGL1	1.84E-39
Macrophages	MCL1	2.99E-39
Macrophages	CLEC10A	3.97E-39
Macrophages	SH3TC1	4.98E-39
Macrophages	HDAC9	1.79E-38
Macrophages	RP11-815J21.4	2.63E-38
Macrophages	FTH1	5.46E-38
Macrophages	SLC1A3	6.44E-38
Macrophages	FCGR2A	1.25E-37
Macrophages	AKAP13	2.98E-37
Macrophages	DOCK8	4.33E-37
Macrophages	ARRB2	1.50E-36
Macrophages	FPR1	2.10E-36
Macrophages	PELI1	2.98E-36
Macrophages	CHN2	4.02E-36
Macrophages	TGFBI	7.65E-36
Macrophages	NAIP	8.18E-36
Macrophages	ACSL1	1.09E-35
Macrophages	IRAK3	1.83E-35
Macrophages	NCF4	3.73E-35
Macrophages	FAM49B	9.29E-35
Macrophages	C10orf11	3.06E-34
Macrophages	MTSS1	3.10E-34
Macrophages	RNF144B	3.32E-34
Macrophages	CSF3R	3.62E-34
Macrophages	PLTP	8.93E-34
Macrophages	MKRN3	1.34E-33
Macrophages	MYO1F	3.29E-33
Macrophages	MGAT1	3.35E-33
Macrophages	FLI1	3.53E-33
Macrophages	SIPA1L1	4.96E-33
Macrophages	IL10RA	5.62E-33
Macrophages	AOAH	6.68E-33
Macrophages	MRC1L1	7.87E-33
Macrophages	CD163L1	1.12E-32
Macrophages	LST1	7.47E-31
Macrophages	C1orf162	7.36E-29
Macrophages	SAMSN1	1.43E-28
Macrophages	FCN1	2.17E-28
Macrophages	C1QB	6.05E-28
Macrophages	RP11-553K8.5	1.32E-27
Macrophages	THEMIS2	1.59E-27
Macrophages	ITGAM	1.88E-25
Macrophages	EMB	2.45E-25
Macrophages	MUC6	1.59E-24
Macrophages	C1QA	4.58E-24
Macrophages	MRC1	4.97E-24
Macrophages	TNFAIP2	5.45E-24
Macrophages	MRVI1-AS1	6.81E-24
Macrophages	FAM177B	5.39E-23
Macrophages	HLA-DQB1	4.60E-22
Macrophages	HLA-DQA1	7.76E-22
Macrophages	TYROBP	2.61E-21
Macrophages	SIRPB2	4.08E-21
Macrophages	FAM196B	5.15E-21
Macrophages	CYTH4	1.08E-20
Macrophages	MIR142	6.89E-20
Macrophages	FOLR2	7.09E-20
Macrophages	RNASE1	4.40E-19

Fibroblast	PLEKHA5	1.49E-20
Fibroblast	MEG8	5.79E-20
Fibroblast	VIPR2	6.11E-20
Fibroblast	TEX26-AS1	2.68E-19
Fibroblast	NRK	4.79E-19
Fibroblast	PCOLCE	8.78E-18
Fibroblast	SLC5A9	2.05E-17
Fibroblast	RP11-99J16__A.2	6.49E-17
Fibroblast	PDGFRA	1.15E-16
Fibroblast	RP11-13N12.2	3.39E-16
Fibroblast	RP11-399D6.2	7.45E-16
Fibroblast	THBS2	4.93E-15
Fibroblast	CXXC5	4.98E-15
Fibroblast	MFGE8	8.98E-15
Fibroblast	HAS2-AS1	2.98E-14
Fibroblast	MCOLN3	3.52E-14
Fibroblast	CYP4A22-AS1	5.18E-14
Fibroblast	C1R	1.29E-13
Fibroblast	SFRP2	1.64E-13
Fibroblast	CYP4Z1	4.13E-13
Fibroblast	MMP2	8.88E-13
Fibroblast	RP11-66B24.4	1.08E-12
Fibroblast	RP11-201E8.1	1.25E-12
Fibroblast	AL132709.5	3.79E-12
Fibroblast	SERPINF1	2.04E-11
Fibroblast	PRRX1	2.26E-11
Fibroblast	ADAMTS16	2.53E-11
Fibroblast	CYP4X1	2.86E-11
Fibroblast	RP11-15M15.2	8.89E-11
Fibroblast	GPNMB	1.41E-10
Fibroblast	CD34	2.09E-10
Fibroblast	HTRA3	2.13E-10
Fibroblast	HAS2	2.60E-10
Fibroblast	PAK3	2.85E-10
Fibroblast	CXCL12	8.30E-10
Fibroblast	ADAMTS15	9.24E-10
Fibroblast	MMP19	1.24E-09
Fibroblast	RP11-554D13.1	1.72E-09
Fibroblast	TPBG	3.19E-09
Fibroblast	NYNRIN	4.54E-09
Fibroblast	ITGA11	4.58E-09
Fibroblast	INSRR	5.95E-09
Fibroblast	MMP23B	1.63E-08
Fibroblast	ADM	4.26E-08
Fibroblast	AP001172.2	4.98E-08
Fibroblast	CYP4B1	1.17E-07
Fibroblast	C10orf55	1.74E-07
Fibroblast	C4orf17	2.52E-07
Fibroblast	AC079742.4	3.96E-07
Fibroblast	RP4-530I15.6	7.85E-07
Fibroblast	SHC3	1.09E-06
Fibroblast	ABCA9-AS1	9.11E-06
Glia	CDH19	0.00E+00
Glia	BAI3	0.00E+00
Glia	PPP2R2B	8.93E-246
Glia	CADM2	2.13E-229
Glia	NRXN3	1.09E-221
Glia	NRXN1	1.22E-157
Glia	ANGPTL1	5.88E-154
Glia	ABCA8	4.94E-144
Glia	SHISA9	3.53E-139
Glia	ANK2	1.66E-128
Glia	NKAIN3	1.77E-128
Glia	ANK3	2.03E-128
Glia	XKR4	1.93E-121
Glia	CHL1	5.42E-117
Glia	RALGPS2	6.33E-116
Glia	SORCS1	1.62E-114
Glia	LRRTM4	3.34E-112
Glia	PRIMA1	4.70E-112
Glia	RP11-242P2.1	1.40E-110
Glia	EPB41L2	2.00E-108
Glia	SLC35F1	1.24E-105
Neuron	MT3	2.76E-24
Neuron	FKBP1B	4.10E-24
Neuron	LINC00599	2.05E-22
Neuron	OGDHL	3.62E-22
Neuron	GNG8	4.08E-21
Neuron	RP11-272L13.3	1.42E-20
Neuron	RP11-650L12.2	5.16E-20
Neuron	POU3F3	1.40E-19
Neuron	NEFM	2.34E-19
Neuron	VSTM2A	1.72E-18
Neuron	GCGR	1.73E-18
Neuron	SLC4A3	5.92E-18
Neuron	NAP1L3	2.05E-16
Neuron	TAC1	4.02E-16
Neuron	PENK	4.32E-16
Neuron	ST8SIA3	5.34E-16
Neuron	KIF26A	5.36E-16
Neuron	TMEM63C	7.40E-16
Neuron	TRPA1	5.84E-15
Neuron	RP11-490G2.2	7.72E-14
Neuron	C12orf68	1.74E-13
Neuron	CDK5R2	2.75E-13
Neuron	LRRC55	5.46E-13
Neuron	NPY	7.17E-13
Neuron	SLC10A4	7.38E-13
Neuron	KCNC1	1.38E-12
Neuron	TCEAL5	2.64E-12
Neuron	PIANP	2.82E-12
Neuron	VGF	4.03E-12
Neuron	GPR42	5.40E-12
Neuron	KLHL34	2.81E-11
Neuron	FFAR3	3.36E-11
Neuron	TUBB4A	5.84E-11
Neuron	TCEAL6	1.08E-10
Neuron	ZDHHC22	1.55E-10
Neuron	LINC00086	2.12E-10
Neuron	SLC35D3	2.25E-10
Neuron	NPY2R	2.87E-10
Neuron	TMEM151A	3.56E-10
Neuron	HR	3.61E-10
Neuron	RPRML	1.28E-09
Neuron	NAT8L	1.61E-09
Neuron	CAMK1G	2.71E-09
Neuron	DIRAS1	2.88E-09
Neuron	RP11-98D18.1	4.89E-09
Neuron	CPNE6	1.09E-08
Neuron	FAM131B	1.30E-08
Neuron	SCRT1	1.87E-08
Neuron	AC079154.1	2.50E-08
Neuron	ASIC3	3.78E-08
Neuron	RP11-122K13.14	5.05E-08
Neuron	RP11-531A24.3	6.31E-08
Neuron	RP4-555D20.2	6.84E-08
Neuron	CELSR3	2.34E-07
Neuron	RP11-284N8.3	5.28E-07
Neuron	HMX2	6.25E-07
Neuron	CAMK2N2	8.21E-07
Neuron	USP35	1.42E-06
Neuron	CCDC78	1.68E-06
Neuron	HOXD1	3.26E-06
Neuron	RP11-1002K11.1	1.52E-05
Neuron	ZCCHC12	3.37E-04
Neuron	C5orf30	8.16E-04
Neuron	LINC00087	9.95E-03
Pericytes	PDGFRB	7.98E-124
Pericytes	RCAN2	4.19E-110
Pericytes	PRKG1	3.32E-107
Pericytes	RGS6	1.30E-103
Pericytes	KCNAB1	3.70E-91
Pericytes	FHL5	3.60E-77
Pericytes	ACTA2	5.05E-76
Pericytes	NR2F2-AS1	4.89E-69
Pericytes	HEYL	3.77E-68
Macrophages	FMNL1	3.39E-18
Macrophages	CD83	3.82E-18
Macrophages	LAPTM5	5.05E-18
Macrophages	CMKLR1	1.49E-17
Macrophages	CTD-2337J16.1	1.62E-16
Macrophages	FCER1G	1.76E-16
Macrophages	MNDA	5.26E-16
Macrophages	LILRB2	6.17E-16
Macrophages	CCL3	1.81E-15
Macrophages	CLEC4E	2.91E-15
Macrophages	LILRB4	1.09E-14
Macrophages	PARVG	1.38E-14
Macrophages	C1QC	5.06E-14
Macrophages	GPR183	1.79E-13
Macrophages	DOK2	2.17E-13
Macrophages	EREG	4.07E-13
Macrophages	MCOLN1	1.79E-12
Macrophages	IRF8	1.93E-12
Macrophages	SCN1B	2.85E-12
Macrophages	OVOL3	4.87E-12
Macrophages	WAS	1.12E-10
Macrophages	TLR2	1.50E-10
Macrophages	TLR1	1.86E-08
Macrophages	HRH2	2.55E-08
Macrophages	LILRB3	3.76E-08
Macrophages	CD68	7.67E-08
Macrophages	UNC93B1	9.71E-08
Macrophages	OSCAR	4.78E-06
Macrophages	CXCL16	6.43E-06
Monocytes	FTL	8.47E-195
Monocytes	TMSB4X	5.91E-185
Monocytes	FTH1	6.81E-176
Monocytes	B2M	5.64E-165
Monocytes	HLA-DRA	1.73E-150
Monocytes	CD74	2.60E-147
Monocytes	TYROBP	2.55E-138
Monocytes	S100A9	2.66E-135
Monocytes	TPT1	1.72E-132
Monocytes	S100A4	1.15E-131
Monocytes	RPLP1	1.15E-131
Monocytes	OAZ1	1.37E-131
Monocytes	GPX1	1.71E-129
Monocytes	CST3	3.75E-129
Monocytes	FCER1G	2.65E-128
Monocytes	LGALS1	6.87E-126
Monocytes	TMSB10	9.09E-126
Monocytes	RPL19	4.30E-124
Monocytes	SH3BGRL3	6.57E-123
Monocytes	SERF2	6.33E-122
Monocytes	CYBA	4.28E-121
Monocytes	RPL15	3.84E-118
Monocytes	S100A11	4.24E-118
Monocytes	RPS19	7.41E-118
Monocytes	RPS9	2.21E-116
Monocytes	RPL13A	2.21E-116
Monocytes	RPS14	3.55E-115
Monocytes	RPL13	2.77E-114
Monocytes	MT-CO1	2.77E-114
Monocytes	RPL11	4.91E-111
Monocytes	RPS27A	9.78E-111
Monocytes	MT-CO3	9.78E-111
Monocytes	NPC2	3.53E-110
Monocytes	RPL28	4.36E-108
Monocytes	MT-ND1	2.48E-107
Monocytes	CFL1	8.36E-107
Monocytes	LYZ	3.59E-104
Monocytes	HLA-DRB1	1.65E-103
Monocytes	RPS15	7.32E-103
Monocytes	RPS23	7.85E-103
Monocytes	RPS12	8.44E-103
Monocytes	RPL7	8.72E-102
Monocytes	UBA52	4.26E-98
Monocytes	PFN1	6.58E-95

Glia	GINS3	1.09E-104
Glia	FRMD5	1.11E-93
Glia	ZNF536	1.44E-93
Glia	NKAIN2	1.29E-92
Glia	PTPRZ1	3.34E-92
Glia	LSAMP	2.11E-90
Glia	LGI4	5.04E-88
Glia	DOCK5	2.45E-87
Glia	WDR86	2.90E-84
Glia	QKI	5.57E-84
Glia	BCL2	8.33E-83
Glia	AP000462.2	2.19E-82
Glia	ASAP2	9.12E-81
Glia	RP3-525N10.2	2.76E-77
Glia	CTNND2	3.14E-77
Glia	LPHN3	2.16E-75
Glia	RP11-242P2.2	1.53E-74
Glia	LRRTM3	2.66E-71
Glia	KIAA1217	2.36E-70
Glia	SYT10	4.99E-70
Glia	KIRREL3	5.38E-70
Glia	KCNMB4	6.81E-68
Glia	NCAM1	2.32E-67
Glia	CASC14	4.54E-67
Glia	LPAR1	1.91E-66
Glia	CADM1	1.64E-65
Glia	SAMHD1	5.44E-65
Glia	LINC00478	5.36E-64
Glia	HMCN1	5.05E-63
Glia	GRIK3	1.28E-62
Glia	HAND2-AS1	1.62E-61
Glia	CTNNA3	1.35E-60
Glia	POLR2F	1.17E-55
Glia	SGIP1	1.36E-55
Glia	PRKCA	1.11E-54
Glia	MEG3	6.08E-53
Glia	SOX6	7.65E-53
Glia	TSPAN11	2.63E-52
Glia	HAND2	1.06E-51
Glia	COL28A1	3.70E-51
Glia	AQP4-AS1	1.11E-50
Glia	GPM6B	5.10E-50
Glia	MARCH10	5.51E-49
Glia	SEMA3C	2.28E-48
Glia	SAT1	3.97E-48
Glia	ST3GAL6	1.01E-47
Glia	TRDN	3.78E-46
Glia	CTD-2544M6.1	5.14E-46
Glia	PLCE1	1.06E-45
Glia	ZSWIM6	1.15E-45
Glia	AC018890.6	1.41E-45
Glia	EHBP1	2.02E-45
Glia	SCN7A	2.73E-45
Glia	HIBCH	1.11E-43
Glia	WIPF1	1.55E-43
Glia	NCAM2	2.71E-43
Glia	INSC	5.35E-43
Glia	RP11-308N19.1	9.60E-42
Glia	NRG3	1.89E-41
Glia	RP11-77K12.4	3.36E-41
Glia	COL21A1	3.89E-41
Glia	COL18A1	1.99E-40
Glia	CD9	3.93E-40
Glia	FIGN	5.69E-40
Glia	RASSF4	1.22E-39
Glia	FADS2	2.75E-38
Glia	RP11-4F22.2	3.18E-37
Glia	GPR155	4.45E-37
Glia	COL9A3	8.81E-37
Glia	RP11-115C10.1	3.94E-36
Glia	SORBS2	5.20E-36
Glia	MICALL2	8.13E-36
Glia	RP11-532N4.2	8.75E-36

Pericytes	SORBS2	2.07E-63
Pericytes	MT2A	5.06E-62
Pericytes	DGKG	2.64E-59
Pericytes	CLMN	3.95E-58
Pericytes	MT1E	8.22E-57
Pericytes	RP11-140I24.1	5.67E-53
Pericytes	DLC1	4.10E-51
Pericytes	LPP	1.06E-49
Pericytes	IGFBP7	1.24E-46
Pericytes	NTRK3	1.62E-46
Pericytes	EDNRA	4.11E-46
Pericytes	INPP4B	9.56E-46
Pericytes	FRY	1.69E-42
Pericytes	RASAL2	2.81E-42
Pericytes	ATP10A	5.00E-41
Pericytes	MT1M	5.00E-41
Pericytes	HES4	5.00E-41
Pericytes	ADCY3	1.40E-40
Pericytes	PTPRG	2.13E-40
Pericytes	ATP1B3	2.13E-40
Pericytes	RBPMS	3.45E-40
Pericytes	TINAGL1	9.30E-40
Pericytes	CTD-2009A10.1	7.25E-39
Pericytes	SPARCL1	2.35E-36
Pericytes	TBX2	3.68E-36
Pericytes	TACC1	3.70E-36
Pericytes	AC007401.2	1.87E-35
Pericytes	FRMD4A	9.09E-35
Pericytes	ZBTB7C	1.05E-34
Pericytes	EBF1	1.98E-34
Pericytes	CALD1	8.87E-34
Pericytes	SLC7A2	1.21E-33
Pericytes	CDH6	3.63E-33
Pericytes	NOTCH3	4.21E-33
Pericytes	SLIT3	5.29E-33
Pericytes	RP11-444D3.1	4.14E-32
Pericytes	HIP1	7.28E-32
Pericytes	ELN	1.18E-31
Pericytes	ARHGEF7	1.15E-30
Pericytes	SYTL2	1.35E-30
Pericytes	PPAP2B	3.84E-30
Pericytes	SLC6A1-AS1	2.81E-29
Pericytes	EPS8	4.47E-29
Pericytes	RNF152	2.28E-28
Pericytes	LDB3	3.00E-28
Pericytes	ZFHX3	4.90E-28
Pericytes	PICALM	1.07E-27
Pericytes	DBR1	1.23E-27
Pericytes	CAV2	1.77E-26
Pericytes	LPHN3	2.60E-26
Pericytes	ID3	4.11E-26
Pericytes	RYR2	6.45E-26
Pericytes	JAG1	6.41E-25
Pericytes	ZNF331	1.53E-24
Pericytes	BAIAP2L2	1.78E-24
Pericytes	EDIL3	2.01E-24
Pericytes	CRIM1	1.20E-23
Pericytes	CPM	1.20E-23
Pericytes	MCAM	1.73E-23
Pericytes	TIMP3	2.18E-23
Pericytes	NPNT	3.20E-23
Pericytes	RP11-223C24.1	7.45E-23
Pericytes	SLC38A11	7.78E-23
Pericytes	ITGA8	1.32E-22
Pericytes	PPFIA2	2.85E-22
Pericytes	CRISPLD2	4.11E-22
Pericytes	PTEN	5.56E-22
Pericytes	ADIRF	1.64E-21
Pericytes	SMIM12	2.95E-21
Pericytes	STEAP4	3.02E-21
Pericytes	GRK5	3.02E-21
Pericytes	AC140912.1	6.03E-21
Pericytes	FKBP5	6.03E-21

Monocytes	HLA-DPB1	7.54E-95
Monocytes	RPS6	8.12E-95
Monocytes	MT-ND4	5.15E-94
Monocytes	RPL29	1.13E-93
Monocytes	ARPC1B	1.42E-93
Monocytes	RPS4X	1.78E-93
Monocytes	S100A6	2.24E-93
Monocytes	RPL30	3.34E-93
Monocytes	EEF1A1	4.04E-93
Monocytes	RPS18	6.45E-93
Monocytes	MT-ND2	8.31E-93
Monocytes	COX4I1	2.07E-92
Monocytes	S100A8	4.33E-92
Monocytes	DBI	1.68E-91
Monocytes	RPL27A	1.14E-90
Monocytes	RPL10	3.80E-90
Monocytes	RPL8	6.24E-90
Monocytes	RPLP0	2.35E-89
Monocytes	RPS13	3.95E-89
Monocytes	RPS7	1.01E-87
Monocytes	RPLP2	2.99E-87
Monocytes	MT-CYB	5.20E-87
Monocytes	RPS24	7.69E-87
Monocytes	RPS20	4.76E-86
Monocytes	RPL6	1.60E-85
Monocytes	AIF1	5.04E-85
Monocytes	CSTB	1.69E-84
Monocytes	RPS8	5.89E-84
Monocytes	HLA-DPA1	3.21E-83
Monocytes	CD63	3.52E-83
Monocytes	RPL14	7.64E-83
Monocytes	SAT1	8.90E-83
Monocytes	EIF1	9.53E-83
Monocytes	SRP14	1.05E-81
Monocytes	ACTB	2.70E-81
Monocytes	YBX1	4.26E-81
Monocytes	RPL3	5.98E-81
Monocytes	MT-CO2	8.87E-81
Monocytes	RPS3A	6.13E-80
Monocytes	RPS5	2.27E-79
Monocytes	RPL27	4.98E-79
Monocytes	GAPDH	3.93E-78
Monocytes	FAU	1.99E-77
Monocytes	PSAP	4.47E-77
Monocytes	MT-ATP6	2.16E-76
Monocytes	TUBA1B	4.48E-76
Monocytes	RPL34	4.48E-76
Monocytes	RPL18	8.94E-76
Monocytes	EEF1B2	1.44E-75
Monocytes	RPS11	1.80E-75
Monocytes	PTPRC	2.55E-75
Monocytes	RPS2	5.03E-75
Monocytes	TSPO	8.26E-75
Monocytes	RPS3	9.37E-75
Monocytes	RPL23A	1.60E-74
Monocytes	RPL35A	6.38E-74
Monocytes	LAPTM5	4.48E-72
Monocytes	CD48	1.73E-64
Monocytes	ATP6V1F	1.38E-63
Monocytes	PYCARD	2.15E-62
Monocytes	LGALS3	5.63E-61
Monocytes	FXYD5	2.59E-59
Monocytes	LY86	1.46E-58
Monocytes	LST1	2.10E-54
Monocytes	HLA-DRB5	4.89E-54
Monocytes	HLA-DQB1	2.49E-51
Monocytes	CTSZ	5.91E-51
Monocytes	C1QC	7.53E-50
Monocytes	GADD45GIP1	2.22E-49
Monocytes	HLA-DQA1	1.02E-48
Monocytes	NKG7	1.56E-48
Monocytes	RHOG	2.13E-47
Monocytes	C1QB	2.45E-46

Glia	CASC15	9.89E-36
Glia	MAPRE2	2.41E-35
Glia	KCNH8	1.41E-34
Glia	CABLES2	2.26E-34
Glia	ATP8A1	2.99E-34
Glia	NLGN4X	3.96E-34
Glia	CA1	2.30E-33
Glia	DMKN	2.61E-32
Glia	ST6GALNAC2	1.51E-31
Glia	RP11-18D7.3	4.73E-30
Glia	RP11-142M10.2	8.19E-30
Glia	GPR126	1.35E-29
Glia	PLEKHB1	4.58E-29
Glia	CRISPLD1	2.16E-27
Glia	GRIK2	3.90E-26
Glia	SHC4	7.54E-26
Glia	CDH2	7.18E-25
Glia	MEGF6	2.67E-24
Glia	RP11-45A16.4	5.31E-24
Glia	ESM1	2.91E-23
Glia	RP11-386G21.1	8.84E-23
Glia	RP11-2E17.1	3.88E-22
Glia	RP4-663N10.1	1.61E-21
Glia	PMEPA1	5.55E-21
Glia	RP11-531H8.2	5.65E-21
Glia	LINC00327	3.04E-20
Glia	PAQR6	3.02E-19
Glia	COL11A1	3.49E-19
Glia	FXYD3	7.20E-18
Glia	S100B	2.92E-16
Glia	ITGB8	6.94E-16
Glia	RLBP1	9.94E-16
Glia	RP11-381K20.2	1.23E-15
Glia	SLC44A3	3.74E-15
Glia	HES1	4.72E-15
Glia	GAP43	1.12E-14
Glia	CDH6	1.22E-13
Glia	WNT16	2.07E-13
Glia	RP4-792G4.2	2.73E-13
Glia	PLP1	4.15E-13
Glia	RP11-391J2.3	8.87E-13
Glia	SRCIN1	2.17E-12
Glia	ACTR5	2.89E-12
Glia	RP11-776H12.1	6.02E-12
Glia	KCNK5	1.41E-11
Glia	CMTM5	1.73E-11
Glia	SOX2	2.07E-11
Glia	HSPA1B	2.13E-11
Glia	RP11-1055B8.3	6.41E-11
Glia	FXYD1	5.72E-10
Glia	PTGDS	9.11E-10
Glia	HEPN1	9.35E-09
Glia	GPC1	6.92E-08
Glia	CTC-255N20.1	1.11E-07
Glia	TBX3	1.34E-07
Glia	L1CAM	1.77E-07
Glia	AC090505.4	2.27E-07
Glia	RP11-202G11.2	2.01E-06
HAS1+	SOD2	3.77E-172
HAS1+	GFPT2	5.27E-171
HAS1+	RP11-66B24.4	6.00E-166
HAS1+	NAMPT	2.74E-155
HAS1+	ALDH1A3	2.44E-145
HAS1+	ACSL4	2.68E-134
HAS1+	C3	5.16E-130
HAS1+	HAS1	1.07E-129
HAS1+	MT2A	2.01E-129
HAS1+	TIMP1	1.13E-127
HAS1+	WWC1	8.53E-106
HAS1+	COBL	3.10E-105
HAS1+	AC016831.7	1.94E-102
HAS1+	FOSL1	5.11E-102
HAS1+	MCTP2	9.38E-101
Pericytes	NTN4	9.43E-21
Pericytes	AC002066.1	1.53E-20
Pericytes	CTGF	1.69E-20
Pericytes	RP11-436F23.1	3.25E-20
Pericytes	MYO1D	4.88E-20
Pericytes	FCHSD2	1.80E-19
Pericytes	MLIP	3.12E-19
Pericytes	RP11-315E17.1	7.47E-19
Pericytes	HIPK2	8.07E-19
Pericytes	RP11-1000B6.3	8.07E-19
Pericytes	ARHGEF10L	1.49E-18
Pericytes	RBMS3	3.09E-18
Pericytes	AGPS	3.57E-18
Pericytes	LINC01088	4.52E-18
Pericytes	LMOD1	4.93E-18
Pericytes	ESYT2	9.13E-18
Pericytes	RBMS3-AS3	1.13E-17
Pericytes	MFGE8	1.26E-17
Pericytes	PRMT10	1.26E-17
Pericytes	CSDC2	2.41E-17
Pericytes	EBF2	7.04E-17
Pericytes	PTP4A3	8.09E-17
Pericytes	LGI4	1.09E-16
Pericytes	CHSY3	1.64E-16
Pericytes	AC097724.3	3.69E-16
Pericytes	RP11-156K13.1	4.65E-16
Pericytes	NTRK2	6.81E-16
Pericytes	FRY-AS1	1.07E-15
Pericytes	MYO1B	1.65E-14
Pericytes	PRDM16	2.66E-14
Pericytes	MARK1	3.38E-14
Pericytes	ZFAND5	4.16E-14
Pericytes	MTHFD2	1.28E-13
Pericytes	CPE	3.06E-13
Pericytes	ALAD	7.01E-13
Pericytes	ISYNA1	9.48E-13
Pericytes	SLC22A3	4.13E-12
Pericytes	WTIP	7.11E-12
Pericytes	C1QTNF1	1.02E-11
Pericytes	LBH	2.19E-11
Pericytes	CENPO	2.34E-11
Pericytes	PTGIR	2.66E-11
Pericytes	PPP1CB	3.02E-11
Pericytes	USP2	1.53E-10
Pericytes	LINC00989	2.58E-10
Pericytes	SCN3A	3.77E-10
Pericytes	NR4A3	3.67E-09
Pericytes	GPRC5C	3.71E-09
Pericytes	HEY2	6.68E-09
Pericytes	LINC00702	8.26E-09
Pericytes	ADRA1A	1.06E-08
Pericytes	RP11-326A19.4	2.40E-08
Pericytes	NR2F2	2.44E-08
Pericytes	GLDN	1.02E-07
Pericytes	MICAL1	1.05E-07
Pericytes	HMGCLL1	2.19E-07
Pericytes	RP5-968D22.1	5.71E-07
Pericytes	RANBP3L	1.15E-06
Pericytes	HES1	1.16E-06
Pericytes	ID4	1.28E-06
Pericytes	GADD45G	3.18E-06
Pericytes	ADAMTS15	3.76E-06
Pericytes	GPR176	5.23E-06
Pericytes	PRRX1	5.69E-06
Pericytes	ADAMTS4	1.15E-05
Pericytes	FRK	1.26E-05
Pericytes	AC005863.2	8.91E-05
Pericytes	MIR22HG	1.27E-04
SDS+	EPHA7	4.53E-69
SDS+	DCC	2.69E-48
SDS+	LSAMP-AS1	1.50E-44
SDS+	SDS	2.28E-42
SDS+	AKAP12	3.28E-41
Monocytes	GPSM3	5.02E-44
Monocytes	CD68	1.40E-42
Monocytes	HLA-DMB	2.91E-42
Monocytes	HCST	7.34E-42
Monocytes	RP11-1143G9.4	2.53E-41
Monocytes	C1QA	4.89E-38
Monocytes	GPNMB	5.68E-38
Monocytes	FABP5	3.04E-36
Monocytes	RNASE6	1.78E-35
Monocytes	ZDHHC12	3.52E-35
Monocytes	USF2	1.27E-33
Monocytes	ARF6	3.73E-32
Monocytes	CXCR4	3.95E-32
Monocytes	S100A12	1.67E-31
Monocytes	EVI2B	1.75E-27
Monocytes	RGS19	4.33E-27
Monocytes	SUPT4H1	9.27E-27
Monocytes	UCP2	3.25E-24
Monocytes	CLEC10A	5.74E-23
Monocytes	RNASE2	8.79E-22
Monocytes	ORAI3	4.86E-21
Monocytes	SEPHS2	5.54E-20
Monocytes	SERPINA1	9.75E-20
Monocytes	FAM26F	3.43E-19
Monocytes	METTL7B	2.65E-18
Monocytes	ARL4C	2.68E-18
Monocytes	ACP5	6.89E-18
Monocytes	IGSF6	1.78E-16
Monocytes	MYO1G	5.44E-16
Monocytes	HMOX1	7.08E-16
Monocytes	RP11-290F20.3	1.16E-15
Monocytes	FCGR1A	3.56E-14
Monocytes	CCR1	7.76E-14
Monocytes	CST7	1.25E-13
Monocytes	CCR2	7.72E-13
Monocytes	GAPT	3.33E-12
Monocytes	CD52	3.95E-12
Monocytes	CENPW	5.13E-12
Monocytes	GCHFR	9.71E-12
Monocytes	HLA-DQA2	1.22E-11
Monocytes	LILRB4	1.33E-11
Monocytes	DCK	4.41E-11
Monocytes	S100B	1.75E-10
Monocytes	ZNF524	2.49E-10
Monocytes	FOLR2	5.68E-10
Monocytes	CFP	1.43E-09
Monocytes	SNX20	2.06E-09
Monocytes	MKI67	2.22E-09
Monocytes	LACC1	2.60E-09
Monocytes	IL1B	3.19E-09
Monocytes	H2AFX	1.17E-08
Monocytes	IL8	1.23E-08
Monocytes	NFE2	2.93E-08
Monocytes	SPP1	7.62E-08
Monocytes	HAMP	1.00E-07
Monocytes	PMAIP1	7.39E-07
Smooth muscle	MYH11	3.68E-240
Smooth muscle	ACTG2	5.72E-193
Smooth muscle	SVIL	3.29E-178
Smooth muscle	SORBS1	2.86E-159
Smooth muscle	CACNA1C	2.37E-127
Smooth muscle	PRUNE2	1.35E-118
Smooth muscle	LPP	1.05E-112
Smooth muscle	DMD	7.65E-111
Smooth muscle	MIR145	2.27E-110
Smooth muscle	NDE1	2.80E-110
Smooth muscle	NT5DC3	1.72E-94
Smooth muscle	SYNPO2	4.78E-89
Smooth muscle	KCNMA1	4.05E-86
Smooth muscle	COL6A2	1.17E-85
Smooth muscle	CCBE1	1.12E-82
Smooth muscle	PDE4D	3.50E-82
Smooth muscle	MYL9	4.00E-81

HAS1+	NFKBIA	5.62E-100
HAS1+	CLDN1	5.65E-95
HAS1+	UGP2	4.68E-92
HAS1+	SAT1	1.94E-89
HAS1+	AP000705.7	5.99E-84
HAS1+	FLRT2	8.31E-83
HAS1+	MIR29A	1.98E-81
HAS1+	MT1E	4.56E-79
HAS1+	SLC7A2	1.12E-78
HAS1+	TJP2	1.25E-78
HAS1+	KLF6	1.94E-78
HAS1+	GPRC5A	2.84E-78
HAS1+	MARCH3	4.56E-77
HAS1+	NABP1	5.77E-77
HAS1+	ERRFI1	2.36E-75
HAS1+	EZR	1.33E-72
HAS1+	SLC20A1	5.27E-72
HAS1+	KRT18	7.40E-70
HAS1+	CLIC4	1.55E-67
HAS1+	NTNG1	1.88E-67
HAS1+	UAP1	1.01E-64
HAS1+	CXCL1	2.91E-61
HAS1+	RP11-286E11.1	6.08E-60
HAS1+	HIF1A-AS2	2.89E-58
HAS1+	FAM153B	2.89E-58
HAS1+	TNFRSF12A	5.79E-57
HAS1+	SOX6	2.80E-56
HAS1+	CCDC64	5.32E-55
HAS1+	HIF1A	3.19E-54
HAS1+	PLA2G2A	3.49E-54
HAS1+	ID2	2.62E-53
HAS1+	EFNA5	1.22E-52
HAS1+	RP11-434I12.2	4.04E-52
HAS1+	CXCL2	6.10E-52
HAS1+	PHLDB2	2.09E-51
HAS1+	CD55	3.70E-50
HAS1+	RP6-99M1.2	5.05E-50
HAS1+	MAST4	2.88E-49
HAS1+	VCAM1	4.73E-49
HAS1+	NFKB1	1.12E-47
HAS1+	CD200	4.22E-47
HAS1+	MEDAG	4.30E-47
HAS1+	SLC39A8	1.15E-46
HAS1+	MAP4K4	4.14E-46
HAS1+	OLR1	8.41E-46
HAS1+	IER3	3.01E-45
HAS1+	LMNA	4.02E-45
HAS1+	DUSP1	4.72E-45
HAS1+	HOMER1	2.20E-44
HAS1+	S100A6	2.23E-44
HAS1+	SGMS2	2.76E-44
HAS1+	CRY1	3.62E-44
HAS1+	ATP2B1	6.59E-44
HAS1+	CCNL1	7.55E-42
HAS1+	ICAM1	8.08E-42
HAS1+	KRT19	2.04E-41
HAS1+	ARAP2	2.83E-41
HAS1+	STAT3	6.81E-41
HAS1+	PIM1	1.17E-40
HAS1+	ERN1	5.76E-40
HAS1+	RDH10	1.44E-39
HAS1+	ITPKC	1.88E-39
HAS1+	CAMSAP2	2.73E-39
HAS1+	THSD4	4.22E-39
HAS1+	KDM6B	6.42E-39
HAS1+	PKHD1L1	8.77E-39
HAS1+	OSMR	2.26E-38
HAS1+	TNFSF14	6.19E-38
HAS1+	ZFPM2	1.82E-37
HAS1+	RP11-281P23.2	1.95E-37
HAS1+	MAP3K8	2.05E-37
HAS1+	SRGAP1	3.70E-37
HAS1+	PLCB1	1.01E-36
SDS+	SVIL	2.33E-34
SDS+	FBXO32	2.63E-31
SDS+	PRUNE2	1.09E-28
SDS+	CTD-3105H18.18	4.61E-28
SDS+	DLG5	5.80E-28
SDS+	PDE9A	1.37E-26
SDS+	MT1E	1.42E-26
SDS+	RP11-707P20.1	1.73E-26
SDS+	SPESP1	2.88E-25
SDS+	RP11-690J15.1	4.70E-25
SDS+	GOLPH3	1.48E-24
SDS+	RP11-680F20.9	1.54E-22
SDS+	CRISPLD2	2.02E-22
SDS+	CACNA1C	3.69E-22
SDS+	FSHR	2.16E-21
SDS+	WWTR1	3.03E-21
SDS+	MYH14	3.29E-21
SDS+	RAD51	8.54E-21
SDS+	NID1	1.04E-20
SDS+	GEM	6.36E-19
SDS+	MON1B	6.62E-19
SDS+	CHD8	1.54E-18
SDS+	SDR42E2	1.70E-18
SDS+	RP11-296K13.4	2.11E-18
SDS+	RP11-169E6.4	2.12E-18
SDS+	LDLRAD2	2.24E-18
SDS+	PACRG	3.65E-18
SDS+	PDZRN3	3.94E-18
SDS+	VSNL1	4.68E-18
SDS+	MT1X	1.31E-17
SDS+	AFMID	1.92E-17
SDS+	C9orf171	2.91E-17
SDS+	SCAI	4.48E-17
SDS+	C15orf52	6.15E-17
SDS+	CASC5	9.51E-17
SDS+	RBM20	1.74E-16
SDS+	SOGA2	1.79E-16
SDS+	MT1M	1.43E-15
SDS+	BMPR1A	1.59E-15
SDS+	LINC00276	2.35E-15
SDS+	STK24	3.73E-15
SDS+	PRSS38	4.53E-15
SDS+	PSMA8	5.74E-15
SDS+	GRM7	6.92E-15
SDS+	RP11-432B6.3	9.06E-15
SDS+	C1orf95	5.61E-14
SDS+	SLC8A1-AS1	6.25E-14
SDS+	RP11-138I17.1	7.01E-14
SDS+	GREM2	8.64E-14
SDS+	ARMC2	1.15E-13
SDS+	CTC-529L17.2	1.34E-13
SDS+	CLCN4	1.87E-13
SDS+	CWC25	2.02E-13
SDS+	RP11-774D14.1	2.31E-13
SDS+	RPGRIP1	3.03E-13
SDS+	MITF	3.65E-13
SDS+	ATP6V0A4	3.70E-13
SDS+	FMN2	4.88E-13
SDS+	GTF2IRD1	4.92E-13
SDS+	GPC3	6.44E-13
SDS+	CDHR3	8.00E-13
SDS+	UNC79	1.07E-12
SDS+	GPN3	1.07E-12
SDS+	DPP6	1.10E-12
SDS+	SGK223	1.18E-12
SDS+	SLC24A3	1.26E-12
SDS+	RBFOX3	1.33E-12
SDS+	TTTY14	1.53E-12
SDS+	RP5-1048B16.1	1.83E-12
SDS+	FAM153B	2.16E-12
SDS+	SORBS2	2.22E-12
SDS+	CDC40	4.57E-12
SDS+	AC004076.9	5.17E-12
Smooth muscle	FBXO32	5.23E-77
Smooth muscle	MIR143HG	2.37E-75
Smooth muscle	FOXP2	8.35E-73
Smooth muscle	TPM2	1.38E-72
Smooth muscle	RBPMS	3.04E-72
Smooth muscle	PDZRN4	2.60E-70
Smooth muscle	SMTN	7.64E-70
Smooth muscle	CNN1	2.21E-67
Smooth muscle	FLNA	3.86E-67
Smooth muscle	TPM1	8.90E-67
Smooth muscle	CTD-3105H18.18	3.92E-64
Smooth muscle	LMOD1	3.12E-61
Smooth muscle	LINC00578	1.77E-60
Smooth muscle	CALD1	1.49E-57
Smooth muscle	ACTA2	2.16E-57
Smooth muscle	PDZRN3	1.75E-56
Smooth muscle	SLMAP	3.85E-55
Smooth muscle	MALAT1	2.43E-54
Smooth muscle	AC005358.3	2.42E-53
Smooth muscle	CACNB2	1.38E-52
Smooth muscle	MYLK	6.11E-50
Smooth muscle	COL6A1	2.47E-49
Smooth muscle	PDLIM7	3.50E-49
Smooth muscle	DES	6.05E-49
Smooth muscle	PRKG1	3.40E-47
Smooth muscle	SLC8A1	1.07E-46
Smooth muscle	DPP6	2.93E-44
Smooth muscle	ROR2	3.02E-44
Smooth muscle	HDAC4	1.46E-43
Smooth muscle	CASKIN1	2.00E-41
Smooth muscle	PCDH7	2.51E-41
Smooth muscle	RBFOX3	7.42E-40
Smooth muscle	NEXN	2.49E-39
Smooth muscle	BNC2	1.18E-38
Smooth muscle	CHRM2	3.34E-38
Smooth muscle	CBR4	3.55E-38
Smooth muscle	CHRM3	6.01E-38
Smooth muscle	PALLD	6.43E-38
Smooth muscle	SLC8A1-AS1	6.58E-36
Smooth muscle	PDK4	6.73E-36
Smooth muscle	STAB2	8.50E-36
Smooth muscle	MON1B	9.64E-36
Smooth muscle	GEM	2.04E-34
Smooth muscle	STT3A-AS1	3.02E-34
Smooth muscle	AP001347.6	3.02E-34
Smooth muscle	hsa-mir-490	3.97E-33
Smooth muscle	ACTN1	8.07E-33
Smooth muscle	RP11-611D20.2	2.68E-32
Smooth muscle	FHL1	3.58E-32
Smooth muscle	CACNA2D1	6.79E-32
Smooth muscle	AF001548.5	3.60E-31
Smooth muscle	RP11-123O10.4	4.40E-31
Smooth muscle	ITGA5	8.79E-30
Smooth muscle	MEIS1	2.02E-29
Smooth muscle	PARVA	2.94E-29
Smooth muscle	SPOP	5.31E-29
Smooth muscle	AC007392.3	5.77E-29
Smooth muscle	MSRB3	1.08E-28
Smooth muscle	PDLIM3	1.27E-28
Smooth muscle	MYOCD	2.08E-28
Smooth muscle	GPM6A	6.73E-28
Smooth muscle	FN1	9.22E-28
Smooth muscle	TAGLN	1.30E-27
Smooth muscle	MYL6	1.83E-27
Smooth muscle	ATP2B4	2.48E-27
Smooth muscle	PPP1R12B	2.74E-27
Smooth muscle	MEIS2	5.82E-27
Smooth muscle	SEMA3A	2.10E-26
Smooth muscle	COL4A3	2.84E-26
Smooth muscle	LHCGR	8.51E-26
Smooth muscle	ENAH	1.09E-25
Smooth muscle	SORBS2	1.38E-25
Smooth muscle	CSRP1	2.85E-25

HAS1+	STEAP2	1.35E-36
HAS1+	RBMS1	5.50E-36
HAS1+	KCTD8	1.03E-35
HAS1+	CTD-2005H7.2	1.21E-35
HAS1+	CA12	1.67E-35
HAS1+	PLAUR	7.82E-35
HAS1+	NFKBIZ	1.55E-34
HAS1+	RNF24	1.91E-34
HAS1+	ANXA1	4.85E-34
HAS1+	LINC00842	3.29E-33
HAS1+	MIR4435-1HG	4.28E-33
HAS1+	CTD-2369P2.5	6.42E-33
HAS1+	TNFRSF21	8.83E-33
HAS1+	PDPN	2.93E-32
HAS1+	IL6	6.53E-32
HAS1+	TRIB1	2.30E-31
HAS1+	SERPINB9	3.25E-31
HAS1+	DUSP2	5.31E-31
HAS1+	RP11-716H6.2	3.67E-30
HAS1+	RP11-707A18.1	2.28E-29
HAS1+	CALB2	8.91E-27
HAS1+	MFSD2A	1.58E-25
HAS1+	CHI3L1	1.62E-25
HAS1+	MT1M	8.09E-25
HAS1+	SLPI	2.64E-24
HAS1+	LIF	4.38E-24
HAS1+	BNC1	3.28E-23
HAS1+	LINC00152	4.74E-23
HAS1+	MTMR7	4.95E-23
HAS1+	FAM110C	3.22E-22
HAS1+	FAM153C	4.47E-22
HAS1+	TNFAIP3	5.04E-21
HAS1+	RP11-277B15.2	8.47E-21
HAS1+	CFB	1.71E-19
HAS1+	MSLN	5.58E-18
HAS1+	RP11-74M11.2	9.27E-18
HAS1+	ZC3H12A	2.75E-17
HAS1+	PRG4	3.36E-17
HAS1+	PLCH2	3.69E-17
HAS1+	ITLN1	4.12E-17
HAS1+	ARC	2.82E-16
HAS1+	TFPI2	2.88E-16
HAS1+	RP11-404P21.3	3.75E-16
HAS1+	GADD45A	5.16E-16
HAS1+	RP11-244K5.8	1.81E-15
HAS1+	RP11-290F20.2	4.00E-15
HAS1+	DAW1	7.58E-15
HAS1+	KLK11	2.17E-13
HAS1+	CLEC4M	3.71E-13
HAS1+	IL20	9.49E-13
HAS1+	CARNS1	1.15E-12
HAS1+	SERPINB2	5.38E-12
HAS1+	SMPD3	1.30E-11
HAS1+	RP11-667K14.3	2.20E-11
HAS1+	IL8	5.42E-11
HAS1+	PROCR	1.03E-10
HAS1+	CCDC71L	1.92E-10
HAS1+	TGM1	1.92E-10
HAS1+	RP5-1022P6.5	2.39E-10
HAS1+	EPS8L1	2.74E-09
HAS1+	HILPDA	4.08E-09
HAS1+	LINC00707	4.37E-09
HAS1+	VNN3	1.56E-08
HAS1+	GATA6-AS1	1.00E-07
HAS1+	ISYNA1	5.39E-06
ICCs	KCNIP4	8.99E-193
ICCs	SGCZ	1.25E-184
ICCs	ANO1	6.43E-138
ICCs	DPP10	1.67E-130
ICCs	PTGER3	2.94E-126
ICCs	RP11-626H12.3	6.51E-122
ICCs	SLC12A2	2.09E-120
ICCs	KIT	8.33E-114
SDS+	AFF3	5.90E-12
SDS+	RP1-209A6.1	7.41E-12
SDS+	ANP32E	8.02E-12
SDS+	ACBD5	8.26E-12
SDS+	FGFR2	1.41E-11
SDS+	SMO	1.75E-11
SDS+	MAMDC2-AS1	2.02E-11
SDS+	ROR2	2.83E-11
SDS+	CCBE1	4.29E-11
SDS+	RP11-545G3.1	4.43E-11
SDS+	SYNPO	4.58E-11
SDS+	AC007389.3	6.25E-11
SDS+	EPB41	7.17E-11
SDS+	COL4A3	7.74E-11
SDS+	TIGD7	7.82E-11
SDS+	DENND5B-AS1	8.69E-11
SDS+	MED22	1.82E-10
SDS+	COL23A1	2.61E-10
SDS+	RIMS2	2.94E-10
SDS+	ESRRG	4.13E-10
SDS+	METTL2B	4.50E-10
SDS+	CCDC62	5.26E-10
SDS+	LY9	1.13E-09
SDS+	PPAPDC1A	3.03E-09
SDS+	DYRK3	5.08E-09
SDS+	RAB5B	8.98E-09
SDS+	AC073635.5	1.31E-08
SDS+	KIAA1644	3.16E-08
SDS+	RP11-818F20.5	4.46E-08
SDS+	AL022476.2	6.58E-08
SDS+	HTRA4	1.27E-07
SDS+	FAM25C	1.83E-07
SDS+	RP3-404K8.2	2.78E-07
SDS+	RP11-195F19.9	4.09E-07
SDS+	RP11-555J4.4	4.90E-07
SDS+	MT1G	6.17E-07
SDS+	RP5-884C9.2	6.96E-07
SDS+	RASGEF1C	7.68E-07
SDS+	C1orf87	1.05E-06
SDS+	VIL1	1.18E-06
SDS+	DBNDD1	1.66E-06
SDS+	SLC34A1	2.40E-06
SDS+	CABYR	4.05E-06
SDS+	GPR133	4.21E-06
SDS+	ALDH3B1	4.21E-06
SDS+	RP11-46I8.3	4.43E-06
SDS+	TUSC5	1.35E-05
SDS+	RP11-297A16.2	2.03E-05
SDS+	RP11-24I21.1	2.50E-05
SDS+	MASP1	2.82E-05
SDS+	CTD-2152M20.2	2.89E-05
SDS+	KCNJ12	3.40E-05
SDS+	SLC1A5	3.71E-05
SDS+	NPFFR1	3.74E-05
SDS+	SPATA12	4.36E-05
SDS+	GRTP1-AS1	5.47E-05
SDS+	ADAM18	5.50E-05
SDS+	GINS2	6.75E-05
SDS+	RP11-32F11.2	1.16E-04
SDS+	DSCR9	1.50E-04
SDS+	KNDC1	1.54E-04
SDS+	NKD1	1.64E-04
SDS+	CTD-2231H16.1	1.78E-04
SDS+	ARSH	2.56E-04
SDS+	CCL24	3.56E-04
SDS+	GAD2	3.89E-04
SDS+	RP11-46H11.3	5.42E-04
SDS+	RP11-167N24.4	5.56E-04
SDS+	RP11-83M16.6	6.42E-04
SDS+	KL	6.59E-04
SDS+	RP11-483H20.6	7.57E-04
SDS+	TPH2	7.60E-04
SDS+	CTD-2251F13.1	1.19E-03
Smooth muscle	LDB3	2.90E-25
Smooth muscle	ITGA1	3.08E-25
Smooth muscle	PNCK	2.56E-24
Smooth muscle	ADAMTS9-AS2	2.79E-24
Smooth muscle	AC100830.3	7.44E-24
Smooth muscle	CKB	3.12E-23
Smooth muscle	RP11-370I10.2	4.18E-23
Smooth muscle	PARD3B	1.39E-22
Smooth muscle	AKAP12	2.29E-22
Smooth muscle	SLFNL1	2.33E-22
Smooth muscle	FGFR2	5.10E-22
Smooth muscle	EPHA7	5.33E-22
Smooth muscle	SDS	5.54E-22
Smooth muscle	RP11-619J20.1	1.02E-19
Smooth muscle	PSMA8	1.30E-19
Smooth muscle	SPEG	3.31E-19
Smooth muscle	SOGA2	9.37E-19
Smooth muscle	PCA3	4.62E-18
Smooth muscle	RP11-166P13.4	5.22E-18
Smooth muscle	WNK2	3.38E-17
Smooth muscle	RP11-374M1.3	4.42E-17
Smooth muscle	RP11-413B19.2	4.16E-16
Smooth muscle	OCEL1	5.59E-16
Smooth muscle	NECAB1	2.53E-15
Smooth muscle	SYNM	2.66E-15
Smooth muscle	ASB2	7.83E-15
Smooth muscle	TIGD7	5.82E-14
Smooth muscle	FBXL22	1.41E-13
Smooth muscle	CTC-529L17.2	2.37E-13
Smooth muscle	WFDC1	6.33E-13
Smooth muscle	C15orf52	1.18E-12
Smooth muscle	HSD17B6	2.09E-12
Smooth muscle	EHBP1L1	6.24E-12
Smooth muscle	RP11-158I9.5	9.79E-12
Smooth muscle	LIPI	1.38E-11
Smooth muscle	HOXD10	6.16E-11
Smooth muscle	RP11-579E24.2	2.50E-10
Smooth muscle	RP11-1069G10.1	5.29E-10
Smooth muscle	ARRDC4	8.03E-10
Smooth muscle	RP11-266N13.2	8.39E-10
Smooth muscle	SLC2A4	8.48E-10
Smooth muscle	CTD-2313P7.1	2.13E-09
Smooth muscle	C20orf166-AS1	3.52E-09
Smooth muscle	ADAM11	8.20E-09
Smooth muscle	AKAP1	1.24E-08
Smooth muscle	NAV2-AS3	2.42E-08
Smooth muscle	PSD	1.07E-07
Smooth muscle	MRVI1	2.08E-07
Smooth muscle	MMP3	4.94E-07
Smooth muscle	LRTM1	5.51E-07
Smooth muscle	CACNA1C-AS1	1.91E-06
Smooth muscle	CTC-296K1.4	3.12E-06
Smooth muscle	CTC-296K1.3	4.58E-06
Smooth muscle	CACNA1H	6.19E-06
Smooth muscle	FAM83D	6.34E-06
Smooth muscle	PI15	1.19E-05
Smooth muscle	FENDRR	1.30E-05
Smooth muscle	CTPS1	1.30E-05
Smooth muscle	POPDC2	1.42E-05
Smooth muscle	AC073635.5	2.14E-05
Smooth muscle	RP11-707P20.1	3.04E-05
Smooth muscle	RP11-131H24.4	7.66E-05
Smooth muscle	ANO5	1.38E-04
Smooth muscle	LPA	3.45E-04
Smooth muscle	TRMT61A	5.68E-04
Vascular endothelial	LDB2	8.82E-186
Vascular endothelial	PTPRB	1.10E-146
Vascular endothelial	MCTP1	1.49E-135
Vascular endothelial	VWF	6.87E-127
Vascular endothelial	EPAS1	9.05E-123
Vascular endothelial	EMP1	2.64E-120
Vascular endothelial	RP3-510L9.1	2.52E-118
Vascular endothelial	MECOM	2.63E-112

ICCs	KIF26B	6.61E-106
ICCs	GPC6	8.52E-103
ICCs	NRG1	8.43E-99
ICCs	IL1RAPL2	6.15E-90
ICCs	PDE1A	1.76E-78
ICCs	FHL2	1.55E-72
ICCs	CAPN15	4.96E-72
ICCs	CPA6	4.58E-69
ICCs	ADAMTSL3	1.22E-67
ICCs	LDB2	5.45E-65
ICCs	BAI3	5.80E-61
ICCs	ETV1	1.24E-58
ICCs	RP11-626H12.1	8.12E-57
ICCs	RP11-62I21.1	1.78E-56
ICCs	CACNB2	1.16E-55
ICCs	DPT	6.73E-55
ICCs	PLCB1	2.68E-53
ICCs	UNC13C	1.44E-52
ICCs	PIEZO2	2.66E-52
ICCs	KCND2	6.42E-51
ICCs	CDH13	2.14E-50
ICCs	PLCL1	1.83E-48
ICCs	GHR	9.75E-48
ICCs	MEIS2	4.43E-44
ICCs	GRIA4	1.38E-41
ICCs	ABCC4	1.27E-39
ICCs	RORA	4.73E-39
ICCs	OBSCN	2.11E-38
ICCs	LINC01091	1.04E-37
ICCs	TMEM132C	2.13E-36
ICCs	STRBP	4.66E-36
ICCs	AFF3	3.23E-35
ICCs	TRPC4	5.18E-35
ICCs	ENOX1	1.45E-34
ICCs	FGF1	3.76E-34
ICCs	ZBTB20	4.20E-34
ICCs	TCF21	6.25E-33
ICCs	DCC	1.18E-31
ICCs	TOX	1.23E-31
ICCs	FAM49B	4.05E-31
ICCs	PDE4C	4.76E-31
ICCs	RP11-140I24.1	1.41E-30
ICCs	PDE3A	1.53E-30
ICCs	MPPED2	1.54E-30
ICCs	RP3-323P13.2	3.70E-30
ICCs	FGF12-AS1	2.27E-29
ICCs	CTD-2009A10.1	3.27E-29
ICCs	FBN1	2.14E-28
ICCs	RP11-39M21.1	1.36E-27
ICCs	PRKG1	1.36E-27
ICCs	RP4-678D15.1	4.05E-27
ICCs	PAM	6.63E-27
ICCs	PRKDC	9.11E-27
ICCs	PDE3B	2.19E-26
ICCs	BMPR1B	3.21E-26
ICCs	ZFHX3	3.21E-26
ICCs	ACSS3	3.39E-26
ICCs	CDH11	3.97E-26
ICCs	CHN2	4.33E-26
ICCs	TSHZ2	2.85E-25
ICCs	MBOAT2	9.37E-25
ICCs	C7	1.78E-24
ICCs	SPATS2L	2.37E-24
ICCs	CUX2	3.00E-24
ICCs	MAPK10	3.29E-24
ICCs	COL13A1	4.40E-24
ICCs	SPRY1	9.66E-24
ICCs	LINGO2	5.71E-23
ICCs	FRAS1	1.81E-22
ICCs	PLAT	5.15E-22
ICCs	NKX3-2	2.78E-21
ICCs	B3GALTL	3.69E-21
ICCs	CSGALNACT1	6.12E-21
SDS+	LDHAL6A	1.46E-03
SDS+	AL161784.1	1.71E-03
SDS+	RP11-133L19.1	1.76E-03
SDS+	RP11-108P20.4	2.32E-03
SDS+	DSC3	2.45E-03
SDS+	ZNF574	2.80E-03
SDS+	C1orf100	2.83E-03
SDS+	FAM189A2	3.59E-03
SDS+	TRIM67	4.53E-03
SDS+	MICALCL	6.29E-03
SDS+	KDM5D	7.36E-03
SDS+	HTR3A	9.13E-03
SDS+	CTD-2377D24.8	9.60E-03
SDS+	VSTM1	1.22E-02
SDS+	CTB-5E10.3	1.62E-02
SDS+	ADRA1B	1.66E-02
SDS+	RP11-3D4.2	1.82E-02
SDS+	IQGAP3	2.10E-02
SPP1+	MT-CO3	1.01E-141
SPP1+	MT-CO1	4.52E-131
SPP1+	MT-CO2	1.02E-114
SPP1+	MT-ND3	4.28E-114
SPP1+	MT-ND4	8.43E-109
SPP1+	MT-ATP6	6.69E-107
SPP1+	MT-CYB	2.19E-105
SPP1+	MT-ND1	2.42E-95
SPP1+	MT-ND2	9.46E-93
SPP1+	MT-ND5	7.78E-73
SPP1+	MTRNR2L8	5.87E-40
SPP1+	SPP1	2.68E-36
SPP1+	MT-ND4L	1.26E-31
SPP1+	DHFR	1.91E-30
SPP1+	MTRNR2L10	6.66E-28
SPP1+	DEFB1	1.19E-23
SPP1+	ATP1B1	8.67E-22
SPP1+	ITM2B	8.23E-20
SPP1+	MTRNR2L12	1.04E-19
SPP1+	MT-ND6	8.65E-19
SPP1+	EGF	1.64E-17
SPP1+	KCNJ16	5.18E-17
SPP1+	ESRRG	7.29E-17
SPP1+	PKHD1	3.14E-16
SPP1+	ERBB4	6.28E-16
SPP1+	KNG1	3.73E-15
SPP1+	SLC12A3	3.73E-15
SPP1+	SLC12A1	1.01E-14
SPP1+	AC013463.2	3.32E-14
SPP1+	UMOD	1.21E-12
SPP1+	CDH16	1.36E-12
SPP1+	PTH1R	4.26E-12
SPP1+	ATP1A1	1.48E-10
SPP1+	AC073218.2	2.79E-10
SPP1+	HINT1	5.64E-10
SPP1+	PAX8	6.35E-10
SPP1+	CCSER1	1.91E-09
SPP1+	TPT1	2.05E-09
SPP1+	MT1G	2.32E-09
SPP1+	CA12	2.61E-09
SPP1+	CYB5A	3.66E-09
SPP1+	COX7B	5.78E-09
SPP1+	HSD11B2	1.57E-08
SPP1+	TMBIM6	1.72E-08
SPP1+	NDUFA4	2.90E-08
SPP1+	RP5-857K21.4	4.77E-08
SPP1+	SLC16A12	4.77E-08
SPP1+	PEBP1	5.98E-08
SPP1+	CGNL1	6.25E-08
SPP1+	RPL34	6.25E-08
SPP1+	COX6C	1.14E-07
SPP1+	TFCP2L1	1.38E-07
SPP1+	COX7C	1.76E-07
SPP1+	SKP1	1.78E-07
SPP1+	OGDHL	2.42E-07
Vascular endothelial	CTA-276F8.2	4.45E-98
Vascular endothelial	PTPRM	5.55E-93
Vascular endothelial	ARL15	2.72E-91
Vascular endothelial	TMTC1	1.64E-89
Vascular endothelial	EGFL7	5.14E-89
Vascular endothelial	PIK3R3	8.57E-89
Vascular endothelial	CYYR1	2.62E-87
Vascular endothelial	ANO2	1.64E-81
Vascular endothelial	MKL2	3.34E-79
Vascular endothelial	LIFR	1.85E-72
Vascular endothelial	EMCN	3.40E-72
Vascular endothelial	ID1	9.99E-71
Vascular endothelial	PALMD	1.42E-69
Vascular endothelial	ELMO1-AS1	1.18E-67
Vascular endothelial	ERG	1.59E-67
Vascular endothelial	SPRY1	1.02E-65
Vascular endothelial	CXCL2	4.01E-64
Vascular endothelial	ELMO1	3.94E-63
Vascular endothelial	PITPNC1	1.38E-62
Vascular endothelial	ARHGAP31	8.80E-61
Vascular endothelial	SPC25	3.33E-60
Vascular endothelial	PREX2	3.80E-60
Vascular endothelial	ABLIM1	2.58E-59
Vascular endothelial	A2M	5.68E-59
Vascular endothelial	PLCB4	1.56E-57
Vascular endothelial	BMPR2	1.59E-57
Vascular endothelial	HIPK3	4.17E-57
Vascular endothelial	ELTD1	1.06E-56
Vascular endothelial	EVA1C	7.35E-56
Vascular endothelial	NEDD9	2.49E-54
Vascular endothelial	AP001597.1	1.81E-53
Vascular endothelial	SOCS3	2.27E-52
Vascular endothelial	PRKCH	4.10E-52
Vascular endothelial	TACC1	6.58E-52
Vascular endothelial	RIN2	2.85E-51
Vascular endothelial	ST6GALNAC3	1.36E-48
Vascular endothelial	SLCO2A1	1.87E-48
Vascular endothelial	TCF4	2.65E-48
Vascular endothelial	TMSB10	1.72E-47
Vascular endothelial	ENTPD1-AS1	2.09E-47
Vascular endothelial	CTD-3222D19.2	3.25E-47
Vascular endothelial	SPARCL1	2.31E-46
Vascular endothelial	ZNF385D	3.21E-46
Vascular endothelial	TPO	5.21E-45
Vascular endothelial	PLEKHG1	4.59E-44
Vascular endothelial	DOCK4	5.52E-44
Vascular endothelial	MAGI1	7.85E-43
Vascular endothelial	RP1-90G24.10	8.01E-42
Vascular endothelial	MYRIP	3.15E-41
Vascular endothelial	ATP8B1	3.84E-40
Vascular endothelial	FLT1	5.49E-40
Vascular endothelial	ID3	1.48E-39
Vascular endothelial	SASH1	5.07E-39
Vascular endothelial	RUNDC3B	5.62E-39
Vascular endothelial	NPDC1	1.78E-38
Vascular endothelial	SYNE2	7.09E-38
Vascular endothelial	PKP4	1.16E-37
Vascular endothelial	NUAK1	1.38E-37
Vascular endothelial	TIMP3	1.39E-37
Vascular endothelial	DARC	1.48E-37
Vascular endothelial	FAM155A	2.57E-37
Vascular endothelial	GFOD1	2.96E-37
Vascular endothelial	SEC14L1	1.80E-36
Vascular endothelial	KIAA0355	2.91E-36
Vascular endothelial	RP4-678D15.1	3.35E-36
Vascular endothelial	RALGAPA2	3.36E-36
Vascular endothelial	MSN	6.72E-36
Vascular endothelial	WNK1	7.78E-36
Vascular endothelial	ADAMTS1	2.86E-35
Vascular endothelial	ARHGAP26	5.46E-35
Vascular endothelial	TM4SF1	6.07E-35
Vascular endothelial	EPHA4	1.17E-34
Vascular endothelial	RP11-588H23.3	1.70E-34

ICCs	NFKBIZ	1.23E-20
ICCs	FGF12	1.43E-20
ICCs	GNG2	2.49E-20
ICCs	NRP1	3.29E-20
ICCs	COL12A1	3.88E-20
ICCs	RP11-222A11.1	4.27E-20
ICCs	FAP	4.65E-20
ICCs	AHCYL2	5.19E-20
ICCs	TMEM100	6.08E-20
ICCs	GUCY1A3	7.53E-20
ICCs	RAB11A	1.49E-19
ICCs	PREX2	3.50E-19
ICCs	ARHGAP24	3.78E-19
ICCs	NBL1	8.47E-19
ICCs	FENDRR	1.38E-18
ICCs	RP11-396J6.1	1.63E-18
ICCs	CA2	2.21E-18
ICCs	RP11-778J15.1	4.81E-18
ICCs	FANCC	5.99E-18
ICCs	RP11-556G22.3	1.27E-17
ICCs	SOX30	6.07E-17
ICCs	RP11-626H12.2	9.03E-17
ICCs	SLC24A2	6.20E-16
ICCs	FBXO48	2.92E-15
ICCs	EYA4	3.37E-15
ICCs	PSG8	1.33E-14
ICCs	VPS37A	1.48E-14
ICCs	CTA-360L10.1	2.50E-14
ICCs	LIN7A	3.05E-14
ICCs	SMAD7	4.33E-14
ICCs	EFCC1	3.70E-13
ICCs	CBR3	7.89E-13
ICCs	LRTM1	1.16E-12
ICCs	PROM1	2.45E-12
ICCs	AC012360.6	6.23E-12
ICCs	SPRY4	9.42E-12
ICCs	HSPA12B	1.60E-11
ICCs	MCOLN2	2.61E-11
ICCs	AC140912.1	3.43E-11
ICCs	ITGA4	1.95E-10
ICCs	CTSL	1.99E-10
ICCs	SYNDIG1L	4.10E-10
ICCs	DPP4	4.63E-10
ICCs	RP11-298D21.1	9.66E-10
ICCs	SYTL2	1.03E-09
ICCs	SULT1C4	1.24E-08
ICCs	TMEM204	1.47E-08
ICCs	MEST	1.61E-08
ICCs	GPC6-AS1	3.66E-08
ICCs	IBA57	1.26E-07
ICCs	CTD-2313P7.1	1.50E-07
ICCs	CTD-3253I12.1	3.15E-07
ICCs	NTF3	1.07E-06
ICCs	CACNA2D3-AS1	1.09E-06
ICCs	CLEC11A	1.86E-06
ICCs	RP11-473O4.3	5.45E-06
ICCs	RP11-391J2.3	2.06E-05
ICCs	LRRC3B	2.15E-05
ICCs	AC072062.3	2.41E-05
ICCs	FOXF1	3.28E-05
ICCs	LINC00571	1.48E-04
ICCs	MCOLN3	6.46E-04
MPO+	BTF3	0.00E+00
MPO+	EEF1B2	0.00E+00
MPO+	GNB2L1	0.00E+00
MPO+	HINT1	0.00E+00
MPO+	RPL14	0.00E+00
MPO+	RPL28	0.00E+00
MPO+	RPL29	0.00E+00
MPO+	RPL35	0.00E+00
MPO+	RPL36AL	0.00E+00
MPO+	RPL8	0.00E+00
MPO+	RPS13	0.00E+00
SPP1+	ATP6V1F	5.05E-07
SPP1+	MTRNR2L1	5.20E-07
SPP1+	PTH2R	7.50E-07
SPP1+	RPS23	7.50E-07
SPP1+	TTTY14	8.13E-07
SPP1+	ISCU	1.33E-06
SPP1+	TMEM52B	1.58E-06
SPP1+	GPC5	1.65E-06
SPP1+	RPL7	1.72E-06
SPP1+	MECOM	2.63E-06
SPP1+	FTH1	2.71E-06
SPP1+	IVNS1ABP	2.73E-06
SPP1+	PCK1	3.71E-06
SPP1+	COBLL1	3.71E-06
SPP1+	RPS27A	4.44E-06
SPP1+	KDM5B	5.77E-06
SPP1+	OOEP	5.86E-06
SPP1+	LAMTOR5	5.94E-06
SPP1+	FTL	6.49E-06
SPP1+	HSP90AB1	7.25E-06
SPP1+	ATP6V1G1	7.74E-06
SPP1+	AHCYL1	8.31E-06
SPP1+	SNX10	8.75E-06
SPP1+	KIF12	8.75E-06
SPP1+	GPX3	9.33E-06
SPP1+	AC002539.1	1.25E-05
SPP1+	ALDOB	1.29E-05
SPP1+	RP1-60O19.1	1.31E-05
SPP1+	HSPD1	1.31E-05
SPP1+	CD164	1.39E-05
SPP1+	MTRNR2L3	1.41E-05
SPP1+	PLCL1	1.57E-05
SPP1+	COX5B	1.59E-05
SPP1+	C14orf105	1.60E-05
SPP1+	NGFRAP1	1.60E-05
SPP1+	S100A10	1.67E-05
SPP1+	DBI	1.68E-05
SPP1+	OXR1	1.93E-05
SPP1+	MT1F	1.98E-05
SPP1+	DUSP9	1.98E-05
SPP1+	TXNIP	2.10E-05
SPP1+	MPC1	2.24E-05
SPP1+	ATP6V0E1	3.13E-05
SPP1+	SOD1	3.13E-05
SPP1+	UGT2B7	3.16E-05
SPP1+	RP4-655J12.4	8.05E-05
SPP1+	WRNIP1	1.09E-04
SPP1+	SFRP1	1.20E-04
SPP1+	KL	1.60E-04
SPP1+	SLC6A8	1.64E-04
SPP1+	GATM	2.31E-04
SPP1+	RP11-465B22.8	3.18E-04
SPP1+	GADD45A	3.22E-04
SPP1+	KLHDC7A	3.70E-04
SPP1+	PPP1R1A	3.77E-04
SPP1+	FXYD2	3.78E-04
SPP1+	PDZK1IP1	4.20E-04
SPP1+	TMEM101	6.06E-04
SPP1+	CA2	6.25E-04
SPP1+	TFAP2A	8.34E-04
SPP1+	PCSK1N	8.70E-04
SPP1+	SFTPD	1.29E-03
SPP1+	SIM1	1.38E-03
SPP1+	CLDN8	1.40E-03
SPP1+	TMEM72	1.52E-03
SPP1+	SMIM5	1.61E-03
SPP1+	SHISA3	1.64E-03
SPP1+	TRIM50	2.01E-03
SPP1+	MT1H	2.24E-03
SPP1+	ACSM2B	2.80E-03
SPP1+	TMEM27	2.99E-03
SPP1+	PROM2	3.02E-03
SPP1+	CYP4A11	3.85E-03
Vascular endothelial	SRGN	2.05E-34
Vascular endothelial	AC007319.1	5.34E-34
Vascular endothelial	RASAL2	6.46E-34
Vascular endothelial	MYO1E	9.22E-34
Vascular endothelial	TSHZ2	2.47E-33
Vascular endothelial	AL035610.2	8.55E-33
Vascular endothelial	PPP1R16B	9.39E-33
Vascular endothelial	ZFP36	2.66E-32
Vascular endothelial	MEF2C	2.90E-32
Vascular endothelial	FLI1	3.82E-32
Vascular endothelial	TNFRSF10D	3.85E-32
Vascular endothelial	CRIM1	1.57E-31
Vascular endothelial	EDN1	1.67E-31
Vascular endothelial	HLA-E	2.56E-31
Vascular endothelial	RASGRF2	3.53E-30
Vascular endothelial	NOTCH4	4.84E-30
Vascular endothelial	FOS	7.95E-30
Vascular endothelial	JUNB	2.20E-29
Vascular endothelial	PTPRG	2.28E-29
Vascular endothelial	POSTN	8.11E-29
Vascular endothelial	TIE1	1.82E-27
Vascular endothelial	SOX17	5.11E-27
Vascular endothelial	IGFBP3	7.90E-27
Vascular endothelial	CD93	2.22E-26
Vascular endothelial	TINAGL1	3.26E-26
Vascular endothelial	CRIP2	1.12E-25
Vascular endothelial	RP11-619L19.1	1.15E-25
Vascular endothelial	DPYS	7.09E-25
Vascular endothelial	LMCD1	4.99E-24
Vascular endothelial	VCAM1	9.92E-24
Vascular endothelial	CLEC14A	5.73E-23
Vascular endothelial	CXorf36	6.11E-23
Vascular endothelial	ECSCR	1.16E-22
Vascular endothelial	RPGR	3.18E-22
Vascular endothelial	CDH5	1.46E-21
Vascular endothelial	RAMP3	4.79E-21
Vascular endothelial	ADAM15	8.21E-21
Vascular endothelial	RAMP2	3.83E-20
Vascular endothelial	LINC00847	2.44E-19
Vascular endothelial	EFNB2	9.40E-19
Vascular endothelial	ELOVL7	2.06E-18
Vascular endothelial	BTNL9	2.17E-18
Vascular endothelial	THBD	9.55E-18
Vascular endothelial	VEGFC	1.09E-17
Vascular endothelial	RAPGEF3	1.05E-16
Vascular endothelial	TEK	2.39E-16
Vascular endothelial	HYAL2	4.00E-16
Vascular endothelial	SNCG	4.38E-16
Vascular endothelial	MEOX2	6.81E-16
Vascular endothelial	DLL4	6.98E-16
Vascular endothelial	IL6	7.04E-16
Vascular endothelial	CTA-134P22.2	1.11E-15
Vascular endothelial	ZNF366	1.73E-15
Vascular endothelial	GJA5	5.18E-15
Vascular endothelial	AQP1	1.00E-14
Vascular endothelial	SMAD7	1.59E-14
Vascular endothelial	AJ006995.3	3.76E-14
Vascular endothelial	CTC-484P3.3	3.90E-14
Vascular endothelial	RP11-355F16.1	8.32E-14
Vascular endothelial	ATOH8	1.57E-13
Vascular endothelial	STC1	2.98E-13
Vascular endothelial	ARHGEF15	9.54E-13
Vascular endothelial	MAPK11	1.02E-12
Vascular endothelial	CX3CL1	1.22E-12
Vascular endothelial	GIMAP8	1.87E-12
Vascular endothelial	SERPINE1	6.31E-12
Vascular endothelial	SHANK3	1.10E-11
Vascular endothelial	RP1-29C18.10	1.29E-11
Vascular endothelial	AJ239322.3	2.08E-11
Vascular endothelial	SELP	3.48E-11
Vascular endothelial	RP11-778O17.4	3.48E-11
Vascular endothelial	SLCO4A1	3.94E-11
Vascular endothelial	RP11-188C12.3	6.38E-11

MPO+	RPS15	0.00E+00
MPO+	RPS5	0.00E+00
MPO+	SLC25A5	0.00E+00
MPO+	UBA52	0.00E+00
MPO+	RPL23	0.00E+00
MPO+	SRP14	0.00E+00
MPO+	RPLP0	0.00E+00
MPO+	YBX1	0.00E+00
MPO+	NACA	0.00E+00
MPO+	GAPDH	0.00E+00
MPO+	RPL15	0.00E+00

SPP1+	GDF15	4.14E-03
SPP1+	TNFRSF11B	4.28E-03
SPP1+	S100A2	4.39E-03
SPP1+	MTRNR2L6	4.86E-03
SPP1+	TSR3	5.82E-03
SPP1+	CYP4F3	6.14E-03
SPP1+	KRT18	6.60E-03
SPP1+	CLCNKA	7.03E-03
SPP1+	COMMD8	9.88E-03
SPP1+	BEX2	1.12E-02

Vascular endothelial	RP11-1070N10.4	7.09E-11
Vascular endothelial	NPR1	1.04E-10
Vascular endothelial	RP11-805F19.2	2.07E-10
Vascular endothelial	ESAM	7.77E-10
Vascular endothelial	KCNJ1	9.81E-10
Vascular endothelial	RP5-1121H13.3	1.99E-09
Vascular endothelial	SYT15	1.85E-08
Vascular endothelial	SLC9A3R2	4.28E-08
Vascular endothelial	CASKIN2	1.39E-07
Vascular endothelial	CTC-459M5.2	5.44E-07

Table 21.

ident	gene	padjH
PEMN_1	RP4-678D15.1	5.98E-104
PEMN_1	TSHZ2	6.27E-101
PEMN_1	RP11-385J1.2	2.35E-70
PEMN_1	ALK	3.07E-66
PEMN_1	TMEM132C	4.93E-65
PEMN_1	GRID2	3.38E-48
PEMN_1	RP3-399L15.3	2.84E-46
PEMN_1	HPSE2	8.30E-44
PEMN_1	CADPS	1.66E-43
PEMN_1	DSCAM	7.53E-41
PEMN_1	RBFOX1	1.40E-38
PEMN_1	KCNMB2	5.28E-38
PEMN_1	GPC6	1.56E-37
PEMN_1	XYLT1	1.63E-37
PEMN_1	HS3ST5	1.31E-35
PEMN_1	SLC24A2	3.07E-35
PEMN_1	LSAMP-AS1	3.19E-34
PEMN_1	RP11-76I14.1	1.07E-32
PEMN_1	CHRNA7	2.91E-32
PEMN_1	CTC-575N7.1	4.21E-32
PEMN_1	RP11-15M15.2	5.43E-32
PEMN_1	ADAMTS19	9.42E-32
PEMN_1	LSAMP	1.18E-31
PEMN_1	RP11-15M15.1	9.77E-31
PEMN_1	RP11-227F19.1	1.75E-30
PEMN_1	CACNA2D1	3.81E-29
PEMN_1	UNC5D	8.01E-29
PEMN_1	BNC2	2.07E-28
PEMN_1	KCNIP4	1.59E-25
PEMN_1	CPNE4	8.67E-24
PEMN_1	LRFN5	5.59E-21
PEMN_1	RYR2	1.64E-20
PEMN_1	DMKN	7.35E-20
PEMN_1	THSD7B	1.41E-19
PEMN_1	CADM1	1.99E-19
PEMN_1	SLC5A7	3.53E-19
PEMN_1	TPD52L1	5.44E-19
PEMN_1	PLCB4	4.19E-18
PEMN_1	FBP1	3.83E-17
PEMN_1	KCNH5	7.20E-17
PEMN_1	EML5	9.89E-17
PEMN_1	AP000462.2	3.03E-16
PEMN_1	NRG3	1.54E-15
PEMN_1	BICD1	5.54E-15
PEMN_1	SORBS2	8.69E-15
PEMN_1	FRMPD4	1.65E-14

ident	gene	padjH
PIMN_2	EMP1	1.95E-07
PIMN_2	HOXD10	2.82E-07
PIMN_2	CTC-510F12.2	3.32E-07
PIMN_2	GADD45B	5.26E-07
PIMN_2	TINAGL1	1.16E-06
PIMN_2	RP11-242P2.2	1.43E-06
PIMN_2	SDC4	2.65E-06
PIMN_2	MRVI1	3.94E-06
PIMN_2	SLC2A4	4.29E-06
PIMN_2	LIPI	8.43E-06
PIMN_2	NFKB2	2.73E-05
PIMN_2	RP11-286H15.1	7.64E-05
PIMN_2	AOC3	7.83E-05
PIMN_2	RP11-893F2.13	1.45E-04
PIMN_2	AC010524.4	1.52E-04
PIMN_2	THBS1	2.55E-04
PIMN_2	SERPINA5	4.65E-04
PIMN_2	C8orf4	5.25E-04
PIMN_2	TNFAIP3	7.02E-04
PIMN_2	MS4A6A	1.03E-03
PIMN_2	ADH6	1.20E-03
PIMN_2	CTC-296K1.3	1.47E-03
PIMN_2	ZCCHC24	1.77E-03
PIMN_2	RHOU	4.12E-03
PIMN_2	RP11-347P5.1	4.81E-03
PIMN_2	PROX1-AS1	5.71E-03
PIMN_2	FKBP10	7.28E-03
PIMN_2	CXCL2	7.33E-03
PIMN_2	ARID5A	7.60E-03
PIMN_2	PPIC	7.99E-03
PIMN_2	MASP1	8.36E-03
PIMN_2	CD163	8.94E-03
PIMN_2	ACKR3	9.13E-03
PIMN_2	SDPR	1.05E-02
PIMN_2	ROBO3	1.08E-02
PIMN_2	RP11-440I14.2	1.50E-02
PIMN_2	NCKAP1L	1.63E-02
PIMN_2	TRPC5OS	1.65E-02
PIMN_2	RP11-326C3.12	1.87E-02
PIMN_2	NFE4	2.12E-02
PIMN_2	FENDRR	2.35E-02
PIMN_2	RP11-343K8.3	2.40E-02
PIMN_2	HOXD9	3.21E-02
PIMN_2	IL6	3.41E-02
PIMN_2	CLCF1	4.18E-02
PIMN_2	CCND1	4.24E-02

ident	gene	padjH
PIN_1	ASTN2	3.22E-10
PIN_1	PDE5A	3.39E-10
PIN_1	DCX	1.18E-09
PIN_1	RGS4	1.49E-09
PIN_1	WBSCR17	3.86E-09
PIN_1	NELL2	8.32E-09
PIN_1	NRP2	8.56E-09
PIN_1	KCNH7	1.38E-08
PIN_1	DNER	2.33E-08
PIN_1	TRPM3	5.97E-08
PIN_1	SCD	9.38E-08
PIN_1	PDZRN3	1.10E-07
PIN_1	FAM19A5	1.52E-07
PIN_1	CALCRL	1.79E-07
PIN_1	ITGB8	1.79E-07
PIN_1	TMC3	1.79E-07
PIN_1	OPRM1	2.22E-07
PIN_1	DHCR24	2.59E-07
PIN_1	KCNQ3	4.14E-07
PIN_1	ZC3H15	4.23E-07
PIN_1	MT3	5.07E-07
PIN_1	AP001604.3	6.80E-07
PIN_1	KCNT2	7.39E-07
PIN_1	ST6GALNAC3	1.12E-06
PIN_1	GPC5	1.14E-06
PIN_1	LBH	1.18E-06
PIN_1	TPD52	1.27E-06
PIN_1	CTB-78F1.1	1.30E-06
PIN_1	RP11-168O10.6	1.34E-06
PIN_1	TMTC1	1.81E-06
PIN_1	LYPD6	2.14E-06
PIN_1	SHISA9	3.01E-06
PIN_1	SNCG	4.06E-06
PIN_1	KCTD8	4.17E-06
PIN_1	NEFM	5.91E-06
PIN_1	GRP	8.32E-06
PIN_1	CHL1	8.55E-06
PIN_1	OGFRL1	9.66E-06
PIN_1	NFATC1	1.19E-05
PIN_1	FABP5	1.19E-05
PIN_1	PRKG1	1.31E-05
PIN_1	RAP1GAP2	1.32E-05
PIN_1	FBP1	1.33E-05
PIN_1	LRRN1	1.71E-05
PIN_1	ST6GALNAC5	1.93E-05
PIN_1	ATRNL1	1.93E-05

PEMN_1	SNAP25-AS1	3.17E-14
PEMN_1	ARHGEF3	4.12E-14
PEMN_1	ADAMTSL1	5.36E-14
PEMN_1	FRMD4B	6.77E-14
PEMN_1	KAZN	2.17E-13
PEMN_1	PDE4B	4.16E-13
PEMN_1	RBMS3	6.66E-13
PEMN_1	CBS	9.62E-13
PEMN_1	HTR4	1.13E-12
PEMN_1	RGS6	1.80E-12
PEMN_1	AP000797.3	2.15E-12
PEMN_1	AL035610.2	2.81E-12
PEMN_1	CLDN11	3.35E-12
PEMN_1	CADM2	6.70E-12
PEMN_1	PPP2R2B	9.13E-12
PEMN_1	PSD3	1.24E-11
PEMN_1	BACH2	2.07E-11
PEMN_1	PRICKLE2	2.19E-11
PEMN_1	LRFN2	4.55E-11
PEMN_1	MAST4	5.50E-11
PEMN_1	BRINP2	8.70E-11
PEMN_1	AMPH	4.09E-10
PEMN_1	MAML3	4.66E-10
PEMN_1	NRP1	8.25E-10
PEMN_1	DAPK2	1.07E-09
PEMN_1	ABTB2	1.07E-09
PEMN_1	NDUFA4L2	1.88E-09
PEMN_1	AJ006995.3	1.91E-09
PEMN_1	ADAMTS9-AS2	3.50E-09
PEMN_1	RP11-390N6.1	3.96E-09
PEMN_1	SYT6	5.10E-09
PEMN_1	AC009120.6	6.34E-09
PEMN_1	RP11-111E14.1	6.44E-09
PEMN_1	CTD-2576D5.4	7.33E-09
PEMN_1	GPR22	1.23E-08
PEMN_1	SLIT3	1.26E-08
PEMN_1	VCAN	1.31E-08
PEMN_1	RP11-383H13.1	1.37E-08
PEMN_1	LHFPL3	1.47E-08
PEMN_1	FBXO48	2.11E-08
PEMN_1	RP4-765H13.1	2.12E-08
PEMN_1	HTR1E	2.31E-08
PEMN_1	PTPRR	2.85E-08
PEMN_1	EPAS1	3.05E-08
PEMN_1	ZDHHC14	3.05E-08
PEMN_1	STXBP5L	3.05E-08
PEMN_1	RP1-34H18.1	3.22E-08
PEMN_1	LPPR5	6.37E-08
PEMN_1	PKNOX2	6.49E-08
PEMN_1	RP11-179K3.2	7.13E-08
PEMN_1	FRK	7.90E-08
PEMN_1	PDE4D	1.13E-07
PEMN_1	SEMA5A	1.18E-07
PEMN_1	AC013463.2	1.21E-07
PEMN_1	GPC6-AS1	1.59E-07
PEMN_1	RHBDL3	5.83E-07
PEMN_1	NNAT	8.08E-07
PEMN_1	RSPO2	1.72E-06
PEMN_1	TRPA1	3.40E-06
PEMN_1	NXPH2	7.26E-06
PIMN_2	AC093639.1	4.75E-02
PIMN_2	AP001053.11	4.81E-02
PIMN_2	RP11-309L24.2	4.81E-02
PIMN_2	HES1	4.90E-02
PIMN_3	PDE1A	2.78E-28
PIMN_3	FSTL5	2.87E-27
PIMN_3	KCNB2	4.91E-27
PIMN_3	RP11-348J24.2	8.13E-26
PIMN_3	ASS1	3.56E-25
PIMN_3	IQCJ-SCHIP1	8.16E-25
PIMN_3	ERBB4	1.24E-22
PIMN_3	RP11-661P17.1	2.31E-21
PIMN_3	CARTPT	4.00E-19
PIMN_3	NPNT	5.99E-19
PIMN_3	NOS1	3.23E-18
PIMN_3	SLC4A4	1.66E-15
PIMN_3	NTNG1	9.18E-15
PIMN_3	PCDH15	5.11E-13
PIMN_3	KCND2	8.52E-13
PIMN_3	CDH2	1.48E-12
PIMN_3	SYN3	1.57E-12
PIMN_3	KIAA1217	4.59E-12
PIMN_3	CNTNAP5	1.14E-11
PIMN_3	HECW1	1.22E-11
PIMN_3	KCNC1	8.29E-11
PIMN_3	CSGALNACT1	8.29E-11
PIMN_3	PARVB	9.91E-11
PIMN_3	NRG3	1.13E-10
PIMN_3	PTPRK	1.26E-10
PIMN_3	FGF14	2.06E-10
PIMN_3	NRXN1	2.21E-10
PIMN_3	ALCAM	2.48E-10
PIMN_3	KLHL1	6.87E-10
PIMN_3	NCAM2	8.21E-10
PIMN_3	KCNH7	9.31E-10
PIMN_3	AP001604.3	1.05E-09
PIMN_3	CHRM3	2.63E-09
PIMN_3	TIMP3	3.48E-09
PIMN_3	THSD4	6.98E-09
PIMN_3	ANXA1	6.99E-09
PIMN_3	AL035610.2	6.99E-09
PIMN_3	VIP	9.94E-09
PIMN_3	PTGIR	1.24E-08
PIMN_3	FLRT2	2.68E-08
PIMN_3	CNTNAP3B	2.68E-08
PIMN_3	SOBP	3.81E-08
PIMN_3	RP11-133F8.2	3.93E-08
PIMN_3	LTK	5.42E-08
PIMN_3	AC007740.1	8.97E-08
PIMN_3	KCNT2	8.99E-08
PIMN_3	B4GALT6	1.04E-07
PIMN_3	ENTPD3	1.24E-07
PIMN_3	TNR	1.42E-07
PIMN_3	FAM155A	1.55E-07
PIMN_3	NECAB1	1.58E-07
PIMN_3	NGB	1.58E-07
PIMN_3	ADCYAP1	2.34E-07
PIMN_3	CNGB1	3.65E-07
PIMN_3	RP11-260M19.2	4.31E-07
PIMN_3	KHDRBS2	4.94E-07
PIN_1	PCDH15	2.02E-05
PIN_1	ANXA1	2.37E-05
PIN_1	TMX4	2.48E-05
PIN_1	PCP4	2.59E-05
PIN_1	B3GNT1	2.66E-05
PIN_1	AC007392.3	3.11E-05
PIN_1	CBLN1	3.13E-05
PIN_1	RP11-38P22.2	3.29E-05
PIN_1	EDIL3	3.42E-05
PIN_1	RORA	3.42E-05
PIN_1	CTB-178M22.1	3.76E-05
PIN_1	GPC5-AS1	4.00E-05
PIN_1	ELMO1-AS1	4.47E-05
PIN_1	MT-CO2	5.28E-05
PIN_1	FRMPD4	5.53E-05
PIN_1	MT-ND5	5.53E-05
PIN_1	CACNA2D1	5.66E-05
PIN_1	RP11-761I4.3	6.51E-05
PIN_1	OVCH1-AS1	6.64E-05
PIN_1	NPY2R	8.63E-05
PIN_1	FRZB	1.01E-04
PIN_1	ADORA1	1.14E-04
PIN_1	MYO1A	1.31E-04
PIN_1	AK4	1.39E-04
PIN_1	FBXL16	1.62E-04
PIN_1	LTK	1.65E-04
PIN_1	TINCR	2.36E-04
PIN_1	SDR16C5	3.75E-04
PIN_1	IMPAD1	5.57E-04
PIN_1	CNTN4-AS2	5.66E-04
PIN_1	CPNE7	7.79E-04
PIN_1	FLRT3	1.20E-03
PIN_1	RP11-31I22.2	2.06E-03
PIN_1	CHST2	2.34E-03
PIN_1	INSIG1	3.38E-03
PIN_1	CTC-265N9.1	3.44E-03
PIN_1	RP11-1002K11.1	5.25E-03
PIN_1	AC068831.10	5.60E-03
PIN_1	C6orf141	5.75E-03
PIN_1	PVRL3	5.87E-03
PIN_1	NUAK1	7.55E-03
PIN_1	ZNF385D-AS2	7.57E-03
PIN_1	POSTN	7.67E-03
PIN_1	MSANTD4	8.59E-03
PIN_1	AC019100.3	1.23E-02
PIN_1	AMER3	1.33E-02
PIN_1	DPH3	1.39E-02
PIN_1	IGIP	1.45E-02
PIN_1	RP11-269F21.3	1.49E-02
PIN_1	RP11-31I22.3	1.60E-02
PIN_1	C2CD4C	1.85E-02
PIN_1	SNPH	2.01E-02
PIN_1	CCR10	2.03E-02
PIN_1	KCNJ2	2.22E-02
PIN_1	RP11-129B22.1	2.27E-02
PIN_1	RP5-1121H13.3	2.75E-02
PIN_1	MAB21L2	2.92E-02
PIN_1	SIGMAR1	3.03E-02
PIN_1	HTRA1	3.21E-02
PIN_1	HPCAL4	3.25E-02

PEMN_1	AP000476.1	1.29E-05
PEMN_1	GLRA3	2.92E-05
PEMN_1	PRELP	7.72E-05
PEMN_1	CLEC18A	8.07E-05
PEMN_1	RP11-402J6.1	8.43E-05
PEMN_1	ANXA10	1.04E-04
PEMN_1	LINC00682	1.14E-04
PEMN_1	GDNF-AS1	2.39E-04
PEMN_1	RP11-556G22.3	3.63E-04
PEMN_1	F3	5.97E-04
PEMN_1	RP11-804L24.2	6.06E-04
PEMN_1	PDGFRB	1.24E-03
PEMN_1	FAM124A	1.88E-03
PEMN_1	MYRFL	1.88E-03
PEMN_1	ABCC11	2.91E-03
PEMN_1	SULT1C4	2.91E-03
PEMN_1	RP11-669N7.2	3.46E-03
PEMN_1	SMIM10	4.36E-03
PEMN_1	FAM180A	4.73E-03
PEMN_1	C9orf24	4.93E-03
PEMN_1	RP11-227H15.4	9.97E-03
PEMN_1	RP11-269G24.3	1.11E-02
PEMN_1	PDZD9	1.29E-02
PEMN_1	HSD11B2	1.40E-02
PEMN_1	FGF10-AS1	1.63E-02
PEMN_1	CTC-419K13.1	1.73E-02
PEMN_1	RP5-944M2.3	1.91E-02
PEMN_1	RP11-2C7.1	2.00E-02
PEMN_1	NPTX1	2.03E-02
PEMN_1	AC010336.1	2.08E-02
PEMN_1	CLEC18B	2.15E-02
PEMN_1	LINC01049	2.53E-02
PEMN_1	ZMAT5	2.66E-02
PEMN_1	RP1-37N7.1	3.22E-02
PEMN_1	RP11-384F7.2	3.24E-02
PEMN_1	SCGB1D2	3.53E-02
PEMN_1	RP11-259P1.1	3.57E-02
PEMN_1	RP4-734G22.3	3.70E-02
PEMN_1	ATP4A	3.78E-02
PEMN_1	KCNK15	3.93E-02
PEMN_1	KCNE3	4.26E-02
PEMN_1	ABHD14A	4.57E-02
PEMN_2	CTA-481E9.4	3.84E-49
PEMN_2	KCNIP4	8.65E-49
PEMN_2	PRKG1	3.97E-48
PEMN_2	CSMD3	9.91E-47
PEMN_2	GALNTL6	5.83E-45
PEMN_2	CHRM2	1.37E-43
PEMN_2	CDH13	5.98E-38
PEMN_2	LSAMP	1.50E-36
PEMN_2	MACROD2	1.56E-35
PEMN_2	ZNF804A	1.21E-34
PEMN_2	GPC6	2.14E-34
PEMN_2	KCNQ3	9.57E-34
PEMN_2	SLC44A5	4.76E-32
PEMN_2	AC067959.1	5.13E-30
PEMN_2	RALYL	1.38E-29
PEMN_2	GRID2	2.47E-29
PEMN_2	BRINP3	2.21E-28
PEMN_2	EFNA5	2.30E-28
PIMN_3	AP001605.4	5.72E-07
PIMN_3	MARCH1	7.17E-07
PIMN_3	EPB41L5	7.36E-07
PIMN_3	RP11-14N7.2	7.38E-07
PIMN_3	P2RY6	9.09E-07
PIMN_3	LINC00284	9.09E-07
PIMN_3	HCN1	9.09E-07
PIMN_3	PCP4	1.07E-06
PIMN_3	SAMD5	1.89E-06
PIMN_3	DPYD	2.18E-06
PIMN_3	FRMPD1	2.30E-06
PIMN_3	RP11-430H10.4	2.64E-06
PIMN_3	ASL	2.64E-06
PIMN_3	NEGR1	2.89E-06
PIMN_3	SIPA1L2	3.91E-06
PIMN_3	DGKB	5.44E-06
PIMN_3	GNG8	5.56E-06
PIMN_3	KCNJ5	5.68E-06
PIMN_3	KCNQ5	6.32E-06
PIMN_3	PHACTR3	9.17E-06
PIMN_3	RP11-257I14.1	1.16E-05
PIMN_3	NCALD	1.32E-05
PIMN_3	SERTM1	1.34E-05
PIMN_3	P2RY14	1.46E-05
PIMN_3	TAGLN3	1.46E-05
PIMN_3	PDE8B	1.59E-05
PIMN_3	PCDH9-AS2	1.95E-05
PIMN_3	PLEKHA6	1.97E-05
PIMN_3	CAMK4	2.11E-05
PIMN_3	HMCN2	2.37E-05
PIMN_3	CTD-2215E18.1	2.48E-05
PIMN_3	SRGAP1	2.84E-05
PIMN_3	GREB1L	2.90E-05
PIMN_3	PRKD1	2.97E-05
PIMN_3	FHIT	2.97E-05
PIMN_3	CACNA1C	2.97E-05
PIMN_3	KCNC2	3.39E-05
PIMN_3	UCN3	3.43E-05
PIMN_3	RFXAP	3.99E-05
PIMN_3	ENC1	4.72E-05
PIMN_3	LEPREL1	4.97E-05
PIMN_3	CTC-499J9.1	5.26E-05
PIMN_3	MYO5A	5.58E-05
PIMN_3	RP11-307P5.1	5.74E-05
PIMN_3	IL12A	6.49E-05
PIMN_3	UCP2	9.12E-05
PIMN_3	PROK2	1.64E-04
PIMN_3	HYI	3.01E-04
PIMN_3	RP11-451M19.3	4.31E-04
PIMN_3	CPNE6	5.92E-04
PIMN_3	AKR1C2	8.14E-04
PIMN_3	MPP4	8.31E-04
PIMN_3	AJ006995.3	9.43E-04
PIMN_3	LINC00314	9.63E-04
PIMN_3	VEGFC	1.07E-03
PIMN_3	BCAT1	1.41E-03
PIMN_3	PCDH19	1.66E-03
PIMN_3	C4orf32	1.72E-03
PIMN_3	TMEM237	1.73E-03
PIMN_3	FSTL4	3.67E-03
PIN_1	GLRA4	3.27E-02
PIN_1	SLC10A4	3.36E-02
PIN_1	CTA-299D3.8	3.67E-02
PIN_1	PRPS1	4.02E-02
PIN_1	TMEM132E	4.29E-02
PIN_1	TOMM34	4.35E-02
PIN_1	SECTM1	4.41E-02
PIN_2	NELL1	2.31E-43
PIN_2	PCDH7	8.50E-40
PIN_2	NRG1	7.25E-20
PIN_2	NTNG1	3.83E-18
PIN_2	ENOX1	3.83E-18
PIN_2	KIF26B	2.10E-17
PIN_2	SPP1	4.16E-17
PIN_2	P4HA3	2.42E-15
PIN_2	HS3ST4	3.76E-15
PIN_2	IQCJ-SCHIP1	1.19E-14
PIN_2	RP11-649G15.2	4.40E-14
PIN_2	PBX3	7.67E-13
PIN_2	ECEL1	2.58E-12
PIN_2	VAT1L	3.44E-12
PIN_2	HECW1	6.68E-12
PIN_2	AC133680.1	2.43E-11
PIN_2	CNTN3	4.72E-11
PIN_2	STRA6	8.50E-11
PIN_2	TNS3	1.32E-10
PIN_2	SAMD3	1.32E-10
PIN_2	OXR1	2.87E-10
PIN_2	FDPS	3.04E-10
PIN_2	NRP1	3.80E-10
PIN_2	TENM2	6.22E-10
PIN_2	XPR1	9.71E-10
PIN_2	GRP	2.19E-09
PIN_2	RARB	4.26E-09
PIN_2	GRIK1	4.26E-09
PIN_2	NEBL	5.44E-09
PIN_2	GLCCI1	5.44E-09
PIN_2	KIAA0922	5.85E-09
PIN_2	FMN1	5.87E-09
PIN_2	AC026202.3	1.18E-08
PIN_2	CYTH3	1.79E-08
PIN_2	SOX30	1.97E-08
PIN_2	TRPS1	1.97E-08
PIN_2	RAB30	1.98E-08
PIN_2	CHRNA7	2.00E-08
PIN_2	DOCK2	2.29E-08
PIN_2	FRMD4A	2.83E-08
PIN_2	RIT2	3.08E-08
PIN_2	SHISA9	4.08E-08
PIN_2	RGS7	4.87E-08
PIN_2	ERBB2IP	5.19E-08
PIN_2	ADAM22	7.02E-08
PIN_2	CCRN4L	8.66E-08
PIN_2	RASGEF1B	1.10E-07
PIN_2	ZNF490	1.16E-07
PIN_2	ATRNL1	1.35E-07
PIN_2	CHST1	2.61E-07
PIN_2	RP11-430H10.4	2.74E-07
PIN_2	RP11-619J20.1	3.17E-07
PIN_2	SEZ6L	4.34E-07

PEMN_2	SEMA3D	4.32E-28
PEMN_2	PTCHD4	2.14E-27
PEMN_2	NBEA	1.85E-26
PEMN_2	CALCRL	8.68E-26
PEMN_2	SNTG1	3.11E-25
PEMN_2	BNC2	5.49E-25
PEMN_2	KCNQ5	6.49E-25
PEMN_2	SORCS3	1.42E-24
PEMN_2	hsa-mir-490	2.34E-24
PEMN_2	SLC5A7	2.27E-23
PEMN_2	UNC5D	4.08E-23
PEMN_2	SGCZ	4.75E-23
PEMN_2	ADAMTS19	7.14E-23
PEMN_2	RYR2	3.71E-22
PEMN_2	COLQ	3.92E-22
PEMN_2	SYT1	1.03E-21
PEMN_2	TPD52L1	3.90E-21
PEMN_2	KCNH5	6.55E-21
PEMN_2	LHFPL3	8.57E-21
PEMN_2	GRIA4	5.38E-20
PEMN_2	HS3ST5	2.81E-19
PEMN_2	ST6GALNAC5	3.57E-19
PEMN_2	SLCO3A1	5.86E-19
PEMN_2	ADAMTS9-AS2	7.53E-19
PEMN_2	PDE4D	1.80E-18
PEMN_2	RP11-76I14.1	2.00E-18
PEMN_2	SLIT3	2.81E-18
PEMN_2	UNC5C	8.42E-18
PEMN_2	ZPLD1	9.38E-18
PEMN_2	ADAMTS9	1.04E-17
PEMN_2	LINC00842	1.25E-17
PEMN_2	GUCY1A3	1.34E-17
PEMN_2	AC074363.1	1.89E-17
PEMN_2	AL035610.2	3.02E-17
PEMN_2	LRRTM3	3.70E-17
PEMN_2	RP11-547I7.1	4.07E-17
PEMN_2	DNM3	8.01E-17
PEMN_2	POSTN	1.84E-16
PEMN_2	LBH	1.88E-16
PEMN_2	LRFN5	2.09E-16
PEMN_2	SYN3	5.28E-16
PEMN_2	GRIA1	9.56E-16
PEMN_2	CA10	2.04E-15
PEMN_2	DIAPH2	2.59E-15
PEMN_2	PEX5L	2.73E-15
PEMN_2	LSAMP-AS1	8.91E-15
PEMN_2	FSTL5	1.06E-14
PEMN_2	NREP	1.36E-14
PEMN_2	PTPRD	1.72E-14
PEMN_2	MEIS1	6.51E-14
PEMN_2	FAM155A	8.34E-14
PEMN_2	CADPS	1.02E-13
PEMN_2	TIMP3	1.15E-13
PEMN_2	IL15	1.15E-13
PEMN_2	RP11-298D21.1	4.69E-13
PEMN_2	SEMA6D	6.46E-13
PEMN_2	DPP6	6.93E-13
PEMN_2	RP11-227F19.1	8.14E-13
PEMN_2	BAI3	1.19E-12
PEMN_2	PIEZO2	1.22E-12

PIMN_3	DLGAP1-AS4	6.83E-03
PIMN_3	ANKRD2	7.20E-03
PIMN_3	GPR42	1.10E-02
PIMN_3	HOTAIRM1	1.14E-02
PIMN_3	FAM162B	1.21E-02
PIMN_3	LINC00113	1.39E-02
PIMN_3	NEFM	1.40E-02
PIMN_3	RP11-19O2.1	1.49E-02
PIMN_3	RP11-103C16.2	1.69E-02
PIMN_3	AC079154.1	1.94E-02
PIMN_3	GP1BA	2.14E-02
PIMN_3	FFAR3	2.28E-02
PIMN_3	FXYD7	2.63E-02
PIMN_3	PLK3	2.63E-02
PIMN_3	GAS6-AS1	2.63E-02
PIMN_3	EME2	2.81E-02
PIMN_3	RP1-257I9.2	3.11E-02
PIMN_3	ZNF654	3.51E-02
PIMN_3	CTD-3051D23.4	3.51E-02
PIMN_3	TP53AIP1	3.84E-02
PIMN_3	RASEF	3.86E-02
PIMN_3	RP11-186N15.3	3.98E-02
PIMN_3	AC007743.1	4.20E-02
PIMN_3	KCNF1	4.49E-02
PIMN_3	TP53INP1	4.50E-02
PIMN_3	AP1G2	4.59E-02
PIMN_3	MAFK	4.79E-02
PIMN_3	RELL2	4.81E-02
PIMN_3	AC004692.4	4.87E-02
PIMN_4	NOS1	2.11E-21
PIMN_4	TMTC2	2.18E-18
PIMN_4	TANC1	2.37E-17
PIMN_4	TPST1	4.47E-16
PIMN_4	DGKB	5.46E-15
PIMN_4	ROBO1	9.76E-15
PIMN_4	RP11-286N3.2	1.20E-14
PIMN_4	ODAM	1.51E-12
PIMN_4	RP11-318M2.2	9.21E-12
PIMN_4	GUCY1A2	7.09E-11
PIMN_4	PRKCE	7.09E-11
PIMN_4	ST18	1.94E-10
PIMN_4	LDLRAD3	9.29E-09
PIMN_4	MAN1A1	2.45E-08
PIMN_4	NLGN1	3.10E-08
PIMN_4	ENTPD3	3.85E-08
PIMN_4	RP11-131L23.1	4.01E-08
PIMN_4	DCLK1	3.82E-07
PIMN_4	PGM2L1	6.02E-07
PIMN_4	ARHGEF28	6.02E-07
PIMN_4	SNTB1	6.51E-07
PIMN_4	PLCB4	7.19E-07
PIMN_4	RIC3	9.79E-07
PIMN_4	NTF3	1.21E-06
PIMN_4	DCC	1.53E-06
PIMN_4	NHLRC3	2.80E-06
PIMN_4	CTC-458I2.2	3.05E-06
PIMN_4	EPB41L3	3.69E-06
PIMN_4	CIT	4.31E-06
PIMN_4	RHOB	4.75E-06
PIMN_4	TSPAN13	4.75E-06

PIN_2	SEMA5A	5.30E-07
PIN_2	GRK5	5.96E-07
PIN_2	FGF12	6.61E-07
PIN_2	RP5-1043L13.1	7.19E-07
PIN_2	ATP8A2	8.15E-07
PIN_2	KLHL1	2.17E-06
PIN_2	DLGAP1	2.93E-06
PIN_2	FSTL4	2.96E-06
PIN_2	DPP6	3.96E-06
PIN_2	PARVB	4.17E-06
PIN_2	KHDRBS3	4.52E-06
PIN_2	GPR158	4.68E-06
PIN_2	OR51E1	5.30E-06
PIN_2	RP11-142M10.2	5.30E-06
PIN_2	EDIL3	6.96E-06
PIN_2	IFI27	7.56E-06
PIN_2	CHL1	7.56E-06
PIN_2	RP11-384F7.1	7.56E-06
PIN_2	CNTN4	7.56E-06
PIN_2	AFF3	7.56E-06
PIN_2	BMPR1B	8.34E-06
PIN_2	ARL8B	8.37E-06
PIN_2	THBS4	1.16E-05
PIN_2	MEIS1	2.02E-05
PIN_2	ZFPM2	2.68E-05
PIN_2	CSMD3	2.79E-05
PIN_2	SYNPO2	3.16E-05
PIN_2	HS6ST2	3.16E-05
PIN_2	NCAM2	3.26E-05
PIN_2	SLC20A2	3.86E-05
PIN_2	ZFHX3	4.10E-05
PIN_2	CALCB	5.73E-05
PIN_2	PGM2L1	5.88E-05
PIN_2	LTK	5.94E-05
PIN_2	LIPH	5.94E-05
PIN_2	TCERG1L	6.94E-05
PIN_2	AC012123.1	1.14E-04
PIN_2	MYLK	1.38E-04
PIN_2	ERC2	1.45E-04
PIN_2	LRRN3	1.75E-04
PIN_2	CPNE8	1.75E-04
PIN_2	OR51E2	1.83E-04
PIN_2	SNAP25	2.05E-04
PIN_2	AC007879.5	2.08E-04
PIN_2	TANC2	2.08E-04
PIN_2	CRB1	2.20E-04
PIN_2	AC026150.5	2.33E-04
PIN_2	NEFM	3.14E-04
PIN_2	HTR2B	4.19E-04
PIN_2	NXPH2	4.27E-04
PIN_2	FAM196B	4.75E-04
PIN_2	PRR16	6.65E-04
PIN_2	LINC00685	8.53E-04
PIN_2	TMC3	1.24E-03
PIN_2	TMEM200A	1.33E-03
PIN_2	CD226	1.39E-03
PIN_2	APOL2	1.39E-03
PIN_2	EHBP1L1	1.68E-03
PIN_2	CALB1	1.77E-03
PIN_2	RP11-62I21.1	1.85E-03

PEMN_2	FBXO48	1.68E-12
PEMN_2	DIAPH2-AS1	3.62E-12
PEMN_2	CCBE1	3.80E-12
PEMN_2	MAGI2	4.79E-12
PEMN_2	TRPA1	7.54E-12
PEMN_2	RP3-399L15.3	1.02E-11
PEMN_2	PRICKLE2	1.14E-11
PEMN_2	HTR4	1.17E-11
PEMN_2	COL5A1	1.42E-11
PEMN_2	UNC79	1.42E-11
PEMN_2	SLC8A1	1.54E-11
PEMN_2	STAC	2.08E-11
PEMN_2	RP11-136K7.2	3.23E-11
PEMN_2	PRB2	4.60E-11
PEMN_2	AC007319.1	5.16E-11
PEMN_2	GABRG3	1.13E-10
PEMN_2	KCNS3	1.69E-10
PEMN_2	CHL1	2.13E-10
PEMN_2	CADM1	2.30E-10
PEMN_2	HTR3A	6.63E-10
PEMN_2	CTC-575N7.1	8.86E-10
PEMN_2	TOX	1.38E-09
PEMN_2	TLL2	5.08E-09
PEMN_2	RGS4	8.65E-09
PEMN_2	CORO6	1.65E-08
PEMN_2	RP11-707P20.1	1.78E-08
PEMN_2	CTD-3253I12.1	2.30E-08
PEMN_2	RP11-556G22.3	2.42E-08
PEMN_2	HTR3B	5.78E-08
PEMN_2	AASS	9.83E-08
PEMN_2	AJ239322.3	2.01E-07
PEMN_2	GHSR	2.69E-07
PEMN_2	DLX6-AS1	5.08E-07
PEMN_2	RP11-429O1.1	5.41E-07
PEMN_2	RP11-162D9.3	5.90E-07
PEMN_2	RP5-952N6.1	7.66E-07
PEMN_2	PHLDA1	1.14E-06
PEMN_2	HTR7	1.61E-06
PEMN_2	SMAD7	2.23E-06
PEMN_2	RP11-362F19.1	5.93E-06
PEMN_2	PNOC	7.06E-06
PEMN_2	SLCO1C1	4.98E-05
PEMN_2	MVB12A	4.98E-05
PEMN_2	MAB21L2	5.08E-05
PEMN_2	RP11-435O5.2	9.28E-05
PEMN_2	RP11-17L5.4	1.02E-04
PEMN_2	ANXA1	1.16E-04
PEMN_2	TMEM100	2.16E-04
PEMN_2	RP11-543D5.1	3.44E-04
PEMN_2	KIAA1024L	4.44E-04
PEMN_2	HES7	8.96E-04
PEMN_2	C12orf39	1.12E-03
PEMN_2	DLX6	1.25E-03
PEMN_2	RP11-168O10.6	1.33E-03
PEMN_2	LINC00494	2.31E-03
PEMN_2	TMEM133	2.44E-03
PEMN_2	B3GALT1	4.23E-03
PEMN_2	NOC3L	4.36E-03
PEMN_2	EVPL	6.05E-03
PEMN_2	CTC-558O2.1	9.80E-03
PIMN_4	AC018890.6	5.78E-06
PIMN_4	AC108142.1	5.80E-06
PIMN_4	RP11-196H14.2	6.12E-06
PIMN_4	MYO1B	6.23E-06
PIMN_4	BAALC	6.47E-06
PIMN_4	RP11-778J15.1	7.10E-06
PIMN_4	SLC25A1	7.24E-06
PIMN_4	SAMD4A	8.63E-06
PIMN_4	PERP	1.08E-05
PIMN_4	CACYBP	1.13E-05
PIMN_4	KIAA1239	1.33E-05
PIMN_4	RP11-252A24.7	1.33E-05
PIMN_4	GAL	1.45E-05
PIMN_4	CTD-2544M6.1	1.57E-05
PIMN_4	ACTN1	2.19E-05
PIMN_4	RP1-15D23.2	3.16E-05
PIMN_4	TCTEX1D1	3.28E-05
PIMN_4	QDPR	4.47E-05
PIMN_4	PHACTR1	4.72E-05
PIMN_4	ASL	5.98E-05
PIMN_4	RP11-452H21.1	6.05E-05
PIMN_4	HSP90B1	7.55E-05
PIMN_4	FAM188A	9.20E-05
PIMN_4	SNRPE	9.36E-05
PIMN_4	EXOC1	9.97E-05
PIMN_4	TRPM3	9.97E-05
PIMN_4	SCML4	1.03E-04
PIMN_4	SERINC5	1.03E-04
PIMN_4	CAMK2N1	1.03E-04
PIMN_4	G6PC3	1.12E-04
PIMN_4	PYURF	1.21E-04
PIMN_4	BUB3	1.27E-04
PIMN_4	VIP	1.28E-04
PIMN_4	EEF1B2	1.28E-04
PIMN_4	RP11-465I4.2	1.32E-04
PIMN_4	PDE8B	1.36E-04
PIMN_4	SLC35A5	1.53E-04
PIMN_4	SMPD3	1.57E-04
PIMN_4	WBSCR22	1.57E-04
PIMN_4	SLC38A2	1.59E-04
PIMN_4	ID4	1.59E-04
PIMN_4	SPCS1	1.59E-04
PIMN_4	ANKRD44	1.59E-04
PIMN_4	DST	1.62E-04
PIMN_4	MAGEH1	1.62E-04
PIMN_4	TMEM241	1.71E-04
PIMN_4	YBX1	1.98E-04
PIMN_4	MAMDC2	2.12E-04
PIMN_4	FAM171A2	2.43E-04
PIMN_4	CTNNA2	2.43E-04
PIMN_4	CYB561	2.53E-04
PIMN_4	CLASP1	2.54E-04
PIMN_4	JPX	2.54E-04
PIMN_4	LSM6	2.56E-04
PIMN_4	C1orf233	2.60E-04
PIMN_4	SRGAP1	2.88E-04
PIMN_4	CDKN2D	3.00E-04
PIMN_4	ABLIM2	3.02E-04
PIMN_4	RP11-3L8.3	3.14E-04
PIMN_4	PCMTD1	3.14E-04
PIN_2	EMB	2.14E-03
PIN_2	RP11-536C10.4	2.54E-03
PIN_2	GPC6-AS1	2.70E-03
PIN_2	BTBD3	2.84E-03
PIN_2	KLHL14	3.18E-03
PIN_2	SLC35G1	3.76E-03
PIN_2	GPR82	5.99E-03
PIN_2	SMAD9	6.03E-03
PIN_2	RP11-1028N23.3	6.05E-03
PIN_2	HMGCR	6.38E-03
PIN_2	ARL6	6.38E-03
PIN_2	DLGAP1-AS5	6.63E-03
PIN_2	RNF144A	7.78E-03
PIN_2	CCDC74B	9.02E-03
PIN_2	RXRG	9.81E-03
PIN_2	ACTR5	9.81E-03
PIN_2	PLK2	9.90E-03
PIN_2	RP11-296E23.1	1.05E-02
PIN_2	CTD-2371O3.2	1.24E-02
PIN_2	CALCA	1.41E-02
PIN_2	ACRV1	1.52E-02
PIN_2	CTB-178M22.1	2.12E-02
PIN_2	TSPAN12	2.36E-02
PIN_2	ITPKA	2.38E-02
PIN_2	VEGFA	2.46E-02
PIN_2	GALR1	2.85E-02
PIN_2	TBX2	3.05E-02
PIN_2	FSIP2	3.11E-02
PIN_2	MIR7-3HG	3.56E-02
PIN_2	IDO2	4.56E-02
PIN_2	CYP4F35P	4.95E-02
PSN	DGKH	4.36E-93
PSN	SPOCK3	4.44E-89
PSN	DGKG	5.26E-75
PSN	CDH6	1.45E-43
PSN	FAM3C	3.89E-40
PSN	LUZP2	5.88E-38
PSN	NTRK3	1.01E-36
PSN	GUCY1A2	4.31E-36
PSN	CBLN2	6.56E-36
PSN	TAC1	1.85E-34
PSN	IFI27	1.32E-31
PSN	ASAP1	1.15E-30
PSN	HTR3A	4.11E-28
PSN	TCF7L2	2.27E-26
PSN	SST	7.27E-26
PSN	SLC2A13	1.90E-25
PSN	TMSB10	2.82E-24
PSN	TRHDE	7.57E-24
PSN	NEDD4L	8.82E-24
PSN	VGLL3	5.04E-23
PSN	OLFM2	1.53E-22
PSN	C6orf141	1.55E-22
PSN	ZNF804A	1.65E-21
PSN	S100A10	4.09E-21
PSN	SCUBE1	5.27E-21
PSN	KCTD16	5.64E-21
PSN	TP53I11	5.84E-21
PSN	OLFM3	7.96E-21
PSN	PLXNA4	5.62E-20

PEMN_2	RP11-923I11.4	1.48E-02
PEMN_2	HGF	1.48E-02
PEMN_2	RP11-284H19.1	1.65E-02
PEMN_2	HHLA1	1.69E-02
PEMN_2	GPR35	2.06E-02
PEMN_2	ITGB5-AS1	2.12E-02
PEMN_2	CBR1	2.31E-02
PEMN_2	SSMEM1	2.45E-02
PEMN_2	AC023115.2	2.50E-02
PEMN_2	EFNB3	3.18E-02
PEMN_2	C5orf47	3.53E-02
PEMN_2	RP11-107D24.2	3.82E-02
PEMN_2	SLC5A9	4.27E-02
PEMN_2	CTD-3023L14.2	4.28E-02
PEMN_2	CTB-178M22.1	4.34E-02
PEMN_2	AL136376.1	4.42E-02
PIMN_1	NOS1	1.66E-25
PIMN_1	DGKB	1.11E-23
PIMN_1	TMTC2	2.21E-19
PIMN_1	EPB41L3	5.46E-19
PIMN_1	LPHN3	4.37E-17
PIMN_1	DCC	1.83E-16
PIMN_1	ALCAM	9.22E-16
PIMN_1	SNTB1	2.98E-15
PIMN_1	ARHGAP26	3.60E-15
PIMN_1	DCLK1	6.34E-15
PIMN_1	PRKCE	7.25E-15
PIMN_1	HDAC9	1.27E-14
PIMN_1	LDLRAD3	1.64E-14
PIMN_1	ST18	2.55E-14
PIMN_1	TCTEX1D1	3.98E-14
PIMN_1	NLGN1	4.96E-14
PIMN_1	PHYHIPL	2.49E-13
PIMN_1	CNTNAP5	2.49E-13
PIMN_1	ALDH1A2	3.62E-13
PIMN_1	GAL	3.47E-12
PIMN_1	FLRT2	4.44E-12
PIMN_1	GUCY1A2	6.31E-12
PIMN_1	SLIT2	7.84E-12
PIMN_1	RP1-15D23.2	7.84E-12
PIMN_1	TPST1	6.93E-11
PIMN_1	PTPRG	4.72E-10
PIMN_1	CTNNA2	2.97E-09
PIMN_1	RP11-286N3.2	4.60E-09
PIMN_1	AC068533.7	4.67E-09
PIMN_1	TRHDE	8.80E-09
PIMN_1	MYRIP	8.80E-09
PIMN_1	GLDN	9.45E-09
PIMN_1	ODAM	1.03E-08
PIMN_1	DMD	1.14E-08
PIMN_1	PPAPDC1A	1.48E-08
PIMN_1	ASL	3.45E-08
PIMN_1	OPRD1	7.81E-08
PIMN_1	TMEM108	8.22E-08
PIMN_1	MAN1A1	8.22E-08
PIMN_1	FOXO3	8.72E-08
PIMN_1	TMEM163	9.68E-08
PIMN_1	MSI2	9.68E-08
PIMN_1	FAM78B	9.96E-08
PIMN_1	RP11-1084J3.4	9.96E-08
PIMN_4	TMEM167A	3.15E-04
PIMN_4	RP11-460H9.1	3.22E-04
PIMN_4	COPE	3.22E-04
PIMN_4	TNS3	3.30E-04
PIMN_4	EIF3I	3.30E-04
PIMN_4	LGALS3BP	3.39E-04
PIMN_4	RP11-320M16.2	3.39E-04
PIMN_4	ABCA2	3.41E-04
PIMN_4	ZNF536	3.46E-04
PIMN_4	RP11-78F17.1	4.09E-04
PIMN_4	RP11-710C12.1	4.17E-04
PIMN_4	POP7	5.57E-04
PIMN_4	AC096772.6	5.87E-04
PIMN_4	NDUFB3	7.37E-04
PIMN_4	CUTA	8.78E-04
PIMN_4	LINC00639	9.63E-04
PIMN_4	CHMP2A	9.64E-04
PIMN_4	MARCKSL1	9.97E-04
PIMN_4	MFSD2A	1.46E-03
PIMN_4	GSTO1	1.60E-03
PIMN_4	BMI1	1.94E-03
PIMN_4	ASPHD2	2.45E-03
PIMN_4	RAMP3	2.48E-03
PIMN_4	ATP2B3	3.09E-03
PIMN_4	UBE2D1	3.30E-03
PIMN_4	MTRNR2L11	3.50E-03
PIMN_4	TMEM60	3.67E-03
PIMN_4	SYNDIG1L	3.88E-03
PIMN_4	SNN	4.61E-03
PIMN_4	VPS4A	4.61E-03
PIMN_4	TCEAL8	4.86E-03
PIMN_4	SLFN13	5.06E-03
PIMN_4	FUNDC1	5.28E-03
PIMN_4	CTD-2336O2.1	5.31E-03
PIMN_4	CDH5	5.40E-03
PIMN_4	JOSD2	5.40E-03
PIMN_4	TM2D2	5.40E-03
PIMN_4	PPP4C	5.50E-03
PIMN_4	RP11-286N3.1	5.55E-03
PIMN_4	SLC25A14	5.55E-03
PIMN_4	HMGA1	5.55E-03
PIMN_4	HSPB7	5.66E-03
PIMN_4	CTD-2165H16.4	6.14E-03
PIMN_4	CAMK1G	6.20E-03
PIMN_4	ARHGEF25	6.81E-03
PIMN_4	WDR74	7.08E-03
PIMN_4	FRG1	7.62E-03
PIMN_4	EPB41L4A-AS1	9.58E-03
PIMN_4	NUDT16	1.14E-02
PIMN_4	CRAT	1.19E-02
PIMN_4	ECHS1	1.22E-02
PIMN_4	NHP2	1.29E-02
PIMN_4	PBDC1	1.38E-02
PIMN_4	USF2	1.39E-02
PIMN_4	MESP1	1.56E-02
PIMN_4	ATXN8OS	1.60E-02
PIMN_4	CCDC106	1.62E-02
PIMN_4	CCDC23	1.66E-02
PIMN_4	FAM150A	1.67E-02
PIMN_4	APOA1BP	1.68E-02
PSN	NECAB2	1.06E-19
PSN	RP11-217C7.1	3.32E-19
PSN	DLX4	3.77E-19
PSN	KANK4	8.22E-19
PSN	CHL1	8.32E-19
PSN	TBPL1	3.25E-18
PSN	CUX2	1.23E-17
PSN	MCTP1	1.49E-17
PSN	C12orf75	1.82E-17
PSN	TSPAN8	6.75E-17
PSN	OLFM1	7.24E-17
PSN	SCN11A	8.01E-17
PSN	RAB3B	8.15E-17
PSN	ADIRF	2.00E-16
PSN	CPNE4	3.18E-16
PSN	HLA-C	3.39E-16
PSN	DLX3	8.90E-16
PSN	PLSCR1	1.14E-15
PSN	SH3BGRL3	1.14E-15
PSN	PHOX2B	1.14E-15
PSN	DIRAS2	2.04E-15
PSN	RP11-138I17.1	2.04E-15
PSN	CDH9	3.81E-15
PSN	KCNH8	6.62E-15
PSN	RPRM	7.73E-15
PSN	ZNF804B	1.26E-14
PSN	SDC3	1.28E-14
PSN	GUCY1A3	1.63E-14
PSN	SLC12A7	2.12E-14
PSN	EPDR1	2.34E-14
PSN	STMN1	2.66E-14
PSN	NGFR	3.45E-14
PSN	KCNAB1	4.84E-14
PSN	UST	6.23E-14
PSN	ANO2	7.64E-14
PSN	SYT4	7.65E-14
PSN	STMN2	2.01E-13
PSN	TUBA1A	3.22E-13
PSN	TMEM160	9.88E-13
PSN	CD9	1.50E-12
PSN	CELF3	1.54E-12
PSN	TTC9B	1.91E-12
PSN	B2M	2.07E-12
PSN	C9orf16	2.17E-12
PSN	SERF2	2.17E-12
PSN	KCNB2	2.58E-12
PSN	THRA	3.91E-12
PSN	ATOX1	3.95E-12
PSN	CALCRL	4.10E-12
PSN	BRINP1	4.82E-12
PSN	YWHAG	4.82E-12
PSN	LGALS1	6.12E-12
PSN	MRPL52	7.53E-12
PSN	GNG3	8.20E-12
PSN	RP11-58B17.2	9.29E-12
PSN	HLA-B	9.46E-12
PSN	C14orf132	1.05E-11
PSN	RP11-531A24.3	1.34E-11
PSN	RBFOX1	1.41E-11
PSN	IFI27L2	1.70E-11

PIMN_1	SCML4	1.16E-07
PIMN_1	KCNJ5	1.68E-07
PIMN_1	TOX	1.68E-07
PIMN_1	KCNC2	1.87E-07
PIMN_1	PDE1C	2.02E-07
PIMN_1	MAGI1	8.38E-07
PIMN_1	ADD3	9.09E-07
PIMN_1	NPY	1.07E-06
PIMN_1	EML6	1.07E-06
PIMN_1	CIT	1.11E-06
PIMN_1	GABRB3	1.28E-06
PIMN_1	PLCB4	1.35E-06
PIMN_1	PTPRE	1.35E-06
PIMN_1	KCNG3	1.53E-06
PIMN_1	WIPF1	1.61E-06
PIMN_1	PAG1	1.69E-06
PIMN_1	AKAP6	1.69E-06
PIMN_1	FMNL2	1.87E-06
PIMN_1	TCF4	2.46E-06
PIMN_1	CHD7	2.53E-06
PIMN_1	RBFOX2	2.55E-06
PIMN_1	TANC1	2.69E-06
PIMN_1	SAMD4A	2.96E-06
PIMN_1	SLC4A4	3.07E-06
PIMN_1	ETV1	4.22E-06
PIMN_1	PDE1A	5.01E-06
PIMN_1	KIAA0319	5.10E-06
PIMN_1	PAM	1.14E-05
PIMN_1	NEAT1	1.14E-05
PIMN_1	NFIA	1.15E-05
PIMN_1	SORCS1	1.26E-05
PIMN_1	ACTN1	1.27E-05
PIMN_1	GFRA1	1.64E-05
PIMN_1	CREB5	2.22E-05
PIMN_1	ANKRD44	2.36E-05
PIMN_1	PPM1H	2.67E-05
PIMN_1	DCBLD2	2.67E-05
PIMN_1	PLCB1	2.68E-05
PIMN_1	ANK3	2.68E-05
PIMN_1	KIF1B	2.89E-05
PIMN_1	FHIT	3.31E-05
PIMN_1	PLS3	4.68E-05
PIMN_1	ARHGEF28	4.68E-05
PIMN_1	PPP2R5C	5.21E-05
PIMN_1	FRMD5	5.34E-05
PIMN_1	MAP3K4	7.34E-05
PIMN_1	SRGAP1	9.31E-05
PIMN_1	SMPD3	1.04E-04
PIMN_1	ASS1	1.04E-04
PIMN_1	DST	1.04E-04
PIMN_1	RPRML	1.40E-04
PIMN_1	CDK6	1.60E-04
PIMN_1	ZEB2	1.64E-04
PIMN_1	TSPAN11	1.72E-04
PIMN_1	ELL2	1.95E-04
PIMN_1	NFIX	2.35E-04
PIMN_1	LFNG	2.45E-04
PIMN_1	CNN2	2.52E-04
PIMN_1	UPF1	4.83E-04
PIMN_1	PDGFB	9.71E-04
PIMN_4	TOPORS-AS1	1.68E-02
PIMN_4	UBBP4	1.73E-02
PIMN_4	DERL1	1.80E-02
PIMN_4	S100A16	2.03E-02
PIMN_4	CKS1B	2.09E-02
PIMN_4	DLX1	2.25E-02
PIMN_4	RSL24D1	2.34E-02
PIMN_4	CTD-2140B24.6	2.40E-02
PIMN_4	PCDH9-AS1	2.42E-02
PIMN_4	hsa-mir-1199	2.63E-02
PIMN_4	SDF2L1	2.64E-02
PIMN_4	GSPT2	2.64E-02
PIMN_4	FBLL1	2.78E-02
PIMN_4	MAL2	2.83E-02
PIMN_4	TMEM185A	3.03E-02
PIMN_4	AKR7A2	3.07E-02
PIMN_4	LCA10	3.50E-02
PIMN_4	SYCP2	3.50E-02
PIMN_4	FAM96A	3.52E-02
PIMN_4	C11orf71	3.67E-02
PIMN_4	SDCCAG3	3.67E-02
PIMN_4	CTD-2050E21.1	3.69E-02
PIMN_4	SOX2	3.72E-02
PIMN_4	TIMM8A	3.89E-02
PIMN_4	MSRB1	4.21E-02
PIMN_4	BMP3	4.30E-02
PIMN_4	RASSF7	4.35E-02
PIMN_4	C6orf47	4.47E-02
PIMN_4	ZSCAN5B	4.51E-02
PIMN_4	ZNF585B	4.58E-02
PIMN_4	SLC41A3	4.64E-02
PIMN_4	FAM43B	4.66E-02
PIMN_4	JAGN1	4.69E-02
PIMN_4	ART4	4.77E-02
PIMN_5	SAT1	8.59E-15
PIMN_5	PLXDC2	8.59E-15
PIMN_5	LINC00478	7.89E-14
PIMN_5	LGI4	6.97E-13
PIMN_5	NKAIN3	2.39E-10
PIMN_5	ABCA8	2.64E-10
PIMN_5	CDH19	2.64E-10
PIMN_5	SPARC	4.71E-10
PIMN_5	ABCA6	7.91E-09
PIMN_5	EPB41L2	1.21E-08
PIMN_5	GRIK3	1.36E-08
PIMN_5	DCN	2.81E-08
PIMN_5	NDRG2	7.96E-08
PIMN_5	PRIMA1	1.75E-07
PIMN_5	CRYAB	1.84E-07
PIMN_5	C7	3.50E-07
PIMN_5	ZMIZ1-AS1	6.23E-07
PIMN_5	MGP	1.01E-06
PIMN_5	NRXN3	1.17E-06
PIMN_5	RP11-466A17.1	1.87E-06
PIMN_5	TNXB	1.87E-06
PIMN_5	SULF1	2.08E-06
PIMN_5	EIF2A	2.08E-06
PIMN_5	NOX4	2.24E-06
PIMN_5	SAMHD1	2.44E-06
PIMN_5	RP11-696N14.1	2.55E-06
PSN	FBXO2	1.79E-11
PSN	LSMD1	1.97E-11
PSN	MAP3K5	2.02E-11
PSN	SNCG	2.60E-11
PSN	FTH1	2.66E-11
PSN	CADM3	2.74E-11
PSN	NEFH	3.41E-11
PSN	AKAP12	3.63E-11
PSN	RP11-509E16.1	3.64E-11
PSN	GUCY1B3	3.64E-11
PSN	PEA15	4.92E-11
PSN	SLC35D3	9.90E-11
PSN	TBX2	1.79E-10
PSN	NMU	8.41E-10
PSN	RP11-361F15.2	2.71E-08
PSN	RP11-909N17.3	2.88E-08
PSN	KCNV1	4.53E-08
PSN	PLSCR5	4.82E-08
PSN	MIR7-3HG	7.50E-08
PSN	DKK1	7.88E-08
PSN	EPHB6	8.34E-08
PSN	PDRG1	8.74E-08
PSN	SUSD2	1.28E-07
PSN	B3GALT6	3.02E-07
PSN	NOG	4.15E-07
PSN	HPCA	6.63E-07
PSN	SPRY1	6.76E-07
PSN	CNTFR	2.39E-05
PSN	HOXB7	3.29E-05
PSN	GALR1	3.52E-05
PSN	FZD1	8.29E-05
PSN	RP11-247C2.2	1.49E-04
PSN	LY6H	2.28E-04
PSN	ENHO	2.53E-04
PSN	CEACAM21	3.69E-04
PSN	FUOM	3.78E-04
PSN	RP3-428L16.2	4.17E-04
PSN	SIGMAR1	4.61E-04
PSN	TMEM229A	7.62E-04
PSN	HRH3	7.89E-04
PSN	NPY5R	1.16E-03
PSN	KCNA4	1.41E-03
PSN	CTD-2086O20.3	1.57E-03
PSN	CTC-338M12.5	1.58E-03
PSN	AC011625.1	2.05E-03
PSN	CYB5R2	2.29E-03
PSN	MYL3	3.96E-03
PSN	THAP1	4.19E-03
PSN	LRRTM1	4.38E-03
PSN	RESP18	4.73E-03
PSN	RP11-797H7.5	7.96E-03
PSN	OTUD6B	8.76E-03
PSN	C8orf48	9.15E-03
PSN	CTD-2256P15.2	1.06E-02
PSN	TMA16	1.10E-02
PSN	CPLX3	1.20E-02
PSN	RP5-908M14.5	1.20E-02
PSN	ZBTB7B	1.48E-02
PSN	CTC-248O19.1	1.52E-02
PSN	AC007126.1	1.52E-02

PIMN_1	AQP9	1.10E-03
PIMN_1	STRIP2	1.11E-03
PIMN_1	LAMA5	1.17E-03
PIMN_1	PLCH2	1.24E-03
PIMN_1	CAPN15	1.55E-03
PIMN_1	GALNT2	1.86E-03
PIMN_1	ROPN1L	1.98E-03
PIMN_1	CDSN	3.04E-03
PIMN_1	GAD2	3.12E-03
PIMN_1	NTF3	3.82E-03
PIMN_1	RP11-453M23.1	4.59E-03
PIMN_1	KCNK17	4.93E-03
PIMN_1	PALD1	5.67E-03
PIMN_1	GABRA4	6.13E-03
PIMN_1	MUC6	7.30E-03
PIMN_1	RP11-993B23.3	7.40E-03
PIMN_1	AC007292.4	7.40E-03
PIMN_1	LURAP1L	7.40E-03
PIMN_1	SOHLH1	8.53E-03
PIMN_1	SRPK3	9.78E-03
PIMN_1	FOSL2	1.07E-02
PIMN_1	CACNA1I	1.09E-02
PIMN_1	EPPK1	1.11E-02
PIMN_1	RP11-318M2.2	1.13E-02
PIMN_1	HTR2A	1.25E-02
PIMN_1	RP11-451M19.3	1.28E-02
PIMN_1	RP11-707A18.1	1.33E-02
PIMN_1	GATA4	1.45E-02
PIMN_1	SLC22A1	1.48E-02
PIMN_1	RP11-23P13.6	1.53E-02
PIMN_1	RP11-631F7.1	1.56E-02
PIMN_1	TNFRSF25	1.58E-02
PIMN_1	RP11-320N7.2	1.69E-02
PIMN_1	MFI2	1.78E-02
PIMN_1	IMPA2	1.83E-02
PIMN_1	DYTN	2.15E-02
PIMN_1	RP11-431M7.2	2.19E-02
PIMN_1	LINC01091	2.39E-02
PIMN_1	CTC-546K23.1	2.45E-02
PIMN_1	RP11-264B14.1	2.96E-02
PIMN_1	RP11-766N7.3	3.03E-02
PIMN_1	RP11-944C7.1	3.31E-02
PIMN_1	FAM126A	3.37E-02
PIMN_1	AC022182.1	3.47E-02
PIMN_1	SPRY2	3.48E-02
PIMN_1	DNAAF3	3.56E-02
PIMN_1	RP11-479J7.2	3.57E-02
PIMN_1	RP11-713M15.1	3.65E-02
PIMN_1	NPTX2	3.72E-02
PIMN_1	RP3-467L1.4	3.73E-02
PIMN_1	RP11-173P15.7	3.73E-02
PIMN_1	MED9	3.74E-02
PIMN_1	RP11-327L3.3	3.77E-02
PIMN_1	CILP	3.88E-02
PIMN_1	ZNF610	4.05E-02
PIMN_1	GCGR	4.24E-02
PIMN_1	AP000640.10	4.44E-02
PIMN_1	OSTN	4.73E-02
PIMN_1	MYCL	4.91E-02
PIMN_2	MYH11	7.96E-105
PIMN_5	DOCK1	3.34E-06
PIMN_5	RP11-242P2.1	4.65E-06
PIMN_5	UFSP2	4.65E-06
PIMN_5	QKI	4.70E-06
PIMN_5	PLEKHG1	6.02E-06
PIMN_5	RUSC1	7.19E-06
PIMN_5	FBLN1	7.77E-06
PIMN_5	PELP1	7.77E-06
PIMN_5	NKAIN2	7.77E-06
PIMN_5	GPRC5A	9.38E-06
PIMN_5	C1orf21	9.38E-06
PIMN_5	COL1A2	9.45E-06
PIMN_5	KCNMB4	9.45E-06
PIMN_5	PLEKHH2	1.12E-05
PIMN_5	RP11-457K10.1	1.25E-05
PIMN_5	UACA	1.33E-05
PIMN_5	COL16A1	1.37E-05
PIMN_5	ANXA5	1.68E-05
PIMN_5	RASSF4	1.89E-05
PIMN_5	C4orf36	2.02E-05
PIMN_5	PPFIBP1	2.06E-05
PIMN_5	MYBL1	2.10E-05
PIMN_5	C1S	2.70E-05
PIMN_5	CBX1	4.95E-05
PIMN_5	CRISPLD2	5.14E-05
PIMN_5	CASC14	5.15E-05
PIMN_5	WEE1	5.15E-05
PIMN_5	S100B	5.35E-05
PIMN_5	GALNT15	5.75E-05
PIMN_5	GPR126	5.91E-05
PIMN_5	NKAP	5.96E-05
PIMN_5	COL27A1	6.06E-05
PIMN_5	MATN2	6.91E-05
PIMN_5	FXYD1	6.91E-05
PIMN_5	WDR86	7.36E-05
PIMN_5	ADAMTS16	8.04E-05
PIMN_5	EBF2	8.28E-05
PIMN_5	PTGIS	8.33E-05
PIMN_5	RP13-143G15.3	8.62E-05
PIMN_5	HMCN1	1.00E-04
PIMN_5	EHD1	1.00E-04
PIMN_5	RSPRY1	1.02E-04
PIMN_5	TOR1B	1.06E-04
PIMN_5	AMDHD2	1.06E-04
PIMN_5	CYP46A1	1.16E-04
PIMN_5	DUSP15	1.58E-04
PIMN_5	RP11-689C9.1	1.65E-04
PIMN_5	COL21A1	1.74E-04
PIMN_5	COL18A1	1.83E-04
PIMN_5	RPS19	2.11E-04
PIMN_5	JUN	2.14E-04
PIMN_5	PRAM1	2.20E-04
PIMN_5	POLR3A	3.01E-04
PIMN_5	ARHGAP24	3.27E-04
PIMN_5	EFEMP1	3.27E-04
PIMN_5	RP11-87M18.2	3.34E-04
PIMN_5	RAB23	3.45E-04
PIMN_5	SLC22A3	3.45E-04
PIMN_5	ZBTB16	3.52E-04
PIMN_5	RPL7	3.52E-04
PSN	AC110619.2	1.55E-02
PSN	LINC00237	1.56E-02
PSN	RP11-13K12.2	1.72E-02
PSN	RNF44	1.78E-02
PSN	CKS2	2.09E-02
PSN	C8orf88	2.30E-02
PSN	CRYBB3	2.49E-02
PSN	FAM26E	2.61E-02
PSN	PCDH18	2.71E-02
PSN	HBA1	2.75E-02
PSN	RP11-126K1.6	2.81E-02
PSN	MFI2-AS1	2.82E-02
PSN	RP11-162J8.2	3.81E-02
PSN	RP11-629G13.1	4.03E-02
PSN	RN7SL1	4.09E-02
PSN	RP4-561L24.3	4.18E-02
PSN	RP11-215H22.1	4.37E-02
PSN	AF124730.4	4.44E-02
PSN	SHISA7	4.81E-02
PSVN	ANO3	7.37E-65
PSVN	LRRC4C	1.91E-46
PSVN	CALB2	4.74E-44
PSVN	DLGAP1	4.04E-43
PSVN	ITGBL1	1.03E-39
PSVN	LAMA2	3.18E-39
PSVN	KCNJ3	3.57E-38
PSVN	FGF14	2.04E-37
PSVN	GRIK2	1.02E-35
PSVN	SCGN	9.00E-34
PSVN	GPR158	9.11E-34
PSVN	DGKI	3.15E-33
PSVN	EXT1	4.45E-31
PSVN	MGAT4C	1.16E-30
PSVN	FAM19A2	2.54E-29
PSVN	CNTNAP2	3.78E-28
PSVN	KCND2	9.85E-28
PSVN	LINGO2	2.74E-25
PSVN	KCNK2	2.81E-24
PSVN	C1orf186	9.95E-23
PSVN	GALNT13	1.62E-22
PSVN	FRMD4A	3.58E-22
PSVN	KCNH8	6.19E-22
PSVN	SYTL3	7.58E-22
PSVN	BRINP3	8.29E-22
PSVN	GPC5	4.16E-21
PSVN	CNGB1	6.08E-21
PSVN	DLC1	6.59E-21
PSVN	IL1RAPL1	1.30E-20
PSVN	KCNMA1	4.87E-20
PSVN	CACNA1D	5.43E-20
PSVN	VIP	1.22E-18
PSVN	AC009227.2	2.94E-18
PSVN	PCSK2	1.18E-17
PSVN	GULP1	1.21E-17
PSVN	AP1S3	6.09E-16
PSVN	RP11-38J22.6	1.05E-15
PSVN	ETV1	2.49E-15
PSVN	LUZP2	2.78E-15
PSVN	CAMK4	2.80E-15
PSVN	LINC00693	9.29E-15

PIMN_2	ACTG2	2.73E-70
PIMN_2	RBPMS	2.80E-54
PIMN_2	SORBS1	2.80E-54
PIMN_2	SVIL	8.75E-53
PIMN_2	LPP	8.95E-52
PIMN_2	NDE1	3.58E-50
PIMN_2	COL6A2	5.92E-50
PIMN_2	MIR145	8.68E-45
PIMN_2	TPM2	2.63E-43
PIMN_2	FOXP2	7.53E-42
PIMN_2	NT5DC3	1.37E-40
PIMN_2	TPM1	1.78E-40
PIMN_2	FBXO32	3.13E-37
PIMN_2	PDK4	6.90E-37
PIMN_2	CTD-3105H18.18	3.99E-34
PIMN_2	LMOD1	4.14E-32
PIMN_2	CALD1	4.13E-31
PIMN_2	MIR143HG	1.28E-29
PIMN_2	MYL9	9.41E-29
PIMN_2	RP11-611D20.2	4.74E-28
PIMN_2	PDZRN4	1.21E-27
PIMN_2	CNN1	1.40E-27
PIMN_2	ARHGAP6	4.76E-27
PIMN_2	SMTN	4.92E-26
PIMN_2	ROR2	4.92E-26
PIMN_2	FLNA	5.40E-26
PIMN_2	ITGA1	8.13E-26
PIMN_2	STAB2	1.72E-25
PIMN_2	ZBTB16	3.42E-25
PIMN_2	ACTA2	4.54E-25
PIMN_2	SPARCL1	7.19E-24
PIMN_2	MEIS2	1.02E-23
PIMN_2	ITGA5	6.84E-23
PIMN_2	HIF3A	1.25E-22
PIMN_2	NEXN	2.90E-22
PIMN_2	COL6A1	1.00E-21
PIMN_2	LINC00578	1.47E-21
PIMN_2	HDAC4	1.11E-20
PIMN_2	FKBP5	1.88E-20
PIMN_2	AC005358.3	2.89E-20
PIMN_2	CBR4	6.19E-20
PIMN_2	MYLK	1.53E-19
PIMN_2	DES	1.97E-19
PIMN_2	FAM129A	3.25E-19
PIMN_2	CCBE1	3.25E-19
PIMN_2	AF001548.5	3.74E-19
PIMN_2	MGST1	1.82E-18
PIMN_2	COL4A2	1.03E-17
PIMN_2	PDLIM7	1.03E-17
PIMN_2	SEMA3A	1.09E-17
PIMN_2	PGM5	4.06E-17
PIMN_2	PDZRN3	4.42E-17
PIMN_2	IGFBP7	2.33E-16
PIMN_2	GNG12-AS1	3.45E-16
PIMN_2	BTG2	3.83E-16
PIMN_2	MBNL1	3.83E-16
PIMN_2	PDLIM3	5.61E-16
PIMN_2	TNC	8.44E-16
PIMN_2	GPM6A	2.55E-15
PIMN_2	FN1	3.62E-15

PIMN_5	LRRTM3	3.78E-04
PIMN_5	TIMP1	4.22E-04
PIMN_5	C9orf37	4.28E-04
PIMN_5	FADS2	4.32E-04
PIMN_5	WIF1	4.32E-04
PIMN_5	LRRC3B	4.32E-04
PIMN_5	SPARCL1	4.45E-04
PIMN_5	RP13-143G15.4	4.45E-04
PIMN_5	SNX32	4.86E-04
PIMN_5	AC018890.6	5.18E-04
PIMN_5	EARS2	5.33E-04
PIMN_5	CFH	5.46E-04
PIMN_5	HEYL	5.72E-04
PIMN_5	IGFBP7	5.72E-04
PIMN_5	ZNF684	6.78E-04
PIMN_5	HAS2	7.01E-04
PIMN_5	ADA	7.04E-04
PIMN_5	MYOC	1.37E-03
PIMN_5	APOE	1.48E-03
PIMN_5	GLUL	2.05E-03
PIMN_5	RP11-387H17.4	2.28E-03
PIMN_5	FAM210B	2.72E-03
PIMN_5	PLP1	3.31E-03
PIMN_5	ARHGAP33	3.31E-03
PIMN_5	CYR61	3.59E-03
PIMN_5	HEY2	3.68E-03
PIMN_5	CTD-2525I3.3	4.82E-03
PIMN_5	ENTPD2	4.98E-03
PIMN_5	ATP13A5	5.08E-03
PIMN_5	KLF2	5.43E-03
PIMN_5	C16orf59	6.19E-03
PIMN_5	VSTM2B	6.78E-03
PIMN_5	C1orf85	6.91E-03
PIMN_5	LPL	7.33E-03
PIMN_5	RP11-27M24.1	7.77E-03
PIMN_5	FEM1C	8.57E-03
PIMN_5	MYBBP1A	8.78E-03
PIMN_5	FAS	9.08E-03
PIMN_5	C1orf213	1.00E-02
PIMN_5	RP11-179A10.1	1.06E-02
PIMN_5	ALG12	1.09E-02
PIMN_5	DPT	1.17E-02
PIMN_5	SLC15A3	1.24E-02
PIMN_5	MXRA8	1.35E-02
PIMN_5	APOBEC2	1.35E-02
PIMN_5	PLEKHS1	1.35E-02
PIMN_5	GPNMB	1.45E-02
PIMN_5	PI16	1.53E-02
PIMN_5	CCDC137	1.68E-02
PIMN_5	RP11-597D13.9	1.78E-02
PIMN_5	RAB39B	1.79E-02
PIMN_5	IGFBP6	1.87E-02
PIMN_5	LEP	1.92E-02
PIMN_5	NPR2	2.00E-02
PIMN_5	PRDM8	2.07E-02
PIMN_5	MEGF6	2.44E-02
PIMN_5	TCTE3	2.54E-02
PIMN_5	RP11-124N14.3	2.58E-02
PIMN_5	PRODH	2.69E-02
PIMN_5	F2RL2	2.79E-02

PSVN	AHR	1.37E-14
PSVN	CPNE8	1.37E-14
PSVN	RP11-707A18.1	3.89E-14
PSVN	CTNNA2	4.43E-14
PSVN	UNC5C	7.41E-14
PSVN	AKAP12	1.20E-13
PSVN	FMN1	1.21E-13
PSVN	EDNRA	1.60E-13
PSVN	COL5A2	2.70E-13
PSVN	LPHN2	7.62E-13
PSVN	SMAD9	1.11E-12
PSVN	KIAA1456	1.18E-12
PSVN	RP11-368L12.1	1.63E-12
PSVN	NEGR1	5.52E-12
PSVN	ELL2	5.93E-12
PSVN	PTPRK	1.25E-11
PSVN	GABRB1	1.25E-11
PSVN	GREB1L	1.25E-11
PSVN	PLXNA4	1.56E-11
PSVN	RP11-118B18.1	1.60E-11
PSVN	RTTN	1.76E-11
PSVN	GFRA1	1.76E-11
PSVN	ANGPT1	2.02E-11
PSVN	SYT10	4.81E-11
PSVN	SUPT3H	5.60E-11
PSVN	GCGR	6.62E-11
PSVN	UNC5B	1.29E-10
PSVN	CD36	1.44E-10
PSVN	CDH10	1.46E-10
PSVN	NCAM2	1.56E-10
PSVN	RP11-260M19.2	1.59E-10
PSVN	FAM20A	1.66E-10
PSVN	PLEKHA5	4.19E-10
PSVN	SPHKAP	4.47E-10
PSVN	GAN	4.74E-10
PSVN	THSD7A	4.74E-10
PSVN	CTD-2054N24.2	8.78E-10
PSVN	VWDE	1.41E-09
PSVN	OSBPL6	1.93E-09
PSVN	ARNT2	2.17E-09
PSVN	CHRM3	2.38E-09
PSVN	C8orf12	3.91E-09
PSVN	ARPP21	4.98E-09
PSVN	NOL4	6.26E-09
PSVN	GAREM	1.00E-08
PSVN	AFF3	1.04E-08
PSVN	SAMD12	1.36E-08
PSVN	ATRNL1	1.90E-08
PSVN	PCDH15	2.59E-08
PSVN	SAV1	2.64E-08
PSVN	RP11-547I7.1	4.48E-08
PSVN	PRKG2	4.53E-08
PSVN	RP5-921G16.1	4.55E-08
PSVN	NLGN4Y	4.79E-08
PSVN	SMARCA2	5.15E-08
PSVN	MCHR2-AS1	9.92E-08
PSVN	PID1	1.15E-07
PSVN	ZEB1	1.20E-07
PSVN	GCLC	1.22E-07
PSVN	AGMO	9.82E-07

PIMN_2	SLMAP	4.18E-15
PIMN_2	ETV6	4.45E-15
PIMN_2	TXNIP	4.91E-15
PIMN_2	PALLD	5.04E-15
PIMN_2	COL1A1	9.21E-15
PIMN_2	ZFP36L1	1.45E-14
PIMN_2	AP001347.6	1.57E-14
PIMN_2	FOXP1	2.26E-14
PIMN_2	TAGLN	2.48E-14
PIMN_2	ITPKB-AS1	3.14E-14
PIMN_2	PARD3	3.14E-14
PIMN_2	PARD3B	5.10E-14
PIMN_2	RBFOX3	6.70E-14
PIMN_2	TPM4	8.01E-14
PIMN_2	SYNPO2	1.94E-13
PIMN_2	FHL1	2.84E-13
PIMN_2	PARVA	3.06E-13
PIMN_2	MON1B	7.60E-13
PIMN_2	CRISPLD2	7.91E-13
PIMN_2	DUSP1	1.88E-12
PIMN_2	RP11-242P2.1	2.38E-12
PIMN_2	LHCGR	2.66E-12
PIMN_2	NID1	4.36E-12
PIMN_2	NRXN3	6.41E-12
PIMN_2	PBX1	7.28E-12
PIMN_2	FBXL7	8.03E-12
PIMN_2	MYOF	8.55E-12
PIMN_2	CACNA1C	8.86E-12
PIMN_2	FAM196A	9.11E-12
PIMN_2	STT3A-AS1	9.46E-12
PIMN_2	PRUNE2	1.82E-11
PIMN_2	ITIH5	1.97E-11
PIMN_2	COL6A3	2.06E-11
PIMN_2	MSRB3	2.16E-11
PIMN_2	MMP3	2.20E-11
PIMN_2	MID1	2.24E-11
PIMN_2	TBC1D1	2.39E-11
PIMN_2	STK38L	3.16E-11
PIMN_2	RP11-166P13.4	3.25E-11
PIMN_2	C20orf166-AS1	1.76E-10
PIMN_2	HOXA11-AS	2.86E-10
PIMN_2	KCNMB1	4.80E-10
PIMN_2	CTC-529L17.2	2.64E-09
PIMN_2	AC007401.2	4.13E-09
PIMN_2	FBXL22	7.87E-09
PIMN_2	HSD17B6	9.16E-09
PIMN_2	BCL11A	1.31E-08
PIMN_2	MT1E	1.95E-08
PIMN_2	SRPX2	3.02E-08
PIMN_2	SOCS3	5.29E-08
PIMN_2	RP11-413B19.2	9.82E-08
PIMN_5	TCF21	2.79E-02
PIMN_5	FGL2	2.84E-02
PIMN_5	HEPN1	2.89E-02
PIMN_5	ARID5A	3.00E-02
PIMN_5	DDIT4	3.47E-02
PIMN_5	C5orf64	3.48E-02
PIMN_5	ESM1	3.63E-02
PIMN_5	AC140912.1	3.68E-02
PIMN_5	ANKRD20A1	3.84E-02
PIMN_5	RP4-543J13.1	4.02E-02
PIMN_5	CFD	4.16E-02
PIMN_5	PRKCDBP	4.46E-02
PIMN_5	RP11-496I9.1	4.51E-02
PIMN_5	TNFAIP2	4.66E-02
PIMN_5	CHTF18	4.69E-02
PIMN_5	CMTM5	4.72E-02
PIN_1	PENK	2.60E-42
PIN_1	LRRTM4	2.56E-37
PIN_1	SGCZ	2.62E-35
PIN_1	CNTN4	1.76E-33
PIN_1	PLCXD3	1.01E-26
PIN_1	CNTN6	4.49E-24
PIN_1	USH1C	4.98E-24
PIN_1	TENM2	4.14E-23
PIN_1	CNTN5	7.28E-22
PIN_1	FAM19A2	7.44E-22
PIN_1	LIN7A	1.21E-21
PIN_1	CLSTN2	2.55E-20
PIN_1	ASIC2	2.55E-20
PIN_1	SNAP25	6.15E-18
PIN_1	ZMAT4	6.15E-18
PIN_1	DLC1	6.75E-17
PIN_1	PIEZO2	7.44E-16
PIN_1	VAT1L	2.78E-15
PIN_1	CACNA1E	1.14E-14
PIN_1	VSTM2A	5.32E-13
PIN_1	TAC3	5.88E-13
PIN_1	BMPER	6.29E-13
PIN_1	SEMA3D	1.14E-12
PIN_1	NDST4	1.30E-12
PIN_1	ZNF804A	1.62E-12
PIN_1	NEBL	1.67E-12
PIN_1	TM4SF4	2.87E-12
PIN_1	PPP2R2B	1.05E-11
PIN_1	SLC16A12	2.78E-11
PIN_1	CHGB	6.83E-11
PIN_1	SEMA3E	8.40E-11
PIN_1	CAMK2A	1.01E-10
PIN_1	AL035610.2	1.64E-10
PIN_1	LINC00871	2.65E-10
PIN_1	RALYL	3.05E-10
PSVN	CHDH	4.86E-06
PSVN	RP11-63C8.1	9.91E-06
PSVN	RP11-374M1.3	1.30E-05
PSVN	NR2F1	1.84E-05
PSVN	SAMD11	2.23E-05
PSVN	NPY2R	2.58E-05
PSVN	COL11A1	3.00E-05
PSVN	BAI1	3.04E-05
PSVN	RP11-148O21.6	5.17E-05
PSVN	RP11-171L9.1	8.87E-05
PSVN	RP11-154H12.3	8.89E-05
PSVN	MCHR2	9.07E-05
PSVN	RP11-145O15.3	2.27E-04
PSVN	RP11-258O13.1	2.56E-04
PSVN	CTC-255N20.1	4.54E-04
PSVN	PGF	4.87E-04
PSVN	SSTR1	4.87E-04
PSVN	BCL2L12	5.95E-04
PSVN	PDLIM2	7.81E-04
PSVN	RP5-837I24.4	8.33E-04
PSVN	PRR16	8.65E-04
PSVN	GTSCR1	1.03E-03
PSVN	UNC5B-AS1	1.06E-03
PSVN	NPY1R	1.13E-03
PSVN	SYT13	1.39E-03
PSVN	PKHD1L1	1.43E-03
PSVN	CTA-373H7.7	1.83E-03
PSVN	UPP1	2.21E-03
PSVN	FAM167A	2.44E-03
PSVN	C21orf91-OT1	3.81E-03
PSVN	LRTM1	4.02E-03
PSVN	SIDT1-AS1	4.02E-03
PSVN	IVNS1ABP	5.98E-03
PSVN	RGS7BP	6.84E-03
PSVN	EPHB6	7.64E-03
PSVN	RP1-200K18.1	1.95E-02
PSVN	FGF12-AS1	2.29E-02
PSVN	RP11-54O7.3	2.53E-02
PSVN	LINC01159	2.61E-02
PSVN	KCTD9	2.64E-02
PSVN	CSN1S1	2.66E-02
PSVN	SFTPB	2.67E-02
PSVN	CTD-3032J10.2	2.77E-02
PSVN	IL13RA2	3.10E-02
PSVN	RP11-47J17.2	3.15E-02
PSVN	MMRN1	3.30E-02
PSVN	TWISTNB	3.98E-02
PSVN	CNGA3	4.29E-02
PSVN	CCDC155	4.29E-02
PSVN	SSSCA1	4.29E-02
PSVN	CD200R1	4.81E-02

Table 22.

ident	gene	padjH
Glia_1	LSAMP	7.01E-59
Glia_1	BAI3	1.46E-48
Glia_1	NKAIN2	5.22E-41
Glia_1	CTNNA3	4.88E-37
Glia_3	RP11-662M24.1	5.09E-03
Glia_3	RP11-736G13.1	5.19E-03
Glia_3	ERCC6	5.21E-03
Glia_3	CTD-2024I7.13	5.35E-03
Glia_6	FBN1	2.17E-20
Glia_6	PLCB1	3.48E-20
Glia_6	BICC1	1.81E-19
Glia_6	TFPI	2.08E-18

Glia_1	CTNND2	7.79E-37
Glia_1	TPD52L1	1.58E-36
Glia_1	ABCA8	1.10E-29
Glia_1	LRRTM3	6.34E-28
Glia_1	PPP2R2B	2.03E-24
Glia_1	FADS2	3.08E-24
Glia_1	RP11-77K12.4	4.80E-24
Glia_1	ATP8A1	1.71E-20
Glia_1	HAND2-AS1	4.88E-20
Glia_1	RALYL	1.62E-18
Glia_1	NRG3	1.97E-18
Glia_1	LRRTM4	5.05E-18
Glia_1	RP11-466A17.1	5.32E-18
Glia_1	TRDN	8.91E-18
Glia_1	RALGPS2	1.51E-17
Glia_1	BCL2L14	4.06E-17
Glia_1	DMKN	6.69E-17
Glia_1	RP11-532N4.2	2.70E-16
Glia_1	PITPNC1	3.78E-16
Glia_1	NKAIN3	8.24E-16
Glia_1	ANGPTL1	1.18E-15
Glia_1	RP3-525N10.2	1.73E-15
Glia_1	AC018890.6	1.77E-15
Glia_1	RP11-3L8.3	9.71E-15
Glia_1	CRISPLD1	1.03E-14
Glia_1	PLCB4	2.08E-14
Glia_1	SAT1	2.74E-14
Glia_1	LINC00478	4.54E-14
Glia_1	SGIP1	8.51E-14
Glia_1	MARCH10	9.82E-14
Glia_1	PPFIBP1	1.97E-13
Glia_1	SASH1	2.77E-13
Glia_1	CERS6	3.53E-13
Glia_1	HMCN1	5.45E-13
Glia_1	HAND2	6.35E-13
Glia_1	LSAMP-AS1	9.44E-13
Glia_1	MPPED2	1.67E-12
Glia_1	SGCD	1.67E-12
Glia_1	MIR181A2HG	5.75E-12
Glia_1	ZBTB7C	2.03E-11
Glia_1	CACNA1D	2.42E-11
Glia_1	MEG3	3.10E-11
Glia_1	RIMS1	3.90E-11
Glia_1	FRAS1	4.40E-11
Glia_1	SOX5	7.25E-11
Glia_1	SLC4A8	1.29E-10
Glia_1	PCDH9	1.39E-10
Glia_1	NGF	2.10E-10
Glia_1	NR6A1	3.07E-10
Glia_1	HIBCH	3.62E-10
Glia_1	AL592284.1	4.60E-10
Glia_1	RP3-510L9.1	4.65E-10
Glia_1	LYRM2	5.85E-10
Glia_1	DPP10	5.85E-10
Glia_1	COL11A1	7.54E-10
Glia_1	LTBP1	1.00E-09
Glia_1	TRHDE	1.19E-09
Glia_1	HEYL	1.69E-09
Glia_1	PRKCA	2.13E-09
Glia_1	SYNPR	2.34E-09
Glia_3	RP11-338E21.3	5.45E-03
Glia_3	CTD-3234P18.2	5.88E-03
Glia_3	ZNF324B	5.88E-03
Glia_3	RP11-10J21.5	5.97E-03
Glia_3	RP11-3D4.3	6.03E-03
Glia_3	HTR2B	7.34E-03
Glia_3	DNM1P35	7.91E-03
Glia_3	HCN3	7.99E-03
Glia_3	MED4-AS1	8.00E-03
Glia_3	RP11-77B22.2	9.03E-03
Glia_3	RP11-265N6.2	9.25E-03
Glia_3	RP11-90J7.4	9.71E-03
Glia_3	RP11-139K4.2	1.06E-02
Glia_3	C12orf77	1.08E-02
Glia_3	RNF44	1.09E-02
Glia_3	RP11-550H2.1	1.09E-02
Glia_3	LL09NC01-251B2.3	1.11E-02
Glia_3	LINC00507	1.14E-02
Glia_3	RP11-876F14.1	1.15E-02
Glia_3	RP11-1028N23.3	1.20E-02
Glia_3	RP11-890B15.3	1.22E-02
Glia_3	RP11-329J18.3	1.23E-02
Glia_3	RP11-930O11.2	1.25E-02
Glia_3	DNAJB7	1.26E-02
Glia_3	RP11-89N17.3	1.32E-02
Glia_3	CES1	1.47E-02
Glia_3	RP4-614C15.2	1.55E-02
Glia_3	E2F1	1.64E-02
Glia_3	IL7R	1.68E-02
Glia_3	AC100830.5	1.76E-02
Glia_3	AL603965.1	1.80E-02
Glia_3	VSIG4	1.80E-02
Glia_3	ALAS2	1.81E-02
Glia_3	RP5-973M2.2	1.82E-02
Glia_3	CDH24	1.86E-02
Glia_3	FCER1A	2.06E-02
Glia_3	AC112693.2	2.06E-02
Glia_3	FAM229A	2.09E-02
Glia_3	A2M-AS1	2.21E-02
Glia_3	INTS5	2.41E-02
Glia_3	RP11-135D11.2	2.42E-02
Glia_3	FAM25B	2.50E-02
Glia_3	RNF112	2.51E-02
Glia_3	RP11-415D17.4	2.56E-02
Glia_3	LAG3	2.59E-02
Glia_3	IER5	2.67E-02
Glia_3	HCG22	2.71E-02
Glia_3	RP11-44F21.2	2.74E-02
Glia_3	METTL18	3.11E-02
Glia_3	ANGPTL2	3.43E-02
Glia_3	RP11-691G17.1	3.47E-02
Glia_3	AC073236.3	3.55E-02
Glia_3	CTC-248O19.1	3.63E-02
Glia_3	C1orf162	3.68E-02
Glia_3	HOXD11	3.83E-02
Glia_3	DNM3OS	3.84E-02
Glia_3	AC025171.1	3.85E-02
Glia_3	LINC00692	3.98E-02
Glia_3	TNFSF14	4.06E-02
Glia_3	RP11-421F16.3	4.17E-02
Glia_6	RP11-14N7.2	1.78E-17
Glia_6	DCLK1	4.55E-17
Glia_6	RP11-39M21.1	1.16E-16
Glia_6	RP11-648L3.2	2.92E-16
Glia_6	FBLN1	1.55E-15
Glia_6	ABCA6	1.61E-15
Glia_6	RP11-219B17.1	2.17E-15
Glia_6	NRK	2.86E-15
Glia_6	RP11-66B24.4	3.36E-15
Glia_6	RP13-143G15.3	1.73E-14
Glia_6	PDE1A	6.90E-14
Glia_6	AC005237.4	1.62E-13
Glia_6	COL5A2	3.44E-13
Glia_6	LAMB1	5.85E-13
Glia_6	NFIA	6.24E-13
Glia_6	ABCA9	1.09E-12
Glia_6	AC007319.1	2.92E-12
Glia_6	STEAP2	2.92E-12
Glia_6	LUM	1.87E-11
Glia_6	FOXO3	9.42E-11
Glia_6	COL6A3	1.26E-10
Glia_6	SVEP1	2.83E-10
Glia_6	PTPRG	3.88E-10
Glia_6	NFKBIZ	4.80E-10
Glia_6	RHOBTB3	4.80E-10
Glia_6	MBP	5.74E-10
Glia_6	RBMS3	8.80E-10
Glia_6	LTBP4	9.05E-10
Glia_6	CBLB	1.15E-09
Glia_6	LINC00478	1.34E-09
Glia_6	TMSB4X	1.81E-09
Glia_6	ADAMTS1	2.25E-09
Glia_6	NAV3	2.25E-09
Glia_6	PLCL2	2.34E-09
Glia_6	CTA-360L10.1	3.45E-09
Glia_6	COL3A1	3.82E-09
Glia_6	BOC	4.20E-09
Glia_6	ANXA10	4.61E-09
Glia_6	ELN	4.85E-09
Glia_6	RP11-15M15.2	4.85E-09
Glia_6	ZBTB16	7.37E-09
Glia_6	DUSP1	7.39E-09
Glia_6	SLC9A9	8.45E-09
Glia_6	PIEZO2	9.90E-09
Glia_6	PDE7B	1.38E-08
Glia_6	ARHGAP26-AS1	1.39E-08
Glia_6	PLCL1	1.58E-08
Glia_6	IGFBP6	2.57E-08
Glia_6	CITED2	2.91E-08
Glia_6	RP11-597D13.9	3.51E-08
Glia_6	MCOLN3	6.59E-08
Glia_6	PBX3	8.08E-08
Glia_6	PRR16	9.47E-08
Glia_6	RP11-160H12.2	1.19E-07
Glia_6	NEAT1	1.20E-07
Glia_6	GRIA4	1.23E-07
Glia_6	GUCY1A3	1.24E-07
Glia_6	KAZN	1.88E-07
Glia_6	CCNI	1.96E-07
Glia_6	ZFPM2	2.53E-07

Glia_1	RP11-318K12.2	2.68E-09
Glia_1	DAPL1	2.79E-09
Glia_1	PTPRZ1	2.79E-09
Glia_1	LRP1B	3.33E-09
Glia_1	PDE4B	3.62E-09
Glia_1	WDR86	4.77E-09
Glia_1	FRMD3	4.77E-09
Glia_1	SYT10	5.06E-09
Glia_1	USP54	5.72E-09
Glia_1	PIEZO2	5.72E-09
Glia_1	RLBP1	8.85E-09
Glia_1	CD47	9.02E-09
Glia_1	LPHN3	1.08E-08
Glia_1	GABRB1	1.29E-08
Glia_1	NRXN3	1.55E-08
Glia_1	RP11-242P2.1	1.59E-08
Glia_1	HPGD	1.68E-08
Glia_1	RP11-379B18.5	1.68E-08
Glia_1	APP	1.68E-08
Glia_1	CXADR	1.76E-08
Glia_1	C9orf3	2.13E-08
Glia_1	MOXD1	2.18E-08
Glia_1	PXDN	3.84E-08
Glia_1	IGSF11	4.03E-08
Glia_1	ANTXR1	4.60E-08
Glia_1	EDIL3	6.10E-08
Glia_1	CTD-2269F5.1	6.65E-08
Glia_1	RP11-4F22.2	8.43E-08
Glia_1	AC037445.1	8.56E-08
Glia_1	CLASP2	1.31E-07
Glia_1	MAML2	2.04E-07
Glia_1	MAPK10	2.29E-07
Glia_1	NLGN1	3.30E-07
Glia_1	AC010127.3	3.30E-07
Glia_1	GNA14	4.71E-07
Glia_1	TOM1L1	4.83E-07
Glia_1	MYBL1	2.55E-06
Glia_1	ZNF680	9.35E-06
Glia_1	PAIP2B	9.99E-06
Glia_1	ST3GAL1	9.99E-06
Glia_1	COL12A1	2.37E-05
Glia_1	LINC00903	2.47E-05
Glia_1	LPL	3.11E-05
Glia_1	MARC1	7.26E-05
Glia_1	MFSD2A	1.47E-04
Glia_1	RP4-663N10.1	1.73E-04
Glia_1	RP11-776H12.1	1.90E-04
Glia_1	WNT16	2.38E-04
Glia_1	SLC16A12	2.70E-04
Glia_1	SOX2	2.70E-04
Glia_1	KIAA1549L	3.31E-04
Glia_1	CISD2	3.38E-04
Glia_1	AL139147.1	4.90E-04
Glia_1	RP11-379B18.6	5.89E-04
Glia_1	SERPINE2	6.26E-04
Glia_1	HES4	6.32E-04
Glia_1	IGDCC3	7.18E-04
Glia_1	ACAP1	1.09E-03
Glia_1	MYO7A	1.26E-03
Glia_1	HMGCLL1	1.76E-03
Glia_3	DCAF11	4.21E-02
Glia_3	RP11-154F14.2	4.25E-02
Glia_3	LINC00473	4.43E-02
Glia_3	ZNF501	4.45E-02
Glia_3	RFPL1	4.92E-02
Glia_3	DOK2	4.94E-02
Glia_3	MIR142	4.97E-02
Glia_4	MYH11	8.47E-187
Glia_4	ACTG2	2.24E-139
Glia_4	SVIL	3.93E-114
Glia_4	CACNA1C	3.06E-93
Glia_4	LPP	1.09E-81
Glia_4	PRUNE2	2.68E-79
Glia_4	MIR145	3.37E-75
Glia_4	PDZRN4	1.62E-71
Glia_4	SYNPO2	7.73E-71
Glia_4	COL6A2	6.28E-70
Glia_4	PRKG1	1.63E-69
Glia_4	FBXO32	1.19E-62
Glia_4	NDE1	1.31E-62
Glia_4	NT5DC3	7.84E-61
Glia_4	TPM1	3.26E-59
Glia_4	RBPMS	5.40E-57
Glia_4	SLC8A1	1.08E-56
Glia_4	MIR143HG	2.98E-53
Glia_4	CCBE1	3.52E-53
Glia_4	TPM2	1.92E-48
Glia_4	SMTN	9.51E-48
Glia_4	PDLIM7	4.67E-46
Glia_4	FOXP2	2.76E-45
Glia_4	PDE4D	1.54E-43
Glia_4	SORBS1	3.25E-43
Glia_4	ACTA2	1.11E-42
Glia_4	PCDH7	9.74E-42
Glia_4	MEIS1	2.50E-41
Glia_4	STAB2	7.28E-40
Glia_4	MEIS2	4.19E-39
Glia_4	CACNB2	1.31E-38
Glia_4	MYL9	1.81E-38
Glia_4	RP11-611D20.2	2.30E-37
Glia_4	LMOD1	1.47E-34
Glia_4	CTD-3105H18.18	5.75E-34
Glia_4	ACTN1	7.70E-34
Glia_4	GEM	2.34E-33
Glia_4	AC005358.3	2.96E-32
Glia_4	DMD	1.05E-31
Glia_4	GPM6A	2.75E-31
Glia_4	SLC8A1-AS1	2.85E-30
Glia_4	PDZRN3	6.94E-30
Glia_4	NEXN	2.66E-29
Glia_4	EPHA7	1.37E-28
Glia_4	hsa-mir-490	4.06E-28
Glia_4	SEMA3A	8.45E-28
Glia_4	ITGA5	1.69E-27
Glia_4	AC007392.3	2.46E-27
Glia_4	FLNA	1.04E-26
Glia_4	SLMAP	2.25E-26
Glia_4	MYLK	2.43E-26
Glia_4	DSTN	1.92E-25
Glia_4	AP001347.6	6.52E-25
Glia_6	PIK3R1	3.19E-07
Glia_6	PLXDC2	3.31E-07
Glia_6	PLAGL1	3.70E-07
Glia_6	RBMS3-AS3	4.28E-07
Glia_6	EPHA3	4.32E-07
Glia_6	PAM	4.63E-07
Glia_6	MN1	4.68E-07
Glia_6	TCF21	5.36E-07
Glia_6	UAP1	5.64E-07
Glia_6	SDC2	6.06E-07
Glia_6	NRP1	6.39E-07
Glia_6	MFAP5	6.48E-07
Glia_6	RP11-15M15.1	8.47E-07
Glia_6	PDGFRA	8.81E-07
Glia_6	AOX1	1.17E-06
Glia_6	PRRX1	2.17E-06
Glia_6	CYP4X1	2.53E-06
Glia_6	ADAMTS5	3.85E-06
Glia_6	CXCL12	4.52E-06
Glia_6	ALDH1A3	9.27E-06
Glia_6	MMP19	1.71E-05
Glia_6	AC012317.1	2.49E-05
Glia_6	CFD	7.16E-05
Glia_6	ADCYAP1R1	9.79E-05
Glia_6	IGF1	9.99E-05
Glia_6	EFCC1	2.27E-04
Glia_6	SFRP2	2.34E-04
Glia_6	RP11-13N12.2	3.30E-04
Glia_6	GSTM3	4.13E-04
Glia_6	DIO3OS	5.08E-04
Glia_6	MEDAG	5.10E-04
Glia_6	ADM	5.94E-04
Glia_6	CILP	6.64E-04
Glia_6	PCOLCE	1.09E-03
Glia_6	EXOC3L4	1.13E-03
Glia_6	TPBG	1.24E-03
Glia_6	AC140912.1	1.28E-03
Glia_6	FGF10	1.58E-03
Glia_6	PLA2G2A	1.89E-03
Glia_6	CD34	2.06E-03
Glia_6	RP11-38P22.2	2.79E-03
Glia_6	SPRY4	2.97E-03
Glia_6	CTD-2363C16.1	3.26E-03
Glia_6	FGF10-AS1	5.11E-03
Glia_6	RP11-140I24.1	6.60E-03
Glia_6	GUCY1B3	7.02E-03
Glia_6	CCL11	7.56E-03
Glia_6	GEMIN4	7.57E-03
Glia_6	CASP1	7.62E-03
Glia_6	KHNYN	1.03E-02
Glia_6	FNDC1	1.04E-02
Glia_6	H2BFM	1.04E-02
Glia_6	MEIS1-AS3	1.06E-02
Glia_6	EXOSC2	1.11E-02
Glia_6	PI16	1.11E-02
Glia_6	RP11-175K6.1	1.29E-02
Glia_6	BMP4	1.38E-02
Glia_6	TNFSF10	1.40E-02
Glia_6	RP11-62I21.1	1.46E-02
Glia_6	GPC6-AS1	1.52E-02

Glia_1	COL9A3	1.84E-03
Glia_1	AC008937.2	2.88E-03
Glia_1	ZC3H8	2.89E-03
Glia_1	HEY1	2.91E-03
Glia_1	PHF21B	2.91E-03
Glia_1	CCDC24	3.59E-03
Glia_1	SHC3	3.78E-03
Glia_1	PAQR6	4.54E-03
Glia_1	PTGDS	8.04E-03
Glia_1	CHDH	9.49E-03
Glia_1	R3HCC1	1.02E-02
Glia_1	RP11-624M8.1	1.13E-02
Glia_1	B3GALT1	1.17E-02
Glia_1	ENTPD2	1.22E-02
Glia_1	RP11-255H23.4	1.36E-02
Glia_1	STRIP2	1.50E-02
Glia_1	APOE	1.52E-02
Glia_1	RHBDL3	1.65E-02
Glia_1	AC079117.1	1.85E-02
Glia_1	LCN12	1.99E-02
Glia_1	LINC00648	2.31E-02
Glia_1	RP11-481A20.11	2.34E-02
Glia_1	MYRFL	2.45E-02
Glia_1	ART3	2.53E-02
Glia_1	GPR37	2.65E-02
Glia_1	AMZ2	2.69E-02
Glia_1	RP11-440I14.2	2.69E-02
Glia_1	CSRP2	3.02E-02
Glia_1	NKAIN4	3.16E-02
Glia_1	RP11-1191J2.5	3.22E-02
Glia_1	GSTO2	3.32E-02
Glia_1	TF	3.32E-02
Glia_1	AC009542.2	3.55E-02
Glia_1	MRPS18B	4.30E-02
Glia_1	GALNT3	4.57E-02
Glia_1	KCNE3	4.73E-02
Glia_1	C5orf64	4.74E-02
Glia_2	NRXN1	9.31E-131
Glia_2	XKR4	1.25E-95
Glia_2	ANK3	3.66E-70
Glia_2	SCN7A	1.37E-67
Glia_2	FRMD4A	4.44E-64
Glia_2	RP11-141M1.3	2.60E-58
Glia_2	PIRT	9.78E-49
Glia_2	GINS3	2.66E-40
Glia_2	EHBP1	2.66E-40
Glia_2	PMP22	1.57E-37
Glia_2	GRIK2	1.36E-34
Glia_2	DLC1	9.43E-34
Glia_2	RP11-429O1.1	1.73E-33
Glia_2	RP11-142M10.2	1.93E-31
Glia_2	KIAA1217	1.02E-30
Glia_2	STARD13	1.94E-30
Glia_2	ARHGAP15	1.94E-30
Glia_2	PTPRJ	7.46E-22
Glia_2	NTM	3.12E-21
Glia_2	GPM6B	1.02E-20
Glia_2	AQP7	2.42E-20
Glia_2	NCAM2	3.55E-20
Glia_2	GPR155	4.95E-19
Glia_4	ROR2	1.39E-24
Glia_4	CHRM3	8.16E-24
Glia_4	LINC00578	4.70E-23
Glia_4	MGST1	1.25E-22
Glia_4	AF001548.5	1.73E-22
Glia_4	DES	5.96E-22
Glia_4	COL6A1	8.32E-22
Glia_4	RBFOX3	1.17E-21
Glia_4	MYL6	3.51E-21
Glia_4	MSRB3	3.63E-21
Glia_4	COL4A2	7.72E-21
Glia_4	NEAT1	1.07E-20
Glia_4	CBR4	4.03E-20
Glia_4	CHRM2	4.98E-20
Glia_4	CASKIN1	9.35E-20
Glia_4	CNN1	9.58E-20
Glia_4	ENAH	1.12E-19
Glia_4	BTG2	1.88E-19
Glia_4	LDB3	7.18E-19
Glia_4	SOGA2	1.39E-18
Glia_4	MON1B	1.74E-18
Glia_4	PNCK	2.87E-18
Glia_4	ATP2B4	4.66E-18
Glia_4	COL6A3	5.54E-18
Glia_4	AKAP12	9.78E-18
Glia_4	RP11-413B19.2	9.78E-18
Glia_4	RP11-619J20.1	1.91E-17
Glia_4	NAV2	1.95E-17
Glia_4	PPP1R12B	2.12E-17
Glia_4	FNBP1	2.94E-17
Glia_4	HIF3A	2.94E-17
Glia_4	STT3A-AS1	4.87E-17
Glia_4	FHL1	1.29E-16
Glia_4	ARHGAP6	1.31E-16
Glia_4	PALLD	1.76E-16
Glia_4	AC100830.3	2.04E-16
Glia_4	THRB	2.69E-16
Glia_4	RP11-123O10.4	2.84E-16
Glia_4	FN1	3.31E-16
Glia_4	RP11-166P13.4	4.77E-16
Glia_4	CKB	6.16E-16
Glia_4	PBX1	7.94E-16
Glia_4	LINC00842	2.23E-15
Glia_4	ACTB	2.57E-15
Glia_4	NRP2	3.18E-15
Glia_4	ITGA7	3.44E-15
Glia_4	CALD1	4.38E-15
Glia_4	CTD-2207O23.3	6.29E-15
Glia_4	C20orf166-AS1	1.23E-14
Glia_4	FBXL22	2.52E-14
Glia_4	ITPKB-AS1	3.77E-14
Glia_4	HOXD10	1.48E-12
Glia_4	SLC2A4	5.85E-12
Glia_4	TSPAN2	2.24E-11
Glia_4	PCA3	9.94E-10
Glia_4	FENDRR	3.11E-09
Glia_4	SLC29A1	2.93E-08
Glia_4	RP11-579E24.2	2.28E-07
Glia_4	GADD45G	2.89E-07
Glia_4	ITGB5-AS1	8.24E-07
Glia_6	GADD45A	1.52E-02
Glia_6	CYP4Z1	1.59E-02
Glia_6	PENK	1.79E-02
Glia_6	PRRG3	1.92E-02
Glia_6	RP11-469L4.1	1.98E-02
Glia_6	IL32	2.31E-02
Glia_6	KMT2E-AS1	2.51E-02
Glia_6	SH2D2A	2.55E-02
Glia_6	WISP2	2.60E-02
Glia_6	NPPC	2.60E-02
Glia_6	CTB-51J22.1	2.66E-02
Glia_6	CH25H	2.77E-02
Glia_6	LTF	2.80E-02
Glia_6	P2RY1	3.01E-02
Glia_6	GSTM5	3.07E-02
Glia_6	SNAI2	3.24E-02
Glia_6	LY6H	3.26E-02
Glia_6	RP11-554D13.1	3.31E-02
Glia_6	RP6-99M1.2	3.80E-02
Glia_6	AR	3.84E-02
Glia_7	NFATC2	5.00E-79
Glia_7	EMP1	1.83E-71
Glia_7	LMNA	9.21E-67
Glia_7	CREB5	5.70E-42
Glia_7	RCAN1	1.44E-36
Glia_7	PGM2L1	1.48E-30
Glia_7	ANXA1	1.93E-27
Glia_7	SAMD4A	4.85E-27
Glia_7	VMP1	2.47E-26
Glia_7	DPYSL3	5.51E-26
Glia_7	MIR24-2	1.00E-22
Glia_7	ELL2	2.03E-22
Glia_7	CDH19	2.32E-22
Glia_7	ATP1B3	4.64E-22
Glia_7	PLAT	1.46E-21
Glia_7	TNFRSF12A	2.99E-21
Glia_7	CD44	8.37E-21
Glia_7	CLIC4	3.88E-20
Glia_7	RP11-815J21.4	1.89E-19
Glia_7	MYOF	3.73E-18
Glia_7	MYO1E	3.73E-18
Glia_7	SAT1	1.57E-17
Glia_7	PFKFB3	1.83E-17
Glia_7	CDK17	1.53E-16
Glia_7	RP11-414H17.5	4.74E-16
Glia_7	AKAP13	1.89E-15
Glia_7	SIK2	2.02E-15
Glia_7	TUBB6	6.33E-15
Glia_7	RP5-1042K10.10	9.28E-15
Glia_7	NUDT4	1.87E-14
Glia_7	RFX2	1.48E-13
Glia_7	STAT3	1.54E-13
Glia_7	RP3-510L9.1	1.86E-13
Glia_7	SIK3	2.26E-13
Glia_7	ZFP36	2.97E-13
Glia_7	AXL	5.02E-13
Glia_7	NFATC1	6.12E-13
Glia_7	PTPRE	1.13E-12
Glia_7	S100A6	1.36E-12
Glia_7	TPPP3	5.14E-12

Glia_2	TGFBR2	1.27E-18
Glia_2	TMEM71	8.93E-18
Glia_2	FRMD5	8.93E-18
Glia_2	CADM2	8.93E-18
Glia_2	RP11-308N19.1	2.99E-17
Glia_2	CBY3	7.87E-17
Glia_2	ARHGAP24	4.93E-16
Glia_2	AC092684.1	6.57E-16
Glia_2	PDE4DIP	1.12E-15
Glia_2	SAV1	1.94E-15
Glia_2	ZNF536	1.94E-15
Glia_2	IL1RAPL2	2.22E-15
Glia_2	POLR3GL	6.33E-15
Glia_2	FNDC3B	6.33E-15
Glia_2	RP11-654A16.3	6.40E-15
Glia_2	PDZD2	6.40E-15
Glia_2	ACTR5	2.05E-14
Glia_2	SAMHD1	3.00E-14
Glia_2	AGAP1	3.00E-14
Glia_2	SCAI	3.26E-14
Glia_2	SHISA9	6.03E-14
Glia_2	ANKRD33B	9.25E-14
Glia_2	HIP1	1.12E-13
Glia_2	MAP4	3.05E-13
Glia_2	RP11-295P9.3	4.84E-13
Glia_2	U91319.1	7.42E-13
Glia_2	CADM1	7.78E-13
Glia_2	ALK	1.57E-12
Glia_2	CAB39L	1.80E-12
Glia_2	SOX6	2.48E-12
Glia_2	HSPG2	3.11E-12
Glia_2	FOXO1	3.59E-12
Glia_2	SPTBN1	4.46E-12
Glia_2	ADK	7.69E-12
Glia_2	ADAMTSL1	1.15E-11
Glia_2	HEG1	1.20E-11
Glia_2	ST6GALNAC5	2.16E-11
Glia_2	LGI4	2.51E-11
Glia_2	B2M	2.61E-11
Glia_2	RBMS3	3.51E-11
Glia_2	ATCAY	4.28E-11
Glia_2	KLHL29	5.08E-11
Glia_2	MATN2	9.25E-11
Glia_2	SLIT2	9.28E-11
Glia_2	PCSK2	1.88E-10
Glia_2	PPP1R12A	1.88E-10
Glia_2	KIRREL3	2.02E-10
Glia_2	CLIC4	3.07E-10
Glia_2	LGALS1	3.74E-10
Glia_2	ADAM19	5.16E-10
Glia_2	ASTN2	5.16E-10
Glia_2	C1orf21	6.06E-10
Glia_2	ABCA6	6.33E-10
Glia_2	IGFBP7	7.34E-10
Glia_2	RPL41	7.38E-10
Glia_2	BEAN1	9.36E-10
Glia_2	SDK2	1.25E-09
Glia_2	ALDH1A1	1.66E-09
Glia_2	RP11-386G21.1	1.67E-09
Glia_2	MAML3	2.10E-09
Glia_4	RP11-753H16.3	8.57E-07
Glia_4	BMP3	1.36E-06
Glia_4	CACNA1H	1.43E-06
Glia_4	PTGS1	3.87E-06
Glia_4	RP11-707P20.1	4.05E-06
Glia_4	HOXA-AS3	9.41E-06
Glia_4	MRVI1	5.79E-05
Glia_4	CCND1	1.28E-04
Glia_4	ARL4D	3.56E-04
Glia_4	ROGDI	3.56E-04
Glia_4	KCNJ12	4.87E-04
Glia_4	RP11-1277A3.1	1.12E-03
Glia_4	NR2F2	1.15E-03
Glia_4	PI15	1.23E-03
Glia_4	BOK	1.29E-03
Glia_4	RRP8	1.37E-03
Glia_4	AC073635.5	2.11E-03
Glia_4	RHOU	2.59E-03
Glia_4	RP11-6O2.3	2.78E-03
Glia_4	Z83851.3	5.92E-03
Glia_4	TACR2	6.19E-03
Glia_4	RP11-790J24.1	6.32E-03
Glia_4	RP13-582O9.5	6.55E-03
Glia_4	GINS2	7.51E-03
Glia_4	RP11-753A21.1	9.09E-03
Glia_4	CTC-296K1.3	9.16E-03
Glia_4	MASP1	9.42E-03
Glia_4	MMP3	9.49E-03
Glia_4	CTC-296K1.4	9.67E-03
Glia_4	SLC26A10	1.16E-02
Glia_4	FAM186B	1.20E-02
Glia_4	LPP-AS1	1.23E-02
Glia_4	LINC00339	1.67E-02
Glia_4	C11orf95	1.67E-02
Glia_4	MBNL1-AS1	1.72E-02
Glia_4	SGOL1	1.76E-02
Glia_4	RP11-158I9.5	1.87E-02
Glia_4	TMCO6	1.87E-02
Glia_4	PPP1R3C	1.97E-02
Glia_4	POPDC3	2.11E-02
Glia_4	GPR183	2.12E-02
Glia_4	OSR1	2.40E-02
Glia_4	FAHD2B	2.55E-02
Glia_4	GTPBP3	2.61E-02
Glia_4	CTD-2576D5.4	2.63E-02
Glia_4	ATP5SL	2.68E-02
Glia_4	RP11-643A5.2	2.72E-02
Glia_4	RP11-515O17.3	2.91E-02
Glia_4	C1orf216	3.14E-02
Glia_4	RP11-514D23.1	3.77E-02
Glia_4	TBRG4	3.83E-02
Glia_4	RP4-800J21.3	3.98E-02
Glia_4	CTD-2184D3.6	4.38E-02
Glia_4	RP11-727A23.11	4.42E-02
Glia_4	CLEC10A	4.43E-02
Glia_4	SHANK2-AS1	4.65E-02
Glia_4	HOXA9	4.73E-02
Glia_4	RP11-152F13.10	4.88E-02
Glia_4	SLC18A1	4.95E-02
Glia_4	TMEM18	4.97E-02
Glia_7	ANXA2	6.07E-12
Glia_7	IL1RAP	6.25E-12
Glia_7	FOSB	6.27E-12
Glia_7	ARC	7.76E-12
Glia_7	VCAN	9.61E-12
Glia_7	FOSL1	2.52E-11
Glia_7	CCL2	4.06E-11
Glia_7	SGIP1	5.01E-11
Glia_7	CTGF	1.40E-10
Glia_7	SEMA4A	1.56E-10
Glia_7	MEG3	3.36E-10
Glia_7	S100A10	3.60E-10
Glia_7	NAMPT	3.77E-10
Glia_7	RP11-2E17.1	4.48E-10
Glia_7	MALAT1	5.02E-10
Glia_7	HAS2-AS1	8.38E-10
Glia_7	NUP98	1.50E-09
Glia_7	MARCH3	4.00E-09
Glia_7	RP11-4F22.2	4.01E-09
Glia_7	RGS16	4.49E-09
Glia_7	RP11-123M6.2	5.66E-09
Glia_7	PLK3	8.37E-09
Glia_7	KLF6	8.81E-09
Glia_7	ALG13	9.79E-09
Glia_7	TMPRSS6	1.14E-08
Glia_7	CLCF1	1.77E-08
Glia_7	CSRNP1	1.77E-08
Glia_7	TACC1	2.16E-08
Glia_7	VIM	2.44E-08
Glia_7	ESYT2	2.86E-08
Glia_7	EIF1	3.84E-08
Glia_7	KCTD20	5.23E-08
Glia_7	NR4A3	5.63E-08
Glia_7	PLEKHG6	7.01E-08
Glia_7	FAM107B	7.07E-08
Glia_7	LEPREL1	7.07E-08
Glia_7	ZNRF2	7.80E-08
Glia_7	FOXO3	7.80E-08
Glia_7	SKIL	7.81E-08
Glia_7	ARIH1	7.82E-08
Glia_7	NPTX2	9.24E-08
Glia_7	NR4A2	1.21E-07
Glia_7	LAMC1	1.23E-07
Glia_7	TNC	1.28E-07
Glia_7	AC016831.7	1.54E-07
Glia_7	CTC-232P5.1	1.55E-07
Glia_7	GPR108	1.76E-07
Glia_7	S100A16	2.07E-07
Glia_7	NOD1	2.20E-07
Glia_7	ANGPTL4	2.59E-07
Glia_7	MIR503HG	2.70E-07
Glia_7	ABCA8	3.20E-07
Glia_7	FAM129A	3.85E-07
Glia_7	BAI3	4.12E-07
Glia_7	NEDD9	4.46E-07
Glia_7	LSAMP-AS1	4.99E-07
Glia_7	FAT1	6.21E-07
Glia_7	IFI16	7.77E-07
Glia_7	IQGAP2	8.36E-07
Glia_7	HTATIP2	1.21E-06

Glia_2	SYNE2	2.10E-09
Glia_2	IFNGR2	2.19E-09
Glia_2	CTDSPL	2.66E-09
Glia_2	NEDD4L	2.82E-09
Glia_2	ELMO1-AS1	2.88E-09
Glia_2	CPEB3	3.28E-09
Glia_2	SPARC	3.70E-09
Glia_2	AP000462.2	4.67E-09
Glia_2	PTK2	4.76E-09
Glia_2	FIGN	5.88E-09
Glia_2	FTH1	5.88E-09
Glia_2	NEGR1	6.83E-09
Glia_2	FAM129A	6.83E-09
Glia_2	OSBPL9	9.95E-09
Glia_2	LY9	9.97E-09
Glia_2	GULP1	9.98E-09
Glia_2	DENND1B	1.04E-08
Glia_2	MAL	1.16E-08
Glia_2	TMEM176B	1.17E-08
Glia_2	SH3RF3	1.28E-08
Glia_2	OTOGL	1.42E-08
Glia_2	ITGB8	2.37E-08
Glia_2	COL5A3	5.39E-08
Glia_2	CTTNBP2	5.48E-08
Glia_2	S100B	1.12E-07
Glia_2	LRAT	1.23E-07
Glia_2	HSPA12A	1.40E-07
Glia_2	AHR	1.99E-07
Glia_2	APCDD1	2.30E-07
Glia_2	MX2	5.42E-07
Glia_2	TRABD2B	6.22E-07
Glia_2	SLC5A7	1.36E-06
Glia_2	SIPA1L2	1.52E-06
Glia_2	COL8A1	3.19E-06
Glia_2	RP11-60A8.1	3.45E-06
Glia_2	KCNK5	5.53E-06
Glia_2	FXYD1	7.74E-06
Glia_2	KANK4	8.70E-06
Glia_2	L1CAM	3.88E-05
Glia_2	RDH10	5.03E-05
Glia_2	CYTL1	6.28E-05
Glia_2	RP11-145O15.3	8.28E-05
Glia_2	ENDOD1	8.99E-05
Glia_2	LONRF1	1.44E-04
Glia_2	B4GALT6	2.38E-04
Glia_2	MYOT	2.68E-04
Glia_2	PMP2	2.99E-04
Glia_2	S100A4	4.03E-04
Glia_2	MPZ	4.21E-04
Glia_2	IFI44L	4.22E-04
Glia_2	RHOC	1.67E-03
Glia_2	MARCKS	1.83E-03
Glia_2	OGFRL1	2.03E-03
Glia_2	RP11-434H14.1	4.17E-03
Glia_2	MTRNR2L10	4.38E-03
Glia_2	RGS16	4.41E-03
Glia_2	DDX60L	4.46E-03
Glia_2	LPCAT2	4.76E-03
Glia_2	CST3	5.24E-03
Glia_2	PRNP	5.37E-03
Glia_5	CTNND2	1.49E-39
Glia_5	BAI3	2.78E-38
Glia_5	LSAMP	1.52E-22
Glia_5	CTNNA3	4.10E-20
Glia_5	COL11A1	3.02E-17
Glia_5	FADS2	7.06E-17
Glia_5	RIMS1	7.09E-17
Glia_5	LRRTM4	7.87E-17
Glia_5	IFI44L	2.37E-15
Glia_5	HSPA1B	1.31E-13
Glia_5	GPR126	1.31E-13
Glia_5	PPP2R2B	1.47E-12
Glia_5	LPHN3	8.10E-12
Glia_5	NKAIN2	1.14E-11
Glia_5	ATP8A1	4.63E-11
Glia_5	IFI6	4.63E-11
Glia_5	KCNT2	4.91E-11
Glia_5	HMCN1	7.43E-11
Glia_5	TRIM9	7.43E-11
Glia_5	LRRTM3	5.73E-10
Glia_5	NKAIN3	3.76E-09
Glia_5	PCDH9	5.15E-09
Glia_5	NRG3	1.20E-08
Glia_5	PITPNC1	1.44E-08
Glia_5	RBFOX1	3.35E-08
Glia_5	APOE	4.39E-08
Glia_5	GRM7	4.49E-08
Glia_5	LINC01057	5.30E-08
Glia_5	EPHA5	1.35E-07
Glia_5	LINC00478	1.82E-07
Glia_5	RALYL	2.14E-07
Glia_5	MYBL1	3.28E-07
Glia_5	PCLO	4.41E-07
Glia_5	GNA14	4.43E-07
Glia_5	RP11-179A16.1	4.43E-07
Glia_5	PXDN	4.82E-07
Glia_5	SLC25A25	5.53E-07
Glia_5	MARCH10	5.97E-07
Glia_5	SLC4A8	8.73E-07
Glia_5	DDIT4	8.73E-07
Glia_5	RP11-466A17.1	1.19E-06
Glia_5	TJP1	1.30E-06
Glia_5	RP11-77K12.4	1.43E-06
Glia_5	HSPA1A	1.51E-06
Glia_5	CHL1	1.73E-06
Glia_5	DPP10	2.10E-06
Glia_5	SYT10	2.13E-06
Glia_5	SGIP1	2.20E-06
Glia_5	CACNA1D	2.85E-06
Glia_5	POLR2F	2.95E-06
Glia_5	LURAP1L	3.03E-06
Glia_5	GABRB1	4.90E-06
Glia_5	PTPN13	4.90E-06
Glia_5	MAPRE2	6.30E-06
Glia_5	KCNH8	6.62E-06
Glia_5	RASSF4	8.58E-06
Glia_5	NR6A1	1.03E-05
Glia_5	MIR146A	1.31E-05
Glia_5	APP	1.36E-05
Glia_5	CERS6	1.36E-05
Glia_7	RP11-286E11.1	1.23E-06
Glia_7	RP11-689B22.2	1.73E-06
Glia_7	RP11-542G1.1	7.15E-06
Glia_7	HAS2	7.60E-06
Glia_7	SGMS2	8.33E-06
Glia_7	MIR155HG	1.25E-05
Glia_7	IL6	1.25E-05
Glia_7	SERPINE1	3.35E-05
Glia_7	ID4	6.97E-05
Glia_7	MLF1	7.45E-05
Glia_7	F3	9.42E-05
Glia_7	SULT1C4	1.19E-04
Glia_7	SLC1A3	3.42E-04
Glia_7	RNF122	3.70E-04
Glia_7	GPR143	4.07E-04
Glia_7	YPEL4	5.87E-04
Glia_7	SPRY2	6.46E-04
Glia_7	ANKRD53	9.80E-04
Glia_7	ACHE	1.14E-03
Glia_7	CADM4	2.54E-03
Glia_7	AP000688.8	2.70E-03
Glia_7	C12orf44	4.01E-03
Glia_7	SPSB1	4.16E-03
Glia_7	AL132709.8	4.82E-03
Glia_7	ODF3L1	5.23E-03
Glia_7	MAPK15	5.24E-03
Glia_7	ATP2B3	5.24E-03
Glia_7	RP11-4C20.3	9.45E-03
Glia_7	ZBTB17	1.00E-02
Glia_7	DBI	1.03E-02
Glia_7	CTC-444N24.11	1.08E-02
Glia_7	PDLIM4	1.19E-02
Glia_7	KB-1732A1.1	1.31E-02
Glia_7	RP11-435O5.2	1.91E-02
Glia_7	DDX3Y	2.01E-02
Glia_7	LINC00152	2.30E-02
Glia_7	TFPI2	2.49E-02
Glia_7	RP3-399L15.2	2.52E-02
Glia_7	RIBC1	2.76E-02
Glia_7	RP11-667K14.3	2.81E-02
Glia_7	RARA	2.82E-02
Glia_7	AC133106.2	2.83E-02
Glia_7	KCNK3	3.27E-02
Glia_7	RP11-123B3.2	3.28E-02
Glia_7	RP11-483H20.6	3.34E-02
Glia_7	TMEM106A	3.34E-02
Glia_7	LINC00205	3.52E-02
Glia_7	GPR56	3.53E-02
Glia_7	EGR3	4.58E-02
Glia_7	LMO2	4.89E-02
Glia_8	MCTP1	1.23E-35
Glia_8	LDB2	1.11E-33
Glia_8	EGFL7	3.45E-33
Glia_8	PTPRB	3.17E-29
Glia_8	VWF	2.18E-23
Glia_8	CTA-276F8.2	8.57E-22
Glia_8	EPAS1	2.53E-21
Glia_8	MECOM	1.20E-19
Glia_8	EMP1	1.88E-19
Glia_8	CALCRL	3.05E-19

Glia_2	TAF5L	6.07E-03
Glia_2	PHLDA3	7.90E-03
Glia_2	CAPN9	8.39E-03
Glia_2	TMEM176A	8.72E-03
Glia_2	FSTL3	9.57E-03
Glia_2	SBSPON	1.01E-02
Glia_2	GFRA3	1.05E-02
Glia_2	SHE	1.05E-02
Glia_2	MFAP3L	1.54E-02
Glia_2	PDGFA	1.61E-02
Glia_2	RP1-249H1.4	1.61E-02
Glia_2	NRN1	1.69E-02
Glia_2	RP5-1121H13.3	1.70E-02
Glia_2	MRE11A	1.71E-02
Glia_2	GAS2L3	1.89E-02
Glia_2	TIMM13	1.91E-02
Glia_2	PMEPA1	1.91E-02
Glia_2	IFIT2	1.97E-02
Glia_2	LL22NC03-2H8.5	2.33E-02
Glia_2	RP11-524F11.2	2.48E-02
Glia_2	RP11-179A7.2	2.61E-02
Glia_2	RP11-381O7.3	2.79E-02
Glia_2	GBP1	3.05E-02
Glia_2	SMPDL3B	3.23E-02
Glia_2	SOD1	3.41E-02
Glia_2	LGALS3BP	3.61E-02
Glia_2	HRASLS5	4.33E-02
Glia_3	MYH11	2.14E-51
Glia_3	ACTG2	3.96E-33
Glia_3	SVIL	1.72E-32
Glia_3	LPP	1.26E-27
Glia_3	MIR145	1.38E-21
Glia_3	FLNA	3.11E-21
Glia_3	RP11-123O10.4	6.59E-21
Glia_3	ITGA5	2.18E-18
Glia_3	SPEG	9.55E-17
Glia_3	SORBS1	1.17E-16
Glia_3	PDLIM7	6.58E-16
Glia_3	GEM	9.89E-16
Glia_3	CACNA1C	9.89E-16
Glia_3	THRB	3.95E-15
Glia_3	TSHZ3	6.86E-15
Glia_3	NEAT1	9.88E-15
Glia_3	RP11-413B19.2	9.88E-15
Glia_3	RBPMS	1.29E-14
Glia_3	PDE4D	1.74E-14
Glia_3	KTN1-AS1	1.80E-14
Glia_3	AC100830.3	2.34E-14
Glia_3	SYNPO2	3.40E-14
Glia_3	MLLT3	3.45E-14
Glia_3	DENND3	4.61E-14
Glia_3	ZFR	6.40E-14
Glia_3	ADAM33	6.96E-14
Glia_3	PDZRN4	7.32E-14
Glia_3	ACTA2	8.59E-14
Glia_3	UBAC2	8.59E-14
Glia_3	COL4A1	1.11E-13
Glia_3	MLLT10	1.11E-13
Glia_3	NT5DC3	1.24E-13
Glia_3	PTCHD3P1	1.38E-13
Glia_5	GAP43	1.36E-05
Glia_5	MAPK10	1.53E-05
Glia_5	HES1	1.57E-05
Glia_5	DNM3	1.67E-05
Glia_5	ZNF804B	1.71E-05
Glia_5	FAS	1.76E-05
Glia_5	CSGALNACT1	2.10E-05
Glia_5	HEPN1	2.13E-05
Glia_5	NTNG2	2.44E-05
Glia_5	PTGDS	3.03E-05
Glia_5	RP11-532N4.2	3.03E-05
Glia_5	RP11-122F24.1	3.26E-05
Glia_5	AXDND1	3.36E-05
Glia_5	DMC1	3.74E-05
Glia_5	WIPF1	3.77E-05
Glia_5	XAF1	3.77E-05
Glia_5	TPD52L1	3.80E-05
Glia_5	PDE11A	3.87E-05
Glia_5	SRGAP3	4.43E-05
Glia_5	PHACTR1	4.59E-05
Glia_5	VCAN	4.59E-05
Glia_5	COL12A1	4.59E-05
Glia_5	PLEKHA5	4.86E-05
Glia_5	CTD-2140G10.2	5.74E-05
Glia_5	TARSL2	6.03E-05
Glia_5	RP11-379B18.6	6.04E-05
Glia_5	PDE3A	6.07E-05
Glia_5	CTD-2026G6.3	6.98E-05
Glia_5	SHC4	6.98E-05
Glia_5	RANBP9	7.06E-05
Glia_5	CD47	7.28E-05
Glia_5	RP11-85M11.2	7.62E-05
Glia_5	MOXD1	7.62E-05
Glia_5	RP11-379B18.5	7.97E-05
Glia_5	DUSP22	8.54E-05
Glia_5	PARP14	8.73E-05
Glia_5	FLT3	9.42E-05
Glia_5	TRHDE	9.53E-05
Glia_5	TANC2	9.65E-05
Glia_5	C8orf46	9.65E-05
Glia_5	RP11-154D6.1	3.25E-04
Glia_5	GLDC	3.94E-04
Glia_5	GFRAL	5.26E-04
Glia_5	RP11-18B16.2	6.05E-04
Glia_5	ALDH8A1	6.91E-04
Glia_5	RP11-390B4.3	9.48E-04
Glia_5	NABP2	1.06E-03
Glia_5	TWIST1	1.15E-03
Glia_5	PRSS35	3.69E-03
Glia_5	C3orf20	3.74E-03
Glia_5	NREP-AS1	3.89E-03
Glia_5	ACPP	3.94E-03
Glia_5	RP4-781K5.4	5.02E-03
Glia_5	HIST1H2BJ	5.02E-03
Glia_5	RP11-789A21.1	5.38E-03
Glia_5	AC005235.1	5.63E-03
Glia_5	EBF3	5.87E-03
Glia_5	CYS1	5.93E-03
Glia_5	SLC23A3	7.51E-03
Glia_5	IGSF10	7.63E-03
Glia_8	EMCN	5.16E-18
Glia_8	MKL2	5.68E-16
Glia_8	ID1	1.43E-15
Glia_8	ZNF385D	3.60E-15
Glia_8	FOS	7.78E-15
Glia_8	PIK3R3	1.25E-14
Glia_8	JUNB	2.78E-14
Glia_8	MT2A	3.58E-14
Glia_8	ELTD1	9.06E-14
Glia_8	ERG	1.09E-13
Glia_8	PREX2	1.09E-13
Glia_8	CYYR1	2.93E-13
Glia_8	TMTC1	7.25E-13
Glia_8	ANO2	1.29E-12
Glia_8	SOCS3	2.64E-12
Glia_8	SPRY1	3.98E-12
Glia_8	ELMO1-AS1	5.84E-12
Glia_8	TSHZ2	8.51E-12
Glia_8	AC005237.4	1.06E-11
Glia_8	A2M	1.30E-11
Glia_8	RP4-678D15.1	1.58E-10
Glia_8	LIFR	1.94E-10
Glia_8	ELMO1	2.30E-10
Glia_8	ID3	3.77E-10
Glia_8	ADAMTS9	1.36E-09
Glia_8	MAGI1	1.60E-09
Glia_8	FES	2.40E-09
Glia_8	TPO	2.40E-09
Glia_8	RUNDC3B	2.79E-09
Glia_8	PKP4	3.93E-09
Glia_8	RALGAPA2	3.93E-09
Glia_8	LMCD1	4.45E-09
Glia_8	ADCY4	4.55E-09
Glia_8	AL035610.2	1.02E-08
Glia_8	AC007319.1	1.02E-08
Glia_8	PALMD	1.11E-08
Glia_8	SLC2A3	1.35E-08
Glia_8	SPC25	1.76E-08
Glia_8	SRGN	4.41E-08
Glia_8	CXCL2	5.17E-08
Glia_8	TMEM100	5.35E-08
Glia_8	FGD4	5.71E-08
Glia_8	CLDN5	1.05E-07
Glia_8	ABLIM1	1.05E-07
Glia_8	TMSB10	1.12E-07
Glia_8	HIPK3	1.82E-07
Glia_8	ZFP36	2.01E-07
Glia_8	ST6GAL1	2.09E-07
Glia_8	NUAK1	2.26E-07
Glia_8	ADAMTS1	2.97E-07
Glia_8	SLCO2A1	4.07E-07
Glia_8	RAPGEF3	8.64E-07
Glia_8	ARHGAP29	8.64E-07
Glia_8	SERPINA5	1.07E-06
Glia_8	RAPGEF5	1.58E-06
Glia_8	PTPRM	1.84E-06
Glia_8	PPP1R16B	2.02E-06
Glia_8	DARC	2.10E-06
Glia_8	HLA-E	2.35E-06
Glia_8	ARHGAP26-AS1	2.62E-06

Glia_3	ITGB1	1.62E-13
Glia_3	RP11-611D20.2	1.62E-13
Glia_3	PDGFC	1.62E-13
Glia_3	ACACB	1.70E-13
Glia_3	AC005358.3	2.17E-13
Glia_3	AC098617.1	2.43E-13
Glia_3	AP001347.6	2.51E-13
Glia_3	ILK	2.64E-13
Glia_3	AF001548.5	3.57E-13
Glia_3	MIR143HG	3.98E-13
Glia_3	PRUNE2	5.11E-13
Glia_3	CCDC57	5.82E-13
Glia_3	SIMC1	6.39E-13
Glia_3	TPM4	6.90E-13
Glia_3	PPP1R13B	7.37E-13
Glia_3	ARHGAP6	8.42E-13
Glia_3	RP11-39M21.1	9.55E-13
Glia_3	ACTN1	1.07E-12
Glia_3	SEC13	1.07E-12
Glia_3	CAP2	1.22E-12
Glia_3	CMSS1	1.25E-12
Glia_3	CNN1	1.50E-12
Glia_3	GABPB2	1.86E-12
Glia_3	MAST2	2.10E-12
Glia_3	CACNB2	2.62E-12
Glia_3	PLEKHO1	2.62E-12
Glia_3	HIBADH	2.65E-12
Glia_3	SNX9	2.65E-12
Glia_3	DGKH	3.04E-12
Glia_3	ADAMTS9-AS1	3.17E-12
Glia_3	PPM1L	3.28E-12
Glia_3	CDK7	3.33E-12
Glia_3	SUCLG2	3.33E-12
Glia_3	PIP5K1B	3.52E-12
Glia_3	DDR2	3.52E-12
Glia_3	C22orf23	3.93E-12
Glia_3	TNS1	5.03E-12
Glia_3	NDE1	5.20E-12
Glia_3	SMTN	5.87E-12
Glia_3	ARMC9	5.97E-12
Glia_3	SLC4A7	6.06E-12
Glia_3	CRYBG3	6.31E-12
Glia_3	PLD5	6.31E-12
Glia_3	IFT140	6.81E-12
Glia_3	RP11-544A12.4	8.38E-12
Glia_3	NRDE2	9.43E-12
Glia_3	VTI1A	9.43E-12
Glia_3	MSRA	1.14E-11
Glia_3	DIRC3	1.20E-11
Glia_3	RP11-238K6.1	1.31E-11
Glia_3	MON1B	1.32E-11
Glia_3	SLC8A1	1.50E-11
Glia_3	CNST	1.63E-11
Glia_3	KIF5B	1.69E-11
Glia_3	NME9	1.79E-11
Glia_3	NPLOC4	1.79E-11
Glia_3	ABL1	1.84E-11
Glia_3	ME2	1.88E-11
Glia_3	PRKG1	1.93E-11
Glia_3	GRAMD1A	2.11E-11
Glia_5	ORMDL3	7.93E-03
Glia_5	AC096574.5	8.07E-03
Glia_5	MPZL3	9.03E-03
Glia_5	RP5-1039K5.16	9.45E-03
Glia_5	AC007106.1	1.04E-02
Glia_5	CDH17	1.06E-02
Glia_5	RP11-597K23.2	1.11E-02
Glia_5	WNT5A	1.23E-02
Glia_5	PLA2G12B	1.27E-02
Glia_5	IGSF1	1.28E-02
Glia_5	C5orf52	1.29E-02
Glia_5	CLEC1B	1.30E-02
Glia_5	LINC00698	1.36E-02
Glia_5	DDX19B	1.41E-02
Glia_5	SCNN1G	1.42E-02
Glia_5	DDR1-AS1	1.57E-02
Glia_5	CLVS2	1.57E-02
Glia_5	COL9A2	1.62E-02
Glia_5	RP11-65D24.2	1.69E-02
Glia_5	RP11-159L20.2	1.80E-02
Glia_5	CHL1-AS1	1.84E-02
Glia_5	RP11-79P5.5	1.93E-02
Glia_5	RP11-138H11.1	1.96E-02
Glia_5	RP11-654C22.2	1.96E-02
Glia_5	RP11-1085N6.4	2.01E-02
Glia_5	MYH8	2.08E-02
Glia_5	AC002127.4	2.36E-02
Glia_5	CAPN14	2.39E-02
Glia_5	RP11-51L5.7	2.42E-02
Glia_5	AWAT2	2.43E-02
Glia_5	AC007966.1	2.43E-02
Glia_5	RP11-815M8.1	2.43E-02
Glia_5	JAKMIP1	2.43E-02
Glia_5	RP11-510M2.6	2.66E-02
Glia_5	SLC16A14	2.68E-02
Glia_5	NCR3LG1	2.84E-02
Glia_5	VN1R2	2.85E-02
Glia_5	C1orf189	2.90E-02
Glia_5	AC083864.3	2.92E-02
Glia_5	AC010890.1	2.98E-02
Glia_5	RP11-433J8.1	3.06E-02
Glia_5	RP11-945C19.4	3.09E-02
Glia_5	KIF19	3.15E-02
Glia_5	RP11-285M22.3	3.18E-02
Glia_5	TGFA	3.29E-02
Glia_5	SLC31A2	3.29E-02
Glia_5	RFPL2	3.32E-02
Glia_5	RP11-64P14.7	3.34E-02
Glia_5	SPATA24	3.35E-02
Glia_5	HSPE1-MOB4	3.37E-02
Glia_5	PRDM9	3.38E-02
Glia_5	RP11-529K1.3	3.49E-02
Glia_5	RDH12	3.54E-02
Glia_5	KLK5	3.54E-02
Glia_5	LINC00160	3.55E-02
Glia_5	RP11-57J16.1	3.56E-02
Glia_5	AC006547.13	3.58E-02
Glia_5	RP11-523L1.2	3.67E-02
Glia_5	RP11-380D11.2	3.68E-02
Glia_5	RP11-486L19.2	3.72E-02
Glia_8	DUSP1	3.40E-06
Glia_8	RIN2	3.94E-06
Glia_8	CAV1	4.35E-06
Glia_8	SIK1	4.39E-06
Glia_8	FLI1	4.40E-06
Glia_8	THSD7A	4.51E-06
Glia_8	SOX17	7.10E-06
Glia_8	CD74	7.30E-06
Glia_8	PRKCH	8.47E-06
Glia_8	FLT1	9.02E-06
Glia_8	AC010524.4	1.02E-05
Glia_8	NEDD9	1.12E-05
Glia_8	MAP3K8	1.13E-05
Glia_8	UTRN	1.25E-05
Glia_8	C4orf32	1.25E-05
Glia_8	ARHGAP26	1.25E-05
Glia_8	SDPR	1.26E-05
Glia_8	PLEKHG1	1.48E-05
Glia_8	HLA-B	1.63E-05
Glia_8	MT1E	1.63E-05
Glia_8	TM4SF1	1.68E-05
Glia_8	PLXNA2	2.36E-05
Glia_8	RASAL2	2.36E-05
Glia_8	ATP8B1	2.43E-05
Glia_8	MT1M	2.62E-05
Glia_8	MSN	2.62E-05
Glia_8	ASAP1	2.64E-05
Glia_8	TENC1	2.99E-05
Glia_8	FAM110D	3.43E-05
Glia_8	RBMS3-AS3	3.79E-05
Glia_8	GPIHBP1	4.21E-05
Glia_8	MYCT1	7.15E-05
Glia_8	ETS2	8.95E-05
Glia_8	RFTN1	1.44E-04
Glia_8	HYAL2	1.58E-04
Glia_8	ATOH8	2.10E-04
Glia_8	SH3BGRL2	2.82E-04
Glia_8	AQP1	5.08E-04
Glia_8	EBF3	5.18E-04
Glia_8	POSTN	5.60E-04
Glia_8	SNCG	6.49E-04
Glia_8	ECSCR	6.53E-04
Glia_8	BCAM	6.85E-04
Glia_8	ARHGEF15	7.41E-04
Glia_8	CLEC1A	7.55E-04
Glia_8	ICAM2	8.46E-04
Glia_8	CD93	9.45E-04
Glia_8	GIMAP6	9.45E-04
Glia_8	MYC	1.25E-03
Glia_8	SLC40A1	1.31E-03
Glia_8	RP11-818O24.3	1.49E-03
Glia_8	RP11-203M5.8	1.75E-03
Glia_8	FRAT2	1.93E-03
Glia_8	TMEM173	1.99E-03
Glia_8	THBD	2.01E-03
Glia_8	KCNJ1	2.02E-03
Glia_8	LRRC32	2.44E-03
Glia_8	AC005550.3	2.44E-03
Glia_8	S1PR1	2.52E-03
Glia_8	EDN1	2.59E-03

Glia_3	DMD	2.12E-11
Glia_3	DSCAM	2.17E-11
Glia_3	PRKAG2	2.26E-11
Glia_3	SULF2	2.42E-11
Glia_3	FMN1	2.42E-11
Glia_3	MEIS2	3.22E-11
Glia_3	TTLL11	3.29E-11
Glia_3	RP11-521M14.2	1.77E-05
Glia_3	EDA2R	1.94E-05
Glia_3	NBL1	1.89E-04
Glia_3	FUOM	3.01E-04
Glia_3	PRSS50	3.02E-04
Glia_3	ANKRD9	7.08E-04
Glia_3	AP000345.2	7.10E-04
Glia_3	NPTX1	7.71E-04
Glia_3	ZNF182	7.81E-04
Glia_3	RP11-789C1.1	1.20E-03
Glia_3	C17orf77	1.67E-03
Glia_3	CETP	1.77E-03
Glia_3	RP11-375H17.1	1.95E-03
Glia_3	CRYBB1	2.00E-03
Glia_3	MUCL1	2.14E-03
Glia_3	RP11-214L13.1	2.33E-03
Glia_3	RP11-818C3.1	2.53E-03
Glia_3	RP11-706C16.7	2.75E-03
Glia_3	RP4-662A9.2	2.76E-03
Glia_3	RAE1	2.81E-03
Glia_3	TEKT2	3.27E-03
Glia_3	RP11-956E11.1	3.42E-03
Glia_3	AMELY	3.55E-03
Glia_3	NNAT	3.94E-03
Glia_3	TMEM201	4.27E-03
Glia_3	RP13-297E16.5	4.54E-03
Glia_3	SERPINB5	4.58E-03
Glia_3	AC114730.7	4.60E-03
Glia_3	CTD-2184D3.7	5.00E-03
Glia_5	HMGB2	3.83E-02
Glia_5	RP11-197K6.1	3.83E-02
Glia_5	ABCC12	3.94E-02
Glia_5	KCNC1	3.95E-02
Glia_5	RP11-945A11.1	4.03E-02
Glia_5	RP11-10H3.1	4.12E-02
Glia_5	GBP6	4.33E-02
Glia_5	RP11-285C1.2	4.34E-02
Glia_5	RP11-285E9.6	4.52E-02
Glia_5	KRT73	4.56E-02
Glia_5	CTC-207P7.1	4.65E-02
Glia_5	RP11-47G4.2	4.71E-02
Glia_5	AADACL4	4.89E-02
Glia_5	RP11-327P2.5	4.99E-02
Glia_6	PID1	1.11E-67
Glia_6	TSHZ2	9.43E-60
Glia_6	RP4-678D15.1	9.43E-60
Glia_6	GPC6	1.36E-56
Glia_6	MGP	5.20E-55
Glia_6	DCN	1.30E-46
Glia_6	C7	1.06E-45
Glia_6	DPT	4.17E-43
Glia_6	LAMA2	2.63E-36
Glia_6	RORA	7.51E-33
Glia_6	EBF1	1.35E-30
Glia_6	SULF1	3.10E-28
Glia_6	ADH1B	4.35E-28
Glia_6	LHFP	1.52E-26
Glia_6	KCNN3	3.40E-26
Glia_6	DLC1	8.96E-26
Glia_6	PREX2	9.32E-26
Glia_6	RP13-143G15.4	7.38E-25
Glia_6	SLIT2	1.09E-23
Glia_6	C1orf21	1.75E-23
Glia_6	VIPR2	2.69E-21
Glia_6	RP11-385J1.2	1.48E-20
Glia_8	CTC-484P3.3	2.63E-03
Glia_8	MPZL2	3.34E-03
Glia_8	LINC00313	4.19E-03
Glia_8	VEGFC	4.71E-03
Glia_8	Z98049.1	5.09E-03
Glia_8	SLCO4A1	5.80E-03
Glia_8	ACVRL1	5.85E-03
Glia_8	DUSP23	6.61E-03
Glia_8	NOTCH4	6.61E-03
Glia_8	B4GALNT1	9.94E-03
Glia_8	NOS3	1.04E-02
Glia_8	MRPL28	1.19E-02
Glia_8	APLNR	1.20E-02
Glia_8	ROBO4	1.34E-02
Glia_8	TAL1	1.37E-02
Glia_8	RP6-99M1.2	1.42E-02
Glia_8	FAM26E	1.48E-02
Glia_8	RP11-1030E3.1	1.56E-02
Glia_8	FABP4	1.68E-02
Glia_8	RP11-64B16.5	1.71E-02
Glia_8	AC116614.1	1.79E-02
Glia_8	ESAM	1.84E-02
Glia_8	GORASP1	1.89E-02
Glia_8	CLEC14A	1.96E-02
Glia_8	HLA-DRB1	2.80E-02
Glia_8	MT1A	2.94E-02
Glia_8	STC1	3.09E-02
Glia_8	FABP5	3.12E-02
Glia_8	BCL3	3.48E-02
Glia_8	SHANK3	3.55E-02
Glia_8	RP11-136H19.1	4.33E-02
Glia_8	GIMAP1	4.49E-02
Glia_8	GATA2	4.59E-02
Glia_8	SMAD7	4.76E-02
Glia_8	HCN3	4.76E-02

[00698] Table 23. Conserved transcriptional programs in human and mouse enteric neurons. Differentially expressed genes for major neuron classes that are shared between human and mouse, including expression statistics for both mouse and human neurons.

ident	gene	mouse_alpha	mouse_mean	mouse_log2fc	human_alpha	human_mean	human_log2fc
Excitatory_Motor	Abcc8	0.91	1.90	1.03	0.55	0.73	1.33
Excitatory_Motor	Abtb2	0.72	0.69	2.02	0.54	0.93	1.12
Excitatory_Motor	Adamtsl1	0.91	1.18	2.93	0.67	1.51	1.54
Excitatory_Motor	Alk	0.98	4.45	2.14	0.86	3.39	1.91
Excitatory_Motor	Bnc2	0.98	4.28	2.30	0.98	3.64	1.95
Excitatory_Motor	Bub3	0.63	-0.18	0.39	0.59	1.03	0.47
Excitatory_Motor	Calcrl	0.83	1.74	1.05	0.67	1.74	1.28
Excitatory_Motor	Car10	0.79	2.20	2.13	0.78	2.13	1.33
Excitatory_Motor	Casz1	0.98	2.48	1.94	0.69	1.22	0.87
Excitatory_Motor	Chat	0.97	2.48	1.95	0.38	-0.48	0.32
Excitatory_Motor	Chrm2	0.99	2.96	0.44	0.50	1.56	1.91
Excitatory_Motor	Cnr1	0.87	2.77	0.68	0.65	1.37	0.78
Excitatory_Motor	Colq	0.76	0.82	2.30	0.69	1.80	1.75
Excitatory_Motor	Cpne8	0.99	2.47	1.32	0.65	1.42	0.54
Excitatory_Motor	Cradd	0.64	-0.40	0.52	0.62	0.88	0.24

ident	gene	mouse_alpha	mouse_mean	mouse_log2fc	human_alpha	human_mean	human_log2fc
Excitatory_Motor	Dlgap2	1.00	3.82	1.88	0.54	0.55	1.34
Excitatory_Motor	Dmkn	0.72	0.06	1.99	0.44	0.35	1.94
Excitatory_Motor	Dock2	0.77	0.14	2.11	0.49	0.14	0.59
Excitatory_Motor	Ebf3	0.95	2.43	1.12	0.59	0.96	0.80
Excitatory_Motor	Efna5	1.00	4.31	0.49	0.83	2.51	1.09
Excitatory_Motor	Elavl2	0.73	0.31	1.04	0.42	0.06	0.91
Excitatory_Motor	Epb4.1l4b	0.59	-0.80	0.17	0.65	1.09	0.72
Excitatory_Motor	Epha4	0.55	0.22	0.73	0.29	-0.68	0.75
Excitatory_Motor	Epha7	0.57	0.34	1.65	0.60	0.94	0.96
Excitatory_Motor	Fam163a	0.76	0.24	0.22	0.68	1.43	0.57
Excitatory_Motor	Fam19a5	0.98	3.53	1.73	0.56	0.66	1.00
Excitatory_Motor	Fbxo44	0.46	-1.46	0.41	0.48	0.21	0.64
Excitatory_Motor	Frmd4b	0.99	3.70	0.90	0.82	2.05	1.19
Excitatory_Motor	Gda	0.49	0.67	3.17	0.51	0.35	0.82
Excitatory_Motor	Gfra2	0.80	1.47	1.51	0.38	-0.12	0.69
Excitatory_Motor	Gpc6	1.00	5.11	1.71	0.99	4.73	2.45
Excitatory_Motor	Gpr22	0.52	-1.39	0.38	0.39	-0.04	1.34
Excitatory_Motor	Gria1	0.95	2.88	1.07	0.46	0.36	1.35
Excitatory_Motor	Gria2	0.98	1.30	0.29	0.49	0.27	0.50
Excitatory_Motor	Grip1	1.00	4.01	1.40	0.76	1.68	1.21
Excitatory_Motor	Hddc2	0.39	-1.73	1.15	0.43	0.36	0.61
Excitatory_Motor	Htr4	0.87	0.76	1.78	0.67	1.34	2.31
Excitatory_Motor	Kcnq2	0.97	2.23	0.80	0.22	-1.32	1.69
Excitatory_Motor	Kcns3	0.72	0.15	2.36	0.54	0.68	1.43
Excitatory_Motor	Klhl29	0.99	3.41	0.57	0.70	1.38	0.95
Excitatory_Motor	Lbh	0.36	-2.40	0.14	0.38	0.39	0.93
Excitatory_Motor	Lgi1	0.80	0.76	0.91	0.35	-0.26	0.71
Excitatory_Motor	Lrfn2	0.75	1.04	0.52	0.53	0.41	2.23
Excitatory_Motor	Lrig3	0.49	-1.39	2.76	0.22	-1.02	0.93
Excitatory_Motor	Nfib	0.94	2.26	1.12	0.62	1.06	0.52
Excitatory_Motor	Ogdhl	0.48	-1.50	0.47	0.32	-0.30	0.70
Excitatory_Motor	Oprk1	0.90	2.82	4.80	0.21	-1.28	1.69
Excitatory_Motor	Pknox2	0.62	0.37	1.28	0.45	0.30	1.31
Excitatory_Motor	Plcxd3	0.99	2.86	1.89	0.57	0.94	0.38
Excitatory_Motor	Plxna2	0.91	1.42	1.53	0.64	1.05	0.66
Excitatory_Motor	Prickle2	0.98	3.21	1.22	0.71	1.37	2.00
Excitatory_Motor	Psd3	0.88	0.81	1.63	0.90	2.61	0.67
Excitatory_Motor	Ptn	0.82	0.59	1.15	0.33	-0.60	0.17
Excitatory_Motor	Ramp1	0.80	0.66	0.12	0.71	1.92	1.09
Excitatory_Motor	Rbfox1	1.00	7.57	1.65	1.00	5.52	1.21
Excitatory_Motor	Rgs4	0.51	0.48	0.65	0.27	-0.69	1.12
Excitatory_Motor	Runx1t1	0.52	-0.71	2.50	0.40	0.19	0.80
Excitatory_Motor	Sec14l5	0.27	-3.25	1.98	0.39	-0.15	0.80
Excitatory_Motor	Sgpp2	1.00	2.78	0.87	0.58	0.67	0.47
Excitatory_Motor	Slc5a7	0.75	0.34	1.42	0.77	1.90	2.31
Excitatory_Motor	Sorbs2	0.82	0.52	0.35	0.86	2.78	0.87
Excitatory_Motor	Spata17	0.65	-2.89	0.52	0.45	0.32	0.73
Excitatory_Motor	Specc1	0.91	1.63	1.23	0.40	-0.32	0.67
Excitatory_Motor	St5	0.49	-1.20	0.52	0.62	0.89	0.49
Excitatory_Motor	St6galnac3	0.98	2.57	2.06	0.64	1.01	0.17
Excitatory_Motor	Syndig1	0.91	1.54	0.18	0.47	0.47	1.16
Excitatory_Motor	Syt6	0.98	3.53	1.41	0.38	-0.20	1.84
Excitatory_Motor	Tmem132c	0.82	1.75	3.09	0.77	2.88	2.63
Excitatory_Motor	Tmem164	0.92	1.78	1.76	0.48	0.35	0.76
Excitatory_Motor	Tox	0.99	3.64	1.61	0.88	2.80	0.85
Excitatory_Motor	Tpd52l1	0.96	1.09	2.42	0.88	2.37	1.82
Excitatory_Motor	Ubash3b	0.82	1.03	1.38	0.48	0.27	0.60
Excitatory_Motor	Unc5d	0.96	4.26	1.97	0.97	4.57	1.98
Excitatory_Motor	Xylt1	0.98	2.95	1.68	0.92	3.31	1.36

ident	gene	mouse_alpha	mouse_mean	mouse_log2fc	human_alpha	human_mean	human_log2fc
Excitatory_Motor	Zfp521	0.99	3.33	1.08	0.59	1.01	0.83
Inhibitory_Motor	Ablim2	1.00	4.43	1.52	0.72	1.95	0.66
Inhibitory_Motor	Adcy2	0.98	0.91	1.11	0.40	-0.14	0.45
Inhibitory_Motor	Add3	0.98	1.70	1.35	0.74	1.93	0.93
Inhibitory_Motor	Aff1	0.69	0.01	0.84	0.61	1.21	0.86
Inhibitory_Motor	Alad	0.44	-1.35	0.86	0.38	0.05	0.62
Inhibitory_Motor	Alcam	1.00	3.30	2.35	0.85	3.41	1.26
Inhibitory_Motor	Aldh1a3	0.40	-0.70	4.57	0.23	-0.87	0.49
Inhibitory_Motor	Ano4	0.80	-1.30	1.85	0.40	-0.13	0.66
Inhibitory_Motor	Arhgef26	0.41	-1.21	1.96	0.28	-0.86	0.63
Inhibitory_Motor	Arid5b	0.99	2.33	1.22	0.45	0.26	0.46
Inhibitory_Motor	Atp2b1	0.98	1.87	0.77	0.46	0.41	0.67
Inhibitory_Motor	Cartpt	0.27	-1.23	1.03	0.41	3.26	3.18
Inhibitory_Motor	Ccdc129	0.49	-4.30	0.57	0.23	-1.25	0.29
Inhibitory_Motor	Chd7	0.95	2.40	0.98	0.39	-0.10	1.06
Inhibitory_Motor	Cit	0.64	-1.53	0.85	0.53	0.70	1.12
Inhibitory_Motor	Clvs1	1.00	3.83	1.19	0.57	0.76	0.38
Inhibitory_Motor	Col5a2	0.91	0.77	4.02	0.52	0.87	0.52
Inhibitory_Motor	Creb3l2	0.53	-1.11	0.56	0.38	-0.04	0.64
Inhibitory_Motor	Cryab	0.25	-2.80	1.63	0.43	0.97	0.88
Inhibitory_Motor	Cygb	0.56	-0.67	2.47	0.23	-0.59	1.75
Inhibitory_Motor	Dach1	0.76	1.46	1.41	0.58	1.36	1.30
Inhibitory_Motor	Dcc	0.91	1.70	1.15	0.70	2.21	1.39
Inhibitory_Motor	Dgkb	1.00	3.89	3.49	0.81	3.88	1.94
Inhibitory_Motor	Entpd3	0.99	2.30	1.64	0.70	2.10	0.78
Inhibitory_Motor	Epb4.1l2	0.83	-0.08	0.24	0.59	1.09	1.34
Inhibitory_Motor	Etv1	1.00	3.30	1.57	0.61	1.47	0.91
Inhibitory_Motor	Fam13c	0.95	0.92	1.09	0.33	-0.54	0.82
Inhibitory_Motor	Fam78b	1.00	2.94	0.72	0.58	1.12	1.13
Inhibitory_Motor	Fgd4	0.99	0.75	0.62	0.72	1.79	0.71
Inhibitory_Motor	Fosl2	0.57	-0.77	1.10	0.24	-0.88	1.13
Inhibitory_Motor	Fsip1	0.36	-3.59	0.47	0.34	-0.36	0.83
Inhibitory_Motor	Gal	0.54	0.86	0.13	0.65	4.03	1.59
Inhibitory_Motor	Gfra1	0.99	3.68	2.93	0.58	1.18	0.60
Inhibitory_Motor	Gpr176	0.78	0.24	1.30	0.59	1.13	0.81
Inhibitory_Motor	Kcnc1	0.85	0.75	1.43	0.23	-0.74	2.71
Inhibitory_Motor	Kcng3	0.94	1.17	0.65	0.43	0.09	0.89
Inhibitory_Motor	Kcnj5	0.85	1.25	2.86	0.31	-0.45	1.99
Inhibitory_Motor	Kcnq4	0.93	0.81	2.13	0.21	-1.36	0.76
Inhibitory_Motor	Kcnt2	1.00	4.08	1.37	0.75	2.35	0.11
Inhibitory_Motor	Kirrel3	0.90	3.72	0.96	0.44	0.20	0.50
Inhibitory_Motor	Klf7	0.97	2.18	0.60	0.48	0.37	0.26
Inhibitory_Motor	Lama5	0.69	0.57	1.67	0.25	-1.05	0.69
Inhibitory_Motor	Lima1	0.80	-0.87	0.21	0.69	1.52	0.52
Inhibitory_Motor	Lrch1	0.95	1.52	0.93	0.45	0.30	0.55
Inhibitory_Motor	Lrig2	0.98	2.24	0.61	0.44	0.19	0.77
Inhibitory_Motor	Lrriq1	0.51	-2.77	0.04	0.43	0.26	0.98
Inhibitory_Motor	Man1a	0.97	2.90	1.97	0.69	2.28	0.82
Inhibitory_Motor	Man2a1	0.99	3.16	0.54	0.48	0.52	0.77
Inhibitory_Motor	Mkx	0.44	-1.14	2.40	0.28	-0.76	0.83
Inhibitory_Motor	Ncald	1.00	2.94	1.49	0.79	2.27	0.72
Inhibitory_Motor	Net1	0.23	-3.20	0.44	0.22	-1.17	1.13
Inhibitory_Motor	Nos1	1.00	4.77	5.29	0.87	4.44	3.19
Inhibitory_Motor	Oprd1	0.90	1.42	2.58	0.43	0.27	1.53
Inhibitory_Motor	Pald1	0.70	-0.47	1.35	0.26	-0.98	1.24
Inhibitory_Motor	Pde1a	0.97	1.64	2.41	0.66	2.31	2.09
Inhibitory_Motor	Pde1c	0.99	3.41	1.52	0.61	1.31	0.42
Inhibitory_Motor	Pik3c2g	0.80	-2.55	0.88	0.51	0.70	0.51
Inhibitory_Motor	Prkg2	0.36	-1.76	0.35	0.33	-0.53	0.26

ident	gene	mouse_alpha	mouse_mean	mouse_log2fc	human_alpha	human_mean	human_log2fc
Inhibitory_Motor	Ptgir	0.23	-1.39	2.23	0.31	-0.25	1.40
Inhibitory_Motor	Ptpn13	0.53	-1.32	0.83	0.44	0.14	0.51
Inhibitory_Motor	Ptprg	1.00	5.00	1.09	0.86	3.36	1.10
Inhibitory_Motor	Pxdn	0.96	1.66	0.79	0.31	-0.33	2.10
Inhibitory_Motor	Qdpr	0.76	0.42	1.60	0.54	1.32	0.84
Inhibitory_Motor	Rnf125	0.41	-3.06	0.84	0.45	0.28	0.68
Inhibitory_Motor	Samd5	0.69	-0.04	1.10	0.27	-0.23	1.54
Inhibitory_Motor	Serinc5	0.70	-0.69	0.40	0.62	1.13	0.80
Inhibitory_Motor	Sipa1l2	0.87	1.13	1.48	0.28	-0.83	0.93
Inhibitory_Motor	Slc16a1	0.42	-1.49	1.47	0.26	-0.86	1.05
Inhibitory_Motor	Slc4a4	0.90	2.08	0.56	0.50	0.62	1.26
Inhibitory_Motor	Sntb1	1.00	3.83	1.35	0.69	1.98	1.68
Inhibitory_Motor	Sobp	0.99	2.62	0.82	0.45	0.37	0.77
Inhibitory_Motor	St18	1.00	1.18	1.42	0.60	1.37	2.26
Inhibitory_Motor	St3gal4	0.42	-1.72	0.46	0.30	-0.55	0.65
Inhibitory_Motor	Stac2	0.70	0.49	0.54	0.23	-0.67	1.10
Inhibitory_Motor	Stard13	0.99	2.33	1.70	0.52	0.72	0.96
Inhibitory_Motor	Tanc1	0.65	-0.53	1.82	0.66	1.70	1.63
Inhibitory_Motor	Tbx3	0.83	0.57	0.78	0.27	-0.50	0.62
Inhibitory_Motor	Tctex1d1	0.51	-2.27	0.93	0.32	-0.26	3.13
Inhibitory_Motor	Tenm3	0.97	2.99	1.62	0.74	2.11	0.40
Inhibitory_Motor	Tmco4	0.38	-2.31	0.80	0.38	-0.22	0.64
Inhibitory_Motor	Tnfrsf25	0.38	-0.92	1.26	0.25	-0.61	1.41
Inhibitory_Motor	Tnr	0.86	1.78	0.38	0.26	-0.79	0.86
Inhibitory_Motor	Tpst1	0.56	-1.06	0.51	0.82	3.31	1.33
Inhibitory_Motor	Utrn	1.00	3.19	0.57	0.60	1.17	0.81
Inhibitory_Motor	Vip	0.41	1.84	0.42	0.56	4.17	0.67
Inhibitory_Motor	Wipi1	0.91	1.05	1.97	0.24	-1.03	0.89
Inhibitory_Motor	Zeb2	0.97	2.29	0.81	0.56	1.00	0.90
Inhibitory_Motor	Zfp536	0.98	3.10	1.73	0.64	1.51	0.64
Inhibitory_Motor	Zfyve16	0.78	-1.01	0.12	0.52	0.60	0.46
Interneuron	Abcc8	1.00	2.75	1.87	0.73	0.91	1.27
Interneuron	Adra2a	0.57	-1.29	2.45	0.30	-1.25	1.65
Interneuron	B3gnt2	0.84	0.79	0.25	0.31	-1.57	1.14
Interneuron	Chgb	0.62	0.43	0.48	0.65	1.78	1.62
Interneuron	Clstn2	0.89	1.47	0.87	0.80	1.61	1.98
Interneuron	Cntn3	0.90	1.08	0.86	0.73	1.07	2.00
Interneuron	Ctxn1	0.67	-0.59	1.29	0.28	-1.51	1.26
Interneuron	Dapk1	0.99	1.54	2.35	0.69	0.45	0.87
Interneuron	Dynlt3	0.61	0.36	1.42	0.61	0.67	0.87
Interneuron	Eef1a2	0.54	-2.19	0.46	0.45	-0.02	0.98
Interneuron	Elovl4	0.66	0.38	1.62	0.47	-0.59	1.14
Interneuron	Emb	0.85	0.64	0.99	0.42	-0.82	1.91
Interneuron	Fam196b	0.63	0.29	1.54	0.27	-1.92	1.96
Interneuron	Fam19a2	0.99	3.36	1.65	0.86	2.75	1.65
Interneuron	Fam219b	0.56	-1.00	0.43	0.70	0.26	0.57
Interneuron	Gabarapl1	0.89	1.68	1.06	0.76	1.76	1.10
Interneuron	Hpcal4	0.58	-0.32	1.01	0.23	-1.18	1.64
Interneuron	Igf2bp2	0.54	-1.30	2.28	0.73	0.59	0.91
Interneuron	Irf2bpl	0.47	-2.15	0.72	0.31	-0.95	1.47
Interneuron	Kcnc4	0.68	-0.40	1.04	0.50	-0.02	1.48
Interneuron	Lbh	0.80	-0.52	2.44	0.49	1.08	1.60
Interneuron	Lin7a	0.91	0.99	1.11	0.62	0.96	2.74
Interneuron	Lnpep	0.99	2.01	1.08	0.77	0.88	0.40
Interneuron	Meis1	0.99	2.39	1.82	0.82	1.82	1.30
Interneuron	Mt3	0.57	-2.69	2.59	0.53	0.54	1.41
Interneuron	Ndufaf3	0.41	-2.25	0.75	0.45	-0.56	0.64
Interneuron	Nefm	0.44	0.99	2.54	0.55	1.34	2.33
Interneuron	Nfatc1	0.65	1.94	7.15	0.41	-0.33	2.06

ident	gene	mouse_alpha	mouse_mean	mouse_log2fc	human_alpha	human_mean	human_log2fc
Interneuron	Nrp2	0.99	3.01	1.21	0.73	1.56	1.90
Interneuron	Ogfrl1	0.47	-1.41	1.27	0.57	-0.14	0.97
Interneuron	Parva	1.00	3.39	1.97	0.78	1.18	0.84
Interneuron	Penk	0.86	5.03	5.99	0.70	4.85	4.89
Interneuron	Phox2a	0.51	-3.10	1.41	0.51	0.23	1.33
Interneuron	Prickle2	0.99	2.90	0.53	0.70	0.70	0.68
Interneuron	Ptprz1	0.73	1.68	1.79	0.68	0.72	1.52
Interneuron	Rgs4	0.55	1.92	2.54	0.32	0.31	2.19
Interneuron	Sdc3	0.77	0.23	0.25	0.38	-0.80	1.30
Interneuron	Sema3e	0.69	3.39	4.88	0.84	2.01	1.74
Interneuron	Slc16a12	0.68	-0.02	1.67	0.51	0.15	1.90
Interneuron	Slc1a4	0.73	0.39	1.10	0.65	0.42	1.36
Interneuron	Sncg	0.87	1.13	1.23	0.91	3.54	0.96
Interneuron	Spock1	0.88	2.54	1.26	0.78	1.56	1.30
Interneuron	Tac1	0.64	3.72	3.62	0.42	1.80	0.40
Interneuron	Tbx2	0.22	-1.97	1.83	0.27	-1.30	1.44
Interneuron	Tenm2	0.96	4.27	0.71	0.96	3.83	2.06
Interneuron	Tlx2	0.42	-1.58	0.73	0.53	0.43	0.95
Interneuron	Tm4sf4	0.93	2.16	1.60	0.70	1.97	2.22
Interneuron	Tmc3	0.73	2.14	1.56	0.69	1.30	2.11
Interneuron	Tns3	1.00	3.98	0.58	0.86	1.63	0.73
Interneuron	Tomm22	0.47	-1.92	0.81	0.42	-0.34	0.99
Interneuron	Trim36	0.70	-0.69	1.76	0.54	-0.19	1.01
Interneuron	Tspyl1	0.63	0.51	0.95	0.61	1.76	1.02
Interneuron	Ush1c	0.94	1.49	2.51	0.51	0.62	3.75
Interneuron	Vstm2a	0.27	-1.87	2.13	0.41	0.44	2.33
Interneuron	Ypel5	0.78	0.61	1.33	0.41	-0.85	0.66
Interneuron	Zfhx3	0.97	2.22	2.50	0.84	1.48	0.81
Interneuron	Zmat4	0.88	0.78	3.07	0.80	1.84	1.73
Secretomotor	Abca5	0.88	0.11	0.05	0.67	1.72	1.03
Secretomotor	Adamts1	0.31	-0.38	1.67	0.36	0.42	1.12
Secretomotor	Arnt2	0.74	-0.69	0.85	0.53	1.14	1.64
Secretomotor	Arpp21	1.00	3.72	2.02	0.57	1.53	1.50
Secretomotor	Calb2	0.97	0.83	1.70	0.85	3.58	3.94
Secretomotor	Camk2a	1.00	3.28	1.59	0.35	0.82	1.50
Secretomotor	Camk4	1.00	3.10	1.47	0.93	3.37	1.34
Secretomotor	Cdh10	0.86	0.50	3.15	0.68	1.77	1.60
Secretomotor	Chdh	0.44	-1.29	0.78	0.33	0.08	2.18
Secretomotor	Clic5	0.30	-1.66	3.75	0.46	0.41	0.98
Secretomotor	Cntn3	0.94	1.09	0.91	0.38	0.31	1.03
Secretomotor	Cux2	0.89	1.52	1.90	0.67	1.86	0.99
Secretomotor	Dennd5a	0.84	-0.03	0.34	0.60	1.23	0.75
Secretomotor	Ell2	0.77	0.41	1.16	0.65	1.87	1.81
Secretomotor	Etv1	1.00	4.13	1.78	0.81	2.51	1.62
Secretomotor	Fmn1	0.97	1.37	1.78	0.58	1.90	1.83
Secretomotor	Gal	0.58	3.72	3.96	0.64	4.64	1.28
Secretomotor	Gan	0.46	-1.19	0.78	0.67	1.79	1.60
Secretomotor	Gfra1	0.98	3.66	1.11	0.71	2.27	1.55
Secretomotor	Gng8	0.25	-3.20	2.55	0.29	-0.22	0.78
Secretomotor	Hcn1	0.93	0.64	0.98	0.63	1.65	1.14
Secretomotor	Kcnc2	1.00	3.90	0.48	0.43	0.67	1.21
Secretomotor	Kcnd2	1.00	6.04	2.65	0.94	4.09	2.01
Secretomotor	Kcnk2	0.89	0.39	0.79	0.69	1.79	2.95
Secretomotor	Kif26a	0.77	-0.06	1.03	0.29	-0.20	1.65
Secretomotor	Lhfpl2	0.42	-1.26	0.93	0.60	1.36	1.14
Secretomotor	Luzp2	0.98	1.49	2.79	0.81	2.48	1.42
Secretomotor	Nol4	0.98	1.44	0.71	0.61	1.47	1.46
Secretomotor	Npy2r	0.28	-1.14	2.33	0.25	-0.30	2.30
Secretomotor	Ntsr1	0.36	-1.52	2.42	0.25	-0.61	1.75

ident	gene	mouse_alpha	mouse_mean	mouse_log2fc	human_alpha	human_mean	human_log2fc
Secretomotor	Pcdh17	0.47	-0.92	1.94	0.44	0.75	0.90
Secretomotor	Plcz1	0.38	-2.12	1.24	0.24	-0.98	1.27
Secretomotor	Plscr4	0.87	0.60	0.75	0.28	-0.66	1.07
Secretomotor	Plxna4	0.80	3.82	1.52	0.61	1.67	1.77
Secretomotor	Prkd1	0.96	1.72	2.79	0.54	0.89	0.50
Secretomotor	Prkg2	0.55	-0.10	2.16	0.49	1.09	2.07
Secretomotor	Robo2	0.97	1.73	0.61	0.88	3.52	0.56
Secretomotor	Scgn	0.94	2.84	4.40	0.90	3.22	2.46
Secretomotor	Scn11a	0.92	0.66	1.27	0.47	0.97	0.93
Secretomotor	Slc16a7	0.78	-0.75	0.68	0.35	0.31	1.64
Secretomotor	Spock3	0.97	2.52	1.15	0.72	2.07	0.76
Secretomotor	Syt10	0.56	-0.90	2.56	0.42	1.23	2.73
Secretomotor	Trps1	0.89	2.71	1.63	0.50	1.35	1.59
Secretomotor	Unc5b	0.50	-0.97	1.74	0.33	0.06	3.20
Secretomotor	Vip	0.65	4.34	3.50	0.88	5.65	2.10
Secretomotor	Zyx	0.45	-2.29	0.56	0.28	-0.31	1.32
Sensory	Ache	0.92	2.25	1.15	0.67	1.41	1.15
Sensory	Acp1	0.88	-0.94	0.49	0.44	0.11	1.86
Sensory	Adamts1	0.34	-0.24	1.88	0.56	1.27	2.04
Sensory	Adap1	0.86	0.38	0.53	0.23	-2.41	1.17
Sensory	Adora1	0.28	-0.98	2.06	0.30	-1.15	2.22
Sensory	Agpat2	0.27	-2.61	0.96	0.28	-1.57	1.74
Sensory	Ano2	0.89	2.02	4.98	0.67	1.37	1.85
Sensory	Anxa2	0.81	0.33	1.80	0.84	1.95	0.95
Sensory	Arf5	0.54	-3.06	0.48	0.47	-0.17	1.59
Sensory	Arhgdig	0.46	-1.68	0.91	0.63	1.38	1.94
Sensory	Atp1a3	0.64	-0.29	0.74	0.67	0.88	0.66
Sensory	B2m	0.59	-2.26	0.79	0.93	5.12	1.84
Sensory	B3galt6	0.21	-2.63	0.75	0.40	-0.16	3.28
Sensory	Boc	0.53	-0.65	1.35	0.58	-0.61	1.98
Sensory	Calb2	0.92	0.61	1.45	0.51	1.99	1.29
Sensory	Calcb	0.71	2.64	5.83	0.53	1.18	1.55
Sensory	Cbln2	0.36	0.81	4.77	0.77	2.96	5.94
Sensory	Cd151	0.59	-0.60	0.73	0.74	0.96	0.80
Sensory	Cdc42ep4	0.26	-2.58	0.76	0.44	-0.56	0.98
Sensory	Cnp	0.39	-0.64	1.02	0.35	-0.72	1.73
Sensory	Cnr1	0.99	3.37	1.26	0.81	1.75	1.03
Sensory	Cntfr	0.69	-1.59	0.66	0.28	-0.34	3.45
Sensory	Cpne5	0.43	-2.08	2.92	0.65	0.79	1.48
Sensory	Cxxc4	0.61	-1.09	0.23	0.58	0.53	1.42
Sensory	Dcx	0.61	-0.14	0.96	0.40	-1.16	1.03
Sensory	Dgkh	0.88	1.19	0.85	0.88	5.29	5.19
Sensory	Dlx3	0.21	-2.69	5.93	0.37	-1.50	7.05
Sensory	Dpf1	0.49	-3.10	0.53	0.51	-0.22	1.29
Sensory	Galr1	0.29	0.32	2.41	0.40	-0.28	2.78
Sensory	Gap43	0.96	1.72	1.11	0.91	3.27	1.33
Sensory	Gse1	0.98	1.62	1.06	0.53	-0.07	1.23
Sensory	Hpca	0.23	-1.10	4.39	0.26	-1.84	4.53
Sensory	Hpcal1	0.84	0.44	1.47	0.63	0.85	1.12
Sensory	Htr3a	0.45	2.40	1.21	0.84	3.02	4.02
Sensory	Lgals3bp	0.54	0.00	1.59	0.49	-0.13	0.64
Sensory	Lin7b	0.39	-2.06	0.46	0.51	-0.08	1.46
Sensory	Maz	0.77	-0.74	1.19	0.40	-0.93	1.00
Sensory	Mmadhc	0.48	-1.93	0.69	0.37	-0.77	1.44
Sensory	Nmu	0.26	0.97	7.11	0.40	0.77	4.44
Sensory	Nt5dc2	0.22	-3.12	1.07	0.49	-0.12	1.03
Sensory	Ntrk3	0.91	3.95	1.09	0.74	2.68	3.51
Sensory	Phox2b	0.88	0.99	1.10	0.65	1.85	2.57
Sensory	Pianp	0.56	-2.08	0.29	0.47	-0.02	2.32

ident	gene	mouse_alpha	mouse_mean	mouse_log2fc	human_alpha	human_mean	human_log2fc
Sensory	Plcb3	0.70	0.12	0.74	0.44	0.25	2.30
Sensory	Plscr4	0.80	0.72	0.93	0.51	0.26	2.09
Sensory	Plxna4	1.00	4.62	2.72	0.74	2.08	2.14
Sensory	Pomp	0.71	-1.78	1.09	0.65	1.30	1.67
Sensory	Psmb8	0.28	-2.83	1.44	0.33	-1.68	1.20
Sensory	Ptpru	0.27	-2.42	1.57	0.30	-1.13	2.38
Sensory	Rab3b	0.56	-0.65	0.39	0.95	3.49	1.74
Sensory	Rac3	0.46	-1.88	1.08	0.53	0.51	1.60
Sensory	Rom1	0.25	-1.93	1.13	0.26	-1.86	1.82
Sensory	Rph3a	0.61	0.12	5.25	0.65	0.83	1.48
Sensory	Samd11	0.60	-1.48	0.41	0.58	0.60	2.50
Sensory	Scn11a	0.93	1.19	2.32	0.77	1.95	2.01
Sensory	Scube1	1.00	3.83	2.79	0.67	1.62	3.11
Sensory	Sdc3	0.76	0.51	0.58	0.58	0.80	3.25
Sensory	Slc12a7	0.58	-0.25	3.38	0.47	0.00	4.73
Sensory	Slc36a1	0.82	0.85	2.10	0.51	-0.34	1.33
Sensory	Smad9	0.60	-1.12	1.52	0.65	0.95	1.55
Sensory	Spock2	0.98	1.70	0.99	0.74	2.72	1.75
Sensory	Ssbp4	0.55	-2.08	0.40	0.56	0.16	0.93
Sensory	Sst	0.68	2.68	6.75	0.63	2.26	6.39
Sensory	Susd2	0.44	0.53	2.72	0.42	-0.53	3.50
Sensory	Syt7	0.88	1.02	1.27	0.60	0.54	1.51
Sensory	Tapbp	0.69	-0.07	0.64	0.67	0.96	1.37
Sensory	Tbx2	0.32	-1.28	2.70	0.49	-0.11	2.81
Sensory	Tcf7l2	0.96	2.87	2.90	0.95	2.90	2.02
Sensory	Thra	0.83	-0.50	0.46	0.67	1.33	1.78
Sensory	Tlx2	0.61	-0.22	2.79	0.63	1.18	1.75
Sensory	Trp53i11	0.71	1.18	1.72	0.77	1.80	2.78
Sensory	Tspan7	0.94	1.22	0.97	0.47	-0.11	0.57
Sensory	Unc5b	0.52	-1.58	1.27	0.35	-1.02	1.46
Sensory	Vgll3	0.29	-0.65	2.74	0.70	1.04	3.92
Sensory	Vipr2	0.70	1.89	4.59	0.58	0.32	2.30
Sensory	Zfp804a	0.69	3.05	2.27	0.88	3.84	2.69

Example 21 - Improved single nuclei RNA-seq analysis

[00699] Applicants provide an improved pipeline to apply single-cell genomics to multiple tissue types and multiple individuals (Fig. 33). Applicants provide for methods to solve problems associated with analyzing single nuclei. Applicants provide examples of how analysis of single nuclei transcriptomic data is different from single cell transcriptomic data. Applicants provide examples showing variation of single cell/single nuclei RNA-seq analysis across preps, individuals, and tissues. Applicants provide methods to scale up the approaches to many individuals. Figure 34 shows the single nuclei RNA-seq analysis pipeline. The pipeline can result in a tSNE plot showing clustering of individual nuclei. The individual nuclei clustered can be classified based on differential expression of genes in each cluster. The clusters can be assigned to a specific cell type based on known marker genes. New cell subtypes can also be identified.

[00700] An important difference in single nuclei RNA-seq compared to single cell RNA-seq is that many reads in single nuclei RNA-seq map to introns. Applicants hypothesized that counting reads that map to introns can allow better recovery of biological processes. Applicants determined that counting reads mapping to introns allows higher detection of genes (Fig. 35). Applicants also determined that counting reads mapping to introns allows higher detection of nuclei (Fig. 36).

[00701] Applicants also determined that filtering using computational methods developed for single cell RNA-seq can lead to low numbers of genes detected and important cell subsets can be lost (Fig. 37 and 38). For example, T cell receptor is expressed in nuclei subset 13 indicating that this subset are nuclei from T cells. Applicants show that by using thresholds from single cell RNA-seq T cells are lost because the number of genes detected is low.

[00702] Another issue to overcome is removing nuclei that are potential doublets (Fig. 39). One computational method that can be used to remove doublets is Scrublet (Wolock, Samuel L., Romain Lopez, and Allon M. Klein. "Scrublet: computational identification of cell doublets in single-cell transcriptomic data." BioRxiv(20l8): 3573). Other filtering methods may be used.

[00703] Another issue to overcome is removing nuclei that potentially only contain ambient RNA (Fig. 40). One computational method that can be used for ambient RNA is EmptyDrops (Lun, Aaron TL, et al. "EmptyDrops: distinguishing cells from empty droplets in droplet-based single-cell RNA sequencing data." Genome biology 20.1 (2019): 63). The total number of unique molecular identifiers (UMI) can be used to distinguish the nuclei, as nuclei encapsulated in droplets have a higher rank and greater total UMIs.

[00704] Applicants successfully clustered lung cell subsets using single nuclei RNA-seq (Fig. 41). Applicants observed variation across different nuclei preparations for the same individuals (Fig. 42) and across individual tissue samples when using the same nuclei preparation (Fig. 43). Applicants also show that there is variation between tissue types that needs to be accounted for. For example, the proportion of reads mapping to mitochondrial genes is much higher in heart tissue (Fig. 44).

[00705] Applicants determined that combining samples increases the power to detect cell subsets, but requires performing batch corrections (Fig. 45). The tSNE plots show that cells cluster by the individuals they came from without using batch correction. Applicants show that using batch correction allows for nuclei to cluster by cell type (Fig. 46). Applicants used 3 different batch

correction methods: COMBAT, CCA, and LIGER. Applicants were able to identify corresponding cell subsets while not over-correcting and losing biological state information. Applicants can demultiplex the 12 samples to produce 12 individual tSNE plots (Fig. 47). The nuclei subsets are consistent across the 12 tSNE plots. Applicants identified cell subsets using differentially expressed genes (Fig. 48). Applicants also identified cell subsets using genes curated from the literature. For example, PTPRC (CD45) is a marker for lymphocytes, CD163 is a marker for macrophages, AGER, PDPN and HOPX are markers for Alveolar Type I cells, SFTPB and SFTPC are markers for Alveolar Type II cells, KRT5, TP63 and KRT14 are markers for basal epithelial (CD271+) cells, FOXJ1, TEIBA1A and CDHR3 are markers for ciliated epithelial cells, and BPIFA1, SCGB1A1, SCGB3A1 and SCGB3A2 are markers for club epithelial cells. Applicants recovered the major subsets of parenchymal, stromal, and immune cells in lung tissue (Fig. 49). The methods also were able to be applied to 8 GTEx tissues (Fig. 50).

[00706] Applicants also determined methods for detecting QTLs (Fig. 51). Applicants determined that for sufficient power to detect QTLs, expression measurements from 10-100s of individuals was required. A quantitative trait locus (QTL) is a region of DNA which is associated with a particular phenotypic trait, which varies in degree and which can be attributed to polygenic effects, i.e., the product of two or more genes, and their environment. Rather than loading each individual on a separate lOx channel (lOx Genomics), the samples are mixed together at high concentration. Cord blood from 8 individuals with sequenced genomes is mixed with cells from all 8 individuals and processed together. Droplet-based cell isolation is used. Applicants can distinguish individuals using their sequenced SNPs and remove doublets based on cells or nuclei having SNPs from multiple individuals. Batch effects from cells being encapsulated in droplets can be controlled for.

[00707] Applicants show genetic demultiplexing to identify which individual each nuclei came from using lung nuclei pooled from 3 individuals. Applicants pooled three different samples and ran them on the same lOx channel.

References

1. 1. B. B. Yoo, S. K. Mazmanian, The Enteric Network: Interactions between the Immune and Nervous Systems of the Gut. *Immunity.* **46,** 910-926 (2017).

2. J. B. Furness, The enteric nervous system and neurogastroenterology. *Nat. Rev. Gastroenterol. Hepatol.* **9,** 286-294 (2012).
3. V. Sasselli, V. Pachnis, A. J. Burns, The enteric nervous system. *Dev. Biol.* **366,** 64-73 (2012).
4. C. E. Bernard *et al.*, Effect of age on the enteric nervous system of the human colon. *Neurogastroenterol. Motil.* **21,** 746-e46 (2009).
5. M. Li *et al.*, Integrative functional genomic analysis of human brain development and neuropsychiatric risks. *Science.* **362** (2018), doi:lO.H26/science.aat76l5.
6. L. A. Scheving, Biological clocks and the digestive system. *Gastroenterology.* **119,** 536-549 (2000).
7. R. De Giorgio *et al.*, Enteric neuropathies: Yesterday, Today and Tomorrow. *Adv. Exp. Med. Biol.* **891,** 123-133 (2016).
8. M. Pesce, O. Borrelli, E. Saliakellis, N. Thapar, Gastrointestinal Neuropathies: New Insights and Emerging Therapies. *Gastroenterol. Clin. North Am.* **47,** 877-894 (2018).
9. C. S. N. Klose *et al.*, The neuropeptide neuromedin E T stimulates innate lymphoid cells and type 2 inflammation. *Nature.* 549, 282-286 (2017).
10. D. Knights, K. G. Lassen, R. J. Xavier, Advances in inflammatory bowel disease pathogenesis: linking host genetics and the microbiome. *Gut.* **62,** 1505-1510 (2013).
11. V. Chaidez, R. L. Hansen, I. Hertz-Picciotto, Gastrointestinal problems in children with autism, developmental delays or typical development. *J. Autism Dev. Disord.* **44,** 1117-1 127 (2014).
12. R. F. Pfeiffer, Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol.* 2, 107-1 16 (2003).
13. J. R. Grider, Neurotransmitters mediating the intestinal peristaltic reflex in the mouse. *J. Pharmacol. Exp. Ther.* **307,** 460-467 (2003).
14. A. B. Rosenberg *et al.*, Single-cell profiling of the developing mouse brain and spinal cord with split-pool barcoding. *Science.* 360, 176-182 (2018).
15. A. Sathyamurthy *et al.*, Massively Parallel Single Nucleus Transcriptional Profiling Defines Spinal Cord Neurons and Their Activity during Behavior. *Cell Rep.* 22, 2216-2225 (2018).
16. N. Habib *et al.*, Massively parallel single-nucleus RNA-seq with DroNc-seq. *Nat. Methods.* **14,** 955-958 (2017).

17. N. Habib *et al.*, Div-Seq: Single-nucleus RNA-Seq reveals dynamics of rare adult newborn neurons. *Science.* 353, 925-928 (2016).

18. B. B. Lake *et al.*, Neuronal subtypes and diversity revealed by single-nucleus RNA sequencing of the human brain. *Science.* 352, 1586-1590 (2016).

19. A. E. Lewis, H. N. Vasudevan, A. K. O'Neill, P. Soriano, J. O. Bush, The widely used Wntl-Cre transgene causes developmental phenotypes by ectopic activation of Wnt signaling. *Dev. Biol.* **379,** 229-234 (2013).

20. T. Matsuoka *et al.*, Neural crest origins of the neck and shoulder. *Nature.* **436,** 347-355 (2005).

21. A. Zeisel *et al.*, Molecular Architecture of the Mouse Nervous System. *Cell.* **174,** 999-1014.e22 (2018).

22. R. Lasrado *et al.*, Lineage-dependent spatial and functional organization of the mammalian enteric nervous system. *Science.* 356, 722-726 (2017).

23. C. B. Wiese, N. Fleming, D. P. Buehler, E. M. Southard-Smith, A Uchll-Histone2BmCherry:GFP-gpi BAC transgene for imaging neuronal progenitors. *Genesis.* **51,** 852-861 (2013).

24. A. Mo *et al.*, Epigenomic Signatures of Neuronal Diversity in the Mammalian Brain. *Neuron.* 86, 1369-1384 (2015).

25. C. Simon, H. Lickert, M. Gotz, L. Dimou, SoxlO-iCreERT2 : a mouse line to inducibly trace the neural crest and oligodendrocyte lineage. *Genesis.* **50,** 506-515 (2012).

26. A. J. Prunuske, K. S. Ullman, The nuclear envelope: form and reformation. *Curr. Opin. Cell Biol.* **18,** 108-116 (2006).

27. P. Betancur, M. Bronner-Fraser, T. Sauka-Spengler, Genomic code for SoxlO activation reveals a key regulatory enhancer for cranial neural crest. *Proc. Natl. Acad. Sci. U. S. A.* **107,** 3570-3575 (2010).

28. A. Herrero, J. M. Duhart, M. F. Ceriani, Neuronal and Glial Clocks Underlying Structural Remodeling of Pacemaker Neurons in. *Front. Physiol.* 8, 918 (2017).

29. B. M. Assas, J. I. Pennock, J. A. Miyan, Calcitonin gene-related peptide is a key neurotransmitter in the neuro-immune axis. *Front. Neurosci.* 8, 23 (2014).

30. I. S. Junttila, Tuning the Cytokine Responses: An Update on Interleukin (IL)-4 and IL-13

Receptor Complexes. *Front. Immunol.* 9, 888 (2018).

31. J. Yan, H. Wang, Y. Liu, C. Shao, Analysis of gene regulatory networks in the mammalian circadian rhythm. *PLoS Comput. Biol.* **4,** el000l93 (2008).
32. N. J. Spencer, D. J. Keating, Is There a Role for Endogenous 5-HT in Gastrointestinal Motility? How Recent Studies Have Changed Our Understanding. *Aciv. Exp. Med. Biol.* **891,** 113-122 (2016).
33. C. Alcaino, G. Farrugia, A. Beyder, Mechanosensitive Piezo Channels in the Gastrointestinal Tract. *Curr. Top. Membr.* 79, 219-244 (2017).
34. G. S. Cottrell *et al.*, Localization of calcitonin receptor-like receptor (CLR) and receptor activity -modifying protein 1 (RAMP1) in human gastrointestinal tract. *Peptides.* **35,** 202-21 1 (2012).
35. A. L. Haber *et al.*, A single-cell survey of the small intestinal epithelium. *Nature.* **551,** 333—339 (2017).
36. J. B. Furness, C. Jones, K. Nurgali, N. Clerc, Intrinsic primary afferent neurons and nerve circuits within the intestine. *Prog. Neurobiol.* **72,** 143-164 (2004).
37. Y.-B. Yu *et al.*, Brain-derived neurotrophic factor contributes to abdominal pain in irritable bowel syndrome. *Gut.* **61,** 685-694 (2012).
38. J. H. Szurszewski, L. G. Ermilov, S. M. Miller, Prevertebral ganglia and intestinofugal afferent neurones. *Gut.* **51 Suppl 1,** i6-10 (2002).
39. V. D. Corleto, Somatostatin and the gastrointestinal tract. *Curr. Opin. Endocrinol. Diabetes Obes.* **17,** 63-68 (2010).
40. A.-P. G. Haramis *et al.*, De novo crypt formation and juvenile polyposis on BMP inhibition in mouse intestine. *Science.* **303,** 1684-1686 (2004).
41. N. Satoh-Takayama *et al.*, IL-7 and IL-15 independently program the differentiation of intestinal CD3-NKp46+ cell subsets from Id2-dependent precursors. *J. Exp. Med.* **207,** 273-280 (2010).
42. S. Degan, G. Y. Lopez, K. Kevill, M. E. Sunday, Gastrin-releasing peptide, immune responses, and lung disease. *Ann. N. Y. Acad. Sci.* **1144,** 136-147 (2008).
43. J. B. Furness, Types of neurons in the enteric nervous system. *J. Auton. Nerv. Syst.* **81,** 87-96 (2000).

44. D. J. Drucker, B. Yusta, Physiology and pharmacology of the enteroendocrine hormone glucagon-like peptide-2. *Annu. Rev. Physiol.* 76, 561-583 (2014).

45. S. Afroze *et al,* The physiological roles of secretin and its receptor. *Ann Transl Med.* **1,** 29 (2013).

46. D. Artis, H. Spits, The biology of innate lymphoid cells. *Nature.* **517,** 293-301 (2015).

47. A. Cianferoni, J. Spergel, The importance of TSLP in allergic disease and its role as a potential therapeutic target. *Expert Rev. Clin. Immunol.* **10,** 1463-1474 (2014).

48. S. A. G. Black, R. J. Rylett, Choline transporter CHT regulation and function in cholinergic neurons. *Cent. Nerv. Syst. Agents Med. Chem.* **12,** 114-121 (2012).

49. C. Legay, Why so many forms of acetylcholinesterase? *Microsc. Res. Tech.* **49,** 56-72 (2000).

50. O. A. Al-Shboul, The importance of interstitial cells of cajal in the gastrointestinal tract. *Saudi J. Gastroenterol.* **19,** 3-15 (2013).

51. P. J. Gomez-Pinilla *etal.* , Anol is a selective marker of interstitial cells of Cajal in the human and mouse gastrointestinal tract. *Am. J. Physiol. Gastrointest. Liver Physiol.* **296,** G1370-81 (2009).

52. P. Konig, D. Groneberg, R. Jager, A. Friebe, NO-sensitive guanylyl cyclase is expressed in pericytes but absent from endothelial cells in the murine lung. *BMC Pharmacol.* **11** (201 1), doi:10.1186/147 1-22 10-11-sl -p38.

53. D. Groneberg, P. Konig, D. Koesling, A. Friebe, Nitric oxide-sensitive guanylyl cyclase is dispensable for nitrergic signaling and gut motility in mouse intestinal smooth muscle. *Gastroenterology.* **140,** 1608-1617 (201 1).

54. C. S. Smillie *et al.* , Rewiring of the cellular and inter-cellular landscape of the human colon during ulcerative colitis. *bioRxiv* (2018), p. 455451.

55. W. G. Lima, G. H. Marques-Oliveira, T. M. da Silva, V. E. Chaves, Role of calcitonin gene-related peptide in energy metabolism. *Endocrine.* **58,** 3-13 (2017).

56. K. Loh, H. Herzog, Y.-C. Shi, Regulation of energy homeostasis by the NPY system. *Trends Endocrinol. Metab.* **26,** 125-135 (2015).

57. V. Athie-Morales, H. H. Smits, D. A. Cantrell, C. M. U. Hilkens, Sustained IL-12 signaling is required for Thl development. *J. Immunol.* **172,** 61-69 (2004).

58. D. Chang *et al.* , A meta-analysis of genome-wide association studies identifies 17 new

Parkinson's disease risk loci. *Nat. Genet.* **49,** 151 1-1516 (2017).

59. S. J. Sanders *et al,* Insights into Autism Spectrum Disorder Genomic Architecture and Biology from 71 Risk Loci. *Neuron.* 87, 1215-1233 (2015).
60. N. Bondurand, E. M. Southard-Smith, Mouse models of Hirschsprung disease and other developmental disorders of the enteric nervous system: Old and new players. *Dev. Biol.* **417,** 139-157 (2016).
61. P. Pla, L. Larue, Involvement of endothelin receptors in normal and pathological development of neural crest cells. *Int. J. Dev. Biol.* 47, 315-325 (2003).
62. J. Ischia, O. Patel, A. Shulkes, G. S. Baldwin, Gastrin-releasing peptide: different forms, different functions. *Biofactors.* 35, 69-75 (2009).
63. L. Tomas-Roca *et al,* De novo mutations in PLXND1 and REV3L cause Mobius syndrome. *Nat. Commun.* 6, 7199 (2015).
64. K. J. Gross, C. Pothoulakis, Role of neuropeptides in inflammatory bowel disease. *Inflamm. Bowel Dis.* **13,** 918-932 (2007).
65. F. R. Cagampang, K. D. Bruce, The role of the circadian clock system in nutrition and metabolism. *Br. J. Nutr.* **108,** 381-392 (2012).
66. T. Vatanen *et al,* Variation in Microbiome LPS Immunogenicity Contributes to Autoimmunity in Humans. *Cell.* **165,** 1551 (2016).
67. V. Gopalakrishnan, B. A. Helmink, C. N. Spencer, A. Reuben, J. A. Wargo, The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy. *Cancer Cell.* 33, 570-580 (2018).
68. A. Deczkowska, M. Schwartz, Targeting neuro-immune communication in neurodegeneration: Challenges and opportunities. *J. Exp. Med.* **215,** 2702-2704 (2018).
69. A. Mo *et al,* Epigenomic Signatures of Neuronal Diversity in the Mammalian Brain. *Neuron.* **86,** 1369-1384 (2015).
70. C. B. Wiese, N. Fleming, D. P. Buehler, E. M. Southard-Smith, A Uchll-Histone2BmCherry:GFP-gpi BAC transgene for imaging neuronal progenitors. *Genesis.* **51,** 852-861 (2013).
71. E. Drokhlyansky *et al,* The brain parenchyma has a type I interferon response that can limit virus spread. *Proc. Natl. Acad. Sci. U. S. A.* **114,** E95-E104 (2017).

72. T. Pietzsch, S. Preibisch, P. Tomancak, S. Saalfeld, ImgLib2—generic image processing in Java. *Bioinformatics.* **28,** 3009-301 1 (2012).

73. J. Schindelin *et al.*, Fiji: an open-source platform for biological-image analysis. *Nat. Methods.* **9,** 676-682 (2012).

74. J. Schindelin, C. T. Rueden, M. C. Hiner, K. W. Eliceiri, The ImageJ ecosystem: An open platform for biomedical image analysis .*Mol. Reprod. Dev.* **82,** 518-529 (2015).

75. C. A. Schneider, W. S. Rasband, K. W. Eliceiri, NIH Image to ImageJ: 25 years of image analysis. *Nat. Methods.* 9, 671-675 (2012).

76. M. Linkert *et al.*, Metadata matters: access to image data in the real world. *J. Cell Biol.* **189,** 777-782 (2010).

77. N. Habib *et al.*, Div-Seq: Single-nucleus RNA-Seq reveals dynamics of rare adult newborn neurons. *Science.* 353, 925-928 (2016).

78. N. Habib *et al.*, Massively parallel single-nucleus RNA-seq with DroNc-seq. *Nat. Methods.* **14,** 955-958 (2017).

79. K. Shekhar *et al.*, Comprehensive Classification of Retinal Bipolar Neurons by Single-Cell Transcriptomics. *Cell.* **166,** 1308-1323. e30 (2016).

80. B. Li, C. N. Dewey, RSEM: accurate transcript quantification from RNA-Seq data with or without a reference genome. *BMC Bioinformatics.* **12,** 323 (201 1).

81. A. L. Haber *et al.*, A single-cell survey of the small intestinal epithelium. *Nature.* **551,** 333—339 (2017).

82. A. Butler, P. Hoffman, P. Smibert, E. Papal exi, R. Satija, Integrating single-cell transcriptomic data across different conditions, technologies, and species. *Nat. Biotechnol.* **36,** 4 11 (2018).

83. A. Schuchardt, V. D'Agati, V. Pachnis, F. Costantini, Renal agenesis and hypodysplasia in ret-k- mutant mice result from defects in ureteric bud development. *Development.* **122,** 1919—1929 (1996).

84. J. Rossi *et al.*, Retarded growth and deficits in the enteric and parasympathetic nervous system in mice lacking GFR alpha2, a functional neurturin receptor. *Neuron.* **22,** 243-252 (1999).

85. S. J. Brookes, P. A. Steele, M. Costa, Identification and immunohistochemistry of cholinergic and non-cholinergic circular muscle motor neurons in the guinea-pig small intestine.

Neuroscience . **42,** 863-878 (1991).

86. S. J. Brookes, P. A. Steele, M. Costa, Calretinin immunoreactivity in cholinergic motor neurones, interneurones and vasomotor neurones in the guinea-pig small intestine. *Cell Tissue Res.* **263,** 471-481 (1991).
87. J. R. Grider, Neurotransmitters mediating the intestinal peristaltic reflex in the mouse. *J. Pharmacol. Exp. Ther.* **307,** 460-467 (2003).
88. Q. Sang, H. M. Young, Chemical coding of neurons in the myenteric plexus and external muscle of the small and large intestine of the mouse. *Cell Tissue Res.* **284,** 39-53 (1996).
89. H. M. Young, J. B. Furness, J. M. Povey, Analysis of connections between nitric oxide synthase neurons in the myenteric plexus of the guinea-pig small intestine. *J. Neurocytol.* **24,** 257-263 (1995).
90. J. B. Furness, The enteric nervous system and neurogastroenterology. *Nat. Rev. Gastroenterol. Hepatol.* **9,** 286-294 (2012).
91. J. R. Grider, Interplay of somatostatin, opioid, and GABA neurons in the regulation of the peristaltic reflex. *Am. J. Physiol.* **267,** G696-701 (1994).
92. J. B. Furness, M. Costa, A. Rokaeus, T. J. McDonald, B. Brooks, Galanin-immunoreactive neurons in the guinea-pig small intestine: their projections and relationships to other enteric neurons. *Cell Tissue Res.* **250,** 607-615 (1987).
93. R. Lasrado *et al.*, Lineage-dependent spatial and functional organization of the mammalian enteric nervous system. *Science.* 356, 722-726 (2017).
94. Y. Benjamini, Y. Hochberg, Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J. R. Stat. Soc. Series B Stat. Methodol.* 57, 289-300 (1995).
95. R. Lopez, J. Regier, M. B. Cole, M. I. Jordan, N. Yosef, Deep generative modeling for single-cell transcriptomics. *Nat. Methods.* **15,** 1053-1058 (2018).
96. J. A. Ramilowski *et al.*, A draft network of ligand-receptor-mediated multicellular signalling in human. *Nat. Commun.* 6, 7866 (2015).
97. R. Vento-Tormo *et al.*, Single-cell reconstruction of the early maternal-fetal interface in humans. *Nature.* **563,** 347-353 (2018).
98. N. Bondurand, E. M. Southard-Smith, Mouse models of Hirschsprung disease and other developmental disorders of the enteric nervous system: Old and new players. *Dev. Biol.* **417,**

139-157 (2016).

99. C. S. Smillie *et al* , Rewiring of the cellular and inter-cellular landscape of the human colon during ulcerative colitis (2018), , doi: 10.1 101/45545 1.

100. S. J. Sanders *et al,* Insights into Autism Spectrum Disorder Genomic Architecture and Biology from 7 1 Risk Loci. *Neuron.* 87, 1215-1233 (2015).

101. D. Chang *et al.*, A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. *Nat. Genet.* **49,** 151 1-1516 (2017).

102. T. Matsuoka *et al.*, Neural crest origins of the neck and shoulder. *Nature.* **436,** 347-355 (2005).

103. A. E. Lewis, H. N. Vasudevan, A. K. O'Neill, P. Soriano, J. O. Bush, The widely used Wntl-Cre transgene causes developmental phenotypes by ectopic activation of Wnt signaling. *Dev. Biol* **379,** 229-234 (2013).

Example 22 - A single-cell and single-nucleus RNA-seq toolbox for fresh and frozen human tumors

[00708] Single cell RNA-Seq (scRNA-Seq) has transformed the ability to analyze tumors, revealing cell types, states, genetic diversity, and interactions in the complex tumor ecosystem 1-6. However, successful scRNA-Seq requires dissociation tailored to the tumor type, and involves enzymatic digestion that can lead to loss of sensitive cells or changes in gene expression. Moreover, obtaining fresh tissue is time-sensitive and requires tight coordination between tissue acquisition and processing teams, posing a challenge in clinical settings. Conversely, single-nucleus RNA-Seq (snRNA-Seq) allows profiling of single nuclei isolated from frozen tissues, decoupling tissue acquisition from immediate sample processing. snRNA-Seq can also handle samples that cannot be successfully dissociated even when fresh, due to size or cell fragility 7,8, as well as multiplexed analysis of longitudinal samples from the same individual9. However, nuclei have lower amounts of mRNA compared to cells, and are more challenging to enrich or deplete. Both scRNA-Seq and snRNA-Seq pose experimental challenges when applied to different tumor types, due to distinct cellular composition and extracellular matrix (ECM) in different tumors.

[00709] To address these challenges, Applicants developed a systematic toolbox for fresh and frozen tumor processing using single cell (sc) and single nucleus (sn) RNA-Seq, respectively (Fig.

53A). Applicants tested eight tumor types with different tissue characteristics (Fig. 53B), including comparisons of matched fresh and frozen preparations from the same tumor specimen. The tumor types span different cell-of-origin (e.g., epithelial, neuronal), solid and non-solid, patient ages, and transitions (e.g., primary, metastatic, Fig. 53B).

[00710] Applicants evaluated and compared protocols based on (i) cell/nucleus quality; (ii) number of recovered vs. expected cells/nuclei; and (iii) cellular composition (Fig. 53A). For "cell/nucleus quality", Applicants considered both experimental and computational metrics. Experimentally, Applicants measured cell viability (for scRNA-Seq), the extent of doublets or aggregates in the cell/nucleus suspension, and cDNA quality recovered after Whole Transcriptome Amplification (Methods). Computationally, Applicants evaluated the overall number of sequencing reads in a library, the percent of reads mapping to the transcriptome, genome, and intergenic regions, the number of cells/nuclei exceeding a minimal number of genes and unique transcripts (reflected by Unique Molecular Identifiers; UMI), the number of reads, transcripts (UMIs), and genes detected per cell/nucleus, and the percent of UMIs from mitochondrial genes (Methods). For "number of recovered vs. expected cells/nuclei", Applicants considered the proportion of droplets scored as likely empty (i.e., containing only ambient RNA rather than the RNA from an encapsulated cell[10]), and the proportion of doublets[11] (Methods). Finally, for "cellular composition", Applicants considered the diversity of cell types captured, the proportion of cells/nuclei recovered from each subset, and the copy number aberration (CNA) pattern classes that are recovered in malignant cells (Methods). Applicants annotated the malignant cells based on the presence of CNAs (when detectable) and the cell type signature they most closely resembled (Methods). Applicants conducted most data analysis using scCloud, a Cloud based single-cell analysis pipeline[12] (https://github.com/klarman-cell-observatory/scCloud, Methods, Fig. 53A and 93).

[00711] For scRNA-seq, Applicants' toolbox encompasses successful protocols for five types of fresh tumors: non-small cell lung carcinoma (NSCLC), metastatic breast cancer (MBC), ovarian cancer, glioblastoma (GBM), and neuroblastoma, as well as a cryopreserved non-solid, chronic lymphocytic leukemia (CLL) (Figs. 53B, 55). Applicants constructed workflows that minimize the time interval between removal of the sample from the patient in a clinical setting and its dissociation into cells, to maximize cell viability and preservation of RNA profiles. Applicants

determined dissociation conditions for each of the tumor types and constructed specific steps as a decision tree to adjust for differences between types of clinical samples (e.g., size, presence of red blood cells) (Fig. 53C, Methods). To choose the best performing dissociation method, Applicants apportioned large tumor specimens into smaller pieces (-0.5-2 cm), dissociating each piece with a different protocol.

[00712] Applicants selected enzymatic mixtures for processing fresh tissues based on the specific characteristics of each tumor type, such as cell type composition and ECM components, and ultimately recommend the method that sufficiently breaks down the ECM and cell-to-cell adhesions, while minimizing processing time and supporting the cell type diversity in the sample. For example, to break down collagen fibers in breast cancer[13,14], Applicants used Liberase™ (Methods), whereas to break down ECM in GBM15 Applicants used papain (cysteine protease). Applicants also included DNase I to digest DNA released from dead cells to decrease viscosity in all dissociation mixtures. Applicants subjected the samples that yielded high quality single cell suspensions to droplet-based scRNA-Seq (Methods).

[00713] As an example of the optimization process, consider NSCLC (sample NSCLC14, Figs. 55-57) where Applicants used three processing protocols: (1) Collagenase 4 [NSCLC-C4]; (2) a mixture of Pronase, Dispase, Elastase, and Collagenases A and 4 [PDEC]; or (3) Liberase™ and Elastase [LE]; each in combination with DNase I and elastase, to break down the elastin fibers found in lung tissue[16,17] (Methods) (Figs. 53D-53G; 56, 57). For the other tumor types, Applicants show the application of the recommended protocol out of those tested (Figs. 53H-53L; 55).

[00714] Protocols often performed similarly on standard quality control measures (e.g., number of cells recovered), but differed markedly in cellular diversity or in the fraction of droplets predicted to contain only ambient RNA ("empty drops") — two evaluation criteria that Applicants prioritized. For example, in the NSCLC resection sample above, all methods yielded a similar number of cells with high-quality expression profiles and similar CNA patterns in malignant cells (Fig. 53D-53G, 56A-56L). However, only the PDEC and LE protocols recovered stromal and endothelial cells (Fig. 53F; 56G), and C4 had a lOO-fold higher fraction of drops called as "empty" (7% vs. 0.08% and 0.04% in PDEC and LE, respectively, 56A). The drops designated "empty" in C4 clustered within macrophages (Figs. 53E; 56E, 56G-56I), the most prevalent cell type, suggesting that these cell barcodes either had lower sequencing saturation or that the sample itself

had higher ambient RNA content. While Applicants estimated similarly low levels of ambient RNA18 across the three protocols (Fig. 56M-560), NCSLC-C4 indeed had lower sequencing saturation and lower reads per cell (Fig. 56A, 56C). Ultimately, taking all of these features into consideration, Applicants recommend the PDEC protocol for processing NSCLC tumor samples.

[00715] Comparing QC metrics across protocols can be challenging due to differences in cell type recovery and in sequencing depth between preparations, which Applicants controlled for by also evaluating QC metrics within each cell type and down-sampling by total reads across protocols (Figs. 56D and 57). For example, overall, for the NSCLC sample, C4 had a significantly higher median number of detected genes (P=l.3*l0-90 vs. PDEC; 1.4*10-62 vs. LE, Mann-Whitney U test), but within B cells, PDEC had a significantly higher number of genes (P=2*l0-15 vs. C4; 2*10-10 vs. LE), whereas within epithelial cells, LE had the highest number (P=5*l0-6 vs. C4; 2*10-4 vs. PDEC) (Figs. 53D; 56D). Because cell type proportions may vary between protocols, and the number of detected genes (and other metrics) varies between cell types, it is important also to assess cell-type specific QCs when choosing a protocol. Down-sampling by total reads did not qualitatively change any of the protocol evaluation metrics (Fig. 57).

[00716] Because in some tumor specimens the proportion of malignant cells is relatively low, Applicants further optimized an immune-cell depletion strategy (Methods). Depletion of CD45+ expressing cells circumvents the need for enriching with specific surface markers (e.g., EpCAM), which might otherwise bias the selection of specific cell populations, such as loss of representation of malignant cells undergoing EMT. Depletion applied to another NSCLC tumor sample (NSCLC17) increased the proportion of malignant epithelial cells from 26% in non-depleted scRNA-seq to 82% (Figs. 53F; 58), and from 1.2% (by FACS) to 29.5% when applied to an ovarian ascites sample (Fig. 53H, sample 727; Fig. 59).

[00717] Applicants also successfully applied the scRNA-Seq toolbox to much smaller core biopsy clinical samples. For example, in MBC, we applied the LD (Liberase™ and DNase I) protocol to a resection (HTAPP-254) and a biopsy (HTAPP-735) from lymph node metastases from two patients, yielding similarly successful QCs (Figs. 53H-53L; 61, 61). The resection and biopsy of the two patients had, however, different cellular compositions (Fig. 53H): a higher proportion of epithelial, endothelial, and fibroblast cells and a lower proportion of T cells in the biopsy compared to the resection. Applicants similarly successfully profiled biopsies of MBC liver

metastases (HTAPP-285, HTAPP-963) with the same protocol (Fig. 53H-53L; 62; 63Fig. 53H). Thus, this protocol can be used across breast cancer metastases from different anatomical metastatic sites.

[00718] The scRNA-Seq toolbox performs well on samples obtained post-treatment, which can be challenging as a result of cell death and changes in cell type composition with treatment. Applicants demonstrate this in profiling a pre-treatment diagnostic biopsy and post-treatment resection from the same neuroblastoma patient using the NB-C4 protocol (Fig. 53H-53L, HTAPP-3l2-pre, HTAPP-3 l2-post; Figs. 64, 65). More cells but of fewer cell types were recovered in the pre-treatment biopsy (4,369 cells: neuroendocrine, T cells, and macrophages) than the post-treatment resection (786 cells: neuroendocrine, T cells, macrophages, as well as endothelial cells, and fibroblasts), consistent with observed post-treatment fibrosis. Applicants tested an additional dissociation protocol in a neuroblastoma orthotopic patient-derived xenograft (O-PDX) sample (O-PDXl) [19,20], which is not expected to include non-malignant human cells, and indeed resulted in high quality malignant cell profiles (Fig. 66).

[00719] In addition to NSCLC, MBC, ovarian cancer ascites, and neuroblastoma samples (Fig. 53H-53L; Figs. 56-67), Applicants established effective scRNA-Seq protocols for GBM, ovarian cancer, and CLL (Figs. 53H-53L; 68-70). In particular, in CLL, Applicants successfully recovered the expected cell types from a cryopreserved sample, containing viable cells. This reflects the increased resilience of immune cells to freezing compared to other cell types, also observed in other settings[21], and the lack of a dissociation step in CLL scRNA-Seq (Methods). Cryopreservation, however, can increase the proportion of damaged cells[22] and may not successfully recover all the malignant and other non-malignant cells in the tumor.

[00720] Thus, for frozen specimens from solid tumors, Applicants optimized snRNA-Seq, focusing on different methods for nucleus isolation (Fig. 54A) across seven tumor types: MBC, neuroblastoma, ovarian cancer, pediatric sarcoma, melanoma, pediatric high-grade glioma, and CLL (Figs. 53B; 55). Applicants initially divided larger samples or used multiple biopsies to compare four isolation methods (EZPrep[8], Nonidet™ P40 with salts and Tris (NST) [modified from Gao, R., et al [23]], CHAPS, with salts and Tris (CST), and Tween with salts and Tris (TST), which differ primarily in the mechanical force (e.g., chopping or douncing), buffer, and/or detergent composition (Fig. 54A, Methods). Because in early tests EZPrep routinely

underperformed CST, NST, and TST (data not shown), Applicants only included it in initial comparisons (below). To evaluate protocols, Applicants used the post-hoc computational criteria above, except Applicants excluded the estimation of empty drops, because it was only developed and tested on single-cell RNA-seq data. Applicants further customized scCloud for snRNA-Seq data, mapping reads to both exons and introns, and adapted the QC thresholds for transcript (UMI) and gene counts to reflect the lower expected mRNA content in nuclei (Methods). Experimentally, Applicants added in-process light microscopy QCs to ensure complete nuclei isolation, and to estimate doublets, aggregates, and debris (Fig. 54A, Methods, Fig. 93).

[00721] Overall, three nucleus isolation methods — TST, CST, and NST — had comparable performance based on the assessed nucleus quality (Fig. 54B-54H), with TST typically yielding the greatest cell type diversity and number of nuclei per cell type, together with highest expression of mitochondrial genes, and NST typically having the fewest genes per nucleus and lowest diversity of types. For example, in neuroblastoma, testing each of the four protocols on a single resection sample (HTAPP-244) (Figs. 54B-54D; 71) yielded a similar number of high-quality nuclei (7,896, 6,157, 7,531, and 7,415 for EZ, CST, NST, and TST, respectively), malignant cells with similarly detectable CNAs, and the expected cell types — with malignant neuroendocrine cells being the most prevalent (Fig. 54C; 71D; 71F-71M). However, nuclei prepared with the EZ protocol had lower numbers of EMIs and genes detected (Fig. 54B), while TST recovered more endothelial cells, fibroblasts, neural crest cells, and T cells than the other protocols (Fig. 54C). TST yielded a higher expression of mitochondrial genes (Fig. 54B), in this and all other tumors tested (Fig. 54H), since the nuclear membrane, ER, and ribosomes remain attached to the nucleus when using this method (unpublished results). The same trends were preserved when down-sampling by the total number of sequencing reads (Fig. 72), as well as for cell-type specific QCs (Fig. 71D).

[00722] The CST, NST, and TST nucleus isolation methods had similar performance characteristics when tested with MBC, ovarian cancer, and pediatric sarcoma samples, with TST again providing the most diversity in cell types, especially in non-malignant cells. In MBC, Applicants compared CST and NST in one metastatic brain resection (HTAPP-394), and CST and TST in another metastatic brain resection (HTAPP-589) and in a metastatic liver biopsy (HTAPP-963) (Fig. 54E-54H; 73-75). In all cases, QC statistics (Figs. 54F-54H; 73; 74; 75A-75D) and CNA

patterns (Figs. 73; 74; 75G-75H) were similar between protocols, and nuclei from epithelial cells were the most prevalent (Fig. 54E). CST and NST captured a very similar distribution of cell types, while TST captured more non-malignant cells, including T cells (Fig. 54E) and a higher fraction of mitochondrial reads (Fig. 54H). In ovarian cancer, CST, NST, and TST recovered similar CNA patterns from the same sample (HTAPP-316, Fig. 76), but NST recovered fewer cells, genes per cell, and EIMIs per cell (Fig. 54E-54G), and had a lower cell type diversity, despite having greater overall sequencing depth, whereas TST captured the greatest cell type diversity (Figs. 54E; 76A). In a rhabdomyosarcoma sample (HTAPP-951), CST and TST captured the same cell types at similar proportions (Fig. 54E) and showed similar CNA patterns (Fig. 77).

[00723] Overall, Applicants recommend the TST protocol for most tumor types, and CST for tumors from neuronal tissues, such as pediatric high-grade glioma (Figs. 55; 78). With the recommended protocols (Fig. 53B, right column), Applicants profiled additional neuroblastoma tumors as well as Ewing sarcoma, melanoma, pediatric high-grade glioma, and CLL tumor samples — spanning biopsies, resections, and treated samples (Figs. 53B; 54E-54H; 78-84). Applicants also tested a pediatric rhabdomyosarcoma sample (HTAPP-951) by two different chemistries for droplet based snRNA-Seq (v2 vs. v3 from lOx Genomics, Methods), obtaining overall similar results in terms of cell types detected, an improved number of recovered vs. expected nuclei and higher complexity per nucleus in v3 (Fig. 85).

[00724] Finally, when Applicants compared scRNA-Seq and snRNA-Seq by testing matching samples from the same specimen each in CLL, MBC, neuroblastoma, and O-PDX (Figs. 54I-54J; 86-89), the methods typically recovered similar cell types with similar transcriptional profiles, but sometimes at varying proportions. In both neuroblastoma and MBC, immune cells were more prevalent in scRNA-Seq, and parenchymal (especially malignant) cells were more prevalent in snRNA-Seq (Figs. 87; 88). Cell and nucleus profiles were comparable based on grouping together when using batch correction by canonical correlation analysis (CCA)24 (Methods) (Figs. 54J; 86-89).

[00725] In conclusion, Applicants developed a toolbox for processing fresh and frozen clinical tumor samples by single cell and single nucleus RNA-Seq, and demonstrated it across eight tumor types. For fresh tissues, Applicants recommend testing 2-3 dissociation methods based on the tumor type, the tissue composition and the decision tree (Fig. 53C), and choose to apply the best

performing protocol by assessing both experimental and computational QC metrics, and, if desired, adding a depletion step. For frozen tissues, Applicants recommend testing the NST, TST, and CST protocols (Fig. 54A). While TST is often favorable due to its superior ability to capture the most diverse set of cells, in some tumors Applicants recommend CST or NST (e.g., CST for pediatric high-grade glioma, Fig. 55). CST also yields fewer mitochondrial reads, reducing sequencing cost. When possible, Applicants recommend testing both scRNA-Seq and snRNA-Seq for the same tumor type, as the two approaches differ in the distribution of cell types detected. Processing frozen samples by snRNA-Seq allows studying many rare, unusual, and longitudinal banked tumor samples. Our toolbox will help researchers systematically profile additional human tumors, leading to a better understanding of tumor biology and ultimately to an era of precision medicine.

Example 23 - Experimental Methods for single-cell and single-nucleus RNA-seq toolbox for fresh and frozen human tumors

[00726] ***Human Patient Samples.*** All work performed for this study was approved by either the Dana-Farber Cancer Institute Institutional Review Board (IRB) [Lung cancer (IRB protocol 98-063), metastatic breast cancer (IRB protocol 05-246), neuroblastoma (IRB protocols 11-104 and 17-104), ovarian cancer (IRB protocol 02-051), melanoma (IRB protocol 11-104), sarcoma (IRB protocol 17-104), GBM(IRB protocol 10-417), and chronic lymphocytic leukemia (IRB protocol 99-224), with secondary use protocol 14-238] or by the St. Jude Children's Research Hospital IRB [pediatric high-grade glioma (IRB protocol 97BANK), neuroblastoma (IRB protocol TBANK [protocol for collecting, banking and distributing human tissue samples: St. Jude Children's Research Hospital Biorepository] for the human samples and MAST [Molecular analysis of solid tumors] for creating O-PDX sample)], and patients were properly consented.

[00727] **Collection of Fresh Tissue for scRNA-Seq.** Collection of fresh solid tumor tissue for lung cancer, ovarian cancer and metastatic breast cancer at BWH/DFCI, was performed following protocols established to reduce the time elapsed between removal of the tumor tissue from the body, placement of the specimen in media, and processing for scRNA-Seq. To this end, Applicants established procedures between the hospital team (surgeon/clinical research coordinator (CRC)/clinical pathologist), the coordinating team (project managers/ pathology technician) and the processing team (staff scientists/research technicians) prior to procedure day. This included

providing the hospital team with collection containers with appropriate media, and pre-defming allocation priorities to ensure quick handling by the pathology technician of the sample received. On the day of the procedure, timely communication between the teams ensured quick specimen transfer from the hospital team to the research team, timely transport to the Broad for processing, and immediate loading of the single cell suspension into the lOx Genomics Single-Cell Chromium Controller (below).

[00728] In all cases, the tissue received from the hospital team was examined by the research pathology technician and following procurement of a specimen for anatomic pathology review, the highest quality portion (or core) was allocated for scRNA-Seq, placed in media and transported to the Broad institute for dissociation following the appropriate protocol (below). Tissue quality is assessed based on visual examination and rapid pathology interpretation at the time of collection, and determined based on tumor content, necrosis, calcification, fat, and hemorrhage.

[00729] For ovarian cancer ascites, approximately -300 mL were usually received from the hospital team within 1 hour after taken out of the body, which contained a vast majority of non-malignant (mainly immune) cells. Hence, all ascites samples were subjected to CD45+ cell depletion (below) to enrich for malignant cells.

[00730] For CLL, samples were generated from peripheral blood mononuclear cells isolated using density centrifugation (Ficoll-Paque) and stored in freezing media (FBS +10% DMSO) in liquid nitrogen until processing.

[00731] For orthotopic PDX of neuroblastoma samples (O-PDX), Foxnl-/- nude mice (Charles River Laboratories) were orthotopically injected via ultrasound-guided para-adrenal injection with cells derived from a patient MYCN-amplified neuroblastoma (available as sample SJNBL046_X 1 through the Childhood Solid Tumor Network [19,20]. A portion of O-PDX tumor was flash-frozen for future single-nucleus RNA-Seq, while the remainder underwent dissociation as described below.

[00732] **Preservation of Tissue for snRNA-Seq.** For those samples that were prospectively collected by Applicants for snRNA-seq (Neuroblastoma HTAP), freezing of tumor samples was performed as quickly as possible after sample collection using standard biobanking technique and the dates when samples were frozen were recorded. (Other samples were obtained from tissue banks with limited record on how they were frozen, which is a typical scenario.) Samples were placed in cryo-tubes without any liquid. Complete removal of liquid from the sample was

accomplished by gently wiping it (not patting, as this would damage the tissue) on the side of the container, before placing in the cryotube. The tubes were then covered in dry-ice and transferred to -80°C for long term storage.

[00733] The other frozen samples from snRNA-Seq were obtained from tissue banks as follows: Ovarian OCT-frozen archival samples were obtained from the Dana-Farber Cancer Institute Gynecology Oncology Tissue Bank; sarcoma snap-frozen samples were obtained from the Boston Children's Hospital Tissue Bank; pediatric snap-frozen glioma samples were obtained from the St. Jude Children's Research Hospital Biorepository; neuroblastoma snap-frozen samples were obtained from the St. Jude Children's Research Hospital Biorepository and the Boston Children's Hospital Precision Link Biobank for Health Discovery; metastatic breast cancer OCT-frozen samples were obtained from the Center for Cancer Precision Medicine Bank; snap-frozen melanoma samples were obtained through the laboratory of Dr. Charles Yoon at BWH.

Example 24 - Dissociation Workflow from Fresh Solid Tumor Samples

[00734] ***MBC, NSCLC (protocols PDEC and LE), ovarian cancer solid tumor, and neuroblastoma workflows.*** Fresh tissue dissociation of MBC, NSCLC (protocols PDEC and LE), ovarian cancer solid tumor, and neuroblastoma were performed using a similar workflow (Fig. 53C), with different components of the dissociation mixture for each tumor type, as described in the next section.

[00735] Samples were transferred from interventional radiology (biopsies) or the operating room (resections) in DMEM (MBC), RPMI (NSCLC), or RPMI with HEPES (ovarian cancer and neuroblastoma) medium. Upon arrival to the laboratory, the sample was washed in cold PBS and transferred into either a 2 mL Eppendorf tube containing dissociation mixture (for biopsies) or a 5 mL Eppendorf tube containing 3 mL dissociation mixture (for resections). Next, the sample was minced in the Eppendorf tube using spring scissors (Fine Science Tools, catalog no. 15514-12) into fragments under ~0.4 mm, and incubated at 37°C, while rotating at approximately 14 RPM, for 10 minutes. After 10 minutes, the sample was pipetted 20 times with a 1 mL pipette tip at room temperature, and placed back into incubation with rotation for an additional 10 minutes. The sample was pipetted again 20 times using a 1 mL pipette tip, and transferred to 1.7 mL Eppendorf tube and centrifuged at 300g for 4 minutes at 4°C. The supernatant was removed and the pellet

was resuspended in 200-500 pL of ACK red blood cell lysis buffer (Thermo Fisher Scientific, A1049201). The ACK volume added depended on the size of the pellet; while pellet size is hard to quantify Applicants suggest adding about 100 pL ACK lysis buffer per 100,000 cells, with a minimum volume of 200 pL. The sample was incubated in ACK red blood cell lysis buffer for 1 minute on ice, followed by the addition of cold PBS at twice the volume of the ACK. The cells were pelleted by a short centrifugation for 8 seconds at 4°C using the short spin setting with centrifugal force ramping up to, but not exceeding, 11,000 g. The supernatant was removed. The pellet color was assessed, if RBCs remained (pellet color pink or red), the ACK step was repeated up to two additional times. To remove cell clumps, the pellet was resuspended in 100 pL of TrypLE (Life Technologies, catalog no. 12604013) and incubated while constantly pipetting at room temperature for 1 minute with a 200 pL pipette tip. TrypLE was inactivated by adding 200 pL of cold RPMI 1640 with 10% FBS. The cells were pelleted using short centrifugation as described above. The pellet was resuspended in 50 pL of 0.4% BSA (Ambion, catalog no. AM2616) in PBS. To assess the single cell suspension, viability, and cell count, 5 pL of Trypan blue (Thermo Fisher Scientific, catalog no. T10282) was mixed with 5 pL of the sample and loaded on INCYTO C-Chip Disposable Hemocytometer, Neubauer Improved (VWR, catalog no. 82030-468). The cell concentration was adjusted if necessary to a range of 200-2,000 cells/pL. A total of 8,000 cells were loaded into each channel of the lOx Genomics Single-Cell Chromium Controller. Due to differences between clinical samples, some steps may need to be repeated or adjusted; for a general overview of guidelines see Fig. 53C.

[00736] ***NSCLC-C4 protocol workflow.*** A similar workflow was used for protocol NSCLC-C4 with the following modifications: Following mechanical chopping as above, sample was dissociated for 15 minutes in a 15 mL falcon tube, with gentle vortex every 5 minutes, followed by filtration through a 70 pm filter, and washed with 20 mL of ice cold PBS and centrifuged at 580 g for 5 minutes. RBS lysis was performed similarly to the above workflow by resuspending the pellet in 1 mL ACK lysis buffer with incubation on ice for 1 minute. 20 mL of ice cold PBS were added to quench the ACK lysis buffer, followed by filtration through a 70 pm filter, and centrifugation at 580 g for 5 minutes. The sample was then cleaned using Viahance™ dead-cell removal kit (BioPAL, catalog no. CP-50VQ02) according to manufacturer's instructions. Cells

were then re-suspended in M199 and loaded on the lOx Genomics Single-Cell Chromium Controller as described above.

[00737] ***GBM workflow.*** All steps were done on ice. Sample was minced thoroughly in Petri dish, thereafter, 4mL HBSS were added (Life Technologies, catalog number 14175095), transferred to 15 mL tubes and centrifuged at 1000 rpm for 2 minutes. After centrifugation, supernatant was removed, pre-heated Buffer X was added, and the sample was incubated while shaking at 37°C for 15 minutes. Sample was pipetted up-down 20 times, incubated at 37°C for an additional 15 minutes, and pipetted again. After dissociation, the sample was filtered through a 100 pm cell strainer (Fisher Scientific, Cat # 22-363-547) into 50 mL tube. Applicants recommend keeping any tissue fragments left in the cell strainer, as they can be reprocessed with the same protocol if initial cell recovery is low. Filtrate was centrifuged at 1000 rpm for 3 minutes, and the supernatant was removed. If the pellet was bloody, RBC removal was performed when needed using LYMPHOLYTE H (CedarLAne, Cat.# CL5015) or Red Blood Cell (RBC) Lysis Solution (lOx) (Miltenyi Biotech, Cat# 130-094-183). The pellet was washed with 10 mL of cold PBS/l% BSA, transferred to 15 mL tube and centrifuged at 1200 rpm for 3 minutes. Supernatant was removed and the pellet was resuspended in 0.4 BSA in PBS. Single cell suspension was visualized, counted and loaded on the lOx Genomics Single-Cell Chromium Controller as described above.

[00738] ***Dissociation mixtures for different tumor types.*** Dissociation mixtures were prepared approximately 5-10 minutes before sample processing from frozen aliquoted stocks, as follows:

[00739] ***MBC, LD Protocol.*** 950 pl of RPMI 1640 (Thermo Fisher Scientific, catalog no. 11875093), 10 pL of 10 mg/mL DNAse I (Sigma Aldrich, catalog no. 11284932001) to a final concentration of 100 pg/mL, and 40 pL of 2.5 mg/mL Liberase™.

[00740] ***Ovarian cancer resection.*** Dissociation mixture was based on Miltenyi Human Tumor Dissociation Kit (Miltenyi Biotec, catalog no. 130-095-929). Before starting, Enzymes H, R, and A were resuspended according to manufacturer's instructions. Dissociation mix containing 2.2 mL RPMI, 100 pL enzyme H, 50 pL enzyme R, and 12.5 enzyme A, was prepared immediately before use.

[00741] ***Neuroblastoma, NB-C4 protocol.*** Medium 199, Hanks Balanced Salts Buffer (Thermo Fisher Scientific) with 100 pg/mL of DNAse I (Millipore Sigma, catalog no. 11284932001), 100 pg/mL Collagenase IV (Worthington; catalog no. LS004186).

[00742] ***Orthotopic PDX neuroblastoma.*** Worthington Papain Dissociation System (catalog no. LK003150). Dissociation was performed according to manufacturer's instructions, with deviation of the dissociation duration, which was shortened to 15 minutes.

[00743] ***NSCLC, PDEC protocol.*** 2692 HBSS (Thermo Fisher Scientific, catalog no. 141701 12), 187.5 µL of 20 mg/mL pronase (Sigma Aldrich, catalog no. 10165921001) to a final concentration of 1,250 pg/mL, 27.6 pL of 1 mg/mL elastase (Thermo Fisher Scientific, catalog no. NC9301601) to a final concentration of 9.2 pg/mL, 30 pL of 10 mg/mL DNase I (Sigma Aldrich, catalog no. 11284932001) to a final concentration of 100 pg/mL, 30 pL of 10 mg/mL Dispase (Sigma Aldrich, catalog no. 4942078001) to a final concentration of 100 pg/mL, 30 pL of 150 mg/mL Collagenase A (Sigma Aldrich, catalog no. 10103578001) to a final concentration of 1,500 pg/mL, 3 pL of 100 pg/mL collagenase IV (Thermo Fisher Scientific, catalog no. NC9836075) to a final concentration of 1250 pg/mL.

[00744] ***NSCLC, LE protocol.*** 5 mL RPMI 1640 (Thermo Fisher Scientific, catalog no. 11875093), 200 pL of 2.5 mg/mL Liberase™ (Millipore Sigma, 5401 119001) to a final concentration of 100 pg/mL, 50 pL of 10 mg/mL DNase I (Sigma Aldrich, catalog no. 11284932001) to a final concentration of 100 pg/mL, 27.6 pL of 1 mg/mL elastase (Thermo Fisher Scientific, catalog number NC9301601) to a final concentration of 9.2 pg/mL.

[00745] ***NSCLC, C4 protocol.*** 5 mL M199 with DNase 1 (final concentration of 10 pg/mL) and Collagenase iv (final concentration of 100 pg/mL).

[00746] GBM. Brain Tumor Dissociation Kit (P) (Miltenyi Biotech. Catalog number 130-095-942). 4 mL Buffer X , 40 pL Buffer Y, 50 p Enzyme N, 20 p Enzyme A.

Processing of non-solid tumor samples for scRNA-Seq

[00747] CLL. Frozen (cryopreserved) cells were thawed in 10 mL RPMI, pelleted and washed with an additional 10 mL RPMI. Live cells were sorted using the MoFlo Astrios EQ Cell Sorter, and 8,000 cells were loaded on one channel of the lOx Genomics Single-Cell Chromium Controller. Remaining cells were pelleted by short centrifugation, the supernatant was discarded and the pellet was frozen on dry ice and stored in -80°C.

[00748] *Ovarian cancer ascites.* Ascites samples without spheres were selected and delivered in six 50 mL conical tubes, for a total of 300 mL of fluid. Tubes were spun down at 580xg for 5 minutes in a 4°C pre-cooled centrifuge and supernatants was aspirated.

[00749] Pellets were resuspended in 5 mL cold ACK Lysing Buffer, and combined from all tubes at this step. ACK lysis was done on ice for 3 minutes, and quenched by adding 10 mL of cold PBS, followed by centrifugation at 580xg for 5 minutes at 4°C. The pellet color was assessed and if it was pink or red, revealing a significant portion of erythrocytes, ACK treatment steps were repeated as needed at most two additional times. Post ACK treatment, the pellet was resuspended in 20 mL cold PBS, filtered through a 70 pm cell strainer into a 50 mL conical tube, and the filter was washed with additional 20 mL cold PBS to recover as many cells as possible. The sample was then centrifuged at 580xg for 5 minutes at 4°C. To reduce the fraction of immune cells in the sample, CD45+ cell depletion was performed using the MACS CD45 depletion protocol described below.

[00750] ***Depletion of CD45+ cellsfor scRNA-Seq.*** Depletion of CD45+ cells in ovarian cancer ascites samples and NSCLC was performed using CD45 MicroBeads (Miltenyi Biotec, catalog no. 130-045-801) according to the manufacturer's protocol. Briefly, following dissociation of ascites or NSCLC samples, cells were counted. The single-cell suspension was centrifuged at 500g for 4 minutes at 4°C. The supernatant was removed and the pellet was resuspended in 80 pL of MACS buffer (PBS supplemented with 0.5% BSA, and 2mM EDTA) per 106 cells. 20 pL of the MACS CD45 microbeads were added to the cell suspension per 10 million cells. The cells incubated on ice for 15 minutes. During the incubation, the LS column was prepared by attaching the column to a MidiMACS separator and rinsing the column with 3 mL MACS buffer. Following the incubation, the cells and bead conjugate was washed with 900 pL MACS buffer per 10 million cells. The cells were centrifuged at 500g for 4 minutes at 4°C. The supernatant was removed and the pellet was resuspended in 500 pL MACS buffer. The cell suspension was transferred to the LS column and the effluent was collected (CD45- fraction). The column was washed three times with 3 mL MACS buffer. The CD45- fraction was centrifuged at 500g for 4 minutes at 4°C. In ascites samples, bead attachment and column separation can be repeated to increase the number of tumor and stromal cells relative to immune cells. The pellet was resuspended in 50 pL of 0.4% BSA (Ambion, catalog no. AM2616) in PBS. Cells were counted by mixing 5 pL of Trypan blue (Thermo Fisher Scientific, catalog no. T10282) with 5 pL of the sample and loaded on INCYTO C-Chip Disposable Hemocytometer, Neubauer Improved (VWR, catalog no. 82030-468). The cell

concentration was adjusted if necessary to a range of 200-2,000 cells/pL. 8,000 cells were loaded into each channel of the lOx Genomics Single-Cell Chromium Controller.

[00751] ***S T based buffers for snRNA-seq.*** 2X stock of salt-Tris solution (ST buffer) containing 146 mMNaCl (Thermo Fisher Scientific, catalog no. AM9759), 10 mM Tris-HCl pH 7.5 (Thermo Fisher Scientific, catalog no. 15567027), 1 mM CaCl2 (Vwr, catalog no. 97062-820), and 2 1 mM MgCl2 (Sigma-Aldrich, catalog no. M1028) was made and used to prepare three buffers. For CST: 1 mL of 2X ST buffer, 980 µL of 1% CHAPS (Millipore), 10 µï of 2% BSA (New England BioLabs), and 10 pL of nuclease-free water. For TST: 1 mL of 2X ST buffer, 60 pL of 1% Tween-20 (Sigma-aldrich, catalog no. P-7949), 10 pL of 2% BSA (New England Biolabs, catalog no. B9000S), and 930 pL of nuclease-free water. For NST: 1 mL of 2X ST buffer, 40 pL of 10% Nonidet™ P40 Substitute (Fisher Scientific), 10 pL of 2% BSA (NEB), and 950 pL of nuclease-free water. lx ST buffer was prepared by dilution 2x ST with ultra-pure water (Thermo Fisher Scientific catalog no. 10977023) in a ratio of 1:1.

[00752] ***Nucleus isolation from frozen samples for snRNA-seq.*** On dry ice, tissue was split and subjected to one of three salt-Tris (ST)-based nucleus isolation protocols (ED, NVW, CS, ORR and AR; unpublished results) and the EZ nuclei isolation buffer8, as detailed below.

[00753] ***Nucleus isolation workflow for ST-based buffers.*** On ice, a piece of frozen tumor tissue was placed into a well of a 6-well plate (Stem cell Technologies, catalog no. 38015) with 1 mL of either CST, TST, or NST buffer. For samples frozen in OCT, an additional step of removing the surrounding OCT, and washing any residual OCT from the sample with PBS was performed in a 10 cm Petri dish. Tissue was then chopped using Noyes Spring Scissors (Fine Science Tools, catalog no. 15514-12) for 10 minutes on ice. For cell pellets, such as for CLL frozen cells, sample was pipetted in the buffer on ice, instead of chopping. The homogenized solution was then filtered through a 40 pm Falcon™ cell strainer (Thermo Fisher Scientific, catalog no. 08-771-2). An additional 1 mL of the detergent buffer solution was used to wash the well and filter. The volume was brought up to 5 mL with 3 mL of IX ST buffer. The sample was then transferred to a 15 mL conical tube and centrifuged at 4°C for 5 minutes at 500g in a swinging bucket centrifuge. The pellet was resuspended in IX ST buffer. Resuspension volume was dependent on the size of the pellet, usually within the range of 100-200 pL. The nucleus solution was then filtered through a 35 pm Falcon™ cell strainer (Corning, catalog no. 352235). Nuclei were counted using C-chip

disposable hemocytometer (VWR International Ltd, catalog no. 22-600-100). 10,000 or 8,000 nuclei (V2 or V3 lOx genomics, receptively) of the single-nucleus suspension were loaded onto the Chromium Chips for the Chromium Single Cell 3' Library (V2, PN-120233; V3 PN-1000075) according to the manufacturer's recommendations (lOx Genomics).

[00754] ***Nucleus isolation workflow using EZ lysis buffer.*** Nucleus isolation was done as previously described8. Briefly, tissue samples were cut into pieces <0.5 cm and homogenized using a glass dounce tissue grinder (Sigma, Catalog no. D8938). The tissue was homogenized 25 times with pestle A and 25 times with pestle B in 2 mL of ice-cold nuclei EZ lysis buffer. The sample was then incubated on ice for 5 minutes, with an additional 3 mL of cold EZ lysis buffer. Nuclei were centrifuged at 500g for 5 minutes at 4°C, washed with 5 mL ice-cold EZ lysis buffer and incubated on ice for 5 minutes. After centrifugation, the nucleus pellet was washed with 5 mL Nuclei Suspension Buffer (NSB; consisting of lx PBS, 0.01% BSA and 0.1% RNAse inhibitor (Clontech, Catalog no. 2313A)). Isolated nuclei were resuspended in 2 mL NSB, filtered through a 35 pm cell strainer (Corning- Falcon, Catalog no. 352235) and counted. A final concentration of 1,000 nuclei/pL was used for loading on lOx v2 channel.

[00755] ***Droplet-based sc/snRNA-seq.*** An input of 8,000 single cells or 10,000 single nuclei (8,000 for v3 lOx technology) were loaded into each channel of the Chromium single cell 3' Chip. Single cells/nuclei were partitioned into droplets with Gel Beads in the Chromium. After emulsions were formed, barcoded reverse transcription of RNA took place. This was followed by cDNA amplification, fragmentation and adaptor and sample index attachment, all according to the manufacturer's recommendations. Libraries from four lOx channels were pooled together and sequenced on one lane of an Illumina HiSeqX with paired end reads, Read 1: 26 nt, Read 2 : 55 nt, Index 1: 8 nt, Index 2 : 0 nt.

Computational Methods

[00756] *scRNA-seq data processing.* Applicants used Cell Ranger mkfastq (v2.0 and v3.0) (lOx Genomics) to generate demultiplexed FASTQ files from the raw sequencing reads. Applicants aligned these reads to the human GRCh38 genome and quantified gene counts as UMIs using Cell Ranger count (v2.0 and v3.0) (lOx Genomics). For single-nucleus RNA-seq reads, Applicants counted reads mapping to introns as well as exons, as this results in a greater number of genes detected per nucleus, more nuclei passing quality control, and better cell type identification, as

previously described[25]. To count introns during read mapping, Applicants followed the approach described at https://support.lOxgenomics.com/single-cell-gene-expression/software/pipelines/latest/advanced/references. Briefly, Applicants built a "pre-mRNA" human GRCh38 reference using Cell Ranger mkref (v3.0) (lOx Genomics) and a modified gene transfer format (GTF) file, where for each transcript, the feature type had been changed from transcript to exon. The starting GTF files came from refdata-cellranger-GRCh38-l.2.0.tar.gz or refdata-cellranger-GRCh38-3.0.0.tar.gz, and are available for download at https://support.l0xgenomics.eom/single-cell-gene-expression/software/downloads/3.0.

[00757] To down-sample sequencing reads or gene counts (UMIs) when comparing protocols, Applicants used downsampleReads and downsampleMatrix, respectively from the R package[10] DropletUtils. Reads were down-sampled to match the protocol with the lowest number of total reads. After down-sampling by total reads, Applicants used write lOxCounts from DropletUtils and a custom python script to generate an HDF5 file for input into the analysis pipelines described below.

[00758] ***Quality control of scRNA-seq data.*** To maintain explicit control over all gene and cell quality control filters, in all the downstream analyses Applicants used the raw feature-barcode matrix, rather than the filtered feature-barcode matrix generated by Cell Ranger. Applicants removed low quality cells by requiring each cell to have a minimal number of UMIs and genes detected. Applicants used different thresholds depending on the experimental modality (single cell or single nucleus) and on the lOx kit (V2 or V3 chemistry). For single nucleus data, Applicants retained nuclei with at least 200 genes and 400 UMIs detected by V2 chemistry and with at least 500 genes and 1,000 UMIs detected by V3 chemistry. For single cell data, Applicants retained cells with at least 500 genes and 1,000 UMIs detected by either V2 or V3 chemistry. For both data types, Applicants filtered out those cells or nuclei where >20% of UMIs came from mitochondrial genes. Finally, Applicants normalized the total UMIs per cell or nucleus to one-hundred thousand (CP100K), and log-transformed these values to report gene expression as E = log(CPlOOK+l).

[00759] Applicants reported the following QC metrics: number of total reads per library sample, sequencing saturation (fraction of reads originating from an already-observed UMI as reported by Cell Ranger count), total recovered cells or nuclei, number of reads per cell or nucleus, number of UMIs per cell or nucleus, number of genes detected per cell or nucleus, fraction of UMIs in a

cell or nucleus aligned to mitochondrial genes, fraction of droplets estimated to contain only ambient RNA ("empty drops"), fraction of cell or nucleus doublets, the number of detected cell types, and the pattern of copy number aberration (CNA) for malignant cells. For a subset of samples, Applicants also calculated the UMI saturation for each cell or nucleus by subsampling from the total number of sequencing reads in the cell or nucleus[26], the number of cells or nuclei per detected cell type, and the estimated level of ambient RNA in droplets containing cells.

[00760] Applicants predicted droplets containing only ambient RNA and no cells using EmptyDrops, with the retain parameter set by the knee of the curve in the barcode rank plot (cell barcodes ranked by their total UMIs)[10]. Applicants predicted potential doublets using Scrublet with expected_doublet_rate = 0.061 1. Applicants estimated the levels of ambient RNA using SoupX and a set of cell-type specific marker genes[18]. Importantly, Applicants flagged the doublets and empty drops and retained them in their analysis, instead of immediately filtering them out. Droplets that appear to contain doublets or empty drops can arise from many different effects, such as cellular differentiation or insufficient sequencing, and by carrying them through the analysis, potential doublets or empty drops can be more clearly interpreted in the context of the full dataset.

[00761] ***Dimensionality reduction, clustering, and visualization.*** For each tumor sample, Applicants analyzed the filtered expression matrix to identify cell subsets, as previously described[27,28]. Applicants chose highly variable genes with a z-score cutoff of **0.5**[29], centered and scaled the expression of each gene to have a mean of zero and standard deviation of one, and performed dimensionality reduction on the variable genes using principal component analysis (PCA). Applicants used the top 50 principal components (PCs) as input to Louvain graph-based clustering, with the resolution parameter set to **1.3.** For each cluster of cells, Applicants identified cluster-specific differentially expressed genes using the following tests: an AUC classifier, Welch's t-test, and Fisher's exact test. For tests that returned a p-value, Applicants controlled the false discovery rate at **5%** with the Benjamini-Hochberg procedure[30]. Applicants visualized gene expression and clustering results by embedding cells or nuclei profiles in a Uniform Manifold Approximation and Projection (UMAP)[31] of the top 50 PCs, with min_dist = **0.5,** spread = **1.0,** the number of neighbors = 15, and the Euclidean distance metric.

[00762] ***Annotating cell subsets.*** For each cell subset identified by clustering, Applicants assigned a cell type from the malignant, parenchymal, stromal, and immune compartments of the

tumor microenvironment using a combination of differentially expressed genes, known gene signatures, and SingleR[32], an automated annotation package. When running SingleR, only cell types assigned to 30 or more cells were considered. When scoring cells for the expression of known gene signatures, Applicants used the AddModuleScore function in Seurat (v2.3.4)[24]. Applicants note that overlapping expression programs between T cells and NK cells make these cell types sometimes more difficult to accurately identify.

[00763] Applicants identified the malignant cells by inferring chromosomal copy number aberrations (CNAs) from the gene-expression data using inferCNV (vl.l.O) [33]. On a sample-by-sample basis, Applicants used the immune and endothelial cells as a healthy reference to estimate CNAs in the malignant cells. Applicants created the count matrix file and annotation file for inferCNV by randomly subsetting the counts data to sample at most 2,000 cells or nuclei. Applicants created a gene ordering file from the human GRCh38 assembly, which contains the chromosomal start and end positions for each gene. To run inferCNV, Applicants used a cutoff of 0.1 for the minimum average read counts per gene among reference cells or nuclei, clustered according to the annotated cell types, denoised our output, ran an HMM to predict CNA level, implemented inferCNV' s i6 HMM model, and requested 8 threads for parallel steps.

[00764] ***Comparing single cell and single nucleus RNA-Seq data.*** To compare profiles between single cell and single nucleus RNA-Seq data collected from the same sample, Applicants used a batch-correction approach.

[00765] For the batch correction approach, Applicants performed batch correction using canonical correlation analysis (CCA) as implemented in Seurat (v2.3.4)[24]. Applicants selected 1,500 genes that were variable across both the cell and nucleus data, used those genes as input to RunCCA to compute the first 20 canonical components, and aligned the first 12 canonical components with AlignSubspace. The aligned canonical components represent a co-embedding of the cell and nucleus data, and Applicants carried out clustering in this dimensionality-reduced space using FindClusters.

[00766] ***Software and data availability.*** Applicants implemented all major analysis steps, from FASTQ files to identifying cell subsets, in pipelines executed in a Cloud environment. Applicants named this collection of pipelines scCloud, which may be executed in both a Cloud-based environment and a local, python environment.

[00767] Pipelines were written in the Workflow Description Language (WDL) and run on Cromwell in the Terra Cloud platform (https://app.terra.bio/), and data was stored in Google Cloud Plaform storage buckets. Applicants wrote two WDL workflows: cellranger_workflow, a wrapper for running Cell Ranger mkfastq and count, and scCloud, a novel, fast, and scalable analysis pipeline for single cell and single nucleus RNA-Seq data. All analysis workflows will be publicly available through https://github.com/klarman-cell-observatory/scCloud.

[00768] Applicants ran additional quality control steps, cell-subset annotations, and protocol comparison steps in R (v3.5) by converting the single-cell AnnData objects from scCloud into Seurat objects. An example script for this analysis will be made available at https://github.com/klarman-cell-observatory/HTAPP-Pipelines.

[00769] Raw data will be available in the controlled access repository DUOS (https://duos.broadinstitute.Org/#/home).

References

1. Jerby-Arnon, L., et al. A Cancer Cell Program Promotes T Cell Exclusion and Resistance to Checkpoint Blockade. Cell 175, 984-997.e924 (2018).
2. Puram, S.V., et al. Single-Cell Transcriptomic Analysis of Primary and Metastatic Tumor Ecosystems in Head and Neck Cancer. Cell 171, 161 1-1624 el624 (2017).
3. Filbin, M.G., et al. Developmental and oncogenic programs in H3K27M gliomas dissected by single-cell RNA-seq. Science 360, 331-335 (2018).
4. Venteicher, A.S., et al. Decoupling genetics, lineages, and microenvironment in IDH-mutant gliomas by single-cell RNA-seq. Science 355(2017).
5. Tirosh, T, et al. Single-cell RNA-seq supports a developmental hierarchy in human oligodendroglioma. Nature 539, 309-313 (2016).
6. Cieslik, M. & Chinnaiyan, A.M. Cancer transcriptome profiling at the juncture of clinical translation. Nat Rev Genet 19, 93-109 (2018).
7. Habib, N., et al. Div-Seq: Single-nucleus RNA-Seq reveals dynamics of rare adult newborn neurons. Science 353, 925-928 (2016).
8. Habib, N., et al. Massively parallel single-nucleus RNA-seq with DroNc-seq. Nat Methods (2017).

9. Gaublomme, J.T., et al. Nuclei multiplexing with barcoded antibodies for single-nucleus genomics. Nat Commun 10, 2907 (2019).
10. Lun, A.T.L., et al. EmptyDrops: distinguishing cells from empty droplets in droplet-based single-cell RNA sequencing data. Genome Biol 20, 63 (2019).
11. Wolock, S.L., Lopez, R. & Klein, A.M. Scrublet: Computational Identification of Cell Doublets in Single-Cell Transcriptomic Data. Cell Syst 8, 281-291 e289 (2019).
12. Li, B., Gould, J., Rosen, Y., Rozenblatt-Rosen, O. & Regev, A. https://github.com/klarman-cell-observatory/KCO. (2019).
13. Al-Hajj, M., Wicha, M.S., Benito-Hernandez, A., Morrison, S.J. & Clarke, M.F. Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci U S A 100, 3983-3988 (2003).
14. McDivitt, R.W., Stone, K.R. & Meyer, J.S. A method for dissociation of viable human breast cancer cells that produces flow cytometric kinetic information similar to that obtained by thymidine labeling. Cancer Res 44, 2628-2633 (1984).
15. Neftel, C., et al. An Integrative Model of Cellular States, Plasticity, and Genetics for Glioblastoma. Cell (2019).
16. Quatromoni, J.G., et al. An optimized disaggregation method for human lung tumors that preserves the phenotype and function of the immune cells. J Leukoc Biol 97, 201-209 (2015).
17. Burgstaller, G., et al. The instructive extracellular matrix of the lung: basic composition and alterations in chronic lung disease. Eur Respir J 50(2017).
18. Young, M.D. & Behjati, S. SoupX removes ambient RNA contamination from droplet based single cell RNA sequencing data. 303727 (2018).
19. Stewart, E., et al. Development and characterization of a human orthotopic neuroblastoma xenograft. Dev Biol 407, 344-355 (2015).
20. Stewart, E., et al. Orthotopic patient-derived xenografts of paediatric solid tumours. Nature 549, 96-100 (2017).
21. Hermansen, J.U., Tjonnfjord, G.E., Munthe, L.A., Tasken, K. & Skanland, S.S. Cryopreservation of primary B cells minimally influences their signaling responses. Sci Rep 8, 17651 (2018).
22. Guillaumet-Adkins, A., et al. Single-cell transcriptome conservation in cryopreserved cells

and tissues. Genome Biol 18, 45 (2017).

23. Gao, R., et al. Nanogrid single-nucleus RNA sequencing reveals phenotypic diversity in breast cancer. Nat Commun 8, 228 (2017).
24. Butler, A., Hoffman, P., Smibert, P., Papalexi, E. & Satija, R. Integrating single-cell transcriptomic data across different conditions, technologies, and species. Nature biotechnology 36, 411-420 (2018).
25. Bakken, T.E., et al. Single-nucleus and single-cell transcriptomes compared in matched cortical cell types. PLoS One 13, e0209648 (2018).
26. Wallrapp, A., et al. The neuropeptide NMU amplifies ILC2-driven allergic lung inflammation. Nature 549, 351-356 (2017).
27. Shekhar, K., et al. Comprehensive Classification of Retinal Bipolar Neurons by Single-Cell Transcriptomics. Cell 166, 1308-1323 el330 (2016).
28. Wolf, F.A., Angerer, P. & Theis, F.J. SCANPY: large-scale single-cell gene expression data analysis. Genome Biol 19, 15 (2018).
29. Macosko, E.Z., et al. Highly Parallel Genome-wide Expression Profiling of Individual Cells Using Nanoliter Droplets. Cell 161, 1202-1214 (2015).
30. Benjamini, Y., and Yosef Hochberg. "Controlling the false discovery rate: a practical and powerful approach to multiple testing". Journal of the Royal statistical society: series B (Methodological) 57.1 289-300 (1995).
31. Leland Mclnnes, J.H., James Melville. UMAP: Uniform Manifold Approximation and Projection for Dimension Reduction. (eprint arXiv: 1802.03426, 2018).
32. Aran, D., et al. Reference-based analysis of lung single-cell sequencing reveals a transitional profibrotic macrophage. Nat Immunol 20, 163-172 (2019).
33. Tickle T, T.I., Georgescu C, Brown M, Haas B inferCNV of the Trinity CTAT Project, https://github.com/broadinstitute/inferCNV. (2019).

Supplemental References

Benjamini, Y., and Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J. R. Stat. Soc. Series B Stat. Methodol. 57, 289-300.

Bondurand, N., and Southard-Smith, E.M. (2016). Mouse models of Hirschsprung disease and

other developmental disorders of the enteric nervous system: Old and new players. Dev. Biol. 417, 139-157.

Brookes, S.J., Steele, P.A., and Costa, M. (l99la). Identification and immunohistochemistry of cholinergic and non-cholinergic circular muscle motor neurons in the guinea-pig small intestine. Neuroscience 42, 863-878.

Brookes, S.J., Steele, P.A., and Costa, M. (l99lb). Calretinin immunoreactivity in cholinergic motor neurones, interneurones and vasomotor neurones in the guinea-pig small intestine. Cell Tissue Res. 263, 471-481.

Butler, A., Hoffman, P., Smibert, P., Papalexi, E., and Satija, R. (2018). Integrating single-cell transcriptomic data across different conditions, technologies, and species. Nat. Biotechnol. 36, 4 1 1.

Chang, D., Nalls, M.A., Hallgrimsdottir, I.B., Hunkapiller, J., van der Brug, M., Cai, F., International Parkinson's Disease Genomics Consortium, 23andMe Research Team, Kerchner, G.A., Ayalon, G., et al. (2017). A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. Nat. Genet. 49, 151 1-1516.

Drokhlyansky, E., Goz Aytiirk, D., Soh, T.K., Chrenek, R., O'Loughlin, E., Madore, C., Butovsky, O., and Cepko, C.L. (2017). The brain parenchyma has a type I interferon response that can limit virus spread. Proc. Natl. Acad. Sci. E[. S. A. 114, E95-E104.

Finak, G , McDavid, A., Yajima, M., Deng, T, Gersuk, V., Shalek, A.K., Slichter, C.K., Miller, H.W., McElrath, M.J., Prlic, M., et al. (2015). MAST: a flexible statistical framework for assessing transcriptional changes and characterizing heterogeneity in single-cell RNA sequencing data. Genome Biol. 16, 278.

Furness, J.B. (2012). The enteric nervous system and neurogastroenterology. Nat. Rev. Gastroenterol. Hepatol. 9, 286-294.

Furness, J.B., Costa, M., Rokaeus, A., McDonald, T.J., and Brooks, B. (1987). Galanin-immunoreactive neurons in the guinea-pig small intestine: their projections and relationships to other enteric neurons. Cell Tissue Res. 250, 607-615.

Grider, J.R. (1994). Interplay of somatostatin, opioid, and GABA neurons in the regulation of the peristaltic reflex. Am. J. Physiol. 267, G696-G701.

Grider, J.R. (2003). Neurotransmitters mediating the intestinal peristaltic reflex in the mouse. J.

Pharmacol. Exp. Ther. 307, 460-467.

Haber, A.L., Biton, M., Rogel, N., Herbst, R.H., Shekhar, K., Smillie, C., Burgin, G., Delorey, T.M., Howitt, M.R., Katz, Y., et al. (2017). A single-cell survey of the small intestinal epithelium. Nature 551, 333-339.

Habib, N., Li, Y., Heidenreich, M., Swiech, L., Avraham-Davidi, I., Trombetta, J.J., Hession, C., Zhang, F., and Regev, A. (2016). Div-Seq: Single-nucleus RNA-Seq reveals dynamics of rare adult newborn neurons. Science 353, 925-928.

Habib, N., Avraham-Davidi, L, Basu, A., Burks, T., Shekhar, K., Hofree, M., Choudhury, S.R., Aguet, F., Gelfand, E., Ardlie, K., et al. (2017). Massively parallel single-nucleus RNA-seq with DroNc-seq. Nat. Methods 14, 955-958.

Lasrado, R., Boesmans, W., Kleinjung, J., Pin, C., Bell, D., Bhaw, L., McCallum, S., Zong, H , Luo, L., Clevers, H., et al. (2017). Lineage-dependent spatial and functional organization of the mammalian enteric nervous system. Science 356, 722-726.

Levine, J.H., Simonds, E.F., Bendall, S.C., Davis, K.L., Amir, E.-A.D., Tadmor, M.D., Litvin, O., Fienberg, H.G., Jager, A., Zunder, E.R., et al. (2015). Data-Driven Phenotypic Dissection of AML Reveals Progenitor-like Cells that Correlate with Prognosis. Cell 162, 184-197.

Lewis, A.E., Vasudevan, H.N., O'Neill, A.K., Soriano, P., and Bush, J.O. (2013). The widely used Wntl-Cre transgene causes developmental phenotypes by ectopic activation of Wnt signaling. Dev. Biol. 379, 229-234.

Li, B., and Dewey, C.N. (201 1). RSEM: accurate transcript quantification from RNA-Seq data with or without a reference genome. BMC Bioinformatics 12, 323.

Linkert, M., Rueden, C.T., Allan, C., Burel, J.-M., Moore, W., Patterson, A., Loranger, B., Moore, J., Neves, C., Macdonald, D., et al. (2010). Metadata matters: access to image data in the real world. J. Cell Biol. 189, 777-782.

Lopez, R., Regier, J., Cole, M.B., Jordan, M.I., and Yosef, N. (2018). Deep generative modeling for single-cell transcriptomics. Nat. Methods 15, 1053-1058.

Madisen, L., Zwingman, T.A., Sunkin, S.M., Oh, S.W., Zariwala, H.A., Gu, H., Ng, L.L., Palmiter, R.D., Hawrylycz, M.J., Jones, A.R., et al. (2010). A robust and high-throughput Cre reporting and characterization system for the whole mouse brain. Nat. Neurosci. 13, 133-140.

Matsuoka, T., Ahlberg, P.E., Kessaris, N., Iannarelli, P., Dennehy, U., Richardson, W.D.,

McMahon, A.P., and Koentges, G. (2005). Neural crest origins of the neck and shoulder. Nature 436, 347-355.

Mo, A., Mukamel, E.A., Davis, F.P., Luo, C., Henry, G.L., Picard, S., Urich, M.A., Nery, J.R., Sejnowski, T.J., Lister, R., et al. (2015). Epigenomic Signatures of Neuronal Diversity in the Mammalian Brain. Neuron 86, 1369-1384.

Pietzsch, T., Preibisch, S., Tomancak, P., and Saalfeld, S. (2012). ImgLib2—generic image processing in Java. Bioinformatics 28, 3009-301 1.

Ramilowski, J.A., Goldberg, T., Harshbarger, J., Kloppmann, E., Lizio, M., Satagopam, V.P., Itoh, M., Kawaji, H., Carninci, P., Rost, B., et al. (2015). A draft network of ligand-receptor-mediated multicellular signalling in human. Nat. Commun. 6, 7866.

Rossi, J., Luukko, K., Poteryaev, D., Laurikainen, A., Sun, Y.F., Laakso, T., Eerikainen, S., Tuominen, R., Lakso, M., Rauvala, H., et al. (1999). Retarded growth and deficits in the enteric and parasympathetic nervous system in mice lacking GFR alpha2, a functional neurturin receptor. Neuron 22, 243-252.

Sanders, S.J., He, X., Willsey, A.J., Ercan-Sencicek, A.G., Samocha, K.E., Cicek, A.E., Murtha, M.T., Bal, V.H., Bishop, S.L., Dong, S., et al. (2015). Insights into Autism Spectrum Disorder Genomic Architecture and Biology from 71 Risk Loci. Neuron 87, 1215-1233.

Sang, Q., and Young, H.M. (1996). Chemical coding of neurons in the myenteric plexus and external muscle of the small and large intestine of the mouse. Cell Tissue Res. 284, 39-53.

Schindelin, J., Arganda-Carreras, F, Frise, E., Kaynig, V., Longair, M., Pietzsch, T., Preibisch, S., Rueden, C., Saalfeld, S., Schmid, B., et al. (2012). Fiji: an open-source platform for biological-image analysis. Nat. Methods 9, 676-682.

Schindelin, J., Rueden, C.T., Hiner, M.C., and Eliceiri, K.W. (2015). The ImageJ ecosystem: An open platform for biomedical image analysis. Mol. Reprod. Dev. 82, 518-529.

Schneider, C.A., Rasband, W.S., and Eliceiri, K.W. (2012). NIH Image to ImageJ: 25 years of image analysis. Nat. Methods 9, 671-675.

Schuchardt, A., D'Agati, V., Pachnis, V., and Costantini, F. (1996). Renal agenesis and hypodysplasia in ret-k- mutant mice result from defects in ureteric bud development. Development 122, 1919-1929.

Shekhar, K., Lapan, S.W., Whitney, I.E., Tran, N.M., Macosko, E.Z., Kowalczyk, M., Adiconis,

X., Levin, J.Z., Nemesh, L, Goldman, M., et al. (2016). Comprehensive Classification of Retinal Bipolar Neurons by Single-Cell Transcriptomics. Cell 166, 1308-1323. e30.

Smillie, C.S., Biton, M., Ordovas-Montanes, L, Sullivan, K.M., Burgin, G., Graham, D.B., Herbst, R.H., Rogel, N., Slyper, M., Waldman, L, et al. (2018). Rewiring of the cellular and inter-cellular landscape of the human colon during ulcerative colitis.

Vento-Tormo, R., Efremova, M., Botting, R.A., Turco, M.Y., Vento-Tormo, M., Meyer, K.B., Park, J.-E., Stephenson, E., Polahski, K., Goncalves, A., et al. (2018). Single-cell reconstruction of the early maternal-fetal interface in humans. Nature 563, 347-353.

Wiese, C.B., Fleming, N., Buehler, D.P., and Southard-Smith, E.M. (2013). A LTchll-Histone2BmCherry:GFP-gpi BAC transgene for imaging neuronal progenitors. Genesis 51, 852-861.

Young, H.M., Furness, J.B., and Povey, J.M. (1995). Analysis of connections between nitric oxide synthase neurons in the myenteric plexus of the guinea-pig small intestine. J. Neurocytol. 24, 257-263.

Example 25 - Expanded single-cell and single-nucleus RNA-Seq toolbox for processing tumors.

[00770] Applicants began by processing fresh tissue. To choose the best performing dissociation method, Applicants apportioned large tumor specimens into smaller pieces (-0.5-2 cm), dissociating each piece with a different protocol for fresh tissue dissociation. Collagenase 4 is NSCLC-C4, PDEC is a mixture of Pronase, Dispase, Elastase, and Collagenases A and 4. LE consists of Liberase™ and Elastase. Each of these was prepared in combination with DNase I. While the QCs looked similar (Fig. 94A) we see that each protocol results in a different proportion of cell types (Fig. 94B). For example C4 does not recover mast cells, endothelial cells, or fibroblasts, while the other two protocols do. In this case Applicants chose the PDEC protocol for future processing and also used this protocol for processing fresh normal lung samples.

[00771] Applicants found that the C4 protocol has the highest number of genes detected per cell overall. However, looking within cell types, Applicants found that similar number of cells were recovered across all three protocols, with C4 having greater cell type proportion of epithelial cells and macrophages. These cells are typically larger, have more starting RNA and more genes

detected per cell, and so overall have the highest number genes detected per cell. Because cell type proportions may vary between protocols, and the number of detected genes (and other metrics) varies between cell types, it is important to also assess cell-type specific QCs when choosing a protocol. For example, while C4 has the highest number of genes detected overall per cell, LE has the greatest number of genes detected per cell in epithelial cells and PDEC has the greatest number of genes detected per cell in B cells (Fig. 95).

[00772] Overall, Applicants processed five types of fresh tumors: non-small cell lung carcinoma (NSCLC), metastatic breast cancer (MBC), ovarian cancer, glioblastoma (GBM), and neuroblastoma, as well as a cryopreserved non-solid, chronic lymphocytic leukemia (CLL) (Fig. 96). Applicants measured QCs for all tissue types, looked at cell proportions and chose a recommended protocol for each tumor type (Fig. 97). While fresh sample processing generally works well, it has several limitations. First, one has to tailor cell dissociation to tumor type (cell type and ECM components). Processing is also time sensitive. Changes in gene expression are also common and there is loss of sensitive cells during dissociation. Moreover, there is no possibility for multiplexing.

[00773] To address these limitations Applicants previously developed a single-nuclei (snRNA-seq) method for profiling expression in single nuclei (Fig. 98). See also WO 2017/0164936, the entirety of which is incorporated by reference herein. snRNA-seq has several advantages. For example, it does not require cell dissociation, can use frozen or lightly fixed tissue, decouples collection from processing, can use banked samples, allows early pooling within and across donors, and allows for massively parallel implementation.

[00774] Application of the protocol tumor tissues required some modification. Buffers, detergent, and force were optimized with over 104 preparations and Applicants developed a nuclei processing toolbox to quickly and effectively profile frozen tissues. The best general approach was testing four different nucleus isolation buffers, three of which were very similar to each other apart from the detergent and the original buffer EZ (Fig. 99).

[00775] To understand the basis for performance differences among nuclei preparations, Applicants compared nuclei structure between the new and published preparations for snRNA-seq electron microscopy. The published methods yielded isolated intact nuclei. In contrast, CST preserved not only the nuclear envelope, but also the ribosomes on the outer nuclear membrane.

Applicants thus termed this method RAISIN (Ribosomes And Intact Single Nucleus) RNA-seq. TST maintained both the rough ER and its attached ribosomes on the outer nuclear membrane, Applicants thus termed this method, INNER Cell (INtact Nucleus and Endoplasmic Reticulum from a single Cell). Consistent with the TEM results, both RAISIN RNA-seq and INNER Cell RNA-seq yielded higher exorrintron ratios than the published methods (41% and 64% increases, respectively), suggesting greater recovery of mRNA relative to pre-mRNA.

[00776] With this toolbox in hand, Applicants tested it on tumors, starting with Neuroblastoma. Applicants observed a similar number of nuclei recovered across protocols, but different cell type proportions, in particular in the T cells, fibroblasts, and zona glomerulosa. Applicants did observe that the EZ buffer did not perform as well. Applicants could apply this across many tumor types, including Neuroblastoma, MBC, glioma, CLL, ovarian cancer, melanoma, and sarcoma (Fig. 100).

[00777] Looking again at QCs and proportions, Applicants observed that in most cases the TST buffer outperforms the other buffers - so while it has more mitochondrial reads - in most cases it detects more immune cells. EZ performed the least well among these tumor types. Applicants next wanted to compare sc/sn RNA-Seq on the same tumor sample, so they took two pieces. One freshly processed by scRNA-seq, one frozen and processed by snRNA-seq. Applicants combined the two datasets, clustered them to identify cell types, and visualized them in UMAP embedding. Applicants observed more T cells in scRNA-seq, more neural crest (cell of origin), endothelial cell in snRNA-seq. Each method has different biases to types of cells recovered.

[00778] Lastly, Applicants wanted to test frozen pre-cancer samples, so a frozen DCIS sample and profile was run using the nuclei toolbox. After analysis, Applicants obtained good QC metrics and could detect several cell types - including two clusters of epithelial cells, immune cells, endothelial cells, and fibroblasts (Fig. 101).

[00779] Applicants also looked at specific breast cancer markers, such as estrogen receptor, progesterone receptor, and ERBB2- HER2. Applicants observed PIP-prolactin induced protein, a biomarker for early stage BC (Fig. 102).

[00780] In summary, to choose the protocol for the cancer type in question, it is best to compare two to three protocols in parallel on the same tissue sample. It is also advisable to check all QCs and if possible, compare sc/snRNA-seq on the same tissue sample. The “best” protocol depends

on the biological question: one must choose the protocol that recovers the greatest cellular diversity (for atlas), and it also depends on whether one is looking at deletion or enrichment of markers.

[00781] To optimize the protocol on FFPE tissues, it is necessary to focus on 4 main steps in the protocol: 1) deparafmization - get rid of the FFPE; 2) decrosslinking; 3) isolation of nuclei; and 4) capture RNA and Library construction (Fig. 103). Some steps may be tissue specific. All steps for the workflow were optimized, as illustrated in Fig. 104. In terms of samples Applicants focused on mouse brain (Fig. 105B). Many methods are developed using this tissue because it has a lot of RNA. All the FFPE blocks were made fresh and processed quickly. Applicants are now also working on getting scrolls from lung cancer patients (Fig. 105A).

[00782] During optimization, Applicants compared different deparaffmization methods. Applicants optimized digestion with ProteinaseK and heat decrosslinking. Applicants also used two different library construction (LC) methods - SCRB-Seq and Smart-seq2 (Fig. 106). Both methods are poly A based, but the main difference is that SMART-Seq2 generates full length transcripts, while SCRB-Seq you get the 3' end of mRNA transcripts. Another difference is that in SMART-Seq2 each cell is processed by itself, while in SCRB-Seq there is early pooling of cells as a barcode is added at the cDNA stage (Fig. 107).

[00783] SCRB-Seq Whole Transcriptome Amplification (WTA) was tested for FFPE because it allows for a high level of multiplexing - barcoding of samples started at reverse transcription (RT). SCRB-Seq has high sensitivity because it amplifies pools of samples (there is more PCR template present). It uses unique molecular identifiers (EIMIs) to detect and quantify unique mRNA transcripts. The cost of constructing sequencing libraries is low - with one library per pool of samples.

[00784] Applicants made the following modifications to the SCRB-Seq protocol for FFPE. RT reaction was done with barcode primers in SMART-Seq2 reaction conditions with less expensive template switching oligos, post-RT PCR conditions were optimized, and cDNA-seq library construction was improved.

[00785] Applicants compared the two methods using the chosen extraction buffer (Xylene RT), used a frozen sample as a positive control and used had a varying number of nuclei. When Applicants looked at the QC they observed that in both SMART-Seq2 and SCRB-Seq libraries a

significant number of genes can be detected. Also, the mitochondrial and ribosomal fractions are considerably low (Fig. 108A).

[00786] Applicants then looked at correlation of expression across library preps, nuclei extraction method and number of nuclei. Applicants observed that when they processed 100 nuclei - there was good correlation between the different frozen samples and between the different FFPE samples. For the FFPE samples, even if the prep was not the same, he samples still clustered together and Applicants also saw that there was a good correlation between FFPE and frozen samples. As expected, the correlation goes down with the numbers of nuclei tested - since cortex mouse is a complex tissue with many cell types. Correlation across preps was as follows: 100/10 frozen nuclei preps tend to cluster together and 100/10 FFPE nuclei preps tend to cluster together but one can see good correlation between frozen and FFPE at 100 nuclei (precision=XXX). Lower correlation was observed at 1 nucleus since brain cortex has many cell types and states and data are sparse (Fig. 109).

[00787] Applicants next tried to cluster the single nuclei and did not observe clear clusters - as the number of cells profiled was too low. However, when looking at known mouse marker genes -expression of specific markers for neurons, glia, and astrocytes in the single cells is observerd (Fig. 110). Moreover, Applicants could use data generated for single cells in mouse cortex brain (from the BICCN) and predict cell types from the FFPE data. Accordingly, Applicants were able to predict several cell types at good accuracy (Figs. 111A, 111B). Applicants used 2,006 genes detected found in both the 10X data (mouse BICCN) and the single nuclei FFPE data to train classifier. First, Applicants split the 10X data in half (train and test data sets), then they ran the classifier on train set, and used it to predict cell type labels on test set.

***

[00788] Various modifications and variations of the described methods, pharmaceutical compositions, and kits of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific embodiments, it will be understood that it is capable of further modifications and that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention that are obvious to those skilled in the art are intended to be within the scope of the invention. This application is

intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure come within known customary practice within the art to which the invention pertains and may be applied to the essential features herein before set forth.

CLAIMS

What is claimed is:

1. A method of recovering nuclei or whole cells from a formalin-fixed paraffin-embedded (FFPE) tissue comprising:

a. dissolving paraffin from a FFPE tissue sample in a solvent, preferably the solvent is selected from the group consisting of xylene and mineral oil, wherein the tissue is dissolved at a temperature between 4C to 90C, preferably room temperature (20 to 25C) for recovering whole cells and 90C for recovering nuclei;

b. rehydrating the tissue using a gradient of ethanol from 100% to 0% ethanol (EtOH);

c. transferring the rehydrated tissue to a volume of a first buffer comprising a buffering agent, a detergent and an ionic strength between lOOmM and 200mM, optionally the first buffer comprises protease inhibitors or proteases and/or BSA;

d. chopping or dounce homogenizing the tissue in the buffer; and

e. removing debris by filtering and/or FACS sorting.

2. The method of claim 1, further comprising isolating nuclei or cell types by FACS sorting.

3. The method of claim 1, wherein dissolving paraffin from a FFPE tissue sample, comprises incubating at least one time in xylene, at room temperature (RT), for about 10 minutes each, and wherein xylene is removed at each change.

4. The method of claim 3, further comprising washing the tissue at least two times with xylene for about 10 min each, wherein the washes are performed at room temperature (RT), 90C, or at least one time at room temperature (RT) and at least one time at 90C, wherein xylene is removed at each change.

5. The method of claim 1, wherein dissolving paraffin from a FFPE tissue sample, comprises incubating at least twice in about 5 ml xylene per 30-100 mg FFPE tissue sample, at room temperature, for about 10 minutes each, wherein xylene is removed at each change.

6. The method of claim 5, further comprising washing the tissue with xylene at 37C for about 10 min.

7. The method of claim 6, further comprising cutting the tissue into two or more pieces and washing at least one piece of the tissue with xylene at 37C for about 10 min.

8. The method of claim 1, wherein dissolving paraffin from a FFPE tissue sample, comprises incubating at least three times in xylene, at room temperature, for about 10 minutes each, and wherein xylene is removed at each change.

9. The method of claim 8, further comprising washing the tissue three additional times with xylene for about 10 min each, wherein the first wash is at room temperature and the second and third washes are at 90C, and wherein xylene is removed at each change.

10. The method of claim 1, wherein rehydrating the tissue comprises a step gradient of ethanol (EtOH) and the tissue is incubated between 1 to 10 minutes at each step.

11. The method of claim 10, wherein the step gradient comprises incubating the tissue for about 2 minutes each in successive washes of 95%, 75%, and 50% ethanol (EtOH).

12. The method of any of the preceding claims, wherein after rehydrating the tissue the method further comprises placing the tissue samples on ice or on a device capable of maintaining the tissue between 4 and 10C, wherein all subsequent steps are performed at a temperature between 4 and 10C.

13. The method of any of the preceding claims, wherein after the step of dissolving paraffin from the tissue or rehydrating the tissue the method further comprises dividing the tissue, preferably in half.

14. The method of claim 1, wherein the first buffer comprises a detergent selected from the group consisting of NP40, CHAPS and Tween-20.

15. The method of claim 14, wherein the NP40 concentration is about 0.2%.

16. The method of claim 14, wherein the Tween-20 concentration is about 0.03%.

17. The method of claim 14, wherein the CHAPS concentration is about 0.49%.

18. The method of claim 1, wherein the first buffer is selected from the group consisting of CST, TST, NST and NSTnPo.

19. The method of claim 1, wherein after the step of chopping or dounce homogenizing the method further comprises centrifuging, preferably, the sample is centrifuged at about 500g for about 5 min, and resuspending the sample in a second buffer comprising a buffering agent and an ionic strength between lOOmM and 200mM, optionally the second buffer comprises protease inhibitors.

20. The method of claim 19, wherein the second buffer is ST, optionally comprising protease inhibitors.

21. The method of claim 1, wherein the sample is filtered through a 40 uM filter.

22. The method of claim 21, further comprising washing the filtered sample in the first buffer.

23. The method of claim 22, further comprising filtering the sample through a 30 uM filter.

24. The method of claim 1, wherein after the step of chopping or dounce homogenizing the method further comprises adding an additional 2 volumes of the first buffer (3 volumes total) and filtering the sample through a 40 uM filter.

25. The method of claim 24, further comprising adding an additional three volumes of the first buffer (6 volumes total), centrifuging, preferably, the sample is centrifuged at about 500g for about 5 min, and resuspending the sample in a second buffer comprising a buffering agent and an ionic strength between lOOmM and 200mM, optionally the second buffer comprises protease inhibitors.

26. The method of claim 25, wherein the second buffer is ST, optionally comprising protease inhibitors.

27. The method of any of the preceding claims, further comprising reversing cross-linking in the tissue sample before or during any step of the method.

28. The method of claim 27, wherein reversing cross-linking comprises proteinase digestion.

29. The method of claim 28, wherein the proteinase is proteinase K or a cold-active protease.

30. The method of any of the preceding claims, further comprising adding a reagent that stabilizes RNA to the tissue sample before or during any step of the method.

31. The method of any of the preceding claims, further comprising lysing recovered cells or nuclei and performing reverse transcription.

32. The method of claim 31, wherein the reverse transcription is performed in individual reaction vessels.

33. The method of claim 31, wherein the reaction vessels are wells, chambers, or droplets.

34. The method of any of the preceding claims, further comprising performing single cell, single nucleus or bulk RNA-seq, DNA-seq, ATAC-seq, or ChIP on the recovered nuclei or whole cells.

35. The method of any of the preceding claims, further comprising staining the recovered cells or nuclei.

36. The method of claim 35, wherein the stain comprises ruby stain.

37. A method of recovering nuclei and attached ribosomes from a tissue sample comprising:

a. chopping the tissue sample at between 0-4 °C in a nuclear extraction buffer comprising Tris buffer, a detergent and salts; and

b. filtering the sample through a filter between 30-50 uM, preferably 40 uM, and optionally washing the filter with fresh nuclear extraction buffer,

wherein the nuclei are present in the supernatant passed through the filter.

38. The method of claim 37, wherein the nuclear extraction buffer comprises 10-20 mM Tris, about 0.49% CHAPS, a salt concentration having an ionic strength of l00-250mM, and about 0.01% BSA, whereby nuclei are recovered that have a preserved nuclear envelope and ribosomes.

39. The method of claim 38, wherein the nuclear extraction buffer is buffer CST.

40. The method of claim 37, wherein the nuclear extraction buffer comprises 10-20 mM Tris, about 0.03% Tween-20, a salt concentration having an ionic strength of l00-250mM, and about 0.01% BSA, whereby nuclei are recovered that have a preserved nuclear envelope, rough ER and ribosomes.

41. The method of claim 40, wherein the nuclear extraction buffer is buffer TST.

42. The method of any of claims 37 to 41, wherein the salts comprise 146 mM NaCl, lmM $CaCl_2$, and 2lmM $MgCl_2$.

43. The method of any of claims 37 to 42, wherein chopping comprises chopping with scissors for 1-10 minutes.

44. The method of any of claims 37 to 43, wherein nuclei from specific cell types are genetically modified to express a detectable label on the nuclear membrane and the method further comprises enriching nuclei from the specific cell types using the detectable label.

45. The method of any of claims 37 to 44, further comprising staining the recovered nuclei.

46. The method of claim 45, wherein the stain comprises ruby stain.

47. The method of any of claims 37 to 46, wherein the nuclei are sorted into discrete volumes by FACS.

48. The method of any of claims 37 to 46, further comprising pelleting the nuclei and resuspending the nuclei in a second buffer consisting of Tris buffer and salts.

49. The method of claim 48, wherein the second buffer is buffer ST.

50. The method of any of claims 37 to 49, further comprising generating a single nuclei barcoded library for the recovered nuclei, wherein the nucleic acid from each nuclei is labeled with a barcode sequence comprising a cell of origin barcode, optionally the barcode sequence includes a cell of origin barcode and a unique molecular identifier (UMI).

51. The method of claim 50, wherein RNA and/or DNA is labeled with the barcode sequence.

52. The method of claim 51, wherein the library is an RNA-seq, DNA-seq, and/or ATAC-seq library.

53. The method of any of claims 50 to 52, further comprising sequencing the library.

54. The method of any of claims 37 to 53, wherein the tissue sample is fresh frozen.

55. The method of any of claims 37 to 54, wherein the tissue sample comprises cells originating from the central nervous system (CNS) or enteric nervous system (ENS).

56. The method of any of claims 37 to 55, wherein the tissue sample is obtained from the gut or the brain.

57. The method of any of claims 37 to 56, wherein the tissue sample is obtained from a subject suffering from a disease.

58. The method of any of claims 37 to 57, wherein the tissue sample is treated with a reagent that stabilizes RNA.

59. The method of any of claims 47 to 58, wherein the discrete volumes are droplets, wells in a plate, or microfluidic chambers.

60. A method of treating a disease selected from the group consisting of Hirschsprung' s disease (HSCR), inflammatory bowel disease (IBD), autism spectrum disorder (ASD), Parkinson's disease (PD) and schizophrenia in a subject in need thereof comprising administering one or more agents capable of modulating the function or activity of:

a) one or more neurons selected from the group consisting of PEMN1, PEMN2, PIMN1, PIMN2, PIMN3, PIMN4, PIMN5, PIN1, PIN2, PSN and PSVN; or

b) one or more cells functionally interacting with the one or more neurons.

61. The method of claim 60, wherein the one or more cells functionally interacting with the one or more neurons are selected from the group consisting of T cells, dendritic cells (DC), B cells, fibroblasts and adipocytes.

62. A method of modulating appetite and energy metabolism in a subject in need thereof comprising administering one or more agents capable of modulating the function or activity of:

a) one or more neurons selected from the group consisting of PIMN4 and PIMN5; or

b) one or more adipose cells functionally interacting with the one or more neurons.

63. The method of any of claims 60 to 62, wherein the one or more neurons are characterized by expression of one or more markers according to Table 14 or Table 21.

64. The method of any of claims 60 to 63, wherein the one or more agents modulate the expression, activity or function of one or more genes according to Table 14 or Table 21.

65. The method of any of claims 60, 61, 63 or 64, wherein the one or more agents modulate the expression, activity or function of one or more genes selected from the group consisting of:

a) NPY, CGRP, Glutamate, GABA, LEP, VIP, PACAP, Nitric oxide, NOS1, FGF1, PDGF, SLIT2, SLIT3, IL15, IL7, IL12A, PENK, CHAT and TPH2; or

b) NPYR1, CALCRL, GRM8, GABRE, LEPR, VIPR2, GRIA4, GUCY1A3, FGFR1, PDGFRB, ROBOl, ROB02, IL15R, IL7R, IL12RB1, OPRM1, CHRNE and HTR3A.

66. The method of claim 62, wherein the one or more agents modulate the expression, activity or function of one or more genes selected from the group consisting of:

c) NPY and CGRP; or

d) NPYR1 and CALCRL.

67. The method of any of claims 60 to 66, wherein the one or more agents modulate the expression, activity or function of one or more core transcriptional programs according to Table 23.

68. The method of claim 67, wherein the one or more agents modulate the expression, activity or function of one or more genes of the one or more core transcriptional programs.

69. The method of any of claims 60 to 68, wherein the one or more agents are administered to the gut.

70. The method of any of claims 60 to 69, wherein the one or more agents comprise an antibody, small molecule, small molecule degrader, genetic modifying agent, nucleic acid agent, antibody-like protein scaffold, aptamer, protein, or any combination thereof.

71. The method of claim 70, wherein the genetic modifying agent comprises a CRISPR system, RNAi system, a zinc finger nuclease system, a TALE, or a meganuclease.

72. The method of claim 71, wherein the CRISPR system comprises Cas9, Casl2, or Casl4.

73. The method of claim 71, wherein the CRISPR system comprises a dCas fused or otherwise linked to a nucleotide deaminase.

74. The method of claim 73, wherein the nucleotide deaminase is a cytidine deaminase or an adenosine deaminase.

75. The method of claim 73, wherein the dCas is a dCas9, dCasl2, dCasl3, or dCasl4.

76. The method of claim 70, wherein the nucleic acid agent or genetic modifying agent is administered with a vector.

77. The method of claim 76, wherein the nucleic acid agent or genetic modifying agent is under the control of a promoter specific to a marker gene for the one or more neurons according to Table 14 or Table 21.

78. A method of detecting one or more cells of the enteric nervous system (ENS) comprising detecting one or more markers according to Table 14-17 or Table 20-22.

79. The method of claim 78, wherein detecting the one or more markers comprises immunohistochemistry.

80. A method of screening for agents capable of modulating expression of a transcription program according to Table 23 comprising:

a) administering an agent to a population of cells comprising neurons selected from the group consisting of PEMN1, PEMN2, PIMN1, PIMN2, PIMN3, PIMN4, PIMN5, PIN1, PIN2, PSN and PSVN; and

b) detecting expression of one or more genes in the transcriptional program.

81. The method of claim 80, wherein detecting expression comprises RT-PCR, RNA-seq, single cell RNA-seq, fluorescently labeled probes, or an immunoassay.

82. The method of claim 80, wherein the neurons express one or more reporter genes under control of a promoter specific to the one or more genes in the transcriptional program and detecting comprises detecting the reporter gene.

83. A method of identifying gene expression in single cells comprising providing sequencing reads from a single nucleus sequencing library and counting sequencing reads mapping to introns and exons.

84. The method of claim 83, further comprising filtering the single nuclei.

85. The method of claim 84, wherein nuclei doublets are removed by filtering.

86. The method of claim 84, wherein nuclei containing ambient RNA or ambient RNA alone is removed by filtering.

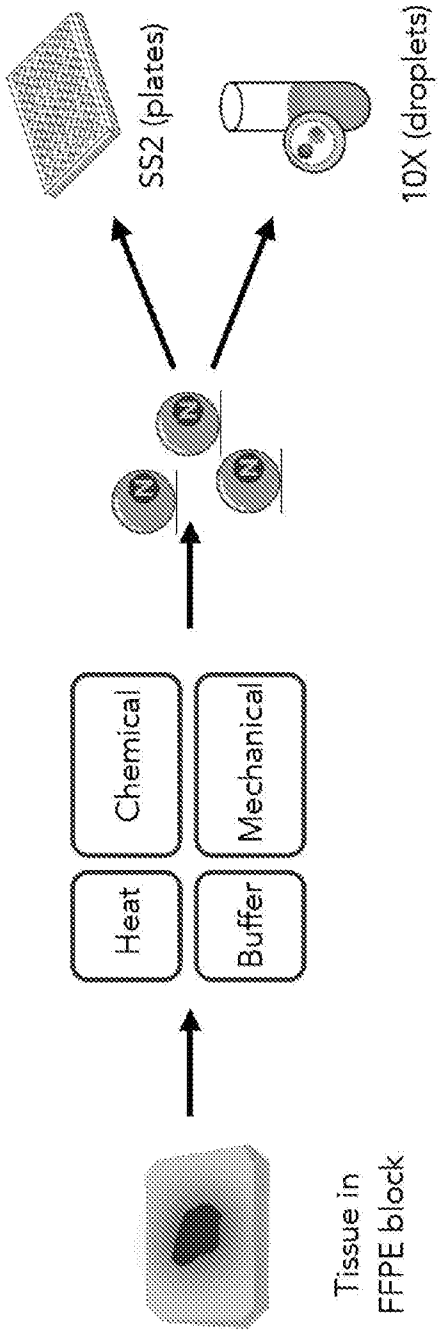

SS2 (plates)
10X (droplets)
Chemical
Mechanical
Heat
Buffer
Tissue in
FFPE block

FIG. 1

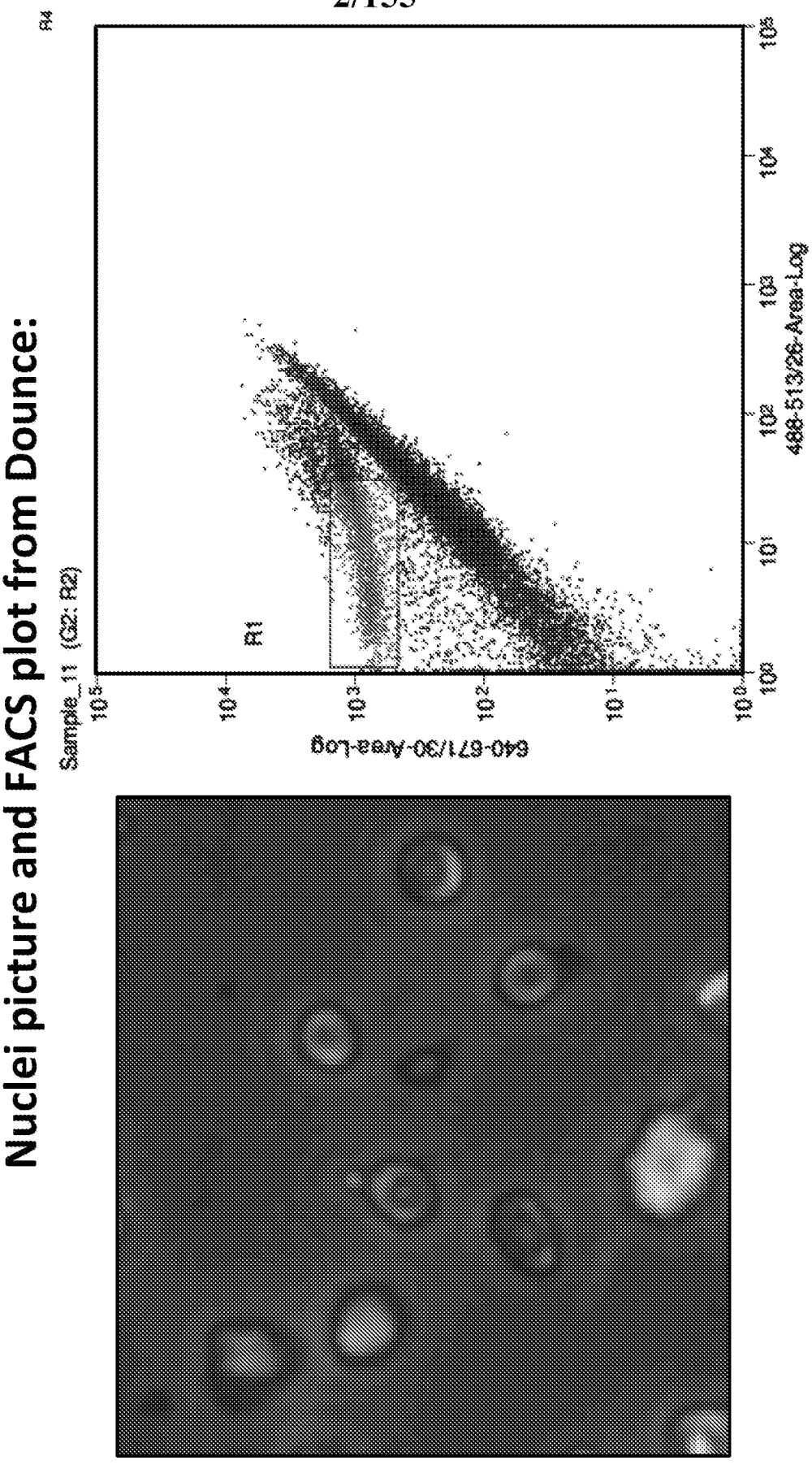

Nuclei picture and FACS plot from Dounce:
R4
Sample_11 (G2: R2)
R1
640-671/30-Area-Log
488-513/26-Area-Log
10^0
10^1
10^2
10^3
10^4
10^5
100
101
102
103
104
105

FIG. 2

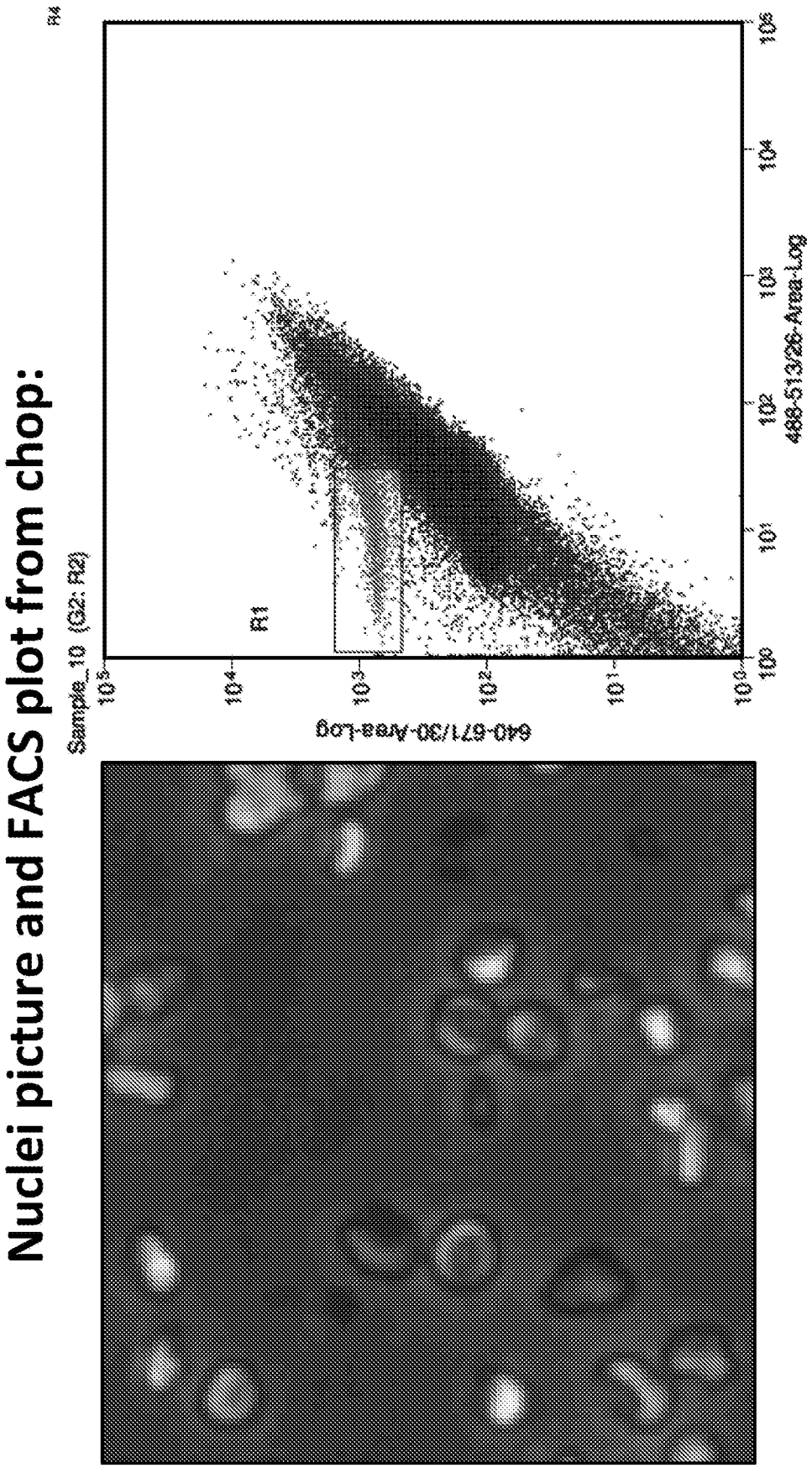

Nuclei picture and FACS plot from chop:
R4
Sample_10 (G2: R2)
R1
640-671/30-Area-Log
488-513/26-Area-Log
10^5
10^4
10^3
10^2
10^1
10^0
100
101
102
103
104
105

FIG. 3

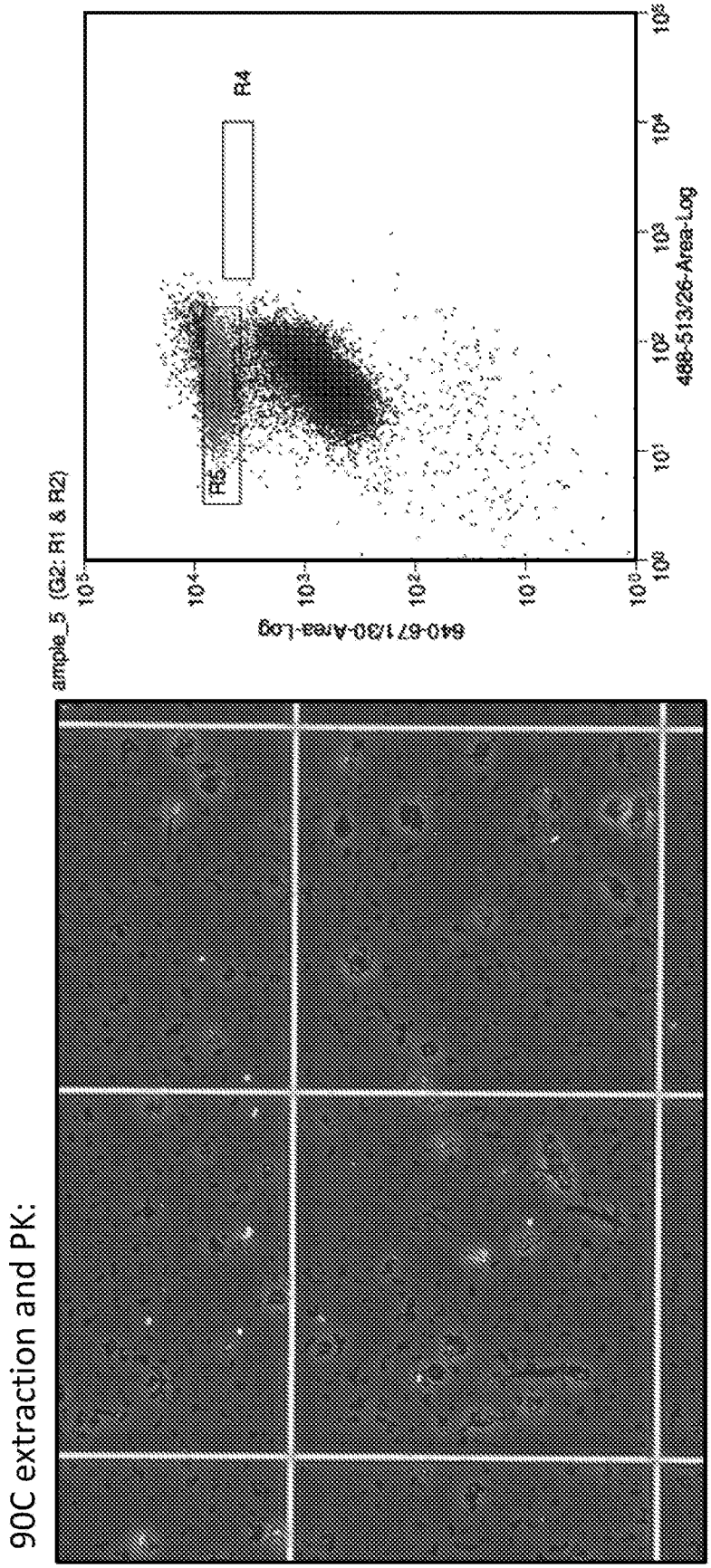

90C extraction and PK:
ample_5 (G2: R1 & R2)
R4
R5
640-671/30-Area-Log
488-513/26-Area-Log

FIG. 4

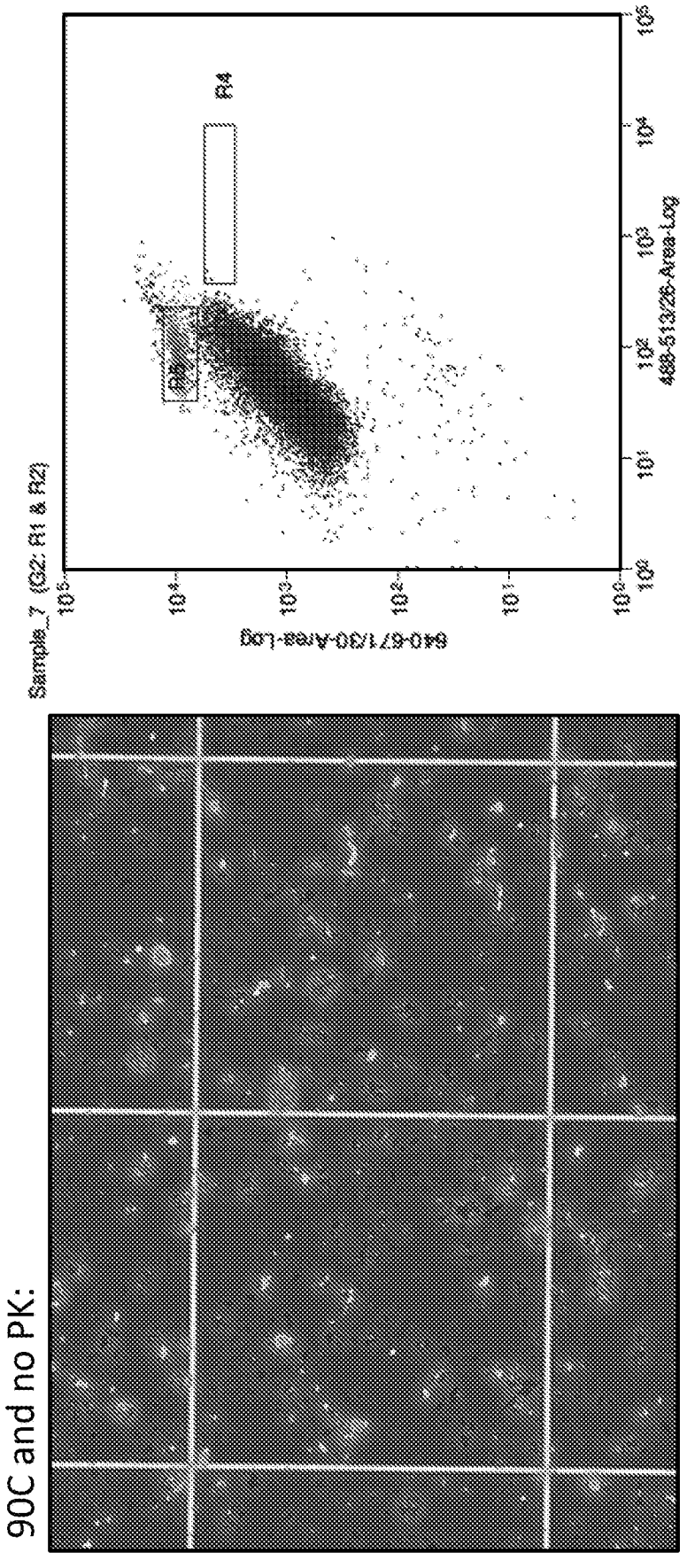

90C and no PK:
Sample_7 (G2: R1 & R2)
R4
R3
640-671/30-Area-Log
488-513/26-Area-Log

FIG. 5

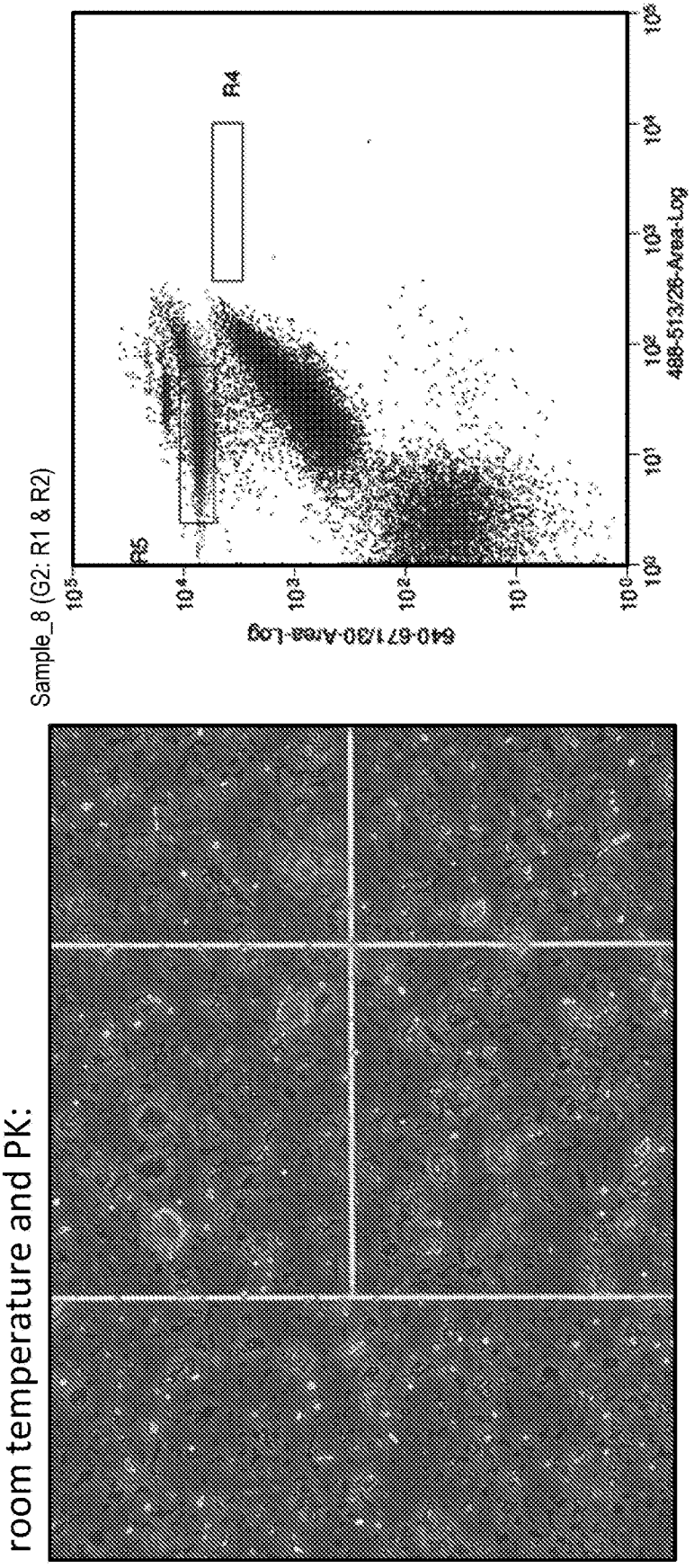

room temperature and PK:
Sample_8 (G2: R1 & R2)
R4
R5
488-513/26-Area-Log
640-671/30-Area-Log

FIG. 6

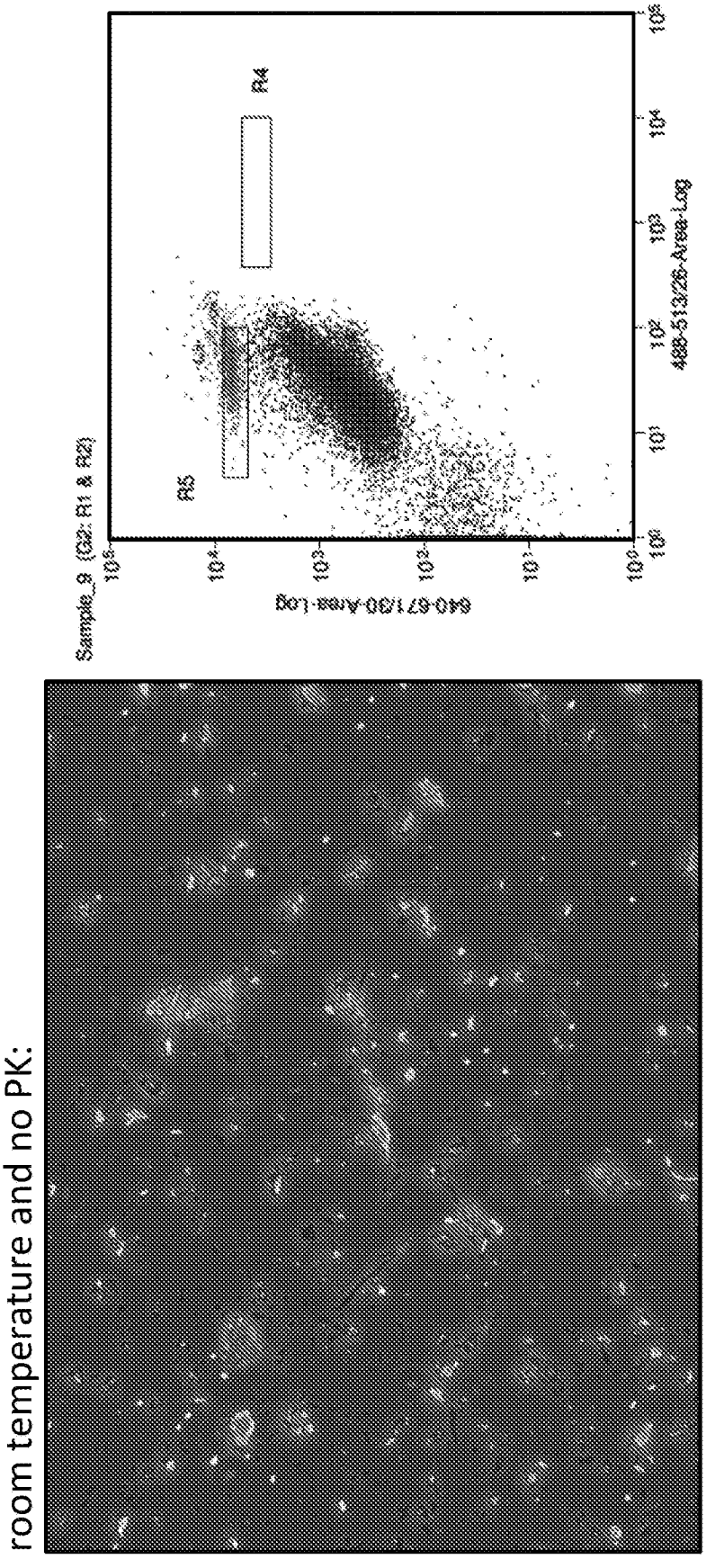

room temperature and no PK:
Sample_9 (G2; R1 & R2)
R4
R5
488-513/26-Area-Log
640-671/30-Area-Log

FIG. 7

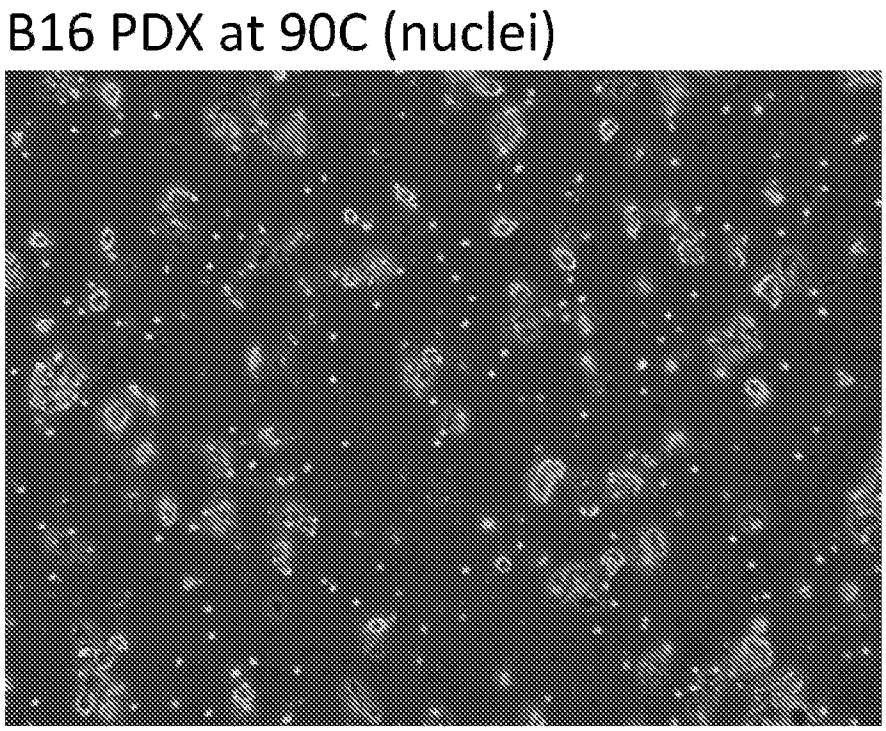


FIG. 8

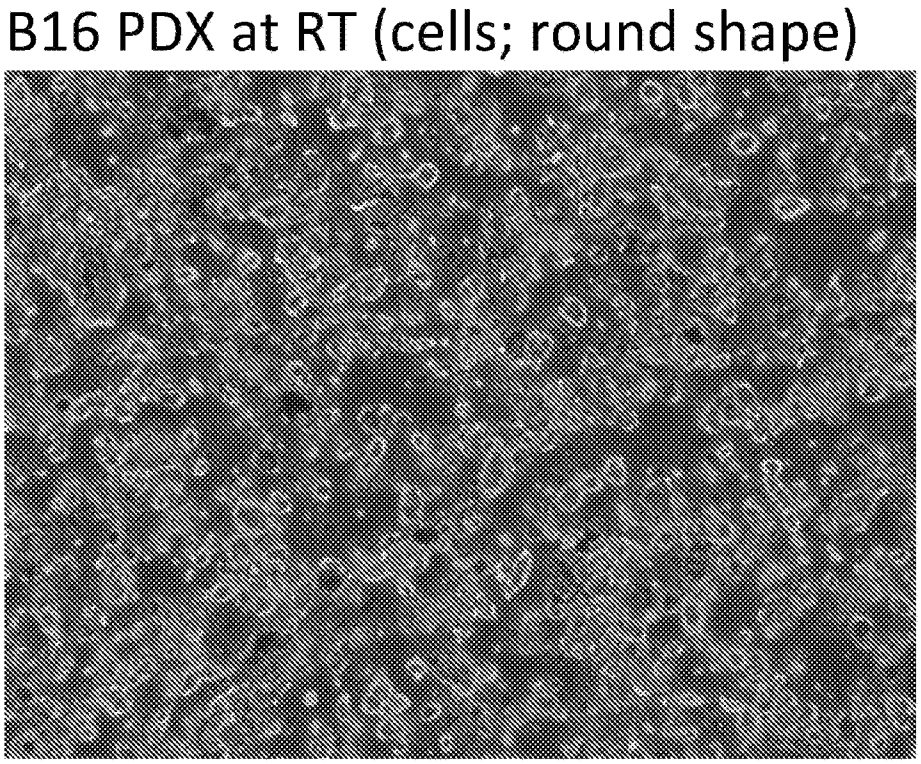


FIG. 9

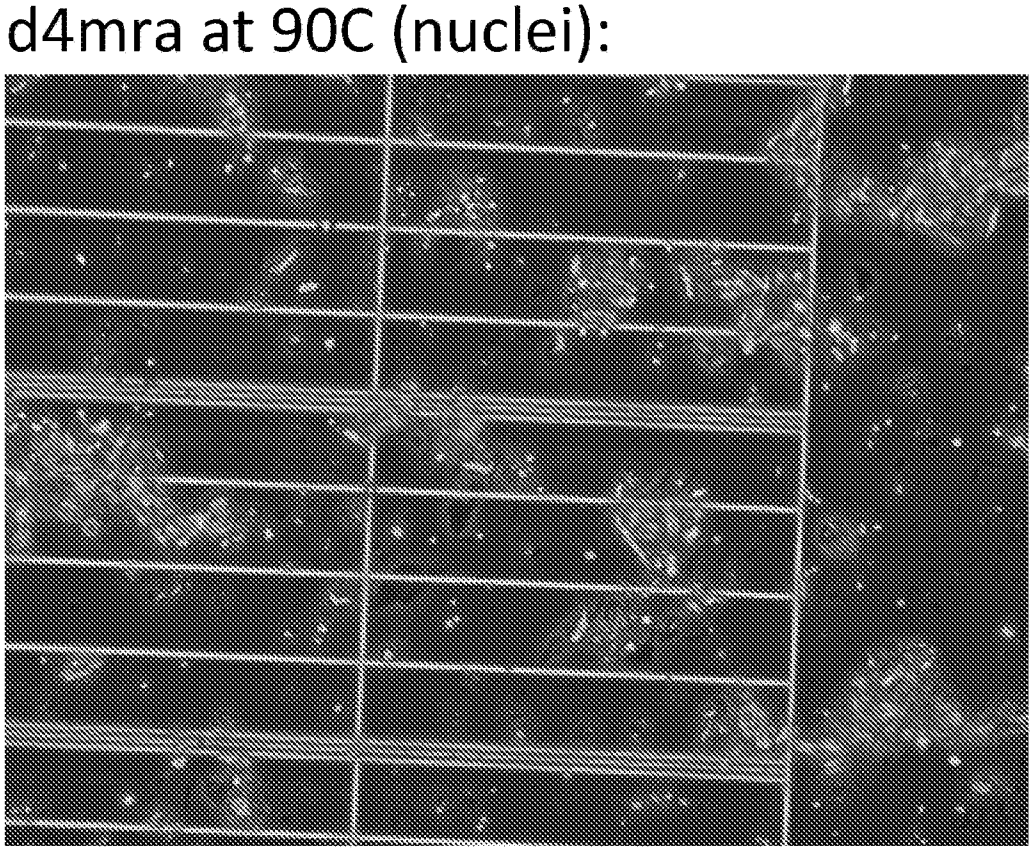


FIG. 10

d4mra at RT (whole cells; elongated shape):

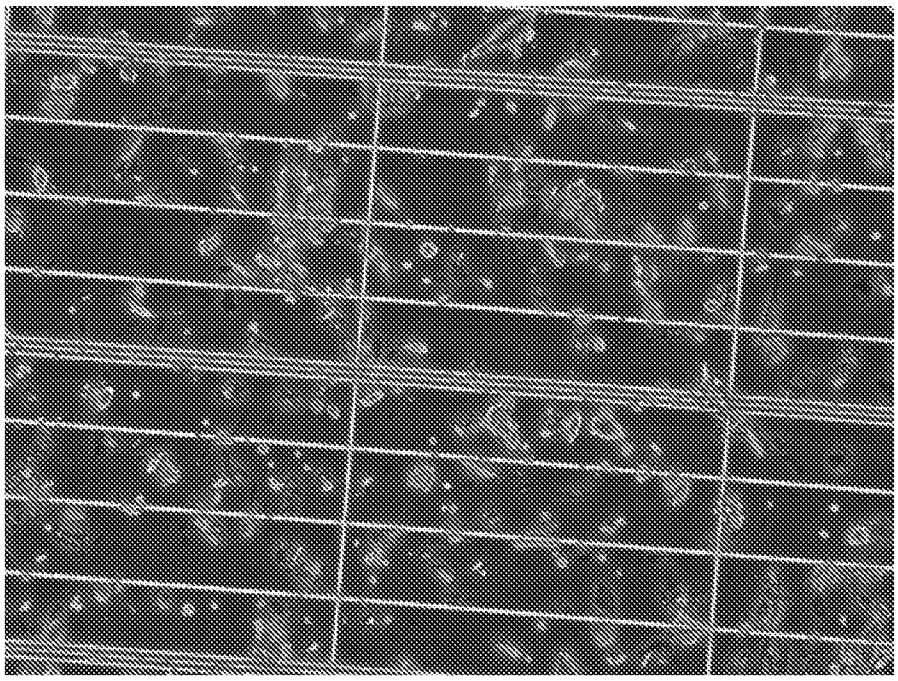


FIG. 11

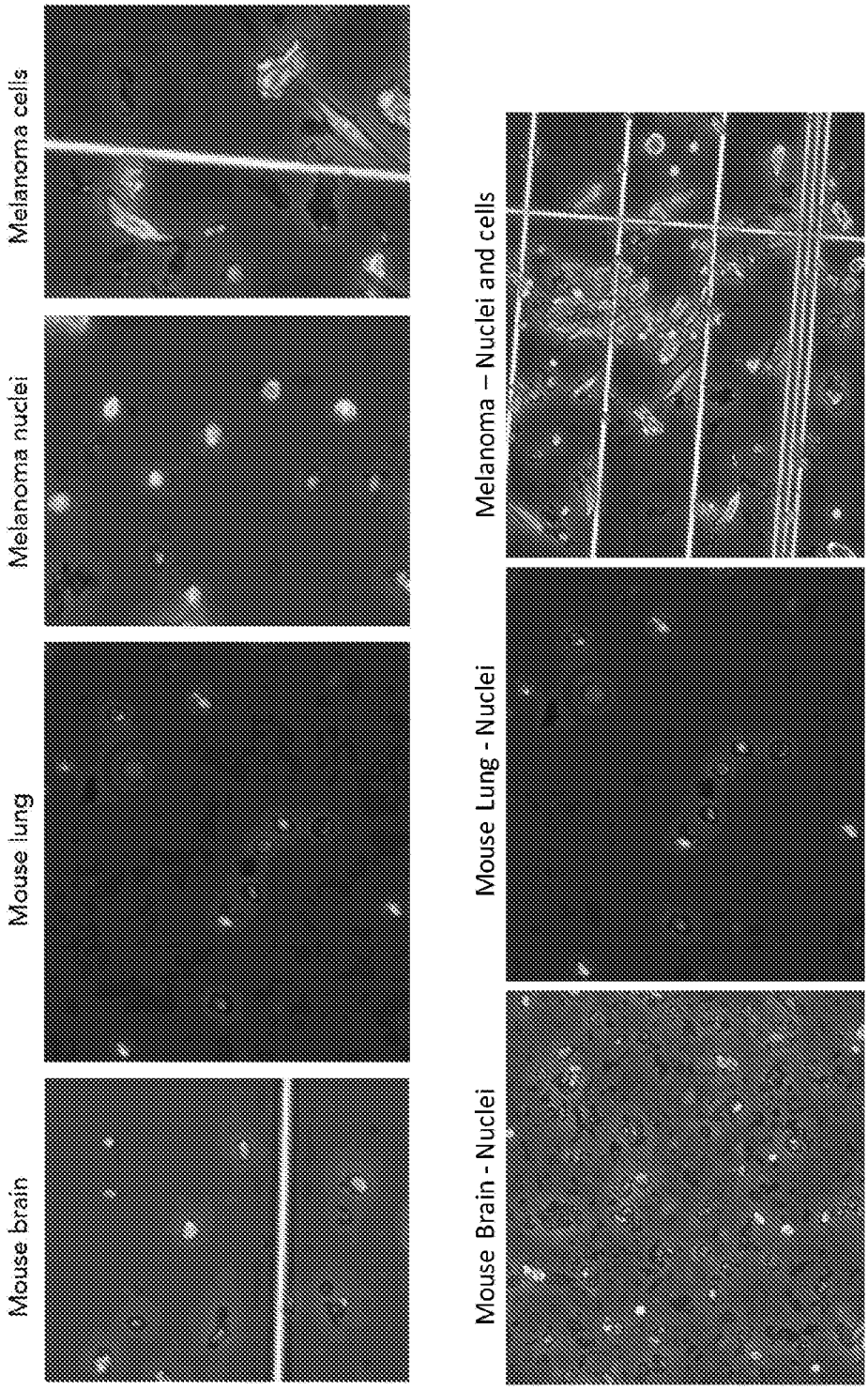

Mouse brain
Mouse lung
Melanoma nuclei
Melanoma cells
Mouse Brain - Nuclei
Mouse Lung - Nuclei
Melanoma – Nuclei and cells

FIG. 12

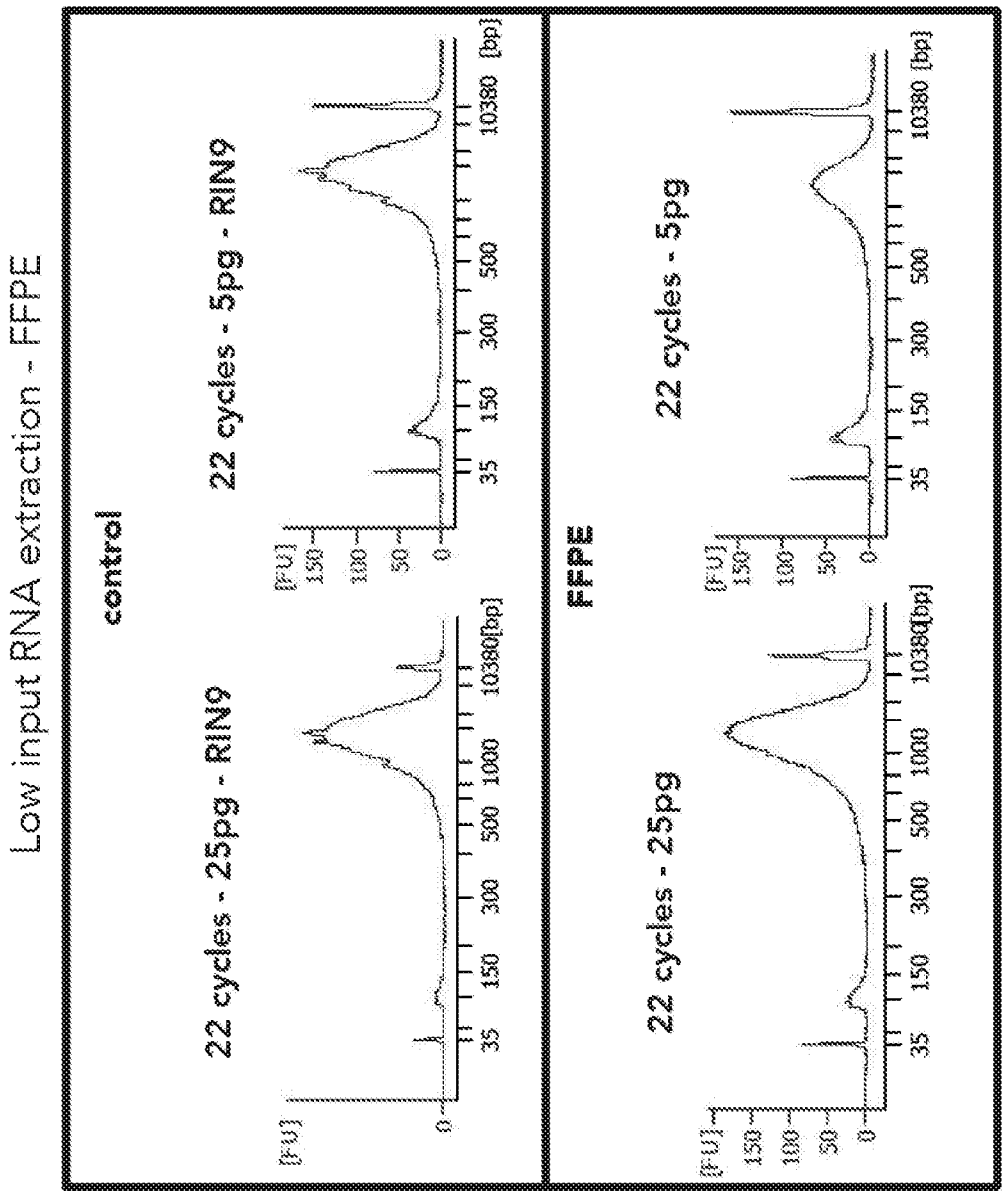

Low input RNA extraction - FFPE
control
22 cycles - 25pg - RIN9
22 cycles - 5pg - RIN9
FFPE
22 cycles - 25pg
22 cycles - 5pg
[FU]
[bp]
10380[bp]
FFPE RNA extraction
Total homogenate control
RIN:9
Xylene FFPE #1
RIN:2.60
Oil FFPE #2
RIN:3.90
[nt]

FIG. 13

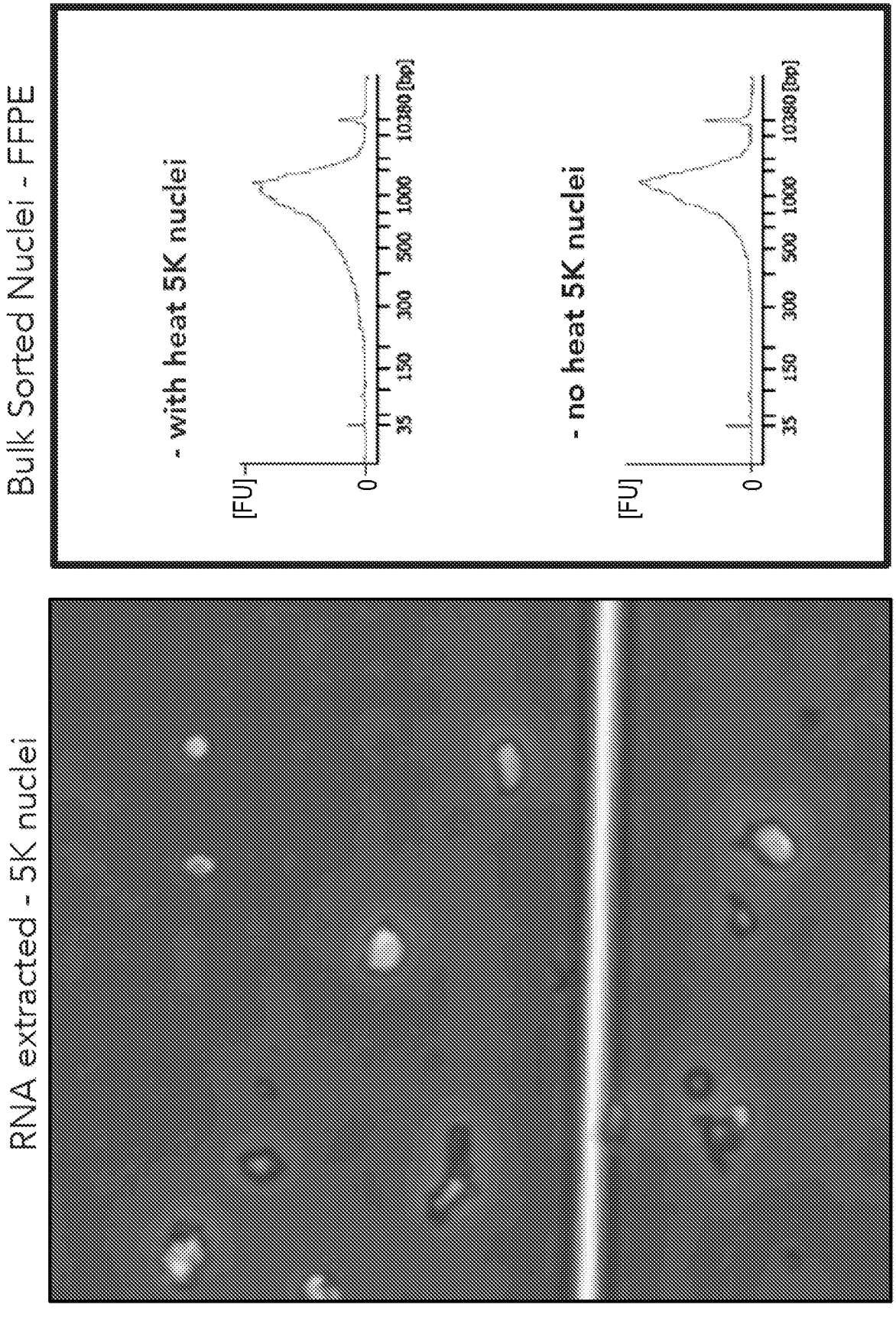

Bulk Sorted Nuclei - FFPE
- with heat 5K nuclei
[FU]
0
35
150
300
500
1000
10380 [bp]
- no heat 5K nuclei
[FU]
0
35
150
300
500
1000
10380 [bp]
RNA extracted - 5K nuclei

FIG. 14

cDNA of Bulk Sorted Nuclei – FFPE Mouse Brain

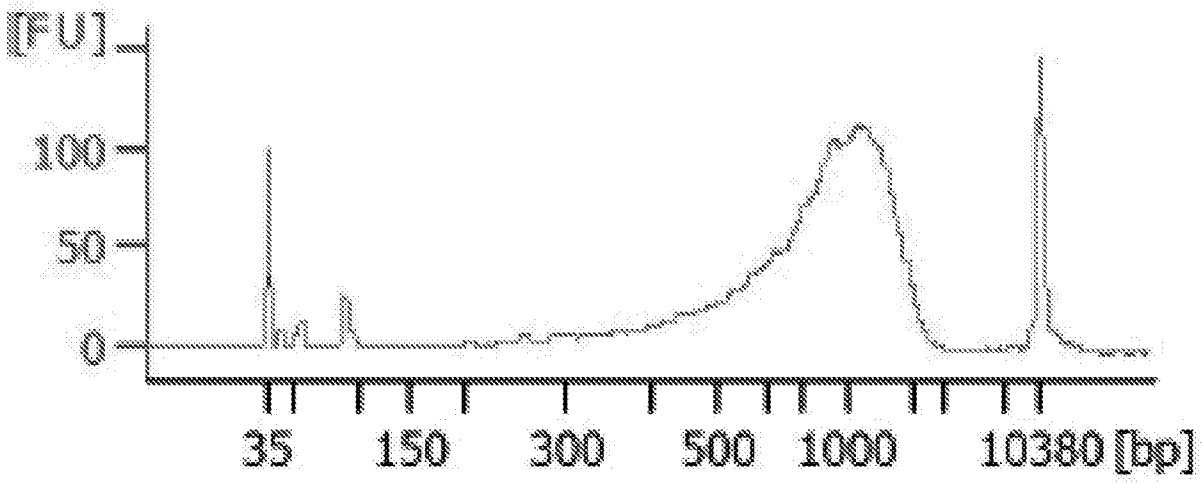


FIG. 15

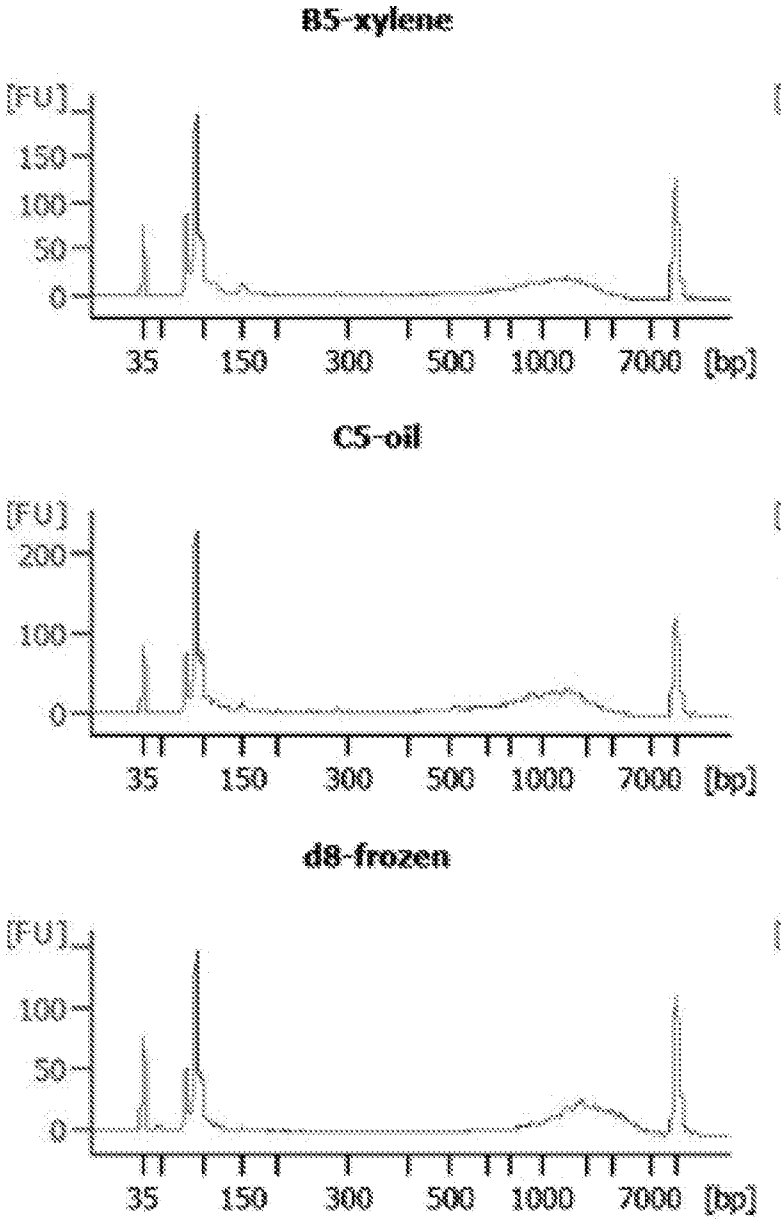

B5-xylene
[FU]
150
100
50
0
35
150
300
500
1000
7000
[bp]
C5-oil
[FU]
200
100
0
35
150
300
500
1000
7000
[bp]
d8-frozen
[FU]
100
50
0
35
150
300
500
1000
7000
[bp]

FIG. 16

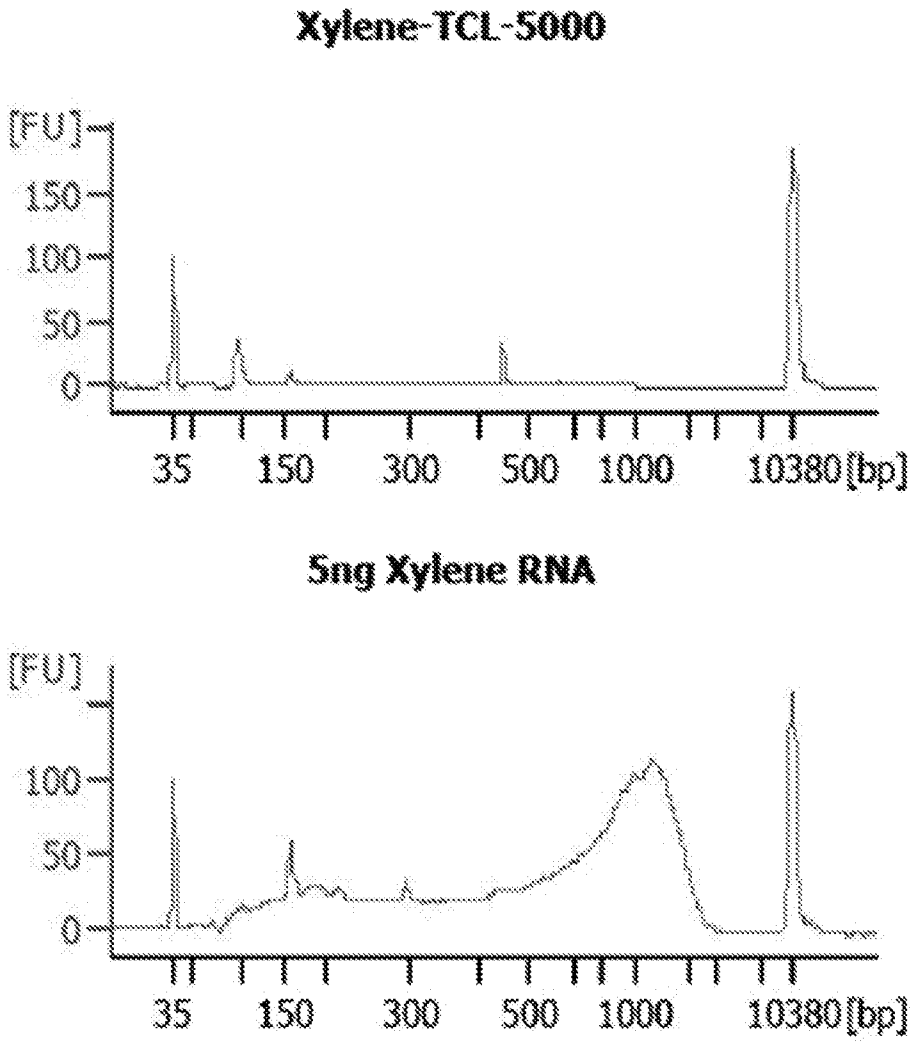

Xylene-TCL-5000
[FU]
150
100
50
0
35
150
300
500
1000
10380
[bp]
5ng Xylene RNA
[FU]
100
50
0
35
150
300
500
1000
10380
[bp]

FIG. 17

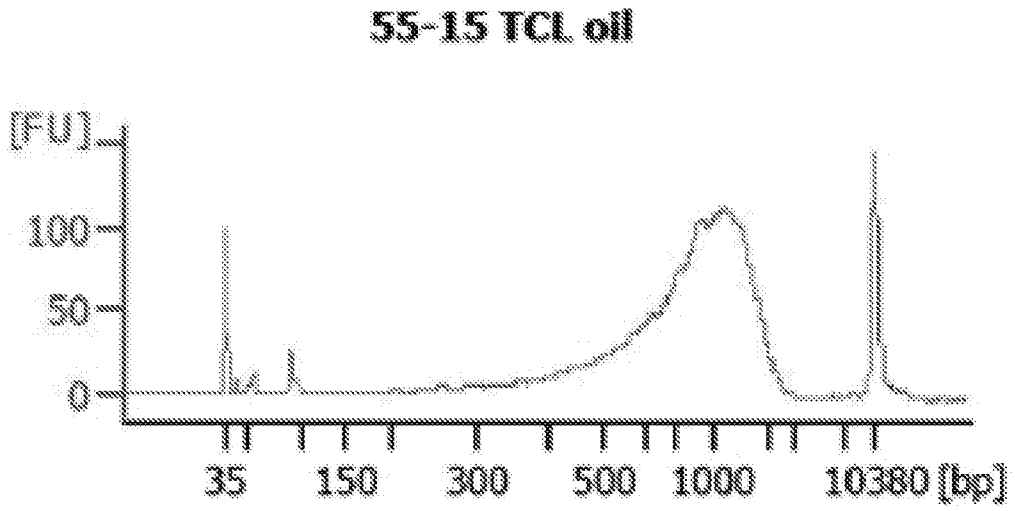

55-15 TCL oil
[FU]
100
50
0
35
150
300
500
1000
10380 [bp]

FIG. 18

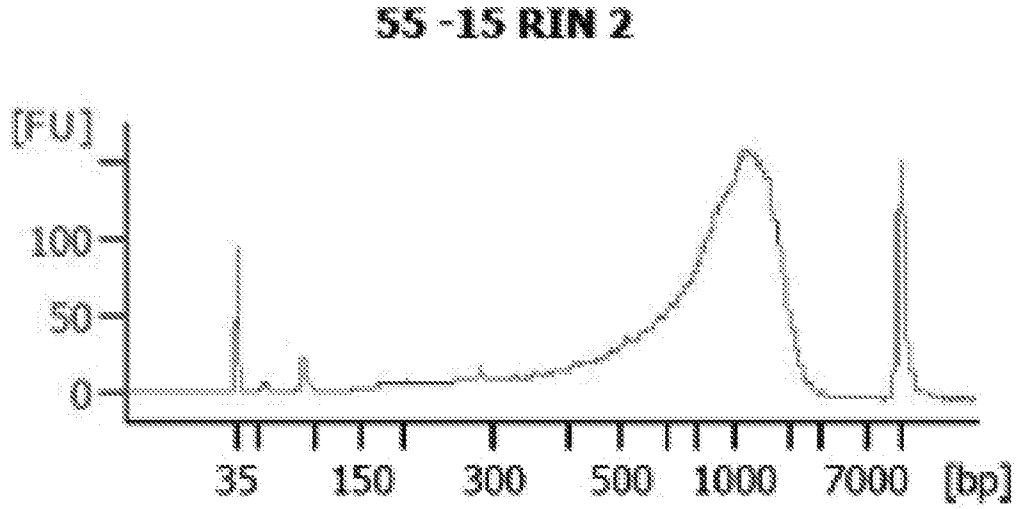

55 -15 RIN 2
[FU]
100
50
0
35
150
300
500
1000
7000
[bp]

FIG. 19

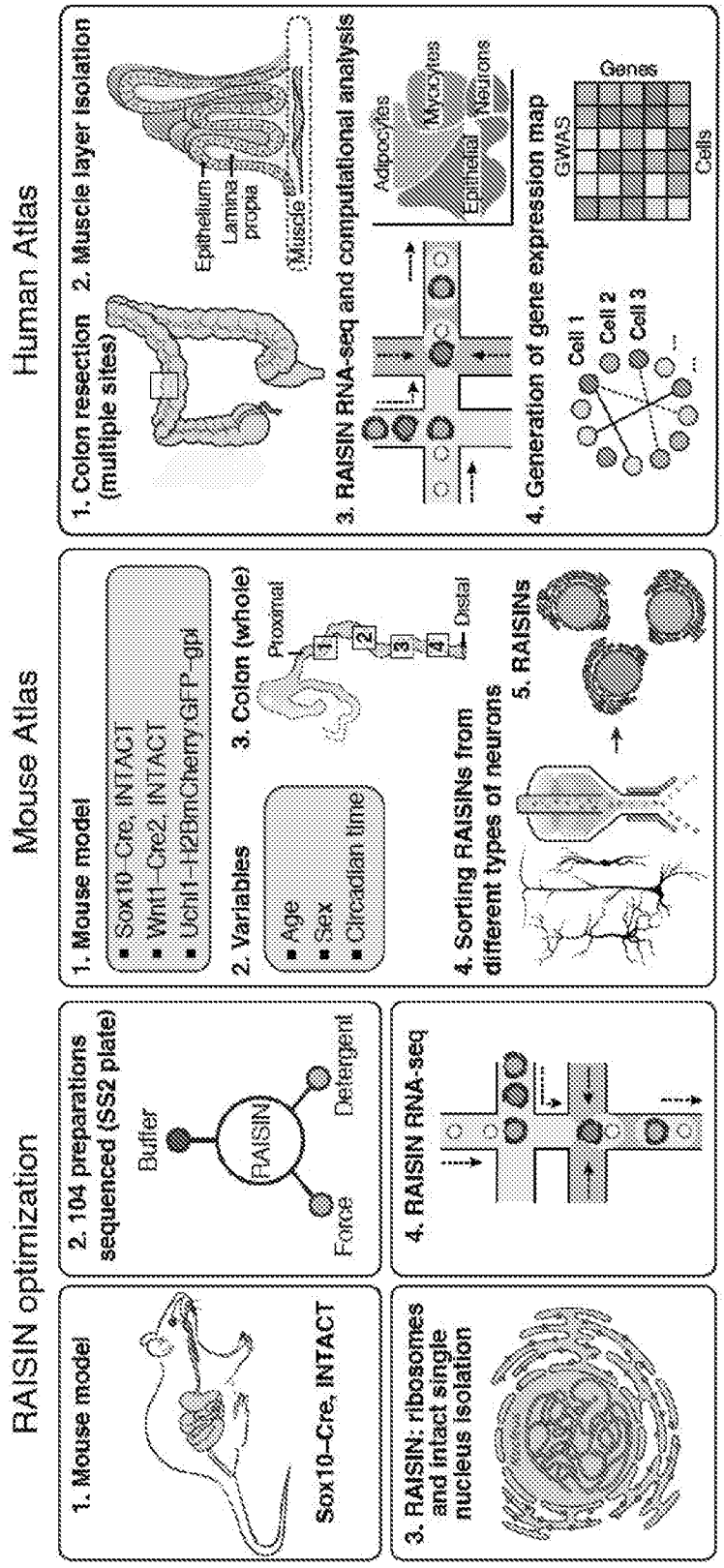

RAISIN optimization
1. Mouse model
Sox10–Cre, INTACT
2. 104 preparations sequenced (SS2 plate)
Buffer
RAISIN
Force
Detergent
3. RAISIN: ribosomes and intact single nucleus isolation
4. RAISIN RNA-seq
Mouse Atlas
1. Mouse model
Sox10–Cre, INTACT
Wnt1–Cre2, INTACT
Ucn1–H2Bmcherry:GFP–gpi
2. Variables
Age
Sex
Circadian time
3. Colon (whole)
Proximal
Distal
4. Sorting RAISINs from different types of neurons
5. RAISINs
Human Atlas
1. Colon resection (multiple sites)
2. Muscle layer isolation
Epithelium
Lamina propia
Muscle
3. RAISIN RNA-seq and computational analysis
Adipocytes
Myocytes
Epithelial
Neurons
4. Generation of gene expression map
GWAS
Cell 1
Cell 2
Cell 3
Genes
Cells

FIG. 20A

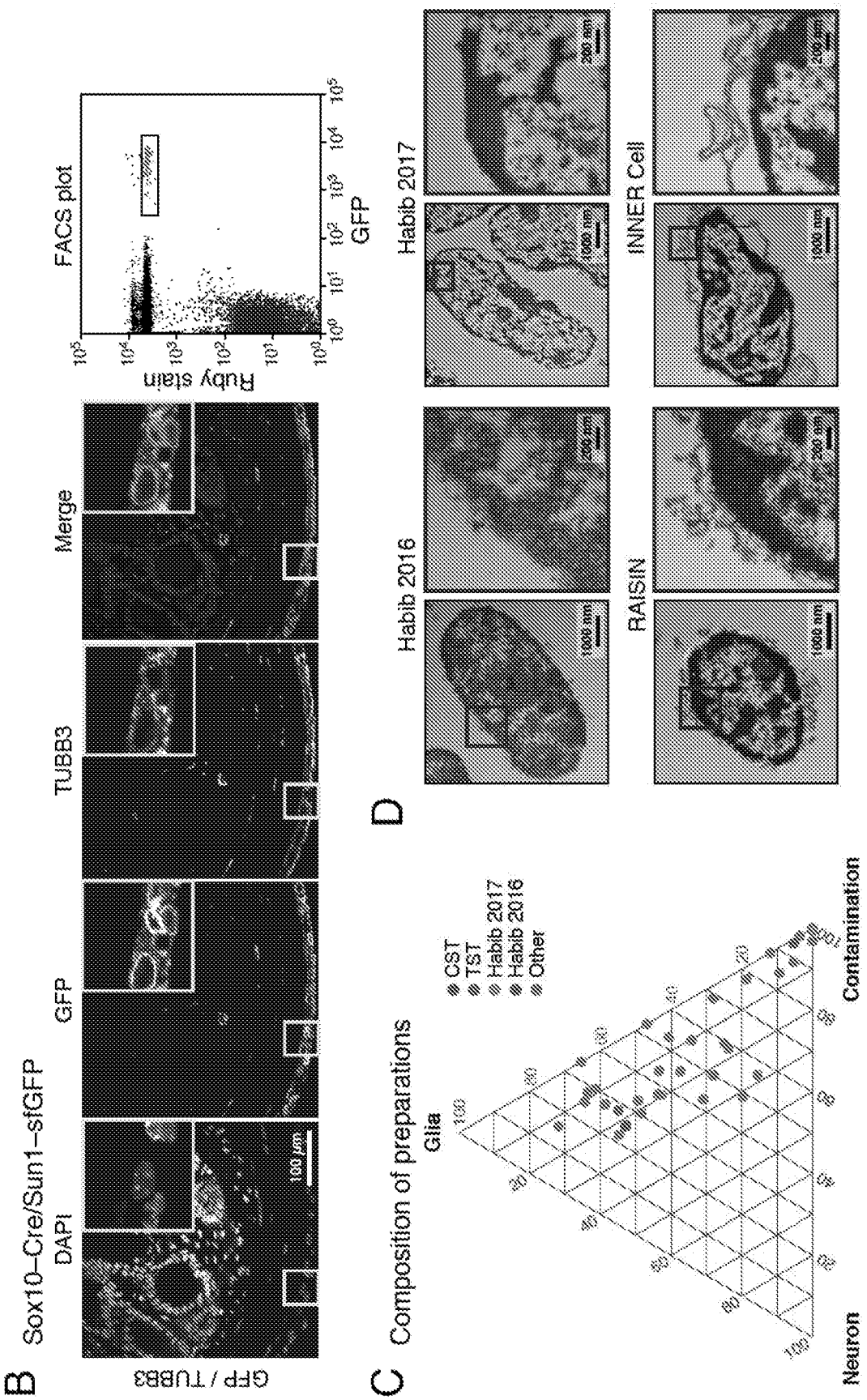

B
Sox10–Cre/Sun1–sfGFP
DAPI
GFP
TUBB3
Merge
GFP / TUBB3
100 μm
FACS plot
Ruby stain
GFP
C
Composition of preparations
Glia
Neuron
Contamination
CST
TST
Habib 2017
Habib 2016
Other
D
Habib 2016
Habib 2017
RAISIN
INNER Cell
1000 nm
250 nm
224 nm
200 nm

FIG. 20B-D

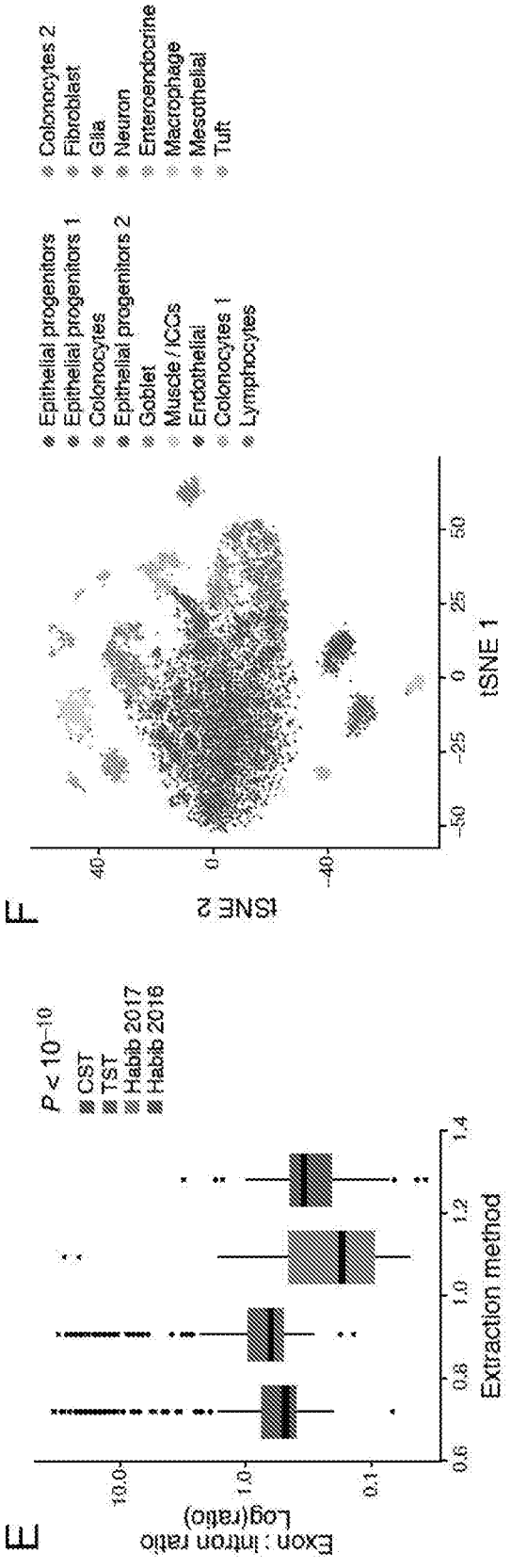

E
Exon : Intron ratio
Log(ratio)
10.0
1.0
0.1
0.6
0.8
1.0
1.2
1.4
Extraction method
P < 10^-10
CST
TST
Habib 2017
Habib 2016
F
tSNE 2
40
0
-40
-50
-25
0
25
50
tSNE 1
Epithelial progenitors
Epithelial progenitors 1
Colonocytes
Epithelial progenitors 2
Goblet
Muscle / ICCs
Endothelial
Colonocytes 1
Lymphocytes
Colonocytes 2
Fibroblast
Glia
Neuron
Enteroendocrine
Macrophage
Mesothelial
Tuft

FIG. 20E-F

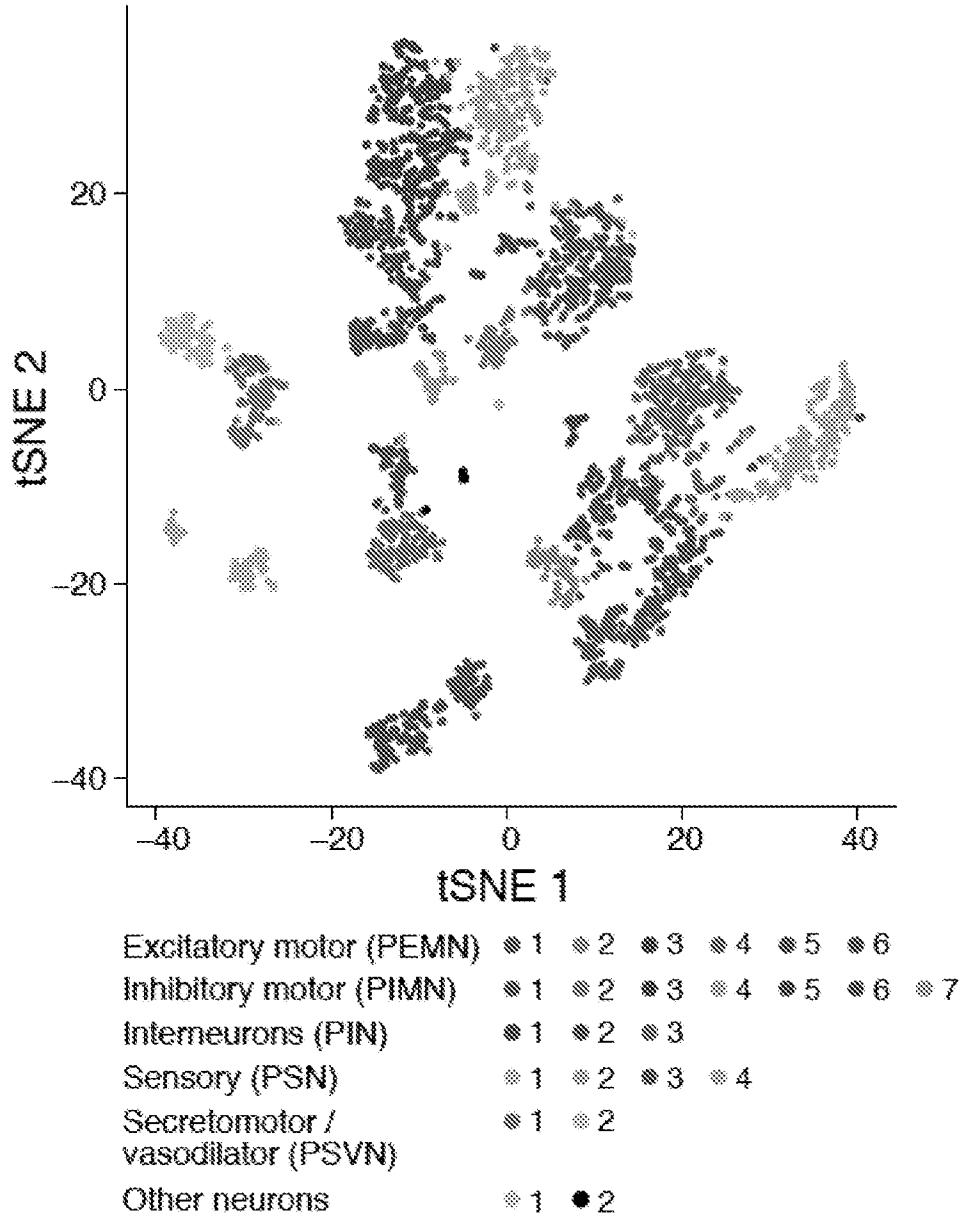

20
0
−20
−40
tSNE 2
−40
−20
0
20
40
tSNE 1
Excitatory motor (PEMN) 1 2 3 4 5 6
Inhibitory motor (PIMN) 1 2 3 4 5 6 7
Interneurons (PIN) 1 2 3
Sensory (PSN) 1 2 3 4
Secretomotor / vasodilator (PSVN) 1 2
Other neurons 1 2

FIG. 21A

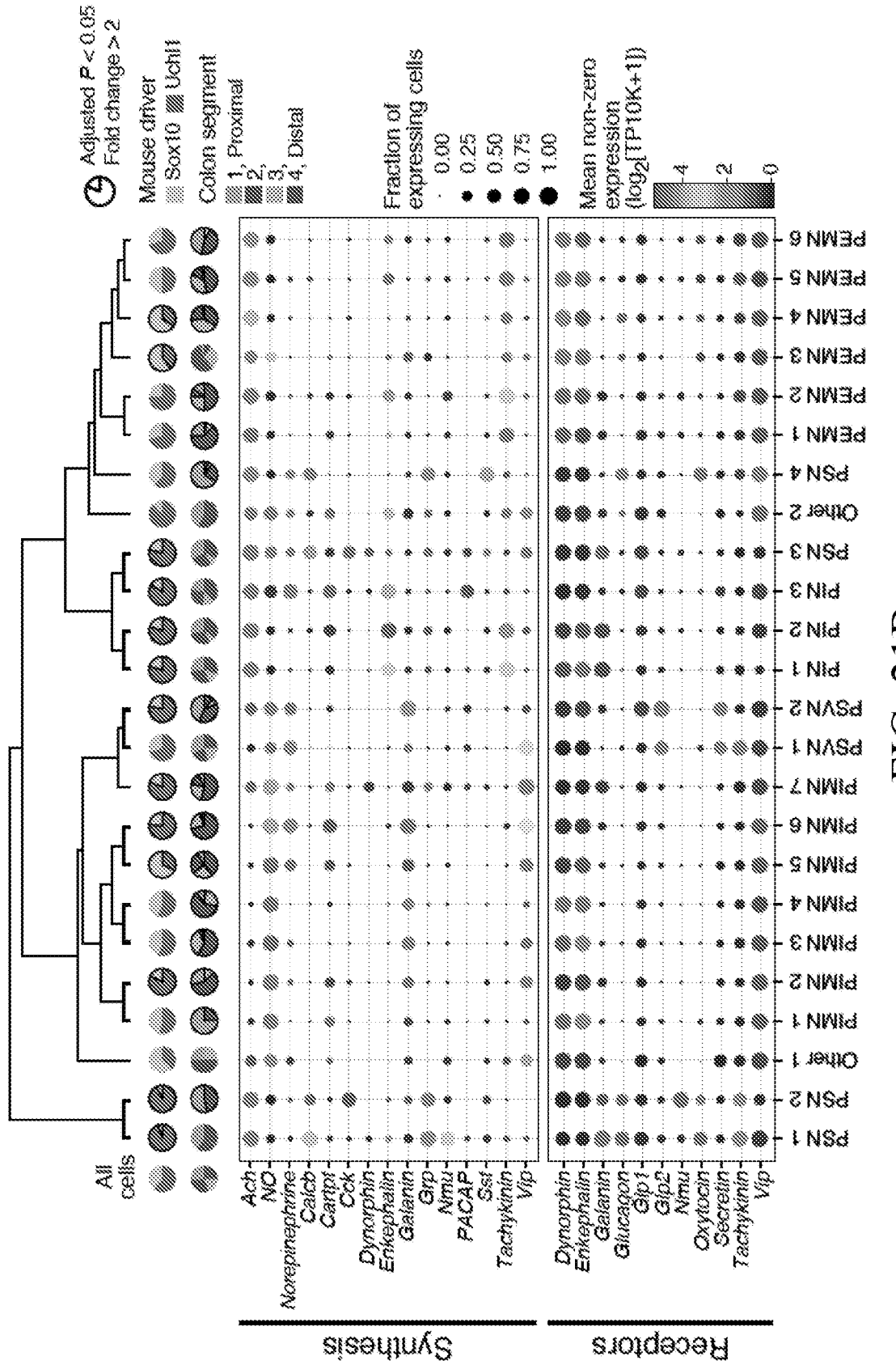

Adjusted P < 0.05
Fold change > 2
Mouse driver
Sox10
Uchl1
Colon segment
1, Proximal
2,
3,
4, Distal
Fraction of expressing cells
0.00
0.25
0.50
0.75
1.00
Mean non-zero expression (log2[TP10K+1])
4
2
0
All cells
Ach
NO
Norepinephrine
Calcb
Cartpt
Cck
Dynorphin
Enkephalin
Galanin
Grp
Nmu
PACAP
Sst
Tachykinin
Vip
Synthesis
Dynorphin
Enkephalin
Galanin
Glucagon
Glp1
Glp2
Nmu
Oxytocin
Secretin
Tachykinin
Vip
Receptors
PSN 1
PSN 2
Other 1
PIMN 1
PIMN 2
PIMN 3
PIMN 4
PIMN 5
PIMN 6
PIMN 7
PSVN 1
PSVN 2
PIN 1
PIN 2
PIN 3
PSN 3
Other 2
PSN 4
PEMN 1
PEMN 2
PEMN 3
PEMN 4
PEMN 5
PEMN 6

FIG. 21B

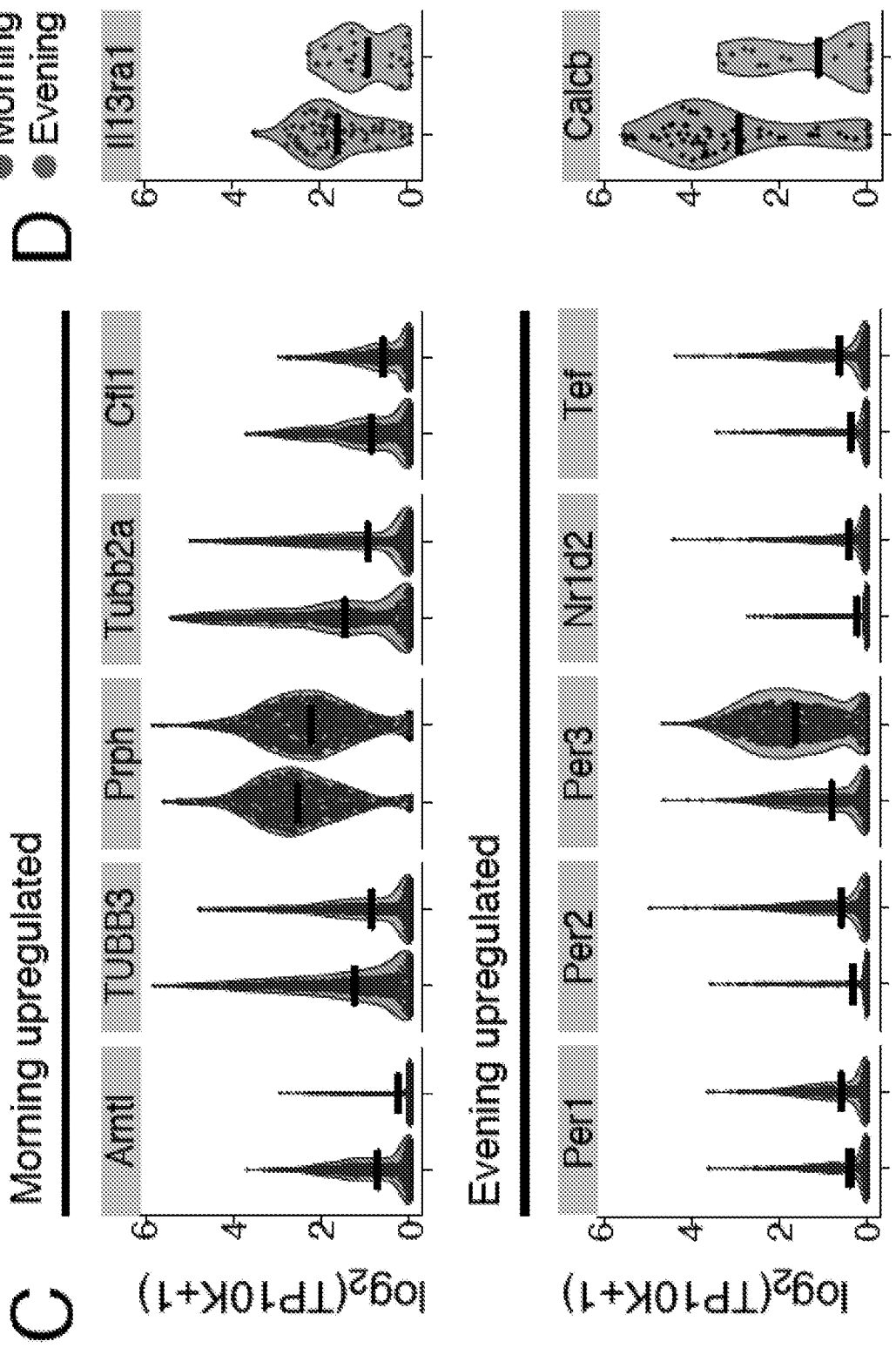

C
Morning upregulated
Amtl
TUBB3
Prpn
Tubb2a
Ctl1
log2(TP10K+1)
Evening upregulated
Per1
Per2
Per3
Nr1d2
Tef
D
Morning
Evening
Il13ra1
Calcb

FIG. 21C-D

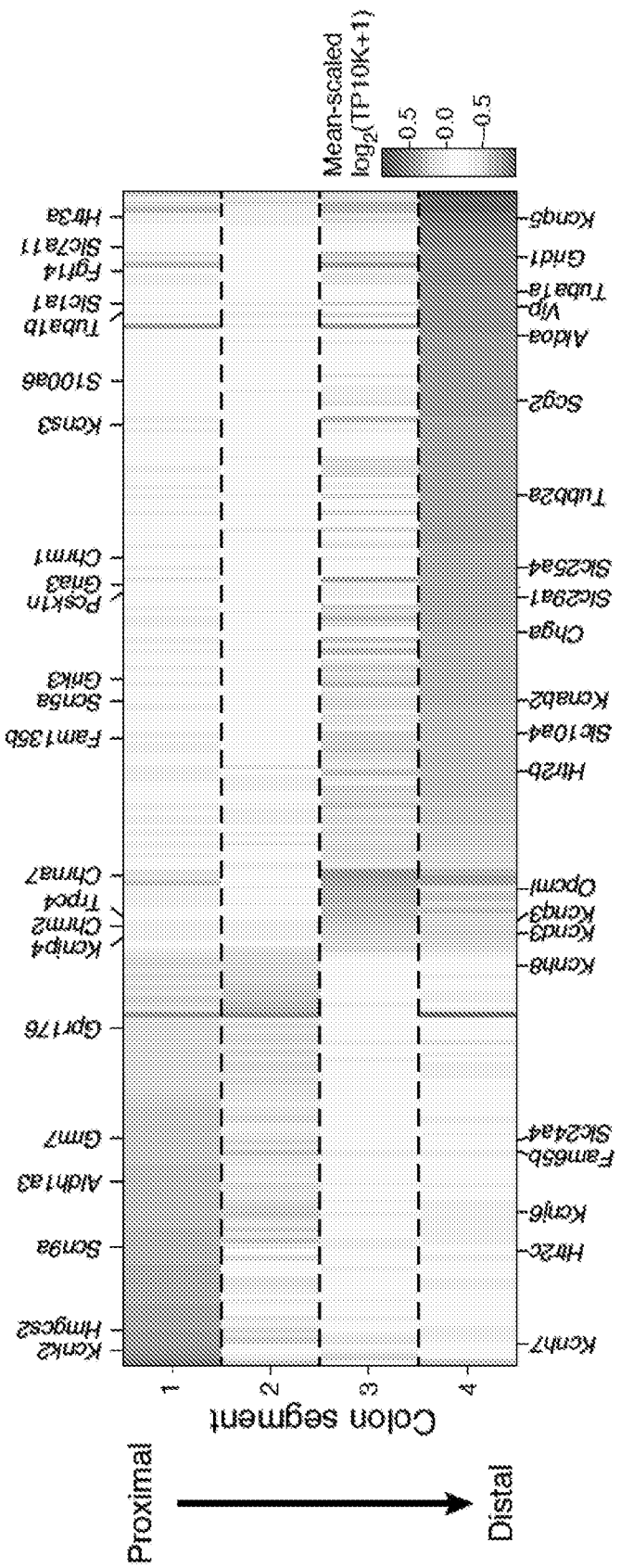

Mean-scaled
log2(TP10K+1)
0.5
0.0
-0.5
Kcnq5
Gnb1
Tuba1a
Vip
Aldoa
Scg2
Tubb2a
Slc25a4
Slc29a1
Chga
Kcnab2
Slc10a4
Hlx2b
Cpcml
Kcnj3
Kcnj3
Kcnh8
Fam65b
Slc24a4
Kcnj6
Hlx2c
Kcnh7
Gpr176
Gmr7
Aldh1a3
Scn9a
Hmgcs2
Kcnk2
Kcnip4
Chrm2
Trpc4
Chrna7
Fam135b
Scn5a
Gnb3
Pgsk1n
Gnai3
Chrm1
S100a6
Kcns3
Tuba1b
Slc1a1
Fgf14
Slc7a11
Htr3a
1
2
3
4
Colon segment
Proximal
Distal

FIG. 21E

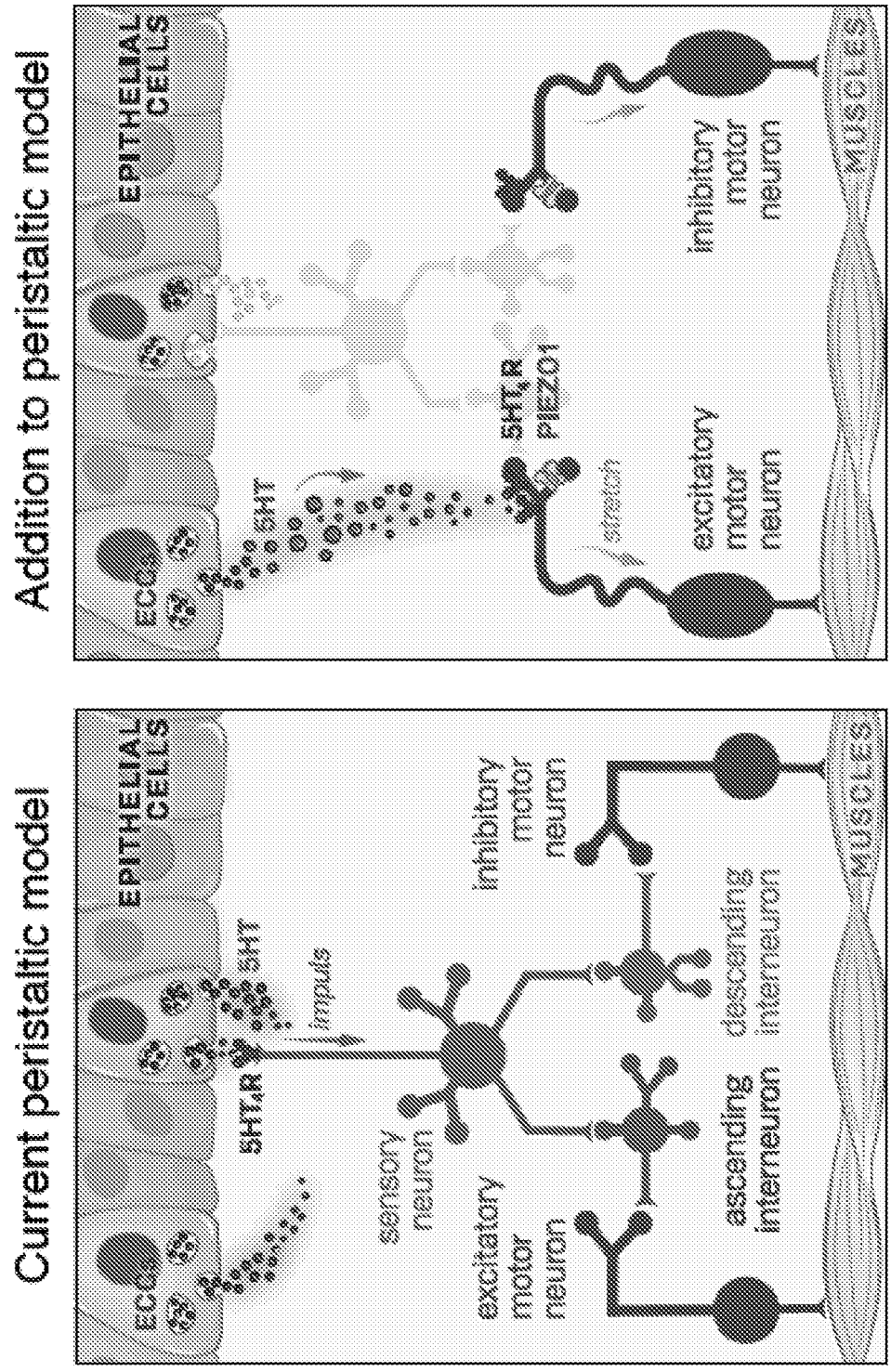

Current peristaltic model
EPITHELIAL CELLS
EC
5HT4R
5HT
impuls
sensory neuron
excitatory motor neuron
inhibitory motor neuron
ascending interneuron
descending interneuron
MUSCLES
Addition to peristaltic model
EPITHELIAL CELLS
EC
5HT
5HT4R
PIEZO1
stretch
excitatory motor neuron
inhibitory motor neuron
MUSCLES

FIG. 21F

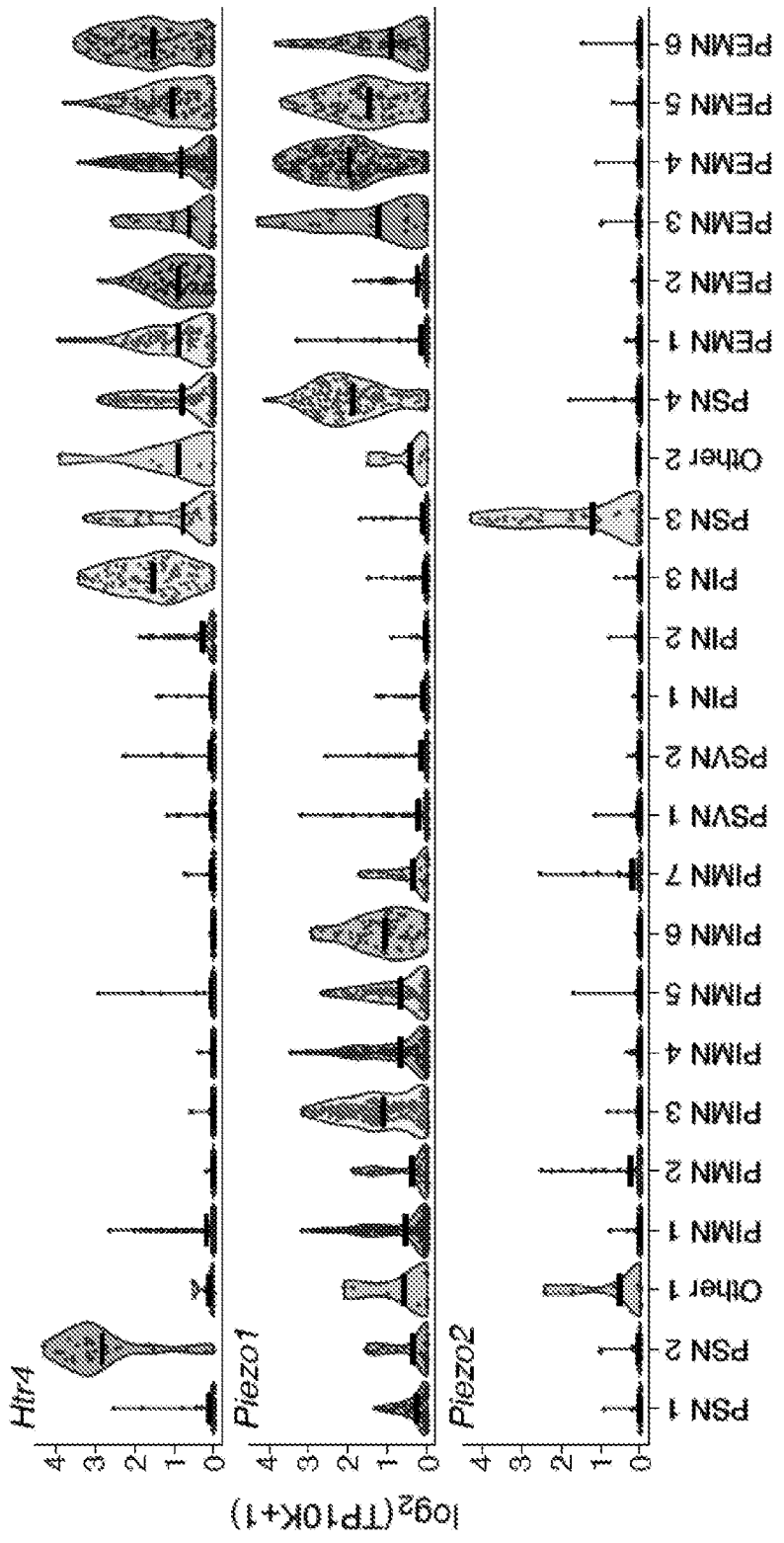

Htr4
Piezo1
Piezo2
log2(TP10K+1)
0
1
2
3
4
PSN 1
PSN 2
Other 1
PIMN 1
PIMN 2
PIMN 3
PIMN 4
PIMN 5
PIMN 6
PIMN 7
PSVN 1
PSVN 2
PIN 1
PIN 2
PIN 3
PSN 3
Other 2
PSN 4
PEMN 1
PEMN 2
PEMN 3
PEMN 4
PEMN 5
PEMN 6

FIG. 21G

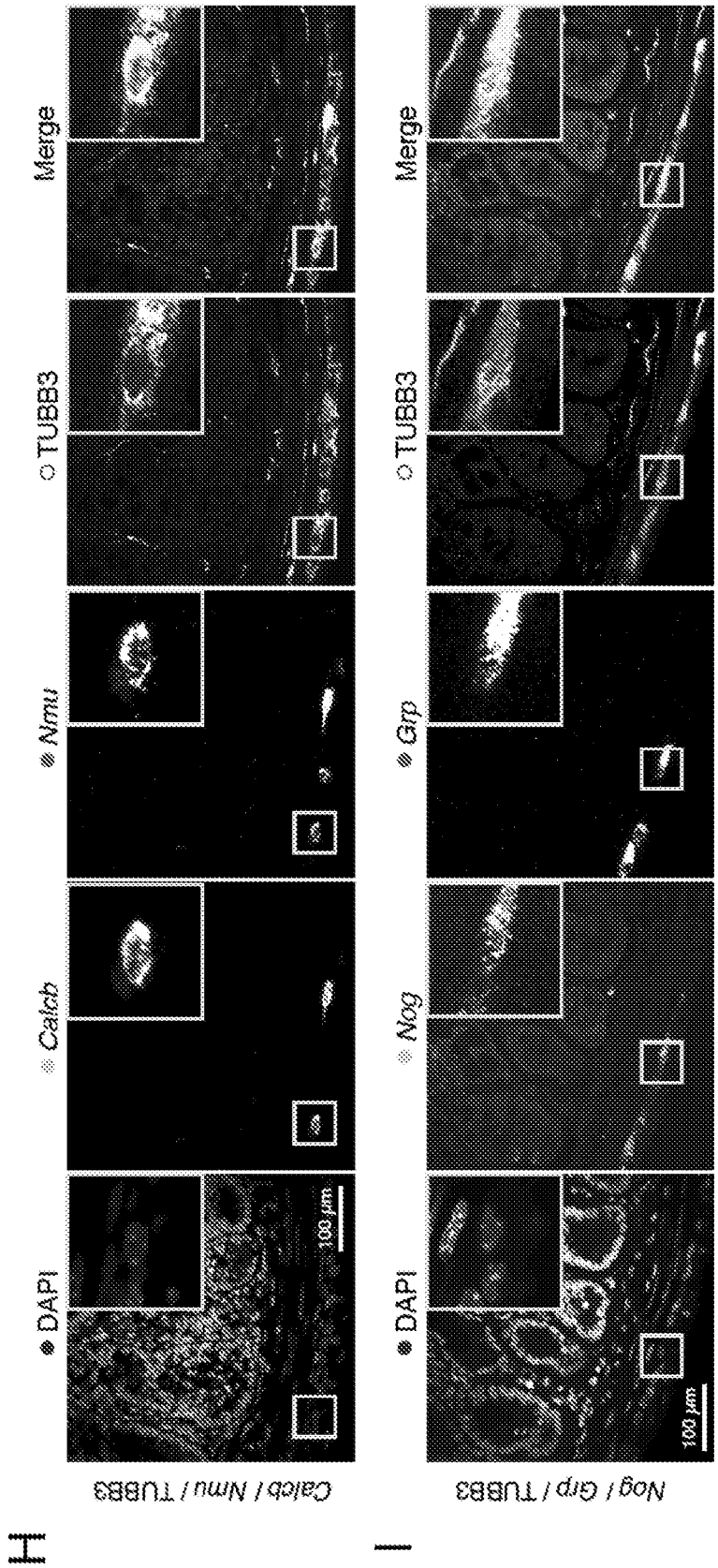

H
I
DAPI
Calcb
Nmu
TUBB3
Merge
Calcb / Nmu / TUBB3
Nog
Grp
Nog / Grp / TUBB3
100 µm

FIG. 21H-I

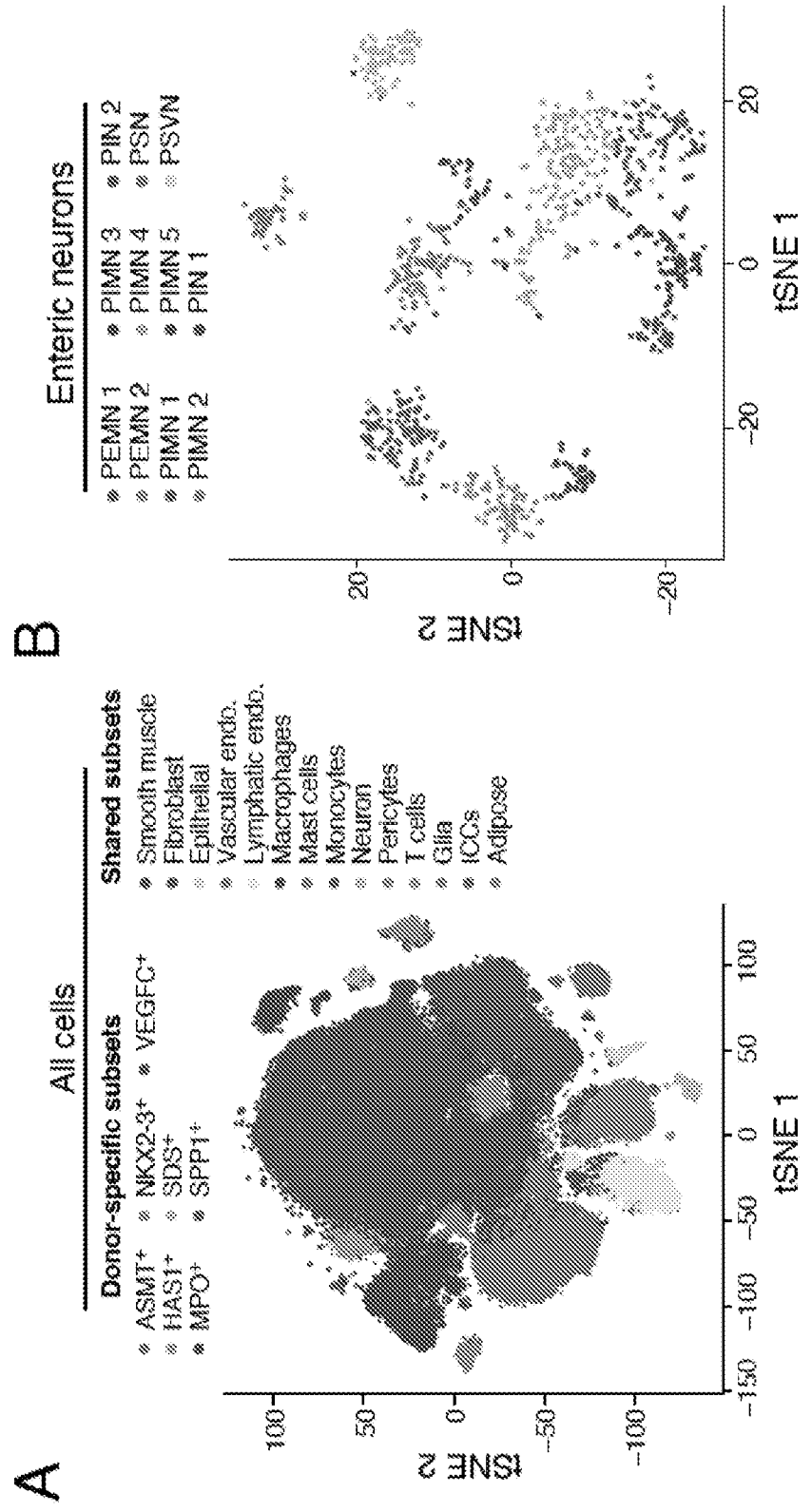

A
All cells
Donor-specific subsets
ASMT+
NKX2-3+
VEGFC+
HAS1+
SDS+
MPO+
SPP1+
Shared subsets
Smooth muscle
Fibroblast
Epithelial
Vascular endo.
Lymphatic endo.
Macrophages
Mast cells
Monocytes
Neuron
Pericytes
T cells
Glia
ICCs
Adipose
tSNE 2
tSNE 1
B
Enteric neurons
PEMN 1
PEMN 2
PIMN 1
PIMN 2
PIMN 3
PIMN 4
PIMN 5
PIN 1
PIN 2
PSN
PSVN
tSNE 2
tSNE 1

FIG. 22A-B

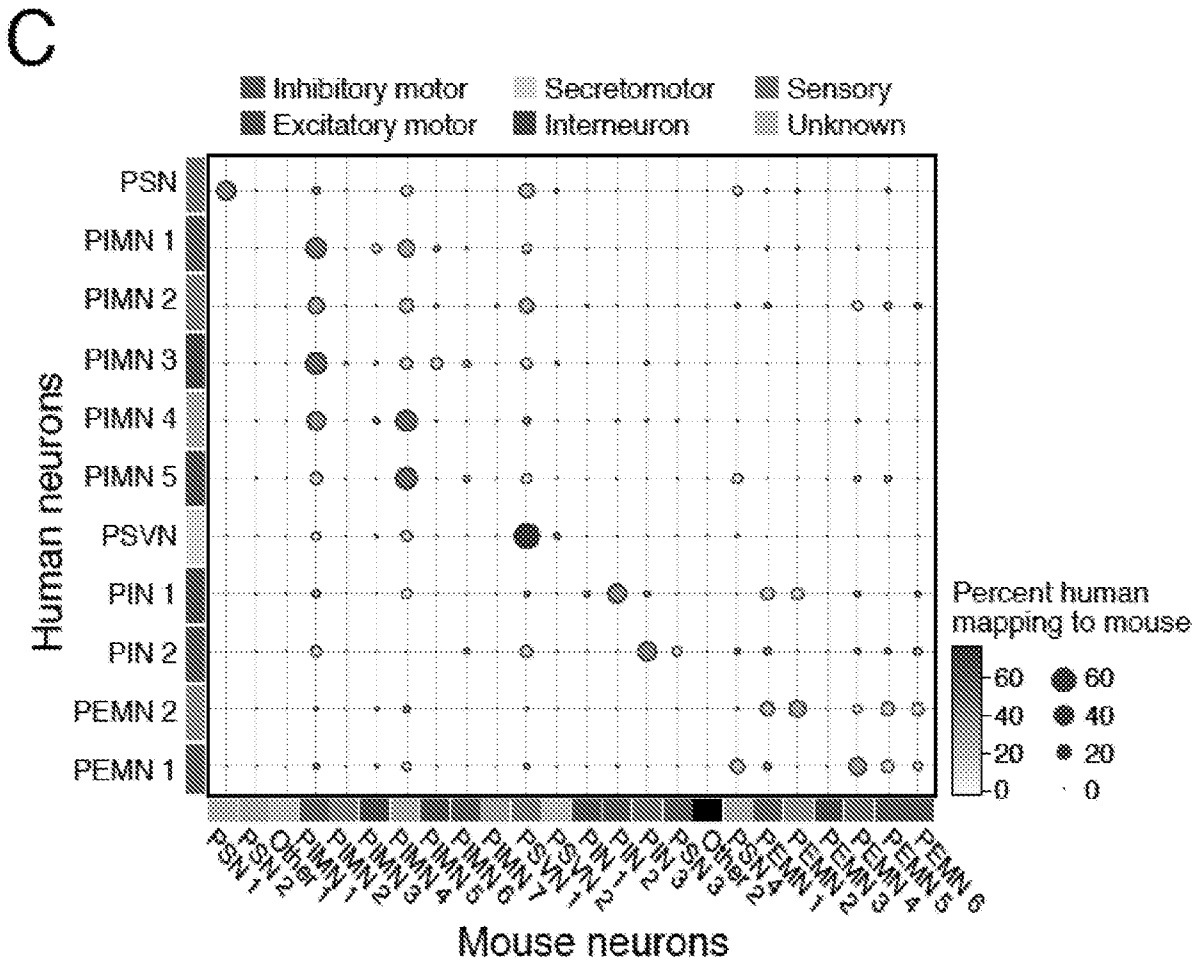

C
Inhibitory motor
Excitatory motor
Secretomotor
Interneuron
Sensory
Unknown
Human neurons
PSN
PIMN 1
PIMN 2
PIMN 3
PIMN 4
PIMN 5
PSVN
PIN 1
PIN 2
PEMN 2
PEMN 1
Percent human mapping to mouse
60
40
20
0
Mouse neurons

FIG. 22C

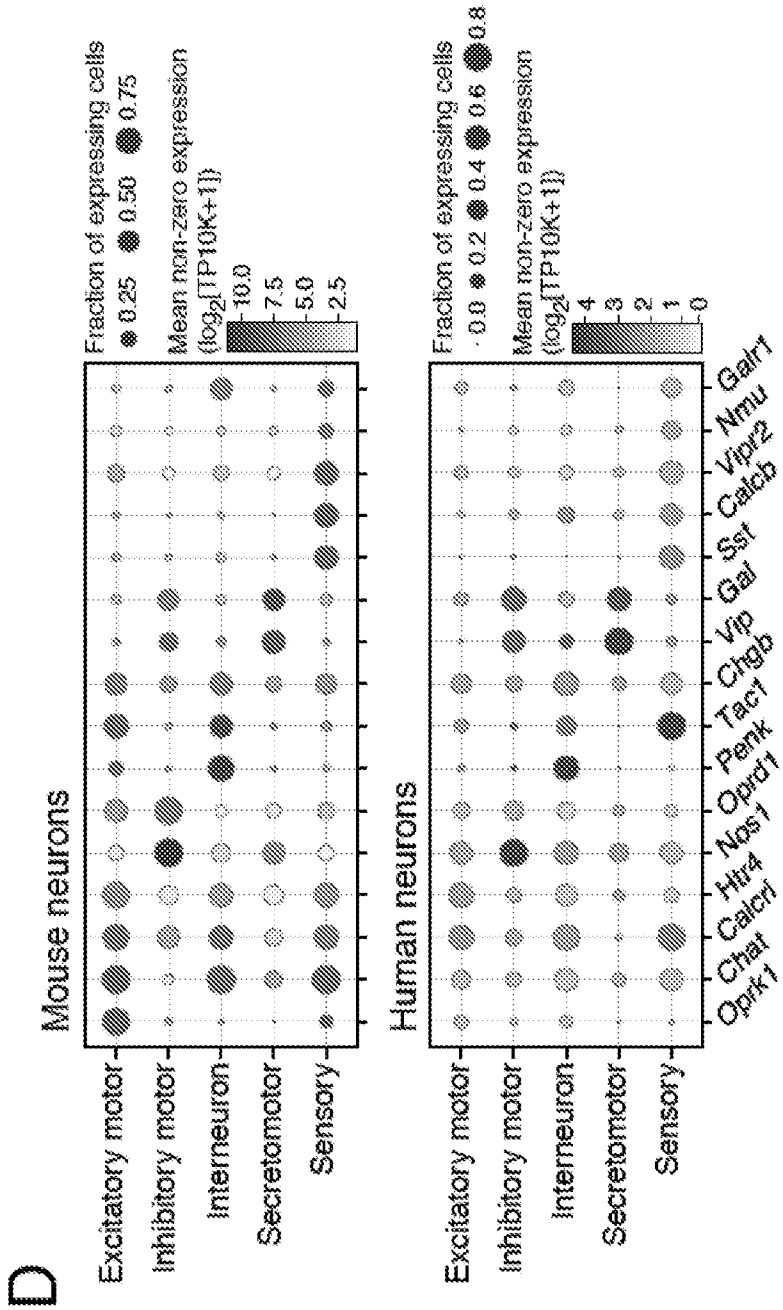

D
Mouse neurons
Human neurons
Excitatory motor
Inhibitory motor
Interneuron
Secretomotor
Sensory
Fraction of expressing cells
0.25
0.50
0.75
Mean non-zero expression
(log2[TP10K+1])
10.0
7.5
5.0
2.5
0.0
0.2
0.4
0.6
0.8
4
3
2
1
0
Oprk1
Chat
Calcrl
Htr4
Nos1
Oprd1
Penk
Tac1
Chgb
Vip
Gal
Sst
Calcb
Vipr2
Nmu
Galr1

FIG. 22D

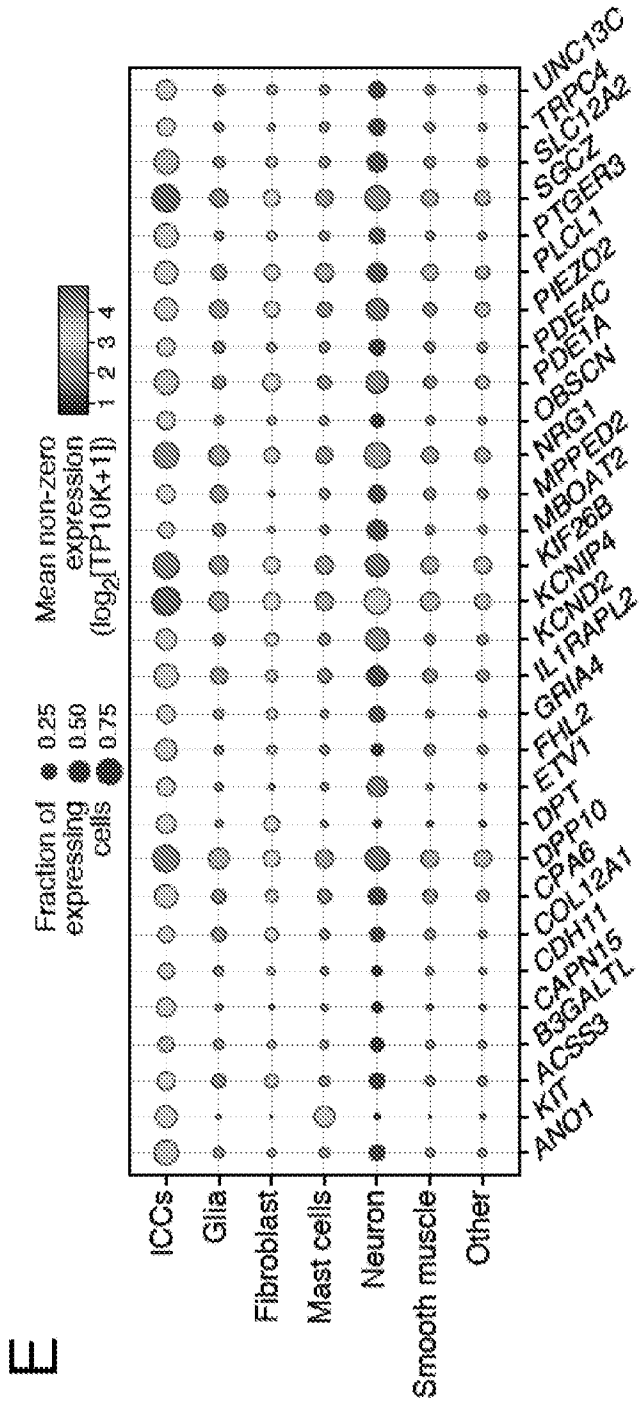

E
Fraction of expressing cells
0.25
0.50
0.75
Mean non-zero expression (log_2[TP10K+1])
1 2 3 4
ICCs
Glia
Fibroblast
Mast cells
Neuron
Smooth muscle
Other
ANO1
KIT
ACSS3
B3GALTL
CAPN15
CDH11
COL12A1
CPA6
DPP10
DPT
ETV1
FHL2
GRIA4
IL1RAPL2
KCND2
KCNIP4
KIF26B
MBOAT2
MPPED2
NRG1
OBSCN
PDE1A
PDE4C
PIEZO2
PLCL1
PTGER3
SGCZ
SLC12A2
TRPC4
UNC13C

FIG. 22E

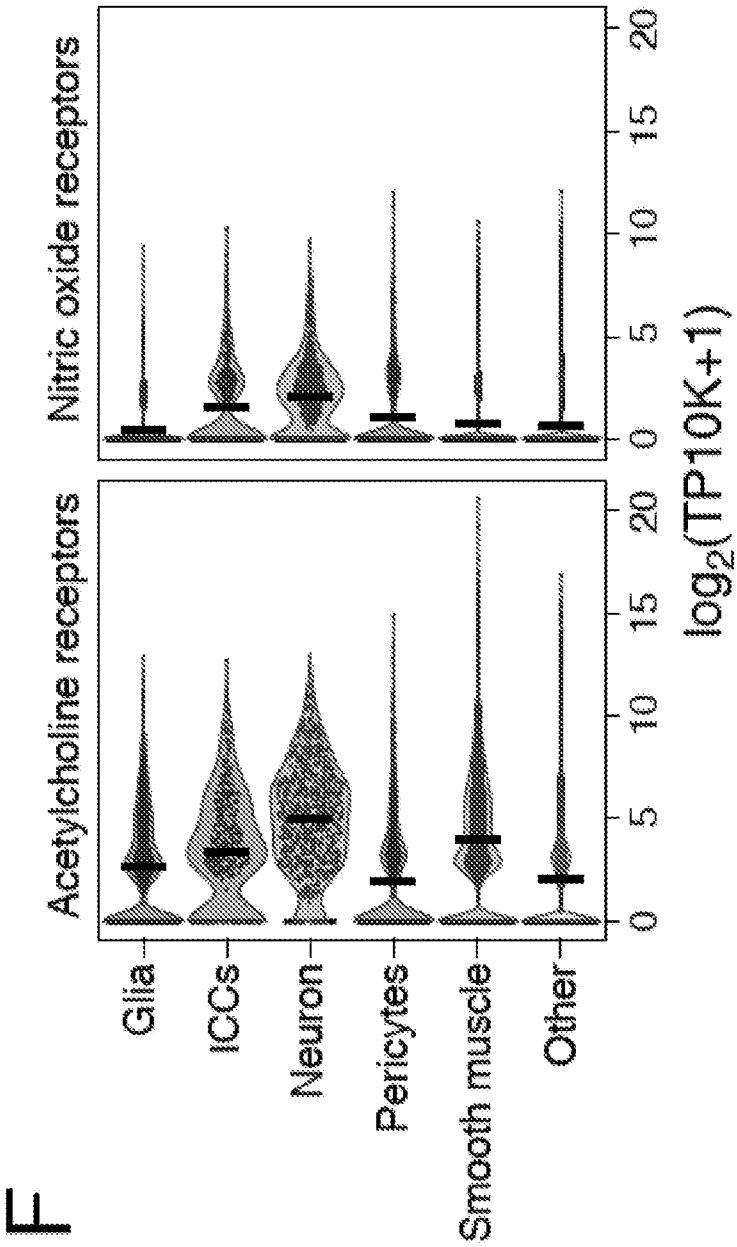

F
Acetylcholine receptors
Nitric oxide receptors
0
5
10
15
20
Glia
ICCs
Neuron
Pericytes
Smooth muscle
Other
log2(TP10K+1)

FIG. 22F

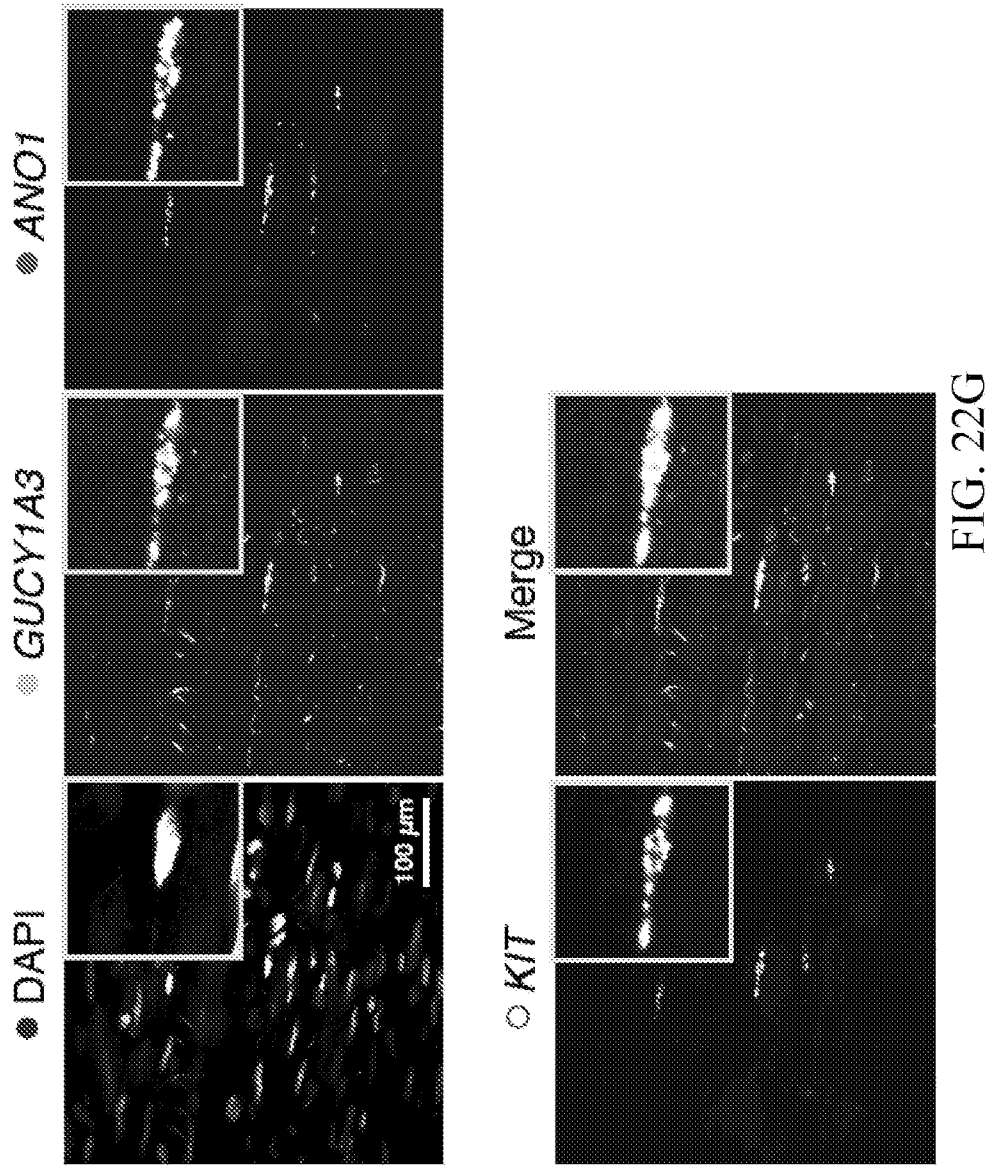


FIG. 22G

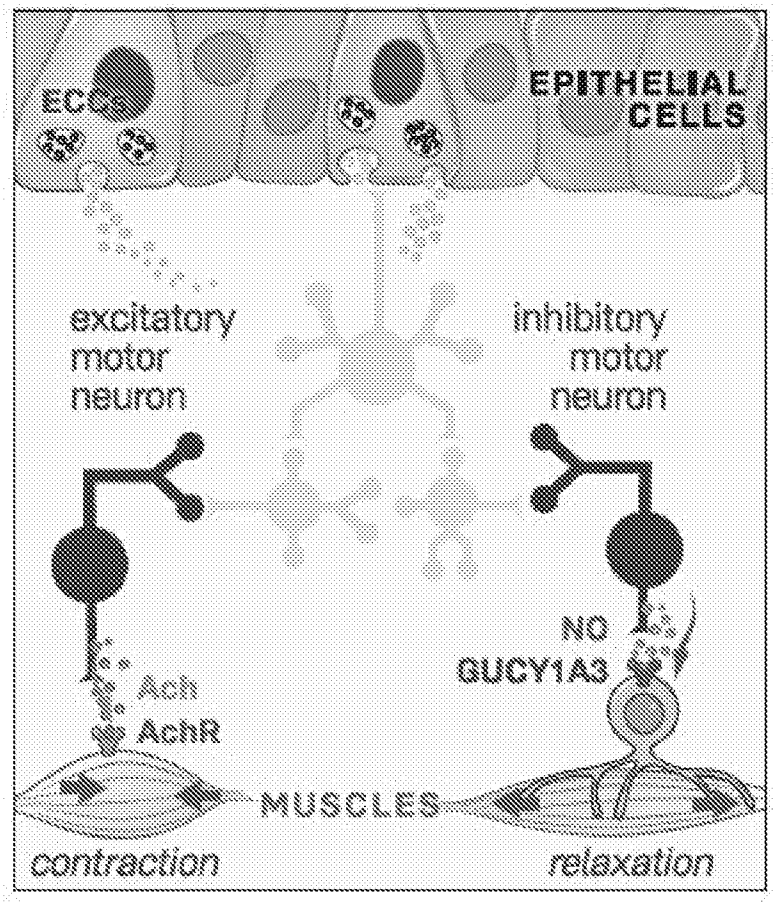

ECCs
EPITHELIAL CELLS
excitatory motor neuron
inhibitory motor neuron
Ach
AchR
NO
GUCY1A3
MUSCLES
contraction
relaxation

FIG. 22H

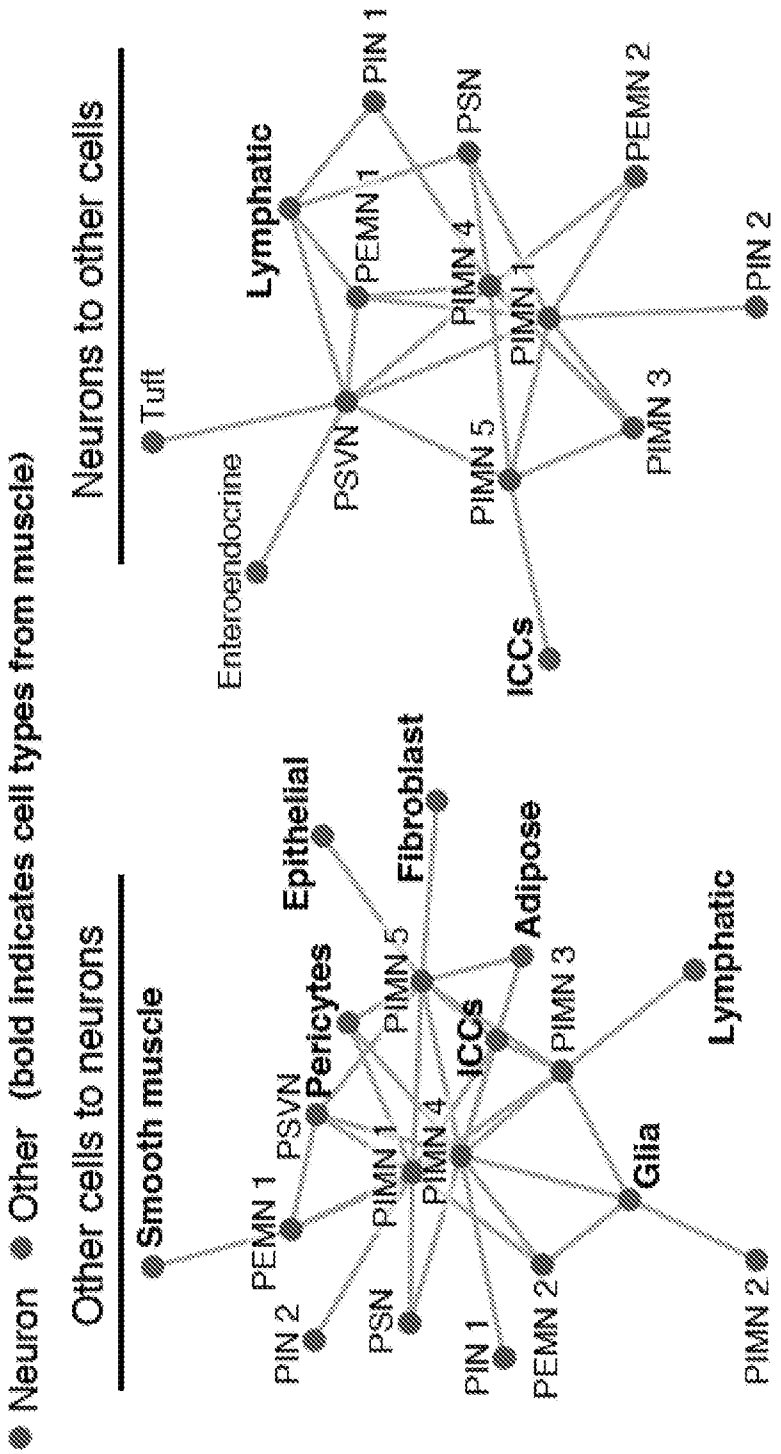

Neuron
Other (bold indicates cell types from muscle)
Other cells to neurons
Smooth muscle
PEMN 1
PIN 2
PSVN
Pericytes
PSN
PIMN 1
Epithelial
PIMN 4
PIN 1
PIMN 5
Fibroblast
ICCs
PEMN 2
Adipose
PIMN 3
Glia
PIMN 2
Lymphatic
Neurons to other cells
Tuft
Enteroendocrine
Lymphatic
PSVN
PIN 1
PEMN 1
PSN
PIMN 4
PIMN 5
ICCs
PIMN 1
PEMN 2
PIMN 3
PIN 2

FIG. 22I

J

Ligand		Receptor	
Cell type	Gene	Cell type	Gene
Neuron	CGRP	Adipocyte	CALCRL
Neuron	NPY	Adipocyte	NPYR1
Neuron	Glutamate	Adipocyte	GRM8
Neuron	GABA	Adipocyte	GABRE
Adipocyte	LEP	Neuron	LEPR
Neuron	VIP/PACAP	Fibroblast	VIPR2
Neuron	Glutamate	Fibroblast	GRIA4
Neuron	Nitric oxide	Fibroblast	GUCY1A3
Neuron	FGF1	Fibroblast	FGFR1
Neuron	PDGF	Fibroblast	PDGFRB
Neuron	SLIT2	Fibroblast	ROBO1
Neuron	SLIT3	Fibroblast	ROBO2
Neuron	IL15	Fibroblast	IL15R
Neuron	IL7	T cell	IL7R
Neuron	IL12A	T cell	IL12RB1
Neuron	PENK	T cell	OPRM1
Neuron	CHAT	Dendritic cell	CHRNE
Neuron	TPH2	B cell	HTR3A

FIG. 22J

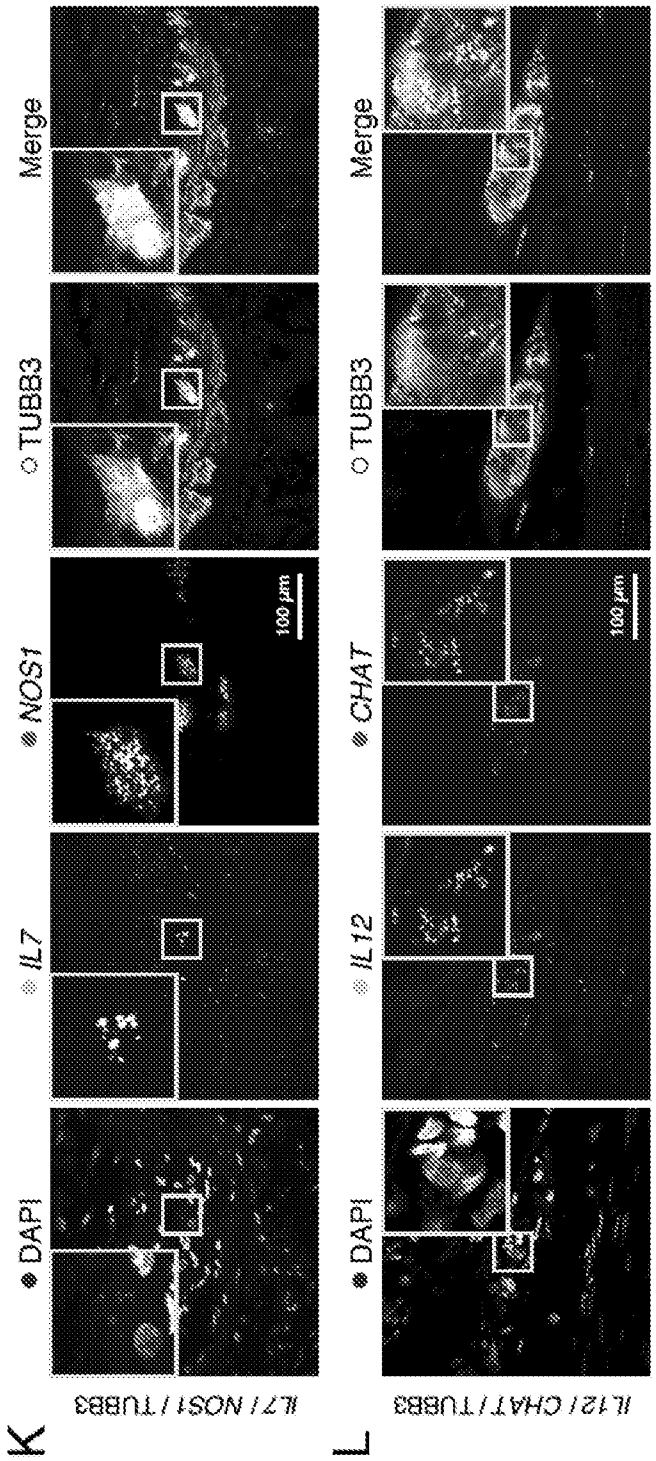

K
IL7 / NOS1 / TUBB3
DAPI
IL7
NOS1
TUBB3
Merge
100 μm
L
IL12 / CHAT / TUBB3
DAPI
IL12
CHAT
TUBB3
Merge
100 μm

FIG. 22K-L

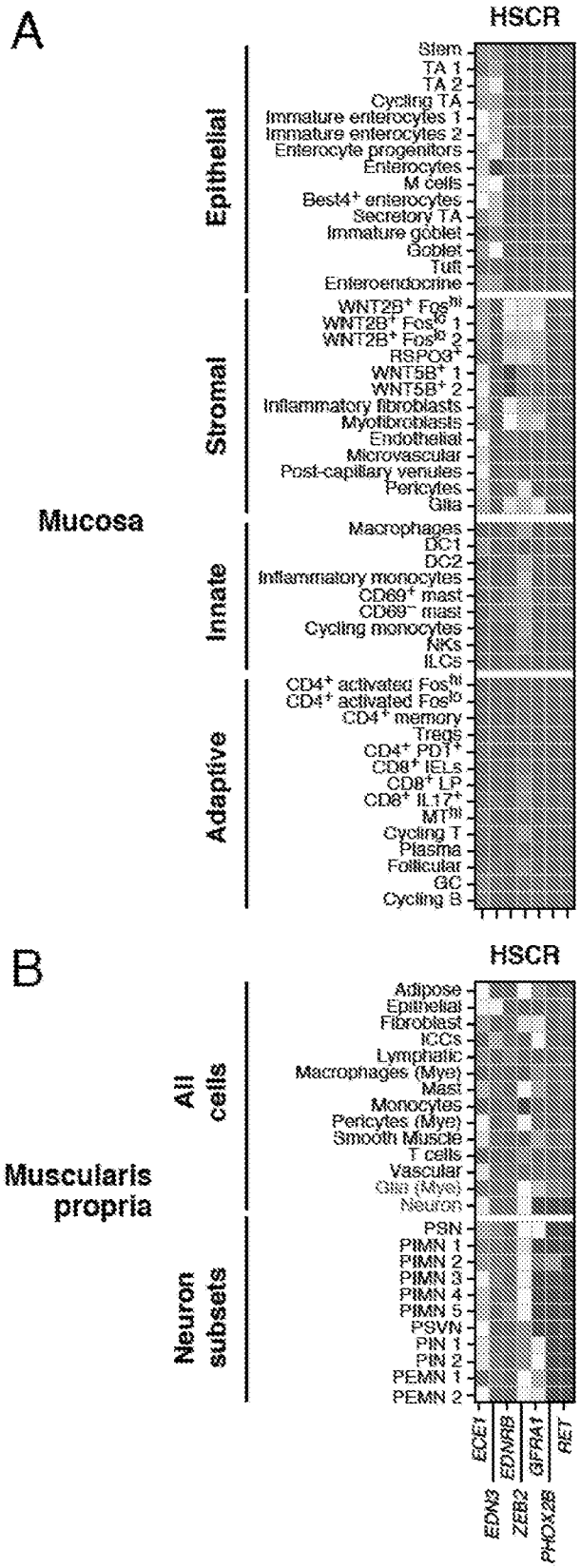

A
HSCR
Mucosa
Epithelial
Stem
TA 1
TA 2
Cycling TA
Immature enterocytes 1
Immature enterocytes 2
Enterocyte progenitors
Enterocytes
M cells
Best4+ enterocytes
Secretory TA
Immature goblet
Goblet
Tuft
Enteroendocrine
Stromal
WNT2B+ Fos hi
WNT2B+ Fos lo 1
WNT2B+ Fos lo 2
RSPO3+
WNT5B+ 1
WNT5B+ 2
Inflammatory fibroblasts
Myofibroblasts
Endothelial
Microvascular
Post-capillary venules
Pericytes
Glia
Innate
Macrophages
DC1
DC2
Inflammatory monocytes
CD69+ mast
CD69− mast
Cycling monocytes
NKs
ILCs
Adaptive
CD4+ activated Fos hi
CD4+ activated Fos lo
CD4+ memory
Tregs
CD4+ PD1+
CD8+ IELs
CD8+ LP
CD8+ IL17+
MThi
Cycling T
Plasma
Follicular
GC
Cycling B
B
HSCR
Muscularis propria
All cells
Adipose
Epithelial
Fibroblast
ICCs
Lymphatic
Macrophages (Mye)
Mast
Monocytes
Pericytes (Mye)
Smooth Muscle
T cells
Vascular
Glia (Mye)
Neuron
Neuron subsets
PSN
PIMN 1
PIMN 2
PIMN 3
PIMN 4
PIMN 5
PSVN
PIN 1
PIN 2
PEMN 1
PEMN 2
ECE1
EDNRB
GFRA1
RET
EDN3
ZEB2
PHOX2B

FIG. 23A-B

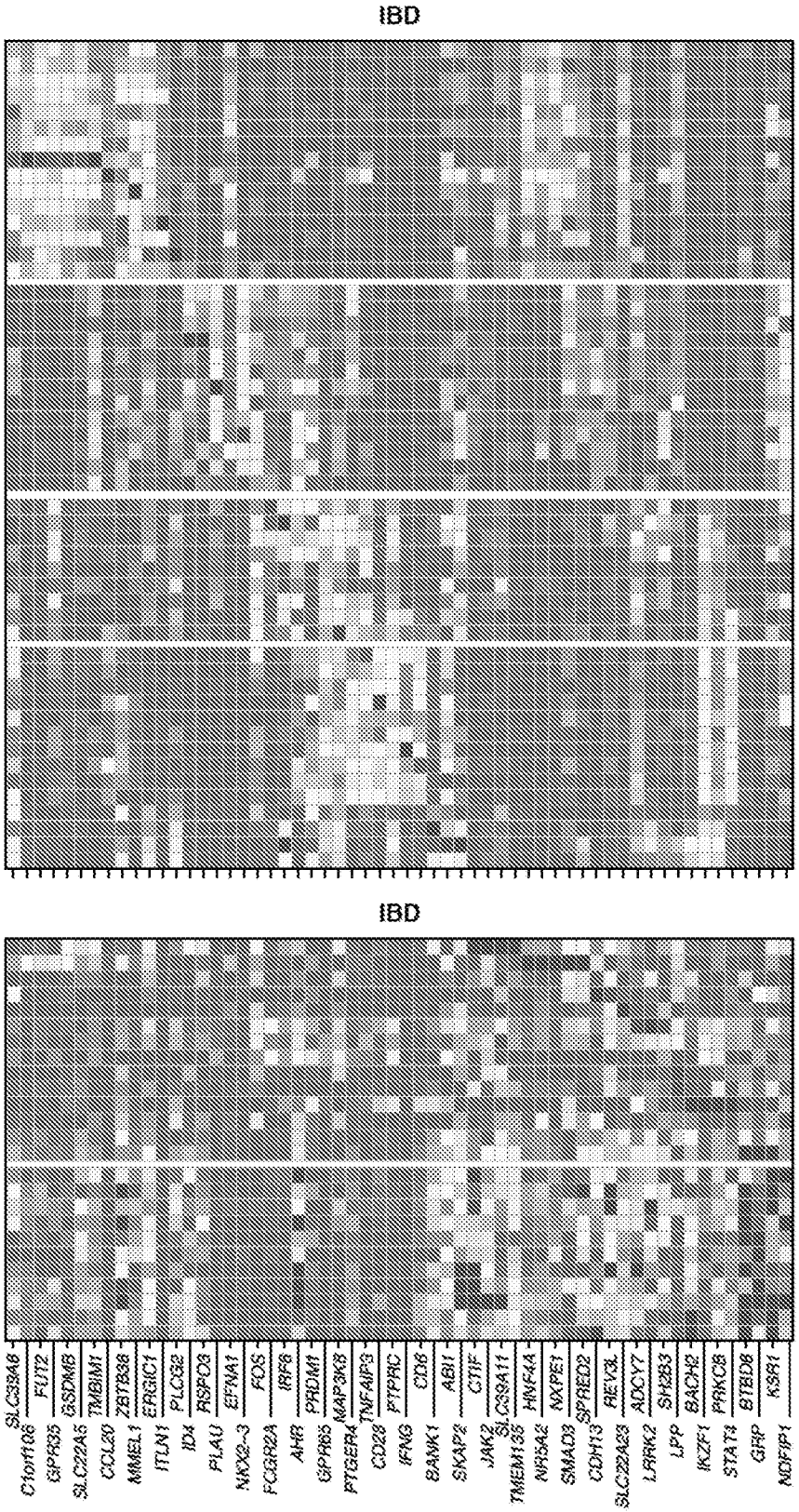


FIG. 23A-B continued

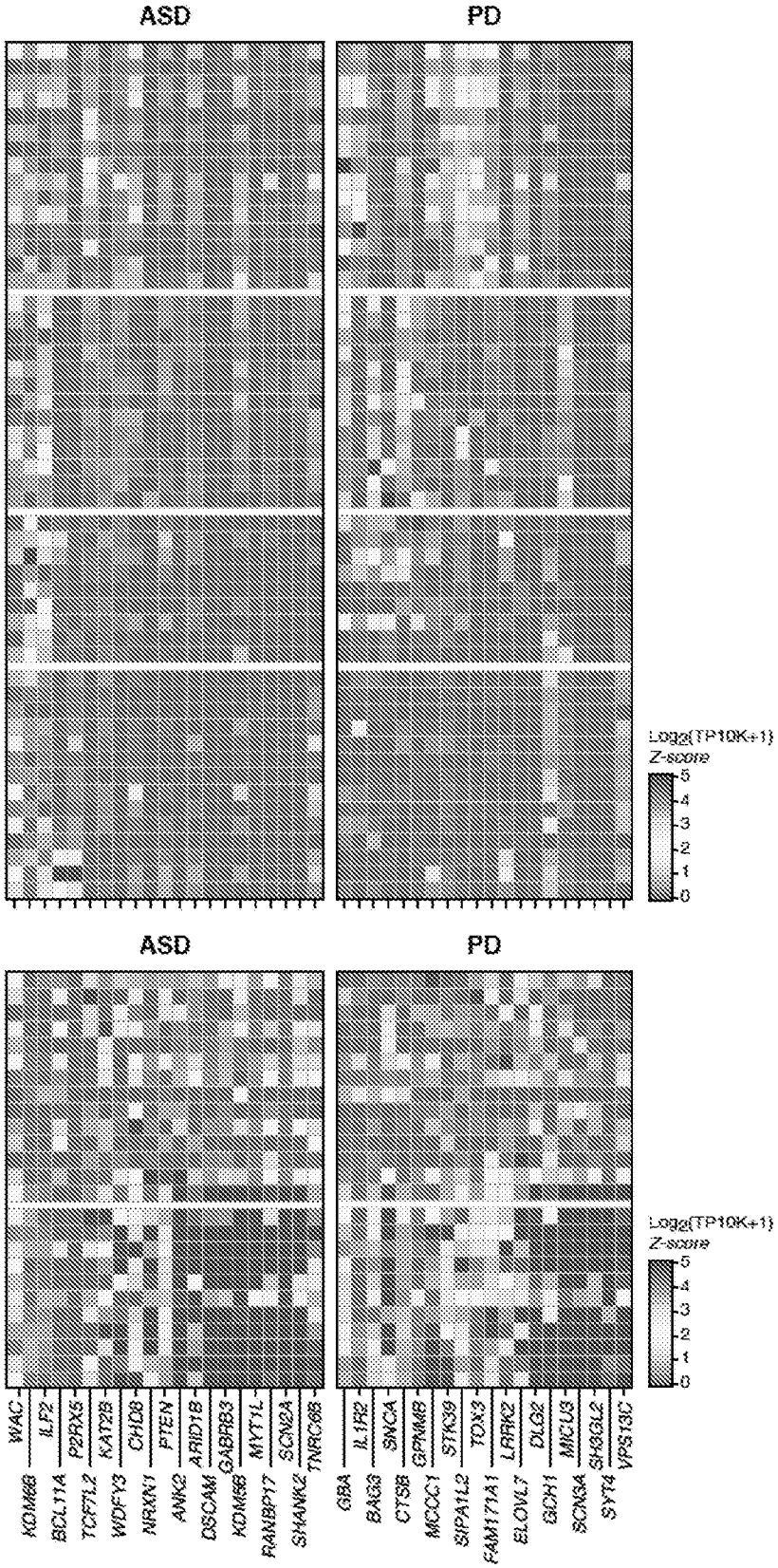


FIG. 23A-B continued

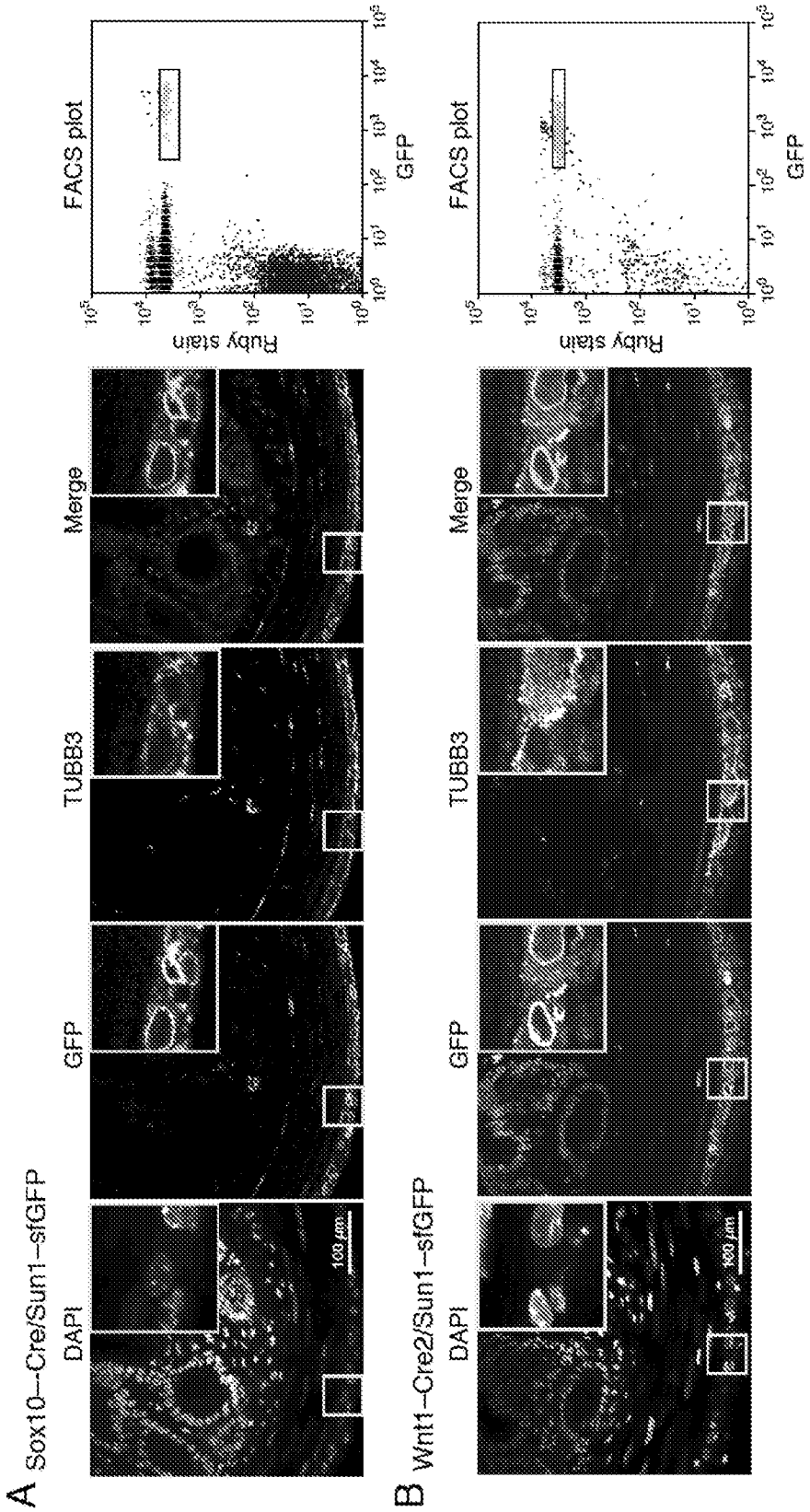

A Sox10–Cre/Sun1–sfGFP
DAPI
GFP
TUBB3
Merge
100 μm
FACS plot
Ruby stain
GFP
B Wnt1–Cre2/Sun1–sfGFP
DAPI
GFP
TUBB3
Merge
100 μm
FACS plot
Ruby stain
GFP

FIG. 24A-B

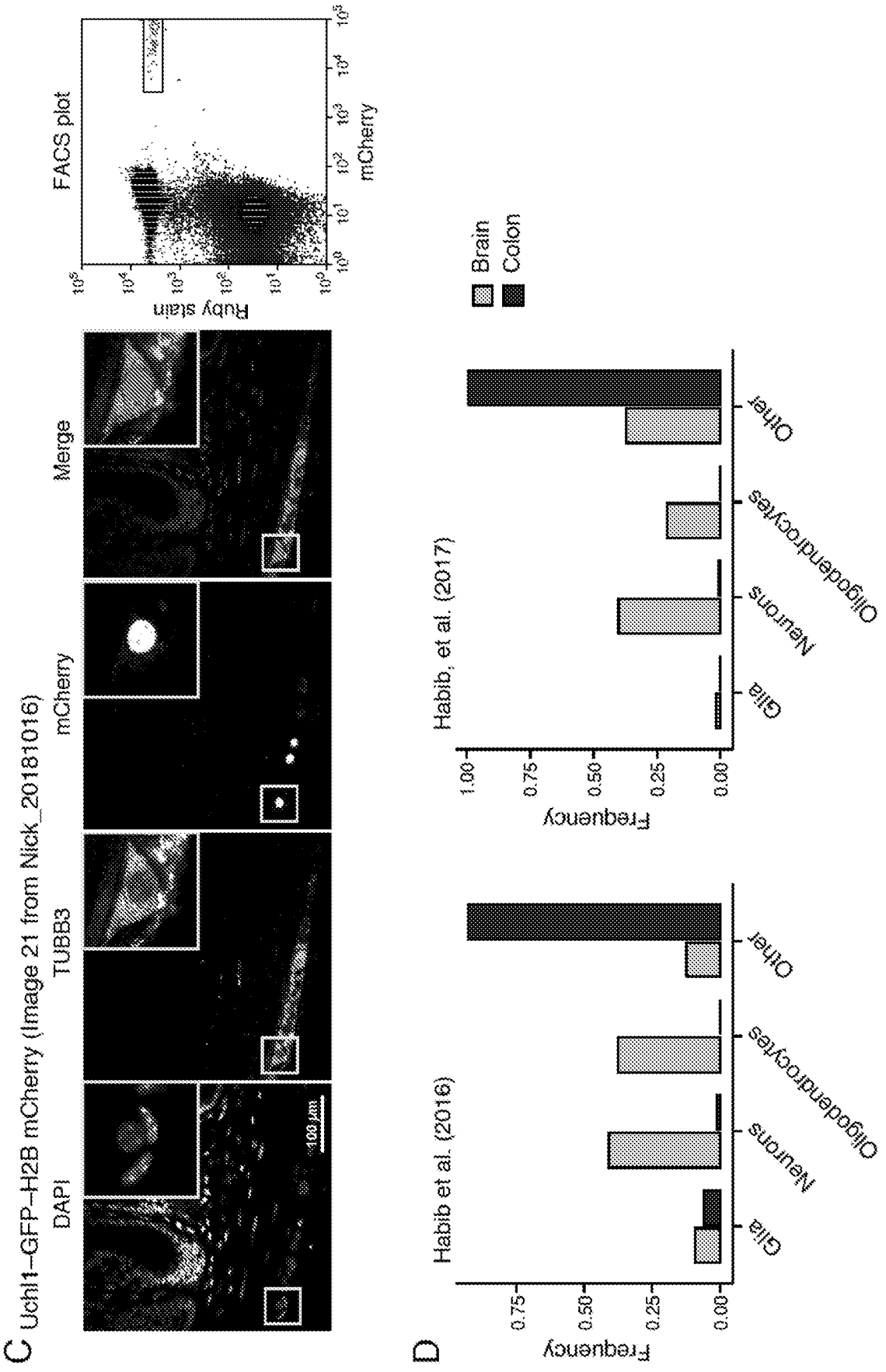

C
Uchl1–GFP–H2B mCherry (Image 21 from Nick_20181016)
DAPI
TUBB3
mCherry
Merge
100 μm
FACS plot
Ruby stain
mCherry
D
Habib et al. (2016)
Habib, et al. (2017)
Brain
Colon
Frequency
Glia
Neurons
Oligodendrocytes
Other

FIG. 24C-D

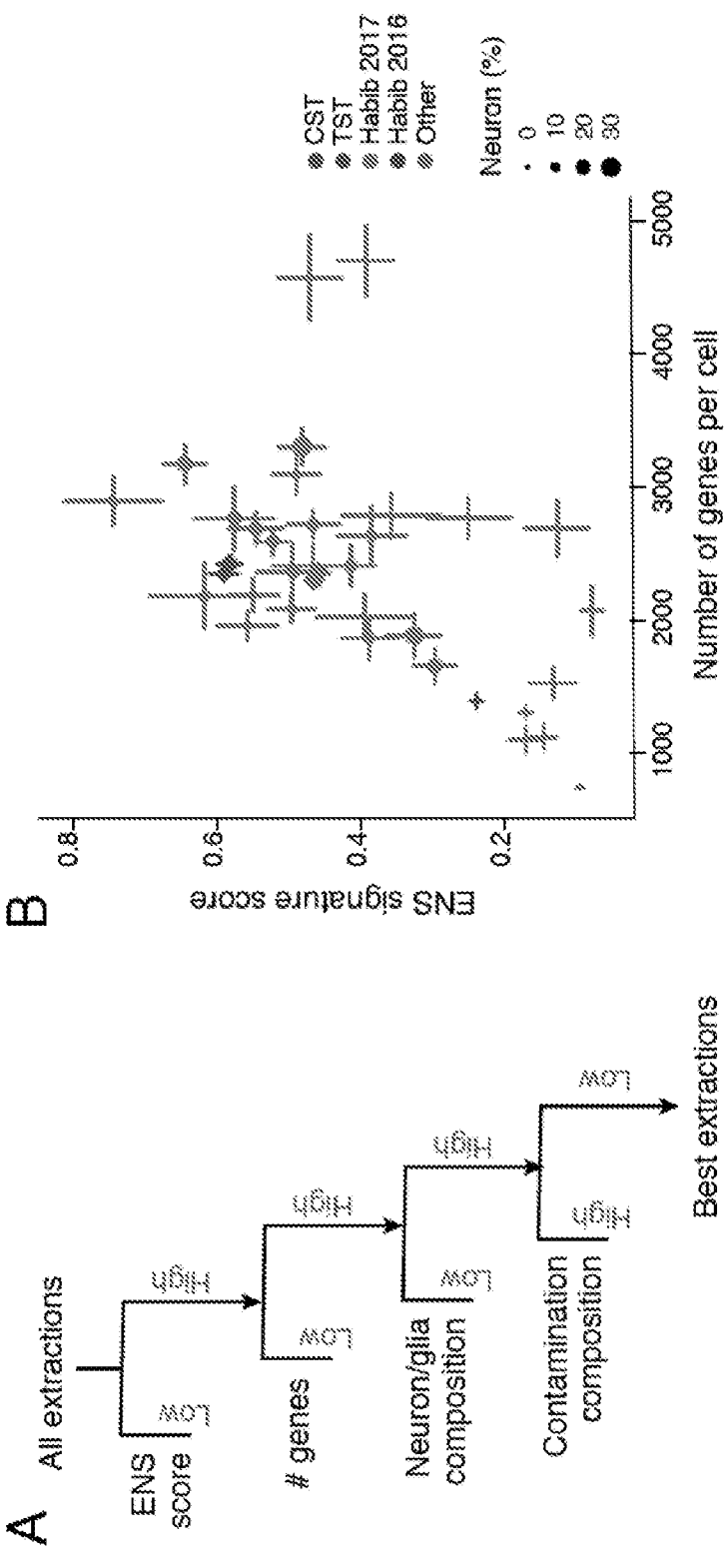

A
All extractions
ENS score
High
Low
genes
High
Low
Neuron/glia composition
High
Low
Contamination composition
High
Low
Best extractions
B
ENS signature score
0.8
0.6
0.4
0.2
1000
2000
3000
4000
5000
Number of genes per cell
CST
TST
Habib 2017
Habib 2016
Other
Neuron (%)
0
10
20
30

FIG. 25A-B

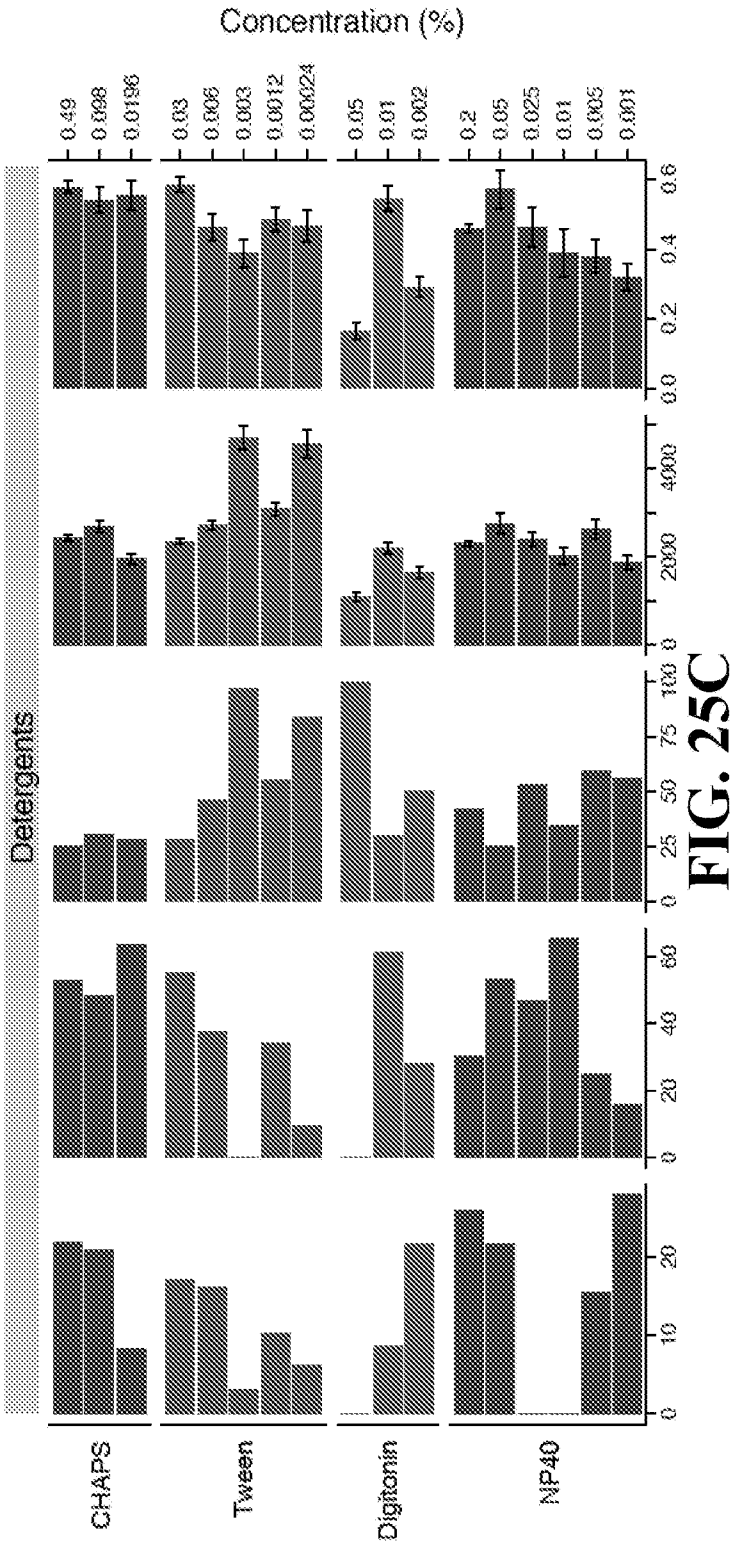


FIG. 25C

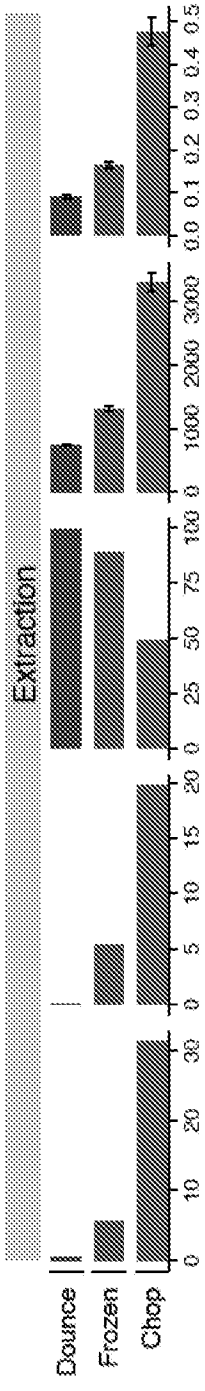


FIG. 25D

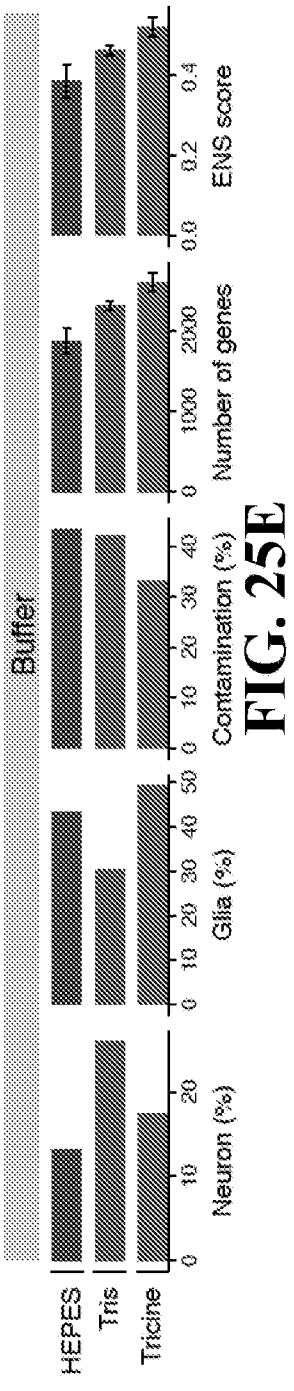


FIG. 25E

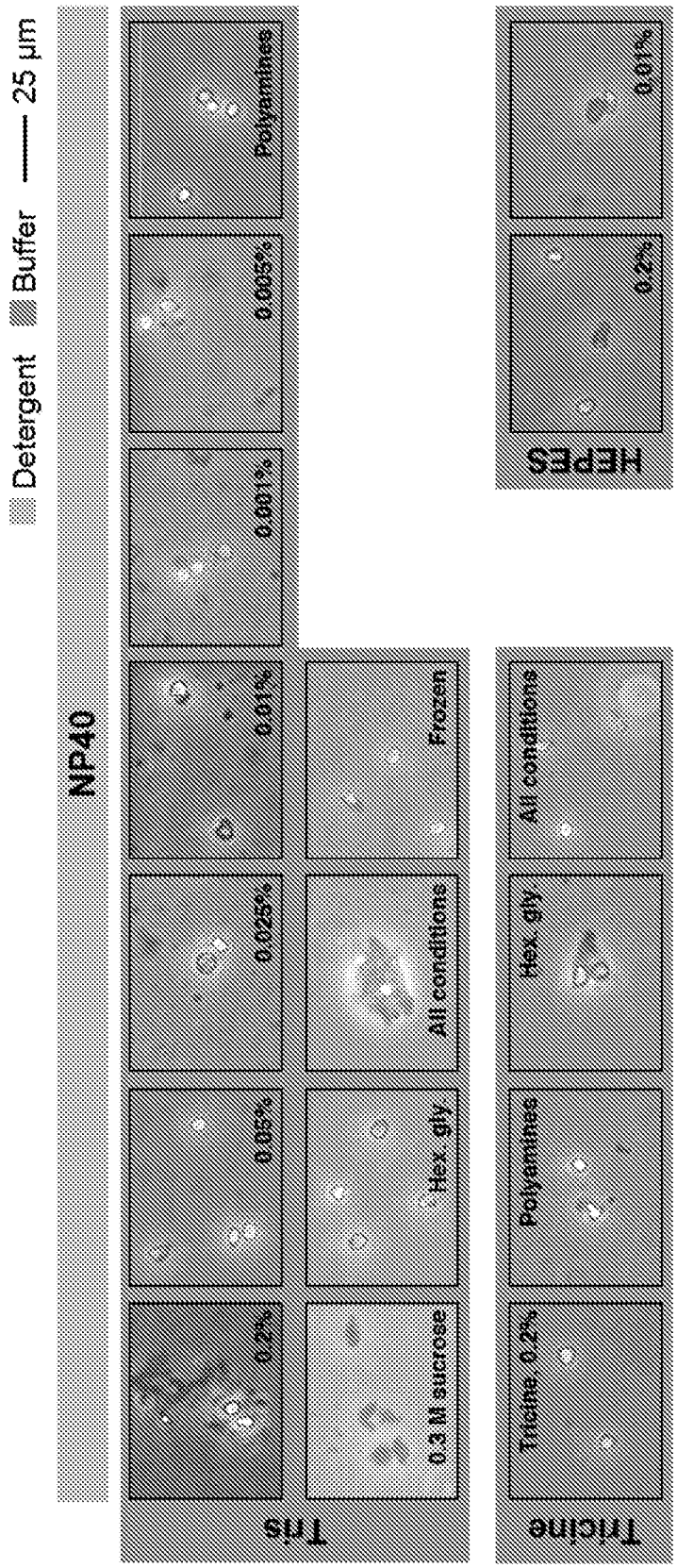

Detergent
Buffer
25 µm
NP40
Tris
Tricine
HEPES
0.2%
0.3 M sucrose
0.05%
Hex. gly
0.025%
All conditions
0.01%
Frozen
0.001%
0.005%
Polyamines
0.01%
0.2%
All conditions
Hex. gly
Polyamines
Tricine 0.2%
0.01%

FIG. 26

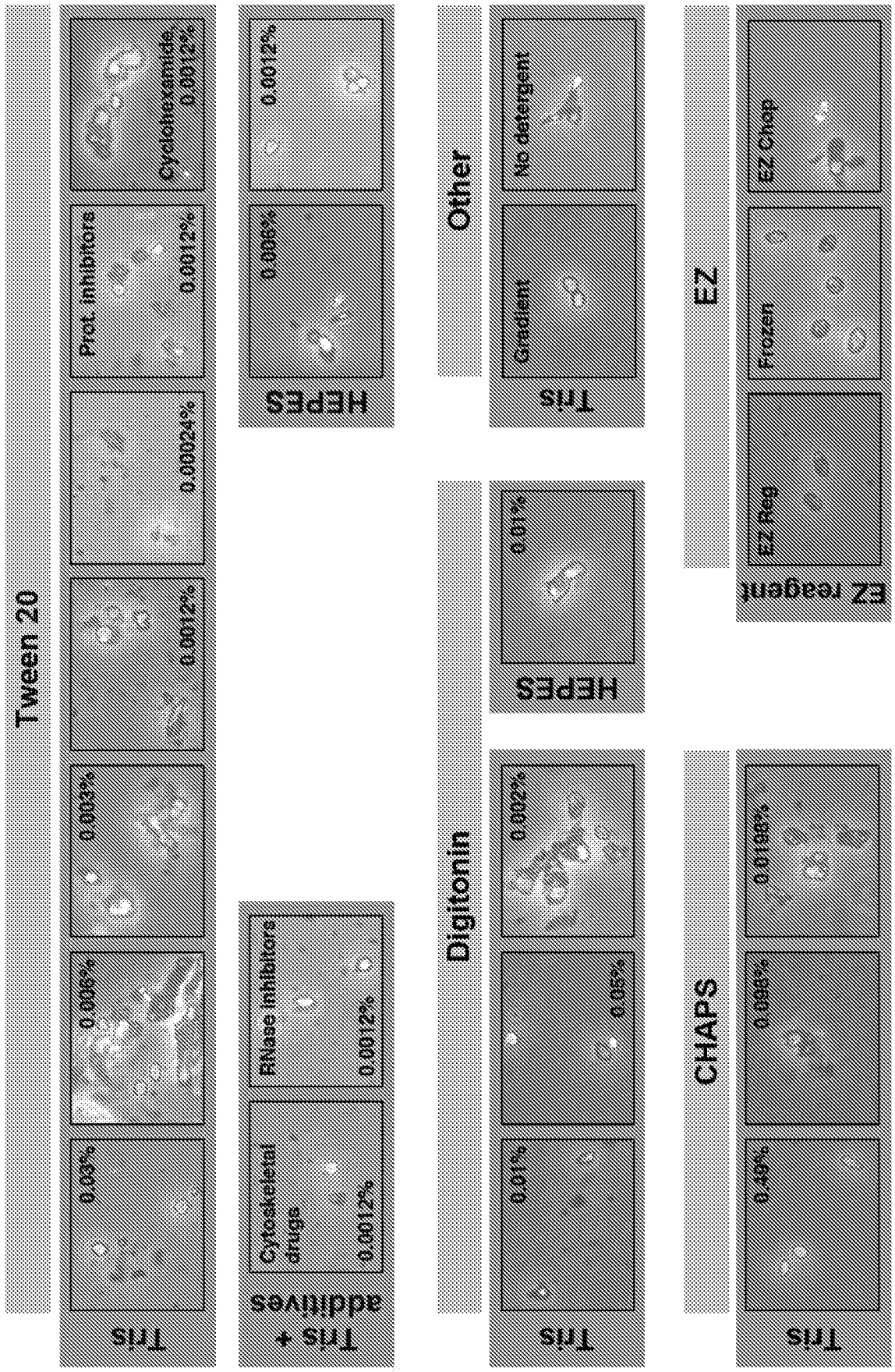


FIG. 26 continued

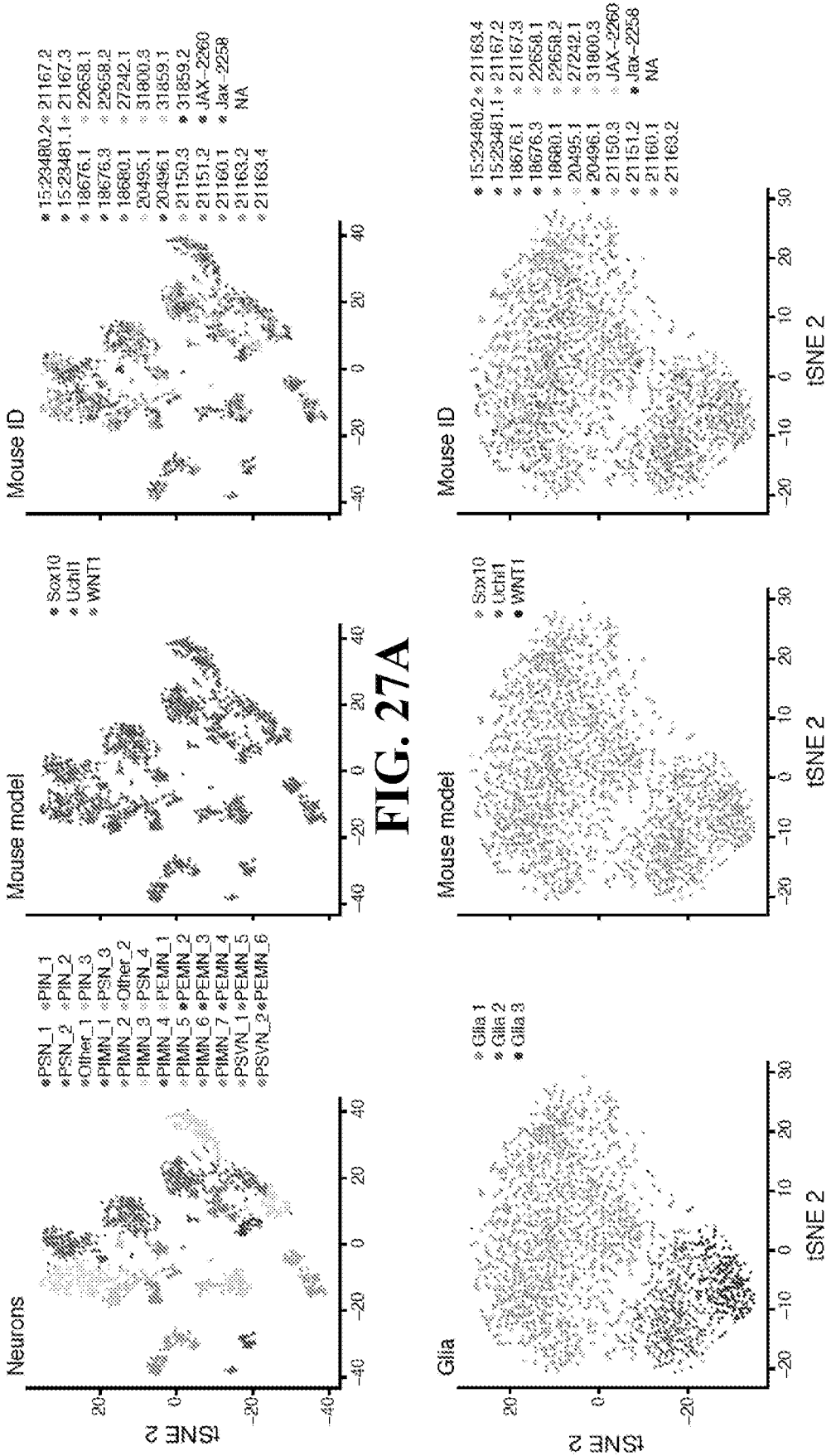


FIG. 27A

FIG. 27B

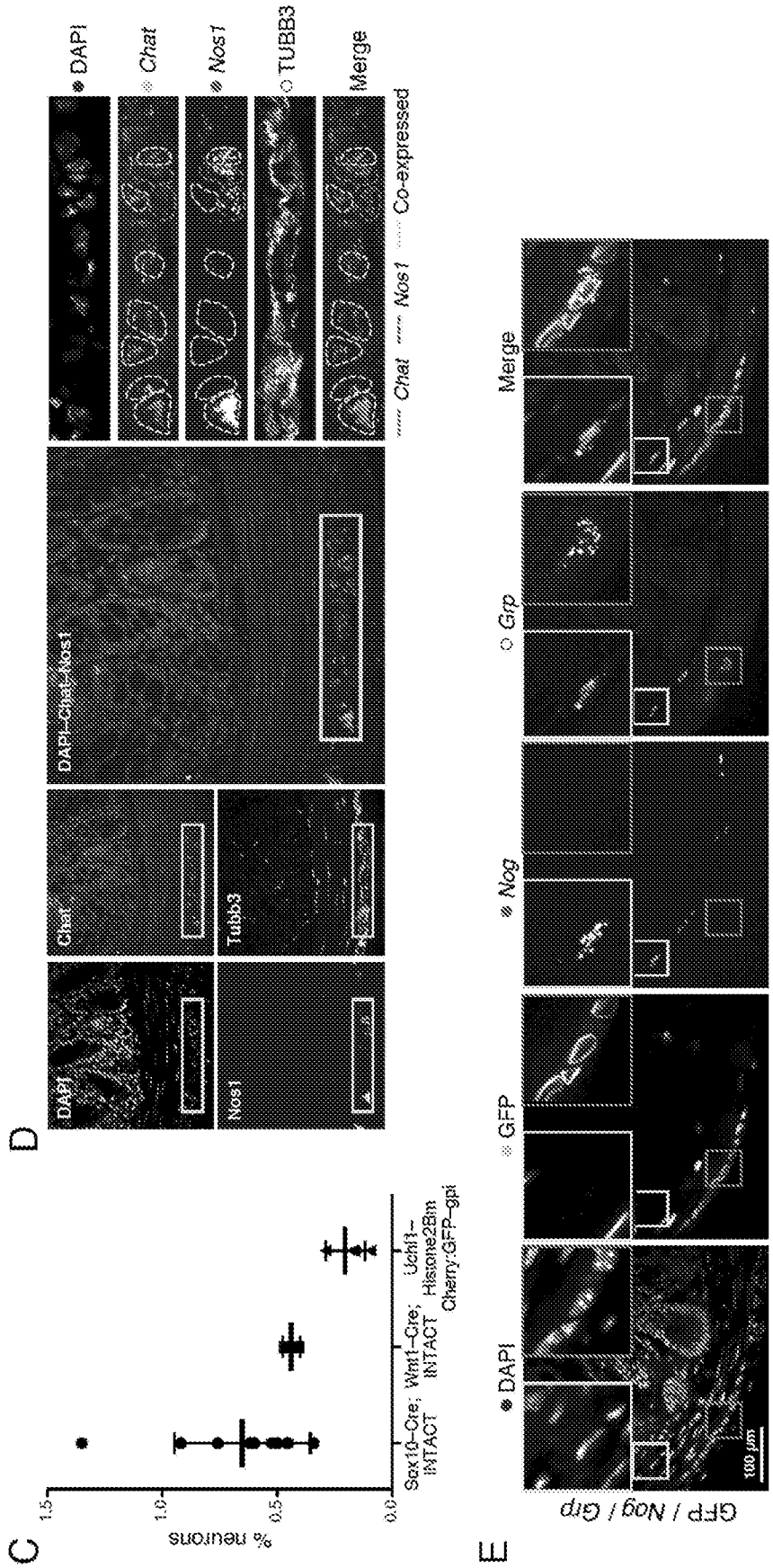

C
% neurons
1.5
1.0
0.5
0.0
Sox10-Cre; INTACT
Wnt1-Cre; INTACT
Uchl1-Histone2Bm Cherry:GFP-gpi
D
DAPI
Chat
Nos1
Tubb3
DAPI–Chat–Nos1
DAPI
Chat
Nos1
TUBB3
Merge
Chat Nos1 Co-expressed
E
DAPI
GFP
Nog
Grp
Merge
100 μm
GFP / Nog / Grp

FIG. 27C-E

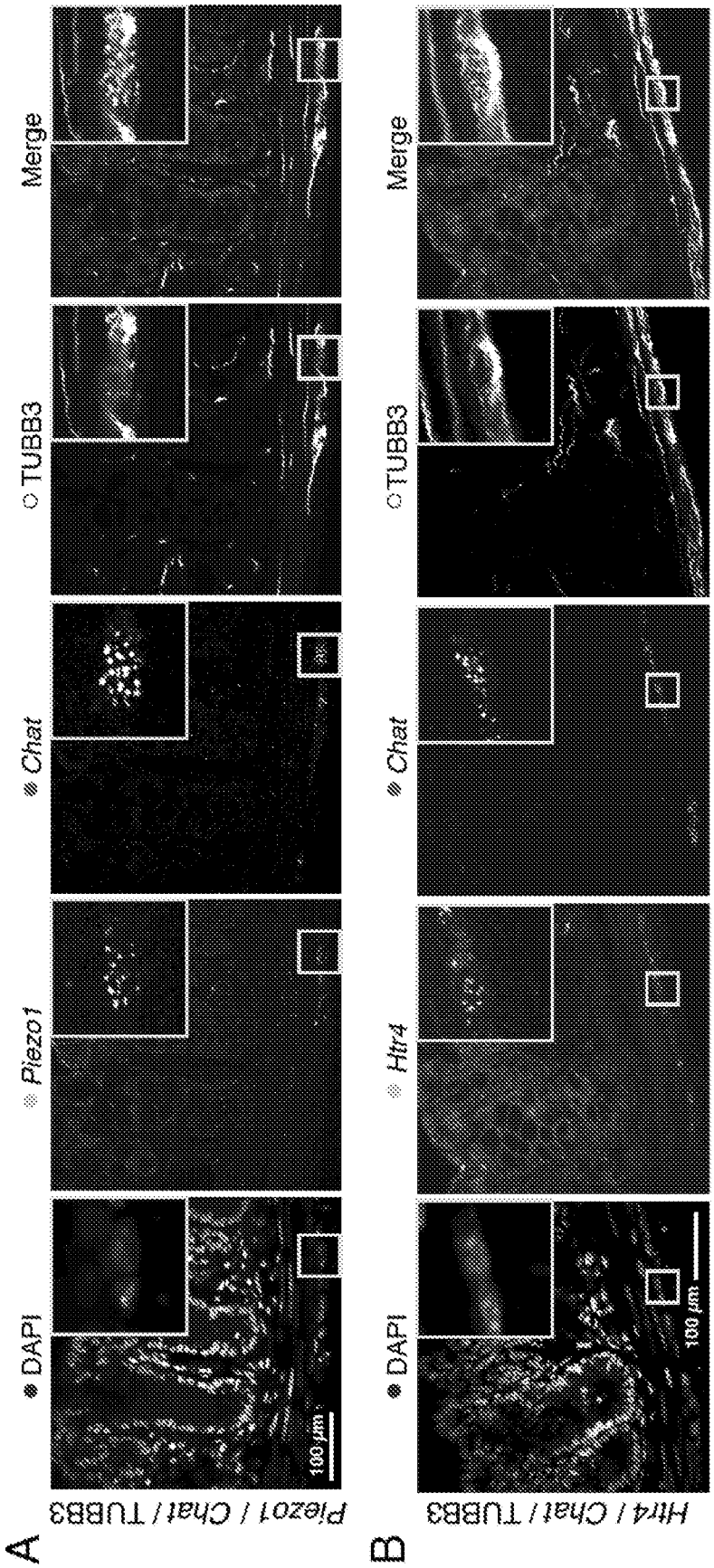

A
Piezo1 / Chat / TUBB3
DAPI
Piezo1
Chat
TUBB3
Merge
100 μm
B
Htr4 / Chat / TUBB3
DAPI
Htr4
Chat
TUBB3
Merge
100 μm

FIG. 28A-B

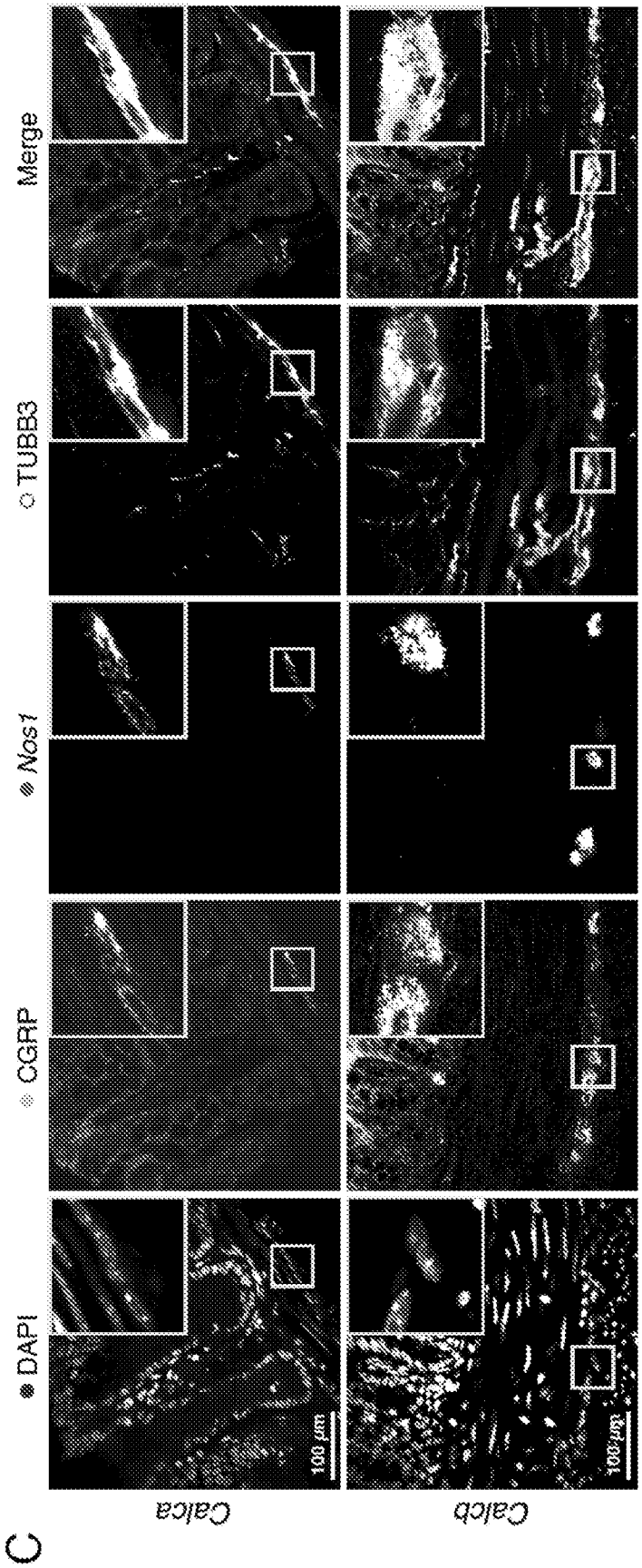


FIG. 28C

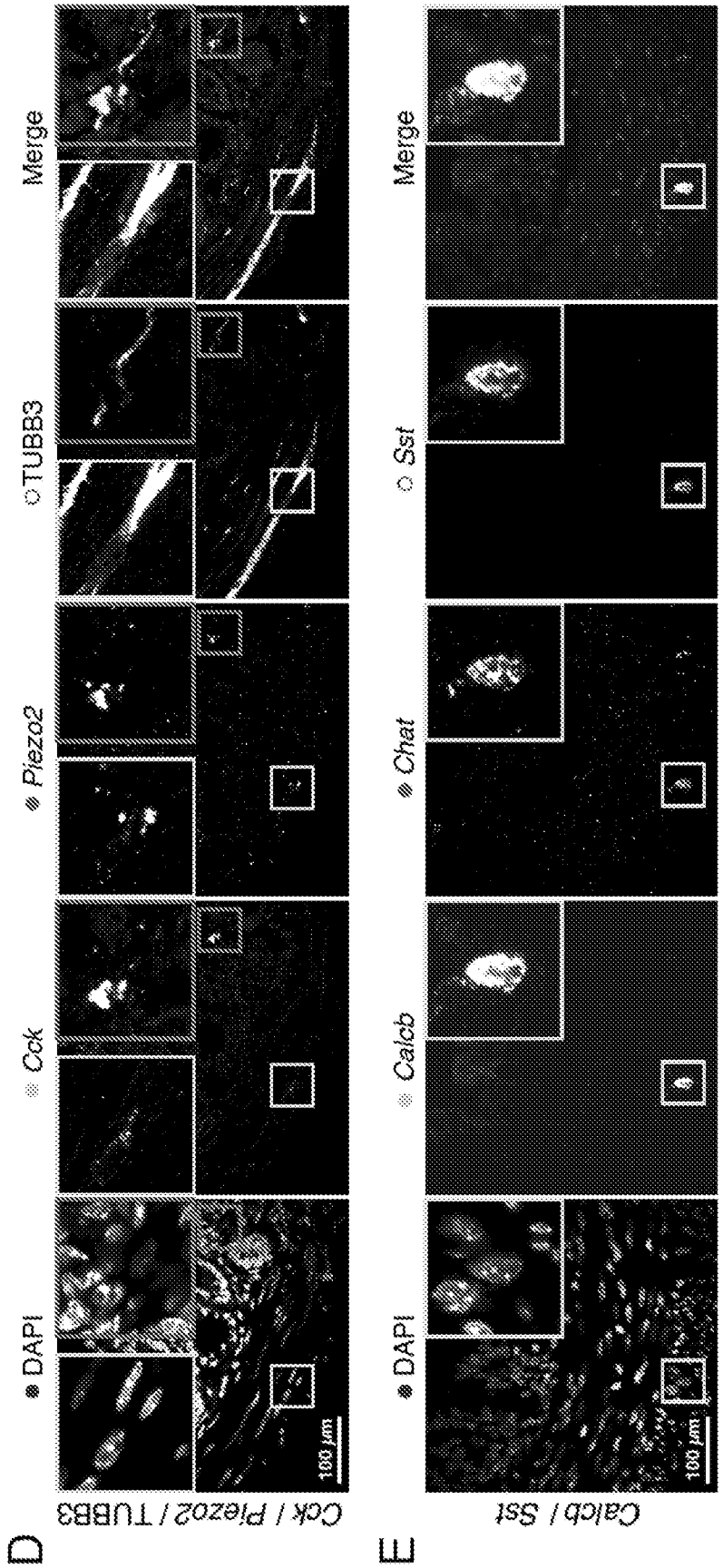

D
DAPI
Cck
Piezo2
TUBB3
Merge
100 μm
Cck / Piezo2 / TUBB3
E
DAPI
Calcb
Chat
Sst
Merge
100 μm
Calcb / Sst

FIG. 28D-E

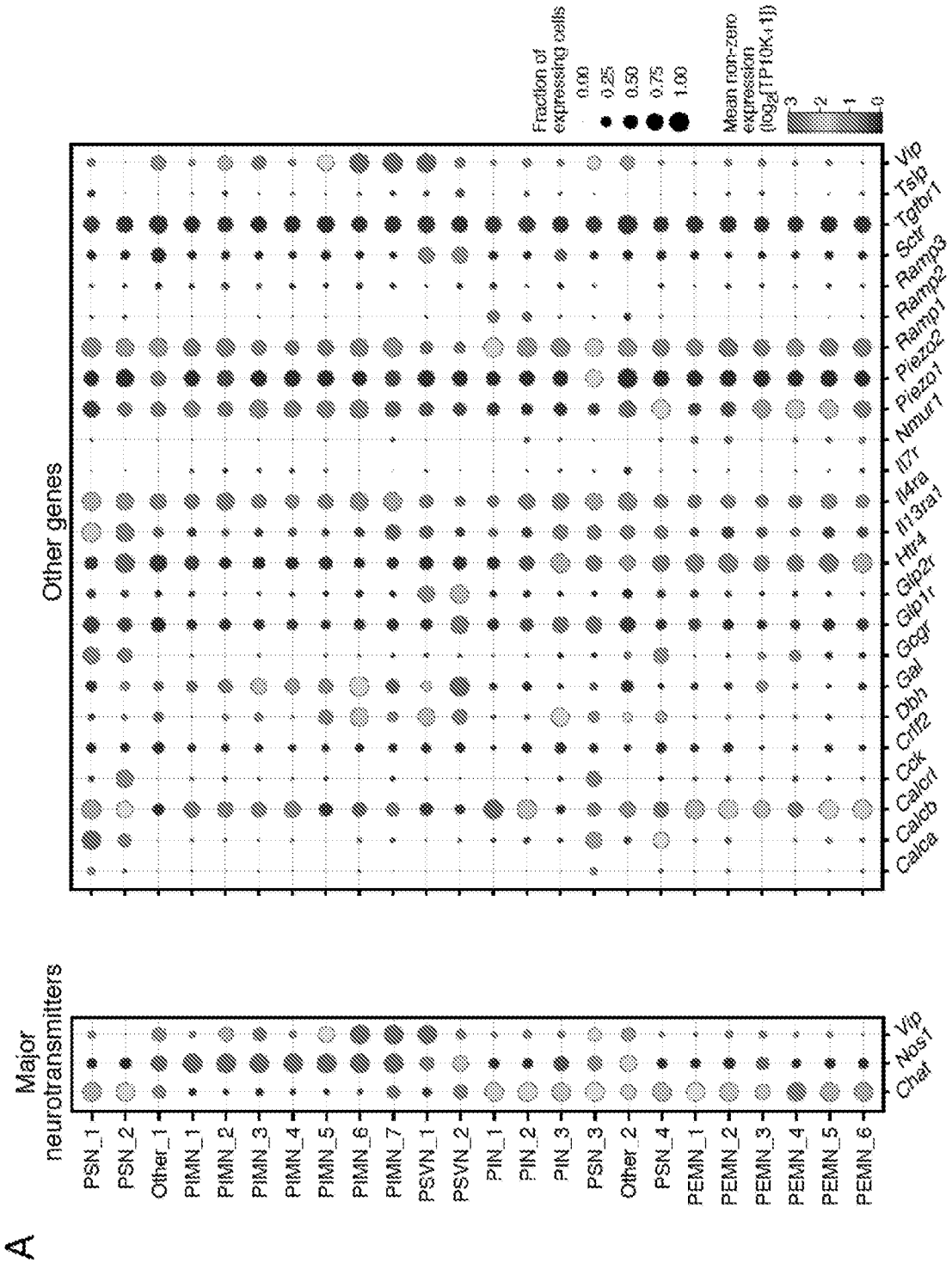

A
Major neurotransmitters
Vip
Nos1
Chat
PSN_1
PSN_2
Other_1
PIMN_1
PIMN_2
PIMN_3
PIMN_4
PIMN_5
PIMN_6
PIMN_7
PSVN_1
PSVN_2
PIN_1
PIN_2
PIN_3
PSN_3
Other_2
PSN_4
PEMN_1
PEMN_2
PEMN_3
PEMN_4
PEMN_5
PEMN_6
Other genes
Calca
Calcb
Calcr
Cck
Crhr2
Dbh
Gal
Galr
Glp1r
Glp2r
Htr4
Il13ra1
Il4ra
Il7r
Nmur1
Piezo1
Piezo2
Ramp1
Ramp2
Ramp3
Sctr
Tgfbr1
Tslp
Vip
Fraction of expressing cells
0.00
0.25
0.50
0.75
1.00
Mean non-zero expression
(log2(TP10K+1))
3
2
1
0

FIG. 29A

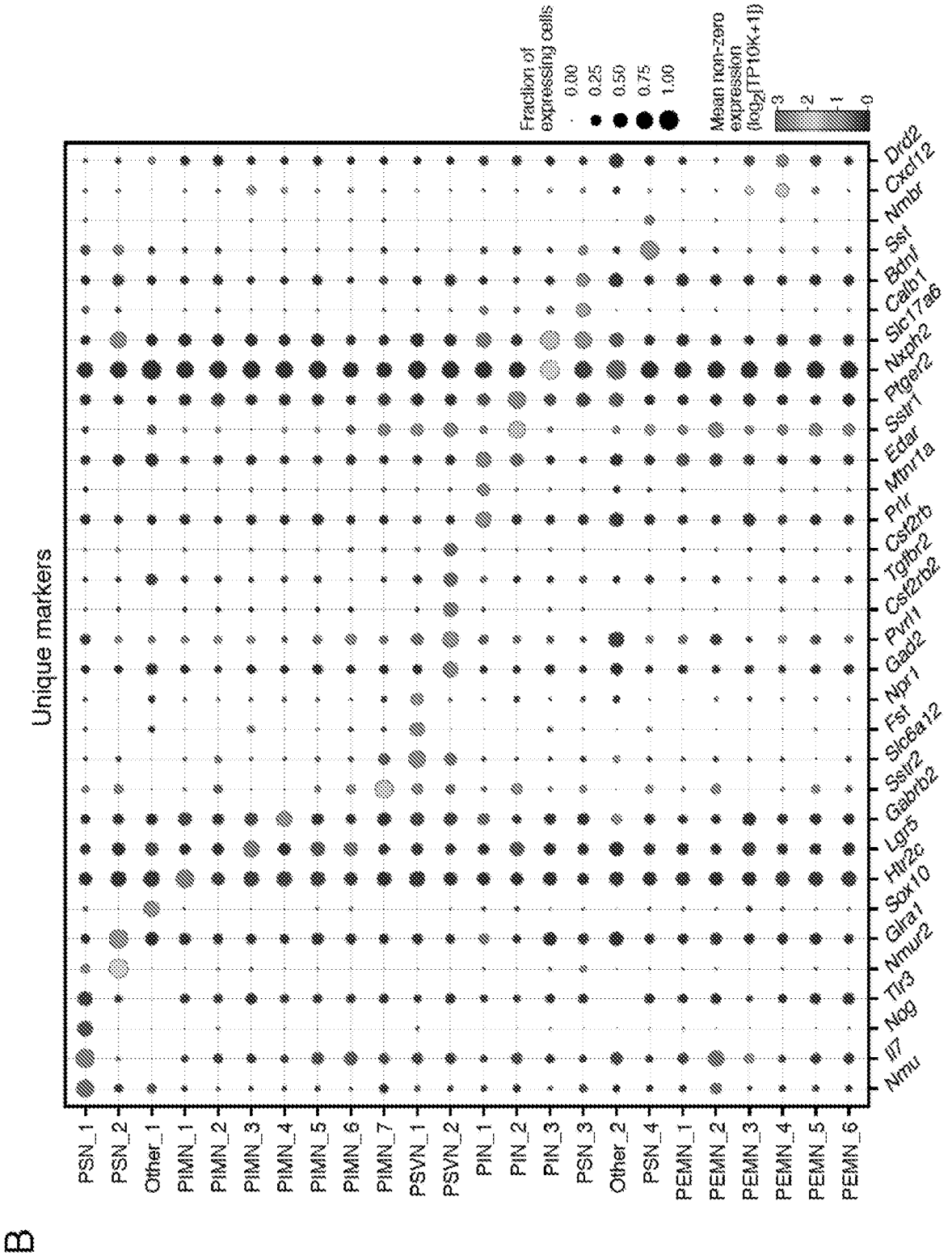

B
Unique markers
PSN_1
PSN_2
Other_1
PIMN_1
PIMN_2
PIMN_3
PIMN_4
PIMN_5
PIMN_6
PIMN_7
PSVN_1
PSVN_2
PIN_1
PIN_2
PIN_3
PSN_3
Other_2
PSN_4
PEMN_1
PEMN_2
PEMN_3
PEMN_4
PEMN_5
PEMN_6
Nmu
Il7
Ndg
Tlr3
Nmur2
Glra1
Sox10
Htr2c
Lgr5
Gabrb2
Sstr2
Slc6a12
Fst
Npr1
Gad2
Pvrl1
Csf2rb2
Tgfbr2
Csf2rb
Prlr
Mmrn1a
Edar
Sstr1
Ptger2
Nxph2
Slc17a6
Calb1
Bdnf
Sst
Nmbr
Cxcl12
Drd2
Fraction of expressing cells
0.00
0.25
0.50
0.75
1.00
Mean non-zero expression (log2[TP10K+1])
3
2
1
0

FIG. 29 B

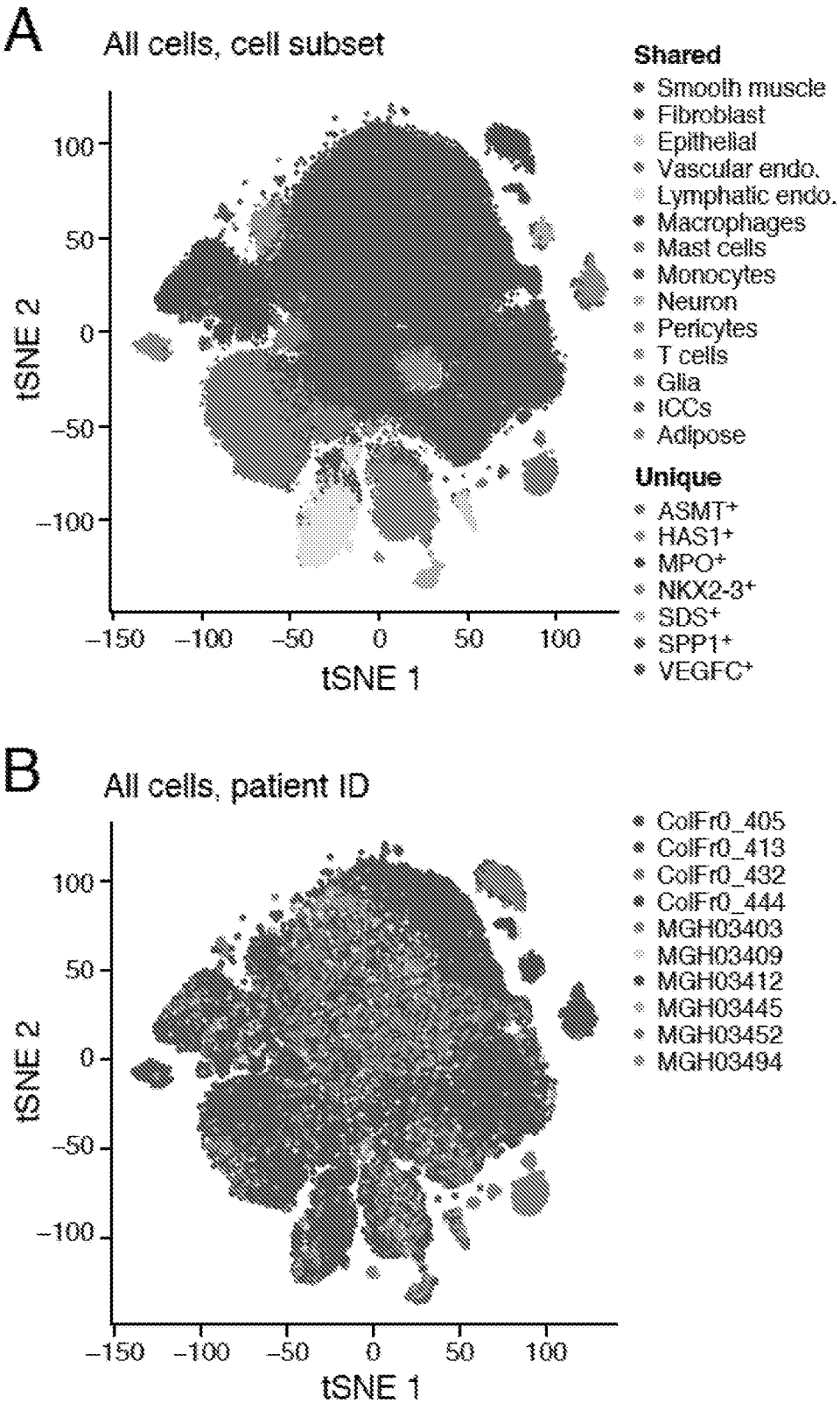

A
All cells, cell subset
Shared
Smooth muscle
Fibroblast
Epithelial
Vascular endo.
Lymphatic endo.
Macrophages
Mast cells
Monocytes
Neuron
Pericytes
T cells
Glia
ICCs
Adipose
Unique
ASMT+
HAS1+
MPO+
NKX2-3+
SDS+
SPP1+
VEGFC+
tSNE 2
tSNE 1
100
50
0
−50
−100
−150
B
All cells, patient ID
ColFr0_405
ColFr0_413
ColFr0_432
ColFr0_444
MGH03403
MGH03409
MGH03412
MGH03445
MGH03452
MGH03494

FIG. 30A-B

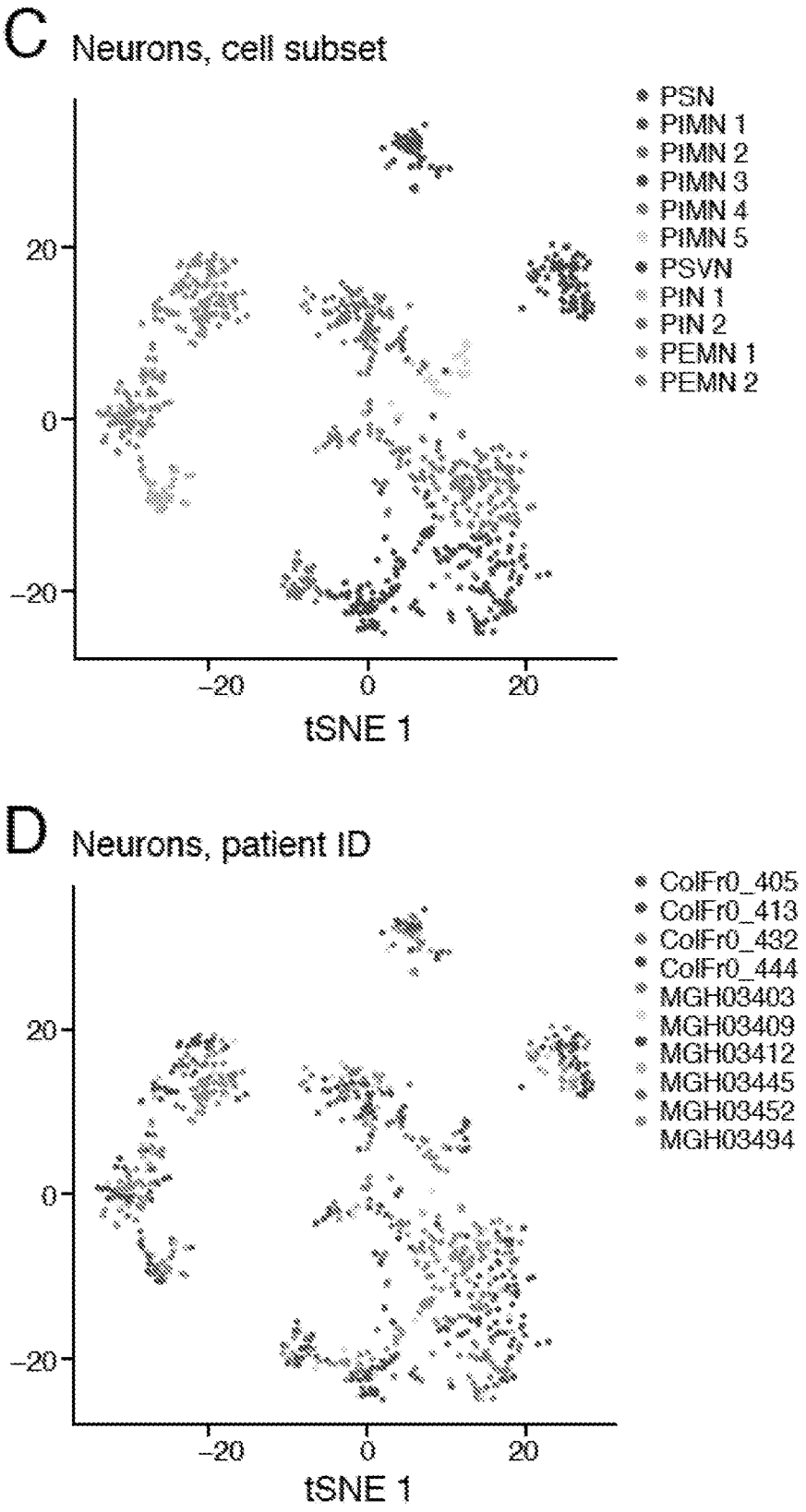

C
Neurons, cell subset
PSN
PIMN 1
PIMN 2
PIMN 3
PIMN 4
PIMN 5
PSVN
PIN 1
PIN 2
PEMN 1
PEMN 2
20
0
−20
−20
0
20
tSNE 1
D
Neurons, patient ID
ColFr0_405
ColFr0_413
ColFr0_432
ColFr0_444
MGH03403
MGH03409
MGH03412
MGH03445
MGH03452
MGH03494
20
0
−20
−20
0
20
tSNE 1

FIG. 30C-D

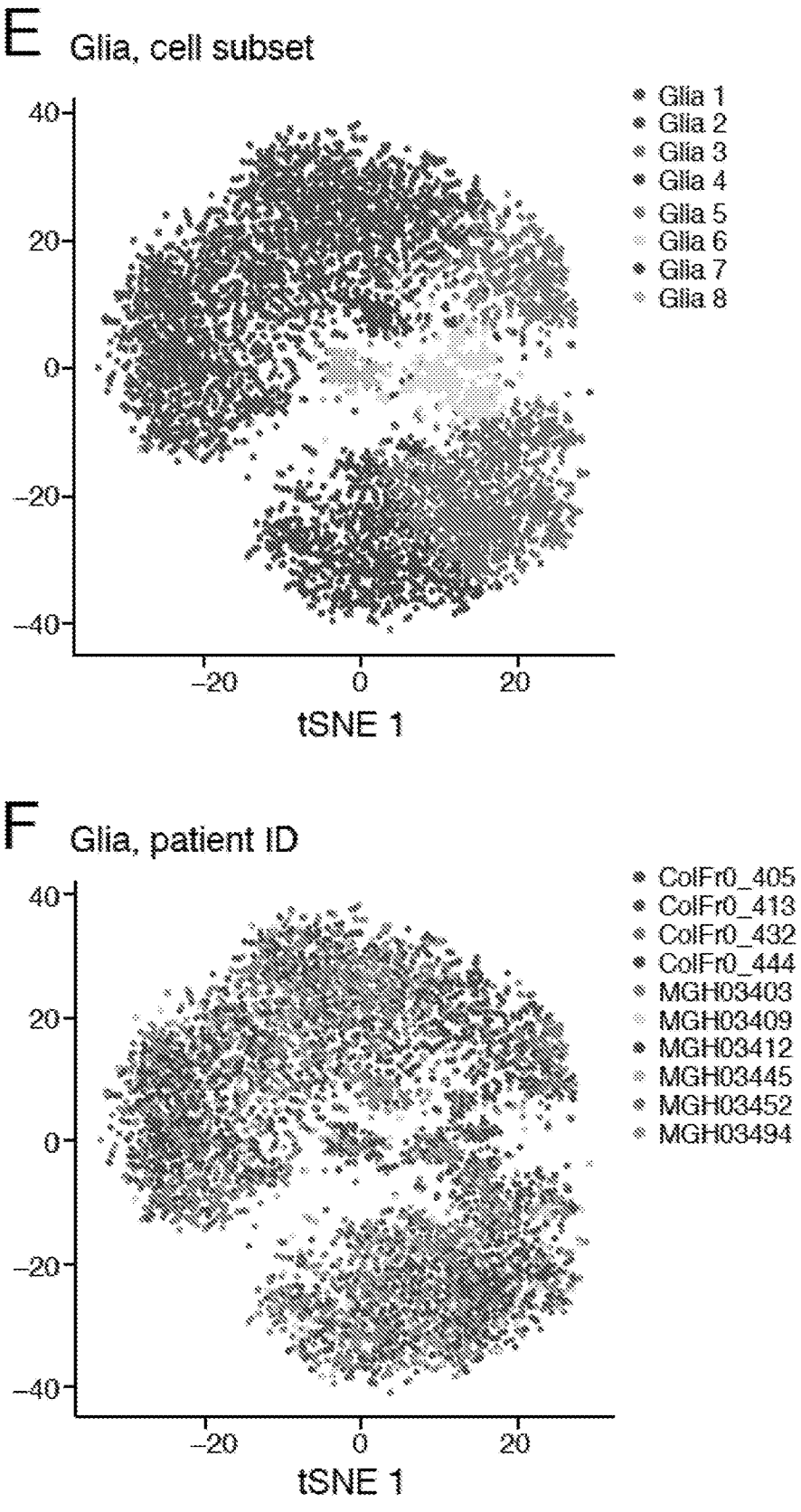

E
Glia, cell subset
Glia 1
Glia 2
Glia 3
Glia 4
Glia 5
Glia 6
Glia 7
Glia 8
40
20
0
−20
−40
−20
0
20
tSNE 1
F
Glia, patient ID
ColFr0_405
ColFr0_413
ColFr0_432
ColFr0_444
MGH03403
MGH03409
MGH03412
MGH03445
MGH03452
MGH03494
40
20
0
−20
−40
−20
0
20
tSNE 1

FIG. 30E-F

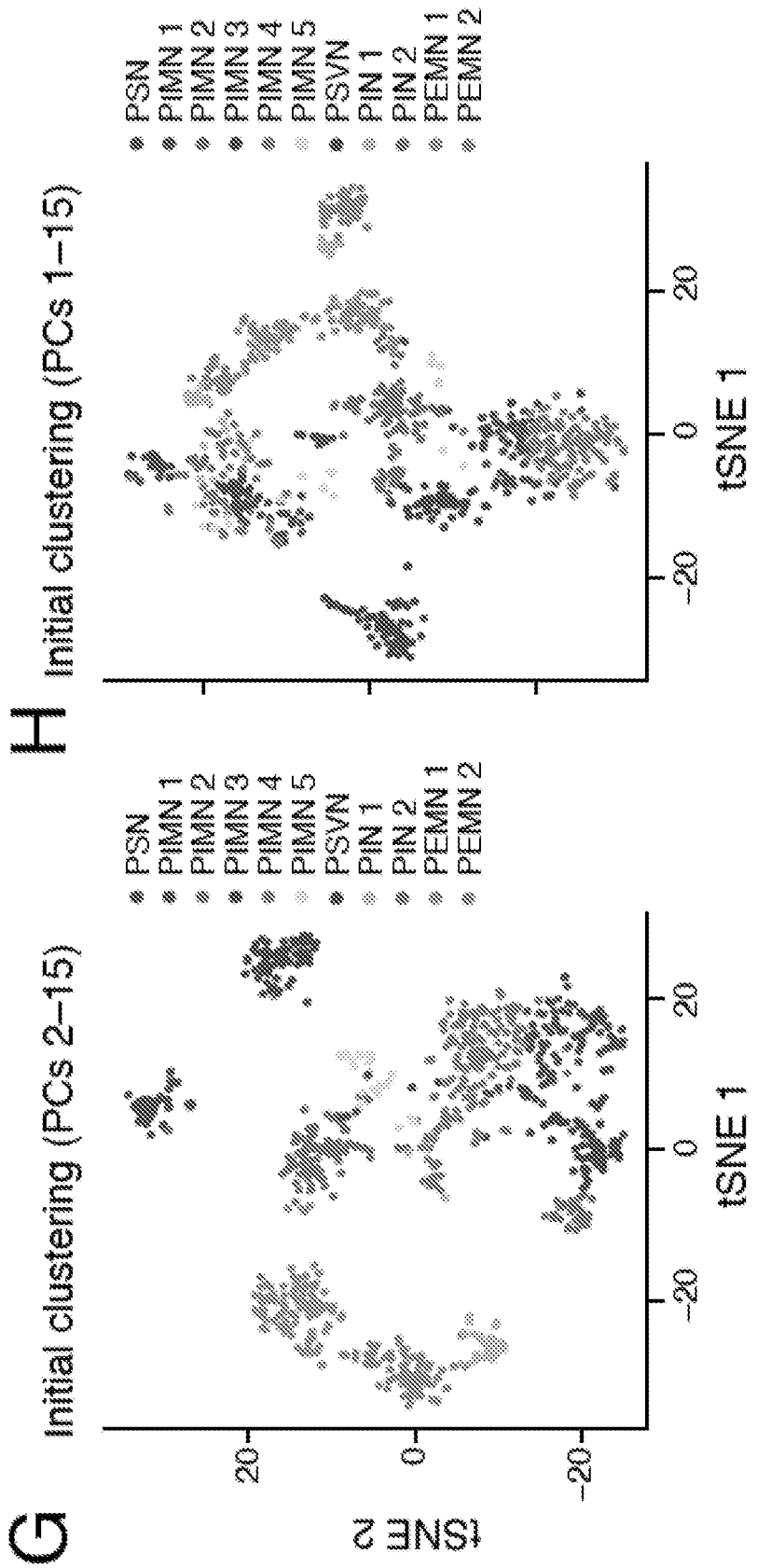

G
Initial clustering (PCs 2–15)
tSNE 2
tSNE 1
20
0
−20
−20
0
20
PSN
PIMN 1
PIMN 2
PIMN 3
PIMN 4
PIMN 5
PSVN
PIN 1
PIN 2
PEMN 1
PEMN 2
H
Initial clustering (PCs 1–15)
tSNE 1
−20
0
20
PSN
PIMN 1
PIMN 2
PIMN 3
PIMN 4
PIMN 5
PSVN
PIN 1
PIN 2
PEMN 1
PEMN 2

FIG. 30G-H

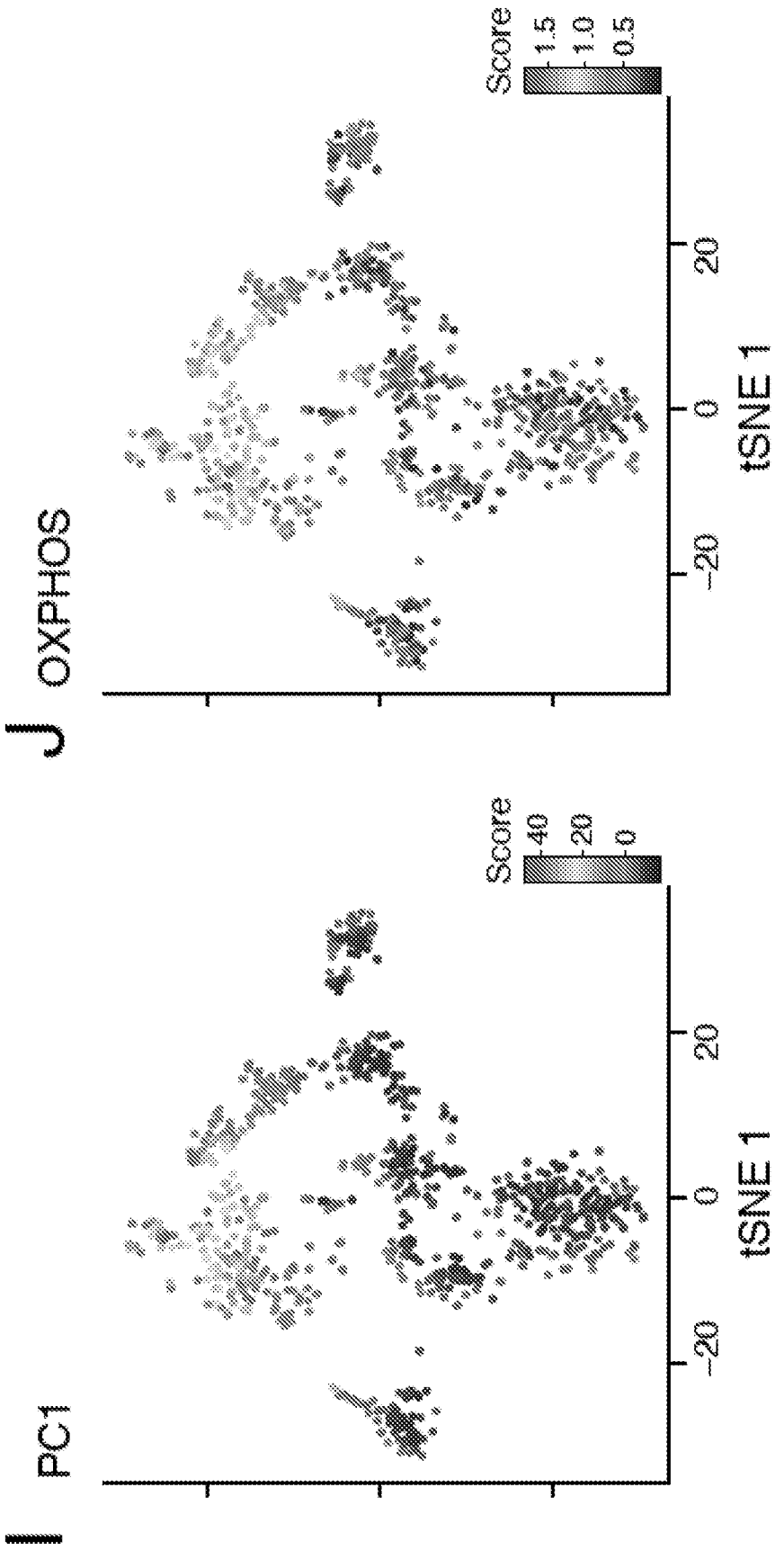

I
PC1
J
OXPHOS
Score
40
20
0
Score
1.5
1.0
0.5
tSNE 1
tSNE 1
20
0
−20
20
0
−20

FIG. 30I-J

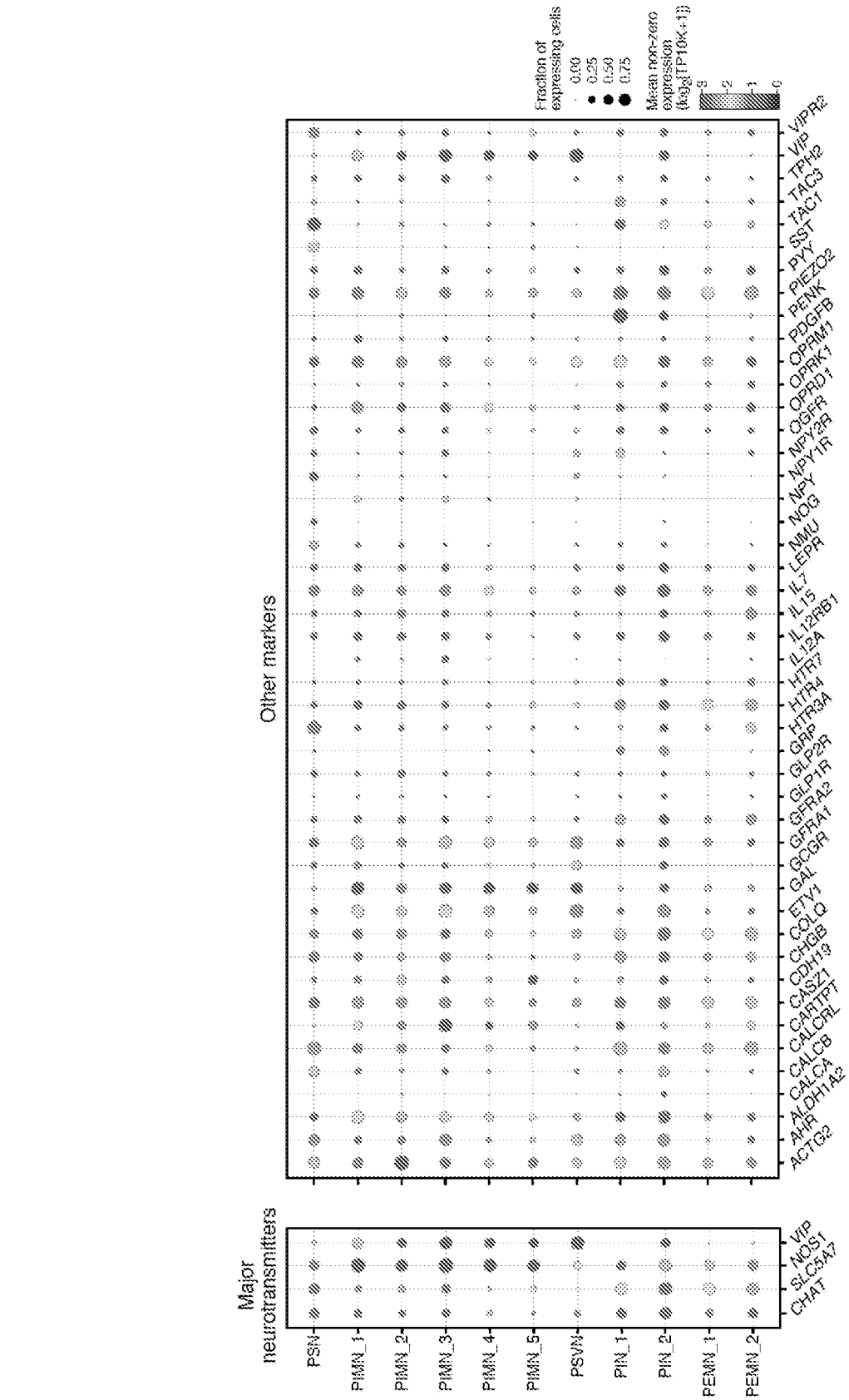


FIG. 31A

FIG. 31B

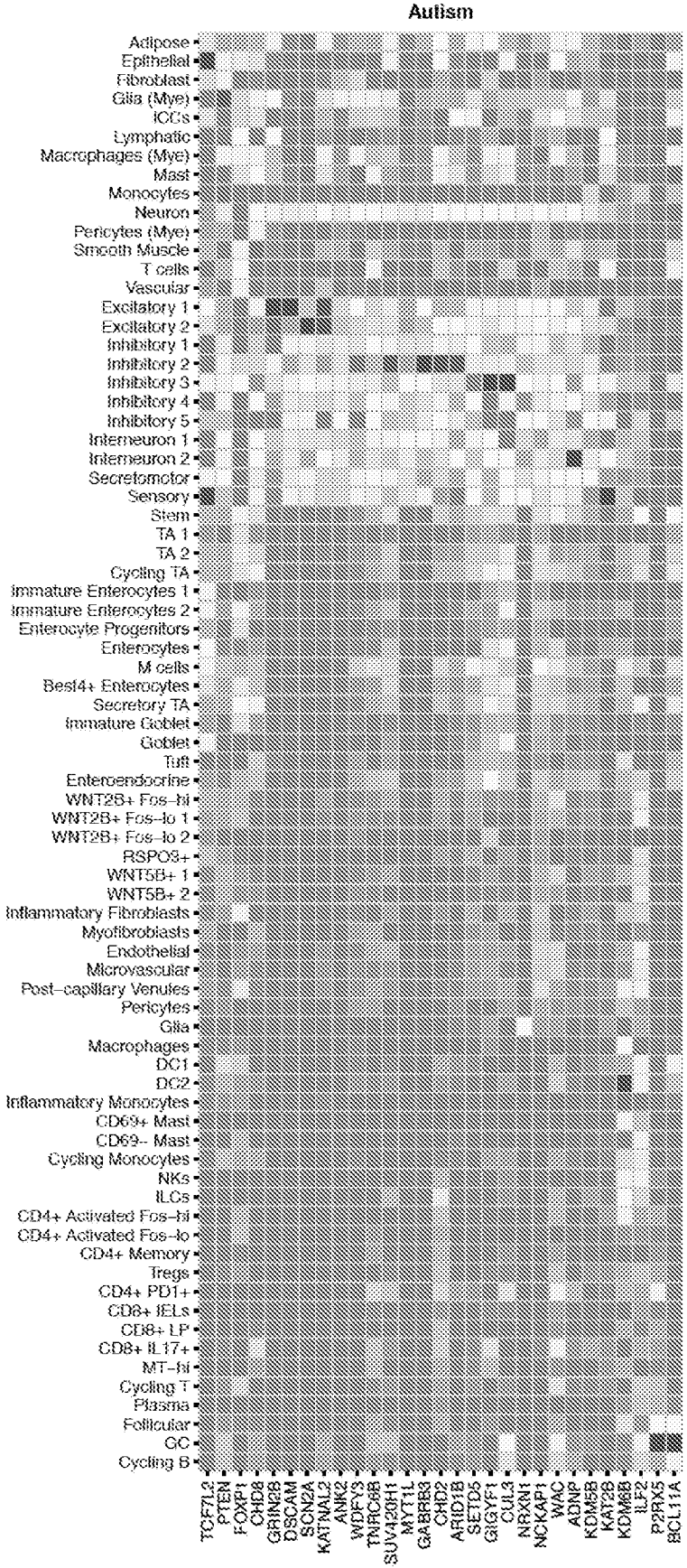

Autism
Adipose
Epithelial
Fibroblast
Glia (Mye)
ICCs
Lymphatic
Macrophages (Mye)
Mast
Monocytes
Neuron
Pericytes (Mye)
Smooth Muscle
T cells
Vascular
Excitatory 1
Excitatory 2
Inhibitory 1
Inhibitory 2
Inhibitory 3
Inhibitory 4
Inhibitory 5
Interneuron 1
Interneuron 2
Secretomotor
Sensory
Stem
TA 1
TA 2
Cycling TA
Immature Enterocytes 1
Immature Enterocytes 2
Enterocyte Progenitors
Enterocytes
M cells
Best4+ Enterocytes
Secretory TA
Immature Goblet
Goblet
Tuft
Enteroendocrine
WNT2B+ Fos–hi
WNT2B+ Fos–lo 1
WNT2B+ Fos–lo 2
RSPO3+
WNT5B+ 1
WNT5B+ 2
Inflammatory Fibroblasts
Myofibroblasts
Endothelial
Microvascular
Post–capillary Venules
Pericytes
Glia
Macrophages
DC1
DC2
Inflammatory Monocytes
CD69+ Mast
CD69– Mast
Cycling Monocytes
NKs
ILCs
CD4+ Activated Fos–hi
CD4+ Activated Fos–lo
CD4+ Memory
Tregs
CD4+ PD1+
CD8+ IELs
CD8+ LP
CD8+ IL17+
MT–hi
Cycling T
Plasma
Follicular
GC
Cycling B
TCF7L2
PTEN
FOXP1
CHD8
GRIN2B
DSCAM
SCN2A
KATNAL2
ANK2
WDFY3
TNRC6B
SUV420H1
MYT1L
GABRB3
CHD2
ARID1B
SETD5
GIGYF1
CUL3
NRXN1
NCKAP1
WAC
ADNP
KDM5B
KAT2B
KDM6B
ILF2
P2RX5
BCL11A

FIG. 32

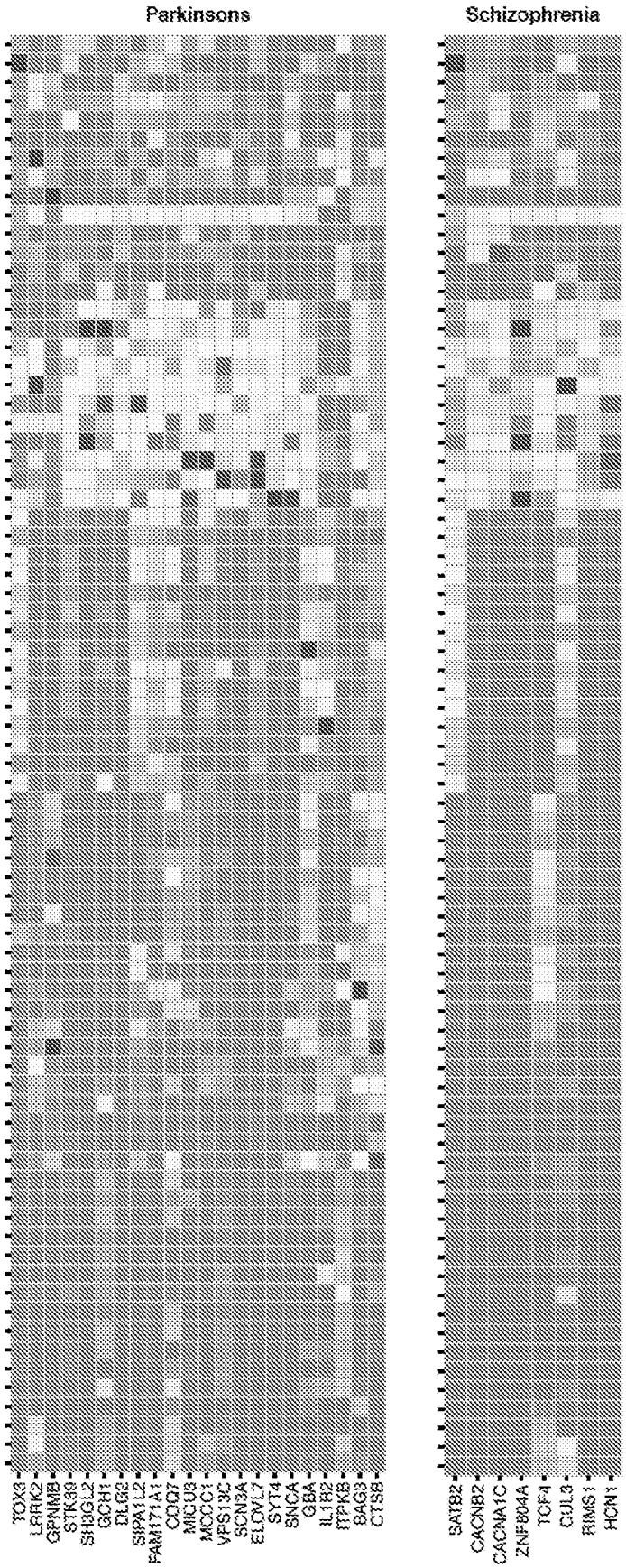


FIG. 32 continued

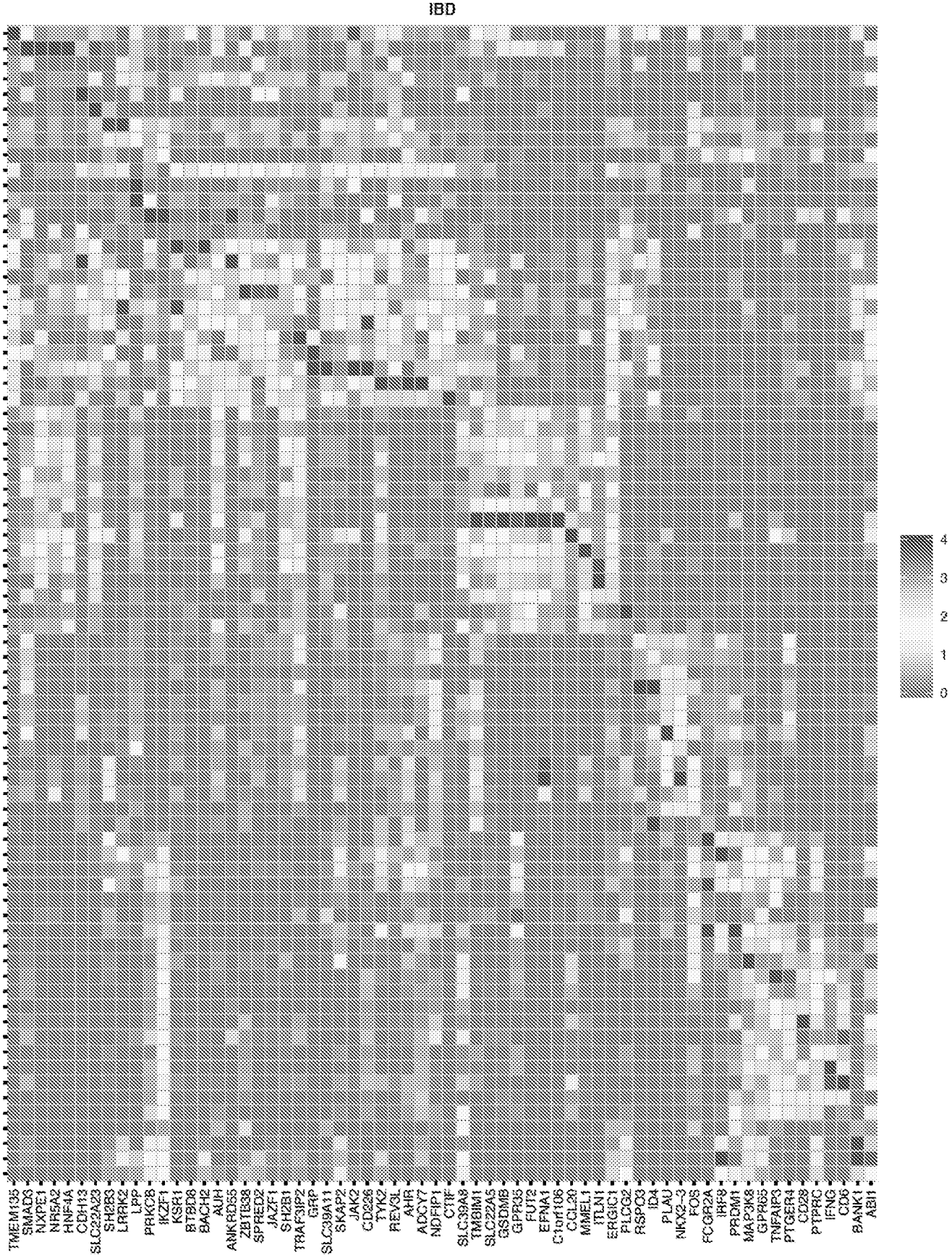


FIG. 32 continued

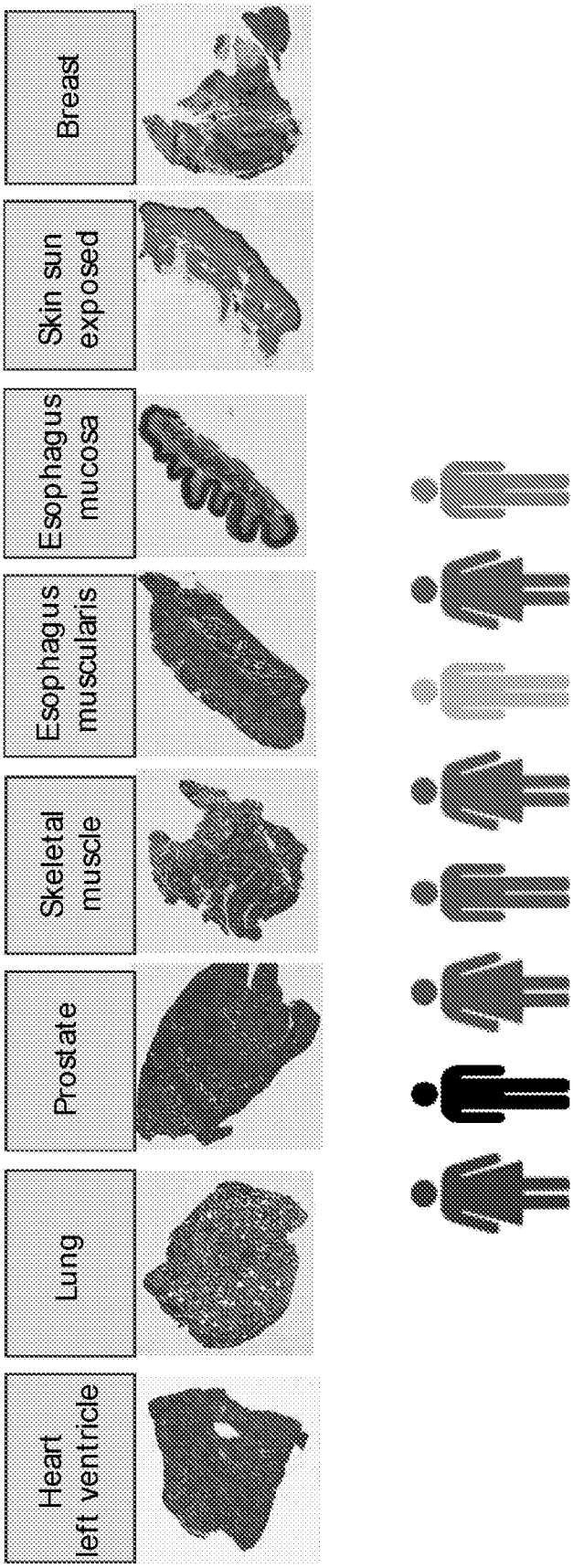

Breast
Skin sun exposed
Esophagus mucosa
Esophagus muscularis
Skeletal muscle
Prostate
Lung
Heart left ventricle

FIG. 33

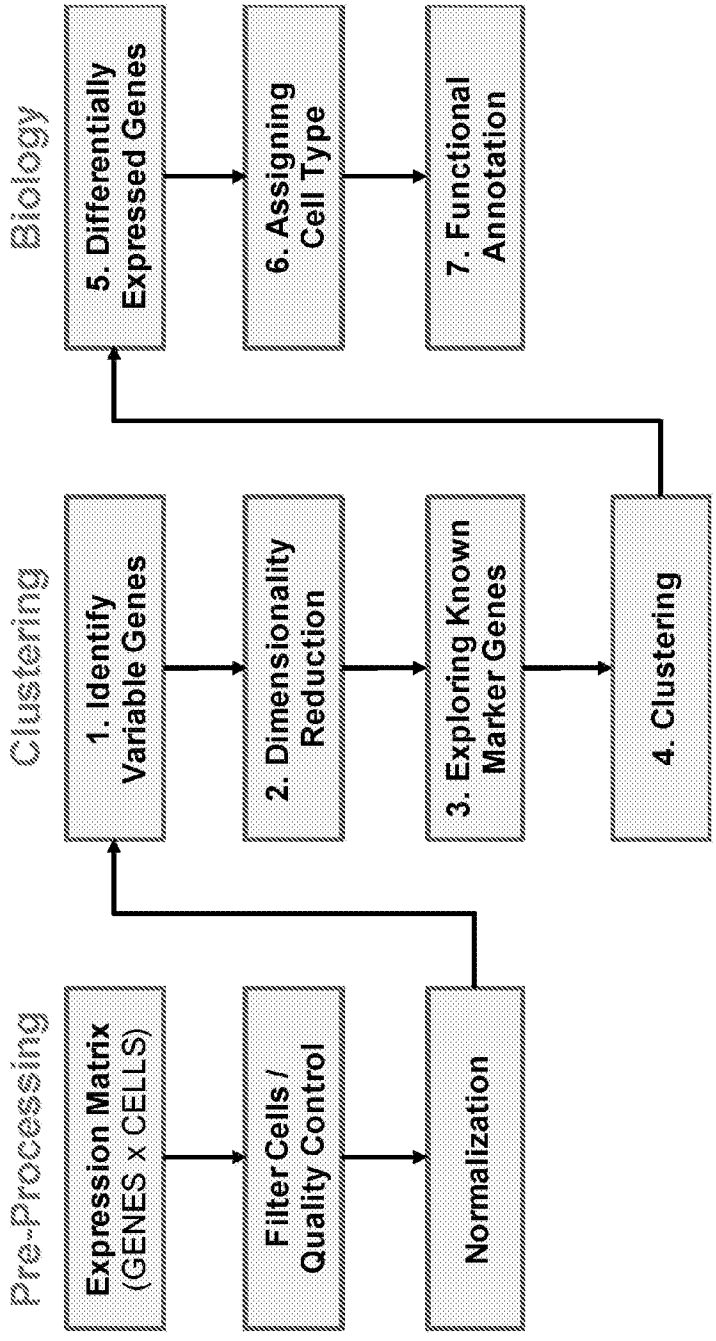

Biology
5. Differentially Expressed Genes
6. Assigning Cell Type
7. Functional Annotation
Clustering
1. Identify Variable Genes
2. Dimensionality Reduction
3. Exploring Known Marker Genes
4. Clustering
Pre-Processing
Expression Matrix (GENES x CELLS)
Filter Cells / Quality Control
Normalization

FIG. 34

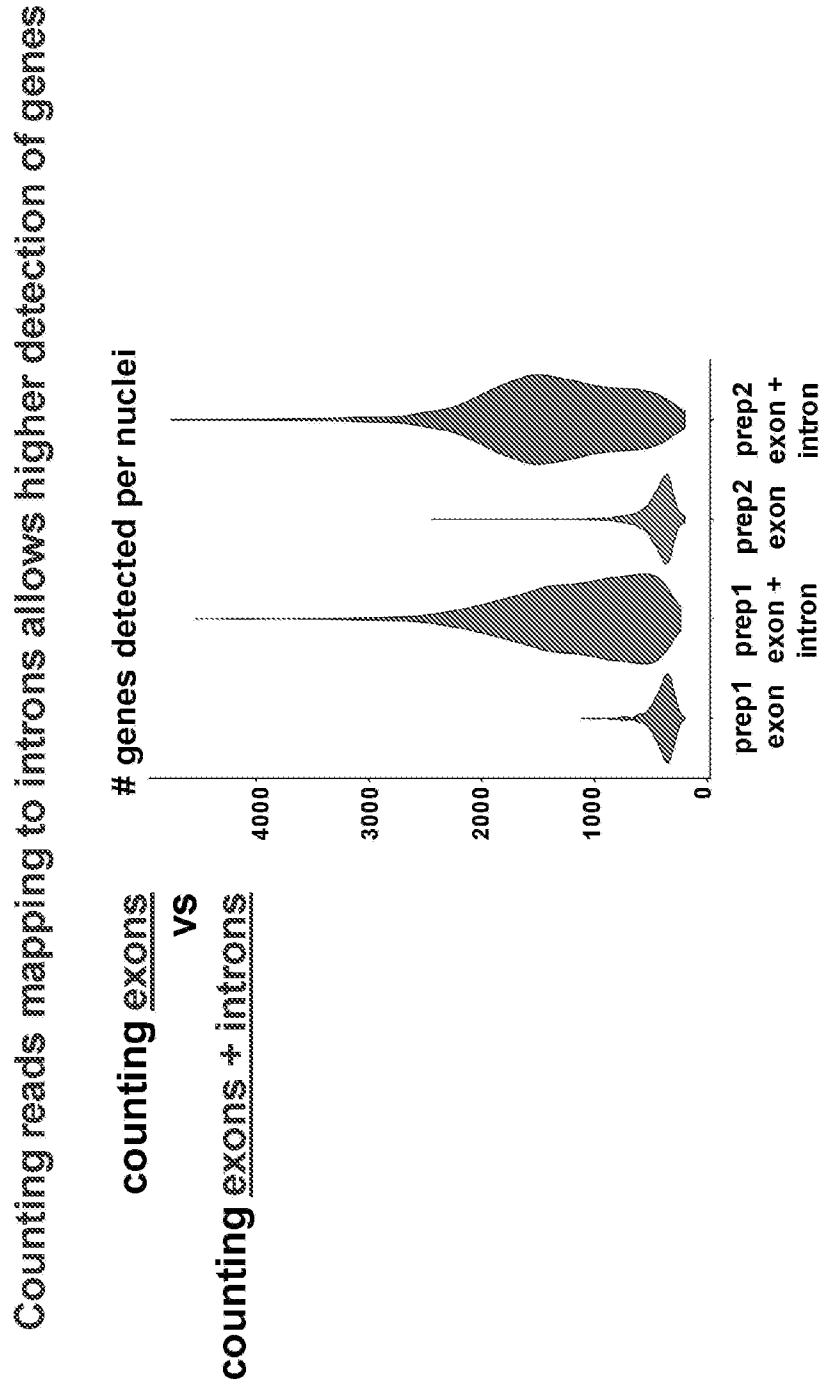

Counting reads mapping to introns allows higher detection of genes
counting exons
vs
counting exons + introns
genes detected per nuclei
4000
3000
2000
1000
0
prep1 exon
prep1 exon + intron
prep2 exon
prep2 exon + intron

FIG. 35

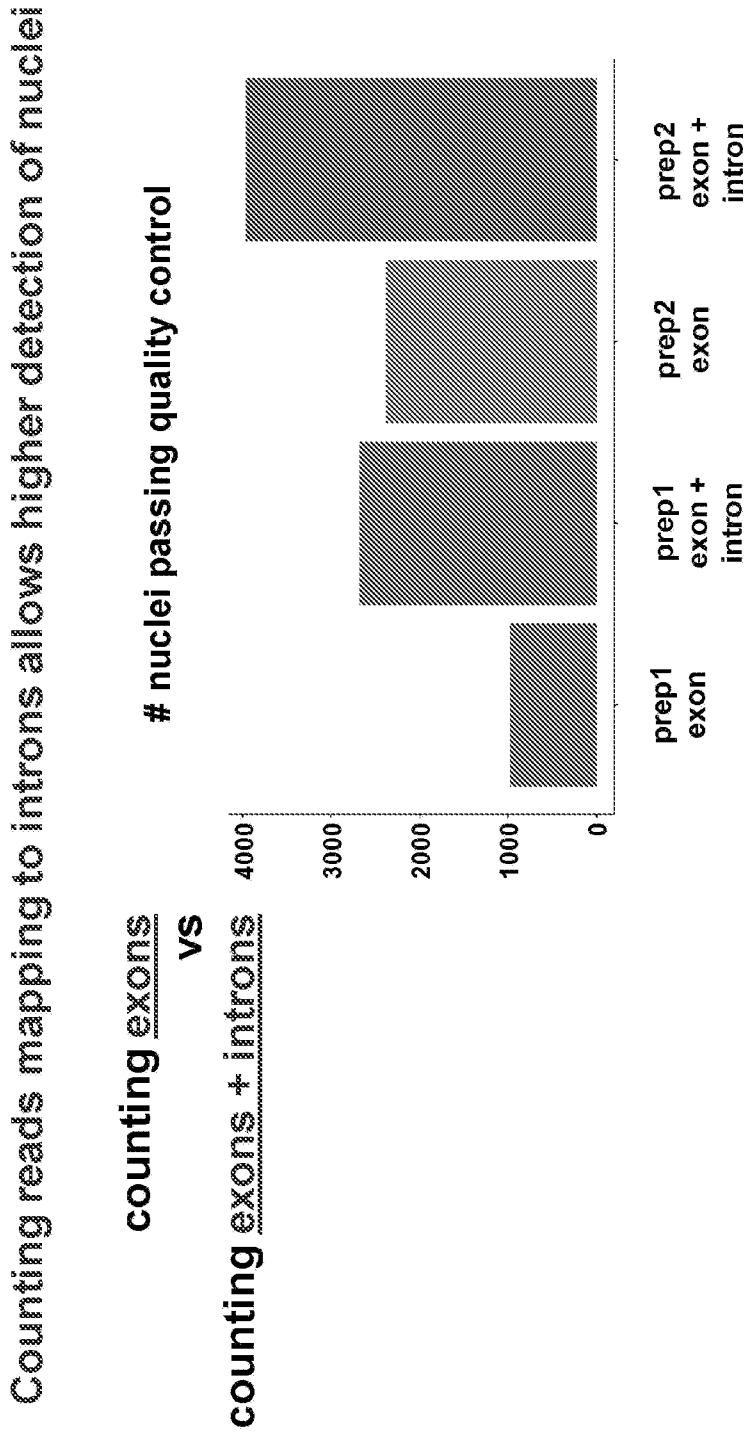

Counting reads mapping to introns allows higher detection of nuclei
counting exons
vs
counting exons + introns
nuclei passing quality control
4000
3000
2000
1000
0
prep1 exon
prep1 exon + intron
prep2 exon
prep2 exon + intron

FIG. 36

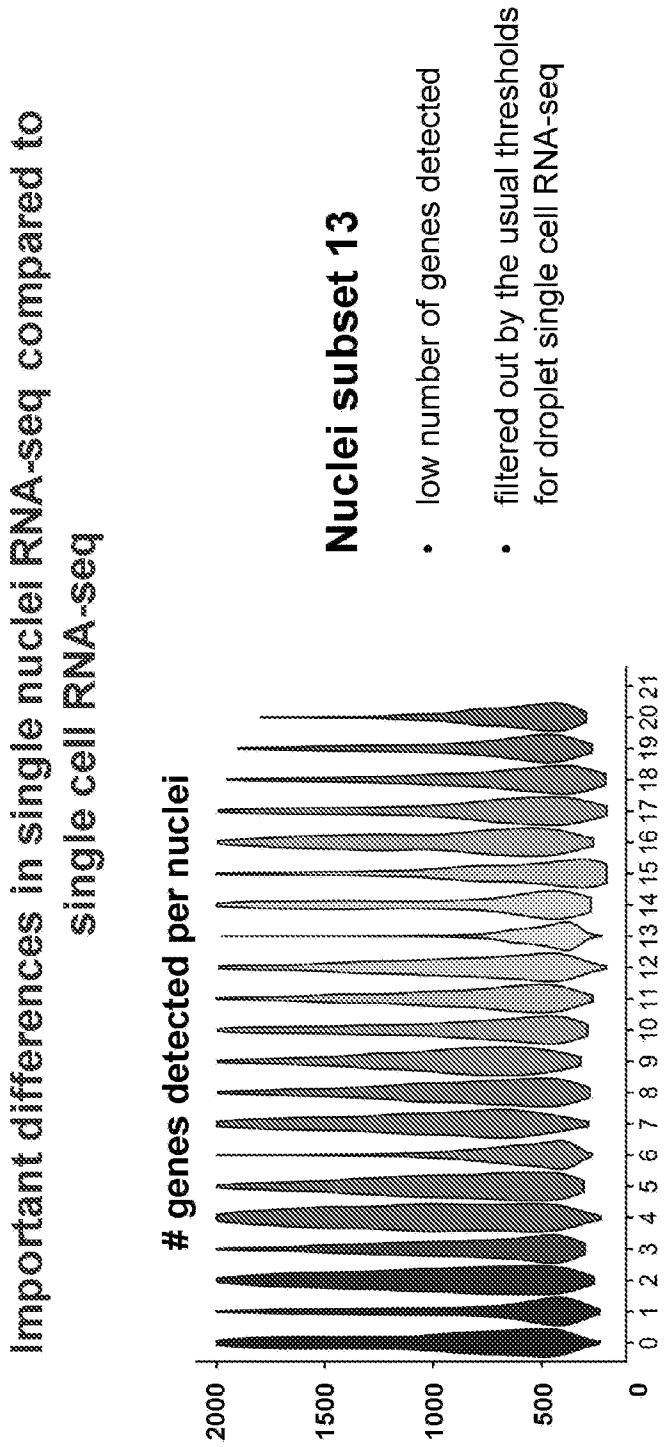

Important differences in single nuclei RNA-seq compared to single cell RNA-seq
genes detected per nuclei
2000
1500
1000
500
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
nuclei subsets
Nuclei subset 13
low number of genes detected
filtered out by the usual thresholds for droplet single cell RNA-seq

FIG. 37

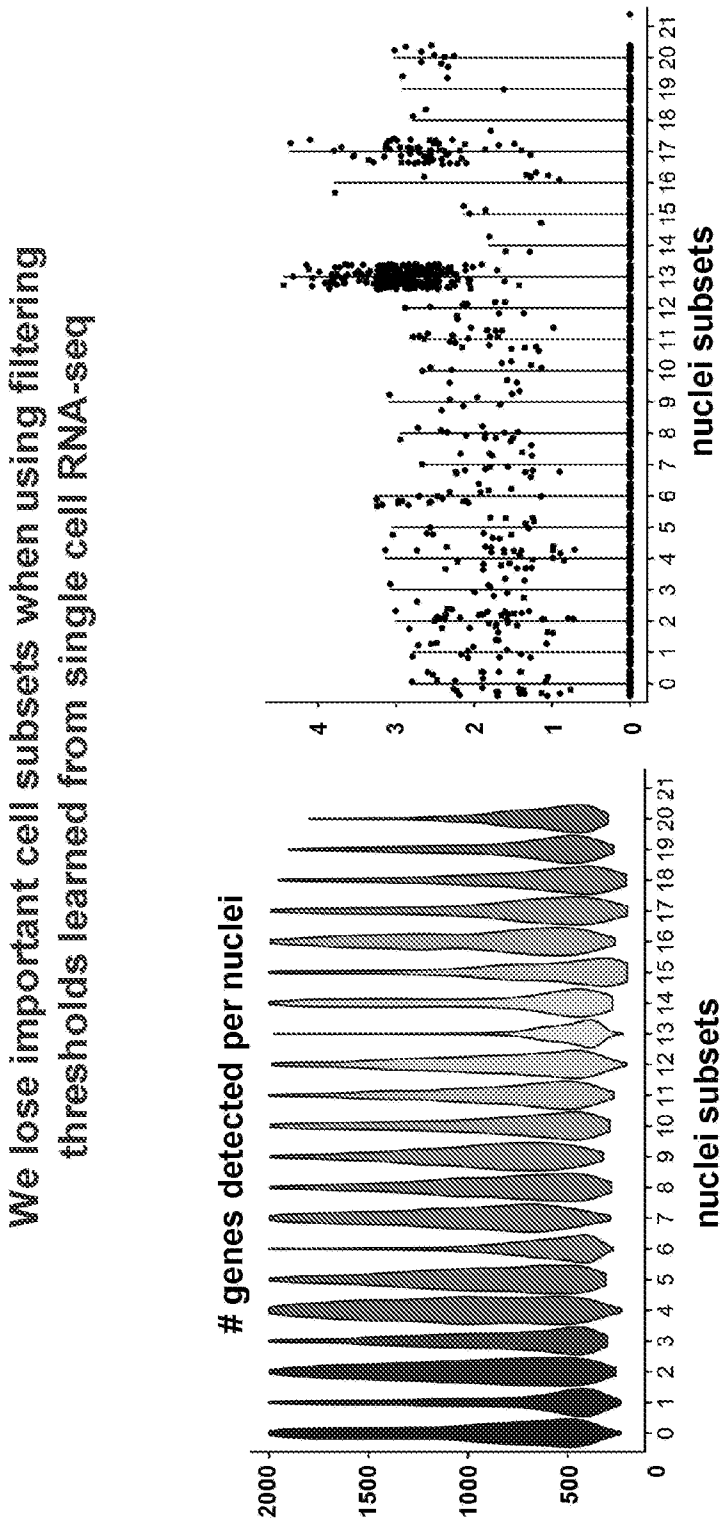

We lose important cell subsets when using filtering thresholds learned from single cell RNA-seq
genes detected per nuclei
2000
1500
1000
500
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
nuclei subsets
4
3
2
1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
nuclei subsets

FIG. 38

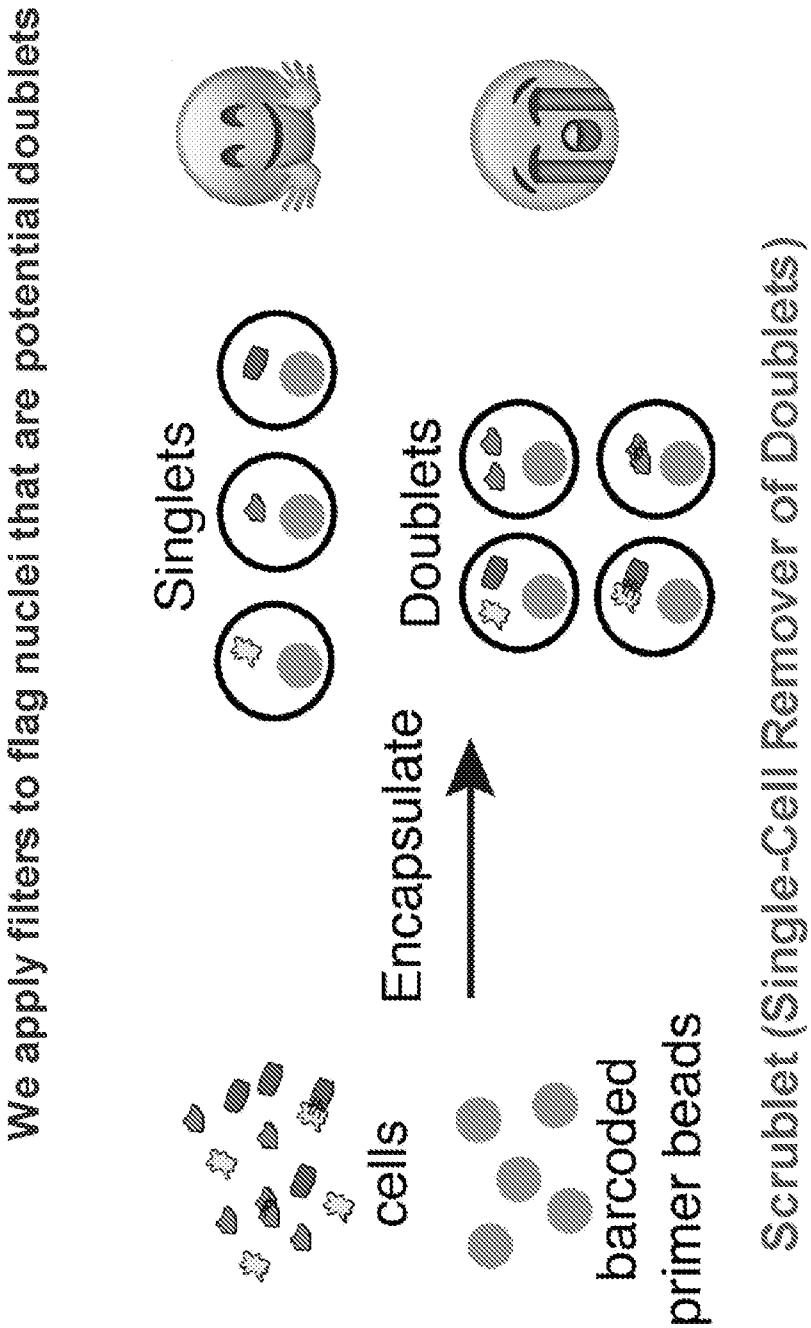

We apply filters to flag nuclei that are potential doublets
Singlets
Doublets
Encapsulate
cells
barcoded
primer beads
Scrublet (Single-Cell Remover of Doublets)

FIG. 39

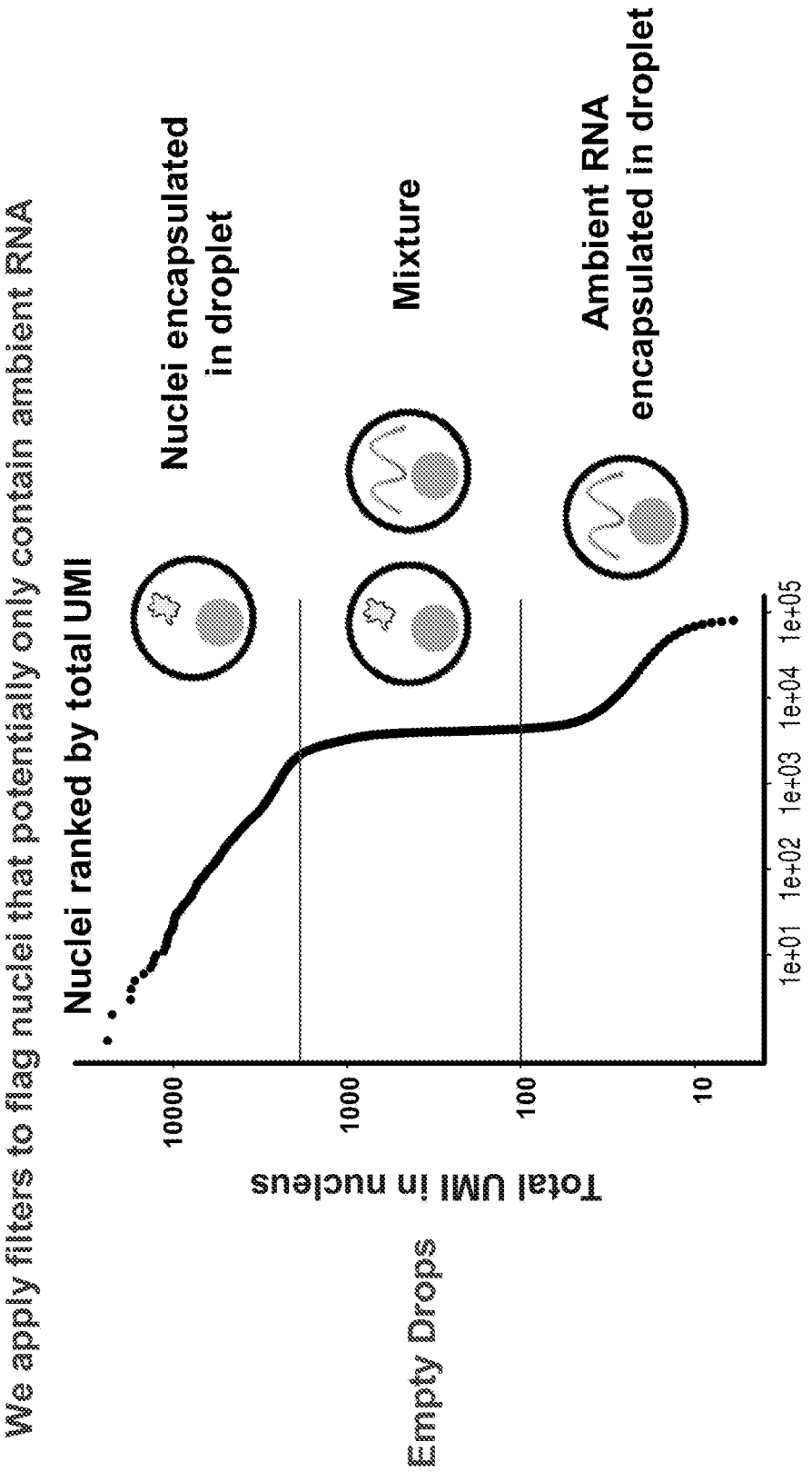

We apply filters to flag nuclei that potentially only contain ambient RNA
Nuclei ranked by total UMI
Nuclei encapsulated in droplet
Mixture
Ambient RNA encapsulated in droplet
Total UMI in nucleus
10000
1000
100
10
1e+01
1e+02
1e+03
1e+04
1e+05
Empty Drops

FIG. 40

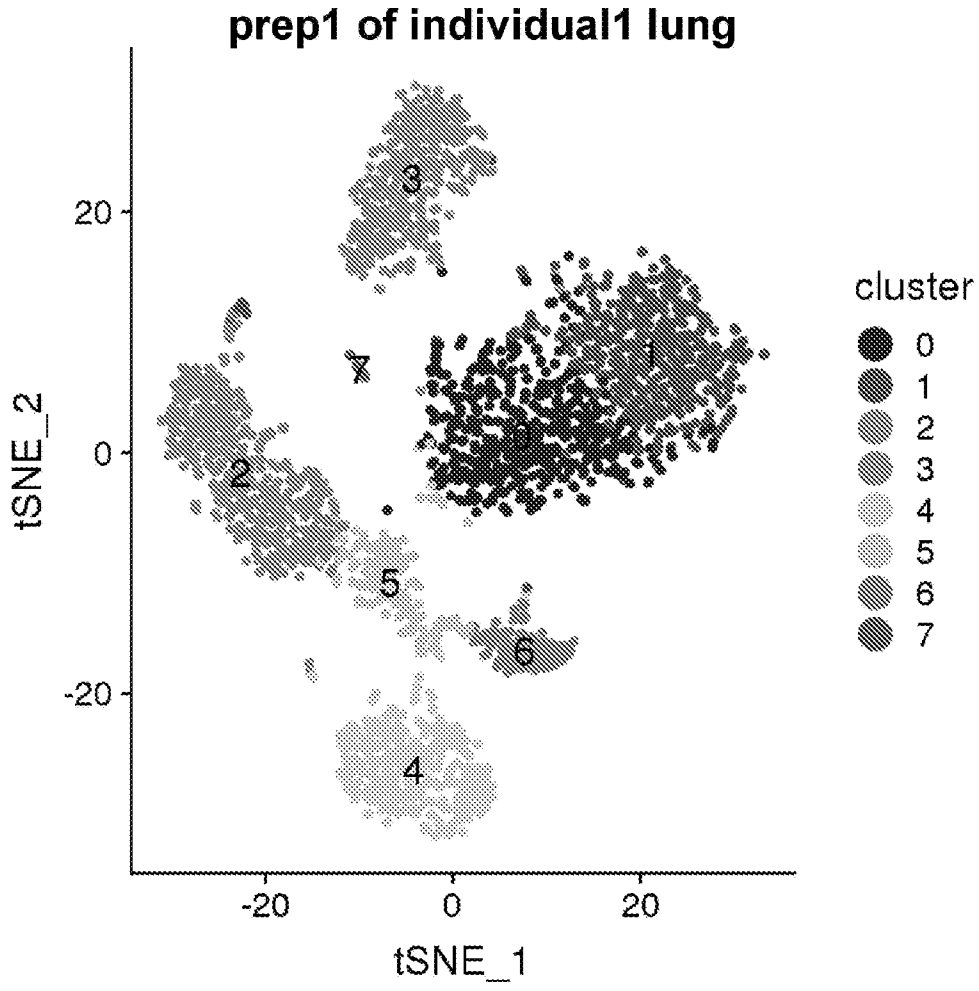

prep1 of individual1 lung
tSNE_2
tSNE_1
20
0
-20
-20
0
20
cluster
0
1
2
3
4
5
6
7

FIG. 41

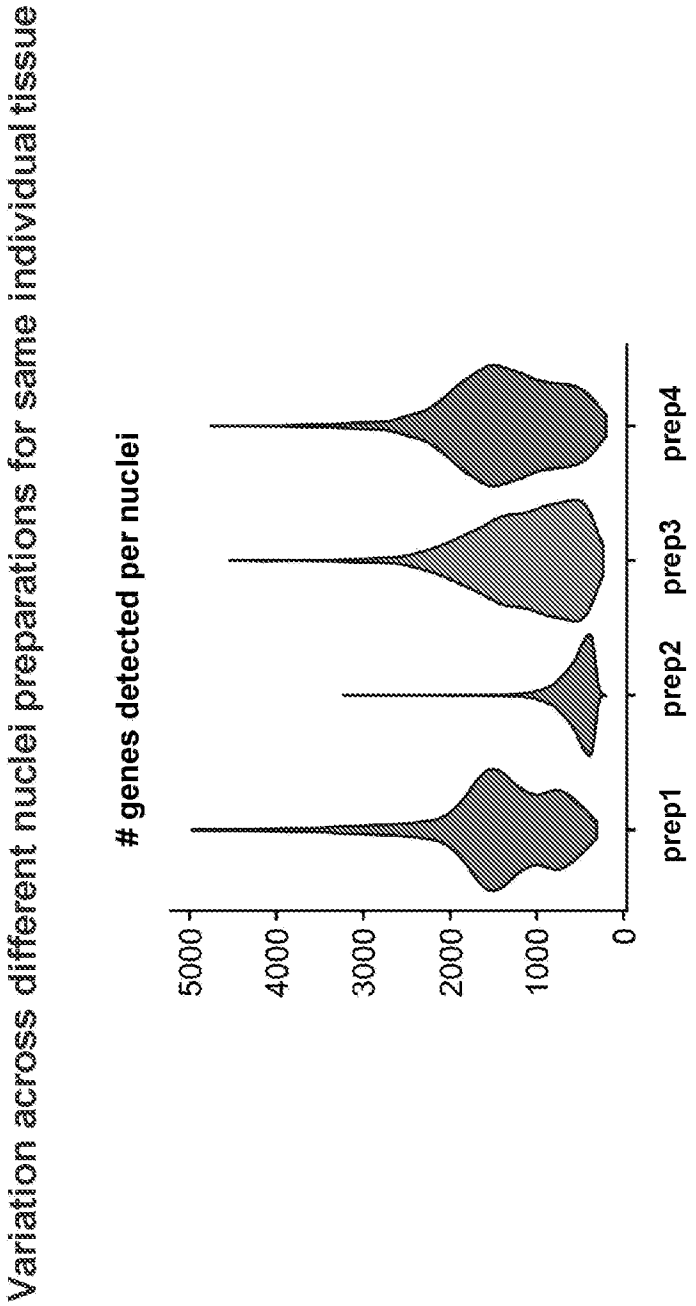

Variation across different nuclei preparations for same individual tissue
genes detected per nuclei
5000
4000
3000
2000
1000
0
prep1
prep2
prep3
prep4

FIG. 42

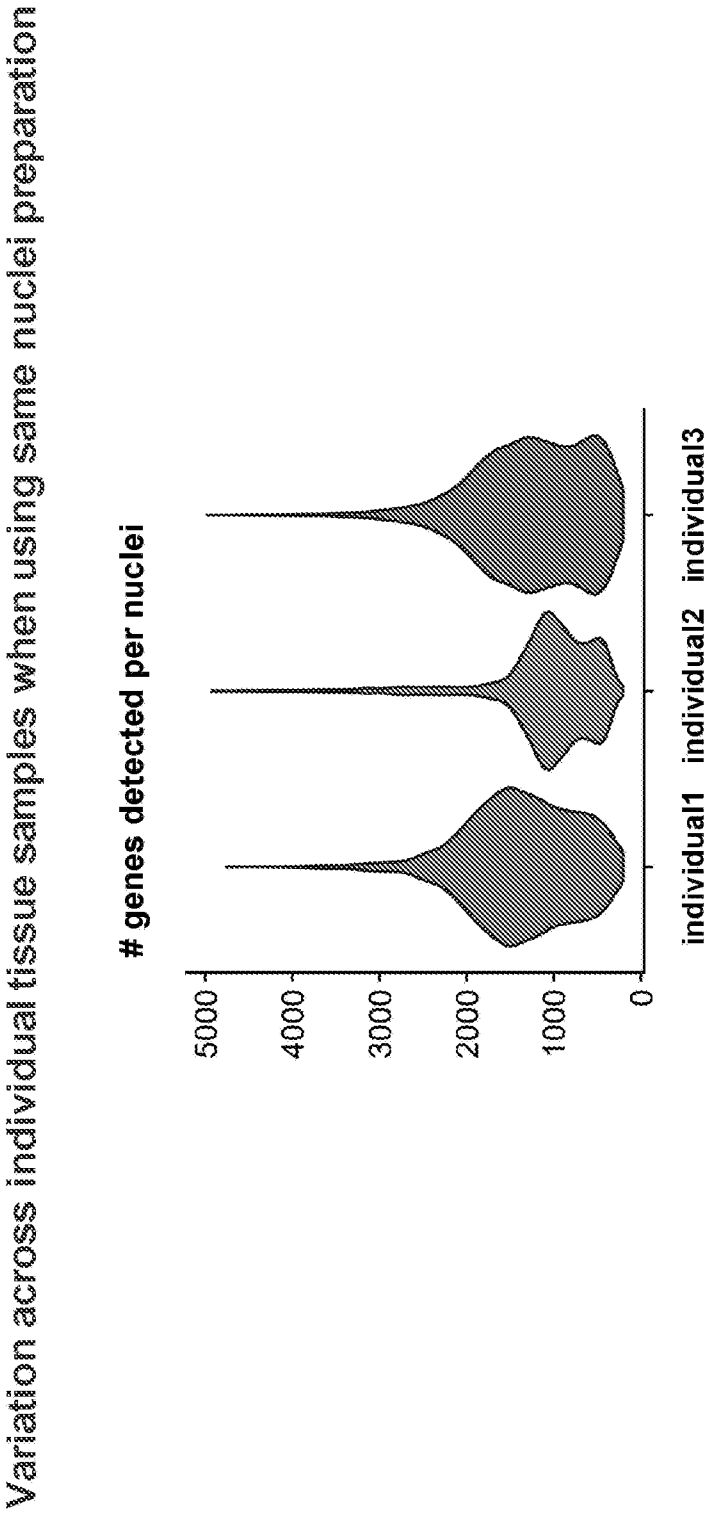

Variation across individual tissue samples when using same nuclei preparation
genes detected per nuclei
5000
4000
3000
2000
1000
0
individual1
individual2
individual3

FIG. 43

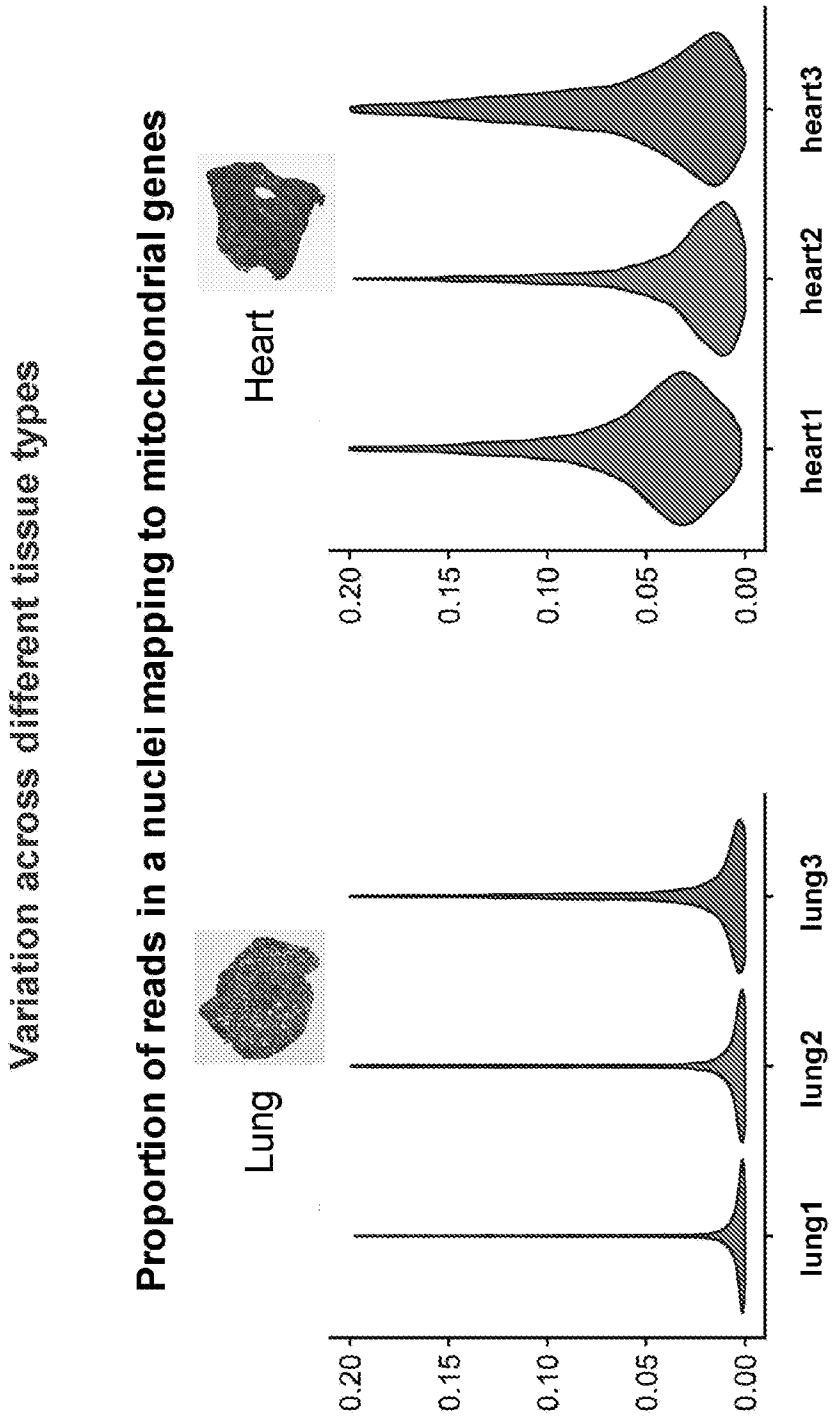
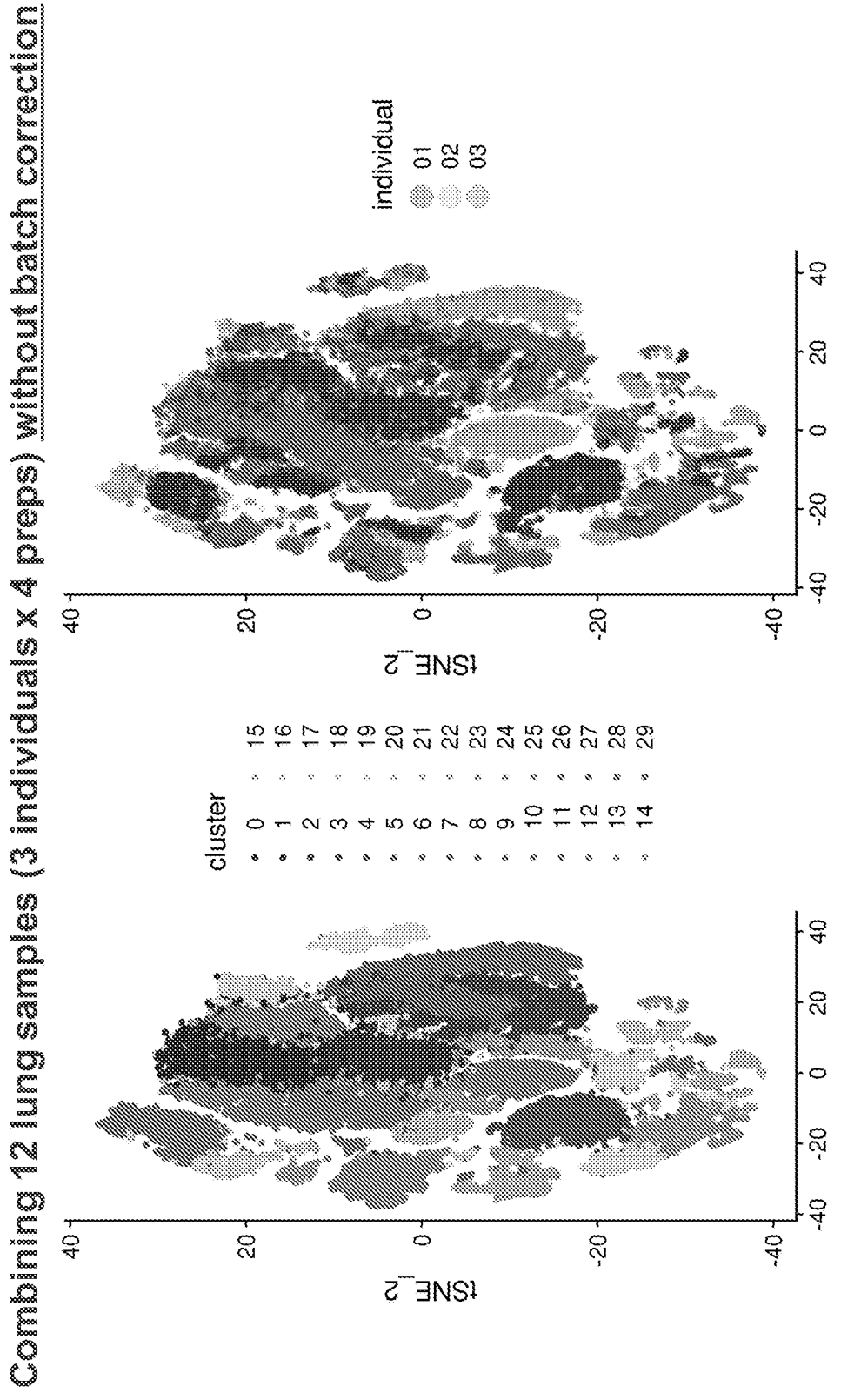
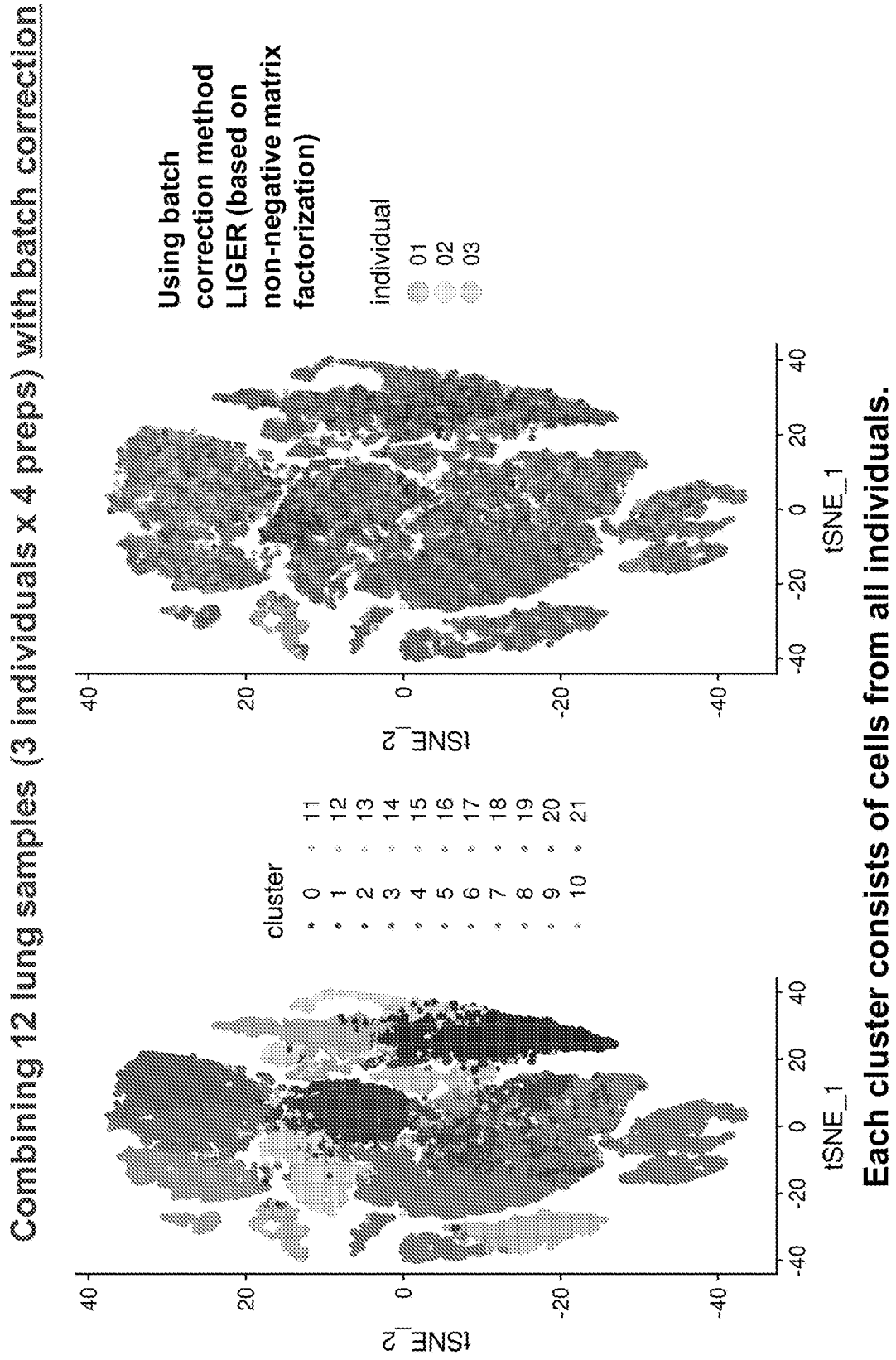

Variation across different tissue types
Proportion of reads in a nuclei mapping to mitochondrial genes
Lung
Heart
0.20
0.15
0.10
0.05
0.00
lung1
lung2
lung3
heart1
heart2
heart3

FIG. 44



Cells cluster by which individual they come from, even though individuals share the same cell types.

FIG. 45



Each cluster consists of cells from all individuals.

FIG. 46

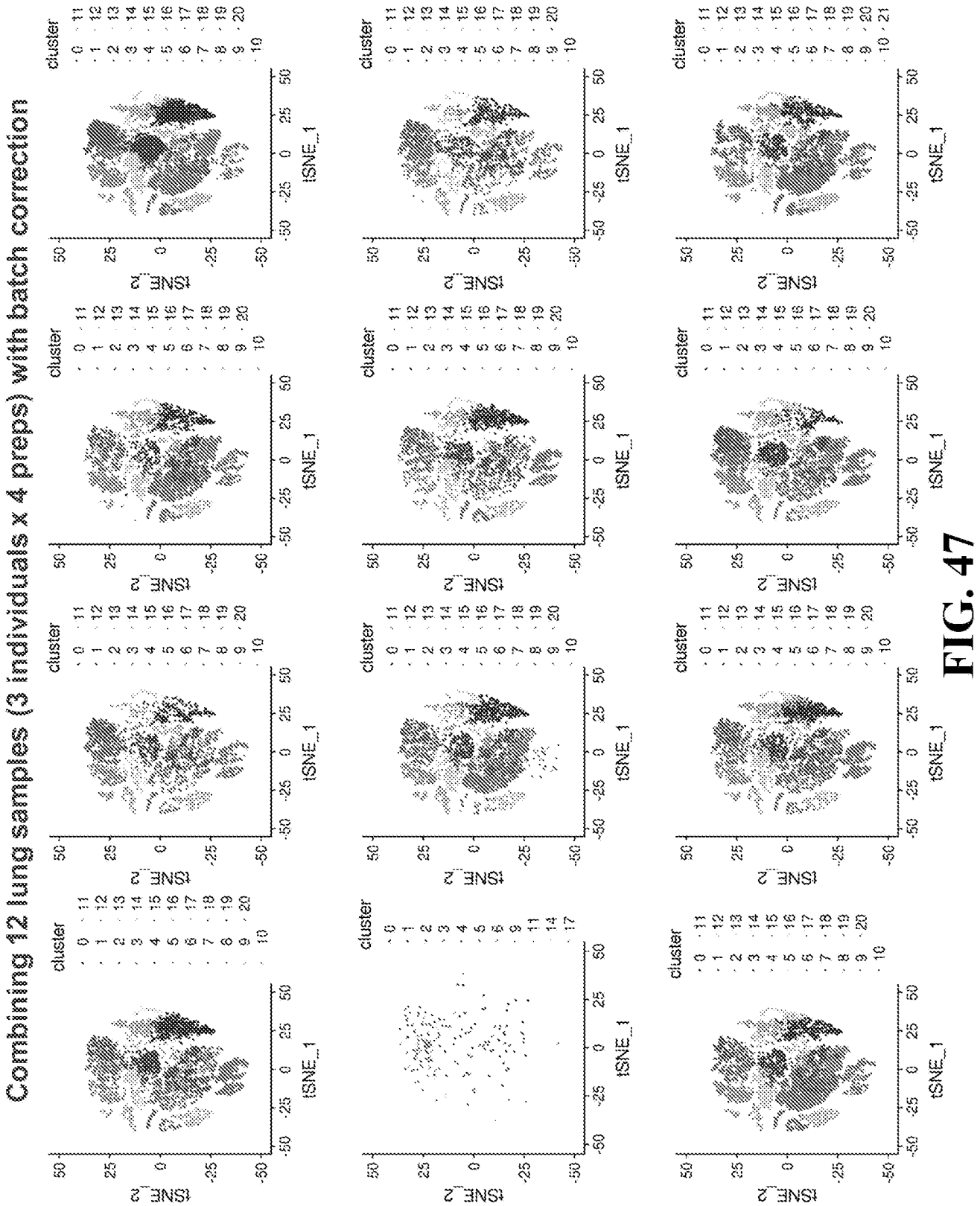

Combining 12 lung samples (3 individuals x 4 preps) with batch correction
cluster
tSNE_1
tSNE_2

FIG. 47

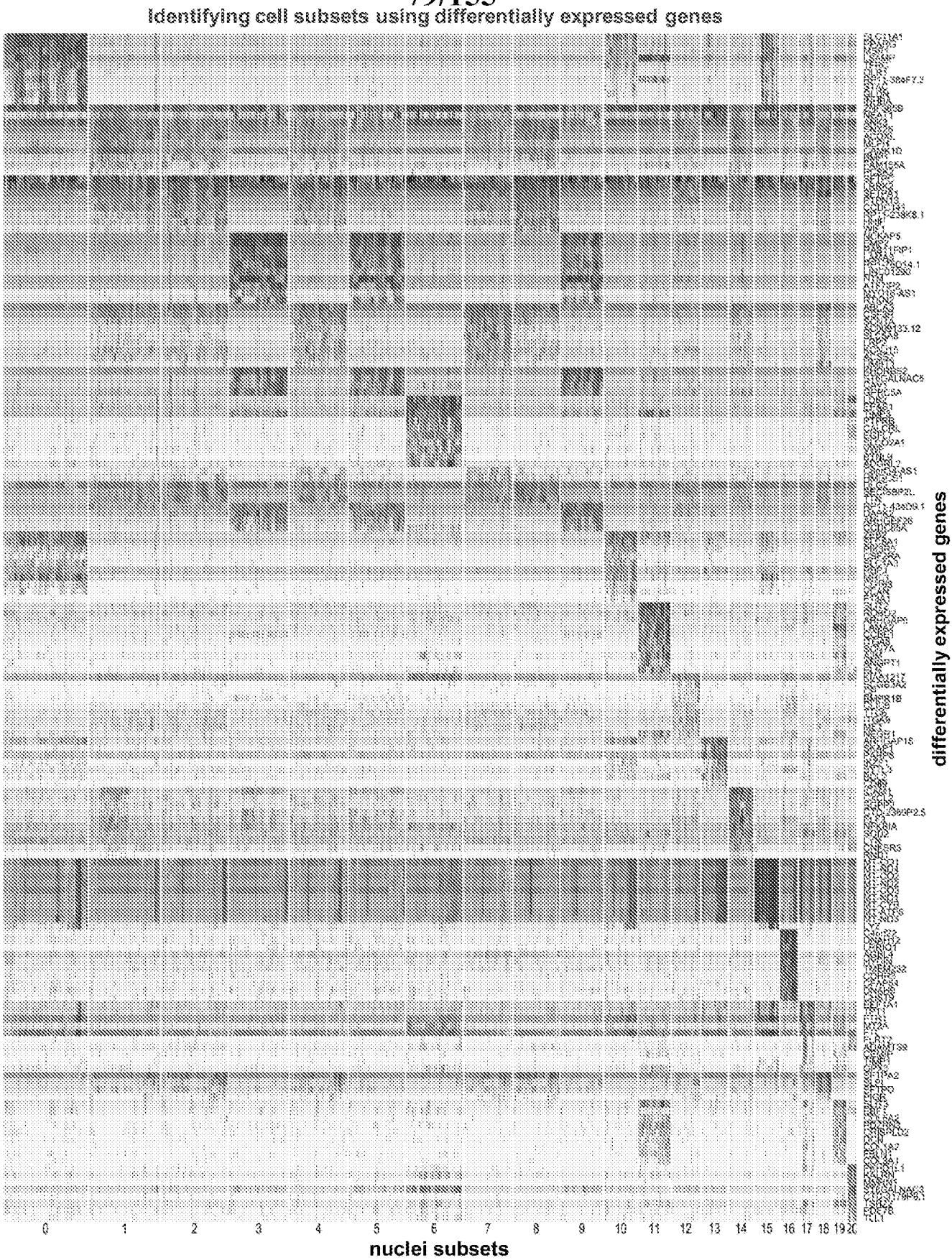

Identifying cell subsets using differentially expressed genes
differentially expressed genes
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
nuclei subsets

FIG. 48

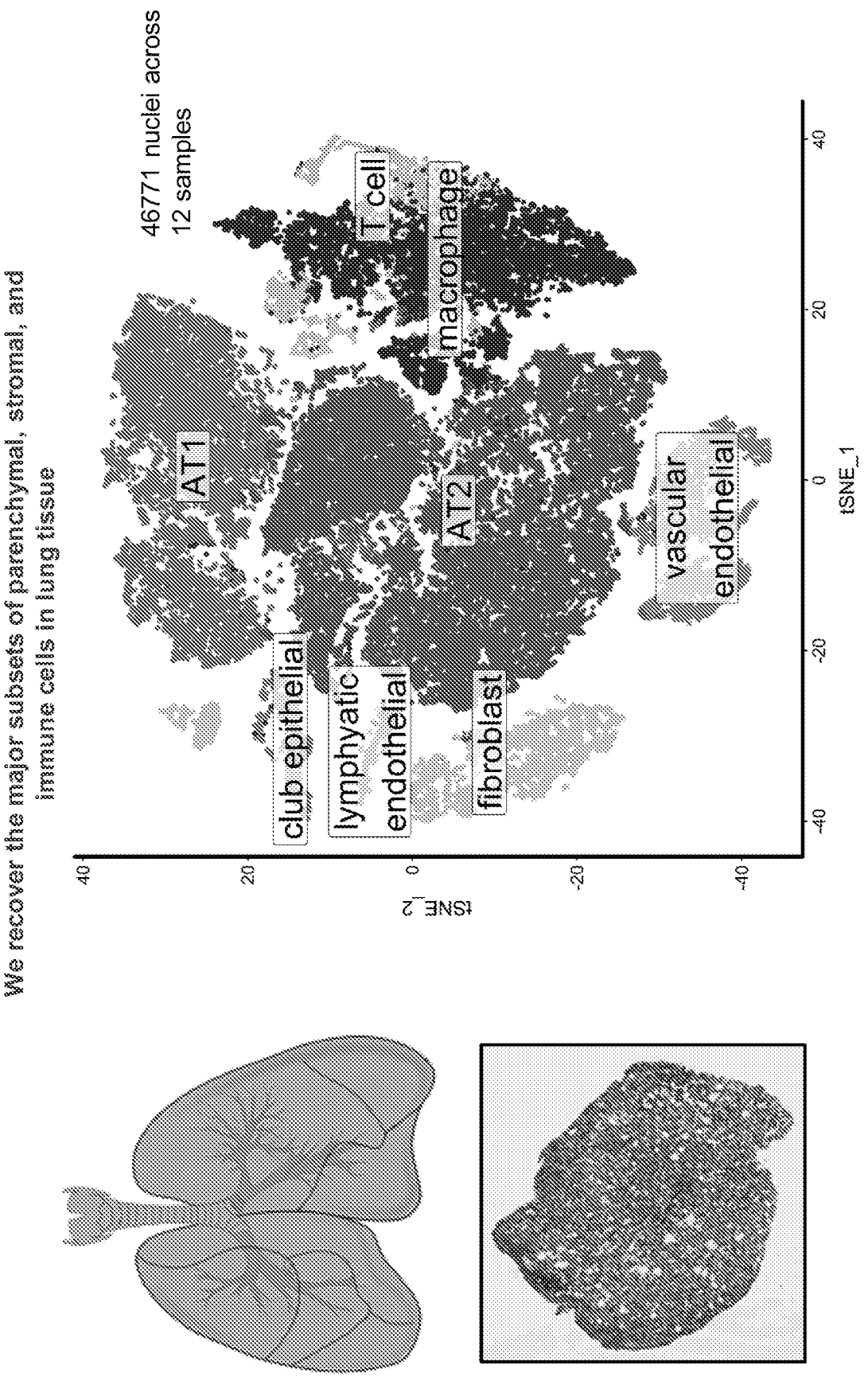

We recover the major subsets of parenchymal, stromal, and immune cells in lung tissue
46771 nuclei across 12 samples
AT1
club epithelial
lymphyatic endothelial
T cell
macrophage
AT2
fibroblast
vascular endothelial
tSNE_1
tSNE_2
40
20
0
-20
-40

FIG. 49

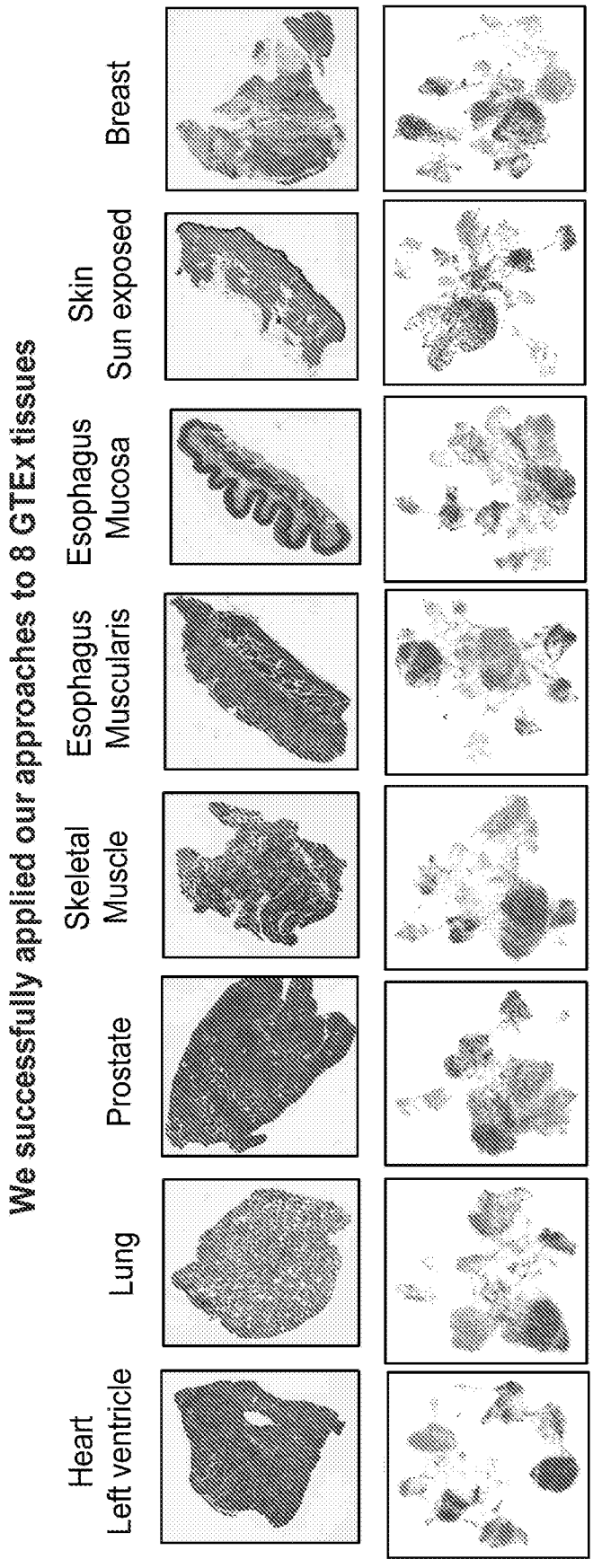

We successfully applied our approaches to 8 GTEx tissues
Heart Left ventricle
Lung
Prostate
Skeletal Muscle
Esophagus Muscularis
Esophagus Mucosa
Skin Sun exposed
Breast

FIG. 50

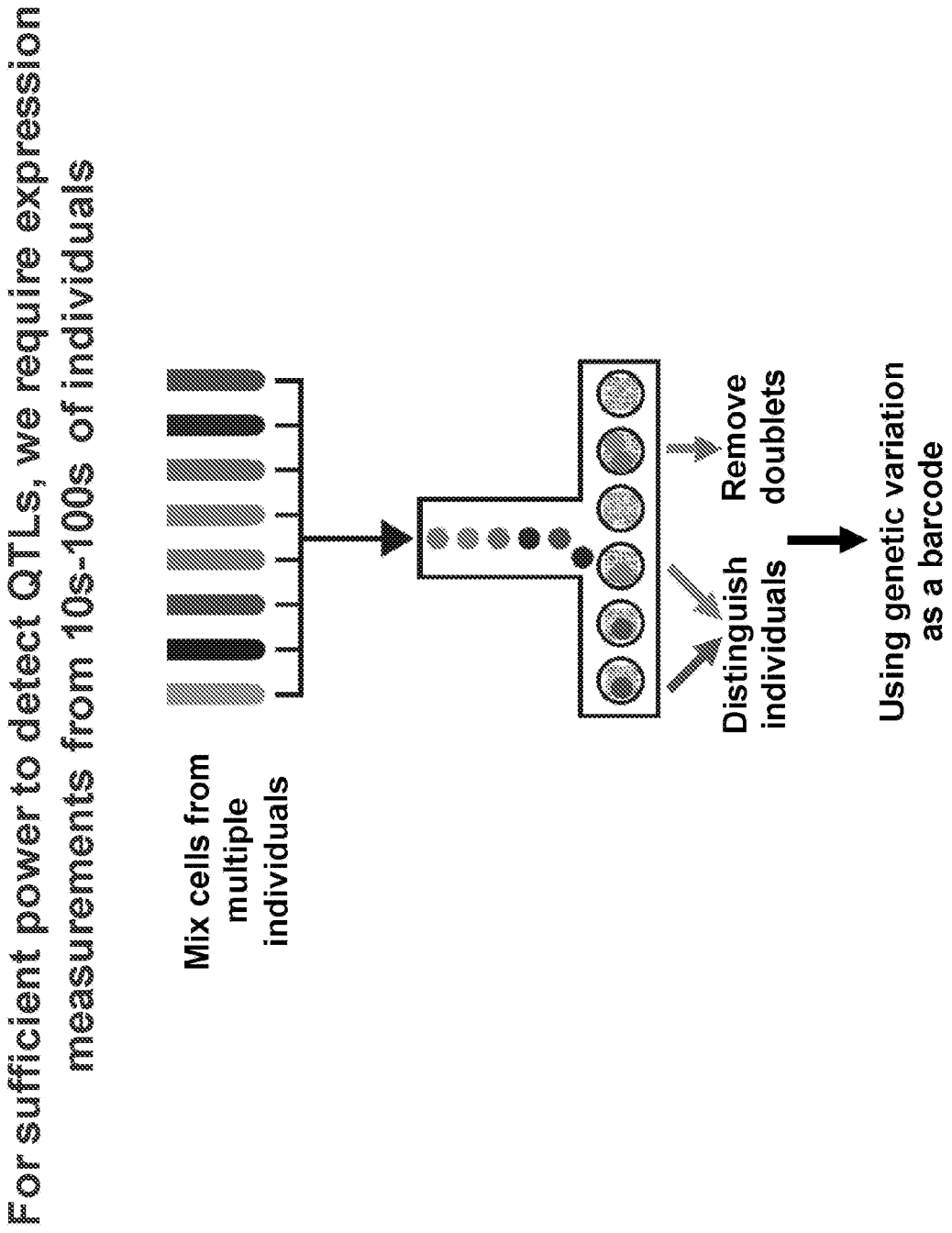

For sufficient power to detect QTLs, we require expression measurements from 10s-100s of individuals
Mix cells from multiple individuals
Distinguish individuals
Remove doublets
Using genetic variation as a barcode

FIG. 51

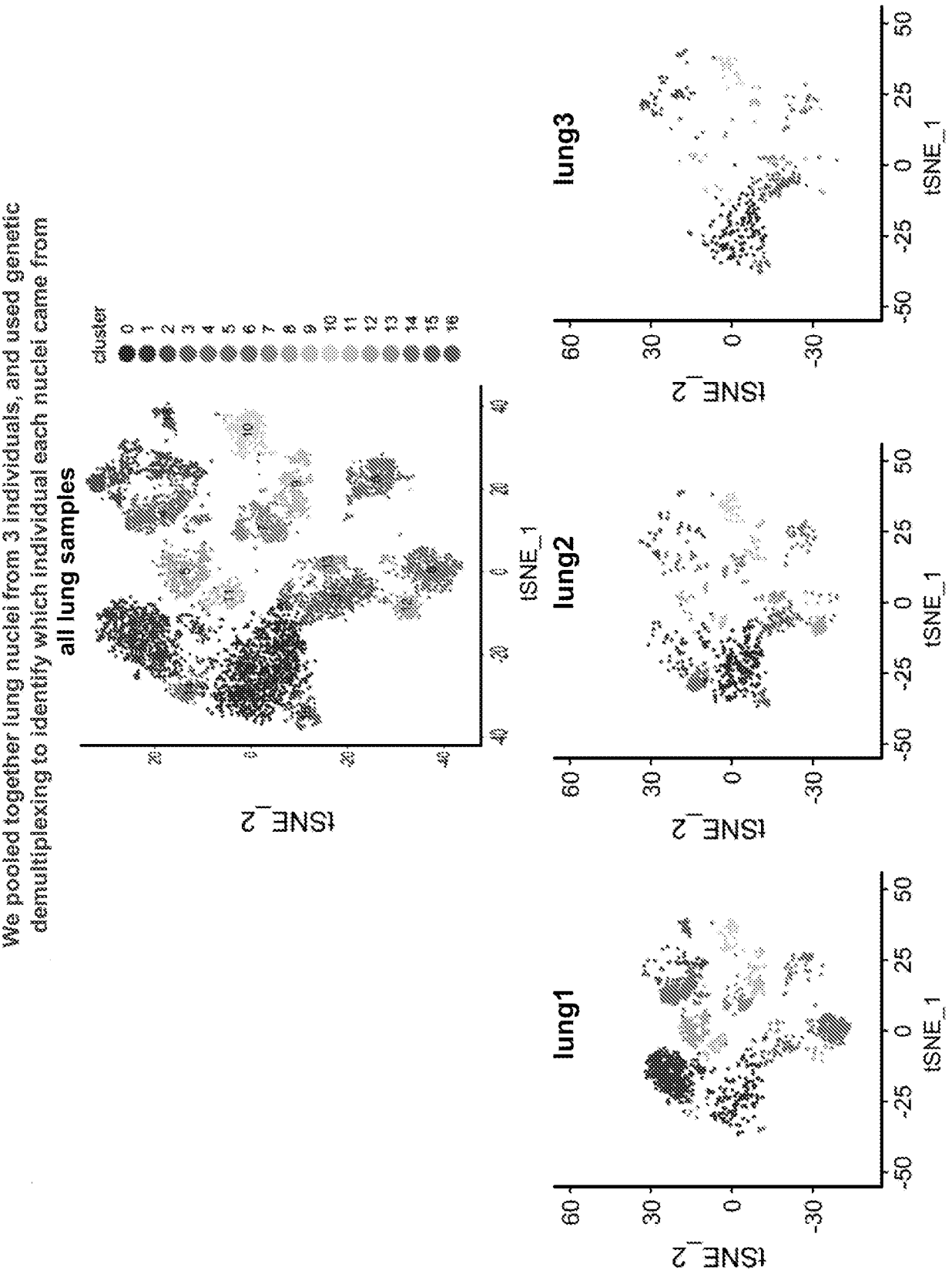

We pooled together lung nuclei from 3 individuals, and used genetic demultiplexing to identify which individual each nuclei came from
all lung samples
cluster
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
tSNE_1
tSNE_2
lung1
lung2
lung3

FIG. 52

FIG. 53A

Cancer Type	Origin	Age	Sample Type	Patients	Cells	Nuclei	Protocol
Lung (NSCLC)	Epithelial	Adult	Resection	2	2	-	PDEC
Neuroblastoma (NB)	Neuroendocrine	Pediatric	Resection Biopsy PDX	3	3	3	Papain Kit TST
Metastatic Breast Cancer (MBC)	Epithelial	Adult	Resection Biopsy	6	4	3	LD / TST
Sarcoma	Mesenchymal	Pediatric	Resection	2	-	2	TST
Ovarian	Epithelial	Adult	Resection Ascites	3	2	1	MHTD Kit TST
Glioma PED HG GBM	Neuronal	Pediatric Adult	Resection	3	1	1	MBTDP Kit CST
Melanoma	Melanocytes	Adult	Resection	2	-	2	TST
CLL	Hematopoietic	Adult	Cryopreserved	1	1	1	TST
							fresh frozen

FIG. 53B

FIG. 53C

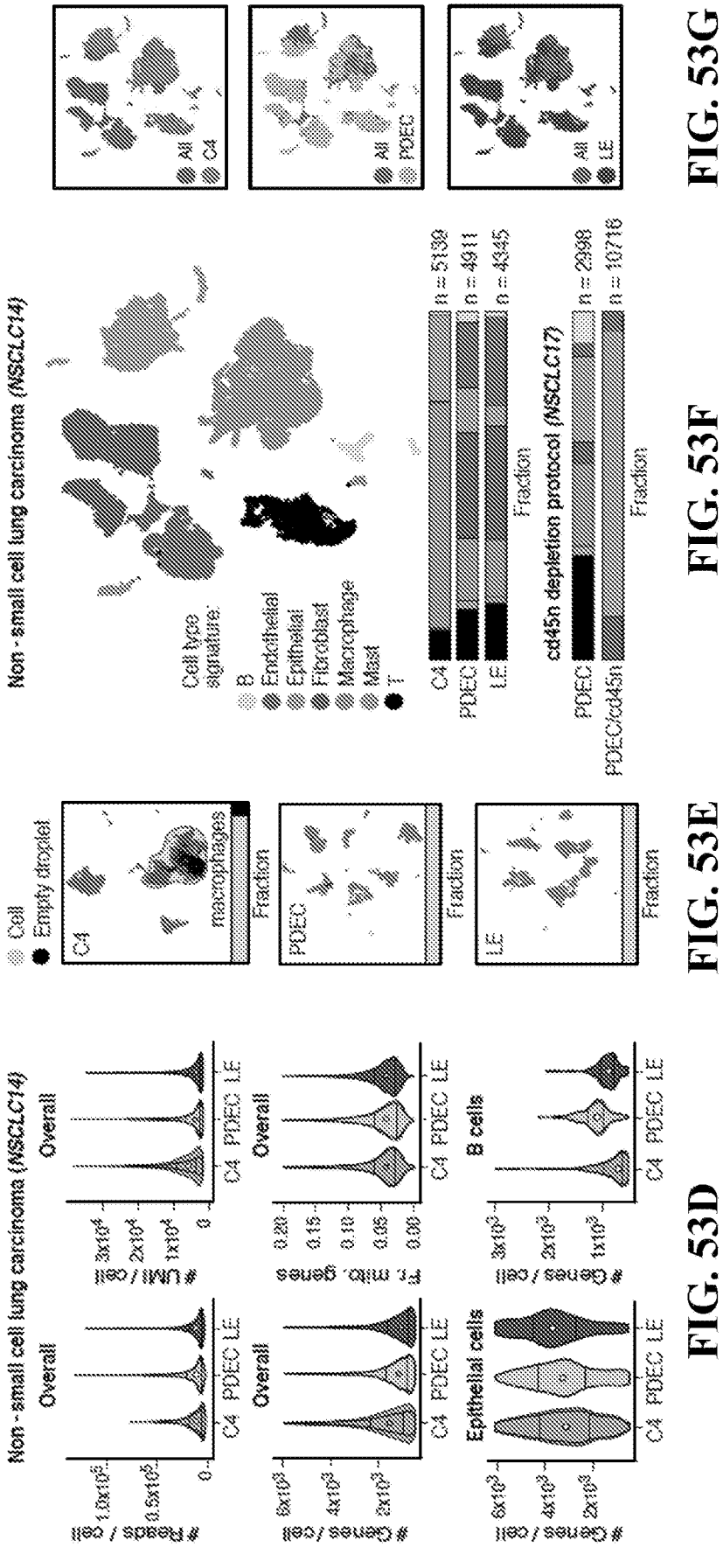


FIG. 53D FIG. 53E FIG. 53F FIG. 53G

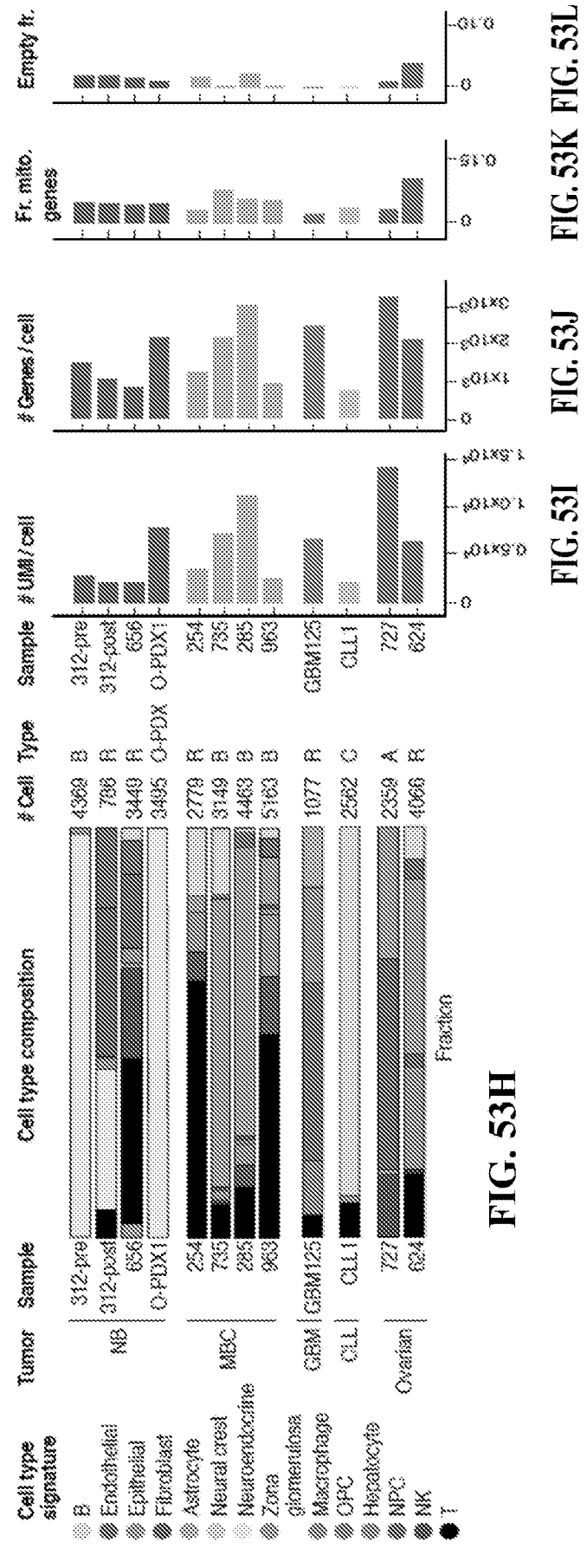


FIG. 53H FIG. 53I FIG. 53J FIG. 53K FIG. 53L

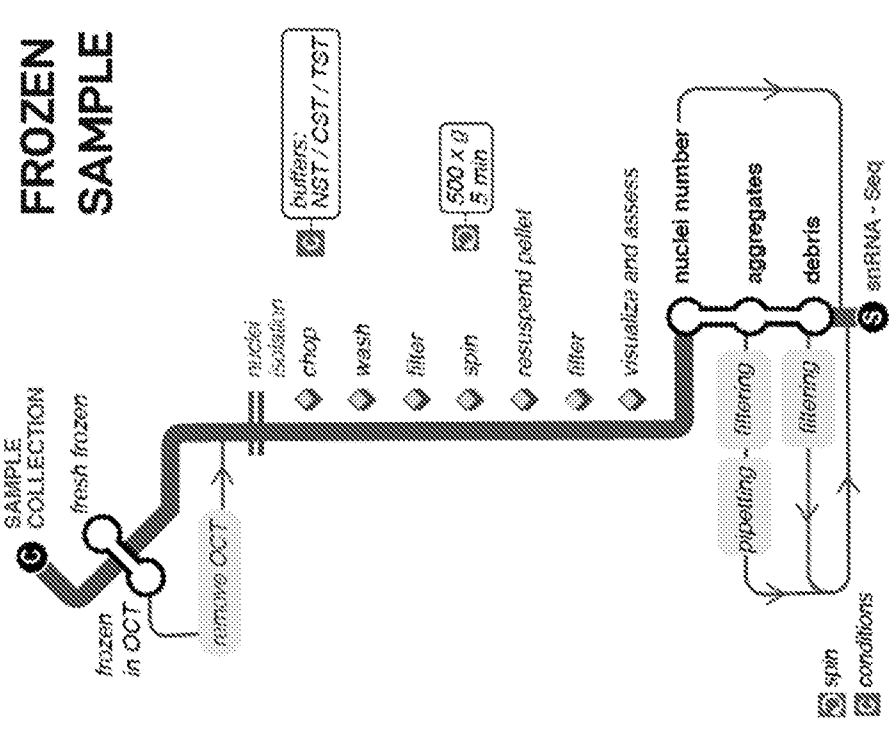


FIG. 54A

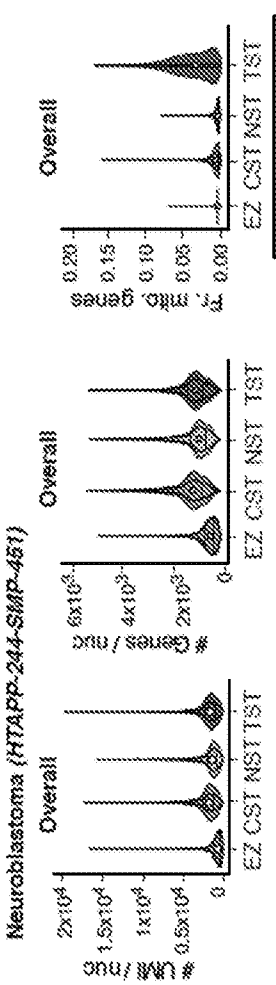


FIG. 54B

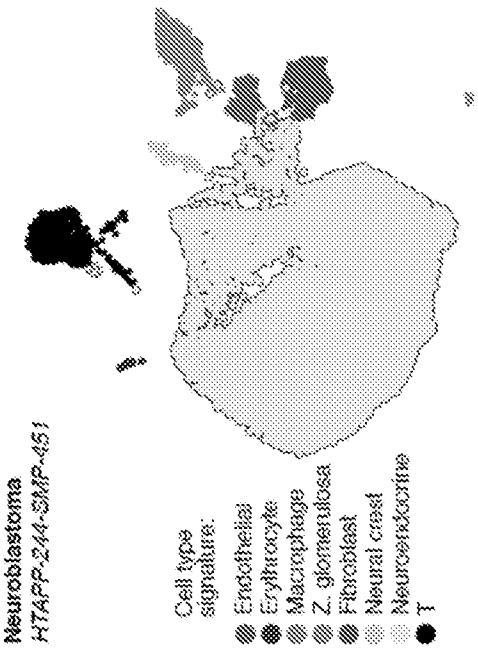


FIG. 54C

FIG. 54D

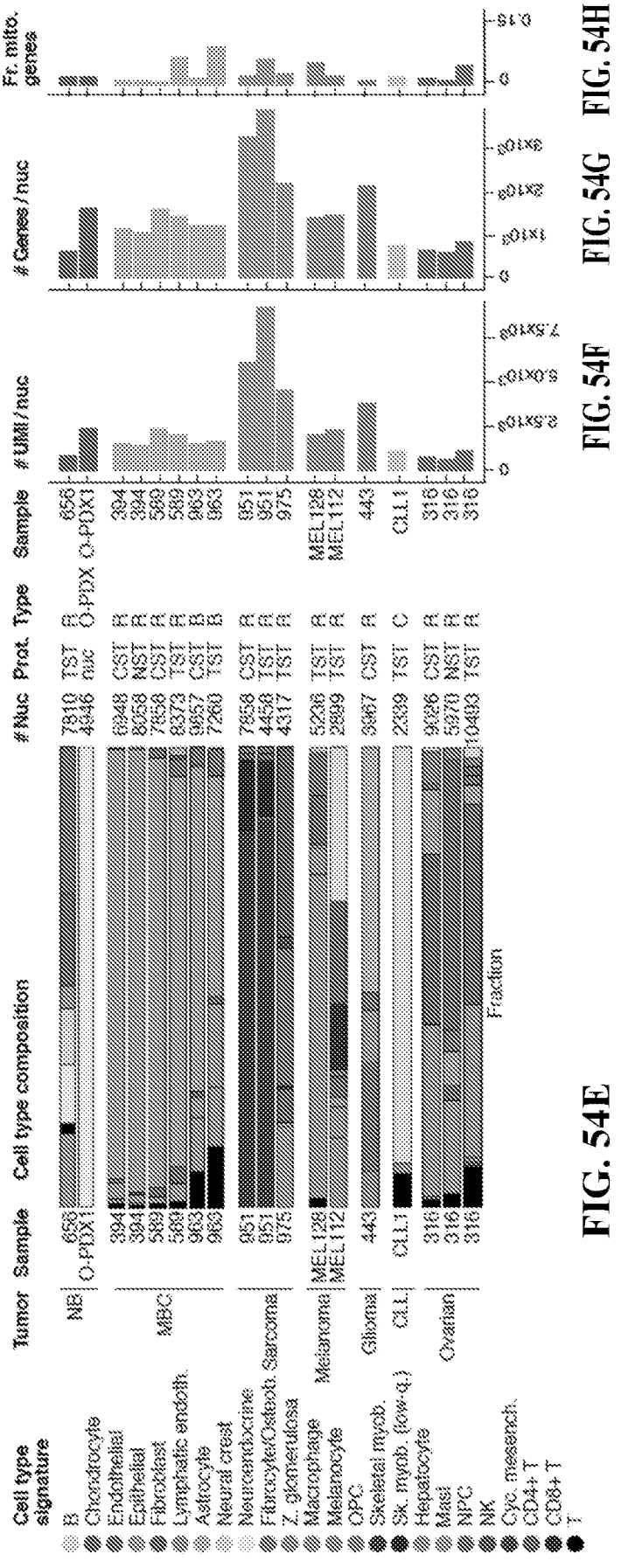


FIG. 54E FIG. 54F FIG. 54G FIG. 54H

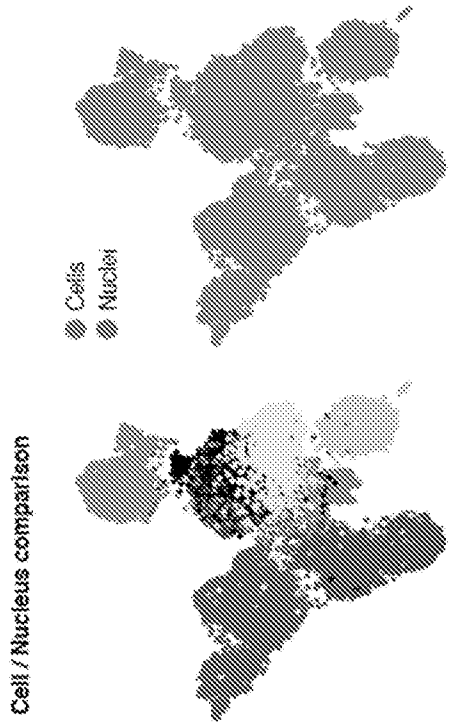


FIG. 54J

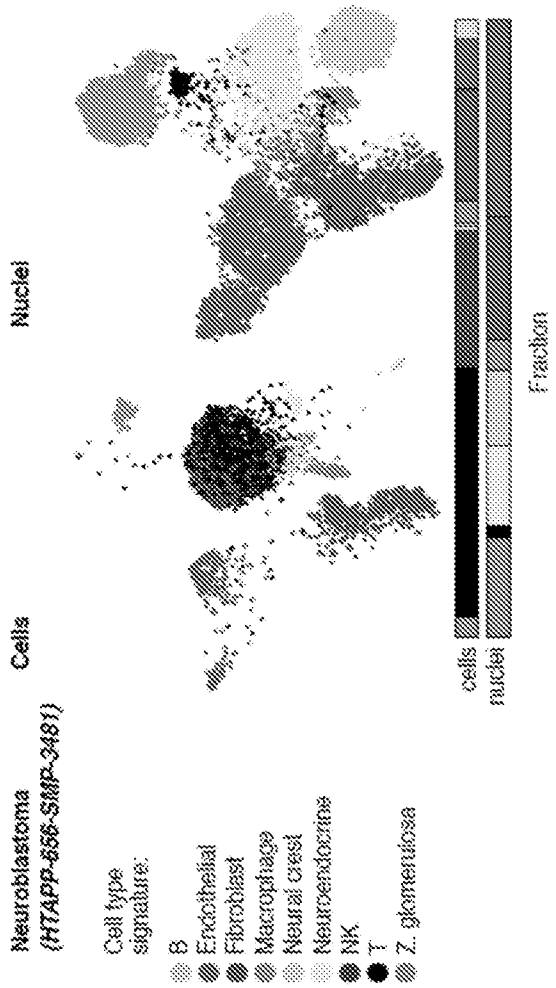


FIG. 54I

Cancer Type	Sample ID	Processing	OCT	Protocols tested	Recommended protocol	Supp Figure No	Supp Figure Page
NSCLC	NSCLC14	fresh		C4 / PDEC / LE	PDEC	S2 - S3	2 - 6
	NSCLC17	fresh		PDEC / cd45n		S4	7 - 8
NB	HTAPP-312-SMP-901	fresh		C4	Papain Kit	S10	14
	HTAPP-312-SMP-902	fresh		C4		S11	15
	HTAPP-656-SMP-3491	fresh		C4		S13	17
	O-PDX1	fresh		Papain Kit		S12	16
	HTAPP-244-SMP-451	frozen		EZ / CST / NST / TST	TST	S17 - S18	21 - 24
	HTAPP-656-SMP-3491	frozen		TST		S26	33
	O-PDX1	frozen		TST		S25	32
MBC	HTAPP-254-SMP-571	fresh		LD	LD	S6	10
	HTAPP-735-SMP-3641	fresh		LD		S7	11
	HTAPP-285-SMP-751	fresh		LD		S8	12
	HTAPP-963-SMP-4741	fresh		LD		S9	13
	HTAPP-394-SMP-1561	frozen	#	CST / NST	TST	S19	25
	HTAPP-589-SMP-2851	frozen	#	CST / TST		S20	26
	HTAPP-963-SMP-4741	frozen	#	CST / TST		S21	27
Glioma	GBM125	fresh		BTD Kit	BTD Kit	S14	18
	HTAPP-443-SMP-5491	frozen		CST	CST	S24	31
CLL	CLL1	fresh		fresh	fresh	S16	20
	CLL1	frozen		TST	TST	S30	37
Ovarian	HTAPP-624-SMP-3212	fresh		MHTD Kit	MHTD Kit	S15	19
	HTAPP-727-SMP-3781	fresh		MHTD Kit / cd45n		S5	9
	HTAPP-316-SMP-891	frozen	#	CST / NST / TST	TST	S22	28 - 29
Melanoma	MEL128	frozen		TST	TST	S28	35
	MEL112	frozen		TST		S29	36
Sarcoma	HTAPP-951-SMP-4632	frozen		CST / TST	TST	S23, S31	30, 38
	HTAPP-975-SMP-4771	frozen		TST		S27	34

FIG. 55

Cancer Type: NSCLC		# Cell	Reads	Sat.	# Read / cell	# UMI / cell	# Gene / cell	Mito fraction	UMI dup. fraction	Empty fraction	Doublet fraction
Sample Type: Resection	C4	5139	128834722	49.4	9498	4729	1478	0.04	0.31	0.07	0.01
Sample ID: NSCLC14	PDEC	4911	162882003	70.8	9675	2712	1156	0.04	0.39	0.00	0.01
Protocol used: C4 / PDEC / LE	LE	4345	120837689	70.0	8968	2801	1083	0.04	0.40	0.00	0.01

FIG. 56A

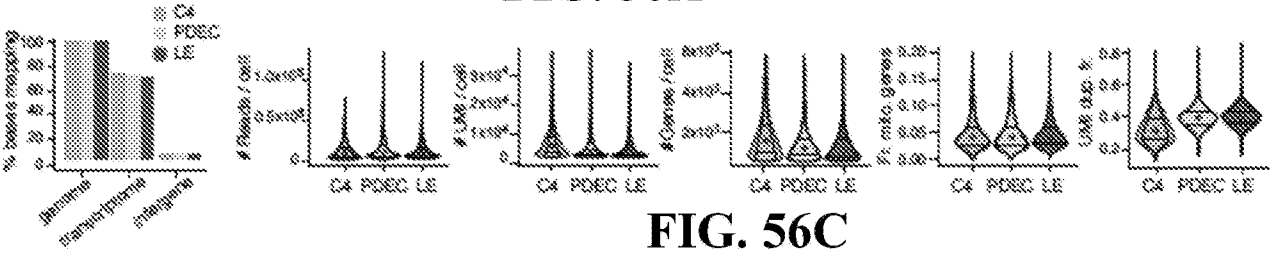


FIG. 56C

FIG. 56B

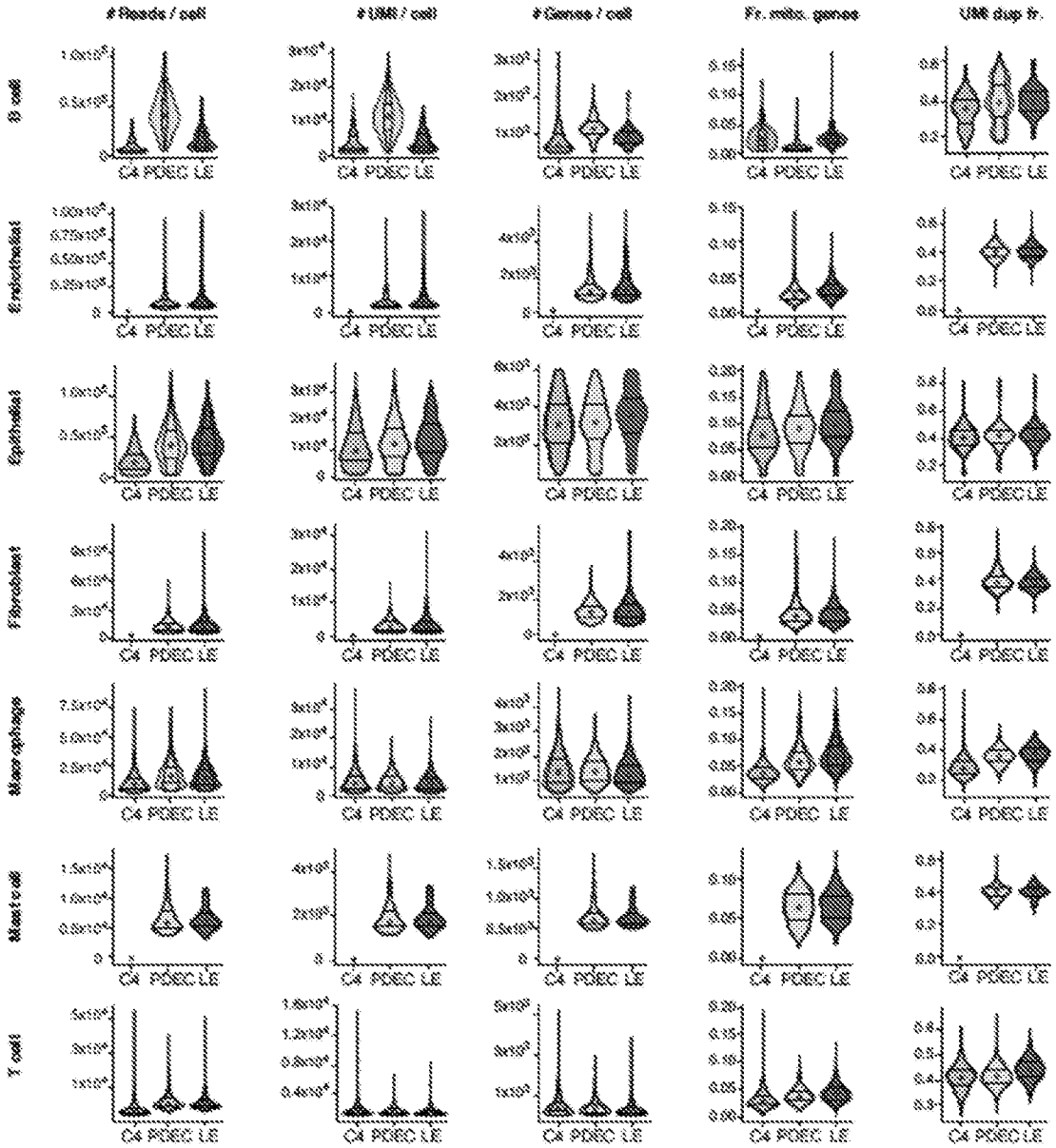


FIG. 56D

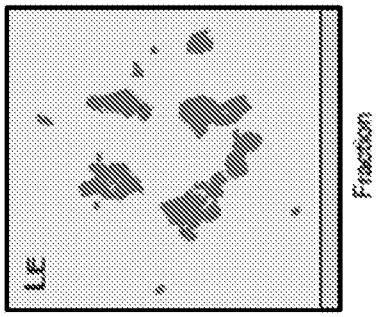


FIG. 56E

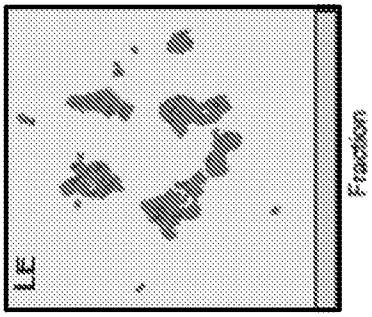


FIG. 56F

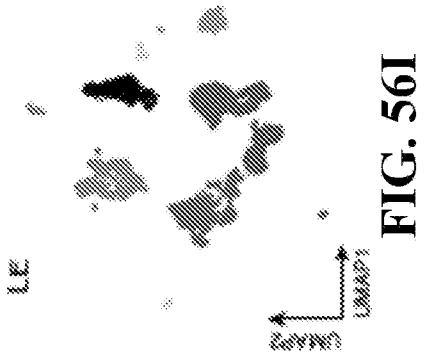


FIG. 56I

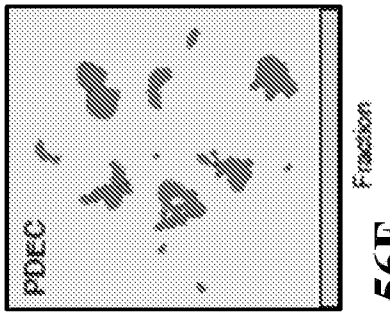


FIG. 56E

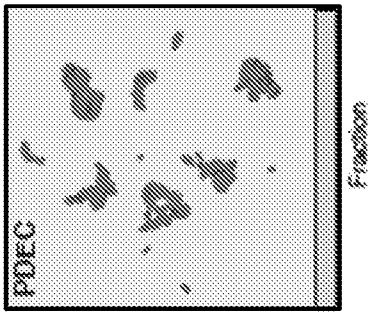


FIG. 56F

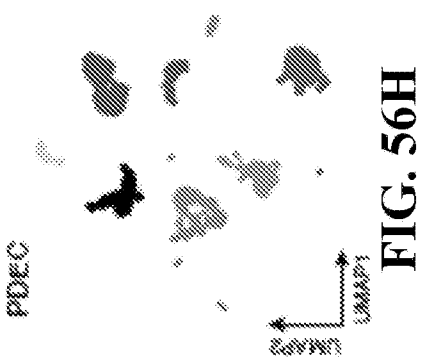


FIG. 56H

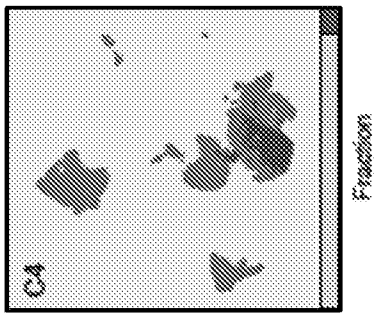


FIG. 56E

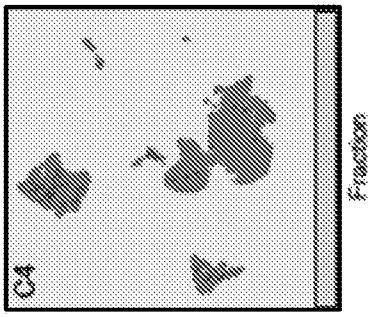
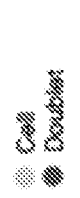
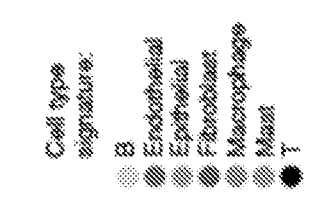


FIG. 56F

FIG. 56G





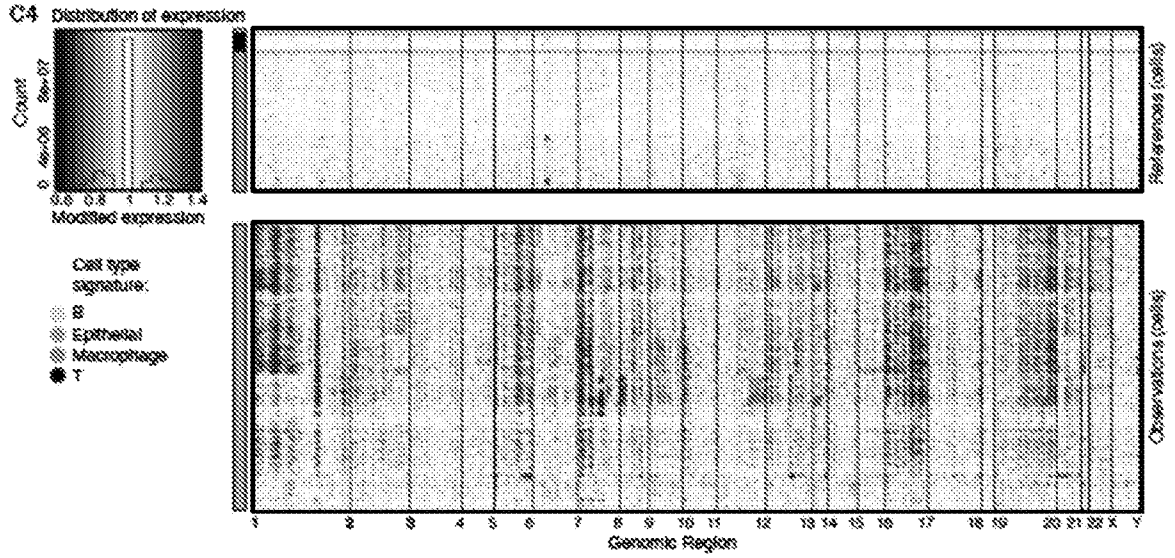


FIG. 56J

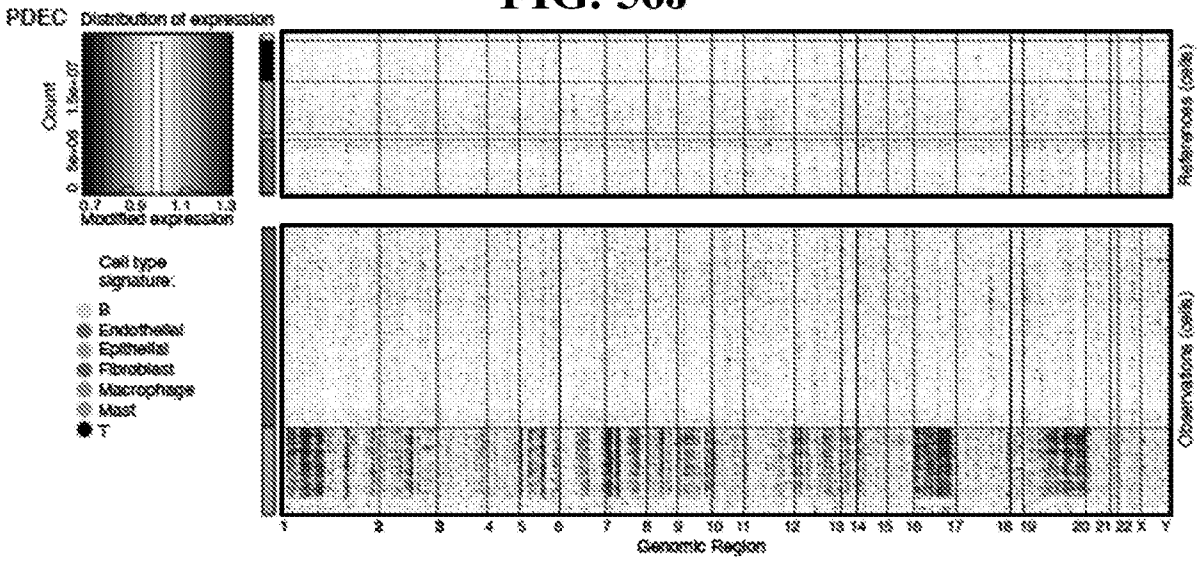


FIG. 56K

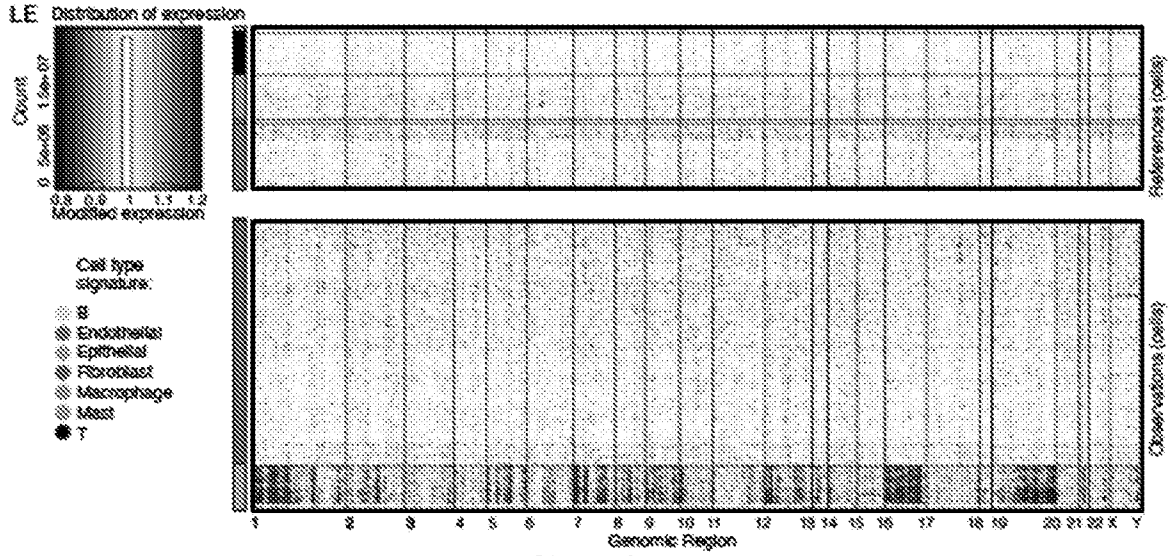


FIG. 56L

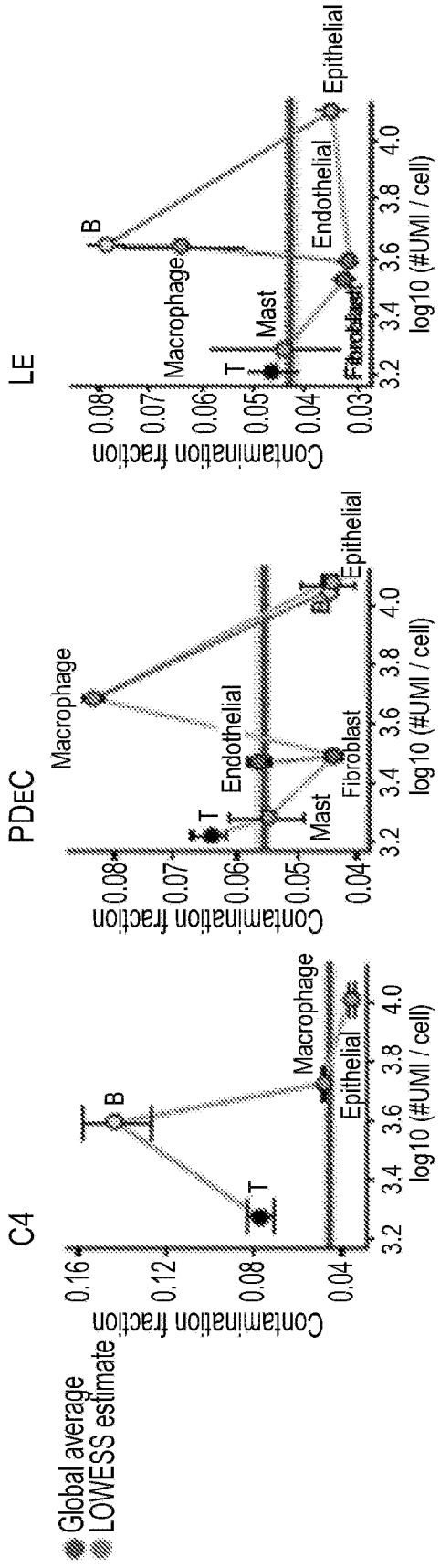


FIG. 56M

FIG. 56N

FIG. 56O

		# Cell	# UMI / cell	# Gene / cell	Mito fraction	Empty fraction	Doublet fraction
Cancer Type: NSCLC							
Sample Type: Resection	C4	3107	4674	1459	0.04	0.11	0.01
Sample ID: NSCLC14	PDEC	4741	2843	1118	0.04	0.00	0.01
Protocol used: Downsampled	LE	4345	2801	1063	0.04	0.00	0.01

FIG. 57A

FIG. 57B

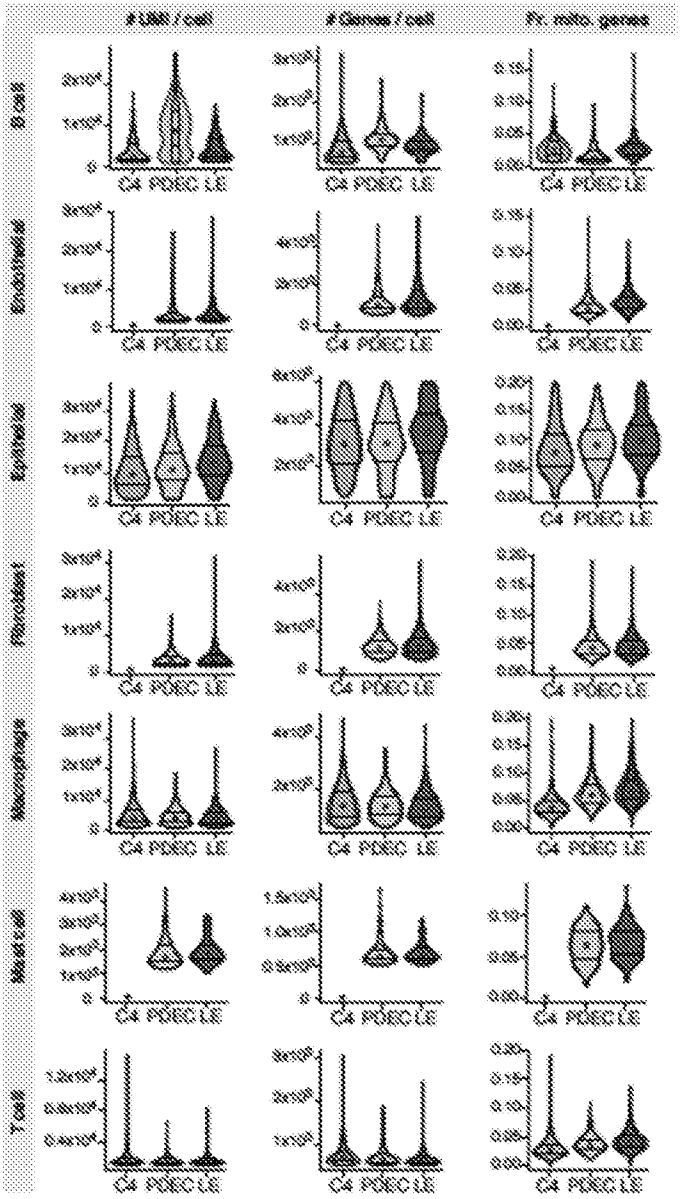


FIG. 57C

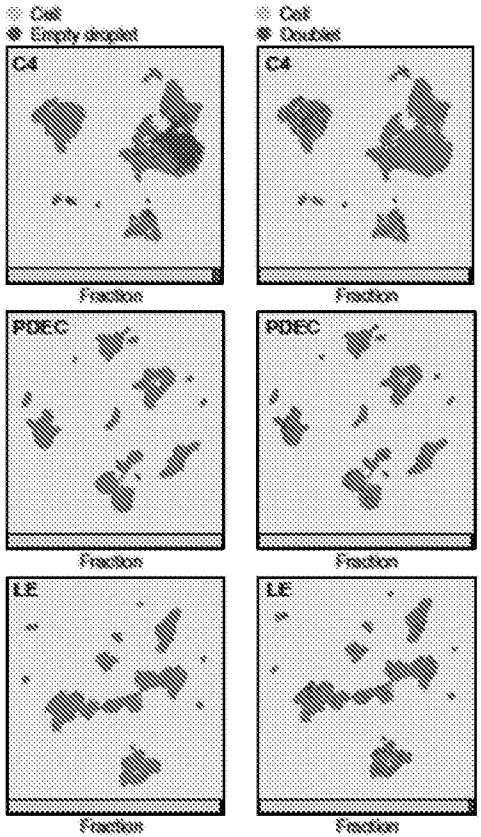


FIG. 57D FIG. 57E

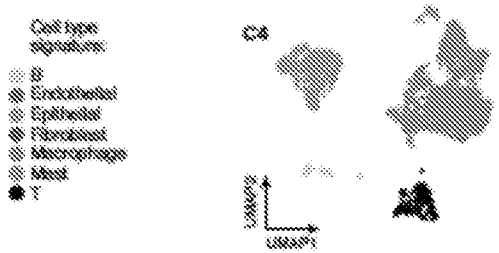
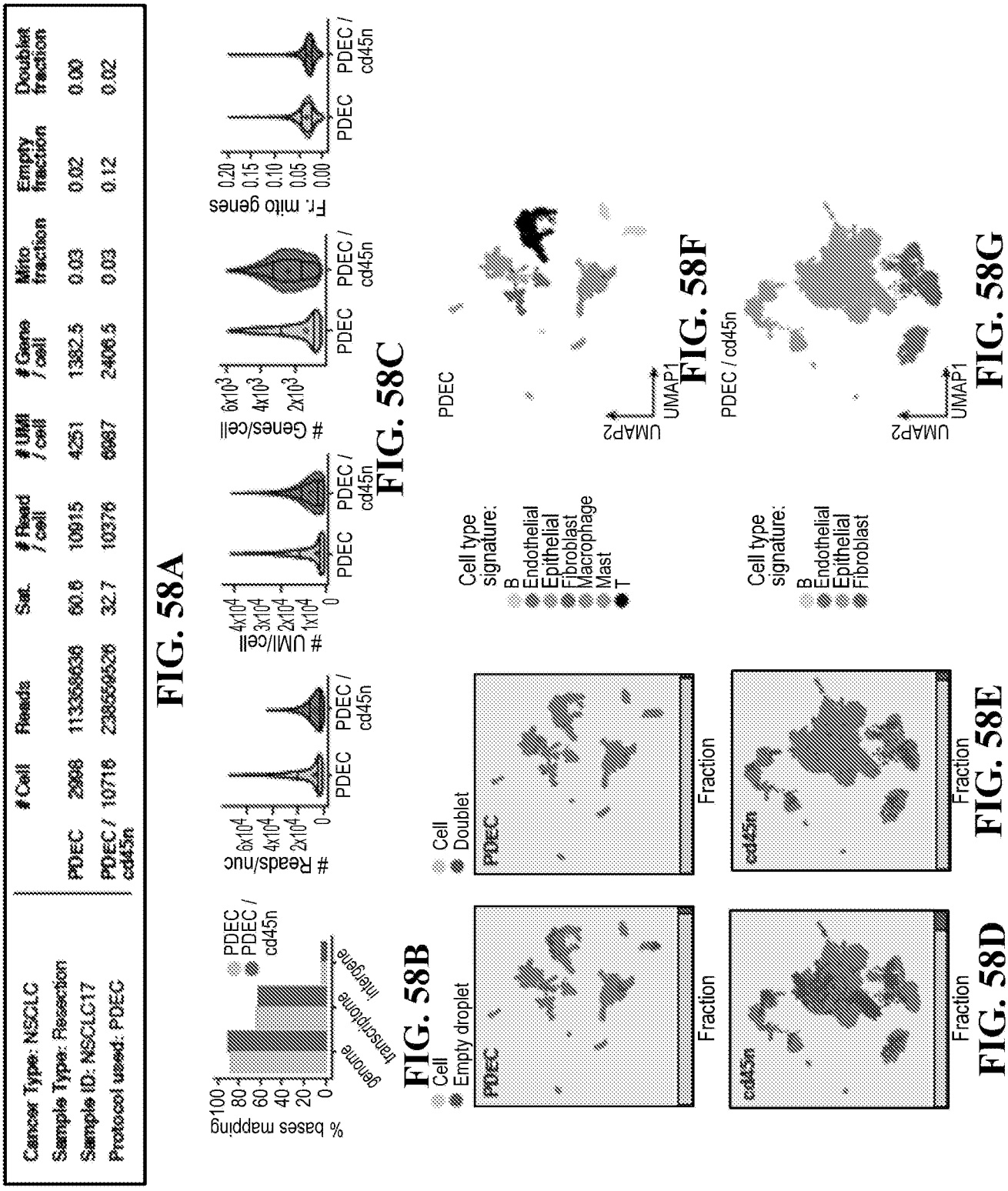


FIG. 57F

FIG. 57G FIG. 57H


Cancer Type: NSCLC
Sample Type: Resection
Sample ID: NSCLC17
Protocol used: PDEC
Cell
Reads
Sat.
Read / cell
UMI / cell
Gene / cell
Mito fraction
Empty fraction
Doublet fraction
PDEC
2966
1133666036
60.8
10915
4251
1382.5
0.03
0.02
0.00
PDEC / cd45n
10718
2385590526
32.7
10376
6687
2406.5
0.03
0.12
0.02
FIG. 58A
% bases mapping
PDEC
PDEC / cd45n
genome
transcriptome
intergene
Reads/nuc
UMI/cell
Genes/cell
Fr. mito genes
FIG. 58B
FIG. 58C
Cell
Empty droplet
Doublet
PDEC
cd45n
Fraction
FIG. 58D
FIG. 58E
Cell type signature:
B
Endothelial
Epithelial
Fibroblast
Macrophage
Mast
T
UMAP1
UMAP2
FIG. 58F
PDEC / cd45n
FIG. 58G

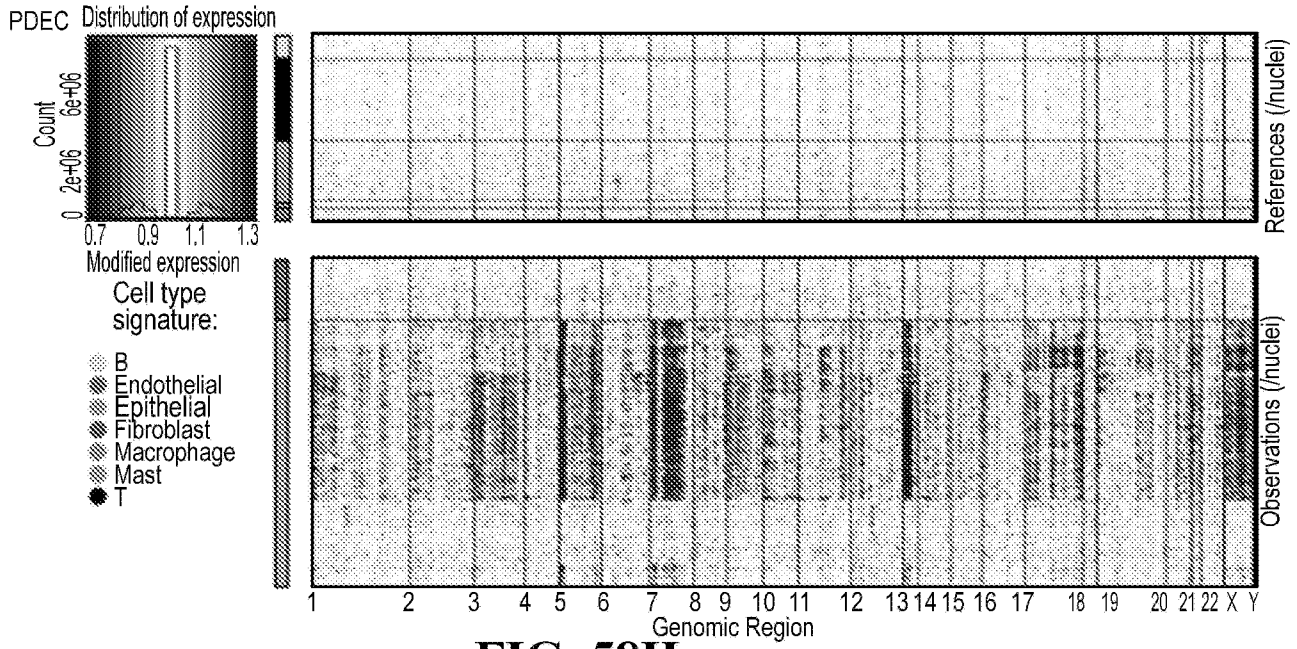


FIG. 58H

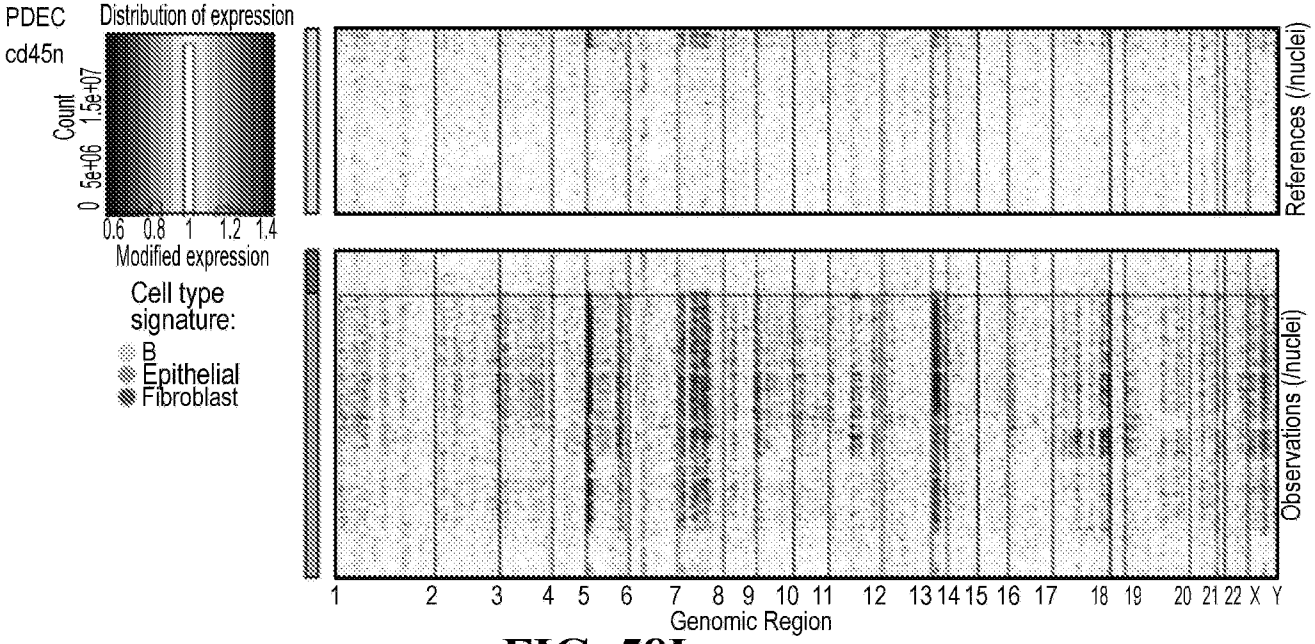


FIG. 58I

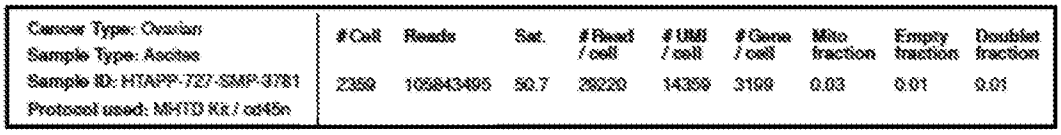


FIG. 59A

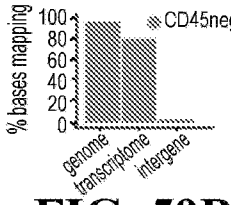


FIG. 59B

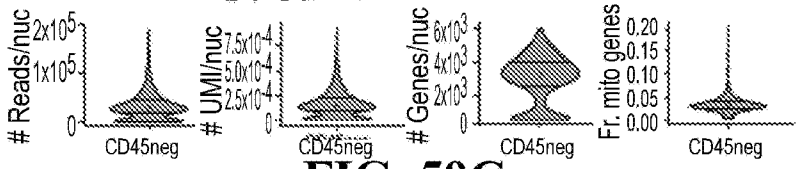


FIG. 59C

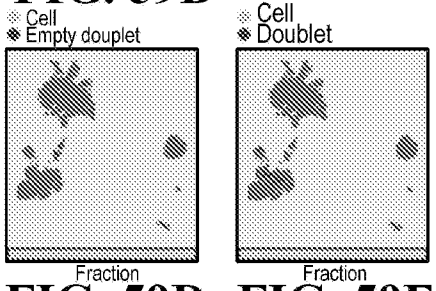


FIG. 59D FIG. 59E

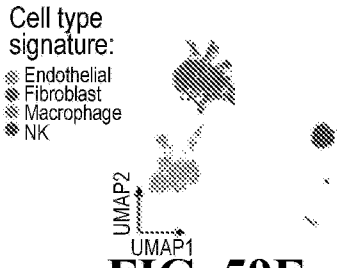


FIG. 59F

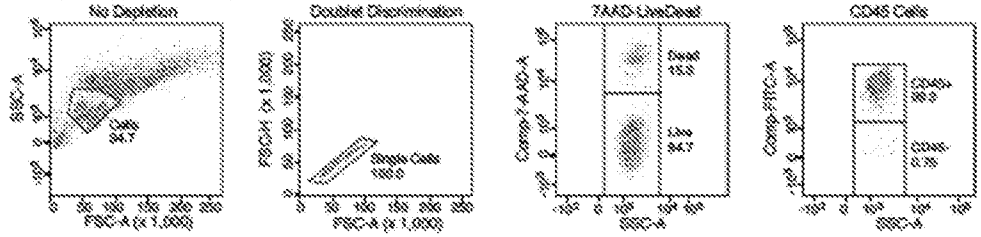


FIG. 59G

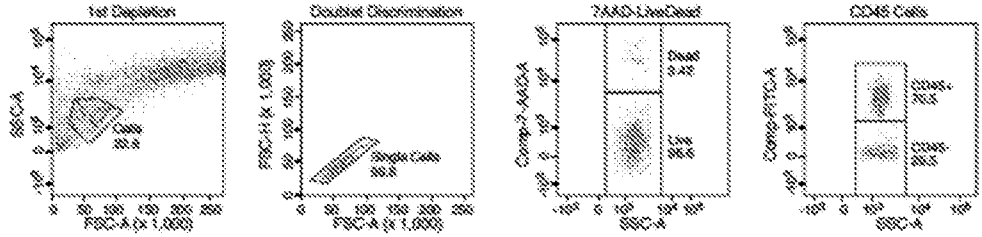


FIG. 59H

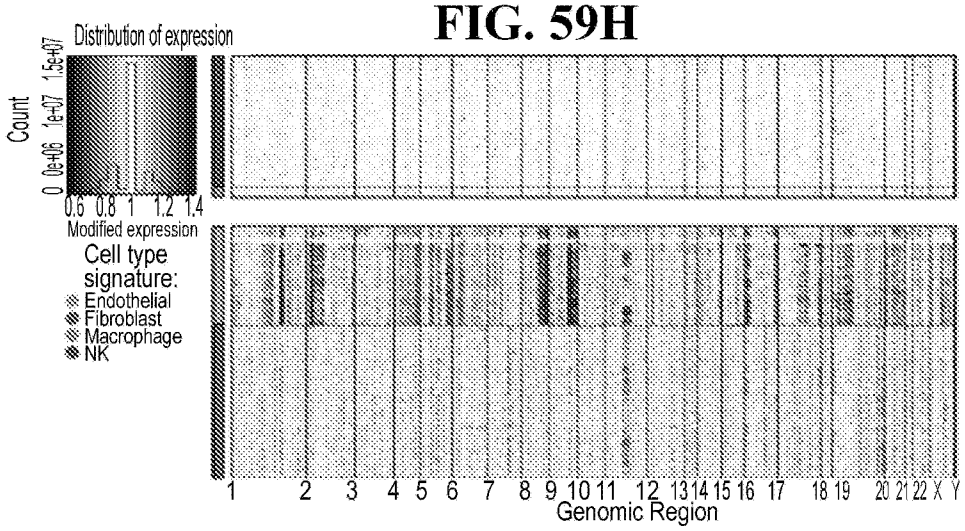


FIG. 59I

Cancer Type: MIBC Sample Type: Resection (LN) Sample ID: HTAPP-254-SMP-571 Protocol used: LD	# Cell	Reads	Sat.	# Read / cell	# UMI / cell	# Gene / cell	Mito fraction	Empty fraction	Doublet fraction
	2779	130243808	59	9412	3841	1201	0.03	0.10	0.01

FIG. 60A

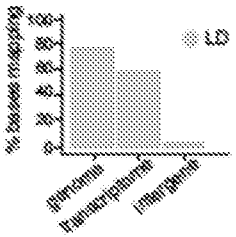


FIG. 60B

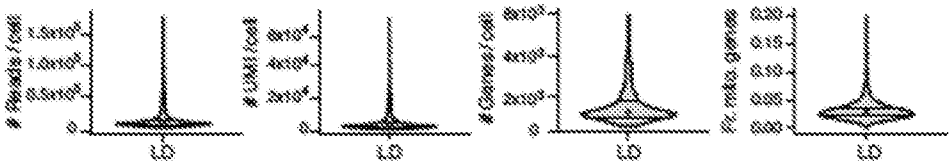


FIG. 60C

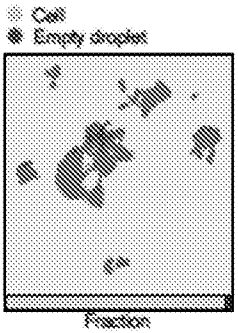


FIG. 60D

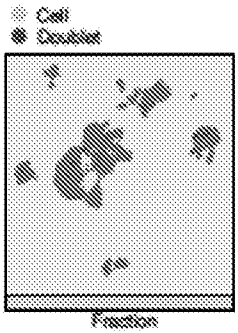


FIG. 60E

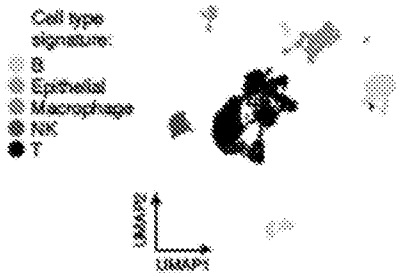


FIG. 60F

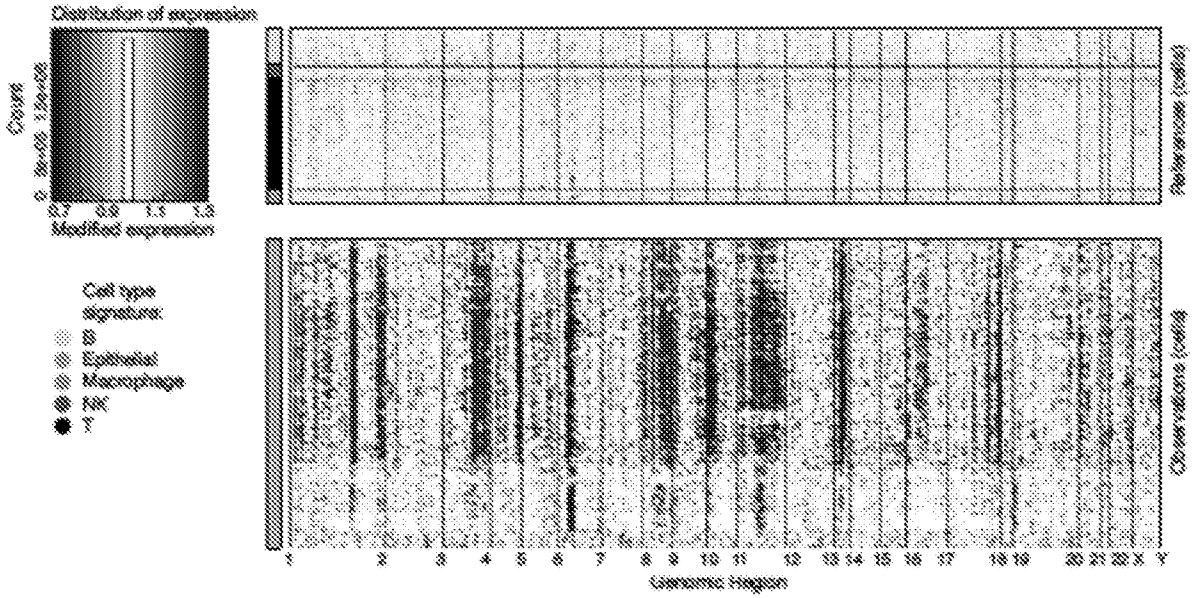


FIG. 60G

Cancer Type: MBC Sample Type: Biopsy (LN) Sample ID: HTAPP-735-SMP-3841 Protocol used: LD	# Cell	Reads	Sat.	# Read / cell	# UMI / cell	# Gene / cell	Mito fraction	Empty fraction	Doublet fraction
	3149	127716334	59.3	17648	7278	2146	0.07	0.00	0.01

FIG. 61A

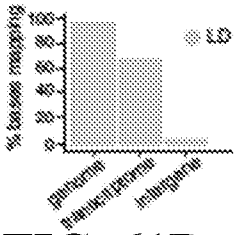


FIG. 61B

FIG. 61C

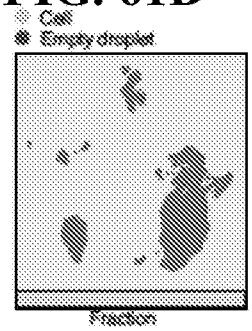


FIG. 61D

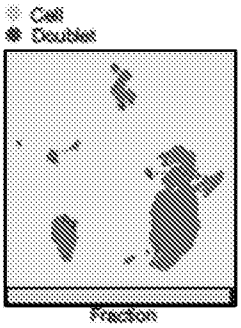


FIG. 61E

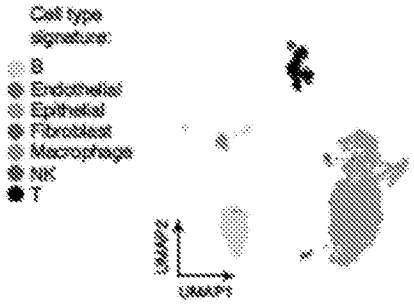


FIG. 61F

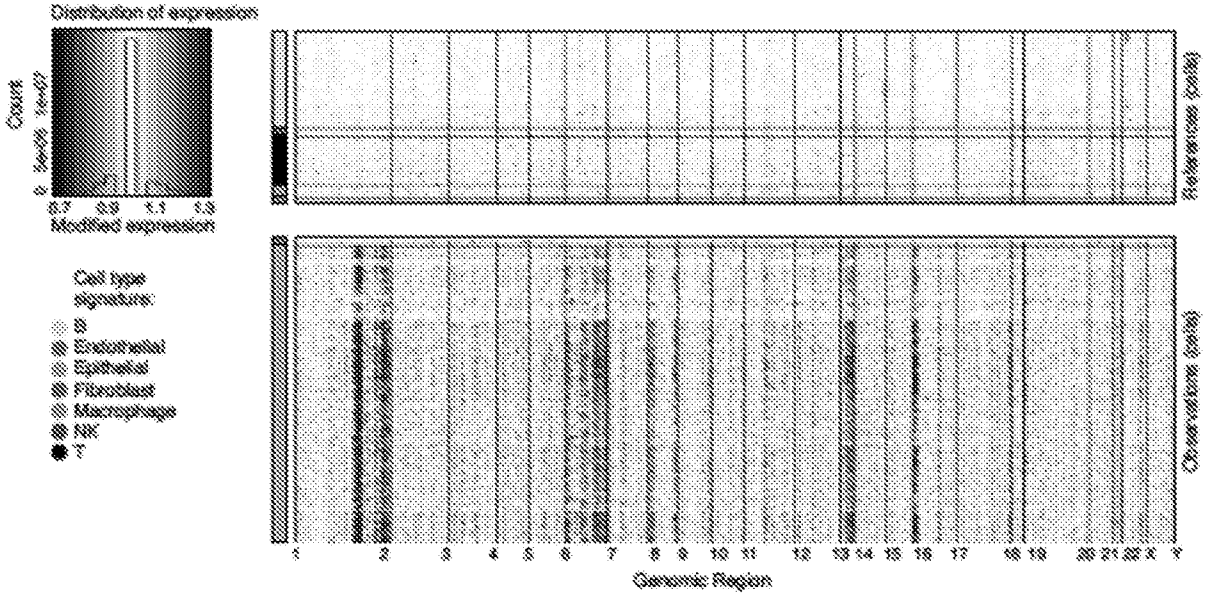


FIG. 61G

Cancer Type: MBC Sample Type: Biopsy (liver) Sample ID: HTAPP-285-SMP-751 Protocol used: LD	# Cell	Reads	Sat.	# Read / cell	# UMI / cell	# Gene / cell	Mito fraction	Empty fraction	Doublet fraction
	4463	208348370	46.4	21358	11297	3004	0.05	0.20	0.01

FIG. 62A

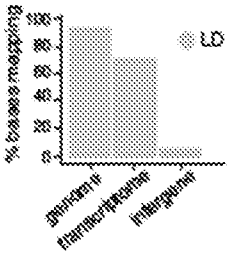


FIG. 62B

FIG. 62C

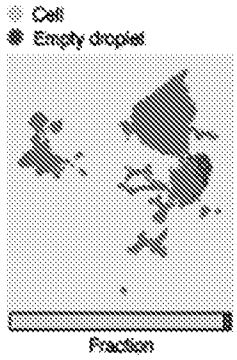


FIG. 62D

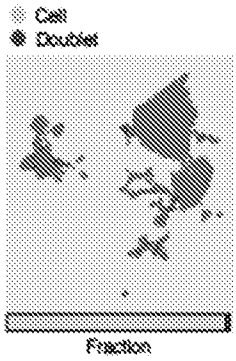


FIG. 62E

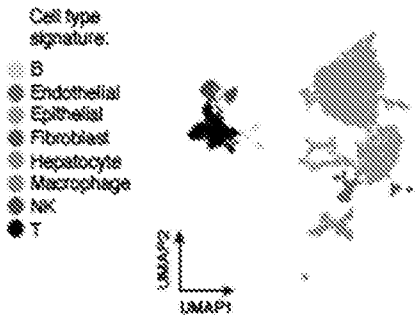


FIG. 62F

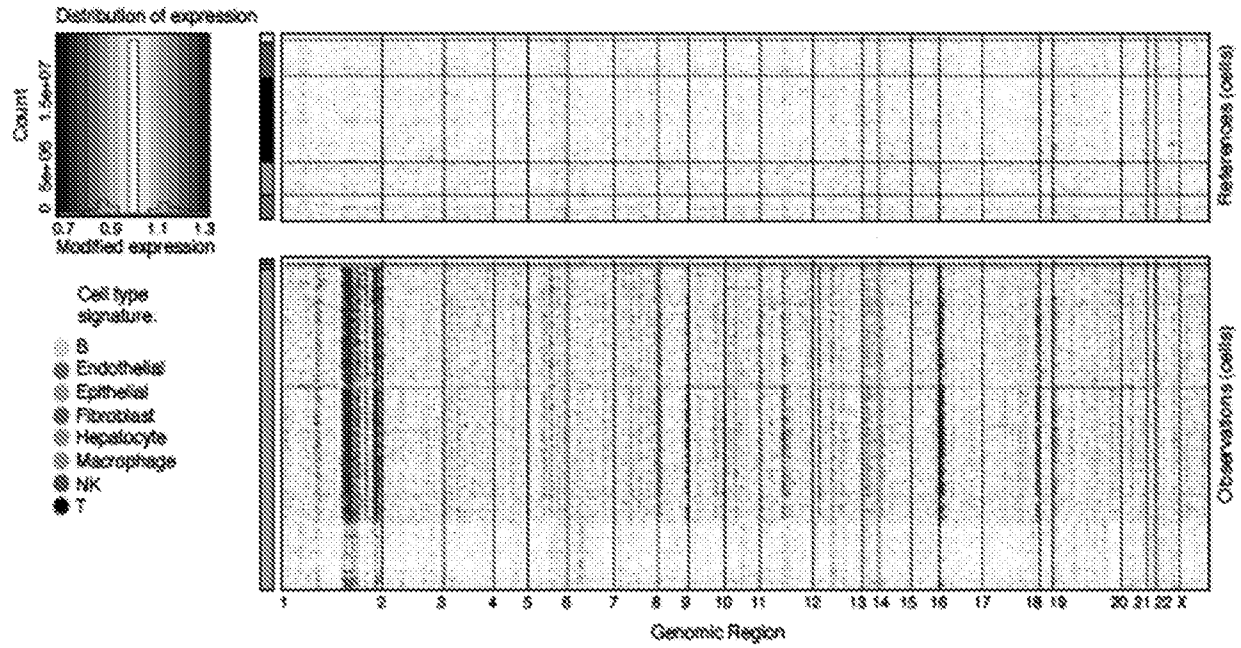


FIG. 62G

Cancer Type: MBC Sample Type: Liver biopsy Sample ID: HTAPP-963-SMP-4741 Protocol used: LD	# Cell	Reads	Sat.	# Read / cell	# UMI / cell	# Gene / cell	Mito fraction	Empty fraction	Doublet fraction
	5163	109660252	58.7	4946	2122	850	0.04	0.00	0.01

FIG. 63A

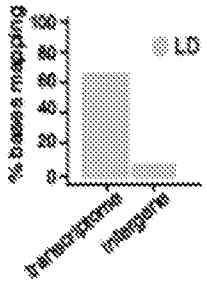


FIG. 63B

FIG. 63C

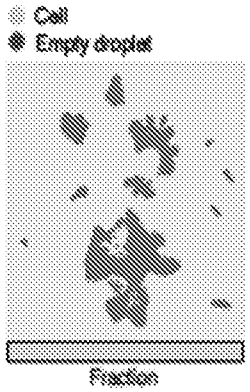


FIG. 63D

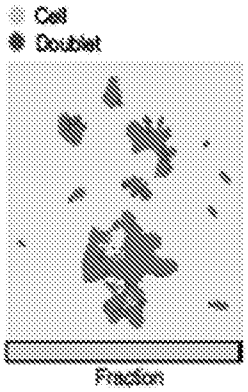


FIG. 63E

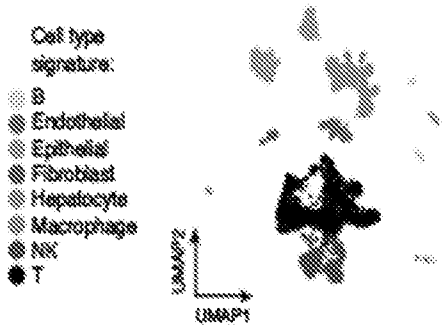


FIG. 63F

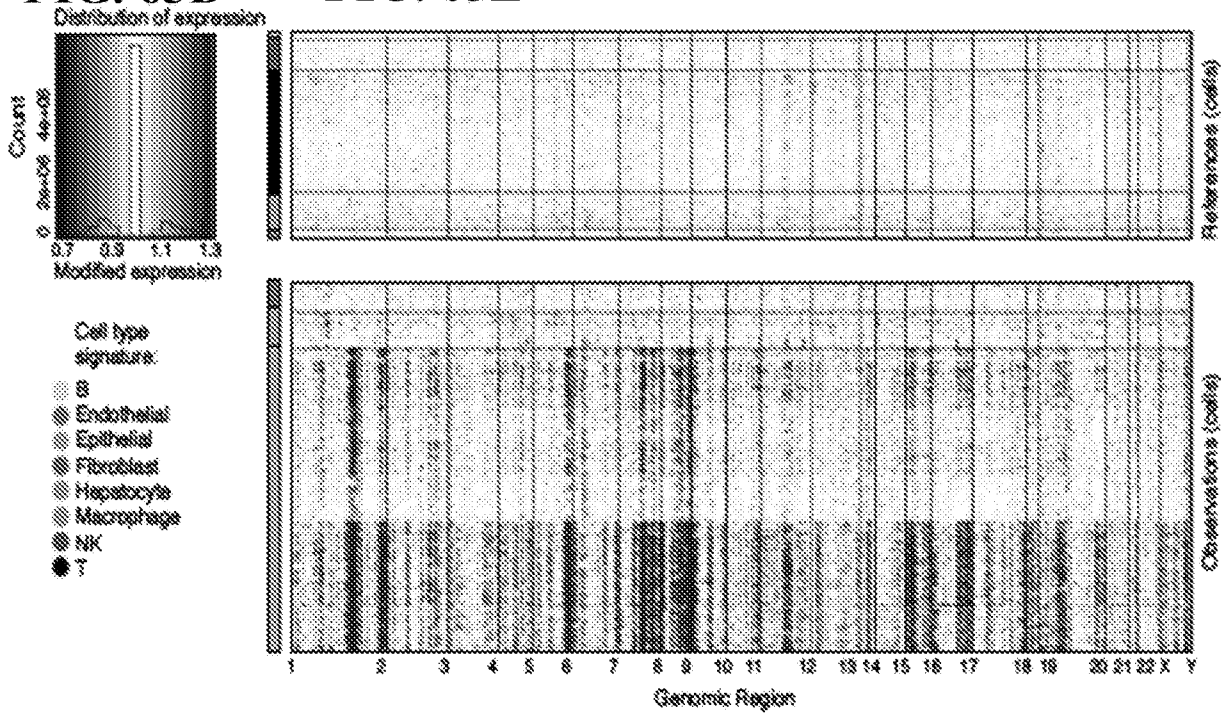


FIG. 63G

Cancer Type: NB Sample Type: Pre-treatment biopsy Sample ID: HTAPP-312-SMP-901 Protocol used: C4	# Cell	Reads	Sat.	# Read / cell	# UMI / cell	# Gene / cell	Mito fraction	Empty fraction	Doublet fraction
	4369	100435380	53.9	6730	3011	1483	0.04	0.02	0.00

FIG. 64A

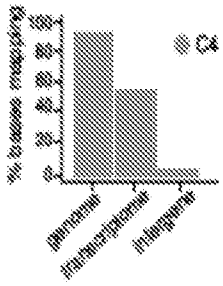


FIG. 64B

FIG. 64C

FIG. 64D

FIG. 64E

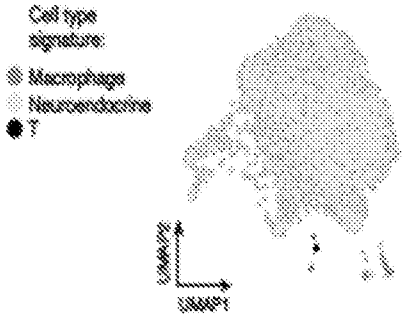


FIG. 64F

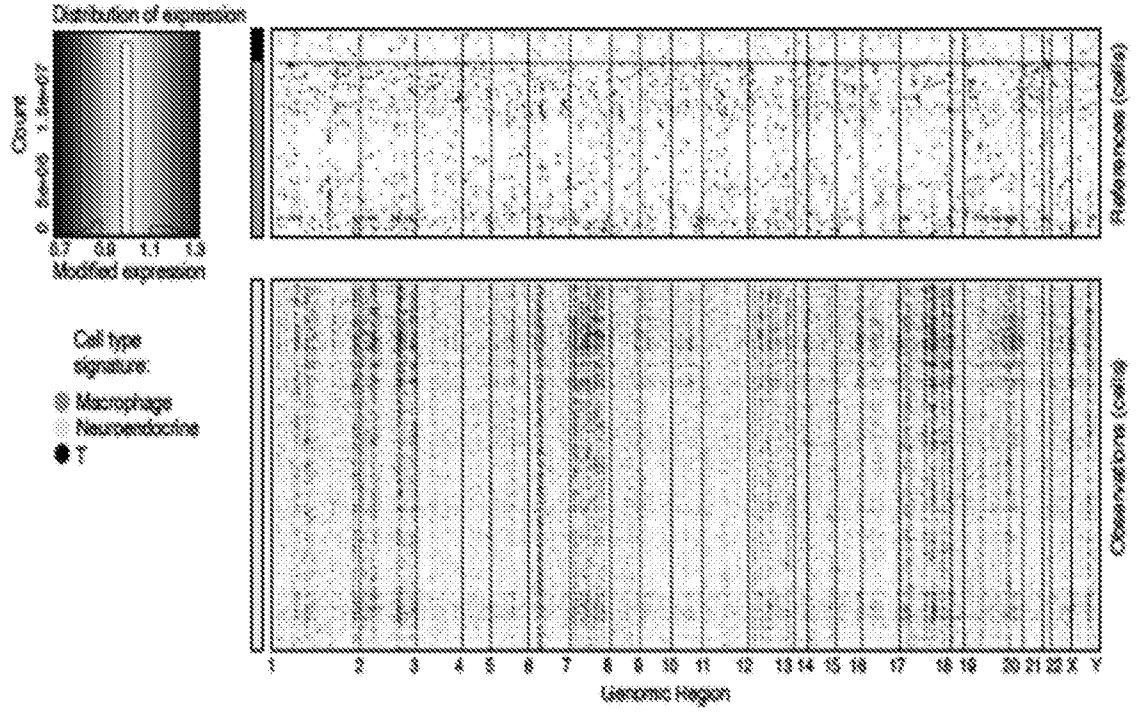


FIG. 64G

Cancer Type: NB Sample Type: Post-treatment resection Sample ID: HTAPP-312-SMP-902 Protocol used: C4	# Cell	Reads	Sat.	# Read / cell	# UMI / cell	# Gene / cell	Mito fraction	Empty fraction	Doublet fraction
	788	95075515	82	35519	2205.5	1028.5	0.04	0.01	0.01

FIG. 65A

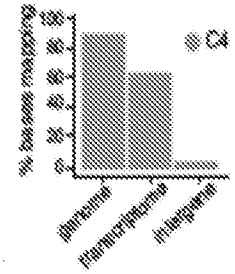


FIG. 65B

FIG. 65C

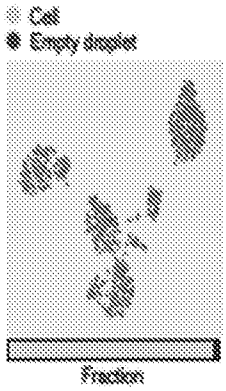


FIG. 65D

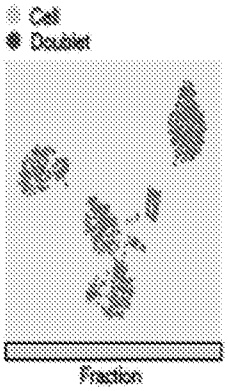


FIG. 65E

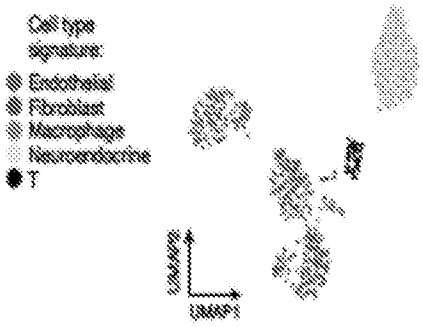


FIG. 65F

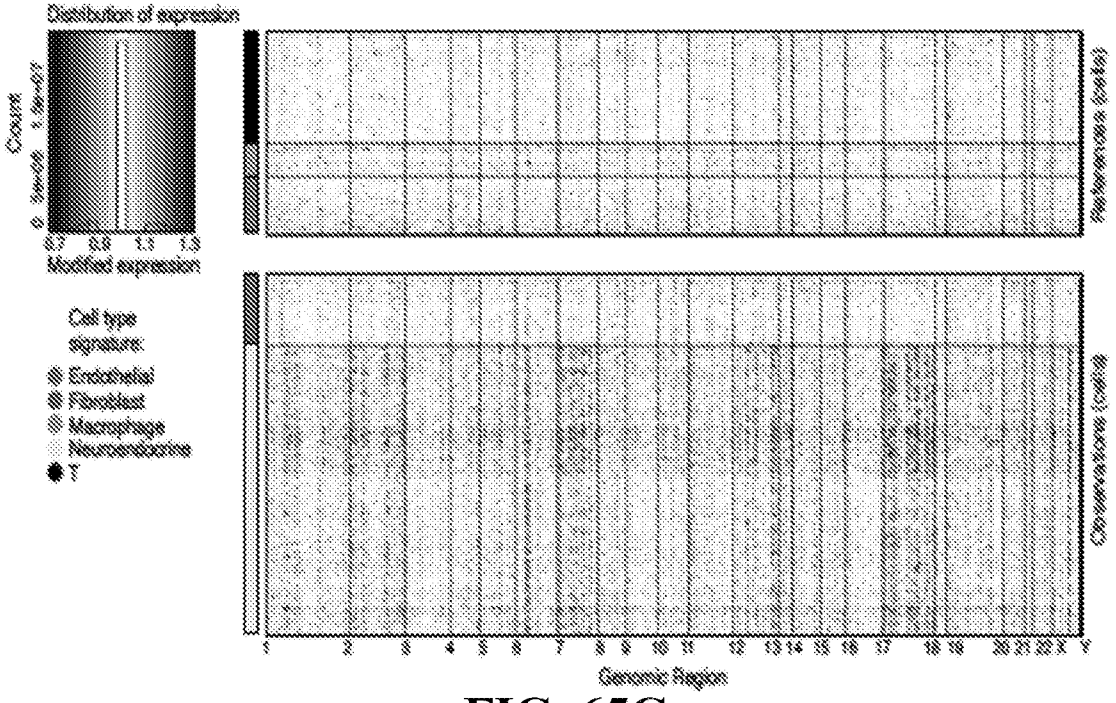


FIG. 65G

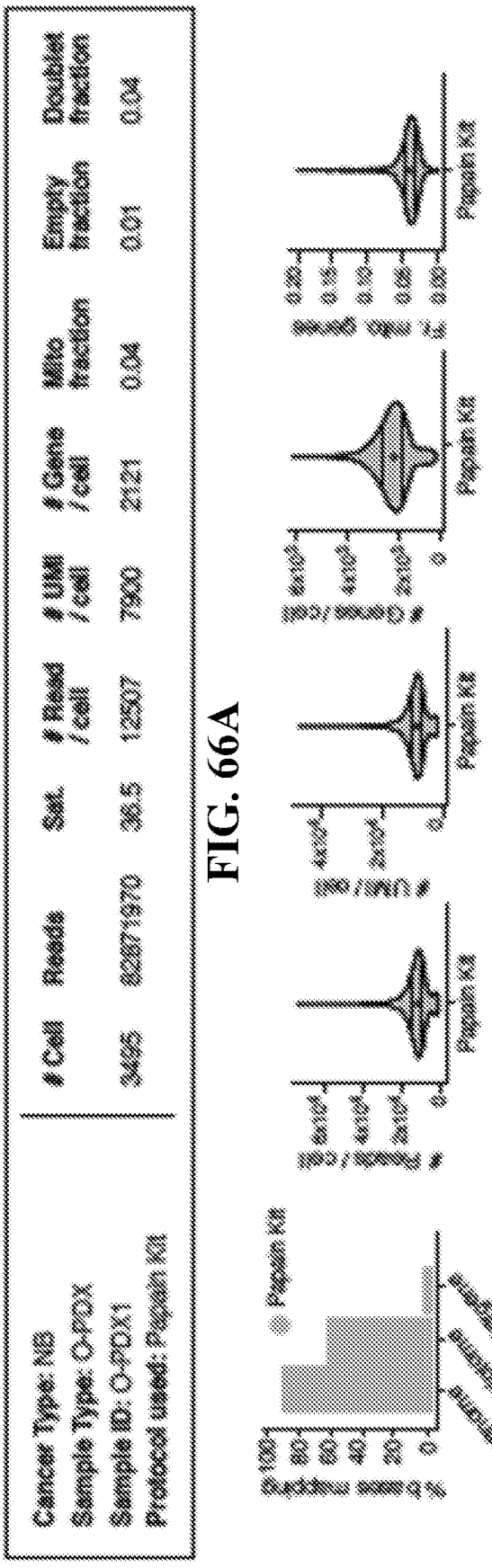


FIG. 66A

FIG. 66C

FIG. 66F

FIG. 66E

FIG. 66D

FIG. 66B

Cancer Type: NB Sample Type: Resection Sample ID: HTAPP-636-SMP-3481 Protocol used: C4	# Cell	Reads	Sat.	# Read / cell	# UMI / cell	# Gene / cell	Mito fraction	Empty fraction	Doublet fraction
	3449	83394710	71.9	8274	2216	817	0.03	0.01	0.01

FIG. 67A

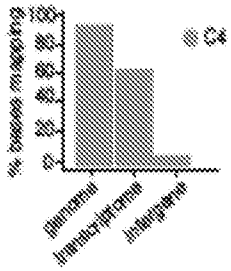


FIG. 67B

FIG. 67C

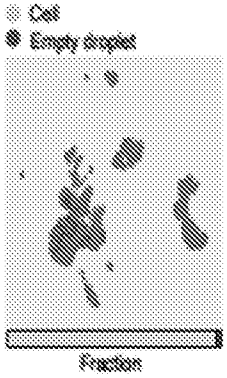


FIG. 67D

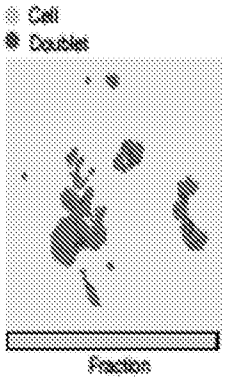


FIG. 67E

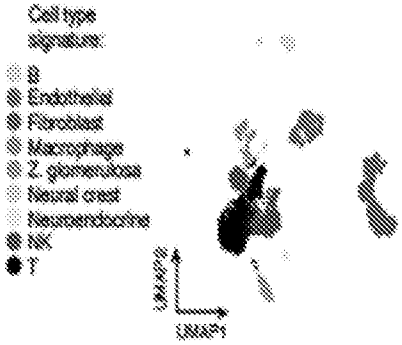


FIG. 67F

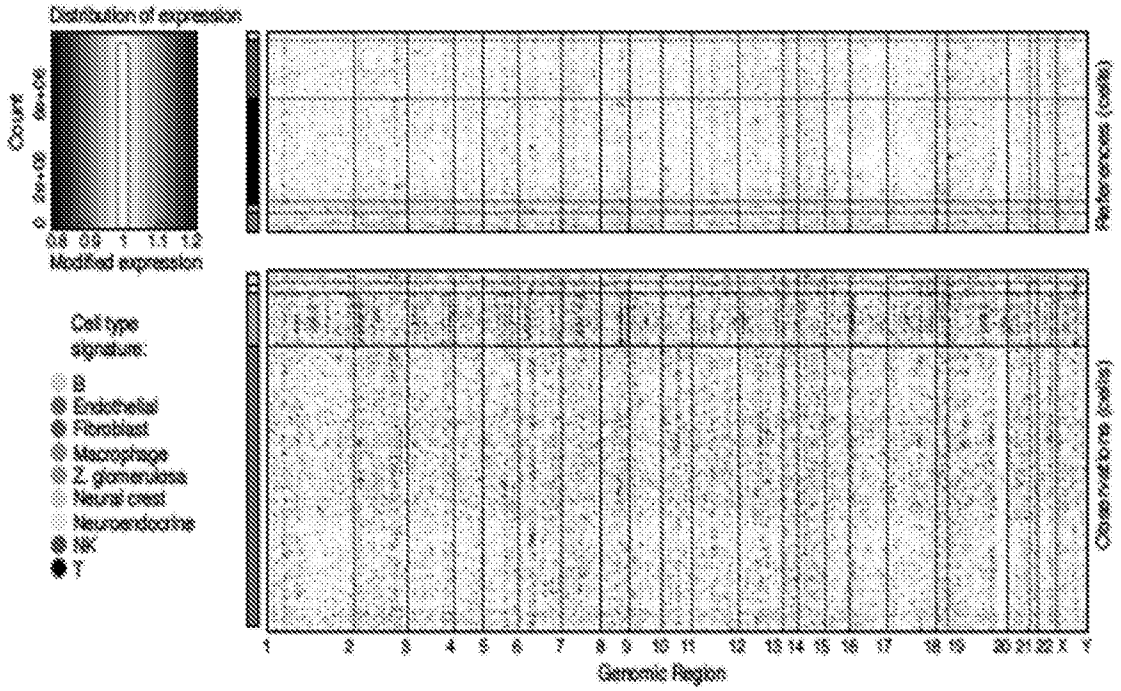


FIG. 67G

Cancer Type: Glioblastoma Sample Type: Resection Sample ID: GBM125 Protocol used: Brain Tumor Diss. Kit	# Cell	Reads	Sat.	# Read / cell	# UMI / cell	# Gene / cell	Mito fraction	Empty fraction	Doublet fraction
	1077	245302862	91.9	92190	6706	2425	0.02	0.90	0.01

FIG. 68A

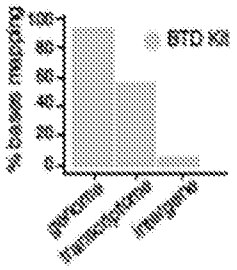


FIG. 68B

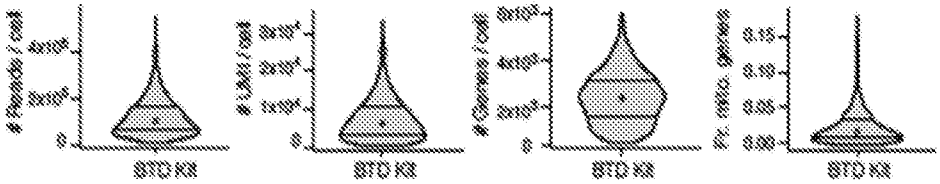


FIG. 68C

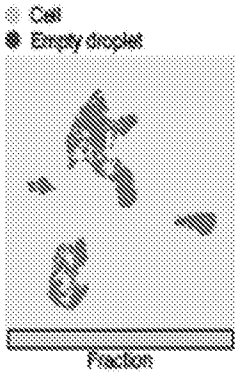


FIG. 68D

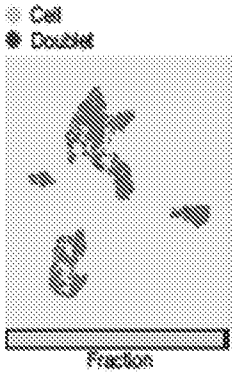


FIG. 68E

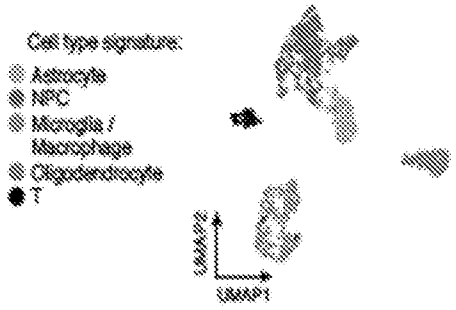


FIG. 68F

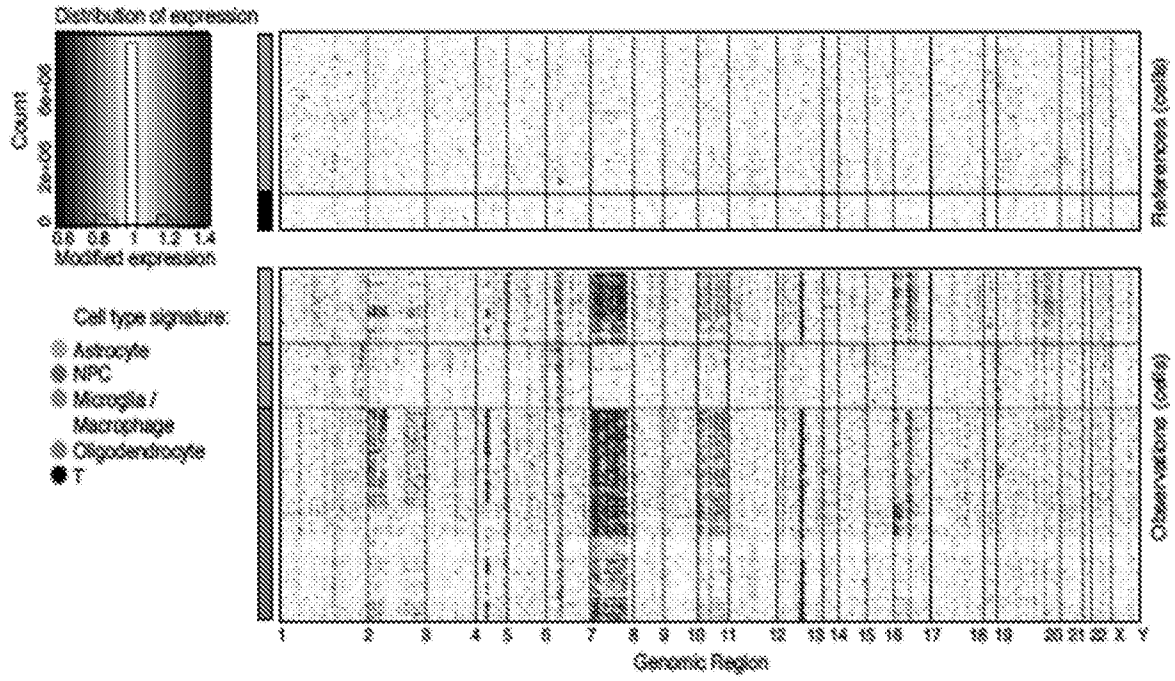


FIG. 68G

Cancer Type: Ovarian Sample Type: Resection Sample ID: HTAPP-824-SMP-3212 Protocol used: MHTD Kit	# Cell	Reads	Sat.	# Read / cell	# UMI / cell	# Gene / cell	Mito fraction	Empty fraction	Doublet fraction
	4066	106716000	13.1	7325	6334	2072	0.09	0.03	0.02

FIG. 69A

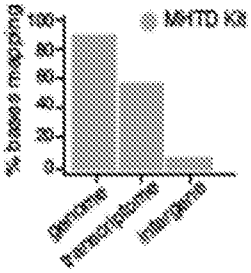


FIG. 69B

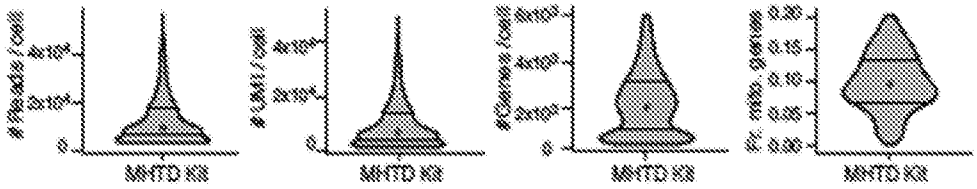


FIG. 69C

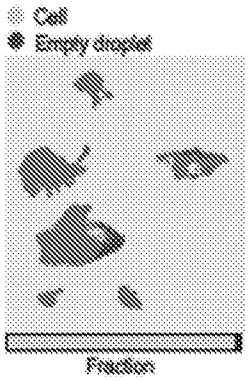


FIG. 69D

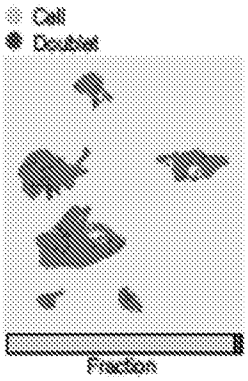


FIG. 69E

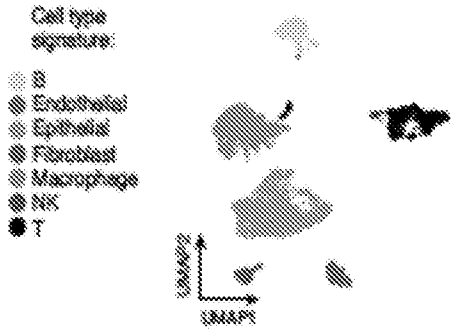


FIG. 69F

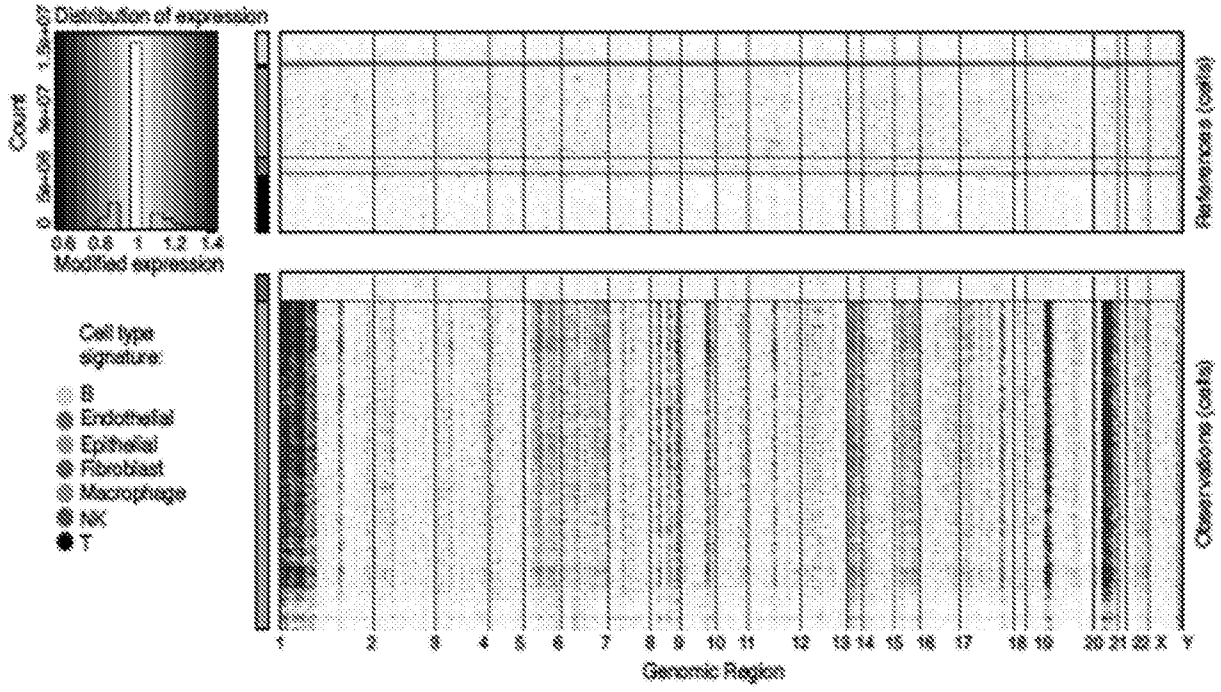


FIG. 69G

Cancer Type: CLL Sample Type: Blood draw Sample ID: CLL1 Protocol used: fresh	# Cell	Reads	Sat.	# Read / cell	# UMI / cell	# Gene / cell	Mito fraction	Empty fraction	Doublet fraction
	2502	111323909	81.3	14346	2210	722	0.03	0.00	0.04

FIG. 70A

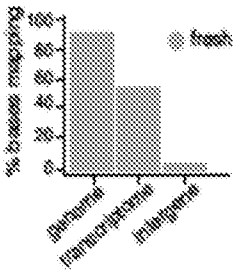


FIG. 70B

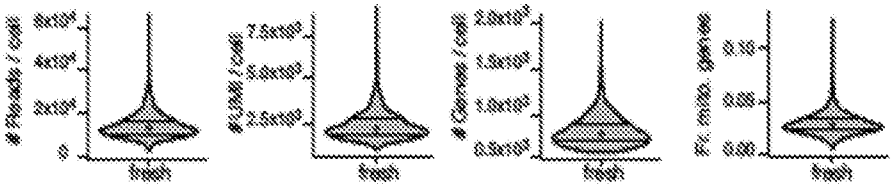


FIG. 70C

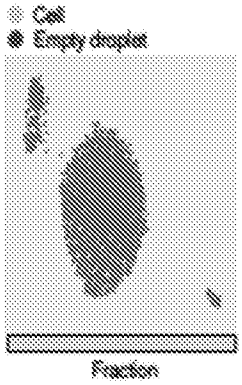


FIG. 70D

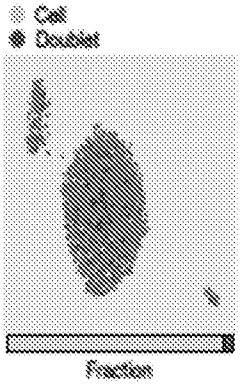


FIG. 70E

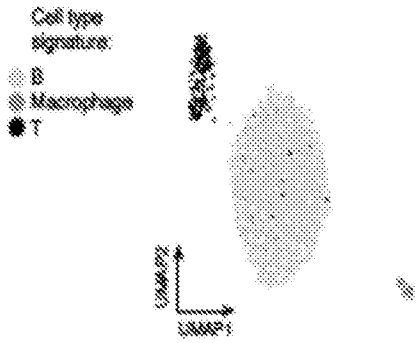


FIG. 70F

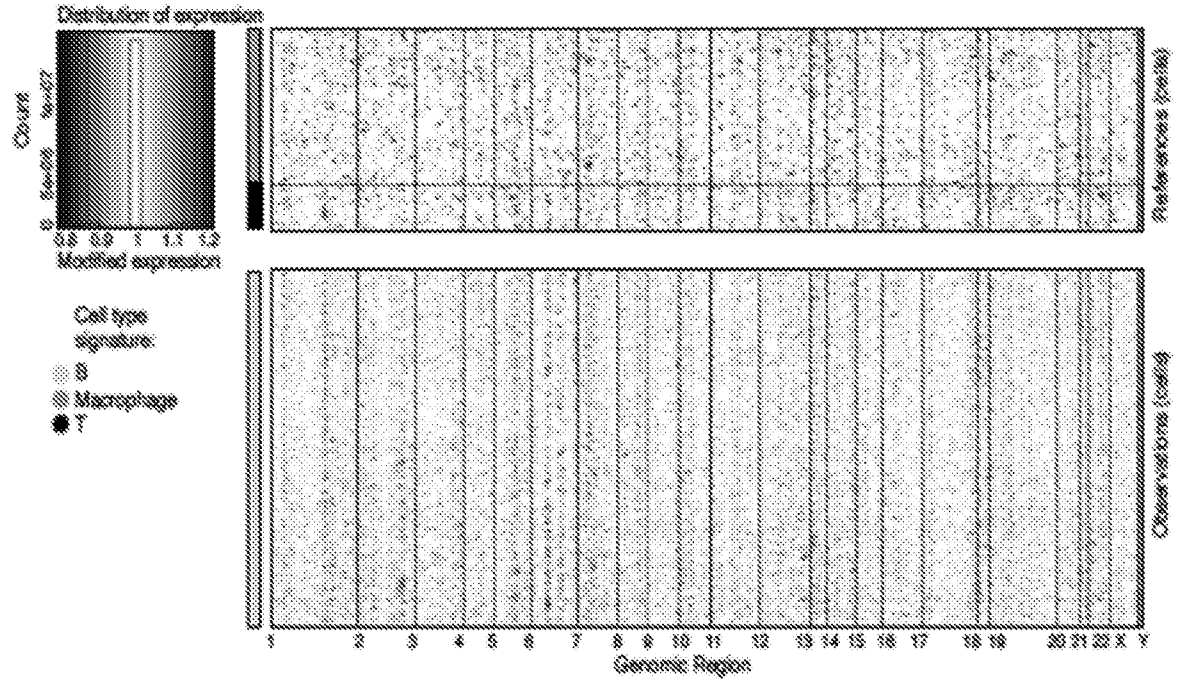


FIG. 70G

Cancer Type: NB
Sample Type: Resection
Sample ID: HTAPP-244-SMP-451
Protocol used: EZ / CST / NST / TST

	# Nuc	Reads	Sat.	# Read / nuc	# UMI / nuc	# Gene / nuc	Mito fraction	UMI dup fraction	Doublet fraction
EZ	7896	1005606624	67.7	3242	989.5	714	0.00	0.47	0.01
CST	6157	1128864753	86.2	4787	2059.0	1385	0.01	0.60	0.01
NST	7931	995700019	48.7	3250	1024.0	1129	0.00	0.63	0.01
TST	7415	982238702	53.5	4217	1903.0	1262	0.04	0.66	0.02

FIG. 71A

FIG. 71B

FIG. 71C

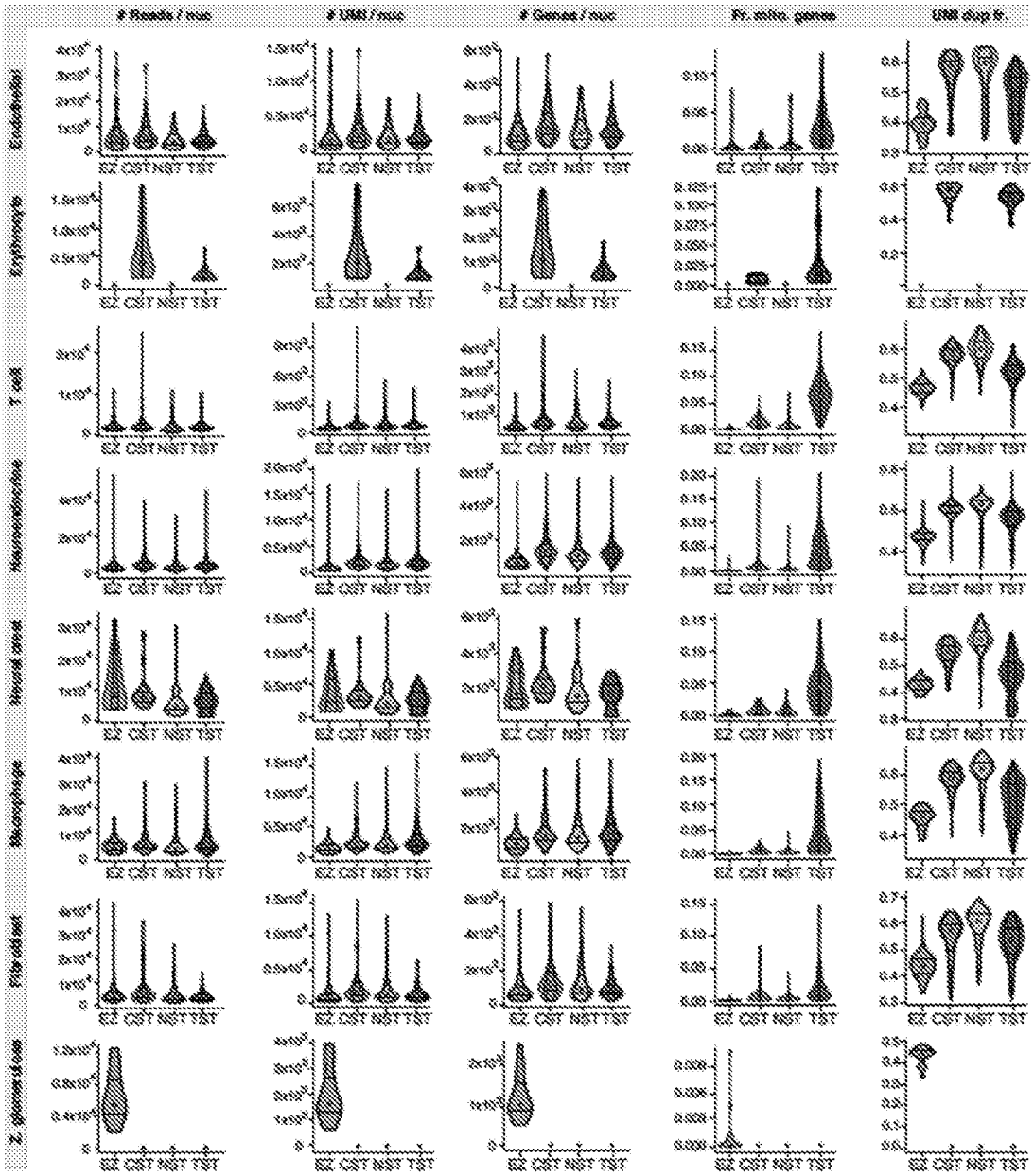


FIG. 71D

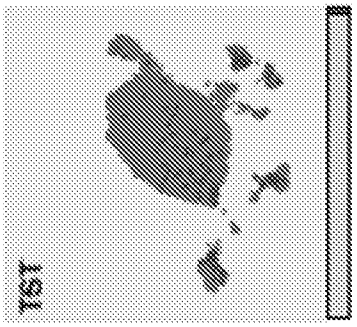


FIG. 71I

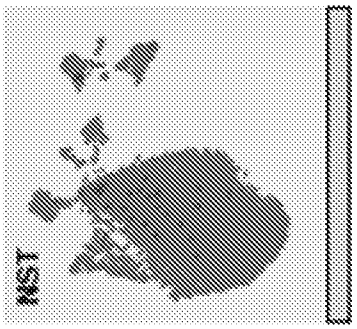


FIG. 71H

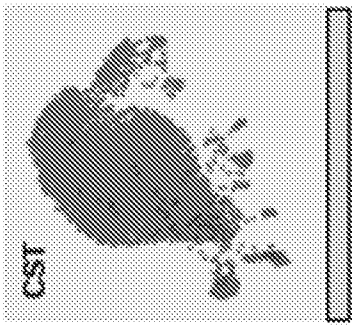


FIG. 71G

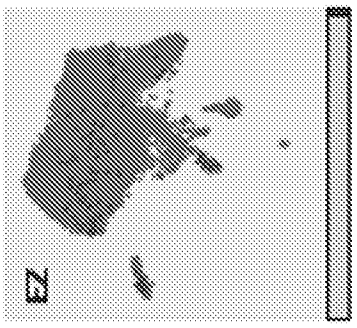


FIG. 71E

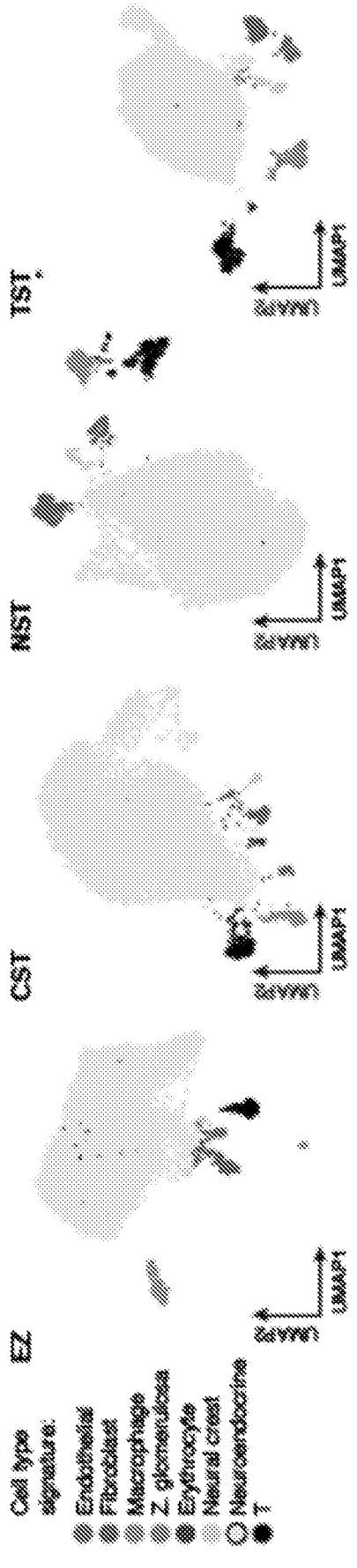


FIG. 71F

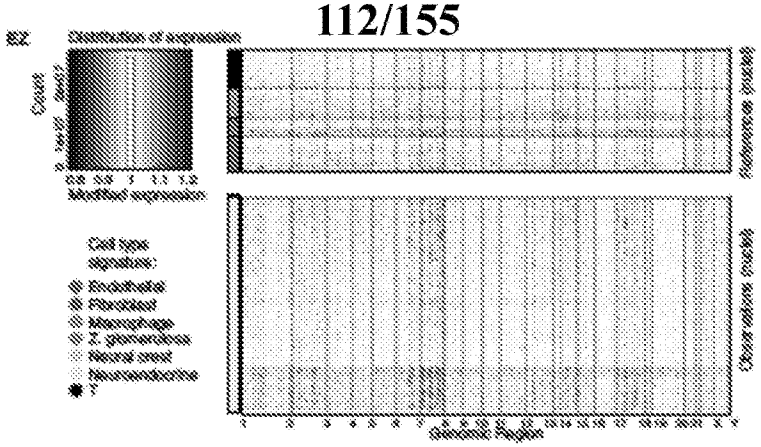


FIG. 71J

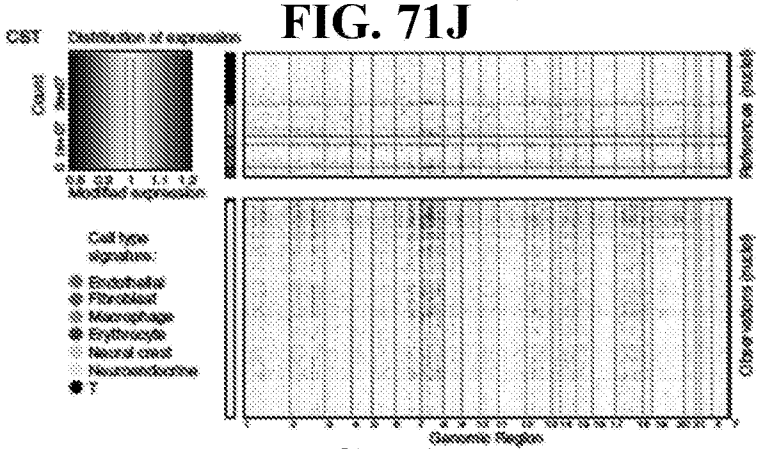


FIG. 71K

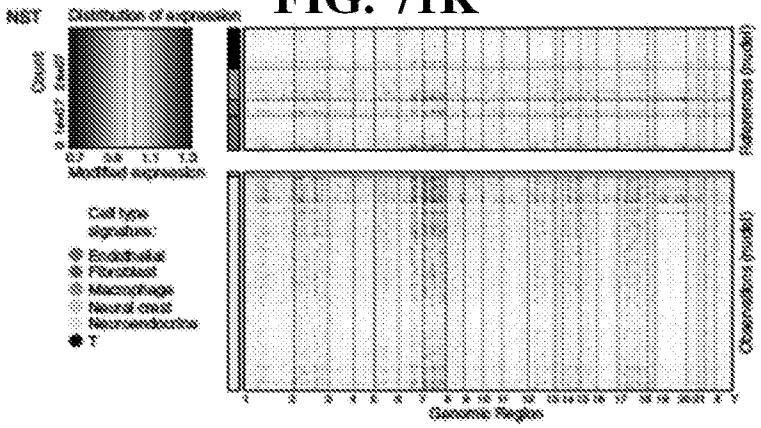


FIG. 71L

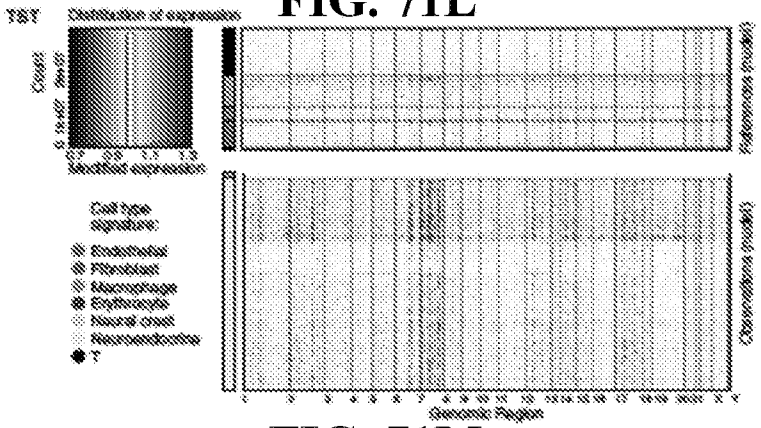


FIG. 71M

		# Nuc	# UMI / nuc	# Gene / nuc	Mito fraction	Doublet fraction
Cancer Type: NB	EZ	7875	984	711	0.00	0.01
Sample Type: Resection	CST	6146	1940	1326	0.01	0.01
Sample ID: HTAPP-244-SMP-451	NST	7524	1614	1124	0.00	0.01
Protocol used: Downsampled	TST	7415	1903	1282	0.04	0.01

FIG. 72A

FIG. 72B

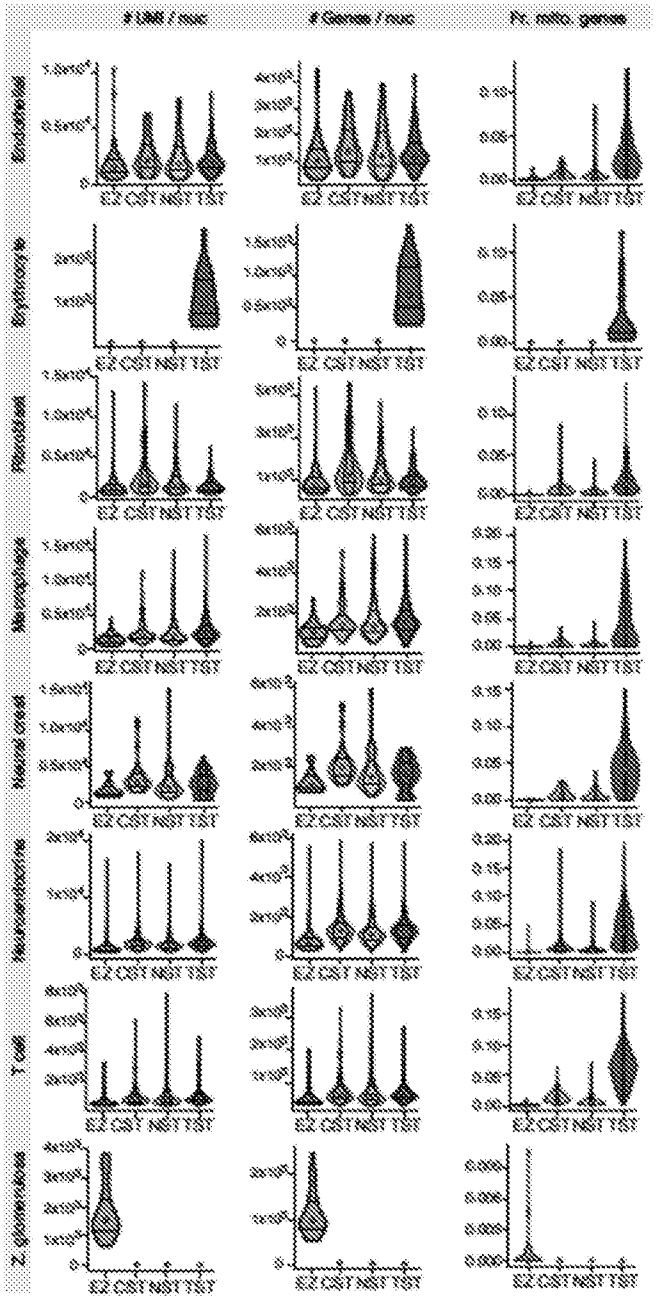


FIG. 72C

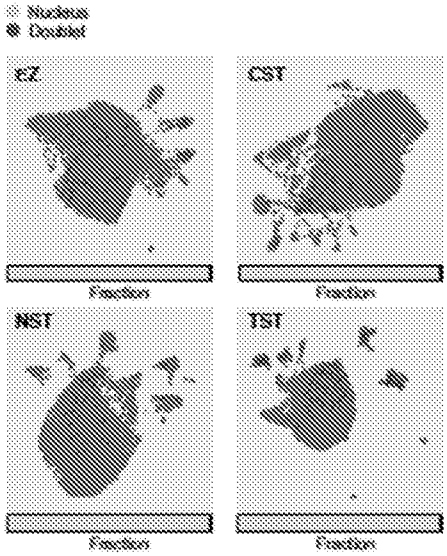


FIG. 72D

FIG. 72E

FIG. 72F

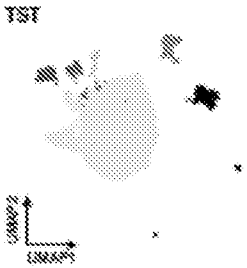


FIG. 72H

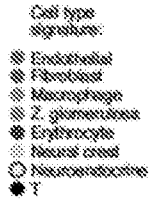


FIG. 72G

Cancer Type: MBC Sample Type: Resection (brain) Sample ID: HTAPP-304-SMP-1381 Protocol used: CST / NST		# Nuc	Reads	Sat.	# Read / nuc	# UMI / nuc	# Gene / nuc	Mito fraction	Doublet fraction
	CST	6948	1159882367	55	3669	1567	1103	0.01	0.01
	NST	8058	1001189421	49	3130	1530	1035	0.01	0.02

FIG. 73A

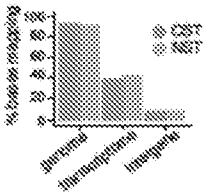


FIG. 73B

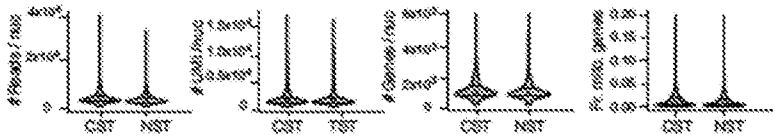


FIG. 73C

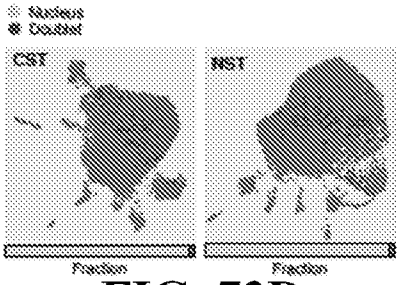


FIG. 73D

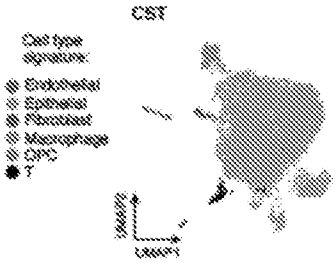


FIG. 73E

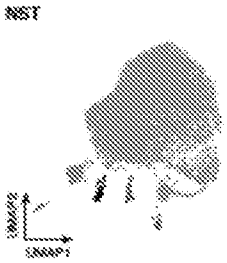


FIG. 73F

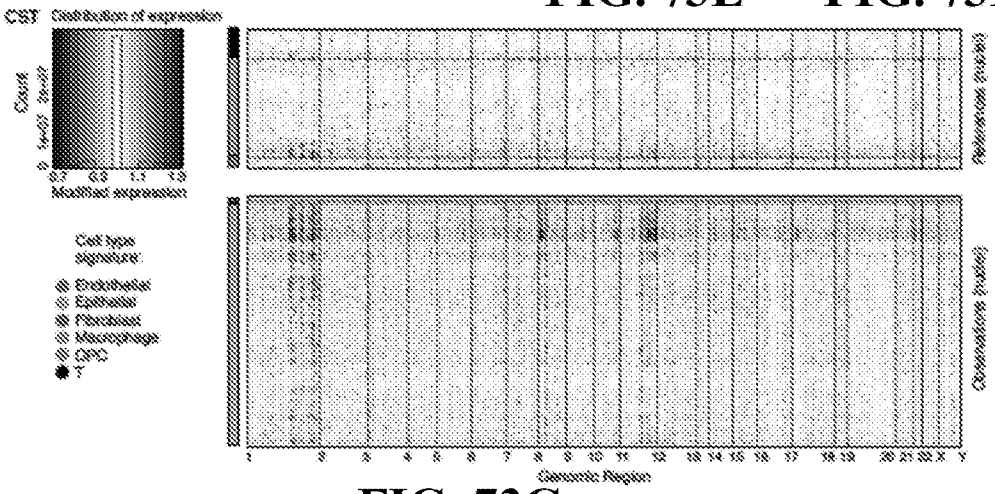


FIG. 73G

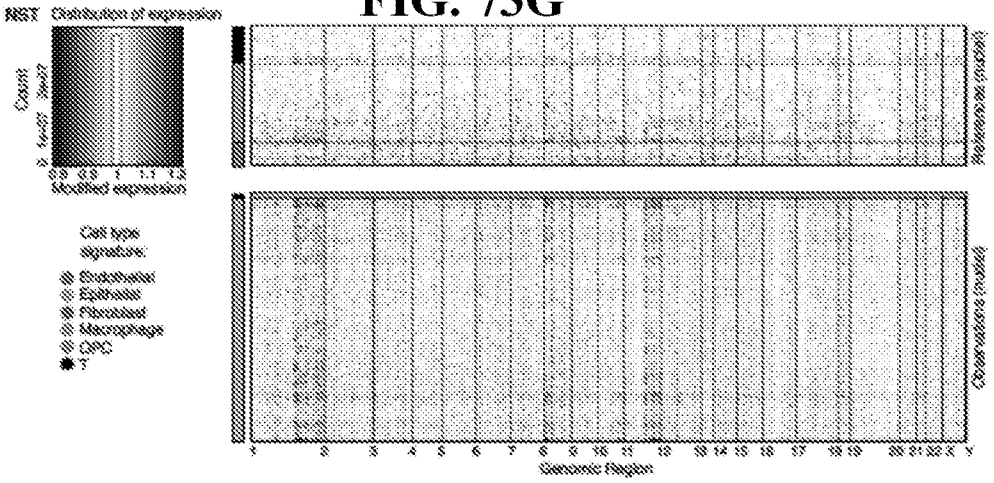


FIG. 73H

Cancer Type: MBC Sample Type: Resection (brain) Sample ID: HTAPP-SBB-SMP-2851 Protocol used: CST / TST		# Nuc	Reads	Sat.	# Read / nuc	# UMI / nuc	# Gene / nuc	Mito fraction	Doublet fraction
	CST	7858	109079277	35.5	3759	2398	1564	0.01	0.01
	TST	8373	117318888	35.1	3348	2137	1396	0.05	0.01

FIG. 74A

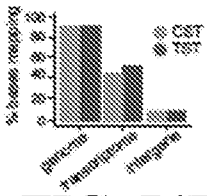


FIG. 74B

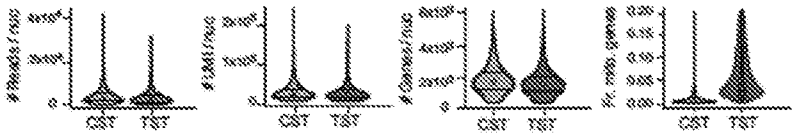


FIG. 74C

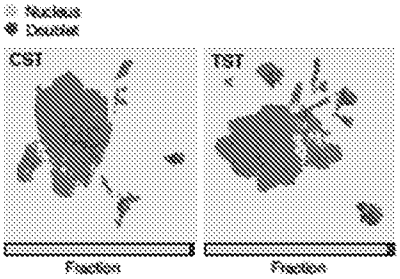


FIG. 74D

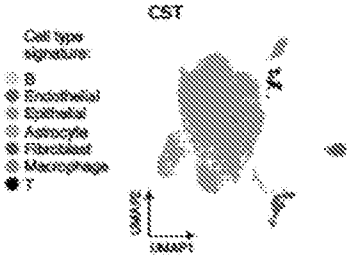


FIG. 74E

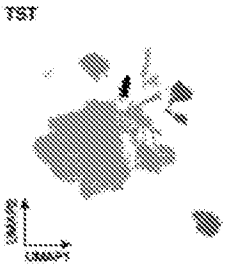


FIG. 74F

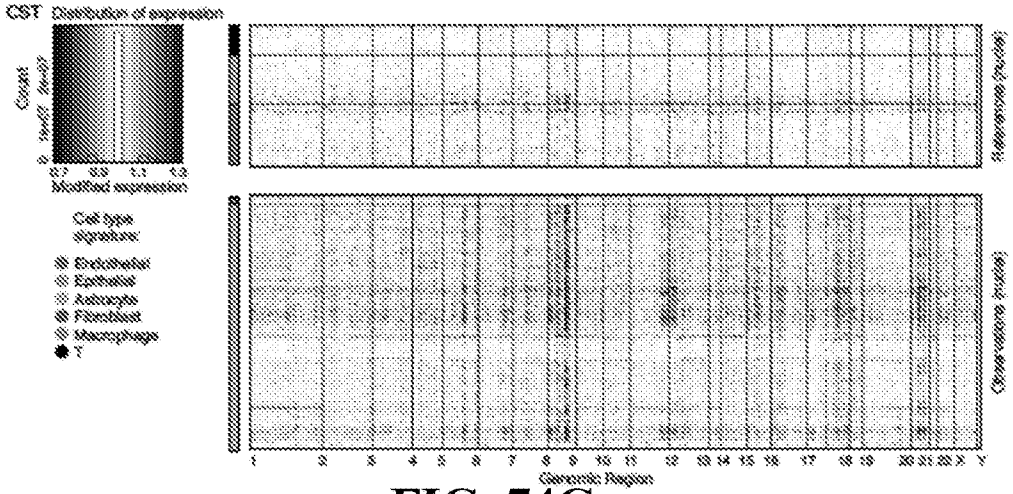


FIG. 74G

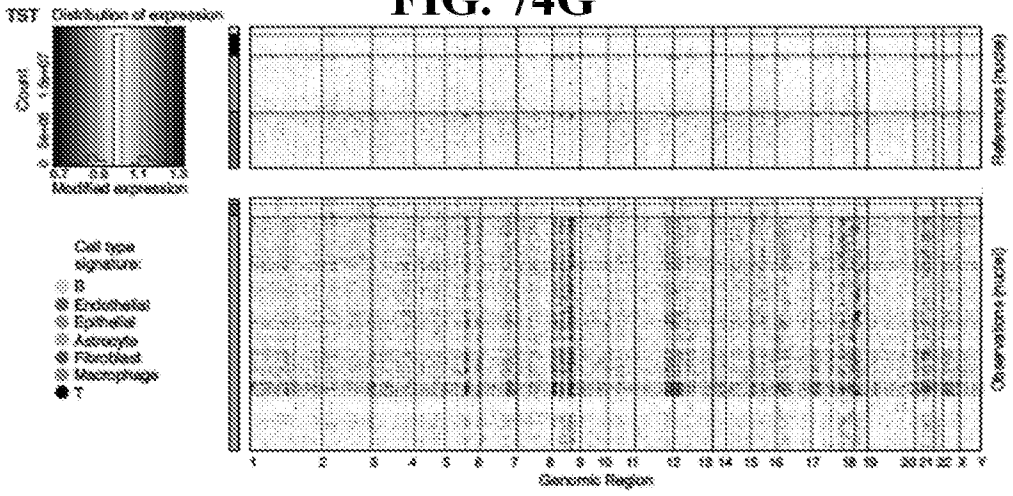


FIG. 74H

Cancer Type: MDC Sample Type: Biopsy (liver) Sample ID: HTAPP-963-SMP-4741 Protocol used: CST / TST		# Nuc	Reads	Sat.	# Read / nuc	# UMI / nuc	# Gene / nuc	Mito fraction	Doublet fraction
	CST	9857	14353/012	56.2	3708	1573	1182	0.01	0.01
	TST	7200	10147/239	84.0	4947	1723	1168	0.05	0.05

FIG. 75A

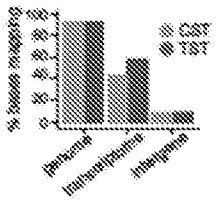


FIG. 75B

FIG. 75C

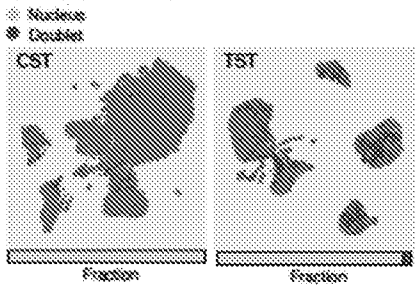


FIG. 75D

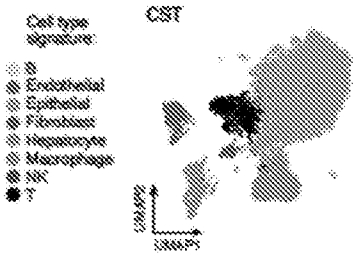


FIG. 75E

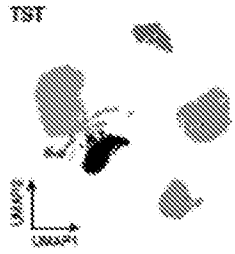


FIG. 75F

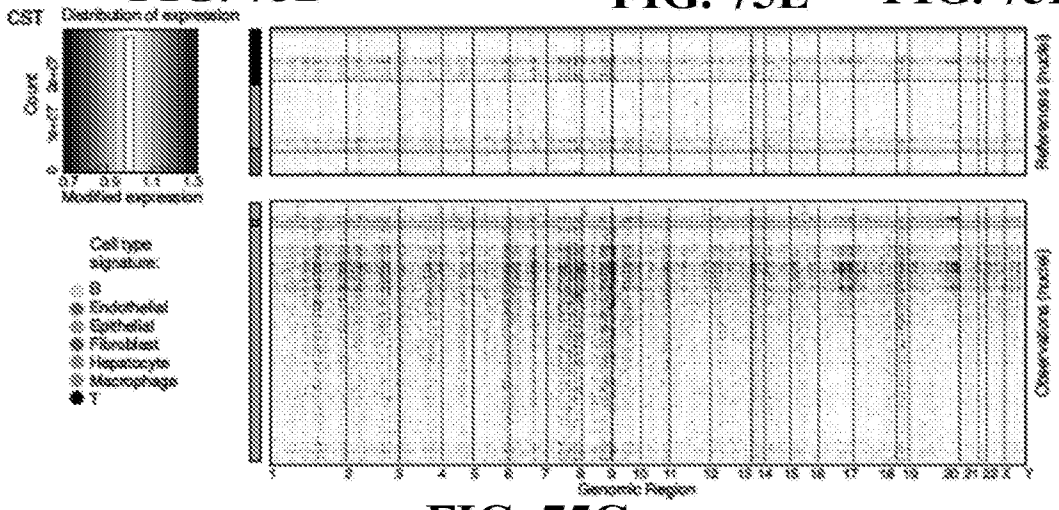


FIG. 75G

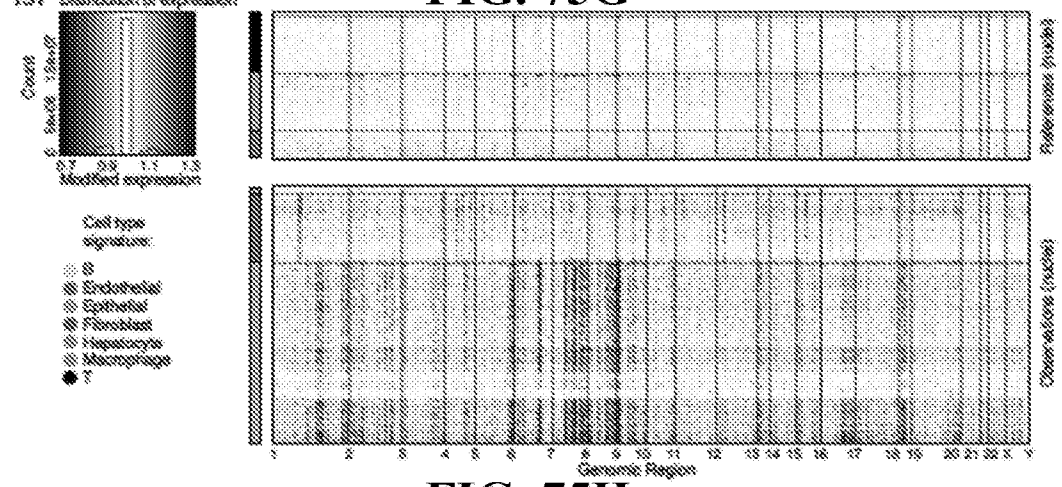


FIG. 75H

Cancer Type: Ovarian		# Nuc	Reads	Sat.	# Read / nuc	# UMI / nuc	# Gene / nuc	Mito fraction	Doublet fraction
Sample Type: Resection	CST	9026	108974203	57.4	1896	788	626	0.0108	0.1011
Sample ID: HTAPP-316-SMP-991	NST	5970	123054527	72.7	2940	726	575	0.0083	0.0149
Protocol used: CST / NST / TST	TST	10493	105768971	49.8	2402	1168	823	0.0320	0.0352

FIG. 76A

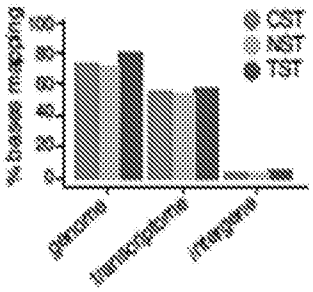


FIG. 76B

FIG. 76C

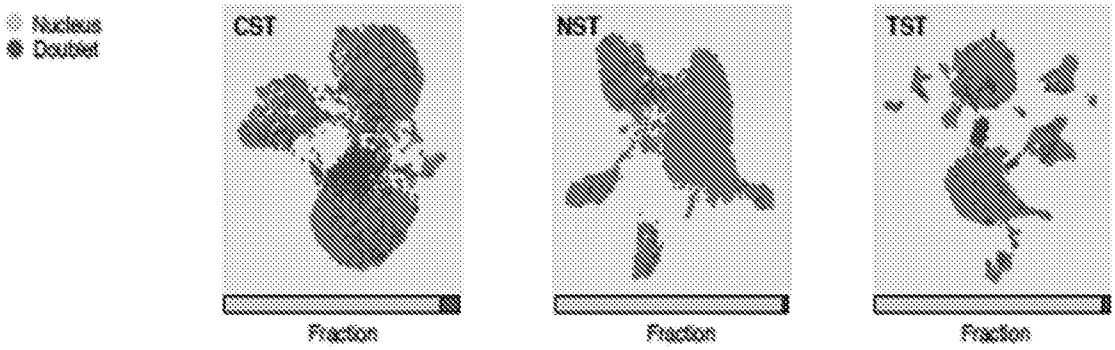


FIG. 76D

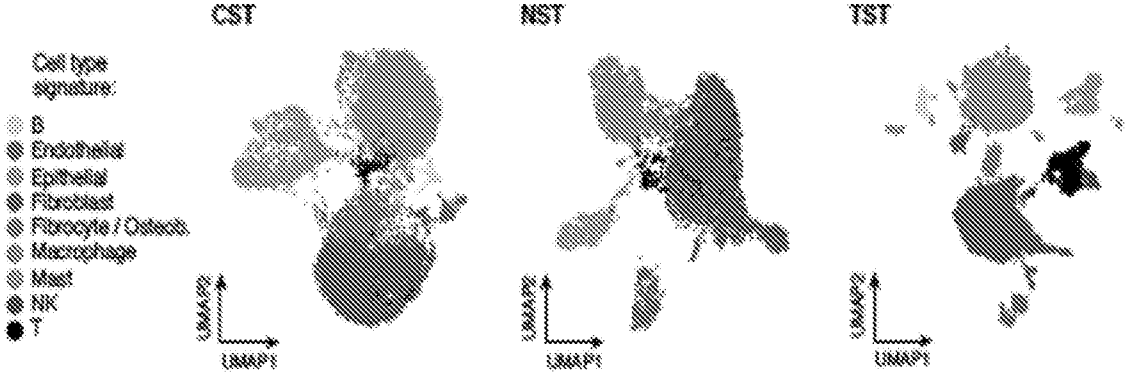


FIG. 76E FIG. 76F FIG. 76G

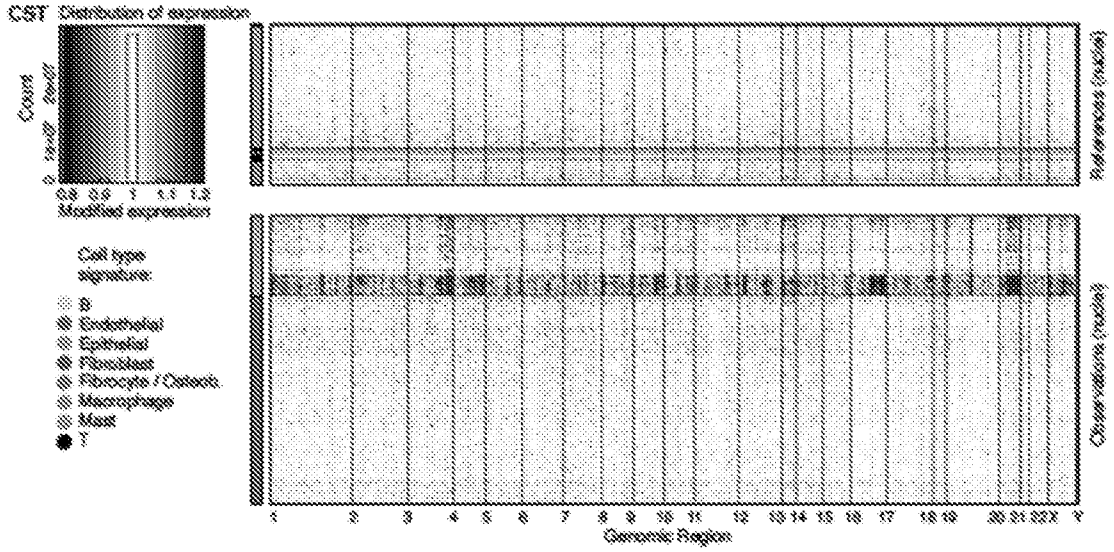


FIG. 76H

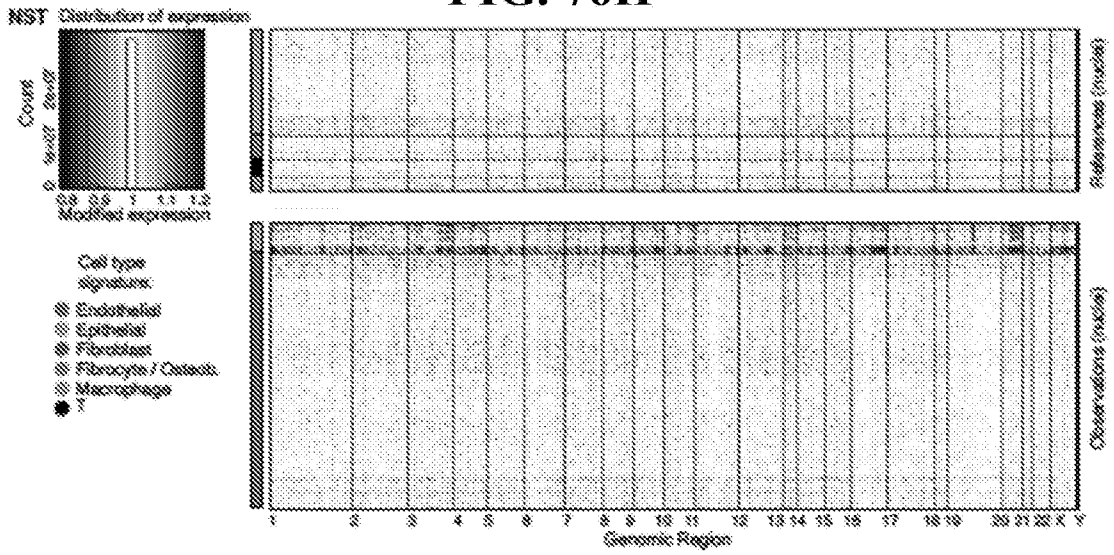


FIG. 76I

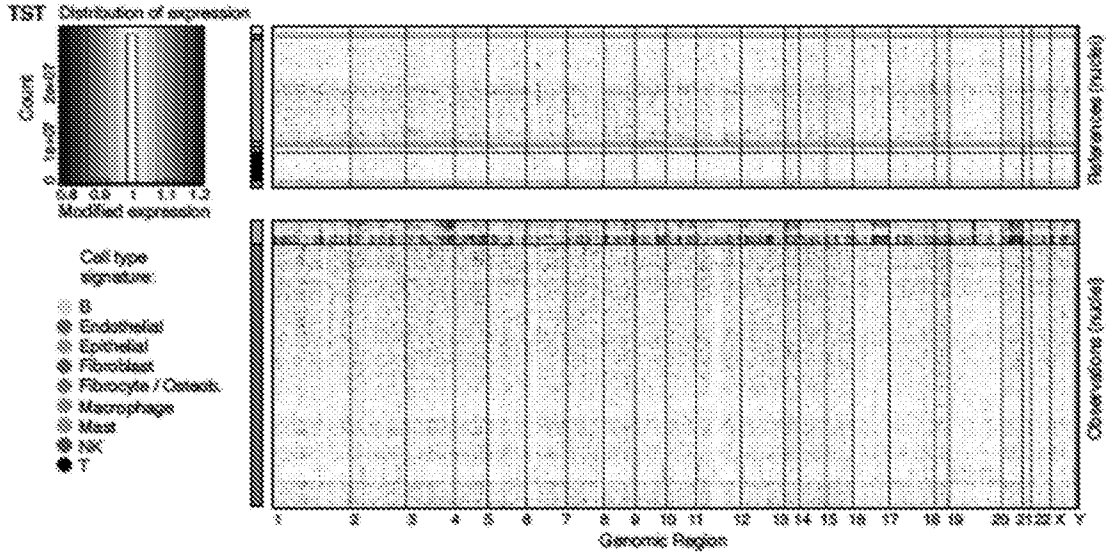


FIG. 76J

Cancer Type: Sarcoma Sample Type: Resection Sample ID: HTAPP-881-SMP-4662 Protocol used: CST / TST		# Nuc	Reads	Sat.	# Read / nuc	# UMI / nuc	# Gene / nuc	Mito fraction	Doublet fraction
	CST	7858	4456265201	37.8	56706	6135	3202	0.02	0.01
	TST	4438	4060011101	58.1	222582	9283	3805	0.04	0.01

FIG. 77A

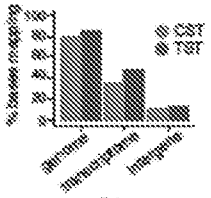


FIG. 77B

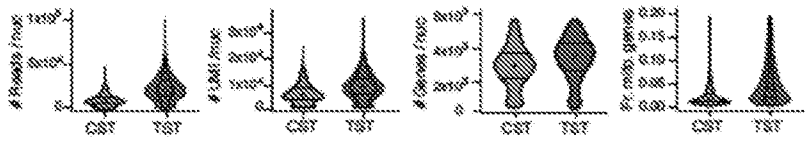


FIG. 77C

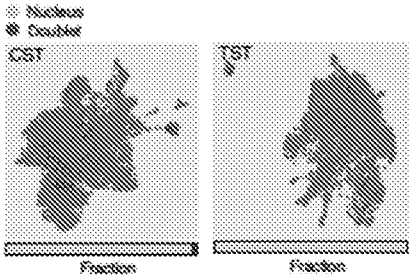


FIG. 77D FIG. 77E

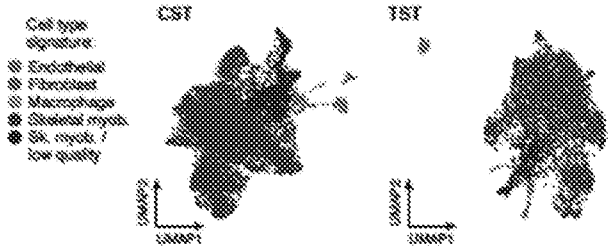


FIG. 77F

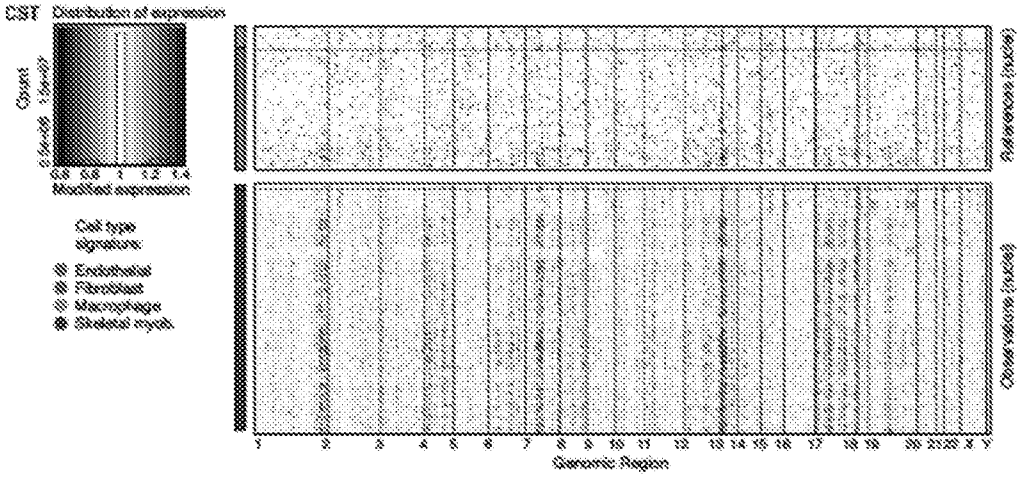


FIG. 77G

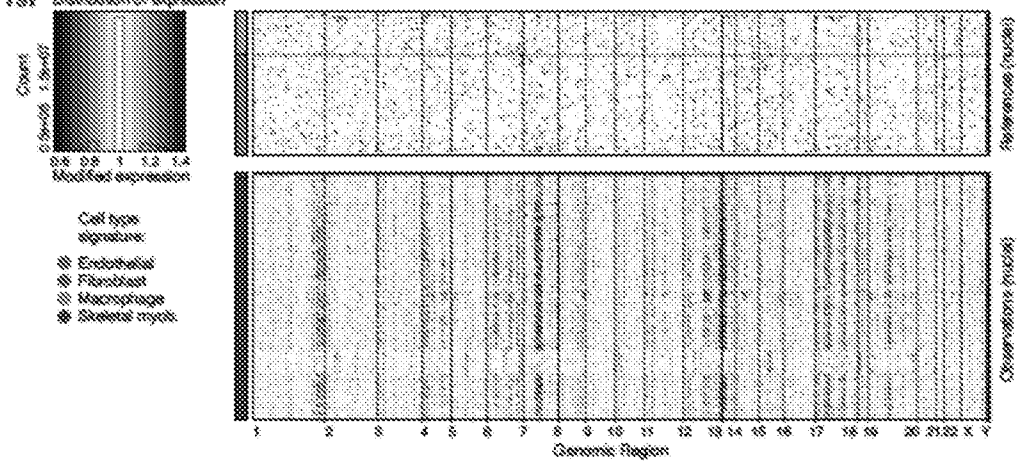


FIG. 77H

Cancer Type: Glioma Sample Type: Resection Sample ID: HTAPP-443-SMP-6401 Protocol used: CST	# Nuc	Reads	Sat.	# Read / nuc	# UMI / med	# Gene / nuc	Mito fraction	Doublet fraction
	3967	108088255	43.4	6930	3304	2099	0.01	0.02

FIG. 78A

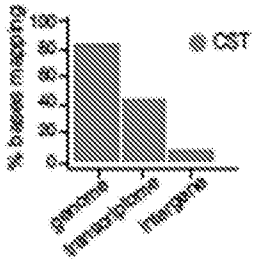


FIG. 78B

FIG. 78C

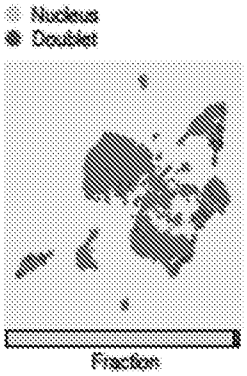


FIG. 78D

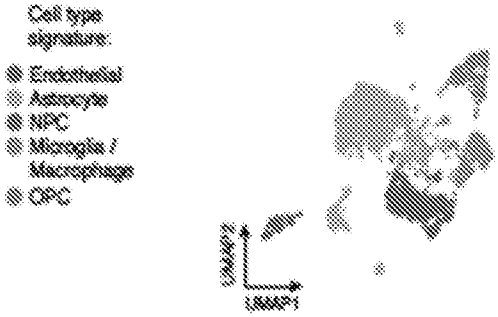


FIG. 78E

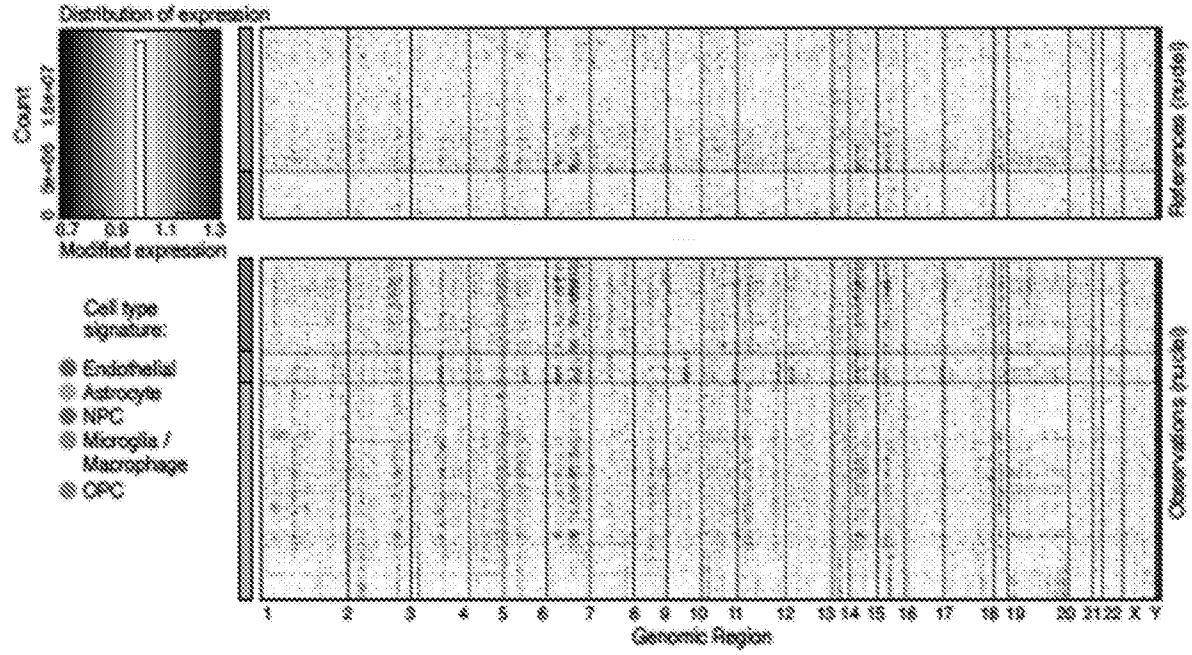
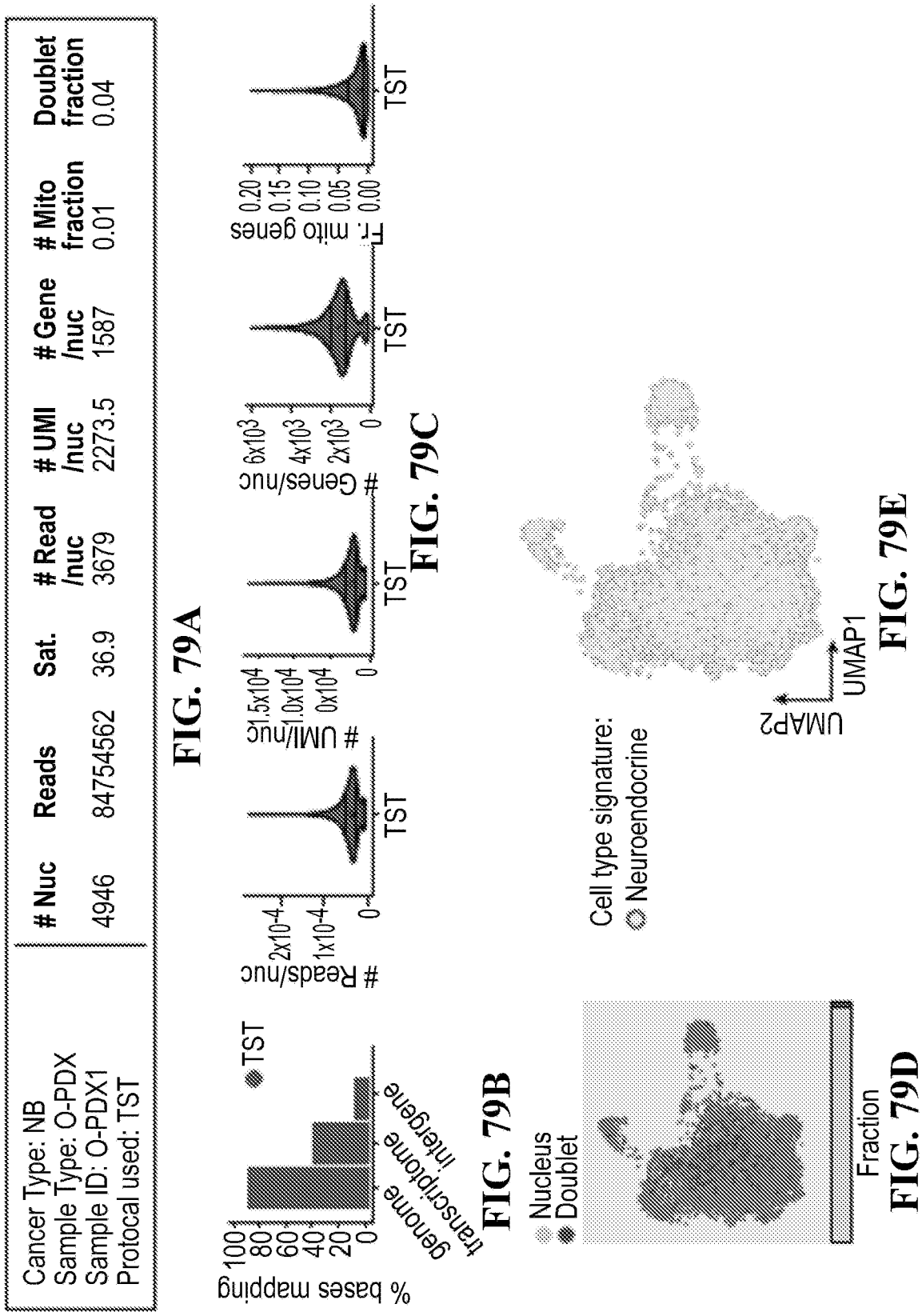


FIG. 78F


Cancer Type: NB
Sample Type: O-PDX
Sample ID: O-PDX1
Protocal used: TST
Nuc
4946
Reads
84754562
Sat.
36.9
Read /nuc
3679
UMI /nuc
2273.5
Gene /nuc
1587
Mito fraction
0.01
Doublet fraction
0.04
FIG. 79A
% bases mapping
genome
transcriptome
intergene
TST
FIG. 79B
Reads/nuc
UMI/nuc
Genes/nuc
Tr. mito genes
TST
FIG. 79C
Nucleus
Doublet
Fraction
FIG. 79D
Cell type signature:
Neuroendocrine
UMAP1
UMAP2
FIG. 79E

Cancer Type: NB Sample Type: Resection Sample ID: HTAPP-656-SMP-3481 Protocal used: TST	# Nuc	Reads	Sat.	# Read /nuc	# UMI /nuc	# Gene /nuc	# Mito fraction	Doublet fraction
	7810	119994153	73.6	3208	795	617	0.01	0.03

FIG. 80A

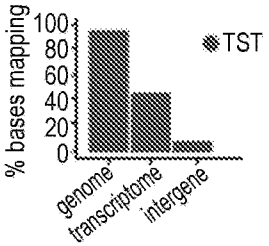


FIG. 80B

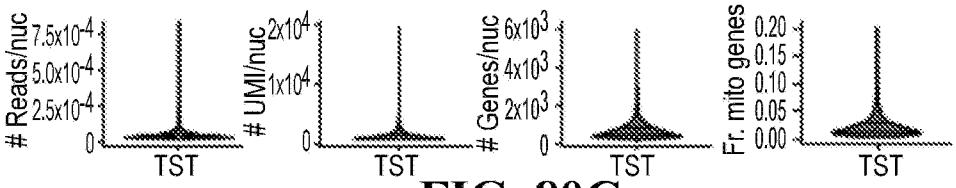


FIG. 80C

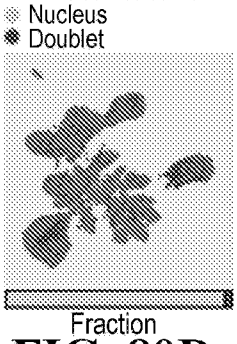


FIG. 80D

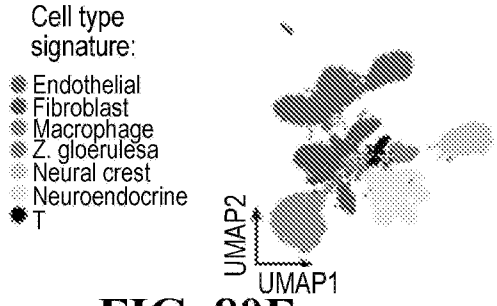


FIG. 80E

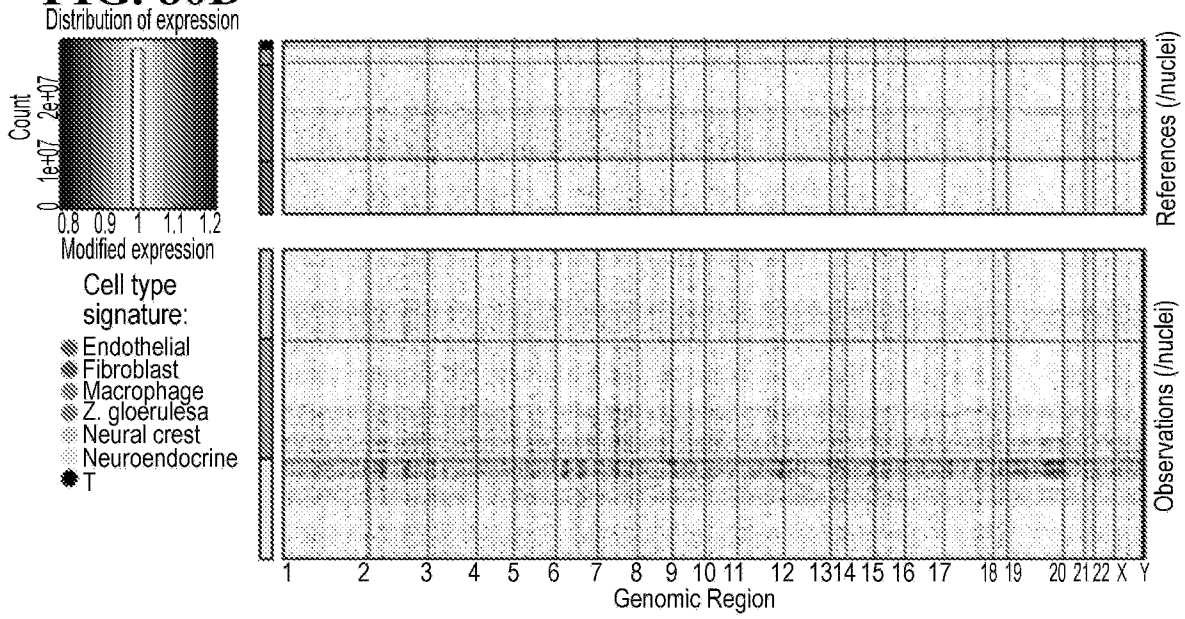


FIG. 80F

Cancer Type: NB Sample Type: Resection Sample ID: HTAPP-975-SMP-4771 Protocal used: TST	# Nuc	Reads	Sat.	# Read /nuc	# UMI /nuc	# Gene /nuc	# Mito fraction	Doublet fraction
	4317	115014299	41.6	7895	4561	2143	0.02	0.01

FIG. 81A

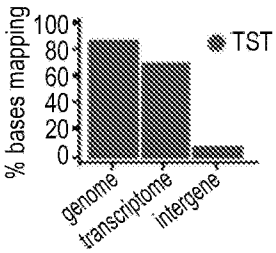


FIG. 81B

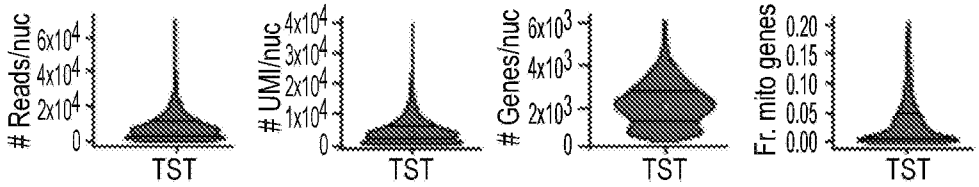


FIG. 81C

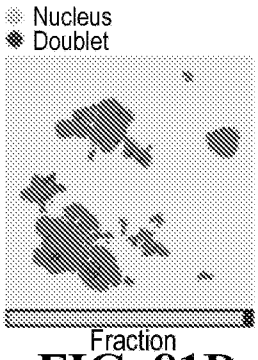


FIG. 81D

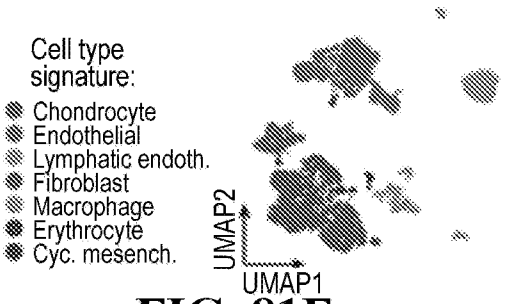


FIG. 81E

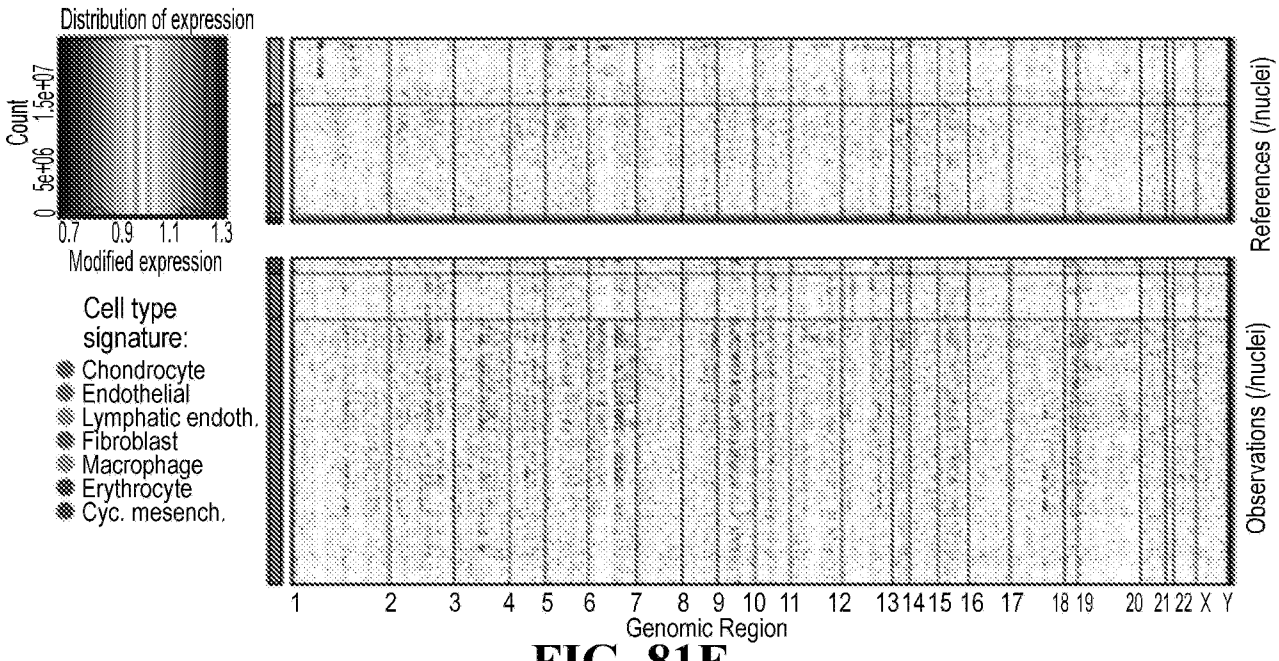


FIG. 81F

Cancer Type: Melanoma Sample Type: Resection Sample ID: MEL128 Protocal used: TST	# Nuc	Reads	Sat.	# Read /nuc	# UMI /nuc	# Gene /nuc	# Mito fraction	Doublet fraction
	5236	64132162	25.5	2669	2034	1374	0.04	0.02

FIG. 82A

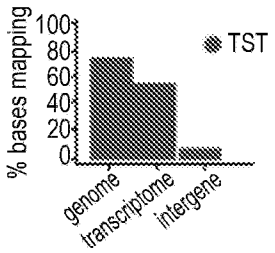


FIG. 82B

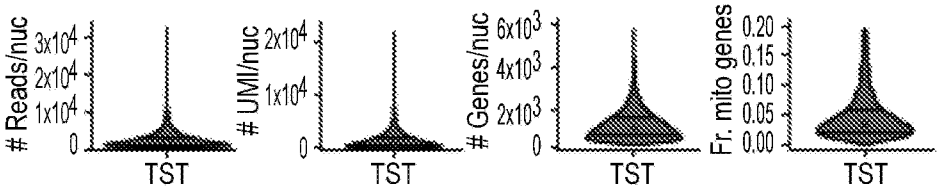


FIG. 82C

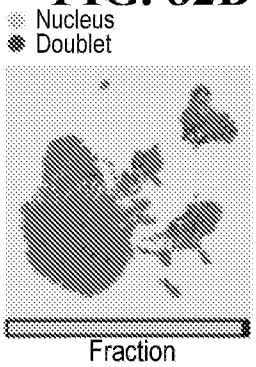


FIG. 82D

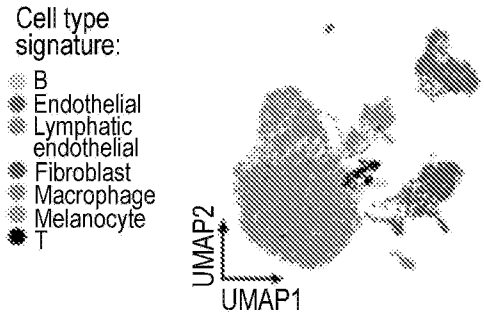


FIG. 82E

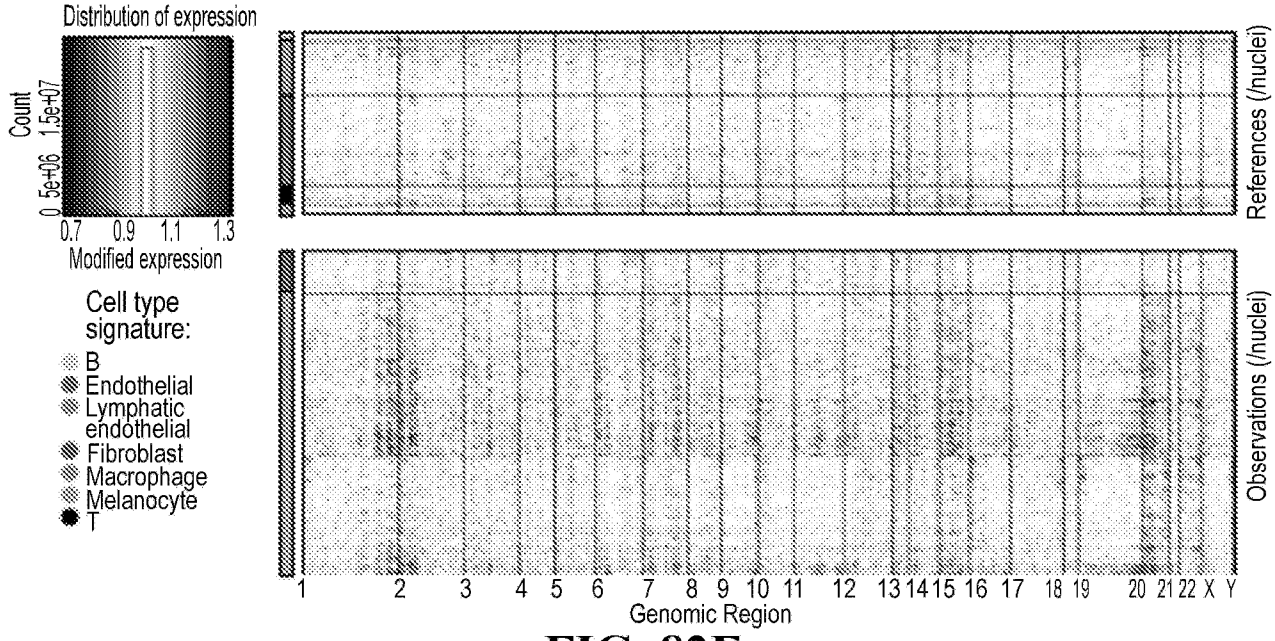


FIG. 82F

Cancer Type: Melanoma Sample Type: Resection Sample ID: MEL112 Protocal used: TST	# Nuc	Reads	Sat.	# Read /nuc	# UMI /nuc	# Gene /nuc	# Mito fraction	Doublet fraction
	2899	54676688	46.6	4484	2378	1430	0.01	0.02

FIG. 83A

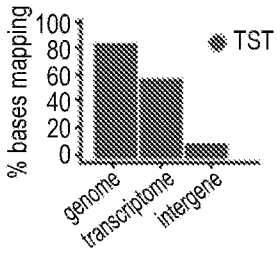


FIG. 83B

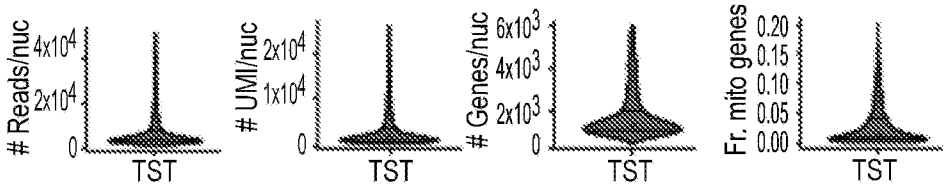


FIG. 83C

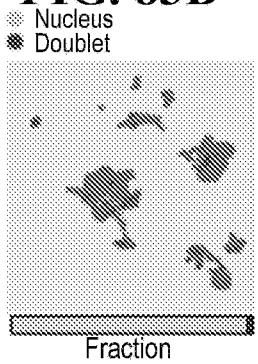


FIG. 83D

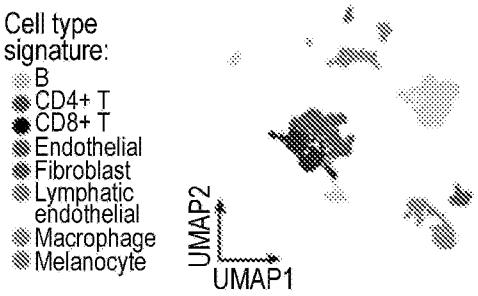


FIG. 83E

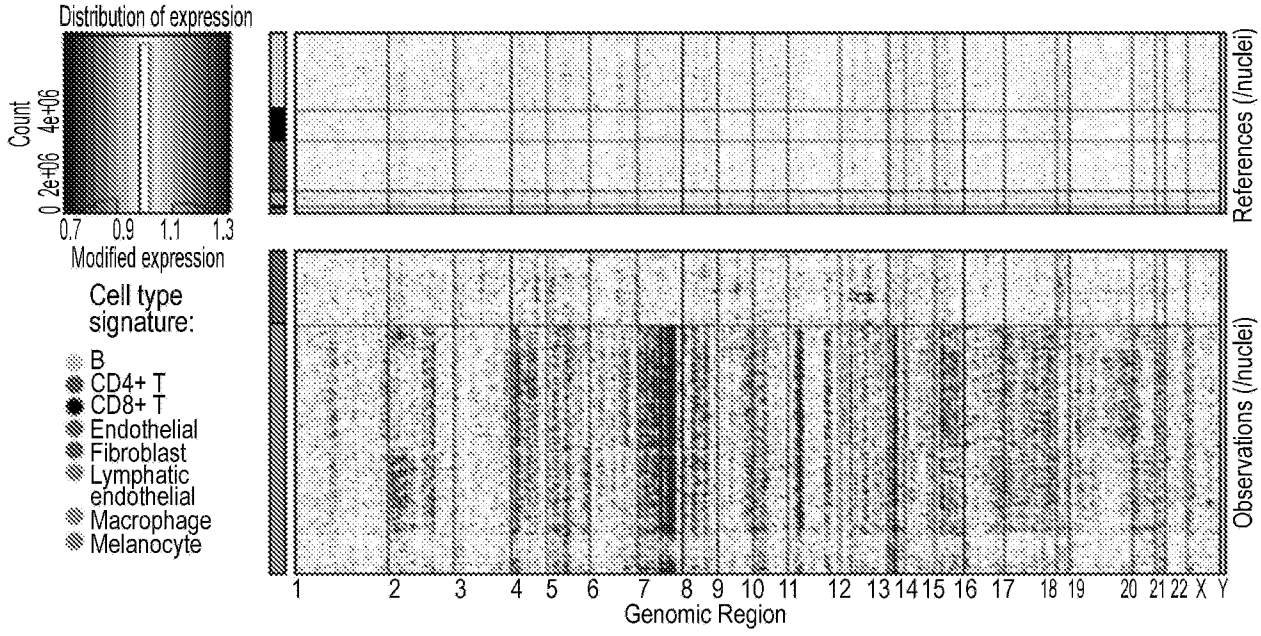


FIG. 83F

Cancer Type: CLL Sample Type: Blood draw Sample ID: CLL1 Protocal used: TST	# Nuc	Reads	Sat.	# Read /nuc	# UMI /nuc	# Gene /nuc	# Mito fraction	Doublet fraction
	2339	94117277	84.6	8934	1126	740	0.01	0.02

FIG. 84A

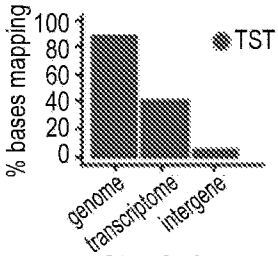


FIG. 84B

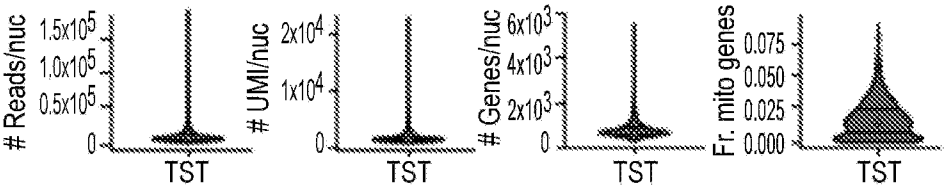


FIG. 84C

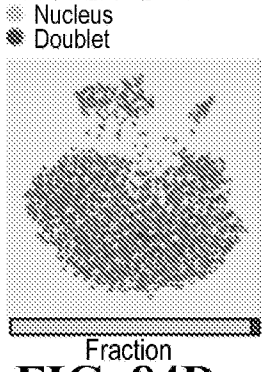


FIG. 84D

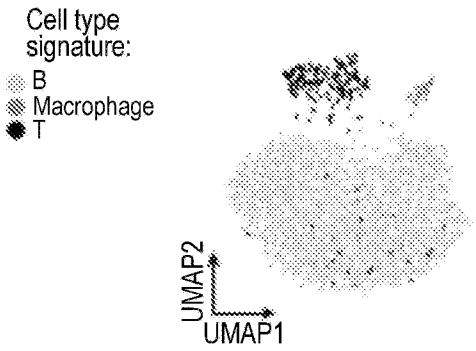


FIG. 84E

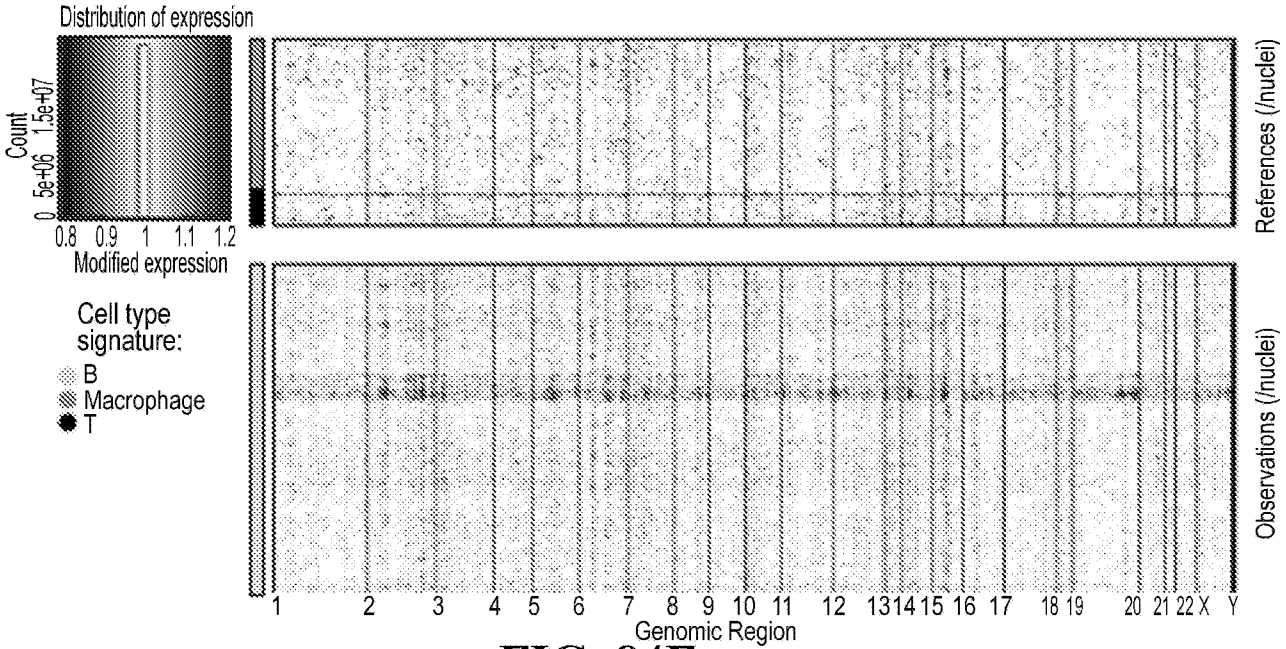
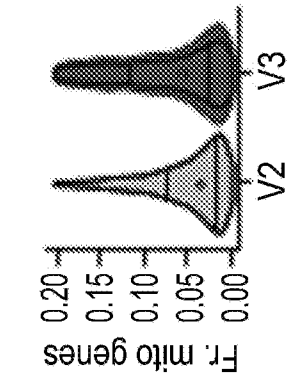


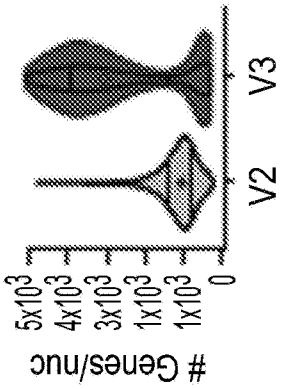
FIG. 84F

Cancer Type: Sarcoma
Sample Type: Resection
Sample ID: HTAPP-951-SMP-4652
Protocal used: TST/V2-V3 comparison

	# Nuc	# Gene /nuc	# UMI /nuc	# Mito fraction	Doublet fraction
V2	3992	1018	1402	0.04	0.01
V3	5312	2979	6310	0.06	0.00

FIG. 85A





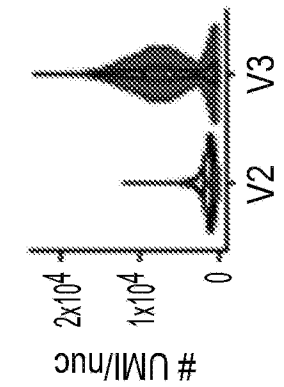


FIG. 85B

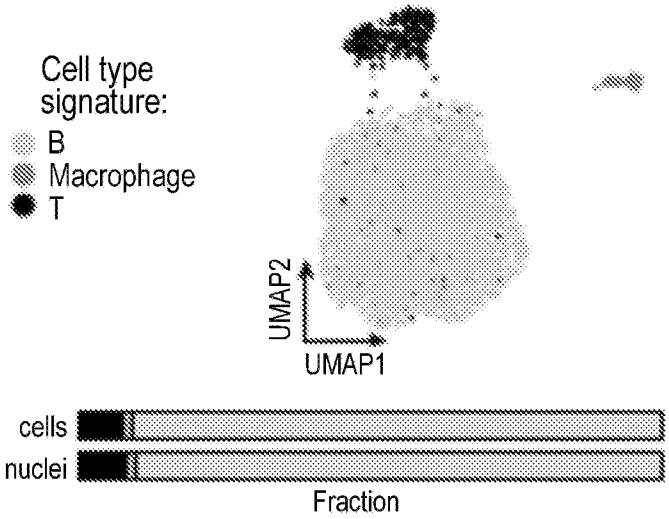


FIG. 86A

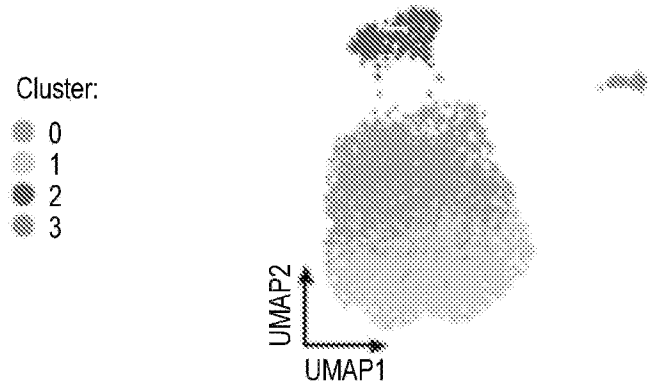


FIG. 86B

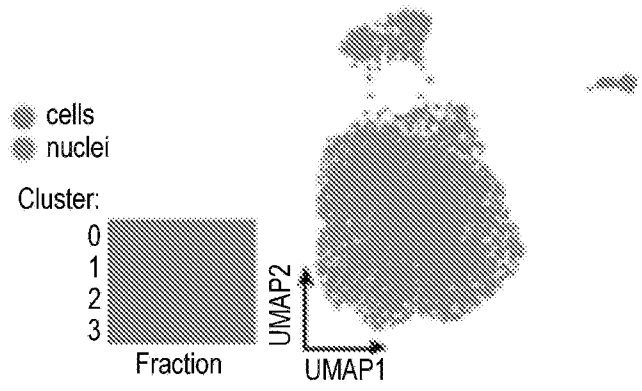


FIG. 86C

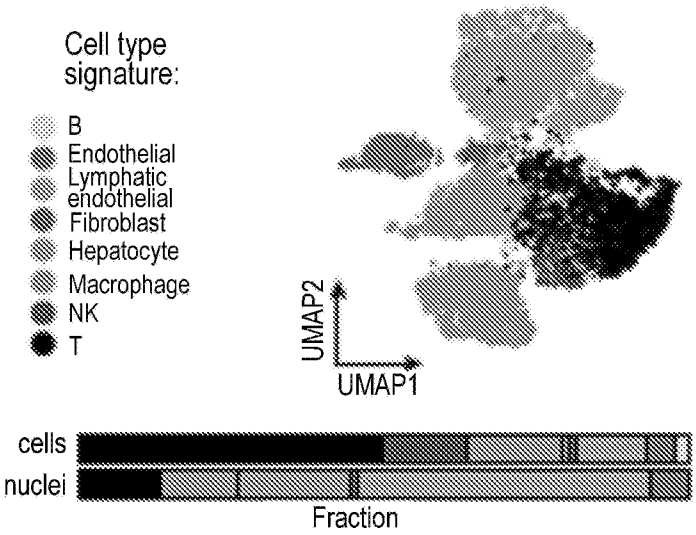


FIG. 87A

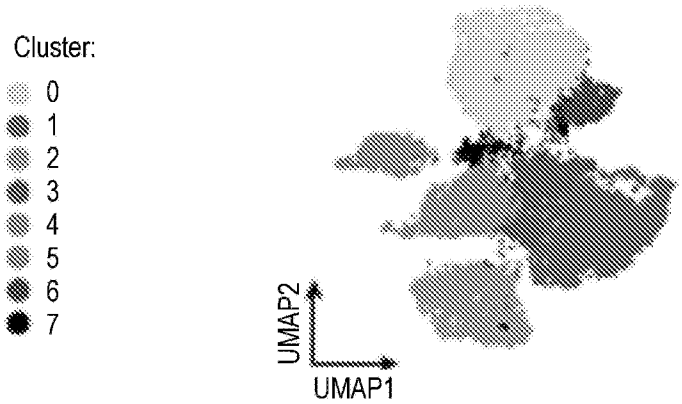


FIG. 87B

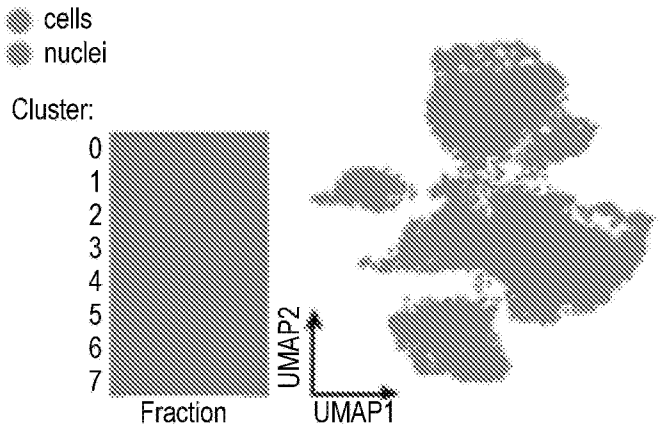


FIG. 87C

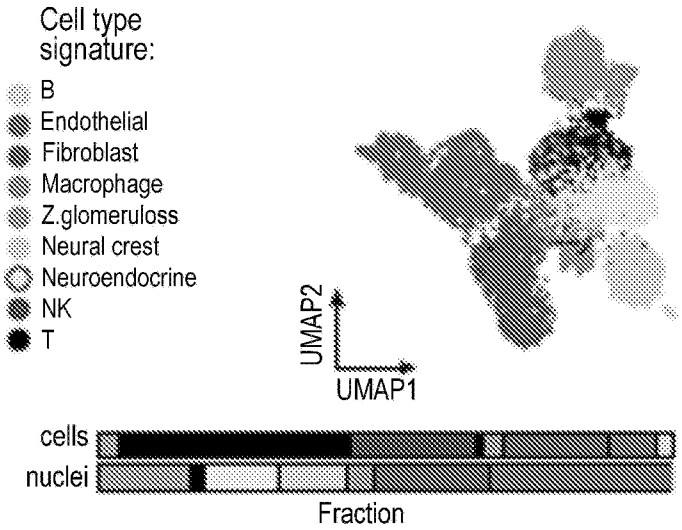


FIG. 88A

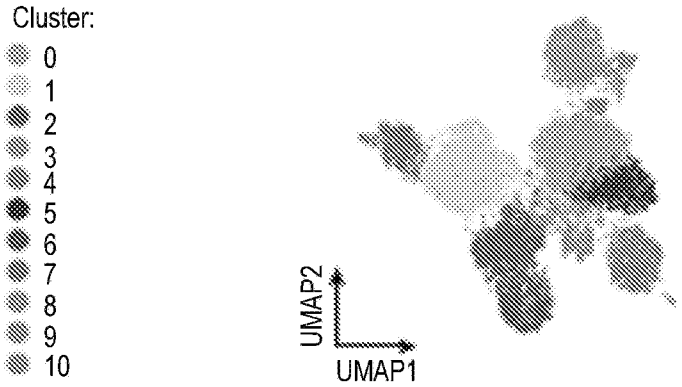


FIG. 88B

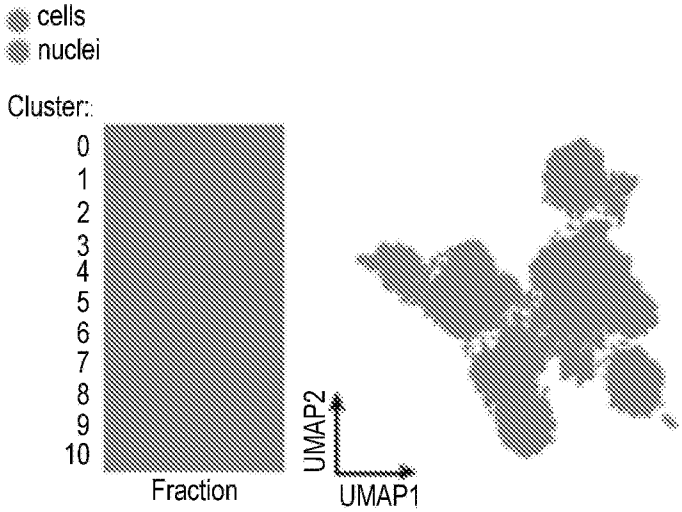


FIG. 88C

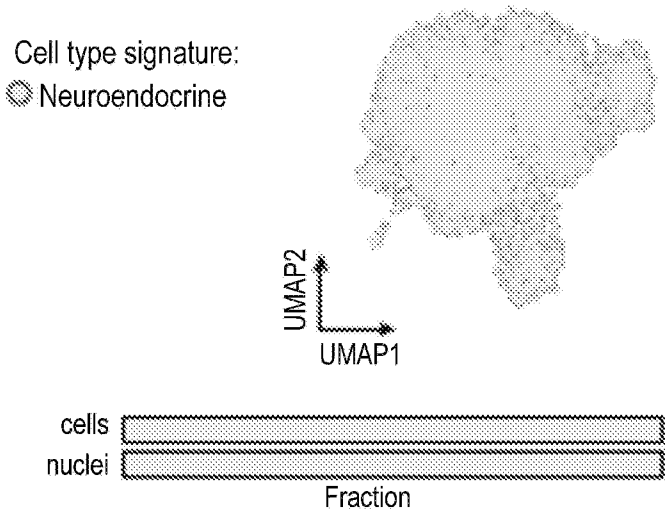


FIG. 89A

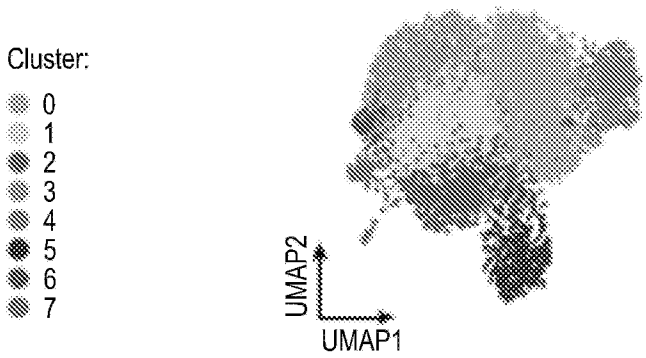


FIG. 89B

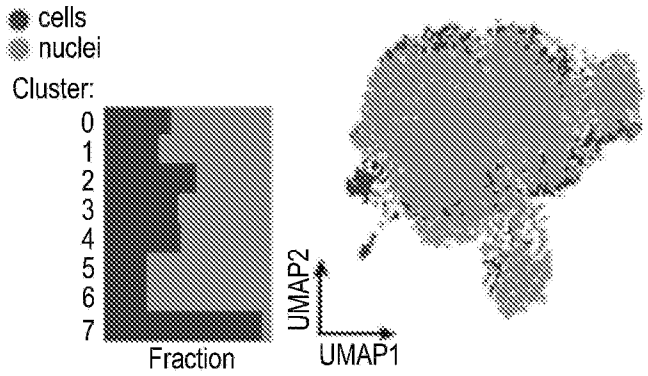


FIG. 89C

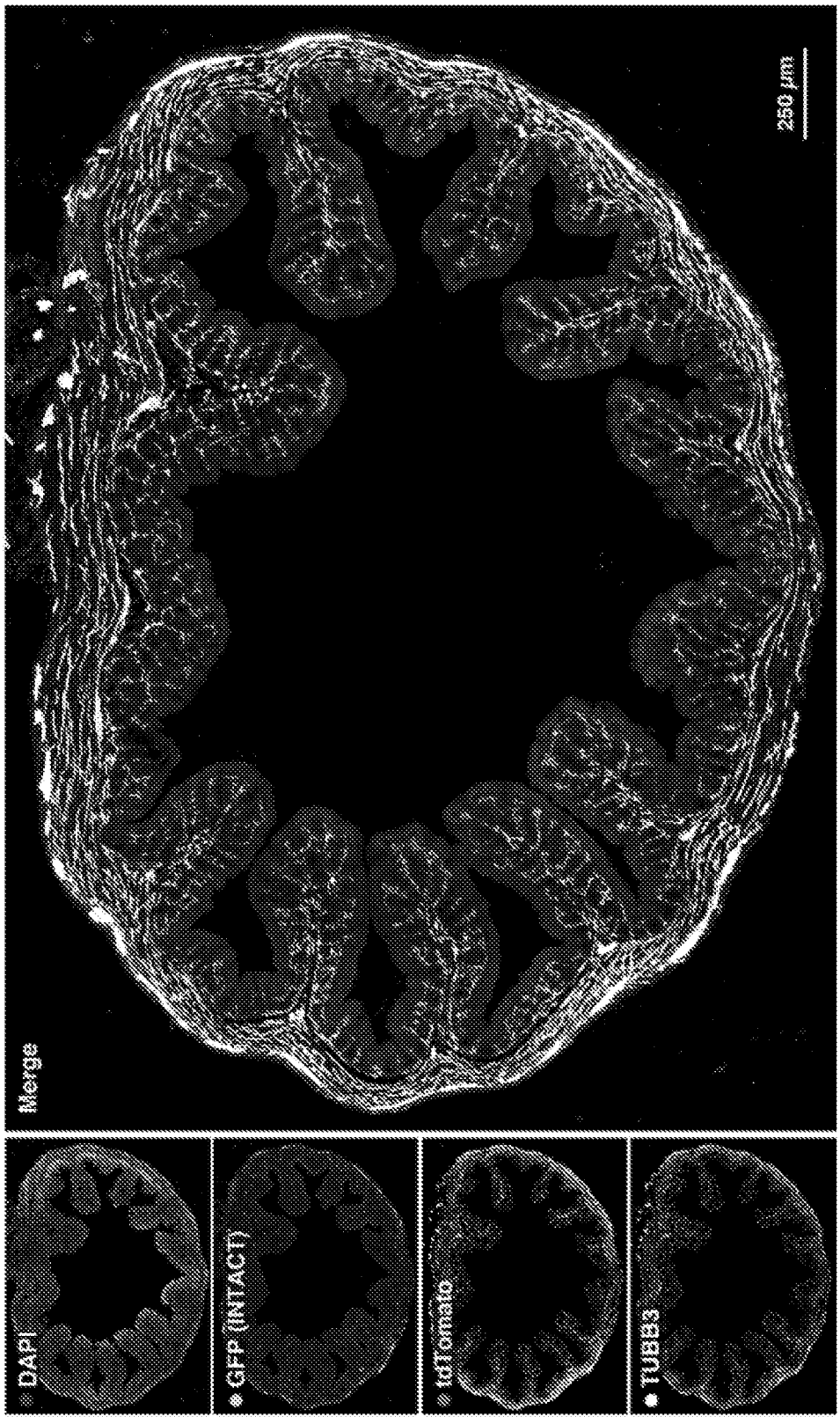

DAPI
GFP (INTACT)
tdTomato
TUBB3
Merge
250 μm
Sox10-Cre; INTACT / conditional tdTomato

Fig. 90

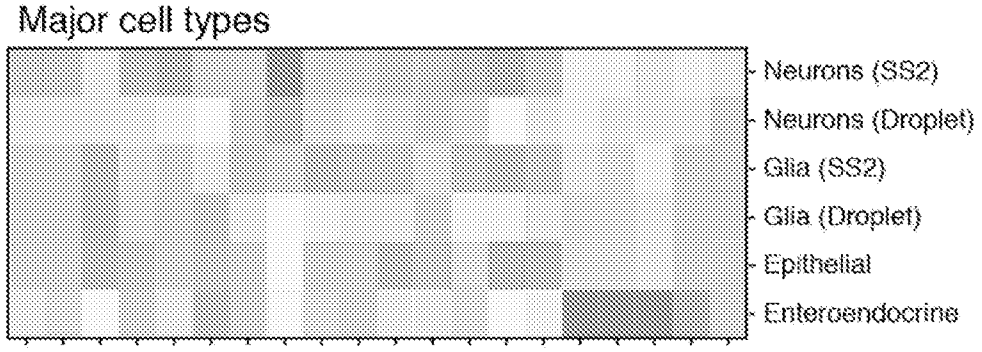


FIG. 91A

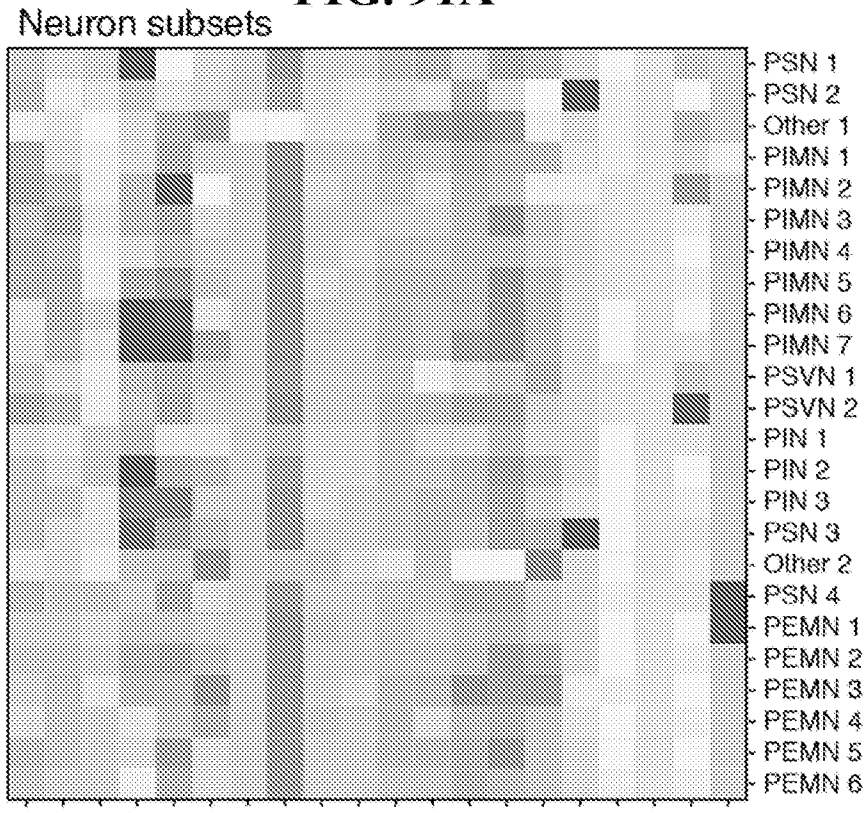


FIG. 91B

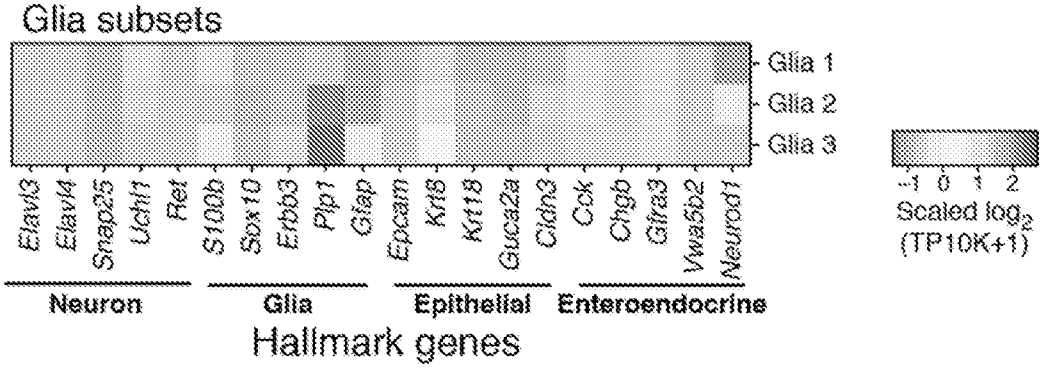


FIG. 91C

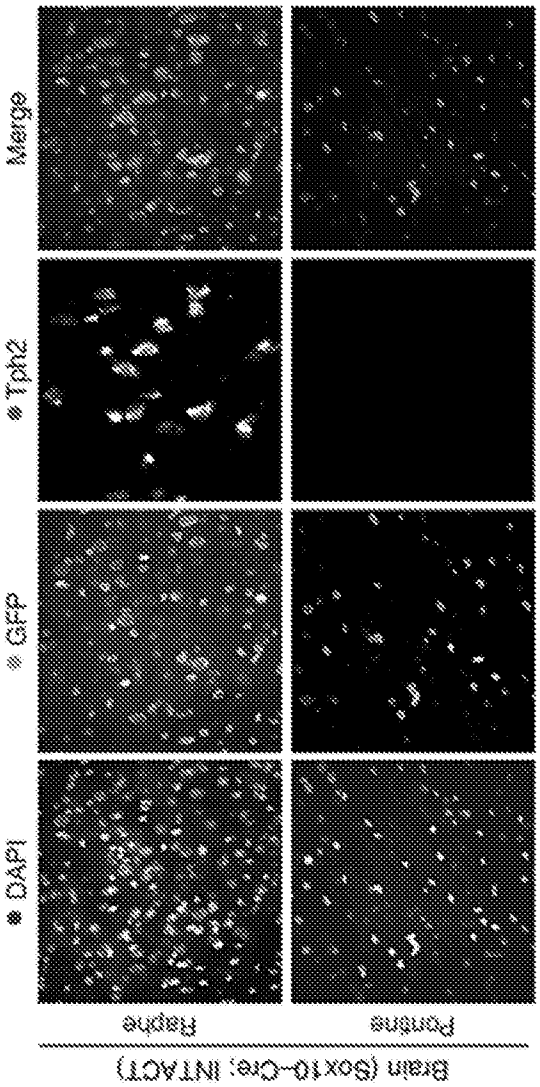


FIG. 92B

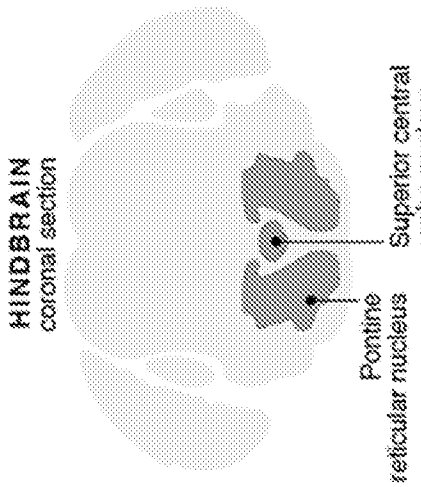


FIG. 92A

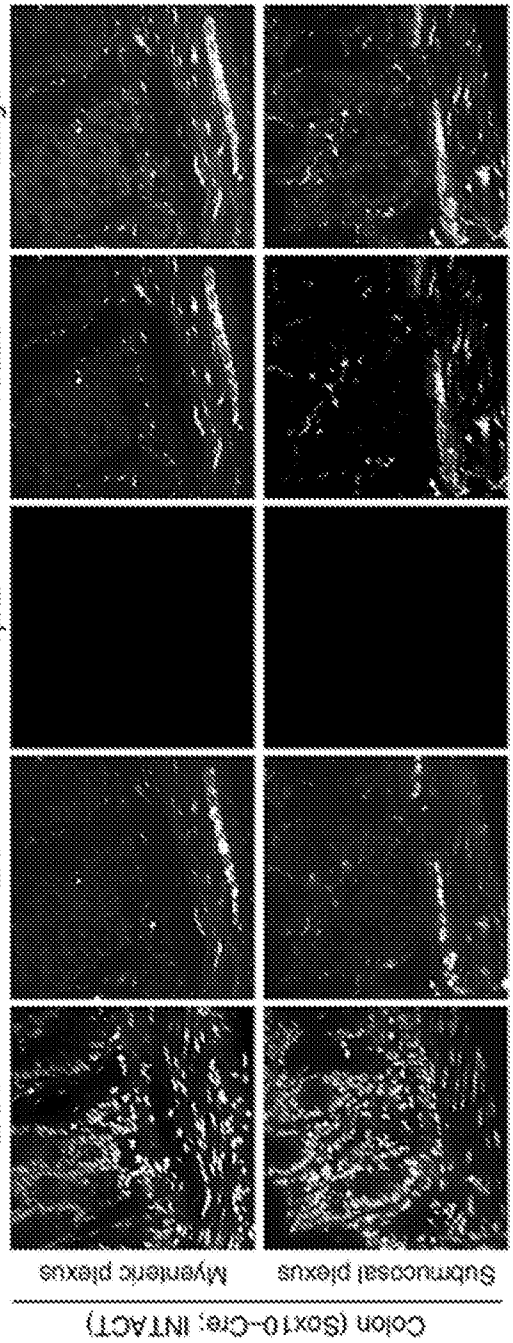


FIG. 92C

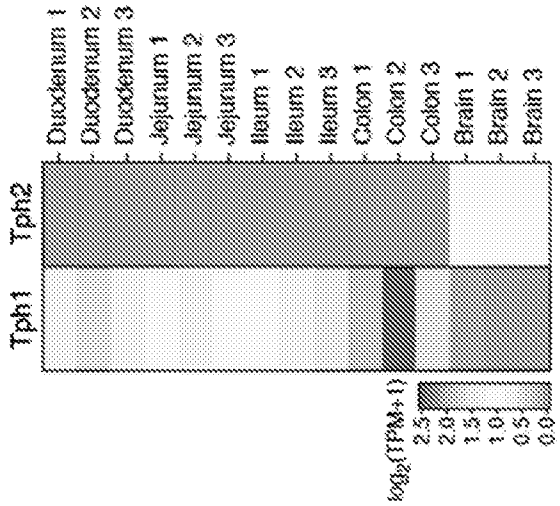


FIG. 92F

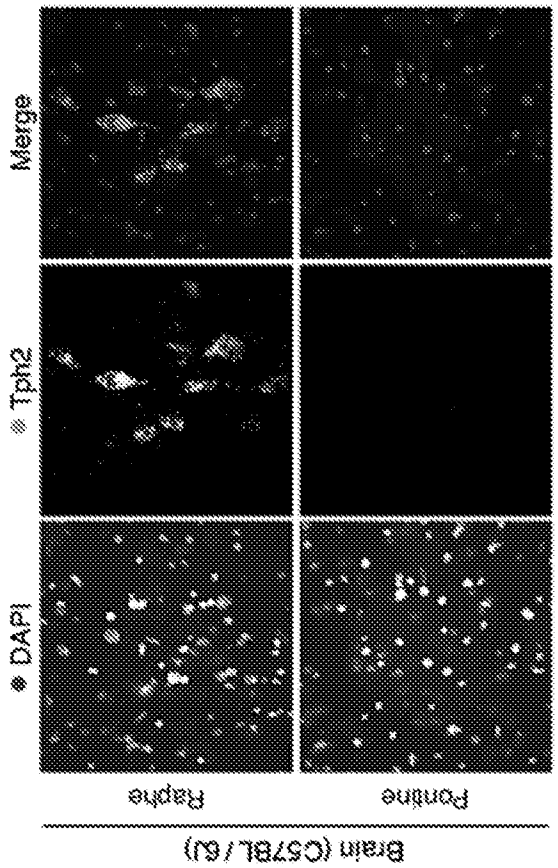


FIG. 92D

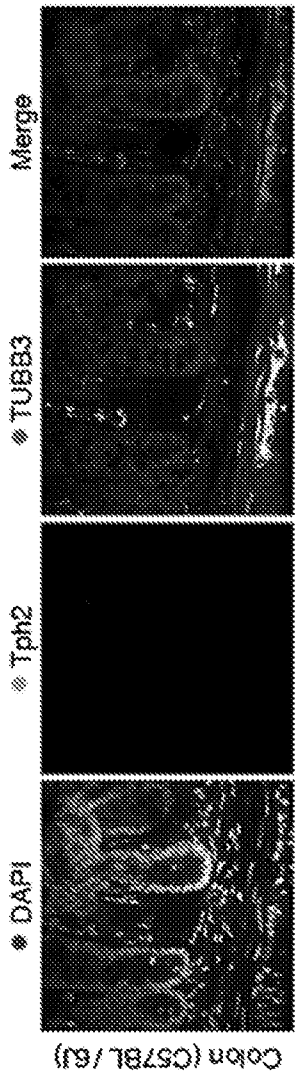


FIG. 92E

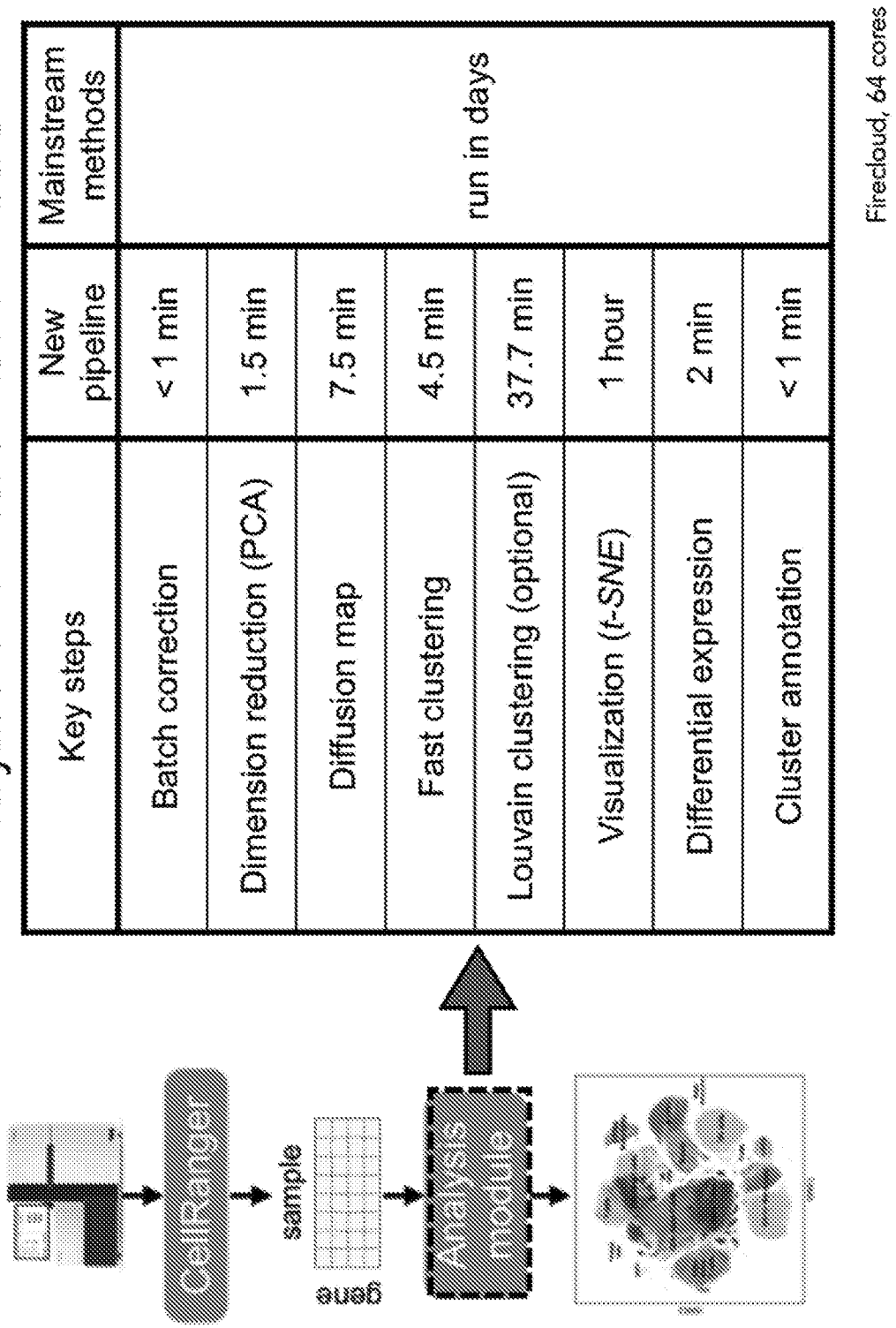

Analyzed 0.9M cells within 2 hours
Key steps
New pipeline
Mainstream methods
Batch correction
< 1 min
run in days
Dimension reduction (PCA)
1.5 min
Diffusion map
7.5 min
Fast clustering
4.5 min
Louvain clustering (optional)
37.7 min
Visualization (t-SNE)
1 hour
Differential expression
2 min
Cluster annotation
< 1 min
Firecloud, 64 cores
CellRanger
sample
gene
Analysis module

FIG. 93

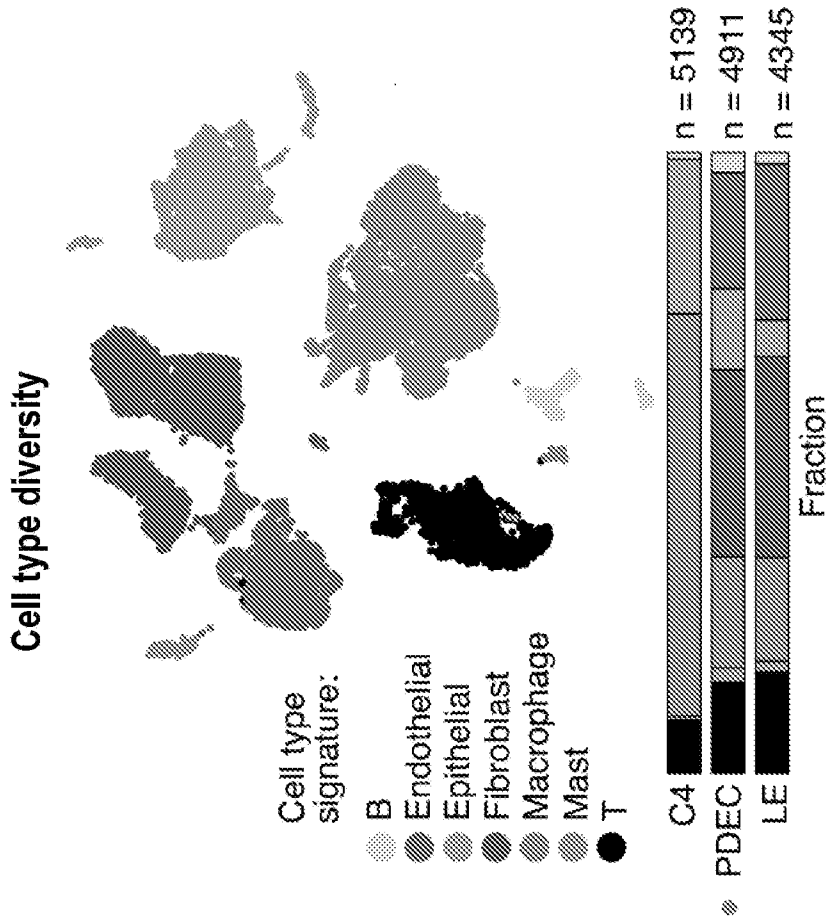


FIG. 94B

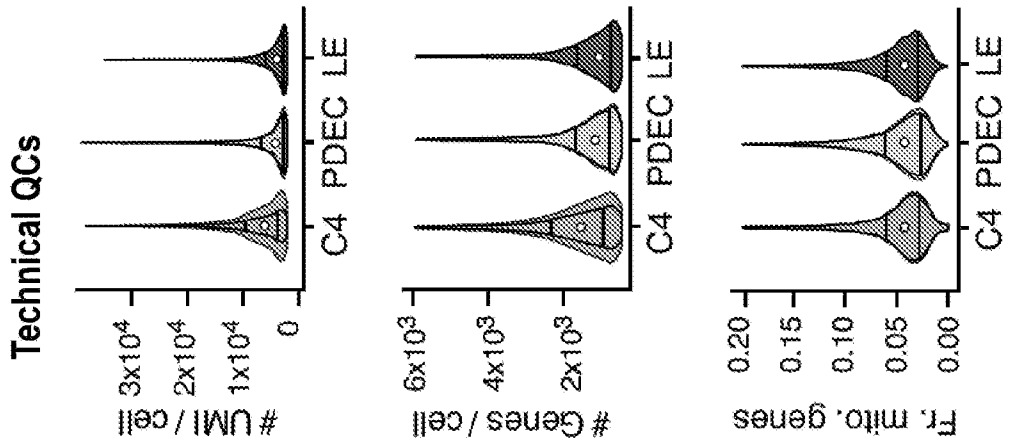


FIG. 94A

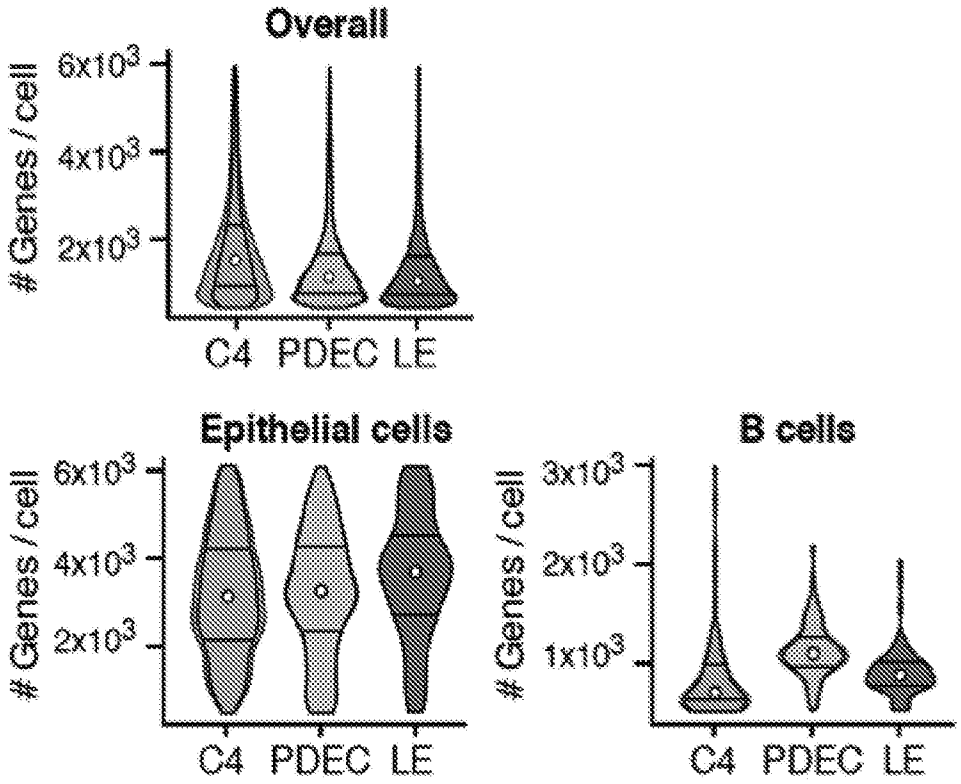

Overall
Genes / cell
6x10^3
4x10^3
2x10^3
C4 PDEC LE
Epithelial cells
Genes / cell
6x10^3
4x10^3
2x10^3
C4 PDEC LE
B cells
Genes / cell
3x10^3
2x10^3
1x10^3
C4 PDEC LE

FIG. 95

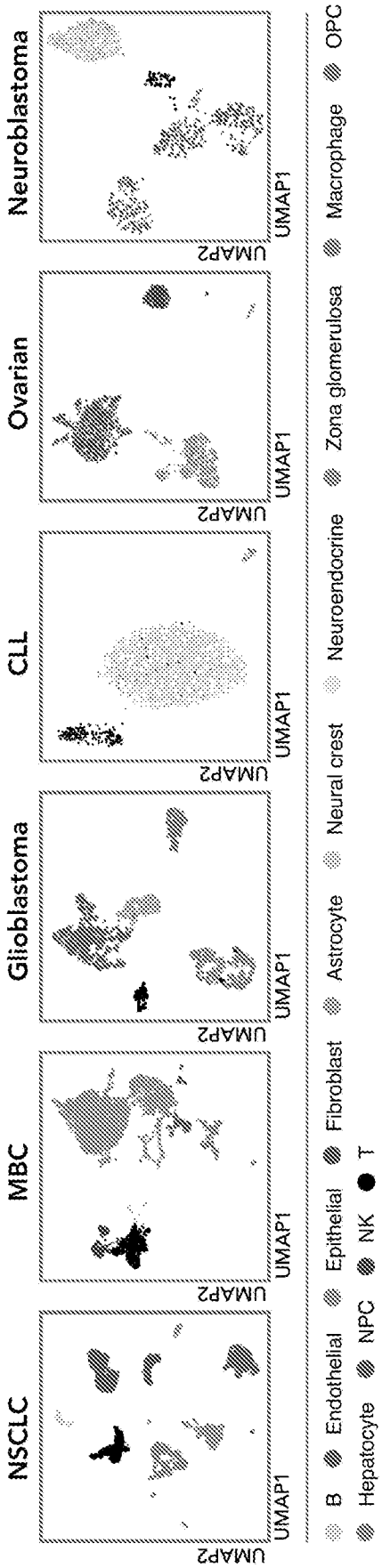

NSCLC
MBC
Glioblastoma
CLL
Ovarian
Neuroblastoma
UMAP1
UMAP2
B
Endothelial
Epithelial
Fibroblast
Astrocyte
Neural crest
Neuroendocrine
Zona glomerulosa
Macrophage
OPC
Hepatocyte
NPC
NK
T

FIG. 96

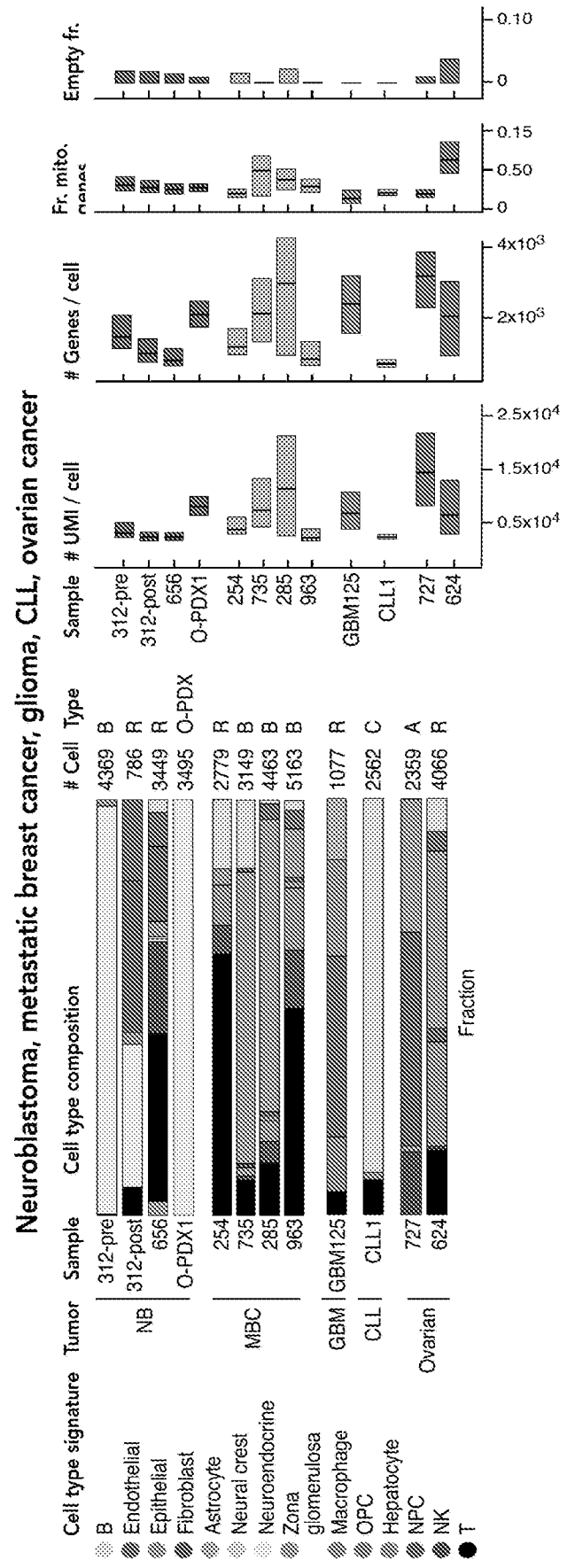

Neuroblastoma, metastatic breast cancer, glioma, CLL, ovarian cancer
Cell type signature
B
Endothelial
Epithelial
Fibroblast
Astrocyte
Neural crest
Neuroendocrine
Zona glomerulosa
Macrophage
OPC
Hepatocyte
NPC
NK
T
Tumor
NB
MBC
GBM
CLL
Ovarian
Sample
312-pre
312-post
656
O-PDX1
254
735
285
963
GBM125
CLL1
727
624
Cell type composition
Fraction
Cell
4369
786
3449
3495
2779
3149
4463
5163
1077
2562
2359
4066
Type
B
R
R
O-PDX
R
B
B
B
R
C
A
R
Sample
312-pre
312-post
656
O-PDX1
254
735
285
963
GBM125
CLL1
727
624
UMI / cell
2.5x10^4
1.5x10^4
0.5x10^4
Genes / cell
4x10^3
2x10^3
Fr. mito.
0.15
0.50
0
Empty fr.
0.10
0

FIG. 97

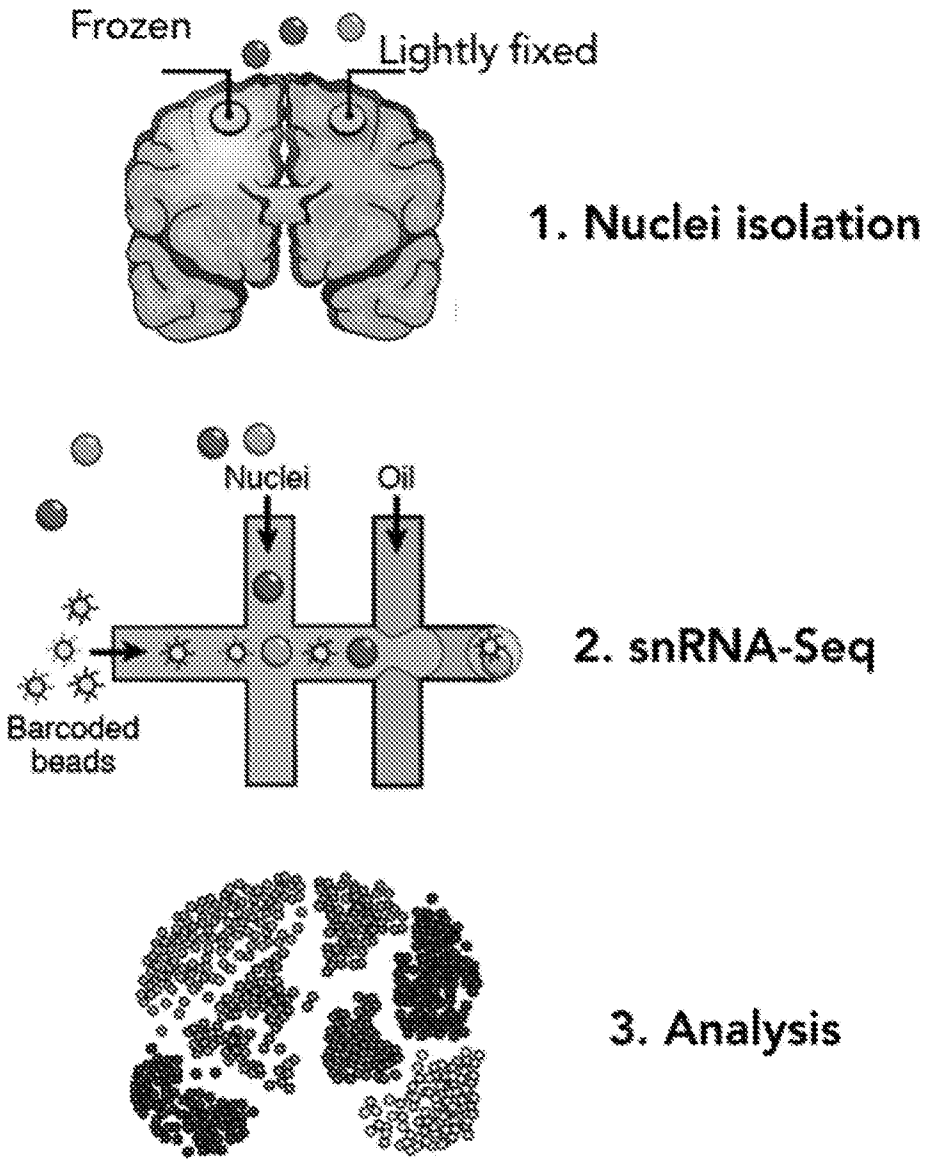

Frozen
Lightly fixed
1. Nuclei isolation
Nuclei
Oil
Barcoded beads
2. snRNA-Seq
3. Analysis

FIG. 98

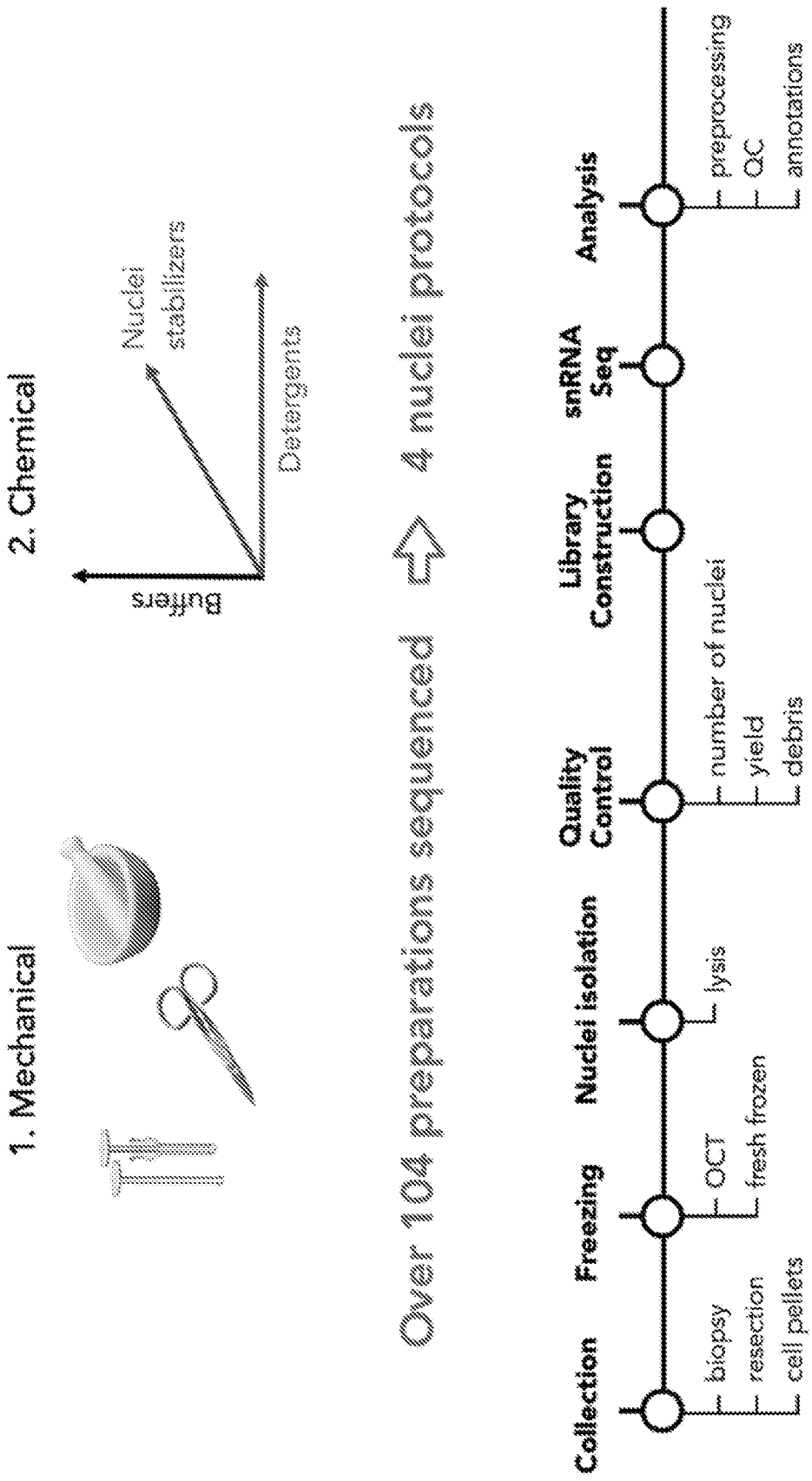

1. Mechanical
2. Chemical
Nuclei stabilizers
Detergents
Buffers
Over 104 preparations sequenced
4 nuclei protocols
Collection
biopsy
resection
cell pellets
Freezing
OCT
fresh frozen
Nuclei isolation
lysis
Quality Control
number of nuclei
yield
debris
Library Construction
snRNA Seq
Analysis
preprocessing
QC
annotations

FIG. 99

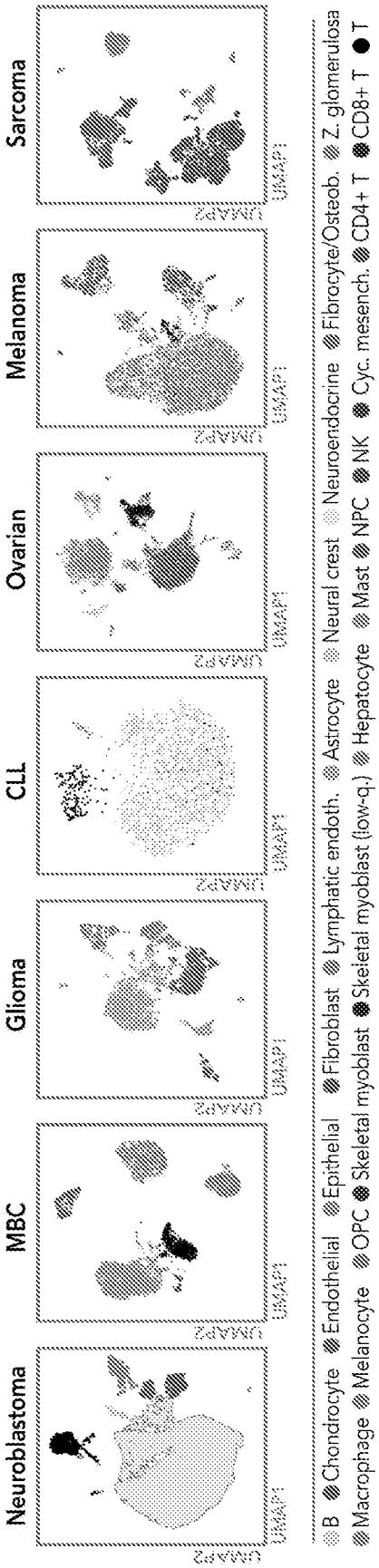
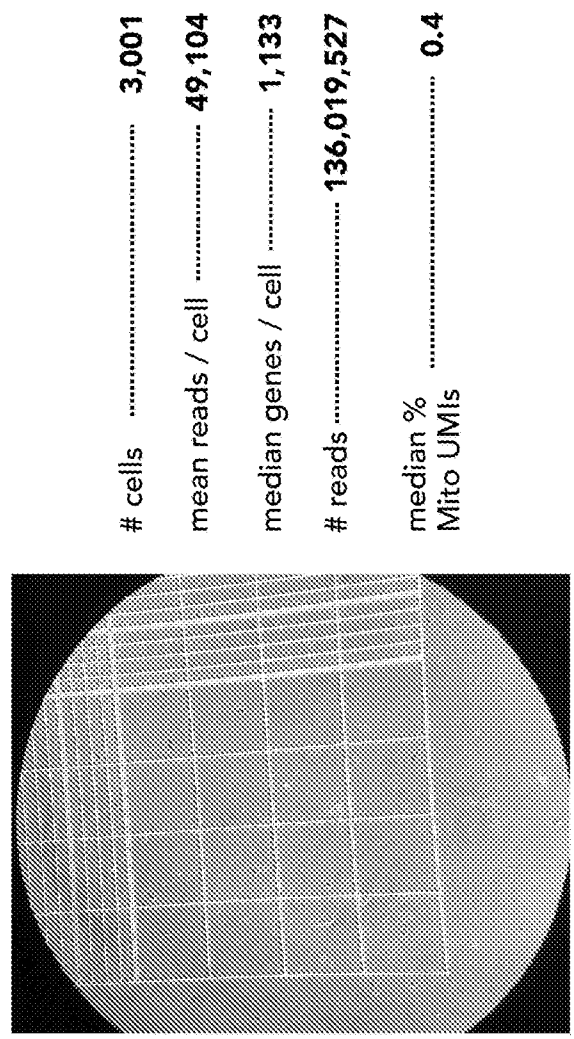

Neuroblastoma
MBC
Glioma
CLL
Ovarian
Melanoma
Sarcoma
UMAP1
UMAP2
B Chondrocyte Endothelial Epithelial Fibroblast Lymphatic endoth. Astrocyte Neural crest Neuroendocrine Fibrocyte/Osteob. Z. glomerulosa
Macrophage Melanocyte OPC Skeletal myoblast Skeletal myoblast (low-q.) Hepatocyte Mast NPC NK Cyc. mesench. CD4+ T CD8+ T T

FIG. 100



# cells	3,001
mean reads / cell	49,104
median genes / cell	1,133
# reads	136,019,527
median % Mito UMIs	0.4

FIG. 101

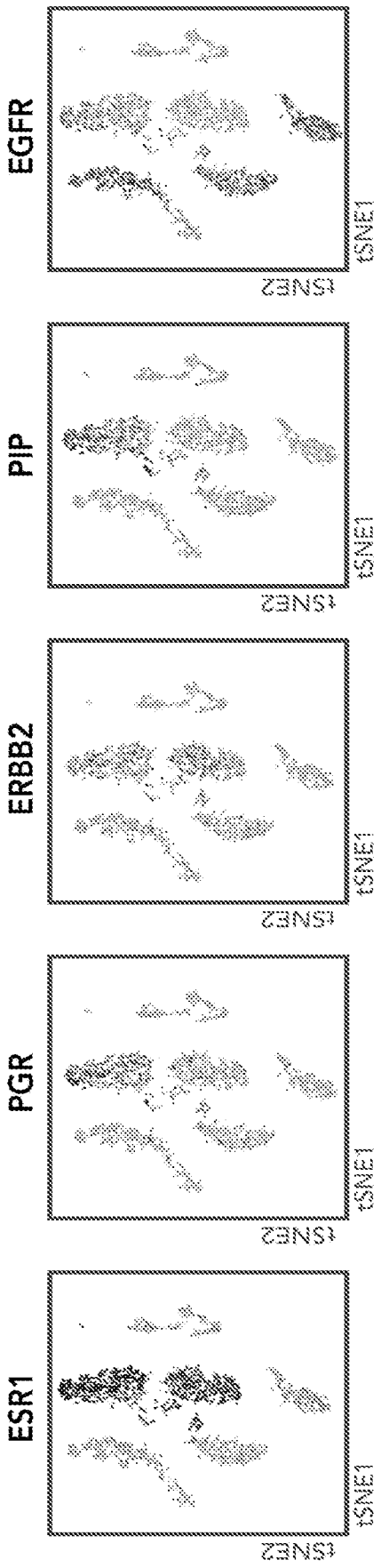

EGFR
tSNE1
tSNE2
PIP
tSNE1
tSNE2
ERBB2
tSNE1
tSNE2
PGR
tSNE1
tSNE2
ESR1
tSNE1
tSNE2

FIG. 102

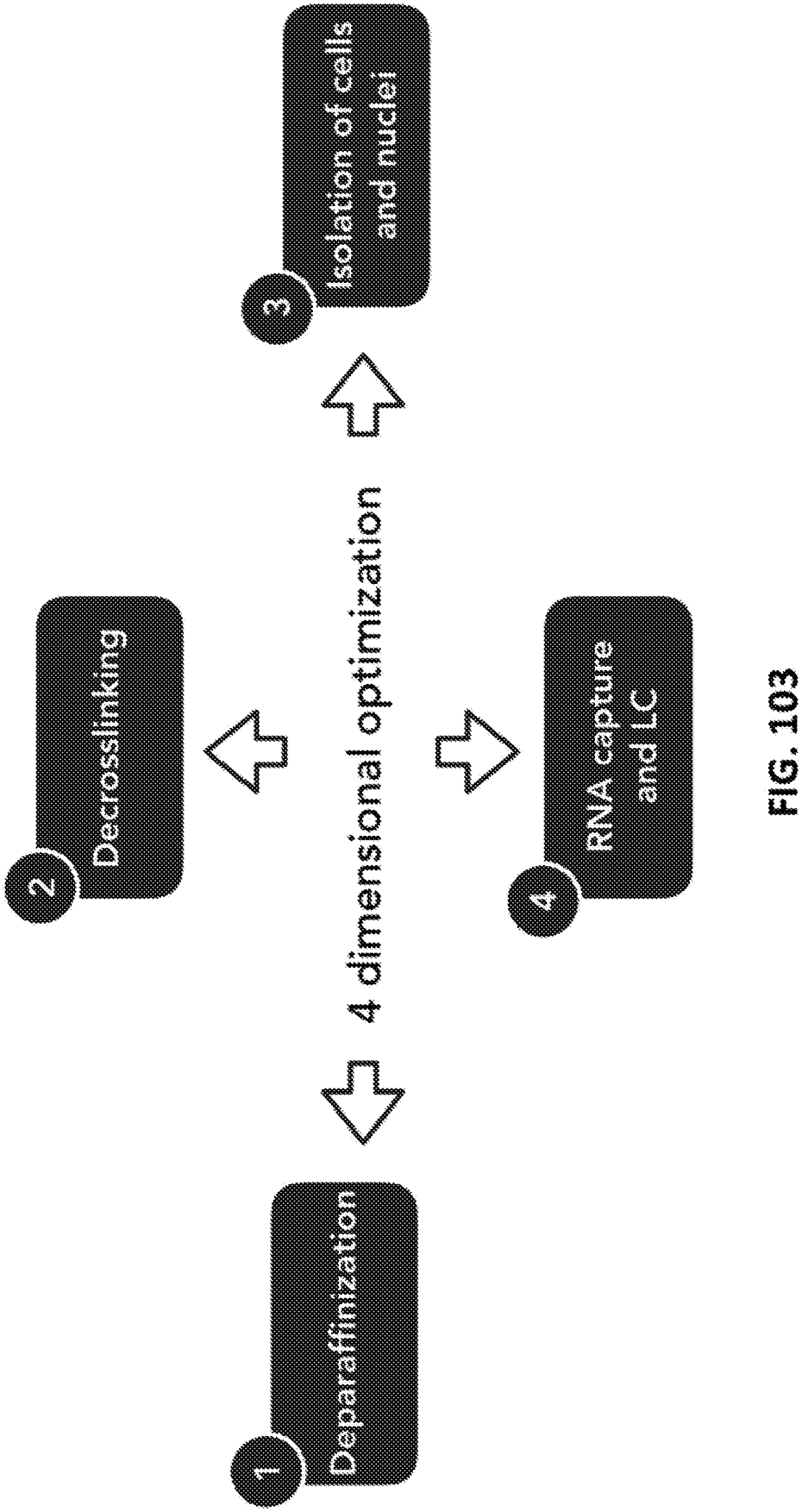

1
Deparaffinization
2
Decrosslinking
3
Isolation of cells and nuclei
4
RNA capture and LC
4 dimensional optimization

FIG. 103

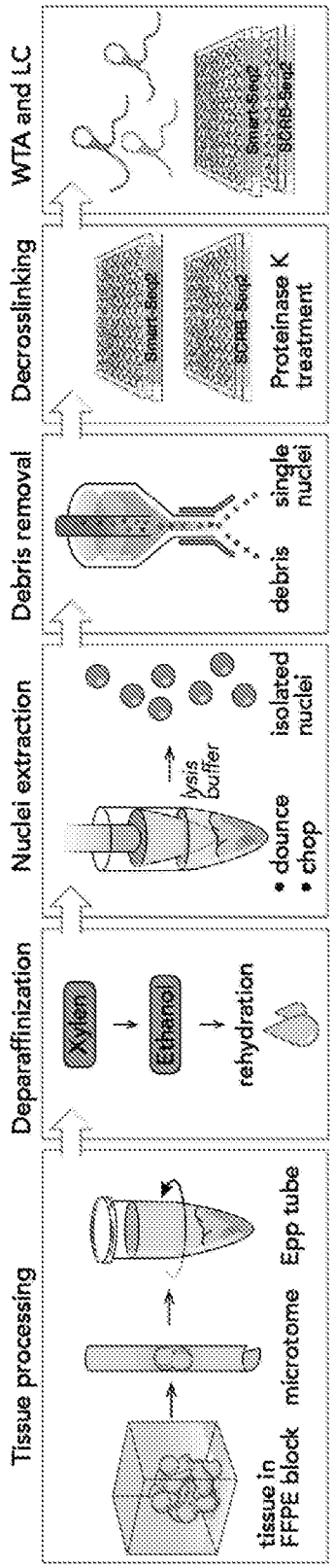

Tissue processing
tissue in FFPE block
microtome
Epp tube
Deparaffinization
Xylen
Ethanol
rehydration
Nuclei extraction
lysis buffer
• dounce
• chop
isolated nuclei
Debris removal
debris
single nuclei
Decrosslinking
Proteinase K treatment
WTA and LC

FIG. 104

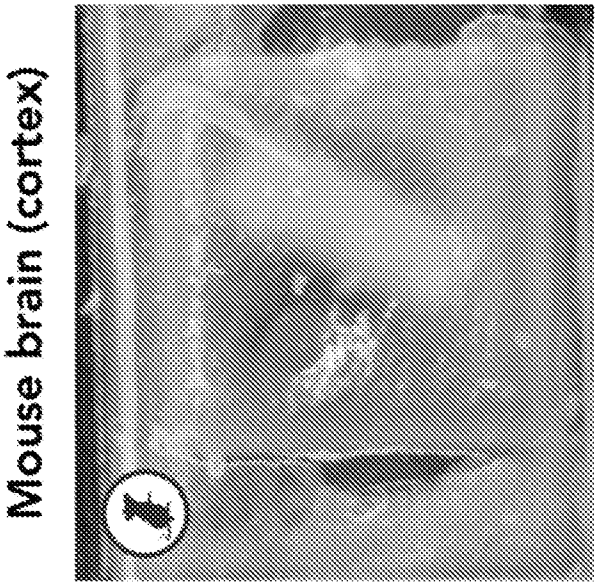


FIG. 105B

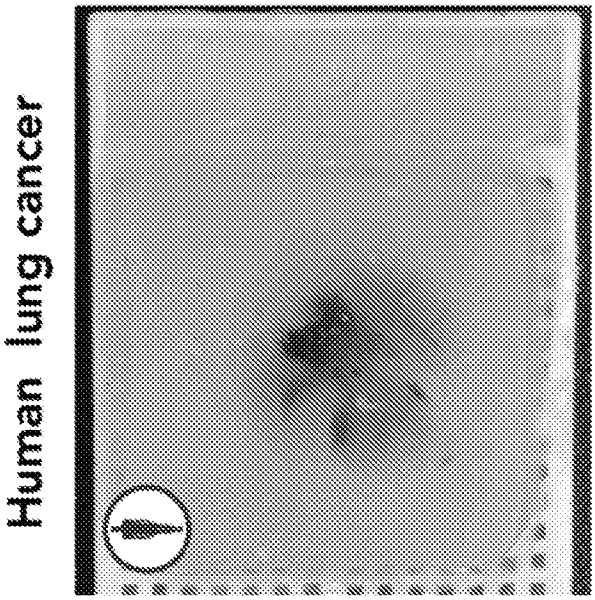


FIG. 105A

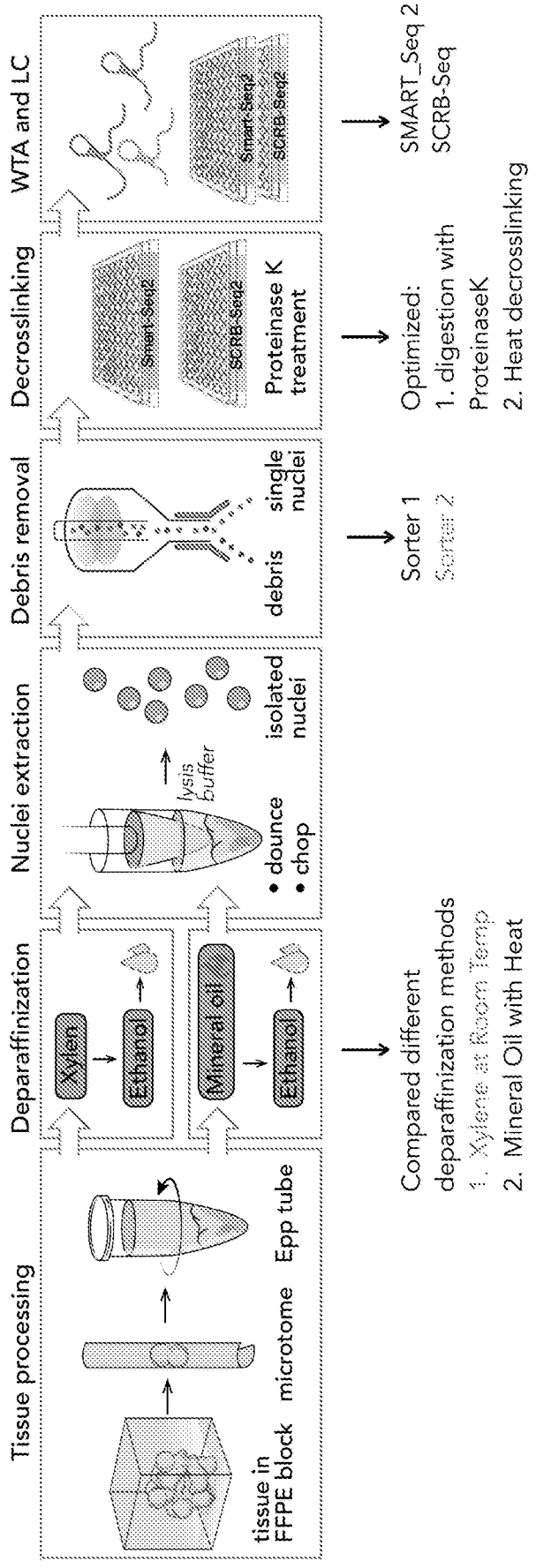

Tissue processing
Deparaffinization
Nuclei extraction
Debris removal
Decrosslinking
WTA and LC
tissue in FFPE block
microtome
Epp tube
Xylen
Ethanol
Mineral oil
Ethanol
• dounce
• chop
lysis buffer
isolated nuclei
debris
single nuclei
Smart-Seq2
SCRB-Seq2
Proteinase K treatment
Smart-Seq2
SCRB-Seq2
Compared different deparaffinization methods
1. Xylene at Room Temp
2. Mineral Oil with Heat
Sorter 1
Sorter 2
Optimized:
1. digestion with ProteinaseK
2. Heat decrosslinking
SMART_Seq 2
SCRB-Seq

FIG. 106

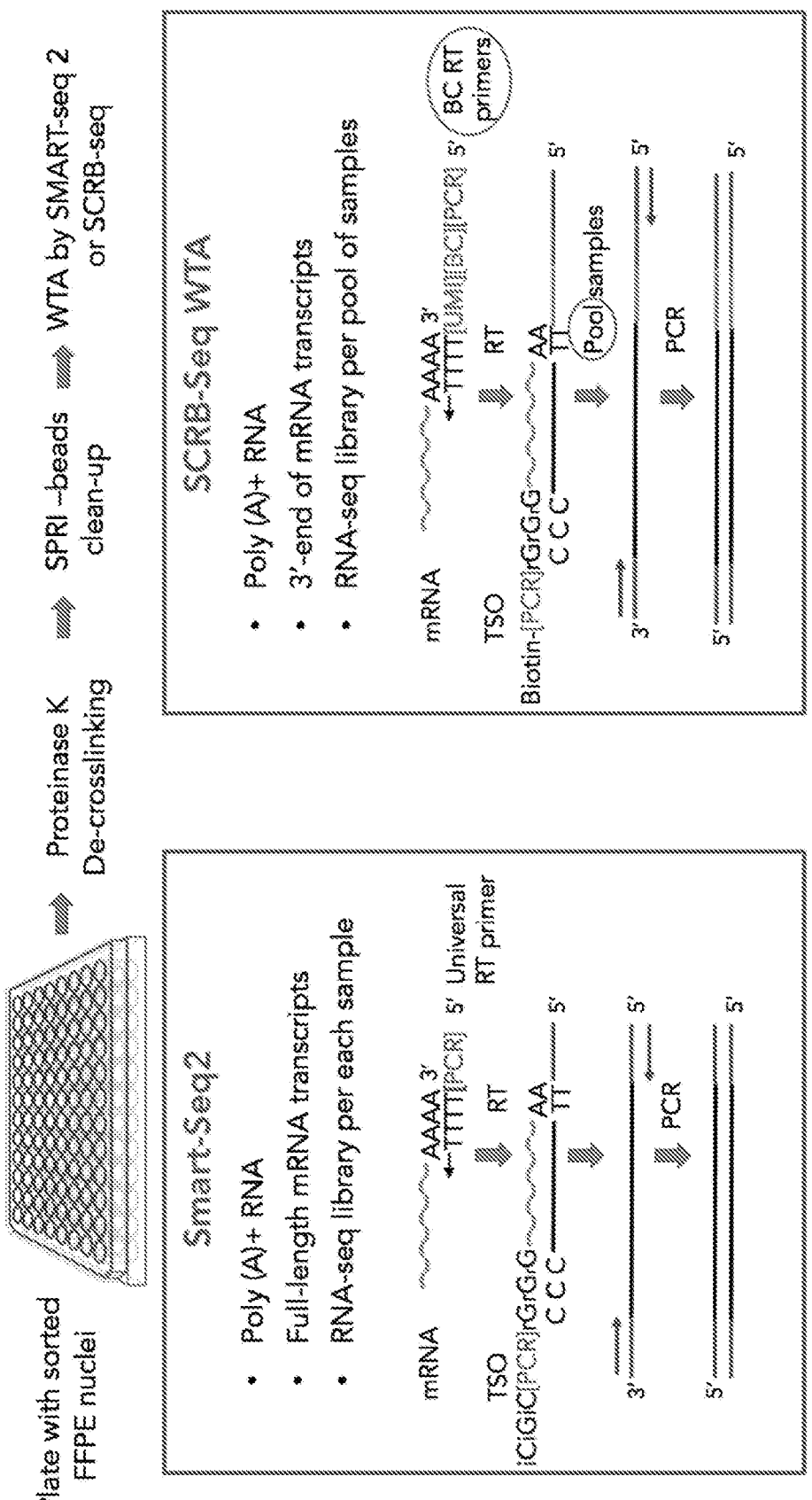


Plate with sorted FFPE nuclei
Proteinase K De-crosslinking
SPRI –beads clean-up
WTA by SMART-seq 2 or SCRB-seq
Smart-Seq2
Poly (A)+ RNA
Full-length mRNA transcripts
RNA-seq library per each sample
mRNA
AAAA 3'
TTTT[PCR]
5' Universal RT primer
TSO
iCiGiC[PCR]rGrGrG
RT
AA
TT
PCR
SCRB-Seq WTA
Poly (A)+ RNA
3'-end of mRNA transcripts
RNA-seq library per pool of samples
TTTT[UMI]BC[PCR]
BC RT primers
Biotin-[PCR]rGrGrG
Pool samples

FIG. 107

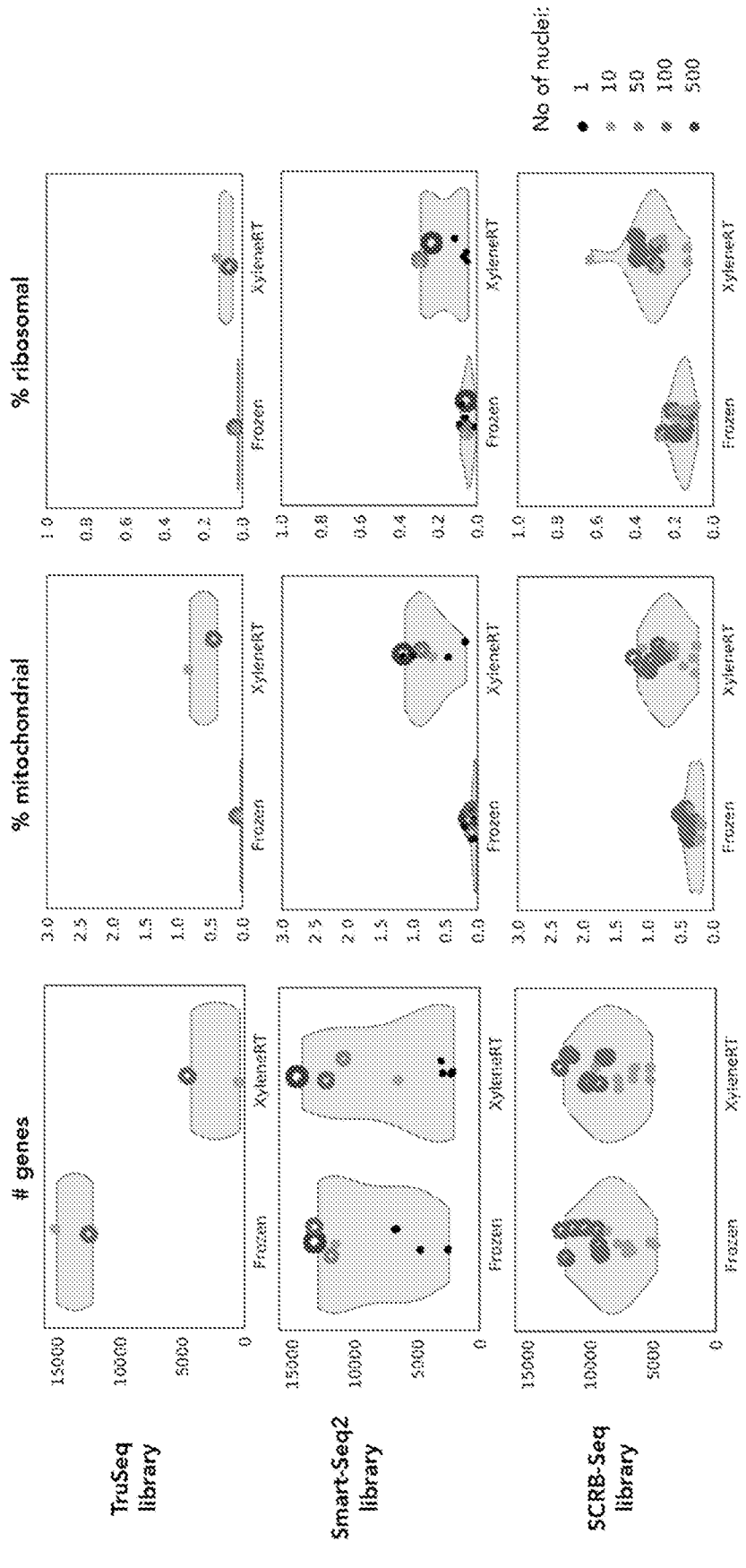

genes
% mitochondrial
% ribosomal
TruSeq library
Smart-Seq2 library
SCRB-Seq library
Frozen
XyleneRT
No of nuclei:
1
10
50
100
500

FIG. 108A

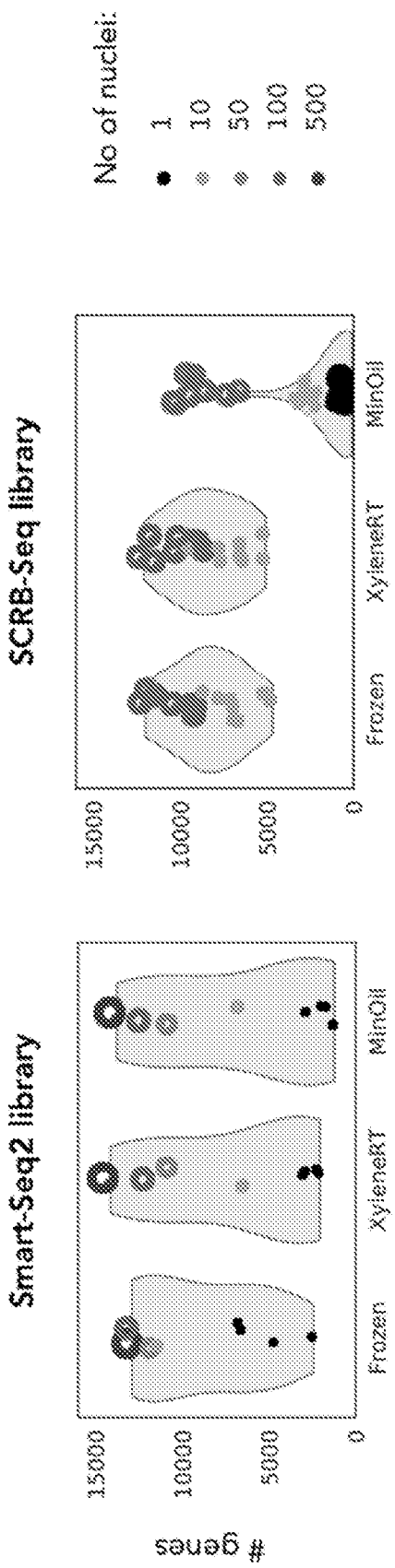

No of nuclei:
1
10
50
100
500
SCRB-Seq library
Smart-Seq2 library
genes
15000
10000
5000
0
Frozen
XyleneRT
MinOil

FIG. 108B

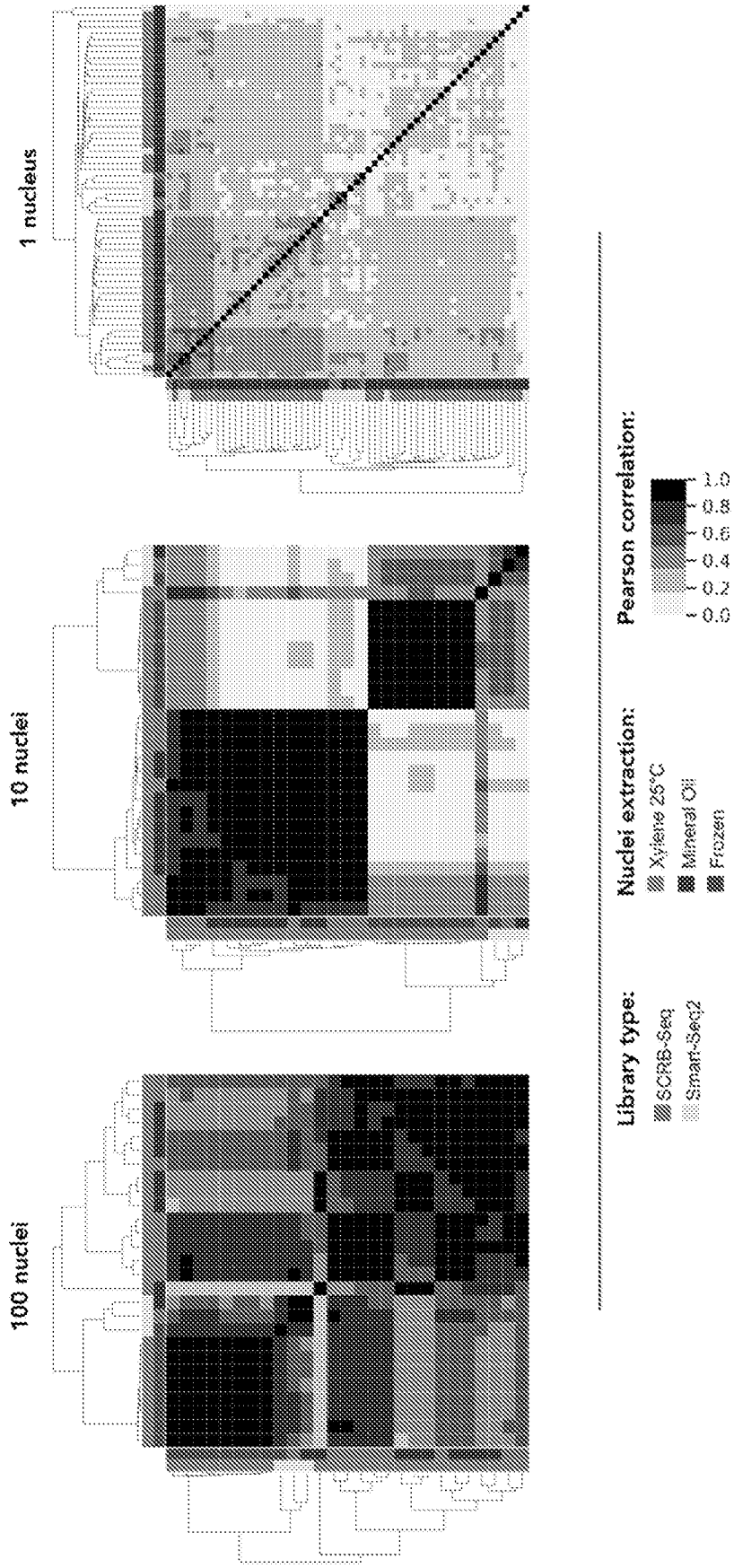

1 nucleus
10 nuclei
100 nuclei
Pearson correlation:
1.0
0.8
0.6
0.4
0.2
0.0
Nuclei extraction:
Xylene 25°C
Mineral Oil
Frozen
Library type:
SCRB-Seq
Smart-Seq2

FIG. 109

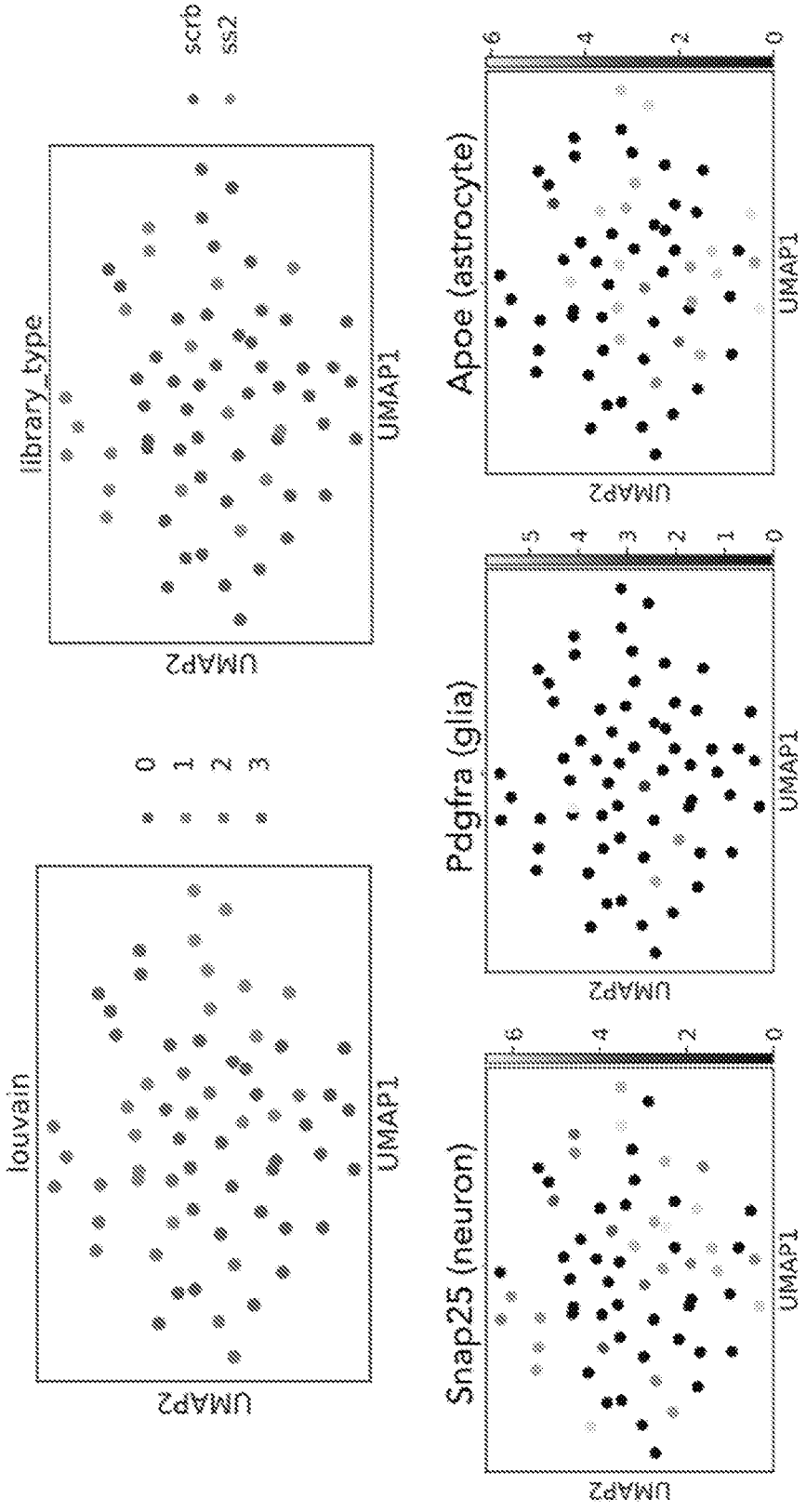

library_type
scrb
ss2
UMAP1
UMAP2
louvain
0
1
2
3
Apoe (astrocyte)
Pdgfra (glia)
Snap25 (neuron)

FIG. 110

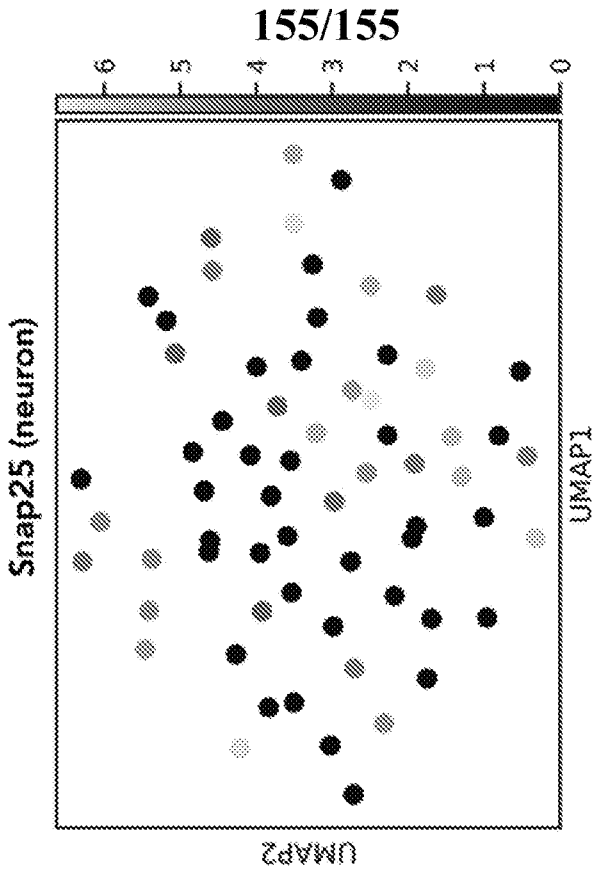


FIG. 111B

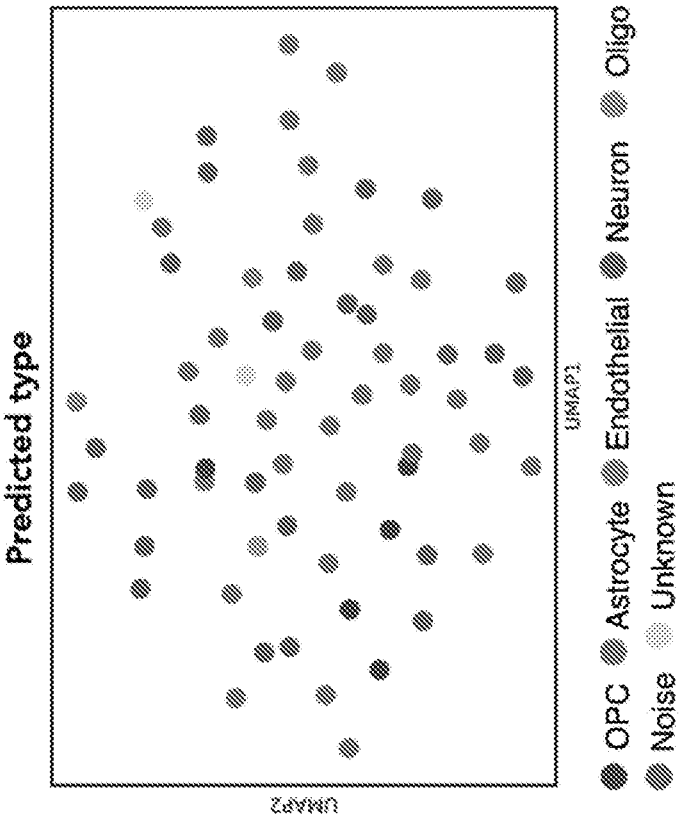


FIG. 111A

INTERNATIONAL SEARCH REPORT

International application No
PCT/US20 19/055894

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N 15/ 10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DAVID W HEDLEY ET AL: "Method for Analysis of Cellular DNA Content of Paraffin-embedded Pathological Material Using Flow Cytometry", THE JOURNAL OF HISTOCHEMISTRY AND CYTOCHEMISTRY, vol. 31, 1 January 1983 (1983-01-01), pages 1333-1335, XP055210784, DOI: 10.1177/31.11.6619538 page 1333, right-hand column, paragraph 2 ----- -/--	1-36

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) orwhich is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 2020	16/03/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Wiesner, Martina

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOÃO LOUREIRO ET AL: "Comparison of Four Nuclear Isolation Buffers for Plant DNA Flow Cytometry", ANNALS OF BOTANY., vol. 98, no. 3, 4 July 2006 (2006-07-04), pages 679-689, XP055656074, GB ISSN: 0305-7364, DOI: 10.1093/aob/mcl141 page 680, right-hand column, paragraph 3; table 2	1-36
A	LUCIANO G MARTELOTTO ET AL: "Whole-genome single-cell copy number profiling from formalin-fixed paraffin-embedded samples", NATURE MEDICINE, vol. 23, no. 3, 6 February 2017 (2017-02-06), pages 376-385, XP055655696, New York ISSN: 1078-8956, DOI: 10.1038/nm.4279 page 10, paragraph 1	1-36
A	HYYTINEN E ET AL: "IMPROVED TECHNIQUE FOR ANALYSIS OF FORMALIN-FIXED, PARAFFIN-EMBEDDED TUMORS BY FLUORESCENCE IN SITU HYBRIDIZATION", CYTOMETRY, ALAN LISS, NEW YORK, US, vol. 16, no. 2, 1 July 1994 (1994-07-01), pages 93-99, XP001094603, ISSN: 0196-4763, DOI: 10.1002/CYTO.990160202 page 94, right-hand column	1-36
A	ZONGMING FU ET AL: "Improved protein extraction and protein identification from archival formalin-fixed paraffin-embedded human aortas", PROTEOMICS - CLINICAL APPLICATIONS, vol. 7, no. 3-4, 1 April 2013 (2013-04-01) , pages 217-224, XP055656426, DE ISSN: 1862-8346, DOI: 10.1002/prca.201200064 point 2.1; page 2	1-36

-/--

1

International application No
PCT/US2019/055894

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	OKELLO J B A ET AL: "Comparison of methods in the recovery of nucleic acids from archival formalin-fixed paraffin-embedded autopsy tissues", ANALYTICAL BIOCHEMISTRY, ELSEVIER, AMSTERDAM, NL, vol. 400, no. 1, 1 May 2010 (2010-05-01), pages 110-117, XP026940236, ISSN: 0003-2697, DOI: 10.1016/J.AB.2010.01.014 [retrieved on 2010-01-15] page 111, right-hand column, paragraph 2; table 1	1-36
A	PALAK G. PATEL ET AL: "Preparation of Formalin-fixed Paraffin-embedded Tissue Cores for both RNA and DNA Extraction", JOURNAL OF VISUALIZED EXPERIMENTS, no. 114, 21 August 2016 (2016-08-21), XP055655976, DOI: 10.3791/54299 points 2 and 3 under the header protocol; page 2	1-36
A	TARA HOLLEY ET AL: "Deep Clonal Profiling of Formalin Fixed Paraffin Embedded Clinical Samples", PLOS ONE, vol. 7, no. 11, 30 November 2012 (2012-11-30), page e50586, XP055210287, DOI: 10.1371/journal.pone.0050586 page 2, left-hand column, paragraph 41 - right-hand column, paragraph 1	1-36

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/055894

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-36

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-36

A method of recovering nuclei or whole cells from a formalin-fixed paraffin-embedded (FFPE) tissue comprising:a. dissolving paraffin from a FFPE tissue sample in a solvent, preferably the solvent is selected from the group consisting of xylene and mineral oil, wherein the tissue is dissolved at a temperature between 4C to 90C, preferably room temperature (20 to 25C) for recovering whole cells and 90C for recovering nuclei;b. rehydrating the tissue using a gradient of ethanol from 100% to 0% ethanol (EtOH);c. transferring the rehydrated tissue to a volume of a first buffer comprising a buffering agent, a detergent and an ionic strength between 100mM and 200mM, optionally the first buffer comprises protease inhibitors or proteases and/or BSA;d. chopping or dounce homogenizing the tissue in the buffer; ande. removing debris by filtering and/or FACS sorting.

---

2. claims: 37-59

A method of recovering nuclei and attached ribosomes from a tissue sample comprising:a. chopping the tissue sample at between 0-4 °C in a nuclear extraction buffer comprising Tris buffer, a detergent and salts; andb. filtering the sample through a filter between 30-50 uM, preferably 40 uM, and optionally washing the filter with fresh nuclear extraction buffer,wherein the nuclei are present in the supernatant passed through the filter.

---

3. claims: 60-77, 80-82

A method of treating a disease selected from the group consisting of Hirschsprung's disease (HSCR), inflammatory bowel disease (IBD), autism spectrum disorder (ASD), Parkinson's disease (PD) and schizophrenia in a subject in need thereof or a method of modulating appetite and energy metabolism in a subject in need thereof comprising administering one or more agents capable of modulating the function or activity off:
a) one or more neurons selected from the group consisting of at least PIMN4 and PIMN5; or
b) one or more cells functionally interacting with the one or more neurons;
and a method of screening for agents capable of modulating expression of a transcription program according to Table 23 comprising:
a) administering an agent to a population of cells comprising neurons selected from the group consisting of PEMN1, PEMN2, PIMN1, PIMN2, PIMN3, PIMN4, PIMN5, PIN1, PIN2,

PSN and PSVN; and
b) detecting expression of one or more genes in the transcriptional program.

---

4. claims: 78, 79

A method of detecting one or more cells of the enteric nervous system (ENS) comprising detecting one or more markers according to Table 14-17 or Table 20-22.

---

5. claims: 83-86

A method of identifying gene expression in single cells comprising providing sequencing reads from a single nucleus sequencing library and counting sequencing reads mapping to introns and exons.
