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#NPCCONF21

25-26 JUNE

KARSTENS MELBOURNE AUSTRALIA

2021 NPC CONFERENCE

A conference for Niemann-Pick type C in Australia attended by patients, families, medical and scientific professionals.

Australian NPC Disease Foundation Inc
Research. Cure. Persevere.

cyclo therapeutics

Funded by the Australian Government Department of Social Services.

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c/- 3 Waller Street
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Australia

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Cerebrospinal fluid neurofilament light chain is elevated in Niemann- Pick type C compared to psychiatric disorders and healthy controls and may be a marker of treatment response

2021 NPC CONFERENCE

The 2021 NPC Conference in Australia is about sharing knowledge and experiences between patient families, clinicians and researchers.

Get the latest information on upcoming Clinical Trials both in Australia and overseas.

Gain new understanding, insights and tools from those who face the same challenges as you.

Share ideas and build new relationships within our Australian Niemann-Pick Community.

EVENT PARTNER

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 including Niemann-Pick Type C1.

cyclo therapeutics

Hosted by

Australian NPC Disease Foundation Inc
Research. Cure. Persevere.

Australian NPC Disease Foundation Inc. (ANPDF) is a not-for-profit organisation dedicated to making a positive difference to the lives of those affected by Niemann-Pick Disease type C.

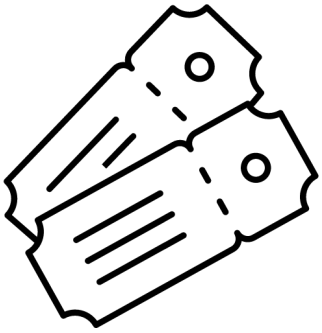
Through activities that raise funds and awareness, we are able to support patients and their families, as well as help fund scientific research towards better treatments.

Follow our journey at www.npcd.org.au

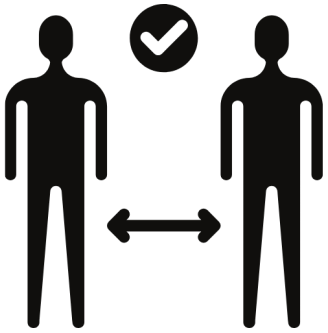
COVID-SAFE VENUE PLAN

All visitors can have the utmost confidence that our chosen venue, Karstens Melbourne, has developed an intelligence-led COVID-Safe Plan, in consultation with industry experts and A-Live Events Agency, that employs risk mitigation principles to ensure health and safety.

AN OVERVIEW ON HOW KARSTENS MELBOURNE IS KEEPING YOU SAFE:

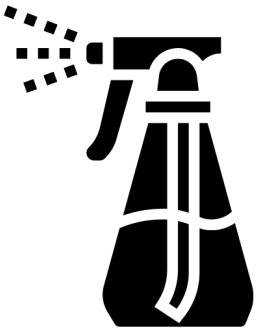


Karstens is only accessible to pre-registered attendees.

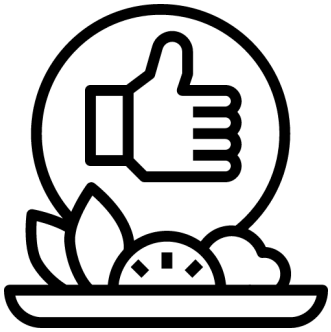


Physical distancing in conference room and break out areas to meet current distancing standards.

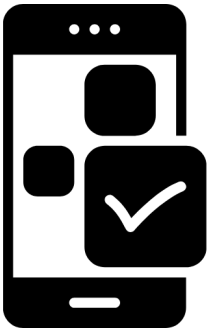
Sanitiser stations throughout the venue and dining areas.



Enhanced venue cleaning concentrated in high traffic areas.



Safe food and beverage service – All food is prepared under a HACCP accredited system.



Digital tickets to support contact tracing and reduce shared contact.

Stay Safe! And enjoy the 2021 NPC Conference in Australia.

SPEAKERS

Discover more about Niemann-Pick Disease type C (NPC) and the people it impacts with our speakers.

FRANCES PLATT
University of Oxford

MARC PATTERSON
Mayo Clinic

LORI GORSKI
Cyclo Therapeutics

CAROLINE HASTINGS
UCSF Benioff Children's Hosp.

JULIAN RAIMAN
Birmingham Women & Children's

GERALD COX
Cyclo Therapeutics

SHARON HRYNKOW
Cyclo Therapeutics

TAYLOR FIELDS
IntraBio

JOY LEE
Royal Children's Hospital

MARK WALTERFANG
Royal Melbourne Hospital

DANIELA CASTIBLANCO
MRC Laboratory of Molecular Biology

YA HUI HUNG
The Florey Institute of Neuroscience and Mental Health

LISETTE CURNOW
VCGS AT MCRI

MARTIN DELATYCKI
VCGS AT MCRI

KIM HEMSLEY
FLINDERS UNIVERSITY

JACKIE IMRIE
INPDR

JOHN LEE TAGGART
NPUK AND INPDA

GAIL HILTON
CHILDHOOD DEMENTIA INITIATIVE

JOANNE BEVILACQUA
NORTHWEST MENTAL HEALTH REGION

DAINA FAIL
NORTHWEST MENTAL HEALTH REGION

MANDY WHITECHURCH
ANPDF

Mistress of Ceremonies

FELICITY MUNRO
ANPDF

DEANNA CARPINO
ANPDF

SCHEDULE OF TALKS

DAY 1: **FRIDAY, JUNE 25**

8:15-8:45	**CONFERENCE CHECK-IN, TEA & COFFEE**
8:45-9:00	**CONFERENCE OPENING AND WELCOME TO COUNTRY** **Felicity Munro** - ANPDF Committee Member, Aust.
9:00-10:00	**UNDERSTANDING & TREATING NIEMANN-PICK TYPE C** **Frances Platt** BSc PhD - Professor of Biochemistry and Pharmacology, Head of Department of Pharmacology - University of Oxford, UK
10:00-10:30	**MORNING TEA BREAK**
10:30-12:30	**NP-C CLINICAL TRIAL UPDATES**
	OVERVIEW OF CLINICAL TRIALS FOR NP-C **Marc Patterson** MD FRACP FAAN FANA - Professor of Neurology, Pediatrics and Medical Genetics - Mayo Clinic, USA
	CYCLO THERAPEUTICS' DEVELOPMENT PROGRAM **Lori Gorski** - Global Head of Patient Advocacy - Cyclo Therapeutics **Caroline Hastings** MD - Director of fellowship program in pediatric hematology and oncology - UCSF Benioff Children's Hospital, USA **Julian Raiman** MD - Consultant, Metabolic Disorders - Birmingham Women & Children's, UK **Gerald Cox** MD PhD - Acting Chief Medical Officer - Cyclo Therapeutics, USA **Sharon Hrynkow** MD - Chief Scientific Officer and Senior VP for Medical Affairs - Cyclo Therapeutics, USA
	INTRABIO UPDATES **Taylor Fields** BA MSt - Senior Vice President - IntraBio Inc, UK
12:30-13:30	**LUNCH + NETWORKING**
13:30-15:30	**NP-C LANDSCAPE IN AUSTRALIA**
	NP-C: THE JOURNEY AFTER THE DIAGNOSIS **Joy Lee** MD FRACP - Metabolic Consultant - Royal Children's Hosp., Aust.
	NP-C: COMMON AND UNCOMMON QUESTIONS **Mark Walterfang** MBBS (Hons) PhD FRANZCP - Professor of Neuropsychiatry - The University of Melbourne; Consultant Neuropsychiatrist - The Royal Melbourne Hospital, Aust.
	CYTOTOXIC LYMPHOCYTE FUNCTION IN NP-C1 **Daniela Castiblanco** PhD - Postdoctoral Fellow - MRC Laboratory of Molecular Biology, UK
	NP-C1: THE QUEST TO FIND A TREATMENT SOLUTION **Ya Hui Hung** BMus BSc (Hons) PhD - Senior Research Officer - The Florey Institute of Neuroscience and Mental Health, Aust.

15:30-16:00	**AFTERNOON TEA BREAK**
16:00-17:30	**GENETICS: A FOCUS ON CARRIERS**

GENETICS & NPC: PUTTING THE PUZZLE PIECES TOGETHER

Lisette Curnow MHSC FHGSA - Senior Genetic Counselor - Victorian Clinical Genetic Services at Murdoch Children's Research Institute, Aust.

REPRODUCTIVE GENETIC CARRIER SCREENING

Martin Delatycki MBBS FRACP PhD - Clinical Director of the Victorian Clinical Genetics Services and co-Director of the Bruce Lefroy Centre at the Murdoch Children's Research Institute, Australia

UNDERSTANDING THE IMPACT OF HETEROZYGOUS MUTATIONS IN SULFAMIDASE & OTHER GENES THAT ENCODE LYSOSOMAL PROTEINS

Kim Hemsley BAppSci (Med. Lab. Sci.) PhD - Head, Childhood Dementia Research Group - Flinders University, Aust.

17:30-18:00	**LIVE Q&A**

with Prof. Frances Platt, Prof. Mark Walterfang & Taylor Fields

DAY 2: **SATURDAY, JUNE 26**

8:00-8:30	**CONFERENCE CHECK-IN, TEA & COFFEE**
8:30-10:00	**COMMUNITY CONNECTIONS**

ACHIEVING INCLUSIVITY IN THE INPDR

Jackie Imrie MSc - Clinical Research Manager - International Niemann-Pick Disease Registry, UK

COMMS & COLLABORATION: NIEMANN-PICK AWARENESS CAMPAIGNS

John Lee Taggart - Communications and Campaigns Manager - Niemann-Pick UK, International Niemann-Pick Disease Alliance, UK

AN INTRODUCTION TO THE CHILDHOOD DEMENTIA INITIATIVE

Gail Hilton - Project Manager - Childhood Dementia Initiative, Aust.

10:00-10:30	**MORNING TEA BREAK**
10:30-11:30	**SUPPORTING THE SUPPORTERS; CARING FOR THE CARERS: WHY WE CAN (AND SHOULD) SECURE OUR OWN OXYGEN MASKS FIRST.**

JoAnne Bevilacqua - Social Work Educator and Research Coordinator and **Daina Fail** BA (Hons) BSW MFST - NorthWest Mental Health Region, Aust.

11:30-12:00	**SHORT TALKS**
12:00-12:30	**ANPDF FUTURE + CONFERENCE CLOSING**

Mandy Whitechurch - Founder and Vice-President and **Deanna Carpino** - President - Australian NPC Disease Foundation, Aust.

VENUE INFORMATION

Karstens Conference Centre is located in the heart of Melbourne's CBD. Conveniently positioned between trams and train routes, the venue is less than an 8-minute walk from Flinders Street and Southern Cross Stations. Parking is available in our building through Secure car park at 410 Little Collins Street.

CONTACT INFORMATION

123 Queen Street
Melbourne, VIC
t 1300 008 710
e info@karstens.com.au
w www.karstens.com.au

PARKING

Secure Parking: Tel. 1300 727 483
In the same Building as Karstens, Enter via Little Collins Street

Car parking for accommodation guests is available for the occupant for $20.00 per vehicle, (which can be extended to include the day of departure for an additional $20.00).

FROM THE AIRPORT

Distance	25 km
Est. Taxi fare	$50
Sky Bus fee	$18

PUBLIC TRANSPORT

Stations	10 mins (Flinders Street or Southern Cross Stations)
Trams	Collins or Bourke Str.
Taxis Silver Top	1300 976 404
Black Cabs	13 22 27
Transport info	www.ptv.vic.gov.au

NEARBY HOTELS

Citiclub Hotel	113 Queen Street (same building as Karstens)
Oaks on Market	60 Market Street
Rendezvous	328 Flinders Street
Adina Apart Hotel	189 Queen Street

GENERAL INFORMATION

CATERING

All day meals will be provided including breakfast, 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 have been forwarded to the caterers to prepare special meals.

Please ask the catering or support staff to find the correct meal option.

MOBILE PHONES

Please respect the presenters and other members of the audience by ensuring your phone is switched off or set to silent whilst in session.

DISABILITY ACCESS

Entrance is via CQ Reception, 412 Little Collins Street. Please call Karstens on 0400 345 983 for access upon arrival.

Disabled toilets are located on level 3 (outside the lifts).

SPEAKER CONTACT DETAILS

We understand there may not be time to answer every question or query within each presentation's timeslot. If your question was unanswered during the conference, we invite you to follow up with our speakers directly at the below email addresses.

DANIELA CASTIBLANCO	daniela.castiblanco@petermac.org
FRANCES PLATT	frances.platt@pharm.ox.ac.uk
GAIL HILTON	gail@childhooddementia.org
ILIA VOSKOBOINIK	ilia.voskoboinik@petermac.org
JACKIE IMRIE	Jackie.Imrie@inpdr.org
JOANNE BEVILACQUA	joanne.bevilacqua@mh.org.au
JOHN TAGGART	john@npuk.org
JOY LEE	joy.lee@rch.org.au
KIM HEMSLEY	kim.hemsley@flinders.edu.au
LISETTE CURNOW	lisette.curnow@vcgs.org.au
LORI GORSKI	lori.gorski@cyclodex.com
MARC PATTERSON	Patterson.Marc@mayo.edu
MARK WALTERFANG	mark.walterfang@mh.org.au
MARTIN DELATIYCKI	martin.delatycki@vcgs.org.au
TAYLOR FIELDS	tfields@intrabiol.com
YA HUI HUNG	yahui.hung@florey.edu.au

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

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Find us online at www.npcd.org.au

KEYNOTE LECTURE

UNDERSTANDING AND TREATING NIEMANN-PICK DISEASE TYPE C

Niemann-Pick disease type C is a rare inherited metabolic disease that affects multiple organ systems in the body, including the brain. It is a complex disease and can be caused by mutations in two different genes, NPC1 or NPC2.

The mutated proteins that are encoded by NPC1 and NPC2 work together in a common pathway but the details of what this pathway does in cells of our bodies remains incompletely understood. In this presentation I will discuss the complexity of NPC disease at the genetic, biochemical and cellular levels and how this complexity offers multiple novel clinical intervention points that could be targeted for therapy. I will explain why the future of treatments for NPC disease will likely be combinations of different therapies.

Frances Platt BSc PhD
Department of Pharmacology, University of Oxford, Oxford, UK

Prof. Frances Platt obtained her BSc from Imperial College London (Zoology) and her PhD from the University of Bath, UK. She was a post-doctoral fellow at Washington University Medical School in St. Louis, USA. She was a Lister Institute Senior Research Fellow and is currently Professor of Biochemistry and Pharmacology at the University of Oxford. Her main research interests include the biology and pathobiology of glycosphingolipids and lysosomal disorders. Her research led to the development of miglustat for the treatment of glycosphingolipid lysosomal storage diseases. Prof. Platt was awarded the Alan Gordon Memorial Award and the Horst Bickel Award for advances in metabolic disease therapy. She was elected a fellow of the Academy of Medical Sciences in 2011 and was the recipient of a Royal Society Wolfson Merit Award in 2013. In 2016 she became a Wellcome Trust Investigator in Science. She was appointed Head of the Department of Pharmacology in 2020 and was elected a Fellow of the Royal Society in 2021.

NP-C CLINICAL TRIAL UPDATES

Marc C. Patterson MD FRACP FAAN FANA
Mayo Clinic Children's Center, USA

Prof. Marc Patterson was born and educated in Australia, and trained in neurology, child neurology and neurometabolic disease at the University of Queensland in Australia, at Mayo Clinic, and at NINDS/NIH under the guidance of Roscoe Brady, MD. He is currently Professor of Neurology, Pediatrics and Medical Genetics. He was Director of the Child Neurology Training program at Mayo 2008-2016), and Chair of the Division of Child and Adolescent Neurology (2008-2017) (Mayo Clinic administrative positions are term-limited). Dr Patterson had previously served as Professor and Director of Pediatric Neurology at Columbia University in New York (2001-2007). He has served as a member of the Neurology Topic Advisory Group for revision of the ICD-10 of the World Health Organization, the Committee on Adverse Effects of Vaccines for the Institute of Medicine, and leads the Education Core of the NIH-funded Lysosomal Disease Network. His research and practice has focused on rare diseases in children, including multiple sclerosis and neurometabolic disorders in general, with special interests in NP-C, other lysosomal diseases (including glycoproteinoses), mitochondrial cytopathies and congenital disorders of glycosylation, areas in which he has published more than 240 peer-reviewed papers and book chapters. He serves on the scientific advisory boards of several rare disease foundations. Dr Patterson has received funding support from NIH, industry and private foundations.

OVERVIEW OF CLINICAL TRIALS FOR NIEMANN-PICK DISEASE TYPE C

Clinical trials are conducted to establish the safety and efficacy of treatments; they are also required by regulatory authorities, whose approval is necessary to ensure that patients have access to safe and effective treatments. Traditionally, trials are conducted in a number of phases. Pre-clinical studies are those performed in tissue culture and in animal models, where candidate drugs for human diseases are discovered. Phase one and two clinical studies involve relatively small numbers of subjects, typically healthy volunteers in early phase studies, and are designed to study the behavior of drugs in the body, and to obtain basic safety data, as well as evidence that they are having the effects claimed; phase three trials, sometimes known as pivotal studies, are double blinded and randomized, and are intended to demonstrate the effectiveness of drugs in the target population. The term 'phase four studies' refers to post approval surveillance, intended to detect evidence of safety concerns not found in earlier studies, and to continue to monitor efficacy. This approach is feasible for common diseases, where potentially large populations of volunteers for studies are available; there are many challenges to traditional clinical trial design in ultra-rare diseases, such as NP-C. The challenges of studying this disease and similar ultra-rare disorders can be overcome with innovative and alternative trial designs. A number of clinical studies have been performed in Niemann-Pick disease over the last 30 years, including studies of drugs whose mechanisms of action include lowering cholesterol levels, inhibiting substrate synthesis, mobilizing and redistributing intracellular cholesterol, enhancing expression of heat shock proteins, enhancing NPC1 protein folding, inhibiting oxidation, enhancing intracellular metabolism, and inhibiting histone deacetylase. No human gene therapy trials have yet been initiated, but extensive pre-clinical work is in process. The results of these studies and the landscape of disease modifying therapy for NP-C, in 2021 will be reviewed.

NP-C CLINICAL TRIAL UPDATES

CYCLO THERAPEUTICS' DEVELOPMENT PROGRAM

This session will present progress in Cyclo Therapeutics' development program of its proprietary hydroxypropyl beta cyclodextrin, Trappsol® Cyclo ™, administered Intravenously for the treatment of Niemann Pick Disease Type C (NPC). The Phase I study in patients 18 years to 69 years showed that the drug has a favorable safety profile, is well tolerated, crosses the blood-brain-barrier and clears cholesterol from cells as observed both histologically and through biomarkers of cholesterol synthesis and metabolism.

"The start of patient enrollment in our pivotal Phase 3 study is an important milestone for both the NPC community and Cyclo Therapeutics."

An ongoing Extension Study in which patients are receiving Intravenous infusions in the home setting, some for close to two years, is characterized by disease stability for most patients and individual improvements for some. The Phase I/II study in patients 2 years to 39 years showed a favorable safety profile and biochemical results similar to the Phase I study as well as encouraging signals of efficacy based on 48-week observations using the 17-Domain NPC Severity Scale, inclusive of improvements in ability to walk, speak, swallow, as well as in fine motor skills and cognition, and Clinical Global Impressions of Improvement. Reductions in hepatosplenomegaly were observed, particularly with respect to spleen size. Based on the Phase I and Phase I/II data, the dose for the Phase III global pivotal trial was selected, 2000 mg/kg. The Phase III trial has been approved for enrolment by FDA and EMA.

The presentation will describe the main features of the Phase III study design and timelines for enrolment, interim analysis and completion. Countries expected to participate in the study include Australia, UK, US, France, Italy, Germany, Spain, Poland and Israel.

NP-C CLINICAL TRIAL UPDATES

Dr. Sharon Hrynkow
Chief Scientific Officer and
Senior VP for Medical Affairs,
Cyclo Therapeutics, Inc., USA

Dr. Hrynkow, a neuroscientist by training, has served in executive leadership roles at the National Institutes of Health, as the inaugural President of the Global Virus Network, a non-profit organization, and as Senior Science Advisor at the Department of State.

Dr. Hrynkow leads the Cyclo Therapeutics, Inc. clinical and scientific programs developing the company's drug, Trappsol® Cyclo™.

In the past Sharon Hrynkow was Associate Director at The National Institute of Environmental Health Sciences, Deputy Director at John E Fogarty International Center, Associate Director-Environmental Health Sciences at National Institutes of Health and President & Director at Global Virus Network.

1. WELCOME REMARKS FROM CYCLO THERAPEUTICS

Lori McKenna Gorski
Global Head of Patient Advocacy and
Engagement, Cyclo Therapeutics, Inc., USA

Ms. Gorski is a well-established biotechnology executive with over 20 years of experience specializing in patient advocacy for rare disease communities, including supporting clinical trial and access strategies, patient engagement and disease awareness communications. She currently serves as a board member of Our Odyssey, an organization dedicated to connecting young adults impacted by a rare or chronic condition with social and emotional support in the hope of improving our quality of life.

NP-C CLINICAL TRIAL UPDATES

2. RESULTS FROM PHASE 1 STUDY TO EVALUATE THE SINGLE- AND MULTIPLE-DOSE PHARMACOKINETICS OF INTRAVENOUS TRAPPSOL® CYCLO IN PATIENTS WITH NIEMANN-PICK DISEASE TYPE C (NPC-1) AND THE EFFECTS OF DOSING UPON BIOMARKERS OF NPC DISEASE

Caroline Hastings MD
Director, Pediatric Hematology Oncology Fellowship Program Children's Hospital & Research Center Oakland; Professor of Pediatrics, University of California, San Francisco, School of Medicine, USA

Dr. Caroline Hastings is a Professor of Pediatrics at UCSF Benioff Children's Hospital Oakland, and serves as the clinical director of NeuroOncology.
She received her M.D. from the University of California, Davis and subsequently completed her Pediatric residency as well as fellowship training in Pediatric Hematology and Oncology at Children's Hospital & Research Center Oakland, California. She is on the clinical faculty at UCSF Benioff Children's Hospital Oakland, and serves as the Director of the Pediatric Hematology/Oncology Fellowship training program.

Her academic interests include clinical trial development in high risk and relapsed leukemia, pediatric brain tumors, and lysosomal storage diseases, in particular Niemann-Pick Disease type C, a progressive fatal metabolic storage disease.

Dr. Hastings is involved with advocacy on a national and regional level. She serves on the Board of Trustees and Treasurer for the American Society of Pediatric Hematology Oncology as well as the chair of the Finance committee.

She leads awareness and philanthropic events and has personally raised several million dollars to support local programs in research, education, and clinical care as well as improving patient access to clinical trials. Dr. Hastings developed an outreach program to bring specialized care to children with blood diseases and cancer in Northern Nevada, based in Reno, beginning in 1992, and this has now become a major center for care in the state.

Dr. Hastings enjoys spending time with her husband and three daughters, traveling, pets, and creating the perfect garden.

NP-C CLINICAL TRIAL UPDATES

3. TOP LINE RESULTS FROM PHASE 1/2 STUDY TO EVALUATE SAFETY AND EFFICACY OF INTRAVENOUS TRAPPSOL® CYCLO™ IN PATIENTS WITH NIEMANN-PICK DISEASE TYPE C1

Julian AJ Raiman MBBS MSc MRCP
Consultant Inherited Metabolic Disease
Birmingham Children's Hospital
Birmingham, UK

Dr Julian Raiman joined the Inherited Metabolic Disease team at Birmingham Children's Hospital in September 2015 as a Consultant and Honorary Senior Clinical Lecturer at the University of Birmingham, where he is also currently the Clinical Lead for the department. This followed 8 years as an Academic Clinician in the Division of Clinical and Metabolic Genetics at the Hospital for Sick Children, Toronto, Canada, and an Associate Professor in the Department of Paediatrics at the University of Toronto.
Having completed his specialty training in 2004, he worked as a Consultant in Metabolic Medicine at the Evelina Children's Hospital, Guys' and St Thomas' NHS Foundation Trust.

Dr Raiman's research interests include treatment and characterization of inherited metabolic diseases, currently with a sub-specialist interest in lysosomal storage disorders in which he is an active Investigator/Co Investigator in over 40 completed and ongoing research studies including others in inborn errors of metabolism. He has authored/co authored in excess of 50 publications and spoken at numerous international, national and local events across his career. He also sits on the International Steering Committee of the Hunter Outcome Survey.

NP-C CLINICAL TRIAL UPDATES

4. PHASE 3 STUDY TO EVALUATE INTRAVENOUS TRAPPSOL® CYCLO™ IN PEDIATRIC AND ADULT PATIENTS WITH NIEMANN-PICK DISEASE TYPE C1

Gerald Cox, MD PhD
Acting Chief Medical Officer,
Cyclo Therapeutics, Inc., USA

Dr. Cox is the founder of Gerald Cox Rare Care Consulting, LLC, where since 2018 he has been providing expert advice to small companies in all phases of clinical development for investigational rare disease drugs. From 2016-2018, Dr. Cox was the Chief Medical Officer of Editas Medicine, where he led the clinical development of CRISPR-based genome editing medicines to treat human diseases, including the first approved IND for a CRISPR-based medicine to be delivered in vivo that is designed to treat a genetic form of blindness called Leber congenital amaurosis type 10. Prior to Editas Medicine, Dr. Cox held increasingly senior roles at Genzyme (now Sanofi Genzyme) for over 15 years, advancing to Vice President of Rare Disease Clinical Development. While at Genzyme, he played an instrumental role in the global development and approval of treatments for several lysosomal storage disorders, including the enzyme replacement therapies Aldurazyme® (laronidase) for Mucopolysaccharidosis type I in 2003, Elaprase® (idursulfase) for Mucopolysaccharidosis type II in Japan and the Asia Pacific region in 2007, and Cerezyme® (imiglucerase) for a label expansion in Gaucher disease type 3 in Australia and China in 2016, as well as the substrate reduction therapy Cerdelga® (eliglustat) for Gaucher disease type 1 in 2014. He also led the early clinical development of the enzyme replacement therapies Myozyme® (alglucosidase alfa) for infantile Pompe disease, which was approved in 2006, and olipudase alfa for Niemann-Pick disease type B, which recently completed a successful Phase 3 study. Dr. Cox has been affiliated with Boston Children's Hospital during his entire career, where he is a Part-time Staff Physician in Genetics. He is also an Instructor in Pediatrics at Harvard Medical School.

Dr. Cox received his MD and PhD from the University of California at San Diego and his B.A. from Harvard College. He completed an internship and residency in pediatrics followed by clinical and post-doctoral research fellowships in genetics at Boston Children's Hospital and was Director of the Medical Genomics Mapping Facility. Dr. Cox is board-certified by the American College of Medical Genetics and Genomics in Clinical, Biochemical, and Molecular Genetics, and he was board-certified by the American Academy of Pediatrics in the past. He serves on the Board of Directors for the National Tay-Sachs and Allied Diseases organization.

NIEMANN-PICK DISEASE TYPE C

#NPCCONF2021

#NC2021

A rare, fatal and progressive genetic disorder characterized by a defect in the NPC1 protein causing cholesterol and lipids to accumulate in cells of major organs leading to cell and tissue dysfunction.

NP-C CLINICAL TRIAL UPDATES

N-ACETYL-L-LEUCINE FOR NIEMANN-PICK DISEASE TYPE C: Results from a Multinational Clinical Trial

Taylor Fields BA MSt
IntraBio, UK

Taylor Fields is the Senior Vice-President of IntraBio Inc. At IntraBio, she leads all efforts related to the development and commercialization of IntraBio's novel treatment and therapies, and is principally responsible for the company's clinical and regulatory development programs. Ms. Fields obtained a B.A. in International Studies and English from the University of Michigan, and received a Masters in Systems Design from the University of Oxford.

N-acetyl-L-leucine (IB1001) is the L-enantiomer of N-acetyl-DL-leucine (racemate), a modified amino acid approved in France since 1957 (TanganilTM) as a treatment for acute vertigo. Prior observational studies assessing the effect of N-acetyl-DL-leucine in NPC patients demonstrated a beneficial symptomatic, and neuroprotective, disease-modifying effect [Bremova et al. 2015; Cortina-Borja et al. 2018; Kaya et al. 2020]. Animal studies in the NPC mouse model (*Npc1*$^{-/-}$) have shown the L-enantiomer (IB1001) has clinical benefits over the racemate. Treatment with N-acetyl-DL-leucine and its enantiomers all significantly reduced ataxia when commenced pre-symptomatically (from 3-weeks of age onward) and symptomatically (for 1-week treatment, starting at 8-weeks of age). However, only IB1001significantly delayed the onset of functional decline (gait abnormalities, motor dysfunction), the decline in general health and condition, slowed disease progression, and prolonged survival—whereas the D-enantiomer did not [Kaya et al. 2020].

In a multi-national clinical trial (IB1001-201), IB1001 demonstrated a statistically significant and clinically meaningful improvement in symptoms, functioning, and quality of life for pediatric and adult patients with NPC. Treatment with IB1001 resulted in a statistically significant change in the primary Clinical Impression of Change in Severity (CI-CS) endpoint (p-value = 0.029) as well as secondary endpoints, including the Scale for the Assessment and Rating of Ataxia (SARA; p-value=0.001), Investigator's Clinical Global Impression of Change (CGI-C; p-value <0.001). IB1001 was safe and well-tolerated, informing a favorable benefit-risk profile for the treatment of NPC.

NP-C LANDSCAPE IN AUSTRALIA

Joy Lee MD FRACP
Royal Children's Hospital, Australia

Dr Joy Lee has been working as a metabolic physician at The Royal Children's Hospital, Melbourne for more than ten years. She completed her fellowship in Biochemical Genetics at the Children's Hospital, Westmead, Sydney and Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Melbourne. She is involved with the diagnosis and management of suspected and known patients with metabolic diseases.

NIEMANN PICK TYPE C: The Journey After the Diagnosis

The challenges and barriers of making a diagnosis of NPC were discussed in a previous symposium. This talk will focus on what happens after a diagnosis is made. Managing the signs and symptoms of NPC requires a multidisciplinary approach with input from neurology, gastroenterology, dietetics, and other allied health services. Dealing with treatment plans and multiple medical appointments while coping with the mental and emotional stresses associated with this diagnosis can be very challenging. This talk will discuss and offer some strategies with the hope of helping navigate these different issues.

NP-C LANDSCAPE IN AUSTRALIA

NIEMANN PICK TYPE C: Common and Uncommon Questions

The diagnosis of the rare disorder NPC can be unexpected for patients, families and clinicians, and brings with it a wealth of questions about the disease, its effects on patients and families, and individuals. This talk will weave together clinical experience and research on NPC, with the aim of answering some of the common, and less common, questions on this disorder.

Mark Walterfang MBBS (Hons) PhD FRANZCP
Royal Melbourne Hospital, Australia

Professor Mark Walterfang has worked as a consultant neuropsychiatrist at the Royal Melbourne Hospital for more than 20 years, having completed specialist training at Neuropsychiatry, RMH, and his PhD at the Melbourne Neuropsychiatry Centre, focusing on neuroimaging. He is completing a second research doctorate in Niemann-Pick Disease type C, having managed adolescent and adult patients with this illness at Neuropsychiatry since 2000.

NP-C LANDSCAPE IN AUSTRALIA

Daniela Castiblanco PhD
MRC Laboratory of Molecular Biology, UK

Daniela is a BSc in Biology and Microbiology as well as a Master of Science from Universidad de Los Andes in Bogotá, Colombia. She recently completed her PhD in the Killer Cell Biology Laboratory at the Peter MacCallum Cancer Centre in Australia under the supervision of Prof. Joe Trapani and A/Prof. Ilia Voskoboinik. During her PhD she studied the biology of cytotoxic secretory granules in cytotoxic lymphocytes in the context of the lysosomal storage disorder, Niemann-Pick type C1. She is currently working as a Postdoctoral Research Fellow at the Laboratory of Molecular Biology – Medical Research Council in the UK.

CYTOTOXIC LYMPHOCYTE FUNCTION IN NIEMANN-PICK TYPE C1 DISEASE

Niemann-Pick disease Type C1 (NPC1) is an autosomal recessive disorder of lipid homeostasis, in which progressive neurological symptoms, including neuroinflammation, dominate the clinical picture. The disease is caused by mutations in a lysosomal cholesterol transporter, the NPC1 protein, whose deficiency results in cholesterol and glycosphingolipid accumulation in the lysosomes. The clinical presentation and severity of NPC1 vary widely, with some patients developing symptoms in infancy or early childhood, and others being diagnosed much later, yet the genotype-phenotype relationship is yet to be fully understood. Importantly, the fact that lysosomes are essential for the function of essential immune cells called cytotoxic lymphocytes remains understudied. Indeed, we have noticed that many non-neurological manifestations of the NPC1 disease - persistent infections, pathological enlargement of the liver and spleen and inflammation in the lungs - are all reminiscent of immunodeficiencies that feature impaired cytotoxic lymphocyte function. We, therefore, explored whether and how NPC1 deficiency influences the function of these essential immune cells.

NP-C LANDSCAPE IN AUSTRALIA

NIEMANN-PICK DISEASE TYPE C1: The quest to find a treatment solution

Pathological mutations in the *NPC1* gene result in the fatal neurodegenerative disorder Niemann-Pick Disease Type C1 (NP-C1).

Currently, there are limited approved treatment options and disease management remains the main clinical care for NP-C1. Therefore, there is an urgent need to explore and develop new treatment options that can halt or reverse the disease progression.

This presentation will summarise the pre-clinical studies at the Florey, in search for an effective treatment solution for NP-C1.

Ya Hui Hung PhD
The Florey Institute of Neuroscience and Mental Health, Australia

Ya Hui Hung is a senior research officer at the Florey Institute of Neuroscience and Mental Health (Australia). Trained in molecular biology and biochemistry, she completed her PhD studies on Menkes disease and copper metabolism at the University of Melbourne (Australia).

Her research interest in Niemann-Pick Disease Type C (NP-C) evolved from her early postdoctoral studies investigating the relationship between copper and cholesterol metabolism in the development of neurodegeneration and Alzheimer's disease.

Her NP-C research has contributed to mapping of the metallobiology landscape in NP-C, and identified early neurological changes in the heterozygous Npc1 mice that may have clinical implications for human NPC1 carriers. She is currently exploring new therapeutic options to treat NP-C.

GENETICS: A FOCUS ON CARRIERS

Lisette Curnow MHSC FHGSA
Victorian Clinical Genetic Services, Murdoch Children's Research Institute, Australia

Lisette is a Senior Genetic Counselor at the Victorian Clinical Genetics Services, based at the Royal Children's Hospital in Melbourne. She has worked at VCGS since 1999 in a range of areas, but predominantly neurology, newborn screening and paediatric oncology.

For the last three years, she has divided her time between a laboratory role involving education of non-genetics specialists and triaging of genetic test requests for the RCH, and clinical work.

She is passionate about genetics and providing support, education and accurate information to families whose lives are impacted in some way by a genetic condition in themselves or their family.

GENETICS AND NPC: Putting the puzzle pieces together

This presentation will discuss our understanding of the genetic cause of NPC, the implications of a new diagnosis for parents and extended family, and testing options available to those at risk. It will also explore the impact of a genetic diagnosis on families.

GENETICS: A FOCUS ON CARRIERS

Martin Delatycki MBBS FRACP PhD
Victorian Clinical Genetic Services & Bruce Lefroy Centre, Murdoch Children's Research Institute, Aust.

Martin is the Clinical Director of the Victorian Clinical Genetics Services (VCGS) and co-Director of the Bruce Lefroy Centre at the Murdoch Children's Research Institute (MCRI). Martin studied medicine at University of Melbourne and trained in paediatrics at the Royal Children's Hospital. He subsequently trained in clinical genetics at the VCGS and then obtained his PhD for work on Friedreich ataxia through the MCRI. His research and clinical interests are neurogenetics and community genetics. Martin has over 250 publications and has obtained over $5 million in research funding.

REPRODUCTIVE GENETIC CARRIER SCREENING

Carrier screening for genetic conditions has been possible since the 1970s. Screening for Tay-Sachs disease and haemoglobinopathies was possible because for each, there is a biochemical/haematological test that identifies carriers. From the late 1980s it became possible to screen for carrier status by genetic testing. This was initially by testing for individual mutations such as those in the CFTR gene in which mutations predispose to cystic fibrosis. Carrier screening programs were set up in communities at risk of autosomal recessive conditions such as Tay-Sachs disease in the Jewish community, haemoglobinopathies in those from Africa, Asia and Mediterranean regions and cystic fibrosis in Caucasian populations. It is now possible to test people for carrier status over one thousand autosomal recessive and X-linked recessive conditions by next generation sequencing. The federal government has funded a project called Mackenzie's Mission where ~8,000 couples will be screened for carrier status for over 1000 genes. Such testing provides choice to couples however it can result in uncertainty and generate ethical concerns. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists and Human Genetics Society of Australasia has developed guidelines in relation > to reproductive genetic carrier screening. These recommend that all women/couples are offered carrier screening pre-pregnancy or in the first trimester for haemoglobinopathies and a panel of other genetic disorders, cystic fibrosis, spinal muscular atrophy and fragile X syndrome at a minimum, with consideration of a large panel of genes, so-called expanded carrier screening.

GENETICS: A FOCUS ON CARRIERS

Kim Hemsley BAppSci (Med. Lab. Sci.) PhD
Flinders University, Australia

For the last 19 years, Kim and the Childhood Dementia Research Group, now at Flinders University, have dedicated themselves to gaining a better understanding of disease pathogenesis in and developing treatments for childhood dementia caused by Sanfilippo syndrome (MPS III). The Group's pre-clinical research has supported establishment of human clinical trials examining the efficacy of intra-CSF-directed enzyme replacement therapy, and first and second-generation AAVrh10-based intra-cerebral gene therapy.

Current research interests include development of small molecule therapies for Sanfilippo syndrome and other childhood dementias, personalised therapy using re-purposed drugs, establishment of prognostic blood-based biomarkers of brain disease progression in Sanfilippo, and understanding the impact of heterozygous mutations in lysosomal genes.

1. Mitsui et al (2009) Arch Neurol 66(5):571-576.
2. Bremova-Ertl et al (2020) Neurology. 94(16): e1702-e1715.
3. Hung et al (2016) Neurotherapeutics. 13(3): 614-622.
4. Douglass et al (2021) J Inherit Metab Dis. doi: 10.1002/jimd.12359.

UNDERSTANDING THE IMPACT OF HETEROZYGOUS MUTATIONS IN SULFAMIDASE & OTHER GENES THAT ENCODE LYSOSOMAL PROTEINS

Carriers of mutations in the gene encoding the lysosomal enzyme glucocerebrosidase *(GBA)* which is deficient in Gaucher disease, are at increased risk of developing Parkinson's disease[1]. Further, carriers of mutations in the Niemann-Pick C1 gene *(NPC1)* have been found to exhibit abnormal brain metabolism and impaired cognition[2], and haploinsufficient *Npc1*$^{+/-}$ mice appear vulnerable to anxiety and motor impairment[3]. To determine whether increased risk of disease is conferred by heterozygous mutations in other lysosomal enzyme-encoding genes, we are evaluating the impact of carrying a mutation in the sulfamidase gene, which in homozygotes causes Sanfilippo syndrome. Our findings to date demonstrate discrete structural aberrations in the dendritic tree of cortical pyramidal neurons in 21-month old animals[4]; the overt disease lesions and resultant phenotypic changes in *Gba*$^{+/-}$ and *Npc1*$^{+/-}$ mice were not observed, and thus may be enzyme dependent. By better understanding why deficiency in, or mutant forms of some but not all lysosomal proteins leads to heightened risk or earlier onset of classical neurodegenerative disorders, novel disease-causing mechanisms may be identified.

CONFERENCE DAY TWO

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MAGNETOM 7T MRI
SIEMENS
THE UNIVERSITY OF MELBOURNE
THE FLOREY

COMMUNITY CONNECTIONS

ACHIEVING INCLUSIVITY IN THE INTERNATIONAL NIEMANN-PICK DISEASE REGISTRY

The INPDR is a single, Niemann-Pick Disease-specific, longitudinal global registry which was conceived and created by patients with support of professionals for worldwide use. It collects clinical data and patient reported data for both acid sphingomyelinase deficiency (Niemann-Pick disease types A and B) and Niemann-Pick type C. It replaces the need for multiple registries which allows for the collection of high volume and high quality data. INPDR has been collecting data on patients with ASMD and Niemann-Pick Disease Type C since September 2014. We currently have 8 countries submitting data from Europe, USA and Canada.

In line with our Strategic Business plan we aim to introduce the INPDR to an additional 28 countries in 2021 with a potential to increase the number of patients enrolled in the Clinical Reported Dataset (CRD) from its current 310 patients to 1000. Initially targeting large centres with known patients we will then be endeavouring to include all patients wherever they may be seen. Additionally we will begin identifying clinical centres that may see a small number of patients to ensure equitable patient access to participation. To enroll into the CRD, patients are only required to have a confirmed diagnosis of NPD and provide informed consent. Traditional barriers to research participation where strict eligibility criteria are in place have > been removed for the INPDR, allowing patients from all background to participate.

Jackie Imrie MSc
International Niemann-Pick Disease Registry

Since qualifying as a paediatric nurse in Leeds in 1981 I have worked in many areas including general paediatrics, oncology, bone marrow transplant unit, cystic fibrosis unit and neonatal intensive care. I moved to Bolton in 1993 and worked in the Willink unit at the Royal Manchester Children's Hospital assisting with clinics for children and adults with a range of metabolic disorders. I was actively involved in the Zavesca trial from the start and have stayed actively involved in research maintaining GCP training. In 1999 I started as the first support nurse for families with Niemann-Pick disease. Having set up the national database and help line I supported families throughout the country with this group of rare disorders. From 1991 to 1996 I completed an Honours degree with the Open University in Biochemistry, Genetics and related subjects. From 2000 to 2003 I studied for the MSc in Genetic Counselling. Since then I have had the opportunity to be lead and joint author on many publications relating to NPDs. Having retired from full time work for NPDG (UK) at the end of 2011 I continued to do Consultancy work in the field of Niemann-Pick Diseases. I currently lead recruitment for the International Niemann-Pick Disease Registry as Clinical Research Manager and am Trustee for NPUK and MLD Support Association UK.

John Lee Taggart
Niemann-Pick UK and International Niemann-Pick Disease Alliance

As the Communications & Campaigns Manager for both Niemann-Pick UK (NPUK) and the International Niemann-Pick Disease Alliance (INPDA), I help to define both charity's content writing and social media strategy, and also develop videos, graphics, and printed publications. More recently I was Executive Producer on the now multi-award winning short film, Go Make Memories (2019), which served to include the wider NPD community in the push for further awareness.

I am privileged to have been asked to feature in this conference, it feels incredible to part of a group who are completely devoted to helping those affected by Niemann-Pick disease. I am hoping through my work we can reach a far wider audience so that more people are conscious of these conditions.

COMMS & COLLABORATION: Niemann-Pick awareness campaigns

After over a year of disruption and displacement as a result of the global COVID-19 pandemic, the role of communication and tech have never been more relevant, and the need for more innovation in the way we interact with one another more urgent than now…as a small rare disease community we feel this even more than most.

In this presentation Niemann-Pick UK and International Niemann-Pick Disease Alliance Communications & Campaigns Manager John Lee Taggart walks us through the many ways in which collaboration between families in their respective home countries and shared efforts with those overseas, has time and time again proven itself to be the best way to inform, educate, and raise awareness of Niemann-Pick disease.

John will also share details of a new upcoming campaign which he hopes NP families in Australia will be excited to take part in!

COMMUNITY CONNECTIONS

AN INTRODUCTION TO THE CHILDHOOD DEMENTIA INITIATIVE

The Childhood Dementia Initiative was set up in 2020 in response to some groundbreaking research that identified more than 70 rare genetic conditions that cause dementia in children, Niemann Pick C is one of these conditions.

This presentation will provide insights from the research that has been published and will explain the goals of Childhood Dementia Initiative and the progress made so far.

Gail Hilton
Childhood Dementia Initiative, Australia

With 15 years experience managing non-profit services in the paediatric health space, Gail now plays a lead role at the Childhood Dementia Initiative.

Her priorities are raising awareness and increasing understanding of childhood dementia in the paediatric health sector and improving quality of life and models of care for these children.

SUPPORTING THE SUPPORTERS; CARING FOR THE CARERS: Why we can (and should) secure our own oxygen masks first.

When a loved one is diagnosed with NPC the immediate concern is for their wellbeing & treatment. This is a normal and natural response. Schedules and priorities change, running around and taking responsibility for making sure that every appointment is made, every recommendation adhered to, every medication change abides by, the list is endless. Yet many people (parents/partners) forget to process the impact on the family but even more importantly on themselves. On every airplane journey, we are instructed to secure our own oxygen masks before attending to our children; new doctors in the emergency room are taught to check their own pulse before stepping in to an emergency. And yet, for this arduous marathon of caring for a loved one, we often neglect ourselves. I will address why our own mental health is equally important, and explore some of the tools and resources that may help.

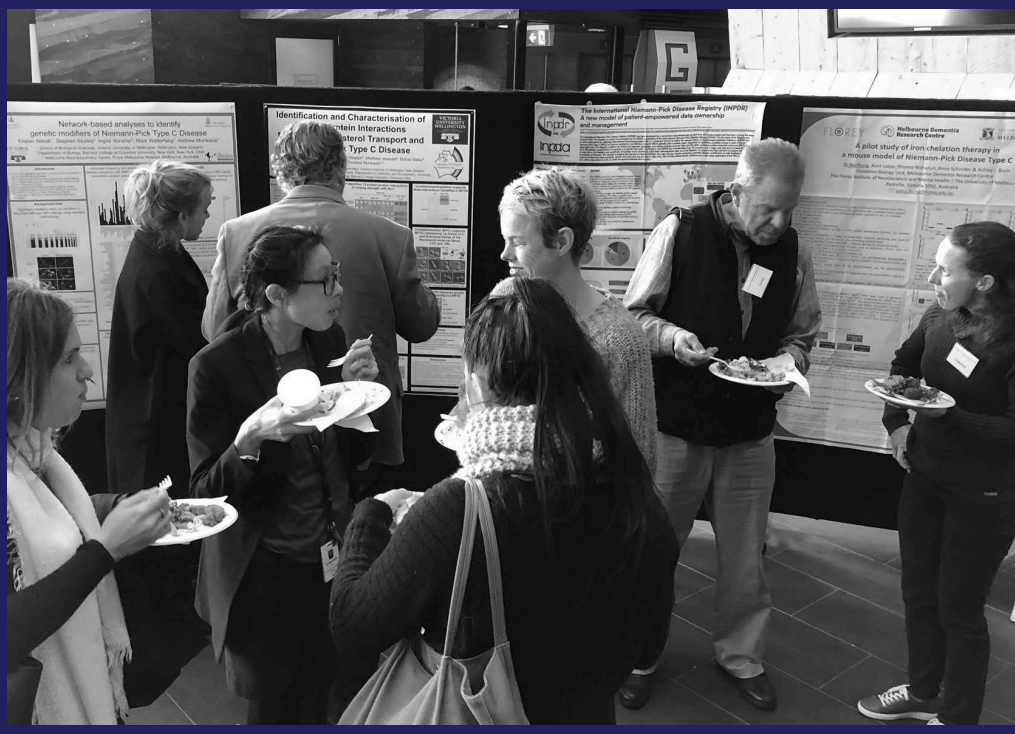
JoAnne Bevilacqua
NorthWest Mental Health Region (NMHR), Aust.

JoAnne is an Accredited Mental Health Social Worker and Family Therapist. Graduating from UOM Social Work in 1988, she began with DHHS Child Protection, specialising in the safety and protection of infants under the SIPW programme. She began the newly created Social Work position with the Neuropsychiatry Team at the RMH in April 2004. From there she completed her Masters in Family Therapy. She worked on building community collaborations and strengthening pathways for those living with Younger Onset Dementias and undertook a secondment with Dementia Australia in 2010 to research the viability of a one stop YOD service for Victoria. Throughout her work, she was involved in supporting families through the initial exploration and implementation of research trials and supported the introductions and connections of Victorian-based parents who were witnessing their children and their lives being impacted by NPC. She has a private practice in counselling and therapy based in Hawthorn since 2009.

Daina Fail BA (Hons) BSW MFST
NorthWest Mental Health Region (NMHR), Aust.

Daina completed her Social Work studies at the University of Melbourne in 1999 and has worked in a variety of settings since- mainly mental health, trauma and Emergency Medicine. It is within these areas that she developed a wide variety of skills required to support and advocate for families, carers and patients alike under diverse circumstances. She joined the Neuropsychiatry Unit in 2014 where she now works as the Senior Social Worker across the inpatient and outpatient clinics. She acquired her Masters of Family Therapy and Systems Theory (ACU) in 2021.

SHORT TALKS #NPCCONF2021 #NC2021



DIFFERENTIAL INVOLVEMENT OF HIPPOCAMPAL SUBREGIONS IN NIEMANN-PICK TYPE C DISEASE: A CASE-CONTROL MRI STUDY

Pierre Wibawa[1,2], Florian Kurth[3], Eileen Luders[3,4], Christos Pantelis[1,5], Vanessa Cropley[1], Maria A. Di Biase[1,6], Dennis Velakoulis[1,2,5], Mark Walterfang[1,2,5]

[1]Melbourne Neuropsychiatry Centre, University of Melbourne, Parkville, Victoria, Australia; [2]Neuropsychiatry Unit, Royal Melbourne Hospital, Parkville, Victoria, Australia;[3]School of Psychology, University of Auckland, Auckland, New Zealand;[4]Laboratory of Neuro Imaging, School of Medicine, University of Southern California, Los Angeles, USA;[5]Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia;[6]Psychiatry Neuroimaging Laboratory, Harvard Medical School, Boston, Massachusetts, USA.

Hippocampal brain regions are commonly affected in Niemann Pick type C disease (NPC), but little is known regarding distinct subregions of the hippocampus and whether these are equally or differentially affected.

Methods: We compared volumes of the hippocampal subregions between 9 adult-onset NPC cases and 9 age- and gender-matched controls using a 3T T1-weighted MRI scan. Gray matter volumes of the cornu ammonis (CA1, CA2 and CA3), dentate gyrus (DG), subiculum, entorhinal cortex and hippocampal-amygdalar transition area (HATA) were calculated by integrating MRI-based image intensities with microscopically defined cytoarchitectonic probabilities.

Results: Compared to healthy individuals, NPC patients showed smaller volumes of the CA1-3 and DG regions bilaterally, with the greatest difference localised to the left DG (Cohen's d=1.993, p = 0.008). There were no significant differences in the subiculum, entorhinal cortex and HATA. We also did not find any significant associations between hippocampal subfield volumes and key clinical features of NPC, including disease duration, symptom severity and psychosis.

Conclusions: The pattern of hippocampal subregional atrophy in NPC differs from those seen in other dementias, which may indicate unique cytoarchitectural vulnerabilities in this earlier-onset disorder.

SHORT TALKS

OBJECTIVE MEASUREMENTS AND CLINICAL CORRELATION OF MOVEMENT DISORDERS IN NIEMANN-PICK TYPE C

Shaddy El-Masri M.D., Andrew Evans M.D. & Mark Walterfang MBBS, PhD.

The Royal Melbourne Hospital, Melbourne, Victoria.

Niemann-Pick Type C (NPC) is an autosomal recessive progressive neurodegenerative disorder caused by mutations in the NPC 1 or 2 genes. Patients with this disorder have variable phenotypic presentations that often include neuropsychiatric manifestations, cognitive decline, and movement disorders. There is considerable significant inter-patient variation in movement disorders, with limited quantitative measurements describing the movements observed. Objective measurements using wearable sensors provide clinically applicable monitoring of patients with Parkinson's Disease, and hence may be utilised in patients with NPC.

Objective: To investigate the relationship between objective measurements obtained via the use of the Personal KinetiGraph (PKG) with the clinical information obtained via questionnaires and clinical rating tools of patients with Niemann-Pick type C.

Methods: 12 patients with Niemann-Pick type C were recruited who wore the PKG for 6 days during regular activities. A 6-day output was provided by the manufacturer, which provided a bradykinesia (BKS), and dyskinesia scores (DKS). BK and DK scores were further divided into their interquartile ranges. A fluctuation score (FDS), percentage time immobile (PTI), and percent time with tremors (PTT) were also provided. Assessments including: Abnormal involuntary movement scale (AIMS), Epworth sleepiness score (ESS), Falls, Neuropsychiatric unit assessment tool (NUCOG), Parkinson's Disease questionnaire (PDQ), and modified Unified Parkinson's Disease Rating Scale (UPDRS) were performed over telehealth within 2 weeks of PKG use. Pearson's correlation analysis were used for correlation assessments.

Results: Significant correlations were demonstrated between BK25 and Falls ($p = 0.032$, R of -0.64), BK50 and Falls ($p = 0.011$, R of -0.73), and BK75 and Falls ($p = 0.0099$, R of -0.74). FDS correlated with NUCOGE ($p = 0.035$, $R = 0.64$), PDQ ($p = 0.015$, $R = -0.7$), UPDRS IV ($p = 0.029$, $R = -0.65$), UPDRS ($p = 0.034$, $R = -0.64$), and AIMS ($p = 0.026$, $R = -0.66$). DK25 on comparison with UPDRSI ($p = 0.04$, R of -0.63) and NUCOGA ($p = 0.041$, R of 0.62), and DK75 on comparison with UPDRSI ($p = 0.015$, $R = -0.71$) and NUCOGA ($p = 0.032$, R of 0.64) demonstrated significant correlations.

Conclusions: Use of PKG demonstrated that bradykinetic patients with NPC were less likely to report concerns regarding falls and that individuals with minimal fluctuations of their movement disorders spent more time dyskinetic. Furthermore, dyskinetic individuals performed poorly in cognitive assessments of attention but with less mood, behaviour, and mentation issues.

APPLICATION OF THE BIOMARKERS IN BIOLOGICAL FLUID MEASURED BY ELECSYS AUTOMATED IMMUNOASSAY AND OTHER IMMUNOASSAY METHOD TO SUPPORT THE CLINICAL DIAGNOSIS IN AUSTRALIA

Qiao-Xin Li[a], James D. Doecke[b], Shiji Varghese[a], Victor Villemagne[c], Christopher Fowler[a], Stephanie R. Rainey-Smith[d], Ralph Martins[d], Christopher Rowe[c], Dhamidhu Eratne[f], Dennis Velakoulis[f], Colin L Masters[a], Steven J Collins[a,e] and the AIBL Research Group

[a]National Dementia Diagnostics Laboratory, Florey Institute, The University of Melbourne, Victoria, Australia 3010; [b]Australian e-Health Research Centre, CSIRO, Brisbane, QLD, 4029, Australia; [c]Austin PET Centre, Austin Health, Heidelberg, VIC, Australia; [d]Centre of Excellence for Alzheimer's Disease Research & Care, School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia; [e]Department of Medicine (RMH), The University of Melbourne, Parkville, Australia 3010; [f]Neuropsychiatry Unit, Royal Melbourne Hospital, Melbourne, VIC, Australia
*presenter's e-mail address: q.li@unimelb.edu.au

Biomarker proteins, amyloid β1-42 (Aβ42), Phospho-tau 181 [pTau] and Total-tau [tTau]), in the cerebrospinal fluid (CSF) are used to support the clinical diagnosis of Alzheimer's disease (AD) at preclinical and clinical stages of the disease, and for enrolment of patients into therapeutic trials. Neurofilament (NfL) protein, a marker of neuronal injury, has shown great promise in diagnosis and differential diagnosis of a range of psychiatric and neurological disorders, including Niemann-Pick type C (NPC). As a National Association of Testing Authorities (NATA) accredited National Dementia Diagnostics Laboratory (NDDL), we are now using the automated Elecsys assay from Roche, recently accredited by NATA. Our group, in collaboration with Roche and international groups, has found that the ratios pTau/Aβ42 and tTau/Aβ42 had areas under the curve of >0.90, and concordance with Aβ-PET (overall percentage agreement >90%). Now we are performing automated Elecsys assay every week. The automated Elecsys has lower day-to-day variations and offers a more precise result. We also perform NfL assay for research and aim to have it accredited by NATA in near future. The panel of Aβ42, Tau, pTau and NfL helps the clinician to differentiate a range of psychiatric and neurological disorders such as AD and NPC in routine practice.

SHORT TALKS

CEREBROSPINAL FLUID NEUROFILAMENT LIGHT CHAIN IS ELEVATED IN NIEMANN- PICK TYPE C COMPARED TO PSYCHIATRIC DISORDERS AND HEALTHY CONTROLS AND MAY BE A MARKER OF TREATMENT RESPONSE

Dhamidhu Eratne[1-4], Samantha M Loi[1-3], Courtney Lewis[1], Wendy Kelso[1,2], Qiao-Xin Li[4], Shiji Varghese[4], Amelia McGlade[4], Steven Collins[4-6], Colin L Masters[4,7], Dennis Velakoulis[1-3], Mark Walterfang[1,2]

[1]Neuropsychiatry Unit, Royal Melbourne Hospital, Melbourne, VIC, Australia; [2]Neuropsychiatry Centre, University of Melbourne & NorthWestern Mental Health, Melbourne, VIC, Australia; [3]Department of Psychiatry, The University of Melbourne, Parkville, VIC, Australia; [4]National Dementia Diagnostics Laboratory, Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia; [5]Department of Medicine, Royal Melbourne Hospital, Melbourne, VIC, Australia; [6]Australian National Creutzfeldt-Jakob Disease Registry, Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia; [7]Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia

Niemann Pick-type C (NPC) is often misdiagnosed as a primary psychiatric illness, with accurate diagnosis coming only after development of frank neurological symptoms such as dystonia or ataxia. Misdiagnosis and diagnostic delay have significant negative implications, especially since treatments are available for NPC. As for many psychiatric and neurological disorders, there is a need for biomarkers for early diagnosis and to aid in differential diagnosis, prognostication and treatment response. Neurofilament light chain (NfL), as a biomarker of neuronal injury that can be measured in cerebrospinal fluid (CSF) and blood, has shown great promise in diagnosis and differential diagnosis of a range of psychiatric and neurological disorders. To our knowledge, NfL has not been explored in NPC.

Methods: We report on three patients with genetically confirmed NPC who had CSF NfL measured using commercially available enzyme-linked immunosorbent assay (NF-light; UmanDiagnostics, Umea, Sweden). The patients with NPC had statistically significantly elevated CSF NfL levels compared to (older) healthy controls and psychiatric disorders (PSY; most with schizophrenia, bipolar and major depressive disorders). NfL perfectly distinguished NPC from healthy controls and NPC with areas under the curve of 1 (695 pg/mL cut-off for NPC vs HC, 1234pg/mL for NPC vs PSY). One patient with severe psychotic symptoms, ataxia and multiple falls had a follow-up level at nine-months after commencing intrathecal cyclodextrin treatment. She had a significant clinical response with dramatic improvements in her psychosis and ataxia, with no further falls. Her CSF NfL level also significantly decreased over this period, essentially halving and returning to levels similar to those of a healthy control.

Discussion: Preliminary data suggests diagnostic utility of CSF NfL in differentiating PSY from NPC. Furthermore, data from one patient may also point to NfL as a marker of treatment response in NPC. A significantly elevated NfL level in a patient with a primary psychiatric diagnosis should prompt a quick review of symptoms and consideration of neurological and neurodegenerative differential diagnoses. Although NfL is a non-specific marker of neuronal injury, this is a strength for a potential screening test for broad neurological/neurodegenerative differential diagnoses, thus allowing for precision medicine approaches to further, more specific and costly investigations, leading to reduced misdiagnosis, diagnostic delay and improved outcomes. For example, more specific biomarkers for NPC such as oxysterols are unlikely to be feasible or cost-effective as broad screening tests in psychiatric settings for a rare disorder like NPC; however, following an abnormal NfL and review of symptoms that in a new light raises suspicions for NPC, a more precise use of specific testing such as oxysterols would then be indicated.

Conclusions: Further studies are warranted of NfL, particularly in blood, which may lead to a simple screening blood test of high utility to psychiatrists, neurologists and general practitioners.

Australian NPC Disease Foundation Inc

Research. Cure. Persevere.

AUSTRALIAN NPC DISEASE FOUNDATION

c/o 3 Waller Street
Benalla, VIC Australia

Email
info@npcd.org.au

Website
www.npcd.org.au