THE FLOREY ANNUAL REPORT 2013

THE FLOREY
INSTITUTE OF NEUROSCIENCE & MENTAL HEALTH

READ

OUR COVER

Associate Professor Julie Bernhardt's career continues to be recognised with a range of awards, fellowships and publications in the field of stroke rehabilitation. In 2013, Julie, left, not only pursued her research, but mentored several young scientists – men and women. Dr Emma Burrows, centre, from the cognitive neuroscience division, is one such beneficiary of Julie's experience.

Julie's support is mirrored by philanthropists like Ms Naomi Milgrom, right, who has made a significant contribution to the Florey's Women in Science program. Naomi has a long relationship with the Florey, dating back to nearly a decade on the Board and more recently, taking an active interest in the Florey's progress towards a more supportive workplace for women.

OUR MISSION

To improve lives through brain research

OUR VISION

To create significant
knowledge about the brain

OUR VALUES

Generate scientific knowledge
to improve global health

Innovate and problem-solve

Work together with integrity

Share our discoveries with
our supporters and partners

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ABOUT US

The Florey Institute of Neuroscience and Mental Health is one of the largest brain research centres in the world and the biggest in Australia. Our scientists share a common goal – to improve people's lives through brain research and, ultimately, to influence global wellbeing and health economics.

We employ 596 staff and educate approximately 120 post-graduate students each year.

Neuroscience is an area of medical research attracting enormous attention as our understanding of the brain rapidly evolves. Internationally, populations are ageing and there is a sense of urgency to find causes, treatments and cures for conditions affecting the brain and mind. We need to address these conditions to avoid suffering and to contain health-related expenditure.

The Florey is a world-leader in imaging technology, genetics, stroke rehabilitation and epidemiological studies. Mental health research is also a growing focus with psychotic illnesses and neurodegenerative diseases demanding attention.

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WHY DO WE STUDY THE BRAIN?

The human brain — a spongy, 1.5kg mass of tissue — is the most complex living structure. It has the capacity to store more information than a supercomputer and to create a network of connections far superior to any social network. The brain has enabled humans to achieve breathtaking milestones — exploring the solar system, mapping the human genome and composing masterpieces of art, literature, and music.

Scientists still have not uncovered the full extent of what the brain can do. This single organ controls every aspect of our lives, ranging from heart rate and appetite to emotion and memory. The brain controls the immune system's response to disease and determines, in part, how well people respond to medical treatments. It shapes our thoughts, beliefs, dreams and imagination.

Neuroscientists specialise in the study of the brain and the nervous system. We are inspired to decipher the brain's command over all its diverse functions. In the last 30 years, the neuroscience field has made enormous progress. We continue to strive for a deeper understanding of how the brain's 100 billion nerve cells are born, grow, and connect. We study how these cells organise themselves into effective, functional circuits that usually remain in working order for life.

Brain researchers are motivated to understand behaviour. How do cell circuits enable us to read and speak? How and why do we form relationships? How do we think, remember, despair, or motivate? We are discovering possible causes of devastating disorders of the brain and body, as well as ways to prevent or cure them. We strive to understand how the world around us works.

Adapted from a piece written by the Society for Neuroscience.

FLOREY IN A FLASH

596 STAFF AND STUDENTS

177 HONORARIES

117 PHD STUDENTS

126 TOTAL STUDENTS

63 FLOREY FACULTY

554 SCIENTIFIC AND TECHNICAL SUPPORT STAFF

1390 ALUMNI

24
Countries represented by our staff and students

538
Papers, chapters, books edited and abstracts in 2013

2823
Scientific publications published over 10 years

349 SCIENTIFIC PAPERS
Scientific papers published in 2013

63,538 CUMULATIVE CITATIONS
Cumulative citations of scientific publications over 10 years

22.51 AVERAGE CITATION
Average citation over 10 years

100
H-index

1.62 AVERAGE CITATIONS
Average citations per item 2013

564
Citations cumulative 2013

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CHAIRMAN'S & DIRECTOR'S REPORT

Report from the Chairman of the Board, Mr Harold Mitchell AC, and the Scientific Director, Professor Geoffrey Donnan

Chairman's & Director's Report

As the Florey Institute of Neuroscience and Mental Health celebrates its 50th anniversary, we have been reflecting on our achievements and also looking forward to a new era in medical research. The Florey has evolved to become part of a sector that is a world-class asset to Australia's economy, delivering significant dividends through highly successful academic activity and biotech ingenuity.

The Florey's work directly benefits the health of Australians. In fact, research conducted during 2013 has had an international impact, by influencing the way people are treated within hours of a stroke as well as encouraging changes in rehabilitation practice to ensure the damaged brain's plasticity is given the very best chance to make new connections. These are just two of the significant pieces of work you will read about in this report.

Within the next five years, investment in translational research into chronic neurological diseases and mental health will be critical to prevent an unprecedented health care crisis. By 2020, 5.5 million baby boomers (20% of current workers) will be leaving the workforce. Longer life expectancy means there will be an increase in the incidence of chronic diseases of brain and mind (stroke, dementia and mental illness) and associated disability in this population. Health care costs are projected to double by 2050.

What we need to avert this crisis is a coordinated frontier program of research focused on translation that changes clinical practice in the treatment of chronic neurological diseases and mental illness. Florey researchers are focussed on the role they will play in helping to maintain healthy brains from adolescence through full maturity and ageing. Our work will contribute to the nation's need for a productive, engaged population with high levels of workforce participation throughout life.

With imaging and genetics now providing fundamental insights to modern medicine, the Florey is beautifully positioned to confront these future health challenges, led by extraordinary scientific leaders.

Today the Florey accommodates 600 people, including more than 120 students, and we work with neuroscientists from 34 countries. We plan to grow even more in the next few years and to collaborate with an even wider range of partners.

During 2013, the Florey joined with the Australian Football League to use our sophisticated imaging equipment to assess the long-term impact of concussion on football players. Professor Graeme Jackson, neurologist and senior deputy director of the Florey, is keen to create a Centre of Research Excellence, bringing key researchers together so that athletes – from little six-year old contenders through to professional players – are offered the best advice to stay safe when competing.

Professor Jackson and his team also refined imaging techniques that not only identify types of epilepsy but help neurosurgeons operate with greater accuracy.

Professor Ingrid Scheffer continued in her extraordinary quest to identify the genes responsible for a range of serious childhood epilepsies, winning a major award on the way.

Our Alzheimer's researchers have contributed to a major advance: we are close to being able to provide a blood test that will identify biological markers associated with the toxic protein called amyloid beta. It could help identify those at risk of dementia

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Chairman's & Director's Report

up to 17 years before symptoms appear, along with scanning and cognitive testing. This opens the way for therapies which may delay disease progression.

Other researchers have undertaken ground-breaking science in so many areas, covering myriad diseases and conditions. Dr Tim Aumann and his colleagues have been analysing human brain specimens from Scotland to assess whether there is a link between levels of dopamine and exposure to light. This work will enhance our understanding of Parkinson's disease, depression, schizophrenia, addiction and seasonal affective disorder. Professor Colin Masters and colleagues published on the relationship between dementia and anaemia. Professor Andrew Lawrence and his team reported new findings into current alcoholism treatments that suggest expensive pharmeceuticals could potentially be replaced by a simple calcium supplement.

We have recruited some great talent including Dr Jess Nithianantharajah (returning from Edinburgh) and Dr Lucy Palmer (joining us from Switzerland). Both have been attracted to Melbourne by the Florey's facilities and talented leaders in their fields.

We continue to build our equipment capabilities. Sophisticated microscopy services and a new mass spectrometer are now operating, providing the ability to image cells and their connections in 3D in living brains, and analyse the precise composition of molecules that are present in healthy and diseased brains, respectively. Along with the University of Melbourne, we have taken delivery of the most powerful magnetic resonance imaging machine in the southern hemisphere which will offer unprecedented clarity when imaging the brain.

While taxpayer-funding remains our main source of revenue through competitive grants won from the National Health and Medical Research Council, we never forget the importance of other sources of support. Patient advocacy organisations, institutional philanthropic trusts and foundations and private philanthropists provide significant support when government funding is static.

We were proud to be included in the book Top 50 Philanthropic Gifts which celebrates major donations that have had the greatest impact on the Australian population. With such overwhelming approbation for our mission by the Australian and international community, we believe the Florey has had, and will continue to have, an important role to play in human health.

As governments wrestle with the age-related health crisis coming our way, there has never been a more important time to invest in medical research.

Mr Harold Mitchell AC, Chairman

Professor Geoffrey Donnan AO, Scientific Director

CHIEF OPERATING OFFICER'S REPORT

Report from the Chief Operating Officer, Gary Gray

The Florey is an amalgamation of four subsidiaries united in a quest for scientific discovery and translation relating to neuroscience and mental health. Its focus is upon diseases which have a substantial and increasing impact upon mortality and morbidity on our own life experiences and those of our family and friends. It is a high order priority for us all. Clearly there is an expectation that government will contribute towards scientific research. And in return, there is the very reasonable expectation that we use taxpayers' funds carefully. Management understands the absolute imperative to ensure financial sustainability.

Not surprisingly, management effort is on maximising income and minimising costs within a structural context for the future.

During the year the Board resolved to eventually collapse the subsidiary structure. A commitment to financial sustainability is the framework for management decision-making and assessment. There has been an impact upon consolidation of building stock, application of resources, enterprise bargaining, branding, and company structure to name a few. The Florey is now accelerating as a single management entity.

Back in 2012, the Florey was operating from five sites. The Florey subsequently vacated the Alan Gilbert Building, substantially vacated Oak Street, and consolidated staff and services from these premises into the Howard Florey Laboratories. By doing this, we have been able to significantly reduce outgoing costs and focus our resources on scientific output at our main three sites.

An exemption from reporting at the subsidiary level to the Australian Securities and Investment Commission was obtained during the year. Concurrently, the process of closing down subsidiaries and associated companies has been initiated. Forty to 50 per cent of all financial transactions within the Florey were attributable to reporting at the subsidiary level. There was a sizeable focus for the finance team upon external compliance at the expense of supporting internal users. This will change during 2014 with supporting software already secured.

In this, the Florey's fiftieth year, a new brand identity was approved which further enhances the Florey's image as a Melbourne institution. Complimentary measures included the formal adoption of a Foundation Council Charter, adoption of a branding strategy and a new web site with significant input from internal stakeholders. The new web site will be launched during 2014.

Comprehensive business plans were developed late 2012 and implemented 2013. They focused upon consolidation of human resource services, finance (including procurement and payroll), information and technology, and marketing and fundraising. Most of the set tasks have been achieved under the leadership of the respective manager with engagement of their staff. They have done a great job. Moving from four independent institutes to amalgamation and now merger is a challenge and experience for most. Together we have supported a new direction while improving outcomes and reducing costs of compliance and other overheads. Management's journey is similar to that of the science. It is ongoing.

Mr Gary Gray, Chief Operating Officer

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REPAIRING A VULNERABLE BRAIN

Photo credit: James Braund, NHMRC.

Professor Seong-Seng Tan

Repairing a vulnerable brain

Professor Seong-Seng Tan and his team were recognised in *Ten of the Best Research Projects 2013* which describes ten Australian health and medical research projects chosen from among the thousands of NHMRC funded medical research projects underway in Australia today.

The book showcases talented researchers who seek to uncover new discoveries that help prevent, treat and cure Australians' health.

While there is currently no effective treatment for brain injury, the brain is armed with some very impressive defence strategies.

The brain can defend itself against dying. Finding out how it does this and exploiting this for treatment is a serious unmet need. Since 1957, more than 1000 drugs have been trialled but none have been effective.

When the brain is injured, such as in an accident or in stroke, the site of the injury is not recoverable due to damage from bleeding and swelling. However, what is not commonly known is that a large number of healthy cells surrounding the injury also die because of signals coming from damaged cells.

This wave of cell death occurs over a few days, providing a small window of opportunity for treatment.

When Professor Seong-Seng Tan and his team looked into healthy brain cells for evidence of protective signals, they discovered a survival protein called Ndfip1.

Ndfip1 behaves like a barcoding tool. By putting a mark on harmful proteins that are produced during injury, these proteins can be recognised by the waste disposal system in the brain cell and removed. It can also regulate other survival proteins.

"When we removed Ndfip1 from healthy brain cells, the cells suffered greater injuries compared to brain cells where the protein was not removed. This showed that Ndfip1 played an important role in cell survival," Seong-Seng says.

The team looked at brain cells damaged following road trauma. Ndfip1 levels were massively increased, showing the traumatised cells had initiated a response to try to protect against the injury.

Seong-Seng and his team's discovery is a world first.

"We have discovered how the brain protects itself by identifying the actual mechanisms involved. Understanding these mechanisms will help us design exciting new drug therapies that will hopefully help people in the first critical hours after stroke or brain injury."

"Even by halving the number of brain cells that normally die after injury, and preserving what is left behind after injury or stroke, we will provide the patient with a stronger foundation for recovery and less functional loss."

NEXT STEPS

Professor Tan and his team are now working on practical therapies to prevent brain cell death following injury, including a compound that will increase Ndfip1.

If methods can make bystander brain cells stronger following injury, there is a strong potential for reducing the number of brain cells that die following trauma or stroke.

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TAKING CARE OF BUSINESS

Dr Henry De Aizpurua

Taking care of business

The Florey's commercial activities have continued to develop during the past year in a number of important discovery and clinical areas. Continued success in partnering our research and clinical discoveries has resulted in significant revenues for our research groups to help them take basic research work from the preclinical discovery stages to investable commercial opportunities.

Relaxin commercial opportunities

Florey's commercial partner, the global pharmaceutical company Novartis, has revealed a successful phase III multi centre trial for relaxin in acute heart failure. This represents a wonderful outcome for a unique Florey discovery and promises to be of enormous benefit to patients suffering from this brutal disease for which there is currently no treatment. The company is currently progressing regulatory approvals for relaxin in the USA and Europe. The Florey stands to benefit from commercial revenues that will be ploughed back into research.

Florey spin outs

NeuProtect Pty Ltd was established by the Florey with investment by Starfish Ventures. The key technologies have proceeded successfully through several preclinical funding rounds and a robust data pack and intellectual property portfolio established. Recent investment by MedImmune LLc (a wholly owned subsidiary of Astra Zeneca) has provided impetus for additional work and the move into phase I clinical trials. The Florey continues to work closely with NeuProtect to move the proprietary technologies through the development phases to increase the value of the company.

Global Kinetics Corporation (GKC) continues from strength to strength as it seeks to develop and commercialise a novel device for Parkinson's Disease management. Investment from a range of parties including the Medical Research Commercialisation Fund has been pivotal in the spectacular progress that the company has enjoyed to date.

Identifying, protecting and exploiting intellectual property

The Florey has a continuing track record of working with our senior faculty to ensure that every research theme is assisted in identifying core intellectual assets. During the year Florey filed three new provisional patents and saw three other fully granted in international jurisdictions. The institute has some level of commercial interaction for every division reflecting the commitment to the translation of our work from basic discovery, through clinical investigation and into new medicines and treatments for the general public.

Engaging the next generation

The Florey along with several other institutes and agencies is a partner in the State government funded program "Molecules to Medicines". This novel initiative seeks to engage young investigators in the activities of commercialising research outcomes. Through a series of syndicate work and seminars as well as practical hands on projects, participants are exposed to all facets of this area. The intent is to form a more rounded graduate or postdoc who can bring new perspectives to their research work.

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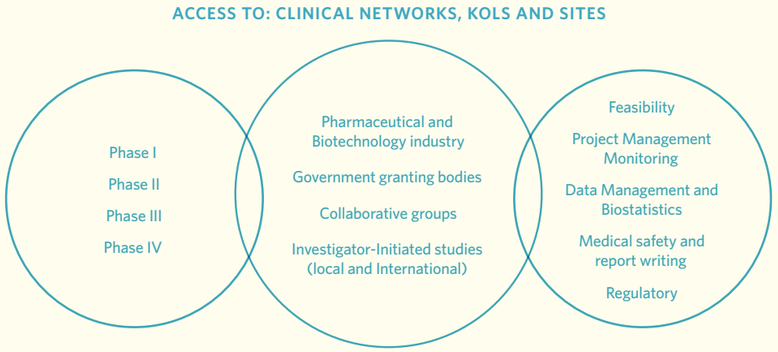
NEUROSCIENCE TRIALS AUSTRALIA



Key services provided by Neurosciences Trials Australia to various stakeholders.

Neuroscience Trials Australia is a niche, not-for-profit, contract research organisation within The Florey Institute of Neuroscience and Mental Health. It offers an Australian approach to global clients seeking economical, smart and timely neuroscientific clinical research.

Neuroscience Trials Australia is co-chaired by two of Australia's most experienced clinicians and medical researchers, Professors Geoffrey Donnan and Stephen Davis. The General Manager, Dr Tina Soulis, oversees all personnel and projects as well as driving business objectives.

The team's areas of expertise include stroke and stroke-related conditions, multiple sclerosis, epilepsy, Parkinson's disease, spinal cord injuries, Huntington's disease, neurosurgery, pain, neuromuscular disease, mental illness and migraine. They have strategic alliances with many therapeutic disease groups and can provide access to key opinion leaders, sites and clinical trial expertise through a range of tailored services. Staff have global management experience in all phases (I to IV), of clinical research.

The services provided include study feasibility, project management, monitoring of studies to global regulatory standards, safety reporting throughout the clinical trial, data management and biostatistics and report writing. The relationship with services provided and key stakeholders are outlines in the diagram below. Key services provided by Neurosciences Trials Australia to various stakeholders

The division continues to expand and has a healthy pipeline of new and ongoing projects with multiple trials in various neuroscience therapeutic areas being conducted at any one time. These projects consist of investigator initiated studies as well as those initiated by commercial interests.

Outlined, below, are examples of the many new projects underway.

Mechanically retrieving clots that occur during strokes: the EXTEND-IA study

Stroke is Australia's second biggest killer after coronary heart disease and a leading cause of disability. According to the National Stroke Foundation, 1 in 6 people will have a stroke in their lifetime. The total financial costs of stroke in Australia are estimated to be $5 billion (2012 figures).

Many of the projects we undertake at Neuroscience Trials Australia are assessing new ways of treating strokes and their effects. Our trials involve developing new drug treatments as well as new devices.

A stroke occurs when a clot blocks one of the blood vessels to the brain. This causes poor blood supply and lack of oxygen to the brain tissue. If blood supply is not restored to the brain there is permanent brain damage. Currently there is only one treatment for stroke caused by a blocked blood vessel. This treatment is a medicine called tissue plasminogen activator (t-PA). t-PA works by dissolving the clot that is blocking blood supply to part of the brain and has been proven to reduce disability after stroke. However, tPA does not always succeed in opening the blocked artery. tPA should be given within the first 4.5 hours after stroke.

The aim the EXTEND-IA study is to test whether mechanical clot retrieval (using a device called Solitaire) after standard intravenous tPA is more effective in opening the blocked blood vessel and improving recovery from stroke than just tPA alone.

This cutting edge multi-centre study is examining the effectiveness of one of the latest clot retrieval devices available globally, the Solitaire FR clot retrieval device.

There are currently 14 sites participating in this pivotal trial in Australia & New Zealand. There have been more than 48 participants recruited to date, and the target sample size is 100 participants.

Neuroscience Trials Australia is the program manager and is responsible for setting up the project, the data management systems and project management.

Stopping bleeding during stroke: the STOP-AUST study

Some types of strokes involve bleeding in the brain. This is called an intracerebral haemorrhage and can be seen on brain scans as a spot. Growth of the haemorrhage is common. It is known to be harmful because it increases mental and physical disability and the chances of death.

There are currently no known effective medications to reduce or prevent haemorrhage growth.

Tranexamic acid is a medication that is known to reduce bleeding in other diseases and therefore it is thought that it may reduce bleeding also in intracerebral haemorrhage.

Although tranexamic acid is approved by the Therapeutic Goods Administration of Australia to reduce blood loss and the need to give extra blood in patients undergoing heart or joint surgery, it is not approved to treat intracerebral haemorrhage.

The purpose of this research project is to evaluate if the medication tranexamic acid reduces the growth of intracerebral haemorrhage.

The project is an international collaboration, with approximately 15 centres in Australia and Finland currently participating. Ten participants are currently enrolled.

Neuroscience Trials Australia is the program manager and is responsible for setting up the project, project and data management systems as well as sourcing and labelling of the study drug.

Making spinal cord injury less traumatic: the ICED (Immediate Cooling and Emergency Decompression) pilot, safety and feasibility studies

Neuroscience Trials Australia is fortunate to play a leading role in this ground breaking set of studies. Our team are involved in setting up project and data management of a unique program which aims to address and change the way that patients who have a spinal cord injury are treated. The main focus of the project is to offer urgent decompression of the injury as close as possible to the time of occurrence.

General manager, Neuroscience Trials Australia, Dr Tina Soulis.

The main causes of traumatic spinal cord injuries (SCI) are road trauma, falls and water related accidents with most spinal cord injuries occurring to men under the age of 35. This type of injury, impacts the majority people at the prime of their lives and it is thought that Australia alone currently has 10,000 people living with spinal cord injury.

The total cost of spinal cord injury in Australia is estimated to be $2 billion annually which includes costs to patients and their families. If just 10% of carers were able to return to the workforce because their family member with a disability had appropriate personal support, there would be a $3 billion boost into the economy.

Even more disheartening, physical injury to the spinal cord results not just from the initial impact, but also from compression of the spinal cord as a consequence of the displaced vertebra.

To date, animal and preliminary human data demonstrate that urgent relief of this compression appears to greatly improve outcome. Urgent decompression in humans is often very difficult to achieve because of logistical difficulties.

Current global data has shown that immediate cooling of the spinal cord as soon as possible after an injury has taken place, can suspend the progressive damage caused. This allows decompressive surgery to be performed in a clinically achievable time frame.

A multicentre clinical trial of immediate cooling followed by emergency decompression (ICED) in patients with spinal cord injuries is being planned. The work currently underway aims at conducting the pilot, safety and feasibility studies necessary before commencing the main trial.

This set of studies aims at addressing how we can effectively stream line the treatment of spinal cord injury to include the complete set of health professionals from paramedics, surgeons and neurologists in a timely and sustainable way.

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NEUROSCIENCE FOR THE NEXT GENERATION

The Florey has a number of initiatives to raise awareness of the brain in the younger generation. Our outreach programs allow neuroscientists to share their experiences with secondary school students and teachers to convey an understanding of why brain research is vital for our community. This opportunity also allows us to showcase how neuroscience research is multidisciplinary in nature and we encourage students to see the wider application of their science subjects. The "THINK ABOUT IT" program was again a success and 40 Florey researchers visited 21 schools and more than 1000 students around Melbourne.

This year saw the commencement of a new collaboration between the Florey and the Gene Technology Access Centre (GTAC). What started as an idea in a discussion between Dr Joanne Britto (Florey Research Fellow) and Jacinta Duncan (Director of GTAC) is now a reality. *Making Connections: neuroscience illuminating the pathways affecting our behaviour and health* is a day-long event where Year 10 and 11 students get hands-on laboratory experience and a tour of the Florey. This was initially designed to be a single annual event during Brain Awareness Week. Due to an overwhelming number of schools wanting to participate, Making Connections will now be run for an additional three days during Education Week and over 400 students and teachers will come to visit the Florey.

The Florey continues to support the Australian Brain Bee Challenge, which is the science equivalent of the spelling bee competition. This year, the finalists were offered a chance for work experience at the Florey and Malini Sivasaththivel and Tracy Doan from The Mac. Robertson Girls' High School welcomed the opportunity. When asked to write about their experience, Tracy wrote "I find that this constant curiosity and passion to learn is truly inspirational, and to see first-hand the commitment of scientists towards their research has led me to see science as a possible career path." This is precisely the reason we continue to place importance on our outreach programs. Thank you to all the scientists who have shared their knowledge and passion with school children this year.

For more information, or to get your school involved, contact schooloutreach@florey.edu.au

Pictured: Mac.Rob student, Tracy Doan and Florey Fellow, Dr Joanne Britto in the lab with Mac.Rob science coordinator, Joey Micallef.

FOUNDATION COUNCIL CHAIRMAN'S REPORT

Report from the Foundation Council Chairman, Trevor Clark OAM

Philanthropy plays a very important part in the life of the Florey. In fact, the Florey owes its existence to two great philanthropists, Sir Ian Potter and Ken Myer. Fifty years ago these two men, inspired by our founding Director Professor Derek Denton, were instrumental in funding and equipping the original Florey. Their families have continued that support to this day.

In 2013 the Foundation raised more than $3.888 million in donations from individuals, community groups, philanthropic trusts, foundations, bequests and from fundraising activities including events and appeals. We are indebted to everyone who has so generously supported our research.

Philanthropic funding is crucial, enabling us to provide our scientists with the latest technologies available, to recruit the best and brightest scientists and to support young emerging scientists. Most importantly, this munificence directly improves the lives of people suffering from illnesses affecting the brain and mind such as Alzheimer's and Parkinson's disease, stroke, depression, schizophrenia, bipolar disorder, epilepsy and multiple sclerosis.

In 2012 the Florey Foundation and its Council were re-formed following the merger of the Florey Neuroscience Institutes and the Mental Health Research Institute. The Council is comprised of myself as Chairman; Julian Clarke, Graeme Kelly, Ross Oakley and Stephen Spargo. Ex officio members are Geoff Donnan, Gary Gray and Ross Johnstone.

I am very grateful for the work being done by Council members who are actively developing several new initiatives to raise significant additional funds to support research at the Florey.

Mr Ross Oakley, Mr Graeme Kelly, Mr Ross Johnstone, Mr Trevor Clark, Mr Gary Gray, Mr Stephen Spargo. (Missing Professor Geoff Donnan and Mr Julian Clarke)

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COMMUNITY SUPPORT

We are fortunate to receive support from many groups and individuals in the community. Some inspiring individual examples include:

- Matt Harry who turned a lifetime ambition into a fundraiser. Matt swam the English Channel and asked family, friends and colleagues to sponsor his swim. His employer, Western Union, was so impressed with his effort they matched the funds he raised. Matt directed his support to research into depression and anxiety.
- Long term supporter Enid Telford's husband Kel died several years ago after a battle with Alzheimer's disease. Kel had a great love of photography and verse so Enid and her daughter Sue decided to make and sell cards as a way of keeping his memory alive. Enid's home is now a cottage industry where the cards are conceived and made. The pair sell the cards at local markets and fairs, with the funds raised supporting Alzheimer's disease research at Florey.
- Tim Blashki is a retired psychoanalyst and psychotherapist, and is also a gifted artist. When planning his first solo exhibition "Beyond Words" he very generously decided to donate the proceeds from sales of his art work to support research into Parkinson's disease at the Florey in memory of his late brother. We look forward to having some of Tim's work hanging in our Parkville building.

Member of the Florey's Foundation Council, Mr Julian Clarke.

In addition to these individuals, it is important to also recognise the wonderful ongoing support we receive from voluntary groups in the community such as One in Five, River's Gift and Charityworks for MS, all of whom work tirelessly to raise funds to support our research. These organisations are often inspired by a family having direct experience of an illness that we are researching. Their support connects us with families living with a relative with a brain disease and brings home to us the great need to better understand the human brain and to use this knowledge to develop effective treatments. Their efforts, along with all our other supporters, provide great encouragement to our researchers.

COMMUNICATING WITH OUR SUPPORTERS

The public affairs office shared the Florey's many achievements through the media and a range of publications, seminars and tours.

The Director, Professor Geoff Donnan, was very active in the media, demonstrating the enormous value provided by the medical research sector to reduce the burden on the nation's health and budgets. Prof Donnan also reinforced the findings of the Strategic Review of Health and Medical Research, released by Simon McKeon AO in April. Prof Donnan called for an increase in medical research funding, stability in career paths for scientists and the need for a significant increase in infrastructure funding.

International and national media reported on a number of our accomplishments during the year. While we promoted our own work, our scientists as respected experts were also contacted regularly by the media for comment.

Media highlights included:

- The Australian Football League and the Florey's collaborative partnership for scientific research into concussion and mild traumatic brain injury. Our neurologists will conduct imaging studies on players following a concussion, assessing the long-term impacts.
- The Florey's imaging capability was explained in the Australian Financial Review following the announcement of US President Barack Obama's $100 million Brain Initiative.
- Professor Andrew Lawrence published a thought-provoking paper, revealing the way a major medication for alcoholism works. The drug, acamprosate, belongs to a small but growing group of pharmaceuticals recognised as beneficial in the treatment of alcohol addiction. While scientists have speculated on the way it works, new research reveals the drug's surprisingly simple key to success. Calcium.
- New approaches to post-stroke recovery by the team at our Austin campus were reported. Professor Leeanne Carey's unique approach to helping her research subjects regain a sense of touch received significant attention.
- The Florey's first and very successful crowdfunding campaign attracted enormous interest in print, radio and TV.

BENEFACTORS

Across Australia it has been a year of significant philanthropy with a number of very large gifts from individuals such as Andrew 'Twiggy' Forrest. In fact, philanthropy has always played a big part in developing this country. In our own case, Sir Ian Potter and Ken Myer were instrumental in the establishment of the Florey back in 1963.

We welcome and are thankful for the growing support of overseas organisations like the New York Academy of Sciences, the Alzheimer's Drug Discovery Foundation and the Michael J. Fox Foundation. We are equally grateful for the wonderful support we receive locally and are proud to have been included in the book Top 50 Philanthropic Gifts which celebrates major gifts that have had the greatest impact on the Australian population. That generous individuals and organisations choose to support our work is a great affirmation for our mission "to improve lives through brain research" and a reflection of the enormous impact of brain illnesses in our community.

In closing I would also like to acknowledge the wonderful work being done by the fundraising and marketing team who work tirelessly across a broad suite of activities to raise funds to support our scientists and to provide the community with information about the research we are doing.

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MR HAROLD MITCHELL AC

Chairman

Mr Harold Mitchell is the founder of Mitchell & Partners and until August 2013 was the Executive Chairman of Aegis Media Australia and New Zealand. Mitchell & Partners is the largest media and communication group in Australia, with growing presence in New Zealand and across the Asia-Pacific region.

Mr Mitchell holds a large number of community roles including Chairman of CARE Australia; Chairman of the Melbourne Symphony Orchestra; Chairman of TVS, University of Western Sydney's television service for Greater Sydney; Chairman of Arts Exhibitions Australia; Vice President of Tennis Australia; Director New York Philharmonic, and Director of Crown Ltd.

He has also been Chairman of the National Gallery Australia; President of the Melbourne International Festival of Arts; President of the Museums Board of Victoria and a Board member of the Opera Australia Council.

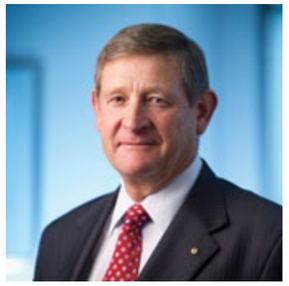
Mr Mitchell was appointed Companion of the Order of Australia in 2010 for eminent service to the community through leadership and philanthropic endeavours in the fields of art, health and education and as a supporter of humanitarian aid in Timor-Leste and Indigenous communities. In 2013 Mr Mitchell was named Victorian of the Year.

BOARD OF DIRECTORS

MR ANDREW ABERCROMBIE

Bec LLb MBA (IMD)

Andrew Abercrombie is the founding Director of FlexiGroup Limited (FXL) and remains on the FlexiGroup Board continuing to work with the CEO and management team. FXL is now a Top 150 company on the ASX. Formerly a commercial lawyer, he oversees a broad range of commercial interests. He is the Regional Chairman of the World Presidents' Organisation and continues to participate in international education programs in various roles. Formerly a member of one of Victoria's Alpine Resort Management Boards, he is also a Director of the Menzies Research Centre, the Melbourne Zoo Foundation and Treasurer of the Liberal Party of Australia (Victorian Division).



PROFESSOR JAMES ANGUS AO

FAA BSc PhD

James Angus is former Dean of the Faculty of Medicine, Dentistry and Health Science at the University of Melbourne. He is also a Fellow and former Member of Council at the Australian Academy of Science. He is currently Professor of Phamacology at the University of Melbourne, a Director of The Peter MacCallum Cancer Institute and Chairs the Victorian Clinical Training Council. Professor Angus is the Vice Chancellor's nominee for appointment in accordance with the Constitution and was previously a non-executive Director of The Mental Health Research Institute (appointed 2003). He was appointed an Officer to The order of Australia in 2010 for distinguished service to biomedical research, particularly in the fields of Pharmacology and cardiovascular disease, as a leading academic and medical educator, and as a contributor to a range of advisory boards and professional organisations both nationally and internationally.

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PROFESSOR GEOFFREY A DONNAN AO

Florey Director
MBBS MD FRACP FRCP (Edin)

Director of The Florey Institute of Neuroscience and Mental Health, Professor Geoffrey Donnan was previously Director of the National Stroke Research Institute and subsequently the Florey Neuroscience Institutes. He is also Professor of Neurology at the University of Melbourne. His research interest is clinical stroke management and he was co-founder of the Australian Stroke Trials Network. He is Past-President of the World Stroke Organisation. He received the American Stroke Association William Feinberg Award for Excellence in Clinical Stroke Research in 2007, the Swedish Karolinska Institute Award for Excellence in Stroke Research and the World Stroke Organization Leadership in Stroke Medicine Award in 2012 and the European Stroke Congress Wepfer Award for stroke research in 2014.

MR CRAIG DRUMMOND

B.Comm (Melb) ACA SFFIN

Craig joined the National Australia Bank in October 2013 as Group Executive, Finance & Strategy and was previously Chief Executive Officer and Country Head of Bank of America Merrill Lynch Australia. Prior to that, Craig joined Goldman Sachs JB Were in 1986 and held various roles including Chief Operating Officer, Chief Executive Officer and Executive Chairman. Craig is a Director of The Geelong Football Club, a Senior Fellow of FINSIA and is a Chartered Accountant.

MR ROB GERRAND

BA, FAICD

Mr Gerrand is Chairman of Healthy Parks People Global Ltd, a Director of Inner North West Melbourne Medicare Local, the Dax Centre and is an AICD Director Nexus Chairman. He heads the marketing and communications consultancy Gerrand & Associates, is a consulting partner with SenateSHJ and was General Manager of Group Public Affairs at ANZ Bank. Previous board appointments include Chairman of Parks Victoria and Director of Alfred Health, the Financial Planning Association of Australia, the Koorie Heritage Trust and the Melbourne Convention and Marketing Bureau. He was the Founding President of the Monash Alumni Association, and in 1994 was appointed Adjunct Professor at Deakin University. He is also a published author.

EMERITUS PROFESSOR ANDREA HULL AO

BA Dip Ed (Univ of Sydney)
MBA (MBS, Univ of Melb) FAICD FAIM

Professor Andrea Hull has had a distinguished career in CEO and executive roles, and also as a non-executive Board member in government and not-for-profit organisations. She is an Emeritus Professor at the University of Melbourne, and is the Deputy Chair of the National Museum of Australia and the Breast Cancer Network of Australia. She is also a Board member of The Melbourne Forum, and The Melbourne Prize. Professor Hull has undertaken numerous international and national assignments, and served on many international, federal and state bodies to advance the integration of economic, social and cultural agendas.

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PROFESSOR GRAEME JACKSON

Florey Deputy Director
(Resigned 31 December 2013)
BSc (Hons) MBBS MD FRACP

Professor Graeme Jackson is the Deputy Director of the Florey, a practising clinical neurologist specializing in epilepsy at the Austin Hospital and a Professorial Fellow of the University of Melbourne. He is recognised as an expert and world authority in understanding brain function and structure using new MR technologies, particularly as they apply to understanding and treating epilepsy. The National Health and Medical Research Council of Australia (NHMRC) awarded him the prestigious Outstanding Achievement Award for research excellence in 2008.

PROFESSOR ANNE KELSO AO

BSc (Hons) Ph D (Melb)

Professor Anne Kelso is Director of the WHO Collaborating Centre for Reference and Research on Influenza at Melbourne Health. She is also an honorary professorial fellow at the University of Melbourne where she undertakes research on immunity to influenza. She is currently a member of the Council of the National Health and Medical Research Council (NHMRC), the Board of the Telethon Institute for Child Health Research and the Board of Trustees of the International Society for Influenza and Other Respiratory Virus Diseases, and a number of committees advising the WHO and the Australian Government on influenza.

BOARD OF DIRECTORS

MR MARK JONES

BA (Hons) (Sheff) MBA (MBS)

Mr Mark Jones is the Ethics and Independence Partner and the Chief Operating Officer of the Risk Management Group at KPMG. He also provides professional services in the areas of corporate governance and internal audit. Mr Jones is a Fellow of both the Institute of Chartered Accountants in England and Wales and the Institute of Chartered Accountants in Australia, and is a member of both CPA Australia and the Australian Institute of Company Directors.

MRS JENNIFER LABOURNE

BBus, FCPA

Jennifer Labourne is the Director of Finance & Business Services at Colac Area Health. She was previously a partner at Ernst & Young, Deputy Chair of Health Purchasing Victoria, Director of Parks Victoria and has been involved on various committees of the Australian Society of Certified Practicing Accountants (CPA).

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PROFESSOR COLIN MASTERS

Florey Deputy Director
BMedSc (Hons) MBBS MD Hon DLitt WAust,
FRCPath FRCPA FAA FTSE

Professor Colin Masters is a Laureate Professor at the University of Melbourne and a former Director of Prana Biotechnology Limited. He is one of the world's best known authorities on Alzheimer's disease.

MR STEPHEN SPARGO

LLB LLM

Mr Stephen Spargo is a Partner practising in the financial services and projects department of Allens. He is a director of Asia Society Australasia Centre, Chairman of The Royal Agricultural Society of Victoria Limited, a Vice-President of the Melbourne Cricket Club and a director of the Committee for the Economic Development of Australia.

BOARD OF DIRECTORS

DR BRENDAN MURPHY

MBBS PhD FRACP FAICD

Dr Brendan Murphy was appointed Chief Executive Officer of Austin Health in January 2005. Prior to that he was Professor/ Director of Nephrology and Chief Medical Officer at St.Vincent's Health. He is currently a member of the Board of Health Workforce Australia and a Professorial Fellow with the title of Professor at Melbourne University.

MR ANDREW STRIPP

MSc (Clinical Psychol) BBSc (Hons)

Andrew Stripp is the Deputy Chief Executive Officer and Chief Operating Officer at Alfred Health where he has worked for 10 years in various roles. He has worked across various settings in the health sector and Victorian State Government including Director Mental Health and has undertaken service and strategic reviews for a range of organizations across Australia.

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“I will do everything I can to help the researchers at the Florey. My wife has frontotemporal dementia. If I can help by participating in an early detection study, of course I will.”

Noel Parkin, one of 1100 people in the Australian Imaging Biomarker and Lifestyle Study of Ageing.

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DR AMY BRODTMANN

Behavioural Neuroscience

Dr Amy Brodtmann is Co-Division Head of Behavioural Neuroscience, consultant neurologist at Austin Health and Director of the Eastern Cognitive Disorders clinic, Eastern Health, Box Hill Hospital. She is a past recipient of a National Health and Medical Research Council Australian Training Research Fellowship, and previous National Brain School Co-ordinator for the Australian and New Zealand Association of Neurologists. She sits on the editorial board of Neurology, the research board of Alzheimer's Australia Victoria, and is the founding director of the Australian Frontotemporal Dementia Association. Her research focuses on imaging correlates of cognitive decline in stroke, the neural basis of neglect, and the diagnosis and management of focal onset dementias.

PROFESSOR ANDREW LAWRENCE

Behavioural Neuroscience

Professor Lawrence is the Co-Division Head of Behavioural Neuroscience, running the Addiction Neuroscience laboratory. His primary research interest is in the development of robust animal models of drug-seeking, drug-taking and drug-induced neural adaptation. In addition, his group uses these models to define new potential therapeutic targets for drug and alcohol abuse disorders. He has published over 180 original articles and reviews. Professor Lawrence is currently Senior Editor of The British Journal of Pharmacology and also sits on the editorial boards of Neurochemical Research, the Journal of Pharmacological Sciences & Addiction Biology. In 2009, Professor Lawrence was awarded the Australian Neuroscience Society medallion for services to the society. In his spare time, Andrew is a keen cyclist and a surf life guard.

DIVISION HEADS

PROFESSOR SEONG-SENG TAN

Brain Development and Regeneration

Professor Tan is the Head of the Division of Brain Development and Regeneration, NH&MRC Senior Principal Research Fellow, and Adjunct Professor at the Melbourne Neuroscience at The University of Melbourne, and University of Queensland Brain Institute. He is interested in understanding how the brain is assembled during development, and what mechanisms protect brain cells from death following brain injury such as trauma and stroke. Professor Tan has published over 100 papers and was awarded the Amgen Australia Medical Research Award (1997). He is on the Editorial Boards of the Journal of Neuroscience (USA) and Experimental Neurology. Professor Tan is a keen swimmer and a member of the Brighton Icebergers.

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PROFESSOR GRAEME JACKSON

Epilepsy and Imaging

Professor Graeme Jackson is the Deputy Director of the Florey, a practising clinical neurologist specialising in epilepsy at the Austin Hospital, and a Professorial Fellow of the University of Melbourne. He is recognised as an expert and world authority in understanding brain function and structure using new MR technologies, particularly as they apply to understanding and treating epilepsy. The National Health and Medical Research Council of Australia (NHMRC) awarded him the prestigious Outstanding Achievement Award for research excellence in 2008.

PROFESSOR ALAN CONNELLY

Imaging

Professor Alan Connelly is an NHMRC Principal Research Fellow. He is the Co-Division Head of the Imaging Division, and Head of the Advanced MRI Development group. He also heads the MRI imaging Facility at the Florey Austin (including two research-only 3T MRI scanners) and the Florey Parkville Small Animal Imaging Facility. Prof Connelly is a development MRI physicist whose work has encompassed a range of MR methods, with current focus primarily on diffusion and perfusion MRI and their application to the investigation of epilepsy, stroke, and cognitive function. His group is internationally recognised as leaders in the field of diffusion MRI fibre tractography, and has developed novel methods to characterise the complex white matter fibre connections in the brain. He has published widely in magnetic resonance, general scientific, and neuroscientific journals, and is a member of the editorial board of Epilepsia.

DIVISION HEADS

ASSOCIATE PROFESSOR STEVEN PETROU

Epilepsy

Associate Professor Petrou is the Co-Division Head of the Division of Epilepsy, and heads the Laboratory of Ion Channels and Human Disease, a multidisciplinary team of researchers with a focus on revealing fundamental mechanisms of disease genesis in the central nervous system. Current major areas of investigation centre on the development and characterisation of genetically engineered mouse models for the study of human familial epilepsy. He works closely with industry and has several patents for his discoveries. In addition, he is the Deputy Director of the Centre for Neural Engineering at University of Melbourne, serves on the editorial board of the Journal Neurobiology of Disease and the Basic Science Committee for the International League Against Epilepsy and is Editor of the Australian and New Zealand Society for Neuroscience.

LAUREATE PROFESSOR COLIN MASTERS

Mental Health

Professor Colin Masters is the Head of the Division of Mental Health, a Fellow of the Royal College of Pathologists, the Royal Australian College of Pathologists and the Australian Academy of Science.

Professor Masters is a world leader in Alzheimer's disease research. His research helped to isolate and characterise elements of the primary pathway causing Alzheimer's disease. This discovery has been important in defining the mechanisms that contribute to the nerve cell degeneration which is the main feature of Alzheimer's disease. His findings are now the subject of intense world-wide research for diagnosis and drug discovery.

Professor Masters has also won many national and international prizes and awards.

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PROFESSOR TREVOR KILPATRICK

Multiple Sclerosis

Professor Trevor Kilpatrick leads the MS Division at the Florey and is a neurologist and Head of the MS Unit at the Royal Melbourne Hospital, in addition to being Director of the Melbourne Neuroscience at The University of Melbourne. His research interests include the neurobiology of multiple sclerosis, neural precursor cell biology and the study of genetic and environmental factors that contribute to MS as well as the translation of basic research discoveries to the clinic.

Professor Kilpatrick has been the recipient of the Sunderland Award, AMRAD Postdoctoral Award and the inaugural Leonard Cox Award. More recently, Professor Kilpatrick and his group were awarded the Australian Museum's Jamie Callachor Eureka Prize for Medical Research (2008) in recognition of their extraordinary contribution to medical research into multiple sclerosis.

ASSOCIATE PROFESSOR ROSS BATHGATE

Neuropeptides

Associate Professor Ross Bathgate is the Head of the Division of Neuropeptides, a NHMRC Senior Research Fellow and an Honorary Principle Research Fellow in the Department of Biochemistry and Molecular Biology at The University of Melbourne. His work focuses on the relaxin family of peptides and their G-protein coupled receptors. These peptide-receptor systems show enormous potential for therapeutic targeting and the hormone relaxin is currently in Phase III clinical trials for the treatment of acute heart failure. He works closely with Novartis who are conducting the clinical trial on relaxin as well as a number of other pharmaceutical companies interested in the clinical development of these peptides. He currently serves on the editorial boards of Molecular and Cellular Endocrinology, Frontiers in Molecular and Structural Endocrinology and Journal of Pharmacological Sciences.

DIVISION HEADS

PROFESSOR PHILIP BEART

Neurodegeneration

Professor Philip Beart (PhD ANU, DSc Melbourne) has been a NH&MRC Research Fellow for 30 years and is currently Professorial Fellow in the Florey and Adjunct Professor in Pharmacology, University of Melbourne. He worked at Cambridge and Harvard Universities, before holding positions at the Austin Hospital and Monash University. Professor Beart has published >200 papers, served on numerous editorial boards and has diverse involvements in learned societies. Awards include the Bethlehem Griffiths Medal (2010), the Lawrie Austin Lectureship of the Australian Neuroscience Society (2009) and in pharmacology the Michael Rand Medal (2009). He has trained numerous honours and post-graduate students. He has a long-term commitment to promoting medical research, particularly neuroscience, in the wider community, and has provided extensive service to the NH&MRC. Professor Beart is currently Chair of the Scientific Promotions Committee and past President of the International Society for Neurochemistry (2011-13).

ASSOCIATE PROFESSOR JULIE BERNHARDT

Stroke

Associate Professor Julie Bernhardt is the Co-Division Head of the Division of Stroke and leads the AVERT Early Intervention Research Program, which includes a multidisciplinary team of researchers committed to the development and testing of new, rehabilitation interventions that can reduce the burden of stroke related disability. AVERT, the largest, international, acute stroke rehabilitation trial ever conducted, sits at the core of the program. Advancing understanding of how exercise-based interventions alter bone, muscle and brain function after stroke is another aim of the program. Julie's clinical career has been devoted to working with people with stroke and other neurological diseases. As a strong proponent of evidence based care, another key theme within her program is the synthesis and translation of evidence into practice. Julie sits on the Board of the National Stroke Foundation and on a number of national and international stroke advisory groups.

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ASSOCIATE PROFESSOR DAVID W HOWELLS

Stroke

Associate Professor David Howells is the Co-Division Head of the Division of Stroke and began his career investigating the biochemical and genetic basis of dopamine and serotonin deficits in children. He went on to describe a new population of dopaminergic neurons, demonstrated that BDNF depletion can cause parkinsonism and that Parkinson's disease patients are deficient in BDNF. His other research interest is in stroke: his studies of neuroprotection in stroke have led to improved modelling of stroke in animals, the development of new methods of imaging, and development of systematic review and analysis as tools for rigorously evaluating basic science literature. The latter have led three leading stroke journals to publish guidelines for Good Laboratory Practice.

DIVISION HEADS

PROFESSOR ROBIN MCALLEN

Systems Neurophysiology

Professor Robin McAllen is the Co-Division Head of the Division of Systems Neurophysiology and a NHMRC Principal Research Fellow. He trained in Physiology in London and Birmingham and in Medicine at Birmingham (UK) before moving to the Florey in 1988. He is a neurophysiologist with an interest in the central nervous regulation on cardiovascular and autonomic functions, and has published extensively of this topic. More recently he has collaborated with Florey colleagues in neuroimaging experiments that aim to translate lessons learned from animal studies to the human brain. He currently serves on the editorial board of the American Journal of Physiology, is a section editor for Clinical and Experimental Pharmacology and Physiology, and is a member of the Faculty of 1000.

PROFESSOR RICHARD MACDONELL

Systems Neurophysiology

Professor Richard Macdonell is Director of Neurology at Austin Health, a Co-Division Head of Systems Neurophysiology and an Honorary Professorial Fellow. He trained in Neurology and Clinical Neurophysiology at Austin Health, Massachusetts General and the London Hospitals and has been in charge of the Neurophysiology and Neuroimmunology services at Austin Health since 1991. His research interests include multiple sclerosis, peripheral nerve and muscle disorders and using transcranial magnetic stimulation to study the pathophysiology of epilepsy.

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EQUALITY IN SCIENCE REPORT

Gender balance at the bench

Pictured: Associate Professor Julie Bernhardt and Dr Emma Burrows, co-chairs of the Equality in Science Committee.

While the number of women and men undertaking PhDs at the Florey has been gender balanced for the past decade, representation at the senior level is skewed, with only 14 per cent of women holding senior research positions. So why does this matter?

Diversity leads to great discoveries, and we can learn a lot about great discoveries from a prominent scientist Karl Deisseroth who gave the 2013 Kenneth Myer lecture at the Florey. When asked the secret to his big ideas he said "bringing people from diverse backgrounds together in the same room". There is a wealth of evidence in support of interdisciplinary teams. They come up with the best ideas because of their diverse range of approaches and thinking styles. The Florey recognises that in order to find cures we must have the biggest ideas, we must think differently and we must certainly engage all our best brains.

The Equality in Science Committee (EQiS) works to create conditions in which staff can operate to their full potential and work together cohesively. This working committee has broad representation of staff to ensure relevant equity issues can be canvassed. We have recently changed our committee structure to allow subgroups to champion change in mentoring, parenting, policy, fundraising and communications.

This year's report celebrates many achievements.

In order to understand how best to address cultural change at the Florey a case study was conducted by Dr Kate White. This report has been endorsed by the executive and the board, and given us an extremely valuable platform to work from.

Professor Ingrid Scheffer was elected to the Australian Academy of Science Fellowship on the back of her prestigious GlaxoSmithKline Award for Research Excellence. Dr Wah Chin Boon, leading the Steroid Neurobiology laboratory, was awarded the Fred P Archer fellowship. PhD student Lizzie Manning was nominated by the Australian Academy of Science to participate in the 64th meeting of the Nobel Laureates in Germany. We are extremely lucky to have many high achievers in our ranks and increasing the visibility of women in science is a key objective of ours. With the generous support of a committed group of supporters we have raised more than $900,000 dollars towards an endowment to support female leaders in our institute.

To improve transparency within our institute, we have developed documents that clearly define leadership positions. We have committed to achieving gender equity on all decision-making bodies, and hope to achieve at least a 30:70 representation on all Institute committees within the next year. Our target of 50 per cent has been supported by Harold Mitchell AC, chair of the Florey Board, who has committed to lead this change, starting with the gender representation on the board.

To reflect a generational shift in the way younger scientists view family responsibilities, we have increased flexibility at work by introducing family friendly meeting times, flexible working hours and part-time positions, and are creating family rooms for working parents. EQiS recognises that diversity in mentoring is key to outcomes. Our mentor and mentee pairs have described mutual benefits as a result of participating in this program.

We are also addressing broader issues by joining forces with three of the largest medical research institutes in Australia; the Walter and Eliza Hall Institute, Peter MacCallum Cancer Institute and Murdoch Children's Research Institute. The 'Women in Science Parkville Precinct' collaboration aims to tackle the broader issues limiting the progression of women in science.

It has been an extremely successful year for the EQiS committee. We thank the committee members who have worked together to develop policies and practices that are helping to encourage diversity at all levels of the Florey.

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The science

THE SCIENCE

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BRAIN DEVELOPMENT AND REGENERATION

Division head: Professor Seong-Seng Tan

A QUICK SNAPSHOT

When the brain is injured, such as in an accident or in stroke, the main area of the brain injury is not recoverable due to massive bleeding and swelling. However, what is not commonly known is that dying brain cells (called neurons) can transmit death signals from the injured area into surrounding healthy tissues, this ripple effect causing death of neighbouring brain cells in large numbers. There is at present no effective cure for brain injury, but scientists have long suspected that evolution has armed the brain with some impressive defensive strategies. We know that the brain can defend itself against dying; finding how it does this remains a mystery. Our work is aimed at identifying these defence strategies and harnessing this information for therapeutic gain.

RESEARCH HIGHLIGHT

We have found that Ndfip1 protects brain cells from death by hijacking an anti-cancer brain protein called PTEN. This protein is normally utilized as a defensive mechanism against tumour formation in brain cells. We found that after brain injury, this mechanism is activated to bolster the longevity of brain cells. The implication of this discovery exposes the PTEN anti-cancer pathway for therapeutic manipulation.

AN IDEA LIKELY TO CHANGE LIVES BY 2033

We are working on practical therapies to prevent neuron death following injury, including a compound that will artificially increase Ndfip1 in recipient neurons.

If this can make brain cells hardier following injury, there is a strong potential for reducing the number of neurons that die following trauma or stroke.

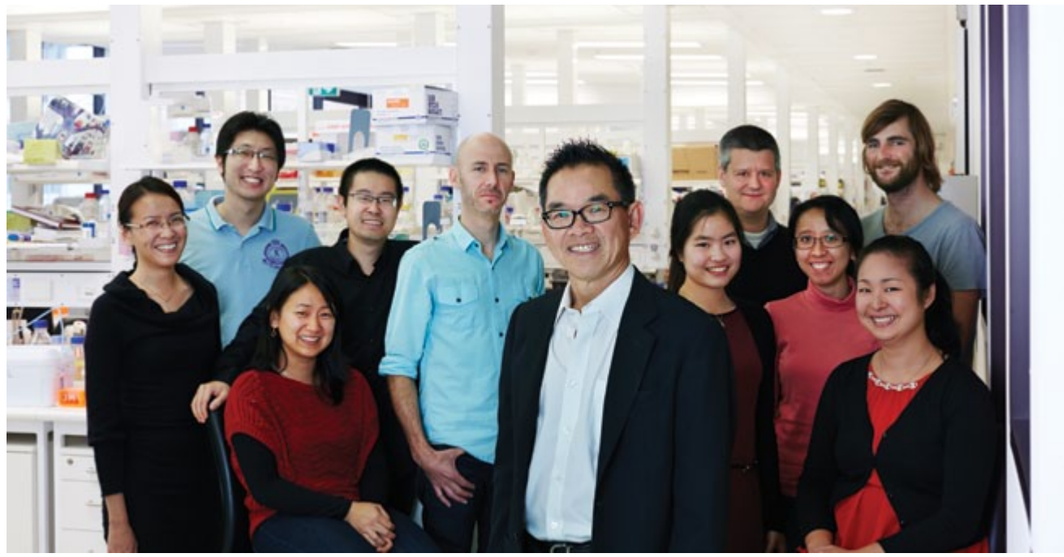
OUR LAB

Our laboratory uses a variety of modern techniques to study how brain cells are able to resist death in a hostile environment produced by injury. Our experiments are driven by questions that are framed around testable hypotheses that may be answerable by experimental tools. These tools include creation of new mouse strains with inserted genes, molecular cloning of brain genes and manipulation of brain proteins. We are performing studies in collaboration with scientists in Australia and overseas.

> “When we removed Ndfip1 from healthy brain cells, the cells suffered greater injuries compared to brain cells where the protein had not been removed.”

SENIOR STAFF

• Seong-Seng Tan • Joanne Britto • Jason Howitt • Ulrich Putz • Ley-Hian Low • Choo-Peng Gohr •

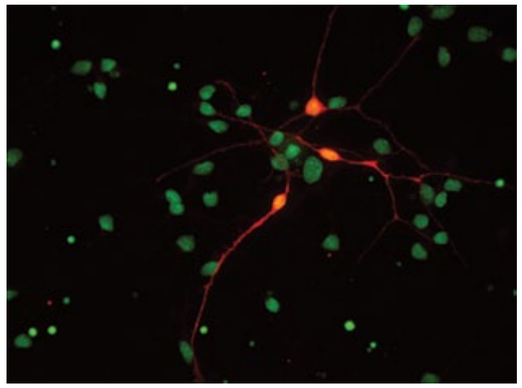


The Brain Development team: Choo-Peng Goh, Ley-Hian Low, Anh Doan, Yijia Li, Jason Howitt, Seong-Seng Tan, Sophia Mah, Ulrich Putz, Yuh-Lit Chow, Michelle Tang, Ulrich Sterzenbach. Absent: Joanne Britto, Hui Xuan Ng, Ean Phing Lee.

BRAIN DEVELOPMENT GROUP

Leader: Joanne Britto

In order for brain cells in the adult brain to function properly, it is important that they are first found in the correct locations. This provides the groundwork for their correct arrangement and interconnection with one another. Failure of brain cells to migrate to their destinations is a frequent cause of many developmental disorders such as autism and schizophrenia. For many years, our group has performed experiments to understand how brain cells are able to correctly migrate to their final positions. Over the last year, our work has uncovered new information on the speed and trajectory of brain cell migration, together with proteins that influence this process.



Brain neurons transplanted into other fetal brains are able to populate their developmental niches.

Research highlights for 2013

We recently focussed on a class of brain cells called interneurons. Although they are in the minority, this class of neurons controls much of our mental processing and sensory experience. Therefore studying the behaviour of interneurons holds the key to understanding the cause of developmental brain disorders. Previously, we showed that interneurons are capable of migrating vast distances to reach their final positions in highly specific addresses. Over the last year, we have been tracking the migration of these neurons, using genetic mice engineered to paint brain cells with artificial colours. This technology allows us to follow the movements of different interneuron classes under a laser microscope. The information from these studies allows us to pinpoint which types of interneurons are most at risk when something goes wrong. Our work has showed that different interneurons destined for different layers have separate rules for movement, dispelling previous notions that all interneurons behave alike.

BRAIN SURVIVAL GROUP

Leader: Jason Howitt

In Australia, there are about 50,000 cases of head injury per year that require hospitalisation. Of these, about 3000 cases are fatal or require life-changing hospitalization. Most cases of brain trauma originate from road traffic accidents; however sports, violence and falls also contribute to the number. Indeed, young males under the age of 35 are more likely to die from brain trauma than any other disease. There is at present no drug treatment to reduce the rate of brain death after trauma. Therefore medical strategies to prevent neurons from succumbing to trauma-induced death is an unmet need.

Research highlights for 2013

Our brain survival team has identified a number of ways to stop brain cell death in animal models. These are all mediated by the brain survival protein called Ndfip1. We found that Ndfip1 activates a number of brain survival pathways. One survival pathway uses a new method that involves an anti-cancer protein called PTEN. We have manipulated PTEN in brain cells and discovered that this leads to increased brain cell survival. An indirect benefit of this discovery is to understand how we can also manipulate PTEN to reverse a form of brain cancer called glioma. We aim to take this further by creating drugs to activate this pathway for the dual benefit of brain cell survival against injury and cancer.

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We have also discovered that Ndfip1 is an important defender against metal accumulation in brain cells. This is important for degenerative brain diseases such as Parkinson's and Alzheimer's disease. We showed that post-mortem brains from Parkinson's disease contain deficient levels of Ndfip1. This deficiency is associated with increase iron accumulation in diseased brain cells. This work opens up the manipulation of Ndfip1 as a way of controlling onset and progress of Parkinson's disease.

BRAIN COMMUNICATION GROUP

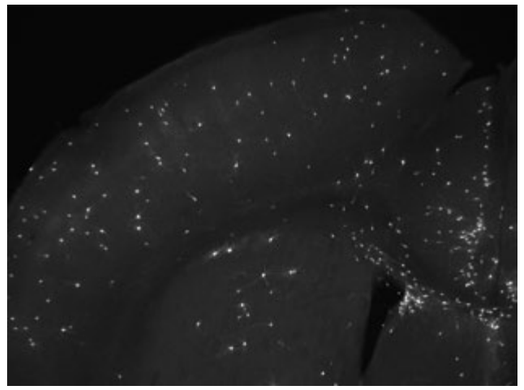
Leader: Ulrich Putz

This group is interested to test a new and bold hypothesis – that brain cells are in constant communication with each other for transmitting electrical and chemical signals during mental activity using exosomes. Exosomes are tiny packets of organelles carrying proteins and nucleic acids. We postulate that exosomes released by neurons may be taken up by neighbouring neurons with functional effects. If our hypothesis is proven, this communication system will be deemed to be as important as the well-known synaptic network of signal (and electrical) transfer between neurons and glia.

However, we believe that certain chemicals are also exchanged between brain cells for purposes that are not related to mental processing, for example for brain repair after injury. Brain communication is also important for protection of nerve cells against brain stress. We are currently engaged in discovering the nature of these communications and under what circumstances are they being transmitted.

Research highlights for 2013

In recent years, our laboratory has discovered an internal system of defence in neurons centred around the Ndfip1/Nedd4 ubiquitination systems. This defence system can be used to equip neighbouring cells at risk from cell death during stress. We showed that the defence system uses exosomes to export survival proteins from healthy cells to unhealthy cells. We also discovered that Ndfip1 can load additional proteins into exosomes following genetic manipulation. This discovery opens up the exciting possibility of creating designer exosomes for biological use.



Embryonic neurons from human brains develop and connect with other another in a culture dish.

EDITORIAL POSITIONS

SEONG-SENG TAN

- Experimental Neurology (USA)
- Journal of Anatomy (UK)
- Journal of Cell Biology (Korea)
- Frontiers in Neuroscience

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

- Australian Neuroscience Society annual meeting, Melbourne Feb 2013. *"PTEN in the brain symposium"*
- Universiti Sains Malaysia, June 2013. "Why brain injury and cancer are two sides of the same coin".
- Kunming University of Science and Technology, August 2013. "Mechanisms to improve neuron survival following injury".

PUBLICATIONS

1. Haas, M., Qu, Z., Kim, T., Vargas, E., Campbell, K., Petrou, S. Tan, S-S., Reid, C., and Heng, J. (2013) Perturbations in cortical development and neuronal network excitability arising from prenatal exposure to benzodiazepines in mice. Eur. J. Neurosci. 37:1584-1593
2. Britto, J.M., Tait, K.J., Lee, E.P., Gamble, R.S. Hattori, M. and Tan, S-S (2013) Exogenous reelin modifies the migratory behavior of neurons depending upon cortical location. Cereb. Cortex (in press)
3. Hammond, V.E., Gunnersen, J.M., Goh, C.P., Low, L.H., Hyakumura, T., Tang, M.M., Britto, J.M., Putz, U., Howitt, J.A., and Tan, S-S (2013) Ndfip1 is required for the development of pyramidal neuron dendrites and spines in the neocortex. Cereb. Cortex (in press)
4. Goh, C.P., Low, L.H., Putz, U., Gunnersen, J., Hammond, V., Howitt, J., and Tan, S-S (2013) Ndfip1 expression in developing neurons indicates a role for protein ubiquitination by Nedd4 E3 ligases during cortical development. Neurosci. Letters (in press)
5. Heng, J.I., Qu, Z., Ohtaka-Maruyama, C., Okado, H., Kasai, M., Castro, D., Guillemot, F. and Tan, S-S (2013) The zinc finger transcription factor RP58 negatively regulates Rnd2 for the control of neuronal migration during cortical development. Cereb. Cortex (in press)
6. Chua J., Nivison-Smith L., Tan S-S., and Kalloniatis M.(2013) Metabolic Profiling of the Mouse Retina Using Amino Acid Signatures: Insight into Developmental Cell Dispersion Patterns Exp. Neurol (in press)
7. Goh, C.P., Putz, U., Howitt, J., Low, L.H., Gunnersen, J., Bye, N., Morganti-Kossmann, C. and Tan, S-S. (2013) Nuclear trafficking of Pten after brain injury leads to neuron survival not death. Exp. Neurol (in press)
8. Nivison-Smith, L., Chua, J., Tan, S-S, and Kalloniatis, M. (2013) Amino acid signatures in the developing mouse retina. Int J. Dev. Neurosci. (in press)
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JESS AND HER IPAD LOVING MICE

After almost six years working abroad, Dr Jess Nithianantharajah has returned to Melbourne to develop her research at the Florey

Jess Nithianantharajah has a long history at the University of Melbourne and the Florey. After completing a Bachelor of Science (Honours), she attained a PhD in Behavioural Neuroscience in 2004 at the Dept of Anatomy and Cell Biology. She commenced her postdoctoral training at the Howard Florey Institute with A/Prof Anthony Hannan before moving in 2008 to work with Prof Seth Grant at the Wellcome Trust Sanger Institute in Cambridge, UK. During this time, she held a joint appointment at the University of Cambridge collaborating with Prof Tim Bussey and Dr Lisa Saksida. She relocated in 2011 with the Grant laboratory to the University of Edinburgh and in 2014, armed with a wealth of experience and contemplating where in the world she would grow her research, she was confident Melbourne was the answer.

Jess has always had a keen interest in understanding how the brain controls behaviour and her recent research has focused on how genes that are required for forming the connections between brain cells are involved in controlling complex behaviour and mental processes. An exciting aspect of her recent studies has been working with the lab in Cambridge that developed an exciting new behavioural tool for mice – iPad-like touchscreen computers – that allow the investigation of complex learning using tests that are very similar to that used in the clinic in patients. These tests have advanced how we can model some of these complex mental processes in animals and has immense significance for medical translation. Jess plans to extend and develop her research using the touchscreen assays at the Florey towards making the Institute a leader within Australia in employing this technology.

A dynamic and critical mass of neuroscientists in Melbourne makes Parkville a thriving place for medical research and a fantastic environment to work in. Having access to diverse and complementary expertise from fellow neuroscientists is something Jess is looking forward to working with. The new Florey Building, which had only commenced construction when Jess left for the UK, has impeccable research facilities to drive exciting and internationally competitive research. Additionally, the Institute is a representation of what many others around the world conceptualise – to bring together a mix of clinical and basic scientists, encouraging a collaborative environment focused on driving research of significance to patients. This was an important aspect that particularly attracted Jess to return to the Florey.

While she admits she will miss the weekend walks in the highlands and the single malt whiskeys, she is very enthusiastic about embarking on her next research phase at the Florey.

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THE GLOBAL HEALTH CHALLENGE OF NEUROLOGICAL DISORDERS

... and how the Florey can contribute

WORLDWIDE, ONE BILLION PEOPLE ARE AFFECTED BY A NEUROLOGICAL DISORDER

50 MILLION

50 million suffer from epilepsy.

44.4 MILLION

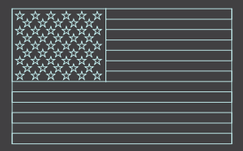
44.4 million suffer from dementia including Alzheimer's.

11%

Neurological diseases make up 11 per cent of the world's disease burden, not including mental health and addiction disorders.

IN EUROPE

The cost of these diseases is high across the globe. For example, the European Brain Council estimated in 2010 that neurological diseases in Europe alone cost one trillion dollars a year.



IN THE UNITED STATES

$500 BILLION

Neurological illnesses affect more than 50 million Americans annually and cost more than $500 billion to treat.

$148 BILLION

Mental disorders strike 44 million American adults a year at a cost of $148 billion.

Advances in research could reduce these costs. Discovering how to delay the onset of Alzheimer's disease by five years could save $50 billion in annual health care costs in the United States alone.

IN AUSTRALIA

STROKE

There are 50,000 strokes in Australia each year – almost 1000 a week; one every 10 minutes.

Annual cost: $49.3 billion.

MENTAL ILLNESS

1 in 5 will have a mental illness in their lifetime.

The prevalence is high and stable.

7.3 million Australians have experience of mental illness.

Burden of disease for anxiety and depression in 2012: $41 billion.

EPILEPSY

800,000

It is estimated that nearly 800,000 people in Australia will be diagnosed with epilepsy at some stage in life.

3.5%

Over 225,000 Australians are living with epilepsy. Up to 3.5 per cent of Australians will experience epilepsy at some point in their lives.

DEMENTIA

Third most common cause of death in Australia and there is no cure.

Three in 10 people over 85 have dementia.

Direct health and aged care support in one year: $4.9 billion.

1,700 NEW CASES

Each week, 1,700 new cases of dementia are diagnosed – one person every six minutes. Some 25,000 have young onset dementia.

4%

Dementia makes up four per cent of the total disease burden in Australia, making it the fourth leading cause of burden of disease for Australians in 2011.

*Source: World Health Organisation

Read article about neurological diseases in Europe alone cost one trillion dollars a year – "CDBE 2010: Backgrounder"

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COGNITIVE NEUROSCIENCE

Division heads: Professor Andrew Lawrence and Dr Amy Brodtmann

A QUICK SNAPSHOT

The Division of Behavioural Neuroscience focuses on the use and development of animal models that reflect aspects of human disorders such as addiction, anxiety, depression, schizophrenia, autism and neurodegenerative conditions such as Huntington's disease. The Cognitive Neuroscience group additionally studies cognitive disorders caused by diseases such as stroke (cerebrovascular disease), Alzheimer disease and other dementias from a clinical perspective.

RESEARCH HIGHLIGHT

There have been a number of highlights within the division during 2013. Professor Andrew Lawrence was part of a multinational collaboration that published a study questioning the efficacy of a frontline medication for the treatment of alcohol use disorders. In addition, research from two PhD students (Phil Ryan & Hanna Kastman), jointly supervised by Professor Andrew Lawrence and Associate Professor Andrew Gundlach (Neuropeptides division), demonstrated that the relaxin-3 system is implicated in stress-induced relapse to alcohol-seeking. Dr Jee Hyun Kim discovered that the bipolar medication, Aripiprazole was effective in facilitating inhibition in adolescents, thereby reducing relapse of drug-seeking and anxiety. Dr Emma Burrows and Associate Professor Anthony Hannan have discovered abnormalities of social interaction and communication in a mouse model of autism spectrum disorder carrying a human gene mutation.

> "Exposure to inhalants during adolescence results in long-term metabolic dysfunction. Adolescent inhalant abuse may increase the risk of adult onset disorders such as diabetes, especially in indigenous populations where there is a high degree of overlap between inhalant abuse and nutrition-related illness."

SENIOR STAFF

• Professor Andrew Lawrence • Associate Professor Anthony Hannan • Associate Professor John Drago • Dr Amy Brodtmann • Associate Professor David Darby •

RESEARCH OVERVIEW

The year 2013 was one of excellence for our scientists and students. Dr Phil Ryan obtained his PhD and was awarded an NMHRC CJ Martin Fellowship to undertake postdoctoral research in the laboratory of Dr Richard Palmiter, a Howard Hughes Investigator in the USA. Dr Nathan Marchant was also awarded a CJ Martin Fellowship to study at the National Institute on Drug Abuse in the USA under the mentorship of Dr Yavin Shaham before returning to the Florey. Dr Heather Madsen commenced postdoctoral training with Dr Serge Ahmed in France while Dr Robyn Brown returned from her spell in the USA. Dr Bianca Jupp was awarded a Fellowship from the AXA Research Fund to extend her postdoctoral training at Cambridge University for two more years. Dr Thibault Renoir was awarded an ARC DECRA Fellowship. Dr Emma Burrows was awarded a Victoria Fellowship, which she used to gain research training at the University of Cambridge. Dr Despina Ganella received her PhD in July and joined the division as a postdoctoral fellow.

Dr Jee Hyun Kim won a NHMRC project grant as the lead investigator, totalling $689,000. She also won the prestigious International Society for Developmental Psychobiology Kucharski young investigator award, given to just one neuroscientist each year, and received an International Society for Neurochemistry young investigator award. Through these achievements in the addiction neuroscience group, Dr Kim received a promotion to Laboratory Head status at the end of 2013 to form her own group within our division in 2014.

Dr Jhodie Duncan was promoted to Florey Senior Research Fellow and was awarded a University of Melbourne Research Grant and HVS Image award.

AN IDEA LIKELY TO CHANGE LIVES BY 2033

By 2033, dementia will be a rare and treatable disease. Patients admitted with stroke will receive dementia risk stratification and be treated with therapies that will recover all functions, including cognitive. People at risk of Alzheimer disease will be identified via online testing or following a sentinel risk event, and treated prior to the development of brain atrophy.

ADDICTION NEUROSCIENCE GROUP

Leader: Andrew Lawrence

The Addiction Neuroscience Group studies how alcohol and other drugs change the brain's chemistry, structure and function. During 2013 we made a number of important findings, many of which are still being actively pursued. As part of their PhDs, Phil Ryan and Hanna Kastman demonstrated for the first time that the neuropeptide, relaxin-3, is implicated in alcohol self-administration and relapse to alcohol-seeking, particularly that precipitated by an acute stressful experience. Subsequently, they commenced a delineation of the neural circuitry involved in this action. This study highlighted that antagonism of the receptor for relaxin-3 (RXFP3) in a part of the brain called the bed nucleus of the stria terminalis could markedly reduce stress-induced relapse to alcohol-seeking. Other important findings include a demonstration that orexin receptors (OX1R and OX2R) differentially modulate alcohol self-administration vs cue-induced relapse. In this case, both receptors are involved in alcohol self-administration whereas only OX1R are implicated in cue-induced relapse.

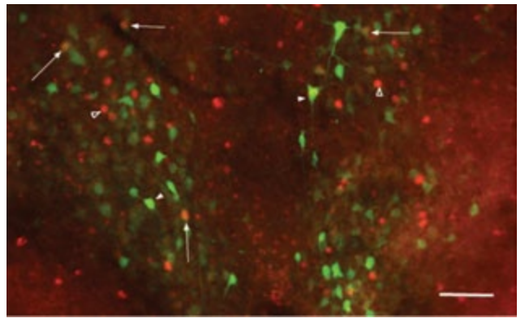

Image of the mouse paraventricular thalamus (PVT) in OX1R-eGFP mice. Green cells (filled arrowheads) are nerves that express the orexin1 receptor (OX1R). Red cells (open arrowheads) are nerves that have been activated during a "relapse" to food-seeking. Filled arrows point to cells that express OX1R and are activated during such a "relapse". Image courtesy of Sarah Sulamain Ch'ng working with Professor Andrew Lawrence.

We also continued with our longstanding project on mGlu5 receptors. The process of behavioural extinction is a form of inhibitory learning that can help to protect against relapse. Dr Christina Perry and Dr Jee Hyun Kim have studied various facets of extinction and shown that mGlu5 signalling is involved in the extinction of contextual and cue memories. This is an important finding as it is potentially translatable by using mGlu5 positive modulators to enhance the rehabilitation of addicts undergoing behavioural therapy.

Other significant new leads on treating addiction were discovered in 2013 by Dr Kim who identified that the popular bipolar medication, Aripiprazole, was effective in facilitating inhibition in adolescents so that there is less relapse of drug-seeking and anxiety. These results suggest that drug addiction and anxiety disorders may be more easily treated during adolescence rather than later in life, and formed the basis of the major NHMRC project grant awarded to Dr Kim. She also recently published on a gene (DCC) that may explain the individual differences in sensitivity to methamphetamine addiction.

The abuse of inhaled chemical vapours to produce self-intoxication is a significant concern, especially among adolescent and indigenous populations. Dr Jhodie Duncan and Mr Alec Dick recently published work demonstrating that exposure to inhalants during adolescence results in specific impairments in aspects of instrumental learning, without altering motor function and spatial learning in late adolescence/early adulthood. These data imply that persistent alterations in reward processing may occur following adolescent inhalant misuse.

Using this model we have also shown that exposure to inhalants during adolescence results in long-term metabolic dysfunction. This includes altering dietary preference and glycemic control. This novel finding suggests that adolescent inhalant abuse may increase the risk of adult onset disorders such as diabetes and has significant implications for our understanding of the long-term consequences, especially in Indigenous populations where there is a high degree of overlap between inhalant abuse and nutrition related illness. The next step in our studies is to determine the underlying mechanisms, including both changes to central or peripheral mediated processes, that drive the adverse outcomes observed in human abusers.

NEURAL PLASTICITY GROUP

Leader: Anthony Hannan

Many neurological and psychiatric disorders, including schizophrenia and autism spectrum disorders (ASD), involve abnormal development of the brain. We are interested in the mechanisms whereby specific genes regulate maturation of the brain and are dynamically regulated by interaction with the environment in conditions like ASD and schizophrenia.

Autism spectrum disorders affect approximately one per cent of children. Dr Emma Burrows has discovered abnormalities of social interaction and communication in a mouse model of ASD carrying a human gene mutation. Ongoing investigations focus on identifying key molecules and cellular changes involved in ASD and testing new therapeutic approaches in this model. With collaborators at the University of Melbourne, we have new evidence that both the central and peripheral nervous system is disrupted in these mice, contributing to a broad array of ASD symptoms.

Schizophrenia is another neurodevelopmental disorder involving a complex combination of genetic and environmental factors which disrupt normal maturation and function of the brain. Using a mouse model of schizophrenia, Dr Emma Burrows has shown that enhanced mental and physical activity can ameliorate cognitive deficits and other behavioural symptoms and benefit specific areas of the brain. Identifying molecules modulated by environmental stimulation has paved the way for future development of new therapeutic approaches. Furthermore, Dr Burrows and a graduate student Faith Lamont have been the first researchers in Australia to generate data using our new automated touchscreen tests (which are directly translatable to human neuropsychological test batteries). They have identified specific aspects of cognitive dysfunction and are testing a therapeutic intervention in this model of schizophrenia.

Huntington's disease (HD) is an inherited single-gene abnormality that involves a triad of psychiatric symptoms (eg depression), cognitive deficits (culminating in dementia) and a movement disorder. Dr Terence Pang, along with PhD student Xin Du, discovered an abnormal stress response associated with depression-like behaviours (which respond to antidepressants) in the mouse model of HD and identified key molecules involved in the disease, the response to environmental stimuli and the increased vulnerability of females. The effects of a major environmental factor, stress, on HD has been explored by Dr Thibault Renoir and a PhD student, Christina Mo, who demonstrated for the first time that stress can accelerate the onset of HD, in particular the cognitive deficits (modelling dementia). These findings will have implications not only for HD, but for depression and dementia in the wider community. Further study of gene-environment interactions and experience-dependent changes in the nervous system may lead to new therapeutic approaches for HD and other brain disorders.

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COGNITIVE NEUROSCIENCE GROUP

Leader: Amy Brodtmann

We are a clinically-based research group examining the cognitive trajectories of patients with stroke and dementia, using advanced imaging techniques in concert with novel testing paradigms developed by our team members.

Cognitive disorders can develop from a range of brain diseases, including stroke, Alzheimer's disease, and other less well known dementias such as frontotemporal dementia. Dementia will overtake all other conditions as the greatest global burden of disease by 2015, greater than stroke, respiratory disease, and depression, the current leaders. One in three Australians will develop dementia after retirement, and the cost of caring for people with dementia is more than $US600 million annually.

The Cognitive Neuroscience group had a year of expansion and consolidation in 2013. The international significance of the Cognition and Neocortical Volume After Stroke (CANVAS) study continued to grow, with conference proceedings and the development of important collaborations with groups in Germany and the United States. The CANVAS project is an NHMRC study where we aim to establish whether stroke patients have increased atrophy (reductions in brain volume) in the first three years post-stroke compared to control subjects, perhaps answering whether stroke can be associated with neurodegenerative mechanisms. This NHMRC-funded project continues to be assisted by help from the Sidney and Fiona Myer Family Foundation. Funding from the Mason foundation was utilised to develop and compare imaging techniques in patients with dementia, and recruitment for this Florey-Royal Melbourne project will commence in 2014. Support from the Collie Trust allowed us to recruit a new post-doctoral research fellow from the UK, Dr Michele Veldsman, who is looking at changes in connectivity in our stroke patient population.

Associate Professor Darby launched the TREAD study in late 2012 to great media interest, and there are now more than 1500 people who log-in monthly for their on-line cognitive testing. This study has been covered by many of the major newspapers nationally, and was a feature on national television. He is in the process of launching a similar project in Brasil, and is working with a long-term collaborator in Oxford, Professor Kia Nobre, on a large community based in the UK.

Dr Brodtmann was appointed to the inaugural Wicking Strategic Panel, a position which, along with her appointments to the Australian Frontotemporal Dementia Association and Alzheimer's Australia – Victoria Dementia Research Grants committee and panel will allow her to lobby and advocate for people with cognitive disorders. She received a prestigious NHMRC Clinical Career Development Fellowship which has supported her work in 2013, and was invited to join the editorial board of the International Journal of Stroke, while continuing her role on the board of Neurology, the world's leading clinical neurology journal.

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

INVITED LECTURES FOR ANDREW LAWRENCE

- Recent Advances in Neuroscience: Plasticity, Imaging, Regeneration & Addiction, Inaugural Meeting of the Sydney Neuroscience Network, University of Sydney. "mGlu5 receptors & extinction of drug-seeking".
- The long and winding road to discovering drugs for brain and mind disorders. ASCEPT annual conference, Melbourne.
- 1st Asia-Pacific Molecular Cell and Cognition Society meeting.
- APSN symposium on Nervous System and diseases: Mechanisms and Models. Singapore.
- 14th Congress of the European Society for Biomedical Research on Alcoholism (ESBRA) Warsaw, Poland –symposium "Are Metabotropic Glutamate Receptors Promising Targets for Alcohol Addiction?".
- Collegium Internationale Neuro-Psychopharmacologicum, special congress on addiction, Kuala Lumpar, Malaysia. Session chair and invited symposium speaker "Addiction neuroscience: emerging new treatments".
- British Pharmacological Society annual meeting, London UK. Symposium "Neuropharmacology & Psychiatric Disorders".
- International Narcotics Research Conference, Cairns. "Orexins & Reward-Seeking".

INVITED LECTURES FOR AMY BRODTMANN

- Visual syndromes after stroke, Masters in Neuroscience Invited Lecture, King's College London, UK (hosted by Professor Marco Catani)
- Vascular contributions to dementia, Dementia Research Centre, London, UK
- ANZAN Annual Scientific Meeting FTD: new controversies Sydney

INVITED LECTURES FOR ANTHONY HANNAN

- CAG Triplet Repeat Disorders Gordon Research Conference, Waterville Valley, NH, USA. 2nd Annual MIND Symposium, 'Molecular Mechanisms of Neurodegeneration', MassGeneral Institute for Neurodegenerative Disease (MIND), MGH, Harvard University, Boston, USA.
- Animal Behaviour Seminar, Animal Research Review Panel of NSW Government, Sydney.
- Research Seminar and Public Lecture, Menzies Institute, University of Tasmania, Hobart.
- Collaborators Day (Rush, Gibbons, Blessing festschrift), Centre for Neuroscience, Adelaide.
- 5th Protein Misfolding and Neurological Disorders Meeting, Heron Island, Queensland.
- Optimising Health Environments Forum, Melbourne.
- Symposium on 'Neural prostheses: harnessing brain plasticity and neural modulation', The Bionics Institute of Australia, Melbourne.
- 3rd Annual Biological Psychiatry Australia (BPA) Scientific Meeting, Brisbane, Queensland.

INVITED LECTURES FOR JHODIE DUNCAN

- International Society for Developmental Psychobiology (ISDP) Annual Conference, San Diego, USA. "The long-term consequences of inhalant abuse during adolescence; potential neuro-adaptations in reward pathways? "
- International Society for Neurochemistry 24th Biennial Meeting, Cancun, Mexico. "The long-term consequences of inhalant abuse during adolescence; potential neuro- adaptations in reward pathways?"

INVITED LECTURES FOR JEE HYUN KIM

- International Society for Developmental Psychobiology (ISDP) Annual Conference, San Diego, USA. " Adolescent susceptibility to drug addiction: a dopamine story."
- International Society for Neurochemistry 24th Biennial Meeting, Cancun, Mexico. "The role of mGlu5 receptor in extinction of drug-seeking behavior"
- 48th Annual Australian Society for Psychology Conference, Cairns, Australia. "Memories of good and bad across development."
- Clinical Expertise in Dementia Care Forum, Alzhemier's Australia, Melbourne, Australia. "Memory and forgetting in the ageing brain."

OTHER ACADEMIC INVITATIONS 2013

ANDREW LAWRENCE

- Hotchkiss Brain Institute, University of Calgary, Canada – invited lecture
- Dept. of Neuroscience, Medical University of South Carolina, USA – invited lecture
- Gene Technology Access Centre, Melbourne – invited lecture
- Convenor & co-Chair, ANS-FAONS symposium on Stress & Addiction
- Faculty member, APSN school in neurochemistry, NUS Singapore
- Member, local organizing committee for International Narcotics Research Conference (INRC), Cairns, Queensland

AMY BRODTMANN

- Institute for Stroke and Dementia Research (ISD), Ludwig-Maximilians-University, Munich hosted by Professor Martin Dichgins, presentation on Cognition and neocortical volume after stroke: the CANVAS study

ANTHONY HANNAN

- NeuRA, UNSW, Sydney (2013) – invited lecture
- School of Medicine, University of Western Sydney (2013) – invited lecture
- Local Organising Committee Member and Session Co-Chair, BioAutism 2013, a satellite to the Australian Neuroscience Society Meeting, Melbourne (2013)
- Chair, Local Organising Committee for Huntington's Disease and other Tandem Repeat Disorders, a satellite to the Australian Neuroscience Society Meeting, Melbourne (2013)
- Scientific Advisory Committee Member, 3rd International Congress on Neurology and Epidemiology, Abu Dhabi, UAE (2013)

JHODIE DUNCAN

- School of Biomedical Sciences and Pharmacy, Uni Newcastle, NSW, Aust –invited lecture

JEE HYUN KIM

- Dept. of Neuroscience, Medical University of South Carolina, USA – invited lecture
- School of Psychology, RMIT (Royal Melbourne Institute of Technology) University, Melbourne, Australia – invited lecture
- Prime Minister's prizes for science awards dinner, Parliament House, Canberra, Australia – invited.
- Australian Academy of Science – Theo Murphy High Flyers Think Tank meeting – invited.
- ABC public lecture "Can you improve your brain" – invited speaker.
- ABC public lecture "Boosting your brain power" – invited speaker.

2013 STUDENTS

- PhD: Nicola Chen, Alec Dick, Rose Chesworth, Phil Ryan, Hanna Kastman, Andrew Walker, Danay Baker-Andresen, Isabel Zbukvic, Xin Du, Christina Mo, Annabel Short, Dean Wright, Jake Rogers, Shlomo Yushuren
- MASTERS: Charlotte Handford, Shawn Tan, Faith Lamont, Emma Giles, Felicia Reed, Katherine Beringer
- HONOURS: Sarah Sulaiman Ch'ng, Suhel Singh, Annabeth Simpson, Russell Coulthard, Marionne Tolentino, Pushba Thangaraju, Uyen (Lavie) Vo, Liliana Laskaris

EDITORIAL BOARDS

ANDREW LAWRENCE

- The British Journal of Pharmacology, Senior Editor
- Neurochemical Research, Associate Editor
- The Journal of Pharmacological Sciences, Associate Editor
- Addiction Biology, Editorial board member
- The Open Neuropsychopharmacology Journal, Editorial board member
- ISRN Addiction, Editorial board member

ANTHONY HANNAN

- Journal of Huntington's Disease, Associate Editor
- European Journal of Neuroscience, Scientific Review Associate
- CNS & Neurological Disorders – Drug Targets, Editorial board member
- Neural Plasticity, Editorial board member
- Neuroscience Letters, Associate Editor
- Frontiers in Neuropharmacology, Review Editor
- Neuroepidemiology, Editorial board member

JHODIE DUNCAN

- Brain Pathology, Editorial board member
- Neurochemical Research, Editorial board member

JEE HYUN KIM

- International Scholarly Research Network: Neuroscience, associate editor
- Pharmacology Research & Perspectives, associate editor

THIBAULT RENOIR

- Frontiers in Neuropharmacology, Associate Editor

AMY BRODTMANN

- Neurology, Editorial Board Member, vascular division
- International Journal of Stroke, Co-Section Editor

EXTERNAL COLLABORATIONS FOR ADDICTION NEUROSCIENCE GROUP

Professor Alon Chen (Weizmann Institute, Israel); Professor Jian-Hui Liang (NIDD, Beijing, China); Professor Bernard Balleine (University of Sydney); Professor Tony Paolini (RMIT); Professor Peter Kalivas (MUSC, USA); Professor Rainer Spanagel (ZIMH, Germany); Professor Caroline Rae (UNSW); Professor Sarah Dunlop (UWA); Assoc Professor Peter Dodd (UQ); Dr Kevin Pfleger (UWA); Dr Amir Rezvani (Duke, USA); Dr. Masa Funada (National Institute of Mental Health, Kohnodai, Japan); Dr. Tim Bredy (The Queensland Brain Institute); Assoc Professor Colin Willis (UNE, Maine); Dr Sarah MacLean (Turning Point Alcohol and Drug Center, Melbourne), Dr Silvia Cruz (Mexico); Dr Andrew Brunn (Melbourne); Dr. Zane Andrews (Monash); Dr. Michael Mathai (Victoria Uni)

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EXTERNAL COLLABORATIONS FOR NEURAL PLASTICITY GROUP

Professor Laurence Lanfumey (INSERM, Paris), Professor Robert Metcalf (Monash University), Professor Margaret Morris (UNSW), Professor Edna Hardeman and Dr Steve Palmer (UNSW), Dr Danny Hatters (Bio21 Institute), Dr Elisa Hill and Professor Joel Bornstein (Melbourne), Dr Jess Nithianantharajah (University of Edinburgh, UK), Dr Laura Gray (Deakin University), Dr Peter Crouch (Melbourne), Dr Nigel Jones and Professor Terry O'Brien (Melbourne), Professor Moira O'Bryan (Monash), Dr Andrew Jenner and Professor Brett Garner (Wollongong), Dr Trent Woodruff and Assoc Professor Peter Noakes (UQ), Assoc Professor Xiao-Jun Du (Baker-IDI), Dr Ghazelah Sadri-Vakili (MGH, Harvard University), Dr Tomris Mustafa (National Institute of Mental Health, USA), Professors Julie Stout and Nellie-Georgiou-Karistianis (Monash), Dr Dan Malone (Monash).

EXTERNAL COLLABORATIONS FOR COGNITIVE NEUROSCIENCE GROUP

AMY BRODTMANN

- Dr Marina Boccardi and Dr Giovanni Frisoni, LENITEM, Fatebenefratelli, IRCSS, Brescia, Italy
- Dr Marco Catani, King's College, London, UK
- Dr Charles DeCarli, University of California Davis, USA
- Professor Trish Desmond, Royal Melbourne Hospital
- Dr Martin Dichgins, Institute for Stroke and Dementia Research (ISD), Ludwig-Maximilians-University, Munich
- Professor John Hodges (FRONTIER, Sydney, Cambridge)
- Dr Tobias Loetscher (Flinders University, Adelaide)

DAVID DARBY

- Professor Kia Nobre, Oxford University,UK
- Dr Moacir Silva Neto, Brasilia, Brazil

PUBLICATIONS

1. Qin, WJ, Wang, YT, Zhang, M, Wen, RT, Liu, Q, Li, YL, Chen, F, Lawrence, AJ & Liang JH (2013) Molecular chaperone Hsp70 participates in the labile phase of development of behavioral sensitization induced by a single morphine exposure in mice. Int. J. Neuropsychopharmacol., 16, 647-659
2. Babovic D, Jiang L, Goto S, Gantois I, Schütz G, Lawrence AJ, Waddington JL & Drago J (2013) Behavioural and anatomical characterisation of mutant mice with targeted deletion of D1 dopamine receptor-expressing cells: response to acute morphine. J. Pharmacol. Sci., 121, 39-47
3. Ryan PR, Buchler E, Shabanpoor F, Hossain MA, Wade JD, Lawrence AJ & Gundlach AL (2013) Central relaxin-3 receptor (RXFP3) activation decreases anxiety- and depressive-like behaviours in the rat. Behav. Brain Res., 244, 142-151
4. Pang TY, Renoir T, Du X, Lawrence AJ & Hannan AJ (2013) Depression-related behaviours displayed by female C57BL/6J mice during abstinence from chronic ethanol consumption are rescued by wheel-running. Eur. J. Neurosci., 37, 1803-1810
5. Brown RM, Khoo SYS & Lawrence AJ (2013) Central orexin (hypocretin) 2 receptor antagonism reduces ethanol self-administration, but not cue-conditioned ethanol-seeking, in ethanol-preferring (iP) rats. Int. J. Neuropsychopharmacol., 16, 2067-2079
6. Chesworth R, Brown RM, Kim JH & Lawrence AJ (2013) The metabotropic glutamate 5 receptor modulates extinction and reinstatement of methamphetamine-seeking in mice. PLoS One, 8(7), e68371
7. Duncan JR, Gibbs SJ & Lawrence AJ (2013) Chronic intermittent toluene inhalation in adolescent rats alters behavioural responses to amphetamine and MK801. Eur. Neuropsychopharmacol., in press
8. Kim JH, Lavan D, Chen N, Flores C, Cooper H & Lawrence AJ (2013) Netrin-1 receptor-deficient mice show age-specific impairment in drug-induced locomotor hyperactivity but still self-administer methamphetamine. Psychopharmacology, 230, 607-616
9. Pang TY, Du X, Catchlove WA, Renoir T, Lawrence AJ & Hannan AJ (2013) Positive environmental modification of depressive phenotype and abnormal hypothalamic-pituitary-adrenal axis activity in female C57BL/6J mice during abstinence from chronic ethanol consumption. Front. Pharmacol., 4, 93 (1-9)
10. Kim HA, Jiang L, Madsen H, Parish, CL, Massalas J, Smardencas A, O'Leary C, O'Tuathaigh C, Waddington JL, Ehrlich ME, Lawrence AJ & Drago J (2013) Resolving pathobiological mechanisms relating to Huntington disease: gait, balance, and involuntary movements in mice with targeted ablation of striatal D1 dopamine receptor cells. Neurobiol. Dis., 62, 323-337
11. Spanagel R, Vengeliene V, Jandeleit B, Fischer WF, Grindstaff K, Zhang X, Gallop M, Krstew EV, Lawrence AJ & Kiefer F (2013) Acamprosate produces its anti-relapse effects via calcium. Neuropsychopharmacology, in press
12. Smardencas A, Rizkalla K, Kim HA, Massalas J, O'Leary C, Ehrlich ME, Schütz G, Lawrence AJ & Drago J (2013) Phenotyping dividing cells in mouse models of neurodegenerative basal ganglia diseases. BMC Neurosci., 14, 111
13. Ryan PR, Kastman HE, Krstew EV, Rosengren KJ, Hossain MA, Churilov L, Wade JD, Gundlach AL & Lawrence AJ (2013) Relaxin-3/RXFP3 system regulates alcohol-seeking. Proc. Natl. Acad. Sci (USA), 110, 20789-20794
14. Dick A, Axelsson, M, Lawrence AJ & Duncan JR (2013) Specific impairments in instrumental learning following chronic intermittent toluene inhalation in adolescent rats. Psychopharmacology, in press
15. Wang YT, Qin WJ, Liu Q, Li YL, Liang H, Chen F, Lawrence AJ, Zhang XL, Liang JH (2013) Chaperone heat shock protein 70 in nucleus accumbens core: a novel biological target of behavioural sensitization to morphine in rats. Int. J. Neuropsychopharmacol., in press
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MEET THE TEAM FROM THE DEVELOPMENTAL PSYCHOBIOLOGY LAB

Our vision is to understand the role of memory and forgetting across development in mental disorders, namely anxiety and substance abuse.

Despite the well-established knowledge that experiences during childhood and adolescence are critical in these disorders, the existing research almost exclusively focuses on memory processes during adulthood. We believe the key to finding effective treatments lies in how we remember and forget emotionally significant events during our development. We use various rodent models that closely resemble human behaviours, and manipulate them using different drugs, viruses, and behavioural approaches to find potential therapeutics. Using animals gives us the opportunity to also find the biological footprints of memory 'engrams' that control our emotions and decisions.

Our research will fundamentally change how we understand anxiety disorders and drug addiction by shifting the focus to pre-adulthood, when our brains are most plastic to environmental influences.

For example, we were the first to discover that fearful memories can be erased during childhood. The meaning of cues that initially evoke signs of fear can be permanently changed so that they no longer evoke any fear in juvenile rodents. These rodents that show 'erased' fear memory are completely immune to reminder treatments that normally retrieve fear memories in adult rodents. This finding shows that we are initially resilient to developing permanent anxious memories early in life (roughly the age of seven, when we acquire large-scale spatial learning abilities). Unfortunately, we also discovered that this resilience quickly turns into vulnerability during adolescence, in that behavioural training that normally reduces fear and anxiety in adult rodents is not effective during adolescence. These findings have since been replicated in humans and we currently have a collaboration with Melbourne Neuropsychiatry Centre to understand how we can reverse such an impairment in fear inhibition during adolescence in humans based on our ongoing rodent studies. We have some evidence now to believe that the communication between cortico-limbic brain regions fundamentally determines whether memories are persistent or erased, and we are now testing novel ways to manipulate such communications in an attempt to erase memories, even past childhood.

We believe that common emotional memory processes underlie both anxiety and addiction. Indeed, we have new findings that show the adolescent vulnerability in inhibition of fear memories extends to inhibition of cocaine-related memories. Although clinically it is known that drug-cues contribute to relapse in adolescent cocaine users, we have the first laboratory demonstration showing disrupted inhibition of a cocaine-associated cue and increased relapse-like behaviours following cocaine self-administration in adolescent animals. We are now working on behaviourally and pharmacologically increasing inhibition of emotionally significant cues in order to discover novel therapeutics for anxiety and addiction. Alongside those translational efforts, we are also working on more basic experiments to delineate the neural mechanisms underlying those good and bad memories that contribute to mental disorders. We want to understand how we can forget or erase any memories that threaten our quality of life. Our research will fundamentally change how we understand anxiety disorders and drug addiction, by shifting the focus to pre-adulthood, when our brains are most plastic to environmental influences.

Watch Jee's TEDx talk

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CLINICAL DISCOVERY UNIT

Division head: Professor Michael Berk

A QUICK SNAPSHOT

The Clinical Discovery Unit in partnership with the IMPACT Strategic Research Centre at Deakin University and Barwon Health, has two predominant foci. Firstly, the development of novel therapies for neuropsychiatric disorders and secondly, understanding risk factors for, and the prevention of, psychiatric disorders. The unit conducts clinical trials, epidemiological studies and biomarker analyses. It is a member of the CRC for Mental Health.

COLLABORATIONS

The unit has multiple state-wide, national and international collaborative partnerships. Among many, these include the University of British Columbia, Canada, Stanford University San Francisco, the Mayo Clinic Rochester, Harvard University Boston, Cambridge University, INSERM Paris, Norwegian University of Science and Technology.

RESEARCH HIGHLIGHT

2013 was a productive year. The quality and quantity of our research output continues to grow with 118 publications in 2013 including a number of high impact publications in the top journals in the field, including Molecular Psychiatry, The American Journal of Psychiatry and The British Journal of Psychiatry. A number of members of the team had particular successes. Ajeet Singh was awarded a Pfizer NSR neuroscience grant and a travel award from the XXIst World Congress on Psychiatric Genetics, Lesley Berk was awarded an Alfred Deakin post-doctoral scholarship, Sharon Brennan was awarded Annual President's Poster Award for most outstanding abstract at the American Society for Bone and Mineral Research (2013) and a Scientists' Research Prize for most outstanding research presentation at the Annual Geelong Research Network research week, Adrienne O'Neil was awarded an NHMRC early career fellowship, Natalie Hyde obtained an APA award, Shae Quirk obtained an NHMRC postgraduate scholarship, Lana Williams was successful in achieving an NHMRC career development fellowship and Michael Berk was given an NHMRC Senior Principal Research fellowship. Lana Williams also won the Smart Geelong "Living with a disability" award. Felice Jacka became the inaugural Chair of the International Society for Nutritional Psychiatry research as well as the Alliance for the Prevention of Mental Disorders. Julie Pasco was appointed to the level of full Professor.

Research highlights include the first proof that N-Acetyl Cysteine has efficacy in unipolar major depression. We were able to show, for the first time, that pre-natal exposure to both cigarette smoking and poor diet increased the risk of mood disorders in offspring. The team demonstrated molecular pathways whereby antidepressants might cause osteoporosis, and provided the first evidence that Paroxynase 1 is a biomarker for depression.

EDITORIAL POSITIONS

PROFESSOR MICHAEL BERK

- Acta Neuropsychiatrica, Issue Editor
- Bipolar Disorders, Editorial review board
- Human Psychopharmacology, Clinical and Experimental, Editor
- Depression and Anxiety, Editor in Chief
- Journal of Psychiatry in Clinical Practice, Editorial review board
- African Journal of Psychiatry, Associate Editor
- Australian & New Zealand Journal of Psychiatry, Member of Advisory Board
- Early Intervention in Psychiatry, Associate Editor
- Clinical Psychopharmacology & Neuroscience
- The Open Psychiatry Journal, Editorial review board
- Clinical Practice (formerly known as Therapy), Editorial review board
- Future Medicine, guest editor
- Therapeutic Advances in Chronic Disease, Editorial Board member
- Australian and New Zealand Journal of Psychiatry (ANZJP), Associate Editor
- World Journal of Psychiatry, Editorial Board Member
- Translational Psychiatry, Editorial Board Member
- Journal of Clinical Medicine, Editorial Board Member
- Current Psychopharmacology, Editorial Board Member
- International Bipolar Foundation, Scientific Advisory Board Member
- International Journal of Bipolar Disorders – Editorial Board Member
- Psychiatry Investigation – Editorial Board Member
- Basic and Clinical Psychiatry – Editorial Board Member
- BMC Medicine – Editorial Board Member
- Current Treatment Options in Psychiatry – Editorial Board Member

MAJOR NATIONAL AND INTERNATIONAL (INVITED) CONFERENCES 2013

- 11th World Congress of Biological Psychiatry Kyoto, Japan,2013
- Australasian Society for Bipolar & Depressive Disorders Conference Melbourne, Australia, 2013
- 26th European College of Neuropsychopharmacology (ECNP) Congress Barcelona Spain,2013
- The Australian Society for Psychiatric Research (ASPR) Conference Melbourne, Australia, 2013
- The Australian Schizophrenia Conference (ASC) Conference Melbourne, Australia, 2013

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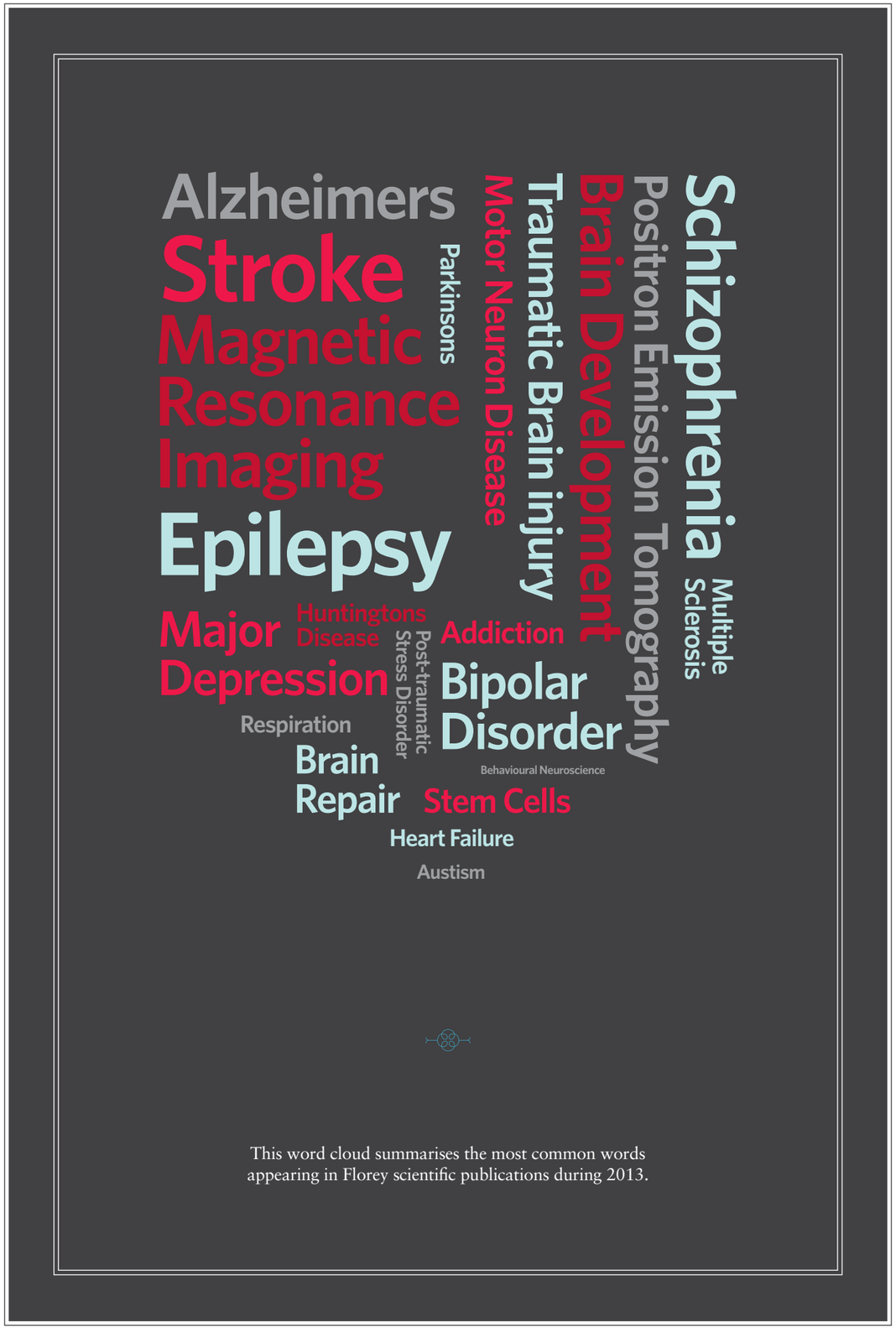

This word cloud summarises the most common words appearing in Florey scientific publications during 2013.

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EPILEPSY

Division heads: Professor Graeme Jackson and Associate Professor Steve Petrou

A QUICK SNAPSHOT

The Florey epilepsy division is a world-leading centre for epilepsy research. The division has major groups at both the Florey's Austin and Parkville campus. The group studies mechanisms that cause epilepsy from cells to the function of the whole brain. We use technologies including advanced MRI and cutting edge cellular physiology techniques to allow us to understand genetic and acquired mechanisms that give rise to epilepsy. Together with our colleagues from The University of Melbourne and across Australia, we are working towards finding a cure for epilepsy.

RESEARCH HIGHLIGHTS

We discovered there are at least six distinct functional brain networks associated with the abnormal brain activity that occurs between seizures in absence epilepsy.

The discovery was made possible by application of novel acquisition and data analysis methods for simultaneous EEG-fMRI that we have developed over the last decade. Two of the networks, which have some spatial overlap, are shown in figure 1. Also displayed for comparison in the figure (hatched in blue) is a more limited result derived using conventional analysis methods. This finding has fundamental implications for our understanding of this epilepsy, and also provides a striking example of the benefits of our advanced methodological approaches.

AN IDEA LIKELY TO CHANGE LIVES BY 2033

Our recent brain imaging studies of epilepsy patients have revealed abnormal functional involvement of complex networks throughout the brain, even when patients are not having a seizure, and even in epilepsy caused by a small focal lesion. Understanding the nature of this activity will likely herald new approaches to treatment, including guiding the placement of implantable neuro-stimulators to help prevent seizures.

> "It is possible to reverse the functional deficit caused by an epilepsy mutation with an already approved drug.... an opportunity to treat a devastating form of epilepsy with a drug specifically targeted to the disease mechanism"

MAIN AREAS OF RESEARCH

- Epilepsy imaging
- Human brain structure and function
- Ion channels and disease
- Neurobiology of epilepsy
- Purinergic signalling

SENIOR STAFF

EPILEPSY IMAGING

• Professor Graeme Jackson (Division Head) • Dr David Abbott • Associate Professor Peter Brotchie • Dr Patrick Carney • Associate Professor Paul McCrory • Dr Saul Mullen • Professor Ingrid Scheffer •

ION CHANNELS AND EPILEPSY LAB

• Associate Professor Steve Petrou • Dr Alison Clarke • Dr Elena Gazina • Dr Carol Milligan • Dr Kay Richards • Dr Robert Richardson • Dr Verena Wimmer •

SYNAPTIC PHYSIOLOGY

• Dr Christopher Reid • Dr Han Shen Tae • Dr Marie Phillips •

PURINERGIC SIGNALLING

• Dr Ben Gu • Professor James Wiley •

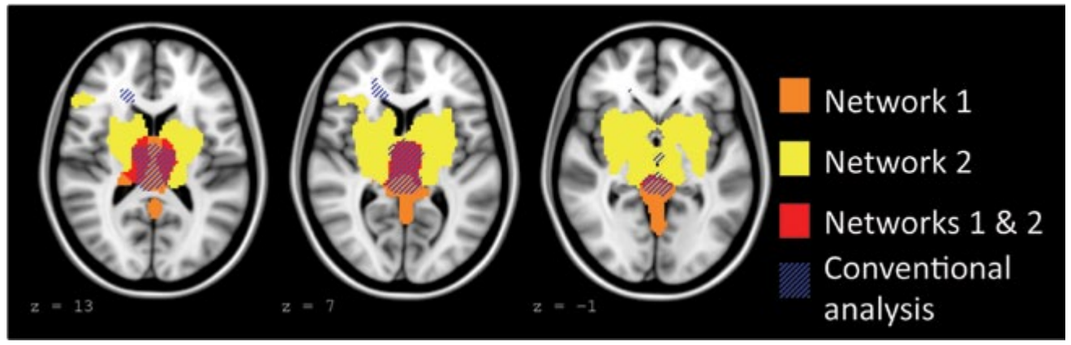

Figure 1. Two of the six functionally distinct networks associated with abnormal brain activity in Absence epilepsy are shown in yellow and orange (and red where they overlap), overlayed upon three axial MRI slices. Our new analysis approach provides evidence for activation in a much larger network of brain regions than seen using conventional model-based analysis (blue hatched region).

EPILEPSY – ION CHANNELS AND HUMAN DISEASE

Leader: Steve Petrou

Our research focus is in the understanding the pathology of ion channel disorders. We use a multidisciplinary approach spanning ion channel biophysics, mouse transgenesis, genetic analysis, computational modeling in vitro and in vivo physiology.

Research highlights for 2013

Our research focus is in understanding the central nervous system pathology of ion channel disorders with a specialised interest in genetic epilepsy. The National Institute of Health-funded Epi4K program continues to reveal the fundamental genetic architecture of the epilepsies. Associate Professor Steve Petrou heads the Epi4K Functional Core and work is underway to understand the mechanisms that underlie genetic epilepsy. Excitingly, we have demonstrated that it is possible to reverse the functional deficit caused by an epilepsy mutation with an already approved drug. This provides an opportunity to treat a devastating form of epilepsy with a drug that is specifically targeted to the disease mechanism. Clinical trials have begun to test this idea.

We have also investigated heterogeneity in the genetic epilepsies using animal models. We provide evidence that 'syndrome-specific' mouse models of epilepsy can recapitulate the genetic principles seen in humans with the disease. Understanding the complexity underlying heterogeneity is central to our ability to predict disease outcome from the personal genome.

The development of new iPS models and TALEN based genome editing continues with the view of creating human neurons for network scale functional genomics analysis as another means of investigating this issue.

These projects are beginning to enable much-needed translational outcomes for improved therapies in the epilepsies.

Research highlights for 2013

This group is primarily based at the Austin node of the Florey and has published more than 80 peer reviewed journal papers in 2013. Our basic work is to understand brain development and function, particularly the disturbances in distributed networks that underlie epileptic disorders. This is done in a translational environment that is immediately relevant to patient care. In addition to the obvious symptomatology of epilepsy (i.e. seizures), cognition, memory and language disturbances are key cognitive areas affected by the disease. We are using EEG/fMRI, advanced diffusion techniques including tractography, functional connectivity and network analysis to investigate the underlying brain mechanisms responsible for the clinical symptoms.

Where necessary, we also develop improved methods for acquisition and data analysis. For example, a recent methodological development from our group assists data-driven (model free) analysis of fMRI by automatically detecting substantial artefact that is often unavoidable in functional MRI acquisitions. The novel classification algorithm is called SOCK and the use of adaptive clustering allows it to be applied to any fMRI data-set. Automatic rejection of artifact reduces manual effort and subjectivity in interpretation of data-driven neuroimaging analysis. The approach has been successfully tested on our own data as well as data from other laboratories.

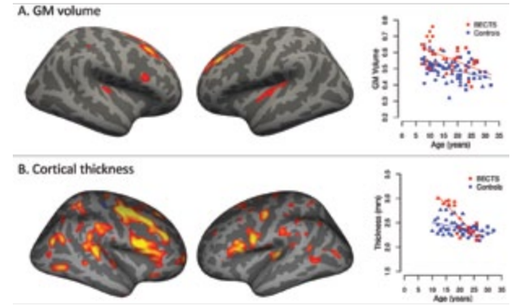

Figure 2. We discovered regional volume and thickness increases in benign epilepsy with centro-temporal spikes (BECTS), the most common epilepsy of childhood. The top row shows volume increases in the BECTS patients compared to control subjects in colour, overlayed upon an "inflated" brain. The bottom row shows increased cortical thickness in BECTS versus control subjects imaged ~9 years after onset. The graphs shows the relationship between change and age. Notice as age increases the effect decreases, which parallels the natural history of the disorder. The areas affected are consistent with the mild neurocognitive dysfunction observed in children with BECTS.

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Advanced neuroimaging methods can also allow quantitative, objective assessment of variations in brain morphology associated with neurological disorders, and can be particularly powerful when studying well defined groups of patients. Using such methods we discovered evidence of structural variation associated with benign epilepsy with centro-temporal spikes (BECTS), the most common epilepsy of childhood. We included patients over a wide age range and discovered the differences compared to healthy controls declined with age, consistent with the distinctive age-dependent profile of this disorder: virtually all children with BECTS remit by age sixteen.

The effect of antiepileptic medication on the brain is also of interest, to help better understand the mechanism of action and also to understand potential side effects. Once again using measures of regional brain volume and cortical thickness derived from structural MRI scans, we established that sodium valproate use in epilepsy is associated with thinning of the parietal lobe, reduced total brain volume, and reduced white matter volume as shown in figure 3. Sodium valproate is a widely used antiepileptic medication, so it is important to understand the potential long term consequences of its use. We therefore also studied past valproate users who no longer take this medication, comparing them to epilepsy patients who had never taken valproate: we found no significant difference, suggesting parietal lobe thinning and volume changes associated with valproate may be transient.

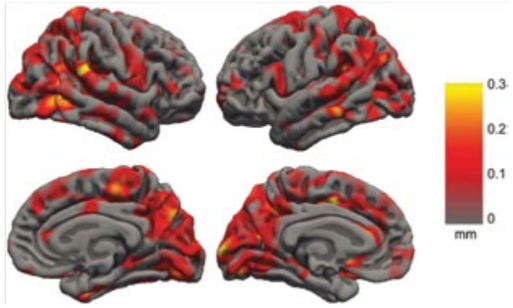

Figure 3. The spatial distribution of cortical thickness decreases in subjects with focal epilepsy taking valproate relative to subjects with epilepsy not taking valproate is shown in colour on the brain renderings. The intensity of the colour overlay indicates the magnitude of the thickness decrease: Hotter colours indicate reduced cortical thickness in subjects taking valproate.

EPILEPSY – ION CHANNELS AND HUMAN DISEASE

EDITORIAL POSITIONS

- Neurobiology of Disease
- Epilepsia

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

- 2013 Dec. pH modulation of neuronal excitability: Towards a molecular mechanism. University of Helsinki.
- 2013 Dec. Translational opportunities in the epileptic encephalopathies. University of Helsinki.
- 2013 Dec. Cell, network and mouse modelling of genetic epilepsies for mechanism, diagnosis and therapy. Translation Research Symposium, American Epilepsy Society. Plenary.
- 2013 Oct. Grant mentoring strategies. John Curtin School Strategic Retreat. Australian National University.
- 2013 Oct. Cell, network and mouse modelling of genetic epilepsies for mechanism, diagnosis and therapy. Australian National University
- 2013 Sep. Epilepsy in a dish: Scalable genome edited stem cell models for neurogenetic disorders. Stems Cells Australia Annual Meeting. Melbourne, Australia.
- 2013 Sep. Oocyte modeling of ATP1A3 mutations in Alternating Hemiplegia of Childhood and Rapid Onset Dystonia Parkinsonism. 2nd International meeting of AHC society. Rome, Italy. Plenary
- 2013. Sep. R43Q mouse. What is good for? Absolutely everything! Melbourne Epilepsy Consortium Meeting.
- 2013 Aug. Stem cell models for diagnosis and therapy. Presentation to Pfizer, Melbourne, Australia.
- 2013 June. High content, high throughput analysis of sodium channel variants in epilepsy. Aurora Biomed Ion Channel Screening Meeting. Vancouver. Canada. Plenary
- 2013 July. Multi-electrode array recording of genome edited human iPS neurons in genetic epilepsy. Melbourne Epilepsy Retreat.
- 2013 April. Channelopathy therapy development. NIH Sponsored Conference on Curing the Epilepsies Benchmarks. Bethesda, MD, USA. Plenary
- 2013. April. Functional mechanisms in the genetic epilepsy. Centre for Human Genome Variation. Duke University, North Carolina. USA
- 2013. Feb. Animal models of the genetic epilepsies. Australian Neuroscience Society Symposium.

EPILEPSY – NEUROIMAGING

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

- Invited plenary speaker: American Epilepsy Society Annual Meeting (Annual Fundamentals of Epilepsy Symposium). Talk title: "New MRI Techniques in Epilepsy". Washington DC, USA 6th Dec 2013
- Invited speaker (international conference, named lecture): Rebecca Hotchkiss International Scholar Exchange Program. Talk title: "Functional and structural connectivity in epilepsy" and "fMRI – where are we now". Calgary, Canada, 17th–20th Sept 2013
- Invited speaker (international conference). Australian American Leadership Obesity Conference. Sydney, 7th Aug 2013
- Plenary speaker (national conference): 22nd Royal Brisbane & Women's Hospital Healthcare Symposium: Lifestyle and Health, Ease and Disease. Talk title: "Brain Networks in Epilepsy". Brisbane, 18th Oct 2013
- Invited Lecture: "Genetic infantile epileptic encephalopathies: Recognition of phenotypes", Pediatric Hot Topics symposium, American Epilepsy Society Annual Meeting, Washington, 9 December 2013.
- Invited Lecture: "Epilepsy Genetics: Translation to clinical practice", American Epilepsy Society Annual Meeting, Washington, 6 December 2013.
- Invited Lecture: "Epilepsy limited to females with mental retardation", American Epilepsy Society Annual Meeting, Washington, 6 December 2013.
- Invited Lecture: "Genetic testing in epilepsy: What should I be doing?", American Epilepsy Society Annual Meeting, Washington, 7 December 2013.
- Invited Lecture: "Fever susceptibility syndromes – predicting outcome". ILAE Progress in Epilepsy Disorders Workshop – Seizures of onset in the first two years of life, Rome, Italy, 16 November 2013.
- Invited Chair: "Epilepsy Genetics: new insights change clinical practice", World Congress of Neurology, Vienna, Austria, 22 September 2013.
- Invited Lecture: "Adult patients with epileptic encephalopathies: not too late to make a genetic diagnosis", World Congress of Neurology, Vienna, Austria, 22 September 2013.
- Invited Lecture: "New Organization of the Epilepsies", Child Neurology course, World Congress of Neurology, Vienna, Austria, 22 September 2013.
- Invited Lecture: "Ion channels in epilepsy", Channelopathies symposium, World Congress of Neurology, Austria, 22 September 2013.

- Plenary Lecture: "Epilepsy genetics: a successful marriage of next generation sequencing and next generation phenotyping", 31st International Australasian Winter Conference on Brain Research, Queenstown, New Zealand, 24 August 2013.
- Invited Lecture: "Listening to the community: modifications to the new organization", 30th International Epilepsy Congress, Montreal, Canada, 26 June 2013.
- Invited Chair: "The new organisation of the epilepsies in daily practice", 30th International Epilepsy Congress, Montreal, Canada, 26 June 2013.
- Invited Lecture: "What's new in diagnostics. What genetic tests should I order today in my patients?" 30th International Epilepsy Congress, Montreal, Canada, 25 June 2013.
- Invited Lecture: "The relationship between paroxsyzmal dyskinesia and epilepsy: Lessons from recent genetic advances", 7th International Congress of Parkinson's Disease and Movement Disorders, Sydney, Australia, 16-20 June 2013.
- Invited Lecture: "Monogenic Epilepsies", Symposium on transition of children to adult medical care, Paris, France 25-26 May 2013.
- Invited Lecture: "Advances in epilepsy genetics: Changing clinical practice", Gesellschaft Neuropädiatrie (GNP), Innsbruck, Austria, 24-28 April 2013.
- Invited Participant: Dinner Debate: Women in science – education, advancement, career opportunities, and the persistent lack of parity in the sciences. L'Oreal-UNESCO For Women in Science 15th Anniversary Events, Paris, France 27 March 2013.
- Invited Participant: BIOVISION Prospective Debate: Can we avoid lifestyle diseases individually or collectively, BIOVISION: The World Life Sciences Forum, Lyon, France, 24-26 March 2013.
- Invited Participant: BIOVISION Prospective Debate: Impact of modern lifestyle on health, BIOVISION: The World Life Sciences Forum, Lyon, France, 24-26 March 2013.
- Invited Lecture: "Genetic testing in epilepsy: what should you be doing?" BIOVISION: The World Life Sciences Forum, Lyon, France, 24-26 March 2013.

EDITORIAL BOARDS

- Annals of Neurology – Ingrid Scheffer
- Epileptic Disorders – Graeme Jackson and Ingrid Scheffer
- Frontiers in Neurology – David Abbott, Patrick Carney, David Vaughan, Graeme Jackson
- Frontiers in Neuroscience – David Abbott, Patrick Carney, David Vaughan, Graeme Jackson
- Progress in Epileptic Disorders series – Ingrid Scheffer

MAJOR AWARDS

The seminal contributions to epilepsy research of Professor Ingrid Scheffer continue to be recognised internationally with six major awards bestowed in 2013:

2013 GlaxoSmithKline Award for Research Excellence
National award for outstanding research: For helping to transform the diagnosis of epilepsy

2013 Ambassador for Epilepsy Award
For outstanding international contribution to epilepsy.
International League Against Epilepsy, Montreal, Canada

2013 Emil Becker Prize
For outstanding contribution to paediatric neurology.
Gesellschaft Neuropädiatrie (German speaking society for neuropaediatrics), Austria

2013 Australian Neuroscience Medallion
Australian Neuroscience Society

2013 Mervyn J Eadie Award
To honour a significant contribution to neuroscience research.
Australian and New Zealand Association of Neurologists

2013 Eccles Lectureship
Australian Neuroscience Society and Australian Neurosurgical Society

EXTERNAL COLLABORATIONS

The epilepsy imaging group co-published this year with many researchers including those from the following institutes:

The University of Melbourne, Monash University, Royal Melbourne Hospital, Royal Womens Hospital (Melbourne), CSIRO, Austin Health, Royal Children's Hospital (Melbourne), Murdoch Childrens Research Institute (Melbourne), Royal Victorian Eye & Ear hospital, Women's & Children's Hospital (Adelaide), The University of Adelaide, The University of Queensland, The Children's Hospital Westmead (NSW), Royal Children's Hospital Herston (Brisbane), NIH (USA), Ann & Robert H. Lurie Children's Hospital of Chicago (USA), Northwestern University Feinberg School of Medicine (USA), Kaohsiung Chung Gung Memorial Hospital (Taiwan), Foothills Medical Centre (Canada), University of Calgary (Canada), New York University School of Medicine (USA), Yale School of Medicine (USA), University of Otago (NZ), University of Pisa (Italy), IRCCS Fondazione Stella Maris (Italy), Prince of Songkla University (Thailand), Gachon University of Medicine and Science (Korea), Eulji University (Korea), University of Pennsylvania (USA), Tel-Aviv University Medical School (Israel), Schneider Children's Medical Center of Israel (Israel), Western Galilee Hospital (Israel), Ginatuna Association (Israel)

PUBLICATIONS

1. Phillips AM, Kim T, Vargas E, Petrou S, Reid CA. Spike-and-wave discharge mediated reduction in hippocampal HCN1 channel function associates with learning deficits in a genetic mouse model of epilepsy. Neurobiol Dis. 2013 Dec 22;64C:30-35
2. Gu BJ, Sun C, Fuller S, Skarratt KK, Petrou S, Wiley JS. A quantitative method for measuring innate phagocytosis by human monocytes using real-time flow cytometry. Cytometry A. 2013 Oct 16. doi: 10.1002/cyto.a.22400. [Epub ahead of print]
3. Kurniawan ND, Richards KL, Yang Z, She D, Ullmann JF, Moldrich RX, Liu S, Yaksic JU, Leanage G, Kharatishvili I, Wimmer V, Calamante F, Galloway GJ, Reutens DC*, Petrou S*. Visualization of Mouse Barrel Cortex using Ex-vivo Track Density Imaging. Neuroimage. 2013 Sep 20. doi:pii: S1053-8119. * Equal Contribution
4. Goldstein DB, Allen A, Keebler J, Margulies EH, Petrou S, Petrovski S, Sunyaev S. Sequence-wide studies in human genetics: design and interpretation. Nature Reviews Genetics 2013 Jul;14(7):460-70
5. Harty RC, Kim TC, Thomas EA, Cardamone L, Jones NC, Wimmer VC*, Petrou S*. Axon initial segment structural plasticity in animal models of genetic and acquired epilepsy. Epilepsy Research. 2013 Apr 17 (Epub). * Equal contribution
6. Olivia M and Petrou S. CELF expression in epilepsy linked to sodium channels. Future Neurology 2013 8(3), 255-257

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7. Thomas EA and Petrou S. Network specific mechanisms may explain the paradoxical effects of carbamazepine and phenytoin. Accepted Epilepsia 2013 Apr 8 (Epub)

8. Richards KL, Kurniawan ND, Yang Z, Kim TH, Keller MD, Low JWJ, Ullmann JFP, Cole S, Foong S, Galloway GJ, Reid CA, Paxinos G, Reutens DC, Petrou S. Hippocampal volume and cell density changes in a mouse model of human genetic epilepsy. Accepted. Neurology. 2013 Mar 26;80(13):1240-6

9. Haas M, Qu Z, Kim TH, Vargas E, Campbell K, Petrou S, Tan SS, Reid CA, Heng J Perturbations in cortical development and neuronal network excitability arising from prenatal exposure to benzodiazepines in mice. Eur J Neurosci. 2013 May;37(10):1584-93

10. Reid CA, Kim TH, Phillips AM, Low JWJ, Berkovic SF, Luscher B, Petrou S. Multiple molecular mechanisms for a single GABAA mutation in epilepsy. Accepted. Neurology 2013 Mar 12;80(11):1003-8

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IMAGING

Division heads: Professor Alan Connelly and Professor Graeme Jackson

A QUICK SNAPSHOT

The Florey Imaging Division encompasses the following research groups: Advanced MRI Development, Epilepsy Imaging, Small Animal MRI, and Interoception. These groups perform neuroscience related MRI research across a wide range of MRI methods, including diffusion MRI, perfusion MRI, functional MRI, and high resolution structural MRI. Most of this work involves the application of up to date MRI acquisition and analysis methods to disease related neuroscience issues, while the work of the Advanced MRI Development Group is at the forefront of developing novel methods to facilitate neuroscience investigations that were previously not possible.

RESEARCH HIGHLIGHT

The Advanced MRI Development team is one of the world leaders in diffusion MRI innovation, and the methodological advances made at the Florey will have a major influence on human connectome investigations.

Following a significant upgrade in 2012 to the 4.7 T animal scanner, thanks to support from the Victorian Biomedical Imaging Capability and the National Imaging Facility, research has progressed during 2013 in areas that were not previously possible (eg animal functional MRI), enabling new scientific collaborations to be established.

The Interoception Group's research includes strong interests in the areas of brain (and brainstem) systems for central pain processing and central cough networks, the latter in particular in patients with cough hypersensitivity and in people with cystic fibrosis.

There are significant cross-relations between the Epilepsy and Imaging divisions, which will be described in detail in the Epilepsy division section of this report.

AN IDEA LIKELY TO CHANGE LIVES BY 2033

Understanding how structural connections relate to brain function is the subject of a major international program of research (the human 'connectome' project). The Florey's methods development achievements will contribute significantly to this effort to move towards a more complete understanding of how the brain works, which has the potential to revolutionise human neuroscience.

> "Major breakthroughs were achieved in 2013 in establishing improved methods to visualise fibre tracts prior to neurosurgery"

SENIOR STAFF

ADVANCED MRI DEVELOPMENT

• Professor Alan Connelly • Professor Graeme Jackson • Associate Professor Fernando Calamante • Dr Donald Tournier • Dr Lisa Willats • Dr David Raffelt • Dr Xiaoyun Liang • Dr Robert Smith • Wai Yen Lo •

ANIMAL MRI

• Dr Leigh Johnston (Honorary) • Professor Roger Ordidge (Honorary) • David Wright • Dr Hong Wang •

INTEROCEPTION

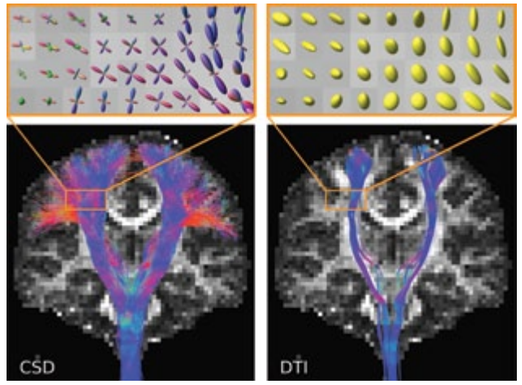
• Dr Michael Farrell • Dr Leonie Cole •

ADVANCED MRI DEVELOPMENT GROUP

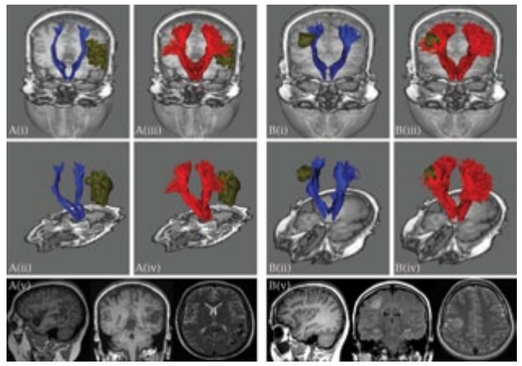
Leader: Alan Connelly

Research highlights for 2013

Major breakthroughs were achieved in 2013 in establishing improved methods to visualise fibre tracts prior to neurosurgery, and in developing a novel method to combine structural and functional information into a single image in order to better understand networks within the brain. Given that networks' abnormalities are increasingly believed to be associated with a number of important disease states, the latter information opens up potentially new areas of neuroscientific enquiry.



Coronal FA images overlaid with fiber tracking results using CSD (left) and DTI (right) from a representative healthy control subject. The magnified regions in the orange boxes show the fiber orientation estimates within individual voxels. The CSD fiber orientation estimates (upper left image) confirm the presence of many voxels containing multiple fiber orientations, within individual voxels. The tensor-derived orientation in equivalent voxels (upper right image) does not represent any of the constituent fiber populations in regions where the DTI-based tractography method failed to produce tracks. Reprinted from Farquharson, s et al. White matter fiber tractography: why we need to move beyond DTI. Journal of Neurosurgery Jun 2013 / Vol. 118 / No. 6 / Pages 1367-1377 with kind permission from AANS.



Results of DTI-based tractography (blue) and CSD-based tractography (red) (derived from the same DWI data set) with segmented pathology volumes (green) overlaid on coronal T1-weighted images for Case A (A) and Case B (B). Case A involved a 49-year-old woman with a large left-sided temporoparietal AVM. See MR images in Panel A(v). Case B involved a 24-year-old woman with a right focal cortical dysplasia situated in the right posterior frontal lobe. See MR images in Panel B(v). The DTI-based tractography results in Case A suggest a clear margin surrounding the lesion (i and ii), whereas the CSD-based tractography results indicate that lateral projections of the corticospinal pathway may be at risk (iii and iv). The DTI-based tractography results in Case B suggest that only the medial aspect of the lesion impinges on the corticospinal tracts (i and ii), whereas the CSD-based tractography results suggest that the lesion is enveloped by medial and lateral projections of corticospinal fibers (iii and iv). Reprinted from Farquharson, s et al. White matter fiber tractography: why we need to move beyond DTI. Journal of Neurosurgery Jun 2013 / Vol. 118 / No. 6 / Pages 1367-1377 with kind permission from AANS.

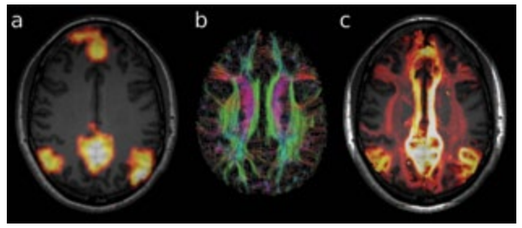
Software

- MRtrix: software package to enable white matter fibre tracking to be done in the brain using our constrained spherical deconvolution algorithm. (>6700 downloads)
- Numerical Fibre Generator: software package to generate realistic arrangements of bundles of fibres, with a complexity similar to that of white matter. Designed to be used as a testbed for the development and evaluation of tractography methods. (>1300 downloads)

Patent

Image processing system: A method for generating super-resolution images of fibrous tissue (such as white matter), based on tractography output.

International patent application no: PCT/AU2010/000257



Track-weighted (TW) functional connectivity (FC) technique. (a) Example FC network (the so-called default mode network) generated using BOLD fMRI data. (b) Whole-brain diffusion MRI fibre-tracking from the same subject. The TW-FC technique combines these two data sets to generate a TW-FC map (c), showing both the functional information and the structural connections. This novel method effectively 'propagates' the FC information along pathways involved in the functional network, highlighting the white matter connections of the network.

ANIMAL MRI

Leaders: Leigh Johnston (University of Melbourne; Hon Florey) and Alan Connelly (Florey)

Research highlights for 2013

The Animal MRI Lab strengthened collaborations with Prof Terry O'Brien and Dr Sandy Shultz (UoM) in imaging rodent models of traumatic brain injury (TBI), which has led to progress in identifying potential neuroprotective agents in experimental TBI.

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INTEROCEPTION

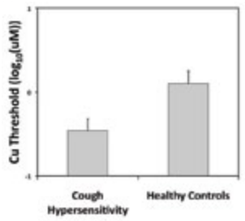
Leader: Michael Farrell

Research highlights for 2013

The Interoception Imaging team provided important insights into two aspects of human homeostasis. In collaboration with Systems Neurobiology, the team was able to accurately locate regions in the brainstem involved in the control of sweating. There has been ongoing debate about whether emotional sweating and heating-related sweating are likely to be related to different brain regions. Our team was able to show that the control of both forms of sweating is mediated by identical structure in the midbrain and medulla.

Another exciting outcome was achieved in collaboration with Dr Stuart Mazzone of the University of Queensland. In another first, the team was able to show substantial decreases in brain regions coding the urge-to-cough after the administration of a placebo. Participants in the study were under the misapprehension that they were inhaling a powerful cough suppressant, which in reality was simply ordinary air. Belief in the suppressant was enough to greatly reduce regional brain responses during inhalation of an irritant, and the team were able to identify associated activity in the prefrontal cortex as a major contributor to the antitussive benefits of deception.

A



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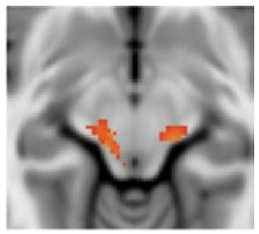

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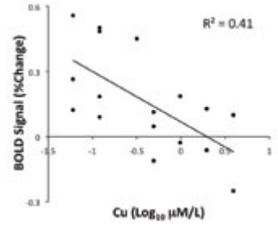

A. Patients suffering from a variety of respiratory disorders can complain of a persistent, non-productive cough. They are also troubled by an urge-to-cough that is not satiated by coughing. These patients are especially sensitive to stimulation of the airways. We found that the dose of inhaled capsaicin to evoke a perceptible urge-to-cough (Cu threshold) was significantly decreased in a group of cough hypersensitive patients compared to healthy controls.

B. The inhalation of capsaicin is associated with an urge-to-cough and activations in a widely distributed network of brain regions. Cough hypersensitive patients show an increased level of activation in the midbrain during capsaicin inhalation compared to healthy people.

C. The increased midbrain activation in cough hypersensitive patients is likely to incorporate the nucleus cunieformis, which also shows activation in response to painful stimulation of sensitised skin (hyperalgesia).

D. Cough hypersensitivity patients with the highest levels of BOLD signal change in the midbrain during capsaicin inhalation were the most sensitive to airways stimulation (had lowest Cu thresholds).

ADVANCED MRI DEVELOPMENT GROUP

COLLABORATIONS

In addition to a range of collaborations within the Florey, the MRI development group has both national and international collaborations with a wide range of institutions, including:

- Universities of Adelaide, Queensland, Sydney, and Melbourne
- MCRI
- Royal Women's Hospital Melbourne
- CSIRO, Brisbane
- University College London
- Stanford University
- Karolinska Institute, Stockholm
- Leiden University
- George Mason University, Washington DC
- Neuroscience Research Institute, Incheon (S Korea)
- Max Planck Institute, Leipzig.

EDITORIAL POSITIONS

- Alan Connelly – Member Editorial Board of Epilepsia

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

ALAN CONNELLY

- Advances in diffusion MRI and their applications to epilepsy. Australia and New Zealand Association of Neurologists (ANZAN) Annual Scientific Meeting, Sydney.
- Diffusion MRI Analysis. Educational Course at the 21st Annual Meeting of the International Society for Magnetic Resonance in Medicine, Salt Lake City, USA.
- Advances in analysis methods for diffusion MRI. 5th Asia-Pacific NMR Symposium in conjunction with ANZMAG 2013, Brisbane.

ANIMAL MRI

COLLABORATIONS

- The Alfred Hospital
- Baker IDI
- Bionics Institute
- CSIRO
- Monash ARMI
- Monash Richie Centre
- Royal Victorian Eye and Ear Hospital
- Royal Women's Hospital
- The University of Melbourne
- MCRI

INTEROCEPTION

COLLABORATIONS

- School of Biomedicine University of Queensland
- Research Imaging Institute, UTHSCSA, USA
- Autonomic Neuroscience, the Florey
- Respiratory and Sleep Disorders Medicine, and Anaesthesia and Pain Management, Royal Melbourne Hospital.

EDITORIAL POSITIONS

- Michael Farrell – Member Editorial Board Human Brain Mapping

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

MICHAEL FARRELL

- Invited Symposium, Australian Pain Society, 33rd ASM, Canberra, Australia.
- Invited Symposium, Australian Society of Anaesthetists National Scientific Congress, Canberra, Australia.

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16. K. Layton, M. Morelande, P.M. Farrell, W. Moran and L.A. Johnston, Modelling and Estimation of Multicomponent T2 Distributions, IEEE Transactions on Medical Imaging, vol.32(8), pp.1423 – 1434
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23. Mazzone, S.B., McGovern, A.E., Yang, S., Phipps, S., Ando, A., Leech, L. Farrell, M.J. Sensorimotor circuitry involved in the higher brain control of coughing, Cough 9(1) 2013 7

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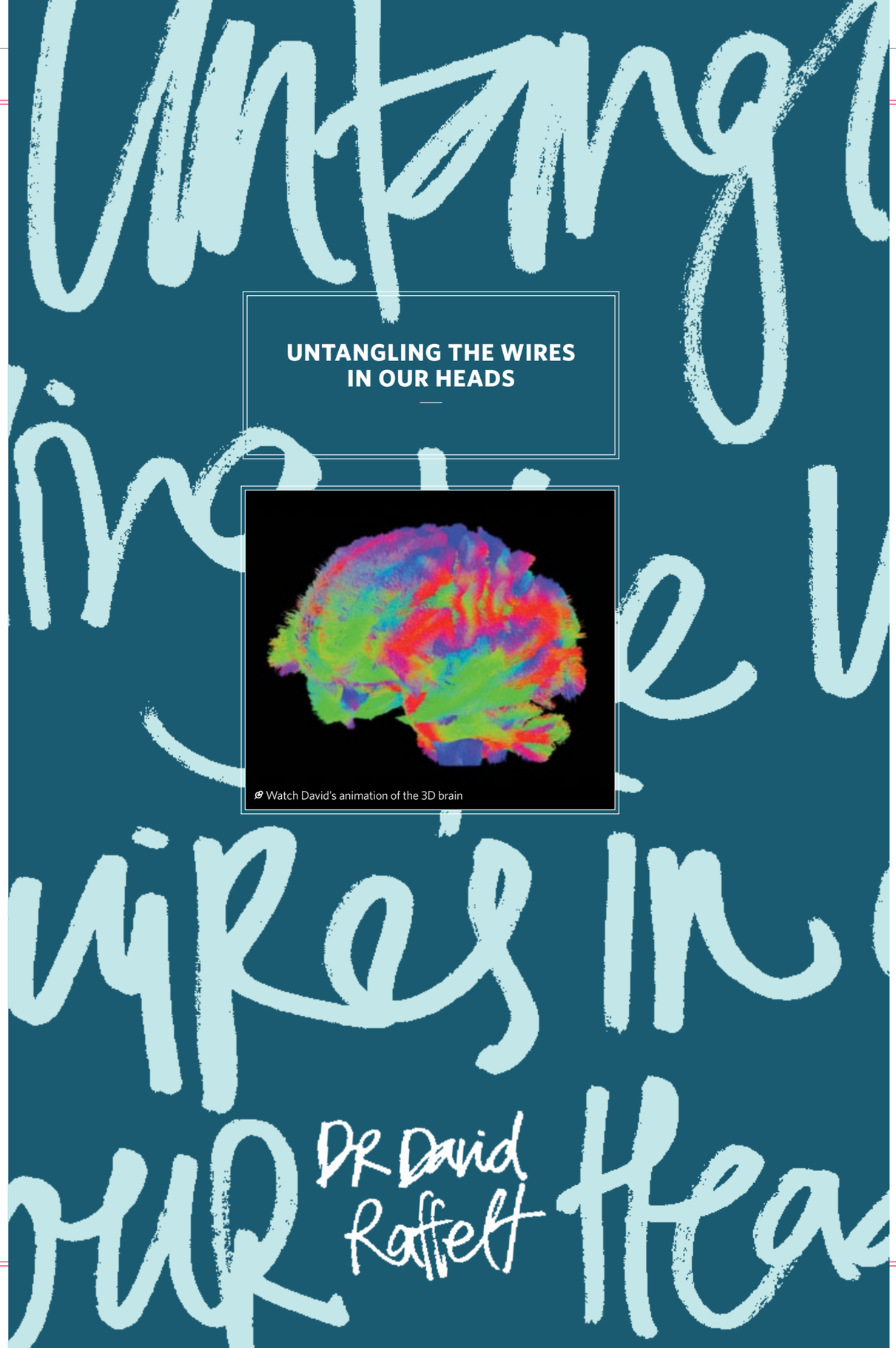

Untangling the wires in our heads

David Raffelt

Imagine if you could look through the skull to see the effect of rehabilitation, medications or singing therapy on the brain. Perhaps the impact of new drugs for Alzheimer's and motor neurone disease could be assessed. And then imagine you could do it using existing technology, with no need to purchase expensive new medical equipment. Dr David Raffelt is a computer scientist at the Florey's Austin campus, who is aiming to do just that.

The brain is a complex system containing billions of inter-connecting neural pathways that communicate with millisecond timing to allow us to sense, process and interact with the world around us. These pathways consist of bundles of wires (called axon tracts) that run in all directions inside the brain; top-to-bottom, side-to-side, front-to-back, and all points in-between. David works closely with the Florey's imaging team to visualise these pathways using Magnetic Resonance Imaging (MRI).

To get some sense of how an MRI machine works, think of the image sensor in your smartphone or digital camera: everyone's a photographer these days, and we're all familiar with the race to produce digital cameras and smartphones with ever increasing numbers of pixels. This has resulted in our ability to capture some amazingly detailed photographs, and we can easily upgrade to a new phone or camera every couple of years.

Magnetic resonance brain scanners are similar, but they image 3-dimensional space, and therefore use "volume pixels" – or voxels. But unlike those of us seeking the latest software, David is creating a new method that disentangles the information from within a single voxel, meaning that existing scanners can now tease apart the characteristics of axon bundles. Thus, he's able to determine which particular axon tracts are affected by a disease or injury, and which have remained healthy.

A powerful illustration of the potential use of this new method is given by comparing MRI scans from patients suffering from Alzheimer's disease with a group of healthy people. David and his team can clearly distinguish axon tracts that have degenerated in Alzheimer's disease. The pathways identified are known to be involved in language and memory, while many other axon tracts are spared in Alzheimer's disease. They can see degeneration of a specific pathway even inside single voxels where multiple tracts cross each other, with their fibres intermingling like crossed electrical wires.

David is enthusiastic about the future of his work.

"The potential uses of this new image analysis method are huge. We'll be able to image which tracts are degenerating in a range of diseases, and then evaluate different treatment effects with better specificity and sensitivity than previous methods."

"The success of new therapies is often measured by the functional outcome in patients – does it help them walk better or improve their memory? This is obviously important, but does little to show us how that therapy has worked within the brain."

"The next challenge is to address the range of diseases where we can detect changes. We'd really like to analyse more diverse types of injury, like concussions or stroke, which can cause damage to varying brain regions in different patients."

NEXT STEPS

David will publish his exciting results in the coming months, and is planning to make his analysis software freely available so it can be widely used to help patients around the world.

BACK TO CONTENTS

HUNTINGTON'S

Searching for a cure

Recently, Prana, a small biotechnology company based in Melbourne announced successful testing of a new drug, PBT2, in a phase II clinical trial of Huntington's disease. While there is still more clinical trial work to be done before the drug will be approved for treatment, the latest trial results are very encouraging. PBT2 was developed on the basis of a 'metals theory' for Alzheimer's, a theory that had its foundations in the research I performed during my PhD studies.

The drug, PBT2, has also shown efficacy after just 12 weeks' treatment of patients with Alzheimer's. While there is more work to be done, we are hopeful the drug will one day provide relief for this incurable and sadly common disorder. I believe we are on the threshold of having the first disease-modifying drug for two major and tragic brain diseases.

It seems timely, then, to reflect on the journey of discovery – some 25 years – that led to this point. Significantly, novel, lab-bench science here in Melbourne has played a seminal role.

I first began working on the role of metals in Alzheimer's during my PhD with Professor Colin Masters between 1989 and 1992. We discovered the interaction of metals with the amyloid precursor, APP, a protein discovered by Colin and implicated in the cause of Alzheimer's disease. After completing my PhD, I went on to perform post-doctoral studies at Harvard Medical School in Boston. There, we discovered that certain metals, in particular zinc, drive the build-up of a peptide, Abeta, to become the amyloid plaque that typifies Alzheimer pathology. It was this discovery that led to the identification of two drug candidates that actually block this reaction – clioquinol and the current drug undergoing trials, PBT2.

In 1995 I was invited to join the faculty of Harvard and set up a laboratory in the Massachusetts General Hospital in Boston. Having filed patents on these discoveries, I set out to source venture capital to set up a biotechnology company in order to develop new drug candidates that target the metal-amyloid interaction as potential therapeutics for Alzheimer's dIsease. This eventually led to the formation of Prana Biotechnology Ltd in 1997 with investors from Melbourne, and with me as as one of three founding scientists. The funds raised were used to test my theory's proof of principle in mouse models of Alzheimer's. Clioquinol, a retired antibiotic, showed profound efficacy in these models. Prana subsequently went public in 2000, and I worked in addition to my full time academic and clinical positions, as the chief scientific consultant for the company from its launch until 2012, when I left the company.

PBT2 is more effective than the old drug, clioquinol, and solved technicalities that thwarted the large scale manufacture of clioquinol. It worked remarkably well in mouse models of Alzheimer's, reversing cognitive loss within days of starting treatment, and lowering Abeta levels in the brain within hours. Passing toxicology checks, it was first tested in a 12-week clinical trial of patients with Alzheimer's. The drug again worked remarkably well, lowering Abeta levels in spinal fluid and reversing aspects of cognitive loss in Alzheimer patients. Despite this enormous promise, the global financial crisis thwarted Prana's ability to engage the kind of big pharmaceutical support needed to drive PBT2 into the phase III trials required to bring a new drug to the public.

Professor Ashley Bush, psychiatrist and neuroscience researcher describes the long road to success – a 25-year journey that may soon prove his once left-field approach has been worth the struggle.

The proposed development of PBT2 for Huntington's disease emerged around the time of my return to a full-time academic position in Australia. In 2005 an investigator in San Francisco came upon our publications that clioquinol may be therapeutic in the treatment of Alzheimer's, and himself tested clioquinol in a mouse model of Huntington's. A prominent paper followed in the Proceedings of the National Academy of Science USA. At the time, I was also collaborating with American colleagues on abnormal metal metabolism in the brain in Huntington's disease and a reaction between metals and the abnormal protein that causes Huntington's disease, huntingtin. So more than one line of evidence indicated that the drugs we had been developing for Alzheimer's disease might also be useful in Huntington's, a terrifying genetic disorder that causes premature dementia.

In 2005, I was fortunate enough to receive a Federation Fellowship from the Australian Research Council – a large grant designed to repatriate Australian scientists who had moved overseas. So I returned to the Florey and built up my laboratory here. I urged Prana to test PBT2 in Huntington's disease mouse models. This success spurred the subsequent testing of the drug in a successful phase II clinical trial.

My decision to return to Australia and to the Florey has been a fortuitous one. I succeeded in achieving an NHMRC Australia Fellowship in 2010 and was appointed as chief scientific officer of the Cooperative Research Center for Mental Health in 2012, just as funding in the USA has become parlous. The metals theory for Alzheimer's has outlived expectations, and despite enormous skepticism that metals have anything to do with brain disease, my work has somehow attracted interest and respect within the broader scientific community, if not the Alzheimer research community itself. I have become the internationally most highly cited neuroscientist in Australia over the last 10 years. I am certainly grateful to my colleagues (particularly Colin Masters) and staff at the Florey who have been tolerant of this risky non-mainstream approach, and even championed it. PBT2 is now regarded as one of a tiny number of drug approaches that is believed to have any chance of arresting the disease. This means that a tiny company, spun out from work at the bench over 25 years, may have outcompeted pharmaceutical giants. We will soon see.

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1:100

EPISODE OF SCHIZOPHRENIA

One in 100 will have an episode of schizophrenia in their lifetime and two thirds of these will go on to have further episodes.

AFFECTED

15 people in every 1000 people will be affected.

15-20

SEVERE MENTAL ILLNESS

People with severe mental illness such as schizophrenia still die 15-20 years earlier than other people.

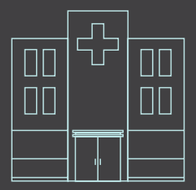
SCHIZOPHRENIA

The push to find some answers

Schizophrenia is the most severe of the mental illnesses. It affects a person's perception, thoughts, judgment, mood, drive and ultimately, their personality. The Florey is committed to improving the lives of those living with this terrible condition.

SYMPTOMS

Symptoms of schizophrenia usually begin in the late teens or early 20s, but can also begin later in life.



TREATMENT

Approximately one quarter of people have one or two episodes and completely recover. The next 50% will have more episodes and will need ongoing medication but will have a reasonable quality of life. The next quarter will have a chronic form of the illness, ie they will have difficulty finding a medication that suits and will be in and out of hospital.

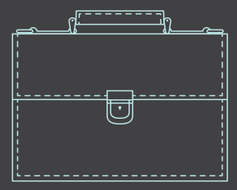
10%

SUICIDE

Up to 10 per cent of people with schizophrenia will end their own lives. This is 12 times the national average and means 18,000 Australians alive today will suicide as a result of schizophrenia.

AUSTRALIANS

Over one million Australians (as family and friends) are directly involved.



EMPLOYMENT

Only 8 per cent of people with schizophrenia are in employment, yet many more could and would like to work.

MADE IMPORTANT DISCOVERIES

Made important discoveries about changes in the biochemistry of the brain in people with schizophrenia, which may provide insights into its underlying mechanism.

THE FLOREY'S IMPACT ON SCHIZOPHRENIA

Our researchers have...

BETTER UNDERSTANDING THE WAY OF STRESS

The Florey's research work has enabled a better understanding of the way stress during development influences brain systems implicated in schizophrenia and depression.

IDENTIFIED

Identified a sub-group of diseases.

NEW INSIGHT

Developed new insight into sex differences and the role of oestrogen in schizophrenia.

$28.6 BILLION

SUPPORT

$28.6 billion supporting people with mental illness each year.

$2.5 BILLION

DIRECT COSTS

It is estimated that schizophrenia costs the community at least $2.5 billion per year in direct costs, which can be multiplied many times to account for the indirect costs.

$3 MILLION

PATIENT DAYS

Total for people with a mental illness: 3 million patient days.

THE FINANCIAL COST OF MENTAL ILLNESS

HOSPITAL DAYS FOR DIFFERENT ILLNESSES

Schizophrenia: 920K

Bipolar affective disorder: 232K

Depression: 500K

Stress-related disorders: 213K

$13.8 BILLION

DIRECT CARE

$13.8 billion spent on direct care. This equates to 2.2% of the Australian GDP.

26.2%

PSYCHIATRIC CONDITION

26.2% of recipients of the Australian Disability Support Pension have a psychiatric condition (second to musculoskeletal conditions).

$1.235 MILLION

MEDICATION EXPENDITURE

Medication expenditure per year: $1.235 million.

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MENTAL HEALTH

Division head: Professor Colin Masters

A QUICK SNAPSHOT

The Mental Health division encompasses research into the causes of neurodegeneration (Alzheimer's disease, Parkinson's disease and other related conditions) and the psychoses (including schizophrenia and mood disorders). Research also extends into discovering biomarkers using longitudinal cohorts of volunteers who are prepared to be followed up over many years. This creates an infrastructure which is then amenable for drug discovery and development.

> "It is now a real possibility that blood biomarkers will contribute to future screening ...for Alzheimer's disease risk."

RESEARCH HIGHLIGHT

Why is one antipsychotic drug, clozapine, effective in people for whom other antipsychotic drugs are not? Our novel finding that clozapine activated the epidermal growth factor (EGF) system in the brain has led us to investigate if this system is dysregulated in people with psychotic disorders. From this we hope to gain insight into the pathology of psychotic disorders and develop more effective ways of treating them.

AN IDEA LIKELY TO CHANGE LIVES BY 2033

Dr Blaine Roberts' group has developed a patentable process for detecting an Alzheimer's disease biomarker in blood which we are developing into an inexpensive diagnostic blood test capable of widespread adoption as a commercial collection kit. Such a test would have significant impacts on patient care by identifying individuals early, on drug development through better patient selection and on the community by reducing the burden of AD on healthcare.

SENIOR STAFF

• Professor Kevin Barnham • Professor Ashley Bush • Professor Robert Cherny • Professor Brian Dean • Professor Colin Masters • Professor Catriona McLean • Associate Professor Suresh Sundram •

OXIDATION BIOLOGY UNIT

Leaders: Ashley Bush and Professor Robert Cherny

This group has a particular interest in uncovering the pathways that lead to a variety of neurodegenerative diseases, especially those pathways in which metal ions (such as zinc, copper and iron) interact with key target proteins. Studies of these pathways have led to new insights for drug therapies for Alzheimer's disease and Huntington disease. In association with Prana Biotechnology, further drug developments for Parkinson's disease are in preclinical development. The Oxidation Biology Unit also contains several laboratories including the Molecular Gerontology Laboratory (Dr Gawain McColl), the Synaptic Neurobiology Laboratory (Dr Paul Adlard), the Parkinson's Laboratory (A/Prof David Finkelstein) and the Prana Biotechnology Research Laboratory (Prof Robert Cherny).

NEUROPATHOLOGY GROUP

Leader: Colin Masters

Understanding the molecular basis of Alzheimer's disease is the main focus of this laboratory. We aim to identify the specific conformer of the Aβ amyloid peptide which accumulates in Alzheimer's disease brain. In both familial early onset Alzheimer's disease (in which Aβ is over-produced) and in late onset sporadic Alzheimer's disease (in which Aβ is poorly cleared from the brain), the same underlying process causes the synapses in the brain to degenerate. Based on this knowledge, we are able to seek biomarkers in the CSF and blood and to discover suitable lead compounds which can target the Aβ oligomer itself.

THE AUSTRALIAN BRAIN BANK NETWORK

Leader: Catriona McLean

An essential component of research into both neurodegenerative disorders and psychotic illness is the provision of brain tissue from donors who have suffered from these afflictions. Thus Brain Banking is fundamental to our research programs.

MEDICINAL CHEMISTRY GROUP

Leader: Kevin Barnham

The Barnham Laboratory has expertise in Medicinal Chemistry (in association with Prana Biotechnology) and in biomarker discovery. More recently, it has focussed on the pathways leading to Parkinson's disease, especially around the oxidative modifications of tau.

The Australian Imaging, Biomarker and Lifestyle (AIBL) Study, the Dementia Collaborative Research Centres (DCRC) and the Cooperative Research Centre for Mental Health (CRCMH)

AIBL, DCRC and the CRCMH are intimately involved in our research programs, relying on patient cohorts for biomarker and imaging discovery in both neurodegenerative and psychotic illness. These consortia involve other groups including Austin Health, Edith Cowan University, National Aging Research Institute, CSIRO, University of Melbourne, University of Western Australia, Mercy Health, Hall and Prior, Cogstate, and Pfizer.

AIBL and the CRCMH have the capacity to generate large data sets, and these are coordinated by Dr Noel Faux working with colleagues at CSIRO. Coordination of biomarkers in the Melbourne node is run by Dr Alan Rembach, the imaging program is directed by Prof C Rowe at Austin Health, and the cognitive stream is coordinated by Prof Paul Maruff at Cogstate.

Clinical research unit (DIAN and A4)

Translation of our research findings into clinical practice will become more important over the next five years, as we move from a series of failed or equivocal phase 3 drug trials sponsored by the Pharmaceutical Industry. There is now general agreement that these drug trials need to be based at the earliest possible stage of Alzheimer's disease, hence our participation in the Dominantly Inherited Alzheimer Network (DIAN) and the Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease (the A4 study). These two pre-clinical trials are designed to administer drugs in the preclinical phases of both familial and sporadic Alzheimer's disease. They are being coordinated by Dr Maree Mastwyk and Ms Lesley Vidaurre.

The NHMRC program in neurodegenerative disease

Also involves collaborators at the University of Melbourne: Prof Andrew Hill (Biochemistry and Molecular Biology), Prof Roberto Cappai (Pathology), Prof Steven Collins (Pathology) and Prof Anthony White (Pathology).

MOLECULAR PSYCHIATRY GROUP

Leader: Brian Dean

Our group seeks to identify the changes in gene expression that contribute to the onset of schizophrenia, bipolar disorder, major depressive disorder and suicide. Our approach is based on the understanding that clinically definable psychiatric disorders occur in people with a genetic predisposition who have encountered as yet unknown environmental factors. This interaction between genes and environment is then known to affect gene expression by a variety of epigenetic mechanisms. As psychiatric disorders primarily affect the human CNS we have a strong focus on studying gene expression in the CNS of people with psychiatric disorders and those who have died by suicide. On identifying changes in gene expression we then use an array of animal and cellular models to better understand the mechanisms that have brought about such a change in expression in the human CNS.

Some drugs have been developed that can be used to treat the symptoms in some people with psychiatric disorders, albeit with varying success. Therefore our group also seeks to understand the mechanisms of action of such drugs, which in the main remain obscure.

The major goal of the group, through the study of the pathophysiology of psychiatric disorders and suicide, as well as the mechanisms of action of psychotropic drugs, is to generate information that may point to new potential drug targets that will either improve outcomes in currently treatment responsive treatment and / or lead to the development of drugs that will be effective in currently treatment resistant people.

Importantly, our group has formed a seamless collaboration with the psychiatric neuropathology laboratory headed by Associate Professor Elizabeth Scarr and with the laboratory of Professor Ian Everall, both at the University of Melborune, to form the Parkville Psychoses group. This grouping ensures we have a coordinated approach to understanding how changes in gene expression in human can cause psychiatric disorders.

MOLECULAR PSYCHOPHARMACOLOGY AND NORTHERN PSYCHIATRY RESEARCH CENTRE

Leader: Suresh Sundram

The molecular psychopharmacology laboratory is dedicated to understanding the molecular pathology of psychotic disorders such as schizophrenia, bipolar disorder and major depression. It aims to develop better and more effective markers and interventions for these illnesses. We do this by investigating how psychotropic medications and drugs interact with receptors and intracellular signalling mechanisms in nerve cells (neurons).

The understanding gained from this work can then be tested in clinical populations through the Northern Psychiatry Research Centre (NPRC) leading to the development of new treatments

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and markers. Moreover, the NPRC can collect clinical material and biological samples that can be examined in the laboratory to better understand these disorders.

Highlights

We are continuing our work to reveal how antipsychotic drugs work; these are the mainstay of treatment for psychotic disorders including schizophrenia, bipolar disorder and major depression. Although these agents have been in use for over 50 years there is still a lot to learn about how they work.

In particular, we continue research into why one antipsychotic drug, clozapine, is effective in people for whom other antipsychotic drugs are not. From this we hope to gain insight into the pathology of psychotic disorders and more effective ways of treating them.

Our novel finding that clozapine activated a growth factor signalling system, the epidermal growth factor (EGF) system in the brain has led us to investigate if this system is dysregulated in people with psychotic disorders.

Avril Pereira and her team identified a number of key proteins that were altered in brain through the EGF system and raised the possibility that the pathways affected by clozapine signalling may interact with more mainstream antipsychotic drug pathways. This creates the potential to identify key target molecules for the development of new therapeutics.

Two PhD students, Vaidy Swaminathan and Sujeevan Sinnatamby have been investigating if the EGF system is disturbed in schizophrenia. This work in collaboration with a number of groups including Cyndi Shannon-Weickert from University of New South Wales, Michael Berk, Deakin University and Ian Everall, University of Melbourne, is looking at how these genes and proteins of the EGF system may be disturbed in the brains and blood of people with schizophrenia. Together with the McIver Family Fellow, Rejhan Idrizi working in the laboratory and support from the CRC for Psychosis has resulted in the identification of a protein that may be associated with schizophrenia and that may provide the basis for a marker for treatment response. These data have been accepted for the Society for Neuroscience Meeting in the USA and Schizophrenia International Research Society Meeting in Italy.

A special thank you

The generous and ongoing support of One in Five continues to make much of our research possible. The One in Five group was formed by the friends and family of Mathew Wardlaw who lost his battle with mental illness on New Years Eve 2001. An entirely voluntary group and now formally established as an organisation they provide much needed funds for our work.

Research highlights for 2013

Vaidy Swaminathan was selected to give oral presentations of his work at the Society for Neuroscience Annual Meeting in the USA in 2013 and the Schizophrenia International Research Society Meeting in Italy in 2014.

Suresh Sundram was invited to give a keynote lecture at the Royal Australian and New Zealand College of Psychiatrists Annual Meeting in 2014; the Asian Schizophrenia Congress, Indonesia in 2013; and a symposium presentation at the Biological Psychiatry Australia Meeting in 2013. He was also appointed to the Physical and Mental Health Sub-Committee of the Joint Advisory Committee to the Governments of Australia and Nauru on Nauruan Regional Processing.

CLINICAL RESEARCH GROUP

Leader: Alan Rembach

The Clinical Research Group (CRG) collects research data and stores biospecimens from human participants involved in neurodegeneration and healthy aging studies. The multi-disciplinary team includes biomarker researchers, neuropsychologists, research nurses, neuro imaging specialists and bioinfomaticians. The group is currently involved in:

- Australian Imaging, Biomarkers and Lifestyle (AIBL) Flagship Study of Ageing
- AIBL Active (exercise intervention trial)
- the CRC for Mental Health
- the Dementia Collaborative Research Centre (DCRC) – Early Risk Diagnosis and Prevention
- the Dominantly Inherited Alzheimer's Network (DIAN) study
- the Rates of Change in Cognition (ROCS) study
- the Older Australian Twin Study (OATS)
- the Woman's Healthy Aging Project (WHAP)
- the A4 study (starting in 2014)

Translation of our research findings into clinical practice will become more important over the next five years, as we move from a series of failed or equivocal Phase III drug trials sponsored by the pharmaceutical industry. There is now general agreement that these drug trials need to be based at the earliest possible stage of Alzheimer's disease, hence our participation in the Dominantly Inherited Alzheimer Network (DIAN) and the Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease (the A4 study). These two pre-clinical trials are designed to administer drugs in the preclinical phases of both familial and sporadic Alzheimer's disease.

SELECTED CONFERENCES AND PRESENTATIONS

- Biological Psychiatry Australia Meeting, Brisbane, Australia (October 2013)
- Asian Schizophrenia Congress, Bali, Indonesia (February 2013)
- Society for Neuroscience Meeting, San Diego, USA (November 2013)

MOLECULAR PSYCHOPHARMACOLOGY LABORATORY

PERSONNEL AND COLLABORATORS

- Head: Associate Professor Suresh Sundram MBBS, MMed, FRANZCP, PhD
- Senior scientist honorary professorial fellow: Professor George Fink MBBS, DPhil, MD, FRCPE, FRSE
- Senior research officer: Dr Avril Pereira BAppSc, MSc, PhD
- Research assistant: Peter Malcolm BSc (Hons)
- PhD students: Sujeevan Sinnatamby MD, FRANZCP and Vaidy Swaminathan MD, FRANZCP
- Advanced medical sciences (AMS) students: Yuanna Zhou and Honam Choi
- Postgraduate student: Hanneke Raaijmakers

NORTHERN PSYCHIATRY RESEARCH CENTRE

PERSONNEL AND COLLABORATORS

- Head: Associate Professor Suresh Sundram MBBS, MMed, FRANZCP, PhD
- Senior research physician: Dr Russell D'Souza MPM, MD
- Research coordinator: Fiona Bole RN
- Research nurse: Sumathy Sathiyamoorthy RN (Div II)
- Research physicians: Dr Rohit Lodhi MD, MRCPsych, FRANZCP and Dr Manish Sharma MD
- PhD student: Jody Stanley
- Postgraduate students: Daniel Bennett and Amy Dluzniak
- Advanced medical sciences (AMS) student: Zexi Allan

COLLABORATORS

- Professor Michael Berk (The University of Melbourne)
- Dr Olivia Carter (The University of Melbourne)
- Dr Gursh Chana (The University of Melbourne)
- Dr Peter Crouch (The University of Melbourne)
- Professor Brian Dean (Mental Health Research Institute)
- Dr Seetal Dodd (The University of Melbourne)
- Professor Ian Everall (The University of Melbourne)
- Dr John Farhall (La Trobe University)
- Ms Marnie Graeco (Northern Hospital)
- Professor Brenda Happell (Central Queensland University)
- Ms Alison Harrington (Northern Area Mental Health Service)
- Dr Alexander Holmes (The University of Melbourne)
- Dr Ana Hutchinson (Northern Clinical Research Centre)
- Dr Nigel Jones (The University of Melbourne)
- A/Professor Gerard Kennedy (Victoria University)
- Dr Ken McAnally (Defense Science Technology Organization)
- Professor Ralph Martins (Edith Cowan University)
- Professor Terence O'Brien (The University of Melbourne)
- Dr Meaghan O'Donnell (The University of Melbourne)
- Dr Elizabeth Scarr (The University of Melbourne)
- Dr Elizabeth Thomas (Scripps Institute, USA)
- Professor Cyndi Shannon-Weickert (Neurosciences Australia)
- Dr Anthony White (The University of Melbourne)

THE CLINICAL RESEARCH GROUP

PERSONNEL AND COLLABORATORS

- Dr Alan Rembach – Manager of the Clinical Research Group.

NEUROPSYCHOLOGY

- Dr Jo Robertson – Neuropsychology coordinator
- Adrian Kamer – Neuropsychology rater
- Fiona Lamb – Neuropsychology rater
- Karra Harrington – CogState/ROCS coordinator
- Dr Yen Yin Limb – Neuropsychology researcher
- Rachel Buckley – PhD candidate

BIOMARKERS

- Brett Trounson BSc (Hons) – Blood Processing Laboratory Manager
- Dr Christopher Fowler BSc (Hons) PhD –Biobank data manager
- Kelly Pertile BSc (Hons) – Recruitment and clinical pathology coordinator
- Rebecca Rumble BBioSc (Hons) – CSF and biospecimen coordinator

CLINICAL TRIAL

- Dr Maree Mastwyk – A4 Clinical trial coordinator
- Ms Lesley Vidaurre – DIAN coordinator

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UNRAVELLING THE SECRETS OF ALZHEIMER'S DISEASE

In Victoria, there are almost 78,000 people living with dementia, most of whom have Alzheimer's disease. This figure is expected to grow to 98,000 by 2020 and over 246,000 by 2050. Australia's largest, longitudinal, prospective studies investigating biomarkers for Alzheimer's disease – the Australian Imaging Biomarker and Lifestyle Study of Ageing (AIBL) – is now in its eighth year.

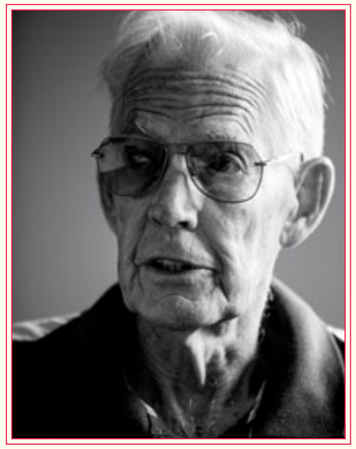
Noel Parkin understands the depredations of Alzheimer's better than many. His wife, Barbara, is living in high-level care as she succumbs to frontal temporal dementia.

"Well-meaning friends ask, 'How's Barb?' and I can never give positive news. It's hard to explain that there is never any improvement. Only bad news," Noel says.

Noel is a passionate advocate of his wife and others who cannot represent themselves due to the relentless progress of dementia.

As well, he is a volunteer participant in the AIBL study. This invaluable study is teaching us about the natural progression of Alzheimer's by monitoring the way human brains age. It is the most comprehensive study of cognition, imaging and measurement of blood-based biomarkers in the world.

"I want to contribute to help the researchers find the cause of this wretched disease."



"I am fighting to see a cure to address the degradation of humanity… I see the full gamut of dementia whenever I visit my wife."

Noel Parkin

The study began in 2006, initially co-funded by CSIRO, by recruiting and collecting data from 1,112 people aged over 60 years of age, every 18 months. The study also includes an enrichment cohort of 397 participants providing data every 18 months. Noel is part of the enrichment group. Those involved have Alzheimer's disease, mild cognitive impairment or are healthy.

The chief aim? Early preclinical detection and the opportunity for potential intervention. The study promises to provide an increasing amount of useful information as the years pass and more longitudinal data is accumulated.

THE AIBL STUDY

In 2013, the AIBL study closed the fourth (54 month) time point assessment of all remaining study volunteers. AIBL also recruited new volunteers to enrich the cohort and over 300 new participants have been screened at baseline. AIBL data has been analysed and presented at multiple international conferences. A number of key, high impact papers have been published in international journals in the last six months and AIBL publications have won international awards.

AIBL SUMMARY OF FINDINGS

The prospective and multidisciplinary approach adopted by AIBL has made substantial contributions to the understanding of cognitive and physiological changes associated with aging in general and the Alzheimer's disease spectrum in particular. Neuroimaging studies have shown that extensive beta-amyloid (Aβ) deposition precedes significant cognitive impairment and grey matter atrophy by more than 15 years (see figure), and Aβ deposition is associated with cognitive decline at the preclinical stages of the disease process, denoting the non-benign nature of Aβ. Thus, by early identification of Alzheimer's pathology, amyloid imaging is likely to have an increasingly important role in clinical management of Alzheimer's provided it can be made accessible and affordable and the scans can be read in a consistent and reliable manner.

It is now a real possibility that blood biomarkers will contribute to future population screening approaches for Alzheimer's risk. Our findings suggest that when properly standardised, peripheral biomarkers represent a rich source of physiological information. A number of different biomarkers have been identified that are expressed in blood and have relationships to changes in the central nervous system, and when combined appropriately these biomarkers may be exploited to develop a population screening tool to triage the community for more intensive and specific examinations such as Aβ Positron Emission Tomography (PET) scanning or Cerebrospinal Fluid (CSF) testing.

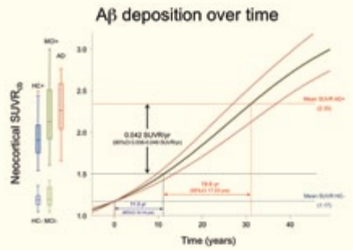
Investigation of lifestyle factors within AIBL has contributed to a developing international literature suggesting that diet and physical activity are related to dementia risk. In addition to physical activity frequency, intensity of physical activity appears important, with higher intensity activity associated with better cognitive function. Relationships between physical activity and age-related hippocampal atrophy, plasma and brain Aβ levels have been observed, and these relationships appear to be moderated by APOE genotype. AIBL data have shown that adherence to a healthy dietary pattern is related to better cognitive function in cognitively unimpaired individuals, and the potential benefit of healthy diet on cognition suggested by observational studies such as AIBL may in time be demonstrated in carefully controlled intervention studies in at risk groups. Overall, diet and physical activity show promise as potential means to slow the rate of cognitive decline and progression towards AD. Further analysis of AIBL data, especially data now being collected at the six-year follow-up should further extend our knowledge in relation to some of these unanswered questions.

In summary, data generated from the AIBL study over the seven years since its inception has helped elucidate some of the pathophysiological mechanisms underpinning the natural history of Alzheimer's disease and contributed to the international effort in setting the groundwork and establishing standards for early diagnosis of the disease and biomarker discovery.

Dr Alan Rembach

HIGHLIGHTS SINCE ITS INCEPTION INCLUDE

- More than 100 scientific publications with over 2,000 citations per year and several papers with more than 500 citations
- The US Alzheimer's Association has awarded our researchers "Best imaging paper in Alzheimer's disease" 2012 and 2013.
- The Florey's significant imaging expertise has provided unique knowledge on biomarker research.
- Landmark paper in Lancet Neurology 2013 (with worldwide media coverage including The Washington Post) demonstrating disease progresses over 20-30 years prior to manifestation of clinical symptoms, by which time there is largely irreversible brain damage. This provides a long window of opportunity for potential disease intervention.



Neocortical amyloid deposition over time. SUVR, standardized uptake value ratio; CDR, clinical dementia rating; CI, confidence interval. The horizontal black dashed line (SUVR of 1.5) represents the threshold for a positive/high A β scan. The horizontal red dashed line (SUVR of 2.21) indicates the medium SUVR for mild AD cases (CDR 1) within AIBL. (Ref: Villemagne et al., (2013). Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study . Lancet Neurology, 12 (4), 357 – 367.)

- Key diagnostic and prognostic blood biomarker papers and patents demonstrating the potential for a low cost blood test for Alzheimer's risk is possible in coming years.
- Demonstration of a protective effect of Mediterranean diet and physical activity from cross-sectional analysis suggesting that lifestyle might delay the onset of disease.
- Provided key baseline data for informing clinical trial design for therapeutics.
- Established an IP portfolio of three patents and licensable software
- Provided training of 18 PhD students and 13 postdoctoral fellows
- Furthered international research collaboration efforts in Alzheimer's disease through data being sharing worldwide via expression of interest and uploading a subset of de-identified AIBL data (AIBL@LONI) through the worldwide Alzheimer's disease Neuroimaging initiative (www.ADNI-info.org) sponsored by the Alzheimer's Association. Through this portal AIBL data has been accessed by over 540 researchers and over 30 industry groups, facilitating international collaboration and co-operation for understanding AD.
- Hosted global leaders' consensus meeting for research and standardisation in AD (RASAD).
- High level of industry support and collaboration (including GE, Pfizer, Merck, Janssen Cogstate, Myriad Rules Based Medicine, Araclon Biotech (Grifols).
- Attracted over $8M foreign industry investment matched by national investment (inc. SIEF, CSIRO, NHMRC, Alzheimer's Association, DCRC).

AIBL JOINS FORCES WITH ALZHEIMER'S AUSTRALIA – VICTORIA

Alzheimer's Australia Victoria is the charity and peak body for dementia and related services and provides education, support, advocacy and information for Victorians living with all forms of dementia, their families and carers and the health profession.

Alzheimer's Australia Victoria produces updated resources and publications in dementia related research and information. Help sheets in community languages are available. All resources are accessible on the website: www.fightdementia.org.au/vic/publications

The organisation is now sharing office space with the Florey AIBL team, enhancing opportunities to combine research with advocacy. The new site houses a dementia learning centre which offers a virtual dementia experience – an interactive environment intended as an experiential learning exercise for professional carers. The opportunities for collaboration are tremendous as AIBL researchers work alongside those operating directly with dementia clients and consumers.

BACK TO CONTENTS

MULTIPLE SCLEROSIS

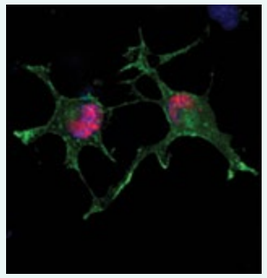
Division head: Professor Trevor Kilpatrick

A QUICK SNAPSHOT

Multiple sclerosis is the commonest neurodegenerative disease affecting young adults in our community. It is a complex disease involving disrupted interactions between the immune and nervous system, resulting in the demyelination and loss of nerve cells. Our division is currently focusing on novel ways by which to manipulate immune activation and/or protect the nervous system in order to limit this damage.

RESEARCH HIGHLIGHT

A major highlight of our work in 2013 is the discovery that a master regulator of myelination known as Myrf, previously identified by Ben Emery and collaborators, undergoes a cleavage event as an essential element of its activation. This knowledge represents essential information necessary to plan how to modulate the expression and activity of Myrf in order to promote myelin repair in MS and related diseases.



Expression of the Myelin Regulatory Factor (Myrf) protein – shown in red- in the nuclei of cultured cells. The Myrf protein acts to turn on the expression of several hundred other genes required for oligodendrocytes to produce myelin, the insulating sheath surrounding neurons in the central nervous system.

Image Credit: Helena Bujalka

AN IDEA LIKELY TO CHANGE LIVES BY 2033

The identification and utilisation of novel therapeutic targets in the brain, which will enable the accurate application of novel treatments to individuals with multiple sclerosis in a personalised and precise manner for improved outcome.

RESEARCH OVERVIEW

Multiple sclerosis has a variable course, with outcomes ranging from negligible to severe disability. Both the cause of the disease and the determinants of disease severity remain uncertain. The MS division, which spans the Florey, University of Melbourne and Royal Melbourne Hospital, is adopting a multifaceted approach to researching the disease. Our approach focuses on understanding the genetic determinants, environmental precipitants and molecular drivers of MS. Our laboratory work, detailed in this report, has provided novel and important insights into how to promote nervous system repair, in particular remyelination; this understanding has been assisted via our research that has focussed on how myelinating cells behave during both development and in the healthy adult, as well as in disease. Our work has also provided important insights into how the immune cells in the brain interact with the myelinating cells during disease, thereby identifying approaches that have therapeutic potential.

We are always aware that our preclinical work needs to be translated into the clinical environment for it to directly benefit people with MS. With this in mind, we continue to collaborate actively with colleagues throughout Australia to interrogate the genetics, epidemiology and pathogenesis of MS, in this way clarifying that our laboratory results are directly pertinent to the human disease. Our collaborative work focusing on patients has also allowed us to develop new paradigms by which to assess the severity of the disease; this is an important preamble to assessing the efficacy of new treatment approaches which work by novel mechanisms, in particular via either neuroprotection or remyelination.

> “Our work has provided novel and important insights into how to reduce the burden of MS by either protecting the nervous system from damage or by promoting its repair.”

SENIOR STAFF

• Professor Trevor Kilpatrick
• Dr Holly Cate • Dr Simon Murray
• Dr Toby Merson • Dr Ben Emery
• Dr Junhua Xiao • Dr Judith Field
• Dr Michele Binder
• Dr Andrew Fox •

OLIGODENDROCYTE BIOLOGY AND NEURONAL-GLIAL INTERACTIONS GROUP

Leader: Toby Merson

The Merson laboratory investigates the life cycle of myelinating glial cells in the nervous system, in particular how they are generated during development, how they are regenerated after injury and their role in supporting the function of axons.

Research highlights for 2013

In 2013, the Merson laboratory made a number of seminal advances in understanding how oligodendrocytes are regenerated after demyelinating injuries targeting CNS white matter. Research by PhD student Lulu Xing has demonstrated that neural precursor cells that are normally involved in the production of neurons in the adult brain can be recruited into demyelinated white matter. Here they produce large numbers of oligodendrocytes that remyelinate broad territories of demyelinated white matter. This finding contrasts with the previously held assumption that more widely distributed oligodendrocyte precursor cells are the principal cell type responsible for remyelination. Our research also raises the remarkable prospect that the quality of myelin generated by these two types of precursor cells could differ, a finding that may have important implications for regenerative strategies targeting demyelinating diseases such as MS.

Research conducted by PhD student Philipp Röth has provided new insights into the mechanisms underlying the generation and organisation of oligodendrocytes in white matter. Developmental analyses have revealed that postnatal myelination is preceded by the emergence of linear arrays of oligodendroglia whose cell bodies align with the axis of nerve fibre tracts. We have shown that complex cellular dynamics underlie linear array formation and that these mechanisms are largely reinstated during the process of remyelination. The work has stimulated us to rethink how myelination and neuronal activity could be coordinately regulated. The topographical organisation of oligodendrocytes into the glial networks that we have described, potentially explain how signals emanating from axons and acting upon single oligodendroglia could become amplified to facilitate broad-scale regional changes in myelination.

In research targeted towards understanding the consequences of a breakdown in neuron-glial cell interactions, Dr Jo Anne Stratton was awarded her PhD in 2013 for developing a transgenic mouse model to study the consequences of the death of Schwann cells, the myelinating cells in the PNS. The inducible model of Schwann cell ablation has enabled us to dissect the incremental steps that trigger neuronal dysfunction, and conversely, the processes associated with restoration of function. The work has revealed that degenerative processes previously thought to be caused by aberrant adaptive immune responses can be initiated by cytotoxic death of Schwann cells in the absence of prior immune dysfunction. This research has also highlighted intriguing points of difference between central and peripheral immune responses to an identical toxic insult, work that has important implications for understanding the basis for differences between neuropathologies affecting the CNS and PNS.

In other developments, results of a collaborative interdisciplinary study investigating the use of nanodiamonds as a potential biomarker for the labeling and fluorescent imaging of neural cells were published in 2013. The research was the first to demonstrate that nanodiamonds containing silicon vacancy centres can be used as fluorescent labels in biomedical imaging due to their extremely stable fluorescence and narrow bandwidth emission.

Awards and research grants

Dr Jo Anne Stratton was awarded her PhD for completion of doctoral studies in 2013. Lulu Xing was the winner of a scientific imaging competition resulting in publication of her image on the cover of the June 2013 issue of Development. Lulu was also the recipient of a student travel award from Students of the Florey Institute Committee (SOFI). Dr Tobias Merson was the recipient of a Melbourne Neuroscience Institute Fellowship in 2013, was appointed to Florey Faculty and was awarded national competitive project grant funding from both the NHMRC and CASS Foundation to commence in 2014.

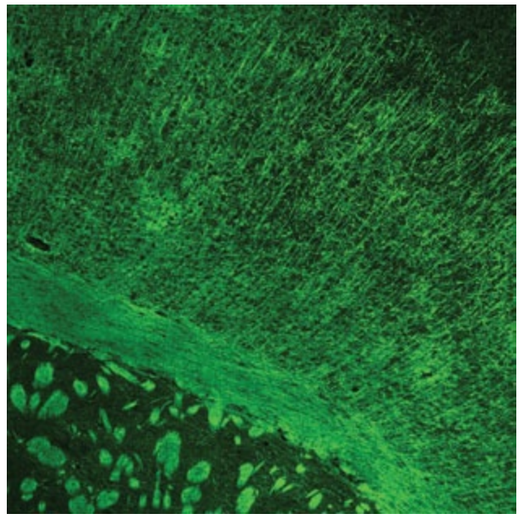
MYELIN DEVELOPMENT AND ITS APPLICATION TO DEMYELINATING DISEASE GROUP

Leader: Ben Emery

The Emery laboratory focuses on understanding the key events that regulate the expression of myelin genes. In particular, the laboratory is focusing on a gene known as Myelin Regulatory Factor (Myrf) that Ben Emery and his collaborators have previously discovered to be vital for the generation of myelin during development.

Research highlights for 2013

In 2013 the group published the finding that Myrf is a novel example of a membrane-associated transcription factor, requiring a cleavage event to free it from the membrane and enable it to function as a transcription factor. Using ChIP-Seq techniques we were able to map the binding of the activated transcription factor to the genome, thus identifying the genes that it targets to promote myelination. These findings were published in the prestigious journal Plos Biology, back-to-back with the complementary findings of another group. Our current research is focussing on trying to understand how to stimulate both the expression and activity of Myrf to promote myelin repair in human diseases.



Myelinating oligodendrocytes in the brain of a mouse. The oligodendrocytes have been genetically modified to express a gene encoding a Green Fluorescent Protein (GFP) originally derived from jellyfish. This enables researchers to visualize the oligodendrocytes and the myelin segments they produce in both the healthy mouse and in mouse models of Multiple Sclerosis. Image credit: Dr Stan Mitew

MYELIN REPAIR GROUP

Leader: Holly Cate

Our lab is interested in enhancing nervous system regeneration following demyelinating disease. During demyelination, there is death of oligodendrocytes, which are the myelin producing cells of the central nervous system. This cell death leads to demyelination of axons, axonal degeneration and progressive impairment of nerve cell function. The pathology is potentially reversible, with a limited amount of cell replacement achieved by local progenitors. Enhancing this process offers a potential for treatment of central demyelinating diseases such as MS.

BACK TO CONTENTS

Our laboratory uses cell culture assays and animal models of demyelination to determine the cellular and molecular changes in neural stem cell and progenitor cell populations in response to myelin damage. We then use this information to identify molecular targets for enhancing nervous system regeneration. As a result of these investigations, the Cate laboratory is currently focussed on clarifying the importance of BMP signaling in modulating the differentiation of neural stem cells of the SVZ as well as oligodendrocyte precursor cells present within and surrounding myelin lesions, and in modulating their potential for differentiation and remyelination in the context of demyelinating disease.

Research highlights for 2013

The Cate lab has identified that BMP signalling is increased in demyelinated lesions in mice. The laboratory has also determined that increases in BMP signalling can transiently increase the population of myelin precursor cells. Furthermore, the laboratory has identified that inhibiting BMP signalling during demyelination can increase myelin repair. These results suggest that time specific modulation of BMP signalling could be utilized to enhance the population of cells needed for myelin repair and could ultimately increase remyelination of demyelinated lesions. The team is further investigating these processes in vitro and in vivo. Along these lines, we have most recently begun investigations to determine whether modulation of the BMP receptor, BMPRIa, enhances OPC differentiation and remyelination, and hence, whether it represents a bona fide therapeutic target. In addition, through collaboration, we have established the presence of BMP signaling within oligodendroglia in human MS lesions, an important precursor to undertaking translational research in this area. Our ultimate aim is for this work to provide important information concerning molecular mechanisms within oligodendrocyte precursor cells that could be targeted for therapeutic benefit in the treatment of MS.

PROMOTING REMYELINATION GROUP AND NEUROTROPHIN LABORATORY

Leaders: Simon Murray and Junhua Xiao

The Murray and Xiao laboratory dissects the cellular and molecular mechanisms that the neurotrophin BDNF utilises to regulate both central and peripheral nervous system myelination, aiming to identify molecules and strategies that can be applied to promote repair in both MS and other demyelinating diseases.

Research highlights for 2013

In 2013, our work continued to identify the molecular mechanisms that BDNF utilises to regulate myelin development and to develop novel neurotrophin-based strategies for promoting myelin repair following a demyelinating insult.

The team has shown that BDNF promotes peripheral nervous system myelination via the neurotrophin receptor p75NTR. Adopting a structural-based drug design approach, Junhua Xiao and Simon Murray, together with their collaborators, have proven that a small molecule BDNF mimetic that specifically targets the p75NTR receptor is extremely effective in promoting peripheral nervous system myelination during development. Using an animal model of peripheral demyelinating neuropathy, our research identified that this peptide limited demyelination and exerted a strong neuroprotective role upon peripheral nerves. Outcomes of this work could develop novel BDNF-based strategies for treating peripheral demyelinating diseases such as Guillain–Barré syndrome.

Work undertaken by a recently graduated PhD student Agnes Wong has yielded substantial novel insights into the influence that BDNF and its receptor TrkB exert upon central nervous system myelination. Using a genetic approach to selectively delete the BDNF receptor TrkB specifically in oligodendrocytes, Agnes has identified that the TrkB receptor plays a key role in promoting central nervous system myelination, which was recently published in the Journal of Neuroscience. Her work has led to additional investigation of the signalling molecules activated by the TrkB receptor that regulate oligodendrocyte myelination, and also novel work on a distinct BDNF mimetic that specifically targets the TrkB receptor, in particular to determine whether the mimetic promotes central nervous system myelination and remyelination. The aim of this work is to develop novel BDNF-based strategies for the treatment of CNS demyelinating diseases such as MS.

Research by PhD students Anita Ferner and Haley Peckham is dissecting the molecular targets that BDNF signalling utilises to regulate central nervous system myelination, and has revealed a key intracellular signaling pathway in oligodendrocytes that is critical in controlling the myelination process. They have also begun to investigate how this signalling pathway regulates myelin formation at the transcriptional level.

NEUROIMMUNOLOGY GROUP

Leaders: Trevor Kilpatrick, Michele Binder and Judith Field

We have identified an important set of three receptors (the TAM family) that is expressed on both immune cells and oligodendrocytes in the brain and which influence the severity of demyelinating disease. We are currently exploring how these receptors and their ligands influence cellular behaviour in order to both limit the extent of demyelination and enhance the capacity for remyelination.

Research highlights for 2013

Our prior research in this area identified that animals deficient in one of the TAM ligands (Gas6) exhibit worse disease when demyelination within the nervous system is induced. Work currently being undertaken by PhD students, Gerry Ma and Rainer Akkermann is exploring how this occurs; in particular, whether TAMs exert their beneficial effects by influencing immune cell activation in the periphery or within the central nervous system, and which of the three receptors is predominantly responsible for exerting each of these effects. We are also exploring strategies that involve activation of the TAM receptors to determine whether this might be a viable strategy to limit disease severity. Finally, we have been focusing on whether expression of the TAM ligands is a determinant of either risk of developing MS or of its severity.

Awards

Trevor Kilpatrick was awarded the prestigious 2013 Bethlehem Griffiths Research Foundation Medal for outstanding contribution to clinical research in progressive neurological disorders, specifically, multiple sclerosis

MS GENETICS GROUP

Leader: Judith Field

Dr Judith Field and colleagues are focusing on key genes that have recently been implicated in the susceptibility to multiple sclerosis. Particular areas of interest include understanding how these genes function, whether perturbations in particular genes might define subsets of people with MS and whether these or other genes are also important determinants of disease severity.

Research highlights for 2013

Research into the genetic contribution to the development of MS within the Multiple Sclerosis Division continues in collaboration with the ANZgene Consortium. Our work also continues to refine the genetic risk association within the TAM receptor gene MERTK, and also the role that the TAM genes play in demyelinating disease. The consequences of the genetic changes that have been shown to lead to increased risk of developing MS are also being investigated in immune cell sub-types isolated from people with MS and healthy volunteers. This work has allowed us to identify gene expression and protein expression changes of potential functional significance, including the CD40 costimulatory molecule, which is expressed on both β lymphocytes and monocytes and their progeny. This work has received ongoing funding by the NHMRC (2014-2016) and is directed to identifying new therapeutic targets for MS and other autoimmune diseases.

OLIGODENDROCYTE BIOLOGY AND NEURONAL-GLIAL INTERACTIONS GROUP

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

- Xing YL, Röth RT, Chuang BHA, Kilpatrick TJ, Merson TD. Adult neural precursor cells are major contributors to oligodendrocyte regeneration and CNS remyelination following cuprizone-induced demyelination. 43rd Annual Meeting of the Society for Neuroscience, 9th-13th November 2013; San Diego, CA, USA.
- Merson TD, Xing YL, Roth P, Kilpatrick TJ. Spatiotemporal and genetic fate-mapping of oligodendrogenesis during normal development and following demyelination. XI European Meeting on Glial Cells in Health and Disease, 3rd-6th July 2013, Berlin, Germany.
- Merson TD, Xing YL, Stratton JS, Wikhe K, Ng SW Kilpatrick TJ. Immune reactivity and influence upon neuronal pathology following oligodendrocyte apoptosis. 33rd Annual Meeting of the Australian Neuroscience Society, 2nd-6th February 2013, Melbourne, Australia. (Symposium presentation)
- Xing YL, Kilpatrick TJ, Merson TD. Spatiotemporal mapping of oligodendrogenesis by neural precursor cells following cuprizone-induced demyelination. 33rd Annual Meeting of the Australian Neuroscience Society, 2nd-6th February 2013, Melbourne, Australia.
- Roth P, Kilpatrick TJ, Merson TD. Understanding linear arrays of myelinating cells in the Central Nervous System . 33rd Annual Meeting of the Australian Neuroscience Society, 2nd-6th February 2013, Melbourne, Australia.
- Kilpatrick TJ, Merson TD, Cate HS, Roth P, Xing YL, Sabo J. Targeting the oligodendrocyte lineage in demyelinative disease. Keystone Symposia on Molecular and Cellular Biology, Multiple Sclerosis (A1), Jan 11-16, 2013; Big Sky, MT, USA.

MYELIN DEVELOPMENT AND ITS APPLICATION TO DEMYELINATING DISEASE GROUP

COLLABORATIONS

- Prof. Matthias Klugmann (University of NSW)
- Prof. John Svaren (University of Wisconsin-Madison)
- Dr. Kaylene Young (University of Tasmania)

EDITORIAL POSITIONS

- Editorial board of Brain Plasticity (IOS Press)

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

- Myelin Repair Foundation Annual meeting, San Francisco, USA, September 2013. Ben Emery, invited speaker.
- Internal Seminar at Biogen Idec, Cambridge, USA. September 2013. Ben Emery, invited speaker.

MYELIN REPAIR GROUP

COLLABORATIONS

- Assoc. Prof. Ann Turnley (Centre for Neuroscience Research, University of Melbourne) Myelin Repair following Traumatic Brain Injury.
- Prof. Patrizia Casaccia (Mt. Sinai School of Medicine, NY, USA) Role of HDACs in oligodendrocyte regeneration.
- Assoc. Prof. Patrick Küry (Heinrich-Heine-University, Düsseldorf, Germany) Role of nucleocytoplasmic translocation cyclin dependent kinases in oligodendroglial differentiation
- Assoc. Prof. Tanja Kuhlmann (University Hospital Munster, Germany) Regulation of BMP signaling in human MS lesions.

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

- Fisher, B., Merlo, D., Sabo, J., Kilpatrick, T.J. Cate, H.S. (2013) Investigation of the role of BMP receptor IA in oligodendrocyte progenitor cells in vitro and during demyelination. Australian Neuroscience Society, Melbourne, Australia.
- Sabo J.K., Aumann T.D., Kilpatrick T.J., Cate, H.S. (2013) Growth factor delivery to the demyelinated mouse brain to enhance myelin repair. Keystone Symposium – Multiple Sclerosis, Montana, USA
- Göttle P., Sabo J.K., Torres K., Heinen A, Tzekova N., Kremer D., Hartung H-P., Cate H.S., Küry P. (2013) Nucleocytoplasmic translocation of p57kip2 promotes oligodendroglial differentiation. Keystone Symposium – Multiple Sclerosis, Montana, USA.

PROMOTING REMYELINATION GROUP AND NEUROTROPHIN LABORATORY

COLLABORATIONS

- A/Prof. Tony Hughes, Dept. Pharmacology, University of Melbourne
- Dr. Mirella Dottori, Dept. Electrical and Electronic Engineering, University of Melbourne
- Dr. Jason Ivanusic, Dept. Anatomy & Neuroscience, University of Melbourne
- A/Prof. Paul Gooley, Bio21 Institute & University of Melbourne
- A/Prof. Maarten van den Buuse, The Florey Institute of Neuroscience and Mental Health
- A/Prof. Paul Adlard, The Florey Institute of Neuroscience and Mental Health
- A/Prof. Martin Scanlon, Monash University
- A/Prof Heung-Chin Cheng, Bio21 Institute
- Dr. Suzanne Hodgkinson, University of New South Wales
- A/Prof. Matthias Klugmann, University of New South Wales
- Prof. Bruce Carter, Vanderbilt University (USA)
- Prof. Rashmi Bansal, University of Connecticut (USA)

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

- Wong A.W., Xiao J., Sabo J., Kemper D., Cate H., Kilpatrick T.J. and Murray S.S. The role of BDNF in CNS myelination and remyelination. Australian Neuroscience Society conference 2013, Melbourne (oral presentation).

BACK TO CONTENTS

- Simon S Murray, Richard A Hughes, Suzanne Hodgkinson, Giang Tran, Paul Gooley, Emma Petrie, Agnes W Wong, Haley Peckham, Anita Ferner, Lauren Giuffrida, Trevor J Kilpatrick and Junhua Xiao. A peptide mimetic of BDNF promotes peripheral myelin development and repair. Australian Neuroscience Society conference, Melbourne, February 2013 (poster presentation).
- Melanie Willingham, Victoria Perreau, Junhua Xiao, Agnes Wong, Trevor Kilpatrick, Simon Murray. proBDNF regulates cholesterol synthesis and myelination by Schwann cells. Australian Neuroscience Society conference, Melbourne, February 2013 (poster presentation).
- Ferner AH, Xiao J, Giuffrida L, Wong AW, Peckham H, Kilpatrick TJ and Murray SS. The influence of TrkB signalling on oligodendrocyte myelination. Australian Neuroscience Society conference, Melbourne, February 2013 (poster presentation).
- Peckham H, Giuffrida L, Wong AW, Ferner AH, Kilpatrick TJ, Murray SS and Xiao J. BDNF promotes oligodendrocyte myelination in vitro via activation of Fyn and Erk kinases. Australian Neuroscience Society conference, Melbourne, February 2013 (poster presentation).
- Simon S Murray, Agnes W Wong, Richard A Hughes, Giang Tran, Suzanne Hodgkinson, Anita Ferner, Trevor J Kilpatrick and Junhua Xiao. A BDNF mimetic promotes peripheral myelin development and ameliorates experimental autoimmune neuritis (EAN). XI European Meeting on Glial Cells in Health and Disease, Berlin, Germany, June 2013 (poster presentation).
- Xiao J., The influence of BDNF upon CNS myelination: mechanisms and mimetics. Glial Biology Workshop, Brain and Spinal Cord Institute, University of Pierre and Marie Curie, Paris, France, June 2013. (Invited talk)
- Agnes Wong, Anita Ferner, Junhua Xiao, Haley Peckham, Lauren Giuffrida, Trevor Kilpatrick. Temporally distinct deletion of TrkB in the oligodendroglial lineage exerts distinct influences upon myelination. Multiple Sclerosis Research Society Biennial Conference, Sydney 2013 (poster presentation).
- Xiao J., Temporal deletion of TrkB receptors in oligodendroglial lineage cells reveals distinct phenotype of myelination. Melbourne Brain Centre second floor symposium, Melbourne, July 2013. (Invited talk)
- Xiao J., A New Strategy for Treating Demyelinating Disease. Melbourne Brain Centre Tuesday Neuroscience Seminar Series, Melbourne, August 2013. (Invited talk)

NEUROIMMUNOLOGY GROUP

COLLABORATIONS

- Greg Lemke, The Salk Institute for Biological Studies.

EDITORIAL POSITIONS

- Therapeutic Advances in Neurological Disorders (International Journal) (2008-)
- Experimental Neurology (International Journal) (2011-)

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

TREVOR KILPATRICK

- Scientific organiser, invited speaker and chair of the Keystone Symposia on Molecular and Cellular Biology – Multiple Sclerosis Conference, Big Sky, Montana, USA
- Invited speaker at the ANS 2013 Satellite Symposium 18, Melbourne Convention Centre, Melbourne
- Symposium co-chair at Euroglia 2013, Berlin
- Invited speaker, DARPA Neural Interface Symposium, Melbourne, May 2013.
- Invited speaker at the Day of Immunology, Melbourne, April 2013.
- Invited speaker and chair of session 'Progressive MS' at PACTRIMS, Kyoto, Japan, November 2013
- Session chair at the MSRA Progress in MS Research Conference, Sydney, November 2013

MICHELE BINDER

- "A MS-associated single nucleotide polymorphism in the MERTK receptor is correlated with altered MERTK expression" at the Progress in MS Research conference (14th – 15th November 2013, Sydney, Australia)

MS GENETICS GROUP

COLLABORATIONS

- Helmut Butzkueven, Department of Medicine, University of Melbourne
- David Booth, University of Sydney
- Jim Wiley, Florey Institute
- ANZgene Consortium
- The International Multiple Sclerosis Genetics Consortium
- Phil Hodgkin, The Walter and Eliza Hall Institute of Medical Research

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

- Field J. et al "TAM receptor signalling, neuroinflammation and demyelination" The 33rd Annual Meeting of the Australian Neuroscience Society. Melbourne February 3 – 6. 2013 (Speaker)
- Field J. et al. "Gene expression in immune cell subsets: A Risk Gene Study for Multiple Sclerosis" Keystone Symposia: Multiple Sclerosis. Big Sky, Montana, U.S.A. January 10 – 16 2013 (Speaker).

PUBLICATIONS

1. Ponsonby AL, Lucas RM, Dear K, van der Mei I, Taylor B, Chapman C, Coulthard A, Dwyer T, Kilpatrick TJ, McMichael AJ, Pender MP, Valery PC, Williams D. The physical anthropometry, lifestyle habits and blood pressure of people presenting with a first clinical demyelinating event compared to controls: The Ausimmune study. Mult Scler. 2013 May 13. [Epub ahead of print] PubMed PMID: 23670542
2. Sabo JK, Aumann TD, Kilpatrick TJ, Cate HS. Investigation of Sequential Growth Factor Delivery during Cuprizone Challenge in Mice Aimed to Enhance Oligodendrogliogenesis and Myelin Repair. PLoS One. 2013 May 1;8(5):e63415. doi: 10.1371/journal.pone.0063415
3. Valery PC, Lucas RM, Williams DB, Pender MP, Chapman C, Coulthard A, Dear K, Dwyer T, Kilpatrick TJ, McMichael AJ, van der Mei I, Taylor BV, Ponsonby AL. Occupational Exposure and Risk of Central Nervous System Demyelination. Am J Epidemiol. 2013 Apr 12. [Epub ahead of print] PubMed PMID: 23585328
4. Wong AW, Xiao J, Kemper D, Kilpatrick TJ, Murray SS. Oligodendroglial expression of TrkB independently regulates myelination and progenitor cell proliferation. J Neurosci. 2013 Mar 13;33(11):4947-57
5. Cortes A, Field J, Glazov EA, Hadler J; ANZgene Consortium, Stankovich J,Brown MA. Resequencing and fine-mapping of the chromosome 12q13-14 locus associated with multiple sclerosis refines the number of implicated genes. Hum Mol Genet. 2013 Jun 1;22(11):2283-92
6. Hughes AM, Lucas RM, McMichael AJ, Dwyer T, Pender MP, van der Mei I, Taylor BV, Valery P, Chapman C, Coulthard A, Dear K, Kilpatrick TJ, Williams D, Ponsonby AL. Early-life hygiene-related factors affect risk of central nervous system demyelination and asthma differentially. Clin Exp Immunol. 2013Jun;172(3):466-74
7. Jokubaitis VG, Spelman T, Lechner-Scott J, Barnett M, Shaw C, Vucic S, Liew D, Butzkueven H, Slee M; Australian Msbase Study Group. The Australian Multiple Sclerosis (MS) immunotherapy study: a prospective, multicentre study of drug utilisation using the MSBase platform. PLoS One. 2013;8(3):e59694. doi: 10.1371/journal.pone.0059694. Epub 2013 Mar 19
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10. Lin R, Charlesworth J, Stankovich J, Perreau VM, Brown MA; ANZgene Consortium, Taylor BV. Identity-by-descent mapping to detect rare variants conferring susceptibility to multiple sclerosis. PLoS One. 2013;8(3):e56379. doi:10.1371/journal.pone.0056379
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NEURODEGENERATION

Division head: Professor Phil Beart

A QUICK SNAPSHOT

Our focus within the Neurodegeneration Division is on how neurons live, die and can be rescued to improve brain function in degenerative conditions such as Parkinson's and Motor neuron diseases. The incidence of Parkinson's disease (PD) is rising alarmingly in our aging community and there is no effective treatment for Motor neuron disease (MND). All such degenerative brain diseases involve a set of generic destructive events that produce a toxic environment for brain cells. These include gene abnormalities, energy deprivation, toxic rubbish accumulation and inflammation. Our various groups study these events in cultured cells and animal models, with a view to translating knowledge into new therapies for human patients.

RESEARCH HIGHLIGHT

The Parkinson's Kinetigraph is a system for measuring the motor aspects of Parkinson's disease and was developed by the team at the Florey. It is being commercialised and is now in routine clinical use in more than 40 major PD centres in Europe, Asia and Australia. Research continues into the detection of impulse control disorders and sleep disorders of Parkinson's and further publications related to the algorithm. There is also ongoing work in using the device to predict the timing of therapy, especially in advanced treatments such as deep brain stimulation.

SENIOR STAFF

• Professor Philip Beart• Professor Malcolm Horne
• Associate Professor Clare Parish • Dr Lachlan Thompson
• Dr Tim Aumann • Dr Wah Chin Boon • Dr Brad Turner •

AN IDEA LIKELY TO CHANGE LIVES BY 2033

The Australian Parkinson's Disease Registry provides vital information on a cohort of comprehensively phenotyped patients around Australia who have had blood and genetic material taken and stored, systematically, for decades. This huge research platform drives major and diverse research projects and provides Florey scientists with important historical data in the race to cure this debilitating disease.

> "We know environmental enrichment works in many animal models and stroke patients, so its possible application in Parkinson's disease represents a stunning advance."

HIGHLIGHTS FOR 2013

Notable successes have occurred in work on Parkinson's disease where Tim Aumann and his team have revealed an amazing plasticity of the neurons involved in this condition. In his model system the number of neurons is increased or decreased following administration of various drugs, but also in mice exposed to different environments. His findings are indicative that in our brains, the number of neurons exhibiting a particular neurochemistry is changing constantly depending upon our environment. Work is planned to determine if this plasticity occurs in the adult human brain to explore the approach as a new therapy for patients. Of course, we know environmental enrichment works in many animal models and stroke patients, so its possible application in Parkinson's disease represents a stunning advance.

Clare Parish and Lachlan Thompson continue to advance their impressive work on stem cell-based therapies for brain repair by generating midbrain dopamine neurons from pluripotent stem cells for use in transplantation-based procedures for Parkinson's disease. Also being explored are engineering strategies with bioscaffolds that can be implanted into the brain to provide physical and trophic support for new neurons, thereby aiding the integration of neural transplants into the local environment.

Sex hormones such as oestrogens and androgens also exert local effects by modulating neuronal function and Wah Chin Boon has shown the key enzyme, aromatase, is discretely localized in limbic brain regions involved overt behaviours.

Malcolm Horne continues his translational success with the Parkinson's Kinetigraph system for measuring the motor symptoms, and disorders of sleep and impulse control in PD. This development is the subject of 2 patents and now in routine clinical use in some 40 major PD Centres in Europe, Asia and Australia.

Abnormal levels or mutations of proteins disrupt brain debris clearance leading to accumulation of toxic intracellular protein aggregates, which have been a special focus in our work in motor neurone disease (MND). Such toxic aggregates and resultant damaged molecules are normally cleared by autophagy. Brad Turner's team is currently translating key mechanistic finding from cellular systems to animal disease models to obtain outcomes beneficial to disease pathology.

In the laboratory of Philip Beart, the focus is on the more fundamental mechanistic aspects of autophagy, where damaged mitochondria are also swallowed up by this rubbish removal system. Brad Turner, Philip Beart and Malcolm Horne in a wide-ranging collaboration with interstate and international colleagues are currently harnessing autophagy to combat motor neuron pathology in mouse models to evaluate its therapeutic potential in MND. This wide-ranging study has also revealed activation of various components of the brain's inflammatory response in both astrocytes and microglia. By focusing on astrocytes, the labs of Malcom Horne and Philip Beart have identified new targets to keep astrocytes healthy which they hope to translate with bioengineering strategies to brain injury models.

MOLECULAR NEUROPHARMACOLOGY GROUP

Leader: Phil Beart

Our laboratory focuses on the pathological mechanisms affecting neurons and the astrocyte which have an interdependent relationship essential to brain health. Our diverse experimental approaches reveal new strategies to rescue threatened neurons and to establish a supportive environment near an injury zone.

Neurons, when they age or become injured, accumulate damaged molecules of all types which affect their function. This process is termed autophagy ("self-eating") and represents one of the cellular rubbish removal mechanisms. If the load becomes too extreme or if the autophagic mechanisms become compromised, the process can become a form of programmed cell death. Most research into the controlling mechanisms has been performed in non-mammalian cells, so our work in primary neurons is groundbreaking. Very recently it has become apparent that damaged mitochondria enter the autophagic cascade through a process termed mitophagy. We have found that disturbed energy generation causes mitochondria to lose their membrane potential with a concomitant drop in ATP production and entry into mitophagy. Since disturbed energetics contributes to various forms of inherited neurodegenerative conditions, we believe that this cascade contributes to many forms of brain injury. We are currently investigating autophagy in other brain injury models.

Inflammation contributes to the advancement of pathology of all forms of brain injury, be it acute (stroke) or a chronic degenerative condition (PD). Astrocytes can display "good" or "bad" responses dependent upon the state of brain injury. We have continued to explore how the biology influencing the "good" component of inflammation can be promoted. By culturing astrocyes in 3D on bioscaffolds, we found what we have defined a healthy astrocyte as displaying GFAP, and increased G-actin, glutamate transport, brain-derived trophic factor (BDNF) and anti-oxidant activity. These "signposts" have guided further studies where via collaboration a novel bioscaffold presenting a covalently bonded sugar moiety has shown great promise in minimizing inflammation in studies performed in cultured astrocytes and in vivo in model of traumatic brain injury. Immunocytochemistry shows non-inflammed astrocytes in both models and the causative molecular signatures are being pursued.

NEURODEGENERATION GROUP

Leader: Tim Aumann

2013 was a watershed year for our studies into plasticity of the adult nigrostriatal pathway. Based on earlier work demonstrating the number of nigrostriatal dopamine neurons increased or decreased following administration of various drugs, this year we found this also occurs in mice exposed to different environments, and that it is abolished by blockade of synaptic input to nigrostriatal neurons (Figure 1 and reference [1]). This evidence indicates that the number of neurons exhibiting a particular neurochemistry (dopamine in this case) in our brains is changing all the time depending upon our environment. This finding is significant because it is a novel form of adult brain plasticity that ought to have major impacts on brain function and behaviour. Moreover, it may lead to new environment-based and drug-free approaches to treating brain diseases and disorders; in this case those associated with imbalances in midbrain dopamine such as PD, schizophrenia, attention deficit and hyperactivity disorder (ADHD) and drug addiction.

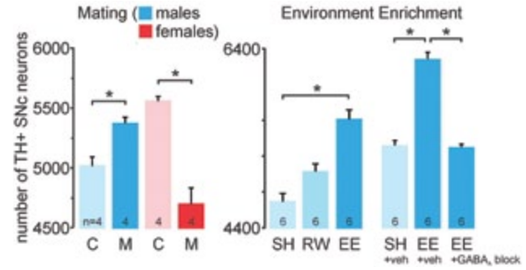

Figure 1: Number (mean±SE) of dopaminergic (TH+) neurones in adult mouse substantia nigra pars compact (SNc) is altered up or down depending on the mouse's environment. Left: Mating paradigm (C=control, M=mated); Right: Environment enrichment (SH=standard housed, RW=running wheel, EE=environment enriched). Furthermore, EE induction of 'newly' DA neurons is abolished by concurrent local blockade of synaptic (GABAA) input. +Veh=vehicle infusion; +GABAA block=10μM picrotoxin infusion. *=p<0.01 one-way ANOVA with Tukey multiple comparisons.

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Research highlights for 2013

We developed a behavioural test for mice which is sensitive to changes in the number of nigrostriatal dopamine neurons, and are about to test whether environmental-induction of different numbers of these cells affects brain function and behaviour. We are also beginning experiments to determine whether the same occurs in the adult human brain, which is crucial for translating this work into new therapies for patients

STEROID NEUROPATHOLOGY GROUP

Leader: Wah Chin Boon

From our everyday experience, we know that sex hormones such as oestrogens and androgens (eg testosterone) affects our behaviour. It has been known for nearly forty years that oestrogens are produced in the brain from testosterone, and that these locally synthesised oestrogens may modulate neuronal functions and provide neuroprotection. The conversion of oestrogens from androgens is catalysed by the enzyme aromatase, but where is this found in the brain?

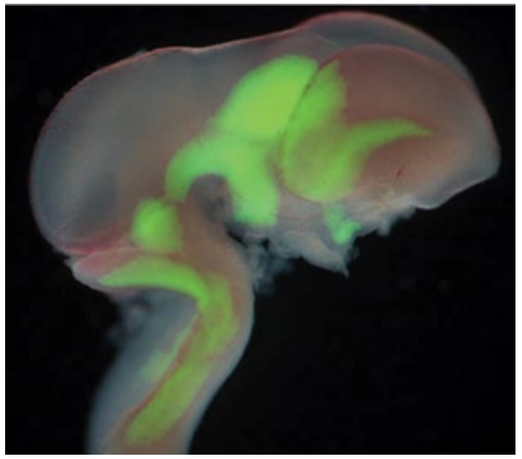
Immunohistochemisty is the common technique used to identify the localisation of a protein in tissues or organs, and this relies on the specificity of the antibody. The aromatase protein shares a similar structure to a cytochrome p450 superfamily, and hence it has been difficult to generate a highly specific anti-aromatase antibody, especially in rodent models. We overcame this problem by using a transgenic mouse model with an enhanced green fluorescence protein (EGFP) tagged to the aromatase.

Our lab has identified EGFP-aromatase expression in the neurons of many brain regions under normal physiological conditions, and these brain regions have been previously reported to be involved in behaviour. Male adult mice have more aromatase-expressing neurons. Furthermore, we noticed that oestrogen receptors are found in neurons expressing aromatase or in close proximity to aromatase-positive neurons, supporting the idea that locally produced oestrogens modulate neuronal functions. As shown in the figure, immunohistochemistry of male medial amygdala detected strong egfp signal (green) in neurons and in close proximity to oestrogen receptor alpha.

NEUROGENESIS AND NEURAL TRANSPLANTATION GROUP

Leader: Lachlan Thompson

Our laboratory is focused on developing regenerative therapies for brain and spinal cord repair. Like many neurobiologists in this field, we share the view that success in this area will be closely aligned with a deeper understanding of the complex processes that underlie brain development. We are particularly interested in the molecular mechanisms that underlie neurogenesis as well as neurite outgrowth and connectivity in the developing brain. Our goal is to adapt key concepts in this area to the development of stem cell-based therapies for brain repair; a central focus is the generation of midbrain dopamine neurons from pluripotent stem cells for use in transplantation-based procedures for Parkinson's disease. We are also working on similar approaches for other neurological conditions including stroke, motor neuron disease and Huntington's disease. In addition to transplantation-based strategies, we are also exploring other novel avenues for brain repair including the use of viral vectors to deliver trophic factors that can protect neurons from injury or even promote 'self-repair' from the brain's own stem cells.



The developing brain of the Ngn2-GFP mouse. This transgenic mouse has been engineered to express green fluorescent proteins in certain types of developing neurons. This means we can isolate and purify this distinct sub-population of cells before transplanting them into the brain as a regenerative approach for brain disease or injury.

STEM CELLS AND NEURAL DEVELOPMENT GROUP

Leader: Clare Parish

The Parish laboratory has a broad research interest relating to repairing the injured brain. The team places a strong emphasis on understanding neural development, with the idea that repairing the injured brain will require recapitulation of many of these early events. Consequently there are a number of major research themes running within the laboratory, including: understanding neural development (notably wnt signalling); directed differentiation of pluripotent stem cells; molecular mechanisms underlying axonal targeting and synaptogenesis and improving cell-replacement therapy for neural injuries.

Horizontal sections through the mouse brain shows the integration of transplanted dopamine progenitor cells in an animal model of Parkinson's disease. This dark-field image showing GFP+ dopamine cells (orange) illustrates the capacity of cells transplanted into the injured midbrain to restore connections with forebrain target tissue. This work was published in the *Journal of Physiology* (2013; 591(1):77-91) and was the cover image of Neuroreport (Dec 18 2013, vol 24(18), pp997-1077), in association with published conference proceeding from the International Neural transplantation and repair meeting, 2013, in Cardiff Wales. Image by PhD student Jessica Kauhausen.

While historically the major focus of the group has been on understanding dopamine development and developing cell replacement therapies for PD, more recently the team has expanded its interests to apply similar approaches for other neural injuries including Huntington's disease and stroke. Much of this work is done in close collaboration with the laboratory of Dr Lachlan Thompson, also at the Florey Institute.

The Parish laboratory has also developed a key interest in neural engineering. The team is developing and testing bioengineered scaffolds that can be implanted into the brain to provide physical and trophic support for new neurons, thereby aiding in the integration of neural transplants.

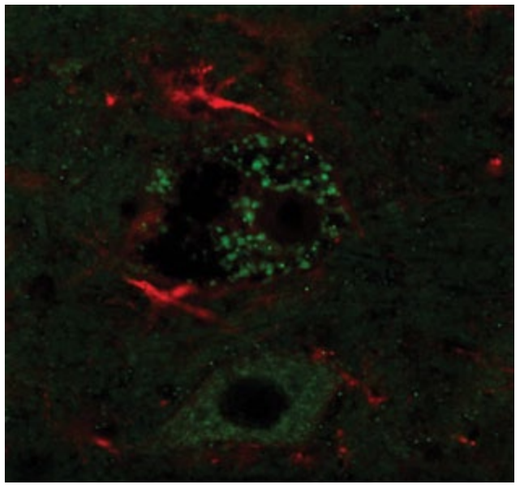
MOTOR NEURON DISEASE GROUP

Leader: Brad Turner

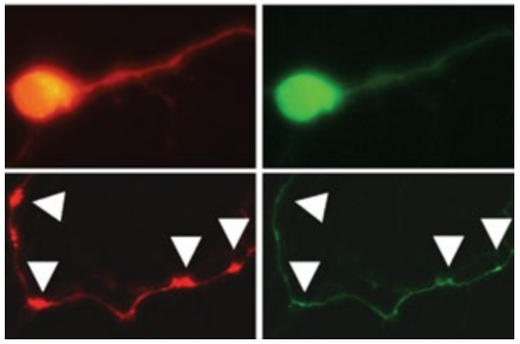
The Turner lab seeks to unravel the molecular pathogenesis of the protein misfolding disorder motor neuron disease (MND) and translate these findings into effective biomarkers and therapeutic strategies. We employ a combination of biochemistry, cell and molecular biology to study the pathogenesis of MND in patient samples, cell culture and mouse models.

Research highlights for 2013

- Our research has identified that autophagy activation occurs in motor neurons of MND patients and genetic mouse models. We have shown that autophagy is triggered by abnormal endosomes which are involved in sorting and transport of proteins, thus coupling endosome pathology to autophagy in MND. We are currently harnessing autophagy to combat protein misfolding and motor neuron pathology in mouse models to test its therapeutic potential in MND.
- We have demonstrated that survival motor neuron (SMN) gene therapy extends survival in mutant TDP-43 mice. This is an important extension of previous work showing that SMN delivery to another MND mouse model, mutant SOD1 mice, is protective to motor neurons. We are now developing a new gene therapy approach for peripheral delivery and sustained motor neuron targeted SMN delivery.



Activated microglia (red) surrounding a motor neuron with abnormal large endosomes (green).



Evidence for mitophagy: Transfected neurons with pH-sensitive mitoRosella (RFP: Localization of mitochondria; GFP: pH indicator of the environment of mitochondrial localization) show even fluorescence of red and green fluorescence in vehicle neurons (upper panels). Rotenone 10nM treatment for 4 hours induced quenching of green fluorescence in axons, indicating the localization of mitochondria in acidic environment (lower panels) of autophagolysosome.

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MOLECULAR NEUROPHARMACOLOGY GROUP

MAJOR COLLABORATIONS

NATIONAL

- Dr David Nisbet, Research School of Engineering, Australian National University. Bioengineering.
- Dr Hakan Mudyerman, Department of Biochemistry, Flinders University. Astrogliosis in MND.
- Dr Steve Cheung, School of Life and Environmental Sciences, Deakin University. Programmed cell death.
- Prof Phillip Nagley, Department of Biochemistry and Molecular Biology, Monash University. Programmed cell death.
- Prof Rod Devenish, Department of Biochemistry and Molecular Biology, Monash University. Autophagy.

INTERNATIONAL

- Prof Ulf Nilsson, Department of Chemistry, University of Lund. Inhibitors of inflammation.

INTERNATIONAL PRESENTATIONS

PHILIP BEART

- Joint conference of the European Society for Neurochemistry and the Biochemical Society, Bath, United Kingdom.
- 11th European Meeting on Glial Cell Function in Health and Disease, Berlin, Germany.
- 12th ISN Advanced School of Neurochemistry, Chichén Itzá, Mexico
- The Brain in Flux: Genetic, Physiologic, and Therapeutic Perspectives on Transporters in the Nervous System", Cancun, Mexico.
- IBRO-ISN School of Neuroscience in Africa, Ibadan, Nigeria.

LINDA LAU

- 24th International Symposium on ALS/MND, Milan, Italy
- Cecilia Cederfur
- Joint conference of the European Society for Neurochemistry and the Biochemical Society, Bath, United King

NEURODEGENERATION GROUP

PAPERS

- Aumann TD, Tomas D. & Horne MK (2013) Brain & Behavior doi: 10.1002/brb3.163.
- Mohammad SS, Sinclair K, Pillai S, Merheb V, Aumann TD, Gill D, Dale RC, Brilot F (2013) Mov Disord. 2014 Jan; 29(1):117-22. doi: 10.1002/mds.25623. Epub 2013 Oct 1.
- Sabo JK; Aumann TD; Kilpatrick TJ; Cate HS (2013) PLoS ONE, May 1;8(5):e63415. doi: 10.1371/journal.pone.0063415.

NEUROGENESIS AND NEURAL TRANSPLANTATION GROUP

SPEAKING INVITATIONS 2013

- American Society for Neural Therapy and Repair (Florida, USA).
- University of Melbourne Department of Pharmacology (Melbourne).

STEM CELLS AND NEURAL DEVELOPMENT GROUP

ORAL PRESENTATIONS

- 2013 Melbourne Brain Symposia, (Nov 2013) "Developing stem cell therapies for Parkinson's disease: A focus on Parkinson's Disease".
- The American Society of Neural Therapy and Repair annual meeting, Clearwater Beach, Florida, USA (April, 2013)
- Australian Neuroscience Society Annual Meeting, Melbourne (Jan, 2013)

MEDIA

- Herald-sun and The Australia newspapers "Peptides and cures for Parkinson's disease" (19 March 2013)
- ABC News and ABC Gold & Tweed Coasts radio interview. "Stem cell researchers exploring brain repair" (31 Jan 2013)

MOTOR NEURON DISEASE GROUP

ORAL PRESENTATIONS

- 33rd Annual Meeting of Australian Neuroscience Society, Melbourne
- 24th Biennial Meeting of ISN-ASN, Cancun, Mexico
- 24th International Symposium on ALS/MND, Milan, Italy

PUBLICATIONS

1. CHEN M.J., NG .JM., PENG Z.F., MANIKANDAN J., YAP Y.W., LLANOS R.M., BEART P.M., CHEUNG N.S. Gene profiling identifies commonalities in neuronal pathways in excitotoxicity: Evidence favouring cell cycle re-activation in concert with oxidative stress. Neurochemistry International 62, 719-730 (2013)
2. SHEEAN R.K., LAU C.L., SHIN Y.S., O'SHEA R.D. & BEART P.M. Links between L-glutamate transporters, Na+/K+-ATPase and cytoskeleton in astrocytes: Evidence following inhibition with rottlerin. Neuroscience 254, 335–346 (2013)
3. YAP Y.W., CHEN M.J., PENG Z.F., MANIKANDAN J., NG J.M., LLANOS R.M., LA FONTAINE S., BEART P.M., CHEUNG N.S. Gene expression profiling of rotenone-mediated cortical neuronal death: Evidence for inhibition of ubiquitin-proteasome system and autophagy-lysosomal pathway, and dysfunction of mitochondrial and calcium signaling. Neurochemistry International 62, 653-663 (2013)
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5. Wright J, Stanic S, Thompson LH. Generation of striatal projection neurons extends into the neonatal period in the rat brain. J Physiol 2013 591(Pt 1):67-76
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NEUROETHICS

Making sense of sincerity and lies…

Professor Neil Levy is the Florey's resident neuroethicist. Neil has published widely in journals, books and in the public sphere, both here and internationally.

Neil travels extensively and has presented on topics relating to free will, consciousness and moral responsibility. The media was quick to call on Neil for comment when Woody Allen was accused of those allegations. Here is his discussion on whether Allen or Farrow were lying.

"It is hard to be agnostic when someone is charged with a terrible crime like child abuse. It is still harder when that person is a beloved filmmaker and symbol of artistic excellence (even if few of his recent films have lived up to expectations). Given the depth of some people's emotional attachment to Allen and his films, many have reacted by refusing to believe Dylan Farrow's claims that she was abused. Others, though, can't believe that she would lie about something like that, and have therefore concluded that the allegations are true.

"But we do not have to choose between branding Allen or Farrow a liar. Whatever the truth of the allegations, they might both be completely sincere in what they say. Decades of research on memory have shown that memory doesn't work like a camera: we don't take snapshots of scenes which we can then consult at will. Rather, memory is a reconstructive processes, in which we retrieve past events by piecing together various cues. That leaves us vulnerable to what psychologists call confabulating memories: making them up, without knowing it.

Decades of research on memory have shown that memory doesn't work like a camera: we don't take snapshots of scenes which we can then consult at will…

"One way in which this happens is when truly recall something, but fail to recall the source of the memory. In one study of convicted felons later freed on conclusive DNA evidence, fully 90 per cent of the convictions were based at least partly on eyewitness testimony. Confusion about the source of memories probably helps explain how this happens: eyewitness might have seen the person in a mugbook, or in a store, and then thought they recalled seeing him at the scene of the crime.

"That's speculation, of course, but it has been demonstrated in a case when a person actually confessed to abusing his daughter in bizarre satanic rituals. A psychologist who interviewed the man made up details of the crimes deliberately. At first the man denied that those details were true, but later he came to recall them. In her work, Elizabeth Loftus has shown that about 30% of people can be led to confabulate memory in the lab. In everyday life, the percentage might be higher, especially when events are emotionally charged and the person is encouraged to imagine them repeatedly. After a while, she may come to mistake her imaginings for recollections. Neither intelligence nor good character seems to protect against this.

"One possibility, therefore, is that having been pressured to recall events, Dylan Farrow came to think they actually happened. Another possibility is that Woody Allen sincerely denies the abuse, but it is he who is confabulating. It is probably more likely that a child would be more vulnerable to confabulation than an adult. In any case, we don't need to decide who is telling the truth (nor is there any good reason to think that lie detecting tests would help). Both sides might be sincere, but one of them is wrong."

PUBLICATIONS AND INVITED LECTURES, PRESENTATIONS AND KEYNOTE ADDRESSES

1. LEVY, N. – Consciousness and Moral Responsibility, Oxford University Press, 2014
2. LEVY, N. (ed). Self-Control and Addiction. New York: Oxford University Press, 2013
3. LEVY, N. Addiction as a Disorder of Belief. Biology & Philosophy, forthcoming
4. LEVY, N. Is Neurolaw Conceptually Confused? Journal of Ethics, forthcoming
5. LEVY, N. Countering Cova: Frankfurt-Style Cases are Still Broken. Ethical Theory and Moral Practice, forthcoming
6. LEVY, N. The Harm of Intraoperative Awareness. Journal of Medical Ethics, forthcoming
7. LEVY, N. Less Blame, Less Crime? The Practical Implications of Moral Responsibility Skepticism, Journal of Practical Ethics, forthcoming
8. Maslen, H., Douglas, T., Cohen Kadosh, R., LEVY, N. & Savulescu, J. Do-it-yourself brain stimulation: a regulatory model. Journal of Medical Ethics, forthcoming
9. LEVY, N. Psychopaths and Blame: The Argument from Content. Philosophical Psychology, forthcoming
10. Maslen, H., Douglas, T., Cohen Kadosh, R., LEVY, N. & Savulescu, J. The regulation of cognitive enhancement devices: Extending the medical model. Journal of Law and Bioscience, forthcoming
11. LEVY, N., Douglas, T., Kahane, G., Terbeck, S., Cowen, P, Hewstone, M. and Savulescu, J. Are You Morally Modified? The Moral Effects of Widely Used Pharmaceuticals. Philosophy, Psychiatry and Psychology, forthcoming
12. LEVY, N. Forced to be Free? Increasing Patient Autonomy by Constraining It. Journal of Medical Ethics, forthcoming
13. LEVY, N. Consciousness, Implicit Attitudes and Moral Responsibility. Noûs, 48 (2014), 21-40
14. LEVY, N. The Value of Consciousness. Journal of Consciousness Studies, 21 (2014), 127-138
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18. LEVY, N. Free will doesn't come for free. American Journal of Bioethics (AJOB-Neuroscience), 4 (2013), 53-4
19. LEVY, N. The Importance of Awareness. Australasian Journal of Philosophy, 91 (2013), 211-229
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23. LEVY, N. Addiction is not a brain disease (and it matters). Frontiers in Addictive Disorders & Behavioral Dyscontrol, 4 (2013): 1-7
24. Barutchu, A., Carter, O., Hester, R. & LEVY, N. Strength in cognitive self-regulation. Frontiers in Cognition, 4 (2013): 1-10
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26. LEVY, N. Zimmerman's The Immorality of Punishment: A Critical Essay. Criminal Law and Philosophy, forthcoming
27. LEVY, N. – Rationality + Consciousness = Free Will. Australasian Journal of Philosophy, 91 (2013), 183-192
28. LEVY, N. Consciousness Matters. In Walter Sinnott-Armstrong (ed). Moral Psychology: Vol. 4, Cambridge, Mass: The MIT Press, 2014
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30. LEVY, N. Naturalism and Free Will. In Kelly James Clark (ed). Blackwell Companion to Naturalism, forthcoming
31. LEVY, N. Does Luck Exist? In CSIRO (ed) The Explainer: From Déjà Vu to Why the Sky Is Blue, and Other Conundrums, CSIRO Publishing, 2013
32. LEVY, N. Free will and Luck. In A. Lavazza, M. De Caro, G. Sartori (eds), Quando siamo responsabili, Turin, Codice Edizioni, 2013
33. LEVY, N. Intuitions and Experimental Philosophy – Comfortable Bedfellows. In Matthew Haug (ed). Philosophical Methods, Routledge, 2013
34. LEVY, N. Be a skeptic, not a metaskeptic. In Gregg Caruso (ed). Exploring the Illusion of Free Will and Moral Responsibility, Lexington Books, 2013
35. LEVY, N. Punishing the Addict: Reflections on Gene Heyman. In Thomas Nadelhoffer (ed). The Future of Punishment. Oxford University Press, 2013
36. LEVY, N. Moral responsibility and consciousness: two challenges, one solution. In Nicole Vincent (ed). Neuroscience and Legal Responsibility, Oxford University Press, 2013
37. Cognitive Enhancement: moral, legal and scientific challenges, Delft, Netherlands (August 2014)
38. Michigan Graduate Student Spring Colloquium (March 2014)
39. Korea Institute for Advanced Study, Seoul (December 2013)
40. Neuroethics: The Birth of a Discipline, Padua, Italy (May 2013)
41. Peter Wall Institute of Advanced Studies International Roundtable, University of British Columbia, Canada (October 2013)
42. Law and Neuroscience, Stanford University, USA (May 2013)
43. Free Will, Southern Methodist University, Dallas, USA (February 2013)
44. Bergamo Science Festival, Italy (October 19 2013). "Moral responsibility and consciousness"
45. Public debate: Is Digital Technology bringing out the best in us? Australia Museum, Sydney (October 8 2013). Pro: Neil Levy; Con: Baroness Susan Greenfield
46. Festival of Ideas, University of Melbourne (October 5 2013). "Teaching Self-Control"
47. Brain awareness week lecture, Kings College London (March 12 2013). "Free will and the brain"
48. Invited Lecture, University of Hamburg (March 7 2013). "Why direct and indirect interventions into the mind are ethically on a par"
49. Guest on The Moral Maze (BBC Radio 4) 12 February 2014. Discussion of memory, 4BC (Brisbane) 23 August 2013
50. Discussion of luck, Life Matters (Radio National) 5 July 2013
51. "Delitti e insidie: I segreti dei sonnambuli" Corriere della Sera, 5 October 2013
52. "Can people really be addicted to sex?" The Conversation, 12 August 2013
53. "Is free will a scientific problem?" The Conversation, 18 July 2013
54. "Caveman ethics? The rights and wrongs of cloning Neanderthals" The Conversation, 26 January 2013
55. "Levy, neuroscienze in affanno quando si parla della coscienza" L'Eco Di Bergamo, 19 October 2013
56. Digital Dementia ABC News 24, July 5, 2013

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NEUROPEPTIDES

Division head: Associate Professor Ross Bathgate

A QUICK SNAPSHOT

The Neuropeptides division conducts multi-disciplinary studies on the relaxin family of peptides/hormones and their receptors. The division focuses on determining the role of these peptides and the receptors they target in a wide range of physiological and disease states. These studies are coupled with fundamental drug discovery research on both the peptides and their G protein-coupled receptors. The aim of this research is to develop therapeutics which target these peptide receptors to treat vascular, fibrotic, metabolic and psychiatric diseases. An exciting outcome for the Neuropeptides Division has been the successful completion of Phase III trials using the hormone relaxin for the treatment of acute heart failure by the Swiss Pharmaceutical Company Novartis. This work demonstrates how fundamental research on the mechanism of action of a hormone, in the case of relaxin pioneered at the Florey by Prof Geoffrey Tregear, can lead to its ultimate use in patients to treat disease.

RESEARCH HIGHLIGHT

The Neuropeptides division was thrilled in 2013 by the successful completion of phase III trials by the Swiss pharmaceutical company Novartis, using the hormone relaxin for the treatment of acute heart failure.

The work demonstrates how fundamental research on a mechanism of action on a hormone, in this case that of relaxin which was pioneered at the Florey more than 30 years ago by Professor Geoffrey Tregear, can lead to its ultimate use in patients to treat disease.

> “
> …We are concentrating on … the development of smaller drugs that can be taken orally for the treatment of heart failure and other diseases.
> ”

AN IDEA LIKELY TO CHANGE LIVES BY 2033

We have shown that relaxin-3 decreases anxiety and depressive-like symptoms in pre-clinical models. By 2033, ‘next generation’ relaxin-3-based therapeutic drugs may be available to treat patients with anxiety and depression.

SENIOR STAFF

• Associate Professor Ross Bathgate • Associate Professor Andrew Gundlach • Dr Mohammed Akhter Hossain • Dr Daniel Scott • Professor John Wade •

Natasha Lam, Fabian Bumbak, Daniel Scott, Rebecca Tan, Natalie Gunn, Brad Hoare from the membrane protein engineering group.

MEMBRANE PROTEIN ENGINEERING GROUP

Leader: Daniel Scott

Many membrane proteins are located on the surface of our cells where they are involved in processes such as sensing neurotransmitters, driving neural impulses and responding to drug treatment. The instability of membrane proteins, however, makes them difficult to study. We engineer stabilised membrane proteins to aid in elucidating the atomic level mechanisms that govern their function and to facilitate novel drug discovery.

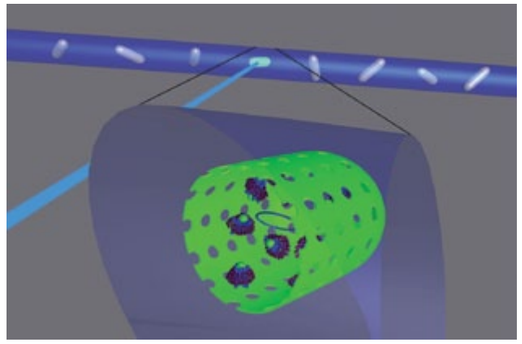
Research highlights for 2013

We are one of only two laboratories in the world with CHESS capability, a membrane protein stabilisation method invented by Dr Scott. This has enabled us to stabilise several G protein-coupled receptors (GPCR) that are key drug targets for central nervous system disorders such as epilepsy, Parkinson’s disease, Alzheimer’s disease, schizophrenia and drug abuse. The generation of these stabilised receptors will provide new avenues for discovering treatments for these diseases.

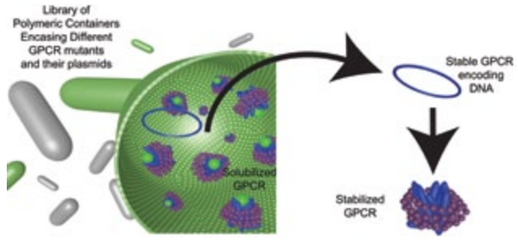
The laboratory is also working on the application of our technology to other membrane proteins such as ion channels, which are responsible for driving neural impulses and are drug targets in many neurological disorders.

Specific research highlights include:

- Published the invention of a novel protein engineering method that was used to stabilise two GPCRs (Scott et. al. J. Mol. Biol. 2013). This technology allows us to engineer membrane proteins that can be easily manipulated in the laboratory, with applications in structural biology, pharmacology and drug discovery. This publication has already received international recognition, being recommended by the Faculty of 1000 (Sexton, P. & Furness, S. F1000 Prime Recommendation of [Scott DJ and Plückthun A, J Mol Biol 2012]. Faculty of 1000, (2012)).
- Published an invited review on membrane protein stabilisation (Scott et. al. Curr. Opin. Chem. Biol. 2013).
- Daniel Scott won an Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) Denis Wade Johnson & Johnson New Investigator Award.
- Daniel Scott won the BPS/ASCEPT Outstanding Young Investigator Prize. Won a paid three-week trip to the UK to visit laboratories and present at the British Pharmacological Society meeting in 2014.
- Two patent applications with IBM research Australia describing GPCR based biosensors for drug discovery.



Cartoon representation of the GPCR stabilisation technology employed in our laboratory. We screen hundreds of millions of nano-capsules, each containing a different GPCR variant, in a fluidic stream using fluorescent activated cell sorting (FACS). The most fluorescent capsules contain stable GPCR variants that can be sorted from the capsule population by the FACS instrument.



We use directed evolution to engineer stabilized GPCRs. Directed evolution works in the same way as natural evolution, but on a single gene level rather than a whole organism. Using molecular biology, we generate a diverse population of our GPCR gene(s) of interest, comprising at least 10 million individual mutants. Each of these individual genes, and the resultant GPCR proteins, are packaged into their own detergent resistant capsules. We can then screen this large population for individuals that exhibit enhanced stability with fluorescence activated cell sorting. Selected genes can then be cycled through further evolutionary rounds, or can be isolated and used to produce stabilized GPCR proteins for biochemical and structural experiments.

NEUROPEPTIDE RECEPTOR GROUP

Leader: Ross Bathgate

The Neuropeptide receptor laboratory studies G protein-coupled receptors (GPCR) which represent the most important class of biomolecules for pharmaceutical development, being targeted by ~30 per cent of current drugs. Our studies on the structure and function of novel neuropeptide GPCRs will enable the development of new drugs to specifically target neurological and other diseases.

Research highlights for 2013

Studies by the group continue to demonstrate the unique mechanism by which the hormone relaxin binds to and activates its receptor, RXFP1. Two recent publications (one in the prestigious Journal of Biological Chemistry) have furthered our understanding of the mechanism of interaction between relaxin and RXFP1 to enable new drug design. Relaxin was recently demonstrated to be an effective treatment for acute heart failure in Phase III clinical trials and will soon be used clinically to treat this disease. However, the patients must be treated by continuous intravenous infusion of relaxin which is not an ideal method to deliver the drug. Studies by our group, which are concentrating on determining the precise mode of interaction of relaxin with RXFP1, will lead to the development of smaller drugs that can be taken orally for the treatment of heart failure and other diseases.

PEPTIDE AND PROTEIN CHEMISTRY GROUP

Leader: John Wade

We employ modern chemical peptide synthesis methods together with structure-based drug design and development to produce novel peptidomimetics with improved receptor selectivity, potency and pharmacokinetics. Our primary research focus is on complex insulin-like peptides including the ovarian peptide, relaxin, and the neuropeptide, relaxin-3.

Research highlights for 2013

Our laboratory has continued to make significant progress in the identification of the key structural features of the insulin-like peptides, relaxin and relaxin-3, that are responsible for the binding and activation of their respective primary G-protein coupled receptors, RXFP1 and 3. Both peptides possess an insulin-like structure in which two peptides chains are linked together by three disulfide bonds.

BACK TO CONTENTS

Relaxin is principally an ovarian hormone that has a number of physiological roles, one of which is to regulate the level of collagen throughout the body. Relaxin-3 possesses a similar overall structure but is a neuropeptide that is expressed by the brain and which appear to have a critical role in regulating mood and stress systems. Because of their similar global structures, relaxin-3 can cross react with the receptor for relaxin; this can potentially complicate our attempts to better understand the role of relaxin-3 in the brain because the relaxin receptor is also present in this organ.

However, by using chemical peptide synthesis, selective amino acid mutation together with sequential truncation was undertaken on each of the two chains that make up each of relaxin-3 to produce novel mimetics. These were shown to possess relaxin-3 receptor selectivity while retaining near-native potency. Importantly, these new analogues are much simpler structurally and therefore easier to make. This will greatly facilitate the neurobiological studies that are being undertaken by our colleagues in the laboratory of Associate Professor Andrew Gundlach.

Such studies will determine whether these analogues possess clinical potential for treating psychiatric disorders such as anxiety and depression. Parallel chemical methods have also led to the development of a novel relaxin analogue which is selective for its own receptor and which has no cross reactivity for the receptor, RXFP2, of related peptide INSL3.

PEPTIDE NEUROBIOLOGY GROUP

Leader: Andrew Gundlach

Our laboratory conducts 'systems neuroscience' research. A primary interest is to understand the role of neuropeptide signalling in the control of complex behaviours – arousal, stress and mood, and associated memory processes – under normal and pathophysiological conditions. We conduct experimental studies in animal models of normal physiology and psychiatric disorders, using a range of biomolecular tools including receptor-selective peptides, viral-vector delivered 'designer' receptors, and a range of transgenic mouse strains.

Research highlights for 2013

Neurological changes which underlie depression, anxiety and other affective disorders are poorly understood, and existing pharmacological treatments for these debilitating diseases are associated with a range of undesirable side effects. Therefore, novel molecular targets in brain that might underpin better treatments for debilitating conditions encompassed by clinical anxiety disorders, major depression, and related psychiatric illnesses need to be identified, and the therapeutic potential of drugs which target them needs to be explored. In this regard, since its discovery at the Florey in 2002, we have been researching the neurobiology of the peptide transmitter relaxin-3. Our laboratory and others have demonstrated that relaxin-3 and its neural receptor RXFP3 appear to play a role in anxiety, cognition, motivation, and other modalities in rodents that are commonly aberrant in human sufferers of affective disorders. In 2013, we again made a number of key observations that have further increased our understanding of this neuropeptide-receptor system.

Importantly, we demonstrated that central activation of RXFP3 by a relaxin-3 mimetic peptide, decreased anxiety- and depressive-like behaviour in adult rats (Ryan PJ et al., 2013a), highlighting the therapeutic potential of targeting the RXFP3 system. In a joint study with members of the Florey Addiction Neuroscience laboratory published in the high-impact Proceedings of the National Academy of Sciences (USA), we demonstrated that central blockade of RXFP3 reduces alcohol self-administration and cue-and stress-induced relapse in alcohol-preferring rats (Ryan PJ et al., 2013b). These findings are important for our understanding of drug seeking behaviour and affective disorders in general, as motivation and reward circuits are often aberrant in clinical depression. We also observed that central RXFP3 blockade also reduced motivational behaviour in mice, such as the consumption of palatable food (Smith CM et al., manuscript submitted).

Valuable insights were also gained using life-long relaxin-3 and RXFP3 gene deletion or 'knockout' mice, reflected by a hypersensitivity to stress-induced insomnia and highly fragmented circadian activity, which is indicative of sleep/wake disturbances. This is commonly observed in a number of pathological conditions including major neurodegenerative disorders and clinical depression. Recent studies suggest this phenotype is related to RXFP3 regulation of non-photic inputs to the circadian system. In this regard, with colleagues in Poland, we identified a major relaxin-3/RXFP3 pathway from midbrain central grey to thalamic 'intergeniculate leaflet' (Blasiak A et al., 2013), an area which contributes to the control of circadian rhythms, particularly in the absence of strong photic drive.

Relaxin-3 positive neurons within the brainstem 'nucleus incertus' are stimulated by the stress hormone corticotrophin-releasing factor (CRF), and the firing of these neurons is synchronised with a unique brain activity that underlies memory processing, known as 'hippocampal theta rhythm' (Ma S et al., 2013). Therefore, as part of a new initiative involving several staff and student members, we have successfully modulated the activity of the nucleus incertus in adult rats using viral-vector delivered 'designer' receptors (DREADDs) and observed strong effects on brain activity (EEG), physiology (body temperature, stress-induced cardiovascular response) and behaviour (locomotor activity, spatial memory). Furthermore, in a new collaboration with scientists at La Trobe University, we are investigating the interactions between brain relaxin-3 and serotonin networks. It is hypothesized that relaxin-3 may play a role in stress-associated changes in anxiety in animals by interactions with serotonin systems in the raphe nuclei. Planned studies will help us model similar changes that occur in stress and trauma induced clinical mood disorders.

These and related studies will continue in 2014 with ongoing support from NHMRC (Australia), and new funding, including a Brain and Behavior Research Foundation (USA) NARSAD Independent Investigator Award to A/Prof Andrew Gundlach, a Commonwealth Endeavour Australia Fellowship awarded to Dr Sherie Ma, and strong student scholarship support from the Bethlehem Griffiths Research Foundation (Cary Zhang), Alzheimer's Australia Dementia Research Foundation (Mouna Haidar) and The University of Melbourne (Hanna Kastman, Valeria Rytova).

MEMBRANE PROTEIN ENGINEERING GROUP

COLLABORATIONS

- Victor Chang Cardiac Research Institute, Australia
- Monash Institute of Pharmaceutical Sciences
- University of Zurich, Switzerland
- Monash University, Australia
- CSIRO, Australia
- Australian Synchrotron
- The University of Melbourne, Australia
- IBM Research Collaboratory in Life Sciences & IBM Australia Research Laboratory

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

- Queenstown Molecular Biology (International), August 2013, Queenstown, NZ. Daniel Scott, invited speaker
- COMBIO, September 2013, Perth, Australia. Daniel Scott, invited speaker
- Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) Annual Scientific Meeting, December 2013, Melbourne. Daniel Scott, invited speaker, Denis Wade award winner and BPS/ASCEPT Outstanding Young Investigator Prize winner

NEUROPEPTIDE RECEPTOR GROUP

COLLABORATIONS

- Department of Biochemistry and Molecular Biology, University of Melbourne
- School of Biomedical Sciences, University of Queensland
- Monash Institute of Pharmacological Sciences, Monash University
- Baker Heart Research Institute, Melbourne
- Department of Pharmacology, University of Melbourne
- Department of Human and Molecular Genetics, Herbert Wertheim College of Medicine, Florida
- International University, USA
- Department of Psychiatry, University of North Carolina, USA
- Corthera (owned by Novartis), San Mateo, USA
- Institute of Protein Research, College of Life Sciences and Technology, Tongji University, Shanghai, China

EDITORIAL POSITIONS

ROSS BATHGATE

- Associate Editor of Frontiers in Molecular and Structural Endocrinology
- Editorial Board Member of Journal of Pharmacological Sciences
- Associate Editor of Molecular and Cellular Endocrinology
- Member – IUPHAR subcommittee on relaxin receptors.

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

- 10th Australian Peptide Symposium, Penang, Malaysia, September 2013
- Plenary speaker, 4th Asia-Pacific International Peptide Symposium, Osaka, Japan, November 2013
- Co-Chair, 4th International Modern Solid Phase Peptide Synthesis & Its Applications Symposium, Kobe, Japan, November 2013

PEPTIDE NEUROBIOLOGY GROUP:

COLLABORATIONS

- Florey Behavioural Neuroscience division
- School of Biomedical Sciences, University of Queensland
- Monash Institute of Pharmaceutical Sciences, Monash University
- School of Psychological Science, La Trobe University
- Department of Human Anatomy and Embryology, University of Valencia, Spain
- Department of Neurophysiology and Chronobiology, Jagiellonian University, Poland
- Department of Neurobiology, Weizmann Institute of Science, Israel
- Department of Pharmacology and Toxicology, University of Innsbruck, Austria
- Department of Psychology, University of Otago, New Zealand
- Diabetes Center, University of California, San Francisco, USA
- Institute François Magendie, University of Bordeaux, France

PEPTIDE AND PROTEIN CHEMISTRY GROUP

COLLABORATIONS

- Bio21 Institute, University of Melbourne
- School of Chemistry, University of Melbourne
- Department of Pharmacology, University of Melbourne
- Department of Pharmacology, Monash University
- Department of Biology, Temple University, USA
- Institute of Bioanalytical Chemistry, Leipzig University, Germany
- Faculty of Medicine, Semmelweis University, Budapest, Hungary
- Leibniz Institute for Farm Animal Biology, Dummerstorf, Germany
- Unemori Corthera (owned by Novartis), San Mateo, USA
- Cooperative Research Center of Life Sciences, Kobe Gakuin University, Japan
- Novartis Institutes for Biomedical Research, Basel, Switzerland
- Institute of Protein Research, Tongji University, Shanghai, China

EDITORIAL POSITIONS

JOHN WADE

- Editor in Chief, Frontiers in Chemical Biology
- Editor in Chief, International Journal of Peptide Research and Therapeutics
- Editor in Chief, Biochemical Compounds
- Editor, Journal of Peptide Science
- Editor, Protein & Peptide Letters
- Editor, Amino Acids
- Editorial Board Member, Chemical Biology and Drug Design
- Editorial Board Member, International Journal of Peptides
- Editorial Board Member, Frontiers in Endocrinology-Molecular and Structural Endocrinology

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

- Australasian Neuroscience Society Annual Scientific Meeting, Melbourne, Australia (2013)
- Students of Brain Research (SOBR) Symposium, Melbourne, Australia (2013)
- Australian Society for Medical Research Student Symposium, Melbourne, Australia (2013)
- Gordon Conference on 'Inhibition in the CNS', Les Diablerets, Switzerland (2013)
- International Behavioural Neuroscience Society Conference, Dublin, Ireland (2013)
- Cardiovascular and Respiratory Control Meeting, Sydney, Australia (2013)
- International Conference on Pharmacology and Drug Development, Singapore (2013)
- Molecular and Cellular Cognition Society Meeting, San Diego, USA (2013)
- Cell Press Symposia 'The Networked Brain', Society for Neuroscience Satellite, San Diego, USA (2013)
- International Galanin Symposium, San Diego, USA (2013)
- Society for Neuroscience Annual Scientific Meeting, San Diego, USA (2013)

EDITORIAL POSITIONS

ANDREW GUNDLACH

- Editorial Board Member, Journal of Chemical Neuroanatomy
- Editorial Board Member, Neuropeptides
- Editorial Board Member, Frontiers in Molecular Neuroscience
- Editorial Board Member, Frontiers in Neuroanatomy
- Editorial Board Member, NeuroSignals
- Chair, IUPHAR Database Committee on Galanin Receptors

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PSYCHOTROPIC DRUG ADVISORY SERVICE

Lead: Associate Professor Suresh Sundram

The Psychotropic Drug Advisory Service is an independent source for information on medicines used to treat mental illnesses and other drugs that affect the way we think, feel and behave. Service users include individuals, medical practitioners, health care professionals, mental health care support organisations and their staff, carers and consumers. Though predominantly telephone based, the service is also accessed via email and facsimile.

Associate Professor Suresh Sundram heads the unit and provides clinical support to pharmacist Christine Culhane who manages the service. We would like to take the opportunity to thank Professor Nicholas Keks for his long involvement as head of the unit and as an ongoing clinical support. The service responds to approximately 2000 enquiries each year.

We gratefully acknowledge the support of the Victorian Department of Health funding the Psychotic Drug Advisory Service which is funded as part of the special mental health annual grant.

HIGHLIGHTS

Each year many people, young and old, are diagnosed with a mental illness. For some, psychosocial interventions adequately control their symptoms. Others will require biological treatments which include medications. Many do not fully understand the implications of the treatments or their role in managing their disorder despite the provision of this information by their prescriber or other healthcare professionals. Others wonder about what to expect from their medication: their benefits, side effects and the possibility of interactions with other medications they may be taking. This service provides a forum for discussion of prescribed medication that is timely and tailored to the needs of the caller. People have the opportunity to talk about their medication concerns in a confidential setting and receive current information.

This is also an important service for carers of people with a mental illness who are concerned about the effects of these drugs on the person with the illness. The service can answer the questions of carers regarding the potential benefits of medications, adverse effects, safety and tolerability and possible interactions with other medications. Enquiries from the general public are nearly half of those recorded by the service.

A range of health care professionals also utilise this service: psychiatrists, other medical practitioners, health care professionals including nurses, pharmacists, psychologists and dieticians, as well as researchers. Electronic databases allow many professionals to research some of their own queries making their calls to the service when the clinical situation is complex or to gain extra insights when there are new medications or other complications involved. The provision of this information to service providers allows them to best manage the changing needs of their clientele.

This service also provides vital information for practitioners and consumers who reside or practice in rural or remote communities as they may not have the immediate resources to provide this extra information.

PRESENTATIONS

Presentations to both professional and consumer groups are also part of the work undertaken by the service.

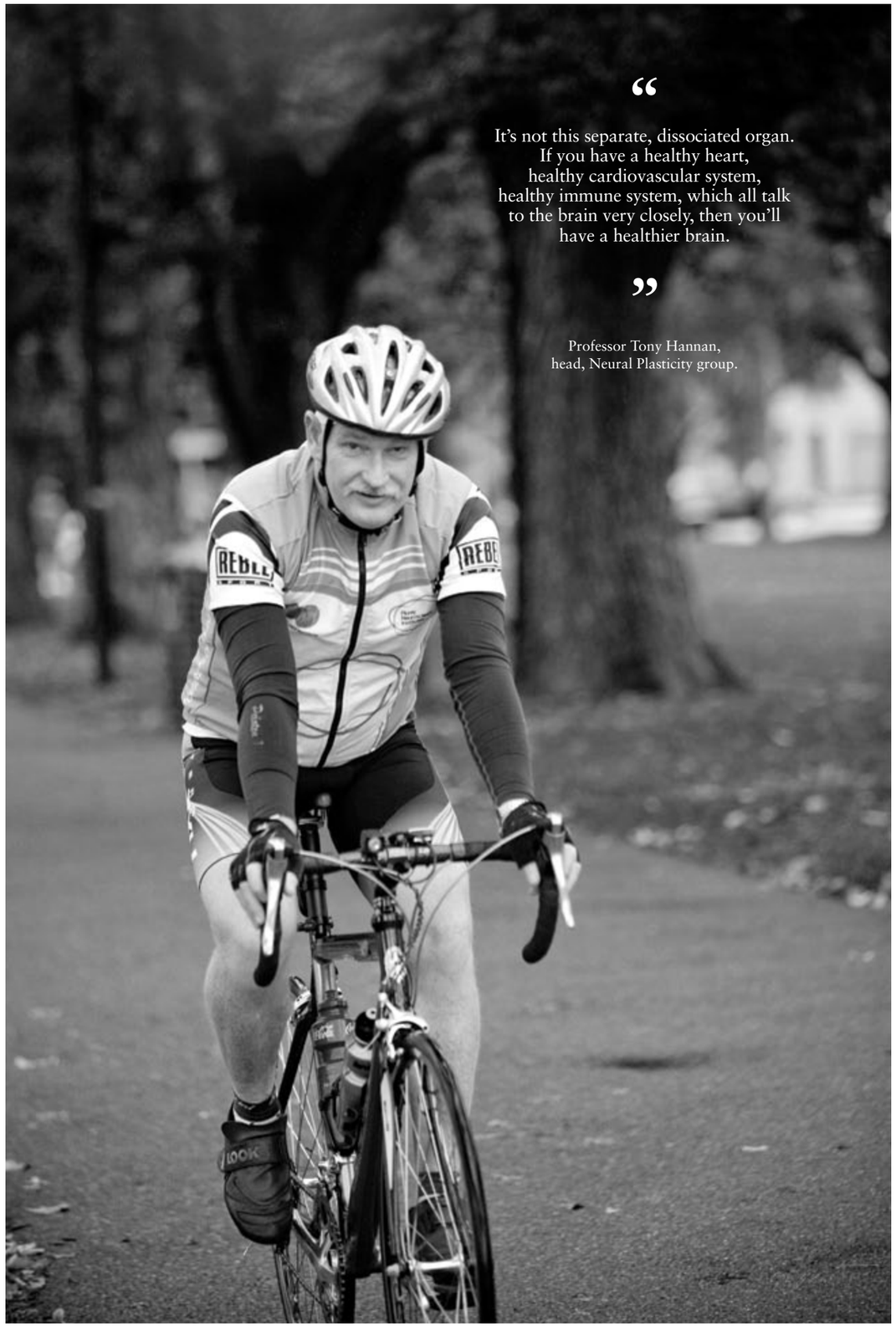
Presentations have been requested by and provided to a number of professional and lay audiences. Christine has ongoing involvement with The Delmont Hospital Psychopharmacology Master classes with Professor Nicholas Keks and Dr Judy Hope. These forums are held twice each year to update the knowledge of practicing psychiatrists and trainees. Tutorials and online discussions for undergraduate and post graduate pharmacists have also been provided.

Christine has also been to a number of carer and consumer support organisations to provide information on medications in a patient sensitive forum.

PROFESSIONAL DEVELOPMENT

The Psychotropic Drug Advisory Services provides a much needed source of specialised information to the broader mental health community in Victoria. Its value is measured by consistency of enquiry numbers and timeliness of responses.

In order to provide the best available information, professional development activities are undertaken including the requirements for continued registration as a pharmacist as well as attending psychiatry and pharmacy specific congresses and symposia.



Pictured: Loyal supporter of the Florey, community fundraiser, Kieran Donlon.

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WHEN CHANGING A NAPPY IS EXCITING

Pictured: (L–R) Damian, Adele and Steph Zammit.

When changing a nappy is exciting

Damian, Stephanie and baby Adele Zammit

Damian Zammit, a young carpenter, suffered a stroke three years ago. The Florey's unique approach to neurorehabilitation has transformed his life in more ways than one.

It's been a tough road to recovery but every day Damian's rehabilitation is helping him regain vital life skills.

One of the most wonderful things about his recovery has been his ability to be more involved with his new daughter Adele. Only six months old Adele, like all young ones, needs attention.

As Damian continues his rehab, he can now hold her, change her nappies, dress her, and his wife Steph is able to go out and leave Damian in charge. They have learned to make small adjustments so Damian can be as involved as possible – even buying zip-up pyjamas so he can prepare Adele for bed.

Damian participated in a specialised rehabilitation program with Professor Leeanne Carey, Head of the Neurorehabilitation and Recovery Research Group in the Stroke Division at the Florey. Following his stroke Damian lost use of the full right side of his body, his speech and his ability to read and write. He also lost his sense of touch. He couldn't feel when his hand made contact with everyday objects and so was unable to use his hand on a day to day basis.

Using the ability of the brain to recover, Professor Carey has helped Damian regain his sense of touch. The rehabilitation program, known as 'Sense' is carefully designed to enhance existing connections and forge new connections in the brain. Damian worked very hard during the program to make sense of any touch information that was coming through, until after only 3 weeks he said 'for the first time since my stroke (18 months ago) I can now feel with my hand'. After 6 weeks of training this improvement showed through with greatly improved scores on sensory tasks, better use of his hand in everyday activities, and evidence that Damian's brain was changing the way it processed touch information... with success!

As Damian says, "it's a slow process." Now he is able to use his hands more and more every day and his legs are nearly completely recovered. He is also able to chat on the phone to his wife and daughter.

And Steph, is of course, one of his greatest supporters.

"Not only is Damian a brilliant, loving and caring husband and dad to Adele but he is the most determined and passionate person I know. Over the past three years Damian has accomplished so much, I think he underestimates himself at times. And even though he has achieved so much, life has its ups and downs. And overcoming his depressive moods can be a tough feat for us both.

And over all this time he has not let go of his passion of carpentry. With assistance he has helped friends renovate their homes, build carports, decks and an outdoor area that he has added to our family home.

With Adele as his new motivation, I watch him, in awe, as he picks himself up and soldiers on hoping that one day he will return to his job."

"The brain is plastic. With specialised rehabilitation a person can learn new skills and recovery even months and years after their stroke. Armed with these skills they can then continue to drive their own recovery in the everyday tasks that matter to them! Damian's story is evidence of this."

Professor Leeanne Carey

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STROKE

Division heads: Associate Professor Julie Bernhardt and Associate Professor David Howells

A QUICK SNAPSHOT

Fifteen million strokes and six million stroke deaths occur each year leaving 55 million survivors suffering the consequences of stroke. The Stroke Division of the Florey Institute of Neuroscience and Mental Health comprises a team of 80 basic and clinical scientists whose aim is to understand the pathophysiology of stroke, optimize existing therapies and develop new treatments to both prevent and reduce the impact of stroke.

The division has five research teams, Stroke Preclinical Science, the AVERT Early Intervention Research Program, the Neurorehabilitation and Recovery group, Epidemiology and Public Health, including the Stroke Telemedicine program and Clinical Trials.

RESEARCH HIGHLIGHT

Country patients suffering a suspected stroke can now receive expert neurological opinion from Melbourne – without leaving their hospital bed thanks to the Florey's Stroke Telemedicine program. The program attracted $7.9 million from state and federal governments in 2012. Patients with a suspected stroke now receive time-critical specialist neurological assessment from Melbourne – via high speed broadband. Other funding partners include Telstra, Monash University and Department of Health through the Victorian Stroke Clinical Network. The result? A greater number of treatment options for patients with stroke, giving the best chance for a successful outcome.

AN IDEA LIKELY TO CHANGE LIVES BY 2033

Our Stroke Telemedicine program is going to improve equity of access to the best available care for Victorians, whether they live in the city or country. It is the most comprehensive program of its kind in Australia and by 2033, we'd hope to see the program spread throughout Australia.

SENIOR STAFF

• Associate Professor David Howells • Associate Professor Julie Bernhardt • Associate Professor Dominique Cadilhac • Professor Christopher Bladin • Professor Geoff Donnan • Professor Leeanne Carey •

> "We led a worldwide review of both the weaknesses and strengths of internationally published data to help improve the rigour and reporting of preclinical neuroscience. These efforts have now been reported in *Nature*. The results press for greater transparency in science and describe how we should avoid wasting the estimated $85 billion a year lost in the production and reporting of research evidence."

STROKE PRECLINICAL SCIENCE

Leader: David Howells

The 17 member preclinical stroke laboratories comprise Australia's leading translational stroke research team with expertise in therapeutic assessment in animal models of stroke, the use of human stem cell derived neurons and glia to explore stroke biology and identify novel drugs and the use of systematic review and meta-analysis to understand why translation to the clinic is so difficult and to provide evidence based selection of agents for clinical trial.

Research highlights for 2013

The CAMARADES collaboration which Associate Professor Howells co-founded and now convene continues to grow. In 2013 we published the first systematic review and met-analyses in preclinical spinal cord injury supporting the hypothesis that early decompression improves neurobehavioural deficits in animal models of silent cerebral infarction (SCI) and that systemic hypothermia appears to be a promising potential method of treating acute SCI. This evidence-based preclinical data led the NHMRC to fund a clinical trial of hypothermia in acute spinal cord injury (ICED, CIA Batchelor).

In both Stroke and SCI, our analyses show that stem cell transplants improve outcome. However, in both circumstances, facets of the disease modelling account for more of detected effect size than stem cell biology. This led us to concentrate on using stem cells as a source of human neurons for drug testing rather than implantation and the demonstration that hypothermia protects human neurons against ischemia via an oxidative and glucose dependent mechanism. This has led to a new collaboration to expand the use of human stem cell derived neurons and glia to explore stroke biology (Dr Cooper-White, UQ; Dr Dottori, UoM; Dr Wilson, CSIRO).

Evidence from meta analysis of the impact of hypothermia and hypertension on outcome in animal models of stroke contributed to the design of experiments which confirm that hypothermia is effective in animal models of stroke and that pethidine, used to suppress shivering in human clinical trials of hypothermia, does not interfere in provision of this benefit.

Cumulative evidence from our analyses of the stroke literature and experimentation in co-morbid animals have contributed to the launch of the Multi-PART consortium (Multicentre Preclinical Animal Research Team; www.multi-part.org), an international in vivo collaboration designed to develop the capacity to undertake international multicentre animal studies to improve the validity and generalizability of current preclinical research to improve the prospects of success for translation of efficacy to human clinical trials. The internal validity of experiments designed to examine candidates prioritized for in vivo testing will be assured by centralized statistical planning, randomization, outcome adjudication, and quality control to reduce the risk of bias. Initial "proof of concept" experiments designed to confirm in vivo activity will be followed by robust exploration of the limits to efficacy (time to treatment, age and sex of animals, efficacy in hypertensive or diabetic animals, efficacy in different models of stroke). The consortium is now established and funded by the EU. A/Prof Howells chairs the project management committee of this EU funded multinational, multidisciplinary consortium and provided guidance for the NINDS call for US researchers to join the initiative (http://tinyurl.com/p6mvjfm).

AVERT EARLY INTERVENTION RESEARCH PROGRAM

Leader: Julie Bernhardt

We believe that the best way to advance science is by collaboration between individuals from a wide range of backgrounds who work together to tackle complex problems. Finding more effective ways to help people affected by stroke recover is a key goal the world over. Our group of 4 post-doctoral researchers, 7 research staff and students are working to develop, test and implement new ways of treating people with stroke. Starting active rehabilitation very early after stroke is a relatively new concept with enormous potential to reduce death and chronic disability. While there is some evidence that exercise and purposeful, task specific activity aids recovery after stroke, currently there are no specific recommendations about post stroke exercise. Pilot work by our group suggests that commencing activity within 24 hours of stroke may lead to faster recovery of function, less disability and better long term quality of life at a lower cost than current care. To test these hypotheses, we are conducting the first randomised controlled trial of very early rehabilitation (AVERT – A Very Early Rehabilitation Trial). Over 2000 patients with stroke will be recruited to this international, multicentre, Phase III efficacy and cost effectiveness clinical trial. The findings of this study have the potential to change clinical practice around the world. Our group also aim to identify key mechanisms by which exercise may improve the physical, cognitive, mood and fatigue outcomes of people affected by stroke.

Research highlights for 2013

The AVERT trial, an international, multicentre (52), randomised controlled trial, moved a step closer to completion in 2013. This single blind, Phase III trial, testing whether starting out of bed mobility training within 24 hours of stroke leads to fewer deaths and less disability than current care, is eagerly awaited by the international stroke community. The final phase of the trial was funded by the National Health and Medical Research Council, and in late 2013 we also got word that the National Institutes of Health, UK were keen to fund the UK arm of the trial. We are now getting very close to the end of recruitment. At December 2013 recruitment sat at 1860 patients from 5 countries (Australia, New Zealand, Malaysia, Singapore, Northern Ireland, Wales, England, Scotland). Further information about the trial can be found at the ANZCRT trials register: http://www.anzctr.org.au or on the Florey website.

Another highlight for 2013 was the development of our new acute exercise laboratory at the Austin Campus. This lab will support our acute exercise testing and training of people affected by stroke, with much of the equipment making bed side assessment and testing a possibility. We are now uniquely positioned to interrogate and develop treatments to help the profound deconditioning that occurs quickly after stroke.

Key research projects and staff

Toby Cumming: Finding new ways to measure cognitive function in acute stroke patients: Assessing cognitive function in those with recent stroke can be challenging. In this study we tested whether a simple computer based task that uses playing cards can be used within days of stroke to measure cognitive function and the relationship between early cognitive deficits and later problems. Better understanding of the problem will help in development and testing of new treatments.

Dose escalation study for stroke survivors with impaired mobility: In partnership with Royal Talbot Rehabilitation Centre, Austin Health, we conducted a dose escalation study of exercise in stroke survivors with significant difficulty with walking. In clinical practice and clinical trials the selection of treatment dose (amount, frequency, intensity) is rarely based on solid data. We aimed to challenge this approach and develop a new way of identifying the best dose of training to get the best results.

Karen Borschmann: Understanding changes in bone, glucose and muscle in the first 6 months after stroke and their relationship to physical activity. Having a stroke often leads to physical inactivity, and the combination of these two things can have a range of negative physiological effects. In this study we track changes in bone density, glucose metabolism and lean muscle mass after stroke and investigates the effect of physical activity on these physiological outcomes. The study has been extended in a subgroup who are being followed out to two years post stroke, making this study one of the first longitudinal studies in this field.

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Coralie English: Exploring the patters of inactivity and use of time in people living with stroke related disability (EPIPS). Long periods of sedentary behaviour in daily activity can increase risk of further stroke and other cardiovascular events. This study explores sedentary behaviour in stroke survivors as baseline to developing an intervention that will aim to change inactivity.

Computer games as a tool for rehabilitation: In collaboration with Melbourne Health and gaming company Current Circus, we have conducted a pilot study with 40 stroke affected individuals in rehabilitation to explore whether computer games (using the Kinect system) can be a useful tool for training in this population. We found that the training was fun, well tolerated and engaging.

NEUROREHABILITATION AND RECOVERY

Leader: Leeanne Carey

The Neurorehabilitation and Recovery research program focuses on stroke recovery: in particular how the brain adapts and how we can harness that potential in rehabilitation. The research involves development of novel rehabilitation approaches based on neuroscience. MRI is used to investigate how changes in the brain can help target rehabilitation most optimally to individual stroke survivors. Our research includes the impact of depression and cognition on stroke recovery. An important focus is to translate these discoveries into clinical practice and better outcomes for stroke survivors.

Research highlights for 2013

In 2013 the Neurorehabilitation and Recovery group continued to build its program of research focused on harnessing real world drivers of neuroplasticity. The major objective of our group is to translate knowledge from neuroscience into evidence-based clinical practice protocols and better outcomes for stroke survivors. This goal represents a paradigm shift for stroke rehabilitation and better outcomes for the 1 in 6 people who experience a stroke. Our research is focussed on: Targeting rehabilitation to the individual based on viable brain networks; Neurobiology of recovery and impact of depression on outcome; and Implementation of evidence-based practice, as outlined below. In 2013, we continued to lead the advanced imaging and clinical arm of the START longitudinal cohort study (reaching 90% recruitment) and expanded the number of sites and therapists involved in our rehabilitation studies. We developed an animation of the translation of neuroscience to rehabilitation (http://youtu.be/7Kns1uObXh8). We hosted and led the Australasian arm of an international initiative to Advance the Science of Rehabilitation and co-lead an international consortium on Stroke Implementation involving UK, Canada and Australia.

Targeting rehabilitation to the individual based on viable brain networks

Few rehabilitation interventions are based on robust principles of neuroscience. With a rare combination of expertise in clinical rehabilitation and neuroscience our program of research is designed to build stroke rehabilitation evidence from clinical discovery to implementation. Our group has demonstrated changes in the brain associated with rehabilitation and how therapy may be used to drive neuroplastic changes. However, as yet, we do not have effective means of identifying individuals who may benefit from therapy nor how to select the optimal therapy for an individual. In our current study we examine for the first time how different training conditions (task-specific vs transfer-enhanced) and different lesion sites (cortical vs subcortical) impact on reorganization of brain networks involved in recovery of touch sensation. This project Effective sensory rehabilitation after stroke: Targeting viable brain networks is funded by an NHMRC Project grant (2012-2015; CIA Carey). In 2013 two new research therapists, Caroline Bailey and Megan Turville, joined the team and we expanded our recruitment sites. We continue to collaborate with expert neurologists in Germany and Newcastle (Aus) and with the Advanced MRI Development team at the Florey. We are also involved in the program of research into neuroimaging outcomes of motor recovery after stroke conducted in Newcastle at the Hunter Medical Research Institute. Our findings will guide therapists in choosing the best therapy for each individual, based on knowledge of brain networks that have capacity to adapt.

Translation: Our systematic approach to development of the SENSe neuroscience-base intervention now provides a template for future development of interventions and is the topic of keynote presentations (see below). We also developed a video animation to depict the translation of neuroscience to an effective rehabilitation intervention: i.e. Connect: Neurogenesis to Neurorehabilitation. The video is available at: http://youtu.be/7Kns1uObXh8. It highlights the value of restorative approach to rehabilitation.

Expected outcomes include: (i) First-ever knowledge of how brain networks alter under different sensory training conditions; and (ii) Evidence-based guidelines to better target sensory rehabilitation to individuals, informed by knowledge of brain networks with capacity to adapt. The clinical value is on identifying strengths of an individual, i.e. neurobiological potential, to use in therapy, and best use of limited resources. Targeting therapy according to viable brain networks is a paradigm shift for stroke rehabilitation.

Neurobiology of recovery and impact of depression on outcome after stroke

One barrier to successful rehabilitation and a major factor impacting recovery and quality of life is post-stroke depression. Despite evidence that depression and stroke are epidemiologically linked, our recent meta-analyses indicate few reliable associates. Our group are using a multimodal approach to investigate the neurobiological associates of recovery and post-stroke depression in a longitudinal stroke cohort. This cohort study is influential in its measurement of a profile of outcomes from mechanisms to participation, and includes blood-based biomarkers, changes in brain structure and function, mood, cognition, lifestyle, and activity participation over 12 months. The cohort, known as START: Stroke Imaging Prevention and Treatment, is funded by a CSIRO preventative health flagship ($3,000,000; 2010-2015). START_PrePARE (Prediction and Prevention to Achieve optimal Recovery Endpoints), the longitudinal cohort arm with advanced imaging and clinical outcomes is led through the Neurorehabilitation and Recovery group. To date 90% of the sample has been recruited. The imaging and biomarker work is supported by teams from CSIRO (Biomedical Imaging and Molecular Biomarkers), the Florey Advanced MRI Development group, and the La Trobe Institute for Molecular Science. Findings are contributing new insights to stroke rehabilitation that is founded in neuroscience.

Expected outcomes include: (i) Novel insight into the neurobiology of post-stroke depression and functional outcome; (ii) Identification of imaging and molecular associates of post-stroke depression to help identify people 'at risk' of depression early, inform personalised approach to rehabilitation, and guide more targeted interventions; (iii) Identification of individual patient characteristics that impact on outcome during the 12-month period; (iv) Quantification of the impact of stroke-associated depression on participation in household, social, and leisure activities.

Implementation of evidence-based practice in clinical practice settings

The main objective of this theme is to develop a template and clinical practice guidelines for implementation of evidence-based rehabilitation in clinical practice settings. This will be achieved in the first instance through implementation of the SENSe intervention. This therapy has been described as 'life changing' from stroke survivors. The SENSe Implement study will address one important knowledge-practice gap in stroke rehabilitation: treatment of sensory loss after stroke. In 2013 we conducted a national survey of current evidence-based assessment and treatment of sensory impairment after stroke: highlighting this important evidence-practice gap. This gap now needs to be systematically and urgently addressed. In 2012-2013 we have produced specialised therapeutic tools, manuals and training videos to teach therapists to effectively use SENSe therapy with their clients. We have continued to develop the tools and resources needed to 'up-skill' therapists. This has been

achieved with funding from philanthropic organisations. We will now implement this effective neuroscience-based sensory intervention in clinical practice settings using recommended 'knowledge-to-action' methods. The SENSe Implement project will be funded in-kind from hospitals and a dedicated SENSe fund. Two experienced therapists who will be involved in the study have enrolled in a PhD and Masters research program. The team also includes a rehabilitation physician/director, senior therapist and 5-10 therapists at each site. Professor Walker will support implementation in the UK.

Expected outcomes include: (i) Improved outcomes for stroke patients receiving evidence-based SENSe rehabilitation; (ii) A community of 'up-skilled' champion therapists; (iii) New evidence of the success of knowledge-transfer methodologies in stroke rehabilitation; and (iv) Dissemination of the implementation template, with application to interventions for other functions.

Application of SENSe in children

The SENSe intervention is now also being applied to children with cerebral palsy using randomised controlled methodology. A research group (n=8) comprising a paediatrician, therapists and PhD students are conducting this research in Perth in collaboration with us.

Building research culture and capacity in occupational therapy and allied health

An ongoing goal within our team is to build a research community and research capacity. This includes growing research capacity and culture in allied health that engages therapists in research that matters, advances the science of rehabilitation, is multidisciplinary, and impacts globally. The Neurorehabilitation and Recovery group involves a multidisciplinary team of experts and emerging researchers. The core group is 24 strong comprising 1 post-doc, 6 research officers/therapists, 7 PhD students and 10 research affiliates from disciplines of occupational therapy, physiotherapy, neurology, neuroscience and physics. In addition, Prof Carey co-leads an international initiative, supported by the McDonnell Foundation, to form 'collaborative research communities' in North America, Israel/Europe and Australasia. The expertise and collective vision of this group (n=70) has far-reaching scope to advance the science of rehabilitation. Prof Carey and key leaders in knowledge-transfer have also formed, and will continue to grow, an international group to promote best-practice stroke implementation research. In 2013, Junichi Uemura, an Associate Professor in Rehabilitation Science from Japan, spent 3 months in the Neurorehabilitation and Recovery research group to build expertise in neuroscience based research. We congratulate Michaela Pascoe and Kate Noonan who successfully completed their PhD in 2013 and Lloyd Pumpa who completed his honors. We welcome Brendon Haslam and Susan Taylor who started in 2013 and Megan Turville and Liana Cahill who will commence in 2014.

PUBLIC HEALTH AND EPIDEMIOLOGY

Leader: Dominique Cadilhac

Our group conducts various projects related to improving the clinical management and outcomes of stroke. Research on the quality of stroke care in public hospitals continues to be a major objective, as well as designing and evaluating systems to improve the delivery of evidence-based care and achieve better health outcomes after stroke.

Research highlights for 2013

In 2013, our team continued to lead the expansion of the Australian Stroke Clinical Registry and the Victorian Stroke Telemedicine Program, which are our major flagship projects. We also continued to provide research support for the National Stroke Foundation 'Know your numbers program' with approximately 146,676 registrants data from 1,740 health check stations (93% were from pharmacy locations) processed for analysis. This program promotes the importance of regular blood pressure checks and the awareness of other stroke risk factors in the community. People who are identified as potentially being at high risk of stroke or cardiovascular disease are referred to their doctor for advice on how to lower their risk and stay healthy. The research program associated with this initiative is being conducted in collaboration with Monash University, where Associate Professor Dominique Cadilhac is also based. A/Prof Dominique Cadilhac was successful in obtaining a large program grant ($3 million) with the Australian Catholic University (ACU International Stroke Research Collaborative) with Professors Sandy Middleton, Caroline Watkins (UK) and Anne Alexandrov (US) to build capacity for international, multidisciplinary stroke research within five years. The funding supports two postdoctoral positions and three PhDs to contribute to an innovative work program, including stroke telemedicine and quality of care research linked to our Florey projects. In 2013, our team also co-hosted a national workshop with the National Stroke Foundation on stroke data and telemedicine which was attended by over 100 delegates.

Stroke Telemedicine (leaders Chris Bladin and Dominique Cadilhac)

The Victorian Stroke Telemedicine initiative is a ground breaking program of work that has the potential to transform the way clinicians collaborate across organisational boundaries to deliver the best care possible to stroke patients irrespective of their location. The objective of the program is to improve the care of acute stroke patients, across Victoria through the use of cutting edge technology. We aim to do this by implementing a seamless videoconference service to 16 regional hospitals providing 24 hour access to a stroke neurologist roster. Professor Chris Bladin and Associate Professor Dominique Cadilhac, who co-lead this work, have secured over $8.96 million in funding for this program. In 2013, a prestigious Victorian Government Public Healthcare Award for "Innovation in Healthcare" was received by our team and project partners for our work to date in this area.

The Victorian Stroke Telemedicine Program includes three projects. The initial project was the VST – Bendigo, a successful single site telemedicine project undertaken at Bendigo Health which concluded in 2013. In this pilot project, use of thrombolysis increased from 8% up to 13% showing direct evidence of a change in practice. Natasha Moloczij did an exceptional job coordinating this initial project with assistance from Emma Tod and Sharon Ermel, and the Florey team has now expanded to four additional staff to establish the larger projects. The VST – Loddon Mallee project commenced in 2013 and is funded by the Victorian Government under the Broadband Enabled Innovation Program (BEIP) grant. This project expands the Bendigo model to include Echuca Regional Health, Swan Hill District Health and Mildura Base Hospital. At the conclusion of the 2 year BEIP funding, Loddon Mallee health services will continue to receive support under the VicStroke Project. The VicStroke Project is funded by the Australian Government Health and Hospital Fund and will continue to support the VST Loddon Mallee project whilst increasing the scope to include a further 12 hospitals across the other regions of Victoria. This will enable state wide coverage of the teleneurology service and is funded until 2018. Together, these projects form the largest acute stroke telemedicine program in Australia. Our project partners include Victorian Stroke Clinical Network (Victorian Department of Health), Monash University, Telstra, Polycom, Ambulance Victoria, National Stroke Foundation and the Loddon Mallee Rural Health Alliance. Boehringer Ingleheim has also provided an educational grant to support adaptions to the AuSCR web-tool and education.

In the Victorian Stroke Telemedicine program there are three key research themes: i) clinical ii) implementation science, and iii) health economics. The data collection has been developed to use the infrastructure available through the Australian Stroke Clinical Registry (A/Prof Cadilhac and The Florey are national data custodians) which has been expanded to include stroke telemedicine variables. In this way, ongoing benefits of the program can be captured to measure sustainability impacts beyond 2018.

BACK TO CONTENTS

Australian Stroke Clinical Registry and Stroke123 NHMRC partnership project (leader Dominique Cadilhac)

Our team leads the consolidation phase of the Australian Stroke Clinical Registry (AuSCR) which is linked to an NHMRC Partnership grant. The main aim of Stroke123 is to demonstrate that integrated and comprehensive data coupled with an active and evidence-based clinical practice improvement program in acute stroke, is more effective than the status quo in enhancing care and treatment outcomes. The achievement of this aim will be facilitated by: expanding the use of the AuSCR across Queensland, establishing high quality, integrated data for stroke using data linkage of AuSCR with state-based hospital data, as well as harmonising AuSCR and National Stroke Foundation Audit data. The data will be used as part of a non-randomised, multi-centre, historical, controlled cohort substudy in Queensland that involves quality improvement interventions (StrokeLink-Queensland) based on clinical performance feedback using the linked AuSCR/National Stroke Foundation and Queensland Health data. Queensland is the pilot for this comprehensive program that is designed to be nationally scalable. Translation of results into policy and practice is occurring through a translation project committee of policy and clinical representatives. Through this work, Associate Professor Cadilhac is leading efforts to advance cross-jurisdictional data linkage in Australia and, as such, has established an eminent working party that includes members of the Australian Institute of Health and Welfare, the Population Health Research Network and lead researchers from various states who have undertaken data linkage projects, and representatives of various State Health Departments. In 2013, she convened a national workshop on cross-jurisdictional data linkage which resulted in an important publication outlining the current issues in Australia for maximising the use of existing data that is held by different organisations (Australasian Epidemiologist 2013;20(1)15-19).

In 2013, there were 47 hospitals with ethical approval to collect data for AuSCR, which is an increase from 31 in 2012 (AuSCR 2012 annual report available at www.auscr.com.au). At the end of 2013, there were nearly 15,000 registered patients, 5674 registered in 2013 with 82% of eligible patients followed-up between 90 and 180 days after stroke and only 1.9% opting out information from the registry. The Florey AuSCR team, in particular registry manager Brenda Grabsch, data manager Francis Kung and Queensland coordinator Renee Stojanovic, have managed to accommodate the expansion of AuSCR efficiently within a very tight budget. At the end of 2013, the team were informed that the Victorian Government, through the Victorian Stroke Clinical Network, had committed about $1 million over four years to support the establishment of AuSCR within Victorian hospitals. This is the largest commitment we have received to date from government to support this initiative.

LABORATORY: CLINICAL TRIALS

Leader: Geoffrey Donnan

The clinical trials platform crosses an array of clinical trial initiatives in stroke. It utilises platform services of Neuroscience Trials Australia (NTA) which is housed within the Florey; these include project management, regulatory and monitoring issues, statistical and data storage.

Research highlights for 2013

The main focus of clinical trial activity continues to be around the extended time window for neurological deficits (EXTEND) series of trials. This is in partnership with Professor Stephen Davis at the Melbourne Brain Centre@RMH and his colleagues. This family of trials is designed to extend the time window for the most commonly used stroke intervention, thrombolysis (clot dissolving). We are testing the hypotheses that the time window may be extended out to nine hours from 4.5 hours and that clot removal with the SOLITAIRE device may improve outcomes. A further study explores the hypothesis that administration of tranexamic acid (a clot promoting agent) may improve outcomes in patients with intracerebral haemorrhagic by minimising further bleeding into the brain. Analysis is being completed on two earlier trials (ARCH trial – prevention of second stroke events in patients with stroke caused by clots coming from the main artery from the heart; DICE trial – Minimising complications post removal of narrowing of the carotid artery (endarterectomy) using the agent dextran given intravenously) and will be submitted for publication.

Collaborations

Clinical trial activity is built upon national and international collaboration. Of the numerous trials conducted at the Florey, the majority are conducted by collaborating with numerous academic colleagues throughout Australia and commonly with those in other countries. Particular collaborations occur with Professors Stephen Davis at the Royal Melbourne Hospital, Christopher Levi and Mark Parson at Newcastle, Greg Albers at Standford University USA, Pierre Amarenco Paris France, and Werner Hacke Heidelberg Germany.

Commercial projects

Clinical trial activity in stroke also includes very important partnerships and collaborations with pharmaceutical and biotechnology companies (both local and global). The trials range from Phase 2 to 3 and include drugs as well as devices. One of the products assessed aims to assist in dissolving clots that are associated with stroke. Another trial is assessing the use of aspirin compared to another agent in the prevention of transient ischaemic attack.

STROKE PRECLINICAL SCIENCE

COLLABORATIONS

- INTERNATIONAL COOPERATION IN PRECLINICAL STROKE RESEARCH: Correcting the problems of bias, lack of statistical power and lack of generalizability in preclinical research requires larger, more rigorously controlled and replicated experiments. Our approach to achieve this is the establishment of the Multi-PART (Multicentre Preclinical Animal Research Team; www.multi-part.org) consortium to conduct experiments across multiple sites. This platform has the potential to transform preclinical animal research across the life sciences, similar to the tremendous improvements in clinical research that occurred through the introduction of multi-center clinical trials. With a team overseen by a consortium steering committee (Howells, Macleod, Allan, Dirnagl and chaired by my post-doc Sena) six working groups are establishing: 1) project management, training and dissemination (led by Howells, Van der Worp); 2) scientific coordination (Dirnagl & Macrae); 3) experimental design (Vivien & Wurbel); 4) data management (Macleod & Planas); 5) statistical analysis (Montaner & Bath); and 6) regulation and ethics (Allan & Percie du Sert). This team will ensure that central randomization, outcome adjudication, and quality control are used to improve validity. Our range of stroke modelling expertise will allow a robust exploration of the limits to efficacy (time to treatment, age and sex of animals, efficacy in hypertensive or diabetic animals). Only under circumstances such as these will we have the power to detect small but translationally significant effects.
- NHMRC PROGRAM (Donnan, Davis, Hankey, Parsons & Howells): Our NHMRC program (AppID's 251525, 454417, 1013612) established a unique vertically integrated program with basic and clinical science elements to select neuroprotectants for clinical trial. We then expanded our basic science so that we had the capacity to identify novel targets for therapy and study the role of long term plasticity. We are now exploring the use of stem cell derived human neurons as a drug screening tool and the use of blood biomarkers to select stroke patients for treatment.
- THE CAMRARADES COLLABORATION (http://www.camarades.info): Co-founded with Macleod (University of Edinburgh) in 2004, this multinational collaboration continues to play a critical role in explaining past translational failure in stroke and now other areas of neuroscience and has provided guidelines for improving reporting and conduct of preclinical research.
- STROKE ON A CHIP: Since our understanding of human stroke pathophysiology is incomplete, we may not have targeted the right cells or the right molecular processes within these cells in our attempts to develop drugs for stroke. A new collaboration with colleagues from University of Queensland (Prof Justin Cooper-White, A/Prof Ernst Wolvetang), University of Melbourne (Dr Mirella Dottori) and CSIRO (Dr William Wilson, Dr Dadong Wang) will use human neurons, astroglia and oligodendroglia derived from embryonic stem cells and microbioreactor arrays to better define the human ischemic cascade. The multifactorial capacity of the MBAs will allow rapid and reproducible examination of complex interactions between the cells and of the effects of ischemia and of the pharmacological injuries, previously used to identify the key steps in the rodent ischemic cascade, on the biology of these cells. This data will allow us to build the first quantitative and statistically robust map of the human ischemic cascade. The nodes of the map most easily disrupted by ischemia and related insults and those that allow for the greatest degree of normalization when treated will be identified as therapeutic targets for future drug testing.
- Eng Lo, Harvard, USA, Novel lipoxygenase inhibitors to reduce oxidative injury after stroke (US Patent 2012/0053220 A1);
- Dave Lambeth, Emory University, USA, Novel NOX inhibitors to treat stroke.
- William Wilson & Lance Macaulay, CSIRO, Biomarkers to generate a stroke clock (Patent PCT/AU2012/000071).

EDITORIAL POSITIONS

- Evidence based preclinical medicine (Editor in chief)
- International Journal of Stroke (Associate Editor)
- Virtual Medical Centre (Editorial board member)
- Journal of Experimental Stroke Translational Medicine (Editorial board member)
- Translational Stroke Research (Editorial board member).

STAFF AND STUDENTS

- Batchelor, Senior Lecturer, Effects of hypothermia on intracranial pressure.
- Jackman, Post-Doc, Role of the blood brain barrier in stroke.
- Sena, Post-doc. Development of Meta-analysis methodologies and Multi-PART Co-ordinator.
- Antonic, Post-doc, Development of models of ischemic injury in human stem cell derived neurons.
- McCann, Post-doc, Systematic review and meta-analysis of antioxidant use in stroke.
- Rewell, Ph.D. student, Long-term consequences of stroke in animals, evaluating the effects of hypothermia.
- Wills, Ph.D student, Cellular mechanisms supporting axonal outgrowth.
- Dagonnier, Clinical Ph.D. student, Validation of rat biomarker discovery in human trials;
- Krenus, Ph.D. student, Biomarkers of bleeding post-stroke and development of Spontaneous Haemorrhagic stroke models.
- Liu, Ph.D. student, Development of models of ischemic injury in human stem cell derived neurons.
- Ho, Ph.D. student, Evaluation of thrombosis biomarkers in predicting stroke risk.
- Ardipradja, RA, Non-invasive induction of ischemic stroke.
- Ho, RA and Skeers RA, both provide stroke modelling expertise.
- Sidon, RA histochemical and protein analysis.
- Durrant, University of Nottingham Masters in Neuroscience.
- Humphrys, University of Nottingham Masters in Neuroscience.

AVERT EARLY INTERVENTION RESEARCH PROGRAM

KEY COLLABORATIONS

Gothenburg University, Sweden; St Olav's University Hospital, Norway; Glasgow University, UK; Edinburgh University, UK; Hunter Medical Research Institute, NSW; Austin Health, Vic; Melbourne Health, Victoria. The AVERT collaboration of 52 hospitals and 700 clinical staff worldwide.

EDITORIAL POSITIONS

- International Journal of Stroke, Section editor Rehabilitation
- Topics in Stroke Rehabilitation
- International Journal of Therapy and Rehabilitation
- Journal for Neurologic Physical Therapy
- American Heart Association writing group "Physical Activity and Exercise Recommendations for Stroke Survivors." (2013)

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

- IX Brazilian Stroke Congress, Fortaleza, Brazil,
- Ever Satellite Symposium, European Stroke Organisation, London.
- World Federation for NeuroRehabilitation,. Neurological Rehabilitation Clinical Trials Special Interest Group – presentation. Pavia, Italy.
- Stroke Centre West Conference, Gothenburg, Sweden. Plenary Speaker. Physical (in)activity in stroke rehabilitation. Is it really important?

BACK TO CONTENTS

- University of Kansas Medical Centre Kansas, USA. Very early rehabilitation. Where are we up to?
- University Hospital of Zurich. Very early rehabilitation – the AVERT Trial progress.
- Swiss Stroke Society 17th Annual Meeting, Switzerland. Very Early Rehabilitation.
- Centre Hospitalier Universitaire Vaudois. Lausanne, Switzerland. When should rehabilitation begin after stroke?
- VasCog, Toronto, Canada
- International Stroke Conference, Honolulu, USA
- Neuroscience Research Australia, Invited seminar series 2013. Transforming stroke rehabilitation care: Plans and progress of an 'enthusiologist'. Sydney.
- Australasian Faculty of Rehabilitation Medicine, Scientific Meeting.
- Stroke Plenary Session. Optimising early mobility: Research and practice. Sydney.
- National Trauma Research Institute, The Alfred Hospital and Monash University.
- NTRI Forum – Transition planning following Acquired Brain Injury. Melbourne.
- Stroke Society of Australasia Scientific Meeting, Darwin
- The Florey Institute of Neuroscience and Mental Health, Stroke Division. Annual Scientific Meeting.

KEY STAFF

- Fiona Ellery, AVERT Trial Manager
- Janice Collier, Post Doc, AVERT Data Manager
- Toby Cumming, Post Doc, Lead Cognition, Mood and Fatigue
- Coralie English, Post Doc, Lead Physical Activity and Sedentary Behaviour
- Julie Luker, Post Doc, Lead Implementation research
- Karen Borschmann, Lead Bone health

NEUROREHABILITATION AND RECOVERY

COLLABORATIONS

INTERNATIONAL

- Washington Uni. St. Louis. USA
- Heinrich Heine University, Germany
- University of Haifa, Israel
- University of Nottingham, UK
- Department of Psychological and Brain Sciences, Indiana Uni, USA
- Department of OT Education, Kansas Medical Centre, USA
- A/Prof Thomas Linden. Neurologist/psychiatrist, Gothenburg, Sweden.
- Dept. of Occupational Science and Occupational Therapy and Graduate Dept. of Rehabilitation Science, University of Toronto, Canada
- Dept. of Clinical and Biological Neurosciences, University. Hospital, Grenobel, France
- McDonnell consortia: Advancing the Science of Rehabilitation. 70 scientists from North America, Israel/Europe and Australasia.
- Implementation Science consortia (UK, Canada, Aus).
- International Post Stroke Upper Extremity Working Group.
- National Institute of Health (NIH) Toolbox: Assessment of Neurological and Behavioural Function group.

NATIONAL

- CSIRO preventative Health Flagship. START program of research.
- Advanced MRI Development, Florey Institute
- La Trobe University: School of Allied Health; Research Focus Area, Sport Exercise and Rehabilitation; and Living with Disability research group (LiDS).
- La Trobe Institute of Molecular Sciences (LIMS)
- School of Paediatric and Child Health, University of Western Australia
- Hunter Medical Research Institute, Newcastle, Centre for Brain and Mental Health Research
- University of Newcastle, NSW
- Australian National University, Canberra
- Allied and Public Health, Australian Catholic University, Melbourne.
- Neurology, Austin Health

EDITORIAL POSITIONS

- Neurorehabilitation and Neural Repair
- Occupational Therapy International
- Australian Occupational Therapy Journal
- Brain Impairment.

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

- Beyond the lesion: targeting viable brain networks for recovery and rehabilitation. UK Stroke Forum. 3-5th Dec. Harrogate, UK.
- Sensory rehabilitation. UK Stroke Forum. 3-5th Dec. Harrogate, UK (workshop x 2).
- Beyond the lesion: Neuroimaging foundations for post-stroke recovery. Seminar Program. 2nd Dec. Manchester University, UK
- Norington Lecture: Transforming stroke rehabilitation in line with neuroscience, best evidence and client expectations. 21st Annual Meeting of the Australasian Faculty of Rehabilitation Medicine. 17-20th September, 2013. Plenary: (oration with prize)
- Building the Evidence for Sensory Rehabilitation after Stroke. University of Haifa, Israel. March
- Neuroscience in the Clinic: An Evidence Based Approach to Sensory Rehabilitation after Stroke. University of Haifa, Israel. March.
- Advancing the Science of Rehabilitation: Translating Neuroscience and Rehabilitation into Everyday Life. James S McDonnell Foundation. Conference Convenor, invited speaker and chair. 21st & 22nd Feb. Melbourne, Australia.
- How to use fMRI to answer clinical research questions. Clinical Neuroscience Research & Neuroimaging for Clinical Research Course, University of Melbourne.
- Stroke Imaging Prevention and Treatment Cohort study: A Focus on Depression. Monash Alfred Psychiatry Research Centre, 6th September.
- Sensory Rehabilitation after Stroke: Neuroscience Foundations, New Evidence and Application to Clinical Practice. Florey Institute of Neuroscience and Mental Health. (2 day national workshop)

PUBLIC HEALTH AND EPIDEMIOLOGY

COLLABORATIONS

Stroke and Ageing Research, Southern Clinical School, Monash University; The George Institute for Global Health; La Trobe University; Hunter Stroke Service, NSW Australia; New South Wales Health, Australia; National Stroke Foundation, Australia; Australian Catholic University, Australia; Centre for Translational Excellence in Neuroscience, Melbourne Health; St Vincent's Hospital, NSW; Southern Clinical School; Queensland Statewide Stroke Clinical Network; Victorian Stroke Clinical Network; Victorian Statewide Stroke Clinical Network; Edith Cowan University, Western Australia; University of Western Australia: South Australian Statewide Stroke Clinical Network; NSW Statewide Stroke Clinical Network; Queensland Health; Michigan State University, USA; Ottawa Hospital Research Institute, Canada; Stroke and Ageing Research, Southern Clinical School,; Telehealth Connect, Australia; NBNCo, Australia; Loddon Mallee Rural Health Alliance, Australia; Bendigo Health, Australia; Telstra, Australia; Polycom, Australia; School of Population Health, University of Melbourne; Health Outcomes Institute, Arizona US; School of Health, University of Central Lancashire, Preston, UK

EDITORIAL POSITIONS

- Cadilhac: International Journal of Stroke, Clinical Audit, Dove Medical Press and World Journal of Hypertension
- Dewey: Stroke journal and International Journal of Stroke
- Bladin: Current Neurology and Neuroscience Reports and British Journal of Sports Medicine

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

CADILHAC

- United Kingdom Stroke Forum, 2013 Harrogate International Centre, Kings Road, Harrogate. Invited by Professor Caroline Watkins to present at this scientific meeting in December on secondary prevention and patient follow up from a nursing perspective. Workshops x 2 provided.
- Distinguished Visitor Program, School of Health, University of Central Lancashire, Preston, England:
  - Overview of A/Prof Cadilhac's research program: health services translational research in stroke (27/11/2013).
  - Stand firm: Secondary prevention, School of Health, University of Central Lancashire, Preston, England. (28/11/2013)
- Economic Implications of not translating evidence: a case study, 3rd International Congress of Neurology and Epidemiology, Abu Dhabi, UAE
- Difficulties in measuring stroke rehabilitation and adherence to best practice: an example from Australia, 3rd International Congress of Neurology and Epidemiology, Abu Dhabi, UAE
- Dissemination and Implementation Forum, Monash School of Population Health. Session: D&I in action – Challenges and opportunities: Telemedicine to increase access to acute stroke thrombolysis in Victoria
- Workshop convenor and presenter: Nurses as change agents to improve health outcomes following stroke, Smart Strokes 9th Australasian Nursing & Allied Health Stroke Conference, Brisbane
- Workshop convenor and presenter: Setting the scene for stroke prevention, Stroke Society of Australasia, Darwin
- National Registries Special Interest group convened by School of Population Health and Preventative Medicine Research Team Meeting, Clayton Campus: Update on the Australian Stroke Clinical Registry to improve the quality of care in hospitals and hurdles found in undertaking data linkage projects. 14/5/2013
- NSW Health Stroke Services Clinical Network Forum "Australian Stroke Clinical Registry: a national system for routine performance measurement" (20 February 2013).
- Invited symposium speaker: International Stroke Conference Honolulu "Nurse as Change agents" February 2013

BLADIN

- VicStroke: The Future of Acute Stroke Telemedicine in Victoria [invited speaker]. 5th Annual National Telemedicine Conference Sydney
- Implementing evidence based acute stroke care in a regional hospital: the Victorian Stroke Telemedicine (VST) Project [oral presentation]. 2nd Annual NHMRC Research Translation Faculty Symposium, From Bench to Bourke: improving practice, policy and commercialisation. Sydney.

OTHER

- Professor Bladin was invited to write a paper for the Hospital and Aged Care magazine: Neuro-network uses ehealth to treat acute stroke patients. Hospital and Aged Care. Surry Hills, NSW, Yaffa Publishing Group Pty Ltd. July-August: 20-22

PUBLICATIONS

1. Ali M, English C, Bernhardt J, Sunnerhagen K, Brady M, VISTA-Rehab Collaboration. More outcomes than trials: a call for consistent data collection across stroke rehabilitation trials. International Journal of Stroke. 8(1):18-24
2. Amarenco P, Bogousslavsky J, Caplan L, Donnan GA, Wolf M & Hennerici M. 2013. The ASCOD phenotyping of ischemic stroke (updated ASCO phenotyping). Cerebrovascular Diseases. 36 (1): 1-5
3. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, Robinson T, Lavados P, Neal B, Hata J, Arima H, Parsons M, Li Y, Wang J, Heritier S, Li Q, Woodward M, Simes RJ, Davis SM, Chalmers J; INTERACT2 Investigators. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013 Jun 20;368(25):2355-65
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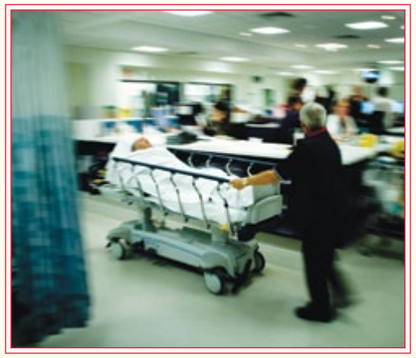
SAVE A MINUTE, SAVE A DAY



Recent number crunching by Florey statisticians has changed the way stroke patients are raced through emergency care, ensuring they receive time-critical scanning and medication.

This is just one example of the Florey's unique service to researchers seeking statistical and decision-making analysis. The service operates with the ultimate goal of improving patient care.

The academic platform makes sense of data, quantitative and statistical aspects of basic science, clinical, imaging, and health services research.

"We are here to support all the staff and postgraduate students with their research, and to assist external public bodies and private companies on a commercial basis," says Professor Leonid Churilov.

Leonid focusses on three major interrelated themes:

- Through collaboration with Florey and university researchers as well as external clients, Leonid provides expert assistance with research study design, analysis, and data management issues through all phases of a research study – from formulating a research plan and a study protocol to writing up the results;
- He offers a range of training and development opportunities in the areas of study design, statistical analysis, and quantitative modelling
- He conducts methodological research with the aim to provide tailored and rigorous quantitative methods to support evidence-based decision making in basic, clinical, and health services research.

The platform serves as a hub for collaboration within the Florey and with other Australian and international research institutions. The Florey collaborates with basic science, clinical, and imaging neuroscience researchers. External collaborators and clients include researchers and clinicians at the Austin, Melbourne, Southern, Eastern, and Barwon health services and Royal Children's Hospital and Murdoch Children's Research Institute in Victoria; Hunter Medical Research Institute in New South Wales; Australian National Stroke Foundation; Australasian Stroke Trials Network; as well as researchers from The University of Melbourne, RMIT University, Monash University, and University of Ballarat in Australia and various universities and research institutes across the globe, including USA, UK, Canada, Hong Kong, Japan, Norway, and Sweden.

Leonid provides consulting services to health policy makers at the Victorian Department of Health and to a number of clinical research organisations, including Neuroscience Trials Australia – an Australian-based, not-for-profit contract research organisation specialising in clinical research.

Of particular interest and practical importance is our work on statistical modelling for health services and clinical decision support. Two world-first collaborative studies in stroke treatment have attracted a lot of attention. One of these studies, "Stroke Thrombolysis: Save a minute – save a day", quantifies the long-term benefits of speedier ischemic stroke treatment, bypassing the emergency department on the way to a scanning suite. It was published in the flagship Stroke journal and attracted worldwide media attention.

The other pioneering study presents the analysis of the key factors in combatting stroke in children. According to the American Heart Association, the news release of the study "More awareness, fast response key to combatting stroke in children" following American Stroke Association International Stroke conference attracted over 4.6 million of readers in just over a month.

The sophisticated modelling work by the Statistics and Decision Analysis Academic platform played a key role in the successful completion of both these studies.

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WHEN STROKE BECOMES DEMENTIA

Dr Amy Brodtmann

In a world-first study, Florey researchers are working with colleagues to investigate why one in three stroke victims – even when they appear to make a good recovery – slides into dementia.

It takes two or three years for symptoms to develop – and the reasons for this have never been explained.

Lead researcher Dr Amy Brodtmann says people typically have problems with thinking, speech and memory immediately after a stroke "but they usually recover".

"What's happening down the track is some people, not everyone, are developing cognitive decline and some people are developing dementia," Amy says.

The project involves studying the brains of 135 Melbourne people, who are being recruited within a day or two of suffering a stroke. Over three years, they will undergo four MRI scans – taken upon recruitment, at three months, one year and three years – to measure any changes in the brain, including shrinkage. The results are correlated with evidence of memory and cognitive impairment.

Amy believes understanding these changes could provide clues as to why stroke patients travel more rapidly into dementia than others.

They may also show how to predict which patients will suffer cognitive impairment and can be assisted by early intervention.

"We'll look at each subject and ask, why did they get worse and why did someone else get better? Was it some kind of medication or lifestyle or was it to do purely with age?"

One aspect of brain degeneration being examined is "white matter hyperintensities"- lesions in the white matter of the brain that have been strongly linked to a reduction in cognitive capacity.

"One of the things we are looking for is whether these hyperintensities are more severe in patients with significant cognitive problems."

This could mean hyperintensities might either be causing the cognitive decline or they may be used as an early detection marker for dementia.

People who present with pre-existing cognitive or memory loss – about a third of stroke victims – are precluded from the project.

Fifty people have already been recruited, including a pilot group who began their scans two years ago. Dr Brodtmann says these people seemed to have undergone changes in the brain that are typical of patients with Alzheimer's disease without the dementia. However, claiming a causal relationship between strokes and dementia remains problematic, largely because the risk factors that predispose a person to having a stroke – smoking, late-onset diabetes, obesity, high cholesterol – can also cause cognitive problems.

The longitudinal study is being assisted by the Victorian Life Sciences Computation Initiative and is funded by the Victorian government.

OUR BRAIN'S FUNDAMENTAL NEED FOR SALT

Florey founder, Emeritus Professor Derek Denton AC, writes of his recent work

This component of the investigations of the Neurobiology group originated some 22 years ago with my work with colleagues in the Florey Institute to explore experimentally the integrative physiological basis of the classic instincts of sodium (salt) appetite and thirst, as far up the evolutionary tree as feasible. The main work to that date had been on sheep, rats and mice.

Experimental work, including intracerebroventricular infusions, was embarked upon at Southwest Foundation in San Antonio, Texas, with Dr. Robert Shade collaborating with Dr. John Blair West and the team at the Florey. Four publications recorded a specific sodium appetite evoked by the brain infusions.

Subsequent work in the international collaborative program included studies of the influence of salt intake on blood pressure of chimpanzees in the Gabon in Equatorial West Africa in collaboration with French and English scientists. This work attracted publication in Nature Medicine. The New York Times described the work as a single variable decisive experiment indicting salt in the causation of high blood pressure in humans. Further, in collaboration with Dr. Peter Fox, Director of the Texas Imaging Research Institute, the first neuroimaging study was made of evocation of thirst, and, following this, other basic instincts involving specific primordial emotions were examined, including hunger for air, pain, temperature change, and also the effect of ageing on thirst. The important novelty embodied in the data gave rise to twelve papers published in the Proceedings of the National Academy of Sciences of the United States (PNAS).

A particularly valuable increment of knowledge and skills embodied in the international collaborative group was involved in the team being joined by Dr. Wolfgang Liedtke (Professor of Translational Neuroscience at Duke University, USA) who had earlier been at Rockefeller University working with Dr. Jeffrey Friedman, the discoverer of the food appetite controlling hormone Leptin. We decided to do the first ever analysis of the genomic changes with the development of sodium deficiency, and the subsequent rapid gratification of the deficit by drinking salt water. The results published in PNAS caused wide international interest with 500 articles in newspapers, magazines and scientific journals in the 7 days following publication. The data revealed the clear-cut upregulation of many genes subserving production of neurotransmitters and receptors involved in activity of a number of nuclei, and rapid reversal of those changes within ten minutes of drinking salt water to satiation. This was much faster than the time needed to absorb the salt solution drunk from the gut. Apart from this most intriguing facet of the gratification process so revealed, it opens up new aspects of the organisation of the gratification process generally for exploration. Disorders of gratification of several basic instincts lie at the genesis of many medical conditions.

A further facet of this study was that with use of the new gene set enrichment analysis (GSEA) developed at Harvard by Dr. Eric Landers, the unexpected finding was made that the population of genes activated in the hypothalamus by sodium deficiency is closely related to the population shown to be activated in experimental animals and humans by addiction to cocaine and the opiate group of drugs, including heroin. We have found that drugs known to antagonize heroin addiction in humans will correspondingly greatly reduce sodium appetite in mice. An hypothesis emerging is that the recently (4,000 years) introduced drugs of addiction have hijacked the neural pathways which subserve sodium appetite, an ancient classic instinctive behavior which emerged at least 200 million year ago, and which is strongly developed in Metatheria (ie kangaroos) as shown in the Snowy Mountains of Australia.

Clearly, a new avenue of approach to drug addiction, a major societal and medical problem, has emerged, and this is currently being followed experimentally.

The evident benefit of an international group is that particular skills and scholarship which would be difficult and extremely expensive to assemble in the one place can be applied to an investigation. Contemporary methods of communication, including email and Skype, make frequent informal exchange and discussion easy and cheap.

Support for this work included grants from The Mathers Charitable Foundation, the Robert and Helen Kleberg Foundation, The Search Foundation, Mr Baillieu Myer, Mr Robert Albert, Mrs. Diana Gibson, Dr. Mark Nelson, Mr. Andrew Abercrombie, Mrs. Nielma Gantner, and the Baker IDI Heart Research Institute.

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SYSTEMS NEUROPHYSIOLOGY

Division heads: Professor Richard Macdonell and Professor Robin McAllen

A QUICK SNAPSHOT

In Systems Neurophysiology we seek to learn how the nervous system controls various bodily functions and how that control is altered in disease. Our disease focus includes not only neurological disorders such as epilepsy and multiple sclerosis, but also how the nervous system impacts on non-neurological diseases such as heart failure and inflammatory diseases. A clear understanding of basic mechanisms is crucial in developing better therapies and reducing the impacts of illness.

As examples, understanding the physiological mechanisms underlying epilepsy and multiple sclerosis (MS) is vital in understanding of how medications work to reduce the risk of seizures and improve physical function in MS and in developing better drugs. The techniques used in our lab are also used to explain the way in which physical therapies such as rehabilitation can be used to enhance neuroplasticity and improve brain recovery after injury. We are also seeking to learn how the nervous system controls the immune system. This has major implications in understanding conditions like MS and possibly providing alternative pathways to treatment.

OUR FOCUS

Professor Robin McAllen heads the Systems Neurophysiology group at Parkville, which researches brain function in health and disease. A particular focus is on how the brain controls basic bodily functions such as blood pressure, body temperature, body fluids and breathing. Prof Richard Macdonell heads the clinical arm at the Austin Hospital which researches the physiological changes underlying various neurological diseases such epilepsy, multiple sclerosis and cerebral palsy and the neurophysiological effects of treatment.

AN IDEA LIKELY TO CHANGE LIVES BY 2033

We recently discovered a nervous reflex pathway that strongly suppresses inflammation – a gateway for the brain to influence the body's immune defences. This 'hard-wired' pathway opens the way to rigorous study of the brain's role in infectious and inflammatory diseases.

> "In hypertension glia cells, supporting cells that help neurons function, withdraw their fine foot-like processes from the surface of microvessels in the brain. This glia retraction contributes to the breakdown of the blood-brain barrier and allows the infiltration of normally excluded blood-borne proteins into the brain. This affects brain function, increases nerve excitability and speeds up disease progression. Understanding the mechanisms leading to blood-brain barrier disruption is vital for the development of new therapies to treat heart failure and hypertension."

SENIOR STAFF

• Professor Robin McAllen • Professor Richard Macdonell • Dr Bradford O. Bratton • Emeritus Professor Derek Denton • Associate Professor Mathias Dutschmann • Dr David Farmer • Dr Davide Martelli • Associate Professor Clive May • Professor Michael McKinley • Dr Rohit Ramchandra • Dr Davor Stanić • Dr Mutsumi Tanaka • Dr Song Yao • Dr Stuart McDougall • Dr Tara Bautista • Dr Lindsay Booth • Dr Dan Tao •

AUTONOMIC NEUROSCIENCE GROUP

Leader: Robin McAllen

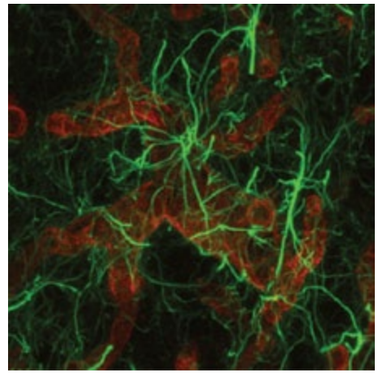
We investigate the central nervous pathways that regulate basic bodily functions such as blood pressure and body temperature, as well as their transmission to bodily targets via autonomic nerves.

Research highlights for 2013

One of our most exciting projects is an investigation of how the brain, acting through sympathetic nerves, regulates the function of the immune system. The mechanism that we are studying is referred to as the 'inflammatory reflex'. Inflammation is the first stage of the body's defence mechanisms to invasion by infectious agents, but this process needs to be tightly controlled. Too weak a response risks inadequate defence against infection, too strong a response leads to organ damage and even death. In the inflammatory reflex, the brain responds to blood-borne chemical signals of infection or inflammation (inflammatory cytokines), and activates a nervous pathway to immune tissues such as the spleen; this pathway damps down the inflammatory process. This is interpreted as a self-limiting, or negative-feedback, response.

In the past year we have completed our first study and published our findings showing that the output pathway for the inflammatory reflex is in the splanchnic sympathetic nerves, not the vagus as had been mistakenly believed for the past 10 years. Moreover, we have found that the reflex is very powerful: it damps down the body's inflammatory response by about 80%. We are currently chasing down which of the several organs contacted by the splanchnic nerve is responsible for the inflammatory suppression. We will then identify the specific brain regions that control this function.

A second highlight was our publication of two companion papers identifying the brainstem nucleus that controls sweating. The first of these presented data taken from experiments performed some years ago on anaesthetised cats. A localized region of the ventromedial medulla in the brain stem was shown to drive sweating responses in the cat's paw. Much more recently, we induced sweating in human volunteers while their brains were scanned by functional MRI. In the human brainstem we found that sweating was linked to brain activation in exactly the position that we predicted from our animal studies, using comparative neuroanatomy. Interestingly, that same region on each side of the brain stem was activated whether the sweating was due to heating or if it was caused by mild mental stress. We have evidently identified the common brain output pathway for sweating in humans.



Glia cells (green) in the brain are in very close contact with brain microvessels (red) and play a critical role in maintaining the blood-brain barrier. When the blood-brain barrier becomes 'leaky' in disease, hormones and other circulating factors, normally only found in the blood, gain access to brain cells and make them hyperactive. Hyperactivity of neurons that stimulate sympathetic nerve activity contributes to the progression of cardiovascular diseases.

NEUROPHYSIOLOGY GROUP

Leader: Richard Macdonell

Our lab studies how diseases such as epilepsy and multiple sclerosis change the excitability of neurons. A second focus is on the physiology of neurorehabilitation and neural repair.

Research highlights for 2013

In the rehabilitation of children who have upper limb dysfunction resulting from cerebral palsy, it is unclear whether constraint induced movement therapy (using a glove on the unaffected hand to prevent the child using it) or bimanual training (allowing the child to use both hands during rehabilitation activities) provide better outcomes. We hypothesised that preventing use of the unaffected hand using a glove would have a greater effect on brain recovery than allowing the child to use both hands and these effects would be retained in the medium term (six months). Sixty-four children with unilateral cerebral palsy were recruited. After random allocation the children were equally divided into either a "glove or no glove" group and enrolled in a training camp in the same environment for a total 60 hours over 10 days.

Children in the gloved group had a greater response within the brain (neuroplasticity) compared with the more conventional two-hand approach using fMRI and transcranial magnetic stimulation. Brain excitability and blood flow in the affected area of the brain improved in the children asked to wear a glove but not in those allowed to use both hands. These physiological changes were accompanied by clinically significant improvement in the ability of the children to use their affected hand, either alone or in combination with the unaffected hand.

This is the first matched pairs randomised trial directly comparing glove or no glove training using measures of neuroscience outcomes in unilateral cerebral palsy. Our study confirms that upper limb training programs for school aged children should commence with a constraint (glove) to drive neuroplastic changes followed by bimanual activities to improve co-ordination.

NEURORESPIRATORY GROUP

Leader: Mathias Dutschmann

We study the basic neural mechanisms underlying breathing, how these patterns of nerve activity adjust to accommodate other behaviours such as swallowing, and how they are modified during development and in neurodegenerative disease.

Research highlights for 2013

A research highlight from the laboratory is the identification of a specific area of the brainstem that protects the airways during swallowing. It achieves this aim by causing coordinated closure of the glottis over the period where fluid in the throat is swallowed. If this mechanism fails, fluid can enter the lungs. Interestingly, this brainstem area is exactly the region that shows severe neurodegenerative changes in dementia. This year we made a thorough study of the region in the brains of mice with mutations that cause dementia and mapped the distribution of degenerating cells in the brainstem. We also found that the identical brainstem nuclei show severe degenerative changes in the brains of humans who suffered from dementia. Our findings are the first to link these degenerative changes in the brainstem with the clinically important symptom of swallowing disorders. Disordered swallowing can cause aspiration pneumonia, a leading cause of death in elderly patients.

NEUROCARDIOVASCULAR GROUP

Leader: Clive May

Heart failure is a complex clinical disorder that constitutes a major health and economic burden in Australia. Despite numerous available therapies the prognosis for these patients remains poor. Patients with heart failure are three times more likely to die within three years than those diagnosed with cancer. Excessive sympathetic nerve activity is associated with reduced survival in patients with heart failure. However, the mechanisms underpinning this long-term hyperactivity are not known

The Neuro-cardiovascular group lead by Associate Professor Clive May is investigating how altered signalling to the brain, breakdown of the barrier between the brain and circulating blood and chemical changes

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in the brain contribute to the increased activity in sympathetic nerves that innervate the heart and kidney. Increased activity in these nerves causes a reduction in the function of these organs and contributes to the progression of heart failure and hypertension.

Research highlights for 2013

The blood-brain barrier is critical for keeping potentially harmful blood-borne substances from reaching brain cells. If this barrier becomes leaky, the substances that cross into the brain can stimulate neurons that increase sympathetic nerve activity and also cause an inflammatory response that can enhance this response. The research led by Dr Song Yao has discovered that, in hypertension, glia cells that support cells helping neurons to function, withdraw their fine foot-like processes from the surface of microvessels in the brain. This glia retraction contributes to the breakdown of the blood-brain barrier and allows the infiltration of normally excluded blood-borne proteins into the brain. This affects brain function, increases nerve excitability and speeds up disease progression. Understanding the mechanisms leading to blood-brain barrier disruption is vital for the development of new therapies to treat heart failure and hypertension.

AUTONOMIC NEUROSCIENCE GROUP

EDITORIAL POSITIONS

- American Journal of Physiology
- Clinical and Experimental Pharmacology and Physiology
- Faculty of 1000

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

- 6th Congress of the International Society for Autonomic Neuroscience, Giessen, Germany. Opening Plenary Lecture.

NEUROPHYSIOLOGY GROUP

COLLABORATIONS

- University of Queensland
- Monash University
- Biogen Idec (Australia)

NEURORESPIRATORY GROUP

COLLABORATIONS

- University of Leuven, Belgium
- University of Munich, Germany
- University of Göttingen, Germany
- Case Western Reserve University, USA

EDITORIAL POSITIONS

- Associate editor of Respiratory Physiology and Neurobiology.
- Frontiers in Integrative Physiology.

NEUROCARDIOVASCULAR GROUP

COLLABORATIONS

- Baker IDI, Melbourne
- University of Lyon, France
- University of Iowa, USA

EDITORIAL POSITIONS

- Clinical and Experimental Pharmacology and Physiology
- Frontiers in Integrative Physiology
- Frontiers in Autonomic Neuroscience
- Faculty of 1000

MAJOR NATIONAL AND INTERNATIONAL CONFERENCES 2013

- Sympathetic nervous system summit, Rome, Italy.

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FLOREY STUDENTS TEAM-UP FOR EXCELLENCE

Students of the Florey Institute, or SOFI, was established in 1999 as a means of bringing students closer together. SOFI aims to enhance the academic and professional life of SOFI postgraduate students, and also to encourage social interaction of students within the Florey, the University of Melbourne, and other postgraduate institutes in Melbourne.

It was a great year for academic development, as SOFI members organised international guest speakers who not only gave formal academic talks, but also relaxed career focussed session with PhD candidates. For example, David Goldstein from Duke University in the USA, gave an enlightening talk on his early career trajectory before opening up an informal Q&A session on anything and everything pertaining to the challenges and opportunities a research career has to offer. We also organised several career days for students focusing on the PhD experience and how to increase productivity, with topics ranging from handling data more effectively, how to network productively, and how to get research published in quality journals.

Additionally, the SOFI mentoring program was a great success, where all Florey honours students were paired with a mid to late PhD candidate mentor, and PhD candidates were paired with post doctorial researchers with a similar research area of expertise. The incentive of free coffee at Dr. Dax café helped get this program off the ground, and it was exciting to see how valuable a resource some mentors became to their mentees, the mark of a worthy endeavour.

VICTORIAN BRAIN BANK NETWORK

Division head: Professor Catriona McLean

AIMS

The Victorian Brain Bank Network (VBBN) collects, processes and stores post-mortem human brains and related samples from individuals who have had neurological diseases (i.e. Alzheimer's disease, motor neurone disease and Parkinson's disease), physichiatric disorders (i.e. bipolar mood disorder, depression and schizophrenia) as well as normal 'control' cases. The VBBN facilitates research into the study of brain diseases by providing tissue to researchers who, using current technologies, aim to unlock our understanding of how brain diseases occur and this will hopefully lead to improvements in diagnosis, the development of early diagnostic tests, therapeutic interventions and development of preventative strategies.

We provide a vital and unique neuropathological diagnostic service that confirms a ante-mortem clinical diagnosis, increases clinicians' awareness and understanding of atypical presentations of certain brain diseases, confirms a diagnosis for donor families, in whom neurological disease may have hereditary or familial association and may be at risk of developing the disease, generates pathological description of brain diseases and advances knowledge of some brain pathologies, thus providing a powerful tool for education and research and importantly, this service is relied on for the validation of research studies.

ACKNOWLEDGMENT

The VBBN would like to acknowledge the generosity shown by the donor and donor families in donating tissue to the VBBN. It is an act of great foresight and kindness to give at a time of loss, so that others may be helped in the future. The clinicians and researchers who benefit from these donations are very grateful to the donors and their families who support them in these decisions.

The VBBN would like to acknowledge the support of the following funeral directors, Bethel, Jensen, Allison Monkhouse, Le Pine, Nelson Bros, Tobin Brothers and WD Rose & Joseph Allison who provide metropolitan transfers for tissue retrieval at no cost to the VBBN.

HIGHLIGHTS

BRAIN AND BRAIN/ SPINAL CORD DONATIONS

The VBBN has a total of 1,093 cases available for research, with 54 new donations received in 2013. The new donations included cases diagnosed with Alzheimer's disease, Frontotemporal dementia, Huntington's disease, Lewy body disease, Motor neurone disease, Multiple sclerosis, Parkinson's disease, schizophrenia, and control 'normal' cases. The VBBN collection makes up 39% of the cases that are available for research within Australia.

TISSUES PROVIDED TO RESEARCHERS

During 2013, the VBBN provided tissue to 47 Australian and international new or continuing research projects, with the main research focus being Alzheimer's disease, Motor neurone disease, schizophrenia and bipolar disorder. This equates to 3,217 diseased and 'control' samples being provided to researchers.

Research groups at The Florey Institute of Neuroscience and Mental Health are among the recipients of this tissue. Seven new research groups have accessed tissues from the VBBN this year with research being performed at Monash University, Murdoch Children's Research Institute, The Florey Institute of Neuroscience and Mental Health, Kyung Hee University, Korea and Kyungpook National University, Korea.

During 2013 research utilising tissue from the VBBN has resulted in 61 Australian and International publications and presentations.

SENIOR STAFF

HEAD
Professor Catriona A McLean BSc, MBBS, FRCPA, MD, FFSc (RCPA)

DIRECTOR
Professor Brian Dean HND ApplBiol, MSc, PhD, FI Biol

CONSULTANTS
Professor Colin Masters BMedSc (Hons), MBBS, MD, HonDLitt WAust, FRCPath, FRACPA, FAA, FTSE

Associate Professor Suresh Sundram MBBS, MMed, FRANZCP, PhD

COORDINATOR
Ms Fairlie Hinton

RESEARCH ASSISTANT
Mr Geoff Pavey BSc (Hons)

CONSULTANT HISTOLOGIST
Dr Ian Birchall BAppSc, MSc, PhD

COLLABORATORS

• Laboratory Manager and Mortuary Technicians, The Alfred • Pathologists and Mortuary Technicians at the Victorian Institute of Forensic Medicine • Ballarat Health Services, Bendigo Health, Royal Hobart Hospital and Launceston General Hospital • Transplant and Family Liaison Coordinators at the Donor Tissue Bank of Victoria •

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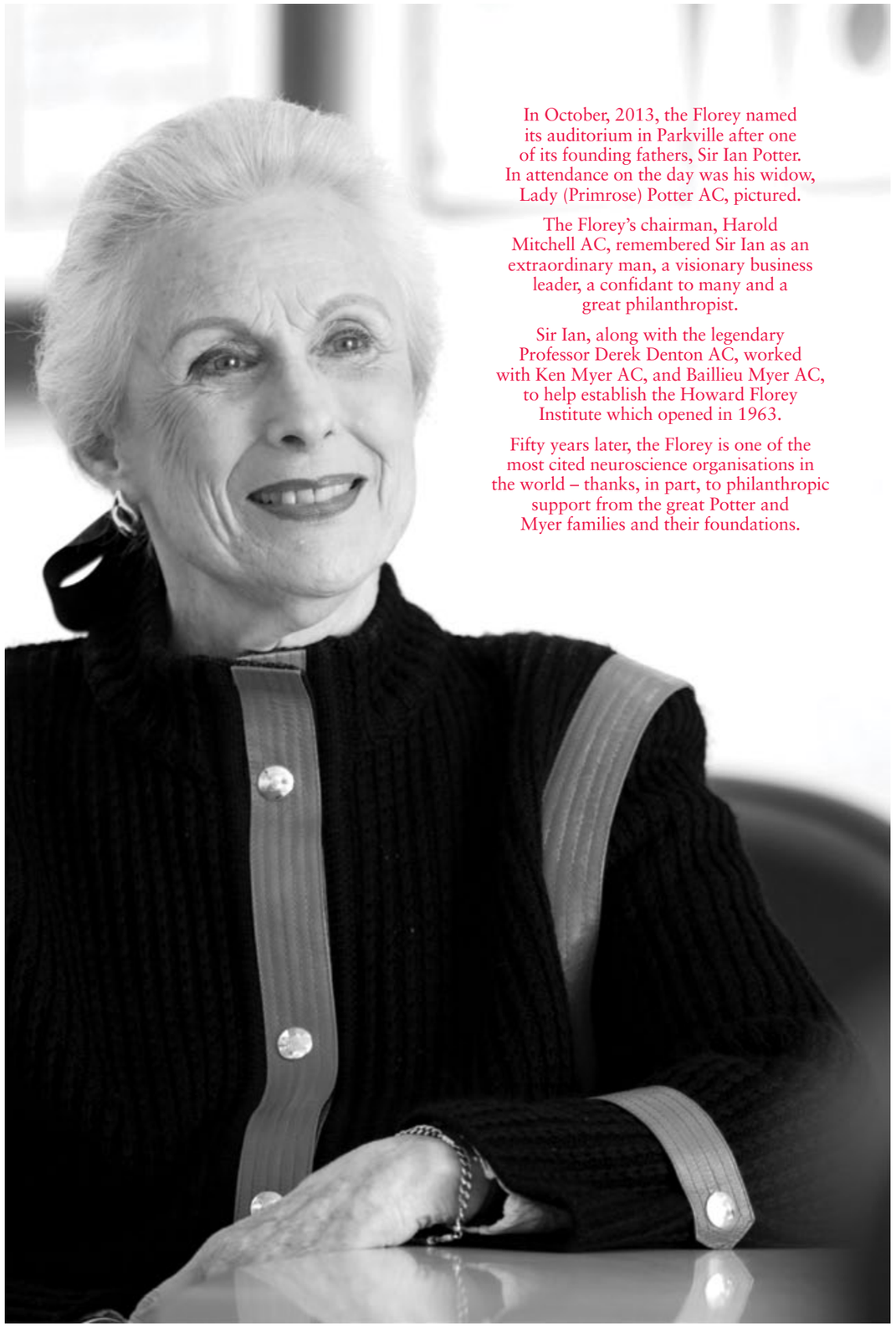

In October, 2013, the Florey named its auditorium in Parkville after one of its founding fathers, Sir Ian Potter. In attendance on the day was his widow, Lady (Primrose) Potter AC, pictured.

The Florey's chairman, Harold Mitchell AC, remembered Sir Ian as an extraordinary man, a visionary business leader, a confidant to many and a great philanthropist.

Sir Ian, along with the legendary Professor Derek Denton AC, worked with Ken Myer AC, and Baillieu Myer AC, to help establish the Howard Florey Institute which opened in 1963.

Fifty years later, the Florey is one of the most cited neuroscience organisations in the world – thanks, in part, to philanthropic support from the great Potter and Myer families and their foundations.

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- Thomas Schneider
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- Loti Smorgon AO (dec 20/8/2013)
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- Meredith Woods
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- Professor Geoffrey Donnan AO
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- Mr Andrew Stripp
- Dr Ross Macdonald
- Dr Ergad Gold
- Mr Wayne McMaster
- Mr Gary Gray

FINANCE AND INVESTMENT

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- Professor Geoffrey Donnan
- Professor Graeme Jackson
- Professor Colin Masters
- Mr Gary Gray
- Mr Andrew Stripp
- Mr Peter Plecher

AUDIT

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- Professor Andrea Hull AO
- Professor Geoffrey Donnan AO
- Professor Graeme Jackson
- Professor Colin Masters
- Mr Gary Gray
- Mr Andrew Stripp
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THE FLOREY FACULTY & SENIOR POSITIONS

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- Associate Professor Steve Petrou
- Mr Gary Gray

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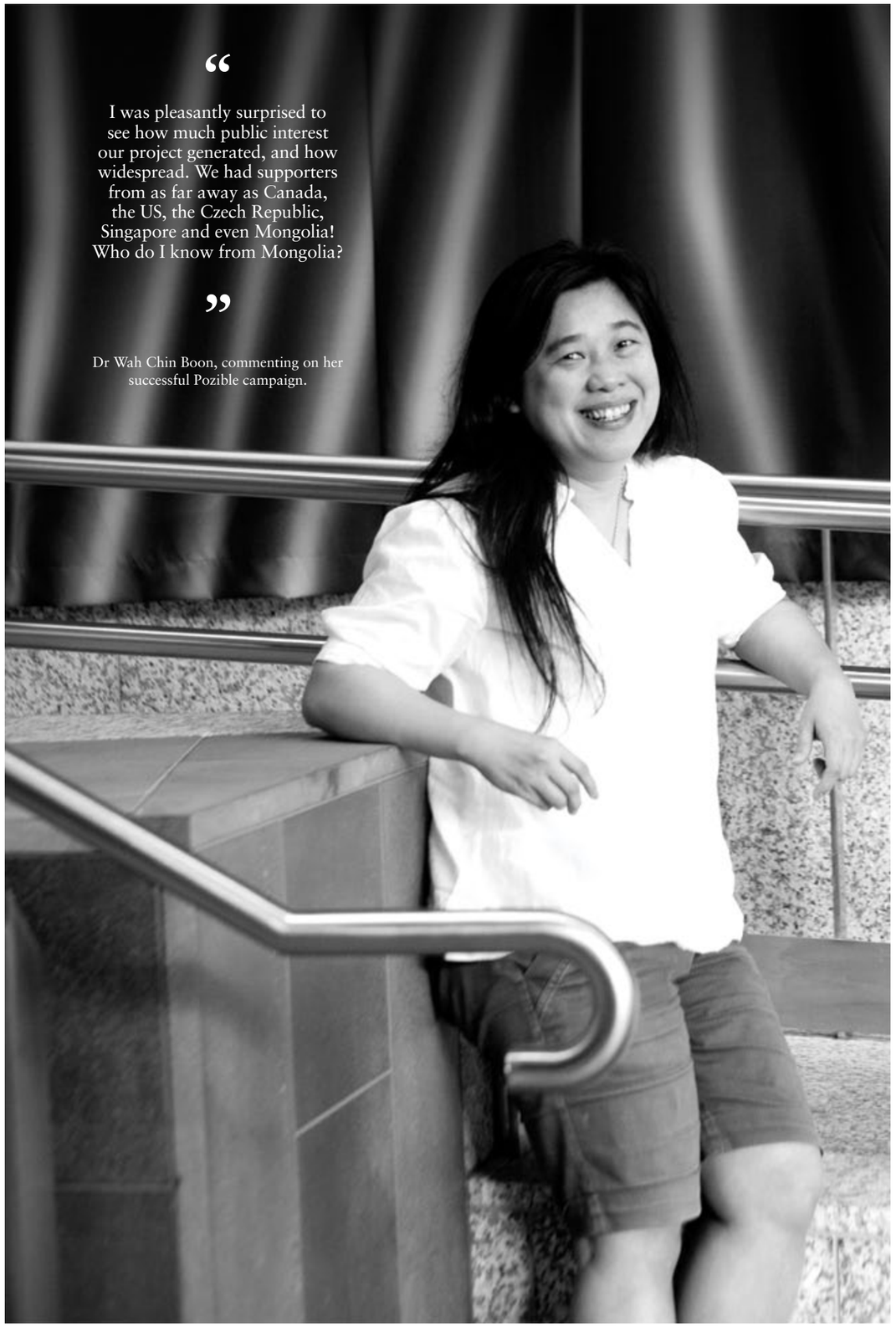

IT IS POZIBLE

It was with a mixture of nervousness and anticipation that the Florey embarked on its inaugural crowdfunding campaign in October 2013. Nervousness, because raising money for medical research in this manner had only been tried a handful of times around the world, and anticipation because if it worked, it would open up a new and exciting way for our scientists to fund their research, and promote it to an entirely new audience.

Seven groups were selected to take part in the campaign, covering disease areas such as stroke, Parkinson's disease, schizophrenia, addiction and autism. Of these groups, four successfully reached their target, raising a combined total of over $70,000 in new research funding. These funds will contribute to new lab equipment, a salary for a new staff member, a student stipend and reagents to create new research tools.

The campaign also raised the public profile of the Florey, generating media interest across national newspapers, radio and television. Social media was also a key driver of the campaign's success, with thousands of hits on Twitter, Facebook and Youtube, exposing our cutting edge science to a new, younger demographic.

Crowdfunding might be an unfamiliar concept to some. The idea is to use the power of the "crowd" to raise funds for a discrete research project by asking hundreds or thousands of backers to each contribute a small amount, thereby reaching your target. If you fail to reach the target in the allotted time, you receive no funds (called the "all-or-none" model).

Until recently, crowdfunding has been used to fund "creative" projects such as filming a documentary, recording an album or shooting a music video, providing travel funds for artists, musicians or writers to attend festivals or developers to create a new game. However, crowdfunding is gaining popularity within the scientific community as a means of raising money beyond traditional, extremely competitive granting agencies.

We used Pozible.com, the biggest crowdfunding website in Australia and the third biggest, worldwide.

One of the successful projects, "DNA: We are what we eat!", was run by Dr Wah Chin Boon and her masters student, Kris Vacy, from the Neurodegeneration division. By raising over $15,000, they'll be able to investigate human DNA changes in response to environmental influences, in an experiment informed by their NHMRC-funded preclinical work in mice.

That work has shown that if certain compounds are present in food, genes thought to be important in normal brain development are 'turned off' leading to an increased risk of developing autism. The $15,000 will be used to run a small pilot study to collect cheek cells from the saliva of autistic and unaffected people, to test if the same mechanism is present in humans. In addition, they will develop a survey to look at whether parents of autistic individuals were heavily exposed to these compounds around the time of conception and while their children were in utero, which will inform public health policy in Australia.

Without the money generated from this campaign, we wouldn't be able to show proof-of-principle in humans at all.

"If successful, this study will form the basis of another NHMRC grant application," says Wah Chin. "Without the money generated from this campaign, we wouldn't be able to show proof-of-principle in humans at all. It was also pleasantly surprising to see how much public interest our project generated, and how widespread. We had supporters from as far way as Canada, the US, the Czech Republic, Singapore and even Mongolia! Who do I know in Mongolia?!"

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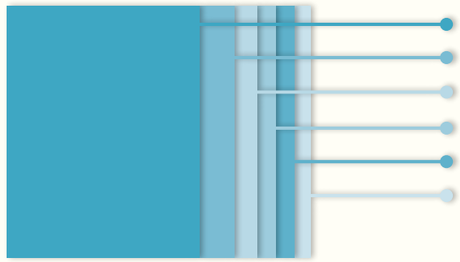
FINANCIAL STATEMENTS

Consolidated Statement of Comprehensive Income
(For the year ended 31 December 2013)

	DEC 2013 $'000
Revenues from ordinary activities	**55,104**
Salaries and employee benefits	(34,914)
Raw materials and consumables used	(4,129)
Conferences and collaborations	(1,686)
Building occupancy	(5,016)
Research support services	(3,331)
General administration	(4,292)
Distribution of grant funds	(3,623)
Net operating deficit before depreciation, amortisation and impairment	**(1,887)**
Depreciation and amortisation	(8,624)
Impairment of non-financial assets	(37,828)
Net operating deficit after depreciation, amortisation and impairment	**(48,339)**
Building project income	205
Expenses related to the building project	(4,647)
Net deficit for the year	**(52,781)**
Other comprehensive income:	
Net gain on revaluation of financial assets	849
Other comprehensive income for the year – surplus	849
Total comprehensive income for the year – deficit	(51,932)
Total comprehensive income attributable to members of the entity – deficit	(51,932)

SOURCES OF REVENUE (Year Ended 31 December 2013)



	$M	% OF TOTAL
Government bodies	33.3	60%
Private donors	6.0	11%
Commercial income	5.3	10%
Peer review funding	4.6	8%
Miscellaneous	3.2	6%
Investment income	2.7	5%
TOTAL	55.1	100%

FINANCIAL STATEMENTS

Consolidated Statement of Financial Position
(As at 31 December 2013)

	DEC 2013 $'000
ASSETS	
Current Assets	
Cash and short-term deposits	25,842
Trade and other receivables	2,961
Available-for-sale financial assets	15,002
Prepayments	133
Inventory	69
Total Current Assets	44,007
Non-Current Assets	
Property, plant and equipment	12,285
Investment property	3,413
Other assets	62,450
Total Non-Current Assets	78,148
TOTAL ASSETS	**122,155**
LIABILITIES	
Current Liabilities	
Trade and other payables	5,774
Provisions	6,528
Income in advance	52
Total Current Liabilities	12,354
Non-Current Liabilities	
Provisions	944
Total Non-Current Liabilities	944
TOTAL LIABILITIES	**13,298**
NET ASSETS	**108,857**
FUNDS	
Retained surplus	47,239
Unrealised investment reserve	579
Merger / reorganisation reserve	61,039
TOTAL FUNDS	**108,857**

We acknowledge the Victorian Government's strong support, particularly through funding from the Operational Infrastructure Support Grant. All funding received through the Department of State Development, Business and Innovation and other government agencies are expended on our research activities and services to support the science. We also thank the State and Federal governments, the Potter Foundation and the Myer Foundation for their huge support for the Melbourne Neuroscience Project including the building of our new facilities. We also gratefully acknowledge the support of the Victorian Department of Health through the provision of an ongoing mental health grant.

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01/04

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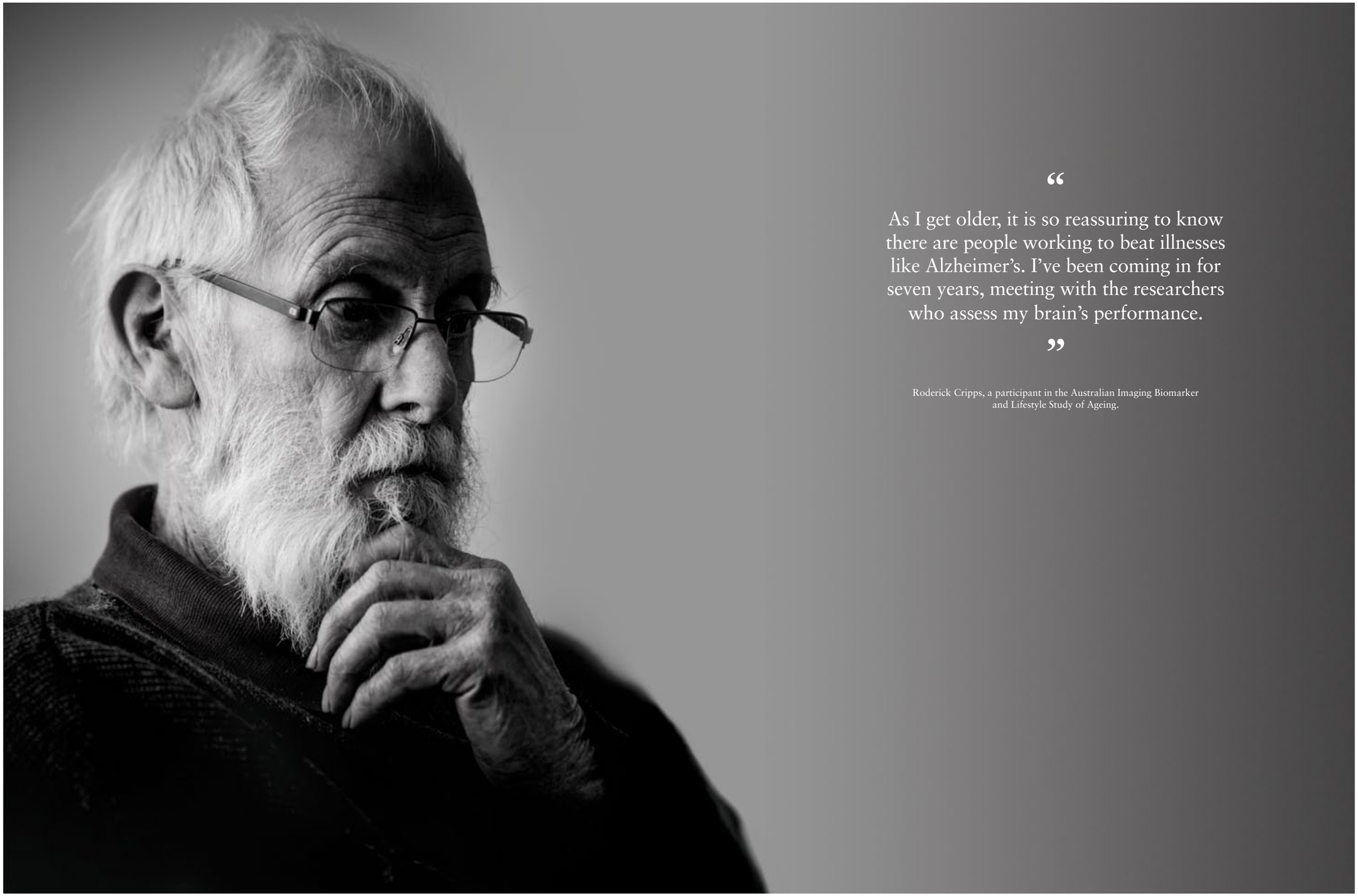

“As I get older, it is so reassuring to know there are people working to beat illnesses like Alzheimer’s. I’ve been coming in for seven years, meeting with the researchers who assess my brain’s performance.”

Roderick Cripps, a participant in the Australian Imaging Biomarker and Lifestyle Study of Ageing.

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The Florey Institute of Neuroscience and Mental Health acknowledges the traditional owners of this land, the people of the Wurundjeri people and the Kulin Nations. We pay our respects to their elders, past and present. We would like to acknowledge that our four sites rest on this precious land.

Parkville Campus

Head Office
30 Royal Parade
Parkville, Victoria 3052
Australia

T +61 3 9035 6789

F +61 3 9035 3107

Howard Florey Laboratories

Royal Parade
Parkville, Victoria 3052
Australia

Oak Street Campus

155 Oak Street
Parkville, Victoria 3052
Australia

Austin Campus

Melbourne Brain Centre
245 Burgundy Street
Heidelberg, Victoria 3084
Australia

T +61 3 9035 7000

F +61 3 9035 7301

FLOREY.EDU.AU

ABN: 92 124 762 027

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