Pfrieger's Digest

Issue 16
January – April 2026

Niemann-Pick Diseases

Summaries of latest research advances related to Niemann-Pick diseases, acid sphingomyelinase deficiency (ASMD) and Niemann-Pick type C disease (NPCD), based on selected peer-reviewed publications in scientific journals.

By Frank W. Pfrieger, PhD
Institute of Cellular and Integrative Neurosciences
Centre National de la Recherche Scientifique / University of Strasbourg
Strasbourg, France

Dear Readers.
Welcome to the **sixteenth** issue covering January 1st 2026 to April 30th 2026. The corresponding links for the PubMed queries are:
- for **NPCD**:

((niemann-pick c OR niemann-pick type C OR niemann-pick type C1 OR niemann-pick type c2 OR npc1 OR npc2) AND (("2026/01/01"[Date - Publication] : "2026/04/30"[Date - Publication]))) NOT (("2020/01/01"[Date - Publication] : "2025/12/31"[Date - Publication]))

- for **ASMD**:

((niemann-pick AND ("type a" OR "type B" OR "type A/B") OR smpd1 OR asmase OR acid sphingomyelinase) AND (("2026/01/01"[Date - Publication] : "2026/04/30"[Date - Publication]))) NOT (("2020/01/01"[Date - Publication] : "2025/12/31"[Date - Publication]))

During this period, 77 (NPCD) and **44** (ASMD) articles were published in scientific journals including **12** (NPCD) and **6** (ASMD) reviews. **Four** articles appear in both queries.

REMINDER!
English versions of the Digest are freely available at the open science archive HAL (some are still missing – *en chantier*!).

Please note: 1) My selection of articles is subjective. 2) I comment only peer-reviewed original articles, and neither preprints nor review articles nor case studies describing single patients. 3) I only include articles that I can read from start to end. 4) I try to ensure correctness of statements, but I cannot guarantee this. 5) Errors of any kind are not excluded. 6) My judgements and interpretations are subjective and reflect my personal opinion, they do not claim any validity. 7) I apologize for any errors in grammar, punctuation and orthography, and for any wrong, quirky or otherwise weird expressions. 8) This text is my translation of my original German version, which was written by myself thanks to my

own natural and naturally limited intelligence without any help from an artificial one. 9) Feel free to distribute this issue, as long as there are no changes to the text or layout. 10) Translations to other languages are welcome, as long as my authorship and the original version are mentioned. 11) The digest does not indicate sources of funding for published studies. This information can be found in a dedicated section of each publication. 12) English versions are freely available from the open science archive HAL, issues 2-6 will be uploaded. 13) I thank the German Niemann-Pick Selbsthilfegruppe e.V. and NPSuisse for support and all others who kindly host the Digest on their websites or distribute it otherwise.
14) Feedback (praise, criticism, giftcards) welcome to: fw-pfrieger@gmx.de.

Patients (NPCD)

PMID: 42106890

Singhal et al. Identification of serum protein biomarkers in individuals with Niemann-Pick disease, type C1. Biomark Res. 2026 May 9. doi: 10.1186/s40364-026-00927-x. Epub ahead of print. PMID: 42106890.

Guess what the first article in this division is about? It's about... so, what? Exactly! High five! Biomarkers, more specifically proteins whose concentration in the blood of patients is higher or lower than in blood of healthy donors. There are lots of studies on this topic, notably from the same corner, the "team Porter". But, remember the Depeche Mode song: "*Just can't get enough*". This is also true for biomarkers, just can't get enough, notably not enough patient data that confirm concentration differences. Markers in blood are notoriously desired, as easily accessible – on tap. Singhal and Kollegen used a sensitive method named *proximal extension assay* (see Digest 8) that measures the relative amounts of 2943 (!) selected proteins. That may sound simple, just measure 68 patients and 20 healthy donors, that's it. The authors took the long road, and they made all sorts of comparisons, biomarker with disease onset, with disease progression, symptoms, miglustat treatment a.s.o. The work confirms previous biomarkers notably neuropeptide Y (Digest 8) and the protein with a terrible name, aka GPNMB (Digest 9). In addition, the work delivers a treasure trove of new markers with wonderful names like TREM2 and HSD17B14. To solidify the results, the newly discovered markers need now to be tested with samples from other NPC patients. Quite striking is the low concentration of BDNF, a well known growth and survival factor for nerve cells (Digest 9), in patients. Is loss of BDNF part of the problem and a possible target for new therapies?

PMID: 41930984

Balcı et al. Childhood Interstitial Lung Disease in Metabolic Disorders: Prevalence, Genotypic and Clinical Characteristics, and Management Approaches: An Analysis of the Child-Turkey Registry. Pediatr Pulmonol. 2026 Apr;61(4):e71603. doi: 10.1002/ppul.71603. PMID: 41930984.

There are registries (databases, tables) for all sorts of entries. This work from Turkey analyses a registry for children with institial lung disease, which can have diverse causes, notably ASMD and NPC. The registry was established in 2021 and lists 706 children. The article describes five NPC and 11 ASMD patients, and patients with other lysosomal diseases.

PMID: 42006583

Hawthorne et al. Dysregulation of Extracellular Vesicle Concentration, MicroRNAs, and Surface Proteins in Patients With Niemann-Pick Disease Type C. J Extracell Biol. 2026 Apr 17;5:e70136. doi: 10.1002/jex2.70136. PMID: 42006583; PMCID: PMC13088877.

We come back to extracellular vesicles, or EVs, hot stuff that becomes notorious in the NPC field (see Digest 6, 9, 11). As reminder, EVs are nanometer-sized "balls" that are secreted by some cells and taken up by others, they are supposed to serve communication between cells, or simply as trashbag. Some EVs are released from the endosomal-lysosomal system. If the latter is perturbed, as in NPCD or other lysosomal disorders, EVs may be affected. There are massive efforts to use EVs as biomarkers, as they are present in all body fluids, and the analysis methods are being refined and standardized. The colleagues observed some differences provoked by NPCD in the number and composition of EVs in cerebrospinal fluid and in the bathtub water of skin fibroblasts in culture. The topic needs further studies with patient samples, but no doubt, there is more to come.

PMID: 42037350

Makrygianni et al. Sertraline Treatment Can Mimic Niemann-Pick Type C Biomarker Profile: A Diagnostic Pitfall. Ann Clin Transl Neurol. 2026 Apr 27. doi: 10.1002/acn3.70411. Epub ahead of print. PMID: 42037350.

We continue with biomarkers and come to a STOP sign. French physicians warn that there may be false-positive NPCD cases, if the person takes – for whatever reason – Sertraline/Zoloft/Lustral. The drug perturbs the endosomal-lysosomal system and

increases the concentration of biomarkers such as oxysterols without any NPCD. It's clear: biomarkers alone cannot replace thorough diagnostic workup.

PMID: 41824299

Tchan et al. An Australian standard of care for Niemann-Pick disease type C. Intern Med J. 2026 May;56(5):832-848. doi: 10.1111/imj.70370. Epub 2026 Mar 13. PMID: 41824299; PMCID: PMC13193484.

Australia delivers a highly welcome contribution for anybody concerned by NPCD, carefully crafted instructions for treatment and care of the disease adapted to Australian conditions, notably the health care system. Curiously, the latter differ widely among countries in contrast to the disease. Starting from internationally agreed and regularly updated recommendations for NPCD treatment, the Australian patient association assembled a group of experts and people affected by the disease to look at the guidelines, to ratify and to either accept, dismiss or adapt them. The pow-wow delivered: a procedure for diagnosis, a framework for multidisciplinary treatment and care (meaning across medical specialties), and general advice how to manage the disease. Impossible to summarize here the advice. The article should be readable by non-experts. In any case, "*downunder*, way ahead!"

PMID: 41936136

Alegretti et al. The p.Ala1035Val variant in Niemann-Pick type C1: Clinical and molecular characterization in Brazilian and Portuguese patients suggests a shared founder effect. Mol Genet Metab. 2026 Jun;148(2):110111. doi: 10.1016/j.ymgme.2026.110111. Epub 2026 Apr 1. PMID: 41936136.

It's a bit complicated, it's about genetics, which is not everone's cup of tea. But with a genetic disease, you can't escape it. Here, DNA of 18 Brazilian and 12 Portuguese patients was examined that all carry the same NPC1 variant, known as Ala1035Val, which is frequent in these countries. The DNA contains small changes, socalled single nucleotide variants or (SNVs), also called single nucleotide polymorphisms. This means that a specific position in the DNA is taken by one or another nucleic acid (see Digest 6). SNVs per se have nothing to do with the disease, they are distributed across the entire genome in all humans as a results of millions of years of natural fiddling with DNA. DNA sequences carrying the same combinations of SNVs are called haplotype. The study shows that the patients homozygous for the Ala1035Val variant carry the same SNV patterns within the NPC1 gene. This suggests that the variant originates from a

common ancestor coming from Portugal to Brazil whenever and for whatever reasons. Whether the SNVs impact the function of NPC1 is not clear. However, the symptoms in this patient cohort are similar. The results underline the importance of SNVs as markers and possibly as disease-modifying factors.

Patients (ASMD)

PMID: 41598527	Giugliani et al. A Retrospective Chart Review Study on the Burden of Illness of Acid Sphingomyelinase Deficiency in Brazil. J Clin Med. 2026 Jan 12;15(2):589. doi: 10.3390/jcm15020589. PMID: 41598527; PMCID: PMC12841961.
PMID: 41692468	Lin et al. Pathogenic Variants and Olipudase Alfa Treatment of Patients With Acid Sphingomyelinase Deficiency in Taiwan. Mol Genet Genomic Med. 2026 Feb;14(2):e70204. doi: 10.1002/mgg3.70204. PMID: 41692468; PMCID: PMC12906976.
PMID: 41716780/	Arafa et al. Olipudase alfa treatment for pediatric acid sphingomyelinase deficiency in Egypt: A prospective, observational cohort study with an interventional subgroup. Mol Genet Metab Rep. 2026 Feb 11;46:101293. doi: 10.1016/j.ymgmr.2026.101293. PMID: 41716780; PMCID: PMC12914850.

Giugliani and colleagues summarize files of 124 Brazilian ASMD patients (94 with type B and 30 with A/B) dating from 1986 to 2021. They show the geographic distribution of patients across Brazil and provide a nice overview regarding disease progression, symptoms, diagnosis and hospital stays.

Lin and colleagues report on nine Taiwanese ASMD patients (1 type A, 4 type A/B und 4 type B), four of which received olipudase treatment. They also summarize the results of a newborn screen of nearly 60.000 babies. 12 of them showed slightler lower ASM activities, and ten of these were heterozygous for pathogenic SMPD1 variants, so no patients.

In the third article, Arafa and colleagues describe comprehensively the clinical picture of 15 infantile and juvenile ASMD patients from Egypt, the majority (10!) with type A/B, the others with type B. In addition, the colleagues report effects of 12-months-long treatment with olipudase alpha in six patients, two of type A/B. Interestingly, treatment of the two A/B patients started early at 1 and 2 years of age. So far, the results look good, curious to see how this goes.

PMID: 41896961

Wiesinger et al. A suspicion index tool to aid the diagnosis and treatment of ASMD. Orphanet J Rare Dis. 2026 Mar 27;21(1):178. doi: 10.1186/s13023-026-04328-z. PMID: 41896961; PMCID: PMC13147735.

A new tool was developed to accomplish a timely diagnosis of ASMD, a socalled suspicion index, which based on symptom combinations indicates how likely it is that the patient has ASMD. Something similar is already in place for NPCD. To establish the new index, the authors combed the literature, they asked experts and they trained a machine brain. Soon, a website should be set up allowing to use the index.

PMID: 42029540

Kato et al. Acid Sphingomyelinase Activity in Dried Blood Spot from Neonatal Intensive Care Unit-Admitted Neonates: A Pilot Study for Expanded Newborn Screening in Japan. Int J Neonatal Screen. 2026 Apr 1;12(2):22. doi: 10.3390/ijns12020022. PMID: 42029540; PMCID: PMC13108211.

New insight in newborn screens for ASMD from Japan. The colleagues focused on a specific group, babies that were treated – for whatever reasons – in neonatal intensive care units of two hospitals. Amon the 244 neonates tested, there was no ASMD case, but the authors show that ASM activity grows with birth weight, gestationale age and the lymphocyte count, and decreases with hematocrit, which is mainly determined by the number of red blood cells. In addition, ASM activity was higher when measured a second time. So, many factors influence ASM activity and reference ranges need to be adapted. Also, ASM activity varies among babies and methods of measurement. The authors propose how to proceed and recommend to use additional biomarkers.

Animal Models (NPCD)

PMID:41853687

Cougnoux et al. Modulation of glutamate metabolism in Niemann-pick disease type C1 mice. Mol Genet Metab Rep. 2026 Mar 5;46:101303. doi: 10.1016/j.ymgmr.2026.101303. PMID: 41853687; PMCID: PMC12993011.

A short story about an ancient topic in neuroscience, the socalled excitotoxicity – what a beautiful word; death by over-excitation. We all know situations where too much excitation is not good... The Porter group asked whether too much glutamate kills nerve cells. No worries, this is not about too much soy sauce. Most synapses in the brain use

glutamate as "excitatory" neurotransmitter. Treatment of NPC1-deficient mice with an inhibitor of specific glutamate receptors prolonged the life-span of female animals but only a bit. Lack of a pump that sucks glutamate into cells (and removes it "from outside") killed more Purkinje cells than NPC1 deficiency alone as expected. However, – it's biology! – disease progression in mice was slower and life spans were increased a bit. Why, is unclear. So glutamate seems to be part of the jigsaw puzzle depicting nerve cell loss.

PMID:41811855	Epstein et al. Comparison of neonatal systemic and intracerebroventricular AAV9 gene therapy delivery demonstrating improved behavioral and phenotypic outcomes in a mouse model of Niemann-Pick disease, type C1. PLoS One. 2026 Mar 11;21(3):e0331275. doi: 10.1371/journal.pone.0331275. PMID: 41811855; PMCID: PMC12978470.
PMID:41912285	Mylvara et al. Optimization of systemic AAV9 gene therapy in Niemann-Pick disease, type C1 mice. Life Sci Alliance. 2026 Mar 30;9(6):e202402874. doi: 10.26508/lsa.202402874. PMID: 41912285; PMCID: PMC13036363.

Two huge studies of the Pavan group concerning gene therapy using the *adeno-associated virus* (aka AAV), truly a recurring topic (Digest 4, 5, 9, 13). The group asked how doses, age of treament (neomatal, 4, 6 or 8 weeks old) and mode of treatment (single injection in the brain or in the blood stream) affect mice lacking NPC1 or mice carrying the famous I1061T variant. These comprehensive studies are a welcome occasion to mention a peculiar phenomenon, namely that in our business, the natural sciences, the results of many years of work and millions of dollars can be summarized in three sentences. Here as well: the earlier the treatment, the higher the dose, the lower is the weight loss of sick mice, the better is their motor coordination and the longer their life span. Note that a lower dose works as well, if the animals are treated as early as possibe. On the other hand, if mice are treated at 4 weeks of age even at the highest does, they develop symptoms and die of the diseases, albeit with a long delay. What counts is how many copies of the normal NPC1 gene delivered by the virus are expressed in the brain. Time for another remark: the manuscript of Epstein was submitted in September 2025 for publication and published in March 2026, so half a year later. Mylvara et al. was submitted in June 2024 and published as well in March

2026, so two years went by. It can take very long/forever to get results published for various reasons.

PMID:41883173 Watanabe et al. An Analysis of Biomarkers for the Evaluation of Gene Therapy in Niemann-Pick Disease Type C1 Mice. Hum Gene Ther. 2026 Apr;37(7-8):300-310. doi: 10.1177/10430342251412391. Epub 2026 Jan 10. PMID: 41883173.

We continue with AAV-based gene therapy. The Japanese group studied which of the known biomarkers is apt to measure success of gene therapy. To this end, one-week-old mice lacking NPC1 received a single injection of AAV carrying the NPC1 gene in their belly cavity. By this way, some virus gets into the brain and improves motor control. The colleagues report that the previously mentioned PPCS (for N-palmitoyl-O-phosphocholineserine; a.k.a. lysosphingomyelin-509) reacts reliably to treatment, its concentration in blood went down.

PMID:41963705 Lee et al. Molecular and histological characterizations reveal two distinct senescent microglia populations in Niemann-Pick disease type C mouse model. Geroscience. 2026 Apr 10. doi: 10.1007/s11357-026-02244-5. Epub ahead of print. PMID: 41963705.

Quiz: what has NPCD to do with aging? Well, one may tend to think: nada. In biomedical research there is a rapidly growing area that deals with aging of cells or cell senescence. The term was coined decades ago when scientists found cells that were dividing (thus producing progeny) stopped doing so at some point. This is understandable. The new work presents hints that some microglial cells in the brain of NPC1-deficient mice show signs of aging, as indicated by the accumulation of specific proteins. The number of these cells increases in brain areas where neurons degenerate. However, the parallel occurrence of two phenomena does not prove any causal relation. In any case, senescence research seeps in the NPC field, this was only a question of time.

PMID:41895381 Miwa et al. Spiral ligament dysfunction and endocochlear potential loss drive hearing impairment in Niemann-Pick C1 mice. Brain Res Bull. 2026 May;238:111846. doi: 10.1016/j.brainresbull.2026.111846. Epub 2026 Mar 25. PMID: 41895381.

Many NPC patients suffer from progressive hearing loss, but the causes are not well understood. An earlier study had shown hearing loss in NPC1-deficient mice starting already at 3 weeks of age, well before other neurologic symptoms. Japanese colleagues studied again the hearing loss in mice. They suggest that the trouble starts not directly in hair cells, which convert acustic waves in electrical signals, but in the socalled spiral ligament of the cochlea, a supporting structure of the inner ear. There are diverging views on this, but in any case, this important symptom deserves more attention, meaning studies, both in patients and in animal models.

PMID:41932416 Mattern et al. Altered bone structure in Niemann-Pick Type C1 mice, especially in females. Bone. 2026 Jul;208:117879. doi: 10.1016/j.bone.2026.117879. Epub 2026 Apr 1. PMID: 41932416.

From time to time, one tends to think about bones, mainly in the context of bouillon (soup broth), probably less in the context of NPCD. The present study reports differences in the femur structure of healthy and NPC1-deficient mice, only in females, not in males. Moreover, they report changes in mouse bones due to different treatments (miglustat, cyclodextrin). A question is whether these changes occur only in the specific mouse colony or whether they emerge in mice from other facilities. Mouse colonies can develop their specific pathologies due to permanent inbreeding which is used to maintain animal colonies at least for a specific period.

Cell-based Models (NPCD)

PMID: 41867897 Halim et al. APOE3 astrocytes can rescue lipid abnormalities and dystrophic neurites of APOE4 human neurons. PNAS Nexus. 2026 Mar 3;5(3):pgag053. doi: 10.1093/pnasnexus/pgag053. PMID: 41867897; PMCID: PMC13003211.

Another quiz: what do the river Nile, stars, fat droplets and NPCD have in common? Nothing so far until the work by Halim et al. They studied whether a well known risk

factor for Alzheimer, the socalled apolipoprotein E4, influences pathologic changes in nerve cells with damaged NPC1. Step-by-step: in the brain, ApoE is made by a specific type of non-neuronal cells, the astrocytes, originally called "star cells" (Digest 13). ApoE is part of lipoproteins – similar to LDL and HDL on your blood exam sheet– that are required for exchange of fats including cholesterol between brain cells. Homo sapiens has several ApoE variants, the most frequent is ApoE3, ApoE4 is more rare. The latter enhances strongly the risk for Alzheimer's disease, but why is still unclear. There have been hints that ApoE is risk factor for NPCD, but that's not ironclad. Why the nile? Because the colleagues used a dye, nile red (Digest 11) to visualize lipid accumulation in nerve cells. Nile red is a relative of nile blue that was first synthesized by the end of the 19th century. Water stained with the dye becomes blue (one could have called it "Danube blue"). Here, nerve and star cells artificially generated from human stem cells were modified to express ApoE3 or ApoE4. The cells were treated with the NPC1 inhibitor U18666A and the fat accumulation was measured in all sorts of combinations. In sum, ApoE3 seems better than ApoE4, it reduced lipid accumulation and the crumbling on neuronal processes after inhibition of NPC1. Lots of work, but still: wouldn't it be useful, to measure electrical activity as important readout of their function? As stated previously, Apo4 is work in progress.

PMID: 41776152

Nguyen et al. Small Molecules to Elevate Rab7-GTPase Activity and Lower Cholesterol Accumulation in Niemann-Pick Type C Disease. Pharm Res. 2026 Apr;43(4):1009-1031. doi: 10.1007/s11095-026-04058-8. Epub 2026 Mar 3. PMID: 41776152; PMCID: PMC13179269.

Australia proposes new drug candidates, a sort of ricochets, as their target is neither NPC1 nor NPC2 nor cholesterol. It's a protein with the highly meaningful name TBC1D15. This is a sort of switch B that switches off switch A. Switch A is a protein named RAB7. This is knowm to help cholesterol out of the endosomal lysosomal system even when NPC1 is broken. So, inhibition of switch B (TBC1D15) disinhibits switch A (Rab7), and we get what we need: activity of Rab7 and less intracellular cholesterol accumulation. The goal was to find inhibitors for switch B. Nowadays, this works *in silico*, with a computer, as structures of proteins can be simulated. So, find an open flank in your target protein, where an inhibitor can bind to, then screen 260000 drug candidates to find a match. This sounds a bit like online dating except that we are looking for inhibitory rather than excitatory partners (!). The colleagues identified four drug candidates that reduced cholesterol accumulation in several cell models of NPCD

and that surived other partner tests. We shall see now: which candidate makes it to the second round? Which one stands the test of real life?

PMID: 41931112 — Salkovski Discovery of Autophagy Modulators that Increase I1061T NPC1 Expression and Promote Cholesterol Efflux in Niemann-Pick Type C Patient-Derived Fibroblasts. ACS Chem Biol. 2026 Apr 17;21(4):812-827. doi: 10.1021/acschembio.6c00039. Epub 2026 Apr 3. PMID: 41931112; PMCID: PMC13097081.

Here, two additional new drug candidates freshly on the lab bench. Their discovery took a different path from the work described above, albeit a path through the biology jungle, where you rarely end where you wanted to. Fine, as long as you get out. The colleagues used a classic wet lab screen, to be precise, they used two. First, they searched for drugs that boost autophagy, the ingenious cell intrinsic degradation/recycling program that is broken in NPC (s. previous issues). Second, they tested whether candidates selected in the first round (312 out of 10,000) can lower cholesterol accumulation in skin fibroblasts from patients. Only 2 candidates survived. The colleagues went through a veritable characterization orgy to address the where-what-how of the candidates. Candidate 1 raises questions. Candidate 2 does what it should, lower cholesterol accumulation, but not how it was thought to. Instead it saves NPC1 from degradation, keyword chaperon. We shall see which candidate survives the next round and shows positive effects in animal models of NPC.

PMID: 42036241 — Chen et al. Curcumin controls lysosomal acidification and exocytosis to ameliorate lysosomal cholesterol accumulation in Niemann-Pick type C disease. Br J Pharmacol. 2026 Aug;183(15):4305-4320. doi: 10.1111/bph.70448. Epub 2026 Apr 26. PMID: 42036241.

There are "comet-like" drugs, they fly towards you, they pass, they fly away and some day, they come back without impact. Curcumin, ingredient of the spice, belongs in this category. There were repeated hints that treatment of NPCD cell models reduces cholesterol accumulation, but in the mouse model it had not major effect. Now, curcumin is back with the new work showing that the drug helps cells to spit out cholesterol. Waiting for the next fly-by.

Cell-based models (ASMD)

PMID: 41342385 — Yi M, Hu J, Zhan X, Zhang H. Identification of Cepharanthine as a Potential Therapy of Acid Sphingomyelinase Deficiency by Reducing Cellular Sphingosylphosphorylcholine. J Inherit Metab Dis. 2026 Jan;49(1):e70125. doi: 10.1002/jimd.70125.

An ancient drug, new for ASMD. It's name is cepharanthine, and its extracted from an Asian plant with the beautiful name Stephania. Ancient, because the drug is approved in Japan since decades (or more) to treat all sorts of ailments ranging from leukocyte deficiency, hair loss, dry mouth and snake bites! The drug seems to turn diverse screws in the cellular gear. The work of Chinese colleagues shows in different cell models of ASMD that treatment with cepharanthine reduces the accumulation of fat (for know-it-alls: sphingosylphosphorylcholine, a derivate of sphingomyeline). Moreover, the energy plants, mitochondria look prettier, as if lifted.

Molecules

PMID: 41934663 — Patel & Elghobashi-Meinhardt. Mechanistic Basis of Cholesterol Binding and Transfer in NPC2: Insights From Molecular Dynamics Simulations. Chembiochem. 2026 Apr 14;27(7):e202500819. doi: 10.1002/cbic.202500819. PMID: 41934663; PMCID: PMC13050278.

There are simulators and simulations, the former are not well liked, the latter of increasing importance. This is about interesting simulations of the structure of molecules. A computer calculates how atoms in a molecule wiggle. The group from Ireland studied how the form of NPC2 changes by disease-provoking mutations, but also after binding cholesterol. NPC2 puts cholesterol in a pocket and hands it over to NPC1 when they meet somewhere in the depths of the lysosome. Variants of NPC2 are rare, but as pathogenic as those of NPC2. The question is why. The 3D structure of the protein has been described previously, but little is known about its dynamics, how the protein structure changes over time, well here, very brief time, nanoseconds, the calculations are computation intense. There are pathogenic variants that inhibit binding of cholesterol and others that preclude the transfer. The simulations show that NPC2 stiffens when it harbors cholesterol in its pocket. The variants change the motility of the mouth where cholesterol goes in and out and of the lips that kiss NPC1. No transfer without kiss!

Miscellaneous

PMID: 41904369 — Liu et al. Lineage-specific expansion and positive selection of NPC2 genes in the crab spider Ebrechtella tricuspidata and other arachnids. BMC Genomics. 2026 Mar 28;27(1):448. doi: 10.1186/s12864-026-12756-1. PMID: 41904369; PMCID: PMC13151251.

Admittedly, spiders are not for everyone, but the present work by Chinese colleagues teaches once again how inventive nature is in general, and spiders in particular. The green crab spider (for pros *Ebrechtella tricuspidata*) has – believe it or not – 13 different versions of NPC2. Why? Digest afficionados may guess, it's about olfaction, smelling. The animals use this or that form of NPC2 for household maintenance (lipid metabolism) as *Homo sapiens et al*. do. But because the creature needs to smell its prey to survive, new NPC2 variants have evolved. They bind different molecules from the air, bring them to the olfactory organ and then: Catch it! In case anyone likes to know how to breed the animals in the lab, they need 25°C, 75% humidty and loads of fruit flies, they love to devour them.

PMID:41957412 — Villani et al. A scalable human-zebrafish xenotransplantation model reveals gastrosome-mediated processing of dying neurons by human microglia. Commun Biol. 2026 Apr 9;9(1):785. doi: 10.1038/s42003-026-09948-6. PMID: 41957412; PMCID: PMC13250125.

New models are exciting! This applies to the one introduced here. It reminds a bit of Ariel, the little mermaid, a combination of fish and human. Human are microglial cells, fish is the rest of the body, a socalled xenotransplantation model. Why this model? Because one wants to study human microglial cells in a "natural" environment" with other cells. Why fish and not mouse? Fish is cheaper and grows faster. So, more experiments in shorter time for less money. The work is not really about NPCD. But, the authors did one experiment related to the disease: if they add the NPC1 inhibitor U18666A to the fish bathwater, the human microglia in the fish brain accumulate lipids from fish nerve cells. Let's see what the future holds for the model.

Out of the box

PMID: 41576950	Ghoochani et al. Cell-type resolved protein atlas of brain lysosomes identifies SLC45A1-associated disease as a lysosomal disorder. Cell. 2026 Feb 5;189(3):765-782.e31. doi: 10.1016/j.cell.2025.12.012.

Here, a new perfect fit for this category. This is about Atlas, but no, neither the mountains nor the big beared man who carries the world nor the old school book that fouls in the basement. It is about cartography, here, attention, cartography of proteins that are humming around in lysosomes of different cells types in the brain. Wow! A dream comes true. Now, go for a hike through the protein forests in the lysosomal landscapes.

PMID: 42085157	Smothers JC, Nguyen CHB, Han Y, Li Y, Chen Z, Radhakrishnan A. Visualization of the interaction between sphingomyelin and cholesterol in lipid bilayer membranes. Proc Natl Acad Sci U S A. 2026 May 12;123(19):e2528400123. doi: 10.1073/pnas.2528400123. Epub 2026 May 5. PMID: 42085157; PMCID: PMC13167793.
PMID: 41850403	Kim et al. Transport of sphingolipids by yeast Npc2 supports phase separation of the vacuole membrane. J Biol Chem. 2026 May;302(5):111370. doi: 10.1016/j.jbc.2026.111370. Epub 2026 Mar 16. PMID: 41850403; PMCID: PMC13092683.

And on we wander in the biology wonderland. The first study shows in unprecedented detail how intimately sphingomyelin and cholesterol are connected in membranes. They embrace each other. The results were obtained in artificial membranes, and the question is how the relationship looks in membranes of specialized cells. In any case, the two are connected. And thus, ASMD and NPCD probably as well. The second study supports the idea that NPC2 is a sort of swiss army knife when it comes to transport of sphingomyelin and cholesterol. The authors show that the yeast version of NPC2 can transport sphingomyelin, probably because its bag is large enough. The human version of NPC2 cannot transport sphingomyelin, so evolution may have led to a sort of specialisation (see Digest 4 and above).

PMID: 41813895

Ye et al. Structures of Marburgvirus glycoprotein and its complex with NPC1 receptor. Nature. 2026 May;653(8114):621-626. doi: 10.1038/s41586-026-10240-0. Epub 2026 Mar 11. PMID: 41813895; PMCID: PMC13171430.

An article in NATURE for this category: it is about infection by Marburg Virus, a more dangerous relative of Ebola. Both use NPC1 to enter cells. The study shows how the viral protein changes when it binds to NPC1 and it uncovers how Marburg escapes the immune defense.