Proudly hosted by:

Australian NPC Disease Foundation Inc
*Research. Cure. Persevere.*

# 2024 NPC CONFERENCE

*In-Person & Virtual*

**JUNE 20-21, 2024**

Online and In-Person at
in Melbourne, Australia

Premier Sponsor:

cyclo therapeutics

Venue Partner:

The Florey

Event subsidised by:

National Disability Conference Intiative Grant funded by the Australian Government Department of Social Services.

**The ANPDF acknowledges the Traditional Owners of the land on which this conference is being held, the Wurundjeri people of the Kulin Nation. We pay our respects to their Elders past, present and emerging.**


**Australian NPC Disease Foundation Inc.**
ABN: 87 767 010 514

c/- 3 Waller Street
Benalla VIC 3672
Australia

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# TO OUR SUPPORTERS

# THANK YOU

The **ANPDF** (**A**ustralian **NP**C **D**isease **F**oundation) is a registered not-for-profit dedicated to improving the lives of Australians diagnosed with Niemann-Pick disease and their families. We endeavour to contribute to advocacy campaigns, provide practical and emotional support, advice and information, and facilitate research into potential therapies.

We rely entirely on voluntary donations, charitable grants, and fundraising to support our work with those affected by Niemann-Pick disease, their families and the health care professionals caring for them.

We are deeply grateful to all who have provided support for this event:

**PREMIER SPONSOR**

cyclo therapeutics

Cyclo Therapeutics, Inc. is a clinical-stage biotechnology company dedicated to developing life-changing medicines through science and innovation for patients and families living with challenging diseases.

**GRANT FUNDING**

**Grant funding provided by the Australian Government Department of Social Services.**

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# CYCLO THERAPEUTICS

## Our Message of Gratitude to the Patient Community

To the heroic study participants and their devoted families throughout Australia, we know it is not easy to commit to a clinical study especially given the day-to-day challenges that come with NPC.

We are making great progress toward completing the TransportNPC™ study and we are working tirelessly to make a treatment available to all who need it. Thank you for sharing your journey with NPC with us - we are devoted to making your efforts and commitment count.

**Learn more at www.cyclotherapeutics.com**

cyclo therapeutics

# DELEGATE

## INFORMATION – THE FLOREY

The Florey Institute of Neuroscience and Mental Health is the largest brain research group in the Southern Hemisphere. With more than 600 research and support staff and educating 90 post-graduates. The conference is located in the Kenneth Myer Building, Cnr Genetics Lane & Royal Parade.

### THE FLOREY

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Parkville, VIC 3052

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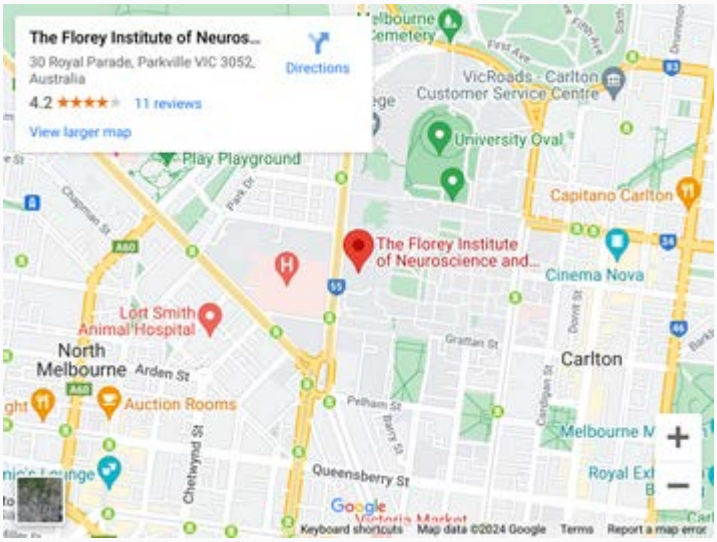


## 1 ON ARRIVAL

The ANPDF registration desk will be available in The Florey entrance area from 12:30pm to 5:00pm on Thursday, 20th June and 8:30am to 5:00pm on Friday, 21st June. ANPDF event team members will be available to assist you with any enquiries. Alternatively, you may contact:
Mandy on 0409 573 740, or
Deanna on 0420 985 510

## 2 GENERAL

All day meals will be provided including lunch and tea breaks. Coffee and tea will be available all day. If you have advised any special dietary requirements on your registration form, these will catered to on the day. Please ask the catering or support staff to find the correct meal option. Access is enabled and available at all entrances.

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# AUSTRALIAN

## NPC DISEASE FOUNDATION

Founded in 2009 by an Aussie mum whose two sons were diagnosed with NP-C, our volunteer-driven charity stands as a beacon of hope in the face of adversity. The ANPDF emerged from the impassioned efforts of parents determined to safeguard their children. Though modest in size, our organization is resolute in its commitment to serve where the need is most acute.

At the heart of our mission lies the aim to provide unwavering support to individuals diagnosed with Niemann-Pick disease and their families. We endeavor to furnish them with the latest, most accurate information available, spanning from cutting-edge research to updates on clinical trials.

Central to our efforts are our annual events, which serve as invaluable forums for knowledge exchange and connection. These events draw together not only affected families but also a diverse array of stakeholders, including allied health professionals, clinicians, researchers, and pharmaceutical industry professionals. Whether attending in person or virtually, participants find themselves immersed in a collaborative environment where expertise is shared, relationships are forged, and hope is renewed.


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The Annual Australian

# Niemann-Pick Conference Programme of Events

**June 20-21, 2024**

Online and In-Person

at The Florey Institute of
Neuroscience and Mental Health
30 Royal Parade, Parkville, VIC 3052

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# WELCOME

## MESSAGE

Dear Families, Friends and Supporters,

It is my pleasure to welcome you to the 2024 NPC Conference hosted by the Australian NPC Disease Foundation. As President and Founder, I am thrilled to see our community come together once again to address the challenges posed by Niemann-Pick Type C (NPC) disease. Whether you're joining us in person or virtually, your participation signifies our collective commitment to advancing research, support, and advocacy efforts for those affected by NPC. This conference serves as a vital platform for collaboration, innovation, and solidarity. Over the next few days, let us seize the opportunity to exchange ideas, share insights, and foster new connections that will propel us forward in our quest for improved treatments and ultimately, a cure for NPC.

Together, we have the power to make a profound and lasting impact on the lives of individuals and families impacted by this disease. Thank you for your dedication and contributions to this important cause.

**Mandy Whitechurch**
Founder and President of
Australian NPC Disease Foundation

CONFERENCE

# SCHEDULE

## Conference Day One

Thursday, 20th June 2024

1.00 PM - 5.00 PM

REGISTRATION FROM 12.30 PM TO BEGIN AT 1.00 PM

| | |
|---|---|
| **1.00 PM** | **Conference Opening & Welcome to Country** by Felicity Munro |
| **1.10 PM** | **From Little Things Big Things Grow** by Michelle and Martin Roberts |
| **2.10 PM** | **Breaking Barriers: Progress and Initiatives of the ANPDF** by Mandy Whitechurch and Deanna Carpino |

AFTERNOON TEA AT 2.40 PM

| | |
|---|---|
| **3.00 PM** | **Childhood Dementia - Progress, Updates and Future Challenges** by Kristina Elvidge |
| **3.30 PM** | **An Update on Clinical NP-C Research in Melbourne** by Mark Walterfang |
| **4.00 PM** | **An update on the Florey mRNA gene therapy project for Niemann-Pick Disease Type C1** by Ya Hui Hung |
| **4.30 PM** | **Pre-Clinical Development of a New Substrate Reduction Strategy to Treat Lysosomal Storage Disorders (LSDs)** by Anthony Cook |

DAY ONE CONFERENCE CLOSING AT 5.00 PM

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# CONFERENCE
# SCHEDULE

## Conference Day Two

Friday, 21st June 2024

9.00 AM - 5.00 PM

REGISTRATION FROM 8.30 AM TO BEGIN AT 9.00 AM

| | |
|---|---|
| **9.10 AM** | **ASMD: Exploring the Other Niemann Pick Disease** by Justin Hopkins |
| **9.40 AM** | **The International Niemann-Pick Disease Registry: A Global Update** by Solomon Mbua |
| **10.10 AM** | **Rare Disease Advocacy: Learnings from RVA** by Nicole Millis |

MORNING TEA AT 10.40 AM

| | |
|---|---|
| **11.00 AM** | **Niemann-Pick C1 (NPC1) in Israel: What Can We Learn From This Unique Population?** by Orna Staretz-Chacham |
| **11.30 AM** | **Ongoing progress of the largest open phase 3 global trial of Trappsol® Cyclo™ (HPβCD) in patients with Niemann-Pick disease type C1 (NPC1)** by Caroline Hastings |
| **12.00 PM** | **N-Acetyl-L-leucine (IB1001) for NPC - Results of a Pivotal, Randomized, Double-blind, placebo-controlled trial** by Tatiana Bremova-Ertl |
| **12.30 PM** | **Clinical update by Azafaros on Nizubaglustat - the development of a small molecule for Niemann-Pick type C** by Christian Freitag and Laura Lopez de Frutos |

LUNCH AT 1.00 PM

| | |
|---|---|
| **2.00 PM** | **Filipin Complex-Reactive Brain Lesions: A Cautionary Tale** by Kim Hemsley |
| **2.30 PM** | **Human Brain Organoids Bring New Insight into Brain Diseases with Developmental Origin** by Silvia Velasco |
| **3.00 PM** | **Genetics and NPC – Putting the Puzzle Pieces Together** by Lisette Curnow |

AFTERNOON TEA AT 3.30 PM

| | |
|---|---|
| **4.00 PM** | **Short Talks from Abstract Posters** |
| **4.30 PM** | **Caring for Carers** by Leah Lonsdale |
| **5.00 PM** | **Live Q+A Session with Pre-recorded Speakers** |

FINAL DAY CLOSING AT 5.15 PM

DAY ONE

# KEYNOTE LECTURE

# FROM LITTLE THINGS BIG THINGS GROW


**Martin and Michelle Roberts**
Cycle 4 Sam


Marty and Michelle Roberts set up the charity "Cycle 4 Sam" following the death of their 4 year old son Sam from Niemann-Pick Disease Type C in 2005. In the 19 years since Sam's passing Cycle 4 Sam has raised nearly $1,000,000 for projects supporting families in South Australia with children with life-limiting rare illnesses. Closely aligned with the Paediatric Palliative Care Service of the Adelaide Women's and Children's Hospital, Cycle 4 Sam has funded numerous initiatives to support families in their most difficult of times. These initiatives include a Family Care Room at the WCH, Art Therapy, Mums, Dads, and Siblings programs, Family Care packages, and were project partners in the construction of a respite holiday facility, Lakinleri, at Victor Harbor. Every 2 years Cycle 4 Sam conducts a 1000km bike ride throughout South Australia and Victoria, but always finishing at the WCH in Adelaide. Since 2021, and in honour of Sam's 21st birthday, Cycle 4 Sam created the event Challenge 21. For the past 3 years participants were encouraged to raise money and awareness for Cycle 4 Sam by choosing any challenge with the number 21 in it. A huge success, Challenge 21 inspired more than 400 participants to create their own personal challenges. We are now working towards supporting the "Bereavement Care for All" program, an initiative supporting families across all areas of the Women's and Children's Hospital who have lost a child. This year we are also approaching a special fundraising milestone. Having currently raised $982,000 our dream of raising $1,000,000 will soon be realised.

### About the Speakers

Marty and Michelle Roberts are the co-directors of Cycle 4 Sam, an Adelaide based charity supporting families in South Australia who have children with life-limiting rare illnesses. Marty is a Geography teacher and Assistant Head of Pembroke Middle School in Adelaide.

Michelle is a School Counsellor at Cabra Dominican College in Adelaide. Marty and Michelle both love cycling and have explored much of Australia and Europe, including some iconic mountain climbs, by bike. They have 3 children, Lucy, Sam, and Charlie. Lucy was 5 years and Charlie was only 3 months when their brother Sam was diagnosed with NP-C in 2002. Sam had just celebrated his 2nd birthday. Marty and Michelle were sadly advised Sam would not see his 5th birthday. Sam died at the age of 4 years and 10 months on April 19, 2005.


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COMMUNITY

# BREAKING BARRIERS: PROGRESS AND INITIATIVES OF THE ANPDF

**Mandy Whitechurch and Deanna Carpino**
Australian NPC Disease Foundation

The Australian NPC Disease Foundation is committed to advancing research, raising awareness, and supporting individuals affected by Niemann-Pick disease. In this presentation, we will share recent developments, initiatives, and organisational updates.

**About the Speakers**

Deanna Carpino has been an integral part of the ANPDF for several years, having served in multiple Executive Committee positions. As the first General Manager of the ANPDF, Deanna oversees the foundation's operations and growth, to raise awareness and funds for research on NP-C. Deanna's journey in the non-profit sector has been shaped by her driven nature and her ability to think outside the box. With over a decade of experience in sales and marketing roles, she brings a unique perspective to her role. Deanna's passion lies in making a positive impact in the lives of individuals and families affected by NP-C. Through collaboration, communication, and hope, she aims to drive meaningful change.

Mandy Whitechurch is the founder and current president of the ANPDF. She is a strong advocate and caregiver for her two sons who have been diagnosed with NPC. Mandy is the Australian Representative of the International Niemann-Pick Disease Alliance (INPDA) and Ambassador for the International Niemann-Pick Disease Registry (INPDR). Mandy's passion for helping others extends to her professional life as well. She works as a Client Services Manager with extensive knowledge around the NDIS for families with NP-C. Her dedication and experience make her an invaluable resource for families and individuals affected by NP-C in Australia. Her story is one of resilience, advocacy, and hope which she shares with our Nieman-Pick community.

DAY ONE

RESEARCH

# CHILDHOOD DEMENTIA – PROGRESS, UPDATES AND FUTURE CHALLENGES

**Dr Kristina Elvidge, PhD**
Childhood Dementia Initiative

Childhood dementia comprises a devastating, under-recognised group of disorders which are individually rare, but a burden study published in Brain in 2023 found that collectively childhood dementia affects 1 in 2,900 births. The shared presentation and impacts of the more than 100 disorders causing childhood dementia present a powerful opportunity to adapt health systems to better care for and support children and families. The development of new, effective therapies can also be accelerated through research that concurrently investigates multiple childhood dementias, or mechanisms common to multiple disorders. Additionally, the shared utilisation of data, technology, and infrastructure can deliver significant efficiencies. This presentation will give an update on recent progress made for childhood dementia and strategic priorities for the future.

**About the Speaker**

Kris has been working with rare disease patient organisations since 2008, to accelerate the development of much needed treatments. She is currently Head of Research at the Childhood Dementia Initiative, an organisation founded in 2020 to drive systemic change to transform outcomes for children with dementia.

She was previously Head of Research at Sanfilippo Children's Foundation which funds research into Sanfilippo syndrome, one of the more than 100 rare diseases that cause childhood dementia, and has also worked with several muscular dystrophy patient organisations both in Australia and the UK. Kris completed a PhD in molecular biology at University of Western Australia and a postdoc at the University of Oxford.

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RESEARCH

# AN UPDATE ON CLINICAL NP-C RESEARCH IN MELBOURNE

**Prof. Mark Walterfang**
The Royal Melbourne Hospital

Participation in research at all levels is crucial to move the NP-C field forward, as greater disease understanding can open up new pathways for treatments. This presentation will focus on recent research in the field, including neuroimaging and biomarker research from the Royal Melbourne Hospital, and collaboration with our research partners. Recent publications will be highlighted to demonstrate how participation in research by patients and their families helps us push the boundaries of knowledge on the disease.

**About the Speaker**

Professor Mark Walterfang has worked as a consultant neuropsychiatrist at the Royal Melbourne Hospital (RMH) for more than 20 years. He completed specialist training at Neuropsychiatry, RMH, and his PhD at the Melbourne Neuropsychiatry Centre, focusing on neuroimaging. He has managed adolescent and adult patients with this Niemann-Pick Disease Type C (NP-C) at Neuropsychiatry since 2000.

He has recently completed a second research doctorate (DMedSci), which focusses on more than 15 years of biomarker research into NP-C at the Royal Melbourne Hospital.

DAY ONE

RESEARCH

# AN UPDATE ON THE FLOREY MRNA GENE THERAPY PROJECT FOR NIEMANN-PICK DISEASE TYPE C1

**Dr. Ya Hui Hung**

The Florey Institute of Neuroscience and Mental Health

Pathological mutations in the *NPC1* gene cause the fatal neurodegenerative disorder Niemann-Pick Disease Type C1 (NP-C1). The *NPC1* gene is responsible for producing the NPC1 protein, which is essential for cellular cholesterol processing. Mutations that disrupt the production of functional NPC1 protein lead to cholesterol build-up within cells, which triggers progressive damage to the brain, liver, spleen, and other organs. There is currently no cure for NP-C1. Gene therapy emerges as a promising therapeutic avenue for NP-C1. By delivering a healthy copy of the *NPC1* gene into affected cells, it can restore the production of functional NPC1 protein and alleviate the detrimental cholesterol build-up.

At The Florey, we are developing a messenger RNA (mRNA)-based gene therapy to treat NP-C1.This approach leverages the same mRNA technology that produced the now FDA-approved COVID-19 mRNA vaccines. Our research, using cell models of NP-C1 demonstrated the transformative potential of an *NPC1* mRNA gene therapy. This presentation will provide an update on our *NPC1* mRNA gene therapy project, highlighting our progress, challenges, and future directions.

**About the Speaker**

Dr. Ya Hui Hung completed her PhD in the Department of Genetics at the University of Melbourne, Australia. Her PhD project on Menkes disease sparked her interest in rare disease research. At The Florey, she leads a research team dedicated to the development of mRNA gene therapy for Niemann-Pick Disease Type C (NP-C) and other genetic diseases that cause childhood dementia. Her research interests include rare genetic diseases, neurodegeneration, childhood dementia and Alzheimer's disease. She is committed to finding treatment solutions for NP-C and other rare genetic diseases. She is a scientific advisor to the Australian NPC Disease Foundation and a co-organiser of the annual Australian NP-C Conference.

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RSEEARCH

# PRE-CLINICAL DEVELOPMENT OF A NEW SUBSTRATE REDUCTION STRATEGY TO TREAT LSDS

**Anthony L Cook, PhD**
University of Tasmania

Many of the diseases that cause childhood dementia involve accumulation of macromolecules within the cells of the brain, resulting in dysfunction of neural pathways that impact the child's ability to learn, play, and recognise family and friends. Lysosomal storage disorders (LSDs) are the cause of most childhood dementias, and this includes Niemann-Pick disease. LSDs are genetic diseases caused by loss-of-function mutation of genes encoding enzymes that function within the lysosome, a component of the cell that breaks down macromolecules. However, in LSDs an enzyme deficiency results in accumulation ('storage') of undegraded macromolecules. One strategy for treating LSDs is to reduce the amount of macromolecules being generated, in what is known as substrate reduction therapy. One such therapy, miglustat (brand name Zavesca), has shown great potential to improve disease outcomes across multiple LSDs that cause childhood dementia. However, miglustat has low blood-brain barrier permeability and a poor side effect profile that limits use for neurological diseases. We have hypothesised that antisense oligonucleotides (ASOs) that target the same pathway as miglustat will overcome these limitations. ASOs are a rapidly growing therapeutic class that can be designed to modulate targeted gene and/or protein expression, and which exhibit many favourable characteristics for treating brain disorders. Here, we describe our progress in development and and pre-clinical testing of an ASO-based approach to substrate reduction therapy that may improve treatment options for children with one of several LSDs.

### About the Speaker

Tony is head of the Stem Cell Models Group at the Wicking Dementia Research and Education Centre, University of Tasmania. He completed his Doctor of Philosophy studies at the University of Queensland in 2004, and following 6 years of post-doctoral research appointments (UQ, and Griffith University), he moved to a teaching-research position at the University of Tasmania in 2009, and then the Wicking Dementia Centre in 2015. Here, he leads and collaborates on projects utilizing pluripotent stem cell cultures and CRISPR/Cas gene editing to study genetic diseases causing neurodegeneration in children, gene-environment interactions in amyotrophic lateral sclerosis, and mechanisms of how axons degenerate.

# JOIN THE CONVERSATION

## STAY CONNECTED

with the Niemann-Pick community in Australia

@NIEMANNPICKOZ

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COMMUNITY

# ACID SPHINGOMYELINASE DEFICIENCY (ASMD): EXPLORING THE OTHER NIEMANN PICK DISEASE

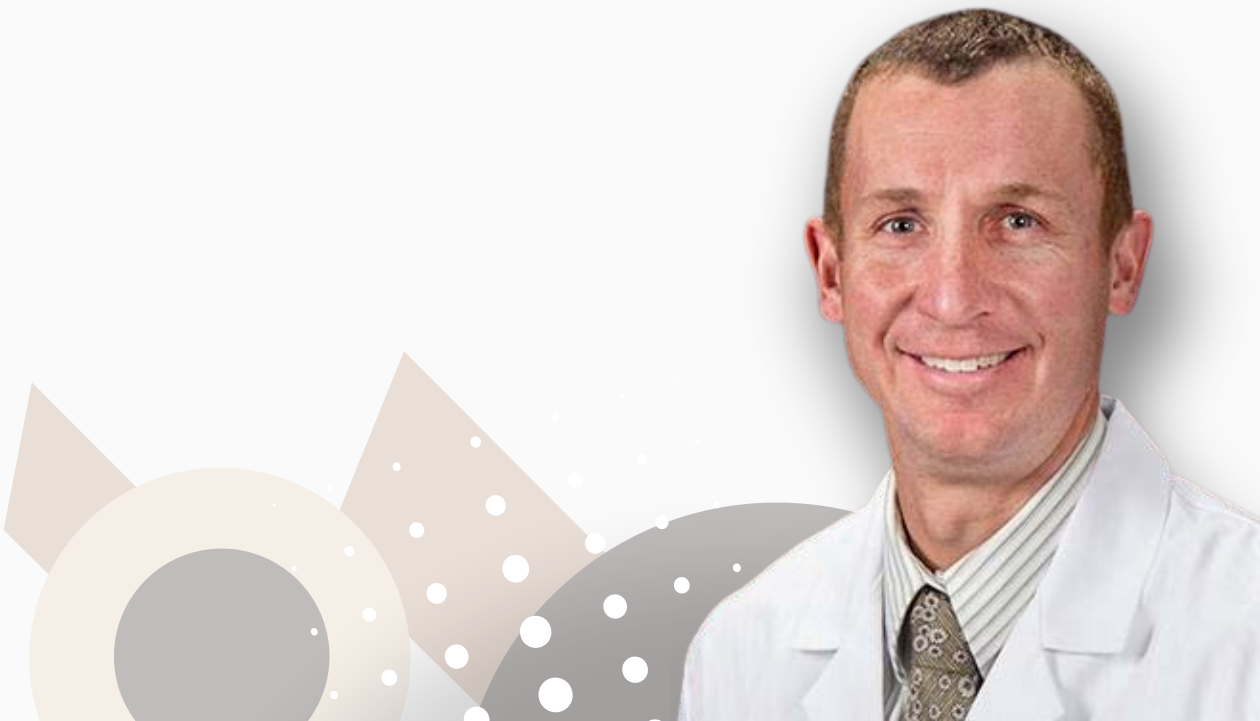
**Justin L. Hopkin, M.D.**
National Niemann-Pick Disease Foundation (NNPDF)

This talk will explore the similarities and differences between ASMD and NPC including why they share the same name. We will also review ASMD prevalence, spectrum of disease, common signs and symptoms, treatments and unmet need.

**About the Speaker**

Dr. Hopkin is a native of Wyoming. He completed his undergraduate studies at the University of Wyoming and medical school at the University of Washington. He was a resident at the University of Colorado where he trained in their primary care tract and was honored to be a chief resident. He went on to practice inpatient and outpatient internal medicine in rural Wyoming for eight years. During this time, he had the pleasure of teaching medical students, working in public health, and providing comprehensive medical care at a critical access hospital in a medically underserved community.

Dr. Hopkin's interest in medical education and serving a diverse population led him to Strong. He is thankful for the opportunity to work with the medical students and residents at the University of Rochester. As chief of the Hospital Medicine Division, he leads a distinguished group of hospitalists that are excelling in the areas of patient care, scholarship and medical education at Strong Memorial Hospital. In his spare time, he is involved in the National Niemann-Pick Disease Foundation and enjoys times with his family.



DAY TWO

COMMUNITY

# RARE DISEASE ADVOCACY: LEARNINGS FROM RARE VOICES AUSTRALIA

**Nicole Millis**
Rare Voices Australia

Advocacy has been an important driver of positive change in rare disease. Since then, RVA has led the Action Plan's collaborative implementation. Rare Voices Australia (RVA), with its focus on systemic advocacy and policy reform has many learnings about influencing change for the rare disease sector. One of the greatest policy wins in recent times was the collaborative development of the Australian Government's National Strategic Action Plan for Rare Disease (the Action Plan) launched in 2020. Since then, RVA has led the Action Plan's collaborative implementation. Nicole will present on how the rare disease sector, including RVA Partners such as the Australian NPC Disease Foundation, continues to utilise the Action Plan to bring about positive change.

**About the Speaker**

Nicole was appointed Chief Executive Officer of RVA in June 2016. An experienced social worker, she has both personal and professional experience in the rare disease sector. Nicole has engaged in systemic rare disease advocacy since 2008 and has extensive experience regarding issues of access to treatments.

Since 2018, Nicole has held the role of consumer nominee on the Life Saving Drugs Program Expert Panel. In 2023, Nicole accepted a health technology assessment appointment to the Enhanced Consumer Engagement Process Co-design Group as a consumer member. Under Nicole's guidance, RVA led the collaborative development of the National Strategic Action Plan for Rare Diseases, the first nationally coordinated effort to address rare diseases in Australia.

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COMMUNITY

# THE INTERNATIONAL NIEMANN-PICK DISEASE REGISTRY: A GLOBAL UPDATE

**Solomon Mbua, Conan Donnelly, Shaun Bolton, Jackie Imrie**
International Niemann-Pick Disease Registry (INPDR)

The International Niemann-Pick Disease Registry is a web-based, patient-led independent registry for the collection of prospective and retrospective clinical data from Niemann-Pick Disease patients. Consisting of a Clinician Reported Database (CRD) and a Patient Reported Database (PRD). The registry has almost doubled in size over the last five years and now includes 430 patients (350 with NPC and 100 with ASMD) across 20 clinical sites in 11 different countries in the CRD including North and South America and Europe. A further 35 sites are in the pipeline, including the Royal Melbourne Hospital in Melbourne, Australia. There are also 148 patients included in the PRD (115 with NPC and 33 with ASMD), 10 of which are from Australia. The INPDR is a community resource used to illuminate the natural history of NPD, to provide insights into the impact Niemann-Pick disease on the lives of patients and their careers and ultimately to improve outcomes for patients and their families. This presentation will describe the patient population included in the INPDR and an outline of the research that the INPDR has supported to date. We will also provide an overview of priorities for the registry for period 2024-2026.

**About the Speaker**

Solomon has over 7 years of clinical research experience within a wide range of therapeutic areas such as oncology, dermatology, rare diseases, cardiology, infectious diseases, as well as medical devices. He has worked in a variety of roles within clinical research including Clinical Research Associate, Associate Clinical Project Manager, and Project Manager. Solomon enjoys the science of planning and executing clinical trials and finds joy in bringing new therapeutics to market. Solomon is currently a Clinical Research Consultant with the INPDR and works with site set up, onboarding, recruitment and data quality initiatives in Australia, The United States, Canada, and South America. He also supports other NPD community led projects and represents the registry at conferences and workshops.

As a speaker for the INPDR, Solomon shares his insights, knowledge, and progress made by the INPDR and their dedication to improving the lives of individuals with NPD. Solomon lives in Buffalo Grove, IL, a few miles outside of Chicago. In his free time, he enjoys spending time with his son, writing children's books, and travelling.

CLINICAL TRIALS

# NIEMANN-PICK C1(NPC1) IN ISRAEL: WHAT CAN WE LEARN FROM THIS UNIQUE POPULATION?

**Orna Staretz- Chacham**
Soroka Medical Center

NPC1 is a pan-ethnic, autosomal recessive, ultra-rare disease. In Israel, several populations are affected by NPC, including the unique Bedouin communities and Ashkenazi Jews in addition to immigrants from eastern Europe (e.g., Russia, Ukraine). The Bedouin patients often harbour homozygous mutations due to consanguinity, leading to earlier diagnosis due to prior affected siblings and large families. This situation has led to the unique ability to diagnose patients at birth and initiate early intervention. Most Israeli patients have the neonatal and early- infantile phenotype, some of whom have interstitial lung disease (often fatal), similar to that seen in NPC2 patients. Premature infants with NPC1 may have a delayed presentation of a severe phenotype. In our population, NPC1 can present antenatally as congenital thrombocytopenia, congenital cholestasis, or hydrops.

We have reported elevated alpha-feto-protein as a marker for NPC1 in cholestatic neonates. There is no definitive treatment for Niemann-Pick disease type C, although there are promising emerging therapies.

Miglustat is not well tolerated by all patients and may be ineffective in very young children. Population studies, such as the NPC Israeli cohort, contribute to our knowledge of the clinical and genetic heterogeneity of the disease, and in this case, also make significant contributions to the natural history and management of the very youngest patients who often have more unusual presentations and severe disease.

The Israeli investigative sites are active participants in international clinical trials and contributing meaningful data needed to assess response to emerging therapeutics as well as assessment of safety in a varied (age, disease manifestations) population.

### About the Speaker

Finished her MD studies in Ben Gurion University in 1995 and headed to Pediatric residency in Soroka Medical Center. After finishing additional subspecialties she serves as senior neonatologist and metabolic diseases specialist, and also is the leader of the Rare Disease Center at Soroka Medical Center, Israel. Dr. Staretz-Chacham is also a senior lecturer at Ben Gurion University and published over 40 publications in different reputable journals, and also serves as the treasurer of the Israeli Society for Metabolic Diseases. She serves as a member of multiple national committees of health education and also of newborn screening and also in international committee of rare diseases of WHO.

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CLINICAL TRIALS

# ONGOING PROGRESS OF THE LARGEST OPEN PHASE 3 GLOBAL TRIAL OF TRAPPSOL® CYCLO™ (HPβCD) IN PATIENTS WITH NIEMANN-PICK DISEASE TYPE C1 (NPC1)

**Dr Caroline Hastings**
UCSF Benioff Children's Hospital

Caroline Hastings, Roberto Giugliani, Faith Ezgu, Beata Kieć-Wilk, Lukasz Pawlinski, Eugen Mengel, Elena Martin-Hernandez, Thorsten Marquardt, Reena Sharma, Nicholas Smith, Nancy Chien, Sema Kalkan Ucar, Mark Walterfang, Moeen Al-Sayed, Victor Fung, Ozlem Goker-Alpan, Norberto Guelbert, Leonardo Mendonça, Julian Raiman, Anna Ardissone, Rita Barone, Alberto Burlina, Cristian Calandra, Jordi Gascón, Loren Pena, Heidi Peters, Ronen Spiegel, Orna Staretz Chacham, Bryan Hurst, Bryan Murray, Andreas Brecht, and Joseph Mejia

NPC is an ultrarare, autosomal recessive monogenic disease with mutations in the NPC1 or NPC2 proteins which alter the transport of cellular unesterified cholesterol. This leads to the toxic accumulation of cholesterol and other lipids, primarily in brain and liver. Clinical severity is highly varied with visceral symptoms predominating in infants and neurologic/neurocognitive deficits in the juveniles and adults. In 2 completed early phase clinical studies, HPβCD administered IV biweekly established safety and tolerability. PK/PD assessments substantiated the MOA and confirmed penetration of the blood-brain-barrier and changes in CNS cholesterol. The ongoing Phase 3 study (96-week, double-blind, placebo-controlled) will evaluate change in 5D-NPC-CSS (ambulation, fine motor, speech, swallow, cognition) between biweekly IV HPβCD (2000 mg/kg) and placebo as primary endpoints for the EU/RoW (4D-NPC-CSS for the US) and collect safety data. Secondary endpoints include validated measures in SCAFI, radiographic swallow visualization, and Vineland-2. Novel exploratory endpoints include speech analytics utilizing IT, caregiver QOL surveys, and assessments of lung/ liver function. To date, 625 adverse events in 63 patients have been reported; 141 having been assessed as possibly related to study treatment; 33 recorded as serious and 9 assessed as being at least possibly related by the investigator. Six events of hearing change and 4 events of tinnitus have been recorded; none were considered serious. Treatment has been well tolerated with a safety profile consistent with prior studies. A particular focus is placed on neurologic outcomes and use of novel assessment technology. A 48-week comparative interim analysis planned for 1H 2025.

## About the Speaker

Dr. Caroline Hastings is a hematologist-oncologist and neuro-oncologist. She earned her medical degree from the University of California, Davis School of Medicine. She completed a residency in pediatrics and a fellowship in pediatric hematology and oncology at UCSF Benioff Children's Hospital Oakland. Dr. Hastings has experience caring for children, adolescents and adults with lysosomal storage disorders and other metabolic diseases. Hasting's research in rare diseases includes projects on relapsed leukemia, brain tumors and Niemann-Pick Type C disease (NPC). She is involved in clinical trials for drugs that show promise for treating NPC and serves on related advisory boards, including foundations dedicated to those affected by the disease.

Dr Hastings currently serves as director of the fellowship program in pediatric hematology and oncology at UCSF Benioff Children's Hospital Oakland.

# CLINICAL TRIALS

## N-ACETYL-L-LEUCINE (IB1001) FOR NPC - RESULTS OF A PIVOTAL, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

**Tatiana Bremova-Ertl**
IntraBio

**Background** Niemann-Pick disease type C (NPC) is a rare lysosomal storage disorder. We evaluated the safety and efficacy of N-acetyl-L-leucine (NALL), an agent that ameliorates lysosomal and metabolic dysfunction, for NPC.

**Methods** In this double-blind, placebo-controlled, crossover trial, patients with genetically confirmed NPC were randomly assigned in a 1:1 ratio to receive orally administered NALL or matching placebo 2-3 times per day in three tiers of weight-based dosing, switching treatments over two consecutive 12-week treatment periods. The primary endpoint was the Scale for the Assessment and Rating of Ataxia (SARA) (range 0-40 points; lower score representing better neurological status). Secondary endpoints included the Clinical Global Impression of Improvement, Spinocerebellar Ataxia Functional Index, and Modified Disability Rating Scale.

**Results** A total of 60 patients aged 5 to 67 years were enrolled. Baseline SARA scores were 15.88 for NALL and 15.68 for placebo. The mean change (standard deviation) on the SARA after treatment was -1.97 (2.43) with NALL and -0.60 (2.39) with placebo (Least Squares mean difference -1.28; 95% Confidence Interval, -1.91 to -0.765; $p<0.001$). The study also met all Secondary endpoints, including the SCAFI, CGI, and mDRS. The frequency of adverse events (AEs) was similar under active and placebo treatment and no treatment-related serious AEs occurred.

**Conclusion** In Niemann Pick Type C, NALL improved neurological signs and symptoms compared to placebo. Sponsored and Funded by IntraBio Inc, ClinicalTrials.gov, NCT05163288; EudraCT, 2021-005356-10).

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CLINICAL TRIALS

# CLINICAL UPDATE BY AZAFAROS ON NIZUBAGLUSTAT: THE DEVELOPMENT OF A SMALL MOLECULE FOR NIEMANN-PICK TYPE C

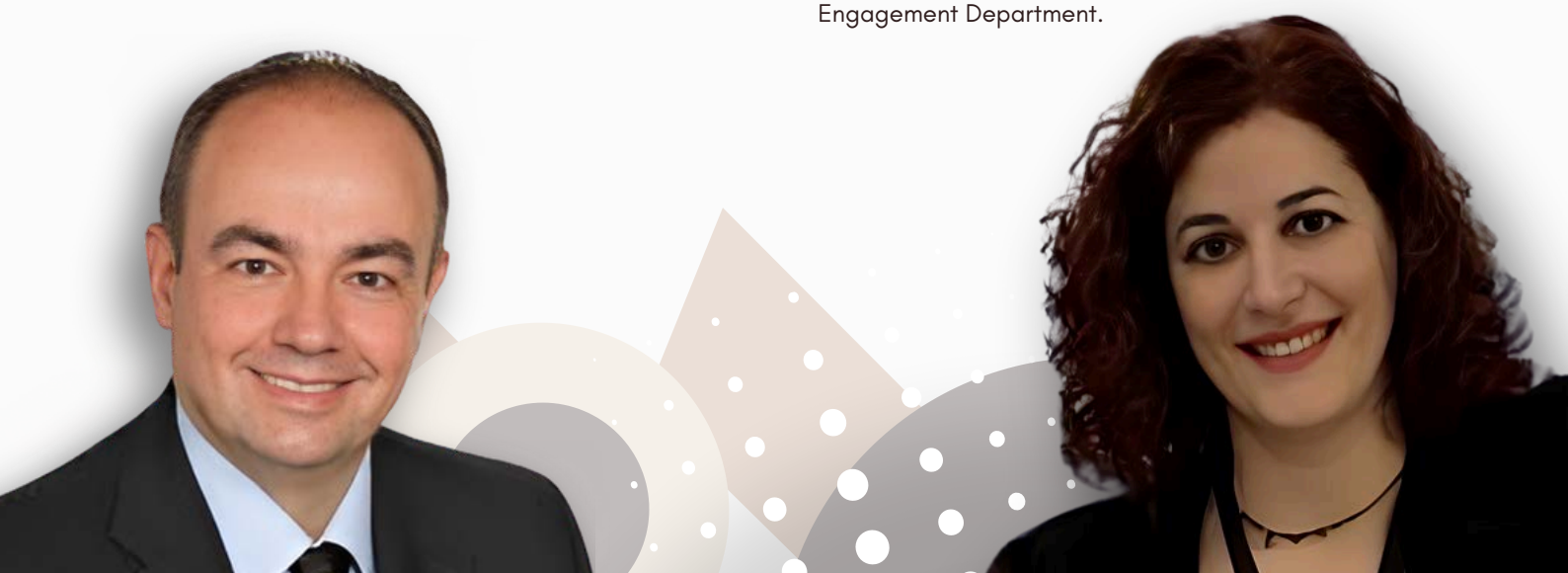
**Christian Freitag and Laura Lopez de Frutos**
Azafaros

Azafaros is a Dutch Swiss start-up company, since 2018 developing a small molecule for lysosomal storage diseases such as NPC, GM1, and GM2. In December 2023 phase 1 data was published without raising any concern regarding safety in human healthy population. Since June 2023 the phase 2 RAINBOW study has been ongoing. The study conducted in NPC and GM2, has two parts: the first part includes 12 weeks of main study with three groups (placebo and two different doses) and the second part includes, an extension with the two doses of active medication without placebo.
Today, the main part is completed, and data is being analyzed to present it to the community as soon as possible. At present, results support the ones observed in the healthy population, showing a positive safety and tolerability profile. Currently, in addition to analyzing the data that will allow us to identify the best dose to perform efficacy studies (phase 3), we are finalizing the design of a NPC study and a GM1/GM2 study. It's our intention to start ín 2025, including sites from different parts of the world such as EU, Australia, US, and LATAM, and assess the impact of nizubaglustat on those symptoms with the highest impact on patients' quality of life. During today's presentation, our Chief Medical Officer Christian Freitag, will update you on the several studies, new data, and our planning for the Phase 3 study.

### About the Speakers

Chris Freitag obtained his medical degree from Kiel University, Germany in 1994. After several years in different hospital positions, he started his career in the pharmaceutical industry at Roche. After A few different roles in different clinical development programs, he started working fully in the rare disease field in 2018. Chris joined Azafaros in 2022 as a Chief Medical Officer with the responsibility for the clinical development and medical management of the clinical program with nizubaglustat.

Laura López de Frutos started her experience with rare diseases 10 years ago, as a researcher in a lysosomal disease translational research lab in Spain, where she pursued his Ph.D. in biochemistry and molecular biology working on Niemann-Pick type C disease. Her professional career moved to the pharmaceutical industry in 2022 when she started working at Azafaros as a Regional Medical Director for Europe where she still maintains a relationship with the scientific community of lysosomal diseases, working in direct contact with clinical experts, and also supporting the Patient Engagement Department.



DAY TWO

GENETIC RESEARCH

# FILIPIN COMPLEX-REACTIVE BRAIN LESIONS: A CAUTIONARY TALE

**Prof. Kim Hemsley**
Flinders Health & Medical Research Institute

Filipin is a fluorescent stain used in the diagnosis of Niemann-Pick Disease Type C (NP-C). It is also widely used by researchers examining the distribution and accumulation of unesterified cholesterol in cell and animal models of neurodegenerative diseases including lysosomal storage disorders (NP-C and MPS IIIA), Alzheimer's and Huntington's disease. Because filipin staining disappears rapidly on exposure to light, we sought to establish a biochemical method to replace it. We bought a fluorometric kit and we also developed a mass spectrometry-based assay. When these tests were applied to NP-C and MPS IIIA mouse tissues, we obtained surprising results. We found no overall difference in the amount of free cholesterol in NP-C or MPS IIIA mouse brain homogenates compared to control tissues. Whilst the observation has previously been made in NP-C tissues and has been explained by alterations in the transport/distribution of cholesterol, it was unexpected for MPS IIIA tissues. Filipin has previously been reported to bind to GM1 ganglioside, and whilst GM1 accumulates in NP-C, this lipid does not accumulate in MPS IIIA cells/tissues. Using a fluorometric assay, we demonstrated for the first time that filipin also cross-reacts with both GM2 and GM3 gangliosides, explaining the filipin-reactive inclusions observed in MPS IIIA brain cells. Filipin is not specific for free cholesterol, and positive staining in any setting should be interpreted with caution.

### About the Speaker

Kim is a PhD neuroscientist. Since establishing the Childhood Dementia Research Group in 2002, she has dedicated her career to the study of disease pathogenesis in and treatment of brain disease in Sanfilippo syndrome, an inherited neurodegenerative lysosomal storage disorder that causes childhood dementia. Kim presently leads a multi-disciplinary team and a comprehensive, innovative translational research program at Flinders University that is seeking to develop tools for predicting the rate of symptom onset and disease progression, evaluate novel treatments and provide biomarkers for monitoring therapeutic efficacy in Sanfilippo. More recently, her teams' research interests have broadened to include other childhood dementia-causing disorders including MPS II, Niemann-Pick C and Peroxisomal disorders. Kim's goal is to enable the implementation of existing technologies for newborn screening for childhood dementia in Australia and beyond, therapeutic intervention at the earliest possible stage and thus the greatest improvement in patient quality and quantity of life to be achieved.

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GENETIC RESEARCH

# HUMAN BRAIN ORGANOIDS BRING NEW INSIGHT INTO BRAIN DISEASES WITH DEVELOPMENTAL ORIGIN

**Assoc. Prof. Silvia Velasco**
Murdoch Children's Research Institute (MCRI)

Pluripotent stem cell-derived organoids represent a significant advance in modelling human brain development in vitro and provide an invaluable opportunity to investigate cellular and molecular processes underlying brain diseases. Mutations in genes encoding epigenetic modifiers have emerged as a leading cause of developmental conditions presenting megalencephaly/ macrocephaly, autism, and intellectual disability, suggesting that the establishment and maintenance of precise epigenetic states is fundamental for normal brain growth, development, and function. However, the biological role of most epigenetic regulators during brain development remains unknown. By leveraging highly reproducible forebrain organoid models and single cell multiomics approaches, gene regulatory network reconstruction analysis, and high-throughput morphometric screenings, we investigated the molecular mechanisms through which haploinsufficiency of the SUV420H1/KMT5B and NSD1/KMT3B genes, which encode histone lysine methyltransferases, are involved in the pathogenesis of neurodevelopmental disorders.
By uncovering cell-type specific abnormalities associated with epigenetic dysregulation during neurodevelopment, our work contributes to shed light on the link between abnormal brain growth and neurocognitive dysfunction and provides an experimental paradigm for investigating the molecular mechanisms, ultimately identify effective therapies for neurodevelopmental disorders.

### About the Speaker

Associate Professor Silvia Velasco leads the Neural Stem Cells Laboratory at the Murdoch Children's Research Institute (MCRI) and is a Principal Investigator at the Novo Nordisk Foundation Center for Stem Cell Medicine, ReNEW, in Melbourne, Australia. With her Team she is interested in studying human brain development and understanding how alterations in this process lead to brain disorders, by using pluripotent stem cell-derived 3D organoid models. Her research interest in stem cell biology and developmental neuroscience began during herpostdoctoral training at New York University and The Broad Institute of MIT and Harvard, in the USA. She received her Ph.D. in Human Biology and B.Sc. and M.Sc. in Medical Biotechnology from the University of Turin in Italy.

DAY TWO

# GENETIC RESEARCH

# GENETICS AND NPC – PUTTING THE PUZZLE PIECES TOGETHER

**Lisette Curnow**
Victorian Clinical Genetics Services

The genetics of NPC should be straightforward (and in many cases is), but sometimes it can be more complicated despite our rapidly improving understanding of the complexities of genetics and genetic disease. This talk gives a summary of what we know about the genetics of NPC and a bit about what we don't and how that can impact families.

**About the Speaker**

Lisette has been working as a Genetic Counsellor with Victorian Clinical Genetics Services at the Royal Children's Hospital since 1999. She has a science background with a Graduate Diploma in Genetic Counselling and a Master of Health Science from Melbourne University.

She coordinated the genetics curriculum of the Graduate Diploma of Genetic Counselling (now the Masters course) for over 10 years and continues to have an interest and role in genetic education. Her work now primarily involves paediatric oncology and neurology, predictive testing for adult-onset neurodegenerative conditions, and developing a new laboratory genetic counselling role in RCH laboratory services. Lisette is the current chairperson of the Australasian society of Genetic Counsellors

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# COMMUNITY
# CARING FOR THE CARER

**Leah Lonsdale**
Carers Victoria

In 2023, Carers Victoria's Carer Engagement team conducted a series of carer polls across Victoria, asking carers about the main issues or challenges they were facing at that point in time. Carer health and wellbeing was in the top 3, along with financial issues and navigating the various service systems. In this session, Leah will explore why carer support is crucial and outlines some supports available to carers and caring families.

*A carer is someone who provides unpaid care and support to a family member or friend with care needs. They are parents, children, partners, other relatives and friends who assist with a variety of personal care, health care, transport, household and other activities.*

**About the Speaker**

Carers Victoria is the peak body representing all unpaid carers in Victoria. Our mission is to ensure that all unpaid carers are recognised, valued and supported. As the only state-wide organisation that focuses on the needs of all unpaid carers, we take pride in assisting carers across the state and championing the voice of all unpaid carers – regardless of the nature of their caring role or the needs of the care recipient.

Prior to working at Carers Victoria, Leah worked with carers across the sector including with Amaze (Autism Victoria), Haemophilia Foundation, Genetic Support Network Victoria and Health Education Australia Ltd (HEAL).

Leah Lonsdale, together with the Carer Engagement & Knowledge Centre team, engage with carers across the state, delivering:

- Education & information – on service navigation, wellbeing and other topics of interest to carers
- Events – so carers can have a break, and connect with other carers
- CarerVoice – opportunities for carers to tell us what matters, so we can reflect themes and messages to government and other stakeholders

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