NCL Research Newsletter

– June 2022 –

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1 MAIN TOPICS

12th NCL Research Award

Prof. Diego Luis Medina

Congratulations to **Prof. Diego Luis Medina** for receiving the 12th NCL Research Award.

Since 2008, the NCL Foundation has regularly awarded the NCL Research Prize. With 50.000 euros, it is the most highly endowed award in the field of Childhood Dementia. With the award, the Foundation's Scientific Advisory Board honors an innovative research idea to further help pave the road for novel therapies to treat CLN3 disease.

This year's 12th NCL Research Prize was awarded to Prof. Diego Luis Medina from the Telethon Institute of Genetics and Medicine (TIGEM) in Pozzuoli, Italy, for his project "**Lysosomal storage-associated Genes in CLN3 Disease**".

The project aims to identify druggable genes and pathways that affect pathological lysosomal storage in CLN3 disease in the hope to find novel routes for developing therapeutics.

We wish Diego lots of success, and we would like to thank the **Joachim Herz Stiftung** for funding the research award again.

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Pioneering papers on CLN3, CLN5, and CLN7

We are always more than happy when research projects which we have funded continue to contribute to a substantial gain in knowledge of CLN3 disease biology and therapeutic insights. Together with Eric Marsh, **Dr. Rebecca Ahrens-Nicklas`** project idea received our 8th NCL Research Award in 2018.

Dr. Rebecca Ahrens-Nicklas

She has now published a second paper that sheds further light on **disease mechanisms underlying neural network dysfunction in CLN3**. The authors show that rescue of CLN3 expression in neurons alone normalizes

neural network function without significantly changing storage histopathology.
This implies a key role for neurons and not glia in CLN3 brain network dysfunction, and also that clearance of the typical storage type seen in CLN3 may neither be an appropriate readout indicative of therapeutic effects nor a reliable biomarker.


Prof. Robert Steinfeld

A team of scientists from **Zürich** and **Göttingen** led by Prof. Robert Steinfeld, member of our NCL Foundation's Scientific Advisory Board, published a paper that describes the **crystal structure of the CLN5 protein**. Furthermore, they also describe a thus far unknown novel enzymatic function of the protein as prototype of a new class of **S-depalmitoylases**.

Mutations in the CLN5 gene generally cause a rapid progressing form of NCL, more rapid than CLN3 disease. Over 50 sequence variations and mutations in the CLN5 gene have been reported and to be associated with variable types of dementias including Alzheimer`s disease. Like CLN5, also CLN1 encodes a depalmitoylase. In patients their functions can clearly not compensate for one another. That implies that CLN1 and CLN5 must have different functions and targets. What it tells us is that **protein depalmitoylation** plays a key role in brain homeostasis and the pathology of neurodegeneration. Future studies will hopefully uncover more precisely the differences and mechanisms underlying neuronal cell death in CLN1 and CLN5.

Another team around **Chunlei Cang** from China and **Dejian Ren** from the University of Pennsylvania recently published that the **CLN7 gene** that is faulty in a form of late-infantile NCL, encodes a protein that serves as a lysosomal **chloride channel** regulating lysosomal ion homeostasis and function.

Altogether, these different findings hopefully open doors to **new promising therapeutic strategies**.

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Three questions to Prof. Robert Steinfeld, University Children's Hospital Zürich

Robert, in in the chapter before we highlight your latest paper on CLN5 – congratulations on this! What do the results mean for understanding pathomechanisms in neurodegenerative diseases and NCL in particular?

Although the CLN5 gene defect was described as early as 1998 as the cause of a variant of late infantile neuronal ceroid Lipofuscinosis (NCL), the function of CLN5 remained unclear for more than 20 years. It was only through our structural and molecular

biology studies that we were able to demonstrate that CLN5 is a novel thioesterase that cleaves palmitoyl residues from proteins. Approximately 10% of all cellular proteins have fatty acids post-translationally attached and are thus anchored in the membrane. The reversible binding of palmitic acid to cysteine residues of proteins is highly regulated by the inter-play of palmitoyl transferases and de-palmitoylases. All S-depalmitoylases identified so far belong to the family of alpha/beta-serine hydrolases. The identification of a new family of cysteine-based S-depalmitoylases is a significant progress that goes beyond the scope of the NCL diseases. Further, the Cln5 variant Asn320Ser segregates with several Alzheimer's disease families, and the activity of proteases such as BACE1, that are involved in the formation of Alzheimer's beta-amyloid plaques, is regulated by their palmitoylation.

What would be your next goals regarding NCL research approaches?
As we hypothesize that decreased depalmitoylation may lead to impaired regulation of cellular protease activity and thus neurodegeneration, one of the major future goals is to prove this hypothesis. It could be the basis for new therapeutic approaches for the NCL diseases.

Currently, studies are ongoing or being initiated using different treatment strategies for various forms of NCL including gene therapy, anti-sense oligonucleotides, or small molecules - for which one(s) do you personally see the greatest chances of success and becoming available to patients in the future?
There is probably no universal therapeutic approach applicable to all NCL disorders. And it may be that we will achieve the best treatment outcomes through a multimodal approach.

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What's new? Project reports from Mainz and Hamburg (Germany)

Our research director **Herman van der Putten** returned highly inspired from a laboratory visit and project update in **Mainz**.

He had an appointment with PhD student **Masood Ahmad Wani** and his supervisor **Benedikt Grünewald** in the Institute of Pathophysiology of the University Medical Centre of the Johannes Gutenberg University in Mainz. Goal, an update, scientific exchange, and discussion about the project we support.

Masood is using **electrophysiological methods** to investigate which pathological changes affect neuronal properties and signal transmission between neurons in the CLN3 brain. Masood and Benedikt have already identified first fundamental changes that could contribute to loss of cognitive function and epilepsy.

New highly interesting data and follow-up experiments were discussed, and we are pleased that the project is revealing novel insights into neuronal dysfunction.

We thank Benedikt and Masood for their great commitment, and we keep a lookout for more findings to come.

A big thank also to our sponsors, the **Helga und Alfred Buchwald Stiftung**, the **Reinhard Frank-Stiftung**, the **Scheck Stiftung**, the **Stiftung Bostelmann**, and **von Poll Immobilien GmbH**.

In **Hamburg**, **Daniela Wünkhaus** successfully defended and completed her **doctoral thesis**. Daniela is a highly committed young scientist whose work was supported by the NCL Foundation. In her work, Daniela established a new **human CLN3 cell model** that shows several CLN3 disease-related changes at various levels including lysosomal storage, lipid and metabolite profiles, and she worked on a lysosomal target and antagonist-based mechanism, that reduces cell pathological changes.

Dr. Daniela Wünkhaus

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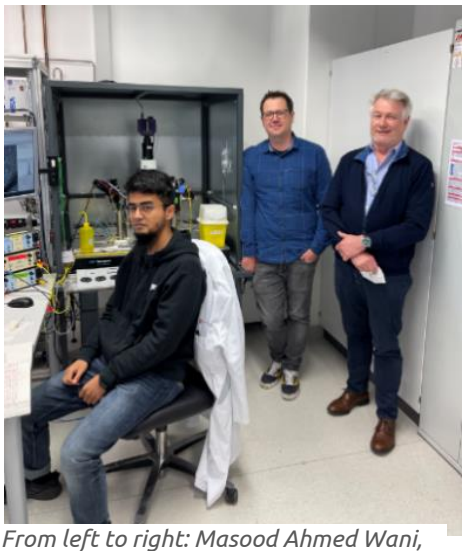

From left to right: Masood Ahmed Wani, Dr. Benedikt Grünewald, Dr. Herman van der Putten

These may lead to novel therapeutic options for CLN3 Batten Disease and related diseases. We thank **Evotec**, the **Heinrich Hartmann Stiftung,** and the "**Krimi-Cup**" for funding the project.

Dani wrote and allowed us to share:

"After the successful defense of my doctoral thesis, an exciting period of researching the NCL diseases is ending for me, hopefully only for now. The NCL-Stiftung is doing incredible work in raising awareness for these childhood dementia diseases. They also fund valuable research projects and kindly support their young researchers. Especially, I want to thank Frank Stehr and Herman van der Putten for their mindful supervision and for introducing me to the NCL research community. It was a great pleasure contributing to the research of these devastating diseases. I am looking forward to any up-coming collaborations and projects".

2 NEW PROJECT GRANT

Prof. Alessia Calcagnì with her team members Tuong Huynh (left) and Niculin Joachim Herz

We are happy to announce that a new project entitled "**Elucidating the impact of Microglia in CLN3**" started June 1st, 2022. The project is carried out by **Prof. Alessia Calcagnì** at Baylor College of Medicine in Houston, Texas, USA.

What is it about? The development of therapeutic strategies for CLN3 disease has been hampered by the very limited understanding of CLN3 function, its role in different brain cell types, and their role in the overall progression of brain pathogenesis. CLN3 patients and CLN3 mouse models show inflammatory microglial cell activation in the brain. Microglia represent the resident innate immune cells of the brain and serve important functions in neuronal homeostasis.

Whether observed changes in CLN3 microglial cells are a direct consequence of CLN3 depletion in these cells, and/or triggered by degeneration of neurons is the subject of Alessia's project. To this end Alessia will characterize brain changes and the microglial compartment in microglia-specific CLN3-KO mice and compare these with mice that lack the CLN3 gene in all brain cells. The aim is to shed light on the contribution of **cell-autonomous versus non-cell-autonomous** changes in the CLN3 brain. Perhaps the study can also point at **biomarkers** for monitoring more specifically the microglial changes during disease progression. In turn, these could help to assess the overall effectiveness of therapeutic approaches in the CLN3 brain, as well as therapies targeting microglia.

The funding period covers 2 years. Cooperating partners are **Dr. Paolo Grumati** and **Dr. Davide Cacchiarelli** (TIGEM, Pozzuoli, Italy), **Prof. Monther Abu-Remaileh** (Stanford University, CA, USA.

We thank the **Werner Reichenberger Stiftung** for sponsoring this important project!

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3 TRAINING, EDUCATION AND EVENTS

We created a new webinar **training for physicians** (in German language). It is dedicated to the topic of diagnosing NCL. The webinar is entitled "Clinical Diagnostics of Neuronal Ceroid Lipofuscinoses (NCL) and the Use of Multiomics". It is presented by two renowned experts:

Angela Schulz, MD, specialist in pediatric and adolescent medicine at the University Medical Center Hamburg Eppendorf and head of the special consultation for pediatric dementia NCL. Dr. Schulz highlights the clinical aspects of diagnosis. **Prof. Peter Bauer, MD**, Chief Genomic Officer of CENTOGENE GmbH in Rostock explains the use of multi-omics approaches to identify biomarkers facilitating genetic diagnosis and monitoring treatment.

The certified webinar is rated with **2 CME** points and is available to physicians on the **MedLearning AG platform**: https://cme.medlearning.de/ncl-stiftung/neuronale_ceroid_lipofuszinosen/index.htm

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We entered into a comprehensive new learning partnership with "**Gläsernes Labor**" on the Berlin-Buch. This is one of the largest and most successful student laboratories in Germany.

We offer a **PCR gene diagnostics** learning project using samples from a fictitious NCL family. The project is offered to students in 10th as well as upper grade levels. It provides teaching material on human genetics and genetic diagnostics in a practice-oriented manner. The aim is also to create awareness for rare diseases amongst students, and provide insight into various scientific professions and careers.

We thank the **Berliner Sparkassen Stiftung Medizin** for supporting this school project!

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On the occasion of this year's **Rare Disease Day**, always held end of February, the German magazine "**Berliner Tagesspiegel**" created awareness and publicity for this topic with a virtual expert health forum entitled "Rare diseases. Ways to a better diagnosis".

Dr. Frank Stehr

Our CEO **Dr. Frank Stehr** participated in a discussion panel dedicated to the topic "**A right to diagnosis: How do the rare become a priority**?"

The meeting focused on opportunities offered by modern laboratory diagnostics, the use of artificial intelligence, improving knowledge transfer, and increasing awareness, with the overall goal to significantly reduce time-to-diagnosis of rare diseases.

Retinal degeneration, cognitive and motor decline, as well as epilepsy are shared clinical phenotypes across NCL disorders. Frank Stehr had the opportunity to present the clinical picture of NCL with its (rare) treatment options on the **60th annual meeting of the German Society for Epileptology (DGfE) e. V.** held April in Leipzig.

His lecture was received with great interest!

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The dates for our upcoming **8th JNCL Young Investigator Symposium** and **19th National NCL Congress** are fixed (attendance is by invitation only):

Mnd 19-Wsnd 21st of September

- 8th JNCL Young Investigator Symposium: Monday & Wednesday
- 19th National NCL Congress: all day Tuesday

We are very grateful to the **Joachim Herz Foundation** which has once again generously offered space and meeting rooms for this event that will take place in the JHF headquarters in Hamburg, Germany.

4 RECENT NEWS AND PUBLICATIONS

CLN1

Kovács et al reported that acidified drinking water attenuates motor deficits and brain pathology in Cln1R151X nonsense mutant mice. Acidified drinking water significantly altered the gut microbiota composition of the mutant mice, suggesting a contribution of gut bacteria to the observed therapeutic effects.

Zhang et al reported seizures occurring in 7-month and older CLN1 (PPT1) knock-in mutant mice. These are associated with inflammatory activation of microglia. Astrocyte activation preceded microglia activation and an antagonist of the ATP-sensitive purinergic P2X7 receptor (P2X7R significantly reduced seizures in PPT1 KI mice.

Taysha Gene Therapies announced the news that Queen's University in Ontario, Canada, received Clinical Trial Application (CTA) approval from Health Canada for the Phase 1/2 clinical trial of TSHA-118, Taysha's investigational gene therapy for infants and children living with CLN1 disease.

Mondal et al described defects in lysosomal Ca++ homeostasis in Ppt1-/- mice. The mice have reduced levels of two palmitoyl acyltransferases which activate the transcription factor NFATC4. The latter regulates expression of the IP3R in the ER, which mediates lysosomal Ca++ refilling.

CLN2

Intravitreal ERT efforts to try and prevent retinal disease progression in children with CLN2 have started in two sites, one in the US (Nationwide Children's Hospital; https://clinicaltrials.gov/ct2/show/NCT05152914), and one in Great Ormond Street hospital in the UK, thanks to a great fund-raising effort by the BDFA. (The Guardian).

Kovacs et al used a commercially available automated segmentation software in optical coherence tomography scans to characterize the inner and outer retinal degeneration in CLN2 patients, and the authors propose this as a biomarker readout.

Iwan et al reported that CLN2 patients on intracerebral ERT continue to show a decrease in CSF NFL levels after 2-year treatment. NFL levels appear to correspond and predict improved clinical status of patients on ERT.

Leal-Pardinas et al present evidence indicating that access to early epilepsy gene panel testing helps to increase yield and shorten time to diagnosis.

Nickel and Schulz discuss the relevance of NCL natural history studies for clinical trials, using experience with CLN2 as an example.

CLN3

Rechtzigel et al demonstrate a substantial overlap in the protein interactomes of CLN3, CLN6, and CLN8, and that the absence of each of these proteins leads to synaptic depletion of SNAREs, tethers, and altered synaptic SNARE complexing in vivo.

Savvidou et al describe four CLN3 patients with several episodes of drug-induced hyperthermia. Possibly provoking drugs included risperidone, clozapine, olanzapine, haloperidol, quetiapine, and sertraline.

Hochstein et al present a natural history study of MRI brain volume changes. The data show that supratentorial grey matter volume changes 4.6% ± 0.2% per year, and is a sensitive parameter for assessment of disease progression that also shows a strong correlation with disease specific clinical scores.

Handrup et al present a long-term follow-up study of patients that received a pacemaker. Treatment is safe and may have great impact on quality of life, but the medical indication is relative. The authors suggest thorough discussion before deciding for this treatment.

Honingh et al present a qualitative and quantitative analysis of patient files and parent interviews on behaviours and emotions. It may provide a lead to adaptable support-modules for children with CLN3 disease.

Ware et al performed exome sequencing in a large cohort of children with cardiomyopathy. They identified a candidate gene set suggesting multigenic mechanisms for cause and presentation. Findings might bear on genetic modifiers in CLN3 cardiomyopathy.

Do et al provide first support of validity of the Vineland-3 adaptive behaviour scale for monitoring changes in CLN3 disease.

Abdennader et al did seizure phenotyping in a CLN3 cohort and report that seizures and epileptic discharges were frequent, often starting by age 10 years. Vineland-3 scores and CSF NFL levels correlated with UBDRS seizure score.

Dev et al report on an unusual case of a 13-year-old CLN3 patient without typical JNCL disease phenotypes but manifesting seizure episodes.

Honasoge and Smith report an unusual a case of bilateral chorio-retinal scarring due to a CLN3 heterozygous deletion in an asymptomatic patient.

Klein et al describe findings that strongly suggest converging roles of PSENEN and CLN3 in the autophagy-lysosome system, and in a γ-secretase-independent manner.

Ahrens-Nicklas et al describe that neuronal genetic rescue of CLN3 alone in CLN3-deficient mice normalizes brain network dynamics despite persistent storage accumulation.

Wibbeler et al report that the UBDRS provides a valid and reliable rating scale that can be used by trained clinicians in different sites to assess the severity and rate of progression of CLN3 disease.

Chear et al describe lysosomal alterations and decreased electrophysiological activity in iPSC-derived cortical neurons, composite heterozygous for the mutant CLN3 alleles delta exon7/9 (966 bp deletion) and the E295K missense mutation.

Relton et al used a HeLa cell CLN3 KO model to show that CLN3-deficiency is associated with an altered metabolic profile, reduced global protein translation, and perturbations in stress granule dynamics.

CLN4

Huang et al identified a novel CLN4 mutation in the DNAJC5/CSPα protein, a membrane associated HSC70 co-chaperone. The mutation leads to autosomal dominant adult-onset NCL. This novel C128Y mutation in a young 20-year-old female with memory loss as first symptom caused abnormal palmitoylation and triggered lipofuscin deposits.

Lee et al reviewed how the deregulation of CLN4/DNAJC5/CSPα perturbs unconventional protein secretion and endosomal micro-autophagy, and contributes to lipofuscin accumulation and neurodegeneration.

Nykanen et al provided further experimental evidence for a role of DNAJC5/CSPα in the processing of APP in cells and an APP mouse model. 5xFAD mice haplo-insufficient for the DNAJC5 gene show increased Aβ plaque burden and a decrease in Aβ plaque latency.

CLN5

Meiman et al describe a novel canine model of CLN5 disease that manifests global brain atrophy and neurological signs, progressing to a level of severity that requires euthanasia by 21-23 months.

Neurogene announced in February the start of recruiting a small number of CLN5 patients in an AAV9-based CLN5 gene therapy trial.

Doccini et al used lysosomal proteomics showing that CLN5-deficiency is linked to disturbances in lipid homeostasis and sphingolipid metabolism.

Basak et al used CLN5-deficient iPSC-derived neurons and showed reduced acidic organelles, reduced lysosomal enzyme activity, and impairments in lysosomal movement.

Luebben et al solved the crystal structure of CLN5 and showed that the CLN5 protein has catalytic properties as a novel cysteine-based S-depalmitoylation enzyme. They show that CLN5-deficient neuronal progenitor cells have reduced thioesterase activity.

CLN6

Amicus Therapeutics announced it will discontinue its investigational gene therapy program of AT-GTX-501 for CLN6 Batten disease. The decision was based on data from a long-term follow-up study (NCT04273243) that showed AT-GTX-501 failed to stabilize disease progression

Rus et al present one of the largest cohorts (97 subjects) to date of genetically diagnosed CLN6 patients screened at a single centre and originating from 20 countries. This study expands the number of published clinical cases and the mutational spectrum of disease associated CLN6 variants.

Koh et al provide experimental results showing that a CLN6-CRMP2-KLC4 complex regulates anterograde ER-derived vesicle trafficking in cortical neurites.

Nicolau et al describe 3 male CLN6 patients from two unrelated Greek-Cypriot families which presented with slightly different symptoms that appeared at the age of 6 years. Unusual, both probands were without initial signs of vision and/or hearing loss.

Murray and Mitchell highlight the differential vulnerability of retinal layers, and the time course of retinal atrophy in ovine models of CLN5 and CLN6 disease. These findings have potential impact on targets and timing for ocular therapies.

Barry et al generated aggregation chimeras that provide evidence of in vivo intercellular/cross-correction in ovine CLN6.

CLN7

Lopez-Fabuel et al describe aberrant upregulation of the glycolytic enzyme PFKFB3 in CLN7, and show that administration of the highly selective PFKFB3 inhibitor AZ67 rectifies key disease hallmarks in the Cln7Δex2 mouse brain in vivo and in CLN7 patients-derived cells.

Garcia-Macia and Bolaños report that CLN7 deficiency in the hypothalamus damages liver lipophagy and results in fat accumulation.

Chen et al report that AAV9/MFSD8 gene therapy is effective in preclinical models of CLN7 disease. A Phase I intrathecal gene transfer trial for AAV9/MFSD8 has been approved by the FDA, and runs at Children's Health in Dallas, TX, in collaboration with UTSW Medical Center, and Taysha Gene Therapies (see: clinicaltrials.gov NCT04737460).

Reith et al report a novel exonic variant of the CLN7 gene that was found in two closely related subjects that are both homozygous for this variant. Both subjects have clinical features of NCL but displayed a great difference in onset of first neurologic as well as ophthalmologic symptoms. This CLN7 variant is silent at the translational level but affects splicing.

CLN10

Liu et al report that intravitreal gene therapy in cathepsin-D deficient mice restores autophagy-lysosomal pathway function and attenuates retinal degeneration.

CLN11

Frydas et al report that functional uORFs in the alternative 5′ UTR of CLN11 (Progranulin) mRNA act as potential regulators of PGRN expression. They also show that genetic variation within the uORFs can increase PGRN protein expression.

Du et al report that sortilin and prosaposin independently regulate lysosomal trafficking of PGRN in vivo. Deletion of both prosaposin and sortilin totally abolishes lysosomal localization of PGRN in neurons but not in microglia. Their data suggest the existence of a novel PGRN lysosomal trafficking pathway in microglia.

Reifschneider et al used genetic and pharmacological (antagonistic Abs) approaches to suppress TREM2-dependent transition of microglia from a homeostatic to a disease-associated state. Trem2 deficiency in PGRN KO mice reduced microglia hyperactivation, but lysosomal dysfunction was not rescued, and synaptic loss and CSF neurofilament light-chain levels were further elevated. Altogether, the findings suggest that TREM2-dependent microglia hyperactivation in models of PGRN deficiency does not promote neurotoxicity, but rather provides neuroprotection.

Tanaka et al report that two drugs (Abemaciclib and vacuolin-1) which both induce autolysosome vacuole formation promote autophagosome-lysosome fusion. Interestingly, vacuole formation was inhibited by knockdown of PGRN, and promoted by its overexpression.

CLN12

Dang et al review the pathological mechanisms of CLN12/ATP13A2 mutations leading to Parkinson's disease, and its role in protecting dopaminergic neurons.

NCL reviews & relevant lysosomal papers related to neurodegeneration.

Medoh et al debate on processes in neurodegenerative LSDs, and possible drivers including toxic substrate accumulation inside lysosomes as well as nutrient deprivation downstream.

Lee et al show that autolysosome acidification declines in Alzheimer`s Disease neurons before extracellular amyloid deposition. They report markedly lowered vATPase activity and build-up of Aβ/APP-βCTF selectively within enlarged de-acidified autolysosomes. They describe Aβ-positive autophagic vacuoles (AV) forming flower-like perikaryal rosettes (PANTHOS), and AVs coalescing into peri-nuclear networks of tubules with intraluminal fibrillar Aβ accumulation. Lysosomal membrane permeabilization, cathepsin release and lysosomal cell death ensue accompanied by microglial invasion. Neurons exhibiting PANTHOS are the principal source of senile plaques in AD models.

Jennings et al present data supporting the hypothesis that LRRK2 inhibition with DNL201 has the potential to correct lysosomal dysfunction in patients with PD at doses that are generally safe and well tolerated. This could be of broader interest as LRRK2 inhibition may ameliorate lysosomal dysfunction more broadly.

Lie et al provide results in Alzheimer-mutant PSEN1 knock-in mice that link dysfunction and mis-trafficking in lysosomal pathways to neuronal dystrophy, which can be rescued by blocking the lysosomal ion channel TRPML1.

Reddy and Brahmbhatt review the application and effectiveness of anti-epileptic drugs, anti-convulsant drugs, and vitamin C, in multiple scenarios to treat Batten disease.

Brudwig and Weimer review breakthroughs in Batten disease research focusing on multiple therapies that show promise in preclinical and clinical studies.

Bantje and Tikkanen discuss splicing therapy options for Lysosomal Storage Disorders including also CLN2.

Simonati and Williams focus on recent advances in NCL research and summarize multi-faceted approaches to deal with clinical issues.

Trivisano et al review neurophysiological findings in NCL, and how these findings may facilitate earlier diagnosis and help follow disease progression.

Kaminiów et al provide an overview of the current knowledge regarding NCL disease pathophysiology, genetics, and clinical manifestation, and also discuss approaches to diagnosis.

Guo et al analysed the contribution of Mendelian disorders in a large population-based pediatric neurodegeneration cohort of approximately 100,000 patients. Out of 69 patients with a neurodegenerative phenotype, 42 patients had a genetic diagnosis, and 32 patients had unique disorders. Common diagnoses included also NCL.

Bartsch and Storch review experimental therapeutic approaches for the treatment of retinal pathology in NCL with special emphasis on ERT and gene therapy.

Gardner and Mole summarize current knowledge and understanding of the genetic basis of NCL and their phenotypic heterogeneity.

Takahashi et al summarize the most up-to-date understanding of glial pathologies and their contribution to the pathogenesis of NCL

Santos et al discuss splicing modulation as a promising therapeutic strategy for lysosomal storage disorders using Mucopolysaccharidoses as an example.

Cao et al discuss current opportunities and challenges of targeting lysosomes in human disease.

Zoncu and Perera review emerging molecular mechanisms of lysosome remodelling and repair in health and disease.

Shibuya et al present a proof-of-concept study suggesting that efficient CNS-wide microglia replacement may have therapeutic efficacy for a variety of neurological diseases.

Drobny et al discuss the role of lysosomal cathepsins in neurodegeneration and summarize the potential role of lysosomal cathepsins as clinical biomarkers and therapeutic approaches.

Tang et al discuss the critical roles of sphingolipid metabolism in regulating lysosomal functions, and how such regulation may contribute to aging and aging-related diseases.

Kim et al review and discuss our understanding of molecular mechanisms underlying the formation and regulation of organelle contact sites, and their role in health, disease, and therapy.

Cisneros et al highlight advances in the field of mitochondria-lysosome contact sites and their mis-regulation across multiple neurodegenerative disorders.

Kuk et al provide arguments for why studying the mitochondrial–lysosomal axis contributes to a better understanding of essential physiological processes underlying LSDs, and propose new LSD treatment strategies.

Meraş et al review the mechanisms that regulate the sorting of soluble proteins to lysosomes, highlighting the effects of mutations in this pathway that cause human disease.

Savini et al used the worm Caenorhabditis elegans as a model, presenting results that reveal lysosomes as a signalling hub coordinating metabolism by mediating inter-tissue communication and promoting longevity.

Hörner et al used a SPG11 mouse model of Hereditary Spastic Paraplegia to show that targeting the adaptive immune system T-lymphocyte component can attenuate the neurodegenerative phenotype. SPG11 dysfunction causes autophagic defects, and the protein is involved in autophagic lysosomal reformation (for review see Pozner et al)

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