

200 YEARS OF CLN3 · 1826 - 2026

Stengel 200

CLN3 Conference

A bicentennial gathering on juvenile neuronal ceroid lipofuscinosis, returning to the town where the disease was first described.

DATES

23-27 August 2026

VENUE

Røros · UNESCO Site



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Welcome to the Stengel 200 CLN3 Conference

It is our great pleasure to welcome you to Røros, Norway, for this unique gathering marking 200 years since Otto Christian Stengel first described what is now recognized as CLN3 disease. Bringing this meeting back to the region where the disease was originally documented provides a meaningful opportunity to reflect on both the history of the field and the remarkable scientific progress achieved over the past two centuries.

Over the coming days, we hope this meeting will foster scientific exchange, encourage new collaborations, and strengthen connections across disciplines and communities. Equally important, it provides an opportunity to recognize the patients and families whose experiences continue to inspire and guide research efforts.

We are grateful to our speakers, sponsors, organizing committee members, and all participants for contributing to this event. We hope you enjoy both the scientific programme and the unique surroundings of historic Røros.



ON BEHALF OF THE ORGANIZING COMMITTEE



Jonathan Cooper
Washington University
School of Medicine



Heather R. Adams
University of Rochester
Medicine



Magnar Bjørås
NTNU



Trine Paus
The Norwegian
NCL Association



Ole Christian Slotten
The Norwegian
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Knut Røthe
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Mirta de Sousa
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Davi Fonseca
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Dagny Døskeland
Nocteva

A platform to converge, share, and collaborate.

The Stengel 200 CLN3 Conference offers a unique platform for world-leading researchers, healthcare providers, industry partners, innovators, and patient advocacy leaders to converge, share knowledge, and collaborate on pioneering advancements. Our goal is to foster an environment of learning, innovation, and partnership to drive forward the understanding and treatment of CLN3 disease.

WHY ATTEND

01 Cutting-Edge Research

Discover the latest breakthroughs in CLN3 research from renowned experts and early-stage investigators.

02 Networking Opportunities

Connect with fellow professionals, industry leaders, and advocates from across the field.

03 Innovative Solutions

Explore new technologies and treatments that are shaping the future of CLN3 patients.

04 Patient Advocacy

Engage with patient advocacy leaders to understand the impact of CLN3 disease on families and communities.

05 A Historical Perspective

Build upon Stengel's original observations, and understand how they inform current and future work and place them in their proper context.



About Røros

Located in the mountains of central Norway, Røros is one of the best-preserved historic mining towns in Europe and has been a UNESCO World Heritage Site since 1980. For more than 300 years, the town's copper mines shaped its history, architecture, and culture.

Today, visitors can experience its distinctive wooden buildings, vibrant local traditions, and unique natural surroundings.

Røros also holds a special place in the history of CLN3 disease. It was here that physician Otto Christian Stengel documented observations in local families that would later become recognized as the first description of what is now known as CLN3 disease, a unique connection between the origins of the disease and the ongoing efforts to understand and treat it.

1980

UNESCO World Heritage Site

300+

Years of copper-mining heritage

1826

First description of CLN3, here in Røros

Otto Christian Stengel

Mining doctor • Røros



Otto Christian Stengel was a physician who served as mining doctor in Røros. In 1826, he documented a devastating neurological disease affecting four siblings from a local family, describing progressive vision loss and cognitive decline.

Published in Norway's first medical journal, his report is now recognized as the earliest known clinical description of juvenile neuronal ceroid lipofuscinosis, **CLN3 disease**.

Although largely forgotten for more than a century, Stengel's observations laid the foundation for our understanding of a disorder that remains the focus of research and clinical efforts today.

1826

FIRST DESCRIPTION

200

YEARS OF PROGRESS

2026

STENGEL 200



Historical review of Dr. Otto Christian Stengel and his description of ceroid lipofuscinosis in humans¹

Contributed by the Stengel family for the first International NCL Conference, Røros 1980

By arranging an International Symposium on Ceroid Lipofuscinosis in Røros, Norway, special interest is put on the first description of the disease which came from this district. Otto Christian Stengel, who first drew attention to the condition in humans 154 years ago, worked as a physician and surgeon at the Røros Copper Mining Company.

The mining company was started in 1644 and gave origin to this settlement in the highlands of Norway. Much of the original atmosphere is still preserved and explains the attraction for visitors to this museum-like little town.

Otto Christian Stengel was born in Schleswig-Holstein in 1794, which was at that time a part of the Kingdom of Denmark. At the age of 17 he was taken out of his training in surgery in Copenhagen and joined the army in the Napoleonic Wars. After practicing at a military hospital in Kiel, he was sent to Norway after the war in 1814. He became a student at the Royal Fredrik University and was graduated in medicine in 1821, ten years after this first Norwegian university was founded. After finishing his medical training, he moved to Røros where he was employed as physician at the Copper Mining Company for 61 years. He died in 1890 at the age of 96 years. One year after his retirement, his son started as a general practitioner in Røros and he remained there with a few interruptions until his death in 1943.

Otto Christian Stengel represents an interesting period of medical history. After two years as a surgical volunteer in a hospital near his home and a couple of months in surgical training in Copenhagen, he was regarded as qualified to work as a military surgeon at the age of 17. Nevertheless he became one of the first with scientific training in medicine in our country.

The extraordinary long period as a practicing physician in the Røros high-land district gave him a superb opportunity to make clinical observations during this time. His continuous knowledge about the local population combined with his diagnostic and clinical awareness seem to be the background for the first description of a condition which was later called juvenile amaurotic familial idiocy, or familial cerebro-macular degeneration. Today, it is best known as ceroid lipofuscinosis.

The first description of this terrifying condition was published in the first volume of the first Norwegian medical journal, *Eyr*, in 1826 (*Eyr*, 1: 347–352, 1826): *Account of a Singular Illness among Four Siblings in the Vicinity of Røraas*.

His report demonstrated a systematic clinical observation coupled with scientific thinking. Four consecutive children in the same family all were taken ill in the same manner. They did well until the age of six years. At that stage the sight diminished and a process started which ended in complete mental retardation and loss of sensory functions. The description includes how the family tried to rid their children of any demonic influences which were destroying their lives. The family then tried to resettle, and a fourth child was sent away to be raised by relatives elsewhere, but neither of these measures showed success. Dr. Stengel concluded that the physical surroundings could not explain the development of the disease.

The first report on this condition in human beings was printed in Norwegian and remained in the darkness of history until attention was brought to its significance by Nissen in 1954 (*Nord. Med.* 52: 1542–1546) and internationally by Nils Koppang (*Erg. Pathol.* 47: 1–43, 1966) and Egill Hansen (*Acta Ophthalmol.* 1: 382–396, 1979). Professionally isolated, Otto Christian Stengel drew the attention to a medical condition nearly one century before any other author (Batten, Mayou, Spielmeyer, Vogt, Stock).

Hopefully this historical review can inspire the present symposium to bring our knowledge on this pathological condition a further step ahead. New scientific progress should not once again remain in the darkness of history, but become a common international possession for the benefit of all individuals involved, animals as well as human beings.

¹ Reprinted from *Ceroid-Lipofuscinosis (Batten's Disease)*, D. Armstrong, N. Koppang & J. A. Rider, eds. © Elsevier Biomedical Press, 1982. Otto Christian Stengel Rø, M.D., D.T.M. & H. · Johannes Stengel Rø, Ph.D., M.D. · John Rø, M.D.

Programme at a Glance

Five days in Røros, from historical perspectives to the future of CLN3 therapy, with a special outing into the historic copper-mining town.

	Sun 23 Aug	Mon 24 Aug	Tue 25 Aug	Wed 26 Aug	Thu 27 Aug
MORNING		09:00 Genetics & Diagnostic Odyssey · Natural History	08:30 Symptoms of CLN3 · II	08:30 Focus on the Future · I	Morning Departures
AFTERNOON	15:00 Mentorship Mixer · Registration	13:30 Symptoms of CLN3 · I · Vision	13:00 Historic Røros Outing	13:30 Focus on the Future · II · Awards	
EVENING	18:15 Welcome Reception 19:30 Dinner	19:00 Dinner	19:00 Dinner	19:00 Closing Dinner	

 Scientific sessions  Special outing  Social & meals

Sunday 23 August 2026

Historical Perspectives on Stengel and CLN3 Disease · Session Chair: Magnar Bjørås

15:30 – 16:30 **Mentorship Mixer**
Early Stage Investigators (ESI) & Mentors

16:00 – 17:00 **Registration**

17:00 – 17:05 **Welcome remarks**
Sadmira Buljubasic, Mayor of Røros

17:05 – 17:25 **Otto Christian Stengel: who he was, what he did; historical conditions in Røros**
Ingeborg Anna Ødegaard, Rørosmuseet

17:25 – 17:45 **From Past to Present: looking back to the 1980 meeting**
Dean Rider, MD

17:45 – 18:00 **A Brief History of CLN3 Disease**
Alfried Kohlschütter, MD

18:00 – 18:15 **Presentation of Stengel's article**
Bergstaden Teaterlag

18:15 – 19:30 **Welcome Reception**

19:30 – 21:00 **Dinner**

☒ PLENARY / SOCIAL ☐ INVITED TALK ☐ MIXER / RECEPTION



Monday 24 August 2026

GENETICS & THE DIAGNOSTIC ODYSSEY

Chair: Susan Cotman, PhD

- 09:00 **Genetics of CLN3 Disease** Sara E. Mole, PhD
- 09:20 **Genetics of CLN3 Disease** ESI Christopher Minnis, PhD
- 09:35 **Genetics of Other Related Disorders** ESI Rabina Dumar, MSc
- 09:50 **The Diagnostic Odyssey** Emma Hietarinta (Finland)
- 10:00 Q&A for Speakers · 10:20 Coffee Break

NATURAL HISTORY & HOW PATIENTS FEEL AND FUNCTION

Chair: Jonathan Mink, MD, PhD

- 10:40 **Natural History of CLN3 Disease** Angela Schulz, MD
- 11:10 **How Individuals with CLN3 Disease Feel and Function** Lars Stensland (Norway)
- 11:20 **Natural History / How Patients Feel and Function** ESI Andrea Miele, PhD
- 11:35 **Natural History / How Patients Feel and Function** ESI Megan Abbott, MD
- 11:50 Q&A for Speakers · 12:10 Lunch

SYMPTOMS OF CLN3 DISEASE: PART I

Chair: Ingrid Helland, MD

- 13:30 **Vision in the Patients** Ruchira Singh, PhD
- 13:50 **Visual Phenotype, Porcine Model of CLN3 Disease** Jill Weimer, PhD
- 14:10 **Vision in CLN3 Disease** Josephine Prener, MD, PhD
- 14:30 Q&A · 14:50 Coffee break
- 15:10 **Retinal Organoids** ESI Synnøve A. Fjeldstad, MSc
- 15:25 **Modeling Dementia in Organoids** ESI Niklas Nonboe Andersen, MSc
- 15:40 **Symptoms of Late Stage CLN3 Disease** John Østergaard, MD, DMSc
- 16:00 **Gastrointestinal Symptoms of CLN3 Disease** Jonathan Cooper, PhD
- 16:20 **The Child and Parent's Experience of Symptoms** Mette Behnke (Denmark)
- 16:40 Q&A for Speakers

19:00 **Dinner**



Tuesday 25 August 2026

SYMPTOMS OF CLN3 DISEASE: PART II

Co-Chairs: Mette Møller-Handrup, MD · Miriam Nickel, MD

- 08:30** **Motor Features of CLN3 Disease** Jonathan W. Mink, MD, PhD
- 08:50** **Seizures, Clinical Features** Scott Demarest, MD
- 09:10** **Cognition and Adaptive Function** Heather R. Adams, PhD
- 09:30** **Clinical Care & Management (incl. Palliative Care)** Miriam Nickel, MD
- 10:00** Q&A · 10:20 Coffee break
- 10:40** **Quality of Life and Family Impact** Jennifer Vermilion, MD
- 11:00** **Symptoms of CLN3 Disease** ESI Heather Brown, MD
- 11:15** **Therapeutic Advances in CLN3** ESI Katy Vecchiato, MD, PhD
- 11:30** **The Child and Parent's Experience of Symptoms** Kjartan Eggen (Norway)
- 11:40** Q&A for Speakers · 12:00 Lunch

SPECIAL EVENT · 13:00 - 17:00

Outing in Historic Røros

A visit to the copper mine, a guided tour of the town, and a visit to Røros Church and Stengel's gravesite. Participants gather promptly at 13:00 for the bus.

19:00 - 21:00

Dinner

Following the historic outing



Wednesday 26 August 2026

FOCUS ON THE FUTURE: PART I

Co-Chairs: Magnar Bjørås, PhD · Jonathan Cooper, PhD

- 08:30** **Cell Biology** Julia Heiby, PhD
- 09:00** **Glial Biology** Susan Cotman, PhD
- 09:30** **Therapeutic Advances in CLN3** **ESI** Jørn-Ove Schjølberg, MSc
- 09:45** **How does CLN3 Relate to Other Diseases?** **ESI** Ewa Ziótkowska, PhD
- 10:00** **Pathomechanisms and Disease Models** **ESI** Destiny Aranovitch, MSc
- 10:15** Q&A · 10:35 Coffee break
- 10:50** **Norwegian Science Showcase, rare disease focus** Katja Scheffler, PhD
- 11:10** **Norwegian Science Showcase, rare disease focus** Anne Simonsen, PhD
- 11:40** **Industry Scientific Showcase** BioMarin, Scenic Biotech
- 12:10** Q&A for Speakers · 12:30 Lunch

FOCUS ON THE FUTURE: PART II

Chair: Dean Rider, MD

- 13:30** **Emerging Therapies, Clinical Trials, Landscape Review** Erika F. Augustine, MD, MSc
- 14:00** **ASOs** Michelle Hastings, PhD
- 14:30** **Symptoms of CLN3 Disease** **ESI** Seda Yasa, PhD
- 14:45** **Therapeutic Advances in CLN3** **ESI** Ramesh Kumar, PhD
- 15:00** **Therapeutic Advances in CLN3** **ESI** Guido Goj, MD
- 15:15** Q&A · 15:35 Coffee break
- 15:55** **Announcements for Future Meetings**
- 9th NCL Translational Science and Therapeutics Conference
 - Nordic NCL Conference
 - 20th International Congress on Neuronal Ceroid Lipofuscinoses
- 16:10** **Awards to best junior investigator talks** ESI Awards Committee
- 16:20** **Recognition of Key Leaders in the field**
- 16:40** **Closing Talk / Summation** Magnar Bjørås & Jonathan Cooper

19:00 **Closing Dinner**

Session Chairs

The scientific sessions are guided by an international panel of clinicians and researchers leading the CLN3 field.



Magnar Bjørås

NTNU – Norwegian University of Science and Technology

Historical Perspectives · Focus on the Future I



Susan Cotman

Massachusetts General Hospital · Harvard Medical School

Genetics & the Diagnostic Odyssey



Jonathan W. Mink

University of Rochester Medical Center

Natural History & How Patients Feel and Function



Ingrid Helland

Oslo University Hospital

Symptoms of CLN3 Disease: Part I



Mette Møller-Handrup

Center for Rare Diseases, Aarhus University Hospital

Symptoms of CLN3 Disease II



Miriam Nickel

University Medical Center Hamburg-Eppendorf

Symptoms of CLN3 Disease: Part II



Jonathan Cooper

Washington University School of Medicine, St. Louis

Focus on the Future: Part I



Dean Rider

Children's Brain Diseases Foundation

Focus on the Future: Part II

Invited Speakers

Leading clinicians and researchers from across the CLN3 community share the latest advances in genetics, natural history, disease models, and therapeutics.



Dean Rider, MD

From Past to Present • 1980 Meeting

Children's Brain Diseases Foundation

Dr. Dean L. Rider, MD, is a gastroenterologist in San Francisco, California (USA), and President of the Children's Brain Diseases Foundation (CBDF). The CBDF was founded in 1978 by Dr. Rider's parents after his brother Charles was diagnosed with CLN3 Batten disease. Since then, CBDF has become a leading force in advancing research on the neuronal ceroid lipofuscinoses (NCLs) through funding, scientific collaboration, and supporting international conferences. The CBDF co-organized the first international Batten disease scientific conference in Røros, Norway, in 1980, laying the foundation for the global NCL research community. Under Dr. Rider's leadership, CBDF continues to support research aimed at improving treatments and ultimately finding a cure for NCL disorders.



Angela Schulz, MD

Natural History of CLN3 Disease

University Medical Center Hamburg-Eppendorf

Dr. Angela Schulz is a Senior Physician in the Department of Pediatrics and Adolescent Medicine at the University Medical Center Hamburg-Eppendorf (UKE). A specialist in neuropaediatrics, palliative medicine, and rare childhood neurodegenerative disorders, her work focuses on the neuronal ceroid lipofuscinoses (NCLs), a group of conditions known as childhood dementias. She leads clinical care and research within UKE's NCL program, coordinating clinical trials, patient registries, and translational research to improve diagnostics and therapies.



Josephine Prener, MD, PhD

Clinical Natural History of Vision Loss in CLN3 Disease: Toward Trial Ready Endpoints

Oslo University Hospital

Josephine Prener, MD, PhD, is a Consultant Ophthalmologist and Head of the ERG Laboratory at the Department of Ophthalmology, Oslo University Hospital, Norway, specialising in inherited retinal dystrophies, electrophysiology, and paediatric retina. She serves as Principal Investigator on several gene therapy and natural history studies in inherited retinal disease, including a natural history programme in non-syndromic CLN3 disease. She is affiliated with the FFB Clinical Research Consortium and ERN-EYE. Her work centres on characterising the clinical course of vision loss in rare retinal disorders and developing robust, trial ready visual outcome measures.



Miriam Nickel, MD

Tailoring Multidisciplinary Care in CLN3 Disease

University Medical Center Hamburg-Eppendorf

Miriam Nickel, MD is a Consultant Palliative Care Pediatrician specialized in rare neurodegenerative brain diseases, especially neuronal ceroid lipofuscinosis (NCL). Her main clinical and research focus for the past 20 years has been in neurodegenerative diseases in childhood. Together with Prof. Angela Schulz (head of the research group for childhood neurodegenerative diseases), she manages the international DEM-CHILD NCL-Database to capture the natural history course for all types of NCLs as well as the Specialty Clinic for Degenerative Brain Disorders in Children and Adolescents, a Center of Excellence for NCL Disorders at the Children's Hospital of the University Medical Center Hamburg-Eppendorf (UKE) in Hamburg, Germany.



Katja Scheffler, PhD

Alzheimer's Disease in a Dish: Personalized Brain Models for Precision Medicine

NTNU & St. Olavs Hospital

Dr. Katja Scheffler is an Associate Professor at the Norwegian University of Science and Technology (NTNU) and Leader of the Neurobiological Laboratory at St. Olavs Hospital in Trondheim, Norway. She holds a PhD from the University of Rostock, Germany and has built an internationally recognized career focused on Alzheimer's disease, genome dynamics, DNA repair, and stem cell-based disease models. Dr. Scheffler leads the translational research initiative Trønderbrain, where she builds a bridge between clinical and basic neuroscience research and oversees an interdisciplinary team of research scientists and clinicians working to advance precision medicine approaches for neurodegenerative diseases.

Invited Speakers continued



Jill Weimer, PhD

Seeing CLN3 Differently: What a Pig Model Is Teaching Us About Vision Loss and Recovery

Sanford Research

A developmental neuroscientist who leads the translational research enterprise at Sanford Research, studying the molecular and cellular mechanisms underlying brain development and pediatric neurological disorders, including Batten disease and NBIA disorders. She has been instrumental in advancing some of the first gene therapy programs for CLN3 and CLN6 Batten disease from preclinical research toward clinical application, and recently served as Chief Science Officer at Amicus Therapeutics.



Jonathan Cooper, PhD

Gastrointestinal Symptoms of CLN3

Washington University School of Medicine

Leads the Pediatric Storage Disorders Laboratory (PSDL) at Washington University in St. Louis, focused on the pathogenesis of multiple forms of NCL, defining affected CNS regions and cell types, and testing preclinical therapies. His work increasingly extends beyond the CNS to treatable enteric, peripheral, and neuromuscular pathologies, including in CLN3 disease. His lab first detailed many of the fundamental pathologies now used as outcome measures across preclinical CLN3 studies.



Ruchira Singh, PhD

Longitudinal Progression of Retinal Degeneration and Vision Loss in CLN3 Disease

University of Rochester

Dean's Professor of Ophthalmology at the University of Rochester. Her research uses patient-derived human pluripotent stem cell (hPSC) models, including 3D hPSC retina systems, to define the cellular mechanisms driving retinal degeneration in CLN3 disease and age-related macular degeneration, advancing understanding of the role of CLN3 in the human retina. Her current work extends these findings to preclinical therapeutic testing in the 3D hPSC retina model and CLN3 miniswine eyes.



John Østergaard, MD, DMSc

Symptoms of Late-Stage CLN3 Disease

Aarhus University Hospital

Senior Consultant at the Department of Communication & Disability, Centre for Rehabilitation, Aarhus. Chief Consultant at the Centre for Rare Diseases, Aarhus University Hospital, from 1989 to 2025, and appointed Professor of Child Neurology at Aarhus University in 2007. His research focuses on clinical aspects of congenital developmental disability disorders and genetically derived neurodegenerative diseases in childhood, including late-stage symptoms in CLN3.



Alfried Kohlschütter, MD

A Brief History of CLN3 Disease

Dept. of Pediatrics, University Medical Center Eppendorf, Hamburg

A retired Professor of Pediatrics with clinical training in pediatrics, pediatric neurology and metabolic diseases. He conducted research on the biochemistry of brain lipids and became interested in the metabolic errors that lead to dementia in young people, among them the neuronal ceroid lipofuscinoses. He developed clinical scoring systems for the quantitative description of the natural course of these diseases, which serve as tools for therapy evaluation.



Jonathan W. Mink, MD, PhD

Motor Features of CLN3 Disease

Dystonia Medical Research Foundation

Pediatric neurologist with special expertise in NCLs and movement disorders affecting children. Former Frederick A. Horner Distinguished Professor in Pediatric Neurology at the University of Rochester, where he directed the University of Rochester Batten Center, and has published extensively on the natural history of CLN3 disease. Since retiring from Rochester in 2023, he serves as Chief Science Officer for the Dystonia Medical Research Foundation.



Anne Simonsen, PhD

Emerging Roles of Autophagy and Lysosomes in Metabolism and Disease

Oslo University Hospital & University of Oslo

Leads the Autophagy research group at the Institute for Cancer Research, Oslo University Hospital, and co-directs the Centre of Excellence CanCell at the University of Oslo. Her lab unravels the molecular mechanisms of autophagy in health and disease using advanced cell biology approaches and zebrafish. She has authored more than 120 papers, holds an H-index of 70, and is a member of the Norwegian Academy of Sciences and an elected member of EMBO.



Susan Cotman, PhD

Delineating Cell-Type Specific Contributions to CLN3 Disease

Mass General Research Institute and Harvard Medical School

Assistant Professor of Neurology at Harvard Medical School and Assistant in Neuroscience at Massachusetts General Hospital. Her research program develops genetic, cell biological, and biochemical tools for investigating neuronal ceroid lipofuscinosis (NCL/Batten disease), with a primary focus on CLN3 disease, delineating the earliest genetic events, identifying disease modifiers toward new therapies, and discovering new NCL genes.

Invited Speakers continued



Scott Demarest, MD

CLN3 Batten – Epilepsy

Precision Medicine Institute, Children's Hospital Colorado

Chief Precision Medicine Officer at Children's Hospital Colorado's Precision Medicine Institute and Associate Professor in Pediatrics, Division of Neurology at the University of Colorado. His clinical practice and research focus on neurogenetic conditions, and he co-directs the Batten Center of Excellence at Children's Hospital Colorado, spanning clinical trials, natural history studies, and outcome measure development.



Heather R. Adams, PhD

Cognition and Adaptive Function in CLN3 Disease: How and Why We Assess These Functions, What We Have Learned, and Where Do We Go Next?

University of Rochester Medicine

Heather Adams is a paediatric neuropsychologist with expertise in paediatric rare diseases and childhood dementia. She has been a researcher with the University of Rochester Batten Center (URBC) since 2003. Her research in the NCLs and other neuronopathic conditions of childhood is focused on characterising neurobehavioral phenotype and natural history, adaptive function, and quality of life impacts for affected individuals and their families.



Michelle Hastings, PhD

Therapeutic Development of Antisense Oligonucleotides Medicines for CLN3 Batten Disease

University of Michigan

Pfizer Upjohn Research Professor of Pharmacology and Director of the Nucleic Acid Therapeutics Core. Her research investigates RNA processing and RNA-based strategies to treat disease, focused on antisense oligonucleotides, and has led to new treatment approaches for CLN3 Batten disease, including the ASO medicine Zebtronkysen. She is an Editor of the journal *RNA* and serves on numerous scientific advisory boards.



Jennifer Vermilion, MD

Beyond Symptom Severity: Quality of Life and Family Impact in CLN3 Disease

University of Rochester

Child Neurologist at the University of Rochester, where she directs the University of Rochester Batten Center of Excellence, and Co-Chair of the BDSRA Foundation Centers of Excellence Program. She provides clinical care for patients with Batten disease and co-leads the longitudinal research project for the U.S. Batten Disease Clinical Research Consortium (BDCRC).



Julia Heiby, PhD

Proteomic Signature in Batten Disease

Leibniz Institute on Aging, Fritz Lipmann Institute

Following a PhD in Molecular Biology at the University of Würzburg with a focus on protein biochemistry, Julia joined the labs of Alessandro Ori at FLI in Jena and Monther Abu-Remaileh at Stanford as a shared postdoc. Her work focuses on lysosomal biology and organelle proteomics, including disease-related changes relevant to the neuronal ceroid lipofuscinoses.



Erika F. Augustine, MD, MSc

Emerging Therapies, Clinical Trials – a Landscape Review

Kennedy Krieger Institute

Associate Chief Science Officer at Kennedy Krieger Institute and Associate Professor of Neurology at Johns Hopkins Medicine, focused on therapeutic development for rare pediatric neurological disorders. Her NIH-funded work examines trial readiness of clinical outcome measures in the NCLs, and she leads the Batten Disease Clinical Research Consortium.



Sara E. Mole, PhD

Genetics of CLN3 – a brief historical perspective to now

University College London (UCL)

Part of the international consortium that identified the CLN3 gene in 1995, and has worked on CLN3 and other Batten and rare diseases ever since. Her interests span disease-causing variants and their effect on gene function, and the transcript complexity of NCL genes. She set up and curates the NCL mutation database.



Emma Hietarinta

Family & Patient Perspective

Finnish JNCL Association

Clinical psychologist specialising in health psychology, and mother of two. Drawing on both professional expertise and personal experience, she reflects on how a CLN3 diagnosis reshaped her family's life, a journey marked by fear and grief, but also courage, resilience, and hope.

Invited Speakers continued



Mette Olin Behnke

Living Through Phase 3: A Family Perspective on CLN3 Symptoms

Founder, Nordic NCL Conference

Mother of three, including a 22-year-old son living with CLN3. She established the Nordic NCL Conference, now a key meeting point for clinicians, researchers, and families across the region, and brings a deeply informed, experience-based perspective on the later phases of CLN3.



Kjartan Eggen

Family & Patient Perspective

Kjartan is the father of Helene (25), who was diagnosed with CLN3 disease at age 7. He is from Oslo, married to Grete, and has three children, of whom Helene is the eldest. Kjartan served on the board of the Norwegian NCL Association for eight years (2015–2023).



Lars Stensland

Family & Patient Perspective

Chairman, Norwegian NCL Association

Father of Julian, now 15, diagnosed at age 6. Married to Kjersti and father of four, with Julian the youngest, living on the west coast of Norway in a small coastal village. Chairman of the board of the Norwegian NCL Association.



Todd Logan, PhD

Elevated TPP1 Enzyme Levels Rescue Disease Phenotypes in a JNCL Mouse Model

BioMarin Pharmaceutical

A translational neurobiologist with over 20 years of experience in neurodegenerative disease. He earned his PhD in Biomedical Sciences from UCSF, studying the Parkinson's-linked protein alpha-synuclein, then joined Denali Therapeutics to co-lead a progranulin protein replacement therapy for Frontotemporal Dementia. For the last 4 years he has directed the Neuroscience Cell Biology group at BioMarin Pharmaceutical, focused on novel therapeutic approaches for neurodevelopmental disorders.



Vincent Blomen, PhD

Industry Scientific Showcase

Scenic Biotech

Vincent leads the Discovery Science at Scenic Biotech, an Amsterdam-based biotechnology company pioneering modifier therapy approaches. His work centers on identifying modifier genes as therapeutic targets for neurometabolic diseases. At the conference, Vincent will present Scenic's lead program focused on targeting the lysosomal hydrolase PLA2G15, highlighting its potential as a novel treatment strategy for lysosomal diseases, including CLN3 Batten.

Abstracts

14 accepted contributions across six themes

From genetics and the diagnostic odyssey to symptoms, disease models, therapeutic approaches, and quality of life, the abstracts trace the full arc of CLN3 research.



■ Genetics & the Diagnostic Odyssey 1

■ Symptoms & Natural History 2

■ Therapeutic Approaches 5

■ Pathomechanisms & Disease Models 3

■ How CLN3 Relates to Other Diseases 2

■ Quality of Life & Adaptive Function 1

Targeted long-read RNA sequencing reveals transcript complexity and variant-specific consequences in CLN3 disease

C. J. Minnis, H-Y. Zhang, E. Gustavsson, J. Lee, C. Anderson, E. Gardner, A. Schulz, M. Nickel, G. Arno, N. Jurkute, A. R. Webster, N. Gammaldi, G. Hermey, F. M. Santorelli, P. Gissen, P. Mills, M. Ryten, S. E. Mole · UCL Institute of Child Health



Christopher Minnis

PRESENTING AUTHOR ESI

UCL Great Ormond Street Institute of Child Health

Early-stage researcher investigating the molecular mechanisms underlying juvenile CLN3 disease, combining long-read RNA sequencing, CRISPR disease models, and RNA therapeutics to define the functional consequences of CLN3 transcript diversity. He also leads SPARTA-CLN3, developing isoform-specific antibodies and targeted mass spectrometry for biomarker discovery and therapeutic monitoring, aiming to translate these discoveries into improved diagnostics and personalised therapies.

Incomplete gene annotation limits understanding of transcript diversity and isoform-specific function, particularly for disease genes. The CLN3 gene causes juvenile CLN3 disease (juvenile neuronal ceroid lipofuscinosis), a rare paediatric neurodegenerative disorder characterised by vision loss and childhood dementia. The most common cause is a 1-kb intragenic deletion removing exons 7 and 8, though the transcriptional consequences of this and other variants remain poorly understood. We performed targeted long-read RNA sequencing of CLN3 transcripts in blood samples from controls and individuals with genetically confirmed juvenile CLN3 disease. We identified substantial transcriptional complexity, with >80 transcripts encoding >35 predicted open reading frames (ORFs), and no dominantly expressed transcript. Likelihood ratio testing and multivariable modelling incorporating age, sex, and disease group demonstrated that disease status is the primary driver of transcript variation, with minimal contributions from age and sex. Principal component-metadata association analyses confirmed that disease variants explain the majority of transcriptomic variance. Patients carrying the common 1-kb deletion showed loss of multiple transcripts, including those encoding the canonical 438aa protein and several shorter isoforms. The most abundant disease-associated transcripts lacked exons 7 and 8 and were predicted to encode a 181aa protein isoform, while additional novel transcripts lacking other coding exons predicted alternative ORFs. Variant-specific transcriptional effects were also observed in individual patients carrying other CLN3 mutations. Functional studies demonstrated that ectopic expression of the 181aa isoform resulted in altered subcellular localisation compared with the canonical 438aa protein and increased accumulation of the disease marker subunit c of mitochondrial ATP synthase, even in the presence of endogenous CLN3. These findings reveal unexpected complexity at the CLN3 locus, demonstrate variant-specific transcriptional consequences, and suggest that disease mechanisms may involve expression of alternative isoforms rather than simple loss of function. This work has important implications for disease modelling, biomarker development, and personalised therapeutic strategies.

Building an Observer-Reported Outcome Measure for the NCLs: Development and Methodology

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Megan Abbott

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Dr. Megan Abbott is a pediatric epileptologist at Children's Hospital Colorado, embarking on a career in clinical research focused on outcome measures in neurogenetic conditions. She is working to establish new multi-disciplinary clinics, generate gene-specific datasets, and devise outcome measures applicable to various neurogenetic populations, in the hope of advancing the field toward clinical trial readiness and disease-modifying therapies.

Background: There is increasing emphasis on incorporating patient and caregiver perspectives into outcome measurement for rare neurodegenerative diseases. Existing clinician-reported outcome measures for neuronal ceroid lipofuscinoses (NCLs) are well developed and validated but may not capture key patient and caregiver perspectives. Because most individuals with NCLs are unable to self-report due to cognitive and communication impairments, observer/caregiver-reported outcomes (ObsROs) are the appropriate approach. However, currently available ObsROs are not disease-specific and do not adequately capture the complex features of NCLs, including motor, cognitive, and visual decline. A patient-centered, disease-specific ObsRO is therefore needed. **Objective:** To develop and preliminarily validate a disease-specific ObsRO measure reflecting caregiver perspectives on disease severity across NCLs. Herein, we outline the planned phased approach for development. **Methodology:** Measure development will follow current regulatory guidance and occur in four phases. Phase 1: Disease-specific focus groups (5-10 participants/group) with caregivers, clinicians, and when feasible, affected individuals, will generate a disease concept model. Purposive sampling will ensure representation across phenotypes and disease stages. Phase 2: Using Phase 1 data, 20-40 draft items will be generated. A 15-25 member multistakeholder panel will complete a modified Delphi process to achieve $\geq 80\%$ consensus on concept inclusion, comprehensiveness, and item relevance. Phase 3: Cognitive ("think-aloud") interviews with caregivers will evaluate item interpretation, clarity, and relevance. Iterative revisions will continue until saturation is reached. Phase 4: The refined ObsRO will be piloted in the natural history cohort through the Batten Disease Clinical Research Consortium. Descriptive statistics, score distribution characteristics, exploratory factor analysis, and test-retest reliability will be assessed. **Conclusions:** This rigorous, patient-centered approach will produce a disease-specific ObsRO suitable for natural history studies and future clinical trials in NCLs.

Development of AAV-Based Gene Therapy for CLN3 Disease Using Human Retinal Organoids

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Retinal organoids derived from human induced pluripotent stem cells are emerging as a robust model for studying inherited retinal disorders, as they recapitulate key aspects of disease pathology. In the case of CLN3 disease, where the disease is caused by a mutation in a single gene, gene therapy is a promising treatment strategy. To explore this, we designed and produced several adeno-associated viruses (AAVs). The AAVs were tested on human retinal organoids derived from two patients and two healthy controls. The retinal organoids were transfected once they displayed mature cell types, twelve weeks after differentiation, and kept for twelve weeks after treatment. The AAV-treatment increased CLN3 protein expression in patients, detected through targeted mass spectrometry. The impact of restored CLN3 expression on cellular health was evaluated by immunohistochemical analysis of SCMAS accumulation and retinal cell layering normalization, alongside single-nucleus RNA sequencing and mass spectrometry to assess pathway-level changes associated with lysosomal function, cellular homeostasis, and stress responses. This study represents an important step towards the development of gene therapy for CLN3 disease, aided by retinal organoids as a preclinical platform for evaluating in-house AAVs.

Early Oligodendrocyte Lineage Alterations in Pre-Symptomatic CLN3 Disease

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Postdoctoral Research Fellow at Massachusetts General Hospital, Harvard Medical School, and the Broad Institute, holding a DHFMR Fellowship. Her CLN3 work spans her PhD on proteostasis and endosome-to-TGN trafficking through to her postdoctoral research characterizing CLN3-deficient brain cell types and testing therapeutic modalities, using single-nucleus RNA-sequencing and multi-omics to map cell-type-specific vulnerability. Her latest paper in *Communications Biology* linked lysosomal dysfunction in microglia to impaired lipid turnover in CLN3 disease.

CLN3 disease is a pediatric lysosomal disorder characterized by progressive neurodegeneration, with early molecular events that remain incompletely understood. To gain unbiased insight into early disease pathomechanisms, we performed single-nucleus RNA-sequencing (snRNA-seq) on the midbrain of homozygous *Cln3* Δ ex7/8 mice and control heterozygous littermates at 2.8 months of age. This pre-symptomatic timepoint was selected to capture early transcriptome-wide changes in this genetically accurate CLN3 disease model, before overt neurodegeneration confounds interpretation. Transcriptomic analysis revealed alterations across multiple cell populations. Notably, the oligodendrocyte (OL) lineage exhibited a reduction in mature OL numbers and detection of an immature OL subpopulation largely absent in control brains. These changes were accompanied by transcriptional changes in myelin-related markers and upregulation of mitochondrial energy and lysosomal stress signatures. Importantly, active oligodendrocyte progenitor cell (OPC)-to-OL differentiation to establish the mature OL pool is ongoing at this age, raising the possibility of impaired OL maturation in homozygous *Cln3* Δ ex7/8 mice. Follow-up qRT-PCR, Western blot, and Olig2 immunohistochemistry confirmed that MBP and PLP1 were significantly reduced at both transcript and protein levels and that OL lineage cell numbers were decreased compared to heterozygous littermate controls. Moreover, intracerebroventricular delivery of an AAV-based CLN3 gene therapy vector at birth (P0) that led to widespread CLN3 expression and correction of hallmark neuropathology and metabolomic markers also corrected OL lineage cell numbers and abnormal OL maturation markers, confirming these abnormalities were responsive to CLN3 absence/presence. Collectively, these findings reveal early OL lineage changes in pre-symptomatic homozygous *Cln3* Δ ex7/8 mice and demonstrate that an AAV-based CLN3 gene therapy vector can correct these abnormalities. Further studies are underway to investigate OL function and the impact of OL abnormalities on CLN3 disease pathophysiology.

Loss of SLITRK2 contributes to synaptic disorganization and neuronal dysfunction in Early Juvenile Metachromatic Leukodystrophy

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PhD candidate under the supervision of Prof. Barbara van Loon at NTNU, holding a Master's degree in Molecular Medicine. Her research focuses on Metachromatic Leukodystrophy (MLD), a rare lysosomal storage neurodegenerative disorder, investigating disease mechanisms and potential therapeutic strategies using 2D and 3D brain models.

Metachromatic leukodystrophy (MLD) is a rare genetic lysosomal storage disorder caused by autosomal recessive pathogenic ARSA variants. ARSA encodes the lysosomal enzyme arylsulfatase A, crucial for sulfatide metabolism. MLD-causative mutations cause loss of ARSA protein or its enzymatic activity, hindering the hydrolysis of sulfatides and leading to their accumulation within lysosomes across multiple cell types, particularly in oligodendrocytes. This results in severe demyelination and progressive neurodegeneration. MLD is classified into several subtypes: late-infantile, early juvenile (EJ), late juvenile and adult MLD. Early juvenile MLD is characterized by disease onset in early childhood, severe clinical manifestations and rapid disease progression. Despite its severity and limited therapeutic options, the disease pathomechanisms remain largely unclear. To investigate the underlying disease mechanism, we employed control- and patient-derived induced pluripotent stem cells (iPSCs), differentiated into mature brain organoids enriched for oligodendrocytes. EJ-MLD patient-specific brain organoids successfully presented disease-specific features including sulfatide overload and reduced ARSA activity, identified by LC-MS/MS analysis, as well as lysosomal expansion indicated by increased LAMP1 mRNA levels compared to healthy control. Subsequent single-cell RNA sequencing revealed that SLIT and NTRK-like protein 2 (SLITRK2), a synaptic adhesion molecule, was the most significantly downregulated gene in EJ-MLD affected OPCs and cycling OPCs. This was accompanied by significant dysregulation of key neuronal and synaptic markers: vGLUT1 (excitatory marker) was reduced, while GABRG1 and SYN1 (pre-synaptic marker) mRNA levels were increased in EJ-MLD organoids. Overall, these results suggest that loss of SLITRK2 in MLD is accompanied by altered synaptic organization and neuronal function in EJ-MLD, further supported by GSEA analysis revealing upregulation of the synaptic assembly pathway in developing EJ-MLD cortical neurons. Taken together, this study using brain organoid models provides novel insights into the molecular alterations underlying EJ-MLD pathology.

Characterisation of the Batten Disease Blood-Brain Barrier and investigating new therapeutic approaches

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Destiny Aranovitch

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A masters student researching the blood-brain barrier using stem cells to understand how the neurodegenerative effects of Batten disease may affect drug delivery. Destiny worked as a nurse at Queensland Children's Hospital for four years and completed both her Bachelors and Masters dissertations in paediatric medical research, with interests spanning drug discovery and delivery, stem cell modelling and therapies, neonatal seizures and EEG analysis, and paediatric clinical research.

Batten disease is a paediatric neurodegenerative lysosomal storage disorder within the group of diseases known as childhood dementia. In CLN3-type Batten disease, children are born asymptomatic and then develop progressive neurodegenerative decline from age 4 until succumbing to premature death in adolescence. Clinical manifestations include blindness, loss of speech, mobility and cognitive abilities, and seizures, all of which significantly impact quality of life. There are no approved treatments for CLN3 Batten disease, with the blood-brain barrier (BBB) posing a major challenge for brain drug delivery. BBB function, or potential dysfunction, has not yet been well-characterised in Batten disease research despite its key relevance to treatment design, delivery, and efficacy. The aim of this study was to use a patient-derived induced pluripotent stem cell (iPSC) model of BBB cells to characterise disease-specific changes in CLN3 Batten disease. As neuroinflammation is a well-recognised characteristic of neurodegenerative diseases, experiments were performed at both baseline and induced inflammatory conditions using tumour necrosis factor- α (TNF- α) and interferon- γ (IFN- γ). Phenotype investigations included measurements of BBB monolayer permeability (dextran delivery), trans-endothelial electrical resistance (TEER), assessment of lipofuscin accumulation, and lysosomal and BBB marker expression (qPCR). Drug repurposing candidates were also tested as additional conditions. Preliminary data suggest increased permeability in Batten disease BBB cells and exacerbation under inflammatory conditions. These changes were significantly different to the healthy control model, which showed low permeability and only mild changes in response to the inflammatory environment. These findings potentially indicate that the BBB in CLN3 Batten disease is dysfunctional at baseline and vulnerable to neuroinflammatory conditions. Further replication is currently underway to validate these findings, as a dysfunctional BBB is a key consideration in the design and delivery of treatments.

Longitudinal CSF NEFL levels in individuals with CLN3 disease

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CLN3 disease (juvenile NCL; Batten), a fatal, blindness-causing and neurodegenerative condition associated with biallelic variants in the CLN3 gene, is the most common of the NCL subtypes. The disease currently lacks fluid biomarkers, which limits therapeutic development. A cross-sectional study from our group previously showed elevated neurofilament light chain (NEFL) levels in individuals with CLN3 disease. To investigate temporal dynamics and clinical utility of the neuronal injury marker NEFL, we assessed its levels in cerebrospinal fluid (CSF) samples (n=119) from 47 participants followed longitudinally in a prospective natural history study (NCT03307304). For comparison, we used CSF from individuals with non-neurodegenerative conditions and from a non-disease commercial sample bank. We used Single Molecule Array (Simoa) to quantify NEFL levels. The cohort included 24 females/23 males, aged 0.1-80 years (median 10), with 40.4% homozygous for the 966-bp deletion. Participants were followed for a median of 4 years, with 27.6% having started miglustat at the time of sample analysis. In aggregate, NEFL levels were significantly elevated in pre-miglustat CLN3 (n=92; mean $\pm$ SD = 808.4 $\pm$ 632.9 pg/mL) vs non-CLN3 (n=39; 520.5 $\pm$ 1208.8 pg/mL; p<0.001) CSF samples. This difference was clear in the 5-20 year-old group (CLN3: 837.7; non-CLN3: 355.3 pg/mL; p<0.001), and less so in other age groups. Paired (n=12) NEFL levels pre- (1129.9 $\pm$ 745.1 pg/mL) and post- (391.3 $\pm$ 163.8 pg/mL) miglustat were significantly different (p=0.005). Additional analyses in progress include longitudinal rates of change and correlations with clinical assessments. This longitudinal study further supports NEFL as a promising fluid biomarker for monitoring CLN3 disease state and response to treatment.

CLN3 Disease: Clinical Characterisation and Early Experience with Repurposed Fingolimod from a UK Paediatric Cohort

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Katy obtained her medical degree from the University of Trieste and specialised in General Paediatrics before completing a PhD in Neuroimaging at King's College London. She is now a Senior Clinical Research Fellow in Paediatric Metabolic Medicine, working on paediatric metabolic clinical trials with a particular interest in neuronal ceroid lipofuscinoses. Her research spans specialist NCL care, translational biomarker studies, and sub-investigator roles across multiple interventional trials.

Background: CLN3 disease is the most common neuronal ceroid lipofuscinosis, characterised by progressive neurodegeneration and premature death. Longitudinal clinical, genetic, neuroimaging, and biomarker data from well-characterised cohorts are essential to understand disease progression and support future clinical trials. Preclinical studies show that fingolimod reduces neuroinflammation and slows neurodegeneration in Batten disease models, and a pilot study in CLN1 demonstrated normalisation of plasma neurofilament light (NfL). **Methods:** Retrospective observational study of CLN3 patients followed at Great Ormond Street Hospital, describing clinical, genetic, and neuroimaging features and early experience with fingolimod as a potential disease-modifying therapy. **Results:** Nineteen patients were included (47% female; median age 12.5 years, range 7-17). Vision loss was the presenting symptom in 95%, followed by behavioural changes and learning difficulties in 58%. Median age at first symptom was 5.5 years and at diagnosis 7 years; median diagnostic delay was 2.1 years. Two patients were diagnosed presymptotically through an affected sibling. Genetic data were available for 14/19: 13 homozygous for the common 1-kb exon 7-8 deletion and one for c.597C>A (p.Tyr199Ter). Seizures occurred in 58%, and 47% were on anti-seizure medications. Of those with documented visual assessment, 76% had only light/dark perception; 79% were independently mobile and 84% fully orally fed. Brain MRI most commonly showed cerebral and cerebellar volume loss with white matter T2 abnormality. Five patients have started fingolimod since October 2025; plasma NfL and clinical data are being collected prospectively. **Conclusions:** This cohort illustrates the characteristic CLN3 trajectory and highlights persistent diagnostic delay. The symptom burden underscores the need for disease-modifying therapy; we will present early experience with fingolimod alongside prospective NfL monitoring.

Nizubaglustat Shows Preclinical Therapeutic Potential in Patient-Derived CLN3 Retinal Organoids

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Nizubaglustat is a brain-penetrant small-molecule inhibitor of GCS and NLGase with therapeutic potential in diseases characterized by lysosomal dysfunction and altered glycolipid handling. These mechanisms are highly relevant to CLN3 Batten disease, a severe neurodegenerative lysosomal storage disorder in which early and progressive retinal degeneration remains untreated. In this study, we evaluated nizubaglustat in patient-derived CLN3 retinal organoids that recapitulate key molecular, cellular, and structural hallmarks of neuronal ceroid lipofuscinosis, including lysosomal dysfunction, disease-associated transcriptional and proteomic signatures, and pathological accumulation of ATP synthase subunit C. Retinal organoids from healthy controls and CLN3 patients were treated with nizubaglustat, miglustat, or eliglustat across therapeutically relevant concentration ranges and analyzed by single-nuclei RNA sequencing, proteomics, pathway analysis, and immunohistochemistry. Across independent analytical layers, nizubaglustat consistently emerged as the most effective compound in reversing disease-associated signatures, with reproducible effects across timepoints, broad activity across retinal cell types, and strongest efficacy at low nanomolar concentration. Nizubaglustat restored pro-neuronal transcriptional programs, corrected proteomic signatures associated with lysosomal dysfunction, reduced disease-relevant pathological features, and improved retinal organoid architecture, whereas miglustat and eliglustat showed more limited or less consistent effects. Collectively, these findings support a multi-level therapeutic effect of nizubaglustat in CLN3 retinal organoids and provide a strong rationale for further preclinical development as a potential disease-modifying strategy for CLN3 Batten disease.

From Childhood to Adult Dementia: Shared Cellular Omics Signatures Reveal Common Disease Mechanisms

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CLN3 juvenile neuronal ceroid lipofuscinosis (JNCL), commonly known as Batten disease, is often described as a form of childhood dementia due to its progressive neurodegenerative course and severe cognitive decline. Despite differences in age of onset, CLN3 disease and Alzheimer's disease may share convergent pathological mechanisms. Identifying overlapping and disease-specific pathways between these disorders could provide important biological insight and support the development of mechanism-based, diagnosis-agnostic therapies. To investigate this, we applied state-of-the-art single-cell transcriptomics and proteomics to brain organoid models of CLN3 disease and Alzheimer's disease across multiple developmental stages. This approach enabled high-resolution mapping of molecular changes during brain development and disease progression in a cell type-specific manner. We identified both shared and distinct cellular responses across the two disorders. Several neural cell populations demonstrated highly similar transcriptional and proteomic signatures in CLN3 and Alzheimer's models, highlighting candidate pathways and cell types that may represent promising therapeutic targets with relevance across neurodegenerative diseases. In parallel, longitudinal analysis of CLN3 organoids revealed altered developmental trajectories, suggesting that disease pathology arises not only from degeneration but also from impaired neurodevelopmental processes. To assess clinical relevance, publicly available single-cell datasets from Alzheimer's disease patients were further analyzed to determine whether specific patient subgroups exhibit molecular profiles most aligned with CLN3 pathology. This stratification may help identify populations most likely to benefit from cross-disease therapeutic strategies. Together, these findings support the concept that CLN3 Batten disease and Alzheimer's disease share key biological features despite distinct clinical presentations. Comparative multi-omics analyses in human brain organoids may therefore accelerate the discovery of broadly effective treatments for neurodegenerative dementia.

Influence of Fingolimod and Miglustat treatment on disease outcome and MRI brain volumes in children with CLN3

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Background: CLN3 is a neurodegenerative disorder leading to progressive loss of vision, motor function and language skills as well as dementia and epilepsy. Loss of brain volume has been shown to be a sensitive marker of disease progression corresponding with clinical scores. Fingolimod, a sphingosine-1-phosphate receptor modulator used in the treatment of MS, ameliorates the disease course in a CLN mouse model. **Objective:** To assess the effects of fingolimod treatment on disease progression in children with CLN3 in an open-label interventional study. **Patients and Methods:** 15 children with CLN3 were included (9 females, 6 males, age 5-16 years). 12 were treated with fingolimod over a period of at least one year, and 9 of these additionally with miglustat in the course of the study; 3 patients were treated only with miglustat from the beginning. MRI studies including MPrage sequences were performed at onset of treatment and after one year. Volumetry data were compared with those of a natural history cohort including 47 MRI sequences. Standardized cognitive testing, the Hamburg JNCL score and a 6-minute walking test were applied at baseline and yearly intervals, with serum NfL measurements at the same intervals. **Results:** Treatment with fingolimod and miglustat was well tolerated. The combined treatment had a beneficial effect on the reduction of brain volume loss over time compared to natural history controls. The predicted NfL values were lower in both treatment groups compared to the natural history group. **Conclusion:** Our results indicate that fingolimod is well tolerated. The combined treatment of miglustat and fingolimod may alleviate brain volume loss and disease progression in CLN3.

Dysphagia in CLN3 disease arises from combined brainstem and peripheral pathology and is amenable to AAV9 gene therapy

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CLN3 disease, a major subtype of neuronal ceroid lipofuscinosis, is characterized by progressive neurodegeneration predominantly affecting the central nervous system (CNS). However, it is becoming increasingly apparent that the effects of disease extend outside the CNS, resulting in symptoms that impair quality of life and can be life-threatening. Among these is progressive failure in the ability to swallow, defined clinically as dysphagia. Despite its clinical relevance, the anatomical basis and temporal progression of dysphagia in CLN3 disease remain incompletely understood. To address this gap, we performed a longitudinal analysis of swallowing-related structures in *Cln3 Δ ex7/8* mice at 9, 12, 15, and 18 months of age. Histological and immunohistochemical assessments included the brainstem, tongue, and cheek musculature at all time points, and the esophagus at 18 months. We identified progressive neurodegenerative changes within brainstem nuclei essential for swallowing control, including the dorsal motor nucleus of the vagus (X), hypoglossal nucleus (XII), and facial nucleus (VII), characterized by storage accumulation and glial activation. These CNS pathologies were accompanied by marked peripheral pathology in orofacial muscles, including reduced myofiber diameter, decreased capillary density, nuclear mislocalization, and increased extracellular matrix deposition, consistent with progressive myopathy. Marked myopathic changes were also evident within the striated muscle layers of the esophagus. To evaluate therapeutic potential, we assessed neonatal intravenous AAV9-mediated CLN3 gene delivery. Gene therapy prevented the majority of pathological changes in both brainstem nuclei and skeletal muscles, indicating these phenotypes are directly driven by CLN3 deficiency and are amenable to intervention. Collectively, these findings demonstrate that dysphagia in CLN3 disease arises from coordinated central and peripheral pathologies and highlight the necessity of therapeutic strategies targeting both CNS and peripheral tissues.

Comparison of Cognitive Trajectories in CLN3 and treated CLN2

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Background: CLN2 Batten disease is the only NCL with an FDA-approved treatment (Brineura, cerliponase alfa); however, there is limited information describing cognition over time. We sought to compare cognitive trajectories of individuals with CLN3 Batten disease to those treated with Brineura for CLN2 Batten. **Method:** Four individuals continually treated for CLN2 (all male, ages 1y6m to 12y7m) and eight individuals with CLN3 (five girls, ages 6y2m to 18y) underwent serial comprehensive neuropsychological evaluations over the past 6 years. Standardized normed scores were compared for the WPPSI-IV and WISC-V Verbal Comprehension Index (VCI), Vineland-3 Adaptive Behavior Composite (ABC), and the Behavior Assessment Scale for Children (BASC-3) indexes. **Results:** Across the CLN2 group, VCI scores were disparate at similar ages, ranging from Below Average to Average. Vineland-3 ABC scores were highest at ages 4 and younger; level of performance declined as children aged. Across the CLN3 group, VCI scores were again disparate but with a wider range, from Exceptionally Low to Average. Vineland-3 ABC scores were higher at younger ages; most scores were in the Exceptionally Low range by around 10 years. BASC-3 Externalizing and Behavioral Symptoms were highest for ages 11 to 13 years, while Internalizing scores were always in the non-clinical range. **Discussion:** The overall cognitive trajectory range for Brineura-treated CLN2 individuals appears similar to individuals with CLN3, though the sample size is small and the CLN2 age range is younger. Behavioral profiles differ in the presence of internalizing symptoms in CLN2 and timing of externalizing symptoms. Continued study of cognitive trajectories in both CLN3 and treated CLN2 is warranted.

Development of a Disease-Specific Quality of Life Screener for Individuals Affected by NCLs: A Collaborative Family-Clinical Framework

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Kennedy Krieger Institute

Heather Brown is a pediatric palliative care doctor at the Kennedy Krieger Institute and Johns Hopkins Children's Center, where she works in inpatient, outpatient, and rehab settings. At Kennedy Krieger, Dr. Brown specializes in neuropalliative care for children with chronic, complex medical conditions, including genetic syndromes, brain injuries, and neurodegenerative conditions. Dr. Brown focuses on quality of life care, symptom management, assisting with difficult decision-making, and supporting families with children with life-limiting conditions.

Introduction: Neuronal ceroid lipofuscinoses (NCLs) are a heterogeneous group of lysosomal storage disorders characterized by accumulation of lysosomal substrates and progressive neurodegeneration. Existing disease rating instruments primarily emphasize functional decline through measures such as expressive language and gross motor performance. While these tools have demonstrated utility in natural history characterization and treatment evaluation, there remains no disease-specific quality of life (QOL) instrument designed to capture the broader lived experience of individuals and families affected by NCLs. **Objective:** This collaborative proposal between family stakeholders, nursing research, and the Kennedy Krieger Institute Batten Center of Excellence seeks to develop a disease-specific QOL screener through qualitative study for individuals affected by NCLs. The proposed tool aims to quantify patient-centered experiences frequently underrepresented in current metrics, including sleep quality, emotional dysregulation, cognitive engagement, seizure burden, appetite, comfort, and overall daily well-being. **Methods:** Families will complete surveys on their priorities in evaluating their child's quality of life, accessible online and in-person at the BDSRA Family Conference. This data will be analyzed and combined with pre-existing, non-disease-specific QOL screening tools to develop an NCL-specific screening tool to appropriately assess QOL for children with Batten disease. **Conclusion:** The development of a disease-specific QOL screener represents an important unmet need within the NCL community. By integrating caregiver perspectives, nursing research principles, palliative care frameworks, and clinical expertise, this initiative seeks a more holistic, patient-centered approach to evaluating disease burden, therapeutic impact, and quality of life. The proposed screener may also provide valuable patient-centered outcome measures within therapeutic trials and longitudinal observational research.

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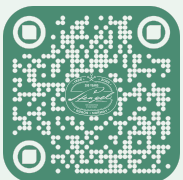
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