Progress in Lipid Research 90 (2023) 101225

Contents lists available at ScienceDirect

Progress in Lipid Research

journal homepage: www.elsevier.com/locate/plipres

Review

The Niemann-Pick type diseases – A synopsis of inborn errors in sphingolipid and cholesterol metabolism

Frank W. Pfrieger *

Centre National de la Recherche Scientifique, Université de Strasbourg, Institute of Cellular and Integrative Neurosciences, Strasbourg, France

ARTICLE INFO

Keywords:
Cholesterol
Lipidosis
Sphingolipids
Ceramide
Lysosome
Lysosomal storage disorder
Neurologic
Psychiatric
Sterol
Neurodegeneration

ABSTRACT

Disturbances of lipid homeostasis in cells provoke human diseases. The elucidation of the underlying mechanisms and the development of efficient therapies represent formidable challenges for biomedical research. Exemplary cases are two rare, autosomal recessive, and ultimately fatal lysosomal diseases historically named "Niemann-Pick" honoring the physicians, whose pioneering observations led to their discovery. Acid sphingomyelinase deficiency (ASMD) and Niemann-Pick type C disease (NPCD) are caused by specific variants of the *sphingomyelin phosphodiesterase 1* (*SMPD1*) and *NPC intracellular cholesterol transporter 1* (*NPC1*) or *NPC intracellular cholesterol transporter 2* (*NPC2*) genes that perturb homeostasis of two key membrane components, sphingomyelin and cholesterol, respectively. Patients with severe forms of these diseases present visceral and neurologic symptoms and succumb to premature death. This synopsis traces the tortuous discovery of the Niemann-Pick diseases, highlights important advances with respect to genetic culprits and cellular mechanisms, and exposes efforts to improve diagnosis and to explore new therapeutic approaches.

1. Introduction

Inborn errors of lipid metabolism cause havoc in vulnerable cells, notably neurons, provoking rare but often fatal diseases [1–5]. Variants of lipid-related genes also increase the risk of prevalent disorders presenting age-dependent neurodegeneration [6–10]. Although the genetic culprits for many pathologic conditions have been uncovered, it is unclear how defective homeostasis of specific lipids provokes progressive neurologic symptoms and shortens the life span of patients, in the most severe cases to just a few months. The elucidation of mechanistic links between the genetic defects and the pathologic changes in specific organs, notably the nervous system, and the development of efficient diagnostic and therapeutic approaches represent formidable challenges for biomedical research. The Niemann-Pick diseases are prime examples for pathologic conditions provoked by deficient lipid homeostasis. This synopsis aims to trace their tortuous discovery, highlights important advances with respect to genetic culprits and disease mechanisms, and exposes efforts to improve diagnosis and to explore new therapeutic approaches.

The historic term "Niemann-Pick" encompasses two rare, autosomal recessive lysosomal disorders [11–13] (Table 1). Acid sphingomyelinase deficiency (ASMD), also known as Niemann-Pick type A, A/B and B disease (Table 1), is caused by mutations in the *sphingomyelin phosphodiesterase 1* (*SMPD1*) gene encoding the enzyme acid sphingomyelinase (ASM; EC 3.1.4.12) [14–20]. The different forms of Niemann-Pick type C disease (NPCD) are caused by mutations in *NPC intracellular cholesterol transporter 1* (NPC1 disease) or–less frequently–in *NPC intracellular cholesterol transporter 2* (NPC2 disease) [21–26] (Table 1).

ASMD and NPCD are rare with estimated birth rates of 1 in 100,000 though higher incidences of specific forms have been reported [27,28]. Numerous variants of the *SMPD1* and *NPC1* or *NPC2* genes (http://www.hgmd.org/) have been identified in ASMD and NPCD patients, respectively, that provoke a wide spectrum of visceral, neurologic and psychiatric symptoms with spleen, liver, lung and brain being the most severely affected organs. Different forms of ASMD [14,16] and NPCD [22,29–31] can be distinguished (Table 1) based on the age of disease onset and the presence of neurologic symptoms, although there is symptomatic overlap between the forms. Patients with the most severe phenotypes present visceral (pre- or perinatal NPCD) and neurovisceral signs (infantile neurovisceral ASMD) during the first months after birth

Abbreviations: ASM, acid sphingomyelinase; ASMD, acid sphingomyelinase deficiency; HPBCD, hydroxypropyl-beta-cyclodextrin; NPCD, Niemann-Pick type C disease; PPCS, N-palmitoyl-O-phosphocholineserine; rhASM, recombinant human ASM.

* Corresponding author at: Institut des Neurosciences Cellulaires et Integratives, CNRS UPR 3212, 8, allée du Général Rouvillois, 67000 Strasbourg; France.
E-mail addresses: frank.pfrieger@unistra.fr, fw-pfrieger@gmx.de.

https://doi.org/10.1016/j.plipres.2023.101225
Received 2 February 2023; Received in revised form 27 March 2023; Accepted 27 March 2023
Available online 31 March 2023

Table 1
Classification of Niemann-Pick diseases.

Disease	OMIM	Genes	Historic	Forms (age of onset)
Acid Sphingomyelinase Deficiency	257200	*SMPD1*	Type A	- Infantile neurovisceral (early infantile)
	–		Type A/B	
	607616		Type B	- Chronic neurovisceral (childhood)
				- Chronic visceral (child-/adulthood)
Niemann-Pick Type C1	257220	*NPC1*	Type C or D	- Perinatal (2 mths)
Niemann-Pick Type C2	607625	*NPC2*		- Early infantile (2-24 mths)
				- Late infantile (2-6 yrs)
				- Juvenile (6-15 yrs)
				- Adolescent/Adult (>15 yrs)

Table 2
Symptoms common to ASMD and NPCD.

Type	Symptom
Systemic	Hepatosplenomegaly
	Liver fibrosis, cirrhosis
	Cholestatic jaundice
	Fetal hydrops
	Portal hypertension
	Interstitial lung disease
	Thrombocytopenia
Neurologic	Dystonia
	Dysphagia
	Hypotonia
	Ataxia
	Intention tremor
	Speech delays
	Delayed motor development
	Loss of motor skills
	Cognitive impairment
	Intellectual decline
Psychiatric	Disruptive/aggressive behaviour
	Depression
	Psychosis

and die within the first years of life. On the other side of the spectrum are NPCD patients presenting neurologic or psychiatric symptoms as adolescents or adults, and ASMD patients with the chronic visceral form presenting progressive visceral symptoms at childhood or later with no neurologic signs. Although individual presentation varies widely, several symptoms are common to both diseases (Table 2). Based on current diagnoses, most NPCD and ASMD patients show the infantile [29,31,32] and the chronic visceral form [33], respectively. Regardless of the form, the relentless progression of ASMD and NPCD degrades the quality of life of patients [34,35] and demands multidisciplinary medical care [36,37].

The primary defects of the diseases concern proteins that ensure the homeostasis of sphingomyelin (ASMD) and cholesterol (NPCD) in cells. These very prominent molecules are intensely studied in numerous biological contexts, as they serve as intimately linked building blocks of eukaryotic membranes [38–42] and as key components of cellular signaling pathways [43–49].

2. Early history

The research history of the diseases bearing the name Niemann-Pick started at the beginning of the 20th century. While working as an intern at the children's hospital of the Charité in Berlin, Germany, the pediatrician Albert Niemann tried to diagnose a 17-months-old girl named Irene. The infant presented a "colossally swollen abdomen (circumference 50 cm)", apathy and a "quite miserable nutritional state". Following the practice and the methods known at the time, Niemann tested and treated the child for congenital syphilis–without success. Irene died within 4 weeks. In 1914, Niemann published a case report with the blatantly honest title "An unknown clinical picture" ["Ein unbekanntes Krankheitsbild"]. He wrote that he never saw or read about a similar case, and he noted differences to morbus Gaucher [50]. Niemann died in 1921 from tuberculosis, but his observations were followed up by other

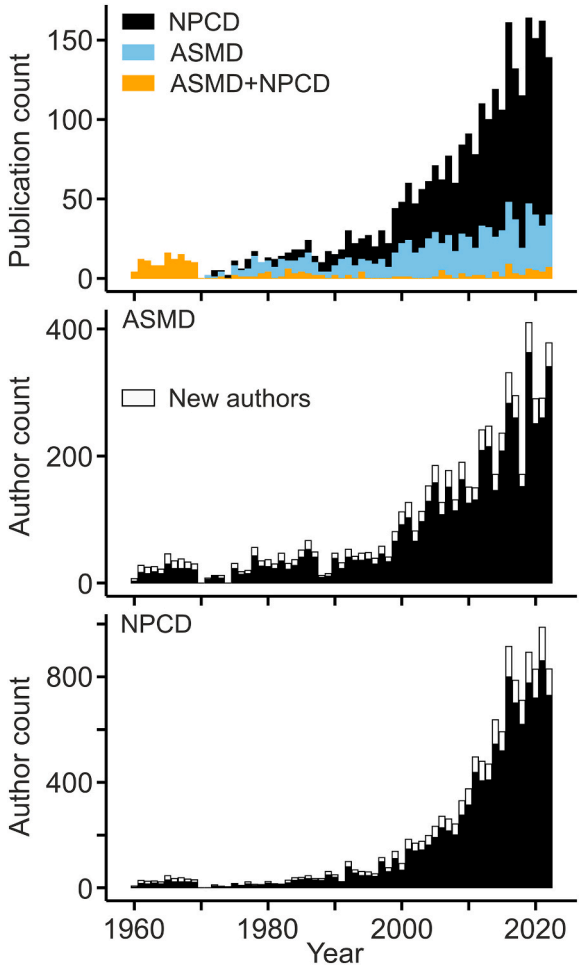

Fig. 1. Development of the ASMD and NPCD field based on publications and authors.
Stacked bar graphs showing (top) the annual count of publications related to both diseases (orange), to ASMD only (sky blue) and to NPCD only (black), and the annual counts of authors contributing articles to ASMD (center) and NPCD (bottom). White bars indicate number of authors publishing for the first time in each field (New authors; see the appendix for the Web of Science queries). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

colleagues, notably the eminent German pathologist Ludwig Pick. The protocol of the scientific discussion following a presentation given by Pick in 1922 documents his clairvoyant assessment. He stated that the cases reported by Niemann and others [51,52] belong to a distinct group of "lipoidcell splenohepatomegaly of infants" ["Lipoidzellige Splenohepatomegalie der Kinder"] [53]. In an article published in 1924, he summarized histopathologic changes in these patients, and he coined the new nosologic term "lipoidcell splenomegaly (type Niemann)" ["lipoidzellige Splenomegalie (Typus Niemann)"] [54]. In a comprehensive review published in 1926, Pick outlined thoroughly what distinguishes the cases with "lipoidcell hepatosplenomegaly type Niemann" from Gaucher disease [55]. He stated that central to the pathogenesis is a primary defect in metabolism, which causes an overload of blood and tissues with fat-like substances ("lipoids"). In the same year, when Pick published his review, the yet-to-become famous pediatrician Erwin Schiff was the first to use the term "type Niemann-Pick" for his diagnosis of a 17-months-old boy. Remarkably, Schiff accomplished this diagnosis *ante-mortem* by splenic biopsy [56]. Curiously, at least one author used transiently the term "Pick-Niemann" disease [57]. In 1927, Brahn and Pick reported several-fold increased levels of cholesterol in spleens of Niemann-Pick patients compared to normal controls [58]. In the 1930s, Ernst Klenk discovered elevated levels of sphingomyelin in their spleen [59], liver and brain [60,61], which were confirmed by other colleagues [62,63]. Fast forward to 1961, when Allen C. Crocker working at the Children's Hospital of the Harvard Medical School (USA) distinguished four forms of the disease (A though D; Table 1) [64] based on a previous review of visceral and neurological symptoms, and biochemical measures in patients [65]. "Type D" comprised exclusively patients from a large Acadian family living in Nova-Scotia since the 17th century [66]. Given the symptomatic variation among patients and the limited diagnostic methods, the classification of Niemann-Pick patients remained problematic until the 1980s (see for example [67]). Two additional categories of Niemann-Pick disease appeared in the 1970s that are now obsolete. Niemann-Pick type E presenting visceral sphingomyelin storage without neurologic involvement and normal ASM activity was proposed in 1972 by Fredrickson and Sloan based on several patients with mostly non-familial disease [68]. Type F was proposed in 1978 by Schneider and colleagues based on their discovery of a heat-labile form of ASM in patients from two families presenting hepatosplenomegaly in their childhood but no neurologic symptoms [69].

3. Foundational research

The nosology established by Crocker started the modern era of research on the Niemann-Pick diseases. Selected publications that provided insight into molecular and cellular mechanisms, that established methods and tools, and that explored diagnostic and therapeutic approaches are mentioned in the following paragraphs. Fig. 1 shows the development of the fields based on annual counts of scientific articles and contributing authors including newcomers.

In 1966, Roscoe O. Brady and colleagues working at the National Institutes of Health in the USA identified a defect in an enzyme that cleaves sphingomyelin, the ASM, as cause for the "classic infantile form of Niemann-Pick disease". This form corresponded to Crocker's type A [70,71]. The group further established a first enzymatic test to diagnose ASMD based on blood samples [72] and on skin or bone marrow cells derived from patient biopsies [73]. These findings marked a breakthrough for ASMD, but they confused research into the cause of NPCD. The latter field squandered for more than 10 years in the labyrinth of the sphingomyelinase hypothesis (see for example [74–78]). Nonetheless, Crocker already presumed distinct genetic causes for the different forms of the disease, and normal levels of ASM activity were detected in organs from Niemann-Pick Type C and D patients [75,79–81]. In the 1980s, evidence for a distinct molecular cause for NPCD came from studies on a strain of mice presenting progressive neurologic symptoms and premature death [82]. They revealed impaired cholesterol esterification [83–85] and disturbed intracellular transport of unesterified cholesterol [86,87] causing its accumulation in late endosomes/lysosomes [88–90]. Together, these findings established NPCD as a distinct nosologic entity.

4. Genetic culprits of the diseases

Key steps to advance research on inherited diseases are the identification of the mutated gene(s) and the characterization of the encoded proteins. In the case of ASMD, the cloning, expression and chromosomal localization of human and mouse *SMPD1* [91–95] allowed for the identification of disease-causing mutations in patients [96–98], measurements of their impact on ASM activity [99], the detection of carriers [100], and a first exploration of genotype-phenotype relations [101,102]. Comparisons of patient-derived cells and organs indicated that the infantile neurovisceral form of ASMD is provoked by extremely low levels of ASM activity [79,103–106]. The discovery of paternal imprinting at the *SMPD1* locus helped to explain at least in part the wide clinical spectrum of ASMD patients [107].

The identification of genes causing NPCD was delayed by several years compared to the breakthroughs on the ASMD front. The existence of distinct genetic culprits causing ASMD and NPCD was indicated by early observations that different genes complement the defects of fibroblasts from Niemann-Pick Type A and B compared to type C patients [103]. The first gene causing NPCD disease, named *NPC1*, was identified in 1997 [108,109]. Patients originally assigned to type D, the so-called "Nova Scotia type", carried a specific allele of *NPC1* [110]. Earlier studies had indicated the presence of a second gene provoking NPCD [111,112], which was subsequently identified as *NPC2* [113]. This gene was identical to *EPI-1* and *HE1* genes that were originally described in the 1990s as major components of epididymal fluid from chimpanzees [114] and humans [115], respectively. The functional collaboration between NPC1 and NPC2 in the lysosome was first indicated by experiments with genetically modified mice [116].

5. The proteins and their functions

The discovery of the defective proteins proceeded in parallel to the identification of the mutated genes. The enzyme defect causing ASMD was known since the 1960s, but the characterization of the protein, ASM, took off in the 1980s with its purification to homogeneity [117–119]. Further research revealed several processing steps generating different forms of the enzyme [120] that are targeted to the lysosome [121–124] or released to the extracellular space [125–127] upon external signals [128]. Other properties of the enzyme, which comprises 631 amino acids, were uncovered. This includes the presence of a saposin-like activator domain thus forgoing the need of co-activator proteins [129,130], and the dependence of its activity on zinc [126,131,132], post-translational modifications [133–135] and the cellular redox status [136–138]. The elucidation of the protein structure brought new insight with respect to conformations, binding sites, and the impact of mutations on protein structure and function [139–141]. Enzyme activity assays revealed that ASM is a promiscuous phosphodiesterase cleaving phospholipids other than sphingomyelin [142].

Starting in the 1980s, interest in ASM was propelled into new spheres by evidence that the enzyme and its product, ceramide, are implicated in different signaling pathways and cellular processes, notably apoptosis [143–150]. These findings provoked studies of ASM in the context of diverse pathologic conditions including atherosclerosis [151], bacterial or viral infections [152–154], dermatitis [155], emphysema [156], Wilson disease [157], cystic fibrosis [158], depression [159], and Alzheimer disease [160]. Evidence that specific variants of ASM enhance the risk for Parkinson disease have opened new avenues for research on this prevalent disorder [161–163].

Characterization of the proteins encoded by *NPC1* and *NPC2* took off after the identification of the genes. Human NPC1 is a relatively large protein comprising 1278 amino acids and 13 transmembrane domains.

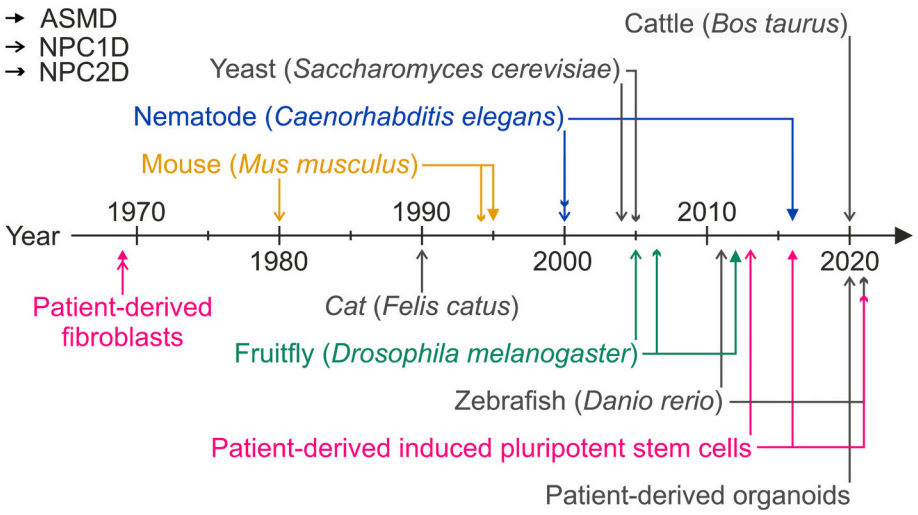

Fig. 2. Development of experimental models.
Timeline showing the development of experimental models for ASMD and NPCD. Model organisms used to study both diseases are indicated in colors, organisms in grey have been established for NPCD only.

Its smaller partner NPC2, made of 151 amino acids, is water-soluble and bears a hydrophobic pocket. Studies revealed the presence of NPC1 [164–167] and NPC2 [113,168–170] in late-endosomes/lysosomes, their glycosylation patterns [171–174], their binding of sterols [173,175–179], their interactions with lipids [180–183] and proteins [174,183–188], their critical domains [189,190], and the destiny of the frequent, disease-causing NPC1 variant I1061T [191–193]. Decisive insight in the molecular functions of NPC1 and NPC2 came from cryo-electron microscopic and x-ray diffraction analyses of their atomic structures [190,194–203]. A key finding was that binding pockets in NPC1 and NPC2 accommodate cholesterol in opposite directions. This insight inspired the "hydrophobic hand-off" model that explains how NPC2 transfers cholesterol to NPC1 [196,204]. The absence of NPC2 may explain the lack of NPC1-mediated cholesterol transport in an artificial system [205]. A next advance was the discovery of a tunnel inside the NPC1 protein, as shown for its distant relative PATCHED [206], enabling cholesterol to crawl through the protein [201–203]. The exact mechanisms how cholesterol exits the endosomal-lysosomal system and reaches other cellular organelles are under investigation. During the last decade, studies on generic cells such as cell lines or fibroblasts proposed several pathways including other carriers such as StARD proteins [207–209] and membrane contact sites [210–218]. The contribution of each pathway probably depends on the specific type of cell and the intracellular targets receiving recycled or imported cholesterol.

Similarly as interest in ASM was boosted in the 1990s by its newly discovered roles in cell signaling, interest in NPC1 was turbocharged during the last decade by its identification as cellular receptor for filovirus [219,220], which spawned an entire new branch of research [221] and incited the development of new tools [222]. In addition, specific NPC1 variants have been identified as risk factor for obesity [223,224].

6. Experimental models

Experimental models are essential to explore disease mechanisms and to develop therapeutic approaches. The first models for ASMD were cells from patient-derived skin and bone marrow biopsies [73] and immortalized lymphoid cells [225] with the more recent addition of induced pluripotent stem cells [226] (Fig. 2). Identification of the *SMPD1* gene enabled the generation of knock-out mice (Fig. 2). These animals show accumulation of lipids in visceral organs [227] and in different brain regions [228] and degeneration of cerebellar Purkinje cells [229], they develop neurologic symptoms between the third and fourth month of age, and they die prematurely [230,231]. Heterozygous *Smpd1* mice also show changes including sperm abnormalities [232], reduced susceptibility to liver disease [233,234], and focal ischemia [235]. ASM-deficient mice are used to study a large variety of cellular processes given the above-mentioned roles of ASM and ceramide in diverse signaling pathways [149,236]. Transgenic mice have also been developed to study specific variants of ASM. Mice expressing a chimeric *SMPD1* targeted to the lysosome show a level of enzymatic activity that is high enough to avoid development of neurologic symptoms [237]. Other transgenic mice express specific human *SMPD1* variants on a *Smpd1*-deficient background [238] or variants that lack a caspase cleavage site [154]. With respect to other mammals, ASMD-like symptoms were described in a Balinese cat [239], a poodle dog [240], a Hereford calf [241], and a juvenile raccoon [242], but no breeding colonies were established. Eukaryotic orthologs of ASM and the outcome of their deficiency were described in the nematode *Caenorhabditis elegans* [243,244] and the fruit fly *Drosophila melanogaster* [245,246] (Fig. 2). Small-molecule inhibitors of ASM [247,248] can be used to interrogate the impact of reduced ASM activity on cells or tissues [249].

The arsenal to explore NPCD is well armed (Fig. 2). Here, selected advances on this front are highlighted, detailed overviews can be found elsewhere [250,251]. As for ASMD, the first models to study NPCD were primary cultures of patient-derived fibroblasts [73] followed by Chinese hamster ovary cell lines bearing defects in NPC1 [252], and neurons derived from embryonic stem cells [253,254]. Protocols to generate pluripotent stem cells from patient fibroblasts and to convert these cells to cell types of interest allowed to study how defects of NPC1 [255–259] and NPC2 [260] affect human neurons and other cell types in vitro [261]. New cell-based disease models allow to investigate the functional impact of NPC1 variants [262–264]. Organoid models help to assess the impact of NPC1 on brain cells and the efficacy of therapeutic approaches at a more integrated level than traditional two-dimensional cell cultures [265]. Pharmacologic induction of a NPCD-like phenotype in cells can be achieved by U186669A [266–268] and itraconazole [201,269,270], which inhibit NPC1 activity albeit through distinct binding sites [201,269].

The parade of animal models for NPCD started in the 1980s with mammals (Fig. 2). Mice of the BALB/C [271] and C57BL strains [272] and a cat [273–275] all bearing spontaneous mutations in the *Npc1* locus [109,276,277] recapitulate some of the neurologic symptoms seen in humans, and they die prematurely. Heterozygous individuals of the mouse strains also present changes such as increased caveolin-1 expression [278], reduced macrophage death due to atherosclerosis

[279], impaired glucose tolerance [280], reduced activity of the cytochrome P450 system [281], and delayed neurodegeneration [282]. The latter change recapitulates neurologic symptoms observed in feline [283] and human heterozygous *NPC1* carriers [284,285]. The mouse models with spontaneous mutations in *Npc1* were complemented by genetically modified mice bearing selected human *NPC1* variants or allowing for cell-specific analyses [286–291]. The latest arrival in the zoo of NPC1-deficient mammals are Angus cattle [292] (Fig. 2). The functions of NPC2 and its interactions with NPC1 in mammals have been studied in *Npc2* knock-down mice [116,181,293], which recapitulate neurovisceral symptoms.

Apart from mammals, a wide range of uni- and multicellular organisms is used to study the impact of NPC1 or NPC2 deficiency (Fig. 2), since NPC1 and NPC2 are "old inventions", and orthologs are present in many phyla [294–297]. This includes workhorses of biological sciences including the plant *Arabidopsis thaliana* (NPC1: [298]), the ciliate *Tetrahymena thermophila* (NPC1: [299]), yeast (NPC1: [300–305]; NPC2: [304,306]), the fruitfly *Drosophila melanogaster* (NPC1: [307–310]; NPC2: [311,312]), the nematode *Caenorhabditis elegans* (NPC1 [313,314]; NPC2 [313,315]), and the fish *Danio rerio* (NPC1: [316–318]; NPC2: [319,320]). Given the diverse functions of NPC1 and NPC2 orthologs, notably as odorant and pheromone carriers in arthropods [321,322], the "ancient" versions of these proteins are of increasing interest in diverse contexts including allergy [323,324], infectious diseases [325–331], and agricultural pest control [332–337].

7. Methods and tools for experimental research

Diverse methods and tools have been developed to study the biologic impact of the genetic variants on cells and to uncover disease mechanisms. The pioneers like Niemann and Pick relied on histologic staining methods and light microscopic inspection of biopsies and post-mortem samples. These techniques revealed a vacuolated appearance of cells due to the presence of "fat-like" substances ("lipoids") [50,55]. Starting in the 1960s, electron microscopy showed very particular membraneous structures named myelin figures, multilamellar bodies or polymorphous cytoplasmic inclusions, in cells from different tissues and organs of ASMD and NPCD patients [338–343] even before the accumulating lipids were identified. Enzymatic activity of ASM has been measured by radiometric [76,344], chromogenic [345], fluorometric [346–349], and mass spectrometric [350] assays, some of which were used for diagnosis and for newborn screens based on dried blood spots [351–357].

The intracellular accumulation of sphingomyelin due to defects in ASM can be tracked by light microscopy using fluorescent analogues [358,359] and by proteins such as lysenin [360,361] and actinoporins [362] that are produced by earth worms and sea anemones, respectively [363,364]. These proteins can be detected by light and electron microscopy after direct or indirect labeling [365]. At present, the intracellular transport activity of the NPC1/NPC2 team cannot be measured directly; cell-free assays were developed to study cholesterol transport by NPC2 between donors and acceptors [180,366]. The accumulation of unesterified cholesterol within cells due to NPC1 or NPC2 dysfunction can be visualized by filipin [83,367], a complex of several fluorescent polyenes secreted by *Staphylococcus filipinensis* [368–370]. Application of this cytochemical stain to patient-derived fibroblasts facilitated the notoriously protracted and difficult diagnosis of NPCD [371–373]. The presence of filipin-stained cholesterol in ultrastructurally defined lamellar inclusions was shown by correlative light and electron microscopic inspection [374]. Additional tools to visualize the distribution of cholesterol in cells are cholesterol-binding proteins derived from theta toxin (perfringolysin O), a cytolysin secreted by *Clostridium perfringens* [375–377], and fluorescent analogues or modified versions of cholesterol (for review see [378]). Other natural, protein-based toxins recognize sphingomyelin/cholesterol complexes [363,364,379]. Additional, indirect approaches to track ASMD- and NPCD-induced defects in cells are based on the accumulation of fluorescent lactosyl-ceramide [380,381], and on the pathologic expansion of the acidic cellular compartment labeled by a pH-dependent fluorophore (Lysotracker). The size of this compartment in patient fibroblasts correlates with disease onset and severity [382–384]. These tools together with biochemical measurements of NPC1 protein levels were used to explore genotype-phenotype correlations for NPC1 [381,385–388] and NPC2 patients [389]. Further additions to the toolbox are functionalized sphingolipids and cholesterol for concentration-clamp, crosslinking and tracking [183,390–394], probes to monitor endosomal-lysosomal function and lipid accumulation in living cells [395–397], and new approaches to analyse the molecular content of lysosomes [398–400]. The latter are critical feats to study diseases affecting this organelle [12].

8. Clinical tests and measures

Clinical research and development require methods to identify and diagnose patients, to measure disease severity, to monitor its progression, and to gauge the efficacy of drug candidates in an objective and quantitative manner. A major breakthrough with respect to genetic tests was the advent of next-generation sequencing of DNA and RNA combined with advanced bioinformatic tools in the beginning of the 2000s. These techniques enabled the detection of new variants, facilitated the diagnosis of patients and led to a revision of carrier frequencies [28,401–408]. The genetic tools have also advanced experimental research as they help to track cell-specific reactions to NPC1 or NPC2 deficiency [320,374,409,410].

Clinical severity scales to quantify disease state and monitor its progression have been developed for ASMD [411] and for NPCD [412–417]. Natural history data summarizing the course of the diseases in individual patients were collected for ASMD [16,411,418–423] and for NPCD [424–434]. Clinical suspicion indices have been developed to identify NPCD patients [435–438]. Databases listing gene variants and patient information (registries) for ASMD [439] and NPCD [412,414,429,440–442] have been established facilitating preclinical and clinical research.

These developments were accompanied by the discovery of molecular biomarker candidates in body fluids of patients. Ideally, these molecules, produced in specific cells and tissues, should serve as surrogate markers of clinical endpoints allowing to monitor disease progression and to gauge the efficacy of therapeutic interventions in patients [443]. Biomarker candidates for ASMD measured in blood were cytokines [444,445], growth hormone and iron [446], 7-ketocholesterol [447], lysosphingomyelin/sphingosylphosphorylcholine [448,449], lysophingomyelin-509 [450]. With respect to NPCD, blood-derived biomarkers were 7-ketocholesterol [451], oxysterols [451–453], 7-ketocholesterol [451], and bile acids [454–456], galectin-3 (LGALS3) and cathepsin D (CTSD) [457], different sphingolipids [458,459], lysophingomyelin-509 [450], later identified as N-palmitoyl-O-phosphocholineserine (PPCS) [460,461], glycoprotein nonmetastatic melanoma protein B (GPNMB) [462–464], neurofilament light chain [465,466], and differences in metabolite profiles [467]. Biomarker candidates in cerebrospinal fluid were calbindin [468], fatty acid binding proteins [469], microglia-derived CD22 [470], neuropeptide Y [471] and neuroinflammation-related molecules [471–473]. In addition, cholesterol metabolites [474] and the small non-coding microRNAs miR-155 [475] may serve as markers in urine and tissues, respectively. Measures of sphingolipids and oxysterols were used to screen for ASMD and NPCD patients [476–480]. Recent studies show that the accurracy and specificity of biomarkers can be increased when several of them are detected in parallel and subjected to multivariate analyses [481,482]. Given the complexity of the Niemann-Pick diseases and the wide symptomatic variability among patients, diagnoses of ASMD and NPCD based on biomarkers must be validated by an ASM activity assay [483] and by genetic tests of NPC1 and NPC2, respectively [373,484,485]. Although non-specific, diverse methods have been proposed to evaluate and monitor disease state in ASMD [17,18] and NPCD patients [22].

Table 3
Cell-specific changes in ASMD and NPCD.

Cell type (source*)	Disease	Change	References
Adipocytes, in vitro (h, m)	NPCD	Impaired differentiation and maintenance (NPC2-dependent)	[572]
Alveolar cells type II (m, c)	NPCD	Perturbation of autophagy and surfactant production	[573,574]
Astrocytes, microglial cells (h, m)	ASMD, NPCD	Different pathologic changes	ASMD: [563]; NPCD [409,470,502,550,563,565–567,575–584]
Generic cells: cell lines (m)	ASMD	Enhanced activator protein 1 (AP1) signaling	[585]
Generic cells: cell lines, fibroblasts (h, m)	ASMD	Impaired endocytosis and plasma membrane repair	[154,586]
Generic cells: cell lines, fibroblasts (h, m)	NPCD	Enhanced fluidity of plasma membrane	[587]
Generic cells: cell lines, fibroblasts (h, m)	NPCD	Impaired motility of endosomal-lysosomal compartments	[397,588–592]
Generic cells: fibroblasts (h)	NPCD	Production of oxysterols	[593]
Generic cells: cell lines, fibroblasts (h)	NPCD	Perturbed RAB9-dependent sorting of mannose 6-phosphate receptors	[594]
Generic cells: fibroblasts (h)	NPCD	Enhanced oxidative stress	[595]
Generic cells: fibroblasts (h)	NPCD	Perturbation of autophagy	[527,596]
Generic cells: cell lines, fibroblasts (h)	NPCD	Impaired lysosomal calcium release	[393,597]
Generic cells: cell lines, fibroblasts (h)	NPCD	Enhanced exosomal cholesterol release	[598]
Generic cells: cell lines, fibroblasts (h)	NPCD	Impaired lysosomal proteolysis	[527,599]
Generic cells: cell lines, fibroblasts (h)	NPCD	Hyperactivation of mechanistic target of rapamycin complex 1 (mTORC1)	[185,599]
Generic cells: cell lines	NPCD	Changes in lysosomal glycocalyx	[600]
Generic cells: cell lines, fibroblasts (h)	ASMD, NPCD	Impaired cellular cholesterol efflux	[218,601,602]
Generic cells: cell lines, fibroblasts (h)	ASMD, NPCD	Increased permeability of lysosomal membranes	[599,603]
Generic cells: cell lines, fibroblasts (h)	ASMD, NPCD	Impaired biogenesis and function of mitochondria	[305,604]
Choroid plexus epithelial cells (m)	NPCD	Enhanced extracellular vesicle secretion	[605]
Coronary arterial smooth muscle cells (m)	ASMD	Perturbation of autophagy	[606]
Germline cells (m)	ASMD, NPCD	Impaired maturation of oocytes and spermatozoa	ASMD: [607]. NPCD: [608–610]
Hepatic stellate cells (m)	ASMD	Enhanced cathepsin activity	[611]
Hepatocytes, liver (m)	NPCD	Impaired peroxisome function	[612]
Hepatocytes, liver (h, m)	NPCD	Perturbation of metal homeostasis (zinc, copper and iron)	[613,614]
Hepatocytes (m)	NPCD	Impaired insulin signaling	[615]
Hepatocytes, liver (m)	NPCD	Impaired mitochondrial function	[604,616–619]
Hepatocytes (h)	NPCD	Perturbation of autophagy	[261]
Macrophages (m)	ASMD	Impaired killing of bacteria	[620,621]
Macrophages (m)	NPCD	Enhanced oxidative stress	[622]
Macrophages (h)	NPCD	Perturbation of autophagy	[623]
Lymphocytes, B type (h)	NPCD	Impaired lysosomal calcium release	[537]
Lymphocytes, B type (h)	ASMD	Perturbation of autophagy	[624]
Lymphocytes, T type (m)	ASMD	Impaired plasma membrane signaling and proliferation	[625]
Lymphocytes, T type (m)	ASMD	Cytotoxic granule secretion	[626]
Lymphocytes, T type (h)	NPCD	Impaired perforin activity	[627]
Lymphocytes, T type (Invariant natural killer cells) (h, m)	ASMD, NPCD	Loss of natural killer T cells; diminished lipid/antigen presentation	ASMD: [628]. NPCD: [181,629–631]
Microglial cells (m)	NPCD	Enhanced cathepsin levels and activity	[564,632]
Neurons, brain (m)	ASMD	Perturbed surface distribution of gangliosides and glycosyl phosphatidyl inositol–anchored proteins	[361]

(*continued on next page*)

Table 3 (*continued*)

Cell type (source*)	Disease	Change	References
Neurons, brain (m)	ASMD	Enhanced neutral sphingomyelinase and vitamin D receptor	[633]
Neurons, brain (h)	NPCD	Presence of neurofibrillary tangles	[634–637]
Neurons, in vitro (m)	NPCD	Impaired neurotrophin signaling	[638]
Neurons, brain (m)	NPCD	Modifications of cytoskeletal proteins including microtubulin-associated tau	[639–641]
Neurons, brain (h, m)	NPCD	Impaired amyloid precursor protein processing	[642–647]
Neurons, in vitro (m, r)	NPCD	Cholesterol depletion from axons	[525,648]
Neurons, brain (h, m)	NPCD	Enhanced tumor necrosis factor-alpha signaling	[649]
Neurons, brain (m)	NPCD	Impaired phosphatidylinositol-3 kinase signaling	[650]
Neurons, brain (m)	NPCD	Impaired self-renewal and differentiation of neural stem cells and neuronal precursor cells	[651,652]
Neurons, brain (m)	NPCD	Enhanced cytosolic proteolysis (cathepsin activity)	[560,632,653]
Neurons, brain (h, m)	NPCD	Impaired vascular epithelial growth factor / sphingosine kinase signaling	[654]
Neurons, brain (m	NPCD	Impaired sonic hedgehog signaling	[652,655]
Neurons, brain (m)	NPCD	Enhanced synthesis of cholesterol	[374]
Neurons, brain (m)	NPCD	Hyperexcitability due to decreased expression of a voltage-gated potassium channel (Potassium Voltage-Gated Channel Subfamily Q Member 2/3, KCNQ2/3)	[656]
Neurons, in vitro (h)	NPCD	Impaired lysosomal proteolysis	[599]
Neurons, in vitro (h)	NPCD	Hyperactivation of mechanistic target of rapamycin complex 1 (mTORC1)	[599]
Neurons, brain (m)	NPCD	Impaired transport of lysosomes along axons	[657]
Neurons, brain (m)	NPCD	Activation of the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway	[188]
Neurons, in vitro (r)	NPCD	Enhanced extracellular vesicle secretion	[658]
Neurons, brain (h, m)	ASMD, NPCD	Impaired mitochondrial function, mitophagy	ASMD: [604]. NPCD: [599,659–662]
Neurons, brain (m)	ASMD, NPCD	Defects in axons, dendrites and synapses	ASMD: [229,663,664]. NPCD: [525,543,581,583,665–676]
Neurons, brain (h, m)	ASMD, NPCD	Perturbation of autophagy	ASMD: [677]. NPCD: [261,286,495,527,596,632,662,678,679]
Neurons, brain (m)	ASMD, NPCD	Perturbation of calcium homeostasis	ASMD: [680]. NPCD: [676,681]
Neurons, brain (m)	ASMD, NPCD	Impaired ABL Proto-Oncogene 1, Non-Receptor Tyrosine Kinase (ABL1) signaling	ASMD: [682]. NPCD: [683,684]
Neurons, brain (m, r)	ASMD, NPCD	Enhanced oxidative stress	ASMD: [685]. NPCD: [686,687]
Neurons, brain (h, m)	ASMD, NPCD	Impaired endocannabinoid signaling	[688,689]
Oligodendroglial precursor cells, in vitro (m)	NPCD	Enhanced exosomal cholesterol release	[598]
Oligodendrocytes, Schwann cells, brain (h, m)	ASMD, NPCD	Impaired development and myelination	ASMD: [690]. NPCD: [277,491,567,576,583,674,691–702]
Pancreatic acinar cells (m)	NPCD	Impaired formation of secretory granules	[703]
Platelets (m)	ASMD	Degranulation and thrombus formation	[704]
Spleenocytes, spleen (h, m)	NPCD	Perturbation of metal homeostasis (zinc, copper and iron)	[613,614]
Umbilical vein endothelial cells (h)	NPCD	Inhibition of mechanistic target of rapamycin complex 1 (mTORC1) signaling	[705]

* Source: h, human; m, mouse; r, rat.

Table 4
Therapeutic targets and approaches tested for Niemann-Pick diseases.

Treatment	Model	References
ASMD		
Transplantation, liver	*Smpd1*-/- mice, patients	[747,784,785]
Transplantation, bone marrow cells	*Smpd1*-/- mice, patients	[786–789]
Transplantion, amniotic cells	Patients	[790,791]
Transplantation, bone marrow-derived stem cells, neural progenitor cells; intracerebral	*Smpd1*-/- mice	[530,748,749,792]
Gene therapy, viral vectors	Patient-derived fibroblasts, *Smpd1*-/- mice, healthy non-human primates	[750,793–797]
Enzyme replacement with rhASM (Olipudase alpha, Xenpozyme)	*Smpd1*-/- mice, patients	[752,754,761,762,798–804]
Neutral sphingomyelinase	*Smpd1*-/- mice	[664]
Phosphoinositide PI(4,5)P2 signaling	*Smpd1*-/- mice	[805]
Histone deacetylases, inhibition	*Smpd1*-/- mice	[685]
High density lipoprotein nanoparticles	*Smpd1*-/- mice	[806]
Endocannabinoid system, activation	*Smpd1*-/- mice	[689]
Apolipoprotein D (APOD)	Patient-derived fibroblasts	[722]
NPCD		
Cholesterol lowering drugs	Patients, *Npc1*-/- mice	[763,807,808]
Dietary restriction	*Npc1*-/- cats	[809]
Hydroxy-propyl-beta-cyclodextrin (VTS-270, Adrabetadex, Trappsol Cyclo)	*Npc1*-/- mice, cats, patients	[771,773–775,810–818]
N-butyl-deoxynojirimycin (OGT918, Miglustat, Zavesca)	*Npc1*-/- mice, cats, patients	[413,433,767,768,819–823]
Apoptosis, inhibition	*Npc1*-/- mice	[824]
RAB7/9 signaling	Patient-derived fibroblasts	[186,825]
Vitamin E	*Npc1*-/- mice	[257,826–828]
Allopregnanolone	*Npc1*-/- mice	[772,773,775]
Nuclear receptors, activation	*Npc1*-/- mice	[829,830]
High-density lipoprotein, release	Patient-derived fibroblasts	[831]
Histone deacetylases, inhibition	$Npc1^{nmf164}$, *Npc1*-/- mice	[253,303,832,833]
Implantation of neural stem cells	*Npc1*-/- mice	[834]
Estradiol	*Npc1*-/- mice	[579]
Transplantation of mesenchymal stem cell	*Npc1*-/- mice	[835–837]
Mitogen-activated protein kinase, inhibition	*Npc1*-/- mice	[838]
Bis(monoacylglyceryl) phosphate / lysobisphosphatidic acid	Patient-derived fibroblasts	[839–841]
ABL proto-oncogene 1, non-receptor tyrosine kinase (ABL1), inhibition (Imatinib)	*Npc1*-/- mice	[684,842]
Curcumin	*Npc1*-/- mice	[537,843–845]
Vitamin C	*Npc1*-/- mice	[846]
Cyclin-dependent kinase-5 (CDK5), inhibition	*Npc1*-/- mice	[847]
Non-steroidal anti-inflammatory drugs	*Npc1*-/- mice	[582,846]
Drug-induced lysosomal exocytosis	*Patient-derived fibroblasts, Npc1*-/- mice	[374,684,827,848–853]
Protein replacement, NPC2	$Npc2^{Gt(LST105)BygNya}$ mice	[293]
UDP-glucose ceramide glucosyltransferase (UGCG), inhibition	*Npc1*-/- mice, cats	[769]
Autophagy, enhancers	Induced pluripotent stem cell-derived cells	[261,678,854]
N-acetyl-cysteine	*Npc1*-/- mice	[855]
Copper chelation	*Npc1*-/- mice	[856]
Acetylcholinesterase (ACHE), inhibition	*Npc1*-/- mice	[857]
Combination miglustat, curcumin, ibuprofen	*Npc1*-/- mice	[858]
N-acetyl-DL-leucine, N-acetyl-L-leucine (IB1001)	*Npc1*-/- mice, patients	[415,777,778,859]
Glucocerebrosidase (GBA2), inhibition	*Npc1*-/- mice	[546]
Cathepsins, inhibition	$Npc1^{I1061T}$	[560,564]
Necroptosis, inhibition	*Npc1*-/- mice	[860,861]
Heat shock protein, activation (Arimoclomol)	*Npc1*-/- mice, patients	[783,862,863]
Gene therapy, viral vectors	*Npc1*-/-, $Npc2^{tm1Plob}$, $Npc1^{I1061T}$ mice	[864–870]
Glutathione	*Npc1*-/- mice	[617]
Adenosine A2A receptor (ADORA2A), activation	*Npc1*-/- mice	[700,871,872]
Metabotropic glutamate receptor, activation	*Npc1*-/- mice	[873]
Polymeric beta-cyclodextrin	$Npc1^{nmf164}$ mice	[874]
Pneumococcal immunization	*Npc1*-/- mice	[875]
Histamine H3 receptor (HRH3), activation	*Npc1*-/- mice	[840]
6-O-alpha-maltosyl-beta-cyclodextrin	*Npc1*-/- mice	[876]
Implantation of VEGF-overexpressing neural stem cells	*Npc1*-/- mice	[877]
Cytochrome P450 family 46 subfamily A member 1 (CYP46A1), activation	$Npc1^{nmf164}$ mice, patients	[675,878]
High-density lipoprotein nanoparticles	$Npc1^{I1061T}$ mice	[806]
Endocannabinoid system, activation	*Npc1*-/- mice	[689]
Iron chelation	*Npc1*-/- mice	[879]
Gene therapy, Trojan horse liposomes	*Npc1*-/- mice	[880]
Transcription factor EB (TFEB), activation (Genistein)	Patient-derived fibroblasts	[852]
Lithium carbonate	Patients	[881]
Heat-shock protein 90 (HSP90), inhibition	Patient-derived fibroblasts	[882]
Extracellular vesicles	*Npc1*-/- mice	[883]
Graphene quantum dots	*Npc1*-/- mice	[884]
Acid ceramidase (ASAH1), activation	Patient-derived fibroblasts	[619]
Two-pore channel 2 (TPC2), activation	Patient-derived fibroblasts	[885]
mRNA encoding NPC1	Patient-derived fibroblasts	[886]

This includes histologic analyses of biopsies [383,444,486–488], and non-invasive measurements to assess for example saccades [489], brain anatomy [490–494], structure and function of sensory organs [495–502], neuroinflammation [503], movement [504], swallowing [505] and cholesterol metabolism [506].

Starting in the 2000s, the development of innovative computational methods and the increase in computation power has opened new

directions for the fields. The use of *in silico* and molecular modeling approaches revealed dynamic properties of the proteins and provided new insight in structure-function and genotype-phenotype relations for *SMPD1* [439,507] and *NPC1/NPC2* [263,508–516]. Computer-based extraction of information from large sets of data or text (mining, machine/deep learning etc.) can help diagnosis [517] and suggest new candidates for biomarkers and therapeutic approaches [512,518–520].

9. Cell-specific changes and disease mechanisms

A pressing question is how pathogenic variants of *SMPD1*, *NPC1* or *NPC2* damage vulnerable cells and organs. By studying postmortem spleen and liver samples from his patient Irene, Niemann observed what became a cellular hallmark of the diseases, the accumulation of lipids within cells [50]. Later on, Bielschowsky and Epstein were the first to describe lipid aggregates in neuronal cell bodies, axons and dendrites in the neocortex and cerebellum of Niemann-Pick patients [521,522]. Obviously, prime suspects causing havoc in ASM- and NPC1- or NPC2-deficient cells are sphingomyelin and unesterified cholesterol, respectively. Depending on the cell type, these accumulating lipids may derive from lipoprotein uptake [83,523], but also from cell-intrinsic pools [374,524–526], for example due to impaired autophagy [527]. Notably, lipids other than the usual suspects accumulate due to defects in ASM, NPC1 or NPC2 as well. ASM deficiency enhances cholesterol levels in visceral organs [81], in macrophages [528], and in neurons [529,530], although absence of accumulation has also been reported [361,531]. Conversely, NPC1-deficiency elevates levels of sphingomyelin [81,532] and other sphingolipids, notably lactosyl- [533] and glycosylceramide [532], and sphingosine [183,393,458,534–538]. Moreover, accumulation of bis(monoacylglyceryl)phosphate (a.k.a. lysobisphosphatidic acid) [81,539] (for review see [540]), and gangliosides (ASMD: [531]; NPCD: [374,458,541–543]) has been observed in both diseases. Why different lipids co-accumulate in the diseases is unclear. Some may accumulate as direct consequence of NPC1 deficiency [183]. On the other hand, sphingolipids and cholesterol appear to mutually influence their processing in late endosomes *in vitro* [142,544–549] suggesting that the late-endosomal handling of different lipids by enzymes and carriers is interdependent and proceeds in a specific order depending on the cell type and the processed material. Whether and how the different lipids damage specialized cell types in ASMD and NPCD, remains to be established.

Apart from lipid accumulation, numerous pathologic changes due to defects in ASM, NPC1 or NPC2 have been documented in generic and specialized cells from different tissues and organs during the last decades (Table 3). The thick catalogue comprises common defects such as impaired recycling of cellular components by autophagy, diminished energy conversion in mitochondria, and enhanced oxidative stress. Moreover, the catalogue lists cell type-specific changes including impaired phagocytosis in macrophages, defective secretion from immune cells, and defects in specialized neuronal structures (Table 3). Some changes observed in cells from animal models have been confirmed in human cells, and vice versa, but a large fraction of data remains to be cross-validated. The importance of this cross-validation is illustrated by recent evidence for differences among brain cells from NPC1-deficient mice and NPCD patients [550] and species-dependent trafficking of NPC1 [193]. In addition, many signaling pathways and cellular processes affected by ASM, NPC1 or NPC2 deficiency were uncovered in generic cells (Table 3), and their contribution to dysfunction of specialized cells remains to be established. Direct comparisons of cells revealed that NPC1 deficiency causes death of primary neurons, but not of cell lines [551], and impairs cholesterol efflux and cathepsin activity in macrophages, but not in hepatocytes [552]. Remarkably, cells differ with respect to their vulnerability to the gene variants. This is exemplified by the differential loss of Purkinje cells located in distinct cerebellar lobules of ASM- [229,529] and NPC1-deficient mice [553–555].

An important question is whether a given type of cell in an affected organ degenerates autonomously or whether neighboring cells contribute to its demise. This applies in particular to neurodegenerative diseases, where the loss of neurons has been shown to depend on non-neuronal (glial) cells [556,557] (for review see [558]). Previous studies of ASMD and NPCD models revealed pathologic changes in different types of glial cells and in the myelin sheath surrounding axons in the peripheral and central nervous system (Table 3). On the other hand, genetic experiments suggested that NPC1 deficiency in neurons is sufficient to induce their death [286,287,559,560]. *In vitro* studies showed normal secretion of lipoproteins from NPC1-deficient glial cells [561]. However, these findings do not exclude a contribution of non-neuronal cells to neurodegeneration. Already in 1954, Paul Diezel suggested that storage material found in microglial cells of Niemann-Pick cases represents remnants of damaged neurons following their uptake by microglial phagocytosis [562]. Recent studies expose microglial cells as key players in neurodegeneration and as possible targets of therapeutic approaches for ASMD [563] and NPCD [409,470,550,563–567]. An emerging question is how defects of ASM, NPC1 or NPC2 affect the complex lymphatic and neuroimmune systems that have been discovered in the meninges and skull bone marrow [568–570] (for review see [571]).

10. Tracking disease modifiers

A long-standing challenge is the identification of genetic [706], epigenetic [707] and environmental factors [708] that account for the substantial phenotypic variability in patients with different lysosomal disorders including ASMD and NPCD. In both diseases, the involvement of protective and deleterious modifiers is indicated by studies of NPC1 mutant mice showing an impact of genetic background on disease severity [289,709–712], and by clinical reports showing divergent symptoms in patients with identical variants [412,424,713–719]. In addition to modifiers that determine inter-individual variation of disease outcome, there are factors that determine the cell type-specific vulnerability to disease-causing gene variants as has been shown in many pathologic conditions [720].

Within the last decade, candidate modifiers have been identified for ASMD and NPCD using a variety of approaches ranging from yeast screens to knock-outs of selected genes and single cell transcriptomics. Notably, some of these pathways may in fact be integral components of the disease mechanisms rather than modifiers. For ASMD, sphingosine kinase has been suggested as modifier of Purkinje cell death based on its expression pattern in the cerebellum [721], whereas endocannabinoid signaling [689] and apolipoprotein D [722] have been shown to modify disease outcome in mice. For NPCD, the list of candidates is long and comprises sigma 2 receptor/TMEM97 [184], cathepsins [653], microtubule-associated protein tau [723,724], histone deacetylases [303], amyloid precursor protein [725], apolipoprotein E [726,727], GM3 synthase [728], non-lysosomal glucosylceramidase (GBA2) [546,729], cystatin B expression [560], heat-shock protein beta 1 (HSPB1) [730], alexidine-dependent signaling [731], endocannabinoid signaling [689], maternal immune activation [732], thrombospondin 1 and a glutamate transporter (SLC1A6) [733], F-box protein 2 [734], quantitative trait loci on mouse chromosomes 1 and 7 [291], annexin A6 [735], cholesterol esterification by corresponding enzymes (sterol O-acyltransferase 2, SOAT2 [736] and sterol o-acyltransferase 1 (ACAT1/SOAT1) [737]), and modulation of peroxisome proliferator-activated receptor-gamma activity [738]. With respect to Purkinje cell vulnerability, potential modifiers are Abelson Helper Integration Site 1 (AHI1), a serine-threonine kinase (ROCK2), a lysosomal cationic amino acid transporter (PQLC2) [388] and a glycosyl transferase (MGAT5) [739]. Other candidates are proteins that may shuttle cholesterol out of the endosomal-lysosomal system independently from NPC1/NPC2 such as lysosomal associated membrane protein 2 (LAMP2) [740,741] and lysosomal integral membrane protein 2 / scavenger receptor class B member 2 (LIMP2/SCARB2) [742].

The long line of candidates implies that numerous modifiers interfere at different molecular and cellular levels ranging from the amount of ASM, NPC1 or NPC2 protein available per cell, to lysosomal function *per se* and the quality and extent of neuroinflammatory responses. Notably, genetic modifiers may act in a cell type-specific manner as shown recently by single-cell analyses of expression quantitative trait loci for autoimmune [743,744] and neurologic diseases [745].

11. Search for therapies

The faulty proteins that cause havoc in ASMD and NPCD differ fundamentally with respect to their location – luminal ASM versus transmembrane NPC1 – and function – enzyme activity versus transporter, respectively. Therefore, the search for therapies in each field has taken distinct paths and time courses [746]. For ASMD, the hunt began in the 1970s with transplantation of liver samples [747] and of mesenchymal cells from different sources (Table 4). These attempts yielded mixed outcomes and little to no effects on neurologic symptoms. Improvement of the latter required intracerebral injection of cells [748,749]. The feasibility of gene therapy was established first *in vitro* using patient-derived fibroblasts [750] and then *in vivo* using different approaches in animal models (Table 4). Enzyme replacement appeared as a promising approach for ASMD, and its preclinical development took off in the 1990s. Biologically active recombinant human ASM (rhASM) could be produced *in vitro* [751] and its systemic administration corrected pathologic changes in livers and spleens of ASM-deficient mice [752]. Intraparenchymal injection of rhASM reduced sphingomyelin accumulation in neurons [753] and its intracerebroventricular administration improved neurologic symptoms in ASM-deficient mice [754]. Better delivery of ASM was explored using nanocarriers coated with a cell adhesion molecule (ICAM1) [755–758] circumventing impaired uptake mechanisms in ASM-deficient macrophages [759] and fibroblasts [760]. However, systemic administration of ASM caused dose-dependent toxicity in ASM-deficient mice due to elevated ceramide levels following bulk cleavage of sphingomyelin. This obstacle was overcome by a debulking/dose escalating regimen in animals [761] and patients [762]. Several clinical trials proved short- and long-term safety and efficacy of rhASM (olipudase alpha/Xenpozyme) in ASMD patients showing significant improvement of visceral symptoms (Tables 4, 5; Fig. 3). These positive results led to its recent approval in several countries including the USA. In parallel to enzyme replacement, alternative therapeutic approaches have been tested for ASMD (Table 4).

The hunt for therapies to combat NPCD began with some delay compared to the efforts in the ASMD field. Starting in the 1990s, cholesterol-lowering drugs were the first approach explored in patients [763] and during the next decades, numerous targets and approaches have been tested preclinically (Table 4) [24]. Only few drug candidates have entered into industry-sponsored clinical development (Tables 4, 5; Fig. 3). The first drug was N-butyl-deoxynojirimycin (OGT918, Miglustat, Zavesca). The compound is a modified version of the bacteria- and plant-derived glucose mimetic nojirimycin. Discovered in Japan, it was shown to inhibit carbohydrate-splitting glucosidases [764]. N-butyl-deoxynojirimycin inhibits glucosylceramide synthase (UDP-glucose ceramide glucosyltransferase, UGCG) [765] and serves as substrate reduction therapy for Gaucher disease [766]. The drug was shown to slow down disease progression in NPC1-deficient mice [767] and cats [768] (Table 4). Several clinical trials proved that long-term treatment with the drug stabilizes neurologic disease progression in many NPCD patients (Tables 4, 5; Fig. 3). Its mechanism of action may involve concurrent inhibition of non-lysosomal glucosylceramidase (GBA2) [546,769,770]. N-butyl-deoxynojirimycin is currently the only drug approved for treatment of NPCD in many countries except for the USA.

Next in line was the cholesterol-binding compound hydroxypropyl-beta-cyclodextrin (HPBCD), which was tested beginning of the 2000s in mice [771] (Tables 4, 5; Fig. 3). Years later, it appeared again on the scene, after the revelation that positive effects on NPC1-deficient mice, originally ascribed to allopregnanolone [772], were mediated by HPBCD serving as vehicle [773–775]. Subsequent studies reported positive effects notably prolongation of life-span in NPC1-deficient mice and cats (Table 4). Clinical trials with HPBCD (named VTS-270, Adrabetadex), showed decelerated neurologic disease progression in patients following intrathecal administration of the compound (Tables 4, 5; Fig. 3).

A third candidate is the modified amino acid N-acetyl-L-leucine (IB1001) (Tables 4, 5; Fig. 3). The racemic version, N-acetyl-DL-leucine, sold in France as over-the-counter drug Tanganil, is used since more than 60 years to treat acute vertigo [776]. Positive effects of the racemic mixture in NPCD patients [777,778] and evidence that the L enantiomer is the active form slowing disease progression in NPC1-deficient mice [778] prompted clinical studies [779], which showed reduced neurologic disease progression after one year of treatment (Tables 4, 5; Fig. 3). With respect to the long-sought mechanism of action, N-acetyl-L-leucine appears to act as prodrug boosting L-leucine-dependent processes, notably energy metabolism, in those cells that can take up the acetylated molecule [780].

A fourth approach tested clinically was based on bimoclomol or arimoclomol, which represent small molecule enhancers of heat-shock protein expression (Tables 4, 5; Fig. 3). The drugs were first explored in preclinical models for diabetic neuropathy [781] and for amyotrophic lateral sclerosis [782]. Encouraging effects of arimoclomol were observed in NPC1-deficient cells and mice [783] and a clinical trial showed decelerated disease progression notably in patients co-treated with arimoclomol and N-butyl-deoxynojirimycin (Tables 4, 5; Fig. 3).

12. Summary and outlook

The Niemann-Pick diseases testify that defects in cellular lipid homeostasis cause dysfunction and death of cells in the brain and other organs, provoke progressive visceral, neurologic and psychiatric symptoms and premature death in animal models and humans. Research has tracked down the genetic culprit causing the "unknown clinical picture" noticed by Albert Niemann more than 100 years ago. Niemann's patient, Irene, most likely suffered from the uniformly fatal infantile neurovisceral form of ASMD invoking an enzymatic defect in sphingomyelin catabolism. Along a meandering path, a second nosologic entity, named Niemann-Pick Type C, was uncovered, where defects in NPC1 or NPC2 impair uptake and recycling of cholesterol and other components. Many candidate pathways and mechanisms have been uncovered yielding converging evidence for defects in lysosomes, autophagy and mitochondria in both diseases [888]. Still, the signal cascades linking the genetic variants with the progressive demise of vulnerable neurons and other specialized cells remain to be established. Further advances require continued efforts to uncover cell-specific reactions to variants of *SMPD1, NPC1* or *NPC2*. The identification of genetic, epigenetic, or environmental disease modifiers that determine the outcome of these variants in specific cell types and individual patients may help to reveal disease mechanisms and deliver new drug targets. From a biological point of view, it is curious that the defective culprits in Niemann-Pick diseases handle two lipids that are intimately linked in their natural habitat, the eukaryotic membrane. Therefore, it may be of value to join forces in the fields and explore whether and how primary defects in either protein impact the other. Integrated research efforts across the fields may help to define cell-specific pathologic pathways common to both diseases and suggest new therapeutic approaches.

Table 5
Clinical studies exploring therapeutic approaches for Niemann-Pick diseases.

Code	Title	Period	Sponsor*	References#
ASMD				
NCT00410566	Safety Study of **rhASM** Enzyme Replacement Therapy in Adults With Acid Sphingomyelinase Deficiency (Niemann-Pick Disease)	12/2006 - 4/2009	Genzyme/Sanofi	–
NCT01722526	Tolerability and Safety Study of **Recombinant Human Acid Sphingomyelinase** in Acid Sphingomyelinase Deficiency Patients	03/2013 - 01/2014	Genzyme/Sanofi	[799,800,802]
NCT02004704	A Long-Term Study of **Olipudase Alfa** in Patients With Acid Sphingomyelinase Deficiency	12/2013 - 02/2024	Genzyme/Sanofi	[801–803]
EudraCT2013-000051-40	A Long-Term Study to Assess the Ongoing Safety and Efficacy of **Olipudase Alfa** in Patients With Acid Sphingomyelinase Deficiency	12/2013	Genzyme/Sanofi	–
EudraCT2010-023953-12	A Phase 2, Multi-Center, Randomized, Open-Label, Repeat Dose, Dose-Comparison Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of **Recombinant Human Acid Sphingomyelinase** in Patients	12/2013	Genzyme/Sanofi	–
EudraCT2014-003198-40	A phase 1/2, multi-center, open-label, ascending dose study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of **olipudase alfa** in pediatric patients	02/2015	Genzyme/Sanofi	–
NCT02292654	Safety, Tolerability, PK, and Efficacy Evaluation of Repeat Ascending Doses of **Olipudase Alfa** in Pediatric Patients <18 Years of Age With Acid Sphingomyelinase Deficiency	05/2015 - 12/2019	Genzyme/Sanofi	[803,887]
EudraCT2015-000371-26	A Phase 2/3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Repeat Dose Study to Evaluate the Efficacy, Safety, Pharmacodynamics and Pharmacokinetics of **olipudase alfa** in Patients...	08/2015	Genzyme/Sanofi	[804]
NCT02004691	Efficacy, Safety, Pharmacodynamic, and Pharmacokinetics Study of **Olipudase Alfa** in Patients With Acid Sphingomyelinase Deficiency	12/2015 - 10/2023	Genzyme/Sanofi	[804]
NCT05359276	Data Analysis of Adult and Pediatric Participants With Acid Sphingomyelinase Deficiency (ASMD) on Early Access to **Olipudase Alfa** in France	06/2022 - 01/2025	Genzyme/Sanofi	–
NPCD				
NCT00517153	**Miglustat** in Niemann-Pick Type C Disease	01/2002–01/2008	Actelion	[819–821]
NCT00316498	Saccadic Eye Movements in Patients With Niemann-Pick Type C Disease	10/2002–08/2007	NEI, NIHCC	–
EudraCT2006-005842-35	Efficacy and safety of treatment with **N-butyl-deoxynojirimycin (NB-DNJ-miglustat**) in patients with Niemann-Pick disease type C	11/2006	Universita` di Napoli Federico II	[822]
NCT01760564	Application of **Miglustat** in Patients With Niemann-Pick Type C	01/2008–12/2010	National Taiwan University Hospital	–
NCT00975689	Biomarker Validation for Niemann-Pick Disease, Type C: Safety and Efficacy of **N-Acetyl Cysteine**	08/2009–11/2010	NICHD, UO, WUSM, NHGRI, NIHCC	–
NCT01747135	**Hydroxypropyl Beta Cyclodextrin** for Niemann-Pick Type C1 Disease	01/2013–03/2017	Vtesse/Mallinckrodt	[816]
NCT02124083	Phase 1/2 Study of **Vorinostat** Therapy in Niemann-Pick Disease, Type C1	04/2014–12/2016	NICHD, WU, WMCCU, NIHCC	–
NCT02534844	**VTS-270** to Treat Niemann-Pick Type C1 (NPC1) Disease	10/2015–10/2021	Mandos LLC	–
EudraCT2014-005194-37	A prospective non-therapeutic study in patients diagnosed with Niemann-Pick disease type C in order to characterise the individual patient disease profile and historic signo-symptomatology progress...	10/2015	Orphazyme ApS	–
NCT04958642	**Adrabetadex** to Treat Niemann-Pick Type C1 (NPC1) Disease	12/2015–11/2021	Mandos LLC	–
EudraCT2015-002548-15	A Phase 2b/3 Prospective, Randomized, Double-blind, Sham-controlled Trial of **VTS-270 (2-hydroxypropyl-β-cyclodextrin)** in Subjects with Neurologic Manifestations of Niemann-Pick Type C1 (NPC1) Disease	12/2015	Vtesse/Mallinckrodt	–
EudraCT2015-004438-93	**Arimoclomol** prospective double blind, randomised, placebo-controlled study in patients diagnosed with Niemann Pick disease type C	05/2016	Orphazyme ApS	–
NCT02612129	**Arimoclomol** Prospective Study in Patients Diagnosed With NiemannPick Disease Type C	06/2016–05/2022	KemPharm Denmark A/S	[416,863]
EudraCT2015-004846-25	**Immunization** against oxLDL in patients with lysosomal lipid diseases and associated metabolic disorders	07/2016	Maastricht University	–
EudraCT2015-005761-23	A Phase I/II study to evaluate the safety and pharmacokinetics of intravenous **Trappsol Cyclo (HP-β-CD)** in patients with Niemann-Pick disease type C (NPC-1) and the pharmacodynamic effects of treatm...	09/2016	Cyclo Therapeutics, Inc.	–
NCT02912793	Safety and Efficacy of Intravenous **Trappsol Cyclo (HPBCD)** in Niemann-Pick Type C Patients	03/2017–03/2021	Cyclo Therapeutics, Inc.	[817]

(*continued on next page*)

Table 5 (*continued*)

Code	Title	Period	Sponsor*	References#
NCT03201627	Study of **Lithium Carbonate** to Treat Niemann-Pick Type C1 Disease	07/2017–06/2021	XHSUSM	[881]
NCT02939547	Study of the Pharmacokinetics of **Trappsol** and Effects on Potential Biomarkers of Niemann-Pick C1 (NPC1)	10/2017–02/2020	Cyclo Therapeutics, Inc.	[818]
NCT03643562	Niemann-Pick Type C Treatment With **Adrabetadex** for Symptoms of Brain and Nervous System	06/2018–11/2021	Mandos LLC	–
NCT03471143	Study of IV **VTS-270** for Infantile Liver Disease Associated With Niemann-Pick Disease, Type C	02/2019–06/2023	WUSM, NICHD	–
NCT03893071	Open-Label Study of Long-Term Safety and Efficacy of Intravenous **Trappsol Cyclo (HPI^{2}CD)** in Niemann-Pick Disease Type C	05/2019–03/2022	Cyclo Therapeutics, Inc.	[818]
EudraCT2018-004331-71	Effects of **N-Acetyl-L-Leucine** on Niemann-Pick type C Disease (NPC): A multinational, multi-center, open-label, rater-blinded Phase II study	05/2019	IntraBio, Inc.	[779]
NCT03759639	**N-Acetyl-L-Leucine** for Niemann-Pick Disease, Type C (NPC)	09/2019–01/2023	IntraBio, Inc.	[779,859]
NCT03879655	Open-label Study of **VTS-270** in Participants With Neurologic Manifestations of Niemann-Pick Type C1	12/2019–11/2021	Mandos LLC	–
NCT03887533	Combined Intrathecal and Intravenous **VTS-270** Therapy for Liver and Neurological Disease Associated With Niemann-Pick Disease, Type C1	01/2020–10/2021	NICHD, NIHCC	–
NCT03910621	Safety and Efficacy of **Miglustat** in Chinese NPC Patients	04/2020–03/2022	Actelion	–
NCT03687476	Safety and Tolerability Study of **VTS-270** in Pediatric Participants With Niemann-Pick Type C (NPC) Disease	05/2020–10/2022	Vtesse/Mallinckrodt	–
EudraCT2019-004498-18	EFFICACY AND SAFETY CLINICAL TRIAL WITH **EFAVIRENZ** IN PATIENTS DIAGNOSED WITH ADULT NIEMANN-PICK TYPE C WITH COGNITIVE IMPAIRMENT	06/2020	Drs. J. Gascón, Lola Ledesma	–
NCT04860960	Phase 3 Study to Evaluate Intravenous **Trappsol(R) Cyclo(TM)** in Pediatric and Adult Patients With Niemann-Pick Disease Type C1	07/2021–12/2025	Cyclo Therapeutics, Inc.	[818]
EudraCT2020-003136-25	A Phase 3, Double blind, Randomized, Placebo controlled, Parallel group, Multicenter Study to Evaluate the Safety, Tolerability, and Efficacy of 2000 mg/kg of **Trappsol® Cyclo™** ...	10/2021	Cyclo Therapeutics, Inc.	–
EudraCT2021-005356-10	Effects of **N-Acetyl-L-Leucine** on Niemann-Pick disease type C (NPC): A Phase III, randomized, placebo-controlled, double-blind, crossover study	03/2022	IntraBio, Ltd.	–
NCT05163288	A Pivotal Study of **N-Acetyl-L-Leucine** on Niemann-Pick Disease Type C	06/2022–11/2024	IntraBio, Inc.	–
EudraCT2022-002514-16	A single-arm uncontrolled 12-month Clinical Study to evaluate the Safety and Efficacy of **miglustat (Zavesca®)** for the Treatment of Niemann-Pick Disease Type C (NPC) in Chinese subjects	07/2022	Actelion Pharmaceuticals Trading Co., Ltd	–

* NEI, National Eye Institute; NIHCC, National Institutes of Health Clinical Center; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; UO, University of Oxford; WUSM, Washington University School of Medicine; NHGRI, National Human Genome Research Institute; WMCCU, Weill Medical College of Cornell University; XHSUSM, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine.

Articles citing the clinical trial (for further references see Table 4).

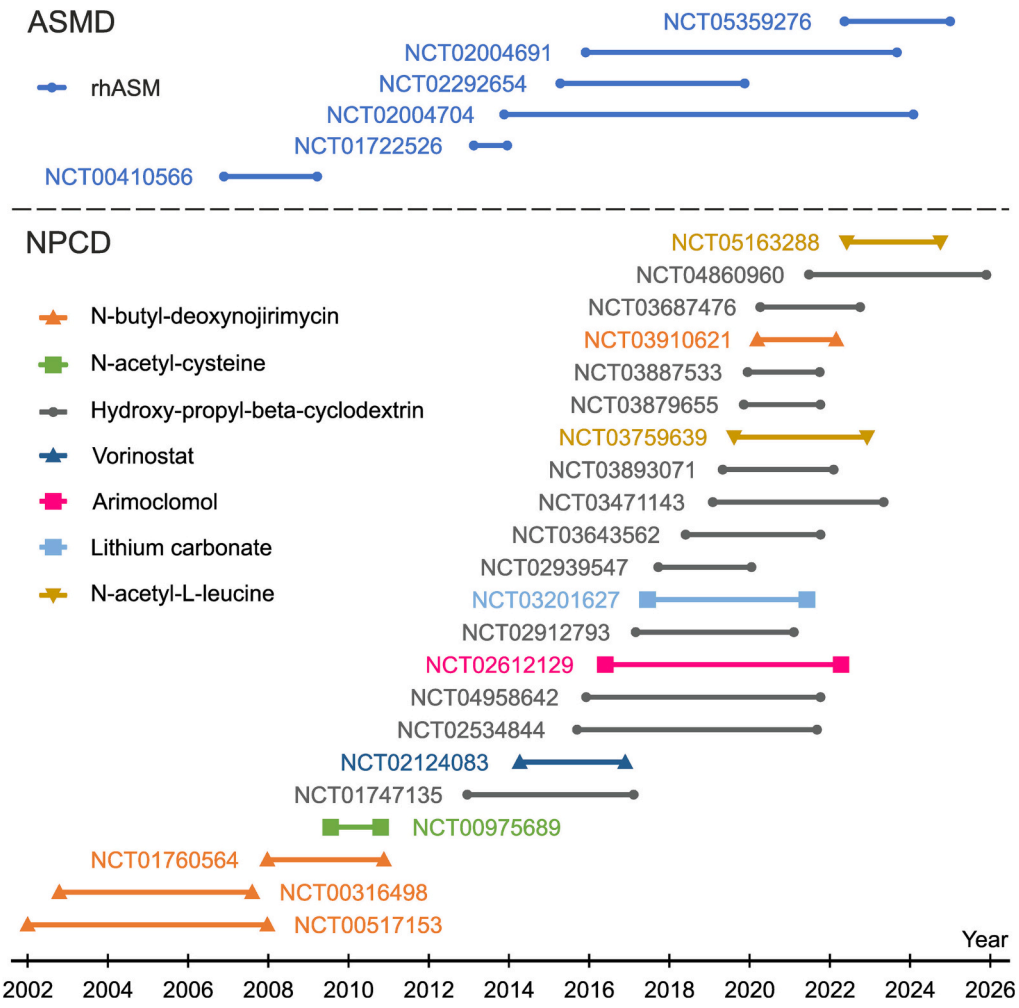

Fig. 3. Clinical trials in ASMD and NPCD.
Timeline of clinical studies testing effects of drug candidates in ASMD (top) and NPCD patients (bottom). The legend indicates the specific drugs tested. Codes indicate clinical trial identification numbers (https://clinicaltrials.gov/). Only interventional studies are shown.

Funding

Subscription-based access to bibliographic information and scientific articles was provided through institutional accounts (University of Strasbourg; Centre National de la Recherche Scientifique). Research in the author's laboratory has been supported by the Niemann-Pick Selbsthilfegruppe e.V. (Germany), the Ara Parseghian Medical Research Foundation (USA), Vaincre les maladies lysosomales (France), and BILD Hilft e.V. (Germany). Open access to this article was made possible by the Niemann-Pick Selbsthilfegruppe e.V. and NPSuisse (Switzerland).

Declaration of Competing Interest

The author declares no conflict of interest.

Acknowledgements

The author thanks Klaus Harzer, Ann-Kathrin Klewer, Valentina Pallottini, Konrad Sandhoff, and Marie Térèse Vanier for valuable comments on earlier versions of the manuscript.

Appendix

Publications relevant to the fields were obtained by queries of a bibliographic database (Web of Science; Clarivate Analytics) using the following terms for ASMD (**QT1**) and NPCD (**QT2**): **QT1**: ((TI=((niemann-pick AND disease AND ("type a" OR "type b" OR "type a/b")) OR ((ASMase OR acid sphingomyelinase OR sphingomyelin phosphodiesterase 1 OR smpd1 OR acidic smase) AND (deficiency OR deficient OR defect OR defective OR niemann-pick)) OR "niemann-pick A" OR "niemann-pick B" OR "niemann-pick A/B" OR "niemann-pick disease a" OR "niemann-pick disease b" OR "niemann-pick disease a/b") OR AB=((niemann-pick AND disease AND ("type a" OR "type b" OR "type a/b")) OR ((ASMase OR acid sphingomyelinase OR sphingomyelin phosphodiesterase 1 OR smpd1 OR acidic smase) AND (deficiency OR deficient OR defect OR defective OR niemann-pick)) OR "niemann-pick A" OR "niemann-pick B" OR "niemann-pick A/B" OR "niemann-pick disease a" OR "niemann-pick disease b" OR "niemann-pick disease a/b")) OR ((TI="niemann-pick" OR AB="Niemann-pick") AND PY=(1920-1969))) AND ((DT==("ARTICLE")) NOT (DT==("REVIEW"))). **QT2**: ((TI=((niemann-pick AND (disease OR disorder) AND ("type c" OR "type c1" OR "type c2" OR "type d" OR "type e")) OR ((npc1 OR npc2) AND (deficiency OR deficient OR defect OR defective OR (niemann-pick AND disease))) OR "niemann-pick c" OR "niemann-pick d" OR "niemann-pick disease c" OR "niemann-pick disease d") OR AB=((niemann-pick AND (disease OR disorder) AND ("type c" OR "type c1" OR "type c2" OR "type d" OR "type e")) OR ((npc1 OR npc2) AND (deficiency OR deficient OR defect OR defective OR (niemann-pick AND disease))) OR "niemann-pick c" OR "niemann-pick d" OR "niemann-pick disease c" OR "niemann-

pick disease d")) OR ((TI="niemann-pick" OR AB="Niemann-pick") AND PY=(1920-1969))) AND ((DT==("ARTICLE")) NOT (DT==("REVIEW"))). Additional queries were performed in MEDLINE using the freely accessible PubMed portal (https://pubmed.ncbi.nlm.nih.gov/). Bibliometric data were analysed and visualized using custom-made R scripts [889,890]. Information about clinical trials related to ASMD or NPCD was retrieved from publicly accessible registers using the terms "niemann-pick" or "sphingomyelinase" (https://www.clinicaltrialsregister.eu/, https://clinicaltrials.gov/).

References

[1] Mochel F. Lipids and synaptic functions. J Inherit Metab Dis 2018;41:1117–22. https://doi.org/10.1007/s10545-018-0204-1.
[2] Dunn TM, Tifft CJ, Proia RL. A perilous path: the inborn errors of sphingolipid metabolism. J Lipid Res 2019;60:475–83. https://doi.org/10.1194/jlr.S091827.
[3] Schönfeld P, Reiser G. How the brain fights fatty acids' toxicity. Neurochem Int 2021;148:105050. https://doi.org/10.1016/j.neuint.2021.105050.
[4] Abed Rabbo M, Khodour Y, Kaguni LS, Stiban J. Sphingolipid lysosomal storage diseases: from bench to bedside. Lipids Health Dis 2021;20:44. https://doi.org/10.1186/s12944-021-01466-0.
[5] Tracey TJ, Kirk SE, Steyn FJ, Ngo ST. The role of lipids in the central nervous system and their pathological implications in amyotrophic lateral sclerosis. Semin Cell Dev Biol 2021;112:69–81. https://doi.org/10.1016/j.semcdb.2020.08.012.
[6] Blauwendraat C, Nalls MA, Singleton AB. The genetic architecture of Parkinson's disease. Lancet Neurol 2020;19:170–8. https://doi.org/10.1016/s1474-4422(19)30287-x.
[7] Duong MT, Nasrallah IM, Wolk DA, Chang CCY, Chang TY. Cholesterol, atherosclerosis, and APOE in vascular contributions to cognitive impairment and dementia (VCID): potential mechanisms and therapy. Front Aging Neurosci 2021:13. https://doi.org/10.3389/fnagi.2021.647990.
[8] Feringa FM, van der Kant R. Cholesterol and Alzheimer's disease; from risk genes to pathological effects. Front Aging Neurosci 2021;13:690372. https://doi.org/10.3389/fnagi.2021.690372.
[9] Gegg ME, Menozzi E, Schapira AHV. Glucocerebrosidase-associated Parkinson disease: pathogenic mechanisms and potential drug treatments. Neurobiol Dis 2022:166. https://doi.org/10.1016/j.nbd.2022.105663.
[10] Martens YA, Zhao N, Liu CC, Kanekiyo T, Yang AJ, Goate AM, et al. ApoE cascade hypothesis in the pathogenesis of Alzheimer's disease and related dementias. Neuron 2022;110:1304–17. https://doi.org/10.1016/j.neuron.2022.03.004.
[11] Platt FM, d'Azzo A, Davidson BL, Neufeld EF, Tifft CJ. Lysosomal storage diseases. Nat Rev Dis Primers 2018:4. https://doi.org/10.1038/s41572-018-0025-4.
[12] Parenti G, Medina DL, Ballabio A. The rapidly evolving view of lysosomal storage diseases. EMBO Mol Med 2021:13. https://doi.org/10.15252/emmm.202012836.
[13] Udayar V, Chen Y, Sidransky E, Jagasia R. Lysosomal dysfunction in neurodegeneration: emerging concepts and methods. Trends Neurosci 2022;45:184–99. https://doi.org/10.1016/j.tins.2021.12.004.
[14] Wasserstein MP, Schuchman EH. Acid sphingomyelinase deficiency. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews(®). Seattle: University of Washington; 2006.
[15] Schuchman EH, Desnick RJ. Types A and B Niemann-Pick disease. Mol Genet Metab 2017;120:27–33. https://doi.org/10.1016/j.ymgme.2016.12.008.
[16] McGovern MM, Avetisyan R, Sanson BJ, Lidove O. Disease manifestations and burden of illness in patients with acid sphingomyelinase deficiency (ASMD). Orphanet J Rare Dis 2017:12. https://doi.org/10.1186/s13023-017-0572-x.
[17] Wasserstein M, Dionisi-Vici C, Giugliani R, Hwu WL, Lidove O, Lukacs Z, et al. Recommendations for clinical monitoring of patients with acid sphingomyelinase deficiency (ASMD). Mol Genet Metab 2019;126:98–105. https://doi.org/10.1016/j.ymgme.2018.11.014.
[18] Eskes ECB, Sjouke B, Vaz FM, Goorden SMI, van Kuilenburg ABP, Aerts J, et al. Biochemical and imaging parameters in acid sphingomyelinase deficiency: potential utility as biomarkers. Mol Genet Metab 2020;130:16–26. https://doi.org/10.1016/j.ymgme.2020.02.002.
[19] Pinto C, Sousa D, Ghilas V, Dardis A, Scarpa M, Macedo MF. Acid sphingomyelinase deficiency: a clinical and immunological perspective. Int J Mol Sci 2021;22:12870. https://doi.org/10.3390/ijms222312870.
[20] Breiden B, Sandhoff K. Acid sphingomyelinase, a lysosomal and secretory phospholipase C, is key for cellular phospholipid catabolism. Int J Mol Sci 2021:22. https://doi.org/10.3390/ijms22169001.
[21] Vanier MT. Niemann-Pick disease type C. Orphanet J Rare Dis 2010;5:16.
[22] Geberhiwot T, Moro A, Dardis A, Ramaswami U, Sirrs S, Marfa MP, et al. Consensus clinical management guidelines for Niemann-Pick disease type C. Orphanet J Rare Dis 2018;13:50. https://doi.org/10.1186/s13023-018-0785-7.
[23] Bräuer AU, Kuhla A, Holzmann C, Wree A, Witt M. Current challenges in understanding the cellular and molecular mechanisms in Niemann-Pick disease type C1. Int J Mol Sci 2019:20. https://doi.org/10.3390/ijms20184392.
[24] Hammond N, Munkacsi AB, Sturley SL. The complexity of a monogenic neurodegenerative disease: More than two decades of therapeutic driven research into Niemann-Pick type C disease. Biochim Biophys Acta Mol Cell Biol Lipids 2019;1864:1109–23. https://doi.org/10.1016/j.bbalip.2019.04.002.
[25] Pfeffer SR. NPC intracellular cholesterol transporter 1 (NPC1)-mediated cholesterol export from lysosomes. J Biol Chem 2019;294:1706–9. https://doi.org/10.1074/jbc.TM118.004165.
[26] Wheeler S, Sillence DJ. Niemann-Pick type C disease: cellular pathology and pharmacotherapy. J Neurochem 2020;153:674–92. https://doi.org/10.1111/jnc.14895.
[27] Acuna M, Martinez P, Moraga C, He XX, Moraga M, Hunter B, et al. Epidemiological, clinical and biochemical characterization of the p.(Ala359Asp) SMPD1 variant causing Niemann-Pick disease type B. Eur J Hum Genet 2016;24:208–13. https://doi.org/10.1038/ejhg.2015.89.
[28] Wassif CA, Cross JL, Iben J, Sanchez-Pulido L, Cougnoux A, Platt FM, et al. High incidence of unrecognized visceral/neurological late-onset Niemann-Pick disease, type C1, predicted by analysis of massively parallel sequencing data sets. Genet Med 2016;18:41–8.
[29] Patterson M. Niemann-Pick disease type C. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews(®). Seattle: University of Washington; 2020.
[30] Rangel DM, Aguiar Melo MC, Pedroso JL, Povoas Barsottini OG, Sobreira-Neto MA, Braga-Neto P. Beyond the typical syndrome: understanding non-motor features in Niemann-Pick type C disease. Cerebellum 2020;19:722–38. https://doi.org/10.1007/s12311-020-01156-0.
[31] Bolton SC, Soran V, Marfa MP, Imrie J, Gissen P, Jahnova H, et al. Clinical disease characteristics of patients with Niemann-Pick Disease Type C: findings from the International Niemann-Pick Disease Registry (INPDR). Orphanet J Rare Dis 2022:17. https://doi.org/10.1186/s13023-022-02200-4.
[32] Yilmaz SB, Baruteau J, Rahim AA, Gissen P. Clinical and molecular features of early infantile Niemann Pick type C disease. Int J Mol Sci 2020:21. https://doi.org/10.3390/ijms21145059.
[33] Cox GF, Clarke LA, Giugliani R, McGovern MM. Burden of illness in acid sphingomyelinase deficiency: a retrospective chart review of 100 patients. JIMD Rep 2018;41:119–29. https://doi.org/10.1007/8904_2018_120.
[34] Pokrzywinski R, Hareendran A, Nalysnyk L, Cowie S, Crowe J, Hopkin J, et al. Impact and burden of acid sphingomyelinase deficiency from a patient and caregiver perspective. Sci Rep 2021:11. https://doi.org/10.1038/s41598-021-99921-6.
[35] Mengel E, Patterson MC, Chladek M, Guldberg C, Dali CÍ, Symonds T, et al. Impacts and burden of Niemann pick type-C: a patient and caregiver perspective. Orphanet J Rare Dis 2021;16:493. https://doi.org/10.1186/s13023-021-02105-8.
[36] Berry-Kravis E. Niemann-Pick disease, type C: diagnosis, management and disease-targeted therapies in development. Semin Pediatr Neurol 2021:37. https://doi.org/10.1016/j.spen.2021.100879.
[37] Mauhin W, Borie R, Dalbies F, Douillard C, Guffon N, Lavigne C, et al. Acid sphingomyelinase deficiency: sharing experience of disease monitoring and severity in France. J Clin Med 2022:11. https://doi.org/10.3390/jcm11040920.
[38] Carquin M, D'Auria L, Pollet H, Bongarzone ER, Tyteca D. Recent progress on lipid lateral heterogeneity in plasma membranes: from rafts to submicrometric domains. Prog Lipid Res 2016;62:1–24. https://doi.org/10.1016/j.plipres.2015.12.004.
[39] Garcia-Arribas AB, Alonso A, Goni FM. Cholesterol interactions with ceramide and sphingomyelin. Chem Phys Lipids 2016;199:26–34. https://doi.org/10.1016/j.chemphyslip.2016.04.002.
[40] Steck TL, Lange Y. Transverse distribution of plasma membrane bilayer cholesterol: Picking sides. Traffic 2018;19:750–60. https://doi.org/10.1111/tra.12586.
[41] Doktorova M, Symons JL, Levental I. Structural and functional consequences of reversible lipid asymmetry in living membranes. Nat Chem Biol 2020;16:1321–30. https://doi.org/10.1038/s41589-020-00688-0.
[42] Dingjan T, Futerman AH. The role of the 'sphingoid motif' in shaping the molecular interactions of sphingolipids in biomembranes. BBA-Biomembranes 2021:1863. https://doi.org/10.1016/j.bbamem.2021.183701.
[43] Kulig W, Cwiklik L, Jurkiewicz P, Rog T, Vattulainen I. Cholesterol oxidation products and their biological importance. Chem Phys Lipids 2016;199:144–60. https://doi.org/10.1016/j.chemphyslip.2016.03.001.
[44] Hannun YA, Obeid LM. Sphingolipids and their metabolism in physiology and disease. Nat Rev Mol Cell Biol 2018;19:175–91. https://doi.org/10.1038/nrm.2017.107.
[45] Radhakrishnan A, Rohatgi R, Siebold C. Cholesterol access in cellular membranes controls Hedgehog signaling. Nat Chem Biol 2020;16:1303–13. https://doi.org/10.1038/s41589-020-00678-2.
[46] Zakany F, Kovacs T, Panyi G, Varga Z. Direct and indirect cholesterol effects on membrane proteins with special focus on potassium channels. Biochim Biophys Acta 2020:1865. https://doi.org/10.1016/j.bbalip.2020.158706.
[47] Wang YQ, Yutuc E, Griffiths WJ. Cholesterol metabolism pathways - are the intermediates more important than the products? FEBS J 2021;288:3727–45. https://doi.org/10.1111/febs.15727.
[48] Goni FM. Sphingomyelin: What is it good for? Biochem Biophys Res Commun 2022;633:23–5. https://doi.org/10.1016/j.bbrc.2022.08.074.
[49] Kalinichenko LS, Gulbins E, Kornhuber J, Müller CP. Sphingolipid control of cognitive functions in health and disease. Prog Lipid Res 2022;86:101162. https://doi.org/10.1016/j.plipres.2022.101162.
[50] Niemann A. Ein unbekanntes Krankheitsbild. Jahrbuch Kinderheilkunde Phys Erziehung 1914;79:1–10.
[51] Knox JHMW, Schmeisser HC. Gauchers disease, a report of two cases in infant. Bull Johns Hopkins Hosp 1916:27.

[52] Siegmund. Lipoidzellenhyperplasie der Milz und Splenomegalie Gaucher. Verh Dtsch Pathol Ges 1921;18.
[53] Pick L. Zur pathologischen Anatomie des Morbus Gaucher. Med Klin 1922;1408.
[54] Pick L. Über den Morbus Gaucher, seine Klinik, pathologische Anatomie und histio-pathogenetische Umgrenzung, nebst Untersuchungen über den Morbus Gaucher der Säuglinge und über die Beteiligung des Skelettsystems. Die lipoidzellige Splenomegalie (Typus Niemann) als neuaufgestelltes Krankheitsbild. Med Klin 1924;20:1561–7.
[55] Der Pick L. Morbus Gaucher und die ihm änlichen Krankheiten (die lipoidzellige Splenohepatomegalie Typus Niemann und die diabetische Lipoidzellenhypoplasie der Milz). Ergeb Inn Med Kinderheilkd 1926;29:519–627.
[56] Schiff E. Im Leben diagnostizierte lipoidzellige Splenohepatomegalie (Typus Niemann-Pick) bei einem 17 Monate alten Knaben. Jahrbuch Kinderheilkunde Phys Erziehung 1926:1.
[57] Epstein E. On the phosphatide and cerebroside content of the spleen and liver of a case of Gaucher disease in babyhood (with comparative values of normal spleen and spleen with Niemann-Pick disease). Virchows Archiv Pathol Anatom Physiol Klinische Med 1930;274:294–300.
[58] Brahn B, Pick L. Zur Chemischen Organanalyse bei der Lipoidzelligen Spleno-Hepatomegalie Typus Niemann-Pick. Klin Wochenschr 1927;6:2367–9. https://doi.org/10.1007/BF01737716.
[59] Klenk E. On the nature of the phosphatides of the spleen in the case of the Niemann-Picksch disease. 10. Announcement on phosphatides. Hoppe-Seylers Zeitschrift Physiol Chem 1934;229:151–6. https://doi.org/10.1515/bchm2.1934.229.4-6.151.
[60] Klenk E. The nature of phosphatide and other lipoids of the brain and liver in Niemann Pick's disease. Hoppe Seylers Z Physiol Chem 1935;235:24–36. https://doi.org/10.1515/bchm2.1935.235.1-2.24.
[61] Klenk E. Beiträge zur Chemie der Lipoidosen [3. Mitteilung]. Niemann-Picksche Krankheit und amaurotische Idiotie262. Biological Chemistry Hoppe-Seyler; 1939. p. 128–43. https://doi.org/10.1515/bchm2.1939.262.3-5.128.
[62] Tropp C, Eckardt B. Sphingomyelin in Niemann-Pick disease. Hoppe Seylers Z Physiol Chem 1936;243:38–42. https://doi.org/10.1515/bchm2.1936.243.1-3.38.
[63] Chargaff E. A study of the spleen in a case of Niemann-Pick disease. J Biol Chem 1939;130:503–11.
[64] Crocker AC. The cerebral defect in Tay-Sachs disease and Niemann-Pick disease. J Neurochem 1961;7:69–80. https://doi.org/10.1111/j.1471-4159.1961.tb13499.x.
[65] Crocker AC, Farber S. Niemann-Pick disease: a review of eighteen patients. Medicine (Baltimore) 1958;37:1–95. https://doi.org/10.1097/00005792-195802000-00001.
[66] Winsor EJ, Welch JP. Genetic and demographic aspects of Nova Scotia Niemann-Pick disease (type D). Am J Hum Genet 1978;30:530–8.
[67] McFarlane J, Murray L, Bradbury K, Cowen PN. Late Niemann-Pick disease with neurovisceral storage: a classification problem. J Clin Pathol 1988;41:619–22. https://doi.org/10.1136/jcp.41.6.619.
[68] Fredrickson DSS. Sphingomyelin lipidoses: Niemann-Pick disease. In: Stanhury JBW, J.B.; Fredrickson, D.S., editors. The Metabolic Basis of Inherited Disease. New York: McGraw-Hill Book; 1972. p. 783–807.
[69] Schneider EL, Pentchev PG, Hibbert SR, Sawitsky A, Brady RO. New form of Niemann-Pick disease characterized by temperature-labile sphingomyelinase. J Med Genet 1978;15:370–4. https://doi.org/10.1136/jmg.15.5.370.
[70] Brady RO, Kanfer JN, Mock MB, Fredrickson DS. The metabolism of sphingomyelin. II. Evidence of an enzymatic deficiency in Niemann-Pick diseae. Proc Natl Acad Sci 1966;55:366–9. https://doi.org/10.1073/pnas.55.2.366.
[71] Patterson MC, Walkley SU. Niemann-Pick disease, type C and Roscoe Brady. Mol Genet Metab 2017;120:34–7. https://doi.org/10.1016/j.ymgme.2016.11.008.
[72] Kampine JP, Brady RO, Kanfer JN, Feld M, Shapiro D. Diagnosis of gaucher's disease and niemann-pick disease with small samples of venous blood. Science 1967;155:86–8. https://doi.org/10.1126/science.155.3758.86.
[73] Sloan HR, Uhlendorf BW, Kanfer JN, Brady RO, Fredrickson DS. Deficiency of sphingomyelin-cleaving enzyme activity in tissue cultures derived from patients with Niemann-Pick disease. Biochem Biophys Res Commun 1969;34:582–8. https://doi.org/10.1016/0006-291x(69)90777-3.
[74] Callahan JW, Khalil M, Gerrie J. Isoenzymes of sphingomyelinase and genetic defect in Niemann-Pick disease, Type-C. Biochem Biophys Res Commun 1974;58:384–90. https://doi.org/10.1016/0006-291x(74)90376-3.
[75] Harzer K, Anzil AP, Schuster I. Resolution of tissue sphingomyelinase isoelectric profile in multiple components is extraction-dependent - evidence for a component defect in Niemann-Pick disease Type-C is spurious. J Neurochem 1977;29:1155–7. https://doi.org/10.1111/j.1471-4159.1977.tb06525.x.
[76] Vanier MT, Revol A, Fichet M. Sphingomyelinase activities of various human-tissues in control subjects and in Niemann-Pick disease - development and evaluation of a microprocedure. Clin Chim Acta 1980;106:257–67. https://doi.org/10.1016/0009-8981(80)90309-5.
[77] Maziere JC, Maziere C, Mora L, Routier JD, Polonovski J. Insitu degradation of sphingomyelin by cultured normal fibroblasts and fibroblasts from patients with Niemann-Pick disease Type-A and Type-C. Biochem Biophys Res Commun 1982;108:1101–6. https://doi.org/10.1016/0006-291x(82)92113-1.
[78] Elleder M. Niemann-Pick disease. Pathol Res Pract 1989;185:293–328. https://doi.org/10.1016/s0344-0338(89)80006-8.
[79] Schneider PB, Kennedy EP. Sphingomyelinase in normal human spleens and in spleens from subjects with Niemann-Pick disease. J Lipid Res 1967;8:202–9.
[80] Harzer K, Benz HU. Simple sphinogomyelinase determination for Niemann-Pick disease - differential diagnosis of types A, B and C. J Neurochem 1973;21:999. https://doi.org/10.1111/j.1471-4159.1973.tb07545.x.
[81] Vanier MT. Biochemical-studies in Niemann-Pick disease. 1. Major sphingolipids of liver and spleen. Biochim Biophys Acta 1983;750:178–84. https://doi.org/10.1016/0005-2760(83)90218-7.
[82] Morris MD, Bhuvaneswaran C, Shio H, Fowler S. Lysosome lipid storage disorder in NCTR-BALB/c mice. I. Description of the disease and genetics. Am J Pathol 1982;108:140–9.
[83] Pentchev PG, Comly ME, Kruth HS, Vanier MT, Wenger DA, Patel S, et al. A defect in cholesterol esterification in Niemann-Pick disease (type C) patients. Proc Natl Acad Sci U S A 1985;82:8247–51.
[84] Pentchev PG, Comly ME, Kruth HS, Patel S, Proestel M, Weintroub H. The cholesterol storage disorder of the mutant BALB/c mouse. A primary genetic lesion closely linked to defective esterification of exogenously derived cholesterol and its relationship to human type C Niemann-Pick disease. J Biol Chem 1986;261:2772–7. https://doi.org/10.1016/S0021-9258(17)35852-0.
[85] Liscum L, Faust JR. Low density lipoprotein (LDL)-mediated suppression of cholesterol synthesis and LDL uptake is defective in Niemann-Pick type C fibroblasts. J Biol Chem 1987;262:17002–8.
[86] Liscum L, Ruggiero RM, Faust JR. The intracellular transport of low density lipoprotein-derived cholesterol is defective in Niemann-Pick type C fibroblasts. J Cell Biol 1989;108:1625–36.
[87] Wojtanik KM, Liscum L. The transport of low density lipoprotein-derived cholesterol to the plasma membrane is defective in NPC1 cells. J Biol Chem 2003;278:14850–6. https://doi.org/10.1074/jbc.M300488200.
[88] Sokol J, Blanchette-Mackie J, Kruth HS, Dwyer NK, Amende LM, Butler JD, et al. Type C Niemann-Pick disease. Lysosomal accumulation and defective intracellular mobilization of low density lipoprotein cholesterol. J Biol Chem 1988;263:3411–7.
[89] Xie C, Turley SD, Pentchev PG, Dietschy JM. Cholesterol balance and metabolism in mice with loss of function of Niemann-Pick C protein. Am J Physiol 1999;276:E336–44.
[90] Kobayashi T, Beuchat MH, Lindsay M, Frias S, Palmiter RD, Sakuraba H, et al. Late endosomal membranes rich in lysobisphosphatidic acid regulate cholesterol transport. Nat Cell Biol 1999;1:113–8.
[91] Quintern LE, Schuchman EH, Levran O, Suchi M, Ferlinz K, Reinke H, et al. Isolation of cDNA clones encoding human acid sphingomyelinase: occurrence of alternatively processed transcripts. EMBO J 1989;8:2469–73. https://doi.org/10.1002/j.1460-2075.1989.tb08382.x.
[92] Schuchman EH, Suchi M, Takahashi T, Sandhoff K, Desnick RJ. Human acid sphingomyelinase. Isolation, nucleotide sequence and expression of the full-length and alternatively spliced cDNAs. J Biol Chem 1991;266:8531–9.
[93] Pereira LD, Desnick RJ, Adler DA, Disteche CM, Schuchman EH. Regional assignment of the human acid sphingomyelinase gene (SMPD1) by PCR analysis of somatic-cell hybrids and insitu hybridization to 11P15.1- P15.4. Genomics 1991;9:229–34. https://doi.org/10.1016/0888-7543(91)90246-b.
[94] Newrzella D, Stoffel W. Molecular-cloning of the acid sphingomyelinase of the mouse and the organization and complete nucleotide-sequence of the gene. Biol Chem Hoppe Seyler 1992;373:1233–8. https://doi.org/10.1515/bchm3.1992.373.2.1233.
[95] Schuchman EH, Levran O, Pereira LV, Desnick RJ. Structural organization and complete nucleotide sequence of the gene encoding human acid sphingomyelinase (SMPD1). Genomics 1992;12:197–205. https://doi.org/10.1016/0888-7543(92)90366-Z.
[96] Ferlinz K, Hurwitz R, Sandhoff K. Molecular basis of acid sphingomyelinase dificiency in a patient with Niemann-Pick disease type A. Biochem Biophys Res Commun 1991;179:1187–91. https://doi.org/10.1016/0006-291X(91)91697-B.
[97] Levran O, Desnick RJ, Schuchman EH. Niemann-Pick disease - a frequent missense mutation in the acid sphingomyelinase gene of Ashkenazi Jewish Type-A and Type-B patients. Proc Natl Acad Sci U S A 1991;88:3748–52. https://doi.org/10.1073/pnas.88.9.3748.
[98] Vanier MT, Ferlinz K, Rousson R, Duthel S, Louisot P, Sandhoff K, et al. Deletion of arginine (608) in acid sphingomyelinase is the prevalent mutation among Niemann-Pick disease type B patients from northern Africa. Hum Genet 1993;92:325–30. https://doi.org/10.1007/bf01247328.
[99] Takahashi T, Suchi M, Desnick RJ, Takada G, Schuchman EH. Identification and expression of five mutations in the human acid sphingomyelinase gene causing types A and B Niemann-Pick disease. Molecular evidence for genetic heterogeneity in the neuronopathic and non-neuronopathic forms. J Biol Chem 1992;267:12552–8.
[100] Levran O, Desnick RJ, Schuchman EH. Identification and expression of a common missense mutation (L302P) in the acid sphingomyelinase gene of Ashkenazi Jewish type-A Niemann-Pick disease patients. Blood 1992;80:2081–7.
[101] Levran O, Desnick RJ, Schuchman EH. Niemann-Pick type-B disease - identification of a single codon deletion in the acid sphingomyelinase gene and genotype phenotype correlations in type-A and type-B patients. J Clin Investig 1991;88:806–10. https://doi.org/10.1172/jci115380.
[102] Simonaro CM, Desnick RJ, McGovern MM, Wasserstein MP, Schuchman EH. The demographics and distribution of type B Niemann-Pick disease: Novel mutations lead to new genotype/phenotype correlations. Am J Hum Genet 2002;71:1413–9. https://doi.org/10.1086/345074.
[103] Besley GTN, Hoogeboom AJM, Hoogeveen A, Kleijer WJ, Galjaard H. Somatic cell hybridisation studies showing different gene mutations in Niemann-Pick variants. Hum Genet 1980;54:409–12. https://doi.org/10.1007/BF00291589.

[104] Beaudet AL, Manschreck AA. Metabolism of sphingomyelin by intact cultured fibroblasts - differentiation of Niemann-Pick disease type-A and type-B. Biochem Biophys Res Commun 1982;105:14–9. https://doi.org/10.1016/s0006-291x(82)80004-1.
[105] Kudoh T, Velkoff MA, Wenger DA. Uptake and metabolism of radioactively labeled sphingomyelin in cultured skin fibroblasts from controls and patients with Niemann-Pick disease and other lysosomal storage diseases. Biochim Biophys Acta 1983;754:82–92. https://doi.org/10.1016/0005-2760(83)90084-x.
[106] Graber D, Salvayre R, Levade T. Accurate differentiation of neuronopathic and nonneuronopathic forms of Niemann-Pick disease by evaluation of the effective residual lysosomal sphingomyelinase activity in intact-cells. J Neurochem 1994;63:1060–8.
[107] Simonaro CM, Park JH, Eliyahu E, Shtraizent N, McGovern MM, Schuchman EH. Imprinting at the SMPD1 locus: Implications for acid sphingomyelinase-deficient Niemann-Pick disease. Am J Hum Genet 2006;78:865–70. https://doi.org/10.1086/503750.
[108] Carstea ED, Morris JA, Coleman KG, Loftus SK, Zhang D, Cummings C, et al. Niemann-Pick C1 disease gene: homology to mediators of cholesterol homeostasis. Science 1997;277:228–31.
[109] Loftus SK, Morris JA, Carstea ED, Gu JZ, Cummings C, Brown A, et al. Murine model of Niemann-Pick C disease: mutation in a cholesterol homeostasis gene. Science 1997;277:232–5.
[110] Greer WL, Riddell DC, Gillan TL, Girouard GS, Sparrow SM, Byers DM, et al. The Nova Scotia (type D) form of Niemann-Pick disease is caused by a G3097–>T transversion in NPC1. Am J Hum Genet 1998;63:52–4. https://doi.org/10.1086/301931.
[111] Steinberg SJ, Ward CP, Fensom AH. Complementation studies in Niemann-Pick disease type C indicate the existence of a second group. J Med Genet 1994;31:317–20. https://doi.org/10.1136/jmg.31.4.317.
[112] Vanier MT, Duthel S, Rodriguez-Lafrasse C, Pentchev P, Carstea ED. Genetic heterogeneity in Niemann-Pick C disease: a study using somatic cell hybridization and linkage analysis. Am J Hum Genet 1996;58:118–25.
[113] Naureckiene S, Sleat D, Lackland H, Fensom A, Vanier MT, Wattiaux R, et al. Identification of HE1 as the second gene of Niemann-Pick C disease. Science 2000;290:2298–301.
[114] Frohlich O, Young LG. Molecular cloning and characterization of EPI-1, the major protein in chimpanzee (Pan troglodytes) cauda epididymal fluid. Biol Reprod 1996;54:857–64. https://doi.org/10.1095/biolreprod54.4.857.
[115] Kirchhoff C, Osterhoff C, Young L. Molecular cloning and characterization of HE1, a major secretory protein of the human epididymis. Biol Reprod 1996;54:847–56. https://doi.org/10.1095/biolreprod54.4.847.
[116] Sleat DE, Wiseman JA, El Banna M, Price SM, Verot L, Shen MM, et al. Genetic evidence for nonredundant functional cooperativity between NPC1 and NPC2 in lipid transport. Proc Natl Acad Sci U S A 2004;101:5886–91.
[117] Jones CS, Shankaran P, Callahan JW. Purification of sphingomyelinase to apparent homogeneity by using hydrophobic chromatography. Biochem J 1981;195:373–82. https://doi.org/10.1042/bj1950373.
[118] Yamanaka T, Suzuki K. Acid sphingomyelinase of human brain: purification to homogeneity. J Neurochem 1982;38:1753–63. https://doi.org/10.1111/j.1471-4159.1982.tb06659.x.
[119] Quintern LE, Weitz G, Nehrkorn H, Tager JM, Schram A, Sandhoff K. Acid sphingomyelinase from human urine: purification and characterization. Biochim Biophys Acta 1987;922:323–36. https://doi.org/10.1016/0005-2760(87)90055-5.
[120] Hurwitz R, Ferlinz K, Vielhaber G, Moczall H, Sandhoff K. Processing of human acid sphingomyelinase in normal and I-cell fibroblasts. J Biol Chem 1994;269:5440–5.
[121] Heller M, Shapiro B. Enzymic hydrolysis of sphingomyelin by rat liver. Biochem J 1966;98. https://doi.org/10.1042/bj0980763. 763-+.
[122] Fowler S. Lysosomal localization of sphingomyelinase in rat liver. Biochim Biophys Acta 1969;191. https://doi.org/10.1016/0005-2744(69)90271-x. 481-+.
[123] Ferlinz K, Hurwitz R, Moczall H, Lansmann S, Schuchman EH, Sandhoff K. Functional characterization of the N-glycosylation sites of human acid sphingomyelinase by site-directed mutagenesis. Eur J Biochem 1997;243:511–7. https://doi.org/10.1111/j.1432-1033.1997.511_1a.x.
[124] Ni XY, Morales CR. The lysosomal trafficking of acid sphingomyelinase is mediated by sortilin and mannose 6-phosphate receptor. Traffic 2006;7:889–902. https://doi.org/10.1111/j.1600-0854.2006.00429.x.
[125] Ferlinz K, Hurwitz R, Vielhaber G, Suzuki K, Sandhoff K. Occurrence of 2 molecular-forms of human acid sphingomyelinase. Biochem J 1994;301:855–62. https://doi.org/10.1042/bj3010855.
[126] Schissel SL, Schuchman EH, Williams KJ, Tabas I. Zn2+-stimulated sphingomyelinase is secreted by many cell types and is a product of the acid sphingomyelinase gene. J Biol Chem 1996;271:18431–6. https://doi.org/10.1074/jbc.271.31.18431.
[127] Grassme H, Jekle A, Riehle A, Schwarz H, Berger J, Sandhoff K, et al. CD95 signaling via ceramide-rich membrane rafts. J Biol Chem 2001;276:20589–96. https://doi.org/10.1074/jbc.M101207200.
[128] Jenkins RW, Canals D, Idkowiak-Baldys J, Simbari F, Roddy P, Perry DM, et al. Regulated secretion of acid sphingomyelinase implications for selectivity of ceramide formation. J Biol Chem 2010;285:35706–18. https://doi.org/10.1074/jbc.M110.125609.
[129] Ponting CP. Acid sphingomyelinase possesses a domain homologous to its activator proteins: saposins B and D. Protein Sci 1994;3:359–61. https://doi.org/10.1002/pro.5560030219.
[130] Kolzer M, Ferlinz K, Bartelsen O, Hoops SL, Lang F, Sandhoff K. Functional characterization of the postulated intramolecular sphingolipid activator protein domain of human acid sphingomyelinase. Biol Chem 2004;385:1193–5. https://doi.org/10.1515/bc.2004.154.
[131] Spence MW, Byers DM, Palmer FBS, Cook HW. A new ZN-2+-stimulated sphingomyelinase in fetal bovine serum. J Biol Chem 1989;264:5358–63.
[132] Schissel SL, Keesler GA, Schuchman EH, Williams KJ, Tabas I. The cellular trafficking and zinc dependence of secretory and lysosomal sphingomyelinase, two products of the acid sphingomyelinase gene. J Biol Chem 1998;273:18250–9. https://doi.org/10.1074/jbc.273.29.18250.
[133] Newrzella D, Stoffel W. Functional analysis of the glycosylation of murine acid sphingomyelinase. J Biol Chem 1996;271:32089–95. https://doi.org/10.1074/jbc.271.50.32089.
[134] Jenkins RW, Idkowiak-Baldys J, Simbari F, Canals D, Roddy P, Riner CD, et al. A novel mechanism of lysosomal acid sphingomyelinase maturation: requirement for carboxyl-terminal proteolytic processing*. J Biol Chem 2011;286:3777–88. https://doi.org/10.1074/jbc.M110.155234.
[135] Edelmann B, Bertsch U, Tchikov V, Winoto-Morbach S, Perrotta C, Jakob M, et al. Caspase-8 and caspase-7 sequentially mediate proteolytic activation of acid sphingomyelinase in TNF-R1 receptosomes. EMBO J 2011;30:379–94. https://doi.org/10.1038/emboj.2010.326.
[136] Qiu HW, Edmunds T, Baker-Malcolm J, Karey KP, Estes S, Schwarz C, et al. Activation of human acid sphingomyelinase through modification or deletion of C-terminal cysteine. J Biol Chem 2003;278:32744–52. https://doi.org/10.1074/jbc.M303022200.
[137] Scheel-Toellner D, Wang KQ, Craddock R, Webb PR, McGettrick HM, Assi LK, et al. Reactive oxygen species limit neutrophil life span by activating death receptor signaling. Blood 2004;104:2557–64. https://doi.org/10.1182/blood-2004-01-0191.
[138] Dumitru CA, Gulbins E. TRAIL activates acid sphingomyelinase via a redox mechanism and releases ceramide to trigger apoptosis. Oncogene 2006;25:5612–25. https://doi.org/10.1038/sj.onc.1209568.
[139] Gorelik A, Illes K, Heinz LX, Superti-Furga G, Nagar B. Crystal structure of mammalian acid sphingomyelinase. Nat Commun 2016:7. https://doi.org/10.1038/ncomms12196.
[140] Xiong Z-J, Huang J, Poda G, Pomès R, Privé GG. Structure of human acid sphingomyelinase reveals the role of the saposin domain in activating substrate hydrolysis. J Mol Biol 2016;428:3026–42. https://doi.org/10.1016/j.jmb.2016.06.012.
[141] Zhou YF, Metcalf MC, Garman SC, Edmunds T, Qiu HW, Wei RR. Human acid sphingomyelinase structures provide insight to molecular basis of Niemann-Pick disease. Nat Commun 2016:7. https://doi.org/10.1038/ncomms13082.
[142] Oninla VO, Breiden B, Babalola JO, Sandhoff K. Acid sphingomyelinase activity is regulated by membrane lipids and facilitates cholesterol transfer by NPC2[S]. J Lipid Res 2014;55:2606–19. https://doi.org/10.1194/jlr.M054528.
[143] Kolesnick RN. 1,2-diacyglycerols but not phorbol esters stimulate sphingomyelin hydrolysis in gh3 pituitary-cells. J Biol Chem 1987;262:16759–62.
[144] Kim MY, Linardic C, Obeid L, Hannun Y. Identification of sphingomyelin turnover as an effector mechanism for the action of tumor-necrosis-factor-alpha and gamma-interferon - specific role in cell-differentiation. J Biol Chem 1991;266:484–9.
[145] Schutze S, Potthoff K, Machleidt T, Berkovic D, Wiegmann K, Kronke M. TNF activates NF-kappa-B by phosphatidylcholine-specific phospholipase-C-induced acidic sphingomyelin breakdown. Cell 1992;71:765–76. https://doi.org/10.1016/0092-8674(92)90553-o.
[146] Cifone MG, Demaria R, Roncaioli P, Rippo MR, Azuma M, Lanier LL, et al. Apoptotic signaling through CD95 (FAS/APO-1) activates an acidic sphingomyelinase. J Exp Med 1994;180:1547–52. https://doi.org/10.1084/jem.180.4.1547.
[147] Haimovitzfriedman A, Kan CC, Ehleiter D, Persaud RS, McLoughlin M, Fuks Z, et al. Ionizing-radiation acts on cellular membranes to generate ceramide and initiate apoptosis. J Exp Med 1994;180:525–35. https://doi.org/10.1084/jem.180.2.525.
[148] Wiegmann K, Schutze S, Machleidt T, Witte D, Kronke M. Functional dichotomy of neutral and acidic sphingomyelinases in tumor-necrosis-factor signaling. Cell 1994;78:1005–15. https://doi.org/10.1016/0092-8674(94)90275-5.
[149] Santana P, Pena LA, HaimovitzFriedman A, Martin S, Green D, McLoughlin M, et al. Acid sphingomyelinase-deficient human lymphoblasts and mice are defective in radiation-induced apoptosis. Cell 1996;86:189–99. https://doi.org/10.1016/s0092-8674(00)80091-4.
[150] Lin T, Genestier L, Pinkoski MJ, Castro A, Nicholas S, Mogil R, et al. Role of acidic sphingomyelinase in Fas/CD95-mediated cell death. J Biol Chem 2000;275:8657–63. https://doi.org/10.1074/jbc.275.12.8657.
[151] Wong ML, Xie BX, Beatini N, Phu P, Marathe S, Johns A, et al. Acute systemic inflammation up-regulates secretory sphingomyelinase in vivo: A possible link between inflammatory cytokines and atherogenesis. Proc Natl Acad Sci U S A 2000;97:8681–6. https://doi.org/10.1073/pnas.150098097.
[152] Esen M, Schreiner B, Jendrossek V, Lang F, Fassbender K, Grassme H, et al. Mechanisms of Staphylococcus aureus induced apoptosis of human endothelial cells. Apoptosis 2001;6:431–9. https://doi.org/10.1023/a:1012445925628.
[153] Grassme H, Riehle A, Wilker B, Gulbins E. Rhinoviruses infect human epithelial cells via ceramide-enriched membrane platforms. J Biol Chem 2005;280:26256–62. https://doi.org/10.1074/jbc.M500835200.
[154] Nozaki K, Maltez VI, Rayamajhi M, Tubbs AL, Mitchell JE, Lacey CA, et al. Caspase-7 activates ASM to repair gasdermin and perforin pores. Nature 2022;606:960–7. https://doi.org/10.1038/s41586-022-04825-8.

[155] Jensen JM, Folster-Holst R, Baranowsky A, Schunck M, Winoto-Morbach S, Neumann C, et al. Impaired sphingomyelinase activity and epidermal differentiation in atopic dermatitis. J Investig Dermatol 2004;122:1423–31. https://doi.org/10.1111/j.0022-202X.2004.22621.x.

[156] Petrache I, Natarajan V, Zhen LJ, Medler TR, Richter AT, Cho C, et al. Ceramide upregulation causes pulmonary cell apoptosis and emphysema-like disease in mice. Nat Med 2005;11:491–8. https://doi.org/10.1038/nm1238.

[157] Lang PA, Schenck M, Nicolay JP, Becker JU, Kempe DS, Lupescu A, et al. Liver cell death and anemia in Wilson disease involve acid sphingomyelinase and ceramide. Nat Med 2007;13:164–70. https://doi.org/10.1038/nm1539.

[158] Teichgraber V, Ulrich M, Endlich N, Riethmuller J, Wilker B, De Oliveira-Munding CC, et al. Ceramide accumulation mediates inflammation, cell death and infection susceptibility in cystic fibrosis. Nat Med 2008;14:382–91. https://doi.org/10.1038/nm1748.

[159] Gulbins E, Palmada M, Reichel M, Luth A, Bohmer C, Amato D, et al. Acid sphingomyelinase-ceramide system mediates effects of antidepressant drugs. Nat Med 2013;19. https://doi.org/10.1038/nm.3214. 934-+.

[160] Lee JK, Jin HK, Park MH, Kim BR, Lee PH, Nakauchi H, et al. Acid sphingomyelinase modulates the autophagic process by controlling lysosomal biogenesis in Alzheimer's disease. J Exp Med 2014;211:1551–70. https://doi.org/10.1084/jem.20132451.

[161] Gan-Or Z, Ozelius LJ, Bar-Shira A, Saunders-Pullman R, Mirelman A, Kornreich R, et al. The p.L302P mutation in the lysosomal enzyme gene SMPD1 is a risk factor for Parkinson disease. Neurology 2013;80:1606–10. https://doi.org/10.1212/WNL.0b013e31828f180e.

[162] Foo JN, Liany H, Bei JX, Yu XQ, Liu JJ, Au WL, et al. A rare lysosomal enzyme gene SMPD1 variant (p.R591C) associates with Parkinson's disease. Neurobiol Aging 2013;34. https://doi.org/10.1016/j.neurobiolaging.2013.06.010.

[163] Mandik F, Vos M. Neurodegenerative Disorders: Spotlight on Sphingolipids. Int J Mol Sci 2021;22:11998.

[164] Higgins ME, Davies JP, Chen FW, Ioannou YA. Niemann-Pick C1 is a late endosome-resident protein that transiently associates with lysosomes and the trans-Golgi network. Mol Genet Metab 1999;68:1–13.

[165] Neufeld EB, Wastney M, Patel S, Suresh S, Cooney AM, Dwyer NK, et al. The Niemann-Pick C1 protein resides in a vesicular compartment linked to retrograde transport of multiple lysosomal cargo. J Biol Chem 1999;274:9627–35. https://doi.org/10.1074/jbc.274.14.9627.

[166] Watari H, Blanchette-Mackie EJ, Dwyer NK, Glick JM, Patel S, Neufeld EB, et al. Niemann-Pick C1 protein: obligatory roles for N-terminal domains and lysosomal targeting in cholesterol mobilization. Proc Natl Acad Sci U S A 1999;96:805–10.

[167] Frolov A, Srivastava K, Daphna-Iken D, Traub LM, Schaffer JE, Ory DS. Cholesterol overload promotes morphogenesis of a Niemann-Pick C (NPC)-like compartment independent of inhibition of NPC1 or HE1/NPC2 function. J Biol Chem 2001;276:46414–21.

[168] Zhang M, Sun M, Dwyer NK, Comly ME, Patel SC, Sundaram R, et al. Differential trafficking of the Niemann-Pick C1 and 2 proteins highlights distinct roles in late endocytic lipid trafficking. Acta Paediatr 2003;92:63–73. https://doi.org/10.1080/08035320310021958.

[169] Blom TS, Linder MD, Snow K, Pihko H, Hess MW, Jokitalo E, et al. Defective endocytic trafficking of NPC1 and NPC2 underlying infantile Niemann-Pick type C disease. Hum Mol Genet 2003;12:257–72. https://doi.org/10.1093/hmg/ddg025.

[170] van der Kant R, Zondervan I, Janssen L, Neefjes J. Cholesterol-binding molecules MLN64 and ORP1L mark distinct late endosomes with transporters ABCA3 and NPC1. J Lipid Res 2013;54:2153–65. https://doi.org/10.1194/jlr.M037325.

[171] Watari H, Blanchette-Mackie EJ, Dwyer NK, Watari M, Neufeld EB, Patel S, et al. Mutations in the leucine zipper motif and sterol-sensing domain inactivate the Niemann-Pick C1 glycoprotein. J Biol Chem 1999;274:21861–6. https://doi.org/10.1074/jbc.274.31.21861.

[172] Chikh K, Vey S, Simonot U, Vanier MT, Millat G. Niemann-Pick type C disease: importance of N-glycosylation sites for function and cellular location of the NPC2 protein. Mol Genet Metab 2004;83:220–30. https://doi.org/10.1016/j.ymgme.2004.06.013.

[173] Liou HL, Dixit SS, Xu SJ, Tint GS, Stock AM, Lobel P. NPC2, the protein deficient in Niemann-Pick C2 disease, consists of multiple glycoforms that bind a variety of sterols. J Biol Chem 2006;281:36710–23. https://doi.org/10.1074/jbc.M608743200.

[174] Anderson J, Walker G, Pu J. BORC-ARL8-HOPS ensemble is required for lysosomal cholesterol Egress through NPC2. Mol Biol Cell 2022. https://doi.org/10.1091/mbc.E21-11-0595-T. mbc.E21-11-0595-T.

[175] Okamura N, Kiuchi S, Tamba M, Kashima T, Hiramoto S, Baba T, et al. A porcine homolog of the major secretory protein of human epididymis, HE1, specifically binds cholesterol. BBA-Mol Cell Biol L 1999;1438:377–87. https://doi.org/10.1016/s1388-1981(99)00070-0.

[176] Ko DC, Binkley J, Sidow A, Scott MP. The integrity of a cholesterol-binding pocket in Niemann-Pick C2 protein is necessary to control lysosome cholesterol levels. Proc Natl Acad Sci U S A 2003;100:2518–25. https://doi.org/10.1073/pnas.0530027100.

[177] Infante RE, Abi-Mosleh L, Radhakrishnan A, Dale JD, Brown MS, Goldstein JL. Purified NPC1 protein - I. Binding of cholesterol and oxysterols to a 1278-amino acid membrane protein. J Biol Chem 2008;283:1052–63. https://doi.org/10.1074/jbc.M707943200.

[178] Infante RE, Radhakrishnan A, Abi-Mosleh L, Kinch LN, Wang ML, Grishin NV, et al. Purified NPC1 protein - II. Localization of sterol binding to a 240-amino acid soluble luminal loop. J Biol Chem 2008;283:1064–75. https://doi.org/10.1074/jbc.M707944200.

[179] Infante RE, Wang ML, Radhakrishnan A, Kwon HJ, Brown MS, Goldstein JL. NPC2 facilitates bidirectional transfer of cholesterol between NPC1 and lipid bilayers, a step in cholesterol egress from lysosomes. Proc Natl Acad Sci 2008;105:15287–92. https://doi.org/10.1073/pnas.0807328105.

[180] Cheruku SR, Xu Z, Dutia R, Lobel P, Storch J. Mechanism of cholesterol transfer from the Niemann-Pick type C2 protein to model membranes supports a role in lysosomal cholesterol transport. J Biol Chem 2006;281:31594–604. https://doi.org/10.1074/jbc.M602765200.

[181] Schrantz N, Sagiv Y, Liu Y, Savage PB, Bendelac A, Teyton L. The Niemann-Pick type C2 protein loads isoglobotrihexosylceramide onto CD1d molecules and contributes to the thymic selection of NKT cells. J Exp Med 2007;204:841–52. https://doi.org/10.1084/jem.20061562.

[182] McCauliff LA, Langan A, Li R, Ilnytska O, Bose D, Waghalter M, et al. Intracellular cholesterol trafficking is dependent upon NPC2 interaction with lysobisphosphatidic acid. Elife 2019:8. https://doi.org/10.7554/eLife.50832.

[183] Altuzar J, Notbohm J, Stein F, Haberkant P, Hempelmann P, Heybrock S, et al. Lysosome-targeted multifunctional lipid probes reveal the sterol transporter NPC1 as a sphingosine interactor. Proc Natl Acad Sci U S A 2023;120:e2213886120. https://doi.org/10.1073/pnas.2213886120.

[184] Bartz F, Kern L, Erz D, Zhu M, Gilbert D, Meinhof T, et al. Identification of cholesterol-regulating genes by targeted RNAi screening. Cell Metab 2009;10:63–75. https://doi.org/10.1016/j.cmet.2009.05.009.

[185] Castellano BM, Thelen AM, Moldavski O, Feltes M, van der Welle RE, Mydock-McGrane L, et al. Lysosomal cholesterol activates mTORC1 via an SLC38A9-Niemann-Pick C1 signaling complex. Science 2017;355:1306–11. https://doi.org/10.1126/science.aag1417.

[186] van den Boomen DJH, Sienkiewicz A, Berlin I, Jongsma MLM, van Elsland DM, Luzio JP, et al. A trimeric Rab7 GEF controls NPC1-dependent lysosomal cholesterol export. Nat Commun 2020:11. https://doi.org/10.1038/s41467-020-19032-0.

[187] Moesgaard L, Petersen D, Szomek M, Reinholdt P, Winkler MBL, Frain KM, et al. Mechanistic insight into lipid binding to yeast Niemann Pick Type C2 protein. Biochemistry 2020;59:4407–20. https://doi.org/10.1021/acs.biochem.0c00574.

[188] Chu T-T, Tu X, Yang K, Wu J, Repa JJ, Yan N. Tonic prime-boost of STING signalling mediates Niemann–Pick disease type C. Nature 2021;596:570–5. https://doi.org/10.1038/s41586-021-03762-2.

[189] Greer WL, Dobson MJ, Girouard GS, Byers DM, Riddell DC, Neumann PE. Mutations in NPC1 highlight a conserved NPC1-specific cysteine-rich domain. Am J Hum Genet 1999;65:1252–60. https://doi.org/10.1086/302620.

[190] Deffieu MS, Pfeffer SR. Niemann-Pick type C 1 function requires lumenal domain residues that mediate cholesterol-dependent NPC2 binding. Proc Natl Acad Sci U S A 2011;108:18932–6.

[191] Gelsthorpe ME, Baumann N, Millard E, Gale SE, Langmade SJ, Schaffer JE, et al. Niemann-Pick type C1 I1061T mutant encodes a functional protein that is selected for endoplasmic reticulum-associated degradation due to protein misfolding. J Biol Chem 2008;283:8229–36. https://doi.org/10.1074/jbc.M708735200.

[192] Schultz ML, Krus KL, Kaushik S, Dang D, Chopra R, Qi L, et al. Coordinate regulation of mutant NPC1 degradation by selective ER autophagy and MARCH6-dependent ERAD. Nat Commun 2018:9. https://doi.org/10.1038/s41467-018-06115-2.

[193] Schultz ML, Schache KJ, Azaria RD, Kuiper EQ, Erwood S, Ivakine EA, et al. Species-specific differences in NPC1 protein trafficking govern therapeutic response in Niemann-Pick type C disease. JCI Insight 2022:7. https://doi.org/10.1172/jci.insight.160308.

[194] Friedland N, Liou H-L, Lobel P, Stock AM. Structure of a cholesterol-binding protein deficient in Niemann-Pick Type C2 disease. Proc Natl Acad Sci U S A 2003;100:2512–7.

[195] Xu S, Benoff B, Liou HL, Lobel P, Stock AM. Structural basis of sterol binding by NPC2, a lysosomal protein deficient in Niemann-Pick type C2 disease. J Biol Chem 2007;282:23525–31. https://doi.org/10.1074/jbc.M703848200.

[196] Kwon HJ, Abi-Mosleh L, Wang ML, Deisenhofer J, Goldstein JL, Brown MS, et al. Structure of N-terminal domain of NPC1 reveals distinct subdomains for binding and transfer of cholesterol. Cell 2009;137:1213–24.

[197] Gong X, Qian H, Zhou X, Wu J, Wan T, Cao P, et al. Structural insights into the Niemann-Pick C1 (NPC1)-mediated cholesterol transfer and Ebola infection. Cell 2016;165:1467–78. https://doi.org/10.1016/j.cell.2016.05.022.

[198] Li X, Saha P, Li J, Blobel G, Pfeffer SR. Clues to the mechanism of cholesterol transfer from the structure of NPC1 middle lumenal domain bound to NPC2. Proc Natl Acad Sci U S A 2016;113:10079–84. https://doi.org/10.1073/pnas.1611956113.

[199] Li X, Wang J, Coutavas E, Shi H, Hao Q, Blobel G. Structure of human Niemann-Pick C1 protein. Proc Natl Acad Sci U S A 2016;113:8212–7. https://doi.org/10.1073/pnas.1607795113.

[200] Li X, Lu F, Trinh MN, Schmiege P, Seemann J, Wang J, et al. 3.3 Å structure of Niemann-Pick C1 protein reveals insights into the function of the C-terminal luminal domain in cholesterol transport. Proc Natl Acad Sci U S A 2017;114:9116–21. https://doi.org/10.1073/pnas.1711716114.

[201] Long T, Qi X, Hassan A, Liang Q, De Brabander JK, Li X. Structural basis for itraconazole-mediated NPC1 inhibition. Nat Commun 2020;11:152. https://doi.org/10.1038/s41467-019-13917-5.

[202] Winkler MBL, Kidmose RT, Szomek M, Thaysen K, Rawson S, Muench SP, et al. Structural insight into Eukaryotic sterol transport through Niemann-Pick Type C proteins. Cell 2019;179:485–497.e18. https://doi.org/10.1016/j.cell.2019.08.038.

[203] Qian H, Wu X, Du X, Yao X, Zhao X, Lee J, et al. Structural basis of low-pH-dependent lysosomal cholesterol Egress by NPC1 and NPC2. Cell 2020;182:98–111.e18. https://doi.org/10.1016/j.cell.2020.05.020.
[204] Wang ML, Motamed M, Infante RE, Abi-Mosleh L, Kwon HJ, Brown MS, et al. Identification of surface residues on Niemann-Pick C2 essential for hydrophobic handoff of cholesterol to NPC1 in lysosomes. Cell Metab 2010;12:166–73. https://doi.org/10.1016/j.cmet.2010.05.016.
[205] Davies JP, Chen FW, Ioannou YA. Transmembrane molecular pump activity of Niemann-Pick C1 protein. Science 2000;290:2295–8. https://doi.org/10.1126/science.290.5500.2295.
[206] Zhang YX, Bulkley DP, Xin Y, Roberts KJ, Asarnow DE, Sharma A, et al. Structural basis for cholesterol transport-like activity of the hedgehog receptor patched. Cell 2018;175. https://doi.org/10.1016/j.cell.2018.10.026. 1352-+.
[207] Alpy F, Stoeckel ME, Dierich A, Escola JM, Wendling C, Chenard MP, et al. The steroidogenic acute regulatory protein homolog MLN64, a late endosomal cholesterol-binding protein. J Biol Chem 2001;276:4261–9.
[208] Zhang M, Liu P, Dwyer NK, Christenson LK, Fujimoto T, Martinez F, et al. MLN64 mediates mobilization of lysosomal cholesterol to steroidogenic mitochondria. J Biol Chem 2002;277:33300–10. https://doi.org/10.1074/jbc.M200003200.
[209] Charman M, Kennedy BE, Osborne N, Karten B. MLN64 mediates egress of cholesterol from endosomes to mitochondria in the absence of functional Niemann-Pick Type C1 protein. J Lipid Res 2010;51:1023–34. https://doi.org/10.1194/jlr.M002345.
[210] Du XM, Kumar J, Ferguson C, Schulz TA, Ong YS, Hong WJ, et al. A role for oxysterol-binding protein-related protein 5 in endosomal cholesterol trafficking. J Cell Biol 2011;192:121–35. https://doi.org/10.1083/jcb.201004142.
[211] Wilhelm LP, Wendling C, Védie B, Kobayashi T, Chenard M-P, Tomasetto C, et al. STARD3 mediates endoplasmic reticulum-to-endosome cholesterol transport at membrane contact sites. EMBO J 2017;36:1412–33. https://doi.org/10.15252/embj.201695917.
[212] Zhao K, Ridgway ND. Oxysterol-binding protein-related protein 1L regulates cholesterol Egress from the endo-lysosomal system. Cell Rep 2017;19:1807–18. https://doi.org/10.1016/j.celrep.2017.05.028.
[213] Dong J, Du X, Wang H, Wang J, Lu C, Chen X, et al. Allosteric enhancement of ORP1-mediated cholesterol transport by PI(4,5)P2/PI(3,4)P2. Nat Commun 2019;10:829. https://doi.org/10.1038/s41467-019-08791-0.
[214] Höglinger D, Burgoyne T, Sanchez-Heras E, Hartwig P, Colaco A, Newton J, et al. NPC1 regulates ER contacts with endocytic organelles to mediate cholesterol egress. Nat Commun 2019;10:4276. https://doi.org/10.1038/s41467-019-12152-2.
[215] Lim C-Y, Davis OB, Shin HR, Zhang J, Berdan CA, Jiang X, et al. ER-lysosome contacts enable cholesterol sensing by mTORC1 and drive aberrant growth signalling in Niemann-Pick type C. Nat Cell Biol 2019;21:1206–18. https://doi.org/10.1038/s41556-019-0391-5.
[216] Meneses-Salas E, Garcia-Melero A, Kanerva K, Blanco-Munoz P, Morales-Paytuvi F, Bonjoch J, et al. Annexin A6 modulates TBC1D15/Rab7/StARD3 axis to control endosomal cholesterol export in NPC1 cells. Cell Mol Life Sci 2020;77:2839–57. https://doi.org/10.1007/s00018-019-03330-y.
[217] Xiao X, Kim Y, Romartinez-Alonso B, Sirvydis K, Ory DS, Schwabe JWR, et al. Selective Aster inhibitors distinguish vesicular and nonvesicular sterol transport mechanisms. Proc Natl Acad Sci 2021;118:e2024149118. https://doi.org/10.1073/pnas.2024149118.
[218] Juhl AD, Lund FW, Jensen MLV, Szomek M, Heegaard CW, Guttmann P, et al. Niemann Pick C2 protein enables cholesterol transfer from endo-lysosomes to the plasma membrane for efflux by shedding of extracellular vesicles. Chem Phys Lipids 2021;235:105047. https://doi.org/10.1016/j.chemphyslip.2020.105047.
[219] Carette JE, Raaben M, Wong AC, Herbert AS, Obernosterer G, Mulherkar N, et al. Ebola virus entry requires the cholesterol transporter Niemann-Pick C1. Nature 2011;477:340–3. https://doi.org/10.1038/nature10348.
[220] Côté M, Misasi J, Ren T, Bruchez A, Lee K, Filone CM, et al. Small molecule inhibitors reveal Niemann-Pick C1 is essential for Ebola virus infection. Nature 2011;477:344–8. https://doi.org/10.1038/nature10380.
[221] Wang H, Shi Y, Song J, Qi J, Lu G, Yan J, et al. Ebola viral glycoprotein bound to its endosomal receptor Niemann-Pick C1. Cell 2016;164:258–68. https://doi.org/10.1016/j.cell.2015.12.044.
[222] Wec AZ, Nyakatura EK, Herbert AS, Howell KA, Holtsberg FW, Bakken RR, et al. A "Trojan horse" bispecific-antibody strategy for broad protection against ebolaviruses. Science (New York, NY) 2016;354:350–4. https://doi.org/10.1126/science.aag3267.
[223] Meyre D, Delplanque J, Chèvre J-C, Lecoeur C, Lobbens S, Gallina S, et al. Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. Nat Genet 2009;41:157–9. https://doi.org/10.1038/ng.301.
[224] Jelinek D, Heidenreich RA, Erickson RP, Garver WS. Decreased Npc1 gene dosage in mice is associated with weight gain. Obesity (Silver Spring) 2010;18:1457–9. https://doi.org/10.1038/oby.2009.415.
[225] Levade T, Salvayre R, Lenoir G, Douste-Blazy L. Sphingomyelinase and nonspecific phosphodiesterase activities in Epstein-Barr virus-transformed lymphoid cell lines from Niemann-Pick disease A, B and C. Biochim Biophys Acta 1984;793:321–4. https://doi.org/10.1016/0005-2760(84)90337-0.
[226] Long Y, Xu M, Li R, Dai S, Beers J, Chen GK, et al. Induced pluripotent stem cells for disease modeling and evaluation of therapeutics for Niemann-Pick disease type A. Stem Cells Transl Med 2016;5:1644–55. https://doi.org/10.5966/sctm.2015-0373.
[227] Kuemmel TA, Thiele J, Schroeder R, Stoffel W. Pathology of visceral organs and bone marrow in an acid sphingomyelinase deficient knock-out mouse line, mimicking human Niemann-Pick disease type A - a light and electron microscopic study. Pathol Res Pract 1997;193:663–71. https://doi.org/10.1016/s0344-0338(97)80025-8.
[228] Kuemmel TA, Schroeder R, Stoffel W. Light and electron microscopic analysis of the central and peripheral nervous systems of acid sphingomyelinase-deficient mice resulting from gene targeting. J Neuropathol Exp Neurol 1997;56:171–9. https://doi.org/10.1097/00005072-199702000-00008.
[229] Macauley SL, Sidman RL, Schuchman EH, Taksir T, Stewart GR. Neuropathology of the acid sphingomyelinase knockout mouse model of Niemann-Pick A disease including structure-function studies associated with cerebellar Purkinje cell degeneration. Exp Neurol 2008;214:181–92. https://doi.org/10.1016/j.expneurol.2008.07.026.
[230] Horinouchi K, Erlich S, Perl DP, Ferlinz K, Bisgaier CL, Sandhoff K, et al. Acid sphingomyelinase deficient mice - a model of type-A and type-B Niemann-Pick disease. Nat Genet 1995;10:288–93. https://doi.org/10.1038/ng0795-288.
[231] Otterbach B, Stoffel W. Acid sphingomyelinase-deficient mice mimic the neurovisceral form of human lysosomal storage disease (Niemann-Pick disease). Cell 1995;81:1053–61. https://doi.org/10.1016/s0092-8674(05)80010-8.
[232] Butler A, Gordon RE, Gatt S, Schuchman EH. Sperm abnormalities in heterozygous acid sphingomyelinase knockout mice reveal a novel approach for the prevention of genetic diseases. Am J Pathol 2007;170:2077–88. https://doi.org/10.2353/ajpath.2007.061002.
[233] Moles A, Tarrats N, Morales A, Domínguez M, Bataller R, Caballería J, et al. Acidic sphingomyelinase controls hepatic stellate cell activation and in vivo liver fibrogenesis. Am J Pathol 2010;177:1214–24. https://doi.org/10.2353/ajpath.2010.091257.
[234] Chung H-Y, Witt CJ, Jbeily N, Hurtado-Oliveros J, Giszas B, Lupp A, et al. Acid sphingomyelinase inhibition prevents development of sepsis sequelae in the murine liver. Sci Rep 2017;7:12348. https://doi.org/10.1038/s41598-017-11837-2.
[235] Hagemann N, Mohamud Yusuf A, Martiny C, Zhang X, Kleinschnitz C, Gunzer M, et al. Homozygous Smpd1 deficiency aggravates brain ischemia/ reperfusion injury by mechanisms involving polymorphonuclear neutrophils, whereas heterozygous Smpd1 deficiency protects against mild focal cerebral ischemia. Basic Res Cardiol 2020;115:64. https://doi.org/10.1007/s00395-020-00823-x.
[236] Garcia-Ruiz C, Colell A, Mari M, Morales A, Calvo M, Enrich C, et al. Defective TNF-alpha-mediated hepatocellular apoptosis and liver damage in acidic sphingomyelinase knockout mice. J Clin Investig 2003;111:197–208. https://doi.org/10.1172/jci200316010.
[237] Marathe S, Miranda SRP, Devlin C, Johns A, Kuriakose G, Williams KJ, et al. Creation of a mouse model for non-neurological (type B) Niemann-Pick disease by stable, low level expression of lysosomal sphingomyelinase in the absence of secretory sphingomyelinase: relationship between brain intra-lysosomal enzyme activity and central nervous system function. Hum Mol Genet 2000;9:1967–76. https://doi.org/10.1093/hmg/9.13.1967.
[238] Jones I, He XX, Katouzian F, Darroch PI, Schuchman EH. Characterization of common SMPD1 mutations causing types A and B Niemann-Pick disease and generation of mutation-specific mouse models. Mol Genet Metab 2008;95:152–62. https://doi.org/10.1016/j.ymgme.2008.08.004.
[239] Wenger DA, Sattler M, Kudoh T, Snyder SP, Kingston RS. Niemann-Pick disease - a genetic model in siamese cats. Science 1980;208:1471–3. https://doi.org/10.1126/science.7189903.
[240] Bundza A, Lowden JA, Charlton KM. Niemann-Pick disease in a poodle dog. Vet Pathol 1979;16:530–8. https://doi.org/10.1177/030098587901600504.
[241] Saunders GK, Wenger DA. Sphingomyelinase deficiency (Niemann-Pick disease) in a Hereford calf. Vet Pathol 2008;45:201–2. https://doi.org/10.1354/vp.45-2-201.
[242] Vapniarsky N, Wenger DA, Scheenstra D, Mete A. Sphingomyelin Lipidosis (Niemann-Pick Disease) in a Juvenile Raccoon (Procyon lotor). J Comp Pathol 2013;149:385–9. https://doi.org/10.1016/j.jcpa.2013.01.011.
[243] Lin XH, Hengartner MO, Kolesnick R. Caenorhabditis elegans contains two distinct acid sphingomyelinases. J Biol Chem 1998;273:14374–9. https://doi.org/10.1074/jbc.273.23.14374.
[244] Schmokel V, Memar N, Wiekenberg A, Trotzmuller M, Schnabel R, Doring F. Genetics of lipid-storage management in caenorhabditis elegans embryos. Genetics 2016;202. https://doi.org/10.1534/genetics.115.179127. 1071-+.
[245] Renault AD, Starz-Gaiano M, Lehmann R. Metabolism of sphingosine 1-phosphate and lysophosphatidic acid: a genome wide analysis of gene expression in Drosophila. Mech Dev 2002;119:S293–301. https://doi.org/10.1016/s0925-4773(03)00131-x.
[246] Kim Y, Sun H. ASM-3 acid sphingomyelinase functions as a positive regulator of the DAF-2/AGE-1 signaling pathway and serves as a novel anti-aging target. PloS One 2012:7. https://doi.org/10.1371/journal.pone.0045890.
[247] Darroch PI, Dagan A, Granot T, He XX, Gatt S, Schuchman EH. A lipid analogue that inhibits sphingomyelin hydrolysis and synthesis, increases ceramide, and leads to cell death. J Lipid Res 2005;46:2315–24. https://doi.org/10.1194/jlr.M500136-JLR200.
[248] Skácel J, Slusher BS, Tsukamoto T. Small molecule inhibitors targeting biosynthesis of ceramide, the central hub of the sphingolipid network. J Med Chem 2021;64:279–97. https://doi.org/10.1021/acs.jmedchem.0c01664.
[249] Lin CH, Kornhuber J, Zheng F, Alzheimer C. Tonic control of secretory acid sphingomyelinase over ventral hippocampal synaptic transmission and neuron excitability. Front Cell Neurosci 2021:15. https://doi.org/10.3389/fncel.2021.660561.

[250] Fog CK, Kirkegaard T. Animal models for Niemann-Pick type C: implications for drug discovery & development. Expert Opin Drug Discovery 2019;14:499–509. https://doi.org/10.1080/17460441.2019.1588882.
[251] Pallottini V, Pfrieger FW. Understanding and treating Niemann-Pick type C disease: models matter. Int J Mol Sci 2020:21. https://doi.org/10.3390/ijms21238979.
[252] Dahl NK, Reed KL, Daunais MA, Faust JR, Liscum L. Isolation and characterization of Chinese hamster ovary cells defective in the intracellular metabolism of low density lipoprotein-derived cholesterol. J Biol Chem 1992;267:4889–96.
[253] Kim SJ, Lee BH, Lee YS, Kang KS. Defective cholesterol traffic and neuronal differentiation in neural stem cells of Niemann-Pick type C disease improved by valproic acid, a histone deacetylase inhibitor. Biochem Biophys Res Commun 2007;360:593–9. https://doi.org/10.1016/j.bbrc.2007.06.116.
[254] Swaroop M, Thorne N, Rao MS, Austin CP, McKew JC, Zheng W. Evaluation of cholesterol reduction activity of methyl-beta-cyclodextrin using differentiated human neurons and astrocytes. J Biomol Screen 2012;17:1243–51.
[255] Bergamin N, Dardis A, Beltrami A, Cesselli D, Rigo S, Zampieri S, et al. A human neuronal model of Niemann Pick C disease developed from stem cells isolated from patient's skin. Orphanet J Rare Dis 2013;8:34. https://doi.org/10.1186/1750-1172-8-34.
[256] Trilck M, Hübner R, Seibler P, Klein C, Rolfs A, Frech MJ. Niemann-Pick type C1 patient-specific induced pluripotent stem cells display disease specific hallmarks. Orphanet J Rare Dis 2013;8:144. https://doi.org/10.1186/1750-1172-8-144.
[257] Yu D, Swaroop M, Wang M, Baxa U, Yang R, Yan Y, et al. Niemann-Pick disease type C: induced pluripotent stem cell-derived neuronal cells for modeling neural disease and evaluating drug efficacy. J Biomol Screen 2014;19:1164–73. https://doi.org/10.1177/1087057114537378.
[258] Sung E-A, Yu K-R, Shin J-H, Seo Y, Kim H-S, Koog MG, et al. Generation of patient specific human neural stem cells from Niemann-Pick disease type C patient-derived fibroblasts. Oncotarget 2017;8:85428–41. https://doi.org/10.18632/oncotarget.19976.
[259] Prabhu AV, Kang I, De Pace R, Wassif CA, Fujiwara H, Kell P, et al. A human iPSC-derived inducible neuronal model of Niemann-Pick disease, type C1. BMC Biol 2021:19. https://doi.org/10.1186/s12915-021-01133-x.
[260] Liedtke M, Volkner C, Jurs AV, Peter F, Rabenstein M, Hermann A, et al. Pathophysiological in vitro profile of neuronal differentiated cells derived from Niemann-Pick disease type C2 patient-specific iPSCs carrying the NPC2 mutations c.58G>T/c.140G>T. Int J Mol Sci 2021:22. https://doi.org/10.3390/ijms22084009.
[261] Maetzel D, Sarkar S, Wang H, Abi-Mosleh L, Xu P, Cheng Albert W, et al. Genetic and chemical correction of cholesterol accumulation and impaired autophagy in hepatic and neural cells derived from Niemann-Pick type C patient-specific iPS cells. Stem Cell Rep 2014;2:866–80. https://doi.org/10.1016/j.stemcr.2014.03.014.
[262] Erwood S, Brewer RA, Bily TMI, Maino E, Zhou L, Cohn RD, et al. Modeling Niemann-Pick disease type C in a human haploid cell line allows for patient variant characterization and clinical interpretation. Genome Res 2019;29:2010–9. https://doi.org/10.1101/gr.250720.119.
[263] Vanharanta L, Peränen J, Pfisterer SG, Enkavi G, Vattulainen I, Ikonen E. High-content imaging and structure-based predictions reveal functional differences between Niemann-Pick C1 variants. Traffic 2020;21:386–97. https://doi.org/10.1111/tra.12727.
[264] Erwood S, Bily TMI, Lequyer J, Yan J, Gulati N, Brewer RA, et al. Saturation variant interpretation using CRISPR prime editing. Nat Biotechnol 2022;40:885–95. https://doi.org/10.1038/s41587-021-01201-1.
[265] Lee SE, Shin N, Kook MG, Kong D, Kim NG, Choi SW, et al. Human iNSC-derived brain organoid model of lysosomal storage disorder in Niemann-Pick disease type C. Cell Death Dis 2020:11. https://doi.org/10.1038/s41419-020-03262-7.
[266] Liscum L, Faust JR. The intracellular transport of low density lipoprotein-derived cholesterol is inhibited in Chinese hamster ovary cells cultured with 3-beta-[2-(diethylamino)ethoxy]androst-5-en-17-one. J Biol Chem 1989;264:11796–806.
[267] Rodriguez-Lafrasse C, Rousson R, Bonnet J, Pentchev PG, Louisot P, Vanier MT. Abnormal cholesterol metabolism in imipramine-treated fibroblast cultures. Similarities with Niemann-Pick type C disease. Biochim Biophys Acta 1990;1043:123–8. https://doi.org/10.1016/0005-2760(90)90284-5.
[268] Lu F, Liang Q, Abi-Mosleh L, Das A, De Brabander JK, Goldstein JL, et al. Identification of NPC1 as the target of U18666A, an inhibitor of lysosomal cholesterol export and Ebola infection. Elife. 2015:4.
[269] Trinh MN, Lu FR, Li XC, Das A, Liang QR, De Brabander JK, et al. Triazoles inhibit cholesterol export from lysosomes by binding to NPC1. Proc Natl Acad Sci U S A 2017;114:89–94. https://doi.org/10.1073/pnas.1619571114.
[270] Head SA, Shi WQ, Yang EJ, Nacev BA, Hong SY, Pasunooti KK, et al. Simultaneous targeting of NPC1 and VDAC1 by itraconazole leads to synergistic inhibition of mTOR signaling and angiogenesis. ACS Chem Biol 2017;12:174–82. https://doi.org/10.1021/acschembio.6b00849.
[271] Pentchev PG, Gal AE, Booth AD, Omodeo-Sale F, Fours J, Neumeyer BA, et al. A lysosomal storage disorder in mice characterized by a dual deficiency of sphingomyelinase and glucocerebrosidase. Biochim Biophys Acta 1980;619:669–79. https://doi.org/10.1016/0005-2760(80)90116-2.
[272] Miyawaki S, Mitsuoka S, Sakiyama T, Kitagawa T. Sphingomyelinosis, a new mutation in the mouse: a model of Niemann-Pick disease in humans. J Hered 1982;73:257–63. https://doi.org/10.1093/oxfordjournals.jhered.a109635.
[273] Lowenthal AC, Cummings JF, Wenger DA, Thrall MA, Wood PA, de Lahunta A. Feline sphingolipidosis resembling Niemann-Pick disease type C. Acta Neuropathol 1990;81:189–97. https://doi.org/10.1007/BF00334507.
[274] Muñana KR, Luttgen PJ, Thrall MA, Mitchell TW, Wenger DA. Neurological manifestations of Niemann-Pick disease type C in cats. J Vet Intern Med 1994;8:117–21. https://doi.org/10.1111/j.1939-1676.1994.tb03208.x.
[275] Vite CH, Ding W, Bryan C, O'Donnell P, Cullen K, Aleman D, et al. Clinical, electrophysiological, and serum biochemical measures of progressive neurological and hepatic dysfunction in feline Niemann-Pick type C disease. Pediatr.Res. 2008;64:544–9.
[276] Somers KL, Royals MA, Carstea ED, Rafi MA, Wenger DA, Thrall MA. Mutation analysis of feline Niemann-Pick C1 disease. Mol Genet Metab 2003;79:99–103. https://doi.org/10.1016/s1096-7192(03)00074-x.
[277] Maue RA, Burgess RW, Wang B, Wooley CM, Seburn KL, Vanier MT, et al. A novel mouse model of Niemann-Pick type C disease carrying a D1005G-Npc1 mutation comparable to commonly observed human mutations. Hum.Mol.Genet. 2012;21:730–50.
[278] Garver WS, Erickson RP, Wilson JM, Colton TL, Hossain GS, Kozloski MA, et al. Altered expression of caveolin-1 and increased cholesterol in detergent insoluble membrane fractions from liver in mice with Niemann–Pick disease type C. Biochim Biophys Acta 1997;1361:272–80. https://doi.org/10.1016/S0925-4439(97)00047-1.
[279] Feng B, Zhang D, Kuriakose G, Devlin CM, Kockx M, Tabas I. Niemann-Pick C heterozygosity confers resistance to lesional necrosis and macrophage apoptosis in murine atherosclerosis. Proc Natl Acad Sci U S A 2003;100:10423–8. https://doi.org/10.1073/pnas.1732494100.
[280] Jelinek D, Castillo JJ, Garver WS. The C57BL/6J Niemann-Pick C1 mouse model with decreased gene dosage has impaired glucose tolerance independent of body weight. Gene 2013;527:65–70. https://doi.org/10.1016/j.gene.2013.05.080.
[281] Nicoli ER, Al Eisa N, Cluzeau CV, Wassif CA, Gray J, Burkert KR, et al. Defective Cytochrome P450-Catalysed Drug Metabolism in Niemann-Pick Type C Disease. PloS One 2016;11:e0152007. https://doi.org/10.1371/journal.pone.0152007.
[282] Yu W, Ko M, Yanagisawa K, Michikawa M. Neurodegeneration in heterozygous Niemann-Pick type C1 (NPC1) mouse: implication of heterozygous npc1 mutations being a risk for tauopathy*. J Biol Chem 2005;280:27296–302. https://doi.org/10.1074/jbc.M503922200.
[283] Brown DE, Thrall MA, Walkley SU, Wurzelmann S, Wenger DA, Allison RW, et al. Metabolic abnormalities in feline Niemann-Pick type C heterozygotes. J Inherit Metab Dis 1996;19:319–30. https://doi.org/10.1007/bf01799262.
[284] Benussi A, Cotelli MS, Cantoni V, Bertasi V, Turla M, Dardis A, et al. Clinical and neurophysiological characteristics of heterozygous NPC1 carriers. JIMD Rep 2019;49:80–8. https://doi.org/10.1002/jmd2.12059.
[285] Bremova-Ertl T, Sztatecsny C, Brendel M, Moser M, Möller B, Clevert DA, et al. Clinical, ocular motor, and imaging profile of Niemann-Pick type C heterozygosity. Neurology 2020;94:e1702–15. https://doi.org/10.1212/wnl.0000000000009290.
[286] Ko DC, Milenkovic L, Beier SM, Manuel H, Buchanan J, Scott MP. Cell-autonomous death of cerebellar purkinje neurons with autophagy in Niemann-Pick type C disease. PLoS.Genet. 2005;1:81–95.
[287] Yu T, Shakkottai VG, Chung C, Lieberman AP. Temporal and cell-specific deletion establishes that neuronal Npc1 deficiency is sufficient to mediate neurodegeneration. Hum.Mol.Genet. 2011;20:4440–51.
[288] Xie X, Brown MS, Shelton JM, Richardson JA, Goldstein JL, Liang G. Amino acid substitution in NPC1 that abolishes cholesterol binding reproduces phenotype of complete NPC1 deficiency in mice. Proc Natl Acad Sci U S A 2011;108:15330–5. https://doi.org/10.1073/pnas.1112751108.
[289] Praggastis M, Tortelli B, Zhang J, Fujiwara H, Sidhu R, Chacko A, et al. A murine Niemann-Pick C1 I1061T knock-in model recapitulates the pathological features of the most prevalent human disease allele. J Neurosci 2015;35:8091–106. https://doi.org/10.1523/jneurosci.4173-14.2015.
[290] Gómez-Grau M, Albaigès J, Casas J, Auladell C, Dierssen M, Vilageliu L, et al. New murine Niemann-Pick type C models bearing a pseudoexon-generating mutation recapitulate the main neurobehavioural and molecular features of the disease. Sci Rep 2017;7:41931. https://doi.org/10.1038/srep41931.
[291] Rodriguez-Gil JL, Watkins-Chow DE, Baxter LL, Elliot G, Harper UL, Wincovitch SM, et al. Genetic background modifies phenotypic severity and longevity in a mouse model of Niemann-Pick disease type C1. Dis Model Mech 2020:13. https://doi.org/10.1242/dmm.042614.
[292] Woolley SA, Tsimnadis ER, Lenghaus C, Healy PJ, Walker K, Morton A, et al. Molecular basis for a new bovine model of Niemann-Pick type C disease. PloS One 2020;15:e0238697. https://doi.org/10.1371/journal.pone.0238697.
[293] Nielsen GK, Dagnaes-Hansen F, Holm IE, Meaney S, Symula D, Andersen NT, et al. Protein replacement therapy partially corrects the cholesterol-storage phenotype in a mouse model of Niemann-Pick type C2 disease. PloS One 2011;6:e27287. https://doi.org/10.1371/journal.pone.0027287.
[294] Higaki K, Almanzar-Paramio D, Sturley SL. Metazoan and microbial models of Niemann-Pick Type C disease. Biochim Biophys Acta 2004;1685:38–47. https://doi.org/10.1016/j.bbalip.2004.08.010.
[295] Adebali O, Reznik AO, Ory DS, Zhulin IB. Establishing the precise evolutionary history of a gene improves prediction of disease-causing missense mutations. Genet Med 2016;18:1029–36. https://doi.org/10.1038/gim.2015.208.
[296] Zhu J, Wang GR, Pelosi P. Plant transcriptomes reveal hidden guests. Biochem Biophys Res Commun 2016;474:497–502. https://doi.org/10.1016/j.bbrc.2016.04.134.
[297] Zheng JC, Sun SL, Yue XR, Liu TX, Jing XF. Phylogeny and evolution of the cholesterol transporter NPC1 in insects. J Insect Physiol 2018;107:157–66. https://doi.org/10.1016/j.jinsphys.2018.04.007.
[298] Feldman MJ, Poirier BC, Lange BM. Misexpression of the Niemann-Pick disease type C1 (NPC1)-like protein in Arabidopsis causes sphingolipid accumulation and

reproductive defects. Planta 2015;242:921–33. https://doi.org/10.1007/s00425-015-2322-4.
[299] Hernandez J, Gabrielli M, Costa J, Uttaro AD. Phagocytic and pinocytic uptake of cholesterol in Tetrahymena thermophila impact differently on gene regulation for sterol homeostasis. Sci Rep 2021:11. https://doi.org/10.1038/s41598-021-88737-z.
[300] Malathi K, Higaki K, Tinkelenberg AH, Balderes DA, Almanzar-Paramio D, Wilcox LJ, et al. Mutagenesis of the putative sterol-sensing domain of yeast Niemann Pick C-related protein reveals a primordial role in subcellular sphingolipid distribution. J Cell Biol 2004;164:547–56. https://doi.org/10.1083/jcb.200310046.
[301] Zhang SC, Ren JH, Li HZ, Zhang Q, Armstrong JS, Munn AL, et al. Ncr1p, the yeast ortholog of mammalian niemann pick C1 protein, is dispensable for endocytic transport. Traffic 2004;5:1017–30. https://doi.org/10.1111/j.1600-0854.2004.00241.x.
[302] Berger AC, Hanson PK, Wylie Nichols J, Corbett AH. A yeast model system for functional analysis of the Niemann-Pick type C protein 1 homolog, Ncr1p: a yeast model for NP-C disease. Traffic 2005;6:907–17. https://doi.org/10.1111/j.1600-0854.2005.00327.x.
[303] Munkacsi AB, Chen FW, Brinkman MA, Higaki K, Gutiérrez GD, Chaudhari J, et al. An "exacerbate-reverse" strategy in yeast identifies histone deacetylase inhibition as a correction for cholesterol and sphingolipid transport defects in human Niemann-Pick type C disease. J Biol Chem 2011;286:23842–51. https://doi.org/10.1074/jbc.M111.227645.
[304] Tsuji T, Fujimoto M, Tatematsu T, Cheng J, Orii M, Takatori S, et al. Niemann-Pick type C proteins promote microautophagy by expanding raft-like membrane domains in the yeast vacuole. Elife 2017:6. https://doi.org/10.7554/eLife.25960.
[305] Colaco A, Fernández-Suárez ME, Shepherd D, Gal L, Bibi C, Chuartzman S, et al. Unbiased yeast screens identify cellular pathways affected in Niemann-Pick disease type C. Life Sci Allianc 2020:3. https://doi.org/10.26508/lsa.201800253.
[306] Berger AC, Vanderford TH, Gernert KM, Nichols JW, Faundez V, Corbett AH. Saccharomyces cerevisiae Npc2p is a functionally conserved homologue of the human Niemann-Pick disease type C 2 protein, hNPC2. Eukaryot Cell 2005;4:1851–62. https://doi.org/10.1128/ec.4.11.1851-1862.2005.
[307] Huang X, Suyama K, Buchanan J, Zhu AJ, Scott MP. A Drosophila model of the Niemann-Pick type C lysosome storage disease: dnpc1a is required for molting and sterol homeostasis. Development 2005;132:5115–24. https://doi.org/10.1242/dev.02079.
[308] Danielsen ET, Moeller ME, Yamanaka N, Ou Q, Laursen JM, Soenderholm C, et al. A drosophila genome-wide screen identifies regulators of steroid hormone production and developmental timing. Dev Cell 2016;37:558–70. https://doi.org/10.1016/j.devcel.2016.05.015.
[309] Bialistoky T, Manry D, Smith P, Ng C, Kim Y, Zamir S, et al. Functional analysis of Niemann-Pick disease type C family protein, NPC1a, in Drosophila melanogaster. Development 2019:146. https://doi.org/10.1242/dev.168427.
[310] Texada MJ, Lassen M, Pedersen LH, Koyama T, Malita A, Rewitz K. Insulin signaling couples growth and early maturation to cholesterol intake in Drosophila. Curr Biol 2022;32. https://doi.org/10.1016/j.cub.2022.02.021. 1548-+.
[311] Huang X, Warren JT, Buchanan J, Gilbert LI, Scott MP. Drosophila Niemann-Pick Type C-2 genes control sterol homeostasis and steroid biosynthesis: a model of human neurodegenerative disease. Development 2007;134:3733–42. https://doi.org/10.1242/dev.004572.
[312] Shi X-Z, Zhong X, Yu X-Q. Drosophila melanogaster NPC2 proteins bind bacterial cell wall components and may function in immune signal pathways. Insect Biochem Mol Biol 2012;42:545–56. https://doi.org/10.1016/j.ibmb.2012.04.002.
[313] Sym M, Basson M, Johnson C. A model for Niemann–Pick type C disease in the nematode Caenorhabditis elegans. Curr Biol 2000;10:527–30. https://doi.org/10.1016/S0960-9822(00)00468-1.
[314] Li J, Brown G, Ailion M, Lee S, Thomas JH. NCR-1 and NCR-2, the C. elegans homologs of the human Niemann-Pick type C1 disease protein, function upstream of DAF-9 in the dauer formation pathways. Development 2004;131:5741–52. https://doi.org/10.1242/dev.01408.
[315] Wüstner D, Landt Larsen A, Faergeman NJ, Brewer JR, Sage D. Selective visualization of fluorescent sterols in Caenorhabditis elegans by bleach-rate-based image segmentation. Traffic 2010;11:440–54. https://doi.org/10.1111/j.1600-0854.2010.01040.x.
[316] Schwend T, Loucks EJ, Snyder D, Ahlgren SC. Requirement of Npc1 and availability of cholesterol for early embryonic cell movements in zebrafish. J Lipid Res 2011;52:1328–44. https://doi.org/10.1194/jlr.M012377.
[317] Lin Y, Cai X, Wang G, Ouyang G, Cao H. Model construction of Niemann-Pick type C disease in zebrafish. Biol Chem 2018;399:903–10. https://doi.org/10.1515/hsz-2018-0118.
[318] Tseng W-C, Loeb HE, Pei W, Tsai-Morris C-H, Xu L, Cluzeau CV, et al. Modeling Niemann-Pick disease type C1 in zebrafish: a robust platform for *in vivo* screening of candidate therapeutic compounds. Dis Model Mech 2018;11. https://doi.org/10.1242/dmm.034165. dmm034165.
[319] Wiweger M, Majewski L, Adamek-Urbanska D, Wasilewska I, Kuznicki J. npc2-deficient Zebrafish reproduce neurological and inflammatory symptoms of Niemann-Pick type C disease. Front Cell Neurosci 2021:15. https://doi.org/10.3389/fncel.2021.647860.
[320] Tseng W-C, Johnson Escauriza AJ, Tsai-Morris C-H, Feldman B, Dale RK, Wassif CA, et al. The role of Niemann-Pick type C2 in zebrafish embryonic development. Development 2021:148. https://doi.org/10.1242/dev.194258.
[321] Pelosi P, Iovinella I, Felicioli A, Dani FR. Soluble proteins of chemical communication: an overview across arthropods. Front Physiol 2014:5. https://doi.org/10.3389/fphys.2014.00320.
[322] Ishida Y, Tsuchiya W, Fujii T, Fujimoto Z, Miyazawa M, Ishibashi J, et al. Niemann-Pick type C2 protein mediating chemical communication in the worker ant. Proc Natl Acad Sci U S A 2014;111:3847–52. https://doi.org/10.1073/pnas.1323928111.
[323] Derewenda U, Li J, Derewenda Z, Dauter Z, Mueller GA, Rule GS, et al. The crystal structure of a major dust mite allergen Der p 2, and its biological implications. J Mol Biol 2002;318:189–97. https://doi.org/10.1016/s0022-2836(02)00027-x.
[324] Iovinella I, Ban L, Song L, Pelosi P, Dani FR. Proteomic analysis of castor bean tick Ixodes ricinus: a focus on chemosensory organs. Insect Biochem Mol Biol 2016;78:58–68. https://doi.org/10.1016/j.ibmb.2016.09.004.
[325] Lige B, Romano JD, Bandaru VVR, Ehrenman K, Levitskaya J, Sampels V, et al. Deficiency of a Niemann-Pick, type C1-related protein in toxoplasma is associated with multiple lipidoses and increased pathogenicity. PLoS Pathog 2011:7. https://doi.org/10.1371/journal.ppat.1002410.
[326] Jupatanakul N, Sim S, Dimopoulos G. Aedes aegypti ML and Niemann-Pick type C family members are agonists of dengue virus infection. Dev Comp Immunol 2014;43:1–9. https://doi.org/10.1016/j.dci.2013.10.002.
[327] Seaman JA, Alout H, Meyers JI, Stenglein MD, Dabiré RK, Lozano-Fuentes S, et al. Age and prior blood feeding of Anopheles gambiae influences their susceptibility and gene expression patterns to ivermectin-containing blood meals. BMC Genomics 2015;16:797. https://doi.org/10.1186/s12864-015-2029-8.
[328] Bolaños J, Betanzos A, Javier-Reyna R, García-Rivera G, Huerta M, Pais-Morales J, et al. EhNPC1 and EhNPC2 proteins participate in trafficking of exogenous cholesterol in entamoeba histolytica trophozoites: relevance for phagocytosis. PLoS Pathog 2016;12:e1006089. https://doi.org/10.1371/journal.ppat.1006089.
[329] Caicedo PA, Serrato IM, Sim S, Dimopoulos G, Coatsworth H, Lowenberger C, et al. Immune response-related genes associated to blocking midgut dengue virus infection in Aedes aegypti strains that differ in susceptibility. Insect Sci 2019;26:635–48. https://doi.org/10.1111/1744-7917.12573.
[330] Istvan E, Das S, Bhatnagar S, Beck JR, Owen E, Llinas M, et al. Plasmodium Niemann-Pick type C1-related protein is a druggable target required for parasite membrane homeostasis. Elife 2019:8. https://doi.org/10.7554/eLife.40529.
[331] Anari M, Stroehlein AJ, Hall RS, Chang BCH, Gasser RB, Young ND. Expanded complement of Niemann-Pick type C2-like protein genes in Clonorchis sinensis suggests functions beyond sterol binding and transport. Parasit Vectors 2020;13:38. https://doi.org/10.1186/s13071-020-3910-0.
[332] Breakspear A, Pasquali M, Broz K, Dong Y, Kistler HC. Npc1 is involved in sterol trafficking in the filamentous fungus Fusarium graminearum. Fungal Genet Biol 2011;48:725–30. https://doi.org/10.1016/j.fgb.2011.03.001.
[333] Xiu CL, Xiao Y, Zhang S, Bao HB, Liu ZW, Zhang YJ. Niemann-Pick proteins type C2 are identified as olfactory related genes of Pardosa pseudoannulata by transcriptome and expression profile analysis. Comp Biochem Physiol D Genom Proteom 2019;29:320–9. https://doi.org/10.1016/j.cbd.2019.01.004.
[334] Wu S, Deng W, Li M, Xiao Y, Li J, Teng K, et al. Analysis of chemosensory genes in full and hungry adults of Arma chinensis (Pentatomidae) through antennal transcriptome. Front Physiol 2020;11:588291. https://doi.org/10.3389/fphys.2020.588291.
[335] Nganso BT, Mani K, Eliash N, Rafaeli A, Soroker V. Towards disrupting Varroa -honey bee chemosensing: a focus on a Niemann-Pick type C2 transcript. Insect Mol Biol 2021;30:519–31. https://doi.org/10.1111/imb.12722.
[336] Ma Y, Guo Z, Wang L, Wang B, Huang T, Tang B, et al. The genome of the rice planthopper egg parasitoid wasps Anagrus nilaparvatae casts light on the chemo- and mechanosensation in parasitism. BMC Genomics 2022;23:541. https://doi.org/10.1186/s12864-022-08656-9.
[337] Kodama S, Kajikawa N, Fukada F, Kubo Y. Niemann-Pick type C proteins are required for sterol transport and appressorium-mediated plant penetration of Colletotrichum orbiculare. mBio 2022;13:e0223622. https://doi.org/10.1128/mbio.02236-22.
[338] Lynn R, Terry RD. Lipid histochemistry and electron microscopy in adult Niemann-Pick disease. Am J Med 1964;37. https://doi.org/10.1016/0002-9343(64)90139-1. 987-+.
[339] Wallace BJ, Schneck L, Kaplan H, Volk BW. Fine structure of cerebellum of children with lipidoses. Arch Pathol 1965;80:466.
[340] Volk BW, Wallace BJ. Liver in lipidosis - an electron microscopic and histochemical study. Am J Pathol 1966;49:203.
[341] Emery JM, Green WR, Huff DS, Sloan HR. Niemann-Pick disease (type C). Histopathology and ultrastructure. Am J Ophthalmol 1972;74:1144–54.
[342] Anzil AP, Blinzinger K, Mehraein P, Dozic S. Niemann-Pick disease type-C - case report with ultrastructural findings. Neuropadiatrie 1973;4:207–25. https://doi.org/10.1055/s-0028-1091741.
[343] Kamensky E, Philippart M, Cancilla P, Frommes SP. Cultured skin fibroblasts in storage disorders. An analysis of ultrastructural features. Am J Pathol 1973;73:59–80.
[344] Kanfer JN, Young OM, Shapiro D, Brady RO. The metabolism of sphingomyelin: I. Purification and properties of a sphingomyelin-cleaving enzyme from rat liver tissue. J Biol Chem 1966;241:1081–4. https://doi.org/10.1016/S0021-9258(18)96805-5.
[345] Gal AE, Brady RO, Hibbert SR, Pentchev PG. Practical chromogenic procedure for detection of homozygotes and heterozygous carriers of Niemann-Pick disease. N Engl J Med 1975;293:632–6. https://doi.org/10.1056/nejm197509252931304.

[346] Gatt S, Dinur T, Barenholz Y. Fluorometric-determination of sphingomyelinase by use of fluorescent derivatives of sphingomyelin, and its application to diagnosis of Niemann-Pick disease. Clin Chem 1980;26:93–6.
[347] He X, Chen F, Dagan A, Gatt S, Schuchman EH. A fluorescence-based, high-performance liquid chromatographic assay to determine acid sphingomyelinase activity and diagnose types A and B Niemann–Pick disease. Anal Biochem 2003; 314:116–20. https://doi.org/10.1016/S0003-2697(02)00629-2.
[348] van Diggelen OP, Voznyi YV, Keulemans JLM, Schoonderwoerd K, Ledvinova J, Mengel E, et al. A new fluorimetric enzyme assay for the diagnosis of Niemann–Pick A/B, with specificity of natural sphingomyelinase substrate. J Inherit Metab Dis 2005;28:733–41. https://doi.org/10.1007/s10545-005-0105-y.
[349] Zhang YY, Wu WJ, Zhang JJ, Li Z, Ma HM, Zhao ZW. Facile method for specifically sensing sphingomyelinase in cells and human urine based on a ratiometric fluorescent nanoliposome probe. Anal Chem 2021;93:11775–84. https://doi.org/10.1021/acs.analchem.1c02197.
[350] Zhou X, Turecek F, Scott CR, Gelb MH. Quantification of cellular acid sphingomyelinase and galactocerebroside beta-galactosidase activities by electrospray ionization mass spectrometry. Clin Chem 2001;47:874–81.
[351] Chamoles NA, Blanco M, Gaggioli D, Casentini C. Gaucher and Niemann-Pick diseases - enzymatic diagnosis in dried blood spots on filter paper: retrospective diagnoses in newborn-screening cards. Clin Chim Acta 2002;317:191–7. https://doi.org/10.1016/s0009-8981(01)00798-7.
[352] Li YJ, Scott CR, Chamoles NA, Ghavami A, Pinto BM, Turecek F, et al. Direct multiplex assay of lysosomal enzymes in dried blood spots for newborn screening. Clin Chem 2004;50:1785–96. https://doi.org/10.1373/clinchem.2004.035907.
[353] Metz TF, Mechtler TP, Orsini JJ, Martin M, Shushan B, Herman JL, et al. Simplified newborn screening protocol for lysosomal storage disorders. Clin Chem 2011;57:1286–94. https://doi.org/10.1373/clinchem.2011.164640.
[354] Mechtler TP, Stary S, Metz TF, De Jesus VR, Greber-Platzer S, Pollak A, et al. Neonatal screening for lysosomal storage disorders: feasibility and incidence from a nationwide study in Austria. Lancet 2012;379:335–41. https://doi.org/10.1016/s0140-6736(11)61266-x.
[355] Elliott S, Buroker N, Cournoyer JJ, Potier AM, Trometer JD, Elbin C, et al. Pilot study of newborn screening for six lysosomal storage diseases using Tandem Mass Spectrometry. Mol Genet Metab 2016;118:304–9. https://doi.org/10.1016/j.ymgme.2016.05.015.
[356] Burton BK, Charrow J, Hoganson GE, Waggoner D, Tinkle B, Braddock SR, et al. Newborn screening for lysosomal storage disorders in Illinois: the initial 15-month experience. J Pediatr 2017;190:130–5. https://doi.org/10.1016/j.jpeds.2017.06.048.
[357] Wasserstein MP, Caggana M, Bailey SM, Desnick RJ, Edelmann L, Estrella L, et al. The New York pilot newborn screening program for lysosomal storage diseases: report of the first 65,000 infants. Genet Med 2019;21:631–40. https://doi.org/10.1038/s41436-018-0129-y.
[358] Koval M, Pagano RE. Sorting of an internalized plasma-membrane lipid between recycling and degradative pathways in normal and Niemann-Pick, type-A fibroblasts. J Cell Biol 1990;111:429–42. https://doi.org/10.1083/jcb.111.2.429.
[359] Levade T, Gatt S, Maret A, Salvayre R. Different pathways of uptake and degradation of sphingomyelin by lymphoblastoid-cells and the potential participation of the neutral sphingomyelinase. J Biol Chem 1991;266:13519–29.
[360] Yamaji A, Sekizawa Y, Emoto K, Sakuraba H, Inoue K, Kobayashi H, et al. Lysenin, a novel sphingomyelin-specific binding protein. J Biol Chem 1998;273:5300–6. https://doi.org/10.1074/jbc.273.9.5300.
[361] Galvan C, Camoletto PG, Cristofani F, Van Veldhoven PP, Ledesma MD. Anomalous surface distribution of glycosyl phosphatidyl inositol-anchored proteins in neurons lacking acid sphingomyelinase. Mol Biol Cell 2008;19: 509–22. https://doi.org/10.1091/mbc.E07-05-0439.
[362] Bernheimer AW, Avigad LS. Properties of a toxin from sea-anemone stoichactis-helianthus, including specific binding to sphingomyelin. Proc Natl Acad Sci U S A 1976;73:467–71. https://doi.org/10.1073/pnas.73.2.467.
[363] Hullin-Matsuda F, Murate M, Kobayashi T. Protein probes to visualize sphingomyelin and ceramide phosphoethanolamine. Chem Phys Lipids 2018;216: 132–41. https://doi.org/10.1016/j.chemphyslip.2018.09.002.
[364] Palacios-Ortega J, Heras-Márquez D, Amigot-Sánchez R, García-Montoya C, Torrijos C, Laxalde D, et al. Sea anemones, actinoporins, and cholesterol. Int J Mol Sci 2022;23:8771.
[365] Makino A, Abe M, Murate M, Inaba T, Yilmaz N, Hullin-Matsuda F, et al. Visualization of the heterogeneous membrane distribution of sphingomyelin associated with cytokinesis, cell polarity, and sphingolipidosis. FASEB J 2015;29: 477–93. https://doi.org/10.1096/fj.13-247585.
[366] Babalola JO, Wendeler M, Breiden B, Arenz C, Schwarzmann G, Locatelli-Hoops S, et al. Development of an assay for the intermembrane transfer of cholesterol by Niemann-Pick C2 protein. Biol Chem 2007;388:617–26. https://doi.org/10.1515/bc.2007.063.
[367] Pipalia NH, Huang A, Ralph H, Rujoi M, Maxfield FR. Automated microscopy screening for compounds that partially revert cholesterol accumulation in Niemann-Pick C cells. J Lipid Res 2006;47:284–301.
[368] Whitfield GB, Brock TD, Ammann A, Gottlieb D, Carter HE. Filipin, an antifungal antibiotic - isolation and properties. J Am Chem Soc 1955;77:4799–801. https://doi.org/10.1021/ja01623a032.
[369] Bergy ME, Eble TE. Filipin complex. Biochemistry 1968;7:653. https://doi.org/10.1021/bi00842a021.
[370] Norman AW, Demel RA, de Kruyff B, van Deenen LL. Studies on the biological properties of polyene antibiotics. Evidence for the direct interaction of filipin with cholesterol. J Biol Chem 1972;247:1918–29.
[371] Vanier MT, Rodriguez-Lafrasse C, Rousson R, Gazzah N, Juge MC, Pentchev PG, et al. Type C Niemann-Pick disease: spectrum of phenotypic variation in disruption of intracellular LDL-derived cholesterol processing. Biochim Biophys Acta 1991;1096:328–37.
[372] Vanier MT, Latour P. Laboratory diagnosis of Niemann-Pick disease type C: the filipin staining test. Methods Cell Biol 2015;126:357–75. https://doi.org/10.1016/bs.mcb.2014.10.028.
[373] Vanier MT, Gissen P, Bauer P, Coll MJ, Burlina A, Hendriksz CJ, et al. Diagnostic tests for Niemann-Pick disease type C (NP-C): a critical review. Mol Genet Metab 2016;118:244–54. https://doi.org/10.1016/j.ymgme.2016.06.004.
[374] Demais V, Barthelemy A, Perraut M, Ungerer N, Keime C, Reibel S, et al. Reversal of pathologic lipid accumulation in NPC1-deficient neurons by drug-promoted release of LAMP1-coated lamellar inclusions. J Neurosci 2016;36:8012–25. https://doi.org/10.1523/jneurosci.0900-16.2016.
[375] Reid PC, Sakashita N, Sugii S, Ohno-Iwashita Y, Shimada Y, Hickey WF, et al. A novel cholesterol stain reveals early neuronal cholesterol accumulation in the Niemann-Pick type C1 mouse brain. J Lipid Res 2004;45:582–91.
[376] Maekawa M, Yang Y, Fairn GD. Perfringolysin O theta toxin as a tool to monitor the distribution and inhomogeneity of cholesterol in cellular membranes. Toxins 2016;8:67.
[377] Liu S-L, Sheng R, Jung JH, Wang L, Stec E, O'Connor MJ, et al. Orthogonal lipid sensors identify transbilayer asymmetry of plasma membrane cholesterol. Nat Chem Biol 2017;13:268–74. https://doi.org/10.1038/nchembio.2268.
[378] Schoop V, Martello A, Eden ER, Hoglinger D. Cellular cholesterol and how to find it. Biochim Biophys Acta 2021:1866. https://doi.org/10.1016/j.bbalip.2021.158989.
[379] Krasevec N, Skocaj M. Towards understanding the function of aegerolysins. Toxins 2022:14. https://doi.org/10.3390/toxins14090629.
[380] Chen C-S, Patterson MC, O'Brien JF, Pagano RE, Wheatley CL. Broad screening test for sphingolipid-storage diseases. Lancet 1999;354:901–5. https://doi.org/10.1016/S0140-6736(98)10034-X.
[381] Sun XF, Marks DL, Park WD, Wheatley CL, Puri V, O'Brien JF, et al. Niemann-Pick C variant detection by altered sphingolipid trafficking and correlation with mutations within a specific domain of NPC1. Am J Hum Genet 2001;68:1361–72. https://doi.org/10.1086/320599.
[382] Rodriguez-Gil JL, Larson DM, Wassif CA, Yanjanin NM, Anderson SM, Kirby MR, et al. A somatic cell defect is associated with the onset of neurological symptoms in a lysosomal storage disease. Mol Genet Metab 2013;110:188–90. https://doi.org/10.1016/j.ymgme.2013.06.010.
[383] te Vruchte D, Speak AO, Wallom KL, Al Eisa N, Smith DA, Hendriksz CJ, et al. Relative acidic compartment volume as a lysosomal storage disorder-associated biomarker. J Clin Investig 2014;124:1320–8. https://doi.org/10.1172/jci72835.
[384] Xu M, Liu K, Swaroop M, Sun W, Dehdashti SJ, McKew JC, et al. A phenotypic compound screening assay for lysosomal storage diseases. J Biomol Screen 2014; 19:168–75. https://doi.org/10.1177/1087057113501197.
[385] Millat G, Marçais C, Tomasetto C, Chikh K, Fensom AH, Harzer K, et al. Niemann-Pick C1 disease: correlations between NPC1 mutations, levels of NPC1 protein, and phenotypes emphasize the functional significance of the putative sterol-sensing domain and of the cysteine-rich luminal loop. Am J Hum Genet 2001;68: 1373–85. https://doi.org/10.1086/320606.
[386] Park WD, O'Brien JF, Lundquist PA, Kraft DL, Vockley CW, Karnes PS, et al. Identification of 58 novel mutations in Niemann-Pick disease type C: correlation with biochemical phenotype and importance of *PTC1* -like domains in *NPC1*. Hum Mutat 2003;22:313–25. https://doi.org/10.1002/humu.10255.
[387] Musalkova D, Majer F, Kuchar L, Luksan O, Asfaw B, Vlaskova H, et al. Transcript, protein, metabolite and cellular studies in skin fibroblasts demonstrate variable pathogenic impacts of NPC1 mutations. Orphanet J Rare Dis 2020:15. https://doi.org/10.1186/s13023-020-01360-5.
[388] Baxter LL, Watkins-Chow DE, Johnson NL, Farhat NY, Platt FM, Dale RK, et al. Correlation of age of onset and clinical severity in Niemann–Pick disease type C1 with lysosomal abnormalities and gene expression. Sci Rep 2022;12:2162. https://doi.org/10.1038/s41598-022-06112-y.
[389] Millat G, Chikh K, Naureckiene S, Sleat DE, Fensom AH, Higaki K, et al. Niemann-Pick disease type C: Spectrum of HE1 mutations and genotype/phenotype correlations in the NPC2 group. Am J Hum Genet 2001;69:1013–21. https://doi.org/10.1086/324068.
[390] Haberkant P, Schmitt O, Contreras FX, Thiele C, Hanada K, Sprong H, et al. Protein-sphingolipid interactions within cellular membranes. J Lipid Res 2008;49: 251–62. https://doi.org/10.1194/jlr.D700023-JLR200.
[391] Windsor K, Genaro-Mattos TC, Kim H-YH, Liu W, Tallman KA, Miyamoto S, et al. Probing lipid-protein adduction with alkynyl surrogates: application to Smith-Lemli-Opitz syndrome. J Lipid Res 2013;54:2842–50. https://doi.org/10.1194/jlr.M041061.
[392] Hofmann K, Thiele C, Schoett H-F, Gaebler A, Schoene M, Kiver Y, et al. A novel alkyne cholesterol to trace cellular cholesterol metabolism and localization. J Lipid Res 2014;55:583–91. https://doi.org/10.1194/jlr.D044727.
[393] Hoglinger D, Haberkant P, Aguilera-Romero A, Riezman H, Porter FD, Platt FM, et al. Intracellular sphingosine releases calcium from lysosomes. Elife 2015:4. https://doi.org/10.7554/eLife.10616.
[394] Hoglinger D, Nadler A, Haberkant P, Kirkpatrick J, Schifferer M, Stein F, et al. Trifunctional lipid probes for comprehensive studies of single lipid species in living cells. Proc Natl Acad Sci U S A 2017;114:1566–71. https://doi.org/10.1073/pnas.1611096114.
[395] Lee HJ, Zhang WD, Zhang DL, Yang Y, Liu B, Barker EL, et al. Assessing cholesterol storage in live cells and C-elegans by stimulated raman scattering

imaging of phenyl-diyne cholesterol. Sci Rep 2015:5. https://doi.org/10.1038/srep07930.
[396] Jena PV, Roxbury D, Galassi TV, Akkari L, Horoszko CP, Iaea DB, et al. A carbon nanotube optical reporter maps endolysosomal lipid flux. ACS Nano 2017;11:10689–703. https://doi.org/10.1021/acsnano.7b04743.
[397] Gupta A, Rivera-Molina F, Xi ZQ, Toomre D, Schepartz A. Endosome motility defects revealed at super-resolution in live cells using HIDE probes. Nat Chem Biol 2020;16. https://doi.org/10.1038/s41589-020-0479-z. 408-+.
[398] Tharkeshwar AK, Trekker J, Vermeire W, Pauwels J, Sannerud R, Priestman DA, et al. A novel approach to analyze lysosomal dysfunctions through subcellular proteomics and lipidomics: the case of NPC1 deficiency. Sci Rep 2017;7:41408. https://doi.org/10.1038/srep41408.
[399] Laqtom NN, Dong W, Medoh UN, Cangelosi AL, Dharamdasani V, Chan SH, et al. CLN3 is required for the clearance of glycerophosphodiesters from lysosomes. Nature 2022;609:1005–11. https://doi.org/10.1038/s41586-022-05221-y.
[400] Tan JX, Finkel T. A phosphoinositide signalling pathway mediates rapid lysosomal repair. Nature 2022;609:815–21. https://doi.org/10.1038/s41586-022-05164-4.
[401] Alavi A, Nafissi S, Shamshiri H, Nejad MM, Elahi E. Identification of mutation in NPC2 by exome sequencing results in diagnosis of Niemann-Pick disease type C. Mol Genet Metab 2013;110:139–44. https://doi.org/10.1016/j.ymgme.2013.05.019.
[402] Chin EL, da Silva C, Hegde M. Assessment of clinical analytical sensitivity and specificity of next-generation sequencing for detection of simple and complex mutations. BMC Genet 2013;14:6. https://doi.org/10.1186/1471-2156-14-6.
[403] Fernández-Marmiesse A, Morey M, Pineda M, Eiris J, Couce ML, Castro-Gago M, et al. Assessment of a targeted resequencing assay as a support tool in the diagnosis of lysosomal storage disorders. Orphanet J Rare Dis 2014;9:59. https://doi.org/10.1186/1750-1172-9-59.
[404] Di Fruscio G, Schulz A, De Cegli R, Savarese M, Mutarelli M, Parenti G, et al. Lysoplex: An efficient toolkit to detect DNA sequence variations in the autophagy-lysosomal pathway. Autophagy 2015;11:928–38. https://doi.org/10.1080/15548627.2015.1043077.
[405] Mudvari P, Movassagh M, Kowsari K, Seyfi A, Kokkinaki M, Edwards NJ, et al. SNPlice: variants that modulate Intron retention from RNA-sequencing data. Bioinformatics 2015;31:1191–8. https://doi.org/10.1093/bioinformatics/btu804.
[406] Synofzik M, Harmuth F, Stampfer M, Müller Vom Hagen J, Schöls L, Bauer P. NPC1 is enriched in unexplained early onset ataxia: a targeted high-throughput screening. J Neurol 2015;262:2557–63. https://doi.org/10.1007/s00415-015-7889-y.
[407] Valencia CA, Husami A, Holle J, Johnson JA, Qian Y, Mathur A, et al. Clinical impact and cost-effectiveness of whole exome sequencing as a diagnostic tool: a pediatric center's experience. Front Pediatr 2015;3:67. https://doi.org/10.3389/fped.2015.00067.
[408] Trujillano D, Bertoli-Avella AM, Kumar Kandaswamy K, Weiss MER, Köster J, Marais A, et al. Clinical exome sequencing: results from 2819 samples reflecting 1000 families. Eur J Hum Genet 2017;25:176–82. https://doi.org/10.1038/ejhg.2016.146.
[409] Cougnoux A, Yerger JC, Fellmeth M, Serra-Vinardell J, Martin K, Navid F, et al. Single cell transcriptome analysis of Niemann-Pick disease, type C1 cerebella. Int J Mol Sci 2020:21. https://doi.org/10.3390/ijms21155368.
[410] Han SQ, Ren M, Kuang TY, Pang M, Guan DW, Liu YS, et al. Cerebellar long noncoding RNA expression profile in a Niemann-Pick C disease mouse model. Mol Neurobiol 2021;58:5826–36. https://doi.org/10.1007/s12035-021-02526-3.
[411] Wasserstein MP, Desnick RJ, Schuchman EH, Hossain S, Wallenstein S, Lamm C, et al. The natural history of type B Niemann-Pick disease: results from a 10-year longitudinal study. Pediatrics 2004;114:e672–7. https://doi.org/10.1542/peds.2004-0887.
[412] Iturriaga C, Pineda M, Fernandez-Valero EM, Vanier MT, Coll MJ. Niemann-Pick C disease in Spain: clinical spectrum and development of a disability scale. J. Neurol.Sci 2006;249:1–6.
[413] Pineda M, Wraith JE, Mengel E, Sedel F, Hwu WL, Rohrbach M, et al. Miglustat in patients with Niemann-Pick disease Type C (NP-C): A multicenter observational retrospective cohort study. Mol Genet Metab 2009;98:243–9. https://doi.org/10.1016/j.ymgme.2009.07.003.
[414] Stampfer M, Theiss S, Amraoui Y, Jiang X, Keller S, Ory DS, et al. Niemann-Pick disease type C clinical database: cognitive and coordination deficits are early disease indicators. Orphanet J Rare Dis 2013;8:35. https://doi.org/10.1186/1750-1172-8-35.
[415] Cortina-Borja M, te Vruchte D, Mengel E, Amraoui Y, Imrie J, Jones SA, et al. Annual severity increment score as a tool for stratifying patients with Niemann-Pick disease type C and for recruitment to clinical trials. Orphanet J Rare Dis 2018:13. https://doi.org/10.1186/s13023-018-0880-9.
[416] Patterson MC, Lloyd-Price L, Guldberg C, Doll H, Burbridge C, Chladek M, et al. Validation of the 5-domain Niemann-Pick type C clinical severity scale. Orphanet J Rare Dis 2021;16. https://doi.org/10.1186/s13023-021-01719-2.
[417] Evans W, Patterson M, Platt F, Guldberg C, Mathieson T, Pacey J, et al. International consensus on clinical severity scale use in evaluating Niemann-Pick disease Type C in paediatric and adult patients: results from a Delphi Study. Orphanet J Rare Dis 2021;16:482. https://doi.org/10.1186/s13023-021-02115-6.
[418] McGovern MM, Aron A, Brodie SE, Desnick RJ, Wasserstein MP. Natural history of Type A Niemann-Pick disease: possible endpoints for therapeutic trials. Neurology 2006;66:228–32. https://doi.org/10.1212/01.wnl.0000194208.08904.0c.
[419] Wasserstein MP, Aron A, Brodie SE, Simonaro C, Desnick RJ, McGovern MM. Acid sphingomyelinase deficiency: Prevalence and characterization of an intermediate phenotype of NIEMANN-PICK disease. J Pediatr 2006;149:554–9. https://doi.org/10.1016/j.jpeds.2006.06.034.
[420] McGovern MM, Wasserstein MP, Giugliani R, Bembi B, Vanier MT, Mengel E, et al. A prospective, cross-sectional survey study of the natural history of Niemann-Pick disease type B. Pediatrics 2008;122:E341–9. https://doi.org/10.1542/peds.2007-3016.
[421] McGovern MM, Lippa N, Bagiella E, Schuchman EH, Desnick RJ, Wasserstein MP. Morbidity and mortality in type B Niemann-Pick disease. Genet Med 2013;15:618–23. https://doi.org/10.1038/gim.2013.4.
[422] Hu JY, Maegawa GHB, Zhan X, Gao XL, Wang Y, Xu F, et al. Clinical, biochemical, and genotype-phenotype correlations of 118 patients with Niemann-Pick disease Types A/B. Hum Mutat 2021;42:614–25. https://doi.org/10.1002/humu.24192.
[423] McGovern MM, Wasserstein MP, Bembi B, Giugliani R, Mengel KE, Vanier MT, et al. Prospective study of the natural history of chronic acid sphingomyelinase deficiency in children and adults: eleven years of observation. Orphanet J Rare Dis 2021;16. https://doi.org/10.1186/s13023-021-01842-0.
[424] Imrie J, Dasgupta S, Besley GT, Harris C, Heptinstall L, Knight S, et al. The natural history of Niemann-Pick disease type C in the UK. J Inherit Metab Dis 2007;30:51–9.
[425] Garver WS, Francis GA, Jelinek D, Shepherd G, Flynn J, Castro G, et al. The National Niemann-Pick C1 disease database: report of clinical features and health problems. Am.J.Med.Genet.A 2007;143A:1204–11.
[426] Wraith JE, Guffon N, Rohrbach M, Hwu WL, Korenke GC, Bembi B, et al. Natural history of Niemann-Pick disease type C in a multicentre observational retrospective cohort study. Mol Genet Metab 2009;98:250–4. https://doi.org/10.1016/j.ymgme.2009.06.009.
[427] Yanjanin NM, Velez JI, Gropman A, King K, Bianconi SE, Conley SK, et al. Linear clinical progression, independent of age of onset, in Niemann-Pick disease, type C. Am J Med Genet B Neuropsychiatr Genet 2010;153B:132–40.
[428] Wyatt K, Henley W, Anderson L, Anderson R, Nikolaou V, Stein K, et al. The effectiveness and cost-effectiveness of enzyme and substrate replacement therapies: a longitudinal cohort study of people with lysosomal storage disorders. Health Technol Assess (Winch Eng) 2012;16:1–543. https://doi.org/10.3310/hta16390.
[429] Patterson MC, Mengel E, Wijburg FA, Muller A, Schwierin B, Drevon H, et al. Disease and patient characteristics in NP-C patients: findings from an international disease registry. Orphanet J Rare Dis 2013;8:12. https://doi.org/10.1186/1750-1172-8-12.
[430] Imrie J, Heptinstall L, Knight S, Strong K. Observational cohort study of the natural history of Niemann-Pick disease type C in the UK: a 5-year update from the UK clinical database. BMC.Neurol. 2015;15:257.
[431] Nadjar Y, Hütter-Moncada AL, Latour P, Ayrignac X, Kaphan E, Tranchant C, et al. Adult Niemann-Pick disease type C in France: clinical phenotypes and long-term miglustat treatment effect. Orphanet J Rare Dis 2018;13:175. https://doi.org/10.1186/s13023-018-0913-4.
[432] Mengel E, Bembi B, del Toro M, Deodato F, Gautschi M, Grunewald S, et al. Clinical disease progression and biomarkers in Niemann-Pick disease type C: a prospective cohort study. Orphanet J Rare Dis 2020:15. https://doi.org/10.1186/s13023-020-01616-0.
[433] Patterson MC, Mengel E, Vanier MT, Moneuse P, Rosenberg D, Pineda M. Treatment outcomes following continuous miglustat therapy in patients with Niemann-Pick disease Type C: a final report of the NPC Registry. Orphanet J Rare Dis 2020:15. https://doi.org/10.1186/s13023-020-01363-2.
[434] Thurm A, Chlebowski C, Joseph L, Farmer C, Adedipe D, Weiss M, et al. Neurodevelopmental characterization of young children diagnosed with Niemann-Pick disease, type C1. J Dev Behav Pediatr 2020;41:388–96. https://doi.org/10.1097/dbp.0000000000000785.
[435] Wijburg FA, Sedel F, Pineda M, Hendriksz CJ, Fahey M, Walterfang M, et al. Development of a suspicion index to aid diagnosis of Niemann-Pick disease type C. Neurology 2012;78:1560–7.
[436] Pineda M, Mengel E, Jahnová H, Héron B, Imrie J, Lourenço CM, et al. A suspicion index to aid screening of early-onset Niemann-Pick disease type C (NP-C). BMC Pediatr 2016;16:107. https://doi.org/10.1186/s12887-016-0641-7.
[437] Synofzik M, Fleszar Z, Schöls L, Just J, Bauer P, Torres Martin JV, et al. Identifying Niemann–Pick type C in early-onset ataxia: two quick clinical screening tools. J Neurol 2016;263:1911–8. https://doi.org/10.1007/s00415-016-8178-0.
[438] Pineda M, Jurickova K, Karimzadeh P, Kolnikova M, Malinova V, Torres J, et al. Evaluation of different suspicion indices in identifying patients with Niemann-Pick disease Type C in clinical practice: a post hoc analysis of a retrospective chart review. Orphanet J Rare Dis 2019:14. https://doi.org/10.1186/s13023-019-1124-3.
[439] Zampieri S, Filocamo M, Pianta A, Lualdi S, Gort L, Coll MJ, et al. SMPD1 mutation update: database and comprehensive analysis of published and novel variants. Hum Mutat 2016;37:139–47. https://doi.org/10.1002/humu.22923.
[440] Runz H, Dolle D, Schlitter AM, Zschocke J. NPC-db, a Niemann-Pick type C disease gene variation database. Hum Mutat 2008;29:345–50. https://doi.org/10.1002/humu.20636.
[441] Garver WS, Jelinek D, Meaney FJ, Flynn J, Pettit KM, Shepherd G, et al. The national Niemann-Pick Type C1 disease database: correlation of lipid profiles, mutations, and biochemical phenotypes. J Lipid Res 2010;51:406–15. https://doi.org/10.1194/jlr.P000331.

[442] Bonnot O, Klünemann HH, Velten C, Torres Martin JV, Walterfang M. Systematic review of psychiatric signs in Niemann-Pick disease type C. World J Biol Psychiatry 2019;20:320–32. https://doi.org/10.1080/15622975.2018.1441548.
[443] Strimbu K, Tavel JA. What are biomarkers? Curr Opin HIV AIDS 2010;5:463–6. https://doi.org/10.1097/COH.0b013e32833ed177.
[444] Dhami R, He XX, Gordon RE, Schuchman EH. Analysis of the lung pathology and alveolar macrophage function in the acid sphingomyelinase-deficient mouse model of Niemann-Pick disease. Lab Invest 2001;81:987–99. https://doi.org/10.1038/labinvest.3780311.
[445] Brinkman J, Wijburg FA, Hollak CE, Groener JE, Verhoek M, Scheij S, et al. Plasma chitotriosidase and CCL18: Early biochemical surrogate markers in type B Niemann-Pick disease. J Inherit Metab Dis 2005;28:13–20. https://doi.org/10.1007/s10545-005-4416-9.
[446] Dhami R, Passini MA, Schuchman EH. Identification of novel biomarkers for Niemann-Pick disease using gene expression analysis of acid sphingomyelinase knockout mice. Mol Ther 2006;13:556–64. https://doi.org/10.1016/j.ymthe.2005.08.020.
[447] Lin N, Zhang HW, Qiu WJ, Ye J, Han LS, Wang Y, et al. Determination of 7-ketocholesterol in plasma by LC-MS for rapid diagnosis of acid SMase-deficient Niemann-Pick disease. J Lipid Res 2014;55:338–43. https://doi.org/10.1194/jlr.D044024.
[448] Chuang WL, Pacheco J, Cooper S, McGovern MM, Cox GF, Keutzer J, et al. Lyso-sphingomyelin is elevated in dried blood spots of Niemann-Pick B patients. Mol Genet Metab 2014;111:209–11. https://doi.org/10.1016/j.ymgme.2013.11.012.
[449] Breilyn MS, Zhang WY, Yu CL, Wasserstein MP. Plasma lyso-sphingomyelin levels are positively associated with clinical severity in acid sphingomyelinase deficiency. Mol Genet Metab Rep 2021:28. https://doi.org/10.1016/j.ymgmr.2021.100780.
[450] Giese AK, Mascher H, Grittner U, Eichler S, Kramp G, Lukas J, et al. A novel, highly sensitive and specific biomarker for Niemann-Pick type C1 disease. Orphanet J Rare Dis 2015;10:78. https://doi.org/10.1186/s13023-015-0274-1.
[451] Jiang X, Sidhu R, Porter FD, Yanjanin NM, Speak AO, te Vruchte DT, et al. A sensitive and specific LC-MS/MS method for rapid diagnosis of Niemann-Pick C1 disease from human plasma. J Lipid Res 2011;52:1435–45. https://doi.org/10.1194/jlr.D015735.
[452] Porter FD, Scherrer DE, Lanier MH, Langmade SJ, Molugu V, Gale SE, et al. Cholesterol oxidation products are sensitive and specific blood-based biomarkers for Niemann-Pick C1 disease. Sci Transl Med 2010;2:56ra81. https://doi.org/10.1126/scitranslmed.3001417.
[453] Tortelli B, Fujiwara H, Bagel JH, Zhang J, Sidhu R, Jiang X, et al. Cholesterol homeostatic responses provide biomarkers for monitoring treatment for the neurodegenerative disease Niemann-Pick C1 (NPC1). Hum Mol Genet 2014;23:6022–33. https://doi.org/10.1093/hmg/ddu331.
[454] Alvelius G, Hjalmarson O, Griffiths WJ, Bjorkhem I, Sjovall J. Identification of unusual 7-oxygenated bile acid sulfates in a patient with Niemann-Pick disease, type C. J Lipid Res 2001;42:1571–7.
[455] Jiang X, Sidhu R, Mydock-McGrane L, Hsu FF, Covey DF, Scherrer DE, et al. Development of a bile acid-based newborn screen for Niemann-Pick disease type C. Sci Transl Med 2016;8:337ra63. https://doi.org/10.1126/scitranslmed.aaf2326.
[456] Mazzacuva F, Mills P, Mills K, Camuzeaux S, Gissen P, Nicoli ER, et al. Identification of novel bile acids as biomarkers for the early diagnosis of Niemann-Pick C disease. FEBS Lett 2016;590:1651–62. https://doi.org/10.1002/1873-3468.12196.
[457] Cluzeau CV, Watkins-Chow DE, Fu R, Borate B, Yanjanin N, Dail MK, et al. Microarray expression analysis and identification of serum biomarkers for Niemann-Pick disease, type C1. Hum.Mol.Genet. 2012;21:3632–46.
[458] Fan M, Sidhu R, Fujiwara H, Tortelli B, Zhang J, Davidson C, et al. Identification of Niemann-Pick C1 disease biomarkers through sphingolipid profiling. J Lipid Res 2013;54:2800–14. https://doi.org/10.1194/jlr.M040618.
[459] Welford RWD, Garzotti M, Lourenco CM, Mengel E, Marquardt T, Reunert J, et al. Plasma lysosphingomyelin demonstrates great potential as a diagnostic biomarker for Niemann-Pick disease type C in a retrospective study. PloS One 2014:9. https://doi.org/10.1371/journal.pone.0114669.
[460] Maekawa M, Jinnoh I, Matsumoto Y, Narita A, Mashima R, Takahashi H, et al. Structural determination of lysosphingomyelin-509 and discovery of novel class lipids from patients with Niemann-Pick disease type C. Int J Mol Sci 2019:20. https://doi.org/10.3390/ijms20205018.
[461] Sidhu R, Mondjinou Y, Qian M, Song H, Kumar AB, Hong X, et al. N-acyl-O-phosphocholineserines: structures of a novel class of lipids that are biomarkers for Niemann-Pick C1 disease. J Lipid Res 2019;60:1410–24. https://doi.org/10.1194/jlr.RA119000157.
[462] Marques ARA, Gabriel TL, Aten J, van Roomen C, Ottenhoff R, Claessen N, et al. Gpnmb is a potential Marker for the visceral pathology in Niemann-Pick type C disease. PloS One 2016:11. https://doi.org/10.1371/journal.pone.0147208.
[463] Rodriguez-Gil JL, Baxter LL, Watkins-Chow DE, Johnson NL, Davidson CD, Carlson SR, et al. Transcriptome of HPβCD-treated Niemann-Pick disease type C1 cells highlights GPNMB as a biomarker for therapeutics. Hum Mol Genet 2021;30:2456–68. https://doi.org/10.1093/hmg/ddab194.
[464] Fukaura M, Ishitsuka Y, Shirakawa S, Ushihama N, Yamada Y, Kondo Y, et al. Intracerebroventricular treatment with 2-hydroxypropyl-β-cyclodextrin decreased cerebellar and hepatic glycoprotein nonmetastatic melanoma protein B (GPNMB) expression in Niemann-Pick disease type C model mice. Int J Mol Sci 2021:22. https://doi.org/10.3390/ijms22010452.
[465] Dardis A, Pavan E, Fabris M, Da Riol RM, Sechi A, Fiumara A, et al. Plasma neurofilament light (NfL) in patients affected by Niemann-Pick type C disease (NPCD). J Clin Med 2021:10. https://doi.org/10.3390/jcm10204796.
[466] Agrawal N, Farhat NY, Sinaii N, Do AD, Xiao C, Berry-Kravis E, et al. Neurofilament light chain in cerebrospinal fluid as a novel biomarker in evaluating both clinical severity and therapeutic response in Niemann-Pick disease type C1. Genet Med 2022;25:100349. https://doi.org/10.1016/j.gim.2022.11.017.
[467] Probert F, Ruiz-Rodado V, Vruchte DT, Nicoli ER, Claridge TDW, Wassif CA, et al. NMR analysis reveals significant differences in the plasma metabolic profiles of Niemann Pick C1 patients, heterozygous carriers, and healthy controls. Sci Rep 2017:7. https://doi.org/10.1038/s41598-017-06264-2.
[468] Bradbury A, Bagel J, Sampson M, Farhat N, Ding WG, Swain G, et al. Cerebrospinal fluid calbindin D concentration as a biomarker of cerebellar disease progression in Niemann-Pick type C1 disease. J Pharmacol Exp Ther 2016;358:254–61. https://doi.org/10.1124/jpet.116.232975.
[469] Cologna SM, Jiang XS, Backlund PS, Cluzeau CV, Dail MK, Yanjanin NM, et al. Quantitative proteomic analysis of Niemann-Pick disease, type C1 cerebellum identifies protein biomarkers and provides pathological insight. PLoS.ONE. 2012;7:e47845.
[470] Cougnoux A, Drummond RA, Collar AL, Iben JR, Salman A, Westgarth H, et al. Microglia activation in Niemann-Pick disease, type C1 is amendable to therapeutic intervention. Hum Mol Genet 2018;27:2076–89. https://doi.org/10.1093/hmg/ddy112.
[471] Li W, Pergande MRR, Crutchfield CAA, Searle BCC, Backlund PSS, Picache JAA, et al. A differential proteomics study of cerebrospinal fluid from individuals with Niemann-Pick disease, Type C1. Proteomics 2023. https://doi.org/10.1002/pmic.202200378.
[472] Cologna SM, Cluzeau CV, Yanjanin NM, Blank PS, Dail MK, Siebel S, et al. Human and mouse neuroinflammation markers in Niemann-Pick disease, type C1. J Inherit Metab Dis 2014;37:83–92.
[473] Campbell K, Cawley NX, Luke R, Scott KEJ, Johnson N, Farhat NY, et al. Identification of cerebral spinal fluid protein biomarkers in Niemann-Pick disease, type C1. Biomark Res 2023:11. https://doi.org/10.1186/s40364-023-00448-x.
[474] Maekawa M, Jinnoh I, Narita A, Iida T, Saigusa D, Iwahori A, et al. Investigation of diagnostic performance of five urinary cholesterol metabolites for Niemann-Pick disease type C S. J Lipid Res 2019;60:2074–81. https://doi.org/10.1194/jlr.M093971.
[475] Pergande MR, Cougnoux A, Rathnayake RAC, Porter FD, Cologna SM. Differential proteomics reveals miR-155 as a novel indicator of liver and spleen pathology in the symptomatic Niemann-Pick disease, type C1 mouse model. Molecules 2019:24. https://doi.org/10.3390/molecules24050994.
[476] Reunert J, Fobker M, Kannenberg F, Du Chesne I, Plate M, Wellhausen J, et al. Rapid diagnosis of 83 patients with Niemann Pick type C disease and related cholesterol transport disorders by cholestantriol screening. Ebiomedicine 2016;4:170–5. https://doi.org/10.1016/j.ebiom.2015.12.018.
[477] Deodato F, Boenzi S, Taurisano R, Semeraro M, Sacchetti E, Carrozzo R, et al. The impact of biomarkers analysis in the diagnosis of Niemann-Pick C disease and acid sphingomyelinase deficiency. Clin Chim Acta 2018;486:387–94. https://doi.org/10.1016/j.cca.2018.08.039.
[478] Voorink-Moret M, Goorden SMI, van Kuilenburg ABP, Wijburg FA, der Vlugt JMM Ghauharali-van, Beers-Stet FS, et al. Rapid screening for lipid storage disorders using biochemical markers. Expert center data and review of the literature. Mol Genet Metab 2018;123:76–84. https://doi.org/10.1016/j.ymgme.2017.12.431.
[479] Mandia D, Plaze M, Le Ber I, Ewenczyk C, Morin A, Carle G, et al. High diagnostic value of plasma Niemann-Pick type C biomarkers in adults with selected neurological and/or psychiatric disorders. J Neurol 2020;267:3371–7. https://doi.org/10.1007/s00415-020-10020-4.
[480] Kubaski F, Burlina A, Polo G, Pereira D, Herbst ZM, Silva C, et al. Experience of the NPC Brazil Network with a comprehensive program for the screening and diagnosis of Niemann-Pick disease type C. Int J Neonatal Screen 2022:8. https://doi.org/10.3390/ijns8030039.
[481] Wu C, Iwamoto T, Hossain MA, Akiyama K, Igarashi J, Miyajima T, et al. A combination of 7-ketocholesterol, lysosphingomyelin and bile acid-408 to diagnose Niemann-Pick disease type C using LC-MS/MS. PloS One 2020:15. https://doi.org/10.1371/journal.pone.0238624.
[482] Papandreou A, Doykov I, Spiewak J, Komarov N, Habermann S, Kurian MA, et al. Niemann-Pick type C disease as proof-of-concept for intelligent biomarker panel selection in neurometabolic disorders. Dev Med Child Neurol 2022;64:1539–46. https://doi.org/10.1111/dmcn.15334.
[483] McGovern MM, Dionisi-Vici C, Giugliani R, Hwu P, Lidove O, Lukacs Z, et al. Consensus recommendation for a diagnostic guideline for acid sphingomyelinase deficiency. Genet Med 2017;19:967–74. https://doi.org/10.1038/gim.2017.7.
[484] Patterson MC, Clayton P, Gissen P, Anheim M, Bauer P, Bonnot O, et al. Recommendations for the detection and diagnosis of Niemann-Pick disease type C: an update. Neurol Clin Pract 2017;7:499–511. https://doi.org/10.1212/cpj.0000000000000399.
[485] Sobrido M-J, Bauer P, de Koning T, Klopstock T, Nadjar Y, Patterson MC, et al. Recommendations for patient screening in ultra-rare inherited metabolic diseases: what have we learned from Niemann-Pick disease type C? Orphanet J Rare Dis 2019;14:20. https://doi.org/10.1186/s13023-018-0985-1.
[486] Thurberg BL, Wasserstein MP, Schiano T, O'Brien F, Richards S, Cox GF, et al. Liver and skin histopathology in adults with acid sphingomyelinase deficiency (Niemann-Pick disease type B). Am J Surg Pathol 2012;36:1234–46. https://doi.org/10.1097/PAS.0b013e31825793ff.

[487] Taksir TV, Johnson J, Maloney CL, Yandl E, Griffiths D, Thurberg BL, et al. Optimization of a histopathological biomarker for sphingomyelin accumulation in acid sphingomyelinase deficiency. J Histochem Cytochem 2012;60:620–9. https://doi.org/10.1369/0022155412451129.
[488] Wang NL, Chen L, Lu Y, Xie XB, Lin J, Abuduxikuer K, et al. The presence of vacuolated Kupffer cells raises a clinical suspicion of Niemann-Pick disease type C in neonatal cholestasis. Front Genet 2022:13. https://doi.org/10.3389/fgene.2022.867413.
[489] Rottach KG, Von Maydell RG, Das VE, Zivotofsky AZ, Discenna AO, Gordon JL, et al. Evidence for independent feedback control of horizontal and vertical saccades from Niemann-Pick type C disease. Vision Res 1997;37:3627–38. https://doi.org/10.1016/s0042-6989(96)00066-1.
[490] Galanaud D, Tourbah A, Lehericy S, Leveque N, Heron B, Billette V, et al. 24 month-treatment with miglustat of three patients with Niemann-Pick disease type C: follow up using brain spectroscopy. Mol.Genet.Metab 2009;96:55–8.
[491] Walterfang M, Fahey M, Desmond P, Wood A, Seal ML, Steward C, et al. White and gray matter alterations in adults with Niemann-Pick disease type C. Cross-sect Study 2010;75:49–56. https://doi.org/10.1212/WNL.0b013e3181e6210e.
[492] Totenhagen JW, Lope-Piedrafita S, Borbon IA, Yoshimaru ES, Erickson RP, Trouard TP. In vivo assessment of neurodegeneration in Niemann-Pick type C mice by quantitative T2 mapping and diffusion tensor imaging. J Magn Reson Imaging 2012;35:528–36.
[493] Masingue M, Adanyeguh I, Nadjar Y, Sedel F, Galanaud D, Mochel F. Evolution of structural neuroimaging biomarkers in a series of adult patients with Niemann-Pick type C under treatment. Orphanet J Rare Dis 2017;12:22. https://doi.org/10.1186/s13023-017-0579-3.
[494] Gburek-Augustat J, Groeschel S, Kern J, Beck-Woedl S, Just J, Harzer K, et al. Comparative analysis of cerebral magnetic resonance imaging changes in nontreated infantile, juvenile and adult patients with Niemann-Pick disease type C. Neuropediatrics 2020;51:037–44.
[495] Claudepierre T, Paques M, Simonutti M, Buard I, Sahel J, Maue RA, et al. Lack of Niemann Pick type C1 induces age-related degeneration in the mouse retina. Mol Cell Neurosci 2010;43:164–76.
[496] Hovakimyan M, Meyer A, Lukas J, Luo J, Gudziol V, Hummel T, et al. Olfactory deficits in Niemann-Pick type C1 (NPC1) disease. PloS One 2013:8. https://doi.org/10.1371/journal.pone.0082216.
[497] Palladino G, Loizzo S, Fortuna A, Canterini S, Palombi F, Erickson RP, et al. Visual evoked potentials of Niemann-Pick type C1 mice reveal an impairment of the visual pathway that is rescued by 2-hydroxypropyl-ß-cyclodextrin. Orphanet J Rare Dis 2015;10:133. https://doi.org/10.1186/s13023-015-0348-0.
[498] Dannhausen K, Karlstetter M, Caramoy A, Volz C, Jägle H, Liebisch G, et al. Acid sphingomyelinase (aSMase) deficiency leads to abnormal microglia behavior and disturbed retinal function. Biochem Biophys Res Commun 2015;464:434–40. https://doi.org/10.1016/j.bbrc.2015.06.133.
[499] Wu BX, Fan J, Boyer NP, Jenkins RW, Koutalos Y, Hannun YA, et al. Lack of acid sphingomyelinase induces age-related retinal degeneration. PloS One 2015;10:e0133032. https://doi.org/10.1371/journal.pone.0133032.
[500] Havla J, Moser M, Sztatecsny C, Lotz-Havla AS, Maier EM, Hizli B, et al. Retinal axonal degeneration in Niemann-Pick type C disease. J Neurol 2020;267:2070–82. https://doi.org/10.1007/s00415-020-09796-2.
[501] Hopf S, Hennermann JB, Schuster AK, Pfeiffer N, Pitz S. Vertical saccadic palsy and foveal retinal thinning in Niemann-Pick disease type C. PloS One 2021;16:e0252825. https://doi.org/10.1371/journal.pone.0252825.
[502] Rava A, La Rosa P, Palladino G, Dragotto J, Totaro A, Tiberi J, et al. The appearance of phagocytic microglia in the postnatal brain of Niemann Pick type C mice is developmentally regulated and underscores shortfalls in fine odor discrimination. J Cell Physiol 2022;237:4563–79. https://doi.org/10.1002/jcp.30909.
[503] Walterfang M, Di Biase MA, Cropley VL, Scott AM, O'Keefe G, Velakoulis D, et al. Imaging of neuroinflammation in adult Niemann-Pick type C disease: A cross-sectional study. Neurology 2020;94:e1716–25. https://doi.org/10.1212/wnl.0000000000009287.
[504] El-Masri S, Malpas CB, Evans A, Walterfang M. Clinical correlates of movement disorders in adult Niemann-Pick type C patients measured via a Personal KinetiGraph. Neurol Sci 2022;43:6339–47. https://doi.org/10.1007/s10072-022-06308-0.
[505] Solomon BI, Munoz AM, Sinaii N, Farhat NM, Smith AC, Bianconi S, et al. Phenotypic expression of swallowing function in Niemann-Pick disease type C1. Orphanet J Rare Dis 2022:17. https://doi.org/10.1186/s13023-022-02472-w.
[506] Haider A, Zhao C, Wang L, Xiao Z, Rong J, Xia X, et al. Assessment of cholesterol homeostasis in the living human brain. Sci Transl Med 2022;14:eadc9967. https://doi.org/10.1126/scitranslmed.adc9967.
[507] Ancien F, Pucci F, Rooman M. In silico analysis of the molecular-level impact of SMPD1 variants on Niemann-Pick disease severity. Int J Mol Sci 2021:22. https://doi.org/10.3390/ijms22094516.
[508] Verot L, Chikh K, Freydiere E, Honore R, Vanier MT, Millat G. Niemann-Pick C disease: functional characterization of three NPC2 mutations and clinical and molecular update on patients with NPC2. Clin Genet 2007;71:320–30. https://doi.org/10.1111/j.1399-0004.2007.00782.x.
[509] Fancello T, Dardis A, Rosano C, Tarugi P, Tappino B, Zampieri S, et al. Molecular analysis of NPC1 and NPC2 gene in 34 Niemann-Pick C Italian Patients: identification and structural modeling of novel mutations. Neurogenetics 2009;10:229–39. https://doi.org/10.1007/s10048-009-0175-3.
[510] Elghobashi-Meinhardt N. Niemann-Pick type C disease: A QM/MM study of conformational changes in cholesterol in the NPC1(NTD) and NPC2 binding pockets. Biochemistry 2014;53:6603–14. https://doi.org/10.1021/bi500548f.
[511] Vadlamudi Y, Muthu K, Kumar MS. Structural exploration of acid sphingomyelinase at different physiological pH through molecular dynamics and docking studies. RSC Adv 2016;6:74859–73. https://doi.org/10.1039/c6ra16584b.
[512] Wang C, Scott SM, Subramanian K, Loguercio S, Zhao P, Hutt DM, et al. Quantitating the epigenetic transformation contributing to cholesterol homeostasis using Gaussian process. Nat Commun 2019:10. https://doi.org/10.1038/s41467-019-12969-x.
[513] Wheeler S, Schmid R, Sillence DJ. Lipid-protein interactions in Niemann-Pick type C disease: insights from molecular modeling. Int J Mol Sci 2019:20. https://doi.org/10.3390/ijms20030717.
[514] Dubey V, Bozorg B, Wustner D, Khandelia H. Cholesterol binding to the sterol-sensing region of Niemann Pick C1 protein confines dynamics of its N-terminal domain. PLoS Comput Biol 2020;16. https://doi.org/10.1371/journal.pcbi.1007554.
[515] Elghobashi-Meinhardt N. Cholesterol transport in wild-type NPC1 and P691S: molecular dynamics simulations reveal changes in dynamical behavior. Int J Mol Sci 2020:21. https://doi.org/10.3390/ijms21082962.
[516] Yoon HJ, Jeong H, Lee HH, Jang S. Molecular dynamics study with mutation shows that N-terminal domain structural re-orientation in Niemann-Pick type C1 is required for proper alignment of cholesterol transport. J Neurochem 2021;156:967–78. https://doi.org/10.1111/jnc.15150.
[517] Schachtner R, Lutter D, Knollmuller P, Tome AM, Theis FJ, Schmitz G, et al. Knowledge-based gene expression classification via matrix factorization. Bioinformatics 2008;24:1688–97. https://doi.org/10.1093/bioinformatics/btn245.
[518] Soufan O, Ba-alawi W, Magana-Mora A, Essack M, Bajic VB. DPubChem: a web tool for QSAR modeling and high-throughput virtual screening. Sci Rep 2018:8. https://doi.org/10.1038/s41598-018-27495-x.
[519] Parolo S, Tomasoni D, Bora P, Ramponi A, Kaddi C, Azer K, et al. Reconstruction of the cytokine signaling in lysosomal storage diseases by literature mining and network analysis. Front Cell Dev Biol 2021:9. https://doi.org/10.3389/fcell.2021.703489.
[520] Moreno-Barea FJ, Franco L, Elizondo D, Grootveld M. Application of data augmentation techniques towards metabolomics. Comput Biol Med 2022:148. https://doi.org/10.1016/j.compbiomed.2022.105916.
[521] Bielschowsky M. Amautorische Idiotie und lipoidzellige Splenohepatomegalie. J Psychol Neur 1928:33.
[522] Epstein E. The causal meaning of the chemical changes for the pathology of the brain with Niemann-pickscher disease. Relationship between Niemann-Pickescher disease and infantile amaurotic Idiocy (typus tay-sachs). Virchows Archiv Pathol Anatom Physiol Klinische Med 1932;284:867–79. https://doi.org/10.1007/bf01944065.
[523] Levade T, Gatt S. Uptake and intracellular degradation of fluorescent sphingomyelin by fibroblasts from normal individuals and a patient with Niemann-Pick disease. Biochim Biophys Acta 1987;918:250–9. https://doi.org/10.1016/0005-2760(87)90228-1.
[524] Levade T, Salvayre R, Maret A, Dousteblazy L. Evidence for both endogenous and exogenous sources of the sphingomyelin storage in lymphoid-cell lines from patients with Niemann-Pick disease type-A and type-B. J Inherit Metab Dis 1988;11:151–7. https://doi.org/10.1007/bf01799864.
[525] Karten B, Vance DE, Campenot RB, Vance JE. Cholesterol accumulates in cell bodies, but is decreased in distal axons, of Niemann-Pick C1-deficient neurons. J. Neurochem. 2002;83:1154–63.
[526] Reid PC, Sugii S, Chang TY. Trafficking defects in endogenously synthesized cholesterol in fibroblasts, macrophages, hepatocytes, and glial cells from Niemann-Pick type C1 mice. J Lipid Res 2003;44:1010–9.
[527] Elrick MJ, Yu T, Chung C, Lieberman AP. Impaired proteolysis underlies autophagic dysfunction in Niemann-Pick type C disease. Hum Mol Genet 2012;21:4876–87. https://doi.org/10.1093/hmg/dds324.
[528] Leventhal AR, Chen WG, Tall AR, Tabas I. Acid sphingomyelinase-deficient macrophages have defective cholesterol trafficking and efflux. J Biol Chem 2001;276:44976–83. https://doi.org/10.1074/jbc.M106455200.
[529] Sarna J, Miranda SRP, Schuchman EH, Hawkes R. Patterned cerebellar Purkinje cell death in a transgenic mouse model of Niemann Pick type A/B disease. Eur J Neurosci 2001;13:1873–80. https://doi.org/10.1046/j.0953-816x.2001.01564.x.
[530] Shihabuddin LS, Numan S, Huff MR, Dodge JC, Clarke J, Macauley SL, et al. Intracerebral transplantation of adult mouse neural progenitor cells into the Niemann-Pick-A mouse leads to a marked decrease in lysosomal storage pathology. J Neurosci 2004;24:10642–51. https://doi.org/10.1523/jneurosci.3584-04.2004.
[531] Scandroglio F, Venkata JK, Loberto N, Prioni S, Schuchman EH, Chigorno V, et al. Lipid content of brain, brain membrane lipid domains, and neurons from acid sphingomyelinase deficient mice. J Neurochem 2008;107:329–38. https://doi.org/10.1111/j.1471-4159.2008.05591.x.
[532] Butler JD, Vanier MT, Pentchev PG. Niemann-Pick C disease: cystine and lipids accumulate in the murine model of this lysosomal cholesterol lipidosis. Biochem Biophys Res Commun 1993;196:154–9. https://doi.org/10.1006/bbrc.1993.2228.
[533] Hulkova H, Ledvinova J, Asfaw B, Koubek K, Kopriva K, Elleder M. Lactosylceramide in lysosomal storage disorders. A comparative immunohistochemical and biochemical study. Virchows Arch 2005;447:31–44. https://doi.org/10.1007/s00428-005-1246-y.
[534] Goldin E, Roff CF, Miller SPF, Rodriguezlafrasse C, Vanier MT, Brady RO, et al. Type-C Niemann-Pick disease - a murine model of the lysosomal cholesterol

lipidosis accumulates sphingosine and sphinganine in liver. Biochim Biophys Acta 1992;1127:303–11. https://doi.org/10.1016/0005-2760(92)90236-o.
[535] Rodriguez-Lafrasse C, Rousson R, Pentchev PG, Louisot P, Vanier MT. Free sphingoid bases in tissues from patients with type-C Niemann-Pick disease and other lysosomal storage disorders. BBA-Mol Basis Dis 1994;1226:138–44. https://doi.org/10.1016/0925-4439(94)90021-3.
[536] te Vruchte D, Lloyd-Evans E, Veldman RJ, Neville DC, Dwek RA, Platt FM, et al. Accumulation of glycosphingolipids in Niemann-Pick C disease disrupts endosomal transport. J.Biol.Chem. 2004;279:26167–75.
[537] Lloyd-Evans E, Morgan AJ, He X, Smith DA, Elliot-Smith E, Sillence DJ, et al. Niemann-Pick disease type C1 is a sphingosine storage disease that causes deregulation of lysosomal calcium. Nat.Med. 2008;14:1247–55.
[538] Gläser A, Hammerl F, Gräler MH, Coldewey SM, Völkner C, Frech MJ, et al. Identification of brain-specific treatment effects in NPC1 disease by focusing on cellular and molecular changes of sphingosine-1-phosphate metabolism. Int J Mol Sci 2020:21. https://doi.org/10.3390/ijms21124502.
[539] Rouser G, Kritchevsky G, Yamamoto A, Knudson AG, Simon G. Accumulation of a glycerolphospholipid in classical Niemann-Pick disease. Lipids 1968;3. https://doi.org/10.1007/bf02531203. 287-+.
[540] Gruenberg J. Life in the lumen: The multivesicular endosome. Traffic 2020;21: 76–93. https://doi.org/10.1111/tra.12715.
[541] Taniguchi M, Shinoda Y, Ninomiya H, Vanier MT, Ohno K. Sites and temporal changes of gangliosides GM1/GM2 storage in the Niemann-Pick disease type C mouse brain. Brain Dev 2001;23:414–21.
[542] Sugimoto Y, Ninomiya H, Ohsaki Y, Higaki K, Davies JP, Ioannou YA, et al. Accumulation of cholera toxin and GM1 ganglioside in the early endosome of Niemann-Pick C1-deficient cells. Proc Natl Acad Sci USA 2001;98:12391–6.
[543] Zervas M, Dobrenis K, Walkley SU. Neurons in Niemann-Pick disease type C accumulate gangliosides as well as unesterified cholesterol and undergo dendritic and axonal alterations. J.Neuropathol.Exp.Neurol. 2001;60:49–64.
[544] Abdul-Hammed M, Breiden B, Adebayo MA, Babalola JO, Schwarzmann G, Sandhoff K. Role of endosomal membrane lipids and NPC2 in cholesterol transfer and membrane fusion. J Lipid Res 2010;51:1747–60. https://doi.org/10.1194/jlr.M003822.
[545] Devlin C, Pipalia NH, Liao X, Schuchman EH, Maxfield FR, Tabas I. Improvement in lipid and protein trafficking in Niemann-Pick C1 cells by correction of a secondary enzyme defect. Traffic 2010;11:601–15.
[546] Marques AR, Aten J, Ottenhoff R, van Roomen CP, Herrera Moro D, Claessen N, et al. Reducing GBA2 activity ameliorates neuropathology in Niemann-Pick type C mice. PloS One 2015;10:e0135889. https://doi.org/10.1371/journal.pone.0135889.
[547] Anheuser S, Breiden B, Sandhoff K. Membrane lipids and their degradation compounds control GM2 catabolism at intralysosomal luminal vesicles. J Lipid Res 2019;60:1099–111. https://doi.org/10.1194/jlr.M092551.
[548] Hashimoto N, Matsumoto I, Takahashi H, Ashikawa H, Nakamura H, Murayama T. Cholesterol-dependent increases in glucosylceramide synthase activity in Niemann-Pick disease type C model cells: Abnormal trafficking of endogenously formed ceramide metabolites by inhibition of the enzyme. Neuropharmacology 2016;110:458–69. https://doi.org/10.1016/j.neuropharm.2016.08.011.
[549] Breiden B, Sandhoff K. Mechanism of secondary ganglioside and lipid accumulation in lysosomal disease. Int J Mol Sci 2020:21. https://doi.org/10.3390/ijms21072566.
[550] Pluvinage JV, Sun J, Claes C, Flynn RA, Haney MS, Iram T, et al. The CD22-IGF2R interaction is a therapeutic target for microglial lysosome dysfunction in Niemann-Pick type C. Sci Transl Med 2021;13. https://doi.org/10.1126/scitranslmed.abg2919. eabg2919.
[551] Cheung NS, Koh CH, Bay BH, Qi RZ, Choy MS, Li QT, et al. Chronic exposure to U18666A induces apoptosis in cultured murine cortical neurons. Biochem. Biophys.Res.Commun. 2004;315:408–17.
[552] Wang MD, Franklin V, Sundaram M, Kiss RS, Ho K, Gallant M, et al. Differential regulation of ATP binding cassette protein A1 expression and ApoA-I lipidation by Niemann-Pick type C1 in murine hepatocytes and macrophages. J.Biol.Chem. 2007;282:22525–33.
[553] Higashi Y, Murayama S, Pentchev PG, Suzuki K. Cerebellar degeneration in the Niemann-Pick type C mouse. Acta Neuropathol (Berl) 1993;85:175–84.
[554] Sarna JR, Larouche M, Marzban H, Sillitoe RV, Rancourt DE, Hawkes R. Patterned Purkinje cell degeneration in mouse models of Niemann-Pick type C disease. J Comp Neurol 2003;456:279–91.
[555] Fiorenza MT, La Rosa P, Canterini S, Erickson RP. The cerebellum in Niemann-Pick C1 disease: mouse versus man. Cerebellum 2022. https://doi.org/10.1007/s12311-021-01347-3.
[556] Nonneman A, Criem N, Lewandowski SA, Nuyts R, Thal DR, Pfrieger FW, et al. Astrocyte-derived Jagged-1 mitigates deleterious Notch signaling in amyotrophic lateral sclerosis. Neurobiol Dis 2018;119:26–40. https://doi.org/10.1016/j.nbd.2018.07.012.
[557] Maatouk L, Yi C, Carrillo-de Sauvage MA, Compagnion AC, Hunot S, Ezan P, et al. Glucocorticoid receptor in astrocytes regulates midbrain dopamine neurodegeneration through connexin hemichannel activity. Cell Death Differ 2019;26:580–96. https://doi.org/10.1038/s41418-018-0150-3.
[558] Brandebura AN, Paumier A, Onur TS, Allen NJ. Astrocyte contribution to dysfunction, risk and progression in neurodegenerative disorders. Nat Rev Neurosci 2022. https://doi.org/10.1038/s41583-022-00641-1.
[559] Elrick MJ, Pacheco CD, Yu T, Dadgar N, Shakkottai VG, Ware C, et al. Conditional Niemann-Pick C mice demonstrate cell autonomous Purkinje cell neurodegeneration. Hum.Mol.Genet. 2010;19:837–47.
[560] Chung C, Puthanveetil P, Ory DS, Lieberman AP. Genetic and pharmacological evidence implicates cathepsins in Niemann-Pick C cerebellar degeneration. Hum Mol Genet 2016;25:1434–46. https://doi.org/10.1093/hmg/ddw025.
[561] Karten B, Hayashi H, Francis GA, Campenot RB, Vance DE, Vance JE. Generation and function of astroglial lipoproteins from Niemann-Pick type C1-deficient mice. Biochem.J. 2005;387:779–88.
[562] Diezel PB. Histochemical studies on primary lipoidoses: amaurotic idiocy, gargoylism, Niemann-Pick's disease, Gaucher's diseases with special reference to the central nervous system. Virchows Archiv Pathol Anatom Physiol Klinische Med 1954;326:89–118. https://doi.org/10.1007/bf02438653.
[563] Gabande-Rodriguez E, Perez-Canamas A, Soto-Huelin B, Mitroi DN, Sanchez-Redondo S, Martinez-Saez E, et al. Lipid-induced lysosomal damage after demyelination corrupts microglia protective function in lysosomal storage disorders. EMBO J 2019:38. https://doi.org/10.15252/embj.201899553.
[564] Seo Y, Kim HS, Kang I, Choi SW, Shin TH, Shin JH, et al. Cathepsin S contributes to microglia-mediated olfactory dysfunction through the regulation of Cx3cl1-Cx3cr1 axis in a Niemann-Pick disease type C1 model. Glia 2016;64:2291–305. https://doi.org/10.1002/glia.23077.
[565] Kavetsky L, Green KK, Boyle BR, Yousufzai FAK, Padron ZM, Melli SE, et al. Increased interactions and engulfment of dendrites by microglia precede Purkinje cell degeneration in a mouse model of Niemann Pick Type-C. Sci Rep 2019;9: 14722. https://doi.org/10.1038/s41598-019-51246-1.
[566] Barthelemy A, Demais V, Stancu I-C, Vasile E, Houben T, Reber M, et al. Glial contribution to cyclodextrin-mediated reversal of cholesterol accumulation in murine NPC1-deficient neurons *in vivo*. bioRxiv 2021. https://doi.org/10.1101/2021.04.08.438990. 2021.04.08.438990.
[567] Colombo A, Dinkel L, Muller SA, Sebastian Monasor L, Schifferer M, Cantuti-Castelvetri L, et al. Loss of NPC1 enhances phagocytic uptake and impairs lipid trafficking in microglia. Nat Commun 2021;12:1158. https://doi.org/10.1038/s41467-021-21428-5.
[568] Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. Nature 2015; 523. https://doi.org/10.1038/nature14432. 337-+.
[569] Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. J Exp Med 2015;212:991–9. https://doi.org/10.1084/jem.20142290.
[570] Møllgård K, Beinlich FRM, Kusk P, Miyakoshi LM, Delle C, Plá V, et al. A mesothelium divides the subarachnoid space into functional compartments. Science 2023;379:84–8. https://doi.org/10.1126/science.adc8810.
[571] Rustenhoven J, Kipnis J. Brain borders at the central stage of neuroimmunology. Nature 2022;612:417–29. https://doi.org/10.1038/s41586-022-05474-7.
[572] Csepeggi C, Jiang M, Frolov A. Somatic cell plasticity and Niemann-pick type C2 protein: adipocyte differentiation and function. J Biol Chem 2010;285:30347–54. https://doi.org/10.1074/jbc.M110.135939.
[573] Roszell BR, Tao J-Q, Yu KJ, Gao L, Huang S, Ning Y, et al. Pulmonary abnormalities in animal models due to Niemann-Pick Type C1 (NPC1) or C2 (NPC2) disease. PloS One 2013;8:e67084. https://doi.org/10.1371/journal.pone.0067084.
[574] Rodriguez-Gil JL, Watkins-Chow DE, Baxter LL, Yokoyama T, Zerfas PM, Starost MF, et al. NPC1 deficiency in mice is associated with fetal growth restriction, neonatal lethality and abnormal lung pathology. J Clin Med 2020:9. https://doi.org/10.3390/jcm9010012.
[575] Suresh S, Yan Z, Patel RC, Patel YC, Patel SC. Cellular cholesterol storage in the Niemann-Pick disease type C mouse is associated with increased expression and defective processing of apolipoprotein D. J.Neurochem. 1998;70:242–51.
[576] German DC, Liang CL, Song T, Yazdani U, Xie C, Dietschy JM. Neurodegeneration in the Niemann-Pick C mouse: glial involvement. Neuroscience 2002;109:437–50.
[577] Suzuki H, Sakiyama T, Harada N, Abe M, Tadokoro M. Pathologic changes of glial cells in murine model of Niemann-Pick disease type C: immunohistochemical, lectin-histochemical and ultrastructural observations. Pediatr.Int. 2003;45:1–4.
[578] Baudry M, Yao Y, Simmons D, Liu J, Bi X. Postnatal development of inflammation in a murine model of Niemann-Pick type C disease: immunohistochemical observations of microglia and astroglia. Exp Neurol 2003;184:887–903. https://doi.org/10.1016/s0014-4886(03)00345-5.
[579] Chen G, Li HM, Chen YR, Gu XS, Duan S. Decreased estradiol release from astrocytes contributes to the neurodegeneration in a mouse model of Niemann-Pick disease type C. GLIA 2007;55:1509–18.
[580] Peake KB, Campenot RB, Vance DE, Vance JE. Niemann-Pick Type C1 deficiency in microglia does not cause neuron death in vitro. Biochim.Biophys.Acta 2011; 1812:1121–9.
[581] Yan X, Yang F, Lukas J, Witt M, Wree A, Rolfs A, et al. Hyperactive glial cells contribute to axonal pathologies in the spinal cord of Npc1 mutant mice. Glia 2014;62:1024–40. https://doi.org/10.1002/glia.22659.
[582] Seo Y, Kim H-S, Shin Y, Kang I, Choi SW, Yu K-R, et al. Excessive microglial activation aggravates olfactory dysfunction by impeding the survival of newborn neurons in the olfactory bulb of Niemann-Pick disease type C1 mice. BBA-Mol Basis Dis 2014;1842:2193–203. https://doi.org/10.1016/j.bbadis.2014.08.005.
[583] Caporali P, Bruno F, Palladino G, Dragotto J, Petrosini L, Mangia F, et al. Developmental delay in motor skill acquisition in Niemann-Pick C1 mice reveals abnormal cerebellar morphogenesis. Acta Neuropathologica. Communications 2016:4. https://doi.org/10.1186/s40478-016-0370-z.
[584] Boyle BR, Melli SE, Altreche RS, Padron ZM, Yousufzai FAK, Kim S, et al. NPC1 deficiency impairs cerebellar postnatal development of microglia and climbing fiber refinement in a mouse mode of Niemann-Pick disease type C. Development 2020:147. https://doi.org/10.1242/dev.189019.

[585] Berger A, Rosenthal D, Spiegel S. Sphingosylphosphocholine, a signaling molecule which accumulates in Niemann-Pick disease type-A, stimulates dna-binding activity of the transcription activator protein AP-1. Proc Natl Acad Sci U S A 1995; 92:5885–9. https://doi.org/10.1073/pnas.92.13.5885.
[586] Tam C, Idone V, Devlin C, Fernandes MC, Flannery A, He XX, et al. Exocytosis of acid sphingomyelinase by wounded cells promotes endocytosis and plasma membrane repair. J Cell Biol 2010;189:1027–38. https://doi.org/10.1083/jcb.201003053.
[587] Koike T, Ishida G, Taniguchi M, Higaki K, Ayaki Y, Saito M, et al. Decreased membrane fluidity and unsaturated fatty acids in Niemann-Pick disease type C fibroblasts. BBA-Mol Basis Dis 1998;1406:327–35. https://doi.org/10.1016/s0925-4439(98)00019-2.
[588] Ko DC, Gordon MD, Jin JY, Scott MP. Dynamic movements of organelles containing Niemann-Pick C1 protein: NPC1 involvement in late endocytic events. Mol.Biol.Cell 2001;12:601–14.
[589] Zhang M, Dwyer NK, Love DC, Cooney A, Comly M, Neufeld E, et al. Cessation of rapid late endosomal tubulovesicular trafficking in Niemann-Pick type C1 disease. Proc Natl Acad Sci U S A 2001;98:4466–71. https://doi.org/10.1073/pnas.081070898.
[590] Lebrand C, Corti M, Goodson H, Cosson P, Cavalli V, Mayran N, et al. Late endosome motility depends on lipids via the small GTPase Rab7. EMBO J 2002; 21:1289–300. https://doi.org/10.1093/emboj/21.6.1289.
[591] Rocha N, Kuijl C, van der Kant R, Janssen L, Houben D, Janssen H, et al. Cholesterol sensor ORP1L contacts the ER protein VAP to control Rab7-RILP-p150 (Glued) and late endosome positioning. J Cell Biol 2009;185:1209–25. https://doi.org/10.1083/jcb.200811005.
[592] Sterling FR, D'Amico J, Brumfield AM, Huegel KL, Vaughan PS, Morris K, et al. StARD9 is a novel lysosomal kinesin required for membrane tubulation, cholesterol transport and Purkinje cell survival. J Cell Sci 2023:136. https://doi.org/10.1242/jcs.260662.
[593] Frolov A, Zielinski SE, Crowley JR, Dudley-Rucker N, Schaffer JE, Ory DS. NPC1 and NPC2 regulate cellular cholesterol homeostasis through generation of low density lipoprotein cholesterol-derived oxysterols. J Biol Chem 2003;278: 25517–25. https://doi.org/10.1074/jbc.M302588200.
[594] Ganley IG, Pfeffer SR. Cholesterol accumulation sequesters Rab9 and disrupts late endosome function in NPC1-deficient cells. J Biol Chem 2006;281:17890–9. https://doi.org/10.1074/jbc.M601679200.
[595] Reddy JV, Ganley IG, Pfeffer SR. Clues to neuro-degeneration in Niemann-Pick Type C disease from global gene expression profiling. PLoS.ONE. 2006;1:e19.
[596] Pacheco CD, Kunkel R, Lieberman AP. Autophagy in Niemann-Pick C disease is dependent upon Beclin-1 and responsive to lipid trafficking defects. Hum.Mol. Genet. 2007;16:1495–503.
[597] Shen D, Wang X, Li X, Zhang X, Yao Z, Dibble S, et al. Lipid storage disorders block lysosomal trafficking by inhibiting a TRP channel and lysosomal calcium release. Nat.Commun. 2012;3:731.
[598] Strauss K, Goebel C, Runz H, Mobius W, Weiss S, Feussner I, et al. Exosome secretion ameliorates lysosomal storage of cholesterol in Niemann-Pick type C disease. J Biol Chem 2010;285:26279–88. https://doi.org/10.1074/jbc.M110.134775.
[599] Davis OB, Shin HR, Lim C-Y, Wu EY, Kukurugya M, Maher CF, et al. NPC1-mTORC1 signaling couples cholesterol sensing to organelle homeostasis and is a targetable pathway in Niemann-Pick type C. Dev Cell 2021;56:260–276.e7. https://doi.org/10.1016/j.devcel.2020.11.016.
[600] Kosicek M, Gudelj I, Horvatic A, Jovic T, Vuckovic F, Lauc G, et al. N-glycome of the lysosomal glycocalyx is altered in Niemann-Pick type C disease (NPC) model cells. Mol Cell Proteomics 2018;17:631–42. https://doi.org/10.1074/mcp.RA117.000129.
[601] Lusa S, Blom TS, Eskelinen EL, Kuismanen E, Mansson JE, Simons K, et al. Depletion of rafts in late endocytic membranes is controlled by NPC1-dependent recycling of cholesterol to the plasma membrane. J Cell Sci 2001;114:1893–900.
[602] Choi HY, Karten B, Chan T, Vance JE, Greer WL, Heidenreich RA, et al. Impaired ABCA1-dependent lipid efflux and hypoalphalipoproteinemia in human Niemann-Pick type C disease. J.Biol.Chem. 2003;278:32569–77.
[603] Kirkegaard T, Roth AG, Petersen NHT, Mahalka AK, Olsen OD, Moilanen I, et al. Hsp70 stabilizes lysosomes and reverts Niemann-Pick disease-associated lysosomal pathology. Nature 2010;463:549–U171. https://doi.org/10.1038/nature08710.
[604] Yambire KF, Fernandez-Mosquera L, Steinfeld R, Muhle C, Ikonen E, Milosevic I, et al. Mitochondrial biogenesis is transcriptionally repressed in lysosomal lipid storage diseases. Elife 2019:8. https://doi.org/10.7554/eLife.39598.
[605] Van Hoecke L, Van Cauwenberghe C, Dominko K, Van Imschoot G, Van Wonterghem E, Castelein J, et al. Involvement of the choroid plexus in the pathogenesis of Niemann-Pick disease type C. Front Cell Neurosci 2021:15. https://doi.org/10.3389/fncel.2021.757482.
[606] Li X, Xu M, Pitzer AL, Xia M, Boini KM, Li PL, et al. Control of autophagy maturation by acid sphingomyelinase in mouse coronary arterial smooth muscle cells: protective role in atherosclerosis. J Mol Med 2014;92:473–85. https://doi.org/10.1007/s00109-014-1120-y.
[607] Butler A, He XX, Gordon RE, Wu HS, Gatt S, Schuchman EH. Reproductive pathology and sperm physiology in acid sphingomyelinase-deficient mice. Am J Pathol 2002;161:1061–75. https://doi.org/10.1016/s0002-9440(10)64267-8.
[608] Fan J, Akabane H, Graham SN, Richardson LL, Zhu GZ. Sperm defects in mice lacking a functional Niemann-Pick C1 protein. Mol Reprod Dev 2006;73:1284–91. https://doi.org/10.1002/mrd.20559.
[609] Busso D, Onate-Alvarado MJ, Balboa E, Zanlungo S, Moreno RD. Female infertility due to anovulation and defective steroidogenesis in NPC2 deficient mice. Mol Cell Endocrinol 2010;315:299–307. https://doi.org/10.1016/j.mce.2009.10.011.
[610] Busso D, Oñate-Alvarado MJ, Balboa E, Castro J, Lizama C, Morales G, et al. Spermatozoa from mice deficient in Niemann-Pick disease type C2 (NPC2) protein have defective cholesterol content and reduced in vitro fertilising ability. Reprod Fertil Dev 2014;26:609–21. https://doi.org/10.1071/rd12059.
[611] Moles A, Tarrats N, Fernandez-Checa JC, Mari M. Cathepsin B overexpression due to acid sphingomyelinase ablation promotes liver fibrosis in Niemann-Pick disease. J Biol Chem 2012;287:1178–88. https://doi.org/10.1074/jbc.M111.272393.
[612] Schedin S, Sindelar PJ, Pentchev P, Brunk U, Dallner G. Peroxisomal impairment in Niemann-Pick type C disease. J Biol Chem 1997;272:6245–51. https://doi.org/10.1074/jbc.272.10.6245.
[613] Christomanou H, Vanier MT, Santambrogio P, Arosio P, Kleijer WJ, Harzer K. Deficient ferritin immunoreactivity in tissues from Niemann–Pick type C patients: extension of findings to fetal tissues, H and L ferritin isoforms, but also one case of the rare Niemann–Pick C2 complementation group. Mol Genet Metab 2000;70: 196–202. https://doi.org/10.1006/mgme.2000.3004.
[614] Hung YH, Faux NG, Killilea DW, Yanjanin N, Firnkes S, Volitakis I, et al. Altered transition metal homeostasis in Niemann-Pick disease, type C1. Metallomics 2014;6:542–53. https://doi.org/10.1039/c3mt00308f.
[615] Vainio S, Bykov I, Hermansson M, Jokitalo E, Somerharju P, Ikonen E. Defective insulin receptor activation and altered lipid rafts in Niemann-Pick type C disease hepatocytes. Biochem J 2005;391:465–72. https://doi.org/10.1042/bj20050460.
[616] Marí M, Caballero F, Colell A, Morales A, Caballeria J, Fernandez A, et al. Mitochondrial free cholesterol loading sensitizes to TNF- and Fas-mediated steatohepatitis. Cell Metab 2006;4:185–98. https://doi.org/10.1016/j.cmet.2006.07.006.
[617] Torres S, Matías N, Baulies A, Nuñez S, Alarcon-Vila C, Martinez L, et al. Mitochondrial GSH replenishment as a potential therapeutic approach for Niemann Pick type C disease. Redox Biol 2017;11:60–72. https://doi.org/10.1016/j.redox.2016.11.010.
[618] Balboa E, Marin T, Oyarzun JE, Contreras PS, Hardt R, Van den Bosch T, et al. Proteomic analysis of Niemann-Pick type C hepatocytes reveals potential therapeutic targets for liver damage. Cells 2021:10. https://doi.org/10.3390/cells10082159.
[619] Torres S, Solsona-Vilarrasa E, Nunez S, Matias N, Insausti-Urkia N, Castro F, et al. Acid ceramidase improves mitochondrial function and oxidative stress in Niemann-Pick type C disease by repressing STARD1 expression and mitochondrial cholesterol accumulation. Redox Biol 2021:45. https://doi.org/10.1016/j.redox.2021.102052.
[620] Utermohlen O, Karow U, Lohler J, Kronke M. Severe impairment in early host defense against Listeria monocytogenes in mice deficient in acid sphingomyelinase. J Immunol 2003;170:2621–8. https://doi.org/10.4049/jimmunol.170.5.2621.
[621] Schramm M, Herz J, Haas A, Kronke M, Utermohlen O. Acid sphingomyelinase is required for efficient phago-lysosomal fusion. Cell Microbiol 2008;10:1839–53. https://doi.org/10.1111/j.1462-5822.2008.01169.x.
[622] Zhang JR, Coleman T, Langmade SJ, Scherrer DE, Lane L, Lanier MH, et al. Niemann-Pick C1 protects against atherosclerosis in mice via regulation of macrophage intracellular cholesterol trafficking. J Clin Invest 2008;118:2281–90. https://doi.org/10.1172/jci32561.
[623] Schwerd T, Pandey S, Yang HT, Bagola K, Jameson E, Jung J, et al. Impaired antibacterial autophagy links granulomatous intestinal inflammation in Niemann-Pick disease type C1 and XIAP deficiency with NOD2 variants in Crohn's disease. Gut 2017;66:1060–73. https://doi.org/10.1136/gutjnl-2015-310382.
[624] Canonico B, Cesarini E, Salucci S, Luchetti F, Falcieri E, Di Sario G, et al. Defective autophagy, mitochondrial clearance and lipophagy in Niemann-Pick type B lymphocytes. PloS One 2016:11. https://doi.org/10.1371/journal.pone.0165780.
[625] Nix M, Stoffel W. Perturbation of membrane microdomains reduces mitogenic signaling and increases susceptibility to apoptosis after T cell receptor stimulation. Cell Death Differ 2000;7:413–24. https://doi.org/10.1038/sj.cdd.4400666.
[626] Herz J, Pardo J, Kashkar H, Schramm M, Kuzmenkina E, Bos E, et al. Acid sphingomyelinase is a key regulator of cytotoxic granule secretion by primary T lymphocytes. Nat Immunol 2009;10:761–U121. https://doi.org/10.1038/ni.1757.
[627] Castiblanco D, Rudd-Schmidt JA, Noori T, Sutton VR, Hung YH, Flinsenberg TWH, et al. Severely impaired CTL killing is a feature of the neurological disorder Niemann-Pick disease type C1. Blood 2022;139:1833–49. https://doi.org/10.1182/blood.2021013477.
[628] Melum E, Jiang XJ, Baker KD, Macedo MF, Fritsch J, Dowds CM, et al. Control of CD1d-restricted antigen presentation and inflammation by sphingomyelin. Nat Immunol 2019;20. https://doi.org/10.1038/s41590-019-0504-0. 1644-+.
[629] Sagiv Y, Hudspeth K, Mattner J, Schrantz N, Stern RK, Zhou D, et al. Cutting edge: impaired glycosphingolipid trafficking and NKT cell development in mice lacking Niemann-Pick type C1 protein. J Immunol 2006;177:26–30. https://doi.org/10.4049/jimmunol.177.1.26.
[630] Schumann J, Facciotti F, Panza L, Michieletti M, Compostella F, Collmann A, et al. Differential alteration of lipid antigen presentation to NKT cells due to imbalances in lipid metabolism. Eur J Immunol 2007;37:1431–41. https://doi.org/10.1002/eji.200737160.
[631] Speak AO, Vruchte DT, Davis LC, Morgan AJ, Smith DA, Yanjanin NM, et al. Altered distribution and function of natural killer cells in murine and human Niemann-Pick disease type C1. Blood 2014;123:51–60. https://doi.org/10.1182/blood-2013-03-488692.

[632] Liao G, Yao Y, Liu J, Yu Z, Cheung S, Xie A, et al. Cholesterol accumulation is associated with lysosomal dysfunction and autophagic stress in Npc1 -/- mouse brain. Am.J.Pathol. 2007;171:962–75.
[633] Conte C, Arcuri C, Cataldi S, Mecca C, Codini M, Ceccarini MR, et al. Niemann-Pick type A disease: behavior of neutral sphingomyelinase and vitamin D receptor. Int J Mol Sci 2019:20. https://doi.org/10.3390/ijms20092365.
[634] Horoupian DS, Yang SS. Paired helical filaments in neurovisceral lipidosis (Juvenile dystonic lipidosis). Ann Neurol 1978;4:404–11. https://doi.org/10.1002/ana.410040504.
[635] Love S, Bridges LR, Case CP. Neurofibrillary tangles in Niemann-Pick disease type C. Brain 1995;118(Pt 1):119–29.
[636] Auer IA, Schmidt ML, Lee VM, Curry B, Suzuki K, Shin RW, et al. Paired helical filament tau (PHFtau) in Niemann-Pick type C disease is similar to PHFtau in Alzheimer's disease. Acta Neuropathol 1995;90:547–51.
[637] Suzuki K, Parker CC, Pentchev PG, Katz D, Ghetti B, D'Agostino AN, et al. Neurofibrillary tangles in Niemann-Pick disease type C. Acta Neuropathol (Berl) 1995;89:227–38.
[638] Henderson LP, Lin L, Prasad A, Paul CA, Chang TY, Maue RA. Embryonic striatal neurons from niemann-pick type C mice exhibit defects in cholesterol metabolism and neurotrophin responsiveness. J.Biol.Chem. 2000;275:20179–87.
[639] Sawamura N, Gong JS, Garver WS, Heidenreich RA, Ninomiya H, Ohno K, et al. Site-specific phosphorylation of tau accompanied by activation of mitogen-activated protein kinase (MAPK) in brains of Niemann-Pick type C mice. J.Biol. Chem. 2001;276:10314–9.
[640] Bu B, Li J, Davies P, Vincent I. Deregulation of cdk5, hyperphosphorylation, and cytoskeletal pathology in the Niemann-Pick type C murine model. J.Neurosci. 2002;22:6515–25.
[641] Tuck BJ, Miller LVC, Katsinelos T, Smith AE, Wilson EL, Keeling S, et al. Cholesterol determines the cytosolic entry and seeded aggregation of tau. Cell Rep 2022;39:110776. https://doi.org/10.1016/j.celrep.2022.110776.
[642] Yamazaki T, Chang TY, Haass C, Ihara Y. Accumulation and aggregation of amyloid beta-protein in late endosomes of Niemann-pick type C cells. J.Biol. Chem. 2001;276:4454–60.
[643] Runz H, Rietdorf J, Tomic I, de Bernard M, Beyreuther K, Pepperkok R, et al. Inhibition of intracellular cholesterol transport alters presenilin localization and amyloid precursor protein processing in neuronal cells. J.Neurosci. 2002;22:1679–89.
[644] Burns M, Gaynor K, Olm V, Mercken M, LaFrancois J, Wang L, et al. Presenilin redistribution associated with aberrant cholesterol transport enhances beta-amyloid production in vivo. J.Neurosci. 2003;23:5645–9. https://doi.org/10.1523/JNEUROSCI.23-13-05645.2003.
[645] Jin LW, Shie FS, Maezawa I, Vincent I, Bird T. Intracellular accumulation of amyloidogenic fragments of amyloid-beta precursor protein in neurons with Niemann-Pick type C defects is associated with endosomal abnormalities. Am.J. Pathol. 2004;164:975–85.
[646] Kodam A, Maulik M, Peake K, Amritraj A, Vetrivel KS, Thinakaran G, et al. Altered levels and distribution of amyloid precursor protein and its processing enzymes in Niemann-Pick type C1-deficient mouse brains. Glia 2010;58:1267–81. https://doi.org/10.1002/glia.21001.
[647] Mattsson N, Olsson M, Gustavsson MK, Kosicek M, Malnar M, Mansson JE, et al. Amyloid-beta metabolism in Niemann-Pick C disease models and patients. Metab Brain Dis 2012;27:573–85.
[648] Tashiro Y, Yamazaki T, Shimada Y, Ohno-Iwashita Y, Okamoto K. Axon-dominant localization of cell-surface cholesterol in cultured hippocampal neurons and its disappearance in Niemann-Pick type C model cells. Eur.J.Neurosci. 2004;20:2015–21.
[649] Wu YP, Mizukami H, Matsuda J, Saito Y, Proia RL, Suzuki K. Apoptosis accompanied by up-regulation of TNF-alpha death pathway genes in the brain of Niemann-Pick type C disease. Mol Genet Metab 2005;84:9–17. https://doi.org/10.1016/j.ymgme.2004.08.017.
[650] Bi XN, Liu JH, Yao YQ, Baudry M, Lynch G. Deregulation of the phosphatidylinositol-3 kinase signaling cascade is associated with neurodegeneration in Npc1-/- mouse brain. Am J Pathol 2005;167:1081–92. https://doi.org/10.1016/s0002-9440(10)61197-2.
[651] Yang SR, Kim SJ, Byun KH, Hutchinson B, Lee BH, Michikawa M, et al. NPC1 gene deficiency leads to lack of neural stem cell self-renewal and abnormal differentiation through activation of p38 mitogen-activated protein kinase signaling. Stem Cells 2006;24:292–8. https://doi.org/10.1634/stemcells.2005-0221.
[652] Nusca S, Canterini S, Palladino G, Bruno F, Mangia F, Erickson RP, et al. A marked paucity of granule cells in the developing cerebellum of the Npc1(-/-) mouse is corrected by a single injection of hydroxypropyl-beta-cyclodextrin. Neurobiol Dis 2014;70:117–26. https://doi.org/10.1016/j.nbd.2014.06.012.
[653] Amritraj A, Peake K, Kodam A, Salio C, Merighi A, Vance JE, et al. Increased activity and altered subcellular distribution of lysosomal enzymes determine neuronal vulnerability in Niemann-Pick type C1-deficient mice. Am.J.Pathol. 2009;175:2540–56.
[654] Lee H, Lee JK, Park MH, Hong YR, Marti HH, Kim H, et al. Pathological roles of the VEGF/SphK pathway in Niemann-Pick type C neurons. Nat Commun 2014;5:5514. https://doi.org/10.1038/ncomms6514.
[655] Canterini S, Dragotto J, Dardis A, Zampieri S, De Stefano ME, Mangia F, et al. Shortened primary cilium length and dysregulated Sonic hedgehog signaling in Niemann-Pick C1 disease. Hum Mol Genet 2017;26:2277–89. https://doi.org/10.1093/hmg/ddx118.
[656] Vivas O, Tiscione SA, Dixon RE, Ory DS, Dickson EJ. Niemann-Pick type C disease reveals a link between lysosomal cholesterol and PtdIns(4,5)P(2) that regulates neuronal excitability. Cell Rep 2019;27:2636–2648.e4. https://doi.org/10.1016/j.celrep.2019.04.099.
[657] Roney JC, Li SA, Farfel-Becker T, Huang N, Sun T, Xie YX, et al. Lipid-mediated motor-adaptor sequestration impairs axonal lysosome delivery leading to autophagic stress and dystrophy in Niemann-Pick type C. Dev Cell 2021;56. https://doi.org/10.1016/j.devcel.2021.03.032. 1452-+.
[658] Guix FX, Capitan AM, Casadome-Perales A, Palomares-Perez I, del Castillo IL, Miguel V, et al. Increased exosome secretion in neurons aging in vitro by NPC1-mediated endosomal cholesterol buildup. Life Sci Allianc 2021:4. https://doi.org/10.26508/lsa.202101055.
[659] Li H, Repa JJ, Valasek MA, Beltroy EP, Turley SD, German DC, et al. Molecular, anatomical, and biochemical events associated with neurodegeneration in mice with Niemann-Pick type C disease. J.Neuropathol.Exp.Neurol. 2005;64:323–33.
[660] Yu W, Gong JS, Ko M, Garver WS, Yanagisawa K, Michikawa M. Altered cholesterol metabolism in Niemann-Pick type C1 mouse brains affects mitochondrial function. J.Biol.Chem. 2005;280:11731–9.
[661] Fernandez A, Llacuna L, Fernandez-Checa JC, Colell A. Mitochondrial cholesterol loading exacerbates amyloid beta peptide-induced inflammation and neurotoxicity. J.Neurosci. 2009;29:6394–405.
[662] Ordonez MP, Roberts EA, Kidwell CU, Yuan SH, Plaisted WC, Goldstein LS. Disruption and therapeutic rescue of autophagy in a human neuronal model of Niemann Pick type C1. Hum.Mol.Genet. 2012;21:2651–62. https://doi.org/10.1093/hmg/dds090.
[663] Camoletto PG, Vara H, Morando L, Connell E, Marletto FP, Giustetto M, et al. Synaptic vesicle docking: sphingosine regulates Syntaxin1 interaction with Munc18. PloS One 2009;4:e5310. https://doi.org/10.1371/journal.pone.0005310.
[664] Arroyo AI, Camoletto PG, Morando L, Sassoe-Pognetto M, Giustetto M, Van Veldhoven PP, et al. Pharmacological reversion of sphingomyelin-induced dendritic spine anomalies in a Niemann Pick disease type A mouse model. EMBO Mol Med 2014;6:398–413. https://doi.org/10.1002/emmm.201302649.
[665] Walkley SU. Pyramidal neurons with ectopic dendrites in storage diseases exhibit increased GM2 ganglioside immunoreactivity. Neuroscience 1995;68:1027–35.
[666] March PA, Thrall MA, Brown DE, Mitchell TW, Lowenthal AC, Walkley SU. GABAergic neuroaxonal dystrophy and other cytopathological alterations in feline Niemann-Pick disease type C. Acta Neuropathol (Berl) 1997;94:164–72.
[667] Karten B, Vance DE, Campenot RB, Vance JE. Trafficking of cholesterol from cell bodies to distal axons in Niemann Pick C1-deficient neurons. J Biol Chem 2003;278:4168–75.
[668] Karten B, Campenot RB, Vance DE, Vance JE. The Niemann-Pick C1 protein in recycling endosomes of presynaptic nerve terminals. J Lipid Res 2006;47:504–14.
[669] Wasser CR, Ertunc M, Liu X, Kavalali ET. Cholesterol-dependent balance between evoked and spontaneous synaptic vesicle recycling. J.Physiol 2007;579:413–29.
[670] Hawes CM, Wiemer H, Krueger SR, Karten B. Pre-synaptic defects of NPC1-deficient hippocampal neurons are not directly related to plasma membrane cholesterol. J.Neurochem. 2010;114:311–22.
[671] Xu S, Zhou S, Xia D, Xia J, Chen G, Duan S, et al. Defects of synaptic vesicle turnover at excitatory and inhibitory synapses in Niemann-Pick C1-deficient neurons. Neuroscience 2010;167:608–20.
[672] Zhou SY, Xu SJ, Yan YG, Yu HM, Ling SC, Luo JH. Decreased purinergic inhibition of synaptic activity in a mouse model of Niemann-Pick disease type C. Hippocampus 2011;21:212–9.
[673] Buard I, Pfrieger FW. Relevance of neuronal and glial NPC1 for synaptic input to cerebellar Purkinje cells. Mol Cell Neurosci 2014;61:65–71. https://doi.org/10.1016/j.mcn.2014.06.003.
[674] Yan X, Ma L, Hovakimyan M, Lukas J, Wree A, Frank M, et al. Defects in the retina of Niemann-pick type C 1 mutant mice. BMC Neurosci 2014;15:126.
[675] Mitroi DN, Pereyra-Gómez G, Soto-Huelin B, Senovilla F, Kobayashi T, Esteban JA, et al. NPC1 enables cholesterol mobilization during long-term potentiation that can be restored in Niemann-Pick disease type C by CYP46A1 activation. EMBO Rep 2019;20:e48143. https://doi.org/10.15252/embr.201948143.
[676] Tiscione SA, Vivas O, Ginsburg KS, Bers DM, Ory DS, Santana LF, et al. Disease-associated mutations in Niemann-Pick type C1 alter ER calcium signaling and neuronal plasticity. J Cell Biol 2019;218:4141–56. https://doi.org/10.1083/jcb.201903018.
[677] Gabande-Rodriguez E, Boya P, Labrador V, Dotti CG, Ledesma MD. High sphingomyelin levels induce lysosomal damage and autophagy dysfunction in Niemann Pick disease type A. Cell Death Differ 2014;21:864–75. https://doi.org/10.1038/cdd.2014.4.
[678] Sarkar S, Carroll B, Buganim Y, Maetzel D, Ng AH, Cassady JP, et al. Impaired autophagy in the lipid-storage disorder Niemann-Pick type C1 disease. Cell Rep 2013;5:1302–15. https://doi.org/10.1016/j.celrep.2013.10.042.
[679] Gurda BL, Bagel JH, Fisher SJ, Schultz ML, Lieberman AP, Hand P, et al. LC3 immunostaining in the inferior olivary nuclei of cats with Niemann-Pick disease type C1 is associated with patterned Purkinje cell loss. J Neuropathol Exp Neurol 2018;77:229–45. https://doi.org/10.1093/jnen/nlx119.
[680] Ginzburg L, Futerman AH. Defective calcium homeostasis in the cerebellum in a mouse model of Niemann-Pick A disease. J Neurochem 2005;95:1619–28. https://doi.org/10.1111/j.1471-4159.2005.03534.x.
[681] Tiscione SA, Casas M, Horvath JD, Lam V, Hino K, Ory DS, et al. IP(3)R-driven increases in mitochondrial Ca(2+) promote neuronal death in NPC disease. Proc Natl Acad Sci U S A 2021;118:e2110629118. https://doi.org/10.1073/pnas.2110629118.
[682] Marin T, Dulcey AE, Campos F, de la Fuente C, Acuna M, Castro J, et al. c-Abl activation linked to autophagy-lysosomal dysfunction contributes to neurological

impairment in Niemann-Pick type A disease. Front Cell Dev Biol 2022:10. https://doi.org/10.3389/fcell.2022.844297.
[683] Alvarez AR, Klein A, Castro J, Cancino GI, Amigo J, Mosqueira M, et al. Imatinib therapy blocks cerebellar apoptosis and improves neurological symptoms in a mouse model of Niemann-Pick type C disease. FASEB J 2008;22:3617–27.
[684] Contreras PS, Tapia PJ, Gonzalez-Hodar L, Peluso I, Soldati C, Napolitano G, et al. c-Abl inhibition activates TFEB and promotes cellular clearance in a lysosomal disorder. Iscience 2020:23. https://doi.org/10.1016/j.isci.2020.101691.
[685] Pérez-Cañamás A, Benvegnù S, Rueda CB, Rábano A, Satrústegui J, Ledesma MD. Sphingomyelin-induced inhibition of the plasma membrane calcium ATPase causes neurodegeneration in type A Niemann–Pick disease. Mol Psychiatry 2017;22:711–23. https://doi.org/10.1038/mp.2016.148.
[686] Klein A, Maldonado C, Vargas LM, Gonzalez M, Robledo F, de Arce KP, et al. Oxidative stress activates the c-Abl/p73 proapoptotic pathway in Niemann-Pick type C neurons. Neurobiol Dis 2011;41:209–18. https://doi.org/10.1016/j.nbd.2010.09.008.
[687] Kennedy BE, LeBlanc VG, Mailman TM, Fice D, Burton I, Karakach TK, et al. Pre-symptomatic activation of antioxidant responses and alterations in glucose and pyruvate metabolism in Niemann-Pick Type C1-deficient murine brain. PloS One 2013;8. https://doi.org/10.1371/journal.pone.0082685. e82685-e82685.
[688] Oddi S, Caporali P, Dragotto J, Totaro A, Maiolati M, Scipioni L, et al. The endocannabinoid system is affected by cholesterol dyshomeostasis: Insights from a murine model of Niemann Pick type C disease. Neurobiol Dis 2019:130. https://doi.org/10.1016/j.nbd.2019.104531.
[689] Bartoll A, Toledano-Zaragoza A, Casas J, Guzmán M, Schuchman EH, Ledesma MD. Inhibition of fatty acid amide hydrolase prevents pathology in neurovisceral acid sphingomyelinase deficiency by rescuing defective endocannabinoid signaling. EMBO Mol Med 2020;12:e11776. https://doi.org/10.15252/emmm.201911776.
[690] Buccinna B, Piccinini M, Prinetti A, Scandroglio F, Prioni S, Valsecchi M, et al. Alterations of myelin-specific proteins and sphingolipids characterize the brains of acid sphingomyelinase-deficient mice, an animal model of Niemann-Pick disease type A. J Neurochem 2009;109:105–15. https://doi.org/10.1111/j.1471-4159.2009.05947.x.
[691] Palmeri S, Battisti C, Federico A, Guazzi GC. Hypoplasia of the corpus-callosum in Niemann-Pick type-C disease. Neuroradiology 1994;36:20–2. https://doi.org/10.1007/bf00599187.
[692] Higashi Y, Murayama S, Pentchev PG, Suzuki K. Peripheral-nerve pathology in Niemann-Pick type-C mouse. Acta Neuropathol 1995;90:158–63.
[693] Weintraub H, Abramovici A, Sandbank U, Pentchev PG, Brady RO, Sekine M, et al. Neurological mutation characterized by dysmyelination in NCTR-BALB/C mouse with lysosomal lipid storage disease. J Neurochem 1985;45:665–72. https://doi.org/10.1111/j.1471-4159.1985.tb04044.x.
[694] Xie CL, Burns DK, Turley SD, Dietschy JM. Cholesterol is sequestered in the brains of mice with Niemann-Pick type C disease but turnover is increased. J Neuropathol Exp Neurol 2000;59:1106–17. https://doi.org/10.1093/jnen/59.12.1106.
[695] Lope-Piedrafita S, Totenhagen JW, Hicks CM, Erickson RP, Trouard TP. MRI detects therapeutic effects in weanling Niemann-Pick type C mice. J Neurosci Res 2008;86:2802–7. https://doi.org/10.1002/jnr.21707.
[696] Yan X, Lukas J, Witt M, Wree A, Hubner R, Frech M, et al. Decreased expression of myelin gene regulatory factor in Niemann-Pick type C 1 mouse. Metab Brain Dis 2011;26:299–306.
[697] Bagel JH, Sikora TU, Prociuk M, Pesayco JP, Mizisin AP, Shelton GD, et al. Electrodiagnostic testing and histopathologic changes confirm peripheral nervous system myelin abnormalities in the feline model of niemann-pick disease type C. J Neuropathol Exp Neurol 2013;72:256–62. https://doi.org/10.1097/NEN.0b013e318286587f.
[698] Yu T, Lieberman AP. Npc1 acting in neurons and glia is essential for the formation and maintenance of CNS myelin. PLoS Genet 2013;9:e1003462. https://doi.org/10.1371/journal.pgen.1003462.
[699] Yang F, Feng X, Rolfs A, Luo J. Lovastatin promotes myelin formation in NPC1 mutant oligodendrocytes. J Neurol Sci 2018;386:56–63. https://doi.org/10.1016/j.jns.2018.01.015.
[700] De Nuccio C, Bernardo A, Ferrante A, Pepponi R, Martire A, Falchi M, et al. Adenosine A(2A) receptor stimulation restores cell functions and differentiation in Niemann-Pick type C-like oligodendrocytes. Sci Rep 2019;9:9782. https://doi.org/10.1038/s41598-019-46268-8.
[701] Yang F, Guan YD, Feng X, Rolfs A, Schluter H, Luo JK. Proteomics of the corpus callosum to identify novel factors involved in hypomyelinated Niemann-Pick type C disease mice. Mol Brain 2019:12. https://doi.org/10.1186/s13041-019-0440-9.
[702] Angelini R, Yutuc E, Wyatt MF, Newton J, Yusuf FA, Griffiths L, et al. Visualizing cholesterol in the brain by on-tissue derivatization and quantitative mass spectrometry imaging. Anal Chem 2021;93:4932–43. https://doi.org/10.1021/acs.analchem.0c05399.
[703] Weintraub H, Abramovici A, Amichai D, Eldar T, Bendor L, Pentchev PG, et al. Morphometric studies of pancreatic acinar granule formation in NCTR-BALB/C mice. J Cell Sci 1992;102:141–7.
[704] Munzer P, Borst O, Walker B, Schmid E, Feijge MAH, Cosemans J, et al. Acid sphingomyelinase regulates platelet cell membrane scrambling, secretion, and thrombus formation. Arterioscler Thromb Vasc Biol 2014;34. https://doi.org/10.1161/atvbaha.112.300210. 61-+.
[705] Xu J, Dang YJ, Ren YRZ, Liu JO. Cholesterol trafficking is required for mTOR activation in endothelial cells. Proc Natl Acad Sci U S A 2010;107:4764–9. https://doi.org/10.1073/pnas.0910872107.
[706] Rahit K, Tarailo-Graovac M. Genetic modifiers and rare mendelian disease. Genes 2020:11. https://doi.org/10.3390/genes11030239.
[707] Hassan S, Sidransky E, Tayebi N. The role of epigenetics in lysosomal storage disorders: Uncharted territory. Mol Genet Metab 2017;122:10–8. https://doi.org/10.1016/j.ymgme.2017.07.012.
[708] Jakobkiewicz-Banecka J, Gabig-Ciminska M, Banecka-Majkutewicz Z, Banecki B, Wegrzyn A, Wegrzyn G. Factors and processes modulating phenotypes in neuronopathic lysosomal storage diseases. Metab Brain Dis 2014;29:1–8. https://doi.org/10.1007/s11011-013-9455-6.
[709] Miyawaki S, Yoshida H, Mitsuoka S, Enomoto H, Ikehara S. A mouse model for Niemann-Pick disease. influence of genetic background on disease expression in spm/spm mice. J Hered 1986;77:379–84. https://doi.org/10.1093/oxfordjournals.jhered.a110265.
[710] Zhang J, Erickson RP. A modifier of Niemann Pick C 1 maps to mouse chromosome 19. Mamm Genome 2000;11:69–71. https://doi.org/10.1007/s003350010013.
[711] Parra J, Klein AD, Castro J, Morales MG, Mosqueira M, Valencia I, et al. Npc1 deficiency in the C57BL/6J genetic background enhances Niemann-Pick disease type C spleen pathology. Biochem Biophys Res Commun 2011;413:400–6. https://doi.org/10.1016/j.bbrc.2011.08.096.
[712] Marshall CA, Watkins-Chow DE, Palladino G, Deutsch G, Chandran K, Pavan WJ, et al. In Niemann-Pick C1 mouse models, glial-only expression of the normal gene extends survival much further than do changes in genetic background or treatment with hydroxypropyl-beta-cyclodextrin. Gene 2018;643:117–23. https://doi.org/10.1016/j.gene.2017.12.006.
[713] Elleder M, Čihula J. Niemann-Pick disease (variation in the sphingomyelinase deficient group). Eur J Pediatr 1983;140:323–8. https://doi.org/10.1007/BF00442673.
[714] Vanier MT, Wenger DA, Comly ME, Rousson R, Brady RO, Pentchev PG. Niemann-Pick disease group C: clinical variability and diagnosis based on defective cholesterol esterification: A collaborative study on 70 patients. Clin Genet 1988;33:331–48. https://doi.org/10.1111/j.1399-0004.1988.tb03460.x.
[715] Moreno R, Lardennois C, Drouin-Garraud V, Verspyck E, Marret S, Laquerrière A. Prenatal revelation of Niemann-Pick disease type C in siblings. Acta Paediatr 2008;97:1136–9. https://doi.org/10.1111/j.1651-2227.2008.00829.x.
[716] Walterfang M, Fietz M, Abel L, Bowman E, Mocellin R, Velakoulis D. Gender dimorphism in siblings with schizophrenia-like psychosis due to Niemann-Pick disease type C. J Inherit Metab Dis 2009;32:S221–6. https://doi.org/10.1007/s10545-009-1173-1.
[717] Anheim M, Lagha-Boukbiza O, Fleury-Lesaunier MC, Valenti-Hirsch MP, Hirsch E, Gervais-Bernard H, et al. Heterogeneity and frequency of movement disorders in juvenile and adult-onset Niemann-Pick C disease. J Neurol 2014;261:174–9. https://doi.org/10.1007/s00415-013-7159-9.
[718] Benussi A, Alberici A, Premi E, Bertasi V, Cotelli MS, Turla M, et al. Phenotypic heterogeneity of Niemann-Pick disease type C in monozygotic twins. J Neurol 2015;262:642–7. https://doi.org/10.1007/s00415-014-7619-x.
[719] Soliani L, Salerno GG, Pisani F, Barigazzi I, Rizzi S, Spagnoli C, et al. Neuropsychological and behavioral disorders as presentation symptoms in two brothers with early-infantile Niemann-Pick type C. Acta Biomed 2020;91:e2020075. https://doi.org/10.23750/abm.v91i3.9272.
[720] Pass T, Wiesner RJ, Pla-Martin D. Selective neuron vulnerability in common and rare diseases-mitochondria in the focus. Front Mol Biosci 2021:8. https://doi.org/10.3389/fmolb.2021.676187.
[721] Terada N, Banno Y, Ohno N, Fujii Y, Murate T, Sarna JUR, et al. Compartmentation of the mouse cerebellar cortex by sphingosine kinase. J Comp Neurol 2004;469:119–27. https://doi.org/10.1002/cne.11002.
[722] Pascua-Maestro R, Corraliza-Gomez M, Fadrique-Rojo C, Ledesma MD, Schuchman EH, Sanchez D, et al. Apolipoprotein D-mediated preservation of lysosomal function promotes cell survival and delays motor impairment in Niemann-Pick type A disease. Neurobiol Dis 2020;144:105046. https://doi.org/10.1016/j.nbd.2020.105046.
[723] Pacheco CD, Elrick MJ, Lieberman AP. Tau deletion exacerbates the phenotype of Niemann-Pick type C mice and implicates autophagy in pathogenesis. Hum.Mol. Genet. 2009;18:956–65.
[724] Smith AF, Vanderah TW, Erickson RP. Haploinsufficiency of tau decreases survival of the mouse model of Niemann-Pick disease type C1 but does not alter tau phosphorylation. J Appl Genet 2020. https://doi.org/10.1007/s13353-020-00572-6.
[725] Nunes A, Pressey SNR, Cooper JD, Soriano S. Loss of amyloid precursor protein in a mouse model of Niemann-Pick type C disease exacerbates its phenotype and disrupts tau homeostasis. Neurobiol Dis 2011;42:349–59. https://doi.org/10.1016/j.nbd.2011.01.028.
[726] Sun Y, Ishibashi M, Seimon T, Lee M, Sharma SM, Fitzgerald KA, et al. Free cholesterol accumulation in macrophage membranes activates toll-like receptors and p38 mitogen-activated protein kinase and induces cathepsin K. Circ Res 2009;104:455–U75. https://doi.org/10.1161/circresaha.108.182568.
[727] Fu R, Yanjanin NM, Elrick MJ, Ware C, Lieberman AP, Porter FD. Apolipoprotein E genotype and neurological disease onset in Niemann–Pick disease, type C1. Am J Med Genet A 2012;158A:2775–80. https://doi.org/10.1002/ajmg.a.35395.
[728] Lee H, Lee JK, Bae YC, Yang SH, Okino N, Schuchman EH, et al. Inhibition of GM3 synthase attenuates neuropathology of Niemann-Pick disease type C. by affecting sphingolipid metabolism. Mol Cells 2014;37:161–71. https://doi.org/10.14348/molcells.2014.2347.
[729] Wheeler S, Haberkant P, Bhardwaj M, Tongue P, Ferraz MJ, Halter D, et al. Cytosolic glucosylceramide regulates endolysosomal function in Niemann-Pick

type C disease. Neurobiol Dis 2019;127:242–52. https://doi.org/10.1016/j.nbd.2019.03.005.
[730] Chung C, Elrick MJ, Dell'Orco JM, Qin ZS, Kalyana-Sundaram S, Chinnaiyan AM, et al. Heat shock protein beta-1 modifies anterior to posterior purkinje cell vulnerability in a mouse model of Niemann-Pick type C disease. PLoS Genet 2016;12:e1006042. https://doi.org/10.1371/journal.pgen.1006042.
[731] Pugach EK, Feltes M, Kaufman RJ, Ory DS, Bang AG. High-content screen for modifiers of Niemann-Pick type C disease in patient cells. Hum Mol Genet 2018;27:2101–12. https://doi.org/10.1093/hmg/ddy117.
[732] Cougnoux A, Fellmeth M, Gu T, Davidson CD, Gibson AL, Pavan WJ, et al. Maternal immune activation modifies the course of Niemann-pick disease, type C1 in a gender specific manner. Mol Genet Metab 2020;129:165–70. https://doi.org/10.1016/j.ymgme.2019.10.004.
[733] Martin KB, Williams IM, Cluzeau CV, Cougnoux A, Dale RK, Iben JR, et al. Identification of novel pathways associated with patterned cerebellar purkinje neuron degeneration in Niemann-Pick disease, type C1. Int J Mol Sci 2020:21. https://doi.org/10.3390/ijms21010292.
[734] Liu EA, Schultz ML, Mochida C, Chung C, Paulson HL, Lieberman AP. Fbxo2 mediates clearance of damaged lysosomes and modifies neurodegeneration in the Niemann-Pick C brain. JCI. Insight 2020. https://doi.org/10.1172/jci.insight.136676.
[735] Meneses-Salas E, Garcia-Forn M, Castany-Pladevall C, Lu A, Fajardo A, Jose J, et al. Lack of annexin A6 exacerbates liver dysfunction and reduces lifespan of Niemann-Pick type C protein-deficient mice. Am J Pathol 2021;191:475–86. https://doi.org/10.1016/j.ajpath.2020.12.009.
[736] Lopez AM, Jones RD, Repa JJ, Turley SD. Niemann-Pick C1-deficient mice lacking sterol O-acyltransferase 2 have less hepatic cholesterol entrapment and improved liver function. Am J Physiol Gastrointest Liver Physiol 2018;315:G454–g463. https://doi.org/10.1152/ajpgi.00124.2018.
[737] Rogers MA, Chang CCY, Maue RA, Melton EM, Peden AA, Garver WS, et al. Acat1/Soat1 knockout extends the mutant Npc1 mouse lifespan and ameliorates functional deficiencies in multiple organelles of mutant cells. Proc Natl Acad Sci U S A 2022;119:e2201646119. https://doi.org/10.1073/pnas.2201646119.
[738] Bernardo A, Malara M, Bertuccini L, De Nuccio C, Visentin S, Minghetti L. The antihypertensive drug telmisartan protects oligodendrocytes from cholesterol accumulation and promotes differentiation by a PPAR-gamma-mediated mechanism. Int J Mol Sci 2021:22. https://doi.org/10.3390/ijms22179434.
[739] Cawley NX, Lyons AT, Abebe D, Luke R, Yerger J, Telese R, et al. Complex N-linked glycosylation: a potential modifier of Niemann-Pick disease, type C1 pathology. Int J Mol Sci 2022;23:5082.
[740] Schneede A, Schmidt CK, Holtta-Vuori M, Heeren J, Willenborg M, Blanz J, et al. Role for LAMP-2 in endosomal cholesterol transport. J Cell Mol Med 2011;15:280–95. https://doi.org/10.1111/j.1582-4934.2009.00973.x.
[741] Li J, Pfeffer SR. Lysosomal membrane glycoproteins bind cholesterol and contribute to lysosomal cholesterol export. Elife 2016:5. https://doi.org/10.7554/eLife.21635.
[742] Heybrock S, Kanerva K, Meng Y, Ing C, Liang A, Xiong ZJ, et al. Lysosomal integral membrane protein-2 (LIMP-2/SCARB2) is involved in lysosomal cholesterol export. Nat Commun 2019;10:3521. https://doi.org/10.1038/s41467-019-11425-0.
[743] Perez RK, Gordon MG, Subramaniam M, Kim MC, Hartoularos GC, Targ SS, et al. Single-cell RNA-seq reveals cell type-specific molecular and genetic associations to lupus. Science 2022;376. https://doi.org/10.1126/science.abf1970. 153-+.
[744] Yazar S, Alquicira-Hernandez J, Wing K, Senabouth A, Gordon MG, Andersen S, et al. Single-cell eQTL mapping identifies cell type-specific genetic control of autoimmune disease. Science 2022;376. https://doi.org/10.1126/science.abf3041. 154-+.
[745] Bryois J, Calini D, Macnair W, Foo L, Urich E, Ortmann W, et al. Cell-type-specific cis-eQTLs in eight human brain cell types identify novel risk genes for psychiatric and neurological disorders. Nat Neurosci 2022;25:1104–12. https://doi.org/10.1038/s41593-022-01128-z.
[746] Toledano-Zaragoza A, Ledesma MD. Addressing neurodegeneration in lysosomal storage disorders: Advances in Niemann Pick diseases. Neuropharmacology 2020:171. https://doi.org/10.1016/j.neuropharm.2019.107851.
[747] Daloze P, Delvin EE, Glorieux FH, Corman JL, Bettez P, Toussi T, et al. Replacement therapy for inherited enzyme deficiency: Liver orthotopic transplantation in Niemann-Pick disease type A. Am J Med Genet 1977;1:229–39. https://doi.org/10.1002/ajmg.1320010209.
[748] Jin HK, Carter JE, Huntley GW, Schuchman EH. Intracerebral transplantation of mesenchymal stem cells into acid sphingomyelinase-deficient mice delays the onset of neurological abnormalities and extends their life span. J Clin Investig 2002;109:1183–91. https://doi.org/10.1072/jci200214862.
[749] Jin HK, Schuchman EH. Ex vivo gene therapy using bone marrow-derived cells: Combined effects of intracerebral and intravenous transplantation in a mouse model of Niemann-Pick disease. Mol Ther 2003;8:876–85. https://doi.org/10.1016/j.ymthe.2003.07.008.
[750] Suchi M, Dinur T, Desnick RJ, Gatt S, Pereira L, Gilboa E, et al. Retroviral-mediated transfer of the human acid sphingomyelinase cDNA: correction of the metabolic defect in cultured Niemann-Pick disease cells. Proc Natl Acad Sci 1992;89:3227–31. https://doi.org/10.1073/pnas.89.8.3227.
[751] He XX, Miranda SRP, Xiong XL, Dagan A, Gatt S, Schuchman EH. Characterization of human acid sphingomyelinase purified from the media of overexpressing Chinese hamster ovary cells. BBA-Protein Struct M 1999;1432:251–64. https://doi.org/10.1016/s0167-4838(99)00069-2.
[752] Miranda SRP, He XX, Simonaro CM, Gatt S, Dagan A, Desnick RJ, et al. Infusion of recombinant human acid sphingomyelinase into Niemann-Pick disease mice leads to visceral, but not neurological, correction of the pathophysiology. FASEB J 2000;14:1988–95. https://doi.org/10.1096/fj.00-0014com.
[753] Yang WW, Dodge JC, Passini MA, Taksir TV, Griffiths D, Schuchman EH, et al. Intraparenchymal injections of acid sphingomyelinase results in regional correction of lysosomal storage pathology in the Niemann-Pick A mouse. Exp Neurol 2007;207:258–66. https://doi.org/10.1016/j.expneurol.2007.06.017.
[754] Dodge JC, Clarke J, Treleaven CM, Taksir TV, Griffiths DA, Yang WD, et al. Intracerebroventricular infusion of acid sphingomyelinase corrects CNS manifestations in a mouse model of Niemann-Pick A disease. Exp Neurol 2009;215:349–57. https://doi.org/10.1016/j.expneurol.2008.10.021.
[755] Muro S, Schuchman EH, Muzykantov VR. Lysosomal enzyme delivery by ICAM-1-targeted nanocarriers bypassing glycosylation- and clathrin-dependent endocytosis. Mol Ther 2006;13:135–41. https://doi.org/10.1016/j.ymthe.2005.07.687.
[756] Muro S, Garnacho C, Champion JA, Leferovich J, Gajewski C, Schuchman EH, et al. Control of endothelial targeting and intracellular delivery of therapeutic enzymes by modulating the size and shape of ICAM-1-targeted carriers. Mol Ther 2008;16:1450–8. https://doi.org/10.1038/mt.2008.127.
[757] Garnacho C, Dhami R, Simone E, Dziubla T, Leferovich J, Schuchman EH, et al. Delivery of acid sphingomyelinase in normal and Niemann-Pick disease mice using intercellular adhesion molecule-1-targeted polymer nanocarriers. J Pharmacol Exp Ther 2008;325:400–8. https://doi.org/10.1124/jpet.107.133298.
[758] Garnacho C, Dhami R, Solomon M, Schuchman EH, Muro S. Enhanced delivery and effects of acid sphingomyelinase by ICAM-1-targeted nanocarriers in type B Niemann-Pick disease mice. Mol Ther 2017;25:1686–96. https://doi.org/10.1016/j.ymthe.2017.05.014.
[759] Dhami R, Schuchman EH. Mannose 6-phosphate receptor-mediated uptake is defective in acid sphingomyelinase-deficient macrophages - implications for Niemann-Pick disease enzyme replacement therapy. J Biol Chem 2004;279:1526–32. https://doi.org/10.1074/jbc.M309465200.
[760] Rappaport J, Garnacho C, Muro S. Clathrin-mediated endocytosis is impaired in type A-B Niemann-Pick disease model cells and can be restored by ICAM-1-mediated enzyme replacement. Mol Pharm 2014;11:2887–95. https://doi.org/10.1021/mp500241y.
[761] Murray JM, Thompson AM, Vitsky A, Hawes M, Chuang WL, Pacheco J, et al. Nonclinical safety assessment of recombinant human acid sphingomyelinase (rhASM) for the treatment of acid sphingomyelinase deficiency: The utility of animal models of disease in the toxicological evaluation of potential therapeutics. Mol Genet Metab 2015;114:217–25. https://doi.org/10.1016/j.ymgme.2014.07.005.
[762] McGovern MM, Wasserstein MP, Kirmse B, Duvall WL, Schiano T, Thurberg BL, et al. Novel first-dose adverse drug reactions during a phase I trial of olipudase alfa (recombinant human acid sphingomyelinase) in adults with Niemann-Pick disease type B (acid sphingomyelinase deficiency). Genet Med 2016;18:34–40. https://doi.org/10.1038/gim.2015.24.
[763] Patterson MC, Dibisceglie AM, Higgins JJ, Abel RB, Schiffmann R, Parker CC, et al. The effect of cholesterol-lowering agents on hepatic and plasma-cholesterol in Niemann-Pick disease type-C. Neurology 1993;43:61–4. https://doi.org/10.1212/WNL.43.1_Part_1.61.
[764] Hughes AB, Rudge AJ. Deoxynojirimycin - synthesis and biological-activity. Nat Prod Rep 1994;11:135–62. https://doi.org/10.1039/np9941100135.
[765] Platt FM, Neises GR, Dwek RA, Butters TD. N-butyldeoxynojirimycin is a novel inhibitor of glycolipid biosynthesis. J Biol Chem 1994;269:8362–5.
[766] Cox T, Lachmann R, Hollak C, Aerts J, van Weely S, Hrebicek M, et al. Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. Lancet 2000;355:1481–5. https://doi.org/10.1016/s0140-6736(00)02161-9.
[767] Zervas M, Somers KL, Thrall MA, Walkley SU. Critical role for glycosphingolipids in Niemann-Pick disease type C. Curr Biol 2001;11:1283–7. https://doi.org/10.1016/s0960-9822(01)00396-7.
[768] Stein VM, Crooks A, Ding W, Prociuk M, O'Donnell P, Bryan C, et al. Miglustat improves purkinje cell survival and alters microglial phenotype in feline niemann-pick disease type C. J.Neuropathol.Exp.Neurol. 2012;71:434–48.
[769] Nietupski JB, Pacheco JJ, Chuang WL, Maratea K, Li L, Foley J, et al. Iminosugar-based inhibitors of glucosylceramide synthase prolong survival but paradoxically increase brain glucosylceramide levels in Niemann-Pick C mice. Mol.Genet.Metab 2012;105:621–8.
[770] Ridley CM, Thur KE, Shanahan J, Thillaiappan NB, Shen A, Uhl K, et al. beta-Glucosidase 2 (GBA2) activity and imino sugar pharmacology. J Biol Chem 2013;288:26052–66. https://doi.org/10.1074/jbc.M113.463562.
[771] Camargo F, Erickson RP, Garver WS, Hossain GS, Carbone PN, Heidenreich RA, et al. Cyclodextrins in the treatment of a mouse model of Niemann-Pick C disease. Life Sci 2001;70:131–42. https://doi.org/10.1016/s0024-3205(01)01384-4.
[772] Griffin LD, Gong W, Verot L, Mellon SH. Niemann-Pick type C disease involves disrupted neurosteroidogenesis and responds to allopregnanolone. Nat Med 2004;10:704–11. https://doi.org/10.1038/nm1073.
[773] Liu B, Li H, Repa JJ, Turley SD, Dietschy JM. Genetic variations and treatments that affect the lifespan of the NPC1 mouse. J Lipid Res 2008;49:663–9.
[774] Abi-Mosleh L, Infante RE, Radhakrishnan A, Goldstein JL, Brown MS. Cyclodextrin overcomes deficient lysosome-to-endoplasmic reticulum transport of cholesterol in Niemann-Pick type C cells. Proc Natl Acad Sci USA 2009;106:19316–21. https://doi.org/10.1073/pnas.0910916106.
[775] Davidson CD, Ali NF, Micsenyi MC, Stephney G, Renault S, Dobrenis K, et al. Chronic cyclodextrin treatment of murine Niemann-Pick C disease ameliorates

neuronal cholesterol and glycosphingolipid storage and disease progression. PloS One 2009;4:e6951.
[776] Leau O, Ducrot R. Action de lacetylleucine sur le vertige experimental de la souris. Compt Rend Seances Soc Biol Ses Filiales 1957;151:1365–7.
[777] Bremova T, Malinová V, Amraoui Y, Mengel E, Reinke J, Kolníková M, et al. Acetyl-dl-leucine in Niemann-Pick type C: A case series. Neurology 2015;85: 1368–75. https://doi.org/10.1212/wnl.0000000000002041.
[778] Kaya E, Smith DA, Smith C, Morris L, Bremova-Ertl T, Cortina-Borja M, et al. Acetyl-leucine slows disease progression in lysosomal storage disorders. Brain Commun 2021:3. https://doi.org/10.1093/braincomms/fcaa148.
[779] Fields T, Patterson M, Bremova-Ertl T, Belcher G, Billington I, Churchill GC, et al. A master protocol to investigate a novel therapy acetyl-l-leucine for three ultra-rare neurodegenerative diseases: Niemann-Pick type C, the GM2 gangliosidoses, and ataxia telangiectasia. Trials 2021:22. https://doi.org/10.1186/s13063-020-05009-3.
[780] Churchill GC, Strupp M, Factor C, Bremova-Ertl T, Factor M, Patterson MC, et al. Acetylation turns leucine into a drug by membrane transporter switching. Sci Rep 2021:11. https://doi.org/10.1038/s41598-021-95255-5.
[781] Vigh L, Literati PN, Horvath I, Torok Z, Balogh G, Glatz A, et al. Bimoclomol: A nontoxic, hydroxylamine derivative with stress protein-inducing activity and cytoprotective effects. Nat Med 1997;3:1150–4. https://doi.org/10.1038/nm1097-1150.
[782] Kieran D, Kalmar B, Dick JRT, Riddoch-Contreras J, Burnstock G, Greensmith L. Treatment with arimoclomol, a coinducer of heat shock proteins, delays disease progression in ALS mice. Nat Med 2004;10:402–5. https://doi.org/10.1038/nm1021.
[783] Kirkegaard T, Gray J, Priestman DA, Wallom KL, Atkins J, Olsen OD, et al. Heat shock protein-based therapy as a potential candidate for treating the sphingolipidoses. Sci Transl Med 2016;8:355ra118. https://doi.org/10.1126/scitranslmed.aad9823.
[784] Sakiyama T, Tsuda M, Owada M, Joh K, Miyawaki S, Kitagawa T. Bone-marrow transplantation for Niemann-Pick mice. Biochem Biophys Res Commun 1983;113: 605–10. https://doi.org/10.1016/0006-291x(83)91769-2.
[785] Smanik EJ, Tavill AS, Jacobs GH, Schafer IA, Farquhar L, Weber FL, et al. Orthotopic liver-transplantation in 2 adults with Niemann-Pick and gauchers diseases - implications for the treatment of inherited metabolic disease. Hepatology 1993;17:42–9. https://doi.org/10.1002/hep.1840170109.
[786] Vellodi A, Hobbs JR, Odonnell NM, Coulter BS, Hughjones K. Treatment of Niemann-Pick disease type-B by allogeneic bone-marrow transplantation. Br Med J 1987;295:1375–6. https://doi.org/10.1136/bmj.295.6610.1375.
[787] Bayever E, Kamani N, Ferreira P, Machin GA, Yudkoff M, Conard K, et al. Bone-marrow transplantation for Niemann-Pick type-1A disease. J Inherit Metab Dis 1992;15:919–28. https://doi.org/10.1007/bf01800234.
[788] Miranda SRP, Erlich S, Visser JWM, Gatt S, Dagan A, Friedrich VL, et al. Bone marrow transplantation in acid sphingomyelinase-deficient mice: Engraftment and cell migration into the brain as a function of radiation, age, and phenotype. Blood 1997;90:444–52.
[789] Miranda SRP, Erlich S, Friedrich VL, Gatt S, Schuchman EH. Hematopoietic stem cell gene therapy leads to marked visceral organ improvements and a delayed onset of neurological abnormalities in the acid sphingomyelinase deficient mouse model of Niemann-Pick disease. Gene Ther 2000;7:1768–76. https://doi.org/10.1038/sj.gt.3301300.
[790] Scaggiante B, Pineschi A, Sustersich M, Andolina M, Agosti E, Romeo D. Successful therapy of Niemann-Pick disease by implantation of human amniotic membrane. Transplantation 1987;44:59–61. https://doi.org/10.1097/00007890-198707000-00014.
[791] Bembi B, Comelli M, Scaggiante B, Pineschi A, Rapelli S, Gornati R, et al. Treatment of sphingomyelinase deficiency by repeated implantations of amniotic epithelial-cells. Am J Med Genet 1992;44:527–33. https://doi.org/10.1002/ajmg.1320440430.
[792] Sidman RL, Li JX, Stewart GR, Clarke J, Yang W, Snyder EY, et al. Injection of mouse and human neural stem cells into neonatal Niemann-Pick A model mice. Brain Res 2007;1140:195–204. https://doi.org/10.1016/j.brainres.2007.01.011.
[793] Barbon CM, Ziegler RJ, Li C, Armentano D, Cherry M, Desnick RJ, et al. AAV8-Mediated hepatic expression of acid sphingomyelinase corrects the metabolic defect in the visceral organs of a mouse model of Niemann-Pick disease. Mol Ther 2005;12:431–40. https://doi.org/10.1016/j.ymthe.2005.03.011.
[794] Passini MA, Macauley SL, Huff MR, Taksir TV, Bu J, Wu IH, et al. AAV vector-mediated correction of brain pathology in a mouse model of Niemann-Pick A disease. Mol Ther 2005;11:754–62. https://doi.org/10.1016/j.ymthe.2005.01.011.
[795] Dodge JC, Clarke J, Song A, Bu J, Yang WD, Taksir TV, et al. Gene transfer of human acid sphingomyelinase corrects neuropathology and motor deficits in a mouse model of Niemann-Pick type A disease. Proc Natl Acad Sci U S A 2005;102: 17822–7. https://doi.org/10.1073/pnas.0509062102.
[796] Bu J, Ashe KM, Bringas J, Marshall J, Dodge JC, Cabrera-Salazar MA, et al. Merits of combination cortical, subcortical, and cerebellar injections for the treatment of Niemann-Pick disease type A. Mol Ther 2012;20:1893–901. https://doi.org/10.1038/mt.2012.118.
[797] Samaranch L, Perez-Canamas A, Soto-Huelin B, Sudhakar V, Jurado-Arjona J, Hadaczek P, et al. Adeno-associated viral vector serotype 9-based gene therapy for Niemann-Pick disease type A. Sci Transl Med 2019:11. https://doi.org/10.1126/scitranslmed.aat3738.
[798] Ziegler RJ, Brown C, Barbon CM, D'Angona AM, Schuchman EH, Andrews L, et al. Pulmonary delivery of recombinant acid sphingomyelinase improves clearance of lysosomal sphingomyelin from the lungs of a murine model of Niemann-Pick disease. Mol Genet Metab 2009;97:35–42. https://doi.org/10.1016/j.ymgme.2009.01.008.
[799] Wasserstein MP, Jones SA, Soran H, Diaz GA, Lippa N, Thurberg BL, et al. Successful within-patient dose escalation of olipudase alfa in acid sphingomyelinase deficiency. Mol Genet Metab 2015;116:88–97. https://doi.org/10.1016/j.ymgme.2015.05.013.
[800] Thurberg BL, Wasserstein MP, Jones SA, Schiano TD, Cox GF, Puga AC. Clearance of hepatic sphingomyelin by olipudase alfa is associated with improvement in lipid profiles in acid sphingomyelinase deficiency. Am J Surg Pathol 2016;40: 1232–42. https://doi.org/10.1097/pas.0000000000000659.
[801] Wasserstein MP, Diaz GA, Lachmann RH, Jouvin MH, Nandy I, Ji AJ, et al. Olipudase alfa for treatment of acid sphingomyelinase deficiency (ASMD): safety and efficacy in adults treated for 30 months. J Inherit Metab Dis 2018;41:829–38. https://doi.org/10.1007/s10545-017-0123-6.
[802] Thurberg BL, Diaz GA, Lachmann RH, Schiano T, Wasserstein MP, Ji AJ, et al. Long-term efficacy of olipudase alfa in adults with acid sphingomyelinase deficiency (ASMD): Further clearance of hepatic sphingomyelin is associated with additional improvements in pro- and anti-atherogenic lipid profiles after 42 months of treatment. Mol Genet Metab 2020;131:245–52. https://doi.org/10.1016/j.ymgme.2020.06.010.
[803] Diaz GA, Giugliani R, Guffon N, Jones SA, Mengel E, Scarpa M, et al. Long-term safety and clinical outcomes of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency: two-year results. Orphanet J Rare Dis 2022:17. https://doi.org/10.1186/s13023-022-02587-0.
[804] Wasserstein M, Lachmann R, Hollak C, Arash-Kaps L, Barbato A, Gallagher RC, et al. A randomized, placebo-controlled clinical trial evaluating olipudase alfa enzyme replacement therapy for chronic acid sphingomyelinase deficiency (ASMD) in adults: One-year results. Genet Med 2022. https://doi.org/10.1016/j.gim.2022.03.021.
[805] Trovò L, Stroobants S, D'Hooge R, Ledesma MD, Dotti CG. Improvement of biochemical and behavioral defects in the Niemann–Pick type A mouse by intraventricular infusion of MARCKS. Neurobiol Dis 2015;73:319–26. https://doi.org/10.1016/j.nbd.2014.09.008.
[806] Schultz ML, Fawaz MV, Azaria RD, Hollon TC, Liu EA, Kunkel TJ, et al. Synthetic high-density lipoprotein nanoparticles for the treatment of Niemann-Pick diseases. BMC Med 2019;17:200. https://doi.org/10.1186/s12916-019-1423-5.
[807] Erickson RP, Garver WS, Camargo F, Hossain GS, Heidenreich RA. Pharmacological and genetic modifications of somatic cholesterol do not substantially alter the course of CNS disease in Niemann-Pick C mice. J Inherit Metab Dis 2000;23:54–62. https://doi.org/10.1023/a:1005650930330.
[808] Reid PC, Lin S, Vanier MT, Ohno-Iwashita Y, Harwood HJ, Hickey WE, et al. Partial blockage of sterol biosynthesis with a squalene synthase inhibitor in early postnatal Niemann-Pick type C npc(nih) null mice brains reduces neuronal cholesterol accumulation, abrogates astrogliosis, but may inhibit myelin maturation. J Neurosci Methods 2008;168:15–25. https://doi.org/10.1016/j.jneumeth.2007.09.002.
[809] Somers KL, Brown DE, Fulton R, Schultheiss PC, Hamar D, Smith MO, et al. Effects of dietary cholesterol restriction in a feline model of Niemann-Pick type C disease. J Inherit Metab Dis 2001;24:427–36. https://doi.org/10.1023/a:1010588112003.
[810] Liu B, Turley SD, Burns DK, Miller AM, Repa JJ, Dietschy JM. Reversal of defective lysosomal transport in NPC disease ameliorates liver dysfunction and neurodegeneration in the npc1-/- mouse. Proc Natl Acad Sci USA 2009;106: 2377–82.
[811] Ramirez CM, Liu B, Taylor AM, Repa JJ, Burns DK, Weinberg AG, et al. Weekly cyclodextrin administration normalizes cholesterol metabolism in nearly every organ of the Niemann-Pick type C1 mouse and markedly prolongs life. Pediatr. Res. 2010;68:309–15.
[812] Rosenbaum AI, Zhang G, Warren JD, Maxfield FR. Endocytosis of beta-cyclodextrins is responsible for cholesterol reduction in Niemann-Pick type C mutant cells. Proc Natl Acad Sci USA 2010;107:5477–82.
[813] Aqul A, Liu B, Ramirez CM, Pieper AA, Estill SJ, Burns DK, et al. Unesterified cholesterol accumulation in late endosomes/lysosomes causes neurodegeneration and is prevented by driving cholesterol export from this compartment. J.Neurosci. 2011;31:9404–13. https://doi.org/10.1523/JNEUROSCI.1317-11.2011.
[814] Vite CH, Bagel JH, Swain GP, Prociuk M, Sikora TU, Stein VM, et al. Intracisternal cyclodextrin prevents cerebellar dysfunction and Purkinje cell death in feline Niemann-Pick type C1 disease. Sci Transl Med 2015;7:276ra26.
[815] Ory DS, Ottinger EA, Farhat NY, King KA, Jiang X, Weissfeld L, et al. Intrathecal 2-hydroxypropyl-β-cyclodextrin decreases neurological disease progression in Niemann-Pick disease, type C1: a non-randomised, open-label, phase 1-2 trial. Lancet 2017;390:1758–68. https://doi.org/10.1016/s0140-6736(17)31465-4.
[816] Farmer CA, Thurm A, Farhat N, Bianconi S, Keener LA, Porter FD. Long-term neuropsychological outcomes from an open-label phase I/IIa trial of 2-hydroxy-propyl-beta-cyclodextrins (VTS-270) in Niemann-Pick disease, type C1. CNS Drugs 2019;33:677–83. https://doi.org/10.1007/s40263-019-00642-2.
[817] Hastings C, Vieira C, Liu B, Bascon C, Gao C, Wang RY, et al. Expanded access with intravenous hydroxypropyl-beta-cyclodextrin to treat children and young adults with Niemann-Pick disease type C1: a case report analysis. Orphanet J Rare Dis 2019:14. https://doi.org/10.1186/s13023-019-1207-1.
[818] Hastings C, Liu B, Hurst B, Cox GF, Hrynkow S. Intravenous 2-hydroxypropyl-beta-cyclodextrin (Trappsol Cyclo) demonstrates biological activity and impacts cholesterol metabolism in the central nervous system and peripheral tissues in adult subjects with Niemann-Pick Disease Type C1: results of a phase 1 trial. Mol Genet Metab 2022;137:309–19. https://doi.org/10.1016/j.ymgme.2022.10.004.

[819] Patterson MC, Vecchio D, Prady H, Abel L, Wraith JE. Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. Lancet Neurol 2007;6:765–72.
[820] Patterson MC, Vecchio D, Jacklin E, Abel L, Chadha-Boreham H, Luzy C, et al. Long-term miglustat therapy in children with Niemann-Pick disease type C. J Child Neurol 2010;25:300–5. https://doi.org/10.1177/0883073809344222.
[821] Wraith JE, Vecchio D, Jacklin E, Abel L, Chadha-Boreham H, Luzy C, et al. Miglustat in adult and juvenile patients with Niemann Pick disease type C: long-term data from a clinical trial. Mol Genet Metab 2010;99:351–7. https://doi.org/10.1016/j.ymgme.2009.12.006.
[822] Fecarotta S, Romano A, Della Casa R, Del Giudice E, Bruschini D, Mansi G, et al. Long term follow-up to evaluate the efficacy of miglustat treatment in Italian patients with Niemann-Pick disease type C. Orphanet J Rare Dis 2015;10:22. https://doi.org/10.1186/s13023-015-0240-y.
[823] Patterson MC, Garver WS, Giugliani R, Imrie J, Jahnova H, Meaney FJ, et al. Long-term survival outcomes of patients with Niemann-Pick disease type C receiving miglustat treatment: A large retrospective observational study. J Inherit Metab Dis 2020;43:1060–9. https://doi.org/10.1002/jimd.12245.
[824] Erickson RP, Bernard O. Studies on neuronal death in the mouse model of Niemann-Pick C disease. J Neurosci Res 2002;68:738–44. https://doi.org/10.1002/jnr.10257.
[825] Choudhury A, Dominguez M, Puri V, Sharma DK, Narita K, Wheatley CL, et al. Rab proteins mediate Golgi transport of caveola-internalized glycosphingolipids and correct lipid trafficking in Niemann-Pick C cells. J Clin Invest 2002;109:1541–50. https://doi.org/10.1172/jci15420.
[826] Bascuñan-Castillo EC, Erickson RP, Howison CM, Hunter RJ, Heidenreich RH, Hicks C, et al. Tamoxifen and vitamin E treatments delay symptoms in the mouse model of Niemann-Pick C. J Appl Genet 2004;45:461–7.
[827] Xu M, Liu K, Swaroop M, Porter FD, Sidhu R, Firnkes S, et al. δ-Tocopherol reduces lipid accumulation in Niemann-Pick type C1 and Wolman cholesterol storage disorders. J Biol Chem 2012;287:39349–60. https://doi.org/10.1074/jbc.M112.357707.
[828] Marín T, Contreras P, Castro JF, Chamorro D, Balboa E, Bosch-Morató M, et al. Vitamin E dietary supplementation improves neurological symptoms and decreases c-Abl/p73 activation in Niemann-Pick C mice. Nutrients 2014;6:3000–17. https://doi.org/10.3390/nu6083000.
[829] Langmade SJ, Gale SE, Frolov A, Mohri I, Suzuki K, Mellon SH, et al. Pregnane X receptor (PXR) activation: a mechanism for neuroprotection in a mouse model of Niemann-Pick C disease. Proc Natl Acad Sci U S A 2006;103:13807–12. https://doi.org/10.1073/pnas.0606218103.
[830] Repa JJ, Li H, Frank-Cannon TC, Valasek MA, Turley SD, Tansey MG, et al. Liver X receptor activation enhances cholesterol loss from the brain, decreases neuroinflammation, and increases survival of the NPC1 mouse. J.Neurosci. 2007;27:14470–80.
[831] Pagler TA, Neuhofer A, Laggner H, Strobl W, Stangl H. Cholesterol efflux via HDL resecretion occurs when cholesterol transport out of the lysosome is impaired. J Lipid Res 2007;48:2141–50. https://doi.org/10.1194/jlr.M700056-JLR200.
[832] Pipalia NH, Cosner CC, Huang A, Chatterjee A, Bourbon P, Farley N, et al. Histone deacetylase inhibitor treatment dramatically reduces cholesterol accumulation in Niemann-Pick type C1 mutant human fibroblasts. Proc Natl Acad Sci U S A 2011;108:5620–5. https://doi.org/10.1073/pnas.1014890108.
[833] Newton J, Hait NC, Maceyka M, Colaco A, Maczis M, Wassif CA, et al. FTY720/fingolimod increases NPC1 and NPC2 expression and reduces cholesterol and sphingolipid accumulation in Niemann-Pick type C mutant fibroblasts. FASEB J 2017;31:1719–30. https://doi.org/10.1096/fj.201601041R.
[834] Ahmad I, Hunter RE, Flax JD, Snyder EY, Erickson RP. Neural stem cell implantation extends life in Niemann-Pick C1 mice. J Appl Genet 2007;48:269–72. https://doi.org/10.1007/bf03195222.
[835] Bae JS, Han HS, Youn DH, Carter JE, Modo M, Schuchman EH, et al. Bone marrow-derived mesenchymal stem cells promote neuronal networks with functional synaptic transmission after transplantation into mice with neurodegeneration. Stem Cells 2007;25:1307–16. https://doi.org/10.1634/stemcells.2006-0561.
[836] Bae JS, Carter JE, Jin HK. Adipose tissue-derived stem cells rescue Purkinje neurons and alleviate inflammatory responses in Niemann-Pick disease type C mice. Cell Tissue Res 2010;340:357–69. https://doi.org/10.1007/s00441-010-0942-3.
[837] Lee H, Bae JS, Jin HK. Human umbilical cord blood-derived mesenchymal stem cells improve neurological abnormalities of Niemann-Pick type C mouse by modulation of neuroinflammatory condition. J Vet Med Sci 2010;72:709–17. https://doi.org/10.1292/jvms.09-0495.
[838] Zhang M, Hallows JL, Wang X, Bu B, Wang W, Vincent I. Mitogen-activated protein kinase activity may not be necessary for the neuropathology of Niemann-Pick type C mice. J Neurochem 2008;107:814–22. https://doi.org/10.1111/j.1471-4159.2008.05657.x.
[839] Chevallier J, Chamoun Z, Jiang GW, Prestwich G, Sakai N, Matile S, et al. Lysobisphosphatidic acid controls endosomal cholesterol levels. J Biol Chem 2008;283:27871–80. https://doi.org/10.1074/jbc.M801463200.
[840] Moreau D, Vacca F, Vossio S, Scott C, Colaco A, Paz Montoya J, et al. Drug-induced increase in lysobisphosphatidic acid reduces the cholesterol overload in Niemann-Pick type C cells and mice. EMBO Rep 2019;20:e47055. https://doi.org/10.15252/embr.201847055.
[841] Ilnytska O, Jeziorek M, Lai K, Altan-Bonnet N, Dobrowolski R, Storch J. Lysobisphosphatidic acid (LBPA) enrichment promotes cholesterol egress via exosomes in Niemann Pick type C1 deficient cells. Biochim Biophys Acta Mol Cell Biol Lipids 2021;1866:158916. https://doi.org/10.1016/j.bbalip.2021.158916.
[842] Alvarez AR, Klein A, Castro J, Cancino GI, Amigo J, Mosqueira M, et al. Imatinib therapy blocks cerebellar apoptosis and improves neurological symptoms in a mouse model of Niemann-Pick type C disease. FASEB J 2008;22:3617–27. https://doi.org/10.1096/fj.07-102715.
[843] Borbon IA, Hillman Z, Duran Jr E, Kiela PR, Frautschy SA, Erickson RP. Lack of efficacy of curcumin on neurodegeneration in the mouse model of Niemann-Pick C1. Pharmacol Biochem Behav 2012;101:125–31. https://doi.org/10.1016/j.pbb.2011.12.009.
[844] Efthymiou AG, Steiner J, Pavan WJ, Wincovitch S, Larson DM, Porter FD, et al. Rescue of an in vitro neuron phenotype identified in Niemann-Pick disease, type C1 induced pluripotent stem cell-derived neurons by modulating the WNT pathway and calcium signaling. Stem Cells Transl Med 2015;4:230–8. https://doi.org/10.5966/sctm.2014-0127.
[845] Garcia-Seisdedos D, Babiy B, Lerma M, Casado ME, Martinez-Botas J, Lasuncion MA, et al. Curcumin stimulates exosome/microvesicle release in an in vitro model of intracellular lipid accumulation by increasing ceramide synthesis. Biochim Biophys Acta 2020:1865. https://doi.org/10.1016/j.bbalip.2020.158638.
[846] Smith D, Wallom KL, Williams IM, Jeyakumar M, Platt FM. Beneficial effects of anti-inflammatory therapy in a mouse model of Niemann-Pick disease type C1. Neurobiol Dis 2009;36:242–51. https://doi.org/10.1016/j.nbd.2009.07.010.
[847] Hao Y, Pan D, Zhang M, Xu J, Li L, Wei J, et al. The neuroprotective effects of cyclin-dependent kinase-5 inhibition in mice with Niemann-Pick disease type C. J Huazhong Univ Sci Technolog Med Sci 2009;29:324–9. https://doi.org/10.1007/s11596-009-0312-0.
[848] Chen FW, Li C, Ioannou YA. Cyclodextrin induces calcium-dependent lysosomal exocytosis. PloS One 2010;5:e15054. https://doi.org/10.1371/journal.pone.0015054.
[849] Cao Q, Zhong XZ, Zou Y, Zhang Z, Toro L, Dong XP. BK Channels alleviate lysosomal storage diseases by providing positive feedback regulation of lysosomal Ca2+ release. Dev Cell 2015;33:427–41. https://doi.org/10.1016/j.devcel.2015.04.010.
[850] Vacca F, Vossio S, Mercier V, Moreau D, Johnson S, Scott CC, et al. Cyclodextrin triggers MCOLN1-dependent endo-lysosome secretion in Niemann-Pick type C cells. J Lipid Res 2019;60:832–43. https://doi.org/10.1194/jlr.M089979.
[851] Feltes M, Gale SE, Moores S, Ory DS, Schaffer JE. Monitoring the itinerary of lysosomal cholesterol in Niemann-Pick Type C1-deficient cells after cyclodextrin treatment. J Lipid Res 2020;61:403–12. https://doi.org/10.1194/jlr.RA119000571.
[852] Arguello G, Balboa E, Tapia PJ, Castro J, Yanez MJ, Mattar P, et al. Genistein activates transcription factor EB and corrects Niemann-Pick C phenotype. Int J Mol Sci 2021:22. https://doi.org/10.3390/ijms22084220.
[853] Barthelemy A, Demais V, Stancu I-C, Vasile E, Houben T, Reber M, et al. Glial contribution to cyclodextrin-mediated reversal of cholesterol accumulation in murine NPC1-deficient neurons in vivo. Neurobiol Dis 2021;158:105469. https://doi.org/10.1016/j.nbd.2021.105469.
[854] Kuo SY, Castoreno AB, Aldrich LN, Lassen KG, Goel G, Dančík V, et al. Small-molecule enhancers of autophagy modulate cellular disease phenotypes suggested by human genetics. Proc Natl Acad Sci U S A 2015;112:E4281–7. https://doi.org/10.1073/pnas.1512289112.
[855] Fu R, Wassif CA, Yanjanin NM, Watkins-Chow DE, Baxter LL, Incao A, et al. Efficacy of N-acetylcysteine in phenotypic suppression of mouse models of Niemann-Pick disease, type C1. Hum Mol Genet 2013;22:3508–23. https://doi.org/10.1093/hmg/ddt206.
[856] Argüello G, Martinez P, Peña J, Chen O, Platt F, Zanlungo S, et al. Hepatic metabolic response to restricted copper intake in a Niemann-Pick C murine model. Metallomics 2014;6:1527–39. https://doi.org/10.1039/c4mt00056k.
[857] Seo Y, Shin Y, Kim HS, Kang I, Hong IS, Choi SW, et al. Donepezil enhances Purkinje cell survival and alleviates motor dysfunction by inhibiting cholesterol synthesis in a murine model of Niemann Pick disease type C. J Neuropathol Exp Neurol 2014;73:234–43. https://doi.org/10.1097/nen.0000000000000045.
[858] Williams IM, Wallom KL, Smith DA, Al Eisa N, Smith C, Platt FM. Improved neuroprotection using miglustat, curcumin and ibuprofen as a triple combination therapy in Niemann-Pick disease type C1 mice. Neurobiol Dis 2014;67:9–17. https://doi.org/10.1016/j.nbd.2014.03.001.
[859] Bremova-Ertl T, Claassen J, Foltan T, Gascon-Bayarri J, Gissen P, Hahn A, et al. Efficacy and safety of N-acetyl-l-leucine in Niemann-Pick disease type C. J Neurol 2022;269:1651–62. https://doi.org/10.1007/s00415-021-10717-0.
[860] Cougnoux A, Cluzeau C, Mitra S, Li R, Williams I, Burkert K, et al. Necroptosis in Niemann-Pick disease, type C1: a potential therapeutic target. Cell Death Dis 2016;7:e2147. https://doi.org/10.1038/cddis.2016.16.
[861] Cougnoux A, Clifford S, Salman A, Ng SL, Bertin J, Porter FD. Necroptosis inhibition as a therapy for Niemann-Pick disease, type C1: Inhibition of RIP kinases and combination therapy with 2-hydroxypropyl-β-cyclodextrin. Mol Genet Metab 2018;125:345–50. https://doi.org/10.1016/j.ymgme.2018.10.009.
[862] Gray J, Fernández-Suárez ME, Falah M, Smith D, Smith C, Kaya E, et al. Heat shock protein amplification improves cerebellar myelination in the Npc1nih mouse model. eBioMedicine 2022;86:104374. https://doi.org/10.1016/j.ebiom.2022.104374.
[863] Mengel E, Patterson MC, Da Riol RM, Del Toro M, Deodato F, Gautschi M, et al. Efficacy and safety of arimoclomol in Niemann-Pick disease type C: Results from a double-blind, randomised, placebo-controlled, multinational phase 2/3 trial of a novel treatment. J Inherit Metab Dis 2021;44:1463–80. https://doi.org/10.1002/jimd.12428.

[864] Xie C, Gong XM, Luo J, Li BL, Song BL. AAV9-NPC1 significantly ameliorates Purkinje cell death and behavioral abnormalities in mouse NPC disease. J Lipid Res 2017;58:512–8. https://doi.org/10.1194/jlr.M071274.
[865] Chandler RJ, Williams IM, Gibson AL, Davidson CD, Incao AA, Hubbard BT, et al. Systemic AAV9 gene therapy improves the lifespan of mice with Niemann-Pick disease, type C1. Hum Mol Genet 2017;26:52–64. https://doi.org/10.1093/hmg/ddw367.
[866] Hughes MP, Smith DA, Morris L, Fletcher C, Colaco A, Huebecker M, et al. AAV9 intracerebroventricular gene therapy improves lifespan, locomotor function and pathology in a mouse model of Niemann-Pick type C1 disease. Hum Mol Genet 2018;27:3079–98. https://doi.org/10.1093/hmg/ddy212.
[867] Markmann S, RJ JC, Rosenberg JB, De BP, Kaminsky SM, Crystal RG, et al. Attenuation of the Niemann-Pick type C2 disease phenotype by intracisternal administration of an AAVrh.10 vector expressing Npc2. Exp Neurol 2018;306:22–33. https://doi.org/10.1016/j.expneurol.2018.04.001.
[868] Levy JM, Yeh WH, Pendse N, Davis JR, Hennessey E, Butcher R, et al. Cytosine and adenine base editing of the brain, liver, retina, heart and skeletal muscle of mice via adeno-associated viruses. Nat Biomed Eng 2020;4:97–110. https://doi.org/10.1038/s41551-019-0501-5.
[869] Davidson CD, Gibson AL, Gu T, Baxter LL, Deverman BE, Beadle K, et al. Improved systemic AAV gene therapy with a neurotrophic capsid in Niemann-Pick disease type C1 mice. Life Sci Allianc 2021:4. https://doi.org/10.26508/lsa.202101040.
[870] Kurokawa Y, Osaka H, Kouga T, Jimbo E, Muramatsu K, Nakamura S, et al. Gene therapy in a mouse model of Niemann-Pick disease type C1. Hum Gene Ther 2021. https://doi.org/10.1089/hum.2020.175.
[871] Ferrante A, Pezzola A, Matteucci A, Di Biase A, Attorri L, Armida M, et al. The adenosine A(2A) receptor agonist T1-11 ameliorates neurovisceral symptoms and extends the lifespan of a mouse model of Niemann-Pick type C disease. Neurobiol Dis 2018;110:1–11. https://doi.org/10.1016/j.nbd.2017.10.013.
[872] Pepponi R, De Simone R, De Nuccio C, Visentin S, Matteucci A, Bernardo A, et al. Repurposing dipyridamole in Niemann Pick type C disease: a proof of concept study. Int J Mol Sci 2022:23. https://doi.org/10.3390/ijms23073456.
[873] Feng X, Bader BM, Yang F, Segura M, Schultz L, Schrooder OHU, et al. Improvement of impaired electrical activity in NPC1 mutant cortical neurons upon DHPG stimulation detected by micro-electrode array. Brain Res 2018;1694:87–93. https://doi.org/10.1016/j.brainres.2018.05.009.
[874] Kulkarni A, Caporali P, Dolas A, Johny S, Goyal S, Dragotto J, et al. Linear cyclodextrin polymer prodrugs as novel therapeutics for Niemann-Pick type C1 disorder. Sci Rep 2018;8:9547. https://doi.org/10.1038/s41598-018-27926-9.
[875] Houben T, Magro Dos Reis I, Oligschlaeger Y, Steinbusch H, Gijbels MJJ, Hendrikx T, et al. Pneumococcal immunization reduces neurological and hepatic symptoms in a mouse model for Niemann-Pick type C1 disease. Front Immunol 2018;9:3089. https://doi.org/10.3389/fimmu.2018.03089.
[876] Yasmin N, Ishitsuka Y, Fukaura M, Yamada Y, Nakahara S, Ishii A, et al. In vitro and in vivo evaluation of 6-O-α-maltosyl-β-cyclodextrin as a potential therapeutic agent against Niemann-Pick disease type C. Int J Mol Sci 2019:20. https://doi.org/10.3390/ijms20051152.
[877] Park MH, Choi BJ, Jeong MS, Lee JY, Jung IK, Park KH, et al. Characterization of the subventricular-thalamo-cortical circuit in the NP-C mouse brain, and new insights regarding treatment. Mol Ther 2019;27:1507–26. https://doi.org/10.1016/j.ymthe.2019.05.008.
[878] Gascon-Bayarri J, Simon PC, Llop R, Carnaval T, Ledesma MD, Rico I, et al. Efficacy and safety clinical trial with efavirenz in patients diagnosed with adult Niemann-pick type C with cognitive impairment. Medicine 2022:101. https://doi.org/10.1097/md.0000000000031471.
[879] Hung YH, Lotan A, Yeshurun S, Schroeder A, Bush AI. Iron chelation by deferiprone does not rescue the Niemann-Pick Disease Type C1 mouse model. Biometals 2020;33:87–95. https://doi.org/10.1007/s10534-020-00233-5.
[880] Jiang D, Lee H, Pardridge WM. Plasmid DNA gene therapy of the Niemann-Pick C1 mouse with transferrin receptor-targeted Trojan horse liposomes. Sci Rep 2020;10:13334. https://doi.org/10.1038/s41598-020-70290-w.
[881] Han SQ, Zhang HW, Yi MN, Liu XQ, Maegawa GHB, Zou YD, et al. Potential disease-modifying effects of lithium carbonate in Niemann-Pick disease, type C1. Front Pharmacol 2021:12. https://doi.org/10.3389/fphar.2021.667361.
[882] Pipalia NH, Saad SZ, Subramanian K, Cross A, Al-Motawa A, Garg K, et al. HSP90 inhibitors reduce cholesterol storage in Niemann-Pick type C1 mutant fibroblasts. J Lipid Res 2021:62. https://doi.org/10.1016/j.jlr.2021.100114.
[883] Van Hoecke L, Van Cauwenberghe C, Boerger V, Bruggeman A, Castelein J, Van Imschoot G, et al. Anti-inflammatory mesenchymal stromal cell-derived extracellular vesicles improve pathology in Niemann-Pick type C disease. Biomedicines 2021:9. https://doi.org/10.3390/biomedicines9121864.
[884] Kang I, Yoo JM, Kim D, Kim J, Cho MK, Lee SE, et al. Graphene quantum dots alleviate impaired functions in Niemann-Pick disease type C in vivo. Nano Lett 2021;21:2339–46. https://doi.org/10.1021/acs.nanolett.0c03741.
[885] Scotto Rosato A, Krogsaeter EK, Jaślan D, Abrahamian C, Montefusco S, Soldati C, et al. TPC2 rescues lysosomal storage in mucolipidosis type IV, Niemann–Pick type C1, and Batten disease. EMBO Mol Med 2022;14:e15377. https://doi.org/10.15252/emmm.202115377.
[886] Furtado D, Cortez-Jugo C, Hung YH, Bush AI, Caruso F. mRNA treatment rescues Niemann-Pick disease type C1 in patient fibroblasts. Mol Pharm 2022;19:3987–99. https://doi.org/10.1021/acs.molpharmaceut.2c00463.
[887] Diaz GA, Jones SA, Scarpa M, Mengel KE, Giugliani R, Guffon N, et al. One-year results of a clinical trial of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency. Genet Med 2021;23:1543–50. https://doi.org/10.1038/s41436-021-01156-3.
[888] Yanez MJ, Marin T, Balboa E, Klein AD, Alvarez AR, Zanlungo S. Finding pathogenic commonalities between Niemann-Pick type C and other lysosomal storage disorders: Opportunities for shared therapeutic interventions. BBA-Mol Basis Dis 2020:1866. https://doi.org/10.1016/j.bbadis.2020.165875.
[889] Pfrieger FW. TeamTree analysis: A new approach to evaluate scientific production. PloS One 2021;16:e0253847. https://doi.org/10.1371/journal.pone.0253847.
[890] Team RC. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2021.