brainWAVES

The Newsletter of the Brain Foundation

Summer 2019-2020

Trevor and 2019 Award Winners

I am very proud to bring to you our 2019 Research Grant edition, the first that I have presided over. Awarding 23 Research Grants this year to some very talented researchers in Australia. You can read all about them on the following pages. I'm sure that you will be as impressed as I was with the quality of the projects they are undertaking.

I would also like to take this opportunity to thank our donors who continue to support these wonderful projects year after year.

Brain Foundation could not do what we do without your steadfast support.

Finally, my best wishes to all over the Christmas and new year holiday period. Have a wonderful and safe time and we look forward to celebrating our 50th year with you in 2020.

Trevor Thompson
C.E.O.

Concussions and you

Everyone will have noticed how much attention to concussion there has been in our media lately. This is a good thing to bring much needed awareness, diagnosis and understanding of treatment. But you could be forgiven for thinking that concussions are in the domain of sportspeople. In fact, over 47% of concussions occur from falls. 17% are from assaults, 14% from motor vehicle accidents and 8% from sporting injuries.

Have you ever bent down to a low cupboard or drawer? When you stood up, you whacked your head on something you had forgotten was there. You 'see stars' and have a headache for a few hours. You may feel like taking an analgesic and lying down. Well, you could have just given yourself a concussion, albeit probably a mild one. However, it seems that some people are predisposed to much more serious concussions due to their genes.

A project at QUT's Genomics Research Centre (GRC) overseen by molecular geneticist Professor Lyn Griffiths is currently studying how genetic differences between individuals can affect their response to concussion.

When a concussion occurs, the electrolytes that brain cells use to maintain electrical balance go through a dramatic change, which disrupts the ability of brain cells to send signals to one another. The process of resetting this balance causes a lot of stress to the brain and is one of the causes of concussion symptoms, including: confusion, memory loss, migraine and mood problems, and difficulty maintaining concentration.

Several genes have already been identified as playing a role in the processes of brain signalling and electrolyte balance and the GRC's current research project examines these genes and their interaction with concussion. One key example of how these genes may interact with a person's response to concussion is related to a genetic condition causing very severe migraine – Familial Hemiplegic Migraine (FHM). People suffering from this rare form of migraine can have severe concussion-like reactions to even very mild head knocks. The GRC's current project recently identified several new genetic mutations that cause high sensitivity to head injury.

The GRC are now planning to extend this research to look for other genes that influence concussion related reactions to head trauma. We are recruiting individuals and families who have suffered from multiple concussions or who have experienced long term concussion effects – professional sports men and women have been targeted as their profession lends itself to this risk but there may be other non-sports people who have been affected by concussion and would like to contribute to this research.

This project ultimately aims to identify genes that influence an individual's risk and their response to concussion so that we can understand concussion in more detail and develop new and more appropriate treatment approaches.

The project is currently recruiting participants who have suffered from concussion. Participation in this research involves filling out a questionnaire and providing a single saliva sample - all conveniently completed via post. If you or someone you know would like to take part in this research project, please contact the Genomics Research Centre and request info on the Concussion Study on: grcclinic@qut.edu.au or (07) 5688 7170 or see the poster on page 14.

FURTHER INFORMATION ON CONCUSSION CAN BE SEEN IN THE HEADACHE SECTION OF THIS NEWSLETTER.

Contact the Brain Foundation
PO Box 579, Crows Nest NSW 1585
Telephone: 02 9437 5967 or 1300 886 660
Email: info@brainfoundation.org.au
Visit our websites brainfoundation.org.au and headacheaustralia.org.au

Fabulous Fundraisers

We thank these fabulous supporters and everyone whose fundraising efforts really inspire us.

City 2 Surf

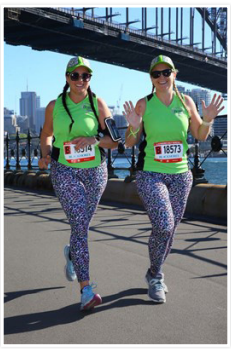
– and they call it a fun run!

Not too sure about this myself, but we are grateful to have 'Team Balken' back again in 2019. Four years in a row and still breaking records! Thanks everyone for your support. Another great result. Dad would be very proud.

Melissa, Nicola, Maddie, Hollie, Brad, Daniel & Carl

Finishing feels great!

More running for fun, I think



Sarah Hollingsworth

Our thanks to Sarah Hollingsworth who along with her sister and friend ran in the Blackmores Half Marathon. Sarah is a survivor of a Brain Tumour – just look at her go now. Thank you ladies for an outstanding effort.

THANKS
TO THE DONORS
OF THE FUTURE

Plenty Parklands Primary School Market Day. Year 6 students excelled themselves to donate to research. Thanks everyone for such a great effort.

Climb every mountain.....

....well, in Canberra anyway

Our supporters will remember a story last year of Nathan Nguyen who suffered a workplace injury and then a stroke, who was supported by his workmates at RAAF Base Edinburgh in his fundraising for Stroke research and awareness. Since then, Nathan has determinedly worked towards his recovery. Now living in Canberra, he was once again supported by these workmates and others as he climbed 5 Mountains in 5 days. This is a feat which would deter most of us, but it did not stop Nathan and his wife Kerrie-Anne who is his greatest supporter.

Nathan and Kerrie Ann

Nathan's greatest supporters

The whole crew

Nothing Trivial about a brain tumour!

'Quiz for a Cause' -use your brain, not your phone

Tumour survivor, Georgia Looner, organized a wonderful fundraising night.

Lovely Georgia is one of the lucky ones who have survived a brain tumour. Many others are not so lucky. Wanting to raise awareness and contribute to research, Georgia organised a very successful Trivia night. Over 150 people attended the event and professionals, who made the event so successful and who also had a close experience of brain tumours, donated their time. I understand that the silent auction became a bit rowdy, with everyone determined to out bid others. This was a good thing for us. Georgia's event was a great night and a great success.

Georgia and friends

Guinness World Record for the World Tandem Bike Riders

After more than 28,000 kms and 281 days circumnavigating the globe on a tandem bike, Lloyd Collier and Louis Snellgrove have been officially recognised by Guinness World Records.

Congratulations to them both! A thoroughly deserved award.

Raising Awareness

Left: Organisers of the Night for Aphasia Georgia and Olivia with Professor Miranda Rose, centre

A Night for Aphasia. What is that you say?

Aphasia is more common than Cerebral Palsy, Parkinson's disease and Multiple Sclerosis, COMBINED... and no one really knows about it. We want to raise awareness and event by event, tell everyone about what Aphasia really is!

This event is a Melbourne first. An evening to celebrate the Aphasia community, and to help shed some light on what Aphasia really is. We strongly believe that our very awareness is the window upon which reality presents itself.

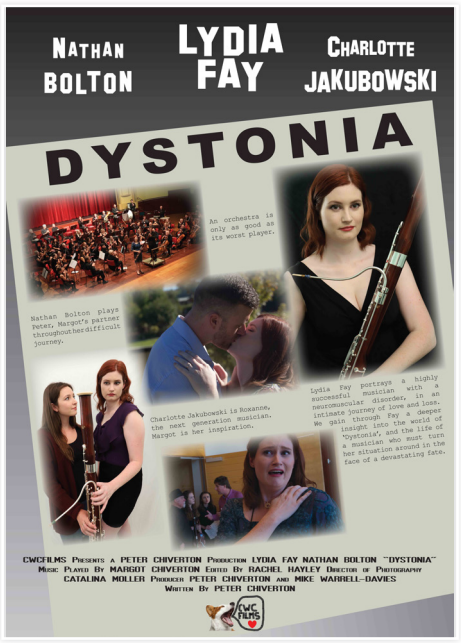
There were 120 people in total at the event and the we had three guest speakers, Professor Miranda Rose, Susie Schulsinger and Georgia Burn, a Speech Pathologist. Thank you to Georgia Harriott and Olivia O'Hare for organising this very successful awareness event.

So, just what is Aphasia?

Aphasia is a neurological disorder caused by damage to the portions of the brain that are responsible for language. Primary signs of the disorder include difficulty in expressing oneself when speaking, trouble understanding speech, and difficulty with reading and writing. Aphasia is not a disease, but a symptom of brain damage. It usually occurs suddenly, often as the result of a stroke or head injury, but it may also develop slowly, as in the case of a brain tumour, infection, or dementia. The type and severity of language dysfunction depends on the precise location and extent of the damaged brain tissue.

If you are looking for help, there are a couple of places you can go for support in Melbourne. The Windy Hill Aphasia group is run by Sam Harvey who is a Speech Pathologist. It runs every second Thursday at Windy Hill, Essendon. The other one is at ACU and it is run by students.

If you are in another state, these groups may be able to steer you in the right direction.



Dystonia

– a movement disorder, and now a moving film

Brain Foundation is pleased to be associated with Dystonia Network of Australia and Dystonia Support Group in helping to gain awareness of this terrible condition.

Dystonia is a movement disorder in which a person's muscles contract uncontrollably. The contraction causes the affected body part to twist involuntarily, resulting in repetitive movements or abnormal postures. Dystonia can affect one muscle, a muscle group, or the entire body.

A short film is available on YouTube telling a personal story about how dystonia impacted a musician's life and raising awareness of dystonia. The film is in drama form and lasts for 19 minutes.

It was featured on the front page of the Parkinson's Australia website and was described as a 'beautiful' film.

PLEASE SUPPORT THE FILM AND RAISE AWARENESS OF DYSTONIA BY SHARING THE LINKS:

Short film 'Dystonia' by CWCFilms: https://www.youtube.com/watch?v=dCapqLSkb60

Subtitled version: https://www.youtube.com/watch?v=QYMBSwxiXrM

Trailer (42 seconds): https://www.youtube.com/watch?v=EVl3k7BoeIs

DYSTONIA SUPPORT GROUP

Dystonia is the third most common movement disorder worldwide.
The cause, while neurological in origin, is unknown.

ADSG Website: australiandystoniasupportgroup.wordpress.com/
ADSG Community Page: facebook.com/AustralianDystoniaSupportGroup
ADSG Closed Support Group on Facebook: facebook.com/groups/AustralianDystoniaSupportGroup/

Headache & Migraine Awareness Week

This year Migraine & Headache Australia ran a series of live talks in 5 major capital cities. We had over 1,100 participants watching the expert seminars in person or on -line. There was a different subject for each talk. We would like to send our sincere thanks to the medical practitioners who donated their time for these videos.

We acknowledge that people who suffer from Migraine and chronic headache do not only live in the big cities, and for this reason, these videos are now available for viewing with no charge on headacheaustralia.org.au until the end of January 2020.

Subjects as follows:

- Hormonal Migraine – Dr Bronwyn Jenkins, Sydney
- High & Low Pressure Headaches – Dr Chantal Baldwin, Sydney
- Prevention strategies & treatments – Dr Christina Sun-Edelstein, Melbourne
- Rebound headache & Medication Overuse Headache – Dr Nicole Limberg, Brisbane
- Natural alternatives – Jacinta Johnson, Adelaide
- 'Concussion, Traumatic Brain Injury and Post Traumatic Headache' – Prof. Melinda Fitzgerald, Perth

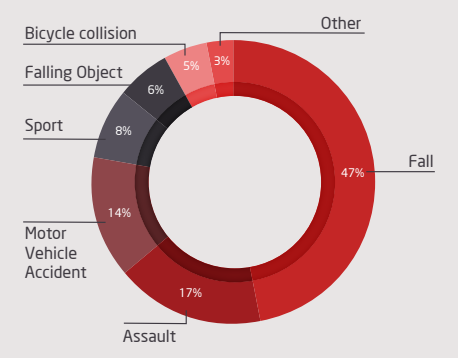
They are all about 30 minutes long. Previous videos of talks on different subjects will be posted also for your convenient viewing.

Concussion and headache

Following on from our front page Concussion story, is the video by Melinda Fitzgerald from Curtin University in Perth. Melinda is a neuro-trauma researcher.

- Did you know that Headache is associated with 90% of people with concussion.
- One in five people with a concussion will go on to get PPCS or Persisting Post Concussion Symptoms. This is where the symptoms last 1 to 3 months or longer.
- People with a history of previous TBI (traumatic brain injury) are five times more likely to develop PPCS after a concussion.
- If you have a history of psychological disorders you are four times more likely to develop PPCS after a concussion.

IF YOU OR PERHAPS YOUR SPORTING CLUB IS INTERESTED IN UNDERSTANDING MORE ABOUT CONCUSSION, CONTACT OUR OFFICE AND WE CAN SEND YOU COPIES OF OUR FACT SHEET, UNDERSTANDING CONCUSSION.



What is Migraine & Headache Australia doing for you?

The Migraine and Headache Australia team recently held a strategy workshop comprising of cross-functional and stakeholder groups including several patient advocates, doctors, researchers, policy experts, a nurse, media and PR experts, and industry representatives to help shape Migraine & Headache Australia's policy priorities and strategy.

Since then the Migraine and Headache Australia team team have been busy developing a government budget submission which will be the first time we have made a formal submission for funding support from the government.

We have also been down in Canberra speaking with key personnel at Parliament House about the urgent and important need for greater support, understanding and research into headache disorders in Australia.

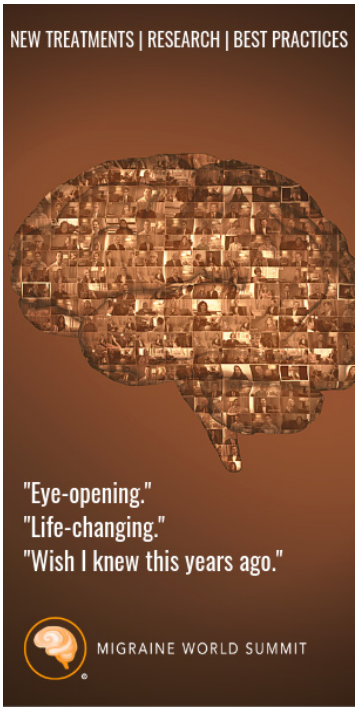
2020 - Migraine World Summit

Yes, returning in March 2020.

Make sure you are registered and you will have access to **32 world leading experts** from leading institutions including the Mayo Clinic, Yale Medical School and The Cleveland Clinic. You will have full access to their expertise and learn how to better manage your migraines without the waiting and cost involved of a face to face appointment.

This is a virtual Summit and it is entirely free during the **live event March 20 – 28**. An incredible opportunity not to be missed. After March 28, the transcripts and interview copies are available to purchase.

Register Now – Migraine World Summit to ensure you get your free ticket.



Trevor and Carl

CGRP on PBS – FYI...

Are you following the action? Roll your sleeves up, here is the latest news.

CGRP Antibody submission to the Pharmaceutical Benefits Scheme (PBS)

Headache Australia has been supporting the submission of a new class of migraine prevention called the CGRP antibodies since 2018. This treatment involves a monoclonal antibody designed to specifically target molecules released during migraine to help prevent attacks. Without PBS support, the cost of this treatment is beyond the affordability of the average patient with migraine. The public and our community have also supported the coverage of these new treatments over several previous submissions.

Full background details available on our website.

UPDATE: September 2019

To date, three CGRP antibodies have been approved by the TGA (Therapeutic Goods Administration – TGA, the Australian medical authority) as safe and effective options for migraine prevention. These are:

ERENUMAB - Aimovig® manufactured by Novartis (withdrawn October 28, 2019)

FREMANEZUMAB - Ajovy® manufactured by Teva Pharmaceuticals

GALCANEZUMAB - Emgality® manufactured by Lilly

None have yet been added to the PBS which means these treatments will only be available for the majority of patients at full cost with a prescription from your doctor.

GALCANEZUMAB - Emgality® has received a positive recommendation from the PBAC (Pharmaceutical Benefits Advisory Committee) for coverage on the PBS subject to some considerations. This is what the PBAC released in their Outcome Statement:

"The PBAC recommended the Authority Required (STREAMLINED) listing of galcanezumab for the treatment of chronic migraine in patients who have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications.

The PBAC considered galcanezumab was an alternative treatment to botulinum toxin type A (Botox®) for patients with chronic migraine and provided a similar reduction in migraine headache days.

The PBAC considered the cost minimisation analysis should be based on equi-effective doses of 120 mg galcanezumab every 30 days and 164IU of Botox every 12 weeks over 2 years of treatment.

Additionally, the PBAC considered it would be appropriate for galcanezumab and Botox to be combined in the same subsidisation caps under a Risk Sharing Arrangement."

Negotiations are now being held between the two parties in relation to this last paragraph that suggests how the government would like to subsidise the new treatment. There is no definite timing on when these negotiations are expected to be concluded, if any agreement will be met or when the subsided treatment drug may be listed on the PBS and available to patients.

Headache Australia hopes for an equitable outcome for all parties that facilitates a fair and reasonable price for patients with appropriate access for those in need of an effective migraine prevention. Updates on this outcome will be posted on our website and via email.

New Submissions made in October 2019

Two treatments have been submitted for the October 2019 PBAC meeting. One is a re-submission of ERENUMAB – Aimovig® (since withdrawn) and the other is the first submission FREMANEZUMAB – Ajovy®. Both these treatments have now been approved by the Australian medical authority (Therapeutic Goods Administration – TGA) as safe and effective options for migraine prevention.

Migraine & Headache Australia shared this information via email, the website and social media to encourage any new submissions. As at the timing of writing we are still awaiting the outcome. To stay tuned for updates please subscribe to Migraine & Headache Australia on our website.

JOIN MIGRAINE AND HEADACHE PRIVATE SUPPORT GROUP ON FACEBOOK TODAY

Connect with other headache and migraine patients.

Join the community to keep up to date with news and latest events. Share, listen and learn from others.

Migraine & Headache Australia support @ facebook - **Facebook.com/groups/headacheaustraliasupportgroup/**

Follow us on Twitter **@HeadacheAus** and

Instagram **headacheaustralia**

And of course, don't forget to register on our **National Headache Register** to receive all the latest up to date news.

ARE YOU A HEADACHE REGISTER MEMBER?

Our Register Members receive regular email updates of current information as we receive it. We send information about new research trials that you can choose to be involved with.

All donations made by Register Members go only to Headache research.
Your email address is required. Register at **headacheaustralia.org.au**

Disclaimer: Headache Australia is not a medical office and cannot offer medical advice. We stress the importance of discussing any issues you have with your medical practitioner.

2019 Research Grant Awards

It gives me the greatest pleasure to present the 2019 Research Grant Award recipients.

This year, 23 wonderful projects have received a grant and you can read all about them on the following pages. We received over 140 applications and would love to be able to fund them all. With your continuing generosity, we look forward to increasing the number of projects selected each year.

Our thanks go to our scientific committee who work tirelessly to assess every application received.

Trevor Thompson

▼ ALZHEIMER'S AND NEURO DEGENERATIVE DISEASES

Analyses of human presynaptic compartments in Alzheimer's Disease

Chief Investigator:
A/Prof Peter Noakes
The University of Queensland

Co-Investigators:
A/Prof Joseph Rothnagel,
A/Prof Peter Dodd

It takes time for proteins made in the cell body of neurons to reach its far compartments, such as "nerve endings" where they communicate with other neurons. Loss of these communication centres is a common feature in brain degeneration in Alzheimer's disease (AD). If they lack key proteins, neurons cannot communicate effectively. This leads to memory impairment, another common feature of AD. One way around this problem, rather than moving proteins from the neuron's cell body to nerve terminal endings, is for the neuron to transport the protein blueprint (RNA) instead. The nerve ending then needs the machinery to make proteins locally. We argue that the transport of RNA to faraway nerve terminals is disrupted in AD, resulting in a loss of the proteins needed for neural communication. To test these ideas, our project will prepare isolated nerve endings from re-thawed frozen human brains from AD and non-AD donors. We have tissue from over 600 AD donors and controls in the Queensland Brain Bank. We will measure RNA, and the machinery needed to make proteins from it. We will also examine the function of these nerve endings to test if nerve endings from AD brains may have poor use of oxygen, which could lead to less release of neurochemicals. Lower neurochemical release will impair the nerve endings' ability to communicate with other neurons. We will also compare and contrast the protein and RNA profiles of human nerve endings isolated from AD regions where nerve communication is poor with regions where it is not, to provide insights into mechanisms for poor neural communication. Our planned research will provide new knowledge of the AD disease process, which is needed to identify new treatment targets.

Next generation gene editing to identify new treatment strategies for motor neuron disease and frontotemporal dementia

Chief Investigator:
Dr Rebecca San Gil
Queensland Brain Institute

Co-Investigator:
Dr Adam Walker

Motor neuron disease (MND) is characterised by the degeneration of motor neurons in the brain and spinal cord that leads to muscle weakness, wasting, and paralysis. It is an inevitably lethal disease with a lifetime risk of ~ 1 in 400 Australians. Interestingly, some people with MND also develop frontotemporal dementia (FTD), suggesting that the two diseases are related. Frontotemporal dementia (FTD) is characterised by the loss of neurons in the brain, which causes changes in personality, emotional state, and language difficulties, accounting for 1 in 20 cases of dementia. The incidence of both of these diseases is increasing and there are no effective treatments that slow or stop the progression of either of these diseases.

One of the first events, at the molecular level, involved in 97% of MND and 50% of FTD cases is the abnormal build-up of a protein called TDP-43 in motor neurons. TDP-43 proteins stick together to form toxic clumps and over time the accumulation of these TDP-43 clumps leads to the death of neurons in MND/FTD. Therefore, one potential therapeutic strategy is to prevent this toxic process of TDP-43 clumping. Unfortunately, there is currently a limited understanding of how TDP-43 clumps in neurons and why it is toxic. The primary aim of this project is to identify the cellular pathways that increase or decrease TDP-43 clumping and its associated toxicity to neurons. This project will use revolutionary gene editing technology to scan every gene in the human genome to identify the genes involved in triggering TDP-43 clumping. This is extremely important because it will broaden the scope of new druggable targets to treat people living with MND and FTD. This approach has great potential to put us on the path towards more effective treatments for people living with MND and FTD.

Rebecca pictured with award sponsors - Lloyd Collier and Louis Snellgrove, our wonderful World Tandem Cyclists

Analysing the effects of an Alzheimer's disease-causing mutation at the level of single cells

Chief Investigator:
Dr Morgan Newman
University of Adelaide, SA

Co-Investigators:
A/Prof Michael Lardelli,
Dr Stephen Pederson

"For decades, the guiding idea for research in Alzheimer's disease (AD) has been the "Amyloid Hypothesis". However, the failures of drugs designed according to this hypothesis imply that it does not explain why AD occurs. AD develops over decades but, when analysing the disease in molecular detail, we only have access to the brains of the deceased. The molecular changes we see in these brains may not represent the initial stresses that caused AD. To identify these causative factors, we must examine young, pre-disease brains. To do this we must use animal models.

Mutations in the PSEN1, PSEN2, and APP genes can lead to early onset AD that is inherited in families (fAD). Many mouse "transgenic models" of AD have been created by inserting multiple mutated genes into mice. However, detailed analysis of the expression of thousands of genes simultaneously in the brains of these models, ("transcriptome analysis"), shows they have little in common with human AD brains. Our approach is different. We assume the most valid way to model AD is to recreate, as closely as possible, the "genetic state" of a person with fAD. People with fAD possess a single mutation in a single fAD gene, so we have created similar animals. Our work uses the zebrafish since it provides numerous advantages in breeding and analysis.

We recently analysed how a single fAD-like mutation in PSEN1 in young, adult zebrafish affects their whole-brain transcriptome. We see dramatic, implied effects on energy production. Energy production is critically important since it supports all other brain functions. But the brain is made up of many cell types, not just neurons, and the energy relationships between these cells are complex. We will repeat our transcriptome analysis at the single-cell level to observe how this fAD-like mutation affects these different cell types."

The role of dopamine in age-related deficits in sensorimotor adaptation

Chief Investigator: Dr Li-Ann Leow
University of Queensland

Co-Investigators: Prof. Timothy Carroll, Dr Eva-Maria Reuter, Prof. Penny Macdonald, Dr Rob Adam, Prof Stephan Riek

We all hope to live independently, for as long as possible. This functional independence requires a form of motor learning called sensorimotor adaptation, which is the capacity to adapt movement to change. For example, problems adapting to changes in the body (e.g., arthritis) or in the environment (e.g., walking onto a slippery floor, manoeuvring obstacles, etc) increases risk of falls. Falls are common and costly: in Australia, a third of community-dwelling older adults (>65 years old) fall at least once a year, with many falls resulting in hospitalization (>100,000 hospitalizations in 2014–15). Unfortunately, sensorimotor adaptation is impaired in older adulthood), even pre-retirement. Why does ageing impair sensorimotor adaptation?

One likely culprit is the profound degeneration of our dopaminergic system. In older adulthood, we lose up to 50% of our dopamine neurons in the substantia nigra/ventral tegmental area. Every decade after age 20, we lose 5-10% of our dopamine receptors and transporters. This project directly tests the idea that deficient dopamine neurotransmission with ageing impairs multiple components of sensorimotor adaptation. Our approach is two-pronged. First, we pharmacologically manipulate dopamine in older adults. Second, we leverage state-of-the-art methods of experimentally dissociating the multiple components of adaptation. Our approach will elucidate the role of dopamine in sensorimotor adaptation, a crucial step towards forming a comprehensive framework of the neural mechanisms that underpin age-related declines in sensorimotor adaptation. More importantly, our work will test the feasibility of remediating age-related decline of sensorimotor adaptation through pharmacological means. Increasing evidence from animal and human clinical studies suggest that dopamine pharmacotherapy can improve outcomes in movement rehabilitation, however, how dopamine pharmacotherapy improves rehabilitation is unknown. This work will fill this knowledge gap by testing how dopamine pharmacotherapy affects the multiple components of sensorimotor adaptation, which forms the basis of many forms of movement rehabilitation.

▼ PARKINSON'S DISEASE

Enhancing mitophagy in Parkinson's disease

Chief Investigator:
Dr Julia Pagan
University of Queensland

Parkinson's disease (PD) is an incurable disease characterised by progressive motor system dysfunction. PD affects 1% of the population over the age of 60 (~110,000 patients in Australia and more than 10 million patients world-wide). Currently, there are no treatments that cure or slow disease progression. The total economic cost of PD is enormous and it is expected to result in an increasing burden on society as the population ages.

The cause of Parkinson's disease is not fully understood. Rare, inherited Parkinson's disease can be caused by mutations in proteins, Pink1 and Parkin, that regulate the removal of mitochondria from cells in a process known as mitophagy. There has been a great deal of research into the development of Parkinson's disease therapies designed to reactivate mutant Parkin through the use of small molecules.

The aim of this project is to activate mitophagy responses through alternative pathways. We have discovered a regulatory pathway that keeps mitophagy levels low in cells. The aim of this project is develop strategies to re-activate the mitophagy pathway in cells. This could lead to the development of activators of mitophagy which could serve as treatments for Parkinson's disease.

2019 Research Grant Awards

▼ CEREBRAL DISEASES

Early detection of cerebral small vessel disease

Chief Investigator:
Dr Lauriane Jugé
Neuroscience Research Australia, NSW

Co-Investigators:
Prof Lynne Bilston,
Dr Lucette Cysique,
Prof Caroline Rae,
Dr Elizabeth Brown,
Dr Peter Burke

Cerebral small vessel disease (CSVD) is a common feature of the ageing brain, associated with up to 45% increased dementia risk and 20% increased risk of strokes. Management of the traditional risk factors of CSVD is still the main approach for treating or preventing CSVD, because there is evidence that brain damage can be reversed or delayed in the early stages of the disease.

Obstructive sleep apnoea (OSA) is a common medical disorder in the general population. It affects at least 3-7% of adult men and 2-5% of women, and the prevalence is increasing as the population ages and becomes more obese. People with OSA have an increased risk of CSVD. If not treated, OSA has been reported to promote CSVD progression.

The diagnosis and monitoring of CSVD relies on imaging findings. However, only severe cases of CSVD in moderate-severe OSA patients have been identified with current routine magnetic resonance imaging (MRI) protocols, and the results have been inconsistent. There is currently no MRI protocol able to identify early stage CSVD or to monitor disease progression in the early stages. In fact, more advanced imaging techniques are required to detect a subtler level of damage, when disease management would be of most benefit.

Thus, the project aims to develop a novel brain MRI protocol able to characterise early CSVD using people with OSA as a high risk population, with the objectives of developing clinical recommendations. Results could be generalised to other high risk populations because CSVD is also frequent in patients with cardiovascular disease and associated risk factors (mainly high blood pressure and high cholesterol). The project will also improve our understanding of

CVSD neuropathology, much needed to improve cognitive ageing, mental health and positive ageing, plus help prevent stroke.

Novel agents for the targeting of abnormal blood vessels in the brain to prevent stroke

Chief Investigator:
Dr Lucinda McRobb
Macquarie University, NSW

Co-Investigators:
Prof Marcus Stoodley

Our goal is to develop new ways to treat a blood vessel disorder that occurs in the brain called arteriovenous malformations, or AVMs. These tangled collections of abnormal blood vessels can form in the brain during early development. They are highly prone to rupturing, leading to release of blood into the brain, causing a type of stroke. This form of stroke occurs primarily in children and young adults, rather than as a result of aging, so has a significant impact on affected individuals and their families. Despite current approaches, one-third of these vulnerable young patients lack safe treatment options and remain susceptible to stroke. To fill this gap, we aim to develop a vascular targeting approach to AVM treatment. This involves delivering a drug through the bloodstream to induce localised clotting and closure of the diseased AVM vessels. Key to this approach is 1) identifying molecular targets unique to the surface of the diseased blood vessels but absent from normal, healthy blood vessels; and 2) developing complementary targeting molecules that recognise and bind these targets to deliver vessel-occluding drugs specifically to the AVMs. The recent discovery that more than half of all AVMs are caused by mutations in a family of genes called RAS, for the first time provides a defined molecular cell type for AVMs that can be easily modelled for study in the laboratory. Our study aims to develop an AVM cell culture model in the laboratory that expresses the RAS mutation and then use it to generate novel targeting molecules (called DNA aptamers) that can specifically recognise and bind RAS-induced molecular targets on the surface of these mutant cells. These novel targeting molecules could then be used to deliver vessel-blocking drugs with high specificity to AVM vessels providing a safe and effective new treatment approach for AVM patients.

WHAT DOES NOVEL MEAN?

Novel is used to describe something new or original. It is a fresh idea which has not been previously reported, to the knowledge of the investigators.

Identifying the role of the immune system in patient outcomes after subarachnoid haemorrhage

Chief Investigator:
Dr Liam Coulthard
Royal Brisbane & Women's Hospital, QLD

Co-Investigators:
A/Prof Trent Woodruff, Prof Kevin Laupland

Aneurysmal subarachnoid haemorrhage (aSAH) is a haemorrhagic stroke resulting from a pre-existing weakness in a blood vessel wall. Overall, the incidence of aSAH is low, affecting around 6-7 people per 100,000 every year. However, given the young age of those affected and the severe disability that can result from this event, the cost to the community is high.

It is difficult to predict who is at risk of aSAH as unruptured aneurysms are largely asymptomatic. We can, however, aim to reduce the adverse effects of aSAH after it has occurred. Whilst, there may be significant injury from the initial bleed, up to 30% of aSAH patients go on to have a further secondary brain injury that is preventable. One of the major causes of secondary injury is vasospasm. This spontaneous constriction of cerebral blood vessels reduces blood flow to otherwise normal areas of brain. Perplexingly, this occurs in a delayed fashion, days after the initial bleed. Patients are at highest risk of vasospasm around 5-9 days after aSAH.

We do know that vasospasm is more likely to occur in those with a higher blood load from the initial bleed. However, the mechanisms that occur between the initial bleed and the onset of vasospasm, almost one week later, are not known.

Our research team aims to look at a group of complement proteins, which function as part of the immune system, during the period after aSAH. These proteins are activated at the point of rupture and they have the potential to cause vessel spasm both directly and indirectly. By examining concentrations of complement proteins in blood and cerebrospinal fluid in the week after aSAH, and comparing this with the clinical data, we may be able to predict who is most at risk in future. We will also develop a tissue and data bank from this collection for future studies into aSAH. Ultimately, the more that is known about the molecular mechanisms underlying vasospasm, the closer the possibility of a prevention or cure.

Sodium selenate – a novel treatment for stroke and post stroke epilepsy

Chief Investigator:
Dr Pablo Miguel Casillas-Espinosa
Monash University, VIC

Co-Investigator:
A/Prof Sandy Shultz

Ischemic stroke is a common neurological condition that often results in debilitating lifelong consequences. One of the most severe, yet understudied consequence of stroke is the development of post-stroke epilepsy. Unfortunately, there is currently no intervention known to prevent the long-term neurological consequences of stroke.

Tau is a protein that plays a critical role in the normal function of the neurons. Tau undergoes phosphorylation and dephosphorylation changes that are tightly regulated by Protein phosphatase 2A (PP2A).

However, we have shown that in a number of neurodegenerative diseases, like traumatic brain injury, Alzheimers, Parkinsons and epilepsy, PP2A dysfunction and tau its hyperphosphorylated. This hyperphosphorylation of tau creates aggregates of the protein which destabilise the structure and function of the neurons, promoting the development of brain diseases.

However, we have previously show that treatment with sodium selenate, which is a drug that improves the function of PP2A, helps to decrease the hyperphosphorylation of tau, to improve memory and mobility, but also prevents the development of epilepsy after traumatic brain injury.

We now have exciting preliminary data showing that tau is hyperphosphorylated and PP2A dysfunctions in a model of ischemic stroke. Based on these promising results, this project will now test the hypotheses that hyperphosphorylated tau and PP2A contribute to the brain damage and consequences of stroke. We will also evaluate if treatment with sodium selenate can prevent the brain damage, mobility impairments, chronic pain, anxiety, social dysfunction, depression, learning and memory deficits and epilepsy after stroke.

Sodium selenate treatment is already in clinical trials in other neurological conditions, thus this project has the strong potential to impact the medical management of stroke patients in the foreseeable future.

Identification of new approaches for the treatment of stroke

Chief Investigator:
A/Prof Simone Schoenwaelder
Heart Research Institute, NSW

Co-Investigators:
Prof Shaun Jackson, Mrs Jessica Maclean, Dr Mike Wu

Acute ischaemic stroke (stroke) is the third most-common cause of death and a leading cause of disability worldwide. The majority (85%) of strokes are caused by blood clots that reduce/stop flow of blood to the brain. The mainstay of stroke treatment is therefore to quickly remove these clots and restore blood flow to the brain, to prevent extensive and permanent damage to brain tissue.

"Clot-busting" drugs that dissolve the blood clot (rtPA) are currently used to treat patients with stroke. However, while administration of rtPA ("Thrombolytic therapy") is the only drug clinically approved for stroke therapy, significant limitations undermine its clinical effectiveness. These include a low success rate in dissolving clots forming in larger vessels, a tendency to promote clot reformation, and an increased risk of life-threatening bleeding. Given that any bleeding in the brain can be catastrophic, strict eligibility criteria surround the use of rtPA for stroke, such that it is only administered in 13% of all stroke patients, with less than half of these achieving a good therapeutic outcome.

A significant problem associated with thrombolysis, is that as a result of breaking down the blood clot, rtPA inadvertently releases thrombin, the very enzyme responsible for clot formation in the first instance. This is thought to be responsible in part for promoting re-clotting events. While the simple addition of an anti-thrombin or anticoagulant drug – of which there are many clinically approved – has the potential to prevent this "re-clotting" phenomena, all existing anticoagulants cause excessive bleeding and are therefore unsafe for use in the treatment of stroke.

We have identified a novel anticoagulant protein found in the saliva of blood feeding insects, which has the unique ability to block clot formation without causing significant bleeding. We will use state-of-the-art preclinical models established in our lab to examine whether this novel anticoagulant can be used to improve the safety and effectiveness of thrombolytic therapy, leading to improved stroke outcomes.

2019 Research Grant Awards

▼ BRAIN TUMOURS

New therapies for glioblastoma: A focus on metabolism

Chief Investigator:
Dr Ayenachew Bezawork-Geleta
University of Melbourne, VIC

Co-Investigators:
Prof Matthew Watt,
Dr Mastura Monif,
Dr Garron Dodd,
Prof Sunghyouk

Gliomas are the most prevalent brain tumours and predominantly arise from glial cells. The World Health Organization (WHO) grades gliomas on a scale of I to IV, reflecting their degree of malignancy. The higher the grade the more severe the tumour in terms of growth and invasion. Grade I tumours are benign and can be cured while grade IV gliomas (also called Glioblastoma or GBM) are very aggressive forms of brain cancer.

Patients with GBM are among the most disadvantaged cancer patients in the healthcare system. The overall survival outcome for GBM is dismal with a median survival of 15 months. Standard GBM management typically involves surgical resection followed by radiotherapy and adjuvant chemotherapy with temozolomide (TMZ), but relapses usually occur within a month after initiating treatments.

The difficulty in effectively treating GBM patients is largely due to a fast-growing malignancy, providing several hindrances to understanding the molecular mechanisms underpinning disease progression and thereby constraining suitable therapeutic development. We have identified a unique requirement for lipid metabolism to support GBM malignancy and show in preclinical models that blocking lipid metabolism slows GBM growth. In this study, we will uncover novel proteins that are requisite for aberrant lipid metabolism and that confer a survival advantage in glioblastoma. Outcomes of this work range from elucidating in-depth mechanisms of tumorigenesis to conducting preclinical translational research. This will provide a rich resource to guide the genesis of a new class of metabolic-based drug for clinical treatment of glioblastoma patients.

Non-invasive blood test for diagnosis and monitoring of brain cancer

Chief Investigator:
Dr Jordan Jones
University of Melbourne, VIC

Co-Investigator:
Dr Andrew Morokoff,
Prof Kate Drummond

Approximately 2000 Australians each year are diagnosed with brain cancer, and despite ongoing interest in the management of these tumours, the most common type, Glioblastoma, is a devastating disease with only 20% of patients surviving beyond 5 years. Current methods of diagnosis and monitoring involve MRI scanning and invasive neurosurgery. Although MRI gives good anatomic and spatial information about the tumour, it is not reliable at predicting how the tumour is going to behave in the future. It is not accurate enough to detect early tumour recurrence in many patients and treatment with radiotherapy can mimic these changes therefore making interpretation of the MRI difficult. Additionally, performing frequent MRI scans is impractical and expensive. A blood test has the potential to solve these clinical challenges by providing a means of frequent, accurate non-invasive monitoring of the tumour that can aid in diagnosis and potentially avoid invasive surgery for some. Circulating biomarkers are starting to be integrated in the care of other cancers including breast and colorectal but to date there has been no validated biomarkers in brain tumours.

We have currently identified a panel of 9 blood markers that can differentiate between patients with brain tumours and healthy controls with over 99% accuracy. We plan to validate this panel during the monitoring of patients with brain tumours by collecting multiple blood samples and comparing these markers to what is seen on subsequent MRIs. We will also investigate whether any of these markers can be used in conjunction with the already known factors that are important for survival to more accurately predict prognosis and identify high-risk patients. More accurate monitoring will help to better inform the timing of MRI's and support decisions when considering further neurosurgical intervention or other treatments as well as adapt a personalized therapy plan, all of which would be a major advance in the lives of those with brain cancer.

BRAIN ANEURYSM SUPPORT AUSTRALIA

This site is for all who are survivors, sufferers, know someone suffering, or supporting someone with an Aneurysm, to share their story and support.

https://www.facebook.com/basa.com.au/

We hope we can help in some small way.

SUPPORT GROUPS WE CAN SUPPORT

Are you part of a support group for another neurological condition that you would like to share with other sufferers.

Please let us know so that we can publish the details.

No one should have to go it alone. Being with others with the same condition offers a great deal of comfort and support!

▼ EPILEPSY

Optimisation of first seizure management

Chief Investigator:
Dr Emma Foster
Alfred Health, VIC

Co-Investigators:
Prof Patrick Kwan, Prof Terence O'Brien, Prof Danny Liew, Dr Patrick Carney, A/Prof Zanfina Ademi, Dr Zhibi

First seizures are a common and important problem, affecting over 14,000 Australians each year, or almost 10% of people over their lifetime. First seizures are associated with increased morbidity, mortality and hospitalisation, as well as substantial costs to individuals, caregivers and society. Many patients require hospitalisation for treatment of seizure-related accidents, injuries and underlying conditions. Healthcare service utilisation, particularly hospitalisation, is far higher in those with first seizures compared to patients with chronic illnesses. Studies demonstrate the benefits of early epileptologist input regarding diagnostic accuracy, adherence to follow up appointments and delay in seizure recurrence. Unfortunately, as our pilot study regarding first seizure presentations at a large metropolitan centre demonstrated, first seizure management often deviates substantially from recommended practice. In this study we will use state-of-the art data linkage to determine first seizure patient health outcomes including recurrent seizure presentations, all-cause hospital attendances and admissions, serious injuries, comorbidities and mortality. Furthermore, we will determine the health and economic benefits of first seizure clinics as a healthcare intervention through reducing potentially avoidable future health service utilisation by reducing seizure recurrence, morbidity and mortality. Lastly, we will develop a multimodality tool using 'real-world' data, including patient and clinical variables and magnetic resonance imaging studies, to predict the chance of seizure recurrence, medical and psychiatric comorbidities, and death, following presentation with a first seizure. This project will establish a solid evidence base for implementation of first seizure clinics into routine practice as an impactful preventative health service intervention, delivering evidence-based care in a cost effective and timely manner. In addition, a robust prognostic model will help identify those at lower risk of seizure recurrence, who may be spared unnecessary workup and costs, as well as those at high risk of seizure recurrence, who may benefit from more intensive monitoring and additional health interventions.

DID YOU KNOW?

Over 14,000 Australians will suffer from a first time seizure each year

▼ CHRONIC HEADACHE & MIGRAINE

The Professor James Lance AO CBE Award

MRI cervical muscles in chronic migraine and cervical dystonia

Chief Investigator:
Dr Lin Zhang

Monash University, VIC

Co-Investigators:
Dr Kelly Bertram,
Prof Meng Law

Migraine is the leading cause of neurological disability in Australia, with significant disruption to work and social engagement producing an annual economic cost estimated at $35.7 billion. Neck pain with muscle tension is a frequent complaint in migraine, often associated with significant symptom related disability. However, the pathophysiological mechanism of this phenomenon is poorly understood, and targeted treatment is lacking.

Our study aims to determine whether there may be a link between the neck muscle spasm in migraine and cervical dystonia. The latter is a much rarer neurological condition occuring in 5-9/100,000 people, producing painful involuntary neck muscle contractions, causing abnormal head postures. Co-exisiting migraine and cervical dystonia has been observed and reported clinically. This probably only explains the minority cases of migraine with neck pain based on published studies as well as premilinary data of our current observational study. The nature of overly active neck muscles in the majority cases of migraine remains unknown.

This project is the first study using magnetic resonance imaging (MRI) to investigate and to compare activated neck muscles in patients with migraine and patients with cervical dystonia. Several early studies have shown that T2 relaxation time sequences can distinguish changes in muscles after exercise compared to resting muscles, due to the shift of water into muscles that are have been actively contracting. Moreover, the degree of muscle activation has a positive correlation to the level of signal shift on MRI. In this study, we will compare the muscle signal changes between patients with chronic migraine with neck muscle tension to healthy individuals and to patients with cervical dystonia, in which the neck muscles are actively contracting involuntarily, which should replicate the effect of voluntary exercise on MRI paradigms.

Knowledge gained from this project will potentially improve understanding of the nature and mechanism of neck pain in chronic migraine and justify consideration of new treatment options for this symptom of migraine, for example botulinum toxin injection into active neck muscles. In addition, it may provide a novel noninvasive tool to allow more precise target identification for botulinum toxin injection in cervical dystonia.

MULTIPLE SYSTEM ATROPHY SUPPORT GROUP

For anyone who is suffering from or supporting a loved one with Multiple System Atrophy, MSA, (also previously known as Shy-Drager Syndrome) or Progressive Supranuclear Palsy, PSP, there is a closed Facebook page you can join to support you on this journey.
Please go to: **https://www.facebook.com/groups/MSAOZNZ**
You may also like to visit these web sites:
www.multiplesystematrophy.org, wwwmsatrust.org.uk and www.psp-australia.org.au

2019 Research Grant Awards

▼ NEUROMUSCULAR DISEASE

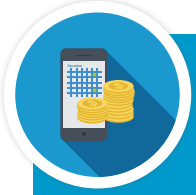
Identifying the genetic basis of neuromuscular disease using the newest advances in genetic technology of RNA sequencing to improve the diagnostic odyssey for patients with inherited muscle disorders

Chief Investigator:
Dr Roula Ghaoui
Royal Adelaide Hospital, SA

Co-Investigators: Dr Karin Kassahn, Prof Hamish Scott, Dr Mark Davis

Identifying the genetic basis of neuromuscular disease is crucial to guide patient care. It enables us to provide more accurate prognostic information to families, and prevent complications, such as heart and lung involvement. By using next generation sequencing (NGS) such as whole exome sequencing (WES) and Neurogenetic Subexomic Supercapture (NSES, also known as targeted neuromuscular panel), this approach has dramatically transformed how we diagnose and deliver health care to Australian myopathy and muscular dystrophy patients - now greater numbers of patients can achieve accurate and timely diagnosis, receive appropriate disease-specific treatments and gain access to informed family planning while still fertile.

Despite these recent advances in genetic testing, more than 50% of patients with hereditary neuromuscular disorders remain undiagnosed. RNA studies via RNA sequencing (also known as transciptome sequencing) is the next step of the diagnostic pathway. This project aims to apply this newest form of NGS testing strategy to clinical practice. We will examine the utility of RNA sequencing (RNA-seq) as a complementary diagnostic tool in a cohort of families with inherited myopathy or limb-girdle muscular dystrophy (LGMD) that have remained undiagnosed despite next generation sequencing (NGS) and who have muscle biopsies available. Previous studies have shown that RNA-seq can provide a substantial diagnosis rate in patients for whom exome or whole genome analysis has not yielded a molecular diagnosis. By taking from my experience of using RNA sequencing, I hope to develop a new diagnostic algorithm with the completion of the project that incorporates NGS and RNA sequencing into the diagnostic pathway for patients with neuromuscular disorders. The ultimate aim of the project is to help inform best practice guidelines for the diagnosis and management of patients with inherited myopathies and LGMD in Australia.



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Regular donations can be made to a specific area of research.

Pathophysiology of Kennedy's Disease

Chief Investigator:
Prof Cindy Lin
Brain & Mind Centre, University of Sydney, NSW

Co-Investigators:
Dr Susanna Park, Dr Thanuja Dharmadasa

Imagine being relatively healthy and normal, then soon after you reach adult-hood you slowly become weak and progressively not able to walk, talk or swallow properly. These are the problems that are faced by patients with Kennedy's disease (KD). Kennedy's disease (KD), also known as X-linked spinal and bulbar muscular atrophy (SBMA), is a rare, recessive, inherited neurodegenerative disorder which causes slowly progressive weakness and wasting of muscles. It also affects the nerves that control bulbar muscles, which control breathing, swallowing, and talking. It can also lead to androgen (male hormones) insensitivity which causes enlarged breasts in men, decreased fertility, and testicular atrophy. However, KD is the most common adult-onset SBMA, disease onset ranges from 18 to 64 ages. Often, individuals with KD are mistakenly thought to have other motor neuron diseases, such as amyotrophic lateral sclerosis (ALS). However, the time from onset to confirmation of diagnosis is on average longer than 5 years. Diagnosis of KD is delayed because there is no explicit biomarkers for the disease and the diagnosis requires the genetic confirmation. There are critical gaps in identifying reliable, sensitive biomarkers across the KD spectrum. There is an urgent need to develop disease-specific, sensitive monitoring biomarkers, to provide clues to the complex underlying pathogenic process in patients with KD.

Neurodegeneration can occur at all levels of the neuraxis, degeneration at the central (brain and the spinal cord) and in the peripheral (nerve) level. The objective is to further research looking at patterns of involvement of both central and peripheral nervous system progression. It is essential to understand both the central and peripheral involvement in KD, when subclinical abnormalities may first become evident.

The present project is designed to address these issues by establishing a comprehensive central and peripheral assessment to investigate the pathophysiology with an initial focus on Kennedy's Disease. This will provide a platform for future studies, to expand scientific knowledge regarding pathophysiology and treatment responses, extending our clinical and neurophysiological prospective studies. The present project is built upon interdisciplinary innovative research. We will use the platform of this grant to promote clinical translational research that meaningfully improves the quality of lives of patients with KD and families affected by this slowly progressive neurodegeneration.

Neuroinflammation in ALS

Chief Investigator:
A/Prof Seth Masters
Walter & Eliza Hall Institute, VIC

Accumulation of a protein known as TDP-43 is a hallmark of disease in almost all patients with amytrophic lateral sclerosis, and many individuals with frontotemporal dementia, Alzheimer's disease, Parkinson's disease, or diffuse Lewy body disease. TDP-43-associated neurodegeneration in general has been linked to inflammation, and interestingly, these inflammatory signals precede symptoms of disease. This suggests that inflammation contributes to disease pathogenesis, rather than simply acting as a marker of disease. We have now identified the primary innate immune pathway in cells that triggers neuroinflammation due to TDP-43. Unexpectedly this is driven by an innate immune pathway which is an immune sensor that recognises stray DNA in the cytoplasm of cells, cGAS/Sting.

TDP-43 releases mitochondrial DNA to activate cGAS/Sting

Normally, DNA remains within the nucleus or mitochondria of cells, but if stray DNA gets into the cytoplasm it can be recognised by cGAS/Sting, leading to inflammation. Indeed, it was already known that TDP-43 can get into mitochondria, and we found that this is what causes mitochondrial DNA to leak into the cytoplasm and trigger inflammation.

Pharmacologic inhibition of cGAS/Sting protects prevents TDP-43 driven inflammation

Critically, we have obtained a small molecule inhibitor of Sting (H-151), and found that it can block neuroinflammation triggered by TDP-43 for cell lines in vitro. H-151 is being commercialised by the company IFM therapeutics (Boston), who have agreed to support our project, looking towards first in man clinical trials.

Therefore, in summary, we suggest that patients with accumulation of TDP-43 suffer from neuroinflammation caused by the cGAS/Sting pathway. This occurs because TDP-43 destabilises mitochondria and the DNA leaks into the cytoplasm, activating cGAS/Sting. We propose to inhibit Sting and thus treat a mouse model of ALS caused by TDP-43, and confirm our results in primary human cells, as important steps towards getting this therapy into the clinic.

Imaging blood flow in nerves in patients with nerve disorders and its relation to treatment approaches

Chief Investigator:
Dr Edrich Rodrigues
Alfred Health, Monash University, VIC

Co-Investigator:
Prof Meng Law

Fatigue is a chronic and debilitating feature of multiple sclerosis (MS) which is not fully understood. It is multifactorial and often reduces quality of life of those individuals. Obstructive sleep apnoea (OSA) is likely to be one of its contributing factors. Its prevalence in MS patients is approximately 20% in newly diagnosed patients and can increase to nearly 90% during disease course. A common screening questionnaire (STOP-BANG) to assess risk of OSA only identifies 56% of those patients. Due to the nature of the central nervous system inflammatory lesions present in MS, majority of the people with OSA are non-obese, which suggests that non-anatomical causes, such as impaired upper airway sensation and poor muscle responsiveness during sleep, are the contributing factors to OSA in MS people. This causes transient disruptions in nocturnal breathing and reductions in overnight oxygen saturation, which characterises OSA. These events apart from leading to daytime sleepiness and feeling of waking up unrefreshed are associated with increased or cardiovascular disease and motor vehicle accidents. Upper airway sensation testing with monofilaments during wakefulness has been routinely used in research protocols. It was shown to have a high sensitivity (80%) to detect nocturnal upper airway occlusion (OSA). Thus, the aim of this project is to recruit 30 fatigued MS patients, fill in 2 groups (low vs high risk) of OSA according to the STOP-BANG questionnaire. Additional upper airway sensation will be tested in all enrolled participants and they will undergo formal gold standard sleep test, polysomnography (PSG), to compare the results. With this protocol we expect to better detect fatigued MS individuals with high propensity to OSA and to facilitate the referral to PSG, rather than referring every single patient. Consequently, a better management of the fatigue in those individuals is likely to be achieved as a reduction to the economic burden to public health in the light of the changes of the billing practices for sleep studies implemented by Medicare in 2017-18.

▼ VESTIBULAR DISORDERS

Using a genetic mouse model to investigate the pathology of Meniere's disease

Chief Investigator:
Dr Aaron Camp
University of Sydney, NSW

Co-Investigators:
Dr Christopher Pastras,
Dr Daniel Brown,
Em Prof Bill Gibson

Balance disorders such as Meniere's disease (MD) are debilitating for sufferers, and pose a significant socio-economic burden on Australia, with an estimated billion-dollar cost. A key clinical observation in MD is a build-up of inner ear fluid called endolymph causing bloating of the membranes within the inner ear, known as 'endolymphatic hydrops' (EH). While EH is present in all Meniere's sufferers across the lifespan of the disorder, the way that hydrops produces clinical symptoms during Meniere's attacks, remains largely unknown. Given the difficulties reconciling abnormal vestibular tests findings with symptoms of MD, a model that bridges the gap between the pathophysiological processes accompanying EH and the observed clinical manifestations of vestibular dysfunction in MD, will provide a direct link between EH and MD, and facilitate continued clinical development of vestibular tests for MD. Our project will use a promising transgenic mouse model that displays characteristics of human EH (the PhexHyp-Duk mouse). Overall, we aim to provide for the first time, a comprehensive examination of the physiological, mechanical, morphological and behavioural correlates of vestibular dysfunction in a novel model of endolymphatic hydrops. The outcome will be new knowledge of the vestibular dysfunction in the model that will a) help to determine the extent of correlation between the physiological phenotype of the transgenic mouse and the known changes in human MD, and b) potentially form the base model for testing new therapies for human MD.

2019 Research Grant Awards

▼ NEURO-TRAUMA

Limiting the damage in Traumatic Brain Injury

Chief Investigator:
Dr Amar Abdullah
University of Melbourne, VIC

Co-Investigator:
Prof Peter Crack

Traumatic brain injury (TBI) remains the leading cause of death and permanent disability in adolescents worldwide. According to the Australian Institute of Health and Welfare, 107 people in every 100,000 Australians suffer a TBI, costing approximately $184 million annually in medical care. Current treatments are inadequate, with the majority of potential therapeutics failing in clinical trials. The failure of potential therapeutics can partly be attributed to the complexities of the secondary damage and that the pathways involved in the neuronal cell death after TBI are not fully understood. Over the past decade it has become clear that the central nervous system (CNS) can exhibit features of neuroinflammation in response to TBI. TBI triggers acute neuroinflammation, which exacerbates primary brain damage. It is important that ways are found to control this neuroinflammation as controlling neuroinflammation will limit the damage the brain suffers after TBI.

Using an animal model of TBI, we have found that type-I interferon (IFN) signaling plays a critical role in regulating neural injury and that mice that lack the receptor for IFN are protected from neural injury. Furthermore, we have extended this work and determined that the detrimental effect of IFN signaling is mediated by its upstream activator stimulator of interferon genes (STING). After TBI STING–/– mice display reduced lesion size as compared to their wild-type (WT) littermates. Importantly, we have also identified increased STING mRNA expression in post-mortem human TBI brain samples, implicating activation of the STING pathway in the human brain after trauma. These data suggest inhibiting type-I IFN signaling through the STING pathway is a potential therapeutic strategy for reducing

cellular damage after TBI. What we are proposing to do is test the neuroprotective ability of novel STING inhibitors in a mouse model of TBI. The advantage of targeting STING is two-fold – 1. Small molecule inhibitors targeting STING are able to cross the blood brain barrier and 2. There are no small molecule inhibitors available to block direct type-I IFN signaling.

HAVE YOU BEEN AFFECTED BY CONCUSSION?

A new research study on the genetics of concussion is now seeking volunteers.

Genes impact the way some people are affected by concussion.

Your involvement could aid in finding better diagnosis and management of concussion by identifying new genes that may play a role.

Participating is simple; fill out a questionnaire and provide a saliva sample.

To participate, contact QUT
Genomics Research Centre
Phone: 07 5688 7170
Email: grcclinic@qut.edu.au
Contact person: Prof Lyn Griffiths, Concussion Study

QUT

This study has been approved by Queensland University of Technology Human Research Ethics Committee (approval number: 1700000811).

Chronic Traumatic Encephalopathy

Chief Investigator:
Dr Claire Shepherd
Neuroscience Research Australia, NSW

Co-Investigator:
Dr Andrew Gardner

There is considerable scientific and community interest in the consequences of repetitive traumatic brain injury (TBI) and global public concern that even mild head injury may lead to a progressive neurodegenerative disorder known as chronic traumatic encephalopathy (CTE) in later life. However, the scientific knowledge in this area is preliminary and there is an urgent need for accelerated research efforts.

The current research program will investigate the presence of CTE in the brain tissue of a large population of well-characterised individuals held by the Sydney Brain Bank and determine any association with TBI exposure. One of the most promising and unique advantages of examining CTE in this large Australian brain bank cohort is that the donors are all collected through longitudinal, prospective brain donor programs.

This study will directly address our understanding of the relationship between TBI and CTE. It will also provide essential validation of current neuropathological diagnostic and staging criteria. In turn, this will help our understanding of potential disease progression. It will also provide essential information required for directing future research efforts to further advance the scientific knowledge, such as developing effective animal models of the disease, which are required to understand disease mechanism and test potential therapeutic strategies.

How does Toxoplasma Gondii, a common worldwide infection, affect brain injury?

Chief Investigator:
Dr Mujun Sun
Monash University, VIC

Co-Investigators:
A/Prof Chris Tonkin, A/Prof Sandy Shultz, Prof Christopher Sobey

Infection with Toxoplasma gondii (T. gondii) is one of the most prevalent infections in humans (i.e., ~30-50% of the global population). T. gondii is a parasite that permanently resides in the brain tissue of infected mammals. T. gondii infection has traditionally been viewed as benign, however recent studies suggest that T. gondii infection in itself may cause subtle behavioural abnormalities, and is associated with neurodegenerative diseases, such as Parkinson's diseases, Alzheimer's disease, as well as neuropsychiatric disorders. Notably, T. gondii infection also results in inflammation in the brain.

Traumatic brain injury (TBI) and stroke are common forms of brain injury that affect millions of people worldwide each year, and both lack effective treatments to improve long-term outcomes. The difficulty in developing effective treatments for brain injuries is in large part due to their heterogeneous nature, as there are factors that can modify how the brain responds to injury. For example, T. gondii infection could result in pre-existing inflammation in the brain, and therefore when the brain is injured the outcomes could be worse. This would affect the optimal treatment strategy required for such patients, and could account for some of the past translational failures in developing interventions for these conditions.

Despite the high prevalence of T. gondii, TBI, and stroke worldwide, how the presence of T. gondii affects TBI or stroke has never been investigated. Therefore, this study will evaluate the possibility that the presence of T. gondii infection modifies TBI and stroke outcomes in rats. Findings from this novel and innovative project will significantly improve our understanding of these prevalent conditions and will provide a foundation for future studies to develop optimized treatment strategies to improve brain injury outcomes.

Investigation of how Zika virus infection causes brain damage in infant and adult brains

Chief Investigator:
A/Prof Heung-Chin Cheng
University of Melbourne, VIC

Co-Investigator:
Dr Prasad Paradkar, A/Prof Nicholas Williamson, Dr Ching-Seng Ang

Zika virus, a mosquito-borne virus, can infect mosquitoes when they feed on an infected human host. The infected mosquitoes then spread the virus to other human hosts through subsequent bites. If a pregnant woman is infected, she can pass the virus to her foetus during pregnancy and birth to cause severe birth defects in the infected infant. One of major defects is microcephaly where the infant's brain shows signs of significant cell death and is much smaller than expected. Following the large outbreak in the Pacific and South Americas in 2015-2016, Zika virus infection has spread to more than 45 countries. With no approved vaccines and efficacious drugs to prevent the spread of the virus and to mitigate Zika virus-induced brain damage, the infection poses a huge public health risk with economic and social impacts. The World Health Organisation in 2018 classified Zika infection as a priority disease in urgent need of accelerated research to identify therapeutic targets for drug development.

Zika virus causes brain damage mainly by targeting a type of immature brain cells called neural progenitor cells (NPCs), which divide and mature to form multiple types of brain cells during foetal and infant development. Upon infection, Zika virus causes these cells to die with an unknown mechanism, leading to microcephaly. Our main objective is to employ a biochemical method called proteomics to investigate how Zika virus infection kills NPCs. Specifically, we aim to identify the proteins in NPCs that are chemically modified as a result of Zika virus infection. Their identification will (i) unveil how Zika virus infection skills NPCs and (ii) benefit the development of drugs to protect against cell death of NPCs in Zika virus-infected patients.

Healthy Brain

Use it or lose it – an active mind is a healthy mind

EASY

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HARD

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					9			7

Solutions on back page

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With your help, we can continue making a difference to many lives for many years to come.

A large proportion of calls we receive are from people who are looking for more information on a particular disease, a family member looking for support after a diagnosis or at the time of a loved ones passing looking to donate to research so that 'no one else needs to go through what they have been through'.

People ring us at their most vulnerable and this is something that we take very seriously. Long term relationships are forged at this time.

Brain disease, disorder and injury is very common. There are so many diseases that affect the brain and spinal column it would be a rare family that has not been touched by one condition or another, or in fact, more than one. Most diseases have no cure.

Many do not have adequate treatment. Many use treatments for a different disease in order to treat symptoms. So, you can see how distressing it is for families to realise the limited options available at the time of diagnosis.

- We would like to fix this terrible state and bring hope to sufferers and families alike.
- We can only do this through more research.
- We can only do this with your help.

A Gift in your Will is a perfect way to honour the memory of a family member or to leave a legacy of hope to children and grand children that they will not have to suffer in the same way. We are able to dedicate your gift to a specific area of research. We can identify the gift (or not) in your memory of that of your loved one.

PLEASE CONSIDER US WHEN NEXT LOOKING AT YOUR FINAL WISHES

Please contact our office if you would like to have a further discussion or to receive one of our brochures to discuss with your legal representative.

IN MEMORIAM

A big thank you to the families and friends of the following who donated in Memory of their loved ones.

Emma CORCORAN
With thanks to Peter Bouchier Butchers

Gerard NASH

Peter Floyd WYLIE

Angela MIRANDA

Yvonne MUNN

Katie FITZGERALD

Harry EFTHYMIOU

Taimi LUBEK

James GIANG

Troy STAUNTON
With thanks to Mount Martha Soccer Club

Richard Joseph DAWSON

Tony PASKINS
With thanks to Lifestyle Tuncurry

Lesley Francis COLLINS

Wendy HURSE

Anne Kathryn HILL

Salvatore PAGLIA

BEQUEST

Our thanks to the estate of the late Joan WILLIS

IN REMEMBRANCE

Mrs Nancy Shugg who donated to dementia research in memory of her husband

Surf City Cranes, Gold Coast. Donated to Aneurysm research in memory.

IN CELEBRATION

Frank Russo on the occasion of his 70th Birthday – donating to Huntington's disease research

Carmel Stephens and Paul Mullins on the occasion of their marriage in memory of Kelly Stephens

Did you know that you can remember your loved ones and make a donation to a specific category of research? Please phone if you would like more details or see our online donation form.

Fundraise for Research

We are often asked "what can we do to fundraise?'

Well, there is no one answer to that question. With the help of fundraising platforms **Everyday Hero**, **My Cause** and **Go Fundraising** you can do just about anything you like.

These sites can take you one of the community events such as a fun run or swim. These are easy to enter and choose to support us. Or, you could do your own event such as a Trivia Night – speak to our office for our 'ready made' trivia pack – or any fun event with your friends. Once you have filled in your details and told everyone why you are fundraising you are on your way. And the best part? If you use these platforms, all donations and receipts are taken care of for you. The money comes straight to our account. Easy!

Brain Foundation

Thank you for supporting brain research through the Brain Foundation

To make a donation please visit our website
brainfoundation.org.au/donate
or use the donation form on the letter enclosed.

REGISTERED CHARITY · acnc.gov.au/charityregister

Healthy Brain Solutions

easy

2	5	3	8	7	1	6	4	9
6	8	1	4	2	9	7	5	3
4	7	9	3	5	6	1	2	8
8	3	7	9	6	5	4	1	2
9	2	6	1	4	3	5	8	7
1	4	5	2	8	7	9	3	6
7	6	4	5	3	2	8	9	1
5	9	2	6	1	8	3	7	4
3	1	8	7	9	4	2	6	5

medium

2	3	4	7	1	9	6	5	8
9	8	5	6	4	2	3	7	1
1	7	6	5	8	3	4	2	9
5	1	2	8	3	7	9	4	6
6	4	3	2	9	1	5	8	7
8	9	7	4	5	6	1	3	2
7	2	1	3	6	5	8	9	4
4	5	9	1	7	8	2	6	3
3	6	8	9	2	4	7	1	5

hard

9	7	3	2	5	4	6	8	1
4	6	8	1	9	3	2	7	5
1	5	2	8	6	7	9	3	4
2	8	5	9	4	1	7	6	3
6	3	1	5	7	2	8	4	9
7	4	9	6	3	8	5	1	2
5	9	4	7	1	6	3	2	8
3	2	7	4	8	5	1	9	6
8	1	6	3	2	9	4	5	7