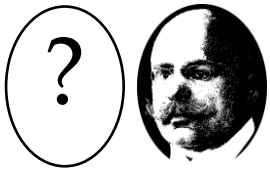
Pfrieger's Digest



Issue 17
May – September 2026

Niemann-Pick Diseases

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

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Dear Readers.
Welcome to the **seventeenth** issue covering May 1st 2026 to September 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 (("2026/05/01"[Date - Publication] : "2026/09/30"[Date - Publication])))) NOT (("2020/01/01"[Date - Publication] : "2026/04/30"[Date - Publication]))

- for **ASMD**:

((niemann-pick AND ("type a" OR "type B" OR "type A/B") OR smpd1 OR asmase OR acid sphingomyelinase) AND (("2026/05/01"[Date - Publication] : "2026/09/30"[Date - Publication])))) NOT (("2020/01/01"[Date - Publication] : "2026/04/30"[Date - Publication]))

During this period, **85** (NPCD) and **55** (ASMD) articles were published in scientific journals including **9** (NPCD) and **9** (ASMD) reviews. **Five** articles appear in both queries.

NEW-NEW-NEW
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NEW-NEW-NEW

All English versions of the Digest are freely available for download from the open science archive HAL.

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Patients (NPCD)

PMID:42036217 — Hiwot et al. 2025 Consensus Clinical Management Guidelines for Niemann-Pick Disease Type C. J Inherit Metab Dis. 2026 May;49(3):e70185. doi: 10.1002/jimd.70185. PMID: 42036217; PMCID: PMC13110917.

There are those, who read user manuals, and there are the others. Indeed, there is a sort of "user manual" for NPCD, an extremely important and regularly updated standard reference that describes comprehensively how to diagnose and treat the disease. An international team of experts has just published the latest version, the last one dates back to 2018.

PMID:42308595 — López de Frutos et al. The RAINBOW study: a phase 2 trial evaluating the 3-month pharmacokinetic and pharmacodynamic data and 18-month clinical and safety outcomes of nizubaglustat in GM2 gangliosidoses or Niemann-Pick type C disease. Mol Genet Metab. 2026 Aug;148(4):110164. doi: 10.1016/j.ymgme.2026.110164. Epub 2026 May 26. PMID: 42308595.

A new drug for NPCD and GM2 Gangliosidosen in sight? The publication contains first results of a well-designed clinical study with Nizubaglustat. What's it? Nizuba is, you may guess, similar to Miglu. These are not names of indigenous tribes, but variants of chemical compounds named iminosugars. They inhibit enzymes at the foot of the big sphingolipid metabolism mountains, among them the enzyme that synthesizes glycosyl ceramide, one of the precursors, and, curiously, its counterpart, one of the enzymes that degrades the precursor. What this does exactly in a cell of desire, is unclear, it depends on the drug concentration, drug affinity, and enzyme levels. Miglu is in the business for quite some time with known effects and side effects. Nizuba is the newcomer, different shape, different affinities. Is it any good? Based on the first results it's difficult to say, the number of patients is low (GM2 gangliosidosis: n = 7; NPCD: n = 6) and the duration of treatment (3 months) short. Wait for more results!

PMID:42693440 Solomon et al. Aspiration and silent aspiration in Niemann-Pick disease type C1: longitudinal findings from the NIH natural history study. Orphanet J Rare Dis. 2026 Aug 22;21(1):312. doi: 10.1186/s13023-026-04543-8. PMID: 42693440; PMCID: PMC13539892.

This is about perturbed swallowing, a massive problem with NPCD, it concerns a majority of patients and represents risk factor for pneumonia, the cause of death for two thirds of patients. The present study complements previous work of the NIH Porter squad (Digest 3, 7, 11). Here, it'Äs about the silent aspiration, aspiration because something gets in the trachea instead of the ??? and slient, because there is no cough reflex or anything similar, it goes unnoticed. The dangerous symptom appears in roughly a fifth of 130 NPCD patients, and it comes with progressive neurologic impairment (high NSS and ASIS values) and weight loss. It is caused by parallel sensory and motor dysfunction, or simply put the sensory cells in the trachea fail to signal that there is something stuck, and at the same time, the motoneurons do not activate the muscles responsible for coughing. Swallowing dysfunction including silent aspiration are important symptoms that should be surveyed regularly and included in clinical studies as outcome measures.

PMID:42376638 Mengel et al. Arimoclomol in infants with Niemann-Pick disease type C: Results from the phase 2/3 open-label pediatric substudy. Mol Genet Metab Rep. 2026 Jun 19;48:101332. doi: 10.1016/j.ymgmr.2026.101332. PMID: 42376638; PMCID: PMC13310637.

PMID:42551329 Berry-Kravis et al. Long-term real-world safety and effectiveness of arimoclomol in individuals with NPC: Outcomes from the US early access program over a 4-year period. Mol Genet Metab. 2026 Sep-Oct;149(1-2):110223. doi: 10.1016/j.ymgme.2026.110223. Epub 2026 Jul 28. PMID: 42551329.

Both publications are about Arimoclomol. Mengel and colleagues report first results of a substudy with infants between 6 to 24 months old. Five patients who all received also miglustat participated, four children with the early- and one with late-infantile form. Four of them received Arimoclomol for more than 12 months. The dosing seems ok, but

with respect to effectiveness, one cannot say much, the number of patients is too small. Three withdrew from the study, one child because of side effects.
There is paint-by-numbers, the second, laborious study resembles something like "guess-by-numbers". Berry-Kravis and colleagues report results from early open access to Arimoclomol bevor its approvement. This is about a whopping 109 patients, half of them over 18, and two thirds treated with miglustat as well, so a relatively large cohort albeit with variable age of treatment start, treatment duration and examination intervals, no results for the few patients with early infantile form. The publication is full of numbers from the five and a further shrinked four domain *NPC clinical severity scale*. If one wants to guess an effect, it may be that the severity scores remained stable over the different treatment durations - on average! It's up to anybody to ponder the meaning of mean values in this disease. Improvements would be better! Both studies list adverse events.

PMID:42324936

Basan et al. Diverse clinical spectrum of Niemann-Pick C: insights from a single center. J Pediatr Endocrinol Metab. 2026 Jun 23;39(9):902-909. doi: 10.1515/jpem-2026-0131. PMID: 42324936.

This publication by colleagues from Turkey describes 14 NPCD patients aged 9 months to 24 years at diagnosis that were examined between 2018 to 2025. As exected, there is a large and fairly common spectrum of symptoms, notable variability between siblings with the same genotype, but consistently elevated levels of N-palmitoyl-O-phosphocholine a.k.a. LysoSM-509 in all patients. The cohort also comprised rare patients with NPC2 variants.

Patients (ASMD)

PMID:42036217

Wasserstein et al. Adults With Acid Sphingomyelinase Deficiency Have Sustained Improvements in Clinical Outcomes With up to 5 Years of Olipudase Alfa Enzyme Replacement Therapy: ASCEND Trial Final Results. J Inherit Metab Dis. 2026 May;49(3):e70192. doi: 10.1002/jimd.70192. PMID: 42047222; PMCID: PMC13122735.

There comes a moment in time, when the wish to cite Shakespeare becomes unbearable, even if it fits only halfway. "All is well that ends well!", but the story continues. Wasserstein and colleagues report the final results of the ASCEND study testing the effects of olipudase alpha (Digest #8, 9, 10, 11, 14–16) in 35 patients from all over the

world. During the up to five years of treatment with fortnightly influsions the outcome measures from liver, spleen, bones, and lung as well as biomarkers in the blood improved with variable degrees from patient to patient and from organ to organ. Liver and spleen seem to score best.

PMID:42375814 — Robin et al. Clinical Characteristics of 19 Patients With Acid Sphingomyelinase Deficiency: A Case Series From Multiple Centers in Argentina. JIMD Rep. 2026 Jun 28;67(4):e70104. doi: 10.1002/jmd2.70104. PMID: 42375814; PMCID: PMC13310959.

This retrospective study describes 19 ASMD patients from different centers in Argentina, who were diagnosed between 1988 bis 2022, four with type A, infantile neurovisceral, most with type B, chronic visceral and the remaining patients with the intermediate form. The study shows the usual: broad spectrum of symptoms, and often endless wait – here up to 35 years – for the correct diagnosis.

PMID:42339202 — Farhan et al. Acid sphingomyelinase deficiency: Phenotypic, biochemical, and molecular heterogeneity in a series of 47 Iraqi patients from a single center. Mol Genet Metab Rep. 2026 Jun 16;48:101328. doi: 10.1016/j.ymgmr.2026.101328. PMID: 42339202; PMCID: PMC13285672.

This comprehensive report from Iraq describes a relatively large cohort of ASMD patients that were diagnosed between 2007 to 2024 in a hospital in Baghdad. The patients (20 type A; 4 type A/B; 23 type B) of mainly consanguineous parents carry 13 variants, three of which are new. Their symptoms and biomarker levels are similar to those in other cohorts with some differences.

PMID:42641356 — Rivaux et al. Multiplex MSMS measurement of lysosomal enzymes enables incidental diagnosis of acid sphingomyelinase deficiency in patients evaluated for Gaucher disease. Mol Genet Metab. 2026 Sep-Oct;149(1-2):110238. doi: 10.1016/j.ymgme.2026.110238. Epub 2026 Aug 19. PMID: 42641356.

Magic word "multiplex", or "many at the same time". That's not everybody's thing, it depends on what is to be done. The work of a French group shows this works with respect to diagnosis. They used a special version of mass spectrometry to measure in

parallel the activities of several lysosomal enzymes in dried blood spots. They identified 56 ASMD patients out of 1.700 suspected ASMD cases, and 8 ASMD patients among suspected Gaucher cases.

PMID:42571428 — Cifuentes-Uribe et al. Plasma KL-6 reflects pulmonary severity and longitudinal response to enzyme replacement therapy in acid sphingomyelinase deficiency type B. Mol Genet Metab Rep. 2026 Jul 30;48:101343. doi: 10.1016/j.ymgmr.2026.101343. PMID: 42571428; PMCID: PMC13452365.

Just briefly, but important: the same group as above introduces a new potential biomarker for lung problems in ASMD (and maybe NPCD?). It's a protein present in lung and blood with the German name "Krebs von den Lungen-6" (KL-6). The data basis is still a bit wobbly, but further studies into this are probably worth it.

PMID:42800888 — Assiri et al. From guidelines to real-world practice: clinical, biochemical, and genetic insights in a series of Moroccan patients with acid sphingomyelinase deficiency. J Pediatr Endocrinol Metab. 2026 Sep 28;39(11):1160-1171. doi: 10.1515/jpem-2026-0194. PMID: 42800888.

This is about clinical practice under "difficult conditions". Clinicians from Morocco show how they could diagnose correctly five ASMD patients using a "cost-efficient" procedure.

Animal models (NPCD)

PMID:42668108 — Luke et al. Lack of cathepsin B increases severity in Niemann-Pick disease, type C1 mice. Neurosci Lett. 2026 Oct 30;886:138716. doi: 10.1016/j.neulet.2026.138716. Epub 2026 Aug 29. PMID: 42668108; PMCID: PMC13540384.

Here's a short, but nice episode from the endless series "It's biology, stupid!" The question was which factors influence how disease progression in NPCD. The candidate here is cathepsin B, a socalled protease. These enzymes destroy specific proteins. Normally, cathepsin B lives in the lysosome, but it can escape and rage in other parts of the rest. The idea was, based on previous work, that cathepsin B is co-responsible for the death of nerve cells and that drugs that inhibit the enzyme would be beneficial. Good! What is to be done to test this – everybody think! If this was the case, mice

lacking both NPC1 and cathepsin B should be better off than mice lacking NPC1 only. So much for the theory. The publication from the Porter group shows exactly the opposite. The mice are worse! They have stronger weight loss, worse neurologic symptoms and more reduced life span. And there floats slowly but surely the earlier hypothesis on the wide river to the large ocean of rejected ideas. But, as always, good that someone did the experiment and published the results!

PMID:42256287 Munkacsi et al. Multi-omics reveal phosphatidic acid phosphatases modify Niemann-Pick type C disease severity. iScience. 2026 May 28;29(6):116121. doi: 10.1016/j.isci.2026.116121. PMID: 42256287; PMCID: PMC13233811.

We continue with the topic, this remarkable study is also about factors that influence severity of NPCD. And it's olympic! The authors practice a venerable olympic sport, the three jump: yeast - mouse - human. First jump: yeast helped here neither in the form of pastry nor alcohol but – once again – as experimental model (Digest 4, 9–12, 14, 16). A conditional synthetic lethalilty screen – sounds unhealthy – uncovered an enzyme named *phosphatidic acid phosphatase*, a.k.a. Lipin, a key component of cellular metabolism, among others, it's required to make triacylglyerol, a key component of body fat serving as energy store. Second jump: mice lacking NPC1 and two of its three lipins die earlier than those lacking only NPC1 or only lipins. So, lipins protect somehow from NPC1 deficiency. Last jump: human carry natural variants of lipin encoding genes (like for NPC1). The authors show based on some patient data that some of the variants may exacerbate disease progression in NPCD. This is a start! Further studies will show whether this is true and what's behind.

PMID:42208871 Kang et al. Npc1 deficiency impairs brain vascular integrity in mouse model of Niemann-Pick disease type C1. Neurobiol Dis. 2026 Aug;226:107462. doi: 10.1016/j.nbd.2026.107462. Epub 2026 May 27. PMID: 42208871.

Here a new edition from the series "Trust doesn't cut it, better look again!". The subject here is the regularly mentioned blood-brain barrier. The present work is not about whether this or that treatment fails due to the barrier, but about the damage to the barrier. A previous study reported no damage to the barrier in NPC1-deficient mice. But, this depends on your scrutiny. A Chinese-German team shows with different methods that the barrier in NPC1-deficient mice is broken at least starting at an

advanced age in selected regions, including thalamus, cortex and cerebellum. Admittedly, these changes may be specific to the mouse colony studied. It would be good to test again in other colonies and animal models, and notably in NPC patients (see also Out-of-the-box).

PMID:42585307

Zhao et al. Mito-TEMPO improves survival rates in npc1-knockout zebrafish by reducing oxidative stress and enhancing mitophagy via Sod2. Sci Adv. 2026 Aug 14;12(33):eaee0509. doi: 10.1126/sciadv.aee0509. Epub 2026 Aug 12. PMID: 42585307; PMCID: PMC13464641.

The study from China looks at oxidative stress and mitochondria in cell and fish models of NPCD. As a reminder: the zebra fish *Danio rerio*, a darling of scientists and aquarianians, has a NPC1 protein and needs it, because if one takes it away it's fish fingers (Digest 3, 4, 8, 16). The antioxidative drug used here is called mito-tempo. It took some time to track the origin of this stuff. The notion that it's also called mito-tempo or mito-tempol or mitotempol helped. In the beginning, there were piperidine nitroxide TEMPO (for freaks: 2,2,6,6-tetramethylpiperidine-1-oxy) and TEMPOL (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxy). They were synthesized in the 1950s. They eliminate dangerous radicals in cells, not in the streets. In 2008, TEMPOL and TEMPO were married to the fatloving triphenylphosphonium (TPP), evidently, with what else?! This stuff likes to be in mitochondria, don't ask why. So, treatment of NPC1-deficient fish with mito-tempo prolonged the life of some, but not all. More experiments in cell culture models of NPCD showed that mito-tempo reduces radicals and cranks up the renewal of damaged mitochondria. The results are probably ultimately not in a way that one would like to dance on tables for extended periods of time, but it's a start.

PMID:42564822

Fioriello et al. Neurodegeneration in the olfactory system in Niemann Pick type C1 disease. iScience. 2026 Jul 27;29(8):116945. doi: 10.1016/j.isci.2026.116945. PMID: 42564822; PMCID: PMC13446202.

Now a topic that comes and goes like a comet. It's about smell or olfaction, and for once not in insects but in mice and humans. Earlier studies had shown damage to the olfactory epithelium in the nose of NPC mouse models. There live the sensory neurons that bind odorants and help to tell whether it smells good or stinks. The new study confirms the damage in another mouse model (I1061T variant). So, what about patients? The study shows "anecdotal evidence", a child and its parents show diminished ability

to smell (doctors call this hyposmia), which can of course have different reasons including a running nose. An earlier study on heterozygous NPC1 allele carriers showed impaired ability to smell. So, is this a biomarker? It can be measured!

PMID:42662950 Koufer et al. Codon-optimized Npc1 mRNA corrects Niemann-Pick type C1 disease phenotypes in vitro and in vivo. Mol Ther Nucleic Acids. 2026 Jul 18;37(3):103022. doi: 10.1016/j.omtn.2026.103022. PMID: 42662950; PMCID: PMC13521171.

No Digest without news from the gene therapy front. Here, for a change not using virus, but with messenger RNA containing fatty droplets. Their advantage is a) cheap, b) non-toxic and c) very flexible. They can be pack with messenger RNA of almost any length, and their surface can be modified. This has been used before (Digest 3 and 7), now a new attempt. The trick here was to optimize the messenger RNA code. To put it simple, some letters of the code, aka triplets, that are rare can be replaced by ones that are more frequent. This doesn't change the text, but it helps cells to read the code and improves production of the protein, in this case of course, NPC1. A similar approach had been tried before but only in cells (Digest 3). The new study shows that the approach works in the mouse model, even after a single injection in blood, however, as expected, only in the liver. The droplets cannot jump the blood-brain barrier. A first step, stay tuned!

Animal models (ASMD)

PMID:42587127 Guerrero-Valero et al. Targeting CD44 reverses sphingomyelin-induced oligodendrocyte maturation arrest in acid sphingomyelinase deficiency. EMBO Mol Med. 2026 Sep;18(9):3767-3789. doi: 10.1038/s44321-026-00503-8. Epub 2026 Aug 12. PMID: 42587127; PMCID: PMC13562706.

Here something heart- or soulwarming. The Ledesma troup found a new therapeutic target for the neurologic forms of ASMD. Their identification is high on the bubble list, no, wrong term, bucket list. The presently partially available enzyme replacement doesn't help the brain and its dying cells. New here is also that this is not about nerve cells, but the oligodendrocytes, the ones with few branches that make the cable isolation. Just as reminder, we are talking about 180,000 km (112,000 miles) of cable tree in every human brain. The study shows that ASM-deficiency in mice perturbs development of these cells, because the new target protein named CD44 is hyperactive.

Treatment of the animals with an inhibitor named Verbascoside gets this back in order, the mice are somewhat better. Verbascoside is a natural substance produced by different plants of the order Lamiales, an example is Verbascum nigrum or dark mullein. The drug has different targets, so it may be not ideal. At least, there's a start, to be continued. If the problems in the brain cannot be tackled at the root by enzyme replacement, there are likely many fires that need to be extinguished.

Cell-based models (NPCD)

PMID:42889954 Men et al. Palmitoyltransferase DHHC13 controls lysosomal cholesterol egress through palmitoylating Niemann-Pick C1. Life Metab. 2026 Sep 10;5(6):loag028. doi: 10.1093/lifemeta/loag028. PMID: 42889954; PMCID: PMC13671750.

With fat or without, and if, with which, where and when? These are the questions behind the present work, a topic that has been tackled previously (Digest #14). The NPC1 protein –like many others – can be married transiently to specific fatty acids, for example palmitic acid, this reversible process is called palmitoylation. Sounds terrible, but it doesn't hurt, and it is important. It ensures that NPC1 gets from its place of birth to its place of work and functions properly. How this works exactly is not clear. Chinese colleagues have identified an enzyme named DHHC13 that attaches palmitic acid to NPC1. If this enzyme is missing in the mouse, cholesterol accumulates in lysosomes as seen in NPC1 deficiency. Why? Probably, because NPC1 cannot be palmitoylated and get to its workplace. Instead, it is degraded. A previous study showed that NPC1 in the lysosome needs to be de-palmitoylated to work. The new study doesn't mention this. Regardless, the reversible attachment of fatty acids to NPC1 is important and defects in these processes can influence disease progression.
Btw, fatty acids are not really sour, they just carry at one end a carboxy group that enables them to bond with other molecules by shedding a hydrogen ion (proton). Similarly chemically speaking, cholesterol is an alcohol because of the characteristic OH group at one end. Evidently, doesn't make you drunk!

PMID:42575437

Panek et al. Activation of pro-survival autophagy by a small molecule promoting p62 oligomerization. J Biol Chem. 2026 Oct;302(10):113430. doi: 10.1016/j.jbc.2026.113430. Epub 2026 Aug 11. PMID: 42575437; PMCID: PMC13570303.

This work from UK and Japan is about a new drug that may prevent NPC1-deficient cells to run out of steam. There are many hints for an energy deficit and there are many ideas why. Cells with broken NPC1 may accumulate junk mitochondria because their recycling via socalled mitophagy doesn't work anymore. The new drug, called SQ-1, activates autophagy and thereby mitophagy and improves the energy metabolism of neurons – as long as the dose is not too high. Does it work in animal models? The team introduced other new therapeutic avenues in 2024 (Digest #11).

PMID:41982147

Mahmoud et al. Differential Trafficking Phenotypes of NPC1 Mutant Proteins Reveal Distinct Cholesterol Accumulation Profiles. J Inherit Metab Dis. 2026 May;49(3):e70186. doi: 10.1002/jimd.70186. PMID: 41982147; PMCID: PMC13080411.

A fundamental question in the NPCD business is how the different gene mutations and the resulting protein variants affect cells, or simply put, how severe is the disease with this or that mutation. The new study prolongs a series of works, principally with cell culture models, that confirm one principle: the amount of NPC1 protein, the accumulation of cholesterol and other biochemical changes vary with the NPC1 variant. But, how these variants affect patients is another story.

PMID:42311208

Szenfeld et al. A Rapamycin Pharmacogenomic Approach for the Childhood Dementia Niemann-Pick C. J Inherit Metab Dis. 2026 Jul;49(4):e70214. doi: 10.1002/jimd.70214. PMID: 42311208; PMCID: PMC13375594.

This work gives rise to a short excursion. The keyword is *pharmacogenomics*, previously a.k.a. *pharmacogenetics*. The question is whether, when which genes influence whether and how a specific drugs affects patient x. If we knew, we could treat more efficiently, though drug sales may plunge. First hints that genes affect drug action appeared in the 1940s from studies on rabbits showing that different rabbit strains reacted differently to the pupil dilating atropine. The reason are strain-specific levels of an atropine inactivating enzyme. The present work used yeast to identify genes that modify the effect of rapamycin on NPC1 deficiency. As reminder, Rapamycin is an inhibitor of mTORC. This protein has key functions in all cells, as it integrates through different

sensors the levels of key components such as oxygen, energy and nutrients but also hormones, and controls basic cellular functions such as growth and cell division. However, Rapamycin showed variable effects on cell models of NPCD. The authors picked up several genes that may determine the response of yeast to rapamycin. Whether they also work in mammals is unclear. In any case, Rapamycin is an unlikely drug candidate for NPCD.

Cell-based models (ASMD)

PMID:42684456	Metkar et al. Targeting of Acid Sphingomyelinase, a Lysosomal Membrane Protein, Using Apolipoprotein E3-containing Nanodiscs. J Membr Biol. 2026 Sep 2;259(1):35. doi: 10.1007/s00232-026-00393-4. PMID: 42684456; PMCID: PMC13538249.

We are approaching Greek mythology and a poor guy named Sisyphos. He was busy with pushing a stone uphill. Nobody knows why, maybe the usual, win over the princess. In any case, the stone kept rolling downhill. Somehow, the present study reminds of this. It's a about an alternative approach for enzyme replacement. Here, the enzyme was tied to an anchor for membranes and wrapped in socalled nanodiscs, which are tiny, nanometer sized slices coated with a specific protein (for specialists: ApoE) that should help uptake by cells. In an ASMD cell culture model, the construct reduced sphingomyelin accumulation. Whether this works in an animal model remains to be seen. Earlier efforts with similar nanocarriers had moderate success (Digest 9). The key question is whether this new stuff can jump the blood-brain barrier. In this case, the stone would stay on the hill!

Miscellaneous

PMID:42198778	Real et al. The Melon Sterol Transporter Niemann-Pick C1 Protein Is a New Interactor of Cucumber mosaic virus Movement Protein. Viruses. 2026 May 20;18(5):577. doi: 10.3390/v18050577. PMID: 42198778; PMCID: PMC13211540.

Melons are like humans, they can become sick, for example by virus. One of them, the cucumber mosaic virus, seems to be able to infect – believe it or not – 1200 different plant species. The study from Spain shows that it uses among others, the two melon versions of NPC1. Indeed, melons have two NPC1 proteins, why is unclear for now.

PMID: 42366915 — Costa et al. A two-component ortholog of the Niemann-Pick C 1 protein is essential for normal growth and sterol trafficking and signaling in Tetrahymena thermophila. FEBS J. 2026 Jun 29. doi: 10.1111/febs.70636. Epub ahead of print. PMID: 42366915.

It would be unfair to compare humans to ciliates, not even if some of the former carry artificial cilia. But, the latter are ahead of humans, and this is shown by this nice work by Chilean colleagues. It's about the warmth-loving ciliate *Tetrahymena thermophila*, a workhorse of biology similar to yeast or mouse. *Tetrahymena* makes its own sterol named tetrahymenol. If it can get cholesterol, it eats it like other animals. Yes, alert readers guess already, the uptake needs NPC1 protein. But, now, attention: the NPC1 protein of Tetrahymena resembles the one of mouse and man, but it's too short, way too short! It misses the tentacle that reaches into the interior of the lysosome and grabs cholesterol from NPC2. So, where is it? Well, it's in the genome, but as a distinct gene! So, the ciliate made two out of one. Why, and how they find each other, is unclear so far.

Out of the box

PMID: 42107486 — Rahman & Zorumski. ARCH × Φ: Sterols and the evolution of gated biological execution. Biosystems. 2026 Jul;265:105812. doi: 10.1016/j.biosystems.2026.105812. Epub 2026 May 8. PMID: 42107486.

Ok, we all know: you can find something or somebody fascinating without ever understanding it, her or him, this may be even *conditio sine qua non*. This publication is an example, and if anybody understands it, please don't tell!

PMID: 42214342	Chayama et al.Physiological brain clearance architecture revealed by neuronal protein tracing. Cell. 2026 Jul 23;189(15):4737-4755.e17. doi: 10.1016/j.cell.2026.04.048. Epub 2026 May 29. PMID: 42214342; PMCID: PMC13225612.
PMID: 43014307	Zhou et al. The blood-brain barrier imports diverse neuroprotective proteins through pathways impaired early in Alzheimer's disease models. Cell. 2026 Nov 11:S0092-8674(26)01326-7. doi: 10.1016/j.cell.2026.10.039. Epub ahead of print. PMID: 43014307.

For all those who care about the blood-brain barrier (BBB), two awesome papers from the same group prominently published in CELL! Briefly, they are about how the brain gets rid of trash and which proteins it imports from blood. There are lots of ideas about this, and some are trashed by the new findings. The first shows with a new approach new and region-specific ways of trash elimination and its dysfunction in a mouse model for Alzheimers disease. The second study shows – again with a new approach – which proteins are imported in the brain from blood. Some candidates are interesting for NPCD, notably Apolipoprotein A1. And here as well, the uptake breaks down in a mouse model of Alzheimer. So, more investigations into BBB and ASMD / NPCD seem to be warranted (see above).

PMID: 42531412	Puszynska et al. Atlas of lysosomal aging reveals a metabolite signature shared with lysosomal storage disorders. Science. 2026 Jul 30;393(6810):eady0832. doi: 10.1126/science.ady0832. Epub 2026 Jul 30. PMID: 42531412.
PMID: 42778605	Fusar Bassini et al. The lipidomic architecture of the mouse brain. Nature. 2026 Oct;658(8134):205-217. doi: 10.1038/s41586-026-11050-0. Epub 2026 Sep 23. PMID: 42778605; PMCID: PMC13626954.

This is once again about two atlases prominently published in SCIENCE and NATURE. The SCIENCE paper is about changes in aging lysosomes and their overlap with changes in lysosomal diseases. The NATURE article is about distribution of fat in the brain. Well, in the rest of the body, you can feel it!