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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 October 2012 (11.10.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/138783 A3

(51) International Patent Classification:
C12Q 1/68 (2006.01)

(21) International Application Number:
PCT/US2012/032202

(22) International Filing Date:
4 April 2012 (04.04.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/471,601	4 April 2011 (04.04.2011)	US
61/472,165	5 April 2011 (05.04.2011)	US
61/610,349	13 March 2012 (13.03.2012)	US

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(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, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, 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, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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, ML, MR, NE, SN, TD, TG).

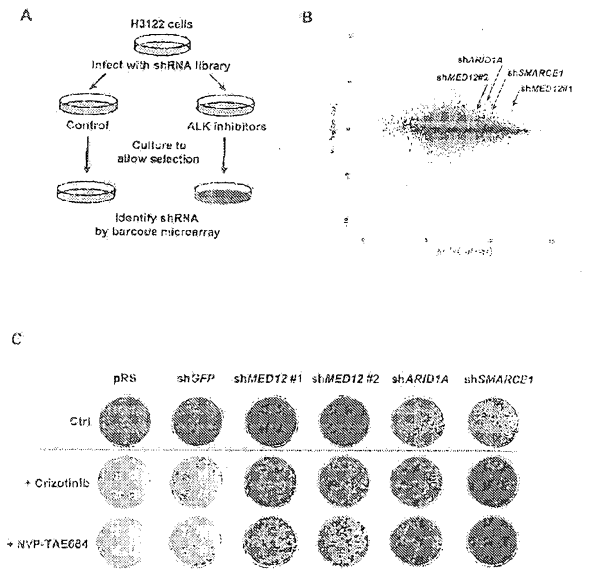
Published:

— *with international search report (Art. 21(3))*

[Continued on next page]

(54) **Title**: METHODS AND COMPOSITIONS FOR PREDICTING RESISTANCE TO ANTICANCER TREATMENT WITH PROTEIN KINASE INHIBITORS

Fig 1



(57) **Abstract**: The instant application provides methods and related compositions pertaining to the identification of resistance to anticancer treatment in a patient. In a particular embodiment, the invention provides biomarkers for the identification of resistance to anticancer treatment in a lung cancer patient, wherein a reduced expression of a MEDIATOR and/or SW1/SNF complex gene in the lung cancer cells of the patient indicates that the lung cancer cells in the patient may be resistant to treatment with a receptor tyrosine kinase inhibitor, such as gefitinib and/or erlotinib. In some embodiments, the invention relates to methods and related compositions for predicting resistance to anticancer treatment by detecting the expression levels of one or more TGF-beta pathway nucleic acids and/or proteins.

WO 2012/138783 A3

(88) Date of publication of the international search report:
14 March 2013

TITLE OF THE INVENTION

METHODS AND COMPOSITIONS FOR PREDICTING RESISTANCE TO ANTICANCER TREATMENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority of U.S. Provisional Application Serial No. 61/471,601 filed April 4, 2011; U.S. Provisional Application Serial No. 61/472,165, filed April 5, 2011; and U.S. Provisional Application Serial No. 61/610,349 filed March 13, 2012, which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The invention relates to the field of methods and related compositions for predicting resistance to anticancer treatment. In certain embodiments, the invention relates to the field of methods and related compositions for predicting resistance to anticancer treatment in a cancer patient by detecting a reduced expression level of a SWI/SNF complex and/or MEDIATOR complex and/or RAS-GAP gene and/or protein in one or more cancer cells of the patient. In other embodiments, the invention relates to the field of methods and related compositions for predicting resistance to anticancer treatment by detecting one or more inactivating mutations in a SWI/SNF complex and/or MEDIATOR complex and/or RAS-GAP gene. In some embodiments, the invention relates to the field of methods and related compositions for predicting resistance to anticancer treatment by detecting dysfunction and/or inactivity of one or more SWI/SNF complex and/or MEDIATOR complex and/or RAS-GAP proteins. In some embodiments, the invention relates to the field of methods and related compositions for predicting resistance to anticancer treatment by detecting the expression levels of one or more TGF-beta pathway nucleic acids and/or proteins.

BACKGROUND OF THE INVENTION

Activation of signaling pathways in cancer is often the result of genomic alterations (mutations, translocations, copy number gains and/or losses) in key components of these pathways. Cancer cells often depend on the continued presence of the signals that emanate from these genomic alterations and sudden inhibition frequently results in death of the cancer cells, a phenomenon coined "oncogene addiction" (Sharma and Settleman, 2007). The presence of specific changes in the genomes of cancer cells can therefore have strong

predictive value for responsiveness to therapies that target these mutations (Pao and Chmielecki).

Such drug response biomarkers are urgently needed for the rational selection of patients for these therapies, as their clinical benefit is often limited due to the fact that only a subset of patients responds. Considering the high cost of targeted therapeutics, response biomarkers are not only a clinical necessity, but also an economic requirement to keep the cost of cancer care in check by reducing the number of patients that receive expensive drugs without experiencing therapeutic benefit.

Lung cancer is a leading cause of cancer deaths worldwide and tobacco smoking remains the major risk factor. Genomic alterations of receptor tyrosine kinases are frequently found in non-small cell lung cancers, the predominant histological subtype, and are particularly enriched (~40%) in non-smokers (Rudin et al., 2009). Lung cancers with activating mutations of the *EGFR* (epidermal growth factor receptor) respond well to treatment with EGFR inhibitors (gefitinib and erlotinib) in the clinic and constitute the largest subgroup of patients (~10%-20%) tractable for an effective tyrosine kinase inhibitor therapy (Lynch et al., 2004; Maemondo et al.; Rosell et al., 2009; Sharma et al., 2007). Recently, EML4-ALK translocations were identified in ~2%-5% of NSCLC providing a second promising molecular target for the treatment of NSCLC (Soda et al., 2007). The fusion of the N-terminal part of EML4 (echinoderm microtubule associated protein like 4) with the C-terminal kinase domain of ALK (anaplastic large cell lymphoma kinase) results in the stable dimerization and constitutive activation of the EML4-ALK fusion kinase. The dual tyrosine kinase inhibitor crizotinib potently inhibits ALK/MET and is currently evaluated in clinical trials. The first phase I study with crizotinib in EML4-ALK positive advanced NSCLC demonstrated remarkable activity (Kwak et al.).

Despite these encouraging clinical results, lung cancers with EGFR mutations or EML4-ALK translocations do not respond equally well to these inhibitors (primary resistance) and all tumors develop resistance (acquired resistance) under prolonged treatment (Jackman et al.). Several acquired resistance mechanisms were identified in pre-clinical studies and also confirmed in specimens from relapsed patients that initially responded well to EGFR or ALK inhibitor treatment. Second site mutations of the EGFR ($EGFR^{T790M}$) and MET amplifications account for ~50% of the cases of acquired resistance to EGFR inhibitors (Engelman et al., 2007; Hammerman et al., 2009; Kobayashi et al., 2005). The $EGFR^{T790M}$ gatekeeper mutation prevents binding of the inhibitors to the kinase domain, but preserves the

activity of the kinase. The frequency of EML4-ALK second site mutations in relapsed tumors is currently unknown and was only found in a single case so far (Choi et al.).

Nevertheless, in a large number of cases the mechanism of resistance to EGFR or ALK inhibitors remains unknown and in particular the determinants of primary resistance are obscure. Understanding the relevant genes and signaling pathways that contribute to resistance of NSCLC cells to tyrosine kinase inhibitors might not only provide drug response markers to stratify treatment options, but might also delineate new therapeutic strategies to overcome the drug resistance.

Citation or identification of any document in this application is not an admission that such document is available as prior art to the present invention.

SUMMARY OF THE INVENTION

In certain embodiments, the invention provides a method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising (a) measuring expression levels of one or more SWI/SNF complex and/or MEDIATOR complex nucleic acid and/or proteins in the patient; and (b) comparing the expression levels of the one or more SWI/SNF complex and/or MEDIATOR complex nucleic acid and/or proteins in (a) with the expression levels of one or more reference SWI/SNF complex and/or MEDIATOR complex nucleic acid and/or proteins, wherein the one or more reference SWI/SNF complex and/or MEDIATOR complex nucleic acid and/or proteins are from a control sample, wherein a reduction in the expression of the one or more SWI/SNF complex and/or MEDIATOR complex nucleic acid and/or proteins in comparison to the one or more reference SWI/SNF complex and/or MEDIATOR complex nucleic acid and/or proteins is indicative of resistance to anticancer treatment in the patient.

In other embodiments, the invention provides a method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising (a) isolating nucleic acid from the patient, wherein the nucleic acid comprises one or more SWI/SNF complex and/or MEDIATOR complex DNA and/or RNA; and (b) analyzing the nucleic acid of (a) for the presence of one or more inactivating mutations in the SWI/SNF complex and/or MEDIATOR complex DNA and/or RNA, wherein the presence of one or more inactivating mutations in the one or more SWI/SNF complex and/or MEDIATOR complex DNA and/or RNA analyzed in (b) is indicative of resistance to anticancer treatment in the patient.

In some embodiments, the invention relates to a method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising (a) isolating protein from the patient, wherein the protein comprises one or more SWI/SNF complex and/or MEDIATOR complex proteins (b) analyzing the activity of the one or more SWI/SNF complex and/or MEDIATOR complex proteins in (a); and (c) comparing the activity of the one or more SWI/SNF complex and/or MEDIATOR complex proteins in (b) with the activity of one or more reference SWI/SNF complex and/or MEDIATOR complex proteins, wherein a difference in activity of the one or more SWI/SNF complex and/or MEDIATOR complex proteins from (b) in comparison to the one or more SWI/SNF complex and/or MEDIATOR complex reference proteins in (c) is indicative of resistance to anticancer treatment in the patient.

In certain embodiments, the expression levels of one or more SWI/SNF complex nucleic acids (e.g., DNA, RNA) and/or proteins are measured.

In certain embodiments, the expression levels of one or more MEDIATOR complex nucleic acids (e.g., DNA, RNA) and/or proteins are measured.

In some embodiments, the invention provides a method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising (a) measuring expression levels of one or more RAS-GAP nucleic acid and/or proteins in the patient; and (b) comparing the expression levels of the one or more RAS-GAP nucleic acid and/or proteins in (a) with the expression levels of one or more reference RAS-GAP nucleic acid and/or proteins, wherein the one or more reference RAS-GAP nucleic acid and/or proteins are from a control sample, wherein a reduction in the expression of the one or more RAS-GAP nucleic acid and/or proteins in comparison to the one or more reference RAS-GAP nucleic acid and/or proteins is indicative of resistance to anticancer treatment in the patient.

In other embodiments, the invention provides a method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising (a) isolating nucleic acid from the patient, wherein the nucleic acid comprises one or more RAS-GAP DNA and/or RNA; and (b) analyzing the nucleic acid of (a) for the presence of one or more inactivating mutations in the RAS-GAP DNA and/or RNA, wherein the presence of one or more inactivating mutations in the one or more RAS-GAP DNA and/or RNA analyzed in (b) is indicative of resistance to anticancer treatment in the patient.

In yet other embodiments, the invention provides a method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising (a)

isolating protein from the patient, wherein the protein comprises one or more RAS-GAP proteins; (b) analyzing the activity of the one or more RAS-GAP proteins in (a); and (c) comparing the activity of the one or more RAS-GAP proteins in (b) with the activity of one or more reference RAS-GAP proteins, wherein a difference in activity of the one or more RAS-GAP proteins from (b) in comparison to the one or more RAS-GAP reference proteins in (c) is indicative of resistance to anticancer treatment in the patient.

In some embodiments the expression levels of one or more RAS-GAP nucleic acids (e.g., DNA, RNA) are measured. In other embodiments, the expression levels of one or more RAS-GAP proteins are measured.

In some embodiments of the methods described herein for evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, the patient has lung cancer (e.g., non-small-cell lung cancer), breast cancer, ovarian cancer, lung cancer, head and neck cancer, bladder cancer, colorectal cancer, cervical cancer, mesothelioma, solid tumors, renal cell carcinoma, stomach cancer, sarcoma, prostate cancer, melanoma, thyroid cancer, brain cancer, adenocarcinoma, glioma, glioblastoma, esophageal cancer, neuroblastoma, and/or lymphoma.

In some embodiments, the resistance to anticancer treatment is resistance to treatment with a receptor tyrosine kinase inhibitor. Examples of receptor tyrosine kinase inhibitors include gefitinib, erlotinib, EKB-569, lapatinib, CI-1033, cetuximab, panitumumab, PKI-166, AEE788, sunitinib, sorafenib, dasatinib, nilotinib, pazopanib, vandetaniv, cediranib, afatinib, motesanib, CUDC-101, imatinib mesylate, crizotinib, ASP-3026, LDK378, AF802, and CEP37440.

In some embodiments, the resistance to anticancer treatment is resistance to treatment with an inhibitor of ERK activation. In certain embodiments, the inhibitor of ERK activation inhibits a cellular protein that interacts directly with ERK. In other embodiments, the inhibitor of ERK activation inhibits a cellular protein that interacts indirectly with ERK. In yet other embodiments, the inhibitor of ERK activation is a receptor tyrosine kinase inhibitor.

Examples of SWI/SNF complex nucleic acids and/or proteins include ARID1A, ARID1B, ARID2, SMARCA2, SMARCA4, PBRM1, SMARCC2, SMARCC1, SMARCD1, SMARCD2, SMARCD3, SMARCE1, ACTL6A, ACTL6B, and SMARCB1.

Examples of MEDIATOR complex nucleic acids and/or proteins include MED22, MED11, MED17, MED20, MED30, MED19, MED18, MED8, MED6, MED28, MED9, MED21, MED4, MED7, MED31, MED10, MED1, MED26, MED2, MED3, MED25,

MED23, MED5, MED14, MED16, MED15, CycC, CDK8, MED13, MED12, MED12L, and MED13L.

Examples of RAS-GAP nucleic acids and/or proteins include DAB2IP, NF1, and RASAL3.

In some embodiments, analyzing nucleic acid comprises sequencing the nucleic acid. In other embodiments, analyzing nucleic acid comprises subjecting the nucleic acid to MLPA. In yet other embodiments, analyzing nucleic acid comprises subjecting the nucleic acid to CGH. In certain embodiments, analyzing nucleic acid comprises subjecting the nucleic acid to FISH.

In certain embodiments, an inactivating mutation is selected from the group consisting of: point mutations, translocations, amplifications, deletions, and hypomorphic mutations.

In certain embodiments, nucleic acid in a method of the invention comprises one or more SWI/SNF complex genes. In other embodiments, the nucleic acid comprises one or more MEDIATOR complex genes. In yet other embodiments, the nucleic acid comprises one or more RAS-GAP genes.

In certain embodiments, one or more SWI/SNF complex and/or MEDIATOR complex proteins analyzed are inactive. In further embodiments, the one or more SWI/SNF complex and/or MEDIATOR complex proteins are inactive due to one or more posttranslational modifications. In some embodiments, one or more RAS-GAP proteins analyzed are inactive. In further embodiments, the one or more RAS-GAP proteins are inactive due to one or more posttranslational modifications

In some embodiments, the invention relates to a microarray comprising a plurality of polynucleotide probes each complementary and hybridizable to a sequence in a different gene that is a SWI/SNF complex gene that is a marker for resistance to anticancer treatment in a patient that has cancer.

In other embodiments, the invention relates to a microarray comprising a plurality of polynucleotide probes each complementary and hybridizable to a sequence in a different gene that is a MEDIATOR complex gene that is a marker for resistance to anticancer treatment in a patient that has cancer.

In some embodiments, the invention relates to a microarray comprising a plurality of polynucleotide probes each complementary and hybridizable to a sequence in a different gene that is a SWI/SNF complex and/or MEDIATOR complex gene that is a marker for resistance to anticancer treatment in a patient that has cancer.

In other embodiments, the invention relates to a microarray comprising a plurality of polynucleotide probes each complementary and hybridizable to a sequence in a different gene that is a RAS-GAP gene that is a marker for resistance to anticancer treatment in a patient that has cancer.

In certain embodiments, a microarray of the invention comprises a plurality of probes, wherein the plurality of probes is at least 70 %, at least 80 %, at least 90 %, at least 95 %, or at least 98 % of the probes on the microarray.

In certain embodiments, in a microarray of the invention, the SWI/SNF complex gene that is a marker for resistance to anticancer treatment is selected from the group consisting of ARID1A, ARID1B, ARID2, SMARCA2, SMARCA4, PBRM1, SMARCC2, SMARCC1, SMARCD1, SMARCD2, SMARCD3, SMARCE1, ACTL6A, ACTL6B, and SMARCB1.

In other embodiments, in a microarray of the invention, the MEDIATOR complex gene that is a marker for resistance to anticancer treatment is selected from the group consisting of MED22, MED11, MED17, MED20, MED30, MED19, MED18, MED8, MED6, MED28, MED9, MED21, MED4, MED7, MED31, MED10, MED1, MED26, MED2, MED3, MED25, MED23, MED5, MED14, MED16, MED15, CycC, CDK8, MED13, MED12, MED13L, and MED12L.

In still other embodiments, in a microarray of the invention, the RAS-GAP gene is selected from the group consisting of: DAB2IP, NF1, and RASAL3.

In some embodiments, the invention relates to a kit, comprising at least one pair of primers specific for a SWI/SNF complex gene that is a marker for resistance to anticancer treatment in a patient that has cancer, at least one reagent for amplification of the SWI/SNF complex gene, and instructions for use.

In other embodiments, the invention relates to a kit, comprising at least one pair of primers specific for a MEDIATOR complex gene that is a marker for resistance to anticancer treatment in a patient that has cancer, at least one reagent for amplification of the MEDIATOR complex gene, and instructions for use.

In some embodiments, the invention relates to a kit, comprising at least one pair of primers specific for a SWI/SNF complex and/or a MEDIATOR complex gene that is a marker for resistance to anticancer treatment in a patient that has cancer, at least one reagent for amplification of the SWI/SNF complex and/or MEDIATOR complex gene, and instructions for use.

In other embodiments, the invention relates to a kit, comprising at least one pair of primers specific for a RAS-GAP gene that is a marker for resistance to anticancer treatment in a patient that has cancer, at least one reagent for amplification of the RAS-GAP gene, and instructions for use.

In certain embodiments, in a kit of the invention, the primers are specific for a SWI/SNF complex gene selected from the group consisting of ARID1A, ARID1B, ARID2, SMARCA2, SMARCA4, PBRM1, SMARCC2, SMARCC1, SMARCD1, SMARCD2, SMARCD3, SMARCE1, ACTL6A, ACTL6B, and SMARCB1.

In certain embodiments, in a kit of the invention, the primers are specific for a MEDIATOR complex gene selected from the group consisting of MED22, MED11, MED17, MED20, MED30, MED19, MED18, MED8, MED6, MED28, MED9, MED21, MED4, MED7, MED31, MED10, MED1, MED26, MED2, MED3, MED25, MED23, MED5, MED14, MED16, MED15, CycC, CDK8, MED13, MED12, MED13L, and MED12L.

In certain embodiments, in a kit of the invention, the primers are specific for a RAS-GAP gene selected from the group consisting of: DAB2IP, NF1, and RASAL3.

In certain embodiments, in a kit of the invention, the marker for resistance to anticancer treatment is a marker for resistance to a receptor tyrosine kinase inhibitor.

In certain embodiments, in a kit of the invention, the marker for resistance to anticancer treatment is a marker for resistance to an inhibitor of ERK activation. In some embodiments, the inhibitor of ERK activation inhibits a cellular protein that interacts directly with ERK. In some embodiments, the inhibitor of ERK activation inhibits a cellular protein that interacts indirectly with ERK. In other embodiments, the inhibitor of ERK activation is a receptor tyrosine kinase inhibitor.

In certain embodiments, the kit is a PCR kit. In other embodiments, the kit is an MLPA kit. In yet other embodiments, the kit is an RT-MLPA kit.

In some embodiments, the level of expression of one or more SWI/SNF complex and/or MEDIATOR complex and/or RAS-GAP genes in a method of the invention is measured by determination of their level of transcription, using a DNA array. In other embodiments, the level of expression of one or more SWI/SNF complex and/or MEDIATOR complex and/or RAS-GAP genes is measured by determination of their level of transcription, using quantitative RT-PCR.

In some embodiments the level of expression of one or more SWI/SNF complex and/or MEDIATOR complex and/or RAS-GAP genes in a method of the invention is

measured in a tumor sample from the patient. In certain further embodiments, the tumor sample is a lung tumor sample.

In some embodiments, the resistance to anticancer treatment is resistance to treatment with a B-RAF inhibitor. Examples of B-RAF inhibitors include CEP-32496, vemurafenib, GSK-2118436, ARQ-736, RG-7256, XL-281, DCC-2036, GDC-0879, AZ628, and antibody fragment EphB4/Raf inhibitors.

In some embodiments, resistance to anticancer treatment is resistance to treatment with a MEK inhibitor. Examples of MEK inhibitors include CKI-27, RO-4987655, RO-5126766, PD-0325901, WX-554, AZD-8330, G-573, RG-7167, SF-2626, GDC-0623, RO-5068760, and AD-GL0001.

In certain embodiments, in a kit of the invention, the marker for resistance to anticancer treatment is a marker for resistance to treatment with a B-RAF inhibitor. In other embodiments, the marker for resistance to anticancer treatment is a marker for resistance to treatment with a MEK inhibitor.

In certain embodiments, in the methods of the invention, the expression levels of SWI/SNF and/or MEDIATOR complex or RAS-GAP nucleic acid and/or proteins are measured in one or more cancer cells of the patient. In some embodiments, nucleic acid is isolated from one or more cancer cells of the patient. In other embodiments, protein is isolated from one or more cancer cells of the patient.

In certain embodiments, in a method of the invention, resistance to anticancer treatment in one or more cancer cells in a patient is primary resistance to anticancer treatment. In other embodiments, the resistance is secondary resistance to anticancer treatment.

In certain embodiments, the instant application relates to a method of treating resistance to one or more inhibitors of ERK activation in a patient in need thereof, comprising administering to the patient at least one inhibitor of the TGF-beta pathway in combination with the one or more inhibitors of ERK activation. In some embodiments, the inhibitor of ERK activation is selected from the group consisting of direct and indirect inhibitors of ERK activation. In certain embodiments, the direct inhibitor of ERK activation is a MEK inhibitor. In certain embodiments, the indirect inhibitor of ERK activation is selected from the group consisting of RTK inhibitors, RAS inhibitors, and B-RAF inhibitors.

In some embodiments, the resistance to one or more inhibitors of ERK activation is primary resistance. In other embodiments, the resistance to one or more inhibitors of ERK activation is secondary resistance. In yet other embodiments, the resistance to one or more

inhibitors of ERK activation is evaluated and/or predicted according to a method as disclosed herein.

In other embodiments, the instant application relates to a method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising (a) measuring expression levels of one or more TGFβ pathway nucleic acid and/or proteins in the patient; and (b) comparing the expression levels of the one or more TGFβ pathway nucleic acid and/or proteins in (a) with the expression levels of one or more reference TGFβ pathway nucleic acid and/or proteins, wherein the one or more reference TGFβ pathway nucleic acid and/or proteins are from a control sample, wherein an increase in the expression of the one or more TGFβ pathway nucleic acid and/or proteins in comparison to the one or more reference TGFβ pathway nucleic acid and/or proteins is indicative of resistance to anticancer treatment in the patient.

In yet other embodiments, the instant application relates to a method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising (a) isolating nucleic acid from the patient, wherein the nucleic acid comprises one or more TGFβ pathway DNA and/or RNA; and (b) analyzing the nucleic acid of (a) for the presence of one or more activating mutations in the TGFβ pathway complex DNA and/or RNA, wherein the presence of one or more activating mutations in the one or more TGFβ pathway DNA and/or RNA analyzed in (b) is indicative of resistance to anticancer treatment in the patient.

In some embodiments, the instant application relates to a method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising (a) isolating protein from the patient, wherein the protein comprises one or more TGFβ pathway proteins; (b) analyzing the activity of the one or more TGFβ pathway proteins in (a); and (c) comparing the activity of the one or more TGFβ pathway proteins in (b) with the activity of one or more reference TGFβ pathway proteins, wherein a difference in activity of the one or more TGFβ pathway proteins from (b) in comparison to the one or more TGFβ pathway reference proteins in (c) is indicative of resistance to anticancer treatment in the patient.

In certain embodiments, the instant application relates to a method of treating cancer in a patient in need thereof, comprising administering to the patient an inhibitor of ERK activation in combination with an inhibitor of TGFβ pathway activation. In certain further embodiments, the cancer is selected from the group consisting of: liver cancer, lung cancer, breast cancer, ovarian cancer, head and neck cancer, bladder cancer, colorectal cancer, cervical cancer, mesothelioma, solid tumors, renal cell carcinoma, stomach cancer, sarcoma,

prostate cancer, melanoma, thyroid cancer, brain cancer, adenocarcinoma, glioma, glioblastoma, esophageal cancer, neuroblastoma, subependymal giant cell astrocytoma, endometrial cancer, a hematological cancer, and lymphoma.

In certain embodiments, the inhibitor of ERK activation is selected from the group consisting of: RTK inhibitors, RAS inhibitors, B-RAF inhibitors, and MEK inhibitors. In a particular embodiment, the inhibitor of ERK activation is a MET inhibitor.

In certain embodiments, the expression levels are measured of one or more of TGFβ pathway nucleic acid that is a TGFβ pathway target gene selected from the group consisting of: ALOX5AP, COL5A1, TAGLN, ANGPTL4, LGALS1, IL11, LBH, and COL4A1.

In some embodiments, the inhibitor of TGFβ pathway activation is LY2157299. In certain embodiments, the inhibitor of TGFβ pathway activation inhibits MED12/TGFβ binding.

In some embodiments, inhibitor of ERK activation is crizotinib or gefitinib. In certain embodiments, the inhibitor of ERK activation inhibits MED12/TGFβ binding.

In some embodiments, the instant application relates to a method of identifying an inhibitor of ERK activation, comprising: measuring MED12/TGFβ binding in the presence and absence of a test compound, wherein a reduction in the amount of MED12/TGFβ binding in the presence of the test compound in comparison to the absence of the test compound indicates an inhibitor of ERK activation has been identified.

In other embodiments, the instant application relates to a method of identifying an inhibitor of TGFβ pathway activation, comprising: measuring MED12/TGFβ binding in the presence and absence of a test compound, wherein a reduction in the amount of MED12/TGFβ binding in the presence of the test compound in comparison to the absence of the test compound indicates an inhibitor of TGFβ pathway activation has been identified.

In yet other embodiments, the instant application relates to a method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising: (a) measuring expression levels of one or more MED12 nucleic acid and/or proteins in the patient; (b) measuring one or more markers of an EMT-like phenotype; and (c) comparing the expression levels of the one or more MED12 nucleic acid and/or proteins in (a) with the expression levels of one or more reference MED12 nucleic acid and/or proteins, wherein a reduction in the expression of the one or more MED12 nucleic acid and/or proteins in comparison to the one or more reference MED12 nucleic acid and/or proteins in (c) and wherein one or more markers are measured of an EMT-like phenotype in (b) is indicative of resistance to anticancer treatment in the patient.

In some embodiments, the nucleic acid in (a) is isolated from one or more cancer cells from the patient. In other embodiments, the protein in (a) is isolated from one or more cancer cells from the patient. In certain embodiments, the one or more markers of an EMT-like phenotype are measured in one or more cancer cells from the patient. In certain further embodiments, the cancer is selected from the group consisting of: liver cancer, lung cancer, breast cancer, ovarian cancer, head and neck cancer, bladder cancer, colorectal cancer, cervical cancer, mesothelioma, solid tumors, renal cell carcinoma, stomach cancer, sarcoma, prostate cancer, melanoma, thyroid cancer, brain cancer, adenocarcinoma, glioma, glioblastoma, esophageal cancer, neuroblastoma, subependymal giant cell astrocytoma, endometrial cancer, a hematological cancer, and lymphoma. In a particular embodiment, the cancer is colorectal cancer.

In certain embodiments, the resistance to anticancer treatment is resistance to treatment with a MEK inhibitor. In further embodiments, the MEK inhibitor is selected from the group consisting of: CKI-27, RO-4987655, RO-5126766, PD-0325901, WX-554, AZD-8330, G-573, RG-7167, SF-2626, GDC-0623, RO-5068760, and AD-GL0001.

In some embodiments, the resistance to anticancer treatment is resistance to treatment with a B-RAF inhibitor. In certain further embodiments, the B-RAF inhibitor is selected from the group consisting of: CEP-32496, vemurafenib, GSK-2118436, ARQ-736, RG-7256, XL-281, DCC-2036, GDC-0879, AZ628, and antibody fragment EphB4/Raf inhibitors.

In some embodiments, the one or more markers of an EMT-like phenotype are selected from mesenchymal markers. In certain embodiments, the one or more mesenchymal markers are selected from vimentin and N-cadherin.

In other embodiments, the instant application relates to a method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising: (a) measuring expression levels of one or more MED12KD signature nucleic acid and/or proteins in one or more cancer cells of the patient; and (b) comparing the expression levels of the one or more MED12KD signature nucleic acid and/or proteins in (a) with the expression levels of one or more positive reference MED12KD signature nucleic acid and/or proteins, wherein if expression of the one or more MED12KD signature nucleic acid and/or proteins in (a) is similar to the one or more positive reference MED12KD signature nucleic acid and/or proteins, then resistance to anticancer treatment is indicated in the patient. In certain embodiments, the expression of the one or more MED12KD signature nucleic acid and/or proteins in (a) is about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, or about 10-fold greater or lesser than the one or more

positive reference MED12KD signature nucleic acid and/or proteins. In other embodiments, the expression of the one or more MED12KD signature nucleic acid and/or proteins in (a) is about the same as the one or more positive reference MED12KD signature nucleic acid and/or proteins.

In yet other embodiments, the instant application relates to a method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising: (a) measuring expression levels of one or more MED12KD signature nucleic acid and/or proteins in one or more cancer cells of the patient; and (b) comparing the expression levels of the one or more MED12KD signature nucleic acid and/or proteins in (a) with the expression levels of one or more negative reference MED12KD signature nucleic acid and/or proteins, wherein if expression of the one or more MED12KD signature nucleic acid and/or proteins in (a) is greater or lesser than the expression of the one or more negative reference MED12KD signature nucleic acid and/or proteins, then resistance to anticancer treatment is indicated in the patient. In some embodiments, the one or more cancer cells of the patient in (a) are from cancer cells of the patient after the anticancer treatment, and wherein the negative reference MED12KD signature nucleic acid and/or proteins are from one or more cancerous cells of the patient prior to the anticancer treatment. In certain embodiments, the expression of the one or more MED12KD signature nucleic acid and/or proteins in (a) is greater than or equal to about 1.2 fold higher or lower than the expression of the one or more negative reference MED12KD signature nucleic acid and/or proteins.

In some embodiments, the one or more cancer cells of the patient in (a) are from one or more cancer cells of the patient prior to the anticancer treatment. In other embodiments, the one or more cancer cells of the patient in (a) are from one or more cancer cells of the patient after the anticancer treatment.

In certain embodiments, the negative reference MED12KD signature nucleic acid and/or proteins are from one or more non-cancerous cells of the patient. In some embodiments, the negative reference MED12KD signature nucleic acid and/or proteins are from one or more cells known to be sensitive to the anticancer treatment. In certain embodiments, the negative reference MED12KD signature nucleic acid and/or proteins is the average expression of the MED12KD signature nucleic acid and/or proteins in one or more tumor or cell line samples known to be sensitive to the anticancer treatment.

In some embodiments, the one or more $MED12^{KD}$ signature nucleic acids are upregulated nucleic acids. In certain embodiments, the upregulated nucleic acids are selected from the upregulated nucleic acids presented in Figure 37. In certain embodiments, the

upregulated nucleic acids are selected from the upregulated nucleic acids presented in Figure 40. In certain embodiments, the upregulated nucleic acids are selected from the upregulated nucleic acids presented in Figure 39.

In other embodiments, the one or more $MED12^{KD}$ signature nucleic acids are downregulated nucleic acids. In certain embodiments, the downregulated nucleic acids are selected from the downregulated nucleic acids presented in Figure 37. In certain embodiments, the downregulated nucleic acids are selected from the downregulated nucleic acids presented in Figure 40. In certain embodiments, the downregulated nucleic acids are selected from the downregulated nucleic acids presented in Figure 39.

In some embodiments, the resistance to anticancer treatment is resistance to treatment with a MEK inhibitor. In certain embodiments, the MEK inhibitor is selected from the group consisting of: CKI-27, RO-4987655, RO-5126766, PD-0325901, WX-554, AZD-8330, G-573, RG-7167, SF-2626, GDC-0623, RO-5068760, and AD-GL0001.

In some embodiments, the resistance to anticancer treatment is resistance to treatment with a B-RAF inhibitor. In certain embodiments, the B-RAF inhibitor is selected from the group consisting of: CEP-32496, vemurafenib, GSK-2118436, ARQ-736, RG-7256, XL-281, DCC-2036, GDC-0879, AZ628, and antibody fragment EphB4/Raf inhibitors.

In certain embodiments, the cancer is selected from the group consisting of: liver cancer, lung cancer, breast cancer, ovarian cancer, head and neck cancer, bladder cancer, colorectal cancer, cervical cancer, mesothelioma, solid tumors, renal cell carcinoma, stomach cancer, sarcoma, prostate cancer, melanoma, thyroid cancer, brain cancer, adenocarcinoma, glioma, glioblastoma, esophageal cancer, neuroblastoma, subependymal giant cell astrocytoma, endometrial cancer, a hematological cancer, and lymphoma.

In some embodiments, the instant application relates to a method of evaluating and/or predicting of resistance to anticancer treatment in a patient in need thereof, comprising: measuring expression levels of one or more MED12KD signature nucleic acid and/or proteins in one or more cancer cells of the patient; and comparing the expression levels of the one or more MED12KD signature nucleic acid and/or proteins in (a) with the expression levels of (i) one or more MED12KD signature nucleic acid and/or proteins from cells known to be resistant to said anticancer treatment AND (ii) one or more MED12KD signature nucleic acid and/or proteins from cells known to be sensitive to said anticancer treatment, whereby the cancer cells of the patient are considered to be resistant if the difference in expression levels between the cells in (a) and the cells in (i) is smaller than the difference in expression levels between the cells in (a) and the cells in (ii).

In other embodiments, the instant application relates to a method of evaluating and/or predicting of resistance to anticancer treatment in a patient in need thereof, comprising measuring expression levels of one or more MED12KD signature nucleic acid and/or proteins in one or more cancer cells of the patient; and comparing the expression levels of the one or more MED12KD signature nucleic acid and/or proteins in (a) with the expression levels of (i) one or more MED12KD signature nucleic acid and/or proteins from cells known to be resistant to said anticancer treatment AND (ii) one or more MED12KD signature nucleic acid and/or proteins from cells known to be sensitive to said anticancer treatment, whereby the cancer cells of the patient are considered to be sensitive if the difference in expression levels between the cells in (a) and the cells in (i) is greater than the difference in expression levels between the cells in (a) and the cells in (ii).

In yet other embodiments, the present application relates to a method of evaluating and/or predicting of resistance to anticancer treatment in a patient in need thereof, comprising measuring expression levels of one or more MED12KD signature nucleic acid and/or proteins in one or more cancer cells of the patient; and comparing the expression levels of the one or more MED12KD signature nucleic acid and/or proteins in (a) with the average expression levels of (i) one or more MED12KD signature nucleic acid and/or proteins taken from two or more cell samples, whereby the cancer cells of the patient are considered to be resistant if the difference in expression levels of the one or more MED12KD signature nucleic acid and/or proteins between the cells in (a) and the average expression levels of the one or more MED12KD signature nucleic acid and/or proteins in (i) is greater than a factor 1.2.

These and other embodiments are disclosed or are obvious from and encompassed by, the following Detailed Description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the results of a genome-wide RNAi screen that identifies MED12, ARID1A and SMARCE1 as critical determinants of drug sensitivity to ALK inhibitors in EML4-ALK mutant NSCLC cells. (A) Schematic outline of the ALK inhibitor resistance barcode screen performed in H3122 cells. Human shRNA library polyclonal virus was produced to infect H3122 cells, which were then left untreated (control) or treated with 5 nM NVP-TAE684. After 4 weeks of selection, shRNA inserts from both populations were recovered, labeled and hybridized to DNA. (B) Analysis of the relative abundance of the recovered shRNA cassettes from ALK inhibitor barcode experiment. Averaged data from three independent experiments were normalized and 2log transformed. Among the 49 top

shRNA candidates (M>1.5 and A>7), two independent sh*MED12*, one sh*ARID1A* and one sh*SMARCE1* vectors were identified. (C) Individual shRNAs from the library targeting *MED12, ARID1A* and *SMARCE1* confer resistance to ALK inhibitors. H3122 cells expressing the empty vector pRS, control sh*GFP*, sh*MED12#1*, sh*MED12#2*, sh*ARID1A* or sh*SMARCE1*, were left untreated for 2 weeks or treated with 300 nM Crizotinib or 2.5 nM NVP-TAE684 for 4 weeks, after which the cells were fixed, stained and photographed.

Figure 2. A genome-wide RNAi screen identifies MED12 as a critical determinant of drug response to tyrosine kinase inhibitors in NSCLCs

(A) Schematic outline of the crizotinib resistance barcode screen performed in H3122 cells. NKI human shRNA library polyclonal virus was produced to infect H3122 cells, which were then left untreated (control) or treated with 300 nM crizotinib for 14 or 28 days, respectively. After selection, shRNA inserts from both populations were recovered, labeled and hybridized to DNA oligonucleotide barcode arrays. (B) Analysis of the relative abundance of the recovered shRNA cassettes from crizotinib barcode experiment. Averaged data from three independent experiments were normalized and 2log transformed. Among the 43 top shRNA candidates (M>2 and A>7), two independent shMED12 vectors (in light gray at end of arrow points) were identified. (F to H) Suppression of MED12 also confers to EGFR inhibitors. F) Colony formation assay of PC9 cells expressing pLKO control or independent lentiviral shMED12 vectors (#4 and #5) were cultured in 50 nM gefitinib or 50 nM erlotinib. The cells were fixed, stained and photographed after 10 (untreated) or 28 days (treated). G) The level of knockdown of MED12 by each of the shRNAs was measured by examining the MED12 mRNA levels by qRT-PCR. Error bars denote SD. H) The level of knockdown of MED12 protein was measured by western blotting.

Figure 3 depicts that suppression of MED12 confers drug resistance to ALK inhibitors in EML4-ALK mutant NSCLC cells. (A) Validation of independent retroviral shRNAs (in pRS vector) targeting *MED12* in H3122 cells. The functional phenotypes of non-overlapping sh*MED12* vectors are indicated by the colony formation assay in 300 nM Crizotinib or 2.5 nM NVP-TAE684. The cells were fixed, stained and photographed after 2 weeks (untreated) or 4 weeks (ALK inhibitors treatment). (B and C) The knockdown ability of each of the shRNAs was measured by examining the *MED12* mRNA levels by qRT-PCR (B) and the MED12 protein levels by western blotting (C). Error bars denote standard deviation (SD). (D) Validation of independent lentiviral shRNAs (in pLKO vector) targeting

MED12. The functional phenotypes of non-overlapping sh*MED12* vectors are indicated by the colony formation assay in 300 nM Crizotinib or 2.5 nM NVP-TAE684. The cells were fixed, stained and photographed after 2 weeks (untreated) or 4 weeks (ALK inhibitors treatment). (E and F) The knockdown ability of each of the shRNAs was measured by examining the *MED12* mRNA levels by qRT-PCR (B) and the MED12 protein levels by western blotting. Error bars denote standard deviation (SD).

Figure 4 shows that restoration of Med12 reverses the resistance to ALK inhibitors driven by MED12 knockdown in EML4-ALK mutant NSCLC cells. (A) Ectopic expression of mouse Med12 re-sensitizes the *MED12* knockdown cells to ALK inhibitors. H3122 cells expressing pLKO control or sh*MED12* vectors were retrovirally infected with viruses containing pMX or pMX-*Med12*, and were grown in the absence or presence of 300 nM Crizotinib or 2.5 nM NVP-TAE684. Cells were then fixed, stained and photographed after 2 weeks (untreated) or 4 weeks (ALK inhibitors treatment). (B) The MED12/Med12 protein levels in H3122 cells (untreated) described in Figure 4A. (C and D) The endogenous *MED12* mRNA (C) and the exogenous *Med12* mRNA were measured by qRT-PCR.

Figure 5 shows that suppression of ARID1A or SMARCE1 confers drug resistance to ALK inhibitors in EML4-ALK mutant NSCLC cells. (A) Validation of independent retroviral shRNAs targeting *ARID1A* or *SMARCE1* in H3122 cells. The functional phenotypes of non-overlapping sh*ARID1A* and sh*SMARCE1* vectors are indicated by the colony formation assay in 300 nM Crizotinib or 2.5 nM NVP-TAE684. The cells were fixed, stained and photographed after 2 weeks (untreated) or 4 weeks (ALK inhibitors treatment). (B and C) The knockdown ability of each of the shRNAs was measured by examining the *ARID1A* mRNA levels by qRT-PCR (B) and the ARID1A protein levels by western blotting (C). Error bars denote standard deviation (SD). (D and E) The knockdown ability of each of the shRNAs was measured by examining the *SMARCE1* mRNA levels by qRT-PCR (D) and the SMARCE1 protein levels by western blotting (E). Error bars denote standard deviation (SD).

Figure 6 shows that restoration of SMARCE1 reverses the resistance to ALK inhibitors driven by SMACRE1 knockdown in EML4-ALK mutant NSCLC cells. (A) Ectopic expression of SMARCE1-ND that cannot be targeted by sh*SMARCE1* vectors re-sensitizes the *SMARCE1* knockdown cells to ALK inhibitors. H3122 cells expressing pRS

control or sh*SMARCE1* vectors were retrovirally infected with viruses containing pMX or pMX-*SMARCE1-ND*, and were grown in the absence or presence of 300 nM Crizotinib or 2.5 nM NVP-TAE684. Cells were then fixed, stained and photographed after 2 weeks (untreated) or 4 weeks (ALK inhibitors treatment). (B) The SMARCE1 protein levels in H3122 cells (untreated) described in Figure 4A. (C and D) The endogenous *SMARCE1* mRNA was measured by qRT-PCR using a 3' UTR specific primer set (C) and the total *SMARCE1* mRNA was measured by qRT-PCR using an ORF specific primer set.

Figure 7 shows that restoration of Med12 reverses the resistance to EGFR inhibitor driven by MED12 knockdown in PC9 EGFR mutant cells. (A) Ectopic expression of mouse Med12 re-sensitizes the otherwise resistant *MED12* knockdown cells to EGFR inhibitors. PC9 cells expressing pLKO control or sh*MED12* vectors were retrovirally infected with viruses containing pMX or pMX-*Med12*, and were grown in the absence or presence of 50 nM Gefitinib. Cells were then fixed, stained and photographed after 2 weeks (untreated) or 3 weeks (EGFR inhibitor treatment). (B) The MED12/Med12 protein levels in PC9 cells (untreated) described in Figure 7A. (C and D) The endogenous *MED12* mRNA (C) and the exogenous *Med12* mRNA were measured by qRT-PCR.

Figure 8 shows that suppression of MED12 confers drug resistance to EGFR inhibitors in H3255 EGFR mutant cells. (A) H3255 cells expressing shRNAs targeting *MED12* are resistant to EGFR inhibitors. The functional phenotypes of sh*MED12* vectors are indicated by the colony formation assay in 25 nM Gefitnib or 25 nM Erlotinib. The cells were fixed, stained and photographed after 2 weeks (untreated) or 4 weeks (EGFR inhibitors treatment). (B) The knockdown ability of each of the shRNAs was measured by examining the *MED12* mRNA levels by qRT-PCR. Error bars denote standard deviation (SD).

Figure 9 shows that suppression of ARID1A confers drug resistance to EGFR and MET inhibitors in NSCLC cells with mutant EGFR or MET amplification. (A) PC9 cells expressing shRNAs targeting *ARID1A* are resistant to EGFR inhibitor. The functional phenotypes of sh*ARID1A* vectors are indicated by the colony formation assay in 25 nM Gefitinib. The cells were fixed, stained and photographed after 2 weeks (untreated) or 4 weeks (EGFR inhibitor treatment). (B) The *ARID1A* mRNA levels for the cells described in Figure 9A were measured by qRT-PCR. Error bars denote standard deviation (SD). (C) H1993 cells expressing shRNAs targeting *ARID1A* are resistance to MET inhibitor. The

functional phenotypes of sh*ARID1A* vectors are indicated by the colony formation assay in 200 nM Crizotinib. The cells were fixed, stained and photographed after 2 weeks (untreated) or 4 weeks (MET inhibitor treatment). (D) The *ARID1A* mRNA levels for the cells described in Figure 9C were measured by qRT-PCR. Error bars denote standard deviation (SD).

Figure 10 shows that restoration of SMARCE1 reverses the resistance to EGFR inhibitor driven by SMACRE1 knockdown in PC9 EGFR mutant cells. (A) Ectopic expression of SMARCE1-ND that cannot be targeted by sh*SMARCE1* vectors re-sensitizes the otherwise resistant *SMARCE1* knockdown cells to EGFR inhibitor. PC9 cells expressing pRS control or sh*SMARCE1* vectors were retrovirally infected with viruses containing pMX or pMX-*SMARCE1-ND*, and were grown in the absence or presence of 50 nM Gefitinib. Cells were then fixed, stained and photographed after 2 weeks (untreated) or 4 weeks (EGFR inhibitor treatment). (B) The SMARCE1 protein levels in PC9 cells (untreated) described in Figure 10A. (C and D) The endogenous *SMARCE1* mRNA was measured by qRT-PCR using a 3' UTR specific primer set (C) and the total *SMARCE1* mRNA was measured by qRT-PCR using an ORF specific primer set.

Figure 11 shows that restoration of SMARCE1 reverses the resistance to MET inhibitor driven by SMACRE1 knockdown in H1993 MET amplified cells. (A) Ectopic expression of SMARCE1-ND that cannot be targeted by sh*SMARCE1* vectors re-sensitizes the otherwise resistant *SMARCE1* knockdown cells to MET inhibitor. H1993 cells expressing pRS control or sh*SMARCE1* vectors were retrovirally infected with viruses containing pMX or pMX-*SMARCE1-ND*, and were grown in the absence or presence of 200 nM Crizotinib. Cells were then fixed, stained and photographed after 2 weeks (untreated) or 4 weeks (MET inhibitor treatment). (B) The SMARCE1 protein levels in H1993 cells (untreated) described in Figure 11A. (C and D) The endogenous *SMARCE1* mRNA was measured by qRT-PCR using a 3' UTR specific primer set (C) and the total *SMARCE1* mRNA was measured by qRT-PCR using an ORF specific primer set.

Figure 12 shows that restoration of SMARCE1 reverses the resistance to MET inhibitor driven by SMACRE1 knockdown in EBC1 MET amplified cells. (A) Ectopic expression of SMARCE1-ND that cannot be targeted by sh*SMARCE1* vectors re-sensitizes the otherwise resistant *SMARCE1* knockdown cells to MET inhibitor. EBC1 cells expressing pRS control or sh*SMARCE1* vectors were retrovirally infected with viruses containing pMX

or pMX-*SMARCE1-ND*, and were grown in the absence or presence of 200 nM Crizotinib. Cells were then fixed, stained and photographed after 2 weeks (untreated) or 4 weeks (MET inhibitor treatment). (B) The SMARCE1 protein levels in H1993 cells (untreated) described in Figure 12A. (C and D) The endogenous *SMARCE1* mRNA was measured by qRT-PCR using a 3' UTR specific primer set (C) and the total *SMARCE1* mRNA was measured by qRT-PCR using an ORF specific primer set.

Figure 13 depicts a RAS-GAP RNAi screen that identifies DAB2IP and NF1 as critical determinants of drug sensitivity to EGFR inhibitors in EGFR mutant NSCLC cells. PC9 cells expressing controls (pLKO or sh*GFP*) or 14 pools of shRNA vectors targeting each RAS-GAP were grown in the absence or presence of 50 nM Gefitinib or Elortinib. Cells were then fixed, stained and photographed after 2 weeks (untreated) or 4 weeks (EGFR inhibitors treatment).

Figure 14 shows that suppression of DAB2IP confers drug resistance to EGFR inhibitors in PC9 EGFR mutant cells. (A) Validation of independent shRNAs (in pLKO vector) targeting *DABP2IP* in PC9 cells. The functional phenotypes of non-overlapping sh*DABP2IP* vectors are indicated by the colony formation assay in 50 nM Gefitinib or Elortinib. The cells were fixed, stained and photographed after 2 weeks (untreated) or 4 weeks (EGFR inhibitors treatment). (B) The knockdown ability of each of the shRNAs was measured by examining the *DAB2IP* mRNA levels by qRT-PCR. Error bars denote standard deviation (SD). (C) Western blotting analysis of PC9 cells expressing controls (pLKO or sh*GFP*) or shRNAs targeting *DAB2IP* treated with vehicle control or 25 nM Gefitinib for 8 hours.

Figure 15 shows that suppression of NF1 confers drug resistance to EGFR inhibitors in PC9 EGFR mutant cells. (A) Validation of independent shRNAs (in pLKO vector) targeting *NF1* in PC9 cells. The functional phenotypes of non-overlapping sh*NF1* vectors are indicated by the colony formation assay in 50 nM Gefitinib or Elortinib. The cells were fixed, stained and photographed after 2 weeks (untreated) or 4 weeks (EGFR inhibitors treatment). (B and C) The knockdown ability of each of the shRNAs was measured by examining the *NF1* mRNA levels by qRT-PCR (B) and the NF1 protein levels by western blotting (C). Error bars denote standard deviation (SD).

Figure 16 shows that suppression of MED12 and SMARCE1 leads to elevated phospho-ERK. (A) *MED12*^{KD} cells retain phospho-ERK levels in the presence of ALK inhibitor in EML4-ALK cells. H3122 cells expressing controls (pRS or sh*GFP*) or sh*MED12* vectors were gown in the absence or presence of 20 nM NVP-TAE684 for 24 hours and the cell lysates were harvested for western blotting analysis. (B) *SMARCE1*^{KD} cells have elevated phospho-ERK in EML4-ALK cells. H3122 cells expressing controls (pRS or sh*GFP*) or sh*SMARCE1* vectors were gown in the absence or presence of 20 nM NVP-TAE684 for 24 hours and the cell lysates were harvested for western blotting analysis. (C) *MED12*^{KD} cells have elevated phospho-ERK levels in EGFR mutant cells. PC9 cells expressing controls (pRS or sh*GFP*) or sh*SMARCE1* vectors were gown in the absence or presence of 25 nM Gefitinib for 8 hours and the cell lysates were harvested for western blotting analysis.

Figure 17 shows that MED12 suppression leads to ERK activation and confers multi-drug resistance in different cancer types (C and D) MED12 knockdown confers resistance to BRAF and MEK inhibitors in melanoma cells. C) BRAFV600E A375 cells expressing pLKO control or shMED12 vectors were cultured in the absence or presence of 2.5 μM PLX4032 or 0.5 μM AZD6244. The cells were fixed, stained and photographed after 10 (untreated) or 28 days (treated). D) MED12 suppression results in elevated level of p-ERK in melanoma cells. A375 cells expressing pLKO control or shMED12 vectors were grown in the absence or presence of 1 μM PLX4032 or 0.5 μM AZD6244 for 6 hours and the cell lysates were harvested for western blotting analysis. E-F) MED12 knockdown confers resistance to MEK inhibitor in colorectal cancer cells. E) KRASV12 SK-CO-1 cells expressing pLKO control or shMED12 vectors were cultured in the absence or presence of 0.5 μM AZD6244. The cells were fixed, stained and photographed after 14 (untreated) or 28 days (treated). F) MED12 suppression results in elevated level of p-ERK in colorectal cancer cells. SK-CO-1 cells expressing pLKO control or shMED12 vectors were grown in the absence or presence of 1 μM AZD6244 for 6 hours and the cell lysates were harvested for western blotting analysis. (G-H) Knockdown of MED12 confers resistance to multi-kinase inhibitor sorafenib in HCC Huh-7 cells. G) Colony formation assay of Huh-7 cells expressing pLKO control or shMED12 vectors (#4 and #5) were cultured in 2 μM sorafenib. The cells were fixed, stained and photographed after 14 (untreated) or 21 days (treated). H) MED12 suppression results in elevated level of p-ERK in HCC cells. Huh-7 cells expressing pLKO

control or shMED12 vectors were grown in the absence or presence of 4 μM sorafenib for 6 hours and the cell lysates were harvested for western blotting analysis.

Figure 18 shows that MED12 suppression confers multi-drug resistance in additional cell lines of different cancer types (A-B) Knockdown of MED12 confers resistance to EGFR inhibitor in NSCLC H3255 (EGFRL858R) cells. A) Colony formation assay of H3255 cells expressing pLKO control or shMED12 vectors (#4 and #5) were cultured in 25 nM gefininib. The cells were fixed, stained and photographed after 14 (untreated) or 28 days (treated). B) The level of knockdown of MED12 by each of the shRNAs was measured by examining the MED12 mRNA levels by qRT-PCR. Error bars denote SD. (C-D) knockdown of MED12 confers resistance to BRAF and MEK inhibitors in melanoma SK-MEL-28 (BRAFV600E) cells. C) Colony formation assay of SK-MEL-28 cells expressing pLKO control or shMED12 vectors (#4 and #5) were cultured in 5 μM PLX4032 or 1 μM AZD6244. The cells were fixed, stained and photographed after 14 (untreated) or 28 days (treated). D) The level of knockdown of MED12 by each of the shRNAs was measured by examining the MED12 mRNA levels by qRT-PCR. Error bars denote SD. (E-F) knockdown of MED12 confers resistance to BRAF and MEK inhibitors in CRC SW1417 (BRAFV600E) cells. E) Colony formation assay of SW1417 cells expressing pLKO control or shMED12 vectors (#4 and #5) were cultured in 2 μM PLX4032 or 150 nM AZD6244. The cells were fixed, stained and photographed after 14 (untreated) or 28 days (treated). F) The level of knockdown of MED12 by each of the shRNAs was measured by examining the MED12 mRNA levels by qRT-PCR. Error bars denote SD.

Figure 19 shows that suppression of MED12 confers drug resistance to BRAF and MEK inhibitors in A375 melanoma cells. A375 (BRAFV600E) melanoma cells expressing shRNAs targeting MED12 are resistance to BRAF and MEK inhibitors. The functional phenotypes of shMED12 vectors are indicated by the colony formation assay in 5 uM PXL4720 or 12.5 nM PD-0325901. The cells were fixed, stained and photographed after 10 days (untreated) or 21 days (BARF and MEK inhibitors treatment).

Figure 20 shows that suppression of TGFβR2 restores the sensitivity to ALK inhibitors in $MED12^{KD}$ cells.

Figure 21 shows that TGFβ signaling is required for the drug resistance driven by MED12 suppression A) Schematic outline of the "drop out" RNAi screen for kinases whose inhibition restores sensitivity to crizotinib in MED12KD cells. Human TRC kinome shRNA library polyclonal virus was produced to infect H3122 cells stably expressing shMED12#3, which were then left untreated (control) or treated with 300 nM crizotinib for 10 days. After selection, shRNA inserts from both populations were recovered by PCR and identified by next generation sequencing. B) Representation of the relative abundance of the shRNA bar code sequences from the shRNA screen experiment depicted in panel A. The y-axis is enrichment (relative abundance of crizotinib treated/untreated) and x-axis is the intensity (average sequence reads in untreated sample) of each shRNA. Among the 51 top shRNA candidates (more than 2.5-fold depleted by crizotinib treatment and more than 200 reads in untreated as indicated by the red dash lines), two independent shTGFβR2 vectors (in light gray near end of arrow points) were identified. C) Suppression of TGFβR2 restores the crizotinib sensitivity in MED12KD cells. Using lentiviral infection, pLKO control or two independent shTGFβR2 vectors were introduced into H3122 control or MED12KD cells. After this, cells were cultured in the absence or presence of 300 nM crizotinib. The cells were fixed, stained and photographed after 14 (untreated) or 21 days (treated). D) The level of knockdown of TGFβR2 by each of the shRNAs was measured by examining the MED12 mRNA levels by qRT-PCR. Error bars denote SD.

Figure 22 shows that TGFβ treatment confers resistance to ALK inhibitors in EML4-ALK NSCLC cells. Activation of TGFβ signaling is sufficient to confer resistance to ALK inhibitors in EML4-ALK cells.

Figure 23 shows that TGFβ treatment confers resistance to EGFR inhibitors in EGFR mutant NSCLC cells. Activation of TGFβ signaling is sufficient to confer resistance to EGFR inhibitors.

Figure 24 shows that TGFβ activation is sufficient to confer multi targeted drug resistance in different cancer types. Recombinant TGFβ treatment leads to resistance to to crizotinib in H3122 cells (A), AZD6244 in SK-CO-1 cells (C) and PLX4032 and AZD6244 in A375 cells (D) in a TGFβ-dosage dependent manner.

Figure 25 shows that MED12^{KD} and TGFβ treatment both lead to elevated phosphor-ERK.

Figure 26 shows that morphological changes in MED12^{KD} cells resemble those of TGFβ.

Figure 27 shows that MED12KD cells morphologically resemble the cells treated with recombinant TGFβ Photographs of Huh-7 (B) cells expressing pLKO control or shMED12 and the control cells treated with recombinant 50 pM of TGFβ. Bar, 25 μm.

Figure 28 is a microarray analysis showing up-regulation of TGFβ target genes in MED12^{KD} cells.

Figure 29 shows that MED12 suppresses TGFβ signaling by negatively regulating TGFβR2 (A-F) Downregulation of MED12 leads to induction of a panel of TGFβ target genes and EMT marker genes. mRNA expression analysis by qRT-PCR of TGFβ target genes ANGPTL4 (A), TAGLN (B), CYR61 (C) and CTGF (D) and EMT marker genes VIM (E) and CDH2 (F) in H3122 and PC9 cells expressing pLKO controls or shRNAs targeting MED12. Cells were cultured in normal condition without TGFβ stimulation. Error bars denote SD. (G-H) MED12 suppression results in strong induction of TGFβR2 protein and SMAD2 phosphorylation. Western blot analysis of H3122 (G) and PC9 (H) cells expressing pLKO control or shMED12 vectors. HSP90 was used as a loading control. I) MED12 localizes to both nucleus and cytoplasm. Western blotting analysis of the nuclear and cytoplasmic fractions prepared from PC9 cells expressing control vector or shMED12 with or without 16 hours of 25 nM gefitinib treatment. Lamin A/C and SP1 were used as marker controls for nuclear fractions, while α-TUBULIN and HSP90 were used as controls for cytoplasmic fractions. J) MED12 is capable of physically interacting with TGFβR2. Western blotting analysis of coimmunoprecipitation experiments using Phoenix cells cotransfected with TGFβR2 and MED12 in a ratio of 5:1.

Figure 30 shows that MED12 suppresses TGF β signaling by negatively regulating TGF β receptor signaling in additional cell line models (A-F) Downregulation of MED12 leads to induction of a panel of TGFβ target genes and EMT marker genes. mRNA expression analysis by qRT-PCR of TGF β target genes ANGPTL4 (A), TAGLN (B), CYR61 (C) and CTGF (D) and EMT marker genes VIM (E) and CDH2 (F) in A375, SK-CO-

1 and Huh-7 cells expressing pLKO controls or shMED12. Cells were cultured in normal condition without TGFβ stimulation. Error bars denote SD. (G) mRNA levels of TGFβR2 in H3122, PC9, A375, SK-CO-1 and Huh-7 cells expressing pLKO control or shMED12 were documented by qRT-PCR. Error bars denote SD. (H-I) MED12 suppression results in strong induction of TGFβR2 protein and SMAD2 phosphorylation. Western blot analysis of A375 (H) and SK-CO-1 (I) cells expressing pLKO control or shMED12 vectors. α-TUBULIN was used as a loading control. J) MED12 localizes to both nucleus and cytoplasm. Western blotting analysis of the nuclear and cytoplasmic fractions prepared from H3122 cells expressing control vector or shMED12 with or without 16 hours of 300 nM crizotinib treatment. Lamin A/C and SP1 were used as marker controls for nuclear fractions, while α-TUBULIN and HSP90 were used as controls for cyctoplasmic fractions. K) Western blotting showing that MED12 knockdown leads to induction of mesenchymal markers Vimentin and N-cadherin in Huh-7 cells.

Figure 31 shows that activation of RAS/ERK pathway confers resistance to tyrosine kinase inhibitors in NSCLC cells.

Figure 32 is a table showing that SWI/SNF and MEDIATOR complexes regulate resistance to a variety of targeted cancer drugs.

Figure 33 shows that MED12KD signature overlaps with an EMT signature and predicts poor outcome in CRC and drug response to MEK inhibitors A) Genes that are frequently upregulated upon MED12 knockdown from the MED12KD signature significantly overlap with a list of genes upregulated during EMT (p=8.9*10-23; see Experimental Procedures). p= hypergeometric p-value. B) Kaplan-Meier analysis of disease specific survival (DSS) for the cohort of 231 CRC. MED12KD gene signature was used to hierarchically cluster the 231 CRC tumors into a cluster with poor DSS (cluster 1, black (bottom) line) and one with significantly better DSS (cluster 2, gray (top) line). C) MED12KD signature predicts drug responses to MEK inhibitors in 152 cell lines of different cancer types harboring the matching RAS or RAF mutations. High expression of subsets of genes upregulated in the MED12KD signature is significantly associated with higher IC50s for all four MEK inhibitors in (AZD6244, p=0.009; CI-1040, p=0.004; PD-0325901, p=0.007; RDEA119, p=0.013). Across these gene sets, each cell line was scored for the percentage of times it had high expression of the gene as well as being resistant to the

inhibitor. The heatmap in the left panel of this figure depicts this percentage for each MEK inhibitor. The cell lines are sorted using hierarchical clustering for visualization. The middle and right panel depict the tissue type of the cell lines and their RAS/RAF mutation status.

Figure 34 shows that IC50 values for AZD6244 and expression levels for ZBED2 across the 152 RAF/RAS mutated lines.
The top panel represents a histogram of IC50 values for the MEK inhibitor, AZD6244, across the 152 cell lines. Below the histogram, the individual IC50 values are plotted using squares (sensitive cell lines) and circles (resistant cell lines). The panel on the left depicts the histogram for the expression levels of gene ZBED2. To the right of the histogram, the individual expression levels are plotted using plus signs (upregulated), crosses (normal expression) and stars (downregulated). The scatter plot depicts the IC50 values and gene expression for each cell line. In this case, there are significantly many cell lines that show resistance to AZD6244 and are upregulated for ZBED2. These cell lines are found in the top-right area of the scatter plot and are indicated by plus signs inside of circles. The MED12 knockdown signature contains a significantly large number of such genes indicating the potential predictive value of this signature.

Figure 35 shows that TGFβR inhibitor and TKIs synergize to suppress proliferation of $MED12^{KD}$ NSCLC cells. A) Combination of TGFβR and ALK inhibitors synergistically inhibits growth of MED12KD NSCLC cells harboring EML4-ALK translocation. H3122 cells expressing pRS control or shMED12 vectors were cultured in the absence and the presence of 1 μM LY2157299, 300 nM crizotinib, or the combination of 1 μM LY2157299 and 300 nM crizotinib. The cells were fixed, stained and photographed after 14 (untreated and LY2157299 alone) or 28 days (crizotinib alone and LY2157299 plus crizotinib).
B) Combination of TGFβR and EGFR inhibitors synergistically inhibits growth of MED12KD NSCLC cells harboring EGFR activating mutation. PC9 cells expressing pLKO control or shMED12 vectors were cultured in the absence and the presence of 1 μM LY2157299, 100 nM gefitinib, or the combination of 1 μM LY2157299 and 100 nM gefitinib. The cells were fixed, stained and photographed after 10 (untreated and LY2157299 alone) or 28 days (gefitinib alone and LY2157299 plus gefitinib).

Figure 36 is a table depicting kinases screened for kinases whose inhibition restores sensitivity to crizotinib in MED12KD cells. Listed are the gene symbols for the genes tested

in the "drop out" RNAi screen and the number of shRNAs for each gene present in the library.

Figure 37 is a table depicting MED12KD signature gene list. Listed are genes deregulated by MED12KD (>2 fold) in at least three out five cell lines (H3122, PC9, SK-CO-1, A375 and Huh-7).

Figure 38 is a table depicting EMT signature gene list. Listed are genes of an EMT signature that was created by combining published EMT expression signatures as described herein.

Figure 39 is a table depicting overlapping genes between MED12KD and EMT signatures. Listed are overlapping genes that are upregulated in both the MED12KD and EMT signatures.

Figure 40 is a table depicting MED12KD signature genes that are significantly associated with higher IC50s for MEK inhibitors in the 152 cell lines. Of the 237 genes that were upregulated by MED12KD as identified by RNA-Seq, Applicants could read the expression levels for 170 genes in these 152 cell lines that have activating mutations in RAS or BRAF. High expression of subsets of these 170 genes is significantly associated with higher IC50s for all four MEK inhibitors in these cell lines.

Figure 41 is a table depicting 152 tumor cell lines used for the COSMIC Cell Line Panel Analysis. Listed are 152 COSMIC cell lines that have activating mutations in RAS or BRAF and their drug response data (IC50 values) to four MEK inhibitors.

DETAILED DESCRIPTION

The instant invention provides methods and related compositions pertaining to the identification of a tumor that will be resistant to treatment by a certain compound or class of compounds. In certain embodiments, the invention provides one or more markers for resistance to anticancer treatment in a patient. In some embodiments, the marker is a MEDIATOR complex and/or SWI/SNF complex gene.

Examples of MEDIATOR complex genes that may serve as a marker for resistance to anticancer treatment in a patient as described herein include MED22, MED11, MED17, MED20, MED30, MED19, MED18, MED8, MED6, MED28, MED9, MED21, MED4,

MED7, MED31, MED10, MED1, MED26, MED2, MED3, MED25, MED23, MED5, MED14, MED16, MED15, CycC, CDK8, MED13, MED12, MED13L, and MED12L (*see e.g.*, MED12L Gene ID: 116931 available from the National Center for Biotechnology Information (NCBI) website). *See, e.g.*, Malik, S, Roeder, RG, "The metazoan Mediator co-activator complex as an integrative hub for transcriptional regulation" Nat Rev Genet. (2010) 11(11):761-72.

Examples of SWI/SNF complex genes that may serve as a marker for resistance to anticancer treatment in a patient as described herein include ARID1A, ARID1B, ARID2, SMARCA2, SMARCA4, PBRM1, SMARCC2, SMARCC1, SMARCD1, SMARCD2, SMARCD3, SMARCE1, ACTL6A, ACTL6B, and SMARCB1. *See, e.g.*, Reisman, D et al. "The SWI/SNF complex and cancer" Oncogene. (2009) 28(14):1653-68.

In some embodiments, the invention provides methods whereby measurement of reduced expression of a MEDIATOR complex and/or SWI/SNF complex gene in one or more cancer cells of a patient identifies these cancer cells as cells that may be resistant to treatment by one or more receptor tyrosine kinase (RTK) inhibitors. RTKs are involved in a number of diverse physiological processes, including proliferation and differentiation, cell survival and metabolism, cell migration, and cell-cycle control (*see, e.g.*, Lemmon, MA, Schlessinger, J "Cell Signaling by Receptor Tyrosine Kinases" Cell (2010) 141:1117-1134).

In addition, an overview of non-small cell lung cancer signaling pathways may be found at www(dot)n-of-one(dot)com/cancer-news-info/egfr/ and the figure presented therein adapted from Herbst, et al. NEJM 2008.

Described herein is the use of a large-scale loss-of-function genetic screen to identify genes whose suppression can confer resistance to crizotinib in a NSCLC cell line harboring an EML4-ALK translocation. Applicants identify a key component of the transcriptional MEDIATOR complex, MED12, as a determinant of crizotinib response in NSCLC. Remarkably, Applicants find that suppression of MED12 also confers resistance to a range of targeted cancer drugs in other cancer types as well, including colon cancer, melanoma and liver cancer. Applicants identify an unexpected activity of MED12 in regulating TGFβ receptor signaling, as the major mechanism of drug resistance induction.

Applicants identify herein MED12 as a candidate biomarker of response to a range of targeted cancer drugs in a variety of cancer types through a previously unappreciated role of this protein in TGFβ receptor signaling. MED12 is a component of the MEDIATOR transcriptional adapter complex that serves as a molecular bridge between the basal transcription machinery and its upstream activators (Conaway et al., 2005). More

specifically, MED12 is a subunit of the "kinase" module of the MEDIATOR complex, which also contains MED13, CYCLIN C and CDK8, whose gene sequence is amplified in some 50% of colon cancers (Firestein et al., 2008). The involvement of MEDIATOR components in responses to TKIs was unexpected, as most of the known genes that influence responses to TKIs involve components of signaling pathways that act downstream or in parallel of these receptors. Applicants reconcile this apparent discrepancy by demonstrating that part of MED12 also resides in the cytosol, where it interacts with the TGFβ type II receptor to inhibit its activity. Consequently, downregulation of MED12 by RNAi strongly activates TGFβ signaling, as evidenced by phosphorylation of SMAD2 and induction of many canonical TGFβ target genes. Activation of TGFβ signaling has been linked previously to activation of ERK signaling (reviewed by (Zhang, 2009)). Consistent with this, Applicants observed activation of ERK signaling by MED12 suppression, which persists in the presence of drugs like crizotinib, gefitinib, vemurafenib, seluteminib and sorafenib (Figures 17, 18 and data not shown), thus providing a rationale for why suppression of MED12 confers resistance to these drugs.

Applicants' data indicate that MED12 suppression also induces an EMT-like phenotype, as judged by the upregulation of the mesenchymal markers Vimentin and N-cadherin (Figures 29 and 30) and the general overlap between genes that are regulated by $MED12^{KD}$ and known EMT signature genes (Figure 33A). Applicants' data are consistent with the findings of others, who also witnessed resistance to EGFR inhibitors in cell lines undergoing EMT (Coldren et al., 2006; Frederick et al., 2007; Fuchs et al., 2008; Rho et al., 2009; Thomson et al., 2005; Yao et al., 2010). In the clinic, EMT transformation was also seen in 3 out of 7 NSCLC patients who developed resistance to EGFR TKIs and did not have one of the well-established secondary EGFR mutations causing drug resistance (Sequist et al., 2011). In some embodiments, such patients have acquired EMT as a result of MED12 loss. For example, MED12 was recently shown to be mutated in some 70% of uterine leiomyomas (Makinen et al., 2011). Applicants note that these mutations are highly clustered in the second exon of MED12, raising the possibility that these mutations are not null alleles. Consistent with this, Applicants observe that MED12 suppression often confers a slow-growth phenotype to cancer cells and that near-complete suppression of MED12 is not tolerated by most cells (Figures 2F, 17C, 17G and data not shown). Thus, in some embodiments, suppression of MED12 may not confer a selective advantage in the absence of drug, but may only become a benefit to the cancer cells when undergoing drug selection pressure. Consistent with this, Applicants observed that PC9 NSCLC, A375 melanoma and

Huh-7 HCC cells are growth-inhibited by $MED12^{KD}$, but this turns into a proliferative advantage when exposed to EGFR, BRAF or MEK inhibitors or the multikinase inhibitor sorafenib (Figures 2F, 17C and 17G). Therefore, in some embodiments, MED12 suppression may not be a marker of intrinsic drug resistance as its constitutive suppression could well be disadvantageous to the cancer cell, but it may be acquired during drug selection to resist the therapy. That cancer cells can transiently assume a reversible drug-tolerant state was recently shown by others (Sharma et al., 2010).

In certain embodiments, cancer cells that undergo an EMT-like process do so through suppression of MED12 expression. Investigation of this would require biopsies of tumors that have progressed following exposure to targeted therapies, which are very rare in today's clinical practice. Applicants' data show that the changes of gene expression triggered by MED12 suppression (through analysis of a set of $MED12^{KD}$ signature genes) are prognostic for disease outcome in colon cancer (Figure 33B) and predictive for responses to MEK inhibitors in a large and heterogeneous cell line panel (Figure 33C). In both of these studies, the mRNA levels of MED12 alone did not predict prognosis or drug responses (data not shown). This may be because MED12 protein levels are primarily regulated at a post-transcriptional level in tumors or because of alterations in MED12 activity as a result of mutation, as seen in leiomyomas (Makinen et al., 2011). Nevertheless, it is clear from Applicants' studies that MED12 suppression triggers activation of TGFβ signaling in tumors of lung, skin, liver and colon and results in an EMT-like phenotype associated with drug resistance. Applicants' data also demonstrate that inhibition of TGFβ signaling with small molecule drugs can reverse resistance to targeted cancer drugs (Figure 35). Accordingly, in some embodiments, EMT arising during drug resistance development, as seen in NSCLC (Sequist et al., 2011), may be countered by combination with a TGFβ antagonist, a notion that can readily be tested in the clinic.

In certain embodiments, identification of a reduced expression of a MEDIATOR complex and/or SWI/SNF complex gene in one or more cancer cells of a patient is indicative that the one or more cancer cells will be resistant to treatment by a compound or class of compounds, such as one or more receptor tyrosine kinase inhibitor compounds. Examples of RTK inhibitor compounds that cells expressing a reduced level of a MEDIATOR complex and/or SWI/SNF complex gene may be resistant to include gefitinib, erlotinib, EKB-569, lapatinib, CI-1033, cetuximab, panitumumab, PKI-166, AEE788, sunitinib, sorafenib, dasatinib, nilotinib, pazopanib, vandetaniv, cediranib, afatinib, motesanib, CUDC-101, and imatinib mesylate. Other RTK inhibitors that cells expressing a reduced level of a

MEDIATOR complex and/or SWI/SNF complex gene may be resistant to include the Alk-1 inhibitors crizotinib, ASP-3026, LDK378, AF802, and CEP37440.

In certain embodiments, identification of a reduced expression of a MEDIATOR complex and/or SWI/SNF complex gene in one or more cancer cells of a patient is indicative that the one or more cancer cells will be resistant to treatment by one or more ERK activation inhibitor compounds. Examples of ERK activation inhibitor compounds that cells expressing a reduced level of a MEDIATOR complex and/or SWI/SNF complex gene may be resistant to include compounds that inhibit the activity of a signaling protein upstream of ERK. Examples of signaling proteins upstream of ERK include MEK1, MEK2, A-RAF, B-RAF, RAF1, MOS, RTKs, and G-protein-coupled receptors. In certain embodiments, the compound that inhibits the activity of a signaling protein upstream of ERK inhibits a direct activator of ERK. Examples of direct ERK activators include MEK1 and MEK2. Examples of MEK inhibitors include CKI-27, RO-4987655, RO-5126766, PD-0325901, WX-554, AZD-8330, G-573, RG-7167, SF-2626, GDC-0623, RO-5068760, and AD-GL0001. In other embodiments, the compound that inhibits the activity of a signaling protein upstream of ERK inhibits an indirect activator of ERK. Examples of indirect ERK activators include A-RAF, B-RAF, RAF1RAF1, MOS, RTKs, and G-protein-coupled receptors. *See, e.g.*, Roux, PP, Blenis, J "ERK and p38 MAPK-activated protein kinases: a family of protein kinases with diverse biological functions" Microbiol Mol Biol Rev. (2004) 68(2):320-44. Examples of B-RAF inhibitors include CEP-32496, vemurafenib, GSK-2118436, ARQ-736, RG-7256, XL-281, DCC-2036, GDC-0879, AZ628, and antibody fragment EphB4/Raf inhibitors.

In some embodiments, an inhibitor inhibits the wild-type version of a protein, such as wild-type B-RAF. In other embodiments, an inhibitor inhibits a mutant form of a protein, such as mutant B-RAF (e.g., V600E). In yet other embodiments, an inhibitor inhibits both the wild-type and mutant form of a protein (e.g., both wild-type B-RAF and B-RAF^{V600E}).

In certain embodiments, identification of a reduced expression of a MEDIATOR complex and/or SWI/SNF complex gene in one or more cancer cells of a patient is indicative that the one or more cancer cells will be resistant to treatment by one or more compounds that are activators of one or more proteins that inactivate ERK. Examples of protein inactivators of ERK include phosphatases, such as the indirect inactivator of ERK, protein phosphatase 5 (PP5), which inactivates the ERK upstream activator, RAF1, by dephosphorylation.

In certain embodiments, the prognostic methods and compositions of the instant invention predict resistance to anticancer treatment to a combination of chemotherapeutic agents, wherein the at least two chemotherapeutic agents are administered at the same time

and/or sequentially. In further embodiments, the invention provides methods wherein a measurement of reduced expression of a MEDIATOR complex and/or SWI/SNF complex and/or RAS-GAP gene in one or more cancer cells of a tumor of a patient identifies the tumor as one that may be resistant to treatment by a combination of at least two ERK activation inhibitors. In other embodiments, the tumor is one that may be resistant to treatment by a combination of at least two compounds that activate one or more proteins upstream of ERK that inactivates ERK signaling.

In some embodiments, activation of the TGF-β (transforming grow factor beta) pathway rescues ERK activation in, for example, a cancer cell. Accordingly, in some embodiments, the prognostic methods and compositions of the instant invention provide methods and compositions wherein a measurement of reduced expression of a MEDIATOR complex and/or SWI/SNF complex and/or RAS-GAP gene in one or more cancer cells of a tumor of a patient identifies the tumor as one that may benefit from treatment with an inhibitor of the TGFβ pathway (e.g., a TGFβ inhibitor and/or inhibitor of one or more downstream signaling proteins in the TGF- β pathway) in combination with one or more ERK activation inhibitors. In other embodiments, the prognostic methods and compositions of the instant invention provide methods and compositions wherein a measurement of reduced expression of a MEDIATOR complex and/or SWI/SNF complex and/or RAS-GAP gene in one or more cancer cells of a tumor of a patient identifies the tumor as one that may benefit from treatment with an inhibitor of the TGF- β pathway in combination with one or more compounds that activate one or more proteins upstream of ERK that inactivates ERK signaling. In certain embodiments, the inhibitor of ERK activation is an RTK inhibitor. In other embodiments, the inhibitor of ERK activation is a B-RAF inhibitor. In yet other embodiments, the inhibitor of ERK activation is a MEK inhibitor. In still other embodiments, the inhibitor of ERK activation is a RAS inhibitor.

In other embodiments, the prognostic methods and compositions of the instant invention provide methods and compositions wherein a measurement of increased expression of a TGFβ pathway gene in one or more cancer cells of a tumor of a patient identifies the tumor as one that may benefit from treatment with an inhibitor of the TGFβ pathway (e.g., a TGFβ inhibitor and/or inhibitor of one or more downstream signaling proteins in the TGFβ pathway) in combination with one or more ERK activation inhibitors. In certain embodiments, the patient is one in need of treatment with an ERK activation inhibitor. In other embodiments, the patient is one in need of treatment with an inhibitor of a TGFβ pathway gene or protein. In other embodiments, the prognostic methods and compositions of

the instant invention provide methods and compositions wherein a measurement of increased expression of a TGFβ pathway gene in one or more cancer cells of a tumor of a patient identifies the tumor as one that may benefit from treatment with an inhibitor of the TGFβ pathway in combination with one or more compounds that activate one or more proteins upstream of ERK that inactivates ERK signaling. In certain embodiments, the inhibitor of ERK activation is an RTK inhibitor. In other embodiments, the inhibitor of ERK activation is a B-RAF inhibitor. In yet other embodiments, the inhibitor of ERK activation is a MEK inhibitor. In still other embodiments, the inhibitor of ERK activation is a RAS inhibitor.

In other embodiments, the prognostic methods and compositions of the instant invention provide methods and compositions wherein a measurement of increased expression of a TGFβ pathway gene in one or more cancer cells of a patient indicates the patient may be resistant to anticancer treatment. In other embodiments, the prognostic methods and compositions of the instant invention provide methods and compositions wherein a measurement of an activating mutation in a TGFβ pathway gene in one or more cancer cells of a patient identifies the one or more cancer cells as cells that may be resistant to anticancer treatment.

In some embodiments, the invention provides methods and compositions for the treatment of primary and/or secondary resistance to one or more anticancer agents in a patient in need thereof, comprising administration of at least one inhibitor of the TGFβ pathway in combination with the one or more anticancer agents to which primary and/or secondary resistance in the patient has developed. For example, in some embodiments, the invention relates to a method of treating secondary resistance to an inhibitor of ERK activation in a patient in need thereof, comprising administering to the patient at least one inhibitor of the TGFβ pathway (e.g., a TGFβ inhibitor) in combination with the inhibitor of ERK activation.

In certain embodiments, the invention provides methods and compositions related to a method of treating cancer in a patient in need thereof, comprising administering to the patient an inhibitor of ERK activation in combination with an inhibitor of TGFβ pathway activation. In some embodiments, the patient is treated without determining whether the patient would be likely to be resistant to one or more of the ERK activation and/or TGFβ pathway activation inhibitors.

In some embodiments, the markers of the instant invention enable the detection of resistance to anticancer treatment in a patient in combination with one or more known markers of hypersensitivity to a chemotherapeutic agent or class of agents. In certain embodiments, expression levels of one or more MEDIATOR complex and/or SWI/SNF

complex genes (e.g., MED12, SMARCE1, and/or ARIDA1) are measured in one or more cancer cells of a patient in combination with an array profile, such as a CGH (comparative genomic hybridization) array analysis.

In certain embodiments, the invention provides methods and compositions for identifying a cancer patient who would likely not benefit from a certain chemotherapeutic treatment. For example, an aspect of the invention is a method of screening cancer patients to determine those cancer patients more likely to benefit from a particular chemotherapy, such as RTK inhibitor chemotherapy, comprising obtaining a sample of genetic material from a tumor of the patient; and assaying for the presence of a genotype in the patient that is associated with resistance to the particular chemotherapy, the genotype characterized by an inactivating mutation in one or more MEDIATOR complex and/or SWI/SNF complex genes. In some embodiments, the genotype is further characterized by an inactivating mutation in one or more known markers for chemotherapeutic resistance. In some embodiments, the genetic material is nucleic acid that is characterized by a reduced expression (e.g., reduced mRNA levels) of one or more MEDIATOR complex and/or SWI/SNF complex genes. In further embodiments, reduced mRNA levels are assessed by the evaluating the corresponding cDNA.

In a particular embodiment, the instant invention provides methods and compositions for the identification of a lung cancer patient who would likely not benefit from RTK inhibitor chemotherapy (e.g., the patient will be recurrence-free for a period of time less than a patient undergoing the same chemotherapy). In some embodiments, the methods of the instant invention predict whether a chemotherapeutic agent or other compound is likely to be cytotoxic to one or more cancer cells.

Cancers for which the prognostic methods and compositions of the instant invention may provide predictive results for resistance to anticancer treatment include cancers such as breast cancer (e.g., BRCA-1 deficient, stage-III HER2-negative), ovarian cancer (e.g., BRCA-1 deficient, epithelial ovarian cancer), lung cancer (e.g., non-small-cell lung cancer or small cell lung cancer, metastatic non-small cell lung cancer), liver cancer (e.g., hepatocellular carcinoma), head and neck cancer (e.g., metastatic squamous cell carcinoma of the head and neck (SCCHN), squamous cell carcinoma, laryngeal cancer, hypopharyngeal cancer, oropharyngeal cancer, and oral cavity cancer), bladder cancer (e.g., transitional cell carcinoma of the bladder), and colorectal cancer (e.g., advanced (non-resectable locally advanced or metastatic) colorectal cancer). Other cancers for which the methods and compositions of the invention may provide predictive results for resistance to anticancer

treatment include cervical cancer (e.g., recurrent and stage IVB), mesothelioma, solid tumors (e.g., advanced solid tumors), renal cell carcinoma (e.g., advanced renal cell carcinoma), stomach cancer, sarcoma, prostate cancer (e.g., hormone refractory prostate cancer), melanoma, thyroid cancer (e.g., papillary thyroid cancer), brain cancer, adenocarcinoma, subependymal giant cell astrocytoma, endometrial cancer, glioma, glioblastoma, and other tumors that have metastasized to the brain, esophageal cancer, neuroblastoma, hematological cancers, and lymphoma.

In some embodiments, the cancer is one in which one or more RTK inhibitor drugs are employed either alone or in combination with other chemotherapeutic agents as a part of an anticancer treatment regimen. In other embodiments, the cancer is one in which one or more RTK inhibitor drugs are employed either alone or in combination with additional treatment regimens, such as surgical procedures, radiation, and/or other anticancer treatments. In certain embodiments, the cancer is one in which one or more RTK inhibitor agents are used as a first-line form of treatment. In yet other embodiments, the one or more RTK inhibitor drugs are employed in combination with an inhibitor of the TGF-beta pathway.

In certain embodiments, the instant invention relates to methods and compositions encompassing the detection of expression levels of a MEDIATOR complex and/or SWI/SNF complex and/or RAS-GAP gene in one or more cells of a subject. Typically, the subject is a human patient who has or is suspected of having at least one type of cancer, and the expression levels of the MEDIATOR complex and/or SWI/SNF complex and/or RAS-GAP gene are detected in a sample of one or more cells, typically one or more tumor cells, from the human patient, which are then compared with the expression levels of the MEDIATOR complex and/or SWI/SNF complex and/or RAS-GAP gene in a control sample. A control sample will generally be one in which the MEDIATOR complex and/or SWI/SNF complex and/or RAS-GAP gene expression levels are known and correlated with resistance to anticancer treatment to a certain drug or group of drugs. In some embodiments, the control sample is one in which the MEDIATOR complex and/or SWI/SNF complex and/or RAS-GAP gene expression levels are known and correlated with a lack of resistance to anticancer treatment to a certain drug or group of drugs. In certain embodiments, the MEDIATOR complex and/or SWI/SNF complex and/or RAS-GAP gene expression levels in one or more tumor cells of a patient are compared with the expression levels in one or more normal cells of the patient, wherein a reduced expression in the one or more tumor cells in comparison to the normal cells of the patient are predictive of resistance to anticancer treatment to a certain drug or group of drugs. In some embodiments, more than one control sample is used for

comparative purposes with the test sample from the subject. In certain embodiments, the expression levels of a MEDIATOR complex gene are detected. In other embodiments, the expression levels of a SWI/SNF complex gene are detected. In yet other embodiments, the expression levels of a RAS-GAP gene are detected.

In certain embodiments, the invention relates to a method for predicting a lung cancer patient's response to RTK inhibitor drug chemotherapy, such as gefitinib or erlotinib treatment. In some embodiments, the lung cancer patient has not yet received RTK inhibitor drug chemotherapy. In further embodiments, a sample of the lung cancer cells from the patient is analyzed for the levels of expression of a MEDIATOR complex and/or SWI/SNF complex gene, such as MED12, SMARCE1, and/or ARIDA1, and or a RAS-GAP gene, such as DAB2IP, NF1, and/or RASAL3. If expression levels of the MEDIATOR complex and/or SWI/SNF complex gene (e.g., MED12, SMARCE1, and/or ARIDA1) and/or RAS-GAP gene (e.g., DAB2IP, NF1, and/or RASAL3) are low compared to expression levels in normal lung tissue, then the lung cancer cells in the patient are likely resistant to RTK inhibitor anticancer treatment.

In certain embodiments, the expression level of the MEDIATOR complex and/or SWI/SNF complex gene, such as MED12, SMARCE1, and/or ARIDA1, and/or RAS-GAP gene, such as DAB2IP, NF1, and/or RASAL3 in cancer tissue is lower than the expression level of the gene in normal tissue. In predicting resistance to anticancer treatment of a tumor, cut-off levels of expression may be determined empirically for the subject cancer for which resistance to anticancer treatment is being assessed.

In other embodiments, the instant invention relates to methods and compositions encompassing the detection of one or more inactivating mutations in a MEDIATOR complex and/or SWI/SNF complex and/or RAS-GAP gene in one or more cells of a subject. Typically, the subject is a human patient who has or is suspected of having at least one type of cancer, and the nucleic acid of the MEDIATOR complex and/or SWI/SNF complex and/or RAS-GAP are isolated from a sample of one or more cells, typically one or more tumor cells, from the human patient, which are then compared with the nucleic acid of the MEDIATOR complex and/or SWI/SNF complex and/or RAS-GAP in a control sample. A control sample will generally be one in which the MEDIATOR complex and/or SWI/SNF complex and/or RAS-GAP nucleic acid sequences are known and correlated with resistance to anticancer treatment to a certain drug or group of drugs. In some embodiments, the control sample is one in which the MEDIATOR complex and/or SWI/SNF complex and/or RAS-GAP nucleic acid sequences are known and correlated with a lack of resistance to anticancer treatment to a

certain drug or group of drugs. In some embodiments, more than one control sample is used for comparative purposes with the test sample from the subject. In certain embodiments, the inactivating mutation is a point mutation. In some embodiments, the inactivating mutation is a hypomorphic mutation. In other embodiments, the inactivating mutation is a gene deletion. In yet other embodiments, the inactivating mutation is an amplification.

In some embodiments, the instant invention relates to methods and compositions encompassing evaluating the protein activity and/or sequence and/or posttranslational modification state of one or more RAS-GAP proteins and/or proteins in a MEDIATOR complex and/or SWI/SNF complex in one or more cells of a subject. Typically, the subject is a human patient who has or is suspected of having at least one type of cancer, and the RAS-GAP protein and/or protein of the MEDIATOR complex and/or SWI/SNF complex is isolated from a sample of one or more cells, typically one or more tumor cells, from the human patient, which are then compared with the RAS-GAP protein and/or protein of the MEDIATOR complex and/or SWI/SNF complex in a control sample. A control sample will generally be one in which the RAS-GAP protein and/or MEDIATOR complex and/or SWI/SNF complex protein sequences and/or activity and/or posttranslational modification state are known and correlated with resistance to anticancer treatment to a certain drug or group of drugs. In some embodiments, the control sample is one in which the RAS-GAP protein and/or MEDIATOR complex and/or SWI/SNF complex protein sequences and/or activity and/or posttranslational modification state are known and correlated with a lack of resistance to anticancer treatment to a certain drug or group of drugs.

Evaluation of protein activity includes assaying the enzymatic activity of the protein. In certain embodiments, the posttranslational modification status of the protein is assessed. In further embodiments, one or more posttranslational modifications (or lack thereof) is associated with protein dysfunction, such as reduced enzymatic activity by the protein. In some embodiments, the RAS-GAP and/or MEDIATOR complex and/or SWI/SNF complex protein in one or more cells of a subject is dysfunctional, and this dysfunction is indicative of resistance to one or more anticancer treatments. Examples of protein dysfunction include reduced or no enzymatic and/or binding activity of the protein; reduced or no protein expression; and/or improper protein modification, such as phosphorylation that results in inactivity of the protein.

The terms "marker" and "biomarker" are used interchangeably herein and refer to a gene, protein, or fragment thereof, the expression or level or activity of which changes between certain conditions. Where the expression or level or activity of the gene, protein, or

fragment thereof correlates with a certain condition, the gene, protein, or fragment thereof is a marker for that condition.

"Resistant," "resistance," or "resistance to anticancer treatment" in the context of treatment of a cancer cell with a chemotherapeutic agent or other compound means that the chemotherapeutic agent or other compound is not likely to have an optimal effect on the cancer cell. In some embodiments, the compound is not likely to have any effect on the cancer cells. In certain embodiments, the effect of a compound on one or more cancer cells is reduced. In certain further embodiments, a tumor is likely to be less sensitive to a compound but not completely resistant to it. In certain embodiments, the compound is not likely to be cytotoxic to the cancer cell. In some embodiments, the compound is not cytotoxic to the cancer cell.

By "primary resistance" with regard to one or more cancer cells in a patient is meant cells that are naïve for anticancer treatment. For example, a tumor that demonstrates primary resistance to an anticancer treatment includes one that has never been treated with the anticancer drug or drugs but demonstrates or is predicted to demonstrate resistance to the anticancer drug or drugs once treatment has begun.

By "secondary resistance" with regard to one or more cancer cells in a patient is meant cells that have acquired resistance to an anticancer treatment. For example, a tumor that demonstrates secondary resistance to an anticancer treatment includes one that has been treated for a prolonged period of time with one or more anticancer drugs but resistance arises to the one or more anticancer drugs after treatment.

By "inactivating mutation" is meant a mutation in, for example, a nucleic acid that encodes a protein that is inactive. This includes, for example, mutations that result in the loss of protein expression and/or activity and includes genetic mutations such as point mutations, translocations, amplifications, deletions (including whole gene deletions), and hypomorphic mutations (e.g., where an altered gene product possesses a reduced level of activity or where the wild-type gene product is expressed at a reduced level). "Inactivating mutation" also includes biomarker dysfunctions due to post-translational protein regulation, for example, where a protein biomarker is inactive or exhibits impaired activity due to, for example, one or more posttranslational modifications, such as phosphorylation that results in protein inactivity.

The term "biomarker dysfunction" with regard to a protein or protein fragment refers to dysfunction of the protein or fragment thereof as a result of improper regulation at the posttranslational level, such as, for example, phosphorylation that results in protein inactivity.

By "MEDIATOR complex gene" is meant any gene encoding for a protein of the MEDIATOR complex.

By "reference MEDIATOR complex gene" is meant a MEDIATOR complex gene in a control sample, e.g., a normal sample such as a non-cancerous tissue sample. Typically, the expression levels of a reference MEDIATOR complex gene serve as a reference for comparative purposes with the levels of expression of the same MEDIATOR complex gene in a different sample, typically a test sample, such as a lung tumor sample.

By "SWI/SNF complex gene" is meant any gene encoding for a protein of the SWI/SNF complex.

By "reference SWI/SNF complex gene" is meant a SWI/SNF complex gene in a control sample, e.g., a normal sample such as a non-cancerous tissue sample. Typically, the expression levels of a reference SWI/SNF complex gene serve as a reference for comparative purposes with the levels of expression of the same SWI/SNF complex gene in a different sample, typically a test sample, such as a lung tumor sample.

By "RAS-GAP gene" is meant any gene encoding for a RAS-GAP protein.

By "reference RAS-GAP gene" is meant a RAS-GAP gene in a control sample, e.g., a normal sample such as a non-cancerous tissue sample. Typically, the expression levels of a reference RAS-GAP gene serve as a reference for comparative purposes with the levels of expression of the same RAS-GAP gene in a different sample, typically a test sample, such as a lung tumor sample.

By "TGFβ pathway gene" is meant any gene encoding for a protein in the TGFβ signaling pathway.

By "TGFβ pathway target gene" is meant any gene whose expression is regulated by TGFβ signaling.

By "reference TGFβ pathway gene" is meant a TGFβ signaling pathway gene in a control sample, e.g., a normal sample such as a non-cancerous tissue sample. Typically, the expression levels of a reference TGFβ pathway gene serve as a reference for comparative purposes with the levels of expression of the same TGFβ pathway gene in a different sample, typically a test sample, such as a lung tumor sample.

By "$MED12^{KD}$ signature" is meant the nucleic acid expression profile depicted in Figure 37. Figure 37 depicts the genes deregulated by $MED12^{KD}$ (>2 fold) in at least three out of five cell lines used. The term "$MED12^{KD}$ signature" includes the 237 upregulated genes and 22 downregulated genes depicted in Figure 37, as well as any protein products of these genes.

By "positive reference MED12KD signature nucleic acid and/or proteins" is meant the nucleic acid expression profile of one or more genes depicted in Figure 37 in one or more independent control sample cells known to be resistant to an anticancer treatment, e.g., one or more cells of a cancer cell line or a tumor sample. Typically, the expression levels of a positive reference MED12KD signature gene serve as a reference for comparative purposes with the levels of expression of the same MED12KD signature gene in a different sample, typically a test sample, such as a lung tumor sample.

By "negative reference MED12KD signature nucleic acid and/or proteins" is meant the nucleic acid expression profile of one or more genes depicted in Figure 37 in one or more independent control sample cells know to be sensitive to an anticancer treatment, e.g., a normal sample such as a non-cancerous tissue sample. Typically, the expression levels of a negative reference MED12KD signature gene serve as a reference for comparative purposes with the levels of expression of the same MED12KD signature gene in a different sample, typically a test sample, such as a lung tumor sample. In some embodiments, the control sample cell is derived from a tumor sample from a patient prior to chemotherapeutic treatment. The control sample in these embodiments can serve as a reference for comparative purposes with the levels of expression of the same MED12KD signature gene in a different sample cell that is derived from a tumor sample from the patient after chemotherapeutic treatment. In other embodiments, the control sample is the average expression of the Figure 37 genes that is determined in a collection of tumor or cell line samples. The term "negative reference MED12KD signature" likewise includes the expression levels of a random set of genes in the test sample. In these embodiments, the random set of genes from the test sample, which may include one or more of the genes depicted in Figure 37, are used for comparative purposes with the expression levels of the genes depicted in Figure 37 in the test sample.

The term "EMT-like phenotype" refers to a partial epithelial–mesenchymal transition (EMT), leading to the induction of mesenchymal markers such as vimentin (VIM) and N-cadherin (CDH2), but not the loss of at least one epithelial marker, such as E-cadherin. As described herein, $MED12^{KD}$ causes expression of the mesenchymal markers VIM and CDH2, indicating that an EMT-like process is initiated in $MED12^{KD}$ cells.

By "interact directly" is meant that a protein or other molecular compound binds and/or enzymatically interacts with a target protein. For example, MEK1 interacts directly with ERK.

By "interact indirectly" is meant that a protein or other molecular compound binds and/or enzymatically interacts with a cellular protein or other molecular compound that may

itself interact with a second cellular protein and so forth until a final cellular protein interacts directly with a target protein. This includes any upstream activators of a target protein, such as ERK, in a signaling cascade, such as a receptor tyrosine kinase signaling cascade. Examples of proteins that interact indirectly with ERK include A-RAF, B-RAF, RAF1, MOS, RTKs, and G-protein-coupled receptors.

By "similar" in the context of the expression of one or more nucleic acid and/or proteins is meant that the expression levels of one or more nucleic acid and/or proteins in one sample is the same as or about the same as the expression levels of the one or more nucleic acid and/or proteins in a second sample. In certain embodiments, the expression levels of a gene are the same (e.g., no measurable difference) between two different samples. In other embodiments, the expression levels of a gene are about the same (e.g., within experimental margins of error) between two different samples.

In various aspects, determination of a level of expression of nucleic acid and/or protein in a test sample that is the same, greater than, or less than that produced by the corresponding nucleic acid and/or protein in a positive reference MED12KD signature is indicative of resitence to anticancer treatment in the tumor from which the test sample was derived. Accordingly, in certain embodiments detection of signal intensity from a test sample that is the same, within experimentally acceptable margins of error, as the signal intensity produced by the positive reference MED12KD signature sample is sufficient to classify the tumor from which the test sample was produced as anticancer treatment resistant. In certain embodiments, detection of signal intensity from a test sample that is greater, within experimentally acceptable margins of error, than the signal intensity produced by the positive reference MED12KD signature sample is sufficient to classify the tumor from which the test sample was produced as anticancer treatment resistant. In certain embodiments, detection of signal intensity from a test sample that is less, within experimentally acceptable margins of error, than the signal intensity produced by the positive reference MED12KD signature sample is sufficient to classify the tumor from which the test sample was produced as anticancer treatment resistant.

In certain embodiments, the deviation of signal intensity of the test sample from the positive reference MED12KD signature sample is measured as a percent difference. In certain embodiments, a test sample is deemed to have produced a signal that is greater than the positive reference MED12KD signature sample if the signal intensity of the test sample measures at a level selected from: the signal intensity of the positive reference MED12KD signature sample greater than 1 %; greater than 2 %; greater than 5%; greater than 10%;

greater than 15%; greater than 20%; the greater than 25%; greater than 30%; greater than 35%; greater than 40%; greater than 45%; greater than 50%; greater than 55%; greater than 60%; greater than 65%; greater than 70%; greater than 75%; greater than 80%; greater than 85%; greater than 90%; greater than 95%; or greater than 100%.

In certain embodiments, a test sample is deemed to have produced a signal that is less than the positive reference MED12KD signature sample if the signal intensity of the test sample measures at a level selected from: the signal intensity of the reference sample less 1 %; less 2 %; less 5%; less 10%; less 15%; less 20%; less 25%; less 30%; less 35%; less 40%; less 45%; less 50%; less 55%; less 60%; less 65%; less 70%; less 75%; less 80%; less 85%; less 90%; less 95%; or less 100% (or no signal produced by the test sample).

In certain embodiments, the deviation of signal intensity of the test sample from the positive reference MED12KD signature sample is measured as a -fold difference, or a difference based upon unit signal production. In certain embodiments, a test sample is deemed to have produced a signal that is greater than the positive reference MED12KD signature sample if the signal intensity of the test sample is selected from: two-fold greater than; three-fold greater than; four-fold greater than; five-fold greater than; six-fold greater than; seven-fold greater than; eight-fold greater than; nine-fold greater than; ten-fold greater; and more than ten-fold greater than the signal intensity of the positive reference MED12KD signature sample.

In certain embodiments, a test sample is deemed to have produced a signal that is less than the positive reference MED12KD signature sample if the signal intensity of the test sample is selected from: two-fold less than; three-fold less than; four-fold less than; five-fold less than; six-fold less than; seven-fold less than; eight-fold less than; nine-fold less than; ten-fold less than; and greater than ten-fold less than the signal intensity of the positive reference MED12KD signature sample.

In certain embodiments where the expression of a nucleic acid and/or protein in a test sample is compared with the expression level of the same nucleic acid and/or protein in a positive reference MED12KD signature nucleic acid and/or protein sample, expression of the test sample nucleic acid and/or protein that is the same as (e.g., no measureable difference) or greater than (e.g., more than 10-fold greater than) the expression level of the nucleic acid and/or protein corresponding to an upregulated gene in the positive reference MED12KD signature, then resistance to anticancer treatment in the test sample is indicated.

In certain embodiments where the expression of a nucleic acid and/or protein in a test sample is compared with the expression level of the same nucleic acid and/or protein in a

positive reference MED12KD signature nucleic acid and/or protein, expression of the test sample nucleic acid and/or protein that is the same as (e.g., no measureable difference) or less than (e.g., more than 10-fold less than) the expression level of the nucleic acid and/or protein corresponding to a downregulated gene in the positive reference MED12KD signature, then resistance to anticancer treatment in the test sample is indicated.

In various aspects, determination of a level of expression of nucleic acid and/or protein in a test sample that is greater than or less than that produced by the corresponding nucleic acid and/or protein in a negative reference MED12KD signature is indicative of resitence to anticancer treatment in the tumor from which the test sample was derived. Accordingly, in certain embodiments, detection of signal intensity from a test sample that is greater, within experimentally acceptable margins of error, than the signal intensity produced by the negative reference MED12KD signature sample is sufficient to classify the tumor from which the test sample was produced as anticancer treatment resistant. In certain embodiments, detection of signal intensity from a test sample that is less, within experimentally acceptable margins of error, than the signal intensity produced by the negative reference MED12KD signature sample is sufficient to classify the tumor from which the test sample was produced as anticancer treatment resistant.

In certain embodiments, the deviation of signal intensity of the test sample from the negative reference MED12KD signature sample is measured as a percent difference. In certain embodiments, a test sample is deemed to have produced a signal that is greater than the positive reference MED12KD signature sample if the signal intensity of the test sample measures at a level selected from: the signal intensity of the positive reference MED12KD signature sample greater than 1%, greater than 2%, greater than 5%; greater than 10%; greater than 15%; greater than 20%; the greater than 25%; greater than 30%; greater than 35%; greater than 40%; greater than 45%; greater than 50%; greater than 55%; greater than 60%; greater than 65%; greater than 70%; greater than 75%; greater than 80%; greater than 85%; greater than 90%; greater than 95%; or greater than 100%.

In certain embodiments, a test sample is deemed to have produced a signal that is less than the negative reference MED12KD signature sample if the signal intensity of the test sample measures at a level selected from: the signal intensity of the reference sample less 1%, less 2 %, less 5%; less 10%; less 15%; less 20%; less 25%; less 30%; less 35%; less 40%; less 45%; less 50%; less 55%; less 60%; less 65%; less 70%; less 75%; less 80%; less 85%; less 90%; less 95%; or less 100% (or no signal produced by the test sample).

In certain embodiments, the deviation of signal intensity of the test sample from the negative reference MED12KD signature sample is measured as a -fold difference, or a difference based upon unit signal production. In certain embodiments, a test sample is deemed to have produced a signal that is greater than the negative reference MED12KD signature sample if the signal intensity of the test sample is selected from: one-fold greater than; one-and-half-fold greater than; two-fold greater than; three-fold greater than; four-fold greater than; five-fold greater than; six-fold greater than; seven-fold greater than; eight-fold greater than; nine-fold greater than; ten-fold greater; and more than ten-fold greater than the signal intensity of the negative reference MED12KD signature sample.

In certain embodiments, a test sample is deemed to have produced a signal that is less than the negative reference MED12KD signature sample if the signal intensity of the test sample is selected from: one-fold less than; one-and-half-fold less than; two-fold less than; three-fold less than; four-fold less than; five-fold less than; six-fold less than; seven-fold less than; eight-fold less than; nine-fold less than; ten-fold less than; and greater than ten-fold less than the signal intensity of the negative reference MED12KD signature sample.

In certain embodiments where the expression of a nucleic acid and/or protein in a test sample is compared with the expression level of the same nucleic acid and/or protein in a negative reference MED12KD signature nucleic acid and/or protein sample, expression of the test sample nucleic acid and/or protein that is greater than (e.g., more than 1.2-fold greater than) the expression level of the nucleic acid and/or protein corresponding to an upregulated gene in the negative reference MED12KD signature, then resistance to anticancer treatment in the test sample is indicated.

In certain embodiments where the expression of a nucleic acid and/or protein in a test sample is compared with the expression level of the same nucleic acid and/or protein in a negative reference MED12KD signature nucleic acid and/or protein, expression of the test sample nucleic acid and/or protein that is less than (e.g., more than 1.2-fold less than) the expression level of the nucleic acid and/or protein corresponding to a downregulated gene in the negative reference MED12KD signature, then resistance to anticancer treatment in the test sample is indicated.

As used herein, the terms "drug," "agent," and "compound," either alone or together with "chemotherapeutic" or "chemotherapy," encompass any composition of matter or mixture which provides some pharmacologic effect that can be demonstrated in-vivo or in vitro. This includes small molecules, antibodies, microbiologicals, vaccines, vitamins, and

other beneficial agents. As used herein, the terms further include any physiologically or pharmacologically active substance that produces a localized or systemic effect in a patient.

The term "nucleic acid" encompasses DNA, RNA (e.g., mRNA, tRNA), heteroduplexes, and synthetic molecules capable of encoding a polypeptide and includes all analogs and backbone substitutes such as PNA that one of ordinary skill in the art would recognize as capable of substituting for naturally occurring nucleotides and backbones thereof. Nucleic acids may be single stranded or double stranded, and may be chemical modifications. The terms "nucleic acid" and "polynucleotide" are used interchangeably. Because the genetic code is degenerate, more than one codon may be used to encode a particular amino acid, and the present compositions and methods encompass nucleotide sequences which encode a particular amino acid sequence.

Unless otherwise indicated, nucleic acids are written left to right in 5′ to 3′ orientation; amino acid sequences are written left to right in amino to carboxy orientation, respectively.

"Antisense" nucleic acids are DNA or RNA molecules that are complementary to at least a portion of a specific mRNA molecule (Weintraub, Scientific American 262 40, 1990). In the cell, the antisense nucleic acids hybridize to the corresponding mRNA, forming a double-stranded molecule. This interferes with the translation of the mRNA since the cell will not translate an mRNA that is double-stranded. Antisense oligomers of at least about 15, about 20, about 25, about 30, about 35, about 40, or of at least about 50 nucleotides are preferred, since they are easily synthesized and are less likely to cause non-specific interference with translation than larger molecules. The use of antisense methods to inhibit the in vitro translation of genes is well known in the art (Marcus-Sakura Anal. Biochem. 172: 289, 1998).

Short double-stranded RNAs (dsRNAs; typically <30 nucleotides) can be used to silence the expression of target genes in animals and animal cells. Upon introduction, the long dsRNAs enter the RNA interference (RNAi) pathway which involves the production of shorter (20-25 nucleotide) small interfering RNAs (siRNAs) and assembly of the siRNAs into RNA-induced silencing complexes (RISCs). The siRNA strands are then unwound to form activated RISCs, which cleave the target RNA. Double stranded RNA has been shown to be extremely effective in silencing a target RNA.

General methods of using antisense, ribozyme technology and RNAi technology, to control gene expression, or of gene therapy methods for expression of an exogenous gene in this manner are well known in the art. Each of these methods utilizes a system, such as a

vector, encoding either an antisense or ribozyme transcript. The term "RNAi" stands for RNA interference. This term is understood in the art to encompass technology using RNA molecules that can silence genes. See, for example, McManus, et al. Nature Reviews Genetics 3: 737, 2002. In this application, the term "RNAi" encompasses molecules such as small interfering or short interfering RNA (siRNA), small hairpin or short hairpin RNA (shRNA), microRNAs, and small temporal RNA (stRNA). Generally speaking, RNA interference results from the interaction of double-stranded RNA with genes.

The antisense oligonucleotides can be of any length; for example, in alternative aspects, the antisense oligonucleotides are between about 5 to 100, about 10 to 80, about 15 to 60, about 18 to 40. The optimal length can be determined by routine screening. The antisense oligonucleotides can be present at any concentration. The optimal concentration can be determined by routine screening. In certain embodiments, siRNA molecules are 12-28 nucleotides long, more preferably 15-25 nucleotides long, still more preferably 19-23 nucleotides long and most preferably 21-23 nucleotides long. In certain embodiments, preferred siRNA molecules are 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 28 or 29 nucleotides in length.

As used herein, the term "amino acid sequence" is synonymous with the terms "polypeptide," "protein," and "peptide," and are used interchangeably. Where such amino acid sequences exhibit activity, they may be referred to as an "enzyme." The conventional one-letter or three-letter code for amino acid residues are used herein.

As used herein, a "synthetic" molecule is produced by *in vitro* chemical or enzymatic synthesis rather than by an organism.

As used herein, the term "expression" refers to the process by which a polypeptide is produced based on the nucleic acid sequence of a gene. The process includes both transcription and translation. The term "expression" also includes the protein product of a translated mRNA. The term "expression" as it refers to protein includes both protein levels and protein activity (e.g., protein binding, enzymatic activity, etc.). The term "expression" also refers to the transcription of non-translated nucleic acid (e.g., non-coding mRNA).

A "gene" refers to the DNA segment encoding a polypeptide or RNA.

By "homolog" is meant an entity having a certain degree of identity with the subject amino acid sequences and the subject nucleotide sequences. As used herein, the term "homolog" covers identity with respect to structure and/or function, for example, the expression product of the resultant nucleotide sequence has the enzymatic activity of a subject amino acid sequence. With respect to sequence identity, preferably there is at least 70%, 75%, 80%, 81%,

82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or even 99% sequence identity. These terms also encompass allelic variations of the sequences. The term, homolog, may apply to the relationship between genes separated by the event of speciation or to the relationship between genes separated by the event of genetic duplication.

Relative sequence identity can be determined by commercially available computer programs that can calculate % identity between two or more sequences using any suitable algorithm for determining identity, using, for example, default parameters. A typical example of such a computer program is CLUSTAL. Advantageously, the BLAST algorithm is employed, with parameters set to default values. The BLAST algorithm is described in detail on the National Center for Biotechnology Information (NCBI) website.

The homologs of the peptides as provided herein typically have structural similarity with such peptides. A homolog of a polypeptide includes one or more conservative amino acid substitutions, which may be selected from the same or different members of the class to which the amino acid belongs.

In one embodiment, the sequences may also have deletions, insertions or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent substance. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues as long as the secondary binding activity of the substance is retained. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine, valine, glycine, alanine, asparagine, glutamine, serine, threonine, phenylalanine, and tyrosine.

The present invention also encompasses conservative substitution (substitution and replacement are both used herein to mean the interchange of an existing amino acid residue with an alternative residue) that may occur e.g., like-for-like substitution such as basic for basic, acidic for acidic, polar for polar, etc. Non-conservative substitution may also occur e.g., from one class of residue to another or alternatively involving the inclusion of unnatural amino acids such as ornithine (hereinafter referred to as Z), diaminobutyric acid ornithine (hereinafter referred to as B), norleucine ornithine (hereinafter referred to as O), pyriylalanine, thienylalanine, naphthylalanine and phenylglycine. Conservative substitutions that may be made are, for example, within the groups of basic amino acids (Arginine, Lysine and Histidine), acidic amino acids (glutamic acid and aspartic acid), aliphatic amino acids (Alanine, Valine,

Leucine, Isoleucine), polar amino acids (Glutamine, Asparagine, Serine, Threonine), aromatic amino acids (Phenylalanine, Tryptophan and Tyrosine), hydroxyl amino acids (Serine, Threonine), large amino acids (Phenylalanine and Tryptophan) and small amino acids (Glycine, Alanine).

The present invention employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA and immunology, which are within the capabilities of a person of ordinary skill in the art. Such techniques are explained in the literature. See, for example, J. Sambrook, E. F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Second Edition, Books 1-3, Cold Spring Harbor Laboratory Press; Ausubel, F. M. et al. (1995 and periodic supplements; *Current Protocols in Molecular Biology*, ch. 9, 13, and 16, John Wiley & Sons, New York, N.Y.); B. Roe, J. Crabtree, and A. Kahn, 1996, *DNA Isolation and Sequencing: Essential Techniques*, John Wiley & Sons; M. J. Gait (Editor), 1984, *Oligonucleotide Synthesis: A Practical Approach*, Irl Press; and, D. M. J. Lilley and J. E. Dahlberg, 1992, *Methods of Enzymology: DNA Structure Part A: Synthesis and Physical Analysis of DNA* Methods in Enzymology, Academic Press. Each of these general texts is herein incorporated by reference.

METHODS OF DETECTING EXPRESSION LEVELS

There are many methods known in the art for determining the genotype of a patient. Any method for determining genotype can be used for determining genotypes in the present invention. Such methods include, but are not limited to, amplimer sequencing, DNA sequencing, fluorescence spectroscopy, fluorescence resonance energy transfer (or "FRET")-based hybridization analysis, high throughput screening, mass spectroscopy, nucleic acid hybridization, polymerase chain reaction (PCR), RFLP analysis and size chromatography (e.g., capillary or gel chromatography), all of which are well known to one of ordinary skill in the art.

Many methods of sequencing genomic DNA are known in the art, and any such method can be used, see for example Sambrook et al., Molecular Cloning; A Laboratory Manual 2d ed. (1989). For example, a DNA fragment of interest can be amplified using the polymerase chain reaction or some other cyclic polymerase mediated amplification reaction. The amplified region of DNA can then be sequenced using any method known in the art. Advantageously, the nucleic acid sequencing is by automated methods (reviewed by Meldrum, Genome Res. September 2000;10(9):1288-303, the disclosure of which is incorporated by reference in its entirety), for example using a Beckman CEQ 8000 Genetic

Analysis System (Beckman Coulter Instruments, Inc.). Methods for sequencing nucleic acids include, but are not limited to, automated fluorescent DNA sequencing (see, e.g., Watts & MacBeath, Methods Mol Biol. 2001;167:153-70 and MacBeath et al., Methods Mol Biol. 2001;167:119-52), capillary electrophoresis (see, e.g., Bosserhoff et al., Comb Chem High Throughput Screen. December 2000;3(6):455-66), DNA sequencing chips (see, e.g., Jain, Pharmacogenomics. August 2000;1(3):289-307), mass spectrometry (see, e.g., Yates, Trends Genet. January 2000;16(1):5-8), pyrosequencing (see, e.g., Ronaghi, Genome Res. January 2001;11(1):3-11), and ultrathin-layer gel electrophoresis (see, e.g., Guttman & Ronai, Electrophoresis. December 2000; 21 (18):3952-64), the disclosures of which are hereby incorporated by reference in their entireties. The sequencing can also be done by any commercial company. Examples of such companies include, but are not limited to, the University of Georgia Molecular Genetics Instrumentation Facility (Athens, Ga.) or SeqWright DNA Technologies Services (Houston, Tex.).

Any one of the methods known in the art for amplification of DNA may be used, such as for example, the polymerase chain reaction (PCR), the ligase chain reaction (LCR) (Barany, F., Proc. Natl. Acad. Sci. (U.S.A.) 88:189-193 (1991)), the strand displacement assay (SDA), or the oligonucleotide ligation assay ("OLA") (Landegren, U. et al., Science 241:1077-1080 (1988)). Nickerson, D. A. et al. have described a nucleic acid detection assay that combines attributes of PCR and OLA (Nickerson, D. A. et al., Proc. Natl. Acad. Sci. (U.S.A.) 87:8923-8927 (1990)). Other known nucleic acid amplification procedures, such as transcription-based amplification systems (Malek, L. T. et al., U.S. Pat. No. 5,130,238; Davey, C. et al., European Patent Application 329,822; Schuster et al., U.S. Pat. No. 5,169,766; Miller, H. I. et al., PCT Application W089/06700; Kwoh, D. et al., Proc. Natl. Acad. Sci. (U.S.A.) 86:1173 (1989); Gingeras, T. R. et al., PCT Application W088/10315)), or isothermal amplification methods (Walker, G. T. et al., Proc. Natl. Acad. Sci. (U.S.A.) 89:392-396 (1992)) may also be used.

To perform a cyclic polymerase mediated amplification reaction according to the present invention, the primers are hybridized or annealed to opposite strands of the target DNA, the temperature is then raised to permit the thermostable DNA polymerase to extend the primers and thus replicate the specific segment of DNA spanning the region between the two primers. Then the reaction is thermocycled so that at each cycle the amount of DNA representing the sequences between the two primers is doubled, and specific amplification of gene DNA sequences, if present, results.

Any of a variety of polymerases can be used in the present invention. For thermocyclic reactions, the polymerases are thermostable polymerases such as Taq, KlenTaq, Stoffel Fragment, Deep Vent, Tth, Pfu, Vent, and UlTma, each of which are readily available from commercial sources. For non-thermocyclic reactions, and in certain thermocyclic reactions, the polymerase will often be one of many polymerases commonly used in the field, and commercially available, such as DNA pol 1, Klenow fragment, T7 DNA polymerase, and T4 DNA polymerase. Guidance for the use of such polymerases can readily be found in product literature and in general molecular biology guides.

Typically, the annealing of the primers to the target DNA sequence is carried out for about 2 minutes at about 37-55° C, extension of the primer sequence by the polymerase enzyme (such as Taq polymerase) in the presence of nucleoside triphosphates is carried out for about 3 minutes at about 70-75° C, and the denaturing step to release the extended primer is carried out for about 1 minute at about 90-95° C. However, these parameters can be varied, and one of skill in the art would readily know how to adjust the temperature and time parameters of the reaction to achieve the desired results. For example, cycles may be as short as 10, 8, 6, 5, 4.5, 4, 2, 1, 0.5 minutes or less.

Also, "two temperature" techniques can be used where the annealing and extension steps may both be carried out at the same temperature, typically between about 60-65° C, thus reducing the length of each amplification cycle and resulting in a shorter assay time.

Typically, the reactions described herein are repeated until a detectable amount of product is generated. Often, such detectable amounts of product are between about 10 ng and about 100 ng, although larger quantities, e.g. 200 ng, 500 ng, 1 mg or more can also, of course, be detected. In terms of concentration, the amount of detectable product can be from about 0.01 pmol, 0.1 pmol, 1 pmol, 10 pmol, or more. Thus, the number of cycles of the reaction that are performed can be varied, the more cycles are performed, the more amplified product is produced. In certain embodiments, the reaction comprises 2, 5, 10, 15, 20, 30, 40, 50, or more cycles.

For example, the PCR reaction may be carried out using about 25-50 μl samples containing about 0.01 to 1.0 ng of template amplification sequence, about 10 to 100 pmol of each generic primer, about 1.5 units of Taq DNA polymerase (Promega Corp.), about 0.2 mM dDATP, about 0.2 mM dCTP, about 0.2 mM dGTP, about 0.2 mM dTTP, about 15 mM MgCl.sub.2, about 10 mM Tris-HCl (pH 9.0), about 50 mM KCl, about 1 μg/ml gelatin, and about 10 μl/ml Triton X-100 (Saiki, 1988).

Those of ordinary skill in the art are aware of the variety of nucleotides available for use in the cyclic polymerase mediated reactions. Typically, the nucleotides will consist at least in part of deoxynucleotide triphosphates (dNTPs), which are readily commercially available. Parameters for optimal use of dNTPs are also known to those of skill, and are described in the literature. In addition, a large number of nucleotide derivatives are known to those of skill and can be used in the present reaction. Such derivatives include fluorescently labeled nucleotides, allowing the detection of the product including such labeled nucleotides, as described below. Also included in this group are nucleotides that allow the sequencing of nucleic acids including such nucleotides, such as chain-terminating nucleotides, dideoxynucleotides and boronated nuclease-resistant nucleotides. Commercial kits containing the reagents most typically used for these methods of DNA sequencing are available and widely used. Other nucleotide analogs include nucleotides with bromo-, iodo-, or other modifying groups, which affect numerous properties of resulting nucleic acids including their antigenicity, their replicatability, their melting temperatures, their binding properties, etc. In addition, certain nucleotides include reactive side groups, such as sulfhydryl groups, amino groups, N-hydroxysuccinimidyl groups, that allow the further modification of nucleic acids comprising them.

In certain embodiments, oligonucleotides that can be used as primers to amplify specific nucleic acid sequences of a gene in cyclic polymerase-mediated amplification reactions, such as PCR reactions, consist of oligonucleotide fragments. Such fragments should be of sufficient length to enable specific annealing or hybridization to the nucleic acid sample. The sequences typically will be about 8 to about 44 nucleotides in length, but may be longer. Longer sequences, e.g., from about 14 to about 50, are advantageous for certain embodiments.

In embodiments where it is desired to amplify a fragment of DNA, primers having contiguous stretches of about 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 nucleotides from a gene sequence are contemplated.

As used herein, "hybridization" refers to the process by which one strand of nucleic acid base pairs with a complementary strand, as occurs during blot hybridization techniques and PCR techniques.

Whichever probe sequences and hybridization methods are used, one ordinarily skilled in the art can readily determine suitable hybridization conditions, such as temperature and chemical conditions. Such hybridization methods are well known in the art. For example, for applications requiring high selectivity, one will typically desire to employ

relatively stringent conditions for the hybridization reactions, e.g., one will select relatively low salt and/or high temperature conditions, such as provided by about 0.02 M to about 0.10 M NaCl at temperatures of about 50° C to about 70° C. Such high stringency conditions tolerate little, if any, mismatch between the probe and the template or target strand. It is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide. Other variations in hybridization reaction conditions are well known in the art (see for example, Sambrook et al., Molecular Cloning; A Laboratory Manual 2d ed. (1989)).

Hybridization conditions are based on the melting temperature (Tm) of the nucleic acid binding complex, as taught, e.g., in Berger and Kimmel (1987, Guide to Molecular Cloning Techniques, Methods in Enzymology, Vol 152, Academic Press, San Diego CA), and confer a defined "stringency" as explained below.

Maximum stringency typically occurs at about Tm-5 °C (5 °C below the Tm of the probe); high stringency at about 5 °C to 10 °C below Tm; intermediate stringency at about 10 °C to 20 °C below Tm; and low stringency at about 20 °C to 25 °C below Tm. As will be understood by those of ordinary skill in the art, a maximum stringency hybridization can be used to identify or detect identical nucleotide sequences while an intermediate (or low) stringency hybridization can be used to identify or detect similar or related polynucleotide sequences.

In one aspect, the present invention employs nucleotide sequences that can hybridize to another nucleotide sequence under stringent conditions (e.g., 65 °C and 0.1xSSC {1xSSC = 0.15 M NaCl, 0.015 M Na3 Citrate pH 7.0). Where the nucleotide sequence is double-stranded, both strands of the duplex, either individually or in combination, may be employed by the present invention. Where the nucleotide sequence is single-stranded, it is to be understood that the complementary sequence of that nucleotide sequence is also included within the scope of the present invention.

Stringency of hybridization refers to conditions under which polynucleic acid hybrids are stable. Such conditions are evident to those of ordinary skill in the field. As known to those of ordinary skill in the art, the stability of hybrids is reflected in the melting temperature (Tm) of the hybrid which decreases approximately 1 to 1.5 °C with every 1 % decrease in sequence homology. In general, the stability of a hybrid is a function of sodium ion concentration and temperature. Typically, the hybridization reaction is performed under conditions of higher stringency, followed by washes of varying stringency.

As used herein, high stringency includes conditions that permit hybridization of only those nucleic acid sequences that form stable hybrids in 1 M Na+ at 65-68 °C. High stringency conditions can be provided, for example, by hybridization in an aqueous solution containing 6x SSC, 5x Denhardt's, 1 % SDS (sodium dodecyl sulphate), 0.1 Na+ pyrophosphate and 0.1 mg/ml denatured salmon sperm DNA as non-specific competitor. Following hybridization, high stringency washing may be done in several steps, with a final wash (about 30 minutes) at the hybridization temperature in 0.2 - 0.1x SSC, 0.1 % SDS.

It is understood that these conditions may be adapted and duplicated using a variety of buffers, e.g., formamide-based buffers, and temperatures. Denhardt's solution and SSC are well known to those of ordinary skill in the art as are other suitable hybridization buffers (see, e.g., Sambrook, et al., eds. (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, New York or Ausubel, et al., eds. (1990) Current Protocols in Molecular Biology, John Wiley & Sons, Inc.). Optimal hybridization conditions are typically determined empirically, as the length and the GC content of the hybridizing pair also play a role.

Nucleic acid molecules that differ from the sequences of the primers and probes disclosed herein, are intended to be within the scope of the invention. Nucleic acid sequences that are complementary to these sequences, or that are hybridizable to the sequences described herein under conditions of standard or stringent hybridization, and also analogs and derivatives are also intended to be within the scope of the invention. Advantageously, such variations will differ from the sequences described herein by only a small number of nucleotides, for example by 1, 2, or 3 nucleotides.

Nucleic acid molecules corresponding to natural allelic variants, homologues (i.e., nucleic acids derived from other species), or other related sequences (e.g., paralogs) of the sequences described herein can be isolated based on their homology to the nucleic acids disclosed herein, for example by performing standard or stringent hybridization reactions using all or a portion of the known sequences as probes. Such methods for nucleic acid hybridization and cloning are well known in the art.

Similarly, a nucleic acid molecule detected in the methods of the invention may include only a fragment of the specific sequences described. Fragments provided herein are defined as sequences of at least 6 (contiguous) nucleic acids, a length sufficient to allow for specific hybridization of nucleic acid primers or probes, and are at most some portion less than a full-length sequence. Fragments may be derived from any contiguous portion of a nucleic acid sequence of choice. Derivatives and analogs may be full length or other than full

length, if the derivative or analog contains a modified nucleic acid or amino acid, as described below.

Derivatives, analogs, homologues, and variants of the nucleic acids of the invention include, but are not limited to, molecules comprising regions that are substantially homologous to the nucleic acids of the invention, in various embodiments, by at least about 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or even 99% identity over a nucleic acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art.

For the purposes of the present invention, sequence identity or homology is determined by comparing the sequences when aligned so as to maximize overlap and identity while minimizing sequence gaps. In particular, sequence identity may be determined using any of a number of mathematical algorithms. A nonlimiting example of a mathematical algorithm used for comparison of two sequences is the algorithm of Karlin & Altschul, Proc. Natl. Acad. Sci. USA 1990;87: 2264-2268, modified as in Karlin & Altschul, Proc. Natl. Acad. Sci. USA 1993;90: 5873-5877.

Another example of a mathematical algorithm used for comparison of sequences is the algorithm of Myers & Miller, CABIOS 1988;4: 11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson & Lipman, Proc. Natl. Acad. Sci. USA 1988;85: 2444-2448.

Advantageous for use according to the present invention is the WU-BLAST (Washington University BLAST) version 2.0 software. WU-BLAST version 2.0 executable programs for several UNIX platforms can be downloaded from ftp://blast.wustl.edu/blast/executables. This program is based on WU-BLAST version 1.4, which in turn is based on the public domain NCBI-BLAST version 1.4 (Altschul & Gish, 1996, Local alignment statistics, Doolittle ed., Methods in Enzymology 266: 460-480; Altschul et al., Journal of Molecular Biology 1990;215: 403-410; Gish & States, 1993;Nature Genetics 3: 266-272; Karlin & Altschul, 1993;Proc. Natl. Acad. Sci. USA 90: 5873-5877; all of which are incorporated by reference herein).

In all search programs in the suite the gapped alignment routines are integral to the database search itself. Gapping can be turned off if desired. The default penalty (Q) for a

gap of length one is Q=9 for proteins and BLASTP, and Q=10 for BLASTN, but may be changed to any integer. The default per-residue penalty for extending a gap (R) is R=2 for proteins and BLASTP, and R=10 for BLASTN, but may be changed to any integer. Any combination of values for Q and R can be used in order to align sequences so as to maximize overlap and identity while minimizing sequence gaps. The default amino acid comparison matrix is BLOSUM62, but other amino acid comparison matrices such as PAM can be utilized.

Alternatively or additionally, the term "homology" or "identity", for instance, with respect to a nucleotide or amino acid sequence, can indicate a quantitative measure of homology between two sequences. The percent sequence homology can be calculated as $(N_{ref}-N_{dif})*100/-N_{ref}$, wherein N_{dif} is the total number of non-identical residues in the two sequences when aligned and wherein N_{ref} is the number of residues in one of the sequences. Hence, the DNA sequence AGTCAGTC will have a sequence identity of 75% with the sequence AATCAATC ($N\ N_{ref}=8$; $N\ N_{dif}=2$). "Homology" or "identity" can refer to the number of positions with identical nucleotides or amino acids divided by the number of nucleotides or amino acids in the shorter of the two sequences wherein alignment of the two sequences can be determined in accordance with the Wilbur and Lipman algorithm (Wilbur & Lipman, Proc Natl Acad Sci USA 1983;80:726, incorporated herein by reference), for instance, using a window size of 20 nucleotides, a word length of 4 nucleotides, and a gap penalty of 4, and computer-assisted analysis and interpretation of the sequence data including alignment can be conveniently performed using commercially available programs (e.g., Intelligenetics.TM. Suite, Intelligenetics Inc. CA). When RNA sequences are said to be similar, or have a degree of sequence identity or homology with DNA sequences, thymidine (T) in the DNA sequence is considered equal to uracil (U) in the RNA sequence. Thus, RNA sequences are within the scope of the invention and can be derived from DNA sequences, by thymidine (T) in the DNA sequence being considered equal to uracil (U) in RNA sequences. Without undue experimentation, the skilled artisan can consult with many other programs or references for determining percent homology.

In embodiments where expression of a particular gene is assessed by determining the expression of the protein product of the gene, any suitable assay for detecting protein levels and/or activity may be employed. For example, suitable protein activity assays include ubiquitination assays, kinase assays, protein-binding assays, DNA-binding and unwinding assays, and any other suitable assay for assessing the activity of the protein product of a translated gene according to the invention.

SAMPLING

In order to determine the genotype or expression level of a particular SWI/SNF complex and/or MEDIATOR complex gene of a patient according to the methods of the present invention, it may be necessary to obtain a sample of genomic DNA or RNA from that patient. That sample of genomic DNA or RNA may be obtained from a sample of tissue or cells taken from that patient.

A sample may comprise any clinically relevant tissue sample, such as a tumor biopsy or fine needle aspirate, hair (including roots), skin, buccal swabs, saliva, or a sample of bodily fluid, such as blood, plasma, serum, lymph, ascitic fluid, cystic fluid, urine or nipple exudate. The sample may be taken from a human, or, in a veterinary context, from non-human animals such as ruminants, horses, swine or sheep, or from domestic companion animals such as felines and canines.

The tissue sample may be marked with an identifying number or other indicia that relates the sample to the individual patient from which the sample was taken. The identity of the sample advantageously remains constant throughout the methods of the invention thereby guaranteeing the integrity and continuity of the sample during extraction and analysis. Alternatively, the indicia may be changed in a regular fashion that ensures that the data, and any other associated data, can be related back to the patient from whom the data was obtained. The amount/size of sample required is known to those ordinarily skilled in the art.

Generally, the tissue sample may be placed in a container that is labeled using a numbering system bearing a code corresponding to the patient. Accordingly, the genotype of a particular patient is easily traceable.

In one embodiment of the invention, a sampling device and/or container may be supplied to the physician. The sampling device advantageously takes a consistent and reproducible sample from individual patients while simultaneously avoiding any cross-contamination of tissue. Accordingly, the size and volume of sample tissues derived from individual patients would be consistent.

According to the present invention, a sample of genomic DNA or RNA is obtained from the tissue sample of the patient of interest. Whatever source of cells or tissue is used, a sufficient amount of cells must be obtained to provide a sufficient amount of DNA or RNA for analysis. This amount will be known or readily determinable by those ordinarily skilled in the art.

DNA or RNA is isolated from the tissue/cells by techniques known to those ordinarily skilled in the art (see, e.g., U.S. Pat. Nos. 6,548,256 and 5,989,431, Hirota et al., Jinrui Idengaku Zasshi. September 1989; 34(3):217-23 and John et al., Nucleic Acids Res. Jan. 25. 1991 ;19(2):408; the disclosures of which are incorporated by reference in their entireties). For example, high molecular weight DNA may be purified from cells or tissue using proteinase K extraction and ethanol precipitation. DNA may be extracted from a patient specimen using any other suitable methods known in the art.

In certain embodiments, target polynucleotide molecules are extracted from a sample taken from an individual afflicted with breast cancer. The sample may be collected in any clinically acceptable manner, but must be collected such that marker-derived polynucleotides (e.g., RNA) are preserved. mRNA or nucleic acids derived therefrom (e.g., cDNA or amplified DNA) are preferably labeled distinguishably from standard or control polynucleotide molecules, and both are simultaneously or independently hybridized to a microarray comprising one or more markers of resistance to anticancer treatment as described above. Alternatively, mRNA or nucleic acids derived therefrom may be labeled with the same label as the standard or control polynucleotide molecules, wherein the intensity of hybridization of each at a particular probe is compared.

Methods for preparing total and poly(A)+ RNA are well known and are described generally in Sambrook et al., MOLECULAR CLONING--A LABORATORY MANUAL (2ND ED.), Vols. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. (1989)) and Ausubel et al., CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, vol. 2, Current Protocols Publishing, New York (1994)).

RNA may be isolated from eukaryotic cells by procedures that involve lysis of the cells and denaturation of the proteins contained therein. Cells of interest include wild-type cells (i.e., non-cancerous), drug-exposed wild-type cells, tumor- or tumor-derived cells, modified cells, normal or tumor cell line cells, and drug-exposed modified cells.

Additional steps may be employed to remove DNA. Cell lysis may be accomplished with a nonionic detergent, followed by microcentrifugation to remove the nuclei and hence the bulk of the cellular DNA. In one embodiment, RNA is extracted from cells of the various types of interest using guanidinium thiocyanate lysis followed by CsCl centrifugation to separate the RNA from DNA (Chirgwin et al., Biochemistry 18:5294-5299 (1979)). Poly(A)+ RNA is selected by selection with oligo-dT cellulose (see Sambrook et al, MOLECULAR CLONING--A LABORATORY MANUAL (2ND ED.), Vols. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. (1989). Alternatively, separation of

RNA from DNA can be accomplished by organic extraction, for example, with hot phenol or phenol/chloroform/isoamyl alcohol.

If desired, RNase inhibitors may be added to the lysis buffer. Likewise, for certain cell types, it may be desirable to add a protein denaturation/digestion step to the protocol.

In certain embodiments, it is desirable to preferentially enrich mRNA with respect to other cellular RNAs, such as transfer RNA (tRNA) and ribosomal RNA (rRNA). Most mRNAs contain a poly(A) tail at their 3' end. This allows them to be enriched by affinity chromatography, for example, using oligo(dT) or poly(U) coupled to a solid support, such as cellulose or Sephadex.TM. (see Ausubel et al., CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, vol. 2, Current Protocols Publishing, New York (1994). Once bound, poly(A)+ mRNA is eluted from the affinity column using 2 mM EDTA/0.1% SDS.

The sample of RNA can comprise a plurality of different mRNA molecules, each different mRNA molecule having a different nucleotide sequence. In a specific embodiment, the RNA sample is a mammalian RNA sample.

In a specific embodiment, total RNA or mRNA from cells are used in the methods of the invention. The source of the RNA can be cells of any animal, human, mammal, primate, non-human animal, dog, cat, mouse, rat, bird, yeast, eukaryote, etc. In specific embodiments, the method of the invention is used with a sample containing total mRNA or total RNA from $1x10^6$ cells or less. In another embodiment, proteins can be isolated from the foregoing sources, by methods known in the art, for use in expression analysis at the protein level.

In certain embodiments, expression of a biomarker according to the invention is measured using multiplex ligation-dependent probe amplification (MLPA) (see, e.g., WO 01/61033 and Schouten, JP et al. (2002) "Relative quantification of 40 nucleic acid sequences by multiplex ligation-dependent probe amplification" Nucleic Acids Res 30, e57) or reverse transcriptase MLPA (RT-MLPA) (see, e.g., Eldering, E et al. (2003) "Expression profiling via novel multiplex assay allows rapid assessment of gene regulation in defined signaling pathways" Nucleic Acids Res 31, e153). In RT-MLPA, mRNA is converted to cDNA by reverse transcriptase, followed by a normal MLPA reaction. In other embodiments, methylation-specific MLPA is employed to detect expression of a biomarker according to the instant invention (see, e.g., Nygren, AO et al. (2005) "Methylation-specific MLPA (MS-MPLA): simultaneous detection of CpG methylation and copy number changes of up to 40 sequences" Nucleic Acids Res 33, 14:e128).

ARRAYS

As defined herein, a "nucleic acid array" refers to a plurality of unique nucleic acids (or "nucleic acid members") attached to a support where each of the nucleic acid members is attached to a support in a unique pre-selected region.

In one embodiment, the nucleic acid member attached to the surface of the support is DNA. In another embodiment, the nucleic acid member attached to the surface of the support is either cDNA or oligonucleotides. In another embodiment, the nucleic acid member attached to the surface of the support is cDNA synthesized by polymerase chain reaction (PCR). In another embodiment, sequences bound to the array can be an isolated oligonucleotide, cDNA, EST or PCR product corresponding to any biomarker of the invention total cellular RNA is applied to the array.

Array technology and the various techniques and applications associated with it is described generally in numerous textbooks and documents. These include Lemieux et al., 1998, Molecular Breeding 4, 277-289, Schena and Davis. Parallel Analysis with Biological Chips. in PCR Methods Manual (eds. M. Innis, D. Gelfand, J. Sninsky), Schena and Davis, 1999, Genes, Genomes and Chips. In DNA Microarrays: A Practical Approach (ed. M. Schena), Oxford University Press, Oxford, UK, 1999), The Chipping Forecast (Nature Genetics special issue; January 1999 Supplement), Mark Schena (Ed.), Microarray Biochip Technology, (Eaton Publishing Company), Cortes, 2000, The Scientist 14[17]:25, Gwynne and Page, Microarray analysis: the next revolution in molecular biology, Science, 1999 August 6; and Eakins and Chu, 1999, Trends in Biotechnology, 17, 217-218.

Major applications for array technology include the identification of sequence (gene/gene mutation) and the determination of expression level (abundance) of genes. Gene expression profiling may make use of array technology, optionally in combination with proteomics techniques (Celis et al, 2000, FEBS Lett, 480(1):2-16; Lockhart and Winzeler, 2000, Nature 405(6788):827-836; Khan et al., 1999, 20(2):223-9). Other applications of array technology are also known in the art; for example, gene discovery, cancer research (Marx, 2000, Science 289: 1670-1672; Scherf, et al, 2000, Nat Genet;24(3):236-44; Ross et al, 2000, Nat Genet. 2000 Mar;24(3):227-35), SNP analysis (Wang et al, 1998, Science, 280(5366):1077-82), drug discovery, pharmacogenomics, disease diagnosis (for example, utilising microfluidics devices: Chemical & Engineering News, February 22, 1999, 77(8):27-36), toxicology (Rockett and Dix (2000), Xenobiotica, 30(2):155-77; Afshari et al., 1999, Cancer Res1;59(19):4759-60) and toxicogenomics (a hybrid of functional genomics and molecular toxicology).

In general, any library may be arranged in an orderly manner into an array, by spatially separating the members of the library. Examples of suitable libraries for arraying include nucleic acid libraries (including DNA, cDNA, oligonucleotide, etc. libraries), peptide, polypeptide and protein libraries, as well as libraries comprising any molecules, such as ligand libraries, among others.

The samples (e.g., members of a library) are generally fixed or immobilized onto a solid phase, preferably a solid substrate, to limit diffusion and admixing of the samples. In particular, the libraries may be immobilized to a substantially planar solid phase, including membranes and non-porous substrates such as plastic and glass. Furthermore, the samples are preferably arranged in such a way that indexing (i.e., reference or access to a particular sample) is facilitated. Typically the samples are applied as spots in a grid formation. Common assay systems may be adapted for this purpose. For example, an array may be immobilized on the surface of a microplate, either with multiple samples in a well, or with a single sample in each well. Furthermore, the solid substrate may be a membrane, such as a nitrocellulose or nylon membrane (for example, membranes used in blotting experiments). Alternative substrates include glass, or silica-based substrates. Thus, the samples are immobilized by any suitable method known in the art, for example, by charge interactions, or by chemical coupling to the walls or bottom of the wells, or the surface of the membrane. Other means of arranging and fixing may be used, for example, pipetting, drop-touch, piezoelectric means, ink-jet and bubblejet technology, electrostatic application, etc. In the case of silicon-based chips, photolithography may be utilised to arrange and fix the samples on the chip.

The samples may be arranged by being "spotted" onto the solid substrate; this may be done by hand or by making use of robotics to deposit the sample. In general, arrays may be described as macroarrays or microarrays, the difference being the size of the sample spots. Macroarrays typically contain sample spot sizes of about 300 microns or larger and may be easily imaged by existing gel and blot scanners. The sample spot sizes in microarrays are typically less than 200 microns in diameter and these arrays usually contain thousands of spots. Thus, microarrays may require specialized robotics and imaging equipment, which may need to be custom made. Instrumentation is described generally in a review by Cortese, 2000, The Scientist 14[11]:26.

Techniques for producing immobilized libraries of DNA molecules have been described in the art. Generally, most prior art methods described how to synthesize single-stranded nucleic acid molecule libraries, using for example masking techniques to build up

various permutations of sequences at the various discrete positions on the solid substrate. U.S. Patent No. 5,837,832 describes an improved method for producing DNA arrays immobilized to silicon substrates based on very large scale integration technology. In particular, U.S. Patent No. 5,837,832 describes a strategy called "tiling" to synthesize specific sets of probes at spatially-defined locations on a substrate which may be used to produced the immobilized DNA libraries of the present invention. U.S. Patent No. 5,837,832 also provides references for earlier techniques that may also be used. Arrays may also be built using photo deposition chemistry.

To aid detection, labels are typically used – such as any readily detectable reporter, for example, a fluorescent, bioluminescent, phosphorescent, radioactive, etc. reporter. Labelling of probes and targets is also disclosed in Shalon et al., 1996, Genome Res 6(7):639-45.

Examples of DNA arrays include where probe cDNA (500~5,000 bases long) is immobilized to a solid surface such as glass using robot spotting and exposed to a set of targets either separately or in a mixture. This method is widely considered as having been developed at Stanford University (Ekins and Chu, 1999, Trends in Biotechnology, 1999, 17, 217-218).

Another example of a DNA array is where an array of oligonucleotides (20-25-mer oligos, preferably, 40-60 mer oligos) or peptide nucleic acid (PNA) probes are synthesized either in situ (on-chip) or by conventional synthesis followed by on-chip immobilization. The array is exposed to labelled sample DNA, hybridized, and the identity/abundance of complementary sequences are determined. Such a DNA chip is sold by Affymetrix, Inc., under the GeneChip® trademark. Agilent and Nimblegen also provide suitable arrays (eg. genomic tiling arrays).

In other embodiments, high throughput DNA sequencing promises to become an affordable and more quantitative alternative for microarrays to analyze large collections of DNA sequences. Examples of high-throughput sequencing approaches are listed in E.Y. Chan, Mutation Reseach 573 (2005) 13-40 and include, but are not limited to, near-term sequencing approaches such as cycle-extension approaches, polymerase reading approaches and exonuclease sequencing, revolutionary sequencing approaches such as DNA scanning and nanopore sequencing and direct linear analysis. Examples of current high-throughput sequencing methods are 454 (pyro)sequencing, Solexa Genome Analysis System, Agencourt SOLiD sequencing method (Applied Biosystems), MS-PET sequencing (Ng et al., 2006, http://nar(dot)oxfordjournals(dot)org/cgi/content/full/34/12/e84).

PROBES

As used herein, the term "probe" refers to a molecule (e.g., an oligonucleotide, whether occurring naturally as in a purified restriction digest or produced synthetically, recombinantly or by PCR amplification), that is capable of hybridizing to another molecule of interest (e.g., another oligonucleotide). When probes are oligonucleotides they may be single-stranded or double-stranded. Probes are useful in the detection, identification and isolation of particular targets (e.g., gene sequences). As described herein, it is contemplated that probes used in the present invention may be labelled with a label so that is detectable in any detection system, including, but not limited to enzyme (e.g., ELISA, as well as enzyme-based histochemical assays), fluorescent, radioactive, and luminescent systems.

With respect to arrays and microarrays, the term "probe" is used to refer to any hybridizable material that is affixed to the array for the purpose of detecting a nucleotide sequence that has hybridized to said probe. Preferably, these probes are 25-60 mers or longer.

The present invention further encompasses probes according to the present invention that are immobilized on a solid or flexible support, such as paper, nylon or other type of membrane, filter, chip, glass slide, microchips, microbeads, or any other such matrix, all of which are within the scope of this invention.

The primers and probes described herein may be readily prepared by, for example, directly synthesizing the fragment by chemical means or by introducing selected sequences into recombinant vectors for recombinant production. Methods for making a vector or recombinants or plasmid for amplification of the fragment either in vivo or in vitro can be any desired method, e.g., a method which is by or analogous to the methods disclosed in, or disclosed in documents cited in: U.S. Pat. Nos. 4,603,112; 4,769,330; 4,394,448; 4,722,848; 4,745,051; 4,769,331; 4,945,050; 5,494,807; 5,514,375; 5,744,140; 5,744,141; 5,756,103; 5,762,938; 5,766,599; 5,990,091; 5,174,993; 5,505,941; 5,338,683; 5,494,807; 5,591,639; 5,589,466; 5,677,178; 5,591,439; 5,552,143; 5,580,859; 6,130,066; 6,004,777; 6,130,066; 6,497,883; 6,464,984; 6,451,770; 6,391,314; 6,387,376; 6,376,473; 6,368,603; 6,348,196; 6,306,400; 6,228,846; 6,221,362; 6,217,883; 6,207,166; 6,207,165; 6,159,477; 6,153,199; 6,090,393; 6,074,649; 6,045,803; 6,033,670; 6,485,729; 6,103,526; 6,224,882; 6,312,682; 6,348,450 and 6; 312,683; U.S. patent application Ser. No. 920,197, filed Oct. 16, 1986; WO 90/01543; W091/11525; WO 94/16716; WO 96/39491; WO 98/33510; EP 265785; EP 0 370 573; Andreansky et al., Proc. Natl. Acad. Sci. USA 1996;93:11313-11318; Ballay et al.,

EMBO J. 1993;4:3861-65; Felgner et al., J. Biol. Chem. 1994;269:2550-2561; Frolov et al., Proc. Natl. Acad. Sci. USA 1996;93:11371-11377; Graham, Tibtech 1990;8:85-87; Grunhaus et al., Sem. Virol. 1992;3:237-52; Ju et al., Diabetologia 1998;41:736-739; Kitson et al., J. Virol. 1991;65:3068-3075; McClements et al., Proc. Natl. Acad. Sci. USA 1996;93:11414-11420; Moss, Proc. Natl. Acad. Sci. USA 1996;93:11341-11348; Paoletti, Proc. Natl. Acad. Sci. USA 1996;93:11349-11353; Pennock et al., Mol. Cell. Biol. 1984;4:399-406; Richardson (Ed), Methods in Molecular Biology 1995;39, "Baculovirus Expression Protocols," Humana Press Inc.; Smith et al. (1983) Mol. Cell. Biol. 1983;3:2156-2165; Robertson et al., Proc. Natl. Acad. Sci. USA 1996;93:11334-11340; Robinson et al., Sem. Immunol. 1997;9:271; and Roizman, Proc. Natl. Acad. Sci. USA 1996;93:11307-11312. Strategies for probe design are described in WO95/11995, EP 717,113 and WO97/29212.

In order to generate data from array-based assays a signal is detected that signifies the presence of or absence of hybridization between a probe and a nucleotide sequence. The present invention further contemplates direct and indirect labelling techniques. For example, direct labelling incorporates fluorescent dyes directly into the nucleotide sequences that hybridize to the array-associated probes (e.g., dyes are incorporated into nucleotide sequence by enzymatic synthesis in the presence of labelled nucleotides or PCR primers). Direct labelling schemes yield strong hybridization signals, typically using families of fluorescent dyes with similar chemical structures and characteristics, and are simple to implement. In some embodiments comprising direct labelling of nucleic acids, cyanine or alexa analogs are utilized in multiple-fluor comparative array analyses. In other embodiments, indirect labelling schemes can be utilized to incorporate epitopes into the nucleic acids either prior to or after hybridization to the microarray probes. One or more staining procedures and reagents are used to label the hybridized complex (e.g., a fluorescent molecule that binds to the epitopes, thereby providing a fluorescent signal by virtue of the conjugation of dye molecule to the epitope of the hybridised species).

Oligonucleotide sequences used as probes according to the present invention may be labeled with a detectable moiety. Various labeling moieties are known in the art. Said moiety may be, for example, a radiolabel (e.g., 3H, 125I, 35S, 14C, 32P, etc.), detectable enzyme (e.g. horse radish peroxidase (HRP), alkaline phosphatase etc.), a fluorescent dye (e.g., fluorescein isothiocyanate, Texas red, rhodamine, Cy3, Cy5, Bodipy, Bodipy Far Red, Lucifer Yellow, Bodipy 630/650-X, Bodipy R6G-X and 5-CR 6G, and the like), a colorimetric label such as colloidal gold or colored glass or plastic (e.g. polystyrene, polypropylene, latex, etc.), beads, or any other moiety capable of generating a detectable

signal such as a colorimetric, fluorescent, chemiluminescent or electrochemiluminescent (ECL) signal.

Probes may be labeled directly or indirectly with a detectable moiety, or synthesized to incorporate the detectable moiety. In one embodiment, a detectable label is incorporated into a nucleic acid during at least one cycle of a cyclic polymerase-mediated amplification reaction. For example, polymerases can be used to incorporate fluorescent nucleotides during the course of polymerase-mediated amplification reactions. Alternatively, fluorescent nucleotides may be incorporated during synthesis of nucleic acid primers or probes. To label an oligonucleotide with the fluorescent dye, one of conventionally-known labeling methods can be used (Nature Biotechnology, 14, 303-308, 1996; Applied and Environmental Microbiology, 63, 1143-1147, 1997; Nucleic Acids Research, 24, 4532-4535, 1996). An advantageous probe is one labeled with a fluorescent dye at the 3' or 5' end and containing G or C as the base at the labeled end. If the 5' end is labeled and the 3' end is not labeled, the OH group on the C atom at the 3'-position of the 3' end ribose or deoxyribose may be modified with a phosphate group or the like although no limitation is imposed in this respect.

Spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means can be used to detect such labels. The detection device and method may include, but is not limited to, optical imaging, electronic imaging, imaging with a CCD camera, integrated optical imaging, and mass spectrometry. Further, the amount of labeled or unlabeled probe bound to the target may be quantified. Such quantification may include statistical analysis. In other embodiments the detection may be via conductivity differences between concordant and discordant sites, by quenching, by fluorescence perturbation analysis, or by electron transport between donor and acceptor molecules.

In yet another embodiment, detection may be via energy transfer between molecules in the hybridization complexes in PCR or hybridization reactions, such as by fluorescence energy transfer (FET) or fluorescence resonance energy transfer (FRET). In FET and FRET methods, one or more nucleic acid probes are labeled with fluorescent molecules, one of which is able to act as an energy donor and the other of which is an energy acceptor molecule. These are sometimes known as a reporter molecule and a quencher molecule respectively. The donor molecule is excited with a specific wavelength of light for which it will normally exhibit a fluorescence emission wavelength. The acceptor molecule is also excited at this wavelength such that it can accept the emission energy of the donor molecule by a variety of distance-dependent energy transfer mechanisms. Generally the acceptor molecule accepts the emission energy of the donor molecule when they are in close proximity

(e.g., on the same, or a neighboring molecule). FET and FRET techniques are well known in the art. See for example U.S. Pat. Nos. 5,668,648, 5,707,804, 5,728,528, 5,853,992, and 5,869,255 (for a description of FRET dyes), Tyagi et al. Nature Biotech. vol. 14, p 303-8 (1996), and Tyagi et al., Nature Biotech. vol 16, p 49-53 (1998) (for a description of molecular beacons for FET), and Mergny et al. Nucleic Acid Res. vol 22, p 920-928, (1994) and Wolf et al. PNAS vol 85, p 8790-94 (1988) (for general descriptions and methods fir FET and FRET), each of which is hereby incorporated by reference.

The probes for use in an array of the invention may be greater than 40 nucleotides in length and may be isothermal.

In some embodiments, the probes, array of probes or set of probes will be immobilized on a support. Supports (e.g., solid supports) can be made of a variety of materials, such as glass, silica, plastic, nylon or nitrocellulose. Supports are preferably rigid and have a planar surface. Supports typically have from about 1-10,000,000 discrete spatially addressable regions, or cells. Supports having about 10-1,000,000 or about 100-100,000 or about 1000-100,000 cells are common. The density of cells is typically at least about 1000, 10,000, 100,000 or 1,000,000 cells within a square centimeter. In some supports, all cells are occupied by pooled mixtures of probes or a set of probes. In other supports, some cells are occupied by pooled mixtures of probes or a set of probes, and other cells are occupied, at least to the degree of purity obtainable by synthesis methods, by a single type of oligonucleotide.

Arrays of probes or sets of probes may be synthesized in a step-by-step manner on a support or can be attached in presynthesized form. One method of synthesis is VLSIPS™ (as described in U.S. 5,143,854 and EP 476,014), which entails the use of light to direct the synthesis of oligonucleotide probes in high-density, miniaturized arrays. Algorithms for design of masks to reduce the number of synthesis cycles are described in U.S. 5,571,639 and U.S. 5,593,839. Arrays can also be synthesized in a combinatorial fashion by delivering monomers to cells of a support by mechanically constrained flowpaths, as described in EP 624,059. Arrays can also be synthesized by spotting reagents on to a support using an ink jet printer (see, for example, EP 728,520).

DATA ANALYSIS

Data analysis is also an important part of an experiment involving arrays. The raw data from an array experiment typically are images, which need to be transformed into matrices - tables where rows represent, for example, genes, columns represent, for example,

various samples such as tissues or experimental conditions, and numbers in each cell for example characterize the expression of a particular sequence (for example, a second sequence that has ligated to the first (target) nucleotide sequence) in the particular sample. These matrices have to be analyzed further, if any knowledge about the underlying biological processes is to be extracted. Methods of data analysis (including supervised and unsupervised data analysis as well as bioinformatics approaches) are disclosed in Brazma and Vilo J (2000) FEBS Lett 480(1):17-24.

KITS

The materials for use in the methods of the present invention are ideally suited for preparation of kits. Oligonucleotides may be provided in containers that can be in any form, e.g., lyophilized, or in solution (e.g., a distilled water or buffered solution), etc. In one aspect of the present invention, there is provided a kit comprising a set of probes as described herein, an array and optionally one or more labels. In another aspect, there is provided an RT-MLPA kit comprising a set of reverse transcriptase primers as described herein, and appropriate ligases, buffers, and PCR primers. In the kits of the invention, a set of instructions will also typically be included.

The oligonucleotide primers and probes of the present invention have commercial applications in prognostic kits for the detection of the expression level of a gene, such as a MEDIATOR complex and/or SWI/SNF complex gene, in the tumor cells of a patient. A test kit according to the invention may comprise any of the oligonucleotide primers or probes according to the invention. Such a test kit may additionally comprise one or more reagents for use in cyclic polymerase mediated amplification reactions, such as DNA polymerases, nucleotides (dNTPs), buffers, and the like. A kit according to the invention may also include, for example, a lysing buffer for lysing cells contained in the specimen.

A test kit according to the invention may comprise a pair of oligonucleotide primers according to the invention and a probe comprising an oligonucleotide according to the invention. Advantageously, the kit further comprises additional means, such as reagents, for detecting or measuring the binding of the primers and probes of the present invention, and also ideally a positive and negative control.

The invention will now be further described by way of the following non-limiting examples.

EXAMPLE 1

Identification of MED12, ARID1A and SMARCE1 as molecular determinants of resistance to ALK inhibitors in an EML4-ALK positive NSCLC cell line using a shRNA barcode screen

The ALK inhibitors crizotinib and NVP-TAE684 potently inhibit the human NSCLC cell lines that harbor EML4-ALK translocations (Galkin et al., 2007; Koivunen et al., 2008; Soda et al., 2007). The NSCLC cell line H3122 carries the EML4-ALK translocation and is exquisitely sensitive to ALK inhibitors. To identify novel determinants of resistance to ALK inhibitors in NSCLC cell lines, Applicants performed a large-scale RNAi-based loss-of-function genetic screen using a collection of 24,000 short hairpin (shRNA) vectors targeting 8,000 human genes (Berns et al., 2004; Brummelkamp et al., 2002). Applicants used a barcoding technology to identify genes whose suppression causes resistance to ALK inhibitors (Brummelkamp et al., 2006; Holzel et al.). The entire shRNA library was introduced into H3122 cells by retroviral infection and cells were plated at low density with or without ALK inhibitors (Figure 1A). After four weeks of incubation with ALK inhibitors and the emergence of resistant cell clones, genomic DNA was isolated from treated and untreated cultures. The stably integrated shRNA cassettes (19-mer bar code sequences) were recovered by PCR from genomic DNA. The relative abundance of individual shRNA vectors was quantified by hybridization of the PCR products to microarrays harboring all 24,000 barcode sequences. The barcode screen was carried out in triplicate and the combined results are shown in Figure 1B. Each dot in the M/A-plot represents one individual shRNA vector in the library. M- and A-values reflect relative enrichment and hybridization signal intensity. Reproducible outliers are generally located in the right upper corner. Low-intensity spots are prone to technical artifacts and thus unreliable. Therefore, Applicants restricted their candidate selection by applying M/A cut-off values of M≥7,5 and A≥7,5 as previously described (Holzel et al.). The identification of independent shRNAs against the same gene or single shRNAs targeting multiple components of the same complex or signaling pathway strongly suggest a genuine hit from the screen. Applying these filter criteria, Applicants identified shRNAs against the genes *MED12*, *ARID1A* and *SMARCE1*.

MED12, ARID1A and SMARCE1 are components of large multi-subunit Mediator and SWI/SNF complexes involved in transcriptional regulation and chromatin remodeling

The MED12 gene encodes for a component of the large mediator complex (~2MDa) that contains at least 33 different subunits and associates with RNA polymerase II at the promoters of genes (Malik and Roeder). Thereby, the Mediator complex is involved in transcriptional regulation. Initially it was thought that the mediator complex is exclusively required for active transcription of genes, but recent studies suggest additional and broader roles in transcriptional regulation, such as epigenetic silencing. In particular, MED12 was implicated in contributing to silencing of neuronal genes in non-neuronal cells by the recruitment of the H3K9 histone methyltransferase EHMT2 (G9a) in a REST dependent manner (Ding et al., 2008). Interestingly, mutations in MED12 are causal for some rare mental retardation syndromes and aberrant gene regulation might contribute to the phenotypic manifestations of these diseases (Risheg et al., 2007; Schwartz et al., 2007). In general, only a few studies have addressed the specific function of individual components of the mediator complex.

ARID1A and SMARCE1 are both components of the SWI/SNF chromatin-remodeling complex (Reisman et al., 2009). The SWI/SNF complex is also a large multi-subunit complex that contains two mutual exclusive but non-redundant subunits with ATPase activity. The ATPases SMARCA2 (BRM1) and SMARCA4 (BRG1) are required for the ATP dependent re-positioning of histones within the chromatin. This ATP-dependent chromatin remodeling activity impacts diverse chromatin related biological processes such as gene transcription and DNA repair. The SWI/SNF complex is conserved throughout evolution from yeast to man. Hence, it is remarkable that several subunits of the SWI/SNF complex have been identified as tumor suppressors. Deletions of SMARCB1 (INI1, BAF47) are found in malignant rhabdoid tumors, a highly aggressive childhood cancer (Versteege et al., 1998). Inactivating truncating mutations of ARID1A and PBRM1 were found in more than 50% and 40% of clear cell ovarian and renal cancer, respectively (Jones et al.; Varela et al.). SMARCA4 (BRG1) is frequently mutated in NSCLC cell lines, but also in primary tumors (Medina et al., 2008; Rodriguez-Nieto et al.). In conclusion, there is substantial evidence in the literature that specific components of the SWI/SNF complex function as tumor suppressors in a tumor type dependent manner, but the molecular basis of this selectivity remains unknown.

Validation of shRNA barcode screen results

To validate the results of their screen, Applicants individually introduced the respective knockdown vectors from the NKI shRNA library against *MED12* (#1 and #2), *ARID1A* and *SMARCE1* into H3122 cells by retroviral infections and confirmed that all four shRNA vectors confer resistance to the ALK inhibitors crizotinib and NVP-TAE684 in H3122 cells (Figure 1C). To rule out 'off-target' effects, a common problem in the field of RNAi screening, Applicants only consider a gene identified from the screen as a genuine hit, if at least two independent shRNAs suppress the expression of the target mRNA and also confer resistance to the ALK inhibitors (Echeverri et al., 2006). In particular, Applicants considered a gene identified in the screen as a genuine hit, if at least two independent shRNAs suppress the expression of the target and also confer crizotinib resistance. Only one gene fulfilled these criteria: MED12, encoding a component of the large MEDIATOR transcriptional adapter complex.

To validate MED12 as a gene whose suppression confers resistance to crizotinib, Applicants individually introduced the two MED12 shRNA vectors (#1 and #2) from the library and one newly generated shRNA (#3) into H3122 cells by retroviral infection. Empty vector (pRS) or shRNA targeting GFP (shGFP) served as controls throughout the study. All three distinct MED12 knockdown vectors conferred resistance to both crizotinib and the second ALK inhibitor NVP-TAE684 in long-term colony formation assays (Figure 3A) and also efficiently suppressed MED12 mRNA and protein expression (Figures 3B, 3C). Similarly, expression of additional independent lentiviral shMED12 vectors (#4 and #5) in H3122 cells also conferred resistance to ALK inhibitors (Figure 4A-C and data not shown). Furthermore, reconstitution of Med12 in MED12 knockdown (MED12KD) H3122 cells by introducing a RNAi-resistant mouse Med12 cDNA restored the sensitivity of these cells to ALK inhibition (Figure 4A).Applicants confirmed that the reconstituted MED12/Med12 total proteins in MED12KD cells were at physiological levels similar to parental cells (Figure 4B), and that knockdown of human MED12 mRNA was maintained in cells expressing both human shMED12 vectors and the mouse Med12 cDNA (Figure 4C, D). Together, these results validate MED12 as a genuine on target hit and establish its role in resistance to ALK inhibition.

Next, Applicants validated that *ARID1A* and *SMARCE1* are on-target hits causally involved in the resistance to ALK inhibitors. As Applicants have only identified single shRNAs (sh*ARID1A*#1, sh*SMARCE1*#1) against these genes from the barcode screen, they generated additional non-overlapping shRNAs against *ARID1A* and *SMARCE1* (sh*ARID1A*#2, sh*SMARCE1*#2) and introduced them into H3122 cells by retroviral infection.

The independent shRNAs recapitulated the resistance to ALK inhibitors (Figure 5A). It is noteworthy that knockdown of either *ARID1A* or *SMARCE1* impaired proliferation of H3122 cells in the absence of the inhibitors. Applicants confirmed the suppression of *ARID1A* and *SMARCE1* mRNA und protein levels by qRT-PCR and immunoblotting (Figure 5B-5E). Again, these results show that *ARID1A* and *SMARCE1* are genuine on-target hits from the screen.

Next, Applicants introduced silent mutations into a human *SMARCE1* cDNA expression construct and thereby generated two separate shRNA resistant (non-degradable, ND) forms of *SMARCE1* (*SMARCE1*-ND) that cannot be targeted by sh*SMARCE1*#1 and sh*SMARCE1*#2. H3122 cells stably infected with pRS, sh*SMARCE1*#1 or #2 were super-infected with retroviral expression constructs encoding for the respective non-degradable forms of *SMARCE1* or the pMx empty control vector. Reconstitution of *SMARCE1* restored sensitivity of *SMARCE1* knockdown cells to ALK inhibitors (Figure 6A). Applicants confirmed reconstituted SMARCE1 protein levels in SMARCE1 knockdown cells by immunoblotting using an SMARCE1 specific antibody, again achieving close to endogenous level of SMARCE1 (Figure 6B). Applicants also verified a persistent knockdown of the endogenous human *SMARCE1* mRNA in cells expressing the non-degradable *SMARCE1* cDNAs by qRT-PCR using a human *SMARCE1* 3'UTR specific primer pair (Figure 6C). In turn, Applicants also confirmed expression of the *SMARCE1* cDNA using an open reading frame specific primer pair detecting endogenous and ectopic (total) *SMARCE1* (Figure 6D). In summary, these experiments demonstrate that *SMARCE1* is a genuine on-target hit from the ALK inhibitor shRNA resistance screen.

MED12, ARID1A and SMARCE1 are molecular determinants of resistance to tyrosine kinase inhibitors in multiple NSCLC cell lines

Next, Applicants addressed the context dependency of their findings by studying independent NSCLC cell lines. The RAS/PI3K signaling cascade is a common denominator of all activated tyrosine kinases in NSCLC such as the EGFR (Pao and Chmielecki). Therefore, Applicants hypothesized that loss of *MED12*, *SMARCE1* and *ARID1A* might also confer resistance to other tyrosine kinase inhibitors in cell lines that harbor respective activating mutations or amplifications.

NSCLC with activating mutations of the EGFR can be effectively treated with the EGFR inhibitors gefitinib and erlotinib. Several NSCLC cell lines with EGFR mutations

(PC9, H3255) were identified that are exquisitely sensitive to gefitinib and erlotinib at low nanomolar concentrations. Applicants introduced *MED12* specific shRNAs (sh*MED12*_TRC#3 and #5) into PC9 cells ($EGFR^{delE746\text{-}A750}$). Suppression of *MED12* rendered PC9 cells insensitive to the EGFR inhibitor gefitinib (Figure 7A, left panel). In addition, reconstitution of PC9 *MED12*-knockdown cells with the mouse Med12 cDNA restored their sensitivity to gefitinib (Figure 7A, right panel). Using an antibody that recognizes human and mouse MED12/Med12, Applicants confirmed the suppression and restoration of MED12 protein level in the indicated PC9 cell lines by immunoblotting (Figure 7B). Applicants also verified persistent knockdown of endogenous *MED12* by qRT-PCR using a human *MED12* specific primer pair (Figure 7C). Likewise, Applicants controlled the ectopic expression of the mouse *Med12* cDNA by qRT-PCR using a mouse *Med12* specific primer pair (Figure 7D). Furthermore, H3255 ($EGFR^{L858R}$) cells were stably infected with three *MED12* shRNA or control constructs (pRS and sh*GFP*) and incubated with two EGFR inhibitors (gefitinib and erlotinib). Control cells were effectively eradicated, whereas sh*MED12* cells were insensitive to the treatment with the inhibitors (Figure 8A). Applicants confirmed suppression of *MED12* by qRT-PCR (Figure 8B). In conclusion, Applicants demonstrated that loss of *MED12* confers resistance to ALK and EGFR tyrosine kinase inhibitors in multiple NSCLC cell lines.

Next, Applicants asked whether *ARID1A* determines sensitivity to tyrosine kinase inhibitors in multiple NSCLC cell lines (context dependency). Applicants introduced the retroviral shRNA vectors against *ARID1A* (#1 and #2) or control vectors (pRS and sh*GFP*) into PC9 ($EGFR^{delE746\text{-}A750}$) and H1993 (*MET*-amplified) cells (Figure 1A and 1C). Suppression of *ARID1A* conferred resistance to the EGFR inhibitor gefitinib and the MET inhibitor crizotinib in PC9 and H1993 cells, respectively. Knockdown of *ARID1A* mRNA was confirmed by qRT-PCR (Figure 3B and 3D).

Now, Applicants addressed whether *SMARCE1* is also determinant of tyrosine kinase inhibitor sensitivity in multiple NSCLC cell lines (context dependency). PC9 ($EGFR^{delE746\text{-}A750}$), H1993 (*MET*-amplified) and EBC-1 (*MET*-amplified) cells were stably infected with the retroviral shRNA constructs pRS, sh*SMARCE1*#1 and #2 and were treated with the EGFR inhibitor geftitinib (PC9) or MET inhibitor crizotinib (H1993, EBC1). In all cases, suppression of *SMARCE1* conferred resistance to the respective inhibitors (Figure 10A, 11A and 12A, left panels). In parallel, the PC9, H1993 and EBC-1 cells expressing sh*SMARCE1*#1 and #2 were infected with retroviral expression constructs encoding for the non-degradable forms of *SMARCE1* (*SMARCE1*-ND). Reconstitution of *SMARCE1* restored

the sensitivity of *SMARCE1*-knockdown cells to the EGFR inhibitor geftitinib or MET inhibitor crizotinib (Figure 10A, 11A and 12A, right panels). Applicants confirmed reconstituted SMARCE1 protein levels in SMARCE1-knockdown cells by immunoblotting using an SMARCE1 specific antibody, again achieving close to endogenous level of SMARCE1 in most of the cases (Figure 10B, 11B and 12B). Applicants also verified a persistent knockdown of the endogenous human *SMARCE1* mRNA in cells expressing the non-degradable *SMARCE1* cDNAs by qRT-PCR using a human *SMARCE1* 3'UTR specific primer pair (Figure 10C, 11C and 12C). In turn, Applicants also confirmed expression of the non-degradable *SMARCE1* cDNAs using an open reading frame specific primer pair detecting endogenous and ectopic (total) *SMARCE1* (Figure 10D, 11D and 12D). It has been shown that excess SMARCE1 protein is rapidly degraded by the proteasome, suggesting that SMARCE1 protein stability requires incorporation into the SWI/SNF complex. This finding is in line with Applicants' observations from the reconstitution experiments that the protein levels of the non-degradable forms SMARCE1 were close to endogenous SMARCE1 protein level despite a significant mRNA overexpression. In conclusion, *SMARCE1* is a determinant of resistance to tyrosine kinase inhibitors in multiple NSCLC cell lines.

The role of RAS-GAPs in the control of tyrosine kinase inhibitor sensitivity in NSCLC cell lines

Constitutive signaling from mutated receptor tyrosine kinases such EGFR leads to activation of the RAS small GTP-binding proteins (KRAS, HRAS, NRAS). In particular *KRAS* is one of the most frequently mutated genes in a variety of cancers including NSCLC. RAS mutations impair the intrinsic GTPase activity and therefore prevent the conversion of active GTP-bound form into the inactive GDP-bound form (Karnoub and Weinberg, 2008). Introduction of constitutive active alleles of RAS in NSCLC cell lines renders the insensitive to tyrosine kinase inhibitors (data not shown). Therefore, inhibition of RAS is key mechanism of the efficacy of tyrosine kinase inhibitors. Applicants reasoned that direct negative regulators of RAS proteins might be critical determinants of sensitivity to tyrosine kinase inhibitors in NSCLC cell lines. The human genome encodes for 14 putative RAS-GTPase activating proteins (RAS-GAPs) that stimulate the GTPase activity of RAS proteins and promote the conversion of active GTP-loaded RAS into the inactive GDP-loaded form (Bernards, 2003). Applicants retrieved shRNAs covering the 14 putative human RAS-GAPs from the TRC shRNA collection and all shRNAs targeting the same gene were pooled

together. Applicants infected PC9 cells with the 14 RAS-GAP pools in addition to the control vectors pLKO and sh*GFP*. The cells were plated at low density and treated with the two EGFR inhibitors gefitinib and erlotinib or left untreated (Figure 13). Several RAS-GAP pools conferred resistance to the EGFR inhibitors in the PC9 cell lines. Applicants observed the strongest resistance phenotype for the pool targeting the RAS-GAP *DAB2IP*. The pools directed against NF1 and RASAL3 also rendered the cells less sensitive to both EGFR inhibitors, whereas the pools targeting RASA2 exhibited inconsistent results.

First, Applicants focused on the RAS-GAPs DAB2IP and NF1. NF1 is bona-fide tumor suppressor mutated in several cancers and also causal for the hereditable disease neurofibromatosis type I, a benign tumor syndrome with strong predisposition to several malignant cancers (Cichowski and Jacks, 2001). DAP2IP plays an important role in prostate cancer and loss of its expression is associated with an aggressive metastatic disease (Min et al.). To validate the results of Applicants' focused shRNA mini-screen, Applicants individually introduced the five *DAB2IP* shRNAs from the TRC shRNA collection into PC9 cells (Figure 14A). Applicants noticed that sh*DAB2IP*#2 and to a lesser extent sh*DAB2IP*#5 exhibited toxicity. Applicants assume that this toxicity is unrelated to the suppression of *DAB2IP*, as sh*DAB2IP*#5 failed to induce a knockdown of *DAB2IP*. The two best shRNA vectors (sh*DAB2IP*#1 and #3) conferred resistance to the EGFR inhibitors gefitinib and erlotinib. Suppression of *DAB2IP* mRNA levels was confirmed by qRT-PCR (Figure 14B). Next, Applicants addressed whether loss of DAB2IP affects the activity of downstream signaling components of the RAS pathway, in particular the phosphorylation (activation) status of ERK. Total cell lysates were prepared from control and sh*DAB2IP* cells (PC9) in the absence or presence of gefitinib (Figure 14C). Applicants confirmed suppression of DAB2IP protein level in sh*DAB2IP* expressing cells. Consistent with the inhibition of RAS by RAS-GAPs, Applicants observed elevated levels of phospho-ERK in sh*DAB2IP* cells indicating hyperactivation of downstream components of the RAS signaling cascade. Importantly, phosphorylation of ERK was maintained in sh*DAB2IP* cells treated with gefitinib being in line with resistance to EGFR inhibitors in the colony formation assays. Next, Applicants individually introduced the five *NF1* shRNAs from the TRC shRNA collection into PC9 cells (Figure 15A). The two best shRNA vectors (sh*NF1*#2 and #5) conferred resistance to the EGFR inhibitors gefitinib and erlotinib. Suppression of *NF1* mRNA and protein levels was confirmed by qRT-PCR and immunoblotting (Figure 15B and 15C). Applicants' results show that the DAB2IP and NF1 are important determinant of sensitivity NSCLC cell to EGFR inhibitors.

Suppression of MED12 and SMARCE1 leads to activation of ERK signaling in NSCLC cells.

Given that loss of MED12 or SMARCE1 causes resistance to multiple tyrosine kinase inhibitors in NSCLC cell lines, Applicants asked whether the activity of downstream components of receptor tyrosine kinase signaling is altered. ERK is a key downstream component and its phosphorylation status positively correlates with its activation that can be determined by specific antibodies against the phosphorylated form of ERK. H3122 cells were infected with two independent controls shRNA vectors or shRNAs targeting either *MED12* or *SMARCE1* and confirmed loss of MED12 or SMARCE1 protein by immunoblotting (Figure 16A and B). The cells were also treated of left untreated with the ALK inhibitor NVP-TAE684, to address the activation status of ERK in the presence or absence of the inhibitor. Interestingly, H3122 MED12 knockdown cells maintained higher levels of ERK phosphorylation in the presence of the inhibitor (Figure 16A). Loss of SMARCE1 resulted in an increased ERK activation even in the absence of the inhibitor and consistently maintained higher levels of phosphorylated ERK in the presence of NVP-TAE684 (Figure 16B). In conclusion, elevated activation of the key downstream component ERK upon suppression of MED12 or SMARCE1 is consistent with resistance to upstream inhibition by tyrosine kinase inhibitors. Further, Applicants could also show that loss of MED12 resulted in elevated levels of ERK phosphorylation and hence activation in PC9 cells (Figure 16C). Applicants conclude that MED12 and SMARCE1 regulate ERK activation in multiple NSCLC lung cancer cell lines. Accordingly, in certain embodiments, MED12 and/or SMARCE1 expression and/or mutation status is an important determinant of treatment responses to tyrosine kinase inhibitors in the clinic.

MED12 loss leads to ERK activation and multi targeted-drug resistance in different cancer types

Applicants' finding that MED12 suppression confers resistance to both ALK and EGFR inhibitors in NSCLCs suggests that MED12 might act on a critical pathway downstream of both ALK and EGFR. As pointed out above, RAS signaling is downstream of all activated RTKs in NSCLC (Pao and Chmielecki, 2010). Applicants first asked which components of the RAS pathway could cause resistance to RTK inhibition in H3122 and PC9 cells by expressing active alleles of these genes (Figure 31). As expected, activation of RAS signaling by expression of KRASV12 conferred resistance to upstream inhibition by TKIs

targeting ALK and EGFR (Figure 31). BRAFV600E and MEK-DD also conferred resistance to TKIs, but PIK3CAH1047R, RALAQ75L and RALBQ72L failed to do so in both cell systems used. These results indicate that activation of the RAS-RAF-MEK cascade is sufficient to cause resistance to ALK and EGFR inhibitors. Applicants therefore asked whether the activity of RAF-MEK-ERK is altered in MED12KD cells. Indeed, H3122 cells expressing shMED12 vectors maintained higher levels of phosphorylated ERK (p-ERK) in the presence of ALK inhibitor (Figure 17A). Similarly, knockdown of MED12 in PC9 and H3255 cells leads to higher levels of p-ERK in both absence and presence of EGFR inhibitors (Figure 17B and data not shown). These findings suggest that MED12 loss confers resistance to ALK and EGFR inhibitors in NSCLCs by enhancing ERK activation.

If suppression of MED12 leads to ERK activation, one would expect that MED12 loss might also confer resistance to other cancer drugs targeting the MAPKs upstream of ERK. The small molecule drug PLX4032 (vemurafenib) has proven to be very effective in the treatment of melanoma with BRAFV600E mutations and the MEK inhibitor AZD6244 (seluteminib) is being tested in the clinical trials for the treatment of several cancers. A375 melanoma cells harboring the BRAFV600E mutation are highly sensitive to PLX4032 and AZD6244. Consistent with Applicants' observations made in NSCLC models, Applicants found that suppression of MED12 in A375 cells caused ERK activation (Figure 17D) and conferred potent resistance to both PLX4032 and AZD6244 (Figure 17C). Similar results were obtained in an additional melanoma cell line SK-MEL-28 (Figure 18C, D). SK-CO-1 colorectal cancer (CRC) cells harbor a KRASV12 mutation and are highly sensitive to MEK inhibition by AZD6244. Knockdown of MED12 also resulted in activation of ERK (Figure 17F) and conferred resistance to AZD6244 in SKCO-1 cells (Figure 17E). Identical results were observed in the CRC cell line SW1417 harboring a BRAFV600E mutation (Figure 18E, F).

To extend their findings even further, Applicants asked whether MED12 also confers resistance to a class of multi-kinase inhibitors. Sorafenib targets multiple tyrosine kinases and RAF kinases and is used clinically to treat advanced renal cell carcinoma and hepatocellular carcinoma (HCC). HCC Huh-7 cells are sensitive to sorafenib, but became resistant after knockdown of MED12 (Figure 17G, H). Taken together, Applicants' data demonstrate that MED12 loss leads to ERK activation and confers resistance to a range of targeted cancer drugs that act upstream of the ERK kinases. Applicants also note that the effects of MED12 suppression appear to be mostly context-independent as its consequences are readily apparent in several major cancer types including NSCLC, melanoma, CRC and HCC.

Results melanoma:

Suppression of MED12 confers drug resistance to BRAF and MEK inhibitors in $BRAF^{V600E}$ melanoma cells

As a first step in expanding Applicants' finding in NSCLC, they examined the potential role of MED12 in drug responses to BRAF and MEK inhibitors in $BRAF^{V600E}$ melanomas where activation of ERK is a common feature of resistant tumors. Since MED12 knockdown leads to higher levels of ERK phosphorylation in NSCLC cells, Applicants asked if MED12 is also critical for drug responses to BRAF and MEK inhibitors in $BRAF^{V600E}$ melanoma cells. A375 ($BRAF^{V600E}$) melanoma cells stably expressing the retroviral shRNA constructs pRS, sh*GFP*, sh*SMARCE*1#1 and #2 were treated with the $BRAF^{V600E}$ inhibitor PLX4720 or MEK inhibitor PD-0325901. In all cases, suppression of *MED12* conferred resistance to the respective inhibitors (Figure 19).

In addition, Applicants observed similar effects in the melanoma cell line, SK-MEL-28, which expresses $BRAF^{V600E}$. In particular, Applicants demonstrate that downregulation of MED12 induces resistance to the BRAF inhibitor, PLX 4032, in SK-MEL-28 cells.

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Experimental Procedures

shRNA Barcode Screen

The human NKI shRNA library and the barcode screen were performed as described (Berns et al., 2004; Brummelkamp et al., 2006). Additional details can be found at http://www(dot)screeninc(dot)nki(dot)nl.

Cell Proliferation Assays

Single cell suspensions of the lung cancer cell lines were seeded into 6-well plates ($2x10^4$ cells/well) and cultured both in the absence and presence of the ALK inhibitors. At the endpoints of colony formation assays, cells were fixed with formaldehyde, stained with

crystal violet (0,1%w/v) and photographed. All relevant assays were performed independently at least three times. All knockdown and overexpression experiments were done by retroviral or lentiviral infections.

Cell Culture and Viral Transduction

H3122, PC9, H1993, EBC-1, H3255, SK-CO-1, and SW1417 cells were cultured in RPMI with 8% heat-inactivated fetal bovine serum, penicillin and streptomycin at 5% CO_2. 293T, Phoenix cells, A375, SK-MEL-28, and Huh-7 cells were cultured in DMEM with 8% heat-inactivated fetal bovine serum, penicillin and streptomycin at 5% CO_2. Subclones of each NSCLC cell line expressing the murine ecotropic receptor were generated and used for all experiments shown. Retroviral infections were performed using Phoenix cells as producers of retroviral supernatants using 2.5-3 μg of plasmid DNA as described (http://www(dot)stanford(dot)edu/group/nolan/retroviral_systems/phx(dot)html). 293T cells were used as producers of lentiviral supernatants by co-transfecting 3rd generation lentiviral packaging constructs (2μg of plasmid DNA) along with the pLKO shRNA vectors (2μg of plasmid DNA). For transfections of 293T cells, Applicants seeded $1.8x10^6$ cells in a 6-well dish in the morning and transfected the cells 6-8 hours later. For transfections of Phoenix cells, Applicants seeded $1.0x10^6$ cells in a 6-well dish in the morning and transfected the cells 6-8 hours later. Cells were refreshed the next day in the morning and afternoon. Viral supernatant was harvested the day thereafter for infections of the target cells. The calcium phosphate method was used for the transfection of Phoenix and 293T cells. Infected NSCLC cells were selected for successful retroviral integration using 2 μg/ml of puromycin.

Reagents and Antibodies

Crizotinib (S1068), NVP-TAE648 (S1108), gefitinib (S1025), erlotinib (S1023), PLX4032 (S1267) and AZD6244 (S1008) were purchased from Selleck Chemicals. TRC human genome-wide shRNA collection (TRC-Hs1.0) was purchased from Open Biosystems (Huntsville, USA). Further information is available at http://www(dot)broad(dot)mit(dot)edu/genome_bio/trc/rnai(dot)html. Antibody against MED12 (A300-774A), SMARCE1 (A300-810A), DAB2IP (A302-439A) and NF1 (A300-140A) was from Bethyl Laboratories; antibody against Vimentin (RV202) was from Abcam; antibody against N-cadherin (ab18203) was from Cell Signaling; antibodies against NF1 (SC-67), HSP90 (H-114), p-ERK (E-4), ERK1 (C-16), ERK2 (C-14), CDK8 (D-9), Lamin A/C (636), SP1 (PEP2) and α-TUBULIN (H-183) were from Santa Cruz Biotechnology; The

antibody against ARID1A (H00008289-M01) was from Abnova. A mixture of ERK1 and ERK2 antibodies was used for detection of total ERK.

Plasmids

All retroviral shRNA vectors were generated by ligating synthetic oligonucleotides (Invitrogen) against the target genes into in the pRetroSuper (pRS) retroviral vector as described (Brummelkamp et al., 2002). The following RNAi target sequences were used for this study.

sh*GFP*	GCTGACCCTGAAGTTCATC
sh*MED12*#1	GTACCATGACTCCAATGAG
sh*MED12*#2	GGAAGAGGTGTTTGGGTAC
sh*MED12*#3	GGAGGAACTGCTTGTGCAC
sh*ARID1A#1*	GGGGTGAGCTGCAACAAAG
sh*ARID1A#2*	AGGAGAAGCTGATCAGTAA
sh*SMARCE1#1*	GGAGAACCGTACATGAGCA
sh*SMARCE1#2*	GGAAGAAAGTCGACAGAGA

All lentiviral shRNA vectors (TRCN number) were retrieved from the arrayed human TRC shRNA library. Additional information about the shRNA vectors can be found at http://www.broadinstitute.org/rnai/public/clone/search using the TRCN number.

pLKO_control		No hairpin insert
sh*GFP*		GCAAGCTGACCCTGAAGTTCA
sh*MED12_TRC*#1	TRCN0000018574	GCAGCATTATTGCAGAGAAAT
sh*MED12_TRC*#2	TRCN0000018575	GCTGTTCTCAAGGCTGTGTTT
sh*MED12_TRC*#3	TRCN0000018576	CGGGTACTTCATACTTTGGAA
sh*MED12_TRC*#4	TRCN0000018577	GCAGTTCATCTTCGACCTCAT
sh*MED12_TRC*#5	TRCN0000018578	GCAGAGAAATTACGTTGTAAT
sh*NF1_TRC*#1	TRCN0000039713	CCATGTTGTAATGCTGCACTT
sh*NF1_TRC*#2	TRCN0000039714	GCCAACCTTAACCTTTCTAAT
sh*NF1_TRC*#3	TRCN0000039715	CCTCACAACAACCAACACTTT
sh*NF1_TRC*#4	TRCN0000039716	CCTGACACTTACAACAGTCAA
sh*NF1_TRC*#5	TRCN0000039717	GCTGGCAGTTTCAAACGTAAT
sh*DAB2IP_TRC*#1	TRCN0000001457	GTAATGTAACTATCTCACCTA
sh*DAB2IP_TRC*#2	TRCN0000001458	GACTCCAAACAGAAGATCATT

sh*DAB2IP_TRC*#3	TRCN0000001459	GAGTTCATCAAAGCGCTGTAT
sh*DAB2IP_TRC*#4	TRCN0000001460	CTGCAAGACTATCAACTCCTA
sh*DAB2IP_TRC*#5	TRCN0000001461	GCACATCACTAACCACTACCT

shTGFβR2#1, TRCN0000000830;
shTGFβR2#2, TRCN0000010445.

The mouse *Med12* expression constructs were generated by the following steps:

1), An linker containing first 89 bp of *Med12* open reading frame (ORF) and multiple restriction sites was cloned into pcDNA3.1(+) vector by NheI and BamHI restriction sites and was sequence verified; The oligo sequences of the top strand for the linker is CTAGCTCGAGTCGACCATGGCGGCTTTCGGGATCTTGAGCTATGAACACCGACCC CTGAAGCGGCTGCGGCTGGGGCCTCCCGATGTGTACCCTCAG and the bottom strand is GATCCTGAGGGTACACATCGGGAGGCCCCAGCCGCAGCCGCTTCAGGGGTCGGT GTTCATAGCTCAAGATCCCGAAAGCCGCCATGGTCGACTCGAG.

2), A PCR fragment of partial Med12 (from 89 to 1777 bp) was generated using a forward primer (CAGGATCCCAAACAGAAGGAGGATGAACTGACGGCTTTGAATGTAA), a reverse primer (TGGGAGAAGACATCATGTCG) and a *Med12* partial cDNA as the template (IMAGE id: 6830443); This PCR fragment was then cloned into the pcDNA3.1(+)-*Med12* (first 89 bp) vector described in step 1 by BamHI and EcoRI restriction sites and was sequence verified. Note that a silence mutation (A to G) at 81 bp of *Med12* ORF was introduced in the forward PCR primer to generate BamHI site in the PCR fragment.

3), An EcoRI/NotI fragment (containing from 1778 to 6573 bp of *Med12* ORF) from the *Med12* partial cDNA (IMAGE id: 6830443) was cloned into the pcDNA3.1(+)-*Med12* (first 1777 bp) described above by EcoRI and NotI restriction sites to generate the pcDNA3.1(+)-*Med12* (full-length).

4), The XhoI/NotI fragment containing the full-length *Med12* ORF from pcDNA3.1(+)-*Med12* was then cloned into the retroviral expression vector pMX-IRES-blasticidine using the XhoI and NotI restriction sites.

The human *SMARCE1* expression construct and the non-degradable (ND) forms of were generated by PCR amplifying *SMARCE1* from H3122 cDNA using the following

primers:
Forward, GTACGAATTCCACCATGTCAAAAAGACCATCTTATGC;
Reverse, GAATAAGTGTTGCCTTGTTTTGTGCTCGAGACTG. The fragment was cloned into the retroviral expression vector pMX-IRES-blasticidine using the EcoRI and XhoI restriction sites in the multiple cloning site and sequence verified. The *SMARCE1-ND* that is resistant against sh*SMARCE1*#1 was generated by site directed mutagenesis using the following primer pair:
Forward, GCATGGAGAAAGGAGAGCCATATATGAGCATTCAGCCTG;
Reverse, CAGGCTGAATGCTCATATATGGCTCTCCTTTCTCCATGC.
The *SMARCE1-ND* that is resistant against sh*SMARCE1#2* was generated by site directed mutagenesis using the following primer pair:
Forward, GAAGCTGCTTTAGAGGAGGAGAGCCGACAGAGACAATCTC;
Reverse, GAGATTGTCTCTGTCGGCTCTCCTCCTCTAAAGCAGCTTC. Both *SMARCE1*-ND clones were sequence verified.

Retroviral expression constructs (pBabe) for KRASG12V (#12544), MEK-DD (#15268), RALAQ75L (#19719), RALBQ72L (#19721), PIK3CAH1047R (#12524) and pCMV5BTGFbeta receptor II (#24801) were obtained from Addgene and sequence validated. The pBabe-BRAFV600E plasmid was a kind gift of Daniel Peeper. The cDNA encoding Myr-AKT was cloned into pBabe-puro and validated by sequencing. These active alleles of RAS effector pathways were also described previously (Holzel et al., 2010)

Quantitative RT–PCR (qRT-PCR)

QRT-PCR assays were carried out to measure mRNA levels of genes using 7500 Fast Real-Time PCR System (Applied Biosystems). Total RNA was isolated using Trizol (Invitrogen) and 1μg of total RNA was used for cDNA synthesis using superscrpipt II reverse transcriptase (Invitrogen) and random hexamer primers (Invitrogen). Relative mRNA levels of each gene shown were normalized to the expression of the house keeping gene *GAPDH*. The sequences of the primers for assays using SYBR® Green master mix (Roche) are listed below (h, human: m, mouse).

hGAPDH_QPCR_Forward	AAGGTGAAGGTCGGAGTCAA
*hGAPDH_QPCR*_Reverse	AATGAAGGGGTCATTGATGG
*hNF1*_QPCR_Forward	TGTCAGTGCATAACCTCTTGC
*hNF1*_QPCR_Reverse	AGTGCCATCACTCTTTTCTGAAG

hMED12_QPCR_Forward	GCTGGTGCACATAGCCACT
*hMED12_QPCR*_Reverse	TACTCCAGCCAGCCTTACCA
mMed12_QPCR_Forward	TCAGGCAGTGGGATTACAATGA
*mMed12_QPCR*_Reverse	TCCAGGGCGTATTTTCTCAAAAC
hSMARCE1_QPCR_Forward	CGGCTTATCTGGTGGCTTT
*hSMARCE1_QPCR*_Reverse	AACAACTACAGGCTGGGAGG
hSMARCE1_3'UTR_QPCR_Forward	GGCTTTTGGACCATTTAGCA
*hSMARCE1_3'UTR_QPCR*_Reverse	GAGGCTTTCAGCAGTTGAGG
hARID1A_QPCR_Forward	CCAACAAAGGAGCCACCAC
*hARID1A_QPCR*_Reverse	TCTTGCCCATCTGATCCATT
*hDAB2IP*_QPCR_Forward	AGCGAGACTCCTTCAGCCTC
hDAB2IP_QPCR_Reverse	GACCGCAACCACAGCTTC

TGFβR2_Forward, GCACGTTCAGAAGTCGGTTA; TGFβR2_Reverse, TCTGGTTGTCACAGGTGGAA;
ANGPTL4_Forward, GGAACAGCTCCTGGCAATC; ANGPTL4_Reverse, GCACCTAGACCATGAGGTGG;
TAGLN_Forward, GTCCGAACCCAGACACAAGT; TAGLN_Reverse, CTCATGCCATAGGAAGGACC;
CYR61_Forward,GCTGGAATGCAACTTCGG; CYR61_Reverse, CCCGTTTTGGTAGATTCTGG;
CTGF_Forward, TACCAATGACAACGCCTCCT; CTGF_Reverse, TGGAGATTTTGGGAGTACGG;
VIM_Forward, CTTCAGAGAGAGGAAGCCGA; VIM_Reverse, ATTCCACTTTGCGTTCAAGG;
CDH2_Forward, CCACCTTAAAATCTGCAGGC; CDH2_Reverse, GTGCATGAAGGACAGCCTCT.

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TGFβ signaling is required for drug resistance caused by MED12 loss

The studies described herein show that suppression of MED12 leads to ERK activation and thus confers what in some embodiments is a "multi targeted-drug resistance" phenotype. To gain further mechanistic insights, Applicants set out to screen a lentiviral shRNA library representing the full complement of 518 human kinases (the "kinome", (Manning et al., 2002)) and 17 additional kinase-related genes (Figure 36) for genes whose inhibition restores sensitivity to ALK inhibitors in $MED12^{KD}$ cells. This "drop out" screen is the inverse of the resistance screen shown in Fig. 2A,B, as here Applicants select for shRNAs that are depleted upon drug treatment rather than enriched. H3122 cells stably expressing shMED12 were infected with the lentiviral kinome shRNA collection and cultured in the presence or absence of crizotinib for 10 days. After this, the relative abundance of shRNA vectors was determined by next generation sequencing of the bar code identifiers present in each shRNA vector (Figure 21A). To prioritize the candidates for study, Applicants arbitrarily considered only shRNA vectors that had been sequenced at least 200 times and which were depleted at least 2.5 fold by the drug treatment. Only very few of the 3388 shRNA vectors in the library met this stringent selection criterion (Figure 21B). Among these candidates, only one gene,transforming growth factor beta receptor II (TGFβR2), was represented by two independent shRNA vectors that met the selection criterion. This suggested that suppression of TGFβR2 synergizes with ALK inhibition in $MED12^{KD}$ cells. To validate this finding, Applicants infected the same $MED12^{KD}$ H3122 cells with each of these two shTGFβR2 vectors (both of which reduced TGFβR2 levels (Figure 21D)) and cultured these cells with or without crizotinib for two weeks. Inhibition of TGFβR2 did not significantly affect proliferation of the parental or $MED12^{KD}$ cells in the absence of crizotinib (Figure 21C). In contrast, suppression of TGFβR2 in combination with ALK inhibitor caused a marked inhibition of proliferation only in $MED12^{KD}$ cells (Figure 21C). These findings indicate that suppression of TGFβR2 re-sensitizes the $MED12^{KD}$ cells to ALK inhibitors and suggest that TGFβ signaling is required for the drug resistance driven by MED12 loss.

TGFβ activation is sufficient to confer resistance to multiple targeted drugs in different cancer types

Next, Applicants asked whether activation of TGFβ signaling alone is sufficient to cause resistance to the cancer drugs studied above. In the absence of exogenous TGFβ, proliferation of the H3122 cells was greatly inhibited by crizotinib. In contrast, cells treated with TGFβ in combination with crizotinib continued to proliferate in a TGFβ-dosage dependent manner (Fig. 4A). These data indicate that TGFβ activation, similar to suppression of MED12, is sufficient to confer resistant to ALK inhibitors in EML4-ALK positive NSCLCs. Interestingly, H3122 cells treated with recombinant TGFβ had a similar large and flat cell morphology as $MED12^{KD}$ cells, which was not seen in parental cells (Figure 26A). Similar morphological observations were seen in other cell types (Figure 26B and data not shown).

Recombinant TGFβ treatment also conferred resistance to EGFR inhibitors in PC9 and H3255 NSCLC cells (Figure 24B and data not shown). Similarly, treatment of TGFβ resulted in a dosage dependent resistance to AZD6244 and PLX4032 in SK-CO-1 CRC cells and A375 melanoma cells (Figure 24C, D). In some cells, such as A375 and Huh-7 cells, (Figure 24D and data not shown), recombinant TGFβ treatment alone resulted in growth inhibition, but clearly became beneficial for proliferation when cells were cultured in the presence of targeted cancer drugs, mimicking the effects of MED12 knock down in the same cells (Figure 17C, G). Collectively, these results demonstrate that activation of TGFβ signaling is sufficient to confer resistance to multiple targeted cancer drugs in the same cancer types in which $MED12^{KD}$ also confers drug resistance.

MED12 loss activates TGFβ signaling by elevating TGFβR2 protein levels

The fact that TGFβ signaling is required for the drug resistance driven by MED12 suppression and that activation of TGFβ signaling phenocopies $MED12^{KD}$ in mediating drug resistance suggested that MED12 can act as a suppressor of TGFβ signaling. Applicants explored this possibility by studying differential gene expression by unbiased transcriptome sequencing analysis using next generation sequencing (RNA-Seq) for the same panel of cells lines tested above (H3122, PC9, SK-CO-1, A375 and Huh-7), for both the parental cells and multiple $MED12^{KD}$ derivatives thereof. The genes deregulated by $MED12^{KD}$ (>2 fold) in at least three out of five cell lines used are listed in Figure 37 and are referred to as $MED12^{KD}$ signature genes henceforth (237 genes up- and 22 genes downregulated). Strikingly, many of these genes are bona fide TGFβ targets. To confirm these observations, Applicants first

examined mRNA expression levels of a panel of TGFβ target genes, including ANGPTL4, TAGLN, CYR61, CTGF, SERPINE1 and CDKN1A in both H3122 and PC9 cells by qRT-PCR (Figure 29A to 29D and data not shown). In agreement with Applicants' RNA-Seq data, all of these TGFβ target genes were significantly induced upon $MED12^{KD}$ in these NSCLC cells. Applicants also observed induction of these TGFβ target genes upon $MED12^{KD}$ in many cell lines of other tumor types, including melanoma A375 and SK-MEL-28, CRC SK-CO-1 and SW1417 and HCC Huh-7 (Figure 30A to 30D and data not shown). It is well-established that TGFβ induces an epithelial–mesenchymal transition (EMT), leading to the induction of several mesenchymal markers such as Vimentin (VIM) and N-cadherin (CDH2) (Thiery et al., 2009). Importantly, $MED12^{KD}$ also caused expression of the mesenchymal markers VIM and CDH2, indicating that an EMT-like process is initiated in $MED12^{KD}$ cells (Figure 29E-F and Figure 30E-F). Accordingly, the protein products of these mesenchymal-specific genes such as Vimentin and N-cadherin were also detected in $MED12^{KD}$ cells by Western blotting (Figure 30I and data not shown). Expression of the epithelial marker E-cadherin (CDH1) was not lost in $MED12^{KD}$ cells (data not shown), suggesting that $MED12^{KD}$ induces a partial EMT. Together, these unbiased gene expression studies support the notion that MED12 is a suppressor of TGFβ signaling in a wide range of cancer types and that its loss activates TGFβ signaling.

To further elucidate the molecular mechanism by which MED12 suppresses TGFβ signaling, Applicants studied the effect of knockdown of MED12 on expression and activation of key components of the TGFβ signaling pathway. Strikingly, Applicants found that suppression of MED12 resulted in a strong induction of TGFβR2 protein levels in H3122 and PC9 cells (Figure 29G, H). Consistently, SMAD2, the key mediator for TGFβ target gene activation, was activated as indicated by a strong increase in SMAD2 phosphorylation upon MED12 knockdown. Similar results were also obtained in A375 melanoma, in SK-CO-1 CRC cells and other cancer cell lines, indicating that this interplay between MED12KD and TGFβ signaling is conserved across different tumor types (Figure 30H-I and data not shown).

Since MED12 is part of the MEDIATOR transcriptional complex that functions in the nucleus, Applicants assumed that MED12 would act on TGFβR2 through a transcriptional step. However, there was only a marginal increase of TGFβR2 mRNA upon MED12 knockdown (Figure 30G), suggesting that MED12 suppresses TGFβR2 in a post-transcriptional manner. To investigate this, Applicants first determined the subcellular localization of MED12. Applicants carried out nuclear and cytoplasmic fractionation of PC9 cells expressing control vector or shMED12, followed by western blotting (Figure 29I).

Lamin A/C and SP1 were used as marker controls for nuclear fractions, while α-TUBULIN and HSP90 were used as controls for cytoplasmic fractions. Abundant nuclear MED12 was detected, in agreement with its known function in a transcriptional complex. Unexpectedly, a significant quantity of MED12 was also present in the cytoplasmic fraction. Applicants confirmed that the cytoplasmic MED12 signal was genuine as it was greatly reduced in the lysate from $MED12^{KD}$ cells. Cytoplasmic MED12 was also seen in H3122 cells (Figure 30J). Interestingly, no significant cytoplasmic CDK8 was detected, another subunit of the MEDIATOR kinase module with which MED12 is known to associate closely. This suggested that cytoplasmic MED12 might have a second function, independent of its role in the MEDIATOR complex.

The observation of the cytoplasmic localization of MED12 prompted Applicants to examine a potential physical interaction between MED12 and TGFβR2. Since low expression of endogenous TGFβRs in most cell types hinders the study of physical interaction with TGFβRs, Applicants performed co-immunoprecipitation experiments using Phoenix cells cotransfected with TGFβR2 and MED12. As indicated in Figure 29J, TGFβR2 coimmunoprecipitated with MED12 and conversely MED12 co-immunoprecipitated with TGFβR2, indicating that MED12 interacts physically with TGFβR2. Thus, in certain embodiments, MED12 is a critical suppressor of TGFβ signaling by negatively regulating TGFβR2 and this effect is mediated in certain embodiments by a novel cytoplasmic function of MED12 in complex with TGFβR2. Hence, without being bound to theory, this finding provides an explanation why MED12 suppression leads to activation of TGFβ signaling.

A MED12KD gene signature has features of EMT and is both prognostic and predictive

As described above, MED12 suppression leads to activation of TGFβ signaling and expression of mesenchymal markers, suggestive of a partial EMT-like process. Recently, EMT has been identified as a program in human CRC that correlates with poor prognosis (Loboda et al., 2011). Applicants therefore asked whether $MED12^{KD}$ indeed induces an EMT-like process and whether the processes induced by $MED12^{KD}$ are likewise associated with poor survival in CRC.

Applicants first compared the 237 genes that were upregulated in the $MED12^{KD}$ signature (as described herein; Figure 37) to the 229 genes upregulated in a more general EMT signature (see Figure 38). Applicants found a significant overlap of 31 genes in both signatures (p=8.9*10-23; Figure 33A and Figure 39).This result further supports the notion that MED12 loss initiates a partial EMT. There was no overlap between the 22 genes

downregulated in the MED12^{KD} signature and the genes downregulated in the EMT signature, most likely due to the small number of genes. Next, Applicants asked whether genes that are deregulated after MED12 knockdown predict survival in CRC. Hierarchical clustering of a set of 231 CRC tumor samples using the MED12^{KD} signature genes led to the identification of two subsets of tumors having significantly different disease-specific survival (Figure 33B). These results indicate that the processes induced by MED12^{KD} result in a poor survival in CRC patients.

To further substantiate Applicants' finding that MED12 suppression confers resistance to cancer drugs targeting the MEK-ERK pathway downstream of RTKs, Applicants asked if the MED12^{KD} signature could predict responses to MEK inhibitors in a large and heterogeneous panel of cancer cell lines of different tissue types. Since MEK inhibitors are currently being evaluated for the treatment of tumors having activating mutations in RAS or BRAF, Applicants focused their studies on 152 tumor cell lines harboring either RAS or BRAF mutations for whom the IC50 values of four different MEK inhibitors and gene expression patterns have been determined (Figure 41). Of the 237 genes that were up-regulated by MED12^{KD} as identified by RNA-Seq, Applicants could read the expression levels for 170 genes in these 152 cell lines (Figure 40). Applicants found that high expression of these 170 genes is significantly associated with higher IC50s for all four MEK inhibitors in these cell lines (AZD6244, p=0.009; CI-1040, p=0.004; PD-0325901, p=0.007; RDEA119, p=0.013; Figure 33C and Figure 40). The analysis of one of these genes, ZBED2, is shown as an example in Figure 34). Thus, the group of genes that is upregulated following MED12^{KD} can predict response to MEK inhibitors in a very heterogeneous panel of cancer cell lines, consistent with the notion that MED12 acts independent of cellular context to influence cancer drug responses (Figure 33C).

TGFβR inhibitor and TKIs synergize to suppress proliferation of MED12KD NSCLC cells

Applicants have demonstrated that TGFβ activation by either MED12 loss or recombinant TGFβ stimulation confers resistance to multiple targeted cancer drugs in a range of cancer types. It is therefore of potential clinical relevance to explore new treatment strategies to target drug resistant tumors having acquired elevated TGFβ signaling. Since inhibition of TGFβR2 by RNAi re-sensitized MED12^{KD} NSCLC cells to TKIs (Figure 21 and data not shown), Applicants reasoned that TGFβR inhibitors would synergize with TKIs to inhibit MED12^{KD} NSCLC cells.

To test this concept, Applicants cultured control or MED12^{KD} H3122 cells in the absence and the presence of crizotinib, the TGFβR inhibitor LY2157299 or the combination of crizotinib and LY2157299 (Figure 35A). LY2157299 is a small molecule inhibitor targeting both TGFβR1and TGFβR2, and is currently being evaluated in clinical trials for the treatment of several cancer types. Consistent with Applicants' previous data, crizotinib alone potently inhibited the proliferation of the control, but not of the MED12^{KD} cells. LY2157299 monotherapy had little effect on all cells. However, strong synergy was seen when crizotinib was combined with LY2157299, consistent with the notion derived from the RNAi experiment that TGFβR2 inhibition restored the sensitivity of MED12^{KD} cells to crizotinib. Importantly, the same synergistic response was also obtained when LY2157299 was combined with gefitinib to suppress proliferation of MED12KD PC9 cells (Figure 35B). Thus, in certain embodiments, the combination of TGFβR inhibitors and TKIs is a strategy for treating tumors with elevated TGFβ signaling.

Experimental Procedures

Pooled "dropout" shRNA Screen

A Kinome shRNA library targeting the full complement of 518 human kinases and 17 kinaserelated genes was constructed from the TRC human genome-wide shRNA collection (TRCHs1.0). The Kinome library was used to generate pools of lentiviral shRNA to infect H3122 cells stably expressing shMED12. Cells were cultured in the presence or absence of crizotinib. Massive parallel sequencing was applied to determine the abundance of shRNA in cells. shRNAs prioritized for further analysis were selected by the fold of depletion by crizotinib treatment.

Long-term Cell Proliferation Assays

Cells were seeded into 6-well plates (2-5 x104 cells/well) and cultured both in the absence and presence of drugs as indicated. More details are described in Huang et al., 2009 (Huang et al.,2009). All knockdown and overexpression experiments were done by retroviral or lentiviral infection. All relevant assays were performed independently at least three times.

Gene expression and statistical analysis

Transcriptome sequencing analysis of cell lines were performed using RNA-Seq. To rule out "off-target" effects, Applicants considered genes that are significantly deregulated in the same direction by two independent shMED12 vectors. The MED12KD gene signature

was then assembled containing genes that were more than 2 folds up- or downregulated upon MED12 knock-down in at least three out of five cell lines. This signature was employed to hierarchically cluster a dataset consisting of gene expression data for 231 which CRC tumor samples. Differences in disease specific survival were determined using the Kaplan-Meier statistics.

EMT signature

An EMT signature was created by combining EMT expression signatures published by Taube et al. (Taube et al., 2010) and Loboda et al. (Loboda et al., 2011), and from the SABiosciences EMT PCR array (SABiosciences, Frederick, MD). All genes were annotated as down- or upregulated during EMT according to the source. Genes with annotation of conflicting expression changes in several sources were excluded. All gene symbols were translated to probe set identifiers.

COSMIC Cell Line Panel Analysis

Drug response data (IC50 values) and gene expression levels were obtained from COSMIC (Forbes et al., 2010) for 152 cell lines that have activating mutations in RAS or BRAF. The IC50 values were classified as sensitive or resistant and gene expression levels were classified as normal, up- or downregulated. For each pair of a gene and a MEK inhibitor an overlap enrichment test was applied to evaluate if significantly many cell lines were both upregulated for the gene and resistant to the MEK inhibitor. The number of significant associations within in the MED12 signature gene set was counted and compared to 100,000 randomly drawn sets of the same size and variance distribution to evaluate the significance of the MED12 signature.

Nuclear and Cytoplasmic Fractionation

Subcellular fractionation experiments were performed according manufacture protocol using the NE-PER Nuclear and Cytoplasmic Extraction Kit (78835) purchased from Thermo Scientific.

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shRNA "Dropout" Screen With a Custom TRC Kinome Library

Lentiviral plasmids (pLKO.1) encoding shRNA that target kinome candidates were listed in Figure 36. The kinome library consists of 7 plasmids pools (TK1-TK7). Lentiviral supernatants were generated as described at

http://www(dot)broadinstitute(dot)org/rnai/public/resources/protocols. H3122 cells stably expressing shMED12#3 were infected separately by the 7 virus pools (Multiplicity Of Infection of 1). Cells were then pooled and plated at 300,000 cells per 15 cm dish in absence or presence of 300 nM crizotinib (5 dishes for each condition) and the medium was refreshed twice per week for 10 days. Genomic DNA was isolated as described (Brummelkamp et al., 2006). shRNA inserts were retrieved from 8ug genomic DNA by PCR amplification (PCR1 and PCR2, see below for primer information) using the following conditions: (1) 98 °C, 30s; (2) 98 °C, 10s; (3) 60 °C, 20s; (4) 72 °C, 1min; (5) to step2, 15 cycles; (6) 72 °C, 5min; (7) 4 °C. Indexes and adaptors for deep sequencing (Illumina) were incorporated into PCR primers. 2.5 ul PCR1 products were used as templates for PCR2 reaction. PCR products were purified using Qiagen PCR purification Kit according to the manufacturer manual. Sample quantification is performed by BioAnalyzer to ensure samples generated at different conditions were pooled at the same molar ratio before analyzed by Illumina genome analyzer.

shRNA stem sequence was segregated from each sequencing reads and aligned to TRC library. The matched reads were counted and the counts were transformed to abundance that was assigned to the corresponding shRNA.

Primers used are as follows:

PCR1_Untreated replicate#1_Forward,
ACACTCTTTCCCTACACGACGCTCTTCCGATCTCTGATCCTTGTGGAAAGGACGA
AACACCGG; PCR1_Untreated replicate#2_Forward,
ACACTCTTTCCCTACACGACGCTCTTCCGATCTAAGCTACTTGTGGAAAGGACGA
AACACCGG; PCR1_PLX treated replicate#1_Forward,
ACACTCTTTCCCTACACGACGCTCTTCCGATCTGTAGCCCTTGTGGAAAGGACGA
AACACCGG; PCR1_PLX treated replicate#1_Forward,
ACACTCTTTCCCTACACGACGCTCTTCCGATCTTACAAGCTTGTGGAAAGGACGA
AACACCGG; PCR1_Reverse (P7_pLKO1_r),
CAAGCAGAAGACGGCATACGAGATTTCTTTCCCCTGCACTGTACCC;
PCR2_Forward,
AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCTTCCGA
TCT: PCR2_Reverse (P5_IlluSeq), CAAGCAGAAGACGGCATACGAGAT.

RNA-Seq Gene Expression Analysis

Total mRNA of each sample was converted into a library of template molecules suitable for subsequent cluster generation using the reagents provided in the Illumina ® TruSeq™ RNA Sample Preparation Kit, following the manufacture protocol. Sequence reads were generated using Illumina HiSeq 2000 with TruSeqTM v3 reagent kits and software. The reads (between 20 - 45 million 50 bp paired-end reads per sample) were mapped to the human reference genome (build 37) using TopHat (v. 1.3.1, (Trapnell et al., 2009)), which allows to span exon-exon splice junctions. The open-source tool HTSeq-count (v. 0.5.3p3), available from EMBL, was then used to generate a list of the total number of uniquely mapped reads (between 16-33 million pairs of reads per sample) for each gene that is present in the provided Gene Transfer Format (GTF) file.

In order to determine which genes are differentially expressed between samples, the R package DEGseq (Wang et al., 2010) was used, which takes the output of HTSeq-count as input. The method used to identify differentially expressed genes is the MA-plot-based method with technical Replicates (MATR), which makes use of the presence of technical replicates. The genes that have no expression for all samples in the comparison were discarded from the dataset. The expression levels of all remaining genes in the dataset were added with 1 in order to avoid negative values after log2 transformation. Normalization for the number of reads is performed within this method and the cut off for differentially expressed genes is based on a p-value of 0.05.

Gene Expression Statistical analysis

Gene expression datasets GSE14333 (Jorissen et al., 2009), GSE17536 and GSE17537 (Smith et al., 2010) were downloaded from the Gene Expression Omnibus (Barrett et al., 2011).

Duplicated samples in GSE14333 and GSE17536 were removed from GSE14333 resulting in a final dataset comprising 389 tumor samples. Expression data were first normalized together using the RMA method as implemented in the affy package (Gautier et al., 2004) for R/Bioconductor (Gentleman et al., 2004) and then mean-centered separately for each dataset. The hclust method was employed for hierarchically clustering the samples based on MED12KD and Pearson correlation distance. The survival and Design packages were used for performing a Kaplan-Meier survival time analysis and plotting survival curves, respectively.

COSMIC Cell Line Panel Analysis

The predictive value of the MED12 knockdown signature was assessed using the Catalogue Of Somatic Mutations In Cancer (COSMIC), which is part of the Cancer Genome Project (CGP) (Forbes et al., 2010). From COSMIC Applicants collected the IC50 values of four MEK inhibitors (AZD6244, CI-1040, PD-0325901 and RDEA119) for 152 cell lines that have a mutation in KRAS, HRAS, NRAS and/or BRAF. For these cell lines Applicants also obtained gene expression levels for 11354 genes from COSMIC.

The IC50 values across the 152 cell lines for each MEK inhibitor were discretized into "sensitive" and "resistant" using a simple discretization strategy. Briefly, if the distribution of IC50 values was not unimodal (using Hartigan's dip test (Hartigan and Hartigan, 1985), $p<0.05$), a two component Gaussian mixture model was used to assign the cell lines to the sensitive or resistant category. Otherwise, an outlier detection strategy was used to call the cell lines that are far to the left of the bulk of the data (i.e., low IC50 values) as sensitive and the others as resistant. Overall, about 18% of the cell lines were called sensitive for each of the MEK inhibitors.

The same strategy was used to discretize the expression levels of each gene into "downregulated", "normal", and "upregulated." In this case, either a two or three component mixture model was used for multimodal distributions (using the BIC to choose the number of components), and for unimodal distributions the outlier scheme called cell lines to the right of the bulk (i.e. high expression levels) as upregulated and those to the left (i.e. low expression levels) as downregulated.

Next, for each pairing of a gene and a MEK inhibitor a simple enrichment test (i.e. hypergeometric test) was applied to evaluate if significantly many cell lines were both upregulated for the gene and resistant to the MEK inhibitor. For the four MEK inhibitors, AZD6244, CI-1040, PD-0325901 and RDEA119, Applicants respectively detected 474, 807, 856 and 681 genes at $p<0.05$.

Applicants evaluated whether there was an overrepresentation of the MED12 signature genes in these sets of genes. Of the 237 genes upregulated after MED12 knockdown, 170 are part of the gene expression set of COSMIC. Of the 22 genes downregulated after MED12 knockdown, only 12 are present in the gene expression set. Because the latter set is very small, Applicants decided to focus only on the set of 170 upregulated genes. In these 170 genes, and the four MEK inhibitors, AZD6244, CI-1040, PD-0325901 and RDEA119, Applicants detected 22, 36, 35, and 26 genes at $p<0.05$, respectively. Seven genes were found in all of the four groups. The association of gene

expression with response to AZD6244 for one of these genes, ZBED2, is depicted in Figure 34.

In order to determine the statistical significance of the number of genes in the MED12 signature whose gene expression was found to be associated with each of the inhibitors, Applicants compared these numbers to what would be expected under the null hypothesis. More specifically, Applicants randomly drew 100,000 sets of 170 genes with the same distribution of expression variance across the dataset as the 170 MED12 upregulated signature genes. Applicants computed a permutation test p-value, which indicates the fraction of times (out of 100,000) that the randomly drawn gene set showed more significantly associated genes than the 170 MED12 signature genes. These p-values are 0.009, 0.004, 0.007 and 0.013 for AZD6244, CI-1040, PD-0325901 and RDEA119, respectively. These numbers are found in Figure 33C and in the main text.

Applicants observed that the variance of genes in the MED12 signature was higher than the average for the complete expression dataset. Applicants focused on random gene sets with the same variance distribution, since genes with no or low variance across the dataset can never be significantly associated with the varying IC50 values, and should therefore not be part of the random gene sets.

* * *

Having thus described in detail embodiments of the present invention, it is to be understood that the invention defined by the above paragraphs is not to be limited to particular details set forth in the above description as many apparent variations thereof are possible without departing from the spirit or scope of the present invention.

Each patent, patent application, and publication cited or described in the present application is hereby incorporated by reference in its entirety as if each individual patent, patent application, or publication was specifically and individually indicated to be incorporated by reference.

WHAT IS CLAIMED IS:

1. A method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising:

(a) measuring expression levels of one or more SWI/SNF complex and/or MEDIATOR complex nucleic acid and/or proteins in the patient; and

(b) comparing the expression levels of the one or more SWI/SNF complex and/or MEDIATOR complex nucleic acid and/or proteins in (a) with the expression levels of one or more reference SWI/SNF complex and/or MEDIATOR complex nucleic acid and/or proteins, wherein the one or more reference SWI/SNF complex and/or MEDIATOR complex nucleic acid and/or proteins are from a control sample, wherein a reduction in the expression of the one or more SWI/SNF complex and/or MEDIATOR complex nucleic acid and/or proteins in comparison to the one or more reference SWI/SNF complex and/or MEDIATOR complex nucleic acid and/or proteins is indicative of resistance to anticancer treatment in the patient.

2. A method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising:

(a) isolating nucleic acid from the patient, wherein the nucleic acid comprises one or more SWI/SNF complex and/or MEDIATOR complex DNA and/or RNA; and

(b) analyzing the nucleic acid of (a) for the presence of one or more inactivating mutations in the SWI/SNF complex and/or MEDIATOR complex DNA and/or RNA, wherein the presence of one or more inactivating mutations in the one or more SWI/SNF complex and/or MEDIATOR complex DNA and/or RNA analyzed in (b) is indicative of resistance to anticancer treatment in the patient.

3. A method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising:

(a) isolating protein from the patient, wherein the protein comprises one or more SWI/SNF complex and/or MEDIATOR complex proteins;

(b) analyzing the activity of the one or more SWI/SNF complex and/or MEDIATOR complex proteins in (a); and

(c) comparing the activity of the one or more SWI/SNF complex and/or MEDIATOR complex proteins in (b) with the activity of one or more reference SWI/SNF complex and/or MEDIATOR complex proteins,

wherein a difference in activity of the one or more SWI/SNF complex and/or MEDIATOR complex proteins from (b) in comparison to the one or more SWI/SNF complex and/or MEDIATOR complex reference proteins in (c) is indicative of resistance to anticancer treatment in the patient.

4. The method of claim 1, wherein the expression levels of one or more SWI/SNF complex nucleic acids and/or proteins are measured in (a).

5. The method of claim 4, wherein the expression levels of one or more SWI/SNF complex DNA are measured in (a).

6. The method of claim 4, wherein the expression levels of one or more SWI/SNF complex RNA are measured in (a).

7. The method of claim 4, wherein the expression levels of one or more SWI/SNF complex proteins are measured in (a).

8. The method of claim 1, wherein the expression levels of one or more MEDIATOR complex nucleic acids and/or proteins are measured in (a).

9. The method of claim 8, wherein the expression levels of one or more MEDIATOR complex DNA are measured in (a).

10. The method of claim 8, wherein the expression levels of one or more MEDIATOR complex RNA are measured in (a).

11. The method of claim 8, wherein the expression levels of one or more MEDIATOR complex proteins are measured in (a).

12. A method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising:

(a) measuring expression levels of one or more RAS-GAP nucleic acid and/or proteins in the patient; and

(b) comparing the expression levels of the one or more RAS-GAP nucleic acid and/or proteins in (a) with the expression levels of one or more reference RAS-GAP nucleic acid and/or proteins, wherein the one or more reference RAS-GAP nucleic acid and/or proteins are from a control sample,

wherein a reduction in the expression of the one or more RAS-GAP nucleic acid and/or proteins in comparison to the one or more reference RAS-GAP nucleic acid and/or proteins is indicative of resistance to anticancer treatment in the patient.

13. A method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising:

(a) isolating nucleic acid from the patient, wherein the nucleic acid comprises one or more RAS-GAP DNA and/or RNA; and

(b) analyzing the nucleic acid of (a) for the presence of one or more inactivating mutations in the RAS-GAP DNA and/or RNA,

wherein the presence of one or more inactivating mutations in the one or more RAS-GAP DNA and/or RNA analyzed in (b) is indicative of resistance to anticancer treatment in the patient.

14. A method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising:

(a) isolating protein from the patient, wherein the protein comprises one or more RAS-GAP proteins;

(b) analyzing the activity of the one or more RAS-GAP proteins in (a); and

(c) comparing the activity of the one or more RAS-GAP proteins in (b) with the activity of one or more reference RAS-GAP proteins,

wherein a difference in activity of the one or more RAS-GAP proteins from (b) in comparison to the one or more RAS-GAP reference proteins in (c) is indicative of resistance to anticancer treatment in the patient.

15. The method of claim 12, wherein the expression levels of one or more RAS-GAP nucleic acids are measured in (a).

16. The method of claim 15, wherein the expression levels of RAS-GAP DNA are measured in (a).

17. The method of claim 15, wherein the expression levels of RAS-GAP RNA are measured in (a).

18. The method of claim 12, wherein the expression levels of one or more RAS-GAP proteins are measured in (a).

19. The method of any of claims 1-3 and 12-14, wherein the patient has liver cancer, lung cancer, breast cancer, ovarian cancer, lung cancer, head and neck cancer, bladder cancer, colorectal cancer, cervical cancer, mesothelioma, solid tumors, renal cell carcinoma, stomach cancer, sarcoma, prostate cancer, melanoma, thyroid cancer, brain cancer, adenocarcinoma, glioma, glioblastoma, esophageal cancer, neuroblastoma, subependymal giant cell astrocytoma, endometrial cancer, a hematological cancer and/or lymphoma.

20. The method of any of claims 1-3 and 12-14, wherein the resistance to anticancer treatment is resistance to treatment with a receptor tyrosine kinase inhibitor.

21. The method of claim 20, wherein the receptor tyrosine kinase inhibitor is selected from the group consisting of: gefitinib, erlotinib, EKB-569, lapatinib, CI-1033, cetuximab, panitumumab, PKI-166, AEE788, sunitinib, sorafenib, dasatinib, nilotinib, pazopanib, vandetaniv, cediranib, afatinib, motesanib, CUDC-101, imatinib mesylate, crizotinib, ASP-3026, LDK378, AF802, and CEP37440.

22. The method of any of claims 1-3 and 12-14, wherein the resistance to anticancer treatment is resistance to treatment with an inhibitor of ERK activation.

23. The method of claim 22, wherein the inhibitor of ERK activation inhibits a cellular protein that interacts directly with ERK.

24. The method of claim 22, wherein the inhibitor of ERK activation inhibits a cellular protein that interacts indirectly with ERK.

25. The method of claim 22, wherein the inhibitor of ERK activation is a receptor tyrosine kinase inhibitor.

26. The method of any of claims 1-3, wherein the SWI/SNF complex nucleic acid and/or protein is selected from the group consisting of: ARID1A, ARID1B, ARID2, SMARCA2, SMARCA4, PBRM1, SMARCC2, SMARCC1, SMARCD1, SMARCD2, SMARCD3, SMARCE1, ACTL6A, ACTL6B, and SMARCB1.

27. The method of claim 26, wherein the SWI/SNF complex nucleic acid and/or protein is selected from the group consisting of: ARID1A and SMARCE1.

28. The method of any of claims 1-3, wherein the MEDIATOR complex nucleic acid and/or protein is selected from the group consisting of: MED22, MED11, MED17, MED20, MED30, MED19, MED18, MED8, MED6, MED28, MED9, MED21, MED4, MED7, MED31, MED10, MED1, MED26, MED2, MED3, MED25, MED23, MED5, MED14, MED16, MED15, CycC, CDK8, MED13, MED12, MED12L, and MED13L.

29. The method of claim 28, wherein the MEDIATOR complex nucleic acid and/or protein is selected from the group consisting of: CycC, CDK8, MED12, MED12L, MED13, and MED13L.

30. The method of claim 29, wherein the MEDIATOR complex nucleic acid and/or protein is MED12.

31. The method of any of claims 12-14, wherein the RAS-GAP is selected from the group consisting of: DAB2IP, NF1, and RASAL3.

32. The method of claim 19, wherein the patient has lung cancer.

33. The method of claim 32, wherein the lung cancer is non-small cell lung cancer.

34. The method of claim 19, wherein the patient has melanoma.

35. The method of claim 2 or 13, wherein analyzing the nucleic acid in (b) comprises sequencing the nucleic acid.

36. The method of any of claims 1, 2, or 13, wherein analyzing the nucleic acid in (b) comprises subjecting the nucleic acid to MLPA.

37. The method of claim 2 or 13, wherein analyzing the nucleic acid in (b) comprises subjecting the nucleic acid to CGH.

38. The method of claim 2 or 13, wherein analyzing the nucleic acid in (b) comprises subjecting the nucleic acid to FISH.

39. The method of claim 2 or 13, wherein the inactivating mutation is selected from the group consisting of: point mutations, translocations, amplifications, deletions, and hypomorphic mutations.

40. The method of claim 2, wherein the nucleic acid of (a) comprises one or more SWI/SNF complex genes.

41. The method of claim 2, wherein the nucleic acid of (a) comprises one or more MEDIATOR complex genes.

42. The method of claim 13, wherein the nucleic acid of (a) comprises one or more RAS-GAP genes.

43. The method of claim 3, wherein the one or more SWI/SNF complex and/or MEDIATOR complex proteins are inactive.

44. The method of claim 43, wherein the one or more SWI/SNF complex and/or MEDIATOR complex proteins are inactive due to one or more posttranslational modifications.

45. The method of claim 14, wherein the one or more RAS-GAP proteins are inactive.

46. The method of claim 45, wherein the one or more RAS-GAP proteins are inactive due to one or more posttranslational modifications

47. A microarray comprising a plurality of polynucleotide probes each complementary and hybridizable to a sequence in a different gene that is a SWI/SNF complex gene that is a marker for resistance to anticancer treatment in a patient that has cancer.

48. A microarray comprising a plurality of polynucleotide probes each complementary and hybridizable to a sequence in a different gene that is a MEDIATOR complex gene that is a marker for resistance to anticancer treatment in a patient that has cancer.

49. A microarray comprising a plurality of polynucleotide probes each complementary and hybridizable to a sequence in a different gene that is a SWI/SNF complex and/or MEDIATOR complex gene that is a marker for resistance to anticancer treatment in a patient that has cancer.

50. A microarray comprising a plurality of polynucleotide probes each complementary and hybridizable to a sequence in a different gene that is a RAS-GAP gene that is a marker for resistance to anticancer treatment in a patient that has cancer.

51. The microarray of any of claims 47-50, wherein the plurality of probes is at least 70 %, at least 80 %, at least 90 %, at least 95 %, or at least 98 % of the probes on the microarray.

52. The microarray of claim 47 or 49, wherein the SWI/SNF complex gene that is a marker for resistance to anticancer treatment is selected from the group consisting of ARID1A, ARID1B, ARID2, SMARCA2, SMARCA4, PBRM1, SMARCC2, SMARCC1, SMARCD1, SMARCD2, SMARCD3, SMARCE1, ACTL6A, ACTL6B, and SMARCB1.

53. The microarray of claim 48 or 49, wherein the MEDIATOR complex gene that is a marker for resistance to anticancer treatment is selected from the group consisting of MED22, MED11, MED17, MED20, MED30, MED19, MED18, MED8, MED6, MED28, MED9, MED21, MED4, MED7, MED31, MED10, MED1, MED26, MED2, MED3, MED25, MED23, MED5, MED14, MED16, MED15, CycC, CDK8, MED13, MED12, MED13L, and MED12L.

54. The microarray of claim 50, wherein the RAS-GAP gene is selected from the group consisting of: DAB2IP, NF1, and RASAL3.

55. A kit, comprising at least one pair of primers specific for a SWI/SNF complex gene that is a marker for resistance to anticancer treatment in a patient that has cancer, at least one reagent for amplification of the SWI/SNF complex gene, and instructions for use.

56. A kit, comprising at least one pair of primers specific for a MEDIATOR complex gene that is a marker for resistance to anticancer treatment in a patient that has cancer, at least one reagent for amplification of the MEDIATOR complex gene, and instructions for use.

57. A kit, comprising at least one pair of primers specific for a SWI/SNF complex and/or a MEDIATOR complex gene that is a marker for resistance to anticancer treatment in a patient that has cancer, at least one reagent for amplification of the SWI/SNF complex and/or MEDIATOR complex gene, and instructions for use.

58. A kit, comprising at least one pair of primers specific for a RAS-GAP gene that is a marker for resistance to anticancer treatment in a patient that has cancer, at least one reagent for amplification of the RAS-GAP gene, and instructions for use.

59. The kit of claim 55 or 57, wherein the primers are specific for a SWI/SNF complex gene selected from the group consisting of ARID1A, ARID1B, ARID2, SMARCA2,

SMARCA4, PBRM1, SMARCC2, SMARCC1, SMARCD1, SMARCD2, SMARCD3, SMARCE1, ACTL6A, ACTL6B, and SMARCB1.

60. The kit of claim 56 or 57, wherein the primers are specific for a MEDIATOR complex gene selected from the group consisting of MED22, MED11, MED17, MED20, MED30, MED19, MED18, MED8, MED6, MED28, MED9, MED21, MED4, MED7, MED31, MED10, MED1, MED26, MED2, MED3, MED25, MED23, MED5, MED14, MED16, MED15, CycC, CDK8, MED13, MED12, MED13L, and MED12L.

61. The kit of claim 58, wherein the primers are specific for a RAS-GAP gene selected from the group consisting of: DAB2IP, NF1, and RASAL3.

62. The kit of any of claims 55-58, wherein the marker for resistance to anticancer treatment is a marker for resistance to a receptor tyrosine kinase inhibitor.

63. The kit of claim 62, wherein the receptor tyrosine kinase inhibitor is selected from the group consisting of: gefitinib, erlotinib, EKB-569, lapatinib, CI-1033, cetuximab, panitumumab, PKI-166, AEE788, sunitinib, sorafenib, dasatinib, nilotinib, pazopanib, vandetaniv, cediranib, afatinib, motesanib, CUDC-101, imatinib mesylate, crizotinib, ASP-3026, LDK378, AF802, and CEP37440.

64. The kit of any of claims 55-58, wherein the marker for resistance to anticancer treatment is a marker for resistance to an inhibitor of ERK activation.

65. The method of claim 64, wherein the inhibitor of ERK activation inhibits a cellular protein that interacts directly with ERK.

66. The method of claim 64, wherein the inhibitor of ERK activation inhibits a cellular protein that interacts indirectly with ERK.

67. The method of claim 64, wherein the inhibitor of ERK activation is a receptor tyrosine kinase inhibitor.

68. The kit of any of claims 55-58, wherein the kit is a PCR kit.

69. The kit of any of claims 55-58, wherein the kit is an MLPA kit.

70. The kit of any of claims 55-58, wherein the kit is an RT-MLPA kit.

71. The method of claim 1, wherein the level of expression of one or more SWI/SNF complex and/or MEDIATOR complex genes is measured by determination of their level of transcription, using a DNA array.

72. The method of claim 1, wherein the level of expression of one or more SWI/SNF complex and/or MEDIATOR complex genes is measured by determination of their level of transcription, using quantitative RT-PCR.

73. The method of claim 1, wherein the level of expression of one or more SWI/SNF complex and/or MEDIATOR complex genes is measured in a tumor sample from the patient.

74. The method of claim 12, wherein the level of expression of one or more RAS-GAP genes is measured by determination of their level of transcription, using a DNA array.

75. The method of claim 12, wherein the level of expression of one or more RAS-GAP genes is measured by determination of their level of transcription, using quantitative RT-PCR.

76. The method of claim 12, wherein the level of expression of one or more RAS-GAP genes is measured in a tumor sample from the patient.

77. The method of claim 73 or claim 76, wherein the tumor sample is a lung tumor sample.

78. The method of any of claims 1-3, 12-14, and 30, wherein the resistance to anticancer treatment is resistance to treatment with a B-RAF inhibitor.

79. The method of claim 78, wherein the B-RAF inhibitor is selected from the group consisting of: CEP-32496, vemurafenib, GSK-2118436, ARQ-736, RG-7256, XL-281, DCC-2036, GDC-0879, AZ628, and antibody fragment EphB4/Raf inhibitors.

80. The method of any of claims 1-3, 12-14, and 30, wherein the resistance to anticancer treatment is resistance to treatment with a MEK inhibitor.

81. The method of claim 80, wherein the MEK inhibitor is selected from the group consisting of: CKI-27, RO-4987655, RO-5126766, PD-0325901, WX-554, AZD-8330, G-573, RG-7167, SF-2626, GDC-0623, RO-5068760, and AD-GL0001.

82. The kit of any of claims 55-58, wherein the marker for resistance to anticancer treatment is a marker for resistance to treatment with a B-RAF inhibitor.

83. The kit of claim 82, wherein the B-RAF inhibitor is selected from the group consisting of: CEP-32496, vemurafenib, GSK-2118436, ARQ-736, RG-7256, XL-281, DCC-2036, GDC-0879, AZ628, and antibody fragment EphB4/Raf inhibitors.

84. The kit of any of claims 55-58, wherein the marker for resistance to anticancer treatment is a marker for resistance to treatment with a MEK inhibitor.

85. The kit of claim 84, wherein the MEK inhibitor is selected from the group consisting of: CKI-27, RO-4987655, RO-5126766, PD-0325901, WX-554, AZD-8330, G-573, RG-7167, SF-2626, GDC-0623, RO-5068760, and AD-GL0001.

86. The method of claim 1 or claim 12, wherein expression levels of SWI/SNF and/or MEDIATOR complex or RAS-GAP nucleic acid and/or proteins are measured in one or more cancer cells of the patient.

87. The method of claim 2 or claim 13, wherein the nucleic acid in (a) is isolated from one or more cancer cells from the patient.

88. The method of claim 3 or claim 14, wherein the protein in (a) is isolated from one or more cancer cells from the patient.

89. The method of claim 86, wherein the resistance is primary resistance to anticancer treatment.

90. The method of claim 86, wherein the resistance is secondary resistance to anticancer treatment.

91. The method of claim 87, wherein the resistance is primary resistance to anticancer treatment.

92. The method of claim 87, wherein the resistance is secondary resistance to anticancer treatment.

93. The method of claim 88, wherein the resistance is primary resistance to anticancer treatment.

94. The method of claim 88, wherein the resistance is secondary resistance to anticancer treatment.

95. A method of treating resistance to one or more inhibitors of ERK activation in a patient in need thereof, comprising administering to the patient at least one inhibitor of the TGF-beta pathway in combination with the one or more inhibitors of ERK activation.

96. The method of claim 95, wherein the inhibitor of ERK activation is selected from the group consisting of direct and indirect inhibitors of ERK activation.

97. The method of claim 96, wherein the direct inhibitor of ERK activation is a MEK inhibitor.

98. The method of claim 96, wherein the indirect inhibitor of ERK activation is selected from the group consisting of RTK inhibitors, RAS inhibitors, and B-RAF inhibitors.

99. The method of claim 95, wherein the resistance to one or more inhibitors of ERK activation is primary resistance.

100. The method of claim 95, wherein the resistance to one or more inhibitors of ERK activation is secondary resistance.

101. The method of claim 95, wherein the resistance to one or more inhibitors of ERK activation is evaluated and/or predicted according to a method of any of claims 1-3 and 12-14.

102. A method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising:

(a) measuring expression levels of one or more TGFβ pathway nucleic acid and/or proteins in the patient; and

(b) comparing the expression levels of the one or more TGFβ pathway nucleic acid and/or proteins in (a) with the expression levels of one or more reference TGFβ pathway nucleic acid and/or proteins, wherein the one or more reference TGFβ pathway nucleic acid and/or proteins are from a control sample,

wherein an increase in the expression of the one or more TGFβ pathway nucleic acid and/or proteins in comparison to the one or more reference TGFβ pathway nucleic acid and/or proteins is indicative of resistance to anticancer treatment in the patient.

103. A method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising:

(a) isolating nucleic acid from the patient, wherein the nucleic acid comprises one or more TGFβ pathway DNA and/or RNA; and

(b) analyzing the nucleic acid of (a) for the presence of one or more activating mutations in the TGFβ pathway complex DNA and/or RNA,

wherein the presence of one or more activating mutations in the one or more TGFβ pathway DNA and/or RNA analyzed in (b) is indicative of resistance to anticancer treatment in the patient.

104. A method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising:

(a) isolating protein from the patient, wherein the protein comprises one or more TGFβ pathway proteins;

(b) analyzing the activity of the one or more TGFβ pathway proteins in (a); and

(c) comparing the activity of the one or more TGFβ pathway proteins in (b) with the activity of one or more reference TGFβ pathway proteins,

wherein a difference in activity of the one or more TGFβ pathway proteins from (b) in comparison to the one or more TGFβ pathway reference proteins in (c) is indicative of resistance to anticancer treatment in the patient.

105. A method of treating cancer in a patient in need thereof, comprising administering to the patient an inhibitor of ERK activation in combination with an inhibitor of TGFβ pathway activation.

106. The method of claim 105, wherein the cancer is selected from the group consisting of: liver cancer, lung cancer, breast cancer, ovarian cancer, head and neck cancer, bladder cancer, colorectal cancer, cervical cancer, mesothelioma, solid tumors, renal cell carcinoma, stomach cancer, sarcoma, prostate cancer, melanoma, thyroid cancer, brain cancer, adenocarcinoma, glioma, glioblastoma, esophageal cancer, neuroblastoma, subependymal giant cell astrocytoma, endometrial cancer, a hematological cancer, and lymphoma.

107. The method of claim 105, wherein the inhibitor of ERK activation is selected from the group consisting of: RTK inhibitors, RAS inhibitors, B-RAF inhibitors, and MEK inhibitors.

108. The method of claim 107, wherein the inhibitor of ERK activation is a MET inhibitor.

109. The method of claim 102, wherein the expression levels are measured of one or more of TGFβ pathway nucleic acid is a TGFβ pathway target gene selected from the group consisting of: ALOX5AP, COL5A1, TAGLN, ANGPTL4, LGALS1, IL11, LBH, and COL4A1.

110. The method of claim 95 or 105, wherein the inhibitor of TGFβ pathway activation is LY2157299.

111. The method of claim 110, wherein the inhibitor of ERK activation is crizotinib or gefitinib.

112. The method of claim 95 or 105, wherein the inhibitor of TGFβ pathway activation inhibits MED12/TGFβ binding.

113. A method of identifying an inhibitor of ERK activation, comprising:
measuring MED12/TGFβ binding in the presence and absence of a test compound, wherein a reduction in the amount of MED12/TGFβ binding in the presence of the test compound in comparison to the absence of the test compound indicates an inhibitor of ERK activation has been identified.

114. A method of identifying an inhibitor of TGFβ pathway activation, comprising:
measuring MED12/TGFβ binding in the presence and absence of a test compound, wherein a reduction in the amount of MED12/TGFβ binding in the presence of the test compound in comparison to the absence of the test compound indicates an inhibitor of TGFβ pathway activation has been identified.

115. A method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising:

(a) measuring expression levels of one or more MED12 nucleic acid and/or proteins in the patient;

(b) measuring one or more markers of an EMT-like phenotype; and

(c) comparing the expression levels of the one or more MED12 nucleic acid and/or proteins in (a) with the expression levels of one or more reference MED12 nucleic acid and/or proteins,

wherein a reduction in the expression of the one or more MED12 nucleic acid and/or proteins in comparison to the one or more reference MED12 nucleic acid and/or proteins in (c) and wherein one or more markers are measured of an EMT-like phenotype in (b) is indicative of resistance to anticancer treatment in the patient.

116. The method of claim 115, wherein the resistance to anticancer treatment is resistance to treatment with a MEK inhibitor.

117. The method of claim 116, wherein the MEK inhibitor is selected from the group consisting of: CKI-27, RO-4987655, RO-5126766, PD-0325901, WX-554, AZD-8330, G-573, RG-7167, SF-2626, GDC-0623, RO-5068760, and AD-GL0001.

118. The method of claim 115, wherein the resistance to anticancer treatment is resistance to treatment with a B-RAF inhibitor.

119. The method of claim 118, wherein the B-RAF inhibitor is selected from the group consisting of: CEP-32496, vemurafenib, GSK-2118436, ARQ-736, RG-7256, XL-281, DCC-2036, GDC-0879, AZ628, and antibody fragment EphB4/Raf inhibitors.

120. The method of claim 115, wherein the nucleic acid in (a) is isolated from one or more cancer cells from the patient.

121. The method of claim 115, wherein the protein in (a) is isolated from one or more cancer cells from the patient.

122. The method of claim 115, wherein the one or more markers of an EMT-like phenotype are measured in one or more cancer cells from the patient.

123. The method of any of claims 120-122, wherein the cancer is selected from the group consisting of: liver cancer, lung cancer, breast cancer, ovarian cancer, head and neck cancer, bladder cancer, colorectal cancer, cervical cancer, mesothelioma, solid tumors, renal cell carcinoma, stomach cancer, sarcoma, prostate cancer, melanoma, thyroid cancer, brain cancer, adenocarcinoma, glioma, glioblastoma, esophageal cancer, neuroblastoma, subependymal giant cell astrocytoma, endometrial cancer, a hematological cancer, and lymphoma.

124. The method of claim 123, wherein the cancer is colorectal cancer.

125. The method of claim 115, wherein the one or more markers of an EMT-like phenotype are selected from mesenchymal markers.

126. The method of claim 125, wherein the one or more mesenchymal markers are selected from vimentin and N-cadherin.

127. A method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising:

(a) measuring expression levels of one or more MED12KD signature nucleic acid and/or proteins in one or more cancer cells of the patient; and

(b) comparing the expression levels of the one or more MED12KD signature nucleic acid and/or proteins in (a) with the expression levels of one or more positive reference MED12KD signature nucleic acid and/or proteins, wherein if expression of the one or more MED12KD signature nucleic acid and/or proteins in (a) is similar to the one or more positive reference MED12KD signature nucleic acid and/or proteins, then resistance to anticancer treatment is indicated in the patient.

128. A method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising:

(a) measuring expression levels of one or more MED12KD signature nucleic acid and/or proteins in one or more cancer cells of the patient; and

(b) comparing the expression levels of the one or more MED12KD signature nucleic acid and/or proteins in (a) with the expression levels of one or more negative reference MED12KD signature nucleic acid and/or proteins, wherein if expression of the one or more MED12KD signature nucleic acid and/or proteins in (a) is greater or lesser than the expression of the one or more negative reference MED12KD signature nucleic acid and/or proteins, then resistance to anticancer treatment is indicated in the patient.

129. The method of claims 127 or 128, wherein the one or more cancer cells of the patient in (a) are from one or more cancer cells of the patient prior to the anticancer treatment.

130. The method of claims 127 or 128, wherein the one or more cancer cells of the patient in (a) are from one or more cancer cells of the patient after the anticancer treatment.

131. The method of claim 128, wherein the negative reference MED12KD signature nucleic acid and/or proteins are from one or more non-cancerous cells of the patient.

132. The method of claim 128, wherein the negative reference MED12KD signature nucleic acid and/or proteins are from one or more cells known to be sensitive to the anticancer treatment.

133. The method of claim 128, wherein the one or more cancer cells of the patient in (a) are from cancer cells of the patient after the anticancer treatment, and wherein the negative reference MED12KD signature nucleic acid and/or proteins are from one or more cancerous cells of the patient prior to the anticancer treatment.

134. The method of claim 128, wherein the negative reference MED12KD signature nucleic acid and/or proteins is the average expression of the MED12KD signature nucleic acid and/or proteins in one or more tumor or cell line samples known to be sensitive to the anticancer treatment.

135. The method of claim 127, wherein the expression of the one or more MED12KD signature nucleic acid and/or proteins in (a) is about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, or about 10-fold greater or lesser than the one or more positive reference MED12KD signature nucleic acid and/or proteins.

136. The method of claim 127, wherein the expression of the one or more MED12KD signature nucleic acid and/or proteins in (a) is about the same as the one or more positive reference MED12KD signature nucleic acid and/or proteins.

137. The method of claim 128, wherein the expression of the one or more MED12KD signature nucleic acid and/or proteins in (a) is greater than or equal to about 1.2 fold higher or lower than the expression of the one or more negative reference MED12KD signature nucleic acid and/or proteins.

138. The method of claim 127, wherein the one or more $MED12^{KD}$ signature nucleic acids are upregulated nucleic acids.

139. The method of claim 138, wherein the upregulated nucleic acids are selected from the upregulated nucleic acids presented in Figure 37.

140. The method of claim 138, wherein the upregulated nucleic acids are selected from the upregulated nucleic acids presented in Figure 40.

141. The method of claim 138, wherein the upregulated nucleic acids are selected from the upregulated nucleic acids presented in Figure 39.

142. The method of claim 127, wherein the one or more $MED12^{KD}$ signature nucleic acids are downregulated nucleic acids.

143. The method of claim 142, wherein the downregulated nucleic acids are selected from the downregulated nucleic acids presented in Figure 37.

144. The method of claim 142, wherein the downregulated nucleic acids are selected from the downregulated nucleic acids presented in Figure 40.

145. The method of claim 142, wherein the downregulated nucleic acids are selected from the downregulated nucleic acids presented in Figure 39.

146. The method of claim 127 or claim 128, wherein the resistance to anticancer treatment is resistance to treatment with a MEK inhibitor.

147. The method of claim 146, wherein the MEK inhibitor is selected from the group consisting of: CKI-27, RO-4987655, RO-5126766, PD-0325901, WX-554, AZD-8330, G-573, RG-7167, SF-2626, GDC-0623, RO-5068760, and AD-GL0001.

148. The method of claim 127 or claim 128, wherein the resistance to anticancer treatment is resistance to treatment with a B-RAF inhibitor.

149. The method of claim 148, wherein the B-RAF inhibitor is selected from the group consisting of: CEP-32496, vemurafenib, GSK-2118436, ARQ-736, RG-7256, XL-281, DCC-2036, GDC-0879, AZ628, and antibody fragment EphB4/Raf inhibitors.

150. The method of claim 127or claim 128, wherein the cancer is selected from the group consisting of: liver cancer, lung cancer, breast cancer, ovarian cancer, head and neck cancer, bladder cancer, colorectal cancer, cervical cancer, mesothelioma, solid tumors, renal cell carcinoma, stomach cancer, sarcoma, prostate cancer, melanoma, thyroid cancer, brain cancer, adenocarcinoma, glioma, glioblastoma, esophageal cancer, neuroblastoma, subependymal giant cell astrocytoma, endometrial cancer, a hematological cancer, and lymphoma.

151. A method of evaluating and/or predicting of resistance to anticancer treatment in a patient in need thereof, comprising:

measuring expression levels of one or more MED12KD signature nucleic acid and/or proteins in one or more cancer cells of the patient; and

comparing the expression levels of the one or more MED12KD signature nucleic acid and/or proteins in (a) with the expression levels of (i) one or more MED12KD signature nucleic acid and/or proteins from cells known to be resistant to said anticancer treatment AND (ii) one or more MED12KD signature nucleic acid and/or proteins from cells known to be sensitive to said anticancer treatment,

whereby the cancer cells of the patient are considered to be resistant if the difference in expression levels between the cells in (a) and the cells in (i) is smaller than the difference in expression levels between the cells in (a) and the cells in (ii).

152. A method of evaluating and/or predicting of resistance to anticancer treatment in a patient in need thereof, comprising:

measuring expression levels of one or more MED12KD signature nucleic acid and/or proteins in one or more cancer cells of the patient; and

comparing the expression levels of the one or more MED12KD signature nucleic acid and/or proteins in (a) with the expression levels of (i) one or more MED12KD signature nucleic acid and/or proteins from cells known to be resistant to said anticancer treatment AND (ii) one or more MED12KD signature nucleic acid and/or proteins from cells known to be sensitive to said anticancer treatment,

whereby the cancer cells of the patient are considered to be sensitive if the difference in expression levels between the cells in (a) and the cells in (i) is greater than the difference in expression levels between the cells in (a) and the cells in (ii).

153. A method of evaluating and/or predicting of resistance to anticancer treatment in a patient in need thereof, comprising:

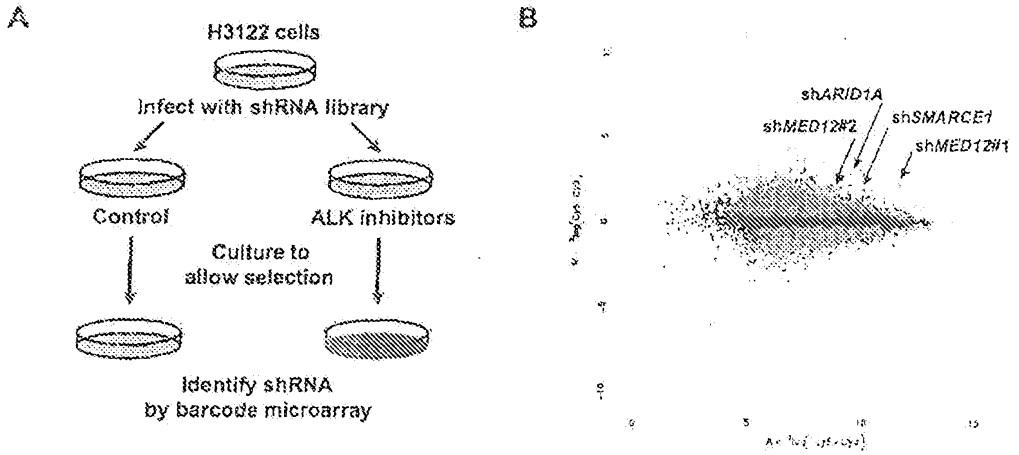
measuring expression levels of one or more MED12KD signature nucleic acid and/or proteins in one or more cancer cells of the patient; and

comparing the expression levels of the one or more MED12KD signature nucleic acid and/or proteins in (a) with the average expression levels of (i) one or more MED12KD signature nucleic acid and/or proteins taken from two or more cell samples,

whereby the cancer cells of the patient are considered to be resistant if the difference in expression levels of the one or more MED12KD signature nucleic acid and/or proteins between the cells in (a) and the average expression levels of the one or more MED12KD signature nucleic acid and/or proteins in (i) is greater than a factor 1.2.

154. The method of claim 95 or 105, wherein the inhibitor of ERK activation inhibits MED12/TGFβ binding.

Fig 1


A
H3122 cells
Infect with shRNA library
Control
ALK inhibitors
Culture to allow selection
Identify shRNA by barcode microarray
B
shARID1A
shMED12#2
shSMARCE1
shMED12#1

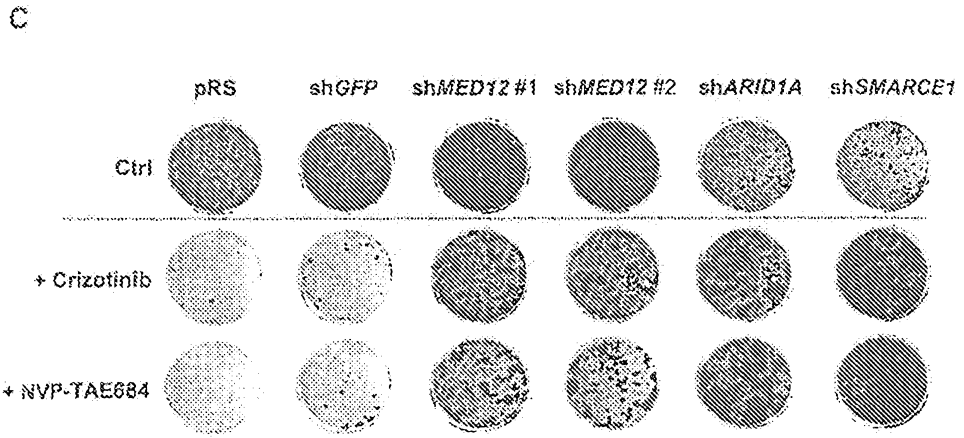
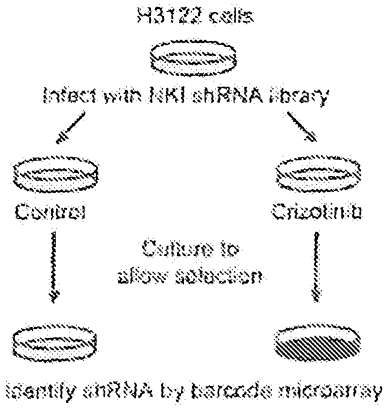
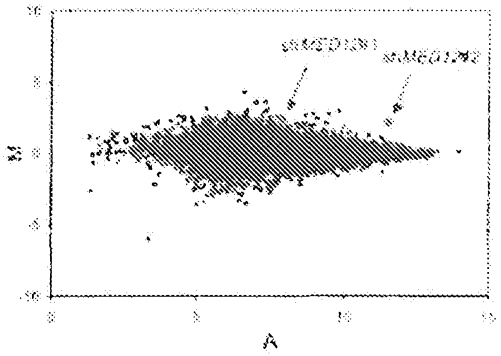

C
pRS
shGFP
shMED12 #1
shMED12 #2
shARID1A
shSMARCE1
Ctrl
+ Crizotinib
+ NVP-TAE684

Fig 2

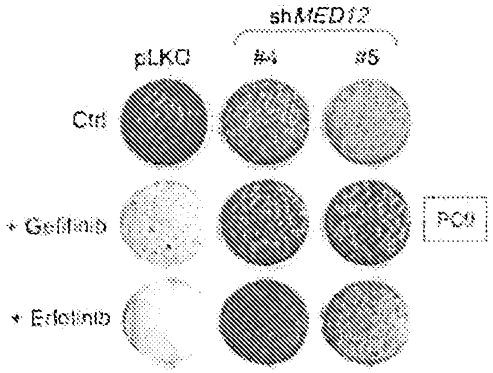
A


H3122 cells
Infect with NKI shRNA library
Control
Crizotinib
Culture to allow selection
Identify shRNA by barcode microarray

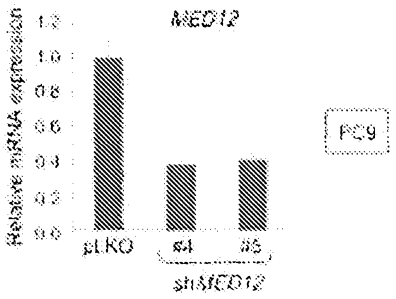
B


shMED12#1
shMED12#2
M
A

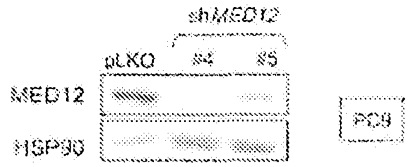
F


shMED12
pLKO
#4
#5
Ctrl
+ Gefitinib
+ Erlotinib
PC9

G


MED12
Relative mRNA expression
1.2
1.0
0.8
0.6
0.4
0.2
0.0
pLKO
#4
#5
shMED12
PC9

H


shMED12
pLKO
#4
#5
MED12
HSP90
PC9

H3122 cells

Fig 3

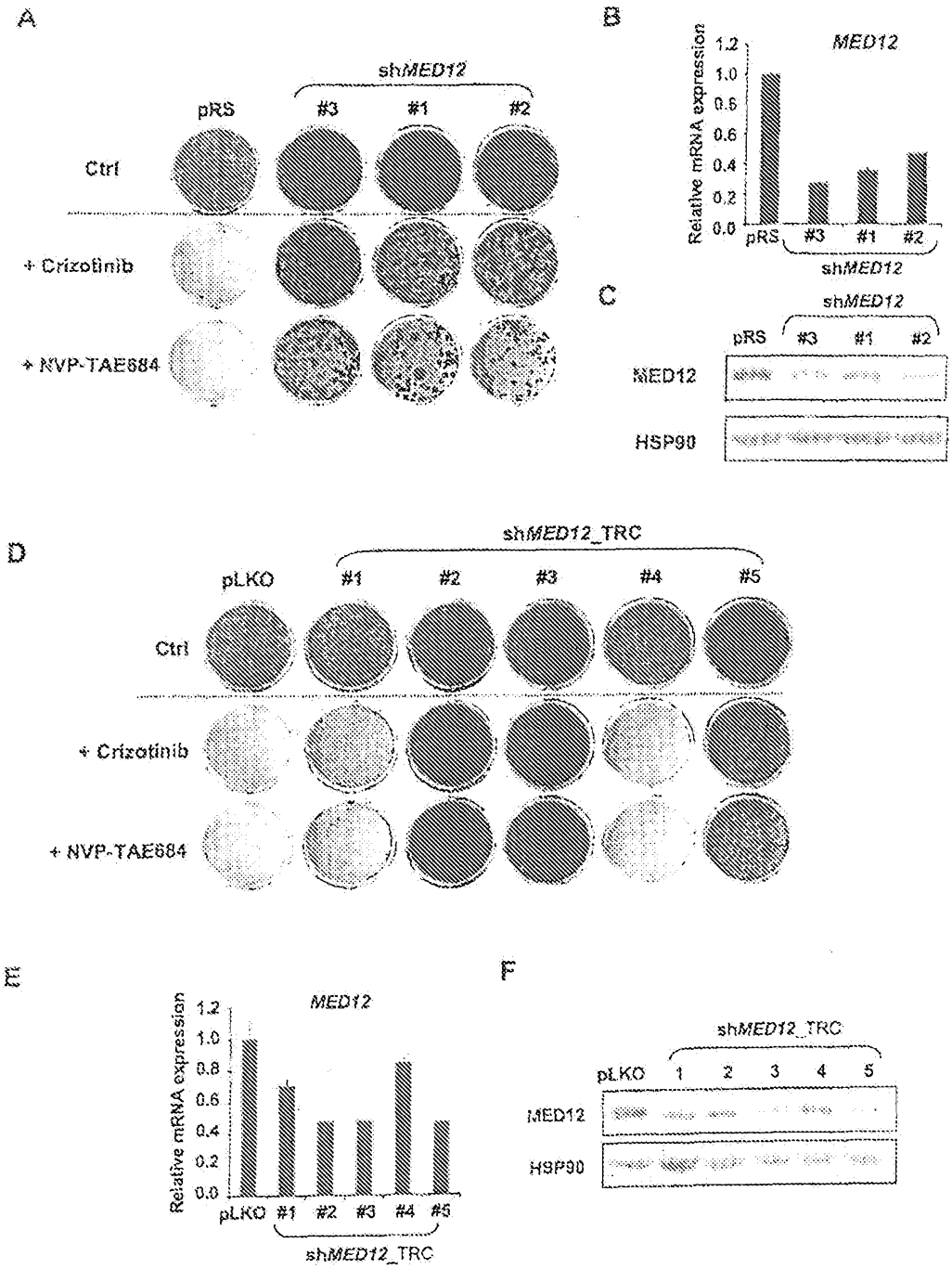


Fig 4

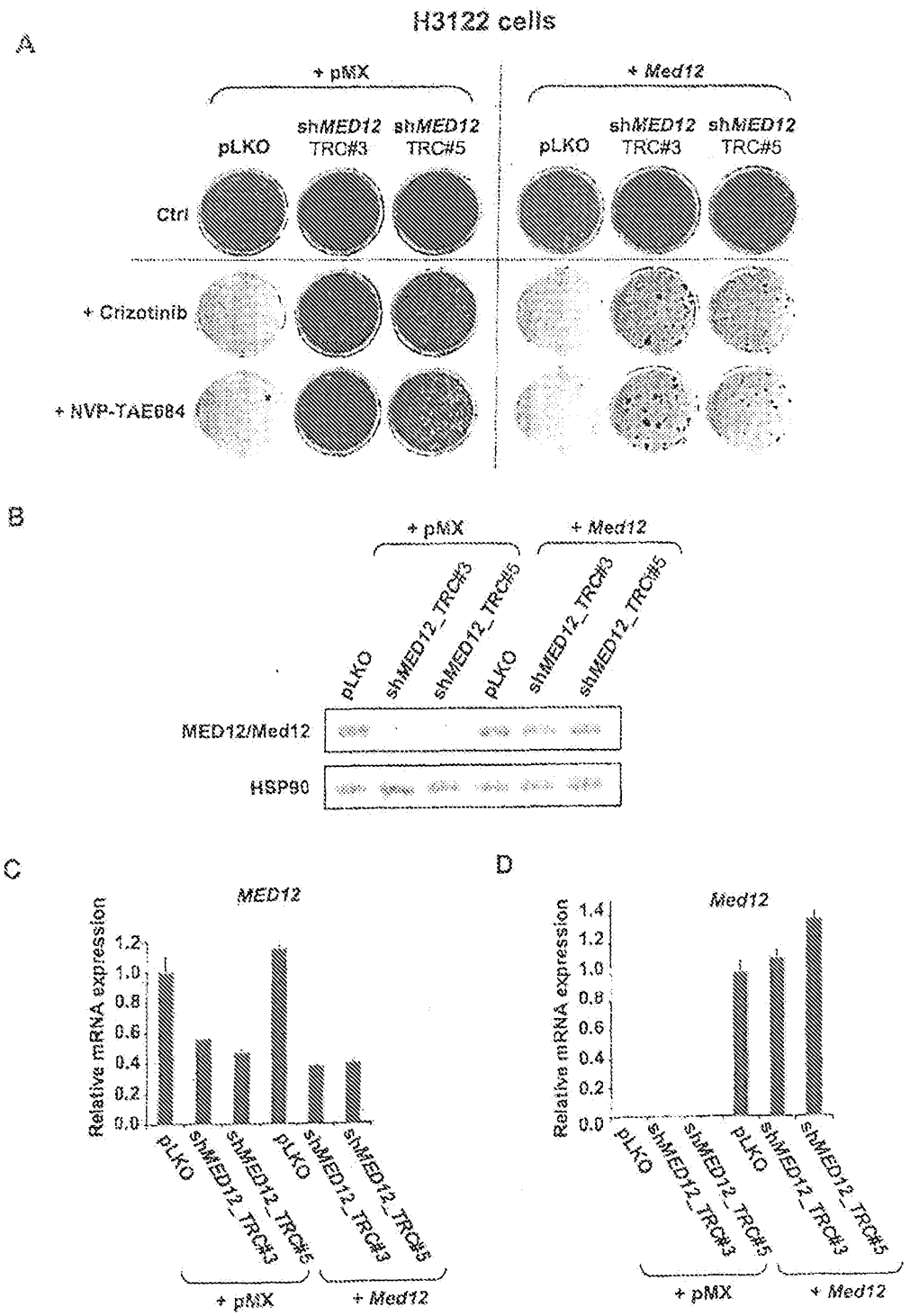

H3122 cells
A
+ pMX
+ Med12
pLKO
shMED12 TRC#3
shMED12 TRC#5
Ctrl
+ Crizotinib
+ NVP-TAE684
B
+ pMX
+ Med12
pLKO
shMED12_TRC#3
shMED12_TRC#5
MED12/Med12
HSP90
C
MED12
Relative mRNA expression
D
Med12

Fig 5

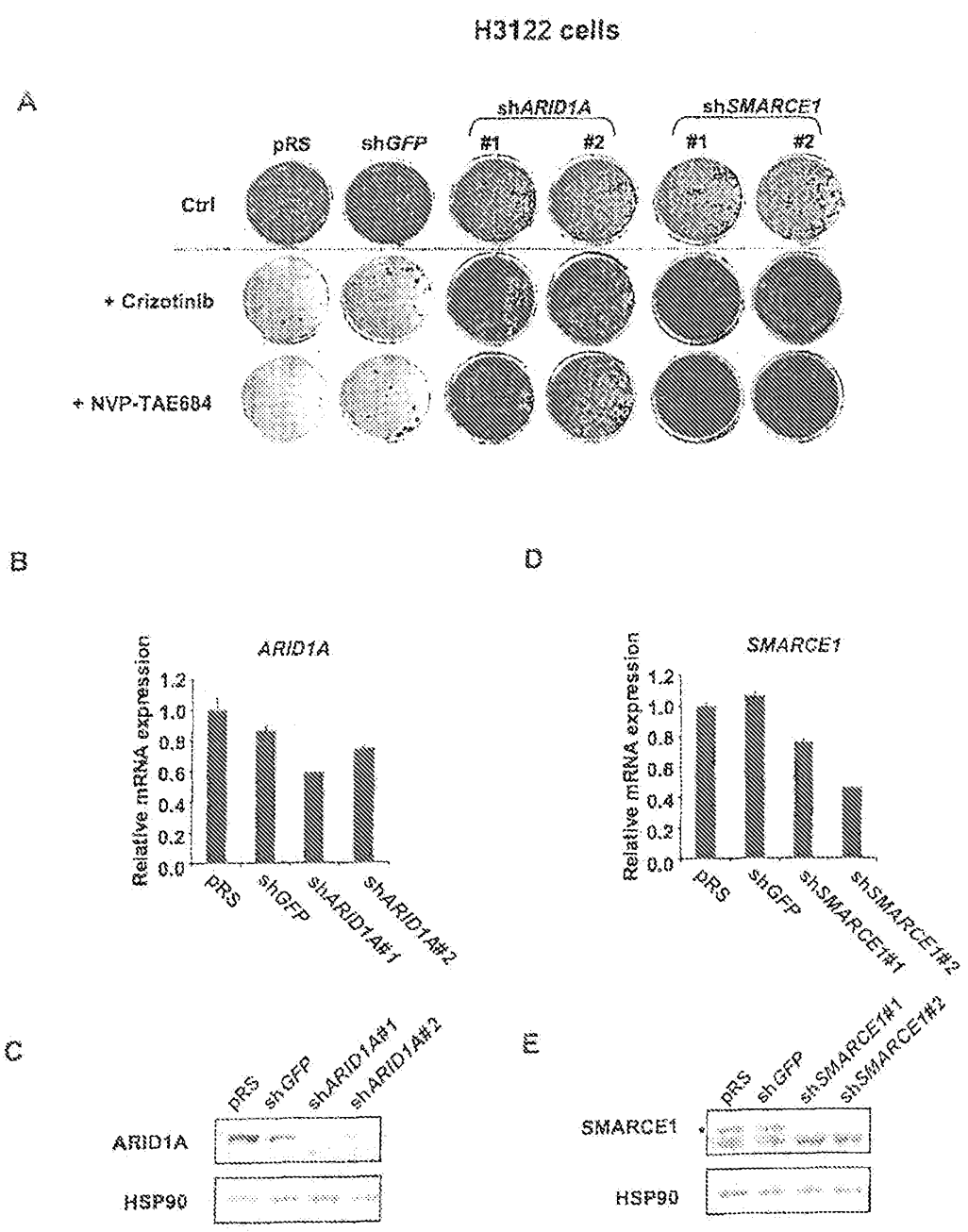

H3122 cells
A
pRS
shGFP
shARID1A
#1
#2
shSMARCE1
#1
#2
Ctrl
+ Crizotinib
+ NVP-TAE684
B
ARID1A
Relative mRNA expression
1.2
1.0
0.8
0.6
0.4
0.2
0.0
pRS
shGFP
shARID1A#1
shARID1A#2
C
pRS
shGFP
shARID1A#1
shARID1A#2
ARID1A
HSP90
D
SMARCE1
Relative mRNA expression
1.2
1.0
0.8
0.6
0.4
0.2
0.0
pRS
shGFP
shSMARCE1#1
shSMARCE1#2
E
pRS
shGFP
shSMARCE1#1
shSMARCE1#2
SMARCE1
HSP90

Fig 6

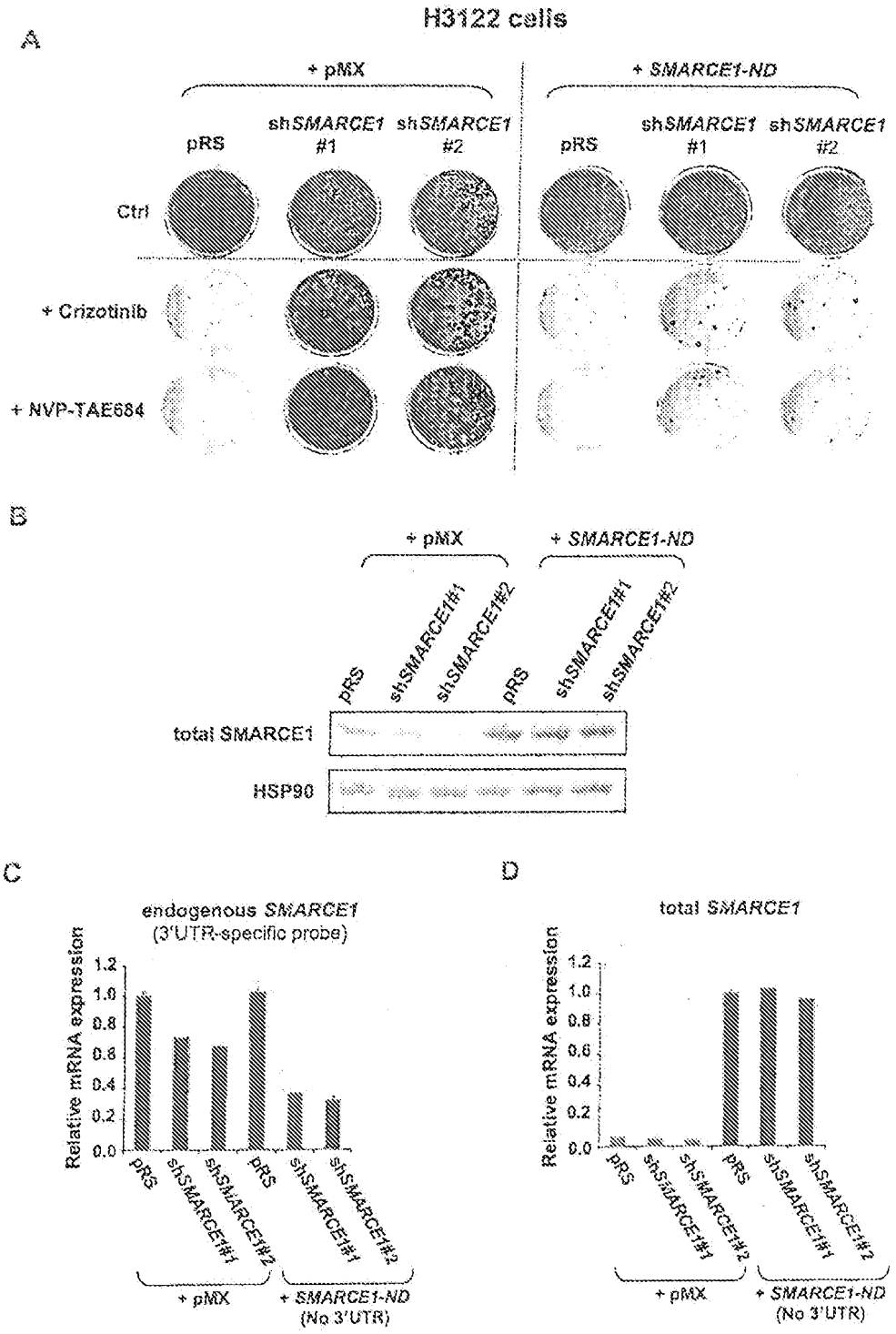

A
H3122 cells
+ pMX
+ SMARCE1-ND
pRS
shSMARCE1 #1
shSMARCE1 #2
Ctrl
+ Crizotinib
+ NVP-TAE684
B
+ pMX
+ SMARCE1-ND
pRS
shSMARCE1#1
shSMARCE1#2
total SMARCE1
HSP90
C
endogenous SMARCE1
(3'UTR-specific probe)
Relative mRNA expression
0.0
0.2
0.4
0.6
0.8
1.0
1.2
+ pMX
+ SMARCE1-ND
(No 3'UTR)
D
total SMARCE1
Relative mRNA expression
+ pMX
+ SMARCE1-ND
(No 3'UTR)

Fig 7

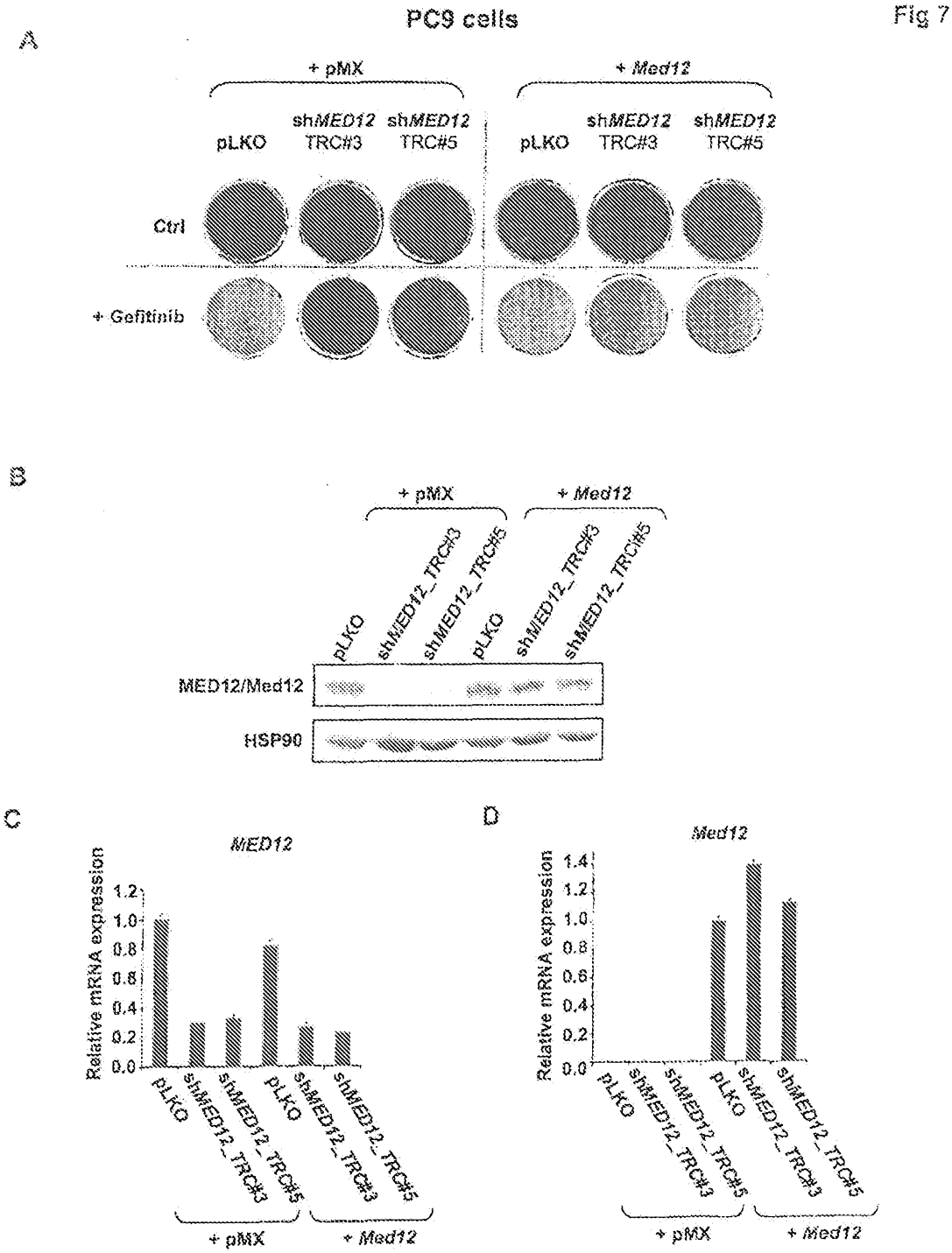
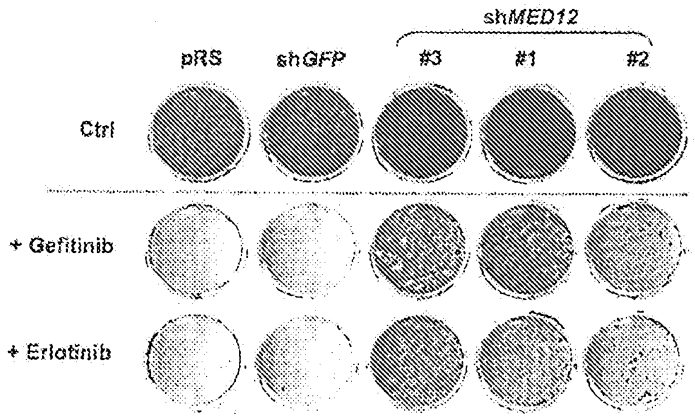

A
PC9 cells
+ pMX
+ Med12
pLKO
shMED12 TRC#3
shMED12 TRC#5
Ctrl
+ Gefitinib
B
MED12/Med12
HSP90
C
MED12
Relative mRNA expression
D
Med12

Fig 8

H3255 cells

A



B

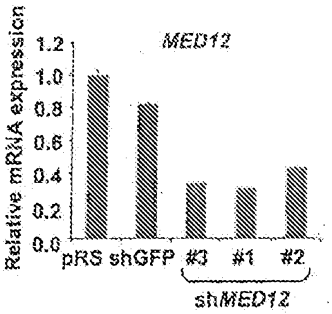


Fig 9

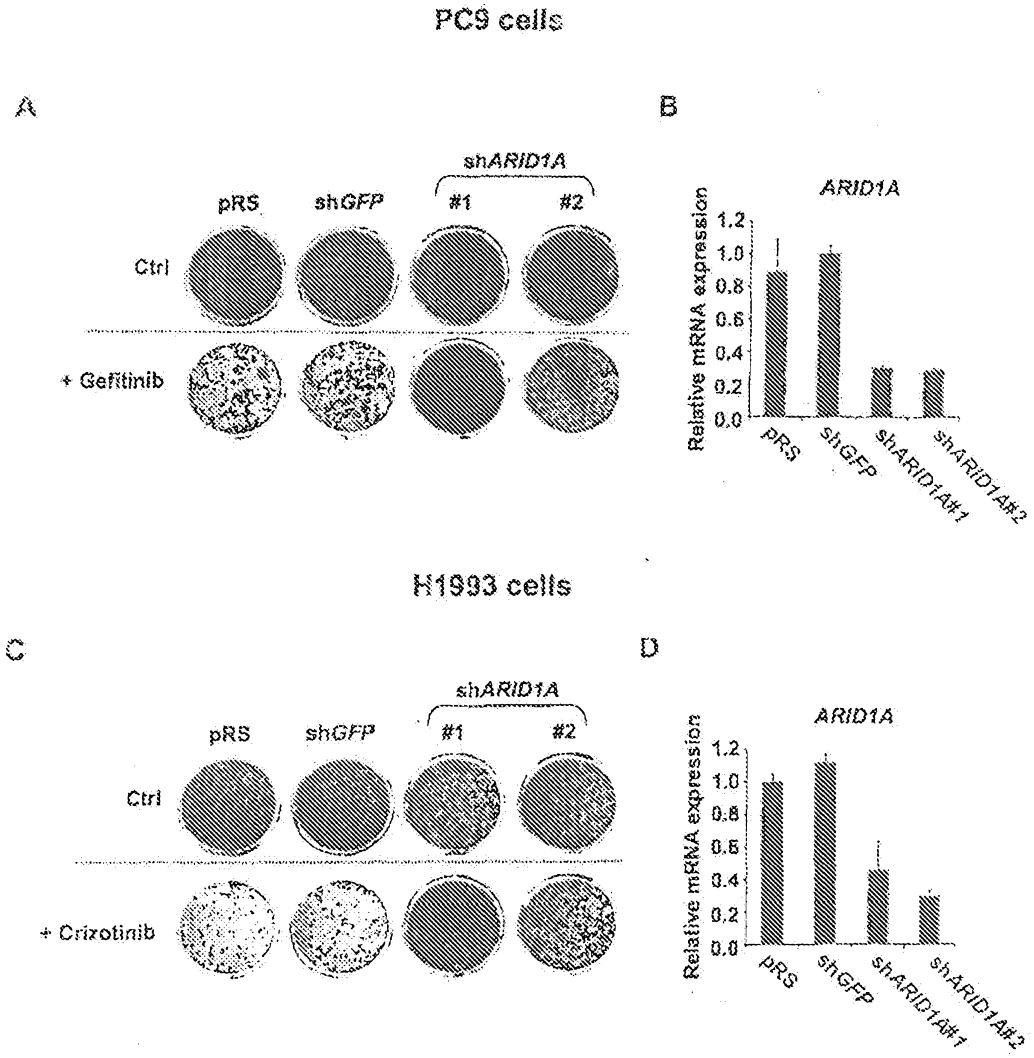

PC9 cells
A
shARID1A
pRS
shGFP
#1
#2
Ctrl
+ Gefitinib
B
ARID1A
Relative mRNA expression
1.2
1.0
0.8
0.6
0.4
0.2
0.0
pRS
shGFP
shARID1A#1
shARID1A#2
H1993 cells
C
shARID1A
pRS
shGFP
#1
#2
Ctrl
+ Crizotinib
D
ARID1A
Relative mRNA expression
1.2
1.0
0.8
0.6
0.4
0.2
0.0
pRS
shGFP
shARID1A#1
shARID1A#2

Fig 10

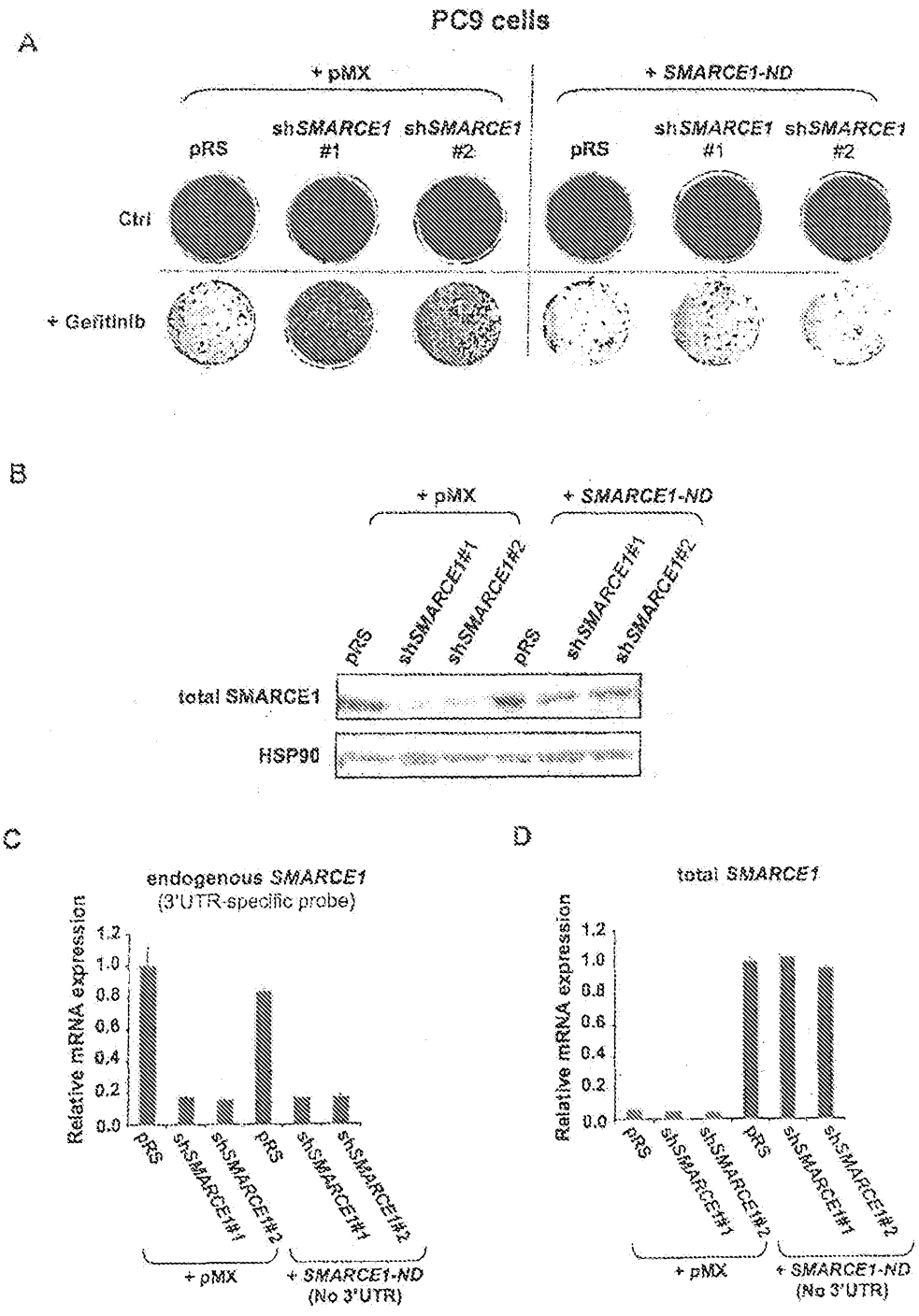

PC9 cells
A
+ pMX
+ SMARCE1-ND
pRS
shSMARCE1 #1
shSMARCE1 #2
Ctrl
+ Gefitinib
B
+ pMX
+ SMARCE1-ND
pRS
shSMARCE1#1
shSMARCE1#2
total SMARCE1
HSP90
C
endogenous SMARCE1
(3'UTR-specific probe)
Relative mRNA expression
0.0
0.2
0.4
0.6
0.8
1.0
1.2
+ pMX
+ SMARCE1-ND
(No 3'UTR)
D
total SMARCE1
Relative mRNA expression
+ pMX
+ SMARCE1-ND
(No 3'UTR)

Fig 11

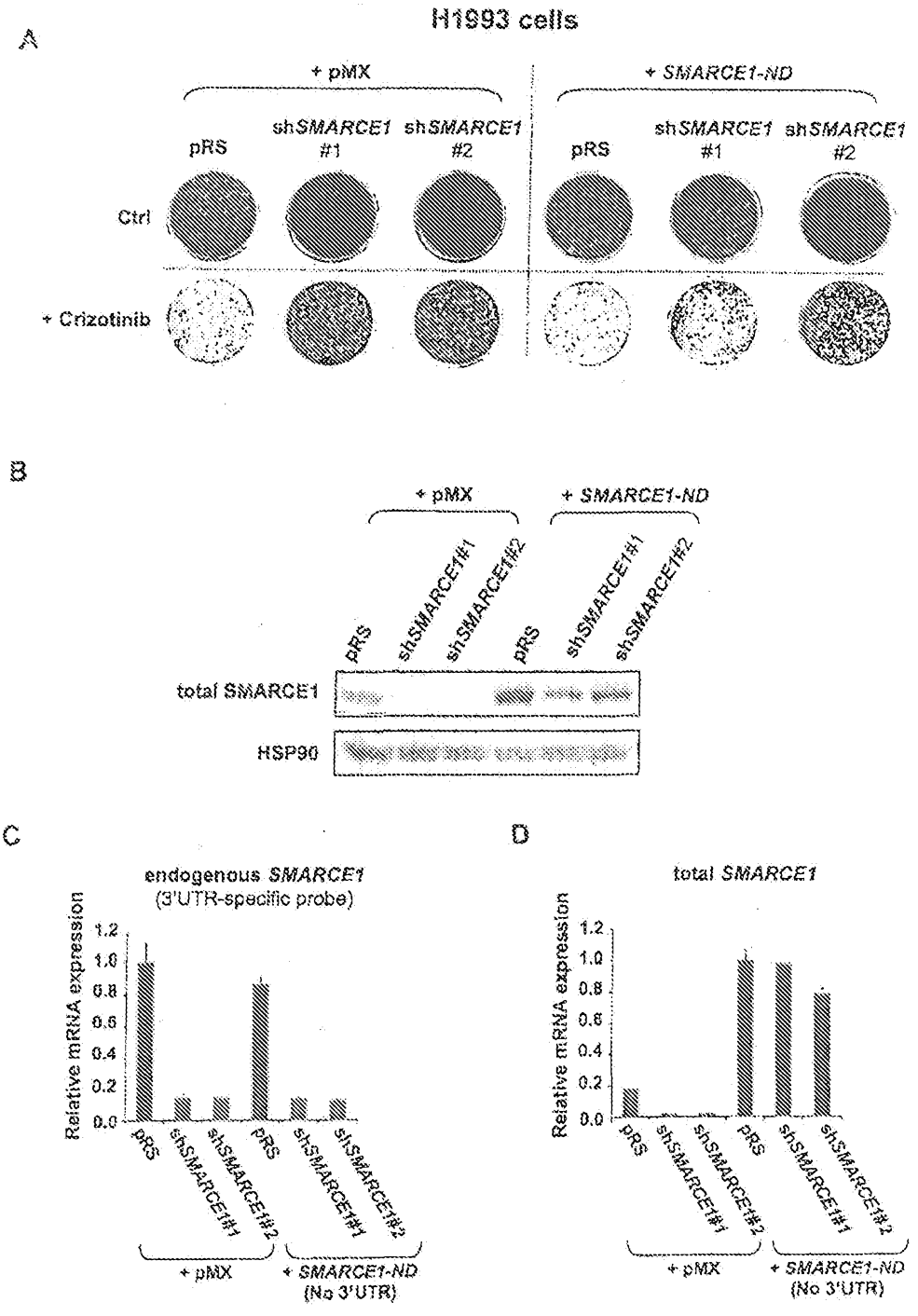

A
H1993 cells
+ pMX
+ SMARCE1-ND
pRS
shSMARCE1 #1
shSMARCE1 #2
Ctrl
+ Crizotinib
B
+ pMX
+ SMARCE1-ND
pRS
shSMARCE1#1
shSMARCE1#2
total SMARCE1
HSP90
C
endogenous SMARCE1
(3'UTR-specific probe)
Relative mRNA expression
+ pMX
+ SMARCE1-ND
(No 3'UTR)
D
total SMARCE1
Relative mRNA expression
+ pMX
+ SMARCE1-ND
(No 3'UTR)

Fig 12

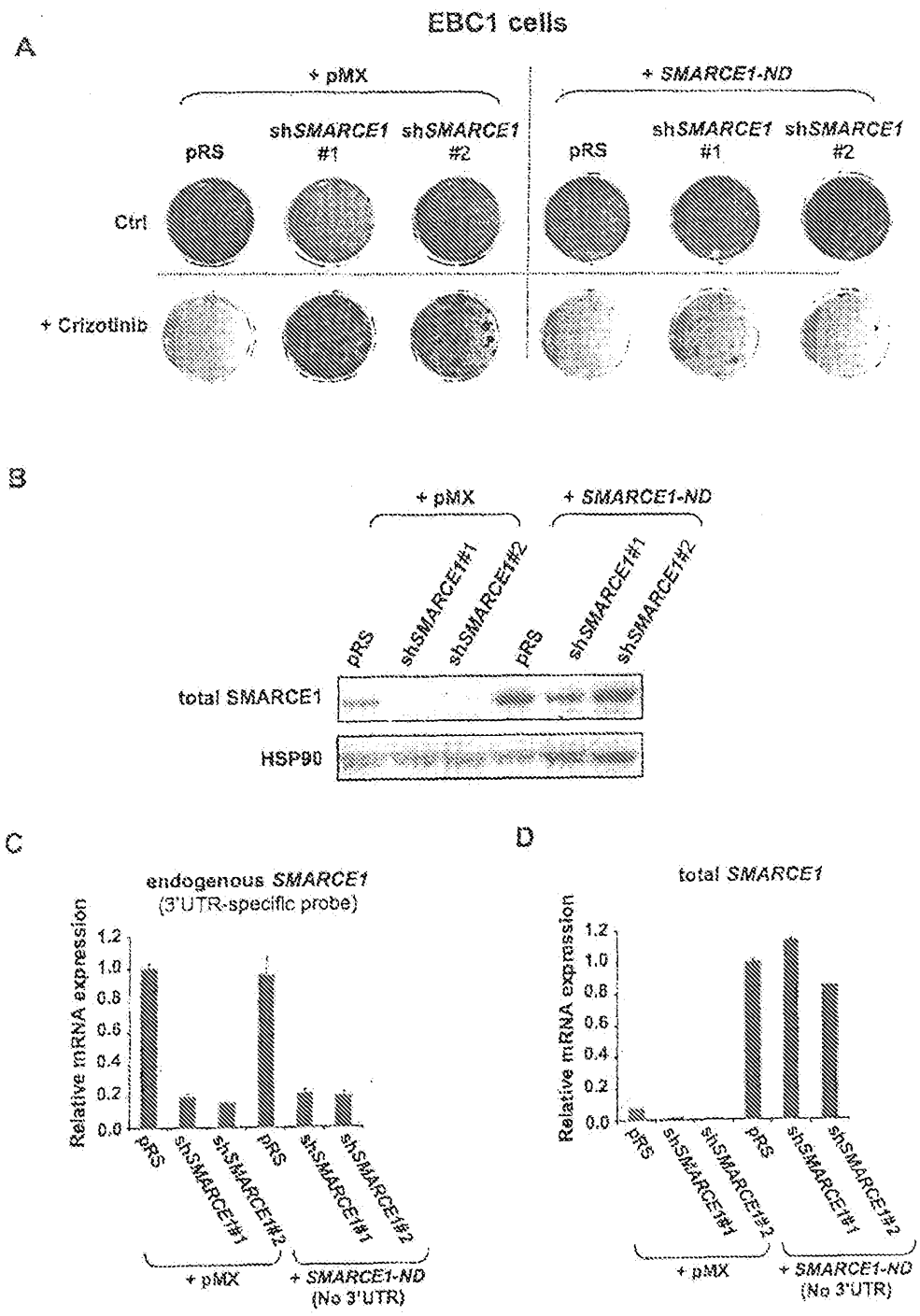

EBC1 cells
A
+ pMX
+ SMARCE1-ND
pRS
shSMARCE1 #1
shSMARCE1 #2
Ctrl
+ Crizotinib
B
+ pMX
+ SMARCE1-ND
pRS
shSMARCE1#1
shSMARCE1#2
total SMARCE1
HSP90
C
endogenous SMARCE1
(3'UTR-specific probe)
Relative mRNA expression
+ pMX
+ SMARCE1-ND
(No 3'UTR)
D
total SMARCE1
Relative mRNA expression
+ pMX
+ SMARCE1-ND
(No 3'UTR)

Fig 13

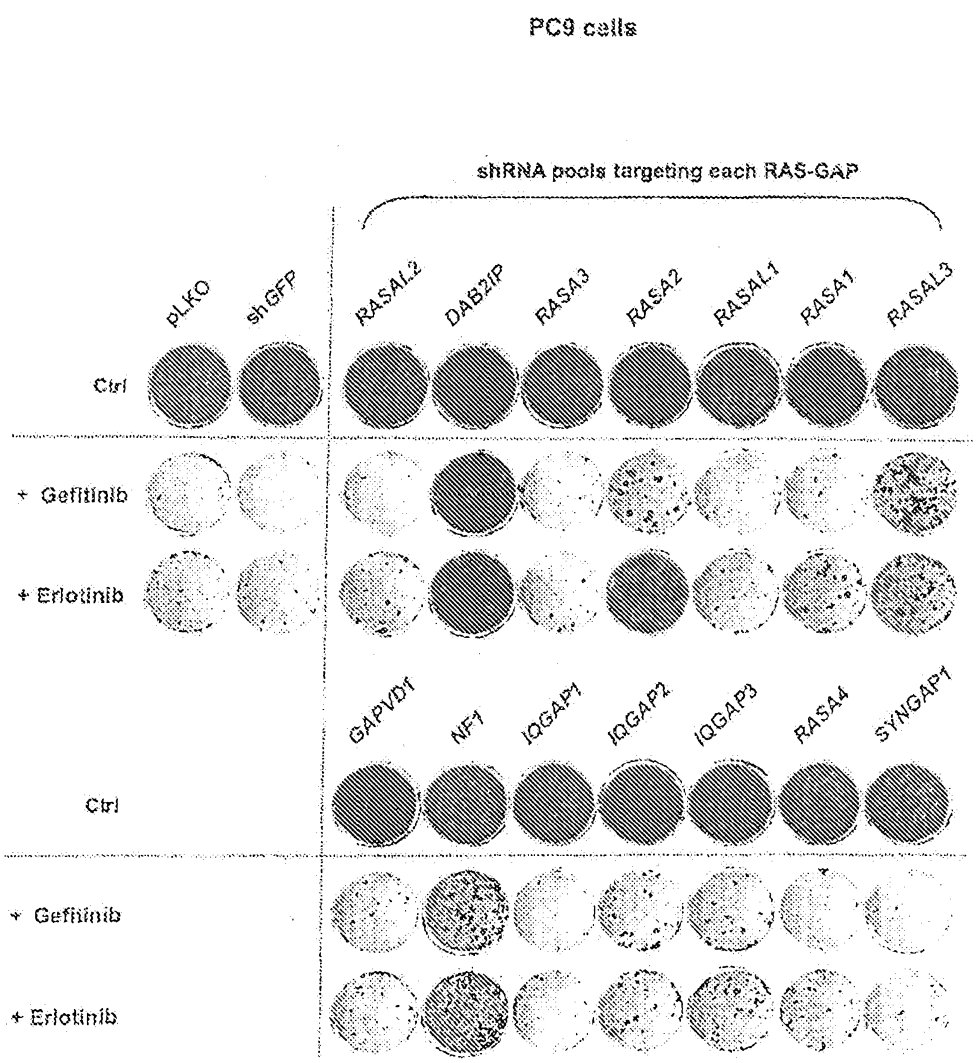

PC9 cells
shRNA pools targeting each RAS-GAP
pLKO
shGFP
RASAL2
DAB2IP
RASA3
RASA2
RASAL1
RASA1
RASAL3
Ctrl
+ Gefitinib
+ Erlotinib
GAPVD1
NF1
IQGAP1
IQGAP2
IQGAP3
RASA4
SYNGAP1
Ctrl
+ Gefitinib
+ Erlotinib

Fig 14

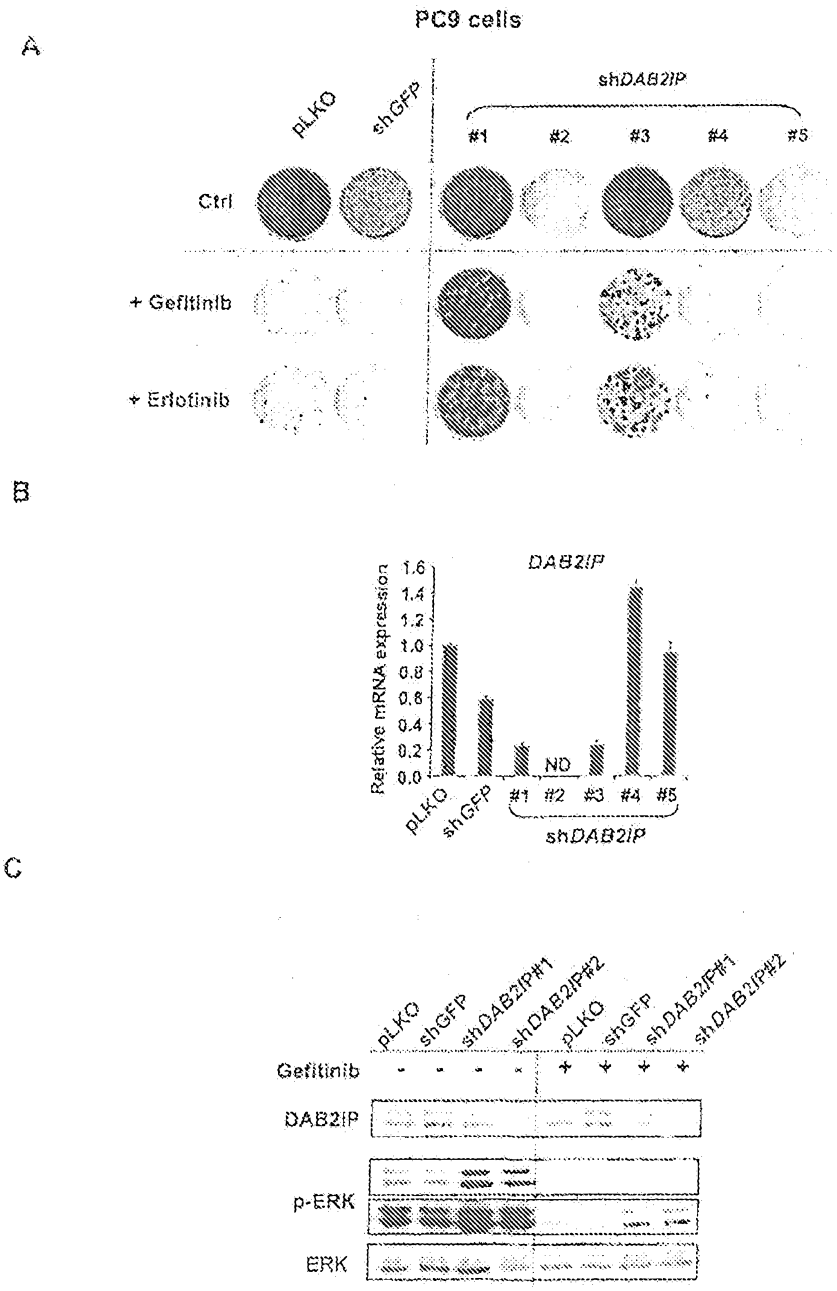

PC9 cells
A
pLKO
shGFP
shDAB2IP
#1
#2
#3
#4
#5
Ctrl
+ Gefitinib
+ Erlotinib
B
DAB2IP
Relative mRNA expression
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
ND
pLKO
shGFP
#1
#2
#3
#4
#5
shDAB2IP
C
pLKO
shGFP
shDAB2IP#1
shDAB2IP#2
pLKO
shGFP
shDAB2IP#1
shDAB2IP#2
Gefitinib
- - - - + + + +
DAB2IP
p-ERK
ERK

Fig 15

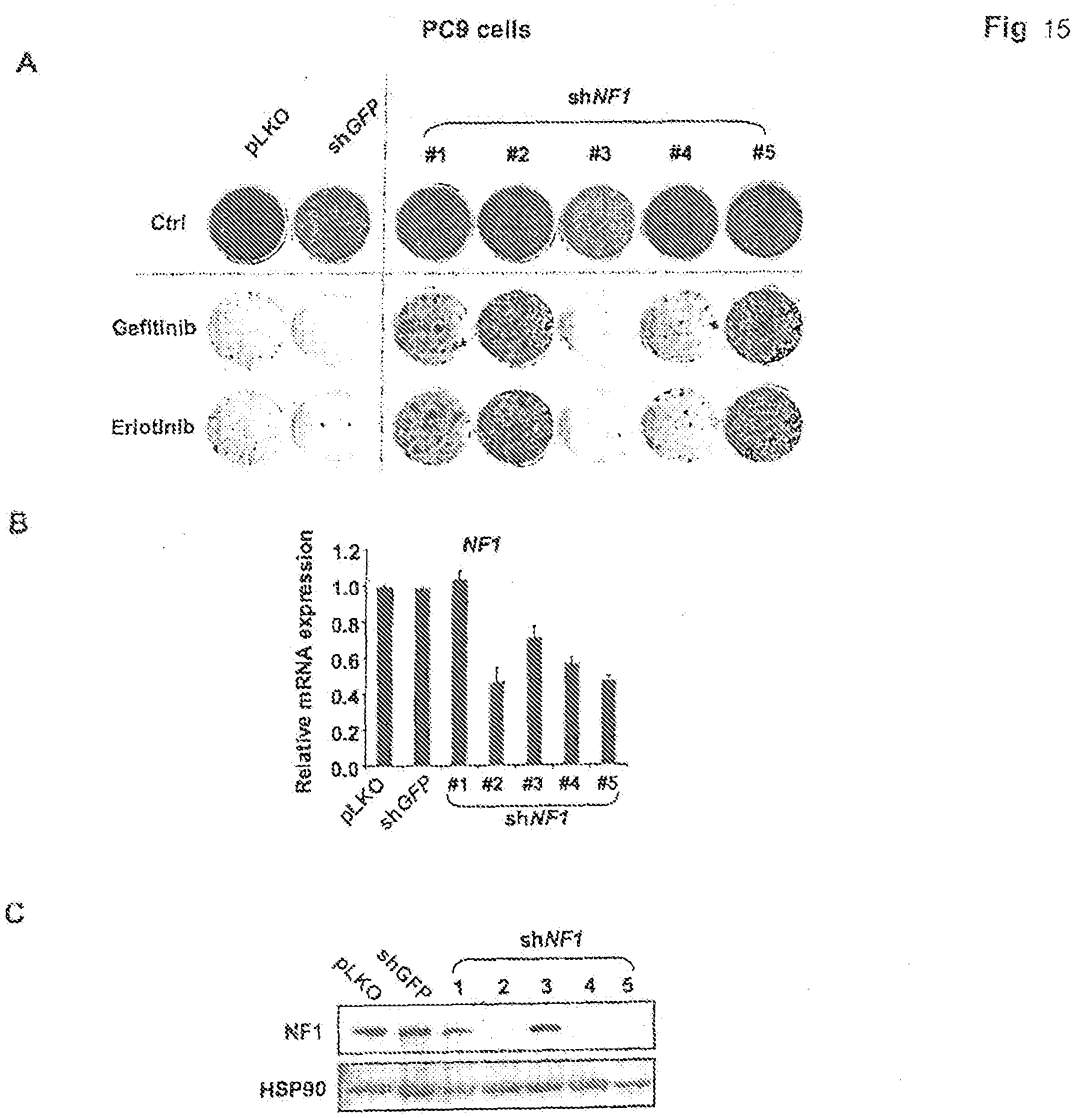

PC9 cells
A
pLKO
shGFP
shNF1
#1
#2
#3
#4
#5
Ctrl
Gefitinib
Erlotinib
B
NF1
Relative mRNA expression
1.2
1.0
0.8
0.6
0.4
0.2
0.0
pLKO
shGFP
#1 #2 #3 #4 #5
shNF1
C
shNF1
pLKO
shGFP
1 2 3 4 5
NF1
HSP90

Fig 16

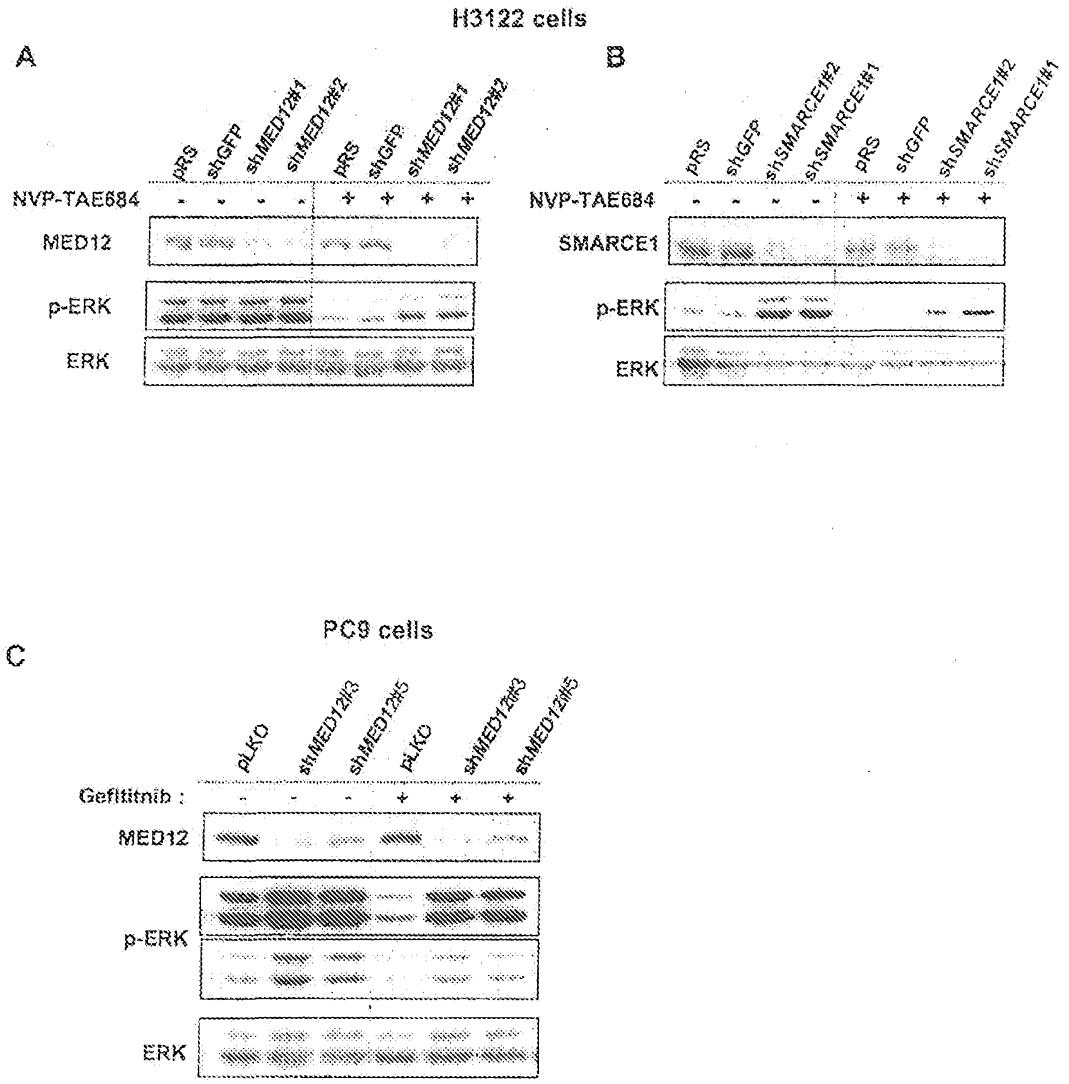

H3122 cells
A
pRS
shGFP
shMED12#1
shMED12#2
pRS
shGFP
shMED12#1
shMED12#2
NVP-TAE684
MED12
p-ERK
ERK
B
pRS
shGFP
shSMARCE1#2
shSMARCE1#1
pRS
shGFP
shSMARCE1#2
shSMARCE1#1
NVP-TAE684
SMARCE1
p-ERK
ERK
C
PC9 cells
pLKO
shMED12#3
shMED12#5
pLKO
shMED12#3
shMED12#5
Gefitinib :
MED12
p-ERK
ERK

Fig 17

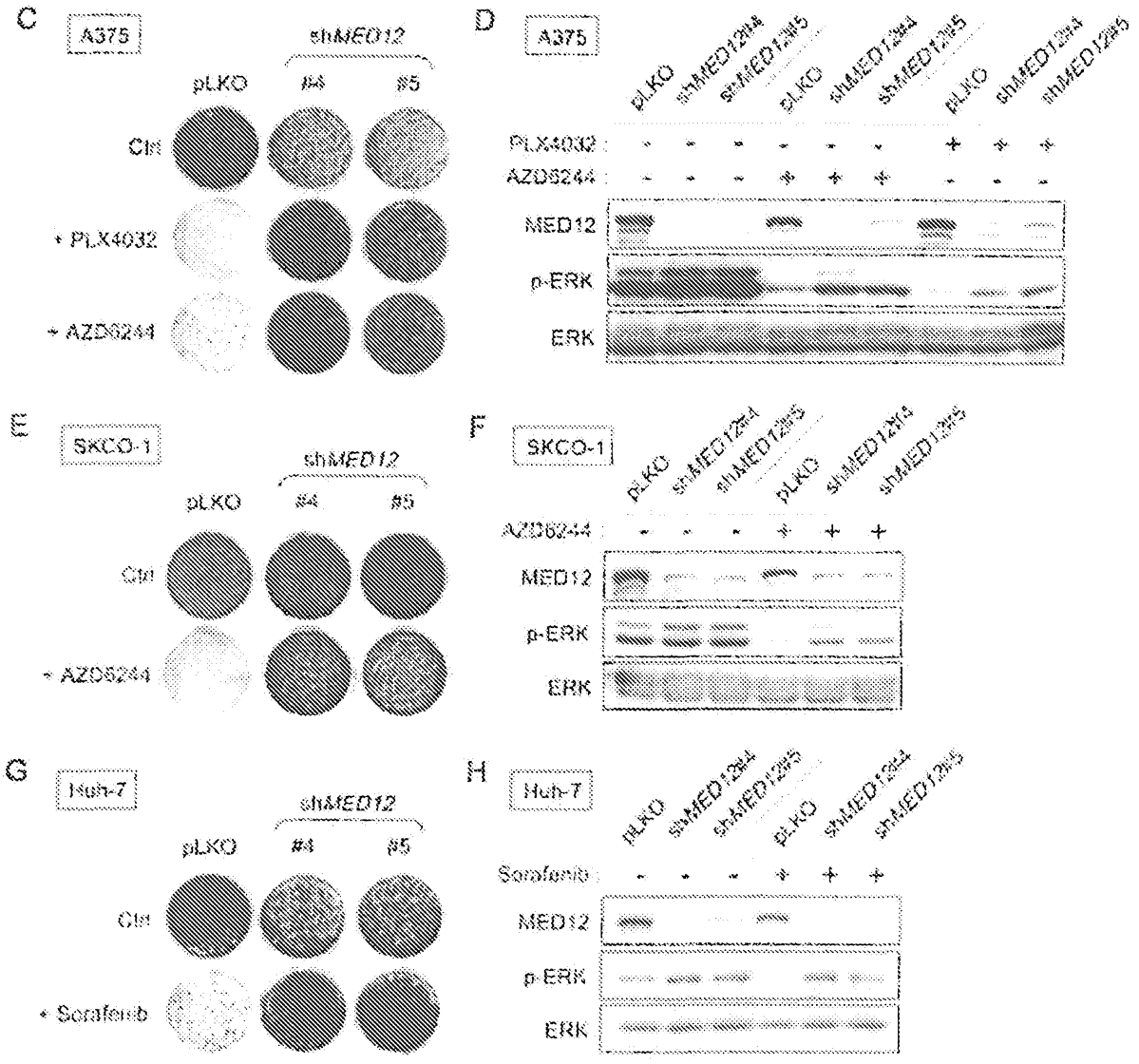
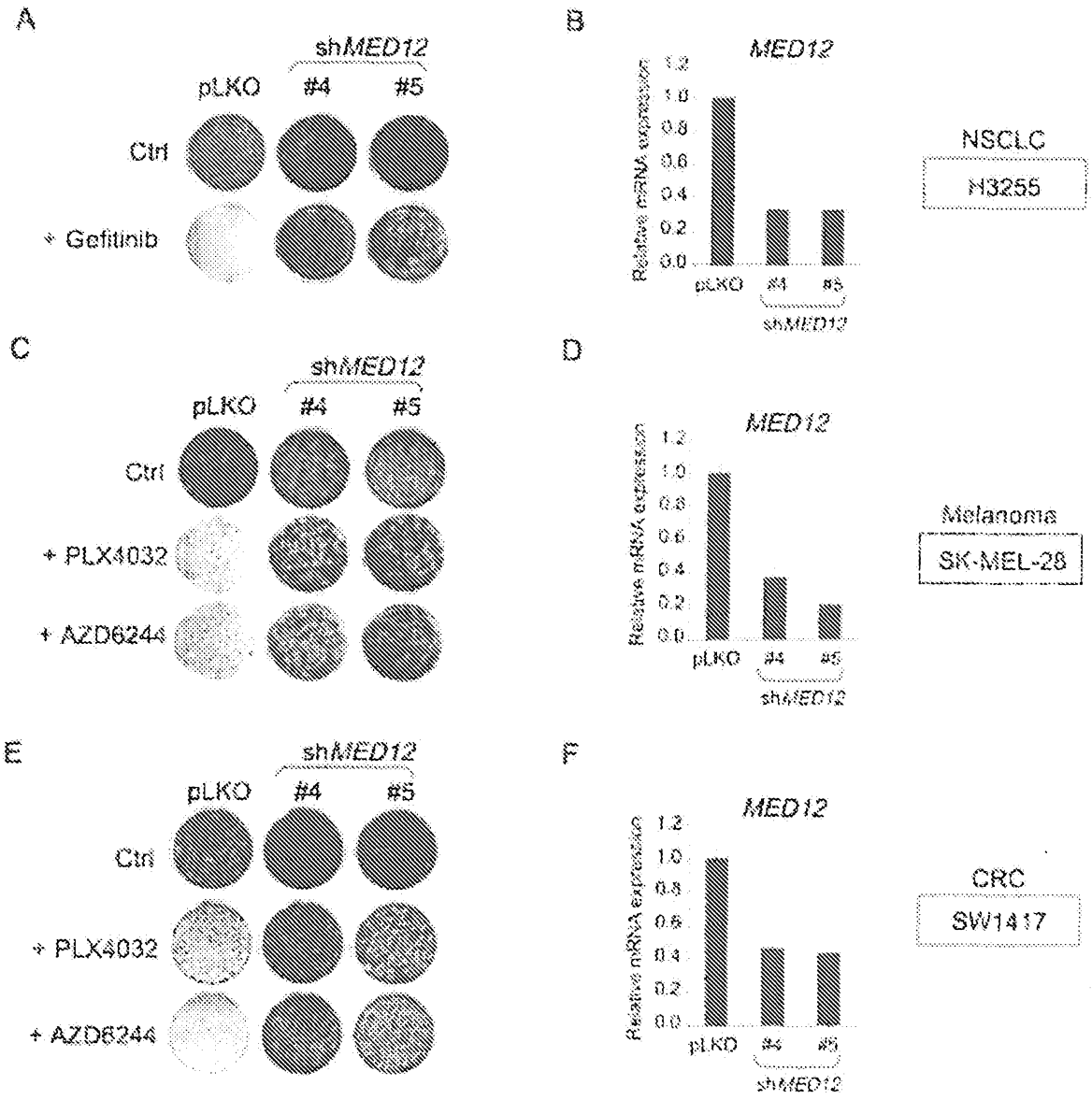

C
A375
shMED12
pLKO
#4
#5
Ctrl
+ PLX4032
+ AZD6244
D
A375
pLKO
shMED12#4
shMED12#5
PLX4032
AZD6244
MED12
p-ERK
ERK
E
SKCO-1
F
SKCO-1
G
Huh-7
+ Sorafenib
H
Huh-7
Sorafenib

Fig 18


A
shMED12
pLKO
#4
#5
Ctrl
+ Gefitinib
B
MED12
Relative mRNA expression
1.2
1.0
0.8
0.6
0.4
0.2
0.0
pLKO
#4
#5
shMED12
NSCLC
H3255
C
shMED12
pLKO
#4
#5
Ctrl
+ PLX4032
+ AZD6244
D
MED12
Relative mRNA expression
1.2
1.0
0.8
0.6
0.4
0.2
0.0
pLKO
#4
#5
shMED12
Melanoma
SK-MEL-28
E
shMED12
pLKO
#4
#5
Ctrl
+ PLX4032
+ AZD6244
F
MED12
Relative mRNA expression
1.2
1.0
0.8
0.6
0.4
0.2
0.0
pLKO
#4
#5
shMED12
CRC
SW1417

A375 cells

Fig 19

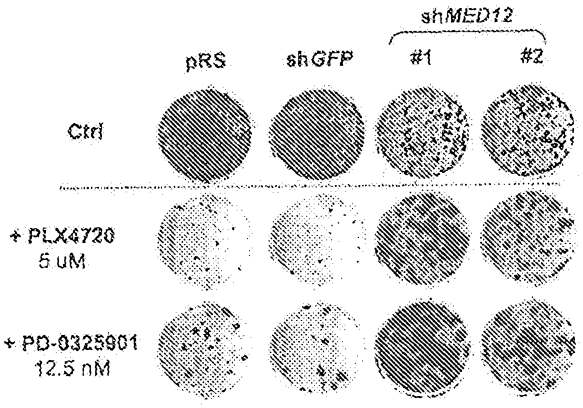


Fig 20

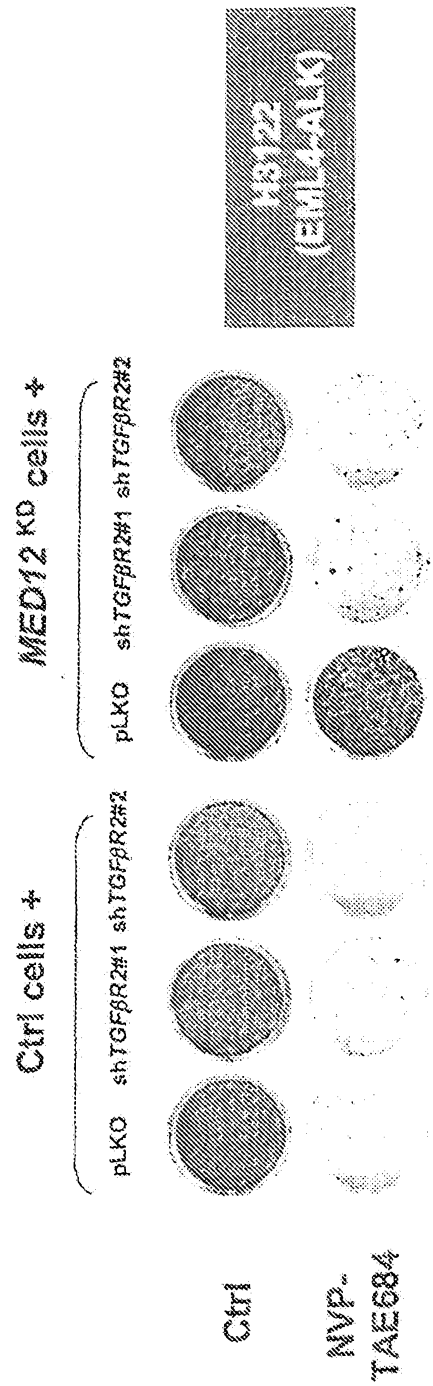

H3122
(EML4-ALK)
MED12 KD cells +
Ctrl cells +
pLKO
shTGFβR2#1
shTGFβR2#2
pLKO
shTGFβR2#1
shTGFβR2#2
Ctrl
NVP-TAE684

Fig 21

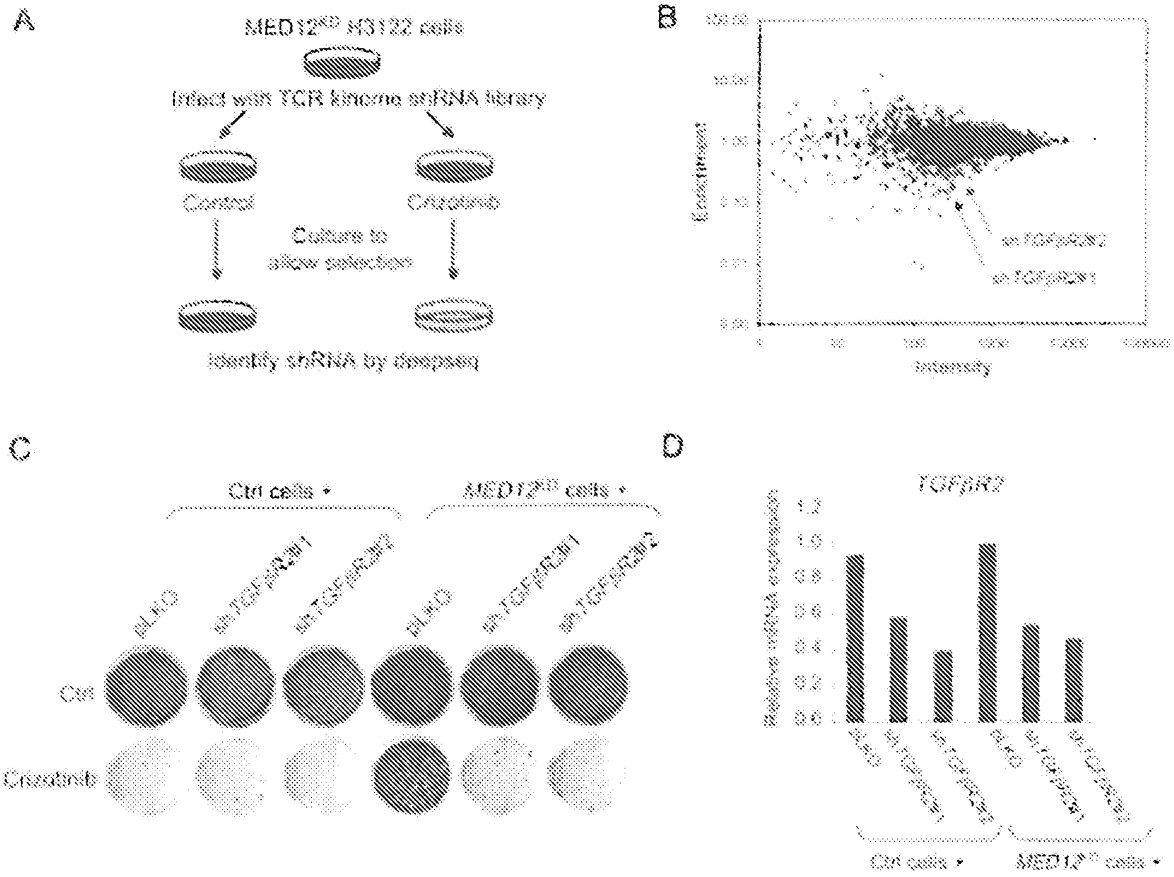

A
MED12KD H3122 cells
Infect with TGR kinome shRNA library
Control
Crizotinib
Culture to allow selection
Identify shRNA by deepseq
B
shTGFβR2#2
shTGFβR2#1
Intensity
C
Ctrl cells
MED12KD cells
shLKO
shTGFβR2#1
shTGFβR2#2
Ctrl
Crizotinib
D
TGFβR2
Ctrl cells
MED12KD cells

Fig 22

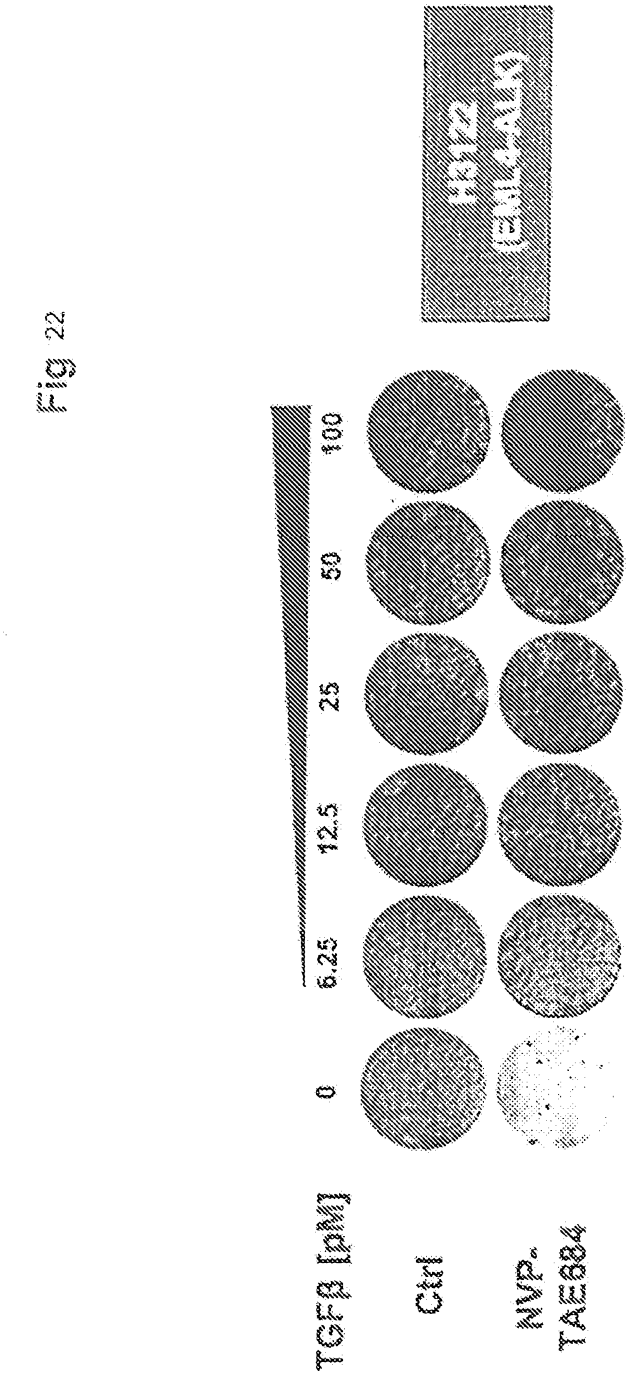


Fig 23

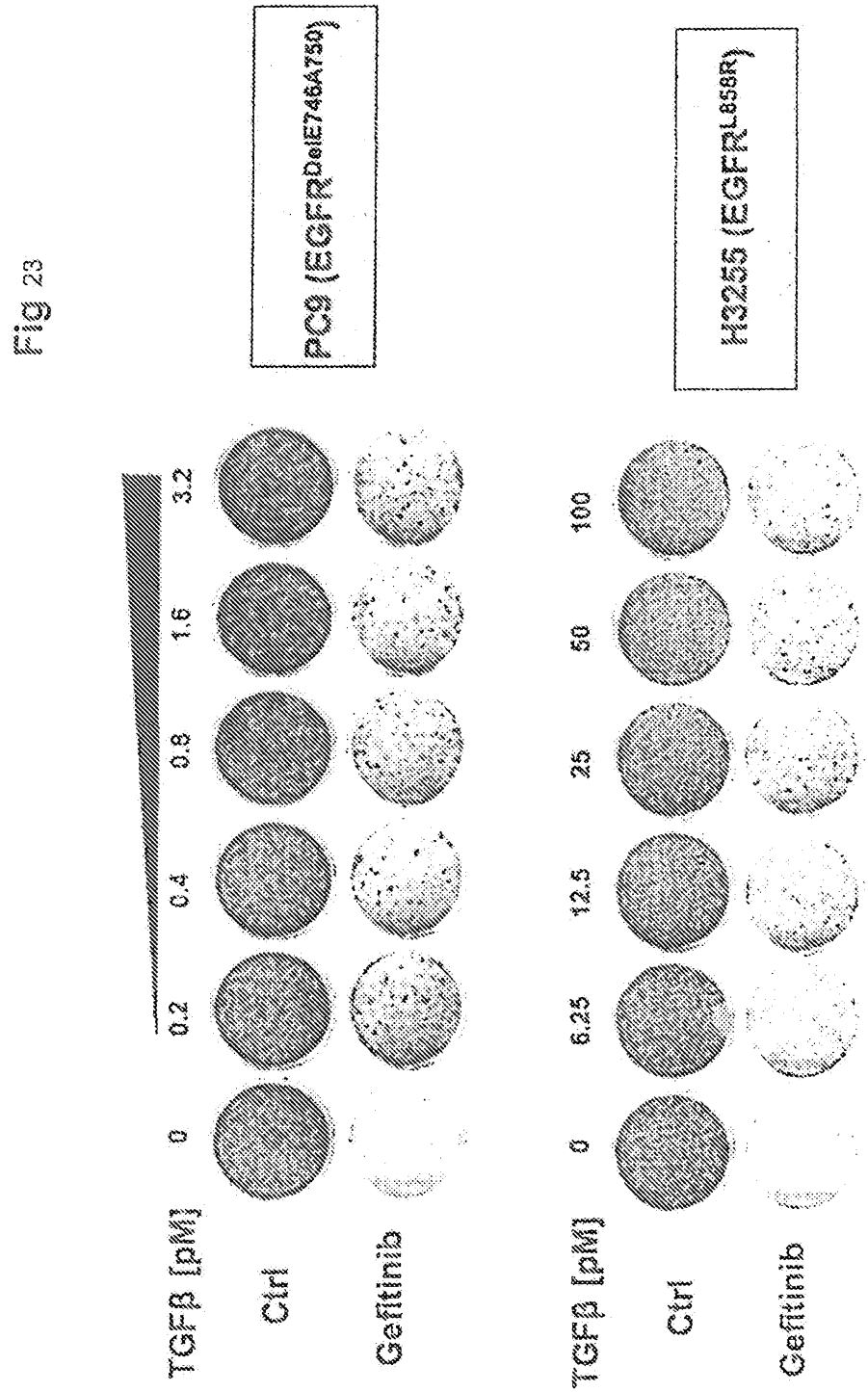

PC9 (EGFRDelE746A750)
H3255 (EGFRL858R)
TGFβ [pM]
0
0.2
0.4
0.8
1.6
3.2
6.25
12.5
25
50
100
Ctrl
Gefitinib

Fig 24

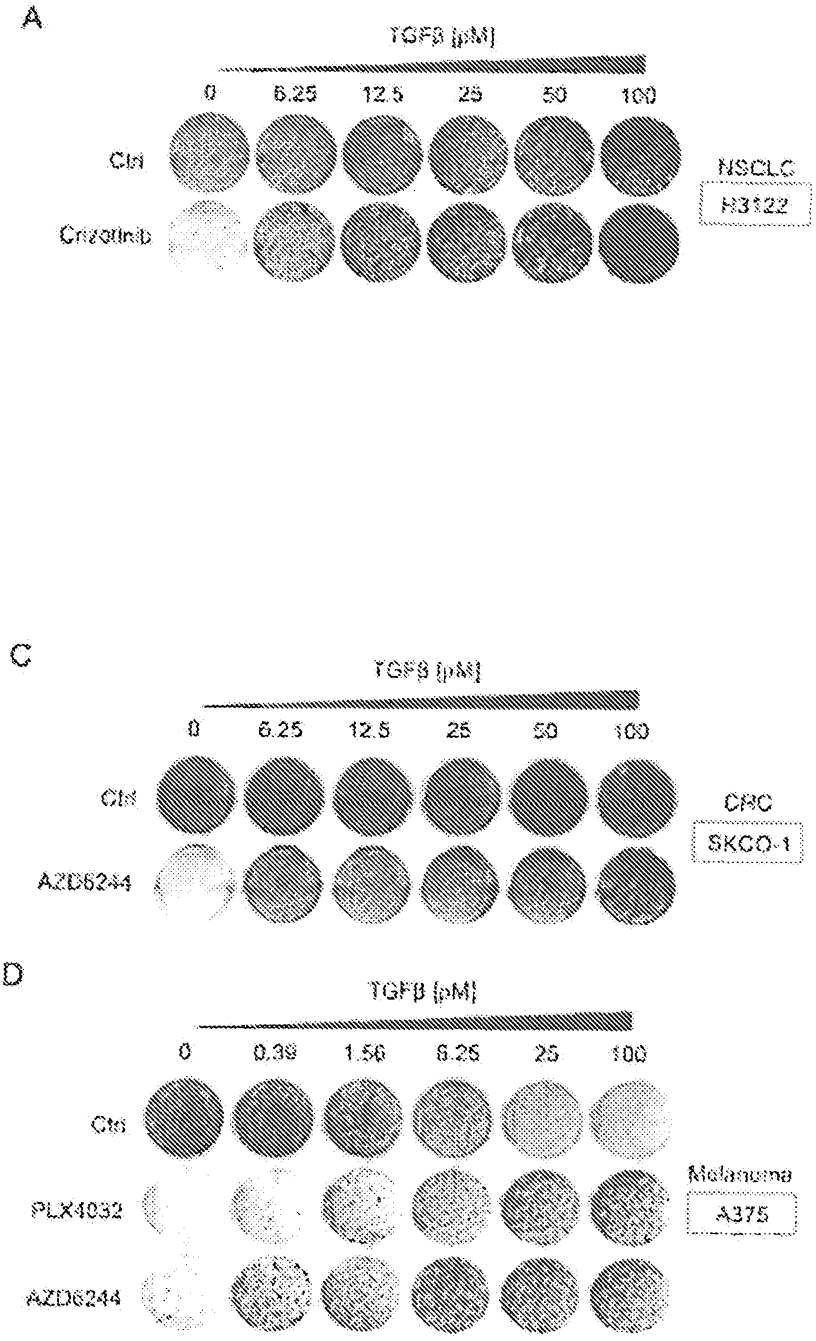

A
TGFβ [pM]
0
6.25
12.5
25
50
100
Ctrl
Crizotinib
NSCLC
H3122
C
TGFβ [pM]
0
6.25
12.5
25
50
100
Ctrl
AZD6244
CRC
SKCO-1
D
TGFβ [pM]
0
0.39
1.56
6.25
25
100
Ctrl
PLX4032
AZD6244
Melanoma
A375

Fig 25

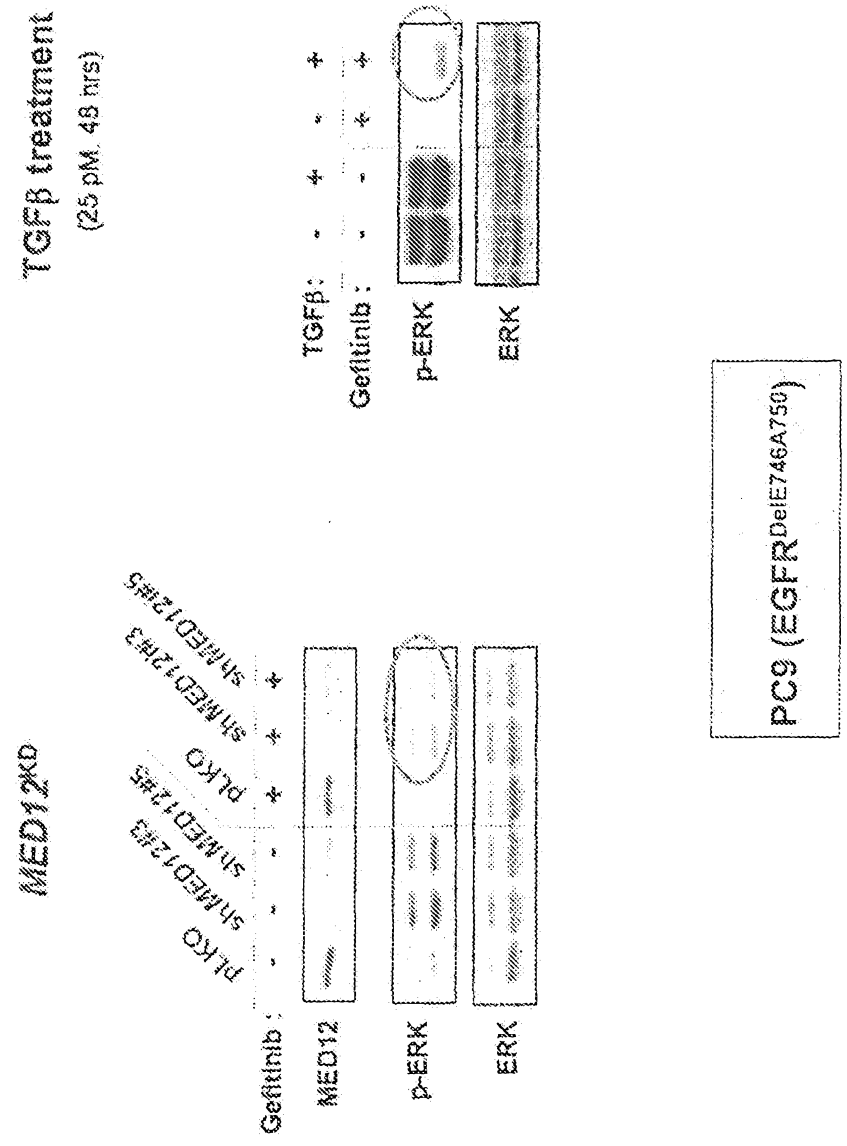

MED12KD
TGFβ treatment
(25 pM, 48 hrs)
Gefitinib : - - - + + +
shLKO
shMED12#3
shLKO
shMED12#5
MED12
p-ERK
ERK
TGFβ: - + - +
Gefitinib : - - + +
p-ERK
ERK
PC9 (EGFRDelE746A750)

Fig 26

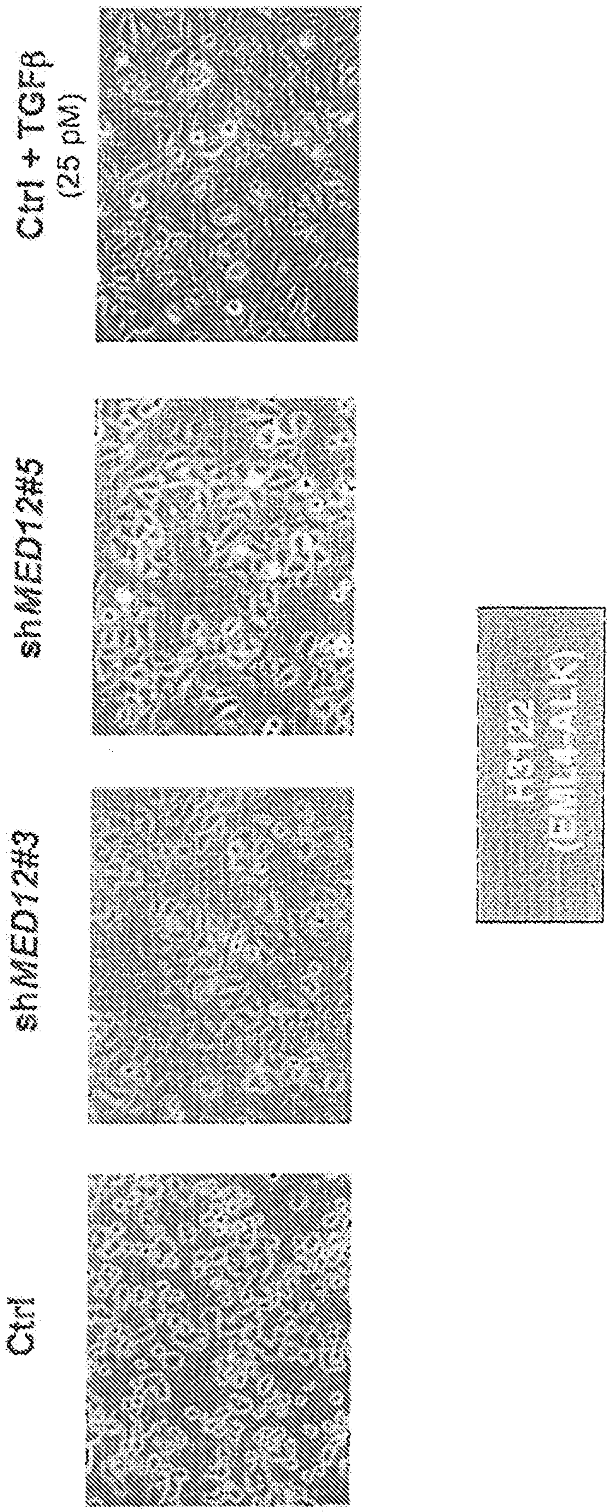


Fig 27

B

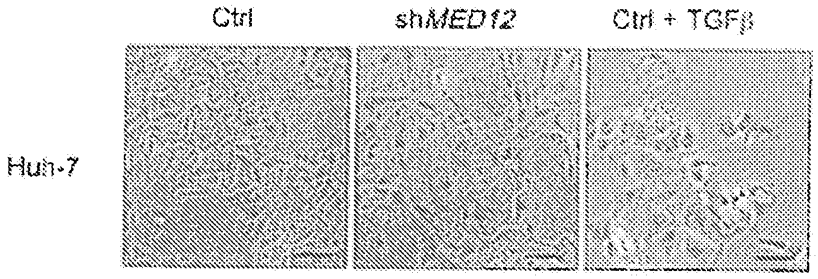
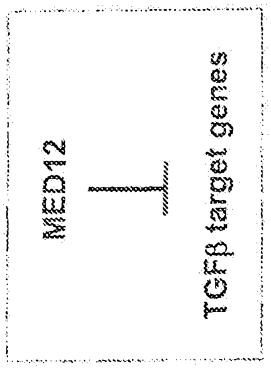


Fig. 28



Rank	Gene symbol	shMED12#3 vs Ctrl	shMED12#5 vs Ctrl
1	LOC100134294	6.0	7.2
2	PTRF	5.8	3.8
3	ANXA9	5.7	4.7
4	SORD3	5.6	3.6
5	PRSS2	5.3	6.3
6	AXONSA6	5.1	5.1
7	CDH2	4.9	3.7
8	TMEM166	4.8	3.6
9	KRT81	4.9	1.8
10	COL5A1	4.9	4.5
11	MAL	4.7	2.2
12	TAGLN	4.7	3.4
13	ANXA10	4.6	4.6
14	RHOD	4.6	6.3
15	HSPB8	4.6	2.2
16	LGALS1	4.5	2.7
17	C6orf15	4.5	2.6
18	PKP2	4.4	3.9
19	ANXA8	4.4	2.7
20	TCHH3	4.4	4.4
21	VGLL1	4.4	0.9
22	EDA	4.4	2.7
23	LOC643008	4.4	3.4
24	IL1R2	4.4	2.8
25	CST6	4.3	3.7
26	AIM1L	4.3	3.4
27	DKK3	4.3	2.8
28	GAS6	4.3	3.3
29	ANXA9	4.2	3.4
30	AOX1	4.2	0.6
31	BTBD11	4.1	2.1
32	ANKRD1	4.1	2.7
33	TRIM29	4.1	2.7
34	LRRC62	4.1	3.7
35	IL11	4.1	3.3
36	SPRR1B	4.1	2.8
37	UNC13D	4.1	3.5
38	FSTL1	4.0	4.4
39	DKK3	4.0	1.3
40	GAS6	4.0	2.8
41	SERPINF1	4.0	4.2
42	L6H	3.9	3.1
43	ADA1	3.9	3.5
44	APOD2L	3.9	4.2
45	VIL1	3.9	3.0
46	SOCS2	3.9	3.1
47	COL4A1	3.8	3.2
48	MX1	3.8	2.6
49	CAV1	3.8	2.9
50	ITGB2	3.8	1.0

Fig 29

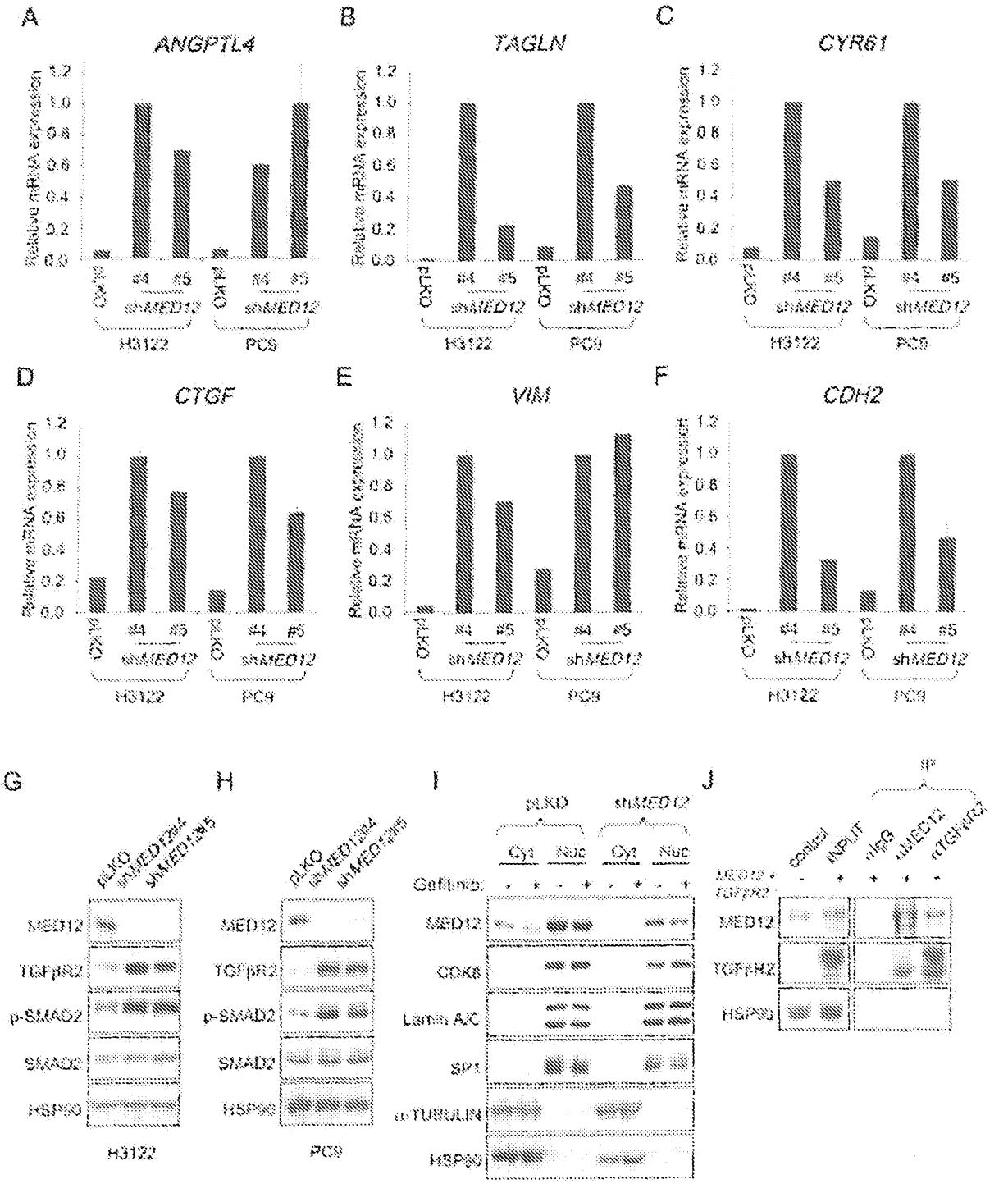

A
ANGPTL4
B
TAGLN
C
CYR61
D
CTGF
E
VIM
F
CDH2
Relative mRNA expression
pLKO
#4
#5
shMED12
H3122
PC9
G
H
I
J
MED12
TGFβR2
p-SMAD2
SMAD2
HSP90
CDK8
Lamin A/C
SP1
α-TUBULIN
Cyt
Nuc
Gefitinib
IP
control
INPUT
rIgG
αMED12
αTGFβR2

Fig 30

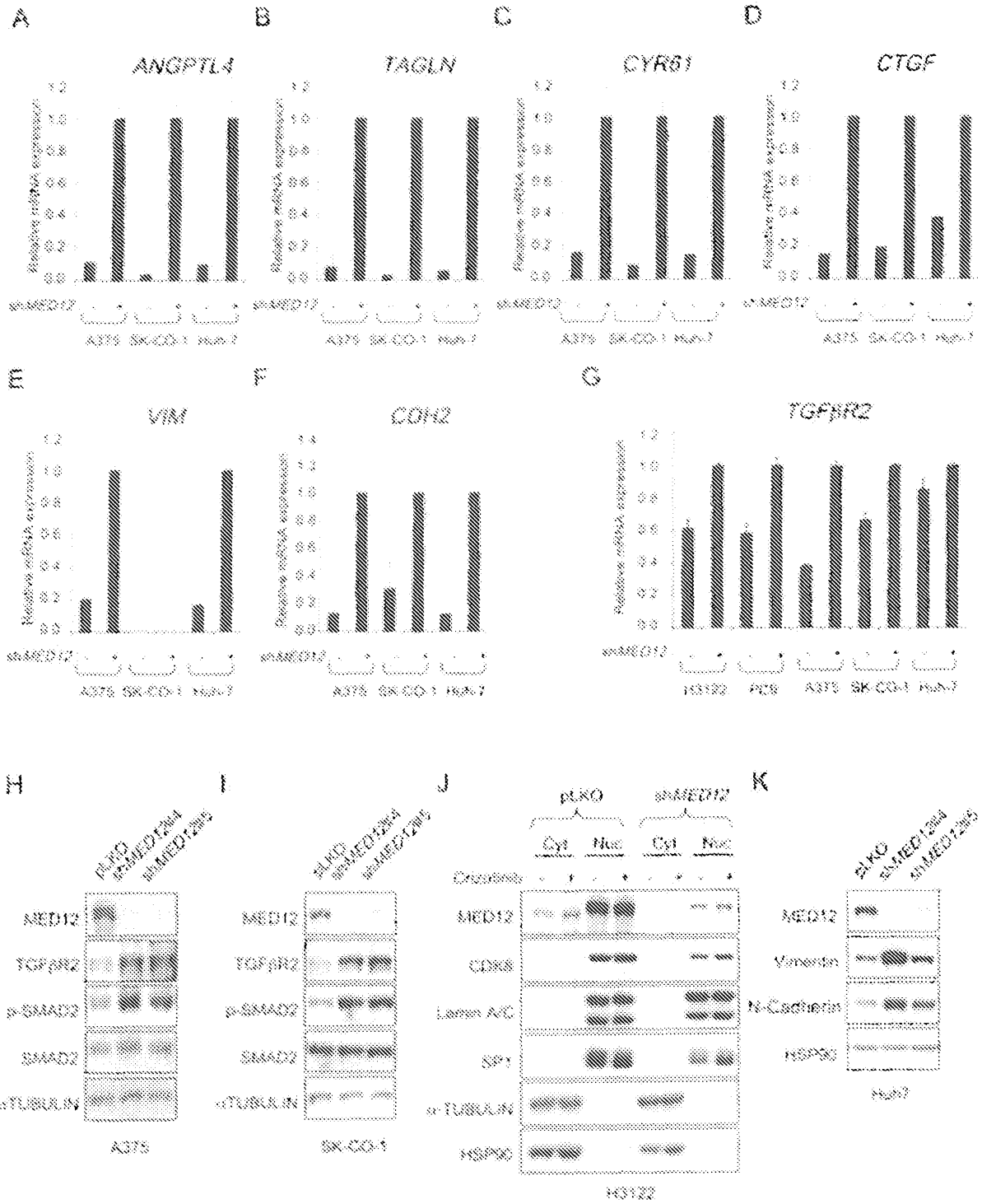

A
ANGPTL4
B
TAGLN
C
CYR61
D
CTGF
shMED12
A375
SK-CO-1
HuH-7
E
VIM
F
COH2
G
TGFBR2
HS132
PC9
H
pLKO
shMED12#4
shMED12#5
MED12
TGFβR2
p-SMAD2
SMAD2
α-TUBULIN
A375
I
SK-CO-1
J
Cyt
Nuc
Crosslink
CDK8
Lamin A/C
SP1
HSP90
HS132
K
Vimentin
N-Cadherin
HuH-7

Fig 31

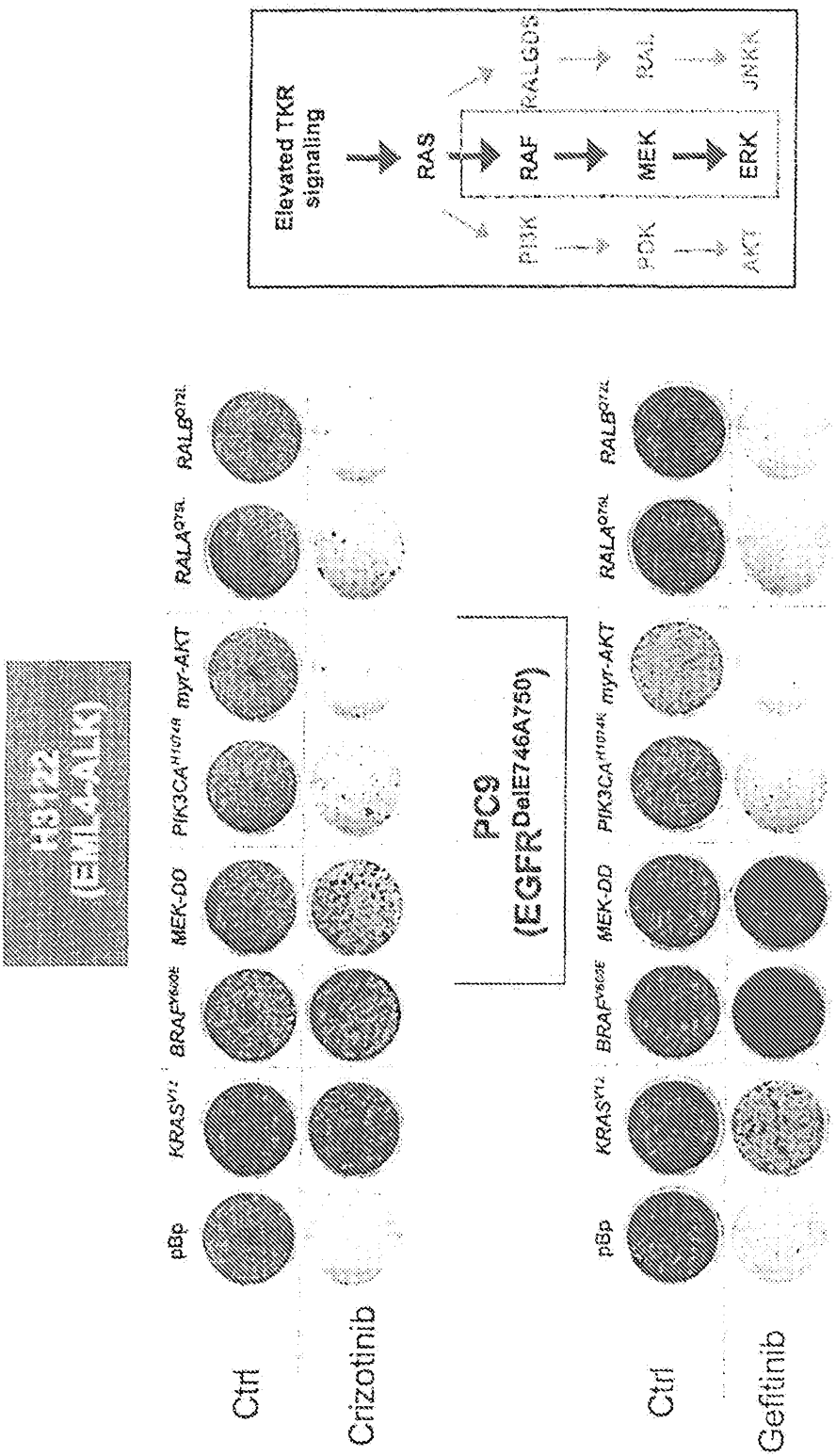
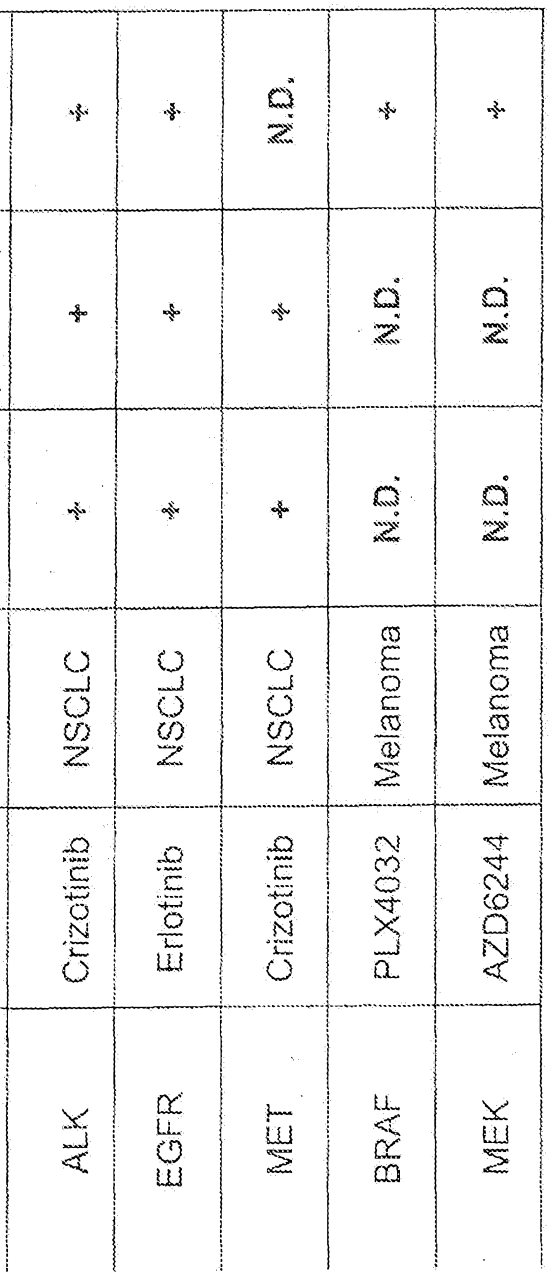

Elevated TKR signaling
RAS
PI3K
PDK
AKT
RAF
MEK
ERK
RALGDS
RAL
JNK
H3122 (EML4-ALK)
PC9 (EGFR DelE746A750)
Ctrl
Crizotinib
Ctrl
Gefitinib
pBp
KRASV12
BRAFV600E
MEK-DD
PIK3CAH1047R
myr-AKT
RALAQ72L
RALBQ72L

Fig 32



Target	Drug	Cancer Type	SMARCE1	SMARCF1 (ARID1A)	MED12
ALK	Crizotinib	NSCLC	+	+	+
EGFR	Erlotinib	NSCLC	+	+	+
MET	Crizotinib	NSCLC	+	+	N.D.
BRAF	PLX4032	Melanoma	N.D.	N.D.	+
MEK	AZD6244	Melanoma	N.D.	N.D.	+

Fig 33

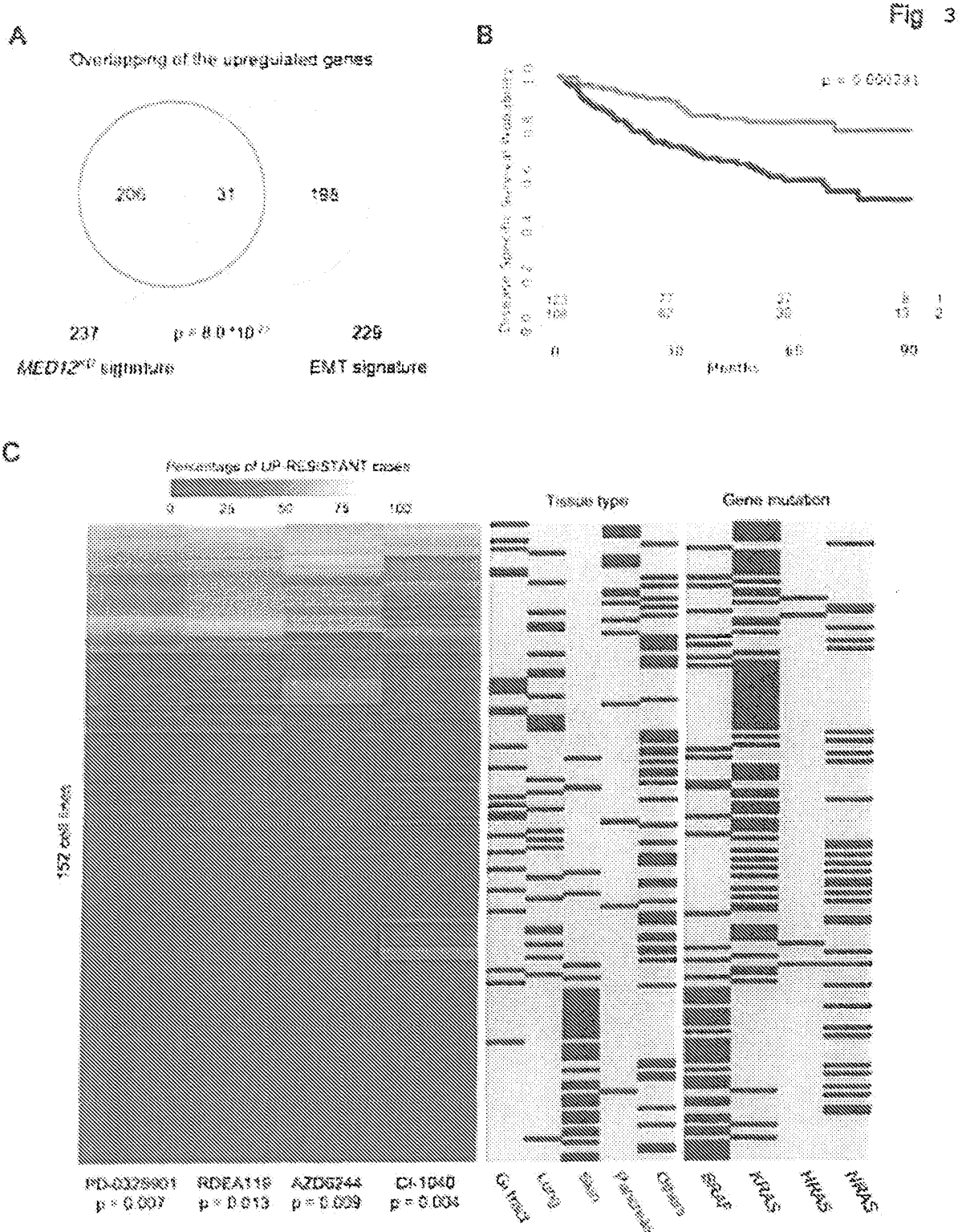

A
Overlapping of the upregulated genes
206
31
188
237
p = 8.0 *10
229
MED12 signature
EMT signature
B
p = 0.000281
Progression
C
Percentage of UP-RESISTANT cases
0
25
50
75
100
152 cell lines
Tissue type
Gene mutation
PD-0325901
p = 0.007
RDEA119
p = 0.013
AZD6244
p = 0.039
CI-1040
p = 0.035
Glioma
Lung
Skin
Pancreas
Others
BRAF
KRAS
HRAS
NRAS

Fig 34

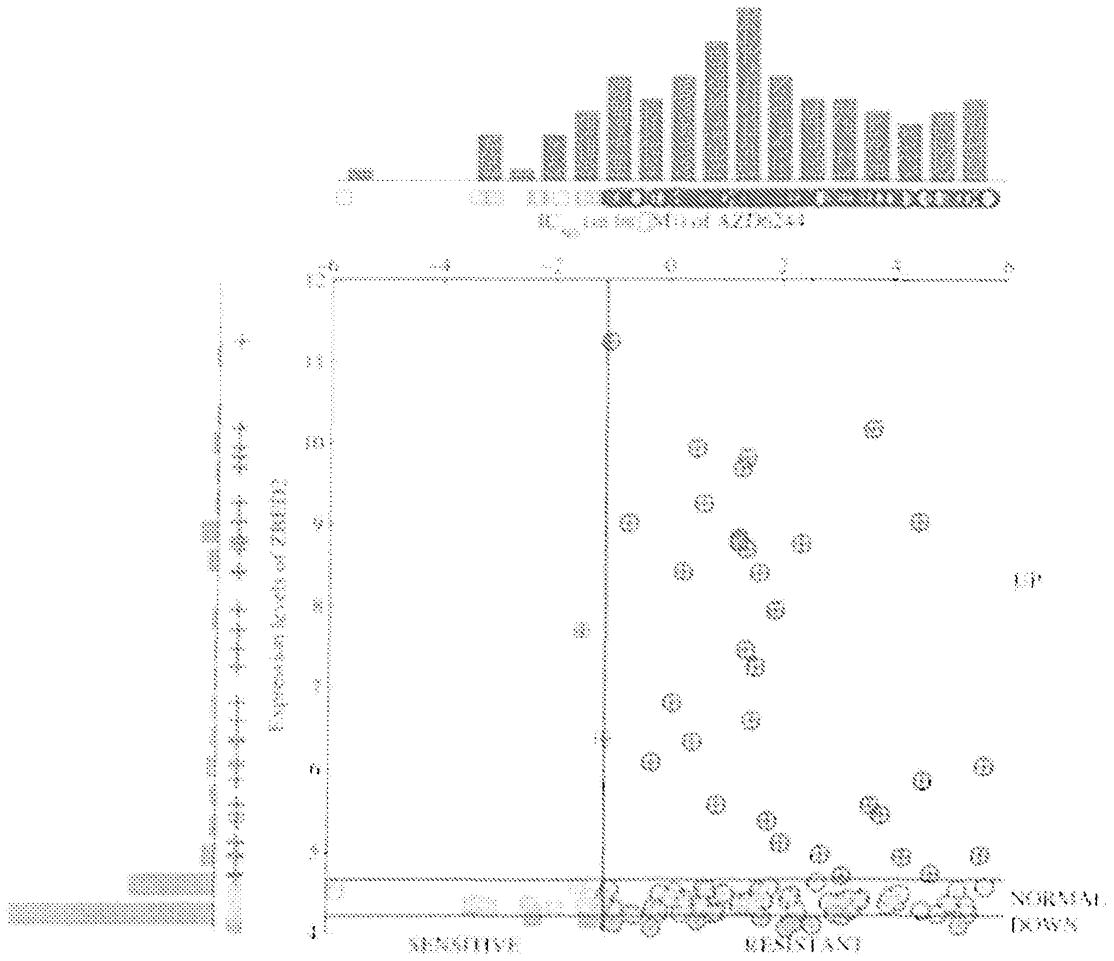


Fig 35

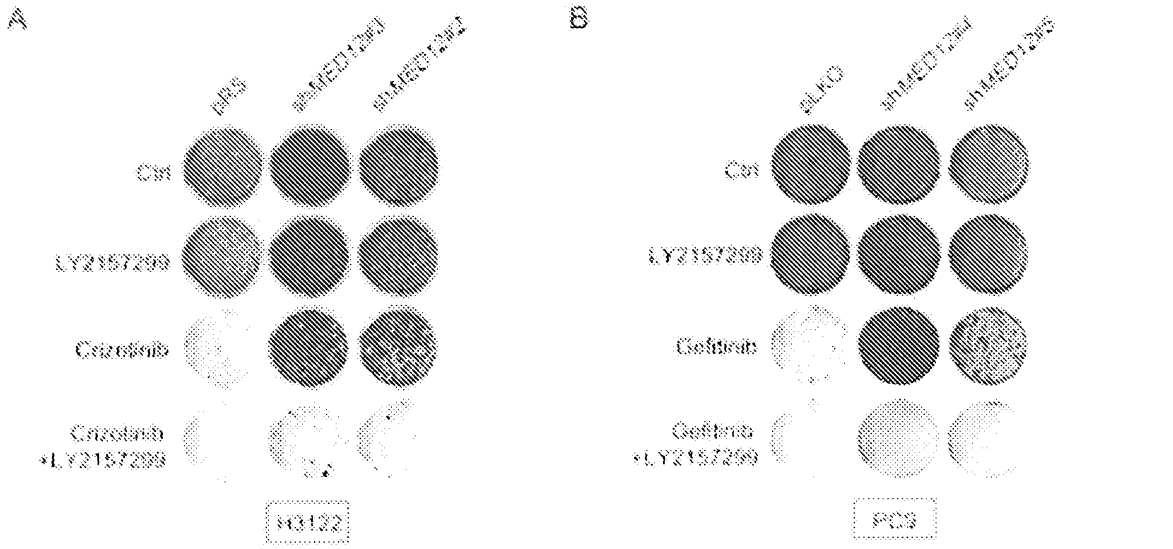

A
pRS
shMED12#3
shMED12#4
Ctrl
LY2157299
Crizotinib
Crizotinib +LY2157299
H3122
B
shLKO
shMED12#3
shMED12#5
Ctrl
LY2157299
Gefitinib
Gefitinib +LY2157299
PC9

Fig. 36

HGNC Symbol	UniGene Id	Oligo ID	TRC Kinome Pool 12oct10
PDK3	Hs.658190	TRCN0000000259	#1
PDK3	Hs.658190	TRCN0000000260	#1
PDK3	Hs.658190	TRCN0000000262	#1
ACVRL1	Hs.591026	TRCN0000000354	#1
ACVRL1	Hs.591026	TRCN0000000356	#1
ACVRL1	Hs.591026	TRCN0000000357	#1
BTK	Hs.159494	TRCN0000000359	#1
BTK	Hs.159494	TRCN0000000360	#1
BTK	Hs.159494	TRCN0000000361	#1
CDK4	Hs.95577	TRCN0000000362	#1
CDK4	Hs.95577	TRCN0000000363	#1
CDK4	Hs.95577	TRCN0000000364	#1
FGFR2	Hs.533683	TRCN0000000367	#1
FGFR2	Hs.533683	TRCN0000000368	#1
FGFR2	Hs.533683	TRCN0000000369	#1
FGFR2	Hs.533683	TRCN0000000370	#1
FGFR3	Hs.1420	TRCN0000000371	#1
FGFR3	Hs.1420	TRCN0000000374	#1
GUCY2D	Hs.592109	TRCN0000000375	#1
GUCY2D	Hs.592109	TRCN0000000378	#1
INSR	Hs.465744	TRCN0000000380	#1
INSR	Hs.465744	TRCN0000000381	#1
JAK3	Hs.515247	TRCN0000000383	#1
JAK3	Hs.515247	TRCN0000000385	#1
JAK3	Hs.515247	TRCN0000000386	#1
JAK3	Hs.515247	TRCN0000000387	#1
KIT	Hs.479754	TRCN0000000388	#1
KIT	Hs.479754	TRCN0000000389	#1
KIT	Hs.479754	TRCN0000000390	#1
KIT	Hs.479754	TRCN0000000391	#1
KIT	Hs.479754	TRCN0000000392	#1
MET	Hs.132966	TRCN0000000393	#1
MET	Hs.132966	TRCN0000000394	#1
MET	Hs.132966	TRCN0000000395	#1
MET	Hs.132966	TRCN0000000396	#1
MET	Hs.132966	TRCN0000000397	#1
PHKG2	Hs.196177	TRCN0000000398	#1
PHKG2	Hs.196177	TRCN0000055433	#1
PHKG2	Hs.196177	TRCN0000000399	#1
PHKG2	Hs.196177	TRCN0000000400	#1
PHKG2	Hs.196177	TRCN0000000401	#1
RET	Hs.350321	TRCN0000000402	#1
RET	Hs.350321	TRCN0000000403	#1
RET	Hs.350321	TRCN0000000404	#1
RET	Hs.350321	TRCN0000000405	#1
RET	Hs.350321	TRCN0000000406	#1
STK11	Hs.515005	TRCN0000000407	#1
STK11	Hs.515005	TRCN0000000408	#1
STK11	Hs.515005	TRCN0000000409	#1
STK11	Hs.515005	TRCN0000000410	#1
STK11	Hs.515005	TRCN0000000411	#1
TEK	Hs.89640	TRCN0000000412	#1
TEK	Hs.89640	TRCN0000000413	#1
TEK	Hs.89640	TRCN0000000414	#1
TEK	Hs.89640	TRCN0000000415	#1
TEK	Hs.89640	TRCN0000000416	#1
FGFR1	Hs.264887	TRCN0000000417	#1
FGFR1	Hs.264887	TRCN0000000418	#1
FGFR1	Hs.264887	TRCN0000000419	#1
FGFR1	Hs.264887	TRCN0000000420	#1
FGFR1	Hs.264887	TRCN0000000421	#1
IGF1R	Hs.643120	TRCN0000000422	#1
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IGF1R	Hs.643120	TRCN0000000424	#1
IGF1R	Hs.643120	TRCN0000000425	#1
IGF1R	Hs.643120	TRCN0000000426	#1
NPR2	Hs.78518	TRCN0000000427	#1
NPR2	Hs.78518	TRCN0000000428	#1
NPR2	Hs.78518	TRCN0000000429	#1
NPR2	Hs.78518	TRCN0000000430	#1
ZAP70	Hs.234569	TRCN0000000436	#1
ZAP70	Hs.234569	TRCN0000000437	#1
ZAP70	Hs.234569	TRCN0000000438	#1
ZAP70	Hs.234569	TRCN0000000439	#1
ZAP70	Hs.234569	TRCN0000000440	#1
ACVR1	Hs.470316	TRCN0000000441	#1
ACVR1	Hs.470316	TRCN0000000442	#1
ACVR1	Hs.470316	TRCN0000000443	#1
ABL1	Hs.431048	TRCN0000000792	#1
ACVR1	Hs.470316	TRCN0000000444	#1
ACVR1	Hs.470316	TRCN0000000445	#1
ACVR2B	Hs.174273	TRCN0000000447	#1
ACVR2B	Hs.174273	TRCN0000000448	#1
ACVR2B	Hs.174273	TRCN0000000450	#1
BMPR1B	Hs.598475	TRCN0000000451	#1
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BMPR1B	Hs.598475	TRCN0000000455	#1
BMPR2	Hs.471119	TRCN0000000456	#1
BMPR2	Hs.471119	TRCN0000000457	#1
BMPR2	Hs.471119	TRCN0000000458	#1
BMPR2	Hs.471119	TRCN0000000459	#1
BMPR2	Hs.471119	TRCN0000000460	#1
BUB1B	Hs.631699	TRCN0000000461	#1
BUB1B	Hs.631699	TRCN0000000462	#1
BUB1B	Hs.631699	TRCN0000000463	#1
BUB1B	Hs.631699	TRCN0000000464	#1
BUB1B	Hs.631699	TRCN0000000465	#1
CAMK2B	Hs.351887	TRCN0000000466	#1
CAMK2B	Hs.351887	TRCN0000000467	#1
CAMK2B	Hs.351887	TRCN0000000468	#1
CAMK2B	Hs.351887	TRCN0000000469	#1
CAMK2B	Hs.351887	TRCN0000000470	#1
CAMK2D	Hs.144114	TRCN0000000471	#1
CAMK2D	Hs.144114	TRCN0000000472	#1
CAMK2D	Hs.144114	TRCN0000000473	#1
CAMK2D	Hs.144114	TRCN0000000474	#1
CAMK2D	Hs.144114	TRCN0000000475	#1
CAMK2G	Hs.523045	TRCN0000000476	#1
CAMK2G	Hs.523045	TRCN0000000477	#1
CAMK2G	Hs.523045	TRCN0000000478	#1
CAMK2G	Hs.523045	TRCN0000000479	#1
CAMK2G	Hs.523045	TRCN0000000480	#1
CDK3	Hs.706766	TRCN0000000481	#1
CDK3	Hs.706766	TRCN0000000482	#1
CDK3	Hs.706766	TRCN0000000483	#1
CDK3	Hs.706766	TRCN0000000484	#1
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CDK6	Hs.119882	TRCN0000055435	#1
CDK6	Hs.119882	TRCN0000000487	#1
CDK6	Hs.119882	TRCN0000000488	#1
CDK8	Hs.382306	TRCN0000000489	#1
CDK8	Hs.382306	TRCN0000000490	#1
CDK8	Hs.382306	TRCN0000000491	#1
CDK8	Hs.382306	TRCN0000000492	#1
CDK8	Hs.382306	TRCN0000000493	#1
CDK9	Hs.150423	TRCN0000000494	#1
CDK9	Hs.150423	TRCN0000000495	#1
CDK9	Hs.150423	TRCN0000000496	#1
CDK9	Hs.150423	TRCN0000000497	#1
CDK9	Hs.150423	TRCN0000000498	#1
CHEK1	Hs.24529	TRCN0000000499	#1
CHEK1	Hs.24529	TRCN0000000500	#1
CHEK1	Hs.24529	TRCN0000000501	#1
CHEK1	Hs.24529	TRCN0000000502	#1
CHEK1	Hs.24529	TRCN0000000503	#1
CHUK	Hs.198998	TRCN0000000504	#1
CHUK	Hs.198998	TRCN0000000505	#1
CHUK	Hs.198998	TRCN0000000506	#1
CHUK	Hs.198998	TRCN0000000507	#1
CHUK	Hs.198998	TRCN0000000508	#1
MAPK14	Hs.485233	TRCN0000000509	#1
MAPK14	Hs.485233	TRCN0000000510	#1
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DGKG	Hs.683449	TRCN0000000514	#1
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DGKG	Hs.683449	TRCN0000000516	#1
DGKG	Hs.683449	TRCN0000000517	#1
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DAPK3	Hs.631844	TRCN0000000521	#1
DAPK3	Hs.631844	TRCN0000000522	#1
DYRK1A	Hs.719269	TRCN0000000523	#1
DYRK1A	Hs.719269	TRCN0000000524	#1
DYRK1A	Hs.719269	TRCN0000000525	#1
DYRK1A	Hs.719269	TRCN0000000526	#1
DYRK1A	Hs.719269	TRCN0000000527	#1
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ERN1	Hs.700027	TRCN0000000529	#1
ERN1	Hs.700027	TRCN0000000530	#1
ERN1	Hs.700027	TRCN0000000531	#1
ERN1	Hs.700027	TRCN0000000532	#1
GUCY2F	Hs.123074	TRCN0000000533	#1
GUCY2F	Hs.123074	TRCN0000000534	#1
GUCY2F	Hs.123074	TRCN0000000535	#1
GUCY2F	Hs.123074	TRCN0000000536	#1
GUCY2F	Hs.123074	TRCN0000000537	#1
IRAK1	Hs.522819	TRCN0000000563	#1

HGNC Symbol	UniGene Id	Oligo ID	TRC Kinome Pool 12oct10
IRAK1	Hs.522819	TRCN0000000544	# 1
IRAK1	Hs.522819	TRCN0000000545	# 1
IRAK1	Hs.522819	TRCN0000000546	# 1
IRAK1	Hs.522819	TRCN0000000547	# 1
IRAK2	Hs.449207	TRCN0000000548	# 1
IRAK2	Hs.449207	TRCN0000000549	# 1
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IRAK2	Hs.449207	TRCN0000000551	# 1
ACVR2A	Hs.470174	TRCN0000000552	# 1
ACVR2A	Hs.470174	TRCN0000000553	# 1
ACVR2A	Hs.470174	TRCN0000000555	# 1
ACVR2A	Hs.470174	TRCN0000000556	# 1
ADRBK1	Hs.83636	TRCN0000000557	# 1
ADRBK1	Hs.83636	TRCN0000000558	# 1
ADRBK1	Hs.83636	TRCN0000000559	# 1
ADRBK1	Hs.83636	TRCN0000000560	# 1
ADRBK1	Hs.83636	TRCN0000000561	# 1
AKT2	Hs.631535	TRCN0000000562	# 1
AKT2	Hs.631535	TRCN0000000563	# 1
AKT2	Hs.631535	TRCN0000000564	# 1
AKT2	Hs.631535	TRCN0000000565	# 1
AKT2	Hs.631535	TRCN0000000566	# 1
ARAF	Hs.446641	TRCN0000000567	# 1
ARAF	Hs.446641	TRCN0000000568	# 1
ARAF	Hs.446641	TRCN0000000569	# 1
ARAF	Hs.446641	TRCN0000000570	# 1
ARAF	Hs.446641	TRCN0000000571	# 1
AXL	Hs.590970	TRCN0000000572	# 1
AXL	Hs.590970	TRCN0000000573	# 1
AXL	Hs.590970	TRCN0000000574	# 1
AXL	Hs.590970	TRCN0000000575	# 1
AXL	Hs.590970	TRCN0000000576	# 1
CAMK4	Hs.591269	TRCN0000000577	# 1
CAMK4	Hs.591269	TRCN0000000578	# 1
CAMK4	Hs.591269	TRCN0000000579	# 1
CAMK4	Hs.591269	TRCN0000000580	# 1
CAMK4	Hs.591269	TRCN0000000581	# 1
CDC2	Hs.334562	TRCN0000000582	# 1
CDC2	Hs.334562	TRCN0000000583	# 1
CDC2	Hs.334562	TRCN0000000584	# 1
CDC2	Hs.334562	TRCN0000000585	# 1
CDC2	Hs.334562	TRCN0000000586	# 1
CDK2	Hs.19192	TRCN0000000587	# 1
CDK2	Hs.19192	TRCN0000000588	# 1
CDK2	Hs.19192	TRCN0000000589	# 1
CDK2	Hs.19192	TRCN0000000590	# 1
CDK2	Hs.19192	TRCN0000000591	# 1
CDK7	Hs.184298	TRCN0000000592	# 1
CDK7	Hs.184298	TRCN0000000593	# 1
CDK7	Hs.184298	TRCN0000000594	# 1
CDK7	Hs.184298	TRCN0000000595	# 1
CDK7	Hs.184298	TRCN0000000596	# 1
CSNK1D	Hs.631725	TRCN0000000597	# 1
CSNK1D	Hs.631725	TRCN0000000598	# 1
CSNK1D	Hs.631725	TRCN0000000599	# 1
CSNK1D	Hs.631725	TRCN0000000600	# 1
CSNK1D	Hs.631725	TRCN0000000601	# 1
CSNK1E	Hs.474833	TRCN0000000602	# 1
CSNK1E	Hs.474833	TRCN0000055427	# 1
CSNK1E	Hs.474833	TRCN0000000603	# 1
CSNK1E	Hs.474833	TRCN0000000604	# 1
CSNK1E	Hs.474833	TRCN0000000605	# 1
CSNK2A1	Hs.644056	TRCN0000000606	# 1
CSNK2A1	Hs.644056	TRCN0000000607	# 1
CSNK2A1	Hs.644056	TRCN0000000608	# 1
CSNK2A1	Hs.644056	TRCN0000000609	# 1
CSNK2A1	Hs.644056	TRCN0000000610	# 1
CSNK2A1	Hs.644056	TRCN0000000611	# 1
CSNK2A1	Hs.644056	TRCN0000000612	# 1
CSNK2A1	Hs.644056	TRCN0000000613	# 1
CSNK2A1	Hs.644056	TRCN0000000614	# 1
CSNK2A1	Hs.644056	TRCN0000000615	# 1
DDR1	Hs.631988	TRCN0000000616	# 1
DDR1	Hs.631988	TRCN0000055436	# 1
DDR1	Hs.631988	TRCN0000000617	# 1
DDR1	Hs.631988	TRCN0000000618	# 1
ERBB3	Hs.118681	TRCN0000000619	# 1
ERBB3	Hs.118681	TRCN0000000620	# 1
ERBB3	Hs.118681	TRCN0000000621	# 1
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FES	Hs.7636	TRCN0000000624	# 1
FES	Hs.7636	TRCN0000000625	# 1
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FGFR4	Hs.165950	TRCN0000000628	# 1
FGFR4	Hs.165950	TRCN0000000629	# 1
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FLT1	Hs.654360	TRCN0000000634	# 1
FLT1	Hs.654360	TRCN0000000635	# 1
FLT4	Hs.646917	TRCN0000000636	# 1
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FLT4	Hs.646917	TRCN0000000638	# 1
FLT4	Hs.646917	TRCN0000000639	# 1
FLT4	Hs.646917	TRCN0000000640	# 1
STK24	Hs.508514	TRCN0000000641	# 1
STK24	Hs.508514	TRCN0000000642	# 1
STK24	Hs.508514	TRCN0000000643	# 1
STK24	Hs.508514	TRCN0000000644	# 1
STK24	Hs.508514	TRCN0000000645	# 1
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DYRK3	Hs.164267	TRCN0000000647	# 1
DYRK3	Hs.164267	TRCN0000000648	# 1
DYRK3	Hs.164267	TRCN0000000649	# 1
DYRK2	Hs.173135	TRCN0000000650	# 1
DYRK2	Hs.173135	TRCN0000000651	# 1
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DYRK2	Hs.173135	TRCN0000000653	# 1
DYRK2	Hs.173135	TRCN0000000654	# 1
AURKA	Hs.250822	TRCN0000000655	# 1
AURKA	Hs.250822	TRCN0000000656	# 1
AURKA	Hs.250822	TRCN0000000657	# 1
AURKA	Hs.250822	TRCN0000000658	# 1
CDC42BPA	Hs.35433	TRCN0000000659	# 1
CDC42BPA	Hs.35433	TRCN0000000660	# 1
CDC42BPA	Hs.35433	TRCN0000000661	# 1
CDC42BPA	Hs.35433	TRCN0000000662	# 1
CDC42BPA	Hs.35433	TRCN0000000663	# 1
MAP4K3	Hs.655750	TRCN0000000664	# 1
MAP4K3	Hs.655750	TRCN0000000665	# 1
MAP4K3	Hs.655750	TRCN0000000666	# 1
MAP4K3	Hs.655750	TRCN0000000667	# 1
DGKZ	Hs.502461	TRCN0000000668	# 1
DGKZ	Hs.502461	TRCN0000000669	# 1
DGKZ	Hs.502461	TRCN0000000670	# 1
DGKD	Hs.471675	TRCN0000000671	# 1
DGKD	Hs.471675	TRCN0000000672	# 1
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DGKD	Hs.471675	TRCN0000000674	# 1
DGKD	Hs.471675	TRCN0000000675	# 1
CAMK1	Hs.434875	TRCN0000000676	# 1
CAMK1	Hs.434875	TRCN0000000677	# 1
CAMK1	Hs.434875	TRCN0000055430	# 1
CAMK1	Hs.434875	TRCN0000000678	# 1
CAMK1	Hs.434875	TRCN0000000679	# 1
MAPKAPK5	Hs.413901	TRCN0000000680	# 1
MAPKAPK5	Hs.413901	TRCN0000000681	# 1
MAPKAPK5	Hs.413901	TRCN0000000682	# 1
MAPKAPK5	Hs.413901	TRCN0000000683	# 1
MAPKAPK5	Hs.413901	TRCN0000000684	# 1
CDK10	Hs.699177	TRCN0000000685	# 1
CDK10	Hs.699177	TRCN0000000686	# 1
CDK10	Hs.699177	TRCN0000000687	# 1
CDK10	Hs.699177	TRCN0000000688	# 1
CDK10	Hs.699177	TRCN0000000689	# 1
CASK	Hs.495984	TRCN0000000690	# 1
CASK	Hs.495984	TRCN0000000691	# 1
CASK	Hs.495984	TRCN0000000692	# 1
CASK	Hs.495984	TRCN0000000693	# 1
CASK	Hs.495984	TRCN0000000694	# 1
STK16	Hs.153003	TRCN0000000695	# 1
STK16	Hs.153003	TRCN0000000696	# 1
STK16	Hs.153003	TRCN0000000697	# 1
STK16	Hs.153003	TRCN0000000698	# 1
STK16	Hs.153003	TRCN0000000699	# 1
CDC2L5	Hs.233552	TRCN0000000700	# 1
CDC2L5	Hs.233552	TRCN0000000701	# 1
CDC2L5	Hs.233552	TRCN0000000702	# 1
CDC2L5	Hs.233552	TRCN0000000703	# 1
CDC2L5	Hs.233552	TRCN0000000704	# 1
RIPK1	Hs.519842	TRCN0000000705	# 1
RIPK1	Hs.519842	TRCN0000000706	# 1
RIPK1	Hs.519842	TRCN0000000707	# 1
RIPK1	Hs.519842	TRCN0000000708	# 1
RIPK1	Hs.519842	TRCN0000000709	# 1
DYRK4	Hs.439530	TRCN0000000710	# 1
DYRK4	Hs.439530	TRCN0000000711	# 1
DYRK4	Hs.439530	TRCN0000000712	# 1
DYRK4	Hs.439530	TRCN0000000713	# 1
PRPF4B	Hs.159014	TRCN0000000719	# 1
PRPF4B	Hs.159014	TRCN0000000720	# 1
PRPF4B	Hs.159014	TRCN0000000721	# 1

HGNC Symbol	UniGene Id	Oligo ID	TRC Kinome Pool 12oct10
PRPF4B	Hs.159014	TRCN0000000722	#1
PRPF4B	Hs.159014	TRCN0000000723	#1
CDKL2	Hs.591698	TRCN0000000724	#1
CDKL2	Hs.591698	TRCN0000000725	#1
CDKL2	Hs.591698	TRCN0000009726	#1
CDKL2	Hs.591698	TRCN0000000727	#1
CDKL2	Hs.591698	TRCN0000000728	#1
RPS6KB2	Hs.534345	TRCN0000000729	#1
RPS6KB2	Hs.534345	TRCN0000000730	#1
MAP3K14	Hs.404183	TRCN0000000731	#1
MAP3K14	Hs.404183	TRCN0000000732	#1
MAP3K14	Hs.404183	TRCN0000000733	#1
MAP3K14	Hs.404183	TRCN0000000734	#1
BRSK2	Hs.170819	TRCN0000000735	#1
BRSK2	Hs.170819	TRCN0000000736	#1
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BRSK2	Hs.170819	TRCN0000000738	#1
BRSK2	Hs.170819	TRCN0000000739	#1
TNK1	Hs.203420	TRCN0000000740	#1
TNK1	Hs.203420	TRCN0000000742	#1
TNK1	Hs.203420	TRCN0000000743	#1
TNK1	Hs.203420	TRCN0000000744	#1
CLK3	Hs.584748	TRCN0000000745	#1
CLK3	Hs.584748	TRCN0000000746	#1
CLK3	Hs.584748	TRCN0000000747	#1
CLK3	Hs.584748	TRCN0000000748	#1
CLK3	Hs.584748	TRCN0000000749	#1
CLK2	Hs.73986	TRCN0000000750	#1
CLK2	Hs.73986	TRCN0000010543	#1
CLK2	Hs.73986	TRCN0000000751	#1
CLK2	Hs.73986	TRCN0000000752	#1
CLK2	Hs.73986	TRCN0000000753	#1
CLK1	Hs.433732	TRCN0000000754	#1
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CLK1	Hs.433732	TRCN0000000756	#1
CLK1	Hs.433732	TRCN0000000757	#1
CLK1	Hs.433732	TRCN0000000758	#1
PLK3	Hs.632415	TRCN0000000759	#1
PLK3	Hs.632415	TRCN0000000760	#1
PLK3	Hs.632415	TRCN0000000761	#1
PLK3	Hs.632415	TRCN0000000762	#1
PLK3	Hs.632415	TRCN0000000763	#1
DGKB	Hs.567255	TRCN0000000764	#1
DGKB	Hs.567255	TRCN0000000765	#1
DGKB	Hs.567255	TRCN0000000766	#1
DGKB	Hs.567255	TRCN0000000767	#1
DGKB	Hs.567255	TRCN0000000768	#1
PTK2B	Hs.491322	TRCN0000000769	#1
PTK2B	Hs.491322	TRCN0000000770	#1
PTK2B	Hs.491322	TRCN0000000771	#1
FLT3	Hs.507590	TRCN0000000772	#1
FLT3	Hs.507590	TRCN0000000773	#1
FLT3	Hs.507590	TRCN0000000775	#1
AURKB	Hs.442658	TRCN0000000776	#1
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STK17B	Hs.88297	TRCN0000000780	#1
STK17B	Hs.88297	TRCN0000000781	#1
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BMPR1A	Hs.524477	TRCN0000000794	#1
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BUB1	Hs.469649	TRCN0000000800	#1
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BUB1	Hs.469649	TRCN0000000802	#1
CSK	Hs.77793	TRCN0000000803	#1
CSK	Hs.77793	TRCN0000000804	#1
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CSNK1G3	Hs.129206	TRCN0000000808	#1
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LIMK1	Hs.647035	TRCN0000000826	#1
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MAPK13	Hs.178695	TRCN0000055428	#1
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PRKCE	Hs.580351	TRCN0000000846	#1
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MAP3K4	Hs.390428	TRCN0000000849	#1
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PRKAA1	Hs.43322	TRCN0000000857	#1
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IRAK3	Hs.369265	TRCN0000000875	#1
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PIK3R4	Hs.149032	TRCN0000000885	#1
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ULK2	Hs.168762	TRCN0000000889	#1
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SLK	Hs.591922	TRCN0000000894	#1
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SLK	Hs.591922	TRCN0000000896	#1
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SLK	Hs.591922	TRCN0000000898	#2
NUAK1	Hs.719171	TRCN0000000899	#2
NUAK1	Hs.719171	TRCN0000000900	#2
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VRK3	Hs.443330	TRCN0000000909	#2
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VRK3	Hs.443330	TRCN0000000912	#2
BMP2K	Hs.146551	TRCN0000000913	#2
BMP2K	Hs.146551	TRCN0000000914	#2
BMP2K	Hs.146551	TRCN0000000915	#2
BMP2K	Hs.146551	TRCN0000000916	#2
BMP2K	Hs.146551	TRCN0000000917	#2
WNK1	Hs.709894	TRCN0000000918	#2
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MYLK	Hs.477375	TRCN0000000936	#2
MYLK	Hs.477375	TRCN0000000937	#2
SRM	Hs.76244	TRCN0000000938	#2
SRM	Hs.76244	TRCN0000000939	#2
SRM	Hs.76244	TRCN0000000940	#2
SRM	Hs.76244	TRCN0000000941	#2
SRM	Hs.76244	TRCN0000000942	#2
MAPK9	Hs.484371	TRCN0000000943	#2
MAPK9	Hs.484371	TRCN0000000944	#2
MAPK9	Hs.484371	TRCN0000000945	#2
MAPK9	Hs.484371	TRCN0000000946	#2
MAPK9	Hs.484371	TRCN0000000947	#2
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NEK2	Hs.153704	TRCN0000000952	#2
ROS1	Hs.1041	TRCN0000000953	#2
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ROS1	Hs.1041	TRCN0000000955	#2
ROS1	Hs.1041	TRCN0000000956	#2
ROS1	Hs.1041	TRCN0000000957	#2
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ILK	Hs.706355	TRCN0000000971	#2
ILK	Hs.706355	TRCN0000000972	#2
STK17A	Hs.709489	TRCN0000000973	#2
STK17A	Hs.709489	TRCN0000000974	#2
STK17A	Hs.709489	TRCN0000000975	#2
STK17A	Hs.709489	TRCN0000000976	#2
ROCK2	Hs.591600	TRCN0000000977	#2
ROCK2	Hs.591600	TRCN0000000978	#2
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GRK4	Hs.32959	TRCN0000000989	#2
GRK4	Hs.32959	TRCN0000000990	#2
MAP3K5	Hs.186486	TRCN0000000991	#2
MAP3K5	Hs.186486	TRCN0000000992	#2
MAP3K5	Hs.186486	TRCN0000000993	#2
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PRKG1	Hs.654556	TRCN0000000996	#2
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PRKG1	Hs.654556	TRCN0000055432	#2
MAP3K12	Hs.713539	TRCN0000000999	#2
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MAP3K12	Hs.713539	TRCN0000001003	#2
PASK	Hs.397891	TRCN0000001004	#2
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PASK	Hs.397891	TRCN0000001008	#2
MAPK9	Hs.484371	TRCN0000001013	#2
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MAPK9	Hs.484371	TRCN0000001015	#2
MAPK9	Hs.484371	TRCN0000001016	#2
MAPK10	Hs.125503	TRCN0000001017	#2
MAPK10	Hs.125503	TRCN0000001018	#2
MAPK10	Hs.125503	TRCN0000001019	#2
MAPK10	Hs.125503	TRCN0000001020	#2
MAPK10	Hs.125503	TRCN0000001021	#2
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MAPK8	Hs.138211	TRCN0000001055	#2
MAPK8	Hs.138211	TRCN0000001056	#2
MAPK8	Hs.138211	TRCN0000001057	#2
RAF1	Hs.159130	TRCN0000001064	#2
RAF1	Hs.159130	TRCN0000001065	#2
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PRKCZ	Hs.496255	TRCN0000001219	#2
PRKCZ	Hs.496255	TRCN0000001220	#2
PRKCZ	Hs.496255	TRCN0000001221	#2
PRKCZ	Hs.496255	TRCN0000001222	#2
SRPK1	Hs.443861	TRCN0000001230	#2
SRPK1	Hs.443861	TRCN0000001232	#2
NPR2	Hs.78518	TRCN0000001312	#2
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NPR2	Hs.78518	TRCN0000001314	#2
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PKN3	Hs.300485	TRCN0000001321	#2
PKN3	Hs.300485	TRCN0000001322	#2
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CLK4	Hs.406557	TRCN0000001350	#2
CLK4	Hs.406557	TRCN0000001352	#2
CLK4	Hs.406557	TRCN0000010605	#2
MAPK7	Hs.150136	TRCN0000001354	#2
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MAPK7	Hs.150136	TRCN0000001355	#2
DGKH	Hs.659437	TRCN0000001357	#2
DGKH	Hs.659437	TRCN0000001358	#2
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GRK6	Hs.235116	TRCN0000001367	#2
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PRKACA	Hs.631630	TRCN0000001371	#2
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MAPK4	Hs.433728	TRCN0000001376	#2
MAPK4	Hs.433728	TRCN0000001378	#2
EIF2AK1	Hs.719136	TRCN0000001381	#2
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EIF2AK1	Hs.719136	TRCN0000001383	#2
RPS6KA1	Hs.149957	TRCN0000001384	#2
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RPS6KA1	Hs.149957	TRCN0000001387	#2
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MAP2K4	Hs.514681	TRCN0000001389	#2
MAP2K4	Hs.514681	TRCN0000001390	#2
MAP2K4	Hs.514681	TRCN0000001391	#2
MAP2K4	Hs.514681	TRCN0000001392	#2
MAP2K4	Hs.514681	TRCN0000001393	#2
RPS6KA3	Hs.445387	TRCN0000001394	#2
RPS6KA3	Hs.445387	TRCN0000001395	#2
RPS6KA3	Hs.445387	TRCN0000001396	#2
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HGNC Symbol	UniGene Id	Oligo ID	TRC Kinome Pool 12oct10
RPS6KA3	Hs.445387	TRCN0000001398	# 2
EIF2AK3	Hs.591589	TRCN0000001399	# 2
EIF2AK3	Hs.591589	TRCN0000001400	# 2
EIF2AK3	Hs.591589	TRCN0000001401	# 2
EIF2AK3	Hs.591589	TRCN0000001402	# 2
EIF2AK3	Hs.591589	TRCN0000001403	# 2
ERBB4	Hs.390729	TRCN0000001407	# 2
ERBB4	Hs.390729	TRCN0000001408	# 2
ERBB4	Hs.390729	TRCN0000001409	# 2
ERBB4	Hs.390729	TRCN0000001410	# 2
PRKD3	Hs.660757	TRCN0000001412	# 2
PRKD3	Hs.660757	TRCN0000001414	# 2
PRKD3	Hs.660757	TRCN0000001415	# 2
DDR2	Hs.593833	TRCN0000001418	# 2
DDR2	Hs.593833	TRCN0000001419	# 2
DDR2	Hs.593833	TRCN0000001420	# 2
DDR2	Hs.593833	TRCN0000001421	# 2
PDGFRA	Hs.74615	TRCN0000001422	# 2
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KALRN	Hs.8004	TRCN0000001427	# 2
KALRN	Hs.8004	TRCN0000001428	# 2
KALRN	Hs.8004	TRCN0000001429	# 2
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KALRN	Hs.8004	TRCN0000001431	# 2
TESK2	Hs.591499	TRCN0000001433	# 2
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NRBP1	Hs.515876	TRCN0000001437	# 2
NRBP1	Hs.515876	TRCN0000001439	# 2
NRBP1	Hs.515876	TRCN0000001440	# 2
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TAOK2	Hs.291623	TRCN0000001442	# 2
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TAOK2	Hs.291623	TRCN0000001445	# 2
CAMK1G	Hs.199068	TRCN0000001452	# 2
CAMK1G	Hs.199068	TRCN0000001453	# 2
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MAP2K5	Hs.114198	TRCN0000001466	# 2
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PDK1	Hs.470633	TRCN0000001476	# 2
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GRK1	Hs.103501	TRCN0000001486	# 2
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ABL1	Hs.431048	TRCN0000001499	# 2
ABL1	Hs.431048	TRCN0000001500	# 2
ABL1	Hs.431048	TRCN0000001502	# 2
PRKG2	Hs.570833	TRCN0000001507	# 2
PRKG2	Hs.570833	TRCN0000001509	# 2
PRKG2	Hs.570833	TRCN0000001510	# 2
PRKG2	Hs.570833	TRCN0000001511	# 2
SGK2	Hs.300863	TRCN0000001518	# 2
SGK2	Hs.300863	TRCN0000001520	# 2
TAOK3	Hs.644420	TRCN0000001527	# 2
TAOK3	Hs.644420	TRCN0000001528	# 2
TAOK3	Hs.644420	TRCN0000001529	# 2
WNK3	Hs.92423	TRCN0000001531	# 2
WNK3	Hs.92423	TRCN0000001532	# 2
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TRIB1	Hs.444947	TRCN0000001535	# 2
TRIB1	Hs.444947	TRCN0000001536	# 2
TRIB1	Hs.444947	TRCN0000001537	# 2
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SGK196	Hs.491646	TRCN0000001542	# 2
SGK196	Hs.491646	TRCN0000001543	# 2
CSNK1D	Hs.631725	TRCN0000001551	# 2
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MAP3K7	Hs.719192	TRCN0000001554	# 2
MAP3K7	Hs.719192	TRCN0000001555	# 2
MAP3K7	Hs.719192	TRCN0000001556	# 2
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MARK3	Hs.35828	TRCN0000001564	# 2
MARK3	Hs.35828	TRCN0000001565	# 2
MAPK6	Hs.411847	TRCN0000001568	# 2
MAPK6	Hs.411847	TRCN0000001569	# 2
MAPK6	Hs.411847	TRCN0000001570	# 2
RYK	Hs.654562	TRCN0000001573	# 2
RYK	Hs.654562	TRCN0000001574	# 2
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MARK2	Hs.567261	TRCN0000001584	# 2
MARK2	Hs.567261	TRCN0000001585	# 2
OXSR1	Hs.475970	TRCN0000001587	# 2
OXSR1	Hs.475970	TRCN0000001588	# 2
OXSR1	Hs.475970	TRCN0000001589	# 2
CSF1R	Hs.586219	TRCN0000001590	# 2
CSF1R	Hs.586219	TRCN0000001591	# 2
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LCK	Hs.470627	TRCN0000001600	# 2
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TIE1	Hs.78824	TRCN0000001602	# 2
TIE1	Hs.78824	TRCN0000001603	# 2
TIE1	Hs.78824	TRCN0000001604	# 2
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YES1	Hs.194148	TRCN0000001608	# 2
YES1	Hs.194148	TRCN0000001609	# 2
YES1	Hs.194148	TRCN0000001610	# 2
YES1	Hs.194148	TRCN0000001611	# 2
AKT3	Hs.498293	TRCN0000001612	# 2
AKT3	Hs.498292	TRCN0000001613	# 2
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MELK	Hs.184339	TRCN0000001642	# 2
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WEE1	Hs.249441	TRCN0000001704	# 2
MOS	Hs.533432	TRCN0000001705	# 2
MOS	Hs.533432	TRCN0000001707	# 2
PSKH1	Hs.513683	TRCN0000001708	# 2

HGNC Symbol	UniGene Id	Oligo ID	TRC Kinome Pool 12oct10
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PSKH1	Hs.513683	TRCN0000001712	# 2
RAGE	Hs.104119	TRCN0000001713	# 2
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MAST2	Hs.319481	TRCN0000001736	# 2
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CAMK1D	Hs.659517	TRCN0000001753	# 2
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EPHA6	Hs.653244	TRCN0000001771	# 2
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MAPK10	Hs.125503	TRCN0000001940	# 3
MAPK10	Hs.125503	TRCN0000001941	# 3
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PRKD2	Hs.466987	TRCN0000001949	# 3
PRKD2	Hs.466987	TRCN0000001950	# 3
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DCLK2	Hs.591683	TRCN0000001972	# 3
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CAMKK1	Hs.8417	TRCN0000001980	# 3
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CSNK2A1	Hs.644056	TRCN0000001986	# 3
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PDGFRB	Hs.509067	TRCN0000002000	# 3
PDGFRB	Hs.509067	TRCN0000002001	# 3
PRKACB	Hs.487325	TRCN0000002002	# 3
PRKACB	Hs.487325	TRCN0000002003	# 3

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PRKACB	Hs.487325	TRCN0000002006	#3
CDKL5	Hs.659851	TRCN0000002011	#3
CDKL5	Hs.659851	TRCN0000002012	#3
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CDKL5	Hs.659851	TRCN0000002014	#3
CDKL5	Hs.659851	TRCN0000002015	#3
EPHB6	Hs.380089	TRCN0000002016	#3
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EPHB6	Hs.380089	TRCN0000002018	#3
GUCY2C	Hs.524278	TRCN0000002019	#3
GUCY2C	Hs.524278	TRCN0000002020	#3
GUCY2C	Hs.524278	TRCN0000002021	#3
GUCY2C	Hs.524278	TRCN0000002022	#3
GUCY2C	Hs.524278	TRCN0000002023	#3
ROR1	Hs.654491	TRCN0000002024	#3
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MAP3K2	Hs.145605	TRCN0000002043	#3
MAP3K2	Hs.145605	TRCN0000002044	#3
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MAP3K2	Hs.145605	TRCN0000002047	#3
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IRAK4	Hs.138499	TRCN0000002064	#3
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STK35	Hs.100057	TRCN0000002091	#3
STK35	Hs.100057	TRCN0000002092	#3
STK35	Hs.100057	TRCN0000002093	#3
STK35	Hs.100057	TRCN0000002094	#3
STK35	Hs.100057	TRCN0000002095	#3
PFTK2	Hs.348711	TRCN0000002096	#3
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SGK2	Hs.300863	TRCN0000002110	#3
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SGK2	Hs.300863	TRCN0000002113	#3
PAK2	Hs.518530	TRCN0000002114	#3
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PIK3C2B	Hs.497487	TRCN0000002119	#3
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PIK3C2B	Hs.497487	TRCN0000002122	#3
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PRKD1	Hs.508999	TRCN0000002124	#3
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PRKD1	Hs.508999	TRCN0000002127	#3
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DYRK1B	Hs.130988	TRCN0000002142	#3
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DCLK1	Hs.507755	TRCN0000002144	#3
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PRKAA2	Hs.437039	TRCN0000002168	#3
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TNNI3K	Hs.480085	TRCN0000002192	#3
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MYO3A	Hs.662630	TRCN0000002197	#3
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ULK4	Hs.656192	TRCN0000002202	#3
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MAPK15	Hs.493169	TRCN0000002214	#3
CCRK	Hs.522274	TRCN0000002215	#3
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MATK	Hs.631845	TRCN0000002220	#3
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PAK1	Hs.435714	TRCN0000002224	#3
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PAK1	Hs.435714	TRCN0000002226	#3
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PIK3C2A	Hs.175343	TRCN0000002228	#3
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PIK3C2A	Hs.175343	TRCN0000002231	#3
PIK3C2A	Hs.175343	TRCN0000002232	#3
GCK	Hs.1270	TRCN0000002233	#3
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GCK	Hs.1270	TRCN0000002235	#3
GCK	Hs.1270	TRCN0000002236	#3
GCK	Hs.1270	TRCN0000002237	#3
NTRK2	Hs.494312	TRCN0000002242	#3

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NTRK2	Hs.494312	TRCN0000002246	# 3
TESK1	Hs.708096	TRCN0000002247	# 3
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CDKL3	Hs.105818	TRCN0000002378	# 3
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FYN	Hs.390567	TRCN0000003097	# 3
FYN	Hs.390567	TRCN0000003098	# 3
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MAPK3	Hs.861	TRCN0000006152	#4
MAPKAPK3	Hs.234521	TRCN0000006153	#4
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STK25	Hs.516807	TRCN0000006269	#4
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STK25	Hs.516807	TRCN0000006271	#4
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TAF1	Hs.158560	TRCN0000006285	#4
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BRD2	Hs.75243	TRCN0000006311	#4
BRD2	Hs.75243	TRCN0000006312	#4
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CIT	Hs.119594	TRCN0000006314	#4
CIT	Hs.119594	TRCN0000006315	#4
CIT	Hs.119594	TRCN0000006316	#4
CIT	Hs.119594	TRCN0000006317	#4
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FASTK	Hs.647094	TRCN0000006321	#4
FASTK	Hs.647094	TRCN0000006322	#4
ICK	Hs.417022	TRCN0000006323	#4
ICK	Hs.417022	TRCN0000006324	#4
ICK	Hs.417022	TRCN0000006325	#4
ICK	Hs.417022	TRCN0000006326	#4
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MARK1	Hs.497806	TRCN0000006331	#4
MARK1	Hs.497806	TRCN0000006332	#4
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PRKY	Hs.632287	TRCN0000006343	#4
PRKX	Hs.390788	TRCN0000006344	#4
RIPK2	Hs.103755	TRCN0000006348	#4
RIPK2	Hs.103755	TRCN0000006349	#4
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RPS6KA2	Hs.719131	TRCN0000006352	#4
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TTK	Hs.169840	TRCN0000006357	#4
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BMX	Hs.495731	TRCN0000006361	#4
BMX	Hs.495731	TRCN0000006362	#4
BMX	Hs.495731	TRCN0000006363	#4
PKLR	Hs.95990	TRCN0000006383	#4
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PKLR	Hs.95990	TRCN0000006387	#4
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EPHA1	Hs.89839	TRCN0000006401	#4
EPHA1	Hs.89839	TRCN0000006402	#4
EPHA2	Hs.171596	TRCN0000006404	#4
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EPHA2	Hs.171596	TRCN0000006407	#4
EPHA3	Hs.123642	TRCN0000006409	#4
EPHA3	Hs.123642	TRCN0000006410	#4
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EPHB2	Hs.523329	TRCN0000006425	#4
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EPHB3	Hs.2913	TRCN0000006427	#4
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EPHB3	Hs.2913	TRCN0000006429	#4
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PTK7	Hs.90572	TRCN0000006431	#4
PTK7	Hs.90572	TRCN0000006433	#4
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STK36	Hs.471404	TRCN0000006989	#4
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CDC2L2	Hs.709182	TRCN0000006993	#4
CDC2L2	Hs.709182	TRCN0000006995	#4
HIPK4	Hs.79363	TRCN0000006996	#4
HIPK4	Hs.79363	TRCN0000006997	#4
HIPK4	Hs.79363	TRCN0000006998	#4
HIPK4	Hs.79363	TRCN0000006999	#4
HIPK4	Hs.79363	TRCN0000007000	#4
MAP2K2	Hs.465627	TRCN0000007006	#4
MAP2K2	Hs.465627	TRCN0000007007	#4
MAP2K2	Hs.465627	TRCN0000007008	#4
WNK4	Hs.105448	TRCN0000007020	#4
WNK4	Hs.105448	TRCN0000007021	#4
WNK4	Hs.105448	TRCN0000007022	#4
WNK4	Hs.105448	TRCN0000007023	#4
CSNK1A1L	Hs.512897	TRCN0000007024	#4
CSNK1A1L	Hs.512897	TRCN0000007025	#4
CSNK1A1L	Hs.512897	TRCN0000007026	#4
CSNK1A1L	Hs.512897	TRCN0000007027	#4
CSNK1A1L	Hs.512897	TRCN0000007028	#4
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LRRK1	Hs.407918	TRCN0000007040	#4
LRRK1	Hs.407918	TRCN0000007041	#4
STK32C	Hs.469002	TRCN0000007043	#4
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MGC16169	Hs.292986	TRCN0000007078	#4
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RPS6KL1	Hs.414481	TRCN0000007082	#4
RPS6KL1	Hs.414481	TRCN0000007083	#4
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MAP3K13	Hs.656069	TRCN0000007104	#4
MAP3K13	Hs.656069	TRCN0000007105	#4
MAP3K13	Hs.656069	TRCN0000007106	#4
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PAK7	Hs.32539	TRCN0000007108	#4
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MARK4	Hs.34314	TRCN0000007159	#4
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HIPK1	Hs.532363	TRCN0000007162	#4
HIPK1	Hs.532363	TRCN0000007163	#4
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NPR1	Hs.490330	TRCN0000007326	#4
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ADCK4	Hs.130712	TRCN0000007330	#4
ADCK4	Hs.130712	TRCN0000007331	#4
ADCK4	Hs.130712	TRCN0000007332	#4
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CDC2	Hs.334562	TRCN0000007923	#4
CDC2	Hs.334562	TRCN0000007924	#4
CDC2	Hs.334562	TRCN0000007925	#4
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MYLK4	Hs.127830	TRCN0000008902	#4
TRIM28	Hs.467408	TRCN0000017998	#4
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IKBKB	Hs.597664	TRCN0000018916	#4
IKBKB	Hs.597664	TRCN0000018917	#4
IKBKB	Hs.597664	TRCN0000018918	#4
IKBKB	Hs.597664	TRCN0000018919	#4
TEC	Hs.479670	TRCN0000019559	#4
TEC	Hs.479670	TRCN0000019560	#4
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TEC	Hs.479670	TRCN0000019562	#4
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PI4KA	Hs.529438	TRCN0000021199	#4
PI4KA	Hs.529438	TRCN0000021200	#4
PI4KA	Hs.529438	TRCN0000021201	#4
PI4KA	Hs.529438	TRCN0000021202	#4
PI4KA	Hs.529438	TRCN0000021203	#4
TRIM24	Hs.490287	TRCN0000021259	#4
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TRIM24	Hs.490287	TRCN0000021262	#4
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BRD3	Hs.522472	TRCN0000021374	#4
BRD3	Hs.522472	TRCN0000021375	#4
BRD3	Hs.522472	TRCN0000021376	#4
BRD3	Hs.522472	TRCN0000021377	#4
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EPHA10	Hs.129435	TRCN0000021384	#4
EPHA10	Hs.129435	TRCN0000021385	#4
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ALPK2	Hs.628152	TRCN0000021389	#4

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ALPK2	Hs.628152	TRCN0000021390	#4
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ALPK2	Hs.628152	TRCN0000021392	#4
ALPK2	Hs.628152	TRCN0000021395	#4
NRBP2	Hs.521926	TRCN0000021399	#4
NRBP2	Hs.521926	TRCN0000021400	#4
NRBP2	Hs.521926	TRCN0000021401	#4
NRBP2	Hs.521926	TRCN0000021402	#4
NRBP2	Hs.521926	TRCN0000021403	#4
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MAP3K15	Hs.713701	TRCN0000021405	#4
MAP3K15	Hs.713701	TRCN0000021406	#4
MAP3K15	Hs.713701	TRCN0000021407	#4
MAP3K15	Hs.713701	TRCN0000021408	#4
NEK5	Hs.672144	TRCN0000021409	#4
NEK5	Hs.672144	TRCN0000021410	#4
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EPHA6	Hs.653244	TRCN0000021418	#4
BRD4	Hs.187763	TRCN0000021424	#4
BRD4	Hs.187763	TRCN0000021425	#4
BRD4	Hs.187763	TRCN0000021426	#4
BRD4	Hs.187763	TRCN0000021427	#4
BRD4	Hs.187763	TRCN0000021428	#4
ERN2	Hs.592041	TRCN0000021429	#4
ERN2	Hs.592041	TRCN0000021430	#4
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ERN2	Hs.592041	TRCN0000021432	#4
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AATK	Hs.514575	TRCN0000021434	#4
AATK	Hs.514575	TRCN0000021435	#4
AATK	Hs.514575	TRCN0000021436	#4
AATK	Hs.514575	TRCN0000021437	#4
MAST3	Hs.466184	TRCN0000021438	#4
MAST3	Hs.466184	TRCN0000021440	#4
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MAST3	Hs.466184	TRCN0000021443	#4
BMPR1A	Hs.524477	TRCN0000021446	#4
BMPR1A	Hs.524477	TRCN0000021447	#4
BMPR1A	Hs.524477	TRCN0000021448	#4
MAST4	Hs.595458	TRCN0000021449	#4
MAST4	Hs.595458	TRCN0000021450	#4
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LRRK2	Hs.187636	TRCN0000021459	#4
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LRRK2	Hs.187636	TRCN0000021461	#4
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CDK5	Hs.647078	TRCN0000021464	#4
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ADCK5	Hs.283374	TRCN0000021482	#4
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LMTK3	Hs.207426	TRCN0000021484	#4
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LMTK3	Hs.207426	TRCN0000021486	#4
LMTK3	Hs.207426	TRCN0000021487	#4
LMTK3	Hs.207426	TRCN0000021488	#4
MAP3K9	Hs.593542	TRCN0000021494	#4
MAP3K9	Hs.593542	TRCN0000021495	#4
MAP3K9	Hs.593542	TRCN0000021496	#4
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ADCK1	Hs.413208	TRCN0000021499	#4
ADCK1	Hs.413208	TRCN0000021500	#4
ADCK1	Hs.413208	TRCN0000021501	#4
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CABC1	Hs.118241	TRCN0000021505	#4
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CABC1	Hs.118241	TRCN0000021507	#4
CABC1	Hs.118241	TRCN0000021508	#4
RPS6KA4	Hs.105584	TRCN0000021514	#4
RPS6KA4	Hs.105584	TRCN0000021515	#4
RPS6KA4	Hs.105584	TRCN0000021517	#4
RPS6KA4	Hs.105584	TRCN0000021518	#4
CDKL4	Hs.403201	TRCN0000021519	#4
CDKL4	Hs.403201	TRCN0000021520	#4
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GSG2	Hs.534059	TRCN0000021533	#5
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PTK6	Hs.51133	TRCN0000021549	#5
PTK6	Hs.51133	TRCN0000021550	#5
PTK6	Hs.51133	TRCN0000021551	#5
PTK6	Hs.51133	TRCN0000021552	#5
PTK6	Hs.51133	TRCN0000021553	#5
DCLK3	Hs.631907	TRCN0000021554	#5
DCLK3	Hs.631907	TRCN0000021555	#5
DCLK3	Hs.631907	TRCN0000021556	#5
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MAP3K11	Hs.502872	TRCN0000021567	#5
MAP3K11	Hs.502872	TRCN0000021568	#5
PNCK	Hs.436667	TRCN0000021569	#5
PNCK	Hs.436667	TRCN0000021570	#5
NEK1	Hs.481181	TRCN0000021580	#5
NEK1	Hs.481181	TRCN0000021581	#5
NEK1	Hs.481181	TRCN0000021582	#5
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CDK8	Hs.382306	TRCN0000023264	#5
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CSNK2A1	Hs.644056	TRCN0000027627	#5
MAP3K15	Hs.713701	TRCN0000032582	#5
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MAPK15	Hs.493369	TRCN0000038659	# 5
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EGFR	Hs.488293	TRCN0000039633	# 5
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SRM	Hs.76244	TRCN0000045728	# 5
SRM	Hs.76244	TRCN0000045731	# 5

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SRM	Hs.76244	TRCN0000045732	#5
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ATR	Hs.271791	TRCN0000052397	#5
BMP2K	Hs.146551	TRCN0000052615	#5
BMP2K	Hs.146551	TRCN0000052616	#5
PI4KA	Hs.529438	TRCN0000052624	#5
PI4KA	Hs.529438	TRCN0000052625	#5
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RAGE	Hs.104119	TRCN0000062662	#5
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AAK1	Hs.468878	TRCN0000127601	#6
SGK2	Hs.300863	TRCN0000121788	#6
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SGK2	Hs.300863	TRCN0000122516	#6
WEE1	Hs.249441	TRCN0000139739	#6
MKNK1	Hs.371594	TRCN0000143831	#6
MKNK1	Hs.371594	TRCN0000122706	#6
ERN2	Hs.592041	TRCN0000138998	#6
ABL2	Hs.159472	TRCN0000140719	#6
TYK	Hs.558348	TRCN0000130981	#6
MAPK10	Hs.125503	TRCN0000149054	#6
AGK	Hs.699361	TRCN0000153828	#6
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NEK1	Hs.481181	TRCN0000155836	#6
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ACVRL1	Hs.591026	TRCN0000019519	#6
CDK4	Hs.95577	TRCN0000010520	#6
FGFR3	Hs.1420	TRCN0000010521	#6
GUCY2D	Hs.593109	TRCN0000010522	#6
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CDK3	Hs.706766	TRCN0000010525	#6
IRAK2	Hs.449207	TRCN0000010527	#6
DDR1	Hs.631988	TRCN0000010528	#6
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FGFR4	Hs.165950	TRCN0000010531	#6
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GSK3B	Hs.445733	TRCN0000010551	#6
LIMK1	Hs.647035	TRCN0000010555	#6
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MAPK13	Hs.178695	TRCN0000010556	#6
DYRK3	Hs.164267	TRCN0000010532	#6
AURKA	Hs.250822	TRCN0000010533	#6
MAP4K3	Hs.655750	TRCN0000010534	#6
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MAP3K14	Hs.464183	TRCN0000010542	#6
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BUB1	Hs.469649	TRCN0000010549	#6
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GRK5	Hs.524625	TRCN0000010557	#6
MAP3K4	Hs.396428	TRCN0000010558	#6
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MARK3	Hs.35828	TRCN0000010641	#6
MAP3K10	Hs.466743	TRCN0000010674	#6
PRKACA	Hs.631630	TRCN0000010620	#6
MAPK6	Hs.411847	TRCN0000010642	#6
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CSF1R	Hs.586219	TRCN0000010645	#6
CSF1R	Hs.586219	TRCN0000010644	#6
MOS	Hs.533432	TRCN0000010649	#6
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MUSK	Hs.521653	TRCN0000010683	#6
TYRO3	Hs.581282	TRCN0000010684	#6
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IRAK4	Hs.138899	TRCN0000010679	#6
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CDK10	Hs.699177	TRCN0000010653	#6
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DYRK1A	Hs.719269	TRCN0000010611	#6
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DYRK1A	Hs.719269	TRCN0000010614	#6
CSNK1D	Hs.631725	TRCN0000010640	#6
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CSNK2A1	Hs.644056	TRCN0000010672	#6
CSNK2A1	Hs.644056	TRCN0000010673	#6
JAK1	Hs.207538	TRCN0000010760	#6
MAP3K3	Hs.29282	TRCN0000010692	#6
PRKCB	Hs.460355	TRCN0000010761	#6
PRKCG	Hs.631564	TRCN0000010693	#6
AURKC	Hs.98358	TRCN0000010694	#6
INSRR	Hs.248138	TRCN0000010765	#6
HIPK2	Hs.197465	TRCN0000010766	#6
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DGKQ	Hs.584858	TRCN0000010995	#6
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PDK1	Hs.470653	TRCN0000011007	#6
MAPK3	Hs.861	TRCN0000010997	#6
MAPK3	Hs.861	TRCN0000010998	#6
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RPS6KA2	Hs.719131	TRCN0000011010	#6
SRPK3	Hs.104865	TRCN0000011067	#6
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PASK	Hs.397893	TRCN0000011065	#6
MAP2K2	Hs.465627	TRCN0000011062	#6
MGC42105	Hs.25845	TRCN0000011068	#6
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STK32C	Hs.469002	TRCN0000011064	#6
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MAST1	Hs.227489	TRCN0000021544	#6
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ALPK3	Hs.459183	TRCN0000021526	#6
EPHA10	Hs.129435	TRCN0000021388	#6
ADCK5	Hs.283374	TRCN0000021479	#6
EPHA6	Hs.653248	TRCN0000021415	#6
CDC42BPG	Hs.293590	TRCN0000021470	#6
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TAF1L	Hs.591086	TRCN0000037502	#6
SBK1	Hs.97837	TRCN0000037395	#6
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AKT2	Hs.631535	TRCN0000039969	#6
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ERBB3	Hs.118681	TRCN0000040110	#6
MAP2K4	Hs.514681	TRCN0000039915	#6
FLT3	Hs.567590	TRCN0000039704	#6
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ERBB4	Hs.390729	TRCN0000039690	#6
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SRM	Hs.76244	TRCN0000045730	#6
PIK4A	Hs.529438	TRCN0000052627	#6
PIK3CD	Hs.518451	TRCN0000054258	#6
PIK3CD	Hs.518451	TRCN0000054262	#6
SCYL2	Hs.506481	TRCN0000057887	#6
CDC42BPA	Hs.35433	TRCN0000072628	#6
ABL2	Hs.159472	TRCN0000073848	#6
ATR	Hs.271791	TRCN0000083904	#6
ABL1	Hs.431048	TRCN0000010289	#6
AKT2	Hs.631535	TRCN0000009819	#6
AKT2	Hs.631535	TRCN0000009820	#6
AKT3	Hs.498292	TRCN0000010181	#6
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ATR	Hs.271791	TRCN0000010300	#6
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BUB1	Hs.469649	TRCN0000010307	#6
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CHEK1	Hs.24529	TRCN0000009828	#6
CHEK2	Hs.291363	TRCN0000010312	#6
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EGFR	Hs.488293	TRCN0000010329	#6
GSK3A	Hs.466828	TRCN0000010339	#6
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ERBB2	Hs.446352	TRCN0000010341	#6
ERBB2	Hs.446352	TRCN0000010342	#6
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ERBB4	Hs.390729	TRCN0000009836	#6
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IGF1R	Hs.643120	TRCN0000010361	#6
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PIK3R2	Hs.371344	TRCN0000018339	#6
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RPS6KA3	Hs.445387	TRCN0000010429	#6
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SGK1	Hs.510078	TRCN0000009866	#6
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TGFBR2	Hs.82028	TRCN0000010444	#6
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CDK4	Hs.95577	TRCN0000018364	#6
CDK4	Hs.95577	TRCN0000009876	#6
CDK6	Hs.119882	TRCN0000009877	#6
CDK6	Hs.119882	TRCN0000009878	#6
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MAP2K4	Hs.514681	TRCN0000010495	#6
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CHEK1	Hs.24529	TRCN0000009947	#7
CHEK1	Hs.24529	TRCN0000009948	#7
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CAMK1	Hs.434875	TRCN0000009994	#7
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CSK	Hs.77793	TRCN0000009996	#7
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ITK	Hs.558348	TRCN0000010023	#7
PIK3CB	Hs.239818	TRCN0000010024	#7
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PIK3CB	Hs.239818	TRCN0000010016	#7
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MAPK1	Hs.431850	TRCN0000010049	#7
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MAPK1	Hs.431850	TRCN0000010041	#7
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PHKG2	Hs.196177	TRCN0000010068	#7
PHKG2	Hs.196177	TRCN0000010069	#7
CDK6	Hs.119882	TRCN0000010081	#7
CDK6	Hs.119882	TRCN0000010082	#7
CDK6	Hs.119882	TRCN0000010074	#7
BLK	Hs.146591	TRCN0000010075	#7
BLK	Hs.146591	TRCN0000010083	#7
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DDR1	Hs.631988	TRCN0000010085	#7
DDR1	Hs.631988	TRCN0000010094	#7
FRK	Hs.89426	TRCN0000010095	#7
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FRK	Hs.89426	TRCN0000010097	#7
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LYN	Hs.699154	TRCN0000010101	#7
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PCTK1	Hs.496068	TRCN0000010259	#7
PCTK1	Hs.496068	TRCN0000010249	#7
PCTK1	Hs.496068	TRCN0000010250	#7
PCTK1	Hs.496068	TRCN0000010251	#7
GCK	Hs.1270	TRCN0000010267	#7
GCK	Hs.1270	TRCN0000010268	#7
GCK	Hs.1270	TRCN0000010269	#7
GCK	Hs.1270	TRCN0000010270	#7
MAPK7	Hs.150136	TRCN0000010261	#7
MAPK7	Hs.150136	TRCN0000010262	#7
MAPK7	Hs.150136	TRCN0000010271	#7
MAPK7	Hs.150136	TRCN0000010275	#7
MAPK9	Hs.484371	TRCN0000010276	#7
MAPK9	Hs.484371	TRCN0000010277	#7
MAPK9	Hs.484371	TRCN0000010278	#7
MAPK9	Hs.484371	TRCN0000010279	#7
MAPK9	Hs.484371	TRCN0000010280	#7
SGK2	Hs.300863	TRCN0000010281	#7
SGK2	Hs.300863	TRCN0000010272	#7
SGK2	Hs.300863	TRCN0000010273	#7
SGK2	Hs.300863	TRCN0000010274	#7
SGK2	Hs.300863	TRCN0000010282	#7
CAMK2A	Hs.716391	TRCN0000010283	#7
CAMK2A	Hs.716391	TRCN0000010284	#7
CAMK2A	Hs.716391	TRCN0000010285	#7
CAMK2A	Hs.716391	TRCN0000010286	#7
LIMK1	Hs.647035	TRCN0000000825	#7
PRKCE	Hs.580351	TRCN0000000845	#7
WNK1	Hs.789894	TRCN0000000922	#7
MYLK2	Hs.86092	TRCN0000000934	#7
SRPK1	Hs.443861	TRCN0000001228	#7
SRPK1	Hs.443861	TRCN0000001231	#7
CLK4	Hs.406557	TRCN0000001351	#7
CLK4	Hs.406557	TRCN0000001353	#7
DGKH	Hs.659437	TRCN0000001360	#7
PRKACA	Hs.631630	TRCN0000001370	#7
MAPK4	Hs.433728	TRCN0000001377	#7

HGNC Symbol	UniGene Id	Oligo ID	TRC Kinome Pool 12oct10
EIF2AK1	Hs.719136	TRCN0000001379	#7
RPS6KA1	Hs.149957	TRCN0000001386	#7
ERBB4	Hs.396729	TRCN0000001411	#7
FRK	Hs.660757	TRCN0000001413	#7
DDR2	Hs.593833	TRCN0000001417	#7
PDGFRA	Hs.74615	TRCN0000001425	#7
TESK2	Hs.591499	TRCN0000001436	#7
NRBP1	Hs.515876	TRCN0000001438	#7
TAOK2	Hs.291623	TRCN0000001443	#7
TAOK2	Hs.291623	TRCN0000001446	#7
MAP2K5	Hs.114198	TRCN0000001469	#7
PDK1	Hs.470633	TRCN0000001478	#7
PDK1	Hs.470633	TRCN0000001479	#7
PDK1	Hs.470633	TRCN0000001480	#7
PAK1	Hs.435714	TRCN0000001481	#7
PAK1	Hs.435714	TRCN0000001482	#7
PAK1	Hs.435714	TRCN0000001483	#7
PAK1	Hs.435714	TRCN0000001485	#7
ROR2	Hs.98255	TRCN0000001493	#7
RPS6KA5	Hs.510225	TRCN0000001495	#7
RPS6KA5	Hs.510225	TRCN0000001497	#7
ABL1	Hs.431048	TRCN0000001501	#7
PRKG2	Hs.570833	TRCN0000001508	#7
TAOK3	Hs.644420	TRCN0000001525	#7
TAOK3	Hs.644420	TRCN0000001526	#7
MARK3	Hs.35828	TRCN0000001567	#7
MAPK6	Hs.631847	TRCN0000001571	#7
TXK	Hs.479869	TRCN0000001578	#7
EPHA6	Hs.653244	TRCN0000001767	#7
MAK	Hs.646125	TRCN0000001788	#7
PBK	Hs.104741	TRCN0000001809	#7
AMHR2	Hs.659889	TRCN0000001956	#7
NEK11	Hs.657336	TRCN0000001962	#7
NEK11	Hs.657336	TRCN0000001964	#7
NEK11	Hs.657336	TRCN0000001965	#7
MAPK15	Hs.493169	TRCN0000002212	#7
MAPK15	Hs.493169	TRCN0000002213	#7
MATK	Hs.631845	TRCN0000002219	#7
FASTK	Hs.647094	TRCN0000006320	#7
RIPK2	Hs.103755	TRCN0000006367	#7
NPR1	Hs.490330	TRCN0000007325	#7
ALPK3	Hs.459383	TRCN0000021524	#7
TRPM7	Hs.512894	TRCN0000021562	#7
TRPM7	Hs.512894	TRCN0000021563	#7
PNCK	Hs.436667	TRCN0000021571	#7
PNCK	Hs.436667	TRCN0000021572	#7
PNCK	Hs.436667	TRCN0000021573	#7
TRPM6	Hs.272225	TRCN0000021586	#7
CLK2	Hs.73986	TRCN0000021590	#7
CLK2	Hs.73986	TRCN0000021592	#7
CDC42BPA	Hs.35433	TRCN0000022979	#7
PIK3R5	Hs.278903	TRCN0000033272	#7
PIK3CD	Hs.518451	TRCN0000035275	#7
TNNI3K	Hs.480085	TRCN0000035807	#7
SPHK1	Hs.68061	TRCN0000036968	#7
IGF1R	Hs.643120	TRCN0000039677	#7
PIK3R2	Hs.371344	TRCN0000039684	#7
PIM1	Hs.81170	TRCN0000046793	#7
PAK3	Hs.656789	TRCN0000047593	#7
PAK3	Hs.656789	TRCN0000047594	#7
PAK3	Hs.656789	TRCN0000047595	#7
PAK3	Hs.656789	TRCN0000047596	#7
PAK3	Hs.656789	TRCN0000047597	#7
KALRN	Hs.8004	TRCN0000048208	#7
KALRN	Hs.8004	TRCN0000048209	#7
KALRN	Hs.8004	TRCN0000048210	#7
KALRN	Hs.8004	TRCN0000048212	#7
ATR	Hs.271791	TRCN0000052394	#7
ATR	Hs.271791	TRCN0000052395	#7
ATR	Hs.271791	TRCN0000052396	#7
PI4KA	Hs.529438	TRCN0000052623	#7
LIMK2	Hs.474596	TRCN0000052680	#7
PIK3CD	Hs.518451	TRCN0000054260	#7
TTBK2	Hs.659846	TRCN0000062387	#7
RAGE	Hs.104119	TRCN0000062638	#7
ATR	Hs.271791	TRCN0000063222	#7
LATS1	Hs.716697	TRCN0000073773	#7
CAMK1D	Hs.659517	TRCN0000074123	#7
PI4KA	Hs.529438	TRCN0000078690	#7
PI4KA	Hs.529438	TRCN0000078692	#7
AAK1	Hs.468878	TRCN0000082348	#7
DDR2	Hs.593833	TRCN0000121321	#7

Fig. 37

Ensembl Gene ID	HGNC symbol	Regulation upon MED12 knock-down
ENSG00000003989	SLC7A2	down
ENSG00000069482	GAL	down
ENSG00000110042	DTX4	down
ENSG00000130600	H19	down
ENSG00000135069	PSAT1	down
ENSG00000136997	MYC	down
ENSG00000138028	CGREF1	down
ENSG00000143333	RGS16	down
ENSG00000163050	ADCK3	down
ENSG00000164362	TERT	down
ENSG00000176387	HSD11B2	down
ENSG00000178821	TMEM52	down
ENSG00000184634	MED12	down
ENSG00000184956	MUC6	down
ENSG00000188883	KLRG2	down
ENSG00000196167	C11orf92	down
ENSG00000215182	MUC5AC	down
ENSG00000224837		down
ENSG00000226942	IL9RP3	down
ENSG00000230787		down
ENSG00000232445		down
ENSG00000253810		down
ENSG00000005238	KIAA1539	up
ENSG00000005884	ITGA3	up
ENSG00000010404	IDS	up
ENSG00000011422	PLAUR	up
ENSG00000013364	MVP	up
ENSG00000014257	ACPP	up
ENSG00000014914	MTMR11	up
ENSG00000018625	ATP1A2	up
ENSG00000023171	GRAMD1B	up
ENSG00000024422	EHD2	up
ENSG00000026025	VIM	up
ENSG00000035862	TIMP2	up
ENSG00000041982	TNC	up
ENSG00000049323	LTBP1	up
ENSG00000050165	DKK3	up
ENSG00000053747	LAMA3	up
ENSG00000056558	TRAF1	up
ENSG00000057704	TMCC3	up
ENSG00000058085	LAMC2	up
ENSG00000060140	STYK1	up
ENSG00000065534	MYLK	up
ENSG00000067798	NAV3	up
ENSG00000070778	PTPN21	up
ENSG00000074527	NTN4	up
ENSG00000074966	TXK	up
ENSG00000075223	SEMA3C	up
ENSG00000075391	RASAL2	up
ENSG00000075461	CACNG4	up
ENSG00000076641	PAGI	up
ENSG00000076706	MCAM	up
ENSG00000078804	TPST2INP2	up
ENSG00000079385	CEACAM1	up
ENSG00000080031	PTPRH	up
ENSG00000084636	COL16A1	up
ENSG00000085063	CD59	up
ENSG00000085117	CD82	up
ENSG00000086730	LAT2	up
ENSG00000087494	PTHLH	up
ENSG00000088538	DOCK3	up
ENSG00000088854	C20orf194	up
ENSG00000091986	CCDC80	up
ENSG00000092929	UNC13D	up
ENSG00000095752	IL11	up
ENSG00000100097	LGALS1	up
ENSG00000100311	PDGFB	up
ENSG00000100647	KIAA0247	up
ENSG00000101335	MYL9	up
ENSG00000102265	TIMP1	up
ENSG00000103647	CORO2B	up
ENSG00000104324		up
ENSG00000105339	DENND3	up
ENSG00000105696	TMEM59L	up
ENSG00000105974	CAV1	up
ENSG00000106366	SERPINE1	up
ENSG00000106868	SUSD1	up
ENSG00000108797	CNTNAP1	up
ENSG00000109472	CPE	up
ENSG00000111348	ARHGDIB	up
ENSG00000111799	COL12A1	up
ENSG00000111913	FAM65B	up
ENSG00000113070	HBEGF	up
ENSG00000113578	FGF1	up
ENSG00000114019	AMOTL2	up
ENSG00000114115	RBP1	up
ENSG00000114529	C3orf52	up
ENSG00000114854	TNNC1	up
ENSG00000115380	EFEMP1	up
ENSG00000115590	IL1R2	up
ENSG00000115641	FHL2	up
ENSG00000115828	QPCT	up
ENSG00000116260	QSOX1	up
ENSG00000116701	NCF2	up
ENSG00000116962	NID1	up
ENSG00000117226	GBP3	up
ENSG00000117228	GBP1	up
ENSG00000118523	CTGF	up
ENSG00000118898	PPL	up
ENSG00000123240	OPTN	up
ENSG00000123342	MMP19	up
ENSG00000123843	C4BPB	up
ENSG00000124116	WFDC3	up
ENSG00000124762	CDKN1A	up
ENSG00000125148	MT2A	up
ENSG00000125775	SDCBP2	up
ENSG00000127328	BEST3	up
ENSG00000127561	SYNGR3	up
ENSG00000127920	GNG11	up
ENSG00000128487	SPECC1	up
ENSG00000128510	CPA4	up
ENSG00000128591	FLNC	up
ENSG00000128849	CGNL1	up
ENSG00000129226	CD68	up
ENSG00000131015	ULBP2	up
ENSG00000131711	MAP1B	up
ENSG00000132334	PTPRE	up
ENSG00000132357	CARD6	up
ENSG00000132535	DLG4	up
ENSG00000133121	STARD13	up
ENSG00000133805	AMPD3	up
ENSG00000133816	MICAL2	up
ENSG00000134668	SPOCD1	up
ENSG00000135046	ANXA1	up
ENSG00000135596	MICAL1	up
ENSG00000135678	CPM	up
ENSG00000135842	FAM129A	up
ENSG00000136378	ADAMTS7	up
ENSG00000136542	GALNT5	up
ENSG00000137193	PIM1	up
ENSG00000137709	POU2F3	up
ENSG00000138271	GPR87	up
ENSG00000138356	AOX1	up
ENSG00000138411	HECW2	up
ENSG00000138613	APH1B	up
ENSG00000138772	ANXA3	up
ENSG00000138829	FBN2	up
ENSG00000139044	B4GALNT3	up
ENSG00000139112	GABARAPL1	up
ENSG00000140545	MFGE8	up
ENSG00000140682	TGFBI	up
ENSG00000140950	KIAA1609	up
ENSG00000142227	EMP3	up
ENSG00000142871	CYR61	up
ENSG00000142910	TINAGL1	up
ENSG00000143127	ITGA10	up
ENSG00000143369	ECM1	up
ENSG00000143669	LYST	up

Ensembl Gene ID	HGNC symbol	Regulation upon MED12 knock-down
ENSG00000143816	WNT9A	up
ENSG00000144655	CSRNP1	up
ENSG00000144681	STAC	up
ENSG00000144810	COL8A1	up
ENSG00000144821	MYH15	up
ENSG00000147852	VLDLR	up
ENSG00000149591	TAGLN	up
ENSG00000150722	PPP1R1C	up
ENSG00000150782	IL18	up
ENSG00000152104	PTPN14	up
ENSG00000152137	HSPB8	up
ENSG00000152377	SPOCK1	up
ENSG00000152503	TRIM36	up
ENSG00000152689	RASGRP3	up
ENSG00000153071	DAB2	up
ENSG00000153208	MERTK	up
ENSG00000153294	GPR115	up
ENSG00000154065	ANKRD29	up
ENSG00000155918	RAET1L	up
ENSG00000157064	NMNAT2	up
ENSG00000158125	XDH	up
ENSG00000158246	FAM46B	up
ENSG00000160469	BRSK1	up
ENSG00000161638	ITGA5	up
ENSG00000162545	CAMK2N1	up
ENSG00000162641	AKNAD1	up
ENSG00000162645	GBP2	up
ENSG00000162840	MT1F2	up
ENSG00000163235	TGFA	up
ENSG00000163346	PBXIP1	up
ENSG00000163395	IGFN1	up
ENSG00000163637	PRICKLE2	up
ENSG00000163898	LIPH	up
ENSG00000163975	MFI2	up
ENSG00000164171	ITGA2	up
ENSG00000164251	F2RL1	up
ENSG00000164465	DCBLD1	up
ENSG00000164520	RAET1E	up
ENSG00000164932	CTHRC1	up
ENSG00000164949	GEM	up
ENSG00000165046	LETM2	up
ENSG00000165124	SVEP1	up
ENSG00000166311	SMPD1	up
ENSG00000166401	SERPINB8	up
ENSG00000166446	CDYL2	up
ENSG00000166920	C15orf48	up
ENSG00000167065	DUSP18	up
ENSG00000167552	TUBA1A	up
ENSG00000167601	AXL	up
ENSG00000167767	KRT80	up
ENSG00000167772	ANGPTL4	up
ENSG00000167972	ABCA3	up
ENSG00000168016	TRANK1	up
ENSG00000168487	BMP1	up
ENSG00000168685	IL7R	up
ENSG00000169184	MN1	up
ENSG00000169213	RAB3B	up
ENSG00000169583	CLIC3	up
ENSG00000170537	TMC7	up
ENSG00000170558	CDH2	up
ENSG00000171522	PTGER4	up
ENSG00000171680	PLEKHG5	up
ENSG00000171992	SYNPO	up
ENSG00000172478	C2orf54	up
ENSG00000172602	RND1	up
ENSG00000172738	TMEM217	up
ENSG00000173267	SNCG	up
ENSG00000173705	SUSD5	up
ENSG00000173706	HEG1	up
ENSG00000174500	GCET2	up
ENSG00000176014	TUBB6	up
ENSG00000176438	C14orf49	up
ENSG00000177469	PTRF	up
ENSG00000177494	ZBED2	up
ENSG00000177694	NAALADL2	up
ENSG00000177839	PCDHB9	up
ENSG00000178038	ALS2CL	up
ENSG00000179674	ARL14	up
ENSG00000181458	TMEM45A	up
ENSG00000181652	ATG9B	up
ENSG00000182568	SATB1	up
ENSG00000182795	C1orf116	up
ENSG00000183044	ABAT	up
ENSG00000184557	SOCS3	up
ENSG00000185567	AHNAK2	up
ENSG00000186594	C17orf91	up
ENSG00000186684	CYP27C1	up
ENSG00000187720	THSD4	up
ENSG00000188015	S100A3	up
ENSG00000188042	ARL4C	up
ENSG00000188153	COL4A5	up
ENSG00000188404	SELL	up
ENSG00000196188	CTSE	up
ENSG00000196352	CD55	up
ENSG00000196878	LAMB3	up
ENSG00000197461	PDGFA	up
ENSG00000198796	ALPK2	up
ENSG00000203780	FANK1	up
ENSG00000204525	HLA-C	up
ENSG00000204540	PSORS1C1	up
ENSG00000205413	SAMD9	up
ENSG00000213626	LBH	up
ENSG00000213949	ITGA1	up
ENSG00000215018	COL28A1	up
ENSG00000221866	PLXNA4	up
ENSG00000222009	BTBD19	up
ENSG00000227825	SLC9A7P1	up
ENSG00000229056		up
ENSG00000234745	HLA-B	up
ENSG00000235471		up
ENSG00000256043	CTSO	up

Fig. 38

Ensembl Gene ID	HGNC symbol	Direction of regulation during EMT	Ensembl Gene ID	HGNC symbol	Direction of regulation during EMT
ENSG00000005243	COPZ2	up	ENSG00000122870	BICC1	up
ENSG00000006118	TMEM132A	up	ENSG00000123080	CDKN2C	up
ENSG00000006638	TBXA2R	up	ENSG00000123416	TUBA1B	up
ENSG00000011465	DCN	up	ENSG00000123496	IL13RA2	up
ENSG00000013297	CLDN11	up	ENSG00000123610	TNFAIP6	up
ENSG00000019549	SNAI2	up	ENSG00000124212	PTGIS	up
ENSG00000022267	FHL1	up	ENSG00000124216	SNAI1	up
ENSG00000026025	VIM	up	ENSG00000124942	AHNAK	up
ENSG00000038427	VCAN	up	ENSG00000125354	SEPT6	up
ENSG00000049323	LTBP1	up	ENSG00000125384	PTGER2	up
ENSG00000050165	DKK3	up	ENSG00000126860	EVI2A	up
ENSG00000059804	SLC2A3	up	ENSG00000126947	ARMCX1	up
ENSG00000065308	TRAM2	up	ENSG00000127863	TNFRSF19	up
ENSG00000067798	NAV3	up	ENSG00000127920	GNG11	up
ENSG00000071282	LMCD1	up	ENSG00000128656	CHN1	up
ENSG00000071967	CYBRD1	up	ENSG00000130270	ATP8B3	up
ENSG00000077782	FGFR1	up	ENSG00000130635	COL5A1	up
ENSG00000077942	FBLN1	up	ENSG00000131016	AKAP12	up
ENSG00000078098	FAP	up	ENSG00000131378	RFTN1	up
ENSG00000078114	NEBL	up	ENSG00000131459	GFPT2	up
ENSG00000086289	EPDR1	up	ENSG00000131711	MAP1B	up
ENSG00000087245	MMP2	up	ENSG00000132429	POPDC3	up
ENSG00000092969	TGFB2	up	ENSG00000133110	POSTN	up
ENSG00000099250	NRP1	up	ENSG00000133121	STARD13	up
ENSG00000100097	LGALS1	up	ENSG00000133937	GSC	up
ENSG00000100146	SOX10	up	ENSG00000134824	FADS2	up
ENSG00000100154	TTC28	up	ENSG00000134986	C5orf13	up
ENSG00000100985	MMP9	up	ENSG00000135111	TBX3	up
ENSG00000101335	MYL9	up	ENSG00000135905	DOCK10	up
ENSG00000101955	SRPX	up	ENSG00000136205	TNS3	up
ENSG00000102265	TIMP1	up	ENSG00000136717	BIN1	up
ENSG00000103489	XYLT1	up	ENSG00000136859	ANGPTL2	up
ENSG00000104321	TRPA1	up	ENSG00000136960	ENPP2	up
ENSG00000105137	SYDE1	up	ENSG00000137941	TTLL7	up
ENSG00000105270	CLIP3	up	ENSG00000138356	AOX1	up
ENSG00000105928	DENAS	up	ENSG00000138448	ITGAV	up
ENSG00000106333	PCOLCE	up	ENSG00000138675	PGES	up
ENSG00000106366	SERPINE1	up	ENSG00000138685	FGF2	up
ENSG00000108691	CCL2	up	ENSG00000139278	GLIPR1	up
ENSG00000109099	PMP22	up	ENSG00000140092	FBLN5	up
ENSG00000109814	UGDH	up	ENSG00000140416	TPM1	up
ENSG00000111186	WNT5B	up	ENSG00000140682	TGFB1I1	up
ENSG00000111799	COL12A1	up	ENSG00000140931	CMTM3	up
ENSG00000112183	RBM24	up	ENSG00000140937	CDH11	up
ENSG00000112186	CAP2	up	ENSG00000141753	IGFBP4	up
ENSG00000112276	BVES	up	ENSG00000142156	COL6A1	up
ENSG00000112769	LAMA4	up	ENSG00000142227	EMP3	up
ENSG00000113902	SEMA5A	up	ENSG00000142494	SLC47A1	up
ENSG00000113083	LOX	up	ENSG00000143196	DPT	up
ENSG00000113140	SPARC	up	ENSG00000143344	RGL1	up
ENSG00000113657	DPYSL3	up	ENSG00000143369	ECM1	up
ENSG00000114251	WNT5A	up	ENSG00000143515	ATP8B2	up
ENSG00000114450	GNB4	up	ENSG00000143653	SCCPDH	up
ENSG00000114948	ADAM23	up	ENSG00000144218	AFF3	up
ENSG00000115109	EPB41L5	up	ENSG00000144642	RBMS3	up
ENSG00000115414	FN1	up	ENSG00000145431	PDGFC	up
ENSG00000115648	MLPH	up	ENSG00000146674	IGFBP3	up
ENSG00000115935	WIPF1	up	ENSG00000147027	TMEM47	up
ENSG00000116132	PRRX1	up	ENSG00000147065	MSN	up
ENSG00000116774	OLFML3	up	ENSG00000148516	ZEB1	up
ENSG00000116962	NID1	up	ENSG00000148677	ANKRD1	up
ENSG00000117152	RGS4	up	ENSG00000149591	TAGLN	up
ENSG00000118495	PLAGL1	up	ENSG00000149968	MMP3	up
ENSG00000118523	CTGF	up	ENSG00000152022	LIX1L	up
ENSG00000119242	CCDC92	up	ENSG00000152377	SPOCK1	up
ENSG00000119681	LTBP2	up	ENSG00000153071	DAB2	up
ENSG00000120658	ENOX1	up	ENSG00000153976	HS3ST3A1	up
ENSG00000122254	HS3ST2	up	ENSG00000154027	AKS	up
ENSG00000122691	TWIST1	up	ENSG00000154096	THY1	up
ENSG00000122707	RECK	up	ENSG00000154734	ADAMTS1	up
ENSG00000122786	CALD1	up	ENSG00000157168	NRG1	up
ENSG00000122862	SRGN	up	ENSG00000157350	ST3GAL2	up

Ensembl Gene ID	HGNC symbol	Direction of regulation during EMT
ENSG00000157613	CREB3L1	up
ENSG00000158186	MRAS	up
ENSG00000159167	STC1	up
ENSG00000161638	ITGA5	up
ENSG00000162407	PPAP2B	up
ENSG00000162545	CAMK2N1	up
ENSG00000162614	NEXN	up
ENSG00000162616	DNAJB4	up
ENSG00000162733	DDR2	up
ENSG00000163430	FSTL1	up
ENSG00000163453	IGFBP7	up
ENSG00000163661	PTX3	up
ENSG00000164176	EDIL3	up
ENSG00000164647	STEAP1	up
ENSG00000164692	COL1A2	up
ENSG00000164741	DLC1	up
ENSG00000166033	HTRA1	up
ENSG00000166073	GPR176	up
ENSG00000166086	JAM3	up
ENSG00000166147	FBN1	up
ENSG00000166402	TUB	up
ENSG00000166780	C16orf45	up
ENSG00000166831	RBPMS2	up
ENSG00000166923	GREM1	up
ENSG00000167552	TUBA1A	up
ENSG00000167601	AXL	up
ENSG00000168386	FILIP1L	up
ENSG00000168487	BMP1	up
ENSG00000168542	COL3A1	up
ENSG00000169554	ZEB2	up
ENSG00000169604	ANTXR1	up
ENSG00000169946	ZFPM2	up
ENSG00000170558	CDH2	up
ENSG00000170836	PPM1D	up
ENSG00000170961	HAS2	up
ENSG00000171408	PDE7B	up
ENSG00000172260	NEGR1	up
ENSG00000173068	BNC2	up
ENSG00000173705	SUSD5	up
ENSG00000173706	HEG1	up
ENSG00000174099	MSRB3	up
ENSG00000175745	NR2F1	up
ENSG00000176692	FOXC2	up
ENSG00000176697	BDNF	up
ENSG00000177311	ZBTB38	up
ENSG00000177469	PTRF	up
ENSG00000177707	PVRL3	up
ENSG00000179242	CDH4	up
ENSG00000179981	TSHZ1	up
ENSG00000181104	F2R	up
ENSG00000182287	AP1S2	up
ENSG00000182326	CIS	up
ENSG00000182492	BGN	up
ENSG00000182636	NDN	up
ENSG00000182752	PAPPA	up
ENSG00000183098	GPC6	up
ENSG00000183688	FAM101B	up
ENSG00000183722	LHFP	up
ENSG00000183853	KIRREL	up
ENSG00000184304	PRKDJ	up
ENSG00000184838	PRR16	up
ENSG00000185070	FLRT2	up
ENSG00000185483	ROR1	up
ENSG00000185669	SNAI3	up
ENSG00000186047	DLEU7	up
ENSG00000186310	NAP1L3	up
ENSG00000187498	COL4A1	up
ENSG00000196159	FAT4	up
ENSG00000196368	NUDT11	up
ENSG00000196549	MME	up
ENSG00000196611	MMP1	up
ENSG00000196628	TCF4	up

Ensembl Gene ID	HGNC symbol	Direction of regulation during EMT
ENSG00000197043	ANXA6	up
ENSG00000197969	VPS13A	up
ENSG00000197977	ELOVL2	up
ENSG00000198053	SIRPA	up
ENSG00000198756	GLT25D2	up
ENSG00000198796	ALPK2	up
ENSG00000204262	COL5A2	up
ENSG00000205426	KRT81	up
ENSG00000211448	DIO2	up
ENSG00000240694	PNMA2	up
ENSG00000241697	TMEFF1	up
ENSG00000249992	TMEM158	up
ENSG00000251349	C9orf30-TMEFF1	up
ENSG00000002587	HS3ST1	down
ENSG00000006555	TTC22	down
ENSG00000011347	SYT7	down
ENSG00000014257	ACPP	down
ENSG00000021355	SERPINB1	down
ENSG00000026036	RTEL1	down
ENSG00000027075	PRKCH	down
ENSG00000035115	SH3YL1	down
ENSG00000039068	CDH1	down
ENSG00000049283	EPN3	down
ENSG00000052344	PRSS8	down
ENSG00000053747	LAMA3	down
ENSG00000058085	LAMC2	down
ENSG00000058404	CAMK2B	down
ENSG00000062038	CDH3	down
ENSG00000064270	ATP2C2	down
ENSG00000065361	ERBB3	down
ENSG00000065618	COL17A1	down
ENSG00000066468	FGFR2	down
ENSG00000068078	FGFR3	down
ENSG00000069764	PLA2G10	down
ENSG00000070159	PTPN3	down
ENSG00000070190	DAPP1	down
ENSG00000076770	MBNL3	down
ENSG00000077238	IL4R	down
ENSG00000083307	GRHL2	down
ENSG00000086300	SNX10	down
ENSG00000086548	CEACAM6	down
ENSG00000086570	FAT2	down
ENSG00000087128	TMPRSS11E	down
ENSG00000087916	SLC6A14	down
ENSG00000088726	TMEM40	down
ENSG00000089356	FXYD3	down
ENSG00000095203	EPB41L4B	down
ENSG00000095585	BLNK	down
ENSG00000096696	DSP	down
ENSG00000099204	ABLIM1	down
ENSG00000099812	C19orf21	down
ENSG00000100290	BIK	down
ENSG00000100418	PPPDE2	down
ENSG00000101443	WFDC2	down
ENSG00000101670	LIPG	down
ENSG00000102879	CORO1A	down
ENSG00000102890	ELMO3	down
ENSG00000103089	FA2H	down
ENSG00000103460	TOX3	down
ENSG00000103534	TMC5	down
ENSG00000104267	CA2	down
ENSG00000104290	FZD3	down
ENSG00000104419	NDRG1	down
ENSG00000104722	NEFM	down
ENSG00000105357	MYH14	down
ENSG00000105388	CEACAM5	down
ENSG00000105699	LSR	down
ENSG00000105825	TFPI2	down
ENSG00000105971	CAV2	down
ENSG00000106537	TSPAN13	down
ENSG00000107014	RLN2	down
ENSG00000107159	CA9	down

Ensembl Gene ID	HGNC symbol	Direction of regulation during EMT
ENSG00000108479	GALK1	down
ENSG00000109255	NMU	down
ENSG00000109452	INPP4B	down
ENSG00000109667	SLC2A9	down
ENSG00000110723	EXPH5	down
ENSG00000111012	CYP27B1	down
ENSG00000111319	SCNN1A	down
ENSG00000111348	ARHGDIB	down
ENSG00000111863	C6orf105	down
ENSG00000112378	PERP	down
ENSG00000113070	HBEGF	down
ENSG00000113356	POLR3G	down
ENSG00000113430	IRX4	down
ENSG00000113645	WWC1	down
ENSG00000113221	ITGB6	down
ENSG00000115339	GALNT3	down
ENSG00000115457	IGFBP2	down
ENSG00000116741	RGS2	down
ENSG00000117407	ARTN	down
ENSG00000117472	TSPAN1	down
ENSG00000117595	IRF6	down
ENSG00000117676	RPS6KA1	down
ENSG00000118785	SPP1	down
ENSG00000118898	PPL	down
ENSG00000118971	CCND2	down
ENSG00000119411	BSPRY	down
ENSG00000120756	PLS1	down
ENSG00000121742	GJB6	down
ENSG00000124102	PI3	down
ENSG00000124107	SLPI	down
ENSG00000125538	IL1B	down
ENSG00000125731	SH2D3A	down
ENSG00000125850	OVOL2	down
ENSG00000127954	STEAP4	down
ENSG00000128422	KRT17	down
ENSG00000128833	MYO5C	down
ENSG00000129354	AP1M2	down
ENSG00000129451	KLK10	down
ENSG00000129455	KLK8	down
ENSG00000129667	RHBDF2	down
ENSG00000130768	SMPDL3B	down
ENSG00000130821	SLC6A8	down
ENSG00000132470	ITGB4	down
ENSG00000132698	RAB25	down
ENSG00000132746	ALDH3B2	down
ENSG00000133135	RNF128	down
ENSG00000133710	SPINK5	down
ENSG00000133740	E2F5	down
ENSG00000133985	TTC9	down
ENSG00000134258	VTCN1	down
ENSG00000134317	GRHL1	down
ENSG00000134363	FST	down
ENSG00000134709	HOOK1	down
ENSG00000134755	DSC2	down
ENSG00000134757	DSG3	down
ENSG00000135373	EHF	down
ENSG00000135374	ELF5	down
ENSG00000135378	PRRG4	down
ENSG00000135423	GLS2	down
ENSG00000135525	MAP7	down
ENSG00000135750	KCNK1	down
ENSG00000136155	SCEL	down
ENSG00000136167	LCP1	down
ENSG00000136237	RAPGEF5	down
ENSG00000136689	IL1RN	down
ENSG00000136943	CTSL2	down
ENSG00000137269	LRRC1	down
ENSG00000137440	FGFBP1	down
ENSG00000137648	TMPRSS4	down
ENSG00000137699	TRIM29	down
ENSG00000137709	POU2F3	down
ENSG00000137747	TMPRSS13	down

Ensembl Gene ID	HGNC symbol	Direction of regulation during EMT
ENSG00000137843	PAK6	down
ENSG00000138271	GPR87	down
ENSG00000138670	RASGEF1B	down
ENSG00000138772	ANXA3	down
ENSG00000139055	ERP27	down
ENSG00000140297	GCNT3	down
ENSG00000140832	MARVELD3	down
ENSG00000141404	GNAL	down
ENSG00000142675	CNKSR1	down
ENSG00000143126	CELSR2	down
ENSG00000143217	PVRL4	down
ENSG00000143375	CGN	down
ENSG00000143412	ANXA9	down
ENSG00000143546	S100A8	down
ENSG00000143556	S100A7	down
ENSG00000144452	ABCA12	down
ENSG00000144681	STAC	down
ENSG00000145103	ILDR1	down
ENSG00000145335	SNCA	down
ENSG00000146192	FGD2	down
ENSG00000146904	EPHA1	down
ENSG00000147676	MAL2	down
ENSG00000147689	FAM83A	down
ENSG00000148346	LCN2	down
ENSG00000148671	C10orf116	down
ENSG00000149300	C11orf52	down
ENSG00000149418	ST14	down
ENSG00000150054	MPP7	down
ENSG00000150782	IL18	down
ENSG00000151150	ANK3	down
ENSG00000151715	TMEM45B	down
ENSG00000151914	DST	down
ENSG00000152766	ANKRD22	down
ENSG00000152939	MARVELD2	down
ENSG00000153292	GPR110	down
ENSG00000154556	SORBS2	down
ENSG00000154639	CXADR	down
ENSG00000154889	MPPE1	down
ENSG00000155066	PROM2	down
ENSG00000156711	MAPK13	down
ENSG00000157992	KRTCAP3	down
ENSG00000158125	XDH	down
ENSG00000158769	F11R	down
ENSG00000159166	LAD1	down
ENSG00000161249	DMKN	down
ENSG00000162069	CCDC64B	down
ENSG00000162777	DENND2D	down
ENSG00000162981	FAM84A	down
ENSG00000163032	VSNL1	down
ENSG00000163209	SPRR3	down
ENSG00000163219	ARHGAP25	down
ENSG00000163220	S100A9	down
ENSG00000163347	CLDN1	down
ENSG00000163362	C1orf106	down
ENSG00000163435	ELF3	down
ENSG00000163624	CDS1	down
ENSG00000163993	S100P	down
ENSG00000164078	MST1R	down
ENSG00000165025	SYK	down
ENSG00000165185	RASEF	down
ENSG00000165140	FBP1	down
ENSG00000165272	AQP3	down
ENSG00000165507	C10orf10	down
ENSG00000165591	FAAH2	down
ENSG00000166145	SPINT1	down
ENSG00000166321	NUDT13	down
ENSG00000166415	WDR72	down
ENSG00000167306	MYO5B	down
ENSG00000167608	TMC4	down
ENSG00000167642	SPINT2	down
ENSG00000167754	KLK5	down
ENSG00000167755	KLK6	down

Ensembl Gene ID	HGNC symbol	Direction of regulation during EMT	Ensembl Gene ID	HGNC symbol	Direction of regulation during EMT
ENSG00000168398	BDKRB2	down			
ENSG00000168672	FAM84B	down			
ENSG00000168743	NPNT	down			
ENSG00000169035	KLK7	down			
ENSG00000169403	PTAFR	down			
ENSG00000169469	SPRR1B	down			
ENSG00000169474	SPRR1A	down			
ENSG00000171004	HS6ST2	down			
ENSG00000171124	FUT3	down			
ENSG00000171345	KRT19	down			
ENSG00000171346	KRT15	down			
ENSG00000173156	RHOD	down			
ENSG00000173467	AGR3	down			
ENSG00000173801	JUP	down			
ENSG00000174469	CNTNAP2	down			
ENSG00000174567	GOLT1A	down			
ENSG00000174951	FUT1	down			
ENSG00000175315	CST6	down			
ENSG00000175318	GRAMD2	down			
ENSG00000176153	GPX2	down			
ENSG00000176393	RNPEP	down			
ENSG00000176532	PRR15	down			
ENSG00000176658	MYO1D	down			
ENSG00000176945	MUC20	down			
ENSG00000177494	ZBED2	down			
ENSG00000178078	STAP2	down			
ENSG00000178726	THBD	down			
ENSG00000178750	STX19	down			
ENSG00000179178	TMEM125	down			
ENSG00000179593	ALOX15B	down			
ENSG00000179913	B3GNT3	down			
ENSG00000180658	OR2A4	down			
ENSG00000181885	CLDN7	down			
ENSG00000182107	TMEM30B	down			
ENSG00000182795	C1orf116	down			
ENSG00000184254	ALDH1A3	down			
ENSG00000184363	PKP3	down			
ENSG00000184731	FAM110C	down			
ENSG00000184916	JAG2	down			
ENSG00000185479	KRT6B	down			
ENSG00000186081	KRT5	down			
ENSG00000186832	KRT16	down			
ENSG00000186847	KRT14	down			
ENSG00000187098	MITF	down			
ENSG00000188910	GJB3	down			
ENSG00000189143	CLDN4	down			
ENSG00000189334	S100A14	down			
ENSG00000196878	LAMB3	down			
ENSG00000197279	ZNF165	down			
ENSG00000197632	SERPINB2	down			
ENSG00000197822	OCLN	down			
ENSG00000198088	NUP62CL	down			
ENSG00000198125	MB	down			
ENSG00000198729	PPP1R14C	down			
ENSG00000206075	SERPINB5	down			
ENSG00000216490	IFI30	down			
ENSG00000227184	EPPK1	down			
ENSG00000236761	CTAGE9	down			
ENSG00000241484	ARHGAP8	down			
ENSG00000248405	PRR5-ARHGAP8	down			
ENSG00000249437	NAIP	down			
ENSG00000253313	C1orf210	down			

Fig. 39

Ensembl Gene ID	HGNC symbol
ENSG00000026025	VIM
ENSG00000049323	LTBP1
ENSG00000050165	DKK3
ENSG00000067798	NAV3
ENSG00000100097	LGALS1
ENSG00000101335	MYL9
ENSG00000102265	TIMP1
ENSG00000106366	SERPINE1
ENSG00000111799	COL12A1
ENSG00000116962	NID1
ENSG00000118523	CTGF
ENSG00000127920	GNG11
ENSG00000131711	MAP1B
ENSG00000133121	STARD13
ENSG00000138356	AOX1
ENSG00000140682	TGFB1I1
ENSG00000142227	EMP3
ENSG00000143369	ECM1
ENSG00000149591	TAGLN
ENSG00000152377	SPOCK1
ENSG00000153071	DAB2
ENSG00000161638	ITGA5
ENSG00000162545	CAMK2N1
ENSG00000167552	TUBA1A
ENSG00000167601	AXL
ENSG00000168487	BMP1
ENSG00000170558	CDH2
ENSG00000173705	SUSD5
ENSG00000173706	HEG1
ENSG00000177469	PTRF
ENSG00000198796	ALPK2

Fig 40

Gene in MED12 signature	Association with drug response (P-value, p<0.05 is yellow)			
Name	AZD6244	CI-1040	PD-0325901	RDEA119
KIAA1539	1	1	1	1
IDS	0.035724124	0.103698283	0.007204722	0.009072613
PLAUR	0.446193324	0.048543765	0.006689257	0.044106897
MVP	1	1	0.052034101	0.062512513
ACPP	1	1	1	1
MTMR11	0.262248423	0.028000689	0.079666149	1
ATP1A2	1	0.151826634	0.149859652	0.356086828
EHD2	1	0.170807202	1	0.522001041
VIM	1	1	1	1
TIMP2	1	1	1	1
TNC	1	1	1	1
LTBP1	1	1	1	0.266201043
DKK3	1	0.321853846	1	0.341471162
LAMA3	1	1	0.014662379	0.019795538
TRAF1	1	1	1	1
LAMC2	0.016993644	0.008295492	0.000611194	0.006561606
STYK1	0.003520393	1.49332E-05	1	3.33448E-05
NAV3	1	0.292703449	0.172931222	1
PTPN21	1	1	1	1
TXK	1	1	0.389754146	0.446949305
SEMA3C	1	1	1	1
RASAL2	1	1	1	1
CACNG4	0.025096835	0.00436873	0.008541368	0.053280351
MCAM	1	1	1	1
CEACAM1	0.4845612	1	1	1
PTPRH	0.27541157	1	1	1
COL16A1	1	1	1	1
CD59	1	1	1	1
CD82	0.138766892	1	0.042179701	1
LAT2	1	1	1	1
PTHLH	1	0.00660059	0.079666149	0.235948164
DOCK3	0.205715804	0.292703449	0.149859652	0.356086828
IL11	1	0.048543765	1	0.522001041
LGALS1	1	1	1	1
PDGFB	0.338787391	0.040583181	1	0.429566594
KIAA0247	0.030605372	0.051187805	0.010861253	0.014236686
MYL9	0.151030068	1	1	0.24950523
TIMP1	1	1	1	1
CORO2B	1	1	1	1
DENND3	1	1	1	1
TMEM59L	1	1	1	1
CAV1	0.373022246	0.182523483	0.067669502	0.076692102
SERPINE1	1	0.051779364	0.149859652	0.182544376
CNTNAP1	1	1	1	1
CPE	0.119650932	0.012660408	0.189043444	0.230289617

ARHGDIB	1	1	1	1
FAM65B	1	1	1	1
HBEGF	0.000478029	0.002602582	0.001849879	0.016019705
FGF1	0.373107019	1	1	1
AMOTL2	0.067224767	1	0.032822032	1
C3orf52	1	1	1	1
TNNC1	1	0.023109238	0.046251047	1
EFEMP1	1	0.251579737	0.124236615	0.06335743
IL1R2	1	0.018990657	1	1
FHL2	0.153467922	0.049145657	0.064009429	0.076002792
QPCT	1	1	1	1
QSOX1	1	1	1	1
NCF2	1	1	1	1
NID1	1	1	1	1
GBP1	0.052598892	0.170807202	0.1291713	0.060071089
CTGF	0.044994363	0.173839749	0.010861253	0.014236686
PPL	0.010914915	0.023109238	1	0.060071089
OPTN	0.05424316	0.000863155	0.001883394	0.002527713
MMP19	0.009433593	0.173839749	0.017347047	0.091369695
C4BPB	0.007028343	0.028000689	0.001849879	0.060071089
CDKN1A	1	1	1	1
MT2A	1	0.173635305	0.090117004	0.108352379
SYNGR3	0.408976565	1	1	0.182544376
GNG11	1	1	1	1
FLNC	1	0.012660408	0.094440033	1
ULBP2	0.087147026	0.084371681	0.02269635	1
MAP1B	1	1	1	1
PTPRE	1	1	1	1
DLG4	1	0.338938111	1	0.507874212
STARD13	1	1	1	1
AMPD3	1	1	1	0.053280351
MICAL2	1	1	1	1
ANXA1	1	0.072909769	0.140239592	0.159171422
MICAL1	1	1	1	1
CPM	1	1	1	1
FAM129A	1	1	1	1
ADAMTS7	0.526955497	1	0.346235667	1
PIM1	0.052598892	0.002100778	1	0.024350312
POU2F3	0.32802469	1	0.326197735	0.370611324
GPR87	0.025216974	0.01027043	0.005776881	0.008259465
AOX1	1	1	1	1
APH1B	1	1	1	1
ANXA3	1	1	1	1
FBN2	1	1	1	1
GABARAPL1	1	1	1	1
MFGE8	1	1	1	1
TGFB1I1	0.101299971	0.029261914	1	0.264010865

KIAA1609	1	1	1	1
EMP3	1	1	1	1
CYR61	0.21221505	0.08094553	0.017347047	0.022158519
TINAGL1	0.030509021	0.004178214	0.001412054	0.002068791
ITGA10	1	1	1	1
ECM1	1	1	1	1
LYST	1	1	1	1
STAC	1	1	1	1
COL8A1	0.446193324	1	0.094518292	0.116528901
MYH15	1	1	0.177729452	0.208818964
VLDLR	1	1	1	1
TAGLN	0.025216974	1	0.025637552	1
IL18	1	1	1	1
PTPN14	0.373107019	1	1	1
HSPB8	1	1	1	1
SPOCK1	0.306180792	1	0.354028137	0.230289617
TRIM36	1	1	1	0.356086828
RASGRP3	1	1	1	1
OAB2	1	1	1	1
MERTK	0.180917105	1	0.273989769	0.32175975
NMNAT2	0.005605271	0.000961068	0.004521321	0.028633774
XDH	0.05424316	0.173839749	0.013754481	0.017796117
ITGA5	1	1	1	1
CAMK2N1	1	0.051187805	0.090117004	0.108352379
GBP2	0.205715804	0.323544668	0.172931222	0.392092059
TGFA	0.035724124	1	1	1
P8XIP1	1	1	1	1
MFI2	1	1	1	1
ITGA2	0.180917105	0.098390417	0.02269635	0.029817575
F2RL1	1	1	1	1
GEM	1	0.236284956	0.172931222	1
SVEP1	1	0.023660762	1	1
SMPD1	1	1	1	1
SERPINB8	1	0.473344876	1	1
TUBA1A	1	1	1	1
AXL	0.05424316	0.00436873	0.013754481	0.017796117
ANGPTL4	1	0.061206117	1	1
ABCA3	0.306180792	0.001267027	0.011700942	0.016019705
TRANK1	1	1	1	1
BMP1	1	1	1	1
IL7R	0.008776445	0.236284956	0.001073038	0.001595687
MN1	0.073972718	0.018990657	0.014662379	0.019795538
RAB3B	0.114825388	0.011539537	0.010854269	0.015594432
CLIC3	0.020748485	0.031508256	0.002728276	0.06335743
TMC7	0.24225212	0.028868468	1	0.022158519
CDH2	1	1	1	1
PTGER4	1	1	1	1

SYNPO	0.180917105	1	0.110744577	0.138384661
C2orf54	0.04406121	0.098390417	0.1291713	0.159341814
RND1	0.119650932	0.040583181	0.1291713	0.159341814
SNCG	0.065142784	0.173839749	0.021788406	0.108352379
SUSD5	1	1	1	1
HEG1	0.205715804	0.113885033	0.306746327	0.356086828
TUBB6	0.153467922	0.032650482	0.078401465	0.092022499
PTRF	1	1	1	1
ZBED2	0.030509021	0.006671083	0.000811713	0.008259465
ALS2CL	0.04406121	0.001267027	0.002412797	0.003433595
ARL14	0.020748485	1	0.003521056	0.023500711
TMEM45A	1	1	0.30646622	1
SATB1	1	1	1	1
C1orf116	0.085589832	0.002668745	0.021748723	0.030913619
ABAT	0.27541157	1	0.243416981	0.484177686
SOCS3	0.077931677	1	1	1
AHNAK2	0.391899113	0.001911241	0.052034101	0.062512513
C17orf91	1	1	1	1
THSD4	1	1	1	1
S100A3	1	1	1	1
ARL4C	0.003674744	0.023660762	0.000810819	0.053280351
COL4A5	0.595498204	0.473344876	1	1
SELL	0.180917105	1	1	1
CTSE	1	1	1	1
CD55	1	1	1	1
LAMB3	0.06251439	0.131989423	0.02269635	0.099469007
PDGFA	1	1	1	1
SAMD9	0.205715804	1	0.066802001	0.084490204
LBH	1	1	0.426853709	1
ITGA1	1	1	1	1
CTSO	1	1	1	0.235948164

Fig. 41

Cell line		IC50 values				Gene mutations			
Name	CTP	AZD6244	CI-1040	PD-0325901	RDEA119	BRAF	KRAS	HRAS	NRAS
A673	Soft tissue	4.978	2.095	1.572	3.083	1	0	0	0
COLO-829	Skin		0.5663	-1.397	0.5201	1	0	0	0
COR-L23	Lung	1.383	1.956	-0.3081	1.003	0	1	0	0
NCI-H2347	Lung	2.354	2.695	-1.371	-0.182	0	0	0	1
NCI-H2030	Lung		2.622	1.059	1.973	0	1	0	0
NCI-H2122	Lung	3.835	1.876	-0.4983	0.8265	0	1	0	0
SK-N-AS	CNS	-2.374	0.05726	-4.803	-3.102	0	0	0	1
NCI-H1299	Lung	4.517	2.848	-1.718	2.617	0	0	0	1
NCI-H2087	Lung	0.323	1.341	-2.315	0.8903	1	0	0	1
UM-UC-3	Bladder		2.308	1.843	3.195	0	1	0	0
NCI-H727	Lung	3.282	1.063	0.6008	3.746	0	1	0	0
Calu-6	Lung	1.685	1.921	-0.1091	2.698	0	1	0	0
NCI-H1355	Lung	3.585	2.045	-2.072	3	0	1	0	0
NCI-H1792	Lung	3.113	2.253	-0.2982	0.8857	0	1	0	0
HPAF-II	pancreas	1.257	1.31	-2.078	0.01164	0	1	0	0
MIA-PaCa-2	pancreas	-0.1121	1.091	-2.777	1.042	0	1	0	0
SHP-77	Lung	4.073	5.771	0.094	6.199	0	1	0	0
NCI-H2009	Lung		2.942			0	1	0	0
NCI-H2291	Lung	-0.2846	0.2849	-3.066	-0.9257	0	1	0	0
SW900	Lung		4.123	1.385	5.475	0	1	0	0
BB49-HNC	upper_aerodigestive_tract	2.707	2.829	-0.419	1.811	0	0	1	0
CP50-MEL-B	Skin	-2.063	-1.736	-5.403	-3.837	1	0	0	0
CP66-MEL	Skin		-0.5167			0	0	0	1
KNS-62	Lung		1.896			0	0	1	0
KP-4	pancreas		2.864	0.4961	3.386	0	1	0	0
KYSE-410	upper_aerodigestive_tract	3.907	2.906	0.4197	1.227	0	1	0	0
LB2518-MEL	Skin	-2.375	-0.3275	-4.496	-2.548	0	0	0	1
LB373-MEL-D	Skin		2.435			0	0	0	1
MZ1-PC	pancreas	1.206	3.248	-1.032	0.3052	0	1	0	0
MZ7-mel	Skin	1.47	-1.67	-3.513	-0.9893	1	0	0	0
CAPAN-1	pancreas	4.678	2.563	-0.3411	1.458	0	1	0	0
HCT-116	GI tract	0.07475	1.927	-1.22	-0.6337	0	1	0	0
HCT-15	GI tract		4.876			0	1	0	0
HL-60	Blood	-3.208	-0.1998	-4.124	-3.062	0	0	0	1
NCI-H23	Lung	3.781	2.768	-1.533	1.969	0	1	0	0
NCI-H460	Lung	1.004	3.674	-1.941	0.8956	0	1	0	0
A549	Lung	-1.573	0.1676	-4.828	-2.157	0	1	0	0
CCRF-CEM	Blood	5.35	2.356	2.972	6.208	0	1	0	0
SK-MEL-28	Skin		-1.187	-6.537	-2.192	1	0	0	0
SK-MEL-2	Skin	-0.9044	0.4594	-3.341	-2.286	0	0	0	1
MOLT-4	Blood	3.403	4.77	0.6441	5.39	0	0	0	1
MDA-MB-231	Breast	1.711	1.453	-1.808	0.1106	1	1	0	0

SW620	GI tract	-1.192	0.1396	-4.213	-1.267	0	1	0	0
RPMI-8226	Blood	-0.271	3.369	-1.087	1.53	0	1	0	0
OVCAR-5	Ovary		1.797			0	1	0	0
HOP-62	Lung		3.019			0	1	0	0
LOXIMVI	Skin	-0.1389	0.582	-3.243	-0.7422	1	0	0	0
MI4	Skin	-3.29	-1.869	-6.575	-3.575	1	0	0	0
UACC-62	Skin	5.196	6.452	1.235	6.049	1	0	0	0
UACC-257	Skin	-1.132	-0.02906	-4.248	-2.729	1	0	0	0
AGS	GI tract	0.105	-1.97	-3.891	-1.415	0	1	0	0
A2058	Skin		0.5167	-0.81	1.326	1	0	0	0
A375	Skin		0.4632	-5.982	-2.128	1	0	0	0
697	Blood	1.824	1.3	2.636	3.041	0	0	0	1
ACN	CNS	-0.5674	-1.553	-4.149	-2.719	1	0	0	0
COLO-800	Skin		2.222			1	0	0	0
COLO-741	GI tract	-0.6582	1.054	-4.927	-0.04502	1	0	0	0
COLO-679	Skin	-1.085	-1.112	-4.615	-1.88	1	0	0	0
CHP-212	CNS	-5.826	-3.516	-7.584	-5.312	0	0	0	1
CFPAC-1	pancreas	2.005	3.118	-0.8254	2.028	0	1	0	0
CAL-62	Other	0.435	0.2094	-2.282	-0.3906	0	1	0	0
C8166	Blood	5.564	3.398	3.018	6.167	0	0	0	1
C32	Skin	-2.32	-1.664	-5.604	-2.877	1	0	0	0
DBTRG-05MG	CNS	2.229	2.213	0.4173	4.205	1	0	0	0
DU-4475	Breast	-3.122		-5.628	-3.328	1	0	0	0
EGI-1	GI tract	0.627	1.283	-2.345	0.2443	0	1	0	0
G-361	Skin		-1.26			1	0	0	0
GCT	Soft tissue	1.292	2.583	2.56	4.387	1	0	0	0
HD-MY-Z	Blood		2.856			0	0	0	1
HEC-1	Uterus	5.622	5.713	2.133	3.986	0	1	0	0
HMV-II	Skin		-0.5522			1	0	0	1
HT-1080	Soft tissue	0.8877	1.104	-2.477	-0.6269	0	0	0	1
HT-1197	Bladder	4.518	5.235	1.484	3.612	0	0	0	1
HT-144	Skin	-2.429	-0.611	-4.726	-3.03	1	0	0	0
HuCCT1	GI tract	0.2612	1.956	-1.333	-0.08974	0	1	0	0
IGR-1	Skin	2.118	3.831	-1.02	1.609	1	0	0	0
IST-MEL1	Skin		-0.4613			1	0	0	0
KE-37	Blood	5.652	2.39	3.02	5.723	0	0	0	1
KMOE-2	Blood		-1.61			0	0	0	1
HuP-T3	pancreas	1.555	1.719	-2.516	1.701	0	1	0	0
GP5d	GI tract	1.572	-0.0386	-1.602	3.978	0	1	0	0
KU-19-19	Bladder	1.252	1.158	-1.329	-1.025	0	0	0	1
LoVo	GI tract	0.05979	0.3968	-2.717	-0.9301	0	1	0	0
LS-123	GI tract	1.319	2.951	-0.5991	0.949	0	1	0	0
LS-411N	GI tract	2.302	0.3378	-1.059	-0.8819	1	0	0	0
LS-513	GI tract	0.3343	0.3822	-2.169	-0.8842	0	1	0	0
LU-99A	Lung	5.061	1.788	1.631	1.47	0	1	0	0

MEL-HO	Skin	-1.969	-1.274	-4.664	-3.224	1	0	0	0
MEL-JUSO	Skin		1.524			0	0	1	1
NCI-SNU-1	GI tract	0.5913	-0.2647	-2.334	0.1759	0	1	0	0
NMC-GI	CNS	3.454	3.253	0.691	1.902	1	0	0	0
NOMO-1	Blood	-3.435	-1.347	-6.164	-1.989	0	1	0	0
NCI-H747	GI tract	-1.051	1.563	-3.38	-0.4337	0	1	0	0
NCI-H441	Lung	1.499	3.145	0.3699	3.455	0	1	0	0
NCI-H358	Lung		-0.08947	-1.161	2.691	0	1	0	0
NCI-H1355	Lung	2.577	1.631	1.758	4.397	0	1	0	0
NCI-H1573	Lung	1.65	2.363	0.5107	1.781	0	1	0	0
ONS-76	CNS		0.4218			0	0	0	1
P12-ICHIKAWA	Blood	0.1629	-0.5027	-2.779	0.5863	0	0	0	1
PA-1	Ovary	4.814	2.76	2.104	5.259	0	0	0	1
RCM-1	GI tract	-0.7	0.2073	-3.055	-1.989	0	1	0	0
RD	Soft tissue	1.516	0.9025	-2.699	1.214	0	0	0	1
RKO	GI tract	-1.402	2.201	-2.958	0.3409	1	0	0	0
RVH-421	Skin	-1.279	-0.01832	-4.376	-3.368	1	0	0	0
SH-4	Skin		0.3905			1	0	0	0
SK-HEP-1	Other	0.8217	1.797	-1.762	0.6682	1	0	0	0
SK-LU-1	Lung	1.327	1.293	-1.26	2.446	0	1	0	0
SK-MEL-1	Skin		0.1979			1	0	0	0
SK-MEL-3	Skin	0.6664		-0.5469	0.9418	1	0	0	0
SK-MEL-28	Skin		-1.082	-0.03023	1.697	1	0	0	0
SK-MEL-30	Skin	-0.2261	1.92	0.2876	2.494	0	0	0	1
SNU-387	Other	3.059	2.909	0.153	2.792	0	0	0	1
SNU-C2B	GI tract	2.87	2.415	-0.6852	2.07	0	1	0	0
SW1116	GI tract	1.904	0.4541	-2.786	1.579	0	1	0	0
SW1417	GI tract	1.615	2.267	-0.8153	1.762	1	0	0	0
SW1463	GI tract	4.143	0.3185	-1.285	1.436	0	1	0	0
SW626	Ovary		1.08			0	1	0	0
SW837	GI tract		2.409	-0.2591	2.772	0	1	0	0
SW872	Soft tissue	0.2673	4.408	-3.495	-0.2346	1	0	0	0
SW948	GI tract	3.095	3.8	-0.9721	1.68	0	1	0	0
SW982	Soft tissue	2.975	2.87	0.6018	-0.8337	1	0	0	0
T84	GI tract	5.321	5.965	2.929	4.682	0	1	0	0
TGBC11TKB	GI tract	2.213	2.788	-1.142	1.655	0	1	0	0
VM-CUB-1	Bladder	1.396	3.271	-0.826	1.314	0	0	1	0
WM-115	Skin	-1.329	-0.7272	-3.037	-0.8586	1	0	0	0
YAPC	pancreas	3.955	5.047	3.177	3.339	0	1	0	0
PSN1	pancreas	-1.006	-0.0455	-3.261	-1.628	0	1	0	0
COLO-678	GI tract	0.5067	2.064	-1.747	0.7564	0	1	0	0
COLO-668	Lung	4.165	5.388	1.23	2.605	0	1	0	0
AsPC-1	pancreas	-1.143	1.647	-3.086	0.09245	0	1	0	0
IA-LM	Lung		3.538			0	1	0	0
C3A	Other	3.199	3.303	0.04142	2.709	0	0	0	1

RPMI-7951	Skin	2.159	1.541	-1.192	-0.3108	1	0	0	0
SW1990	pancreas	1.394	2.523	-0.02852	2.954	0	1	0	0
Capan-2	pancreas	3.626	2.723	-1.324	4.381	0	1	0	0
A101D	Skin	-1.417	-1.559	-4.468	-2.961	1	0	0	0
BFTC-905	Bladder	0.8748	1.043	-2.047	-0.3296	0	0	0	1
GAK	Skin	0.6507	0.1816	-2.701	-0.5825	0	0	0	1
AM-38	CNS	5.152	2.68	0.3405	2.423	1	0	0	0
8505C	Other		4.507			1	0	0	0
BCPAP	Other	0.7337	1.733	-2.043	0.7375	1	0	0	0
HTC-C3	Other	-1.532	-0.7758	-5.119	-2.119	1	0	0	0
KS	Other		-0.8277			1	0	0	0
L-363	Blood	2.651	1.013	2.314	5.043	0	0	0	1
MMAC-SF	Skin		-2.226			1	0	0	0
MFH-ino	Soft tissue		5.66			0	0	0	1
PANC-03-27	pancreas	1.484	1.199	-1.632	-0.2798	0	1	0	0
PANC-08-13	pancreas	4.446	3.369	0.2521	4.662	0	1	0	0
PANC-10-05	pancreas	1.772	1.896	-0.6389	4.21	0	1	0	0
HAL-01	Blood	0.5493	4.553	-0.8092	2.867	0	0	0	1
LAN-6	CNS	1.035	1.465	-2.078	-0.659	0	1	0	0
MZ2-MEL	Skin	-0.937	0.7456	-3.34	-1.144	0	0	0	1