ANAESTHESIA – THE HIDDEN IMPACT
WE’RE SEEKING THE SAFEST WAY TO PUT PATIENTS INTO A DEEP SLEEP
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As the year charges along, I’d like to welcome you to the first edition of Brain Matters for 2019. In this issue we outline many exciting things that are happening at the Institute.

We’re pleased to share with you that a rare syndrome has been named after one of our talented researchers, Dr Sarah Gordon. This is a wonderful recognition of her commitment to improving our understanding of this rare condition. The search for new treatments can be a long and complicated road. I have no doubt Sarah will continue to play an important role in this research which can improve the lives of children around the world.

In this issue we reflect on advances in drug development for motor neurone disease thanks to a collaboration with the University of Melbourne and Bio21. Almost two centuries after anaesthetics revolutionised surgery, we hear how Florey scientists are working with surgical teams from nearby hospitals to examine the impact of anaesthesia on the immune system, the brain and other major organs.

As you may have seen in the media, Praxis Precision Medicines will soon establish their Asia Pacific headquarters in Melbourne. We expect this will generate 100 to 150 new jobs within Victoria. Importantly this achievement was born from over a decade of research at the Florey. Praxis will focus on clinical trials and drug development to treat neurological disorders including epilepsy and mental illnesses. We look forward to continuing to work alongside them and contribute to the future of precision medicine.

The journey of a medical researcher is not possible without the support and encouragement of those who share in our quest. I’d like to thank one of our major donors, Dr Mark Nelson, for his ongoing support and his latest initiative to support our research. Mark was a former PhD student here at the Florey and remains an important contributor to our research through his philanthropic efforts.

I hope you enjoy this issue of Brain Matters.

Director's Report

Floreys researchers, with colleagues in Europe, the UK and US have uncovered the first gene that determines how successful someone's stroke recovery will be.

Professor Vincent Thijs, Florey neurologist and co-head of stroke believes the discovery is just the start of a new journey.

“All this work over many years, with thousands of patients from various international genetic studies, has given us this one gene to work with. Now we need to work out what the variations are doing," Vincent says.

Ischaemic strokes, caused by a blocked artery in the brain, account for 85 per cent of all strokes. Stroke is the leading cause of adult disability and the second leading cause of death in Australia. It affects 56,000 people every year. Almost 500,000 Australians are currently living with the effects of a stroke, and these numbers are set to double to a million people by 2050.

To discover if any genes were involved in stroke recovery, the researchers analysed the DNA of over 3500 stroke survivors and closely matched the results to their recovery three months after their strokes.

Excitingly, the discovery identified numerous genetic variations involved in stroke recovery, all located in one particular gene. More studies are now required on how we use that information to aid rehabilitation.

While this study demonstrates there is a genetic component to stroke recovery, the overwhelming majority of strokes are caused by lifestyle issues. Smoking, obesity, diabetes, heart disease, high cholesterol and high stress levels are all strongly linked to stroke.

“We can’t control our genetics – we have our parents to thank for those – but we can control how much exercise we do, what we eat, and whether we smoke or not. A lot of society’s recent gains in stroke and dementia risk factors like controlling blood pressure and lowering cholesterol are under threat from rising obesity and diabetes,” Vincent says. Read more of Vincent’s funding success on page 6.
Improving lives through brain research

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Anaesthesia – the hidden impact

While anaesthetics revolutionised surgery 200 years ago, Florey scientists are busy investigating the hidden effects of this “very abnormal sleep”.

Approximately 300 million major surgical procedures happen worldwide every year.

Few people realise that acute kidney injury is a common complication in up to one-third of people undergoing major surgery. When this happens, patients face poor short- and long-term outcomes.

What actually causes the kidney injury is unknown but recent findings from Florey researchers suggest it is almost certainly due to a disruption in the kidney’s blood supply and oxygen levels.

Dr Yugeesh Lankadeva and Prof Clive May, in collaboration with Japanese clinical anaesthesiologists from Osaka and Okayama Universities, have now published their findings on anaesthesia and kidney health, and they have important implications for patients undergoing major surgical procedures.

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Every anaesthesiologist has a personal favourite anaesthetic technique and recipe – gas mask or IV infusion - for putting people to sleep before surgery. These decisions are guided by institutional protocols and the anaesthesiologist’s preferences based on their previous experience.

But the consequences for patients of using a particular anaesthetic regime can have severe outcomes such as acute kidney injury, which can lead to chronic kidney disease.

Using a large animal model that closely replicates common human surgical procedures, the researchers set out to answer the seemingly simple question of what happens to the kidney in response to different anaesthetics.

The answers surprised even them.

Using advanced probes they developed in conjunction with a medical device company, they observed a 50 per cent reduction in kidney blood flow when an injected anaesthetic was used and 80 per cent when a gas anaesthetic was delivered.

This reduction in kidney blood flow - to dangerously low levels under anaesthetic - can increase the risk of damage to the kidney when a large increase in blood flow returns after anaesthesia is withdrawn, a so-called reperfusion injury.

The researchers also measured the amount of nerve activity from the brain to the kidney. They found that the activity was increased substantially with gas delivered anaesthesia, but not with injected anaesthesia. The increased nerve activity constricts blood vessels in the kidney and reduces blood flow, thereby damaging the kidney.

These results show a clear risk of damaging the kidney with all anaesthetics, and especially with inhaled ones. Of course, very sick patients absolutely need surgery, so the team’s next steps are to begin human trials comparing different types of anaesthetic to track their effects on kidney function.

It’s possible that the nerve activation associated with anaesthesia, especially the inhaled gas form, is also impairing the immune system, according to Clive, head of the preclinical critical care unit.

“There is a well-known link between the nervous system and the immune system, and activation of the nervous system can inhibit the immune system,” he says.

For older people, the news is perhaps even more concerning. Dr Liz Evered from St Vincent’s Hospital showed that two markers of brain cell injury increase in the first 48 hours after surgery in people aged 60 and over.

The research was funded by the National Health and Medical Research Council and the National Heart Foundation of Australia.
Turning up T-cells to tone down MND

Florey research into motor neurone disease is in the fast lane, thanks to our supporters.

Five years ago, Associate Professor Brad Turner’s research career was transformed after speaking to the Inner Wheel and Rotary Clubs of Pakenham about his motor neurone disease research at the Florey.

He attracted the attention of members of the Stafford Fox Medical Research Foundation who invited him to submit a research proposal. He was subsequently awarded a $3 million research grant. Now in the final year of the grant, he and his team have made promising progress in their pursuit of effective treatments for MND.

One key achievement from the Stafford Fox Medical Research Foundation grant was the exciting discovery that a specific type of immune cell, regulatory T-cells (Tregs), may help slow MND’s progress. Tregs are part of the normal immune system and shut down harmful immune responses after eliminating invading organisms from the body. They also play a critical role in regulating other immune cells, preventing them from attacking healthy cells and tissues in the body by fighting inflammation. It is well known that inflammation builds up in the brain of MND patients, amplifying damage to motor neurons.

“Exploiting Tregs to fine-tune brain inflammation in MND seemed an innovative and exciting approach to take,” says Brad.

Brad and his team, in collaboration with neurologist Professor Steve Vucic at the Westmead Hospital, first demonstrated a significant relationship between Tregs and progression rate of MND in patients.

“The faster MND was progressing, the fewer inflammation fighting Tregs there were in blood. Likewise, the disease progressed more slowly in patients who had higher numbers of Tregs in their blood.”

Intrigued by this observation, Brad and his team tested a new cocktail therapy to amplify Treg numbers in a mouse model of MND. They tested a chronic treatment which dramatically boosted spinal cord Treg levels - the major site of motor neuron death in MND. Importantly, the treatment protected motor neurons and dampened harmful inflammatory responses in the spinal cord, resulting in a significant extension of lifespan in MND mice.

“These results from MND patients and mice confirm the importance of Tregs in MND and demonstrate an effective therapeutic approach to suppress toxic inflammation in the spinal cord from the circulation.

“We are now keenly pursuing new strategies to boost Treg levels and protective activity in MND patients, with the ultimate goal of developing new therapies to effectively treat MND, as demonstrated by the current trial of Tecfidera in Australian MND patients.”

This study was the culmination of a national collaboration between the Florey, leading MND clinics, medical research institutes and universities, made possible by the Stafford Fox Medical Research Foundation.

“The generous support has accelerated our research pace and fast-tracked candidate drug development for MND. This philanthropic funding has been transformative for my lab and expanded the research team and tools to aggressively tackle MND. We are extremely grateful for the tremendous support of the Stafford Fox Medical Research Foundation”.

Brad and his team, in collaboration with neurologist Professor Steve Vucic at the Westmead Hospital, first demonstrated a significant relationship between Tregs and progression rate of MND in patients.
Dr Sarah Gordon, head of the Presynaptic Physiology laboratory.

**A chance encounter**

Dr Sarah Gordon was a postdoctoral researcher in the UK when a chance encounter with a clinician transformed her career.

While Sarah was researching a protein called SYT1 a clinician, Dr Kate Baker, was treating a child in her clinic with a rare, severe neurodevelopmental disorder. Lucas couldn’t walk, talk or feed himself – and he had a mutation to the very gene Sarah was investigating.

A potent collaboration was forged. Two years later Sarah and Kate published a ground-breaking paper on the disorder - a new form of intellectual disability in children. Late last year the syndrome they discovered was named after them. Few scientists enjoy that honour.

Sarah had been fascinated by SYT1 for many years, passionate about her research drilling down and teasing apart what the protein does in different regions of the brain.

“It’s a multi-faceted protein – it has so many different roles and proposed roles in mediating brain health,” she says.

It is essential for communication between brain cells.

Mutations to the gene encoding the protein can have devastating effects. Symptoms vary but children with Baker-Gordon syndrome typically don’t use speech to communicate, and can suddenly switch from being calm to agitated for no apparent reason. Some are engaged with the world; others can’t recognise their own parents.

Lucas provided the first known SYT1 mutation for the syndrome. Sarah and Kate then identified 10 more families with kids with the condition after clinicians from all over the world read about their work and genetically tested children with similar symptoms.

“My job was to work out how that mutation leads to the dysfunction in brain communication between neurons,” Sarah says.

Using ‘brains in a dish’ she found that the mutations slowed down the ability of neurons to communicate with each other. The mutations causing the biggest slowdown in the model were found in children with the most severe disabilities.

“It’s something I’ve been really passionate about characterising. What happens to these kids is really important to us because we’re the only ones in the world doing this research.”

Excitingly, the researchers found they could ‘speed up’ communication using calcium.

They are now investigating possible treatments involving manipulating calcium and changing the activity of brain cells.

Sarah put a face to the disorder she has so assiduously pursued last year when she invited a Melbourne family into her lab whose daughter had the disease. The experience was profound. “This family appreciated so much that there was someone out there who is actually trying to do something for them.”

Typically, families with a child with the disorder spend vast amounts of time and emotional energy trying to find out what their child has and then trying a battery of treatments.

The knowledge gained will, however, have impact beyond the cases involved, she says.

Sarah, who heads the Presynaptic Physiology laboratory, says she chose the Florey as the best place for her work when she returned from overseas in 2015 and that her research success has benefitted from the diversity in researchers at the institute.

Sarah is also investigating mutations involved in disorders at the other end of the spectrum: diseases where brain cells die later in life such as Parkinson’s and Alzheimer’s disease.

She hopes that her work will one day lead to that other rare distinction for a scientist: finding a treatment that helps these young patients within her own lifetime.

**What is a rare disease?**

A rare disease is any life-threatening or chronically debilitating disorder or condition which, as the name suggests, is uncommon in the general population. They often involve many complex symptoms and as a result, they require a range of specialised treatments.

Worldwide, 6,000 to 8,000 rare diseases have so far been identified, with new disorders diagnosed and described in the medical literature on a weekly basis. A rare disease is a specific, clinically serious disorder affecting fewer than 1 in 2000 people, i.e. less than 0.05% of the population.

Some 80 per cent of rare diseases are genetic in origin, with the age of onset of symptoms ranging from early childhood to adulthood. The diagnosis of a rare disease is often delayed because of their individual small numbers and complex nature.

Funding for medical research into rare diseases is often hard to secure so groups like Rare Voices Australia are important as they advocate for those living with rare disease.

https://www.rarevoices.org.au
Thank you to the Stroke Foundation

Four Florey researchers are set to improve stroke treatment and care thanks to funding in the 2019 Stroke Foundation research grant round.

The Florey thanks the Stroke Foundation for helping us improve care for people who have experienced a stroke. A new funding round provides essential support for four of our talented researchers.

Professor Vincent Thijs, co-head of Stroke at the Florey, will investigate the causes of stroke in younger people in a screening study to take place in four hospitals in Melbourne with stroke patients under the age of 60.

Vincent will carry out this important research after being awarded the first Gavin Paul Bennier Memorial Grant of $240,000 over three years as part of the Stroke Foundation’s 2019 Research Grant Program.

The Gavin Paul Bennier Memorial Grant has been offered on behalf of the Bennier family who established a fund in their son’s honour after he tragically lost his life to a rare form of stroke called Cerebral Amyloid Angiopathy in 2017 at the age of 45. Vincent thanked the Bennier family, supporters of the grant and the Stroke Foundation.

Too often, according to Vincent, stroke goes unexplained in younger people.

“The uncertainty is devastating for the individual and their family because they do not know if a stroke will happen again,” Vincent says.

“I believe my project will provide valuable insights into abnormal blood vessel structure in young people, which may be the cause of more unexplained strokes than we realise.”

Other Florey recipients include Dr Karen Borschmann, who will study rehabilitation services for young stroke survivors and Dr Matthew Pase who will study the role of exercise in stroke recovery as part of Florey neurologist Associate Professor Amy Brodtmann’s ongoing PISCES study.

Karen received the inaugural Tim Glendinning Memorial Grant of $50,000 and Matthew received a $50,000 Stroke Foundation seed grant.

In a ground-breaking study, Matthew will explore whether doctors should prescribe exercise to stroke patients to help with their mental and physical recovery.

It has the potential to pave the way for a larger, more definitive study which could challenge and change current practice.

Positive results could see exercise recognised as a medicine for stroke treatment.

“Research shows, three years after a stroke, 30 per cent of patients experience cognitive decline (thinking and memory impairments) or dementia, but there are no current therapies to prevent it,” Matthew says.

“We know exercise improves physical health, but the benefits are likely to be much broader. It seems like common sense, but it’s a concept that has been neglected in a clinical setting.

“I am thankful for the Stroke Foundation Seed Grant of $50,000 which will help get this important research started. The research would not be possible without it.”

Around 100 stroke patients will be part on the initial study. Some will complete an aerobic exercise program while others will be in a control group involving stretching exercises for two months.

Amanda Thrift said this project has the potential to make a real difference for people with stroke.

"After a stroke, cognitive decline can be an incredibly challenging issue for people. It can impact their independence and ability to live well,” Amanda says.

Currently around 20 strokes a day are impacting Australians of working age. International evidence shows the number of working age people impacted by stroke will increase in the coming years, largely due to lifestyle factors. Effective research takes time, perseverance and a great deal of funding.
Winning Hearts and Minds

The generosity of a great supporter means the Florey will reap benefits from a novel investment concept.

Dr Mark Nelson looks back at his time as a student at the Florey with great fondness. As a student of neuroscience and applied physiology in the 1980s, Mark was overwhelmed to be surrounded by geneticists and other specialists who had been lured to the Florey from Harvard and other renowned research hubs. “It was an enormous privilege to undertake a PhD at the Florey as it was considered to be such a very fine institute,” Mark says.

So when he was offered the irresistible chance to do a Masters of Philosophy in the UK at Cambridge University, it was with some trepidation that the young Florey PhD student went to visit the top brass, the intimidating Director, Professor Derek (Dick) Denton. Mark hoped to receive a leave of absence but had no idea how the idea would be received.

“As a poor student, I tentatively approached the Director’s office. He sat and listened and said nothing. He just listened and listened. Then he said, ‘Hmmm...’. He reached into his desk, pulled out a chequebook and wrote out a cheque for $1000 and said, ‘Here you are. You might find this useful.’”

For a young Mark Nelson, this was a huge sum and the generosity has never been forgotten.

These days, Mark is Chairman of the Caledonia Investments funds management group, a company he co-founded back in 1992 after he left science to chase a world of finance and investment. But his link to Prof Denton has remained strong. Mark is a Florey Governor and was on the board of the Institute from 2001 to 2007.

That $1000 cheque has been paid back to the Florey many thousands of times.

“What goes around comes around and I’ve been very happy to support Dick’s research over the years. The Florey was very good to me so obviously, I’ve been keen to help whenever I can.”

Caledonia is a global investment management firm that aims to achieve high returns over a long-term timeframe. It focuses on deep, fundamental research and high conviction investing.

In an exciting move with long term implications, Mark recently nominated the Florey to receive a share of Caledonia’s management fees through a new company known as Hearts and Minds Investments Limited. Hearts and Minds offers shareholders concentrated portfolios of the highest conviction ideas from leading fund managers, one of which is Caledonia. The donation of fees supports medical research and is designed to encourage the development of medicines and to drive a new generation of medical research in Australia. Every six months, Caledonia will forego their fees, and will instead have them directed to the Florey and the Charlie Teo Foundation.

“Neuroscience is an area that the world really needs to focus on,” Mark says. “Any investor will think very carefully about where they want their money to go. This initiative isn’t a band-aid. This aims at big ideas, at prevention and ways we can have far-reaching effects on human health. It’s almost at the stage that if we don’t fund brain research now and wait 20 years, we’ll look back and think ‘oh, that was a mistake. If only we’d done something at the time’. With our ageing population, we need to act now. The prevalence of neurodegenerative disorders increases with age, and the United Nations tells us that globally there will be 2.1 billion people aged over 60 by 2050.”

“From a commercial perspective, too, you ask, ‘Well, who should I back?’. I’m looking for infrastructure, private benefaction, government support, talented scientists...the Florey has all of that. It’s well worth supporting.”

“The Hearts and Minds initiative shouldn’t fail because it’s a sensible structure, and it attracts investors who are very clear on what we’re trying to do.”

To read about the inspiration behind Hearts and Minds, visit the Sohn Conference Foundation: http://www.heartsandmindsinvestments.com.au/site/content/
The Florey thanks our recent donors who kindly donated $250 or more between 06 September 2018 and 05 March 2019:

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