CELEBRATING 30 YEARS OF IMPACT

NeuRA
Discover. Conquer. Cure.

the NeuRA magazine

Issue 41 | Spring 2022

How science is helping families plan for the future

Our neurodegeneration experts test a novel approach to an age old problem

IN THIS ISSUE:

Message from our CEO Professor Peter Schofield AO


Prof Peter Schofield AO

While our previous editions this year have focused on celebrating our three decades of historical impact, in this issue of NeuRA magazine we're putting the spotlight on examples of our research which underpin our newly adopted strategic plan. Our goal is to discover solutions for neurodegeneration, mental health and translational neuroscience through world-class medical research.

To mark Dementia Action Week (19-25 September), we highlight a number of our projects in neurodegeneration that cover our multi-faceted approach to dementia prevention, risk reduction and care.

We learn more about whether it's possible to "retrain" the brain to reduce chronic back pain via the findings from Professor James McAuley's RESOLVE trial. The paper on his collaborative team's novel sensorimotor retraining intervention was published last month in the Journal of the American Medical Association, and has since garnered international attention and media interest.

We hear from PhD candidate Kerith-Rae Dias on the novel gene discovery that will mean individuals and families with a rare intellectual disability will be able to gain access to rapid diagnostics and vital NDIS funding and support.

We also cover a recent study from the Sydney Brain Bank on the prevalence of chronic traumatic encephalopathy (CTE) and impact of head injury using one of the world's largest, and clinically well-defined, brain bank populations.

I'd also like to take this opportunity to introduce and welcome Prof Carolyn Sue AM and her team to NeuRA. Professor Sue is an internationally recognised clinical research leader in Parkinson's and mitochondrial disease and has been appointed as the inaugural Kinghorn Chair, Neurodegeneration. You can read more about her and her work on page 6.

I hope you enjoy this edition. My sincere thanks for your ongoing support.

Prof Peter R Schofield AO FAHMS PhD DSc
CEO


Carole Renouf

Carole's Column

As the sister of a person with an intellectual disability, I was particularly interested to learn about A/Prof Tony Roscioli and Kerith-Rae Dias' research (featured on page 3). I learnt from Kerith-Rae that parents typically only get a diagnosis in 50% of cases with intellectual disability.

This certainly reflects my own family's experience. My mother, who was a psychologist, knew something was wrong from the beginning but it took over two years of wondering and anxiety before a diagnosis of the rare Aicardi Syndrome (only 4,000 cases in the world) was made. Though this seemed an endless time to my mother, this is apparently shorter than the average 'diagnostic odyssey' which is eight years. And parents cannot access the NDIS without a diagnosis.

Around 80% of intellectual disability is caused by a genetic variant. Importantly, most genetic variants that cause intellectual disability are de novo and not inherited. To understand this would relieve the burden of guilt experienced by many parents – and around 3% of the world's population has some form of intellectual disability.

Studying the genomics of intellectual disability may at first sound abstruse, but this research has very "real world" applications. A correct and timely diagnosis will enable the right management of the condition and access to funding and support, as well as early intervention for co-morbidity risks. And families won't be left wondering – thank you, Kerith-Rae!

Carole Renouf
Executive Director of the NeuRA Foundation

"Diagnostic odyssey" over for individuals with rare intellectual disability thanks to novel gene discovery at NeuRA

An international collaboration of clinical and translational genomics researchers led by NeuRA's Associate Professor Tony Roscioli, Carey-Anne Evans and PhD candidate Kerith-Rae Dias, has discovered 11 novel variants in the gene ZMYND8 associated with a new neurodevelopmental disorder. Kerith-Rae shares her insights on this breakthrough discovery.

Kerith-Rae Dias

Can you tell us about the ZMYND8 gene?

The ZMYND8 gene – Zinc Finger MYND-Type Containing 8 – is known to have important functions in humans such as in DNA repair, transcription regulation and suppressing tumours, but hadn't previously been linked to human cognition and learning. We identified an international cohort of individuals with intellectual disability and damaging alterations in this gene. We discovered that these patient-specific ZMYND8 variants abolish interactions with other proteins involved in synaptic plasticity and disrupt responses to DNA damage. This study shows that ZMYND8 has multiple protein domain-specific mechanisms of disease and is a central hub in a molecular network important to human cognition.

What does this discovery mean for kids and their families who carry this gene?

Living with a rare disease can be a challenging and isolating experience. Difficulties in obtaining an accurate diagnosis can mean living with ongoing uncertainty in terms of how the disease will progress, and without access to funding that a specific diagnosis can facilitate. Knowing the genetic basis for a condition also opens door to future research about therapies and treatments that could dramatically improve their quality of life.

The publication of our research means Australians with alterations in ZMYND8 can finally get a diagnosis and gain access to critical NDIS funding and support. It also means future families with ZMYND8 variants can access a rapid diagnosis after genetic testing (in some cases within a few days).

Where does this discovery sit in the emerging field of neurogenomics?

Advances in genomic and multi-omics technologies are accelerating the discovery of disease genes. As these technologies become more integrated in healthcare, identifying genetic variation is no longer the main issue – it's ensuring that there are sufficient resources in the health system to allow access to genomic testing for all families who need it.

The research challenge in confirming the role of new genes is identifying individuals with similar genetic variation and disease features and collaborating with other health professionals to understand how the disease works. Multidisciplinary collaboration is key – which is why we believed it was important to link up with experts from across the globe for this study, including from Boston Children's Hospital, Harvard Medical School, Radboud University Medical Center, University of the Sunshine Coast and UNSW Sydney.

What's next for your research?

We will continue to collect more ZMYND8 cases to describe the phenotypic spectrum of this novel disorder. There is ongoing work to define more protein-protein interactors in this hub and how they contribute to disease. We've also developed a human brain organoid model which allows us to assess what effect knocking out ZMYND8 has on the architecture of the developing (prenatal) brain as well as how the expression of genes downstream of ZMYND8 are impacted.

Neurogenomics at NeuRA

The Neurogenomics Group at NeuRA, led by Associate Professor Tony Roscioli, combines expertise in neuroscience, clinical genetics, translational genomics, paediatric medicine and bioinformatics. Their goal is to better understand the genetic causes of neurocognitive disorders and advance the way these are diagnosed, understood and managed. Since the group was established in 2018 they have contributed to the discovery of more than 20 genes relating to rare diseases and intellectual disorders, helping countless families gain access to answers, funding and vital support.

To read about two of their landmark projects go to: **pregen.neura.edu.au** and **neura.edu.au/project/cre-neurocognitive-disorders**

Planning EARLI for some of life's most difficult decisions

There are many wicked problems in this world – Dr Craig Sinclair, researcher at NeuRA and UNSW School of Psychology, is currently tackling one of the biggest individuals and families can face: how to plan for end-of-life decisions before they become urgent.

By the time someone is experiencing mild to significant cognitive decline, or is very unwell – which is when families usually start having these conversations – the weight of potentially losing a loved one can feel too heavy to even broach the topic.

This was the precise scenario faced by communications consultant Michelle.

"My mum was an eternal optimist who never outwardly acknowledged how sick she was – we couldn't talk directly with her about her cancer let alone discuss what she might want when things got really bad."

"When the end came up very quickly last year, we felt completely lost as to what decisions she would want us to make. It was a sad and actually quite a terrifying experience."

"With dad now facing his own serious health challenges, as a family we've agreed advance care planning is something we need to do to avoid history repeating itself. But every time we sit down together to do it, everything becomes overwhelmingly emotional and we don't get very far."

Dr Sinclair says this is a common issue that many individuals and families face.

"The psychological process of becoming ready to have these conversations can be complex," says Dr Sinclair. "Nearly everyone agrees planning ahead is a good idea, but only 5-10% of people actually do it in a formal way."

Through his upcoming NHMRC-funded EARLI trial, Dr Sinclair is exploring whether 'life story work' can make the process less daunting for individuals and their families alike.

By the time someone is experiencing mild to significant cognitive decline, or is very unwell – which is when families usually start having these conversations – the weight of potentially losing a loved one can feel too heavy to even broach the topic.

Life story work is a way of capturing and recording details about a person, the life they've lived and what matters to them to share with family members and caregivers. On its own, it's a commonly used care strategy in a range of aged care and dementia care settings. The novel approach in this project is combining the process with advance care planning.

Over four visits, researchers will conduct a life story interview. By asking people to share things like meaningful photographs, favourite songs, books or recipes, and the places they've been or lived, the team will seek to capture the person's own story of who they are. They will also facilitate future planning discussions with the person, their family, GP and aged care provider.

"The ultimate goal is to get someone to look back across their life, in order to think about what they'll value most in the future," says Dr Sinclair.

"The trial will test whether this strength-based approach, focused on sustaining personal identity, helps people get clearer about their wishes for future care, and whether it also improves wellbeing."

Commencing early next year, the EARLI trial is partnering with home care providers in Sydney and Perth, and aims to recruit more than 300 participants, over a two-year period.

Right now, the research team are conducting an online survey to better understand people's experiences and attitudes towards planning for future health care needs. If you are over 65, living in Australia independently in the community – in your own home, rented accommodation or a retirement village – you can complete the survey here: **redcap.link/earli-pilot-survey**

Our dementia research

Every day NeuRA's dementia researchers are looking for answers and solutions in prevention, risk reduction and care. Here are three of their current projects...

MyCOACH: Connected Advice for Cognitive Health

Researchers are assessing the effectiveness of a healthy lifestyle intervention in supporting healthy brain ageing and reducing dementia risk.

How it works: A 12-week intervention is tailored for people experiencing changes or concerns in thinking, memory or cognition. It provides education and practical support on memory strategies, the role of diet, social and cognitive activity and stress on brain ageing, and general information about memory impairment and dementia.

Am I eligible? If you've noticed changes in your memory or thinking, or have a diagnosis of Mild Cognitive Impairment (MCI) you may be eligible to participate in this trial.

Call 02 9399 1853 or email mycoach@neura.edu.au to express your interest.

STIGMA

We're investigating the experiences of family caregivers of people with dementia, particularly the impact of negative attitudes or disbeliefs – or stigma – and which factors can act as a buffer against it.

How it works: An anonymous online survey that takes approximately 30-35 minutes to complete.

Am I eligible? If you're over 18, are currently looking after a family member who is formally diagnosed with dementia, and would be willing to complete a short online survey, you could be eligible to participate.

Contact Jana Koch at stigma@neura.edu.au

MEMTECH: Changing Memory, Technology and Driving Study

Driving is critical for most people's independence and life participation. However, identifying the right time to cease driving is very difficult for drivers with cognitive decline, their families and their clinicians.

There are currently no accurate methods for objectively monitoring driver safety changes in the early stages of cognitive decline.

To combat this, researchers are leveraging advances in technology to investigate whether in-vehicle devices could help drivers and clinicians to objectively monitor safety, balancing independence and safety as people age.

For more information go to: neura.edu.au/project/memtech

Five minutes with... Jacob Mamutil

Jacob Mamutil, his mother and daughter

NeuRA supporter Jacob Mamutil shares his journey to philanthropy and why he believes science could unlock a brighter future.

What led you to support NeuRA?
My mum is 89 and was diagnosed with dementia about four to five years ago. Her older sister also had dementia, so my brother and I are both aware there may be a hereditary element to the disease. We want to learn more about it for our own sake as well as for future generations.

What inspires you about NeuRA's research?
Your research is all about looking to the future and finding answers for what we don't understand today. That concept of having an inquiring mind and looking for answers resonates with me. My mum used to be a science and maths teacher so in a way, scientific exploration has always been in our family.

What motivates you to give to research?
I am fascinated by the brain. It's an amazing organ and if my brother and I can support a cause that enables us, along with the broader community, to understand it a bit better, there's a mutual benefit.

What impact do you hope NeuRA will have in the next 30 years?
I hope we can identify the early markers for dementia to arrest the decline for people with the disease. At the end of the day, it's all about improving quality of life. If science can help us on this path, I'm hopeful we'll create a better and brighter future for all. ●

Professor Carolyn Sue AM

Welcoming Professor Carolyn Sue AM to NeuRA

NeuRA, together with our precinct partners UNSW and the South Eastern Sydney Local Health District, are proud to welcome Professor Carolyn Sue AM as the inaugural Kinghorn Chair, Neurodegeneration. Prof Sue commenced at NeuRA this month and will relocate with over 20 of her research and clinical team.

Based at NeuRA, Prof Sue and her team will work to establish an internationally acclaimed centre for Parkinson's disease research as well as an Australian flagship of mitochondrial clinical services and laboratory-based research.

"This position will allow me to focus and devote my time to clinical research," said Professor Sue. "I want to improve health outcomes for those living with Parkinson's and mitochondrial disease. The innovations my team can deliver have the potential to slow the progression of Parkinson's disease, and perhaps even to stop it."

Her appointment was possible through the generous support of the Kinghorn Foundation and their five-year, multi-million dollar philanthropic commitment to her work to discover and implement new therapeutic solutions to Parkinson's and mitochondrial disease.

Sydney Brain Bank conducts world's largest study examining the prevalence of CTE in a brain bank population

Dr Claire Shepherd, Sydney Brain Bank Director

Researchers at the SBB recently conducted one of the world's largest studies examining the prevalence of chronic traumatic encephalopathy (CTE) neuropathology published to date.

Clinical and research neuropathologists with over 50 years of collective experience in neurodegenerative pathologies analysed 636 donated brains for CTE neuropathology. This included a subset of 109 cases with a known history of isolated or repetitive head injury.

"However, we did see indications that isolated traumatic brain injury could lead to increased brain ageing, which warrants further scientific investigation."

Out of the total cohort, five were identified as having CTE neuropathology. Three of these cases were former athletes who were known to have sustained traumatic brain injuries and had significant exposure to repetitive head impacts in collision and combat sports. The other two cases had no known history of neurotrauma (traumatic brain injury or repetitive head impacts).

"Our evidence from this study suggests that a single brain injury is unlikely to cause chronic traumatic encephalopathy neuropathologic change," said Dr Claire Shepherd, Sydney Brain Bank Director. "However, we did see indications that isolated traumatic brain injury could lead to increased brain ageing, which warrants further scientific investigation."

CTE can only be definitively defined after death. The characteristic neuropathology is the presence of a protein called tau, which accumulates in neurons and the support cells of the brain (astrocytes). These tau-containing cells are located around blood vessels in the folds of the brain known as the cortical sulci.

As the body of research and interest in CTE in professional sport increases in Australia and around the world, Dr Shepherd and her team's work provides a vital general population baseline which can now be used as a comparison for more specific cohorts.

Is it possible to retrain your nervous system to reduce chronic back pain?

Findings from a landmark trial conducted here at NeuRA say yes!

Professor James McAuley, Director at NeuRA's Centre for Pain IMPACT

People with chronic back pain have been given new hope with a treatment that challenges traditional treatments such as drugs, spinal manipulation, injections and surgery, by focusing instead on retraining how the back and the brain communicate.

Professor James McAuley, RESOLVE trial lead and Director at NeuRA's Centre for Pain IMPACT, said this new treatment, known as 'graded sensorimotor retraining', aims to achieve three goals.

"The first is to help people in pain understand that it is safe and helpful to move, then to refine neural representations of the back so that it feels safe to move and finally to load the back to promote positive tissue adaptation and experience safety with movement, as they progress towards re-engagement with meaningful functional goals."

The NHMRC-funded, randomised controlled trial divided 276 participants into two groups: one undertook a 12-week course of sensorimotor retraining and the other received a 12-week course of sham treatments designed to control for placebo effects, which are common in low back pain trials.

"What we observed in our trial was a clinically meaningful effect on pain intensity and a clinically meaningful effect on disability," says Prof McAuley. "People were happier, they reported their backs felt better, their quality of life was improved and twice as many people said they were completely recovered compared to the control group."

> **"People were happier, they reported their backs felt better, their quality of life was improved and twice as many people said they were completely recovered compared to the control group." — *Prof James McAuley, RESOLVE trial lead***

Carla Pennini is one of those participants. A nurse and mother of three, she was 13 years old when she was diagnosed with scoliosis — a sideways curvature of the spine that has no known cause. She has struggled with chronic low back pain for more than 20 years.

"My family is very active," Carla says. "Before taking part in this trial I tended to have to do things separately from them. Since taking part in RESOLVE my children, who are now adults, no longer see me as 'mum with the sore back'. It's now 'mum can do whatever we do' — and that's unified us."

According to Prof McAuley, the nervous system of people with chronic low back pain behaves differently to those without pain.

"People with back pain are often told their back is vulnerable and needs protecting. This changes how our brain filters and appraises information from our back and how we move our back. Over time, the back becomes less fit, and the way the back and brain communicate is disrupted in ways that seem to reinforce the notion that the back is vulnerable and needs protecting. The treatment we devised breaks this cycle," Prof McAuley said.

This was certainly the case for Carla. After the RESOLVE treatment, she did something she would never have even contemplated before it — climbing Mount Kinabalu on the Borneo-Malaysia border with her family.

"When I reached the summit at 4am I felt a sense of great achievement and empowerment," says Carla. "It wasn't just about reducing pain for me, it was realising that my medical diagnoses are not chains that tie me down anymore."

While further testing is needed to replicate these results in different settings and populations, researchers are optimistic about rolling out a training package to clinics and have already enlisted partner organisations to start that process.

For further information go to: resolve.neura.edu.au

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Thank you for generously supporting our research into diseases

If you wish to update your preferred communications from NeuRA, please call 1300 888 019.

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NeuRA in the spotlight

From ABC Radio with Richard Glover, to the front page of The Times in the UK, NeuRA researchers have been featured in the media more than 600 times so far this year.

Did you see a familiar face or two in ABC TV's *Our Brain* series? Associate Professor Justine Gatt and Dr Steve Kassem share their insights on the neuroscience of wellbeing and mental health amongst a line-up of international experts in Episode 4: Happier.

▶ **Make sure you tune into upcoming ABC docu-series *Keep on Dancing* (airing Oct 4) for more NeuRA cameos.**

Thank you for your continued support

Thank you to everyone who has supported our fundraising appeals in 2022 and gave by mail, online or over the phone.

Our winter appeal raised over **$175,000** to support the operating costs of our MRI facility and the non-invasive research it enables across so many disease conditions. Our appeal for schizophrenia research raised over **$40,000** which will be vital in progressing potential new therapies with fewer side-effects.

We are very grateful for your generosity, and look forward to keeping you informed of progress through this magazine. •

If you would like to discuss in confidence leaving a gift in your Will to NeuRA please call **Deborah Smith, Gifts in Wills Manager on 02 9399 1270,** email **d.smith@neura.edu.au** or visit **wills.gatheredhere.com.au/c/neura** to start your online Will now.