NCL Research Newsletter May 2021

Content

1. Main Topic

1.1 Goodbye and thank you Rudolf Martini!

Rudolf Martini

We thank Rudolf Martini for more than 8 years of dedicated work as SAB member for the NCL Foundation! He added neuroinflammation as an important novel scientific direction to the NCL field and our project portfolio. He once described to us his commitment and clear motivation to support the foundation as follows: "Funding in the field of rare disorders in particular is limited and deciding which projects should receive this money is something which has to be considered very carefully. Being able to make a contribution in this regard was just as important to me as bringing together international top researchers from a variety of highly specialised neuroscientific subdisciplines in order to, in the best case, develop viable concepts".
History shows, that he had excellent success in doing so and we wish him all the best for the future while opening joyful new chapters in life!

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1.2 Review of the 18th National NCL Congress

18th National NCL Congress as a virtual meeting

Our 18th National NCL Congress took place mid-April. This annual meeting serves to share current research results in the NCL field with an emphasis on CLN3 disease. The meeting promotes networking between researchers and clinicians in academia and biotech sharing the goal to facilitate the development of therapies. More than 50 invited participants attended the meeting, including researchers from the NCL field, members of our Foundation's Scientific Advisory Board, members of Batten disease Foundations in the USA and Europe, as well as parents of affected children or adults. This time, the meeting was virtual and split into a Sunday and a Monday session, each covering a different topic (see agenda). **The first day focused on retinal**

degeneration with sessions on clinical aspects, gene therapy approaches, and CLN3 retinal animal models. **The second day was devoted to the role of adaptive and innate immune cells** in Batten disease.

Retinal degeneration is the earliest and most consistent clinical hallmark in children with CLN3 disease. It typically starts as a bilateral maculopathy, is diagnosed around school age, and progresses rapidly within 1-3 years to legal blindness. Even today most children are diagnosed at a stage when retinal degeneration has progressed significantly. This is of great concern and will continue to hamper treating retinal aspects in CLN3 patients, unless we are able to move diagnosis to a pre-symptomatic stage before retinal degeneration has progressed beyond a stage when halting the loss of function and cells is no longer effective.
In some countries, CLN3 and other NCLs have been added to retinal degeneration Next-Generation-Sequencing (NGS) panels. This is one step forward towards identifying patients early. Newborn screening is of course ultimately the ideal approach but still faces ethical hurdles. Patients perceive vision loss as a major loss of quality of life and handicap because it severely limits social, educational, and daily-life capabilities. Maintaining even just light sensation would already be a blessing. With the advancement of new therapies, earliest possible diagnosis remains key.
Some therapies already in the clinic or on the horizon have potential for treating besides the CNS also CLN3 retinal degeneration. A one-fits-all solution, however, seems unlikely. There are some indications that CNS directed **gene therapy** using AAV can also reach the retina, but species differences in retina-brain neural network circuitry make clinically relevant predictions from animal models unreliable. Retina-directed therapies using AAV and perhaps also **anti-sense oligonucleotides (ASOs)** will likely have to be dealt with specifically and in combination with CNS directed therapy. Exceptions might be therapies based on the use of low molecular weight compounds. Successful gene therapy in the retina requires either expression of the transduced gene in most or all retinal cell types, or at least in those cell types, that mainly drive the retinal degeneration. It remains unclear whether and which retinal cell types are mainly at the root of retinal degeneration in CLN3 disease in patients. Experimental evidence from human iPSC-derived retinal pigment epithelial (RPE) cell models suggests clear deficits in RPE. On the other hand, experimental gene therapy directed towards bipolar cells in the mouse model suggest that this inner layer cell type plays a major role. Major species differences between rodent and primate retina make it very hard to predict which cell type(s) need targeting in patients.

What is the role of adaptive and innate immune cells in CLN3 disease? This question was addressed in the meeting on Monday. Genetics and experimental evidence from other neurodegenerative diseases including Alzheimer`s disease and forms of frontotemporal dementia caused by haploid insufficiency of progranulin (CLN11) point at clear roles for **microglia,** the innate immune cells of the brain. In multiple sclerosis (MS), clinical efficacy of drugs like **Fingolimod** targeting adaptive immune cells show that these cells play a key role in the disease process.

Experimental evidence in preclinical demyelination models furthermore support more and more also a role of innate immune cells in disease progression. Therefore, dampening disease amplifying mechanisms caused by immune cells might be a broadly applicable therapeutic principle in neurodegenerative diseases including NCL.
Data gathered in preclinical mouse models - including models of CLN1 and CLN3 disease - support roles of both adaptive and innate immune cells in amplifying disease. Furthermore, also crosstalk between these types of immune cells seems to play a role. Some NCL patients including a few CLN3 patients have received or still receive Fingolimod. However, without a well monitored and multi-center conducted efforts involving sufficient numbers of patients and a rigorous use of appropriate rating scales and well defined outcome measures we will likely never know whether drugs like Fingolimod can improve quality of life in CLN3 patients.
In contrast to therapies like gene therapy and exon skipping ASOs that attempt to correct the lack of CLN3 function at its roots, immune modulators likely cannot play a major disease modifying or transforming role. This perception of a subordinate role as compared to potential disease-modifying therapies plays likely a major role in decision processes of whether or not to conduct immune-modulation based trials in CLN3 patients. This despite the fact that such treatments might have a significant impact on quality-of-life of patients as disease progresses. Worth emphasizing also that currently used AAV9 **gene therapy** vectors essentially fail to correct gene defects in microglia with consequences, we can only speculate on today.
Speakers in the innate immune cell session highlighted CLN3 disease-associated changes in microglia. The jury is still out on what contribution microglia play in CLN3 disease and we support further investigations into defining their role. Promising data were presented on maintaining **neural network function** in CLN3 mice following AAV9 based gene therapy. If AAV9 GT eventually proves promising in CLN3 patients, novel microglia-related disease aspects could emerge in patients and that may require add-on treatments.

In brief, lots remains unknown and to be done. Recent developments raise hope for novel therapeutic routes as well as biomarkers, and we hope that our joint efforts and mutual support to fight Batten disease will eventually bear fruit and improve the lives of our patients.

We thank all the dedicated presenters: Szilárd Kiss, Simon Dulz, Michalis Georgiou, Dominik Fischer, Sophia kleine Holthaus, Shaomei Wang, Qingjun Wang, Ruchira Singh, Jill Weimer, Rudolf Martini, Kevin Rostásy, Janos Groh, Susan Cotman, Sabina Tahirovic, Jeremy Burns, Anja Capell, Markus Damme, Rebecca Ahrens-Nicklas. A big thank you also to our sponsor and partner Joachim Herz Stiftung for the generous support!

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1.3 Three questions for Graeme Bilbe, new member of our Scientific Advisory Board

We welcome Graeme Bilbe as a new member of our Scientific Advisory Board! Graeme was Global Head of Neuroscience Discovery at Novartis before joining the Drugs for Neglected Diseases initiative (DNDi) as R&D Director in 2012.

Graeme Bilbe

1. Graeme, welcome to the NCL Foundation! You have an impressive career in neuroscience and neglected diseases - what has been for you personally the highlight of your work so far?

Developing therapies that can successfully treat and even cure disease is a tremendous challenge. If I was to choose the most impactful disease therapy I have been involved in for treating patients, I would have to choose fexinidazole, the first oral, safe therapy for sleeping sickness, a scourge of mankind for millenia. The introduction of fexinidazole, will hopefully drive the elimination of sleeping sickness in the world.

2. What is your motivation for joining the Honorary Scientific Advisory Board of the NCL Foundation and where do you see the focus of your work here?

I was first attracted to the idea of making a drug for treating disease when I entered University. It is a very challenging and complex endeavour which I have spent almost my entire career first learning, then applying, and in recent years having some success in bringing life-changing new therapies to patients. Along the way, I have learnt many of the driving principles and intricacies of drug discovery and development. I hope I can apply my experience and knowledge to find ways to get life-changing therapies to the NCL patient, particularly in helping to identify and chaperone a new therapy through the many hurdles between discovery and efficacy in clinical trials.

3. How do you assess the state of NCL research - where do you see the most opportunities, where the biggest challenges?

Finding a therapy to change the course of disease in NCL is very challenging. Fortunately, we know the genetic cause of disease and are beginning to understand the mechanisms underlying disease manifestation and we know disease cell types and target organs but still need to understand better the biology of the disease. I am also very impressed with the incredible scientists, clinicians, motivated parents, patients and caregivers who will be central to developing new therapies. Although these are very good tools in our armoury, we will face many challenges to implement a new therapy from understanding how our new therapies perform in animal models

of the disease through advancing our understanding of disease biology to enable development of a clinical tool chest such as biomarkers. We also need to develop objective measurements of therapeutic action to demonstrate efficacy in clinical trials which can objectively define success in slowing or stopping disease progression and hopefully leading to a cure. Although this may look like a daunting task at first, it is only by doing that we can expand our knowledge and discover novel therapeutic avenues that will make our work a success.

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2. Scientific and Medical Meetings

The NCL Foundation is organizing two **German-language symposia** at two big annual conferences, addressing pediatricians:

1. Kongress für Kinder- und Jugendmedizin in Berlin (06.-09.10.2021)
   Our symposium entitled „Lysosomale Speicherkrankheiten – meist unerkannt? Vom klinischen Bild zur Pathophysiologie und Therapie“ will take place on **Saturday, October 09, 2021 (15:00 – 17:00)**. This is the current **agenda:**

   - Herausforderung NCL Diagnose - kann eine KI-App wie Ada helfen? (Stefanie Brückner)
   - Lysosomale Speichererkrankungen - wann daran denken? (Julia B. Hennermann)
   - Frühe Anzeichen einer neurodegenerativen Erkrankung am Beispiel der NCL (Angela Schulz)
   - Leben mit NCL (Sabine Rosenlöcher)
   - Lysosomale Erkrankungen mit Beteiligung des Gehirns – aktuelle & zukünftige Therapiemöglichkeiten (Andreas Hahn)

2. 46. Jahrestagung der Gesellschaft für Neuropädiatrie in Salzburg, Austria (05.-07.11.2021)
   Our symposium will take place on **Friday, November 5, 2021 (17:30 – 18:30)**. This is the current **agenda**:

   - Neurodegeneration im Kindesalter: Update zu den NCL-Erkrankungen (Robert Steinfeld)
   - Erfahrungen und Empfehlungen bei juveniler NCL (Michael Freilinger)
   - CLN2 – eine nun behandelbare Erkrankung (Andreas Hahn)

Further upcoming conferences:

- **7th JNCL Young Investigator Symposium**
  Our next young investigator meeting will be held in **December 2021 in Hamburg, Germany**. We invite young researchers working on CLN3 trying to facilitate a scientific exchange and foster new collaborations.

- **17th International Congress on NCL**
  Dr. Jon Cooper is organizing the next international NCL conference which will take place from **October 6-10, 2021 in St. Louis, USA**. Registration is now open. It will be held as a hybrid meeting.

Update medical information & training:

- We have updated our medical **information leaflets** for ophthalmologists and pediatricians. Additionally, we would like to point out that we have also updated our **certified online training** on NCL for physicians (in German).

- A **training webinar** in German for physicians on the topic "**Update zur Diagnostik frühkindlicher Speichererkrankungen – Fokus NCL**" is organized by our cooperation partner amedes. Frank Stehr will talk about clinical aspects and therapy options for NCL. **Date: June 16, 2021, 18:00-19:30**.

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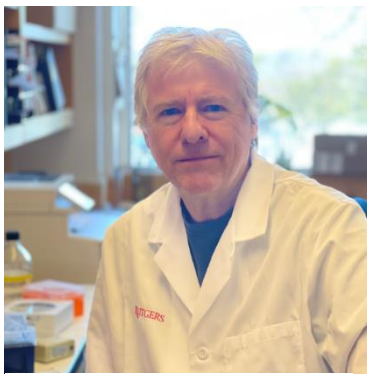
3. Grants and Awards


David Sleat

On the occasion of rare disease day at the end of February this year, we awarded our **11th NCL Research Prize**. The winners are Drs. An Dang Do and Forbes D. Porter from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH), Bethesda and David Sleat from Rutgers University, Piscataway (all USA) for their project "Identifying Proteomic Biomarkers for CLN3 Disease". Developing therapeutic options for CLN3 remains a challenge as long as there are no biomarkers that can be used for reliable disease diagnosis and monitoring. The awardees will analyze a large collection of cerebrospinal fluid (CSF) samples from CLN3 patients with the aim of finding such biochemical markers that correlate with the disease pattern and

progression of CLN3 disease. With the help of the 50,000 US-Dollars prize money, the project will be implemented in cooperation between the NIH and Rutgers University, where the analyses will be carried out. This collaboration came about through our biomarker webinar last year. The collection of patient CSF samples available to the researchers from the NIH is unique and we are very excited about the results!

Masood Ahmad Wani

We started funding a **new NCL research project** in Prof. Jakob von Engelhardt's laboratory at the Institute of Pathophysiology, Johannes Gutenberg University of Mainz, Germany beginning of this year: Masood Ahmad Wani will investigate for his PhD project early neuronal deficits in CLN3 using a combination of electrophysiological approaches in CLN3 mouse model. Through this project we hope to gain insights into the early disturbances in the neuronal activity and mechanisms that contribute to abnormal spiking behavior in CLN3 neurons. Furthermore, the identified neuronal defects can serve as useful biomarkers in preclinical animal studies of early and late phase therapeutic interventions. Our funding partners are: Buchwald Stiftung, Reinhard Frank-Stiftung, Scheck-Stiftung, von Poll Immobilien, Stiftung Bostelmann. Thanks a lot!

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4. Recent Publications

CLN1

Balouch et al. presented a comprehensive cellular characterization of human PPT1-deficient fibroblast cells harboring Met1Ile and Tyr247His compound heterozygous mutations. The authors report a heightened susceptibility to exogenous reactive oxygen species (ROS)-induced cell death and suggest elevated basal levels of endogenous ROS and disturbed of intracellular organellar networks in INCL pathology.

Berve et al. provide evidence for a detrimental impact of innate immune reactions in the CNS of CLN1 mice. The authors show that treatment with the potent CSF-1R inhibitor PLX3397 depletes pro-inflammatory microglia/macrophages and attenuates neuroinflammation in CLN1 ($Ppt1^{-/-}$) mice. However, with a sex- and region-biased efficacy.

Groh et al. reported that disease outcome can be attenuated in a CLN1 mouse model also when treatment with the immunomodulators fingolimod and teriflunomide starts after disease onset. Earlier the authors had shown that both drugs attenuate the neurodegenerative phenotype when applied preventively.

Ługowska et al. examined DPP-IV activity in plasma samples from 307 patients affected with 24 different LSDs and observed an elevated activity in patients with alpha-mannosidosis and some forms of mucolipidosis and mucopolysaccharidoses, but not in CLN1 patients.

Nelvagal et al. provide new insights into the early onset and spatio-temporal staging of CLN1 pathogenesis in spinal cord during postnatal maturation. Microglial activation is already significant at 1 month, followed by astrocytosis, selective interneuron loss, and before significant storage material accumulation and lymphocyte infiltration occurs at 3 months.

Parker et al. report disease-associated alterations in gut microbiota composition of $Cln1^{R151X}$ and $Cln2^{R207X}$ mice. The authors also highlight remarkable strain-specific differences that likely contribute to differences in behaviour and disease susceptibility between strains.

Perez-Canamas et al. described that deficiency of the lysosomal transmembrane protein TMEM106B rescues neurodegeneration in a pharmacological model of Gaucher disease model while exacerbating neurodegeneration in a PPT1-dependent NCL model.

Sadhukhan et al. describe a novel pathway to neuropathology in CLN1 that might explain the neuroprotective action of N-tert(Butyl)hydroxylamine (NtBuHA) by reducing neuroinflammation. APT1 depalmitoylates H-ras. In CLN1, two APT1 S-palmitoylation enzymes and S-palmitoylation of APT1 are reduced. This correlated with increased plasma membrane-localized H-Ras, microglial proliferation, and neuroinflammation which is reversed by treatment with NtBuHA.

Vergoten and Bailly modelled the interaction of three potent inhibitors of PPT1, hydroxychloroquine (HCQ), and the dimeric analogues Lys05 and DC661.

Yuan et al. provided experimental evidence for accumulation of palmitoylated GFAP and its contribution to the pathogenesis of astrogliosis and neurodegeneration in PPT1-deficient mice.

CLN2

Baradaran-Heravi et al. investigated the effect of small molecule eRF3a degraders on premature termination codon (PTC) read through in several genetic disease models. CC-885 and CC-90009 reduced not only the levels of eRF3a, but also those of eRF3b and eRF1. Furthermore, they act synergistically with aminoglycosides to suppress nonsense-mediated mRNA decay (NMD) and increase PTC readthrough also in TPP1 mutant cells.

Kim et al. report the results of a small CLN2 safety and efficacy clinical trial of cerliponase alfa. In brief, the authors report no relationship between magnitude of CSF exposure and efficacy, maximum benefit obtained across the range of exposures with 300 mg Q2W, hence supporting 300 mg i.c.v. Q2W for CLN2 treatment.

Ma et al. generated human H9 embryonic stem cell models of CLN2 disease by introducing two of the most prevalent *TPP1* mutations using CRISPR/Cas9 editing. These cell models are available for sharing.

Mole et al. provide a guideline for healthcare professionals involved in the management of patients with CLN2 disease. This guideline is based on robust evidence-based, expert-agreed recommendations on risks/benefits of disease-modifying treatments and the medical interventions.

Schwering et al. developed a Hamburg Best Practice Guidelines for ICV–Enzyme Replacement Therapy (ERT) in CLN2 Disease based on 6 years of enzyme replacement therapy of 48 CLN2-patients.

Sondhi et al. injected an AAV vector encoding human CLN2 into the brain parenchyma of children with CLN2 disease. Disease progression was slowed but not to the same degree as in children that received recombinant TPP1 emphasizing further improvements in gene therapy needed.

CLN3

Abdennadher et al. performed seizure phenotyping in a cohort of 20 CLN3 patients using clinical history, EEG, and the Unified Batten Disease Rating Scale (UBDRS). Seizures and epileptiform discharges were frequent, often started by age 10 years, and without significant difference between genotypes. Adaptive behaviour composite (ABC) scores and CSF neurofilament light chain (NEFL) levels correlated with UBDRS seizure score suggesting a role of seizures in the neurodegenerative process.

Ahrens-Nicklas et al. determined the impact of genetic rescue in distinct cell types on neural circuit dysfunction in CLN3 disease. The authors restored *Cln3* expression via AAV-mediated gene delivery in a CLN3 mouse model, and performed conditional genetic rescue selectively either in neurons or astrocytes. Rescue of *Cln3* expression

in neurons alone but not astrocytes normalized clinically-relevant electrophysiologic markers of network dysfunction while histopathology (storage) remained substantial.

Dang Do et al. showed that CSF and serum NEFL levels are significantly increased in CLN3 patients and correlate with other disease-relevant measures such as BDDRS and ABC scores. Therefore, NEFL levels may serve as one potential biomarker in CLN3 clinical trials and management.

Dulz et al. established an ophthalmic rating scale to assess ocular disease severity in juvenile CLN3 disease. Ophthalmic manifestations of *CLN3* patients correlated closely with the severity of neurological symptoms and age of the patient. The rating may be valuable tool for the evaluation of novel therapeutic strategies for *CLN3* disease.

Gilani et al. described a novel biallelic frame shift variant of CLN3 (p.Leu376Argfs*15) in exon 14 in a large Iraqi consanguineous family and that most probably led to JNCL with variable expressivity of the phenotype.

Hildenbrand et al. characterized upper limb motor function during activities of daily living in a cohort of 22 CLN3 patients. Poorer visual ability, disease severity, and cognitive function were associated with worse performance on coordination, speed and fine motor control, whereas age had limited impact.

Kinarivala et al. reported a CLN3 iPSC-derived model of the blood-brain barrier that displays hallmarks of CLN3 disease including lipofuscin and subunit C accumulation as well as mitochondrial dysfunction. Utility in screening was shown by identifying compounds reversing defects.

Kuper et al. reported that upon presentation at the ophthalmologist the retina in CLN3 disease is extensively and more severely affected. Also, it shows differentiating early clinical features that should facilitate the identification of children with CLN3 disease.

Langin et al. generated and characterized a novel CLN3^{Q352X} mouse model and describe its potential utility as a novel model to test therapeutics.

Minnis et al. performed synthetic genetic array analyses in yeast to delineate functional signatures for three disease-causing mutations in the yeast CLN3 orthologue *btn1*. The results imply that the minor 1-kb deletion transcript both loses and retains some inherent functions and acquires abnormal characteristics with implications for genotype-phenotype correlations.

Nonkes et al. described an automation of an otherwise cumbersome task of manually quantifying CLN3 lymphocyte vacuolization, thereby aiding prompt clinical decisions in relation to disease.

Shematorova and Shpakovski reviewed changes in cell metabolism and human-specific molecular features of *CLN3* gene expression and discuss possible molecular mechanisms of CLN3 disease.

Smirnov et al. examined 1533 French patients with inherited retinal disorders (IRDs) and identified 15 cases with biallelic *CLN3* variants and two distinct patterns of retinal disease. A mild rod-cone degeneration and a severe retinal degeneration with early macular atrophic changes. Eleven distinct and four novel pathogenic variants were detected. All but one (R405W) were distinct between JNCL and retina-restricted disease.

Tang et al. demonstrated a novel role of CLN3 in regulating photoreceptor outer segment (POS) phagocytosis in iPSC-derived retinal pigment epithelium (RPE). The findings suggest a contribution of primary RPE dysfunction in CLN3 disease that might be targeted by gene therapy.

Yasa et al. showed that CLN5, which interacts with CLN3, regulates retromer function by modulating key interactions between CLN3, Rab7A, retromer, and sortilin. CLN3 and CLN5 serve as an endosomal switch regulating the itinerary of lysosomal sorting receptors.

Zhang et al. investigated the molecular consequences of a compound heterozygous *CLN3* mutation ($CLN3^{c.175G>A/\Delta 1kb}$) in iPSC-derived neural retinoids (NROs) from a patient with non-syndromic CLN3 disease. Correction of the c.175G>A variant restored *CLN3* mRNA and protein expression, prevented accumulation of SCMAS, and reduced vacuolization of photoreceptor inner segments.

Zhong et al. described that CLN3 mutant mice displayed vision impairment and retinal abnormalities including RPE atrophy and degeneration. Downregulating CLN3 in RPE cells led to signaling and transcriptional alterations, autophagy induction, and metabolic abnormalities including ATP depletion and glycogen accumulation. These findings suggest links between RPE dysfunction and vision loss in JNCL.

CLN4

Naseri et al. reviewed and discussed a possible iron chelation therapy for autosomal dominant CLN4 disease based on CSPα oligomerization via ectopic Fe-S cluster binding.

CLN5

Basak et al. reviewed the CLN5 literature and discussed the missing pieces of the puzzle that need to be addressed to develop an efficient therapy for CLN5 Batten disease.

Doccini et al. described a mitochondria-focused quantitative proteomics approach showing the involvement of CLN5 in activation of mitophagy and mitochondrial homeostasis, and perhaps relevant to CLN5 disease treatment.

Xing et al. reported that CLN5-knockdown in human glioblastoma cell lines inhibited proliferation, promoted apoptosis, and inhibited Akt and mTOR signaling pathways.

CLN6

Best et al. investigated the secretome of cultured CLN6 mouse neurons and glia. Their results suggest that the secretome plays a role in CLN6 pathogenesis and highlights also its potential to identify biomarkers for monitoring disease and assessing potential therapeutics.

Courage et al. performed whole-exome sequencing in 84 cases of individuals with unsolved progressive myoclonus epilepsies and identified also cases with intronic or copy-number changes in CLN6.

White et al. showed that cerebrospinal fluid (CSF) delivery of scAAV9.CB.CLN6 rescues both brain and retinal pathology and ameliorates visual deficits in *Cln6*^{nclf} mice.

CLN7

Lopez-Fabuel et al. reported that *Cln7*$^{\Delta ex2}$ mice show failure in the autophagy-lysosomal pathway and accumulation of structurally and bioenergetically impaired ROS-producing neuronal mitochondria. A metabolic shift in neurons mediated by a pro-glycolytic enzyme and its inhibition in *Cln7*$^{\Delta}$*ex2* mice and patient-derived cells rectified key disease hallmarks.

CLN8

Johnson et al. tested the safety and efficacy of neonatal i.c.v. AAV9-CLN8 gene therapy in a CLN8 mouse model and their results demonstrate improvements in histopathological and behavioural hallmarks and lifespan.

CLN10

Bassal et al. analysed retinal degeneration in CLN10 mutant mice lacking Cathepsin D (CTSD). CTSD deficiency resulted in an early-onset and rapidly progressing retinal dystrophy that involved all retinal cell types and cone photoreceptor loss as early as postnatal day 5.

Bunk et al. characterized eleven CTSD variants associated with neurodegenerative diseases including CLN10, AD and PD. The results suggest that CLN10 but not AD and PD-associated CTSD variants are significantly impaired in lysosomal maturation.

CLN12

Anand et al. showed that mutations in the *C. elegans* CLN12 orthologue *catp-6* result in defective autophagy and lysosomal function, reduced motor function, dysregulated iron metabolism and defective mitochondrial health, which is rescuable via iron chelation or mitophagy induction.

Odake et al. using exome sequencing, the authors diagnosed a novel CLN12 homozygous mutation (Ala885Asp) in a family with patients showing a complicated form of autosomal recessive hereditary spastic paraplegia.

NCL in general

Atiskova et al. provided an overview of the characteristic ocular alterations and the general disease course of the 13 currently known NCL forms.

Bartsch et al. reviewed preclinical studies to evaluate therapeutic strategies for the treatment of retinal dystrophy in animal models of NCL.

Behnke and Langmann summarized recent research and concepts regarding NCL-related neuroinflammation as a basis for both biomarker discovery and the development of immunotherapies.

Iwan et al. described urine proteome alterions in humans and animals with NCL. CLN1, CLN2, CLN3, CLN5, CLN6, and CLN7 demonstrated increases in hexosaminidase-A, aspartate aminotransferase-1, and LAMP1 whereas betaine-homocysteine S-methyltransferase-1 was specifically increased in patients with CLN2.

Specchio et al. discussed the current understanding of studying and developing potential therapeutics while also emphasizing the lack of such studies for several NCLs.

Spitzer and Bartsch wrote an editorial on three reviews describing morphologic and functional changes in NCL retina.

Yap et al. surveyed data from The Cancer Genome Atlas and literature on NCL genes observed in oncogenic processes in order to reveal pathway links.

Others

Colombo et al. described that the loss of the Niemann-Pick protein NPC1 enhances phagocytic uptake and impairs lipid trafficking in microglia pointing at an essential cell autonomous role for NPC1 in immune cells having potential relevance for therapy.

Colombo et al. demonstrated that microbiota-derived short chain fatty acids (SCFA) are critical mediators along the gut-brain axis which promote Aβ deposition likely via modulation of the microglial phenotype.

Amodeo et al. discovered that mitochondrial ATPase subunit C can spontaneously fold into β-sheets and self-assemble into fibrils and oligomers in a Ca^{2+}-dependent manner. Accordingly, the authors proposed that toxic effects of subunit C might be linked to participation in inner mitochondrial membrane permeabilization. Whether this bears on potential SubC tox in lysosomes is unclear.

Kaya et al. identified an unanticipated neuroprotective effect of acetyl-l-leucine in lysosomal storage diseases including NPC1 that support its further evaluation in clinical trials in lysosomal disorders.

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