

2011 Grants and Christmas Edition

The Directors and Staff of the Brain Foundation and Headache Australia would like to thank all our supporters, members and donors and wish you all the very best for the coming holiday season. Without your support, we could not continue with the vital Research Grant Programme. Read all about the 2011 Awards in this edition.



Mates' deeds fund research needs

As many of our donors would know, losing a close family member or friend to a disease outside of your control, at any age, is a devastating event to deal with in your life.

However, it is even more devastating when the person involved is a teenager and just beginning their journey of life's many and varied experiences.



The St Augustine's Team before the big event

Such was the case this year, when a student, Christopher Hanavan, from St. Augustine's College on Sydney's northern beaches suffered a haemorrhage from an Arteriovenous Malformation (AVM) in class. Although rushed to hospital, he never regained consciousness and died the following day in hospital.

After the initial shock of this terrible event subsided, Christopher's friends and the school community decided that they would like to do

something positive in Christopher's memory and raise funds for a research project into AVMs.



Christopher's brothers and friends with the Governor at the Award Ceremony.

Affecting 3 out of every 10,000 people, AVMs form accidentally prior to birth. A tangled mesh of abnormal blood vessels which directly connect arteries to veins in the brain, they are more common in men and problems are most likely to occur between the ages of 10 and 30. However, many people will have AVMs that never cause a problem.

Christopher's friends got together to raise funds for research into AVMs by entering the Pub to Pub Fun Run and Walk from Dee Why to Newport on Sydney's northern beaches. Only 1 km shorter than the better known City to Surf, this is also a challenging event, and attracted many thousands of entrants. The boys were sponsored by family and friends

and the final school team of 150 entrants was supported by the administration staff and teachers from the school. The Brain Foundation supplied caps to the entrants for that extra 'team' feel. The event raised over \$9,700 in sponsorship and the Brain Foundation also collected the 'largest team' prize of \$2,000 from Brookvale Rotary who sponsored the event.

The Brain Foundation would also like to thank the Caledonia Foundation for their extraordinary contribution which, together with the funds raised by the boys, allowed us to fund a research grant into "Molecular imaging in brain AVMs". (Read more about this research later in this newsletter.)



Gerald receiving the 'Cheque' from Principal, Tim Cleary

The award was made at this year's Research Grant Ceremony in September which was officiated by the Governor, Her Excellency Professor Marie Bashir AO CVO.

Fundraising and Events

Zombies rise from the dead for the Annual Brisbane Zombie Walk

Once again, Brisbane City was overtaken by the 'living dead' for the Annual Zombie Walk. This family friendly afternoon saw at least 15,000 and maybe as many as 20,000 zombies turn out to 'walk' the streets in support of the Brain Foundation. After successful walks in previous years, the (volunteer) organising committee was hoping for a Guinness Book of Records, and with crowds like this, I think that Brisbane must be declared the Zombie capital of the world.

Starting in Wickham Terrace and walking through the city's shopping area, the streets were lined by thousands of photo taking spectators who were entertained by the many and varied costumes, make up and antics of the Zombies.

We are extremely grateful to the organising committee and the many

volunteers on the day, Brisbane City Council and Qld Police for their support and sponsorship of this ever more popular event, the public and of course the weird and wonderful participants, who so generously supported the Brain Foundation.

Special thanks must go to all the wonderful Zombie teams who raised over \$9,000 through the My Cause fundraising web site.

Brain Foundation would like to thank all the other sponsors of the event: Crazy Contacts, Bifrost Studios, Beserk Clothing, 24 Hour Wristbands and TUH, as well as the venues around the Valley who sponsored us and became zombie-

friendly venues: RGs/Ric's/Bank, Birdee Num Num's and Kaliber and the many other people who sponsored and promoted the event. We are extremely grateful to the Tempo Hotel for hosting the official After Party again this year and for allowing us to have an all-ages section for our younger fans.



Sydney Zombies are a little shy. Not.

Sydney also plays host to the Zombies with a walk from Hyde Park to Central Station on October 29. Held along with the Sydney Food and Wine Fair, although Zombies are not likely to partake of the delicious offerings, the Sydney Zombies are becoming less shy and numbers are growing significantly. This year saw many more gruesome ghouls turn out much to the delight of the many tourists in the Park.

We would like to thank the organising committee for their dedicated efforts to organise this event and raise funds for us, and look forward to the event becoming bigger and better – perhaps even some friendly Zombie rivalry with the Brisbane ghouls.



Zombies may love Braaaains, but the Brain Foundation loves Zombies!

Golfers on target with 'perfect' performance

The Brain Foundation was lucky to have perfect spring weather for the third annual Charity Golf Day at Pymble Golf Course in September. It was heartening to see most of the players who have been supporting the Brain Foundation in attendance again and there was an opportunity to renew acquaintances over breakfast.

The competition was keen, but the organisers from Bullant Sports, Gary "Smokey" Dawson and Matthew Laverty, and their team managed to wrangle a prize for every foursome. Bullant Sports

also arrange Golf Days for other charities throughout the year, and the fundraising culminates with the Annual Gala Charity Ball held in November each year.

Pictured is one of the winning teams, compensating for being too tall next to Brain Foundation Director, Val Gibson, who is the 'driving' force behind our Foundation's involvement.

From left they are: Neil Elliott of Elliott & Assoc, Mitchell & Ben Hancock, Val Gibson, Gerald and Martin.



The Brain Foundation is fortunate to have a wonderful number of supporters who, although having been affected by the devastating diagnosis of Brain Tumours in their families, have put their energy to raising awareness and funds for us to go toward research into this terrible condition.

These 6 enterprising people together have raised enough to fund a Brain Tumour Research project on their own! Thank you all so much.

Girls Night In

Tamara Sanderson from Maryborough in Queensland had some terrible news early this year when her husband was diagnosed with a Glioblastoma Multiforme IV; one of the most common and aggressive forms of Brain Tumour. As her husband is only 26, this made the news even harder to bear.

Tamara decided to hold a 'girls night in' in October and invited friends and family to attend wearing purple or grey. Sourcing raffle items from the local area, Tamara and the girls had a great night and raised over \$2,800 to go towards Brain Tumour research.



Tamara, centre, with her sisters

Melbourne Cup Luncheon – and the winner is... the Brain Foundation!

Melbourne Cup is always a great time to have a get together, and Brain Foundation supporters from Brisbane, Louisâ Coote and Fiona Greenwood decided they could put together a lunch to rival those south of the border! They held a Cup Luncheon with 15 friends attending, many of whom have a family member affected by a brain tumour or acoustic neuroma. Holding a raffle and, of course, the obligatory sweep, a great time was had by all and the Brain Foundation was the beneficiary of the (over) \$1,300 raised.



Louisâ (left) and Fiona.

Hair Today – Gone Tomorrow

What is making our beautiful young girls shave their heads?

Well, you guessed it, Brain Tumours!

Holly Adams (pictured)

Holly from the Sunshine Coast in Queensland is only 14 years old yet she has bravely shaved her beautiful long hair off in the name of fundraising! Her uncle has been diagnosed with a Brain Tumour and Holly really wanted to do something positive to help people who are diagnosed in the future. With the help of her school community, teachers and friends and the community, Holly raised an outstanding \$3,000.

Just as well she lives in a warm part of the country so her head won't be too cold!



Isobel Jones

16 year old Isobel is from Balmain in Sydney and sadly her family has a history of cancer. But it was the 9 year fight and subsequent death of her Uncle Josh which inspired her to shave her head to raise funds for Brain Tumour research. Choosing the anniversary of her grandfathers death in July, also from cancer, Isobel went head first. Raising a very impressive \$1800 we unfortunately did not have a Brain Foundation beanie available to keep her head warm! Thank you Isobel.

You can have your cake and eat it too!

Year 7 House Captain from The Southport School on the Gold Coast, Yash Bhoola, showed his initiative recently, raising funds for Brain Tumour research.

Following the devastating diagnosis of what would be a fatal brain tumour in his grandfather, Yash decided to take some positive action. Raising money at fetes, holding cake stalls and seeking donations, Yash was able to raise \$2,300 to go towards research into this terrible disease. What a fabulous effort!

In Surfers Paradise on business, Gerald Edmunds was able to attend a school assembly to receive a cheque from Yash and promote the Brain Foundation to parents, students and staff at the school.



Erin has a 'Pickled Brain'

Well not really, but you couldn't blame her if she did!

Erin's father passed away earlier this year after a mole on his face turned cancerous, sending tumours to all parts of his body, including more than 15 in his brain. After watching him fight and seeing the loss of the person he was, Erin was determined to see something good come from her father's experience. She decided to join the Brisbane Zombie Walk and registered as the 'Pickled Brains' team, through the

My Cause web site, with a friend. They have raised nearly \$6,300 for Brain Tumour research and still counting.



Gerald and Erin at the Brisbane Zombie Walk

Headache and Migraine News

BOTOX®: help for Chronic Migraine!

BOTOX® is the latest therapy available in Australia for the prevention of headache and migraine and has been found a valid treatment for adults suffering from Chronic Migraine.



Migraine is more than just a severe headache. It is more common than asthma or diabetes, and is the leading cause of lost productivity at work and social activity.

About 2 million Australians or 10% of the population can be expected to suffer from migraine.

There are two types of Migraine – Episodic and Chronic.

Chronic Migraine is a debilitating condition where patients suffer headaches for 15 days or more a month, with migraine on at least 8 of those days.

Approx 350,000 people suffer from chronic migraine. However, many more sufferers may meet the criteria. These people would not be aware that they are eligible to seek BOTOX® treatment for the condition.

BOTOX® has not been proven effective for sufferers of headache and migraine that do not meet this criteria.

To understand your headache and migraine pattern, it is essential for sufferers to track their migraines by keeping a headache diary – see www.headacheaustralia.org.au.

If you meet the chronic migraine criteria you should ask your doctor for a referral to a neurologist.

Other treatment options are avoiding potential triggers and medicinal treatments as have been prescribed by your physician.

BOTOX® is a neuromuscular blocking agent. It works by blocking peripheral signals to the central nervous system. For headache and migraine relief it is not injected into muscles but rather into the area around the nerves, particularly the Trigeminal Nerve, which are transmitting the pain signals. The product itself is no different to that used cosmetically.

BOTOX® needs to be administered by a trained neurologist or pain specialist and it is expected to produce results lasting up to 3 months, depending on the patient.

The effects of BOTOX® may be seen beyond the site of the local injection.

Adverse reactions are usually transient and occur within the first week of the injection and can include pain, tenderness and bruising.

Results from studies show that BOTOX® treatment significantly reduced the number of headache days and migraine days per month. It enabled sufferers to reduce medication use and improved overall health related quality of life.

It is essential that sufferers are referred to a neurologist or pain management specialist for treatment. Currently there are no rebates available for this treatment from either Medicare or Health Insurance Companies.

The costs for treatments of BOTOX® include the cost of the BOTOX® itself – the recommended dose being two vials – plus the fee for injecting. The total cost could be \$1,000 to \$1,200 per course approx, depending on your physician. There is no limit on the number of courses a patient can access.

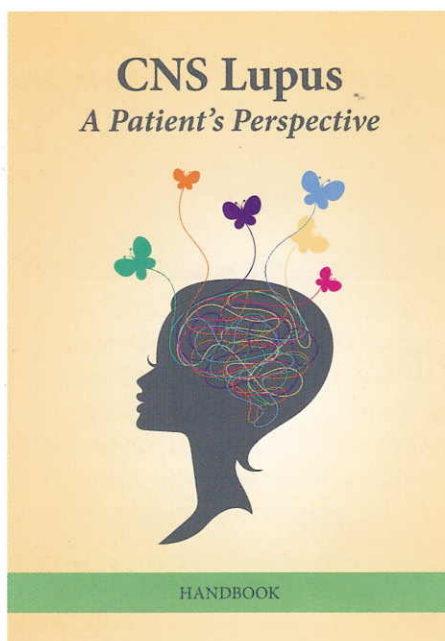
All medicines have risks and benefits. Your physician will weigh the risks of using Botox injections against the benefits expected from using it for each individual.



Please join the Headache Register at
www.headacheaustralia.org.au

Publications

Cerebral Lupus? Read all about it!



Lupus is an autoimmune disease which alters the immune system so that antibodies attack the bodies' tissues instead of protecting them.

By far, the most serious form of Lupus is Cerebral Lupus. While not the most common form, this disease targets the brain as well as the rest of the body.

The Brain Foundation was approached earlier in the year by supporter Venette Hedges from Yamba in NSW (pictured with Gerald Edmunds). Diagnosed with Cerebral Lupus 16 years ago, Venette had realised that while her doctors were supportive and gave a very good medical account of her condition, there was no literature available to tell her what living with Cerebral Lupus would be like. So, having felt the terrible effects of this awful condition for many years, Venette decided to put her experiences down for all sufferers to read and understand what the road ahead may look like. But, like all authors, it was to be a little while longer before the dream of

publishing her booklet was realised.

We are happy to announce that, with a lot of help from her friends and a little assistance from the Brain Foundation, Venette will be publishing her book in the New Year. If you or anyone you know suffers from Cerebral Lupus and you would like a copy of her book, please contact the Brain Foundation office in early 2012.



2011 Research Grant Awards

This edition of Brainwaves provides a showcase for the recently awarded Research Grants for 2011. This year, we have funded 15 research projects to a value of \$500,000. This is made possible by the support of our donors, both individual and corporate and our sponsors. We would like to thank everyone who donates towards these grants each year. Your ongoing support is greatly appreciated.

We would also like to take this opportunity to thank the members of the Scientific Committee who volunteer their time to assess the many applications we receive and arrive at the final candidates.

Our Award Ceremony was held in The Great Hall at Sydney University. The Governor of New South Wales, Her Excellency Professor Marie Bashir AC CVO presented the awards to the recipients and attendees were again charmed by the wonderful piano playing of international pianist Ambre Hammond, who has supported the Brain Foundation for many years.

Non-invasive cerebellar stimulation for focal hand dystonia

Chief Investigator:
Ms Lynley Bradnam

Co-Investigator: Associate Professor
Michael Ridding

Lynley's research focus is in the mechanisms underlying, and treatment of, movement disorders such as focal hand Dystonia and upper limb spasticity after stroke. Her technical expertise is based around using Transcranial Magnetic Stimulation (TMS) to study motor control and her novel findings from experiments investigating upper limb control in healthy humans and in stroke survivors have increased understanding of mechanisms underlying coordination of the upper limb. Lynley's research involves using treatment

interventions based on principles of neuroplasticity, such as noninvasive brain stimulation and peripheral nerve stimulation, as a therapeutic approach for the rehabilitation of movement disorders. Noninvasive brain stimulation has the potential for translation into clinical the clinical setting however, further systematic investigation is required to understand the mechanisms of action and efficacy in individual disorders. Lynley is also interested in the potential use of clinical tests and biomarkers to individualize upper limb therapy for stroke survivors and patients with movement disorders. Lynley has established a Human Neurophysiology Laboratory located within the Repatriation General Hospital in Adelaide. She is working with medical and physiotherapy

clinicians in the hospital setting and her work is supported by the Departments of Physiotherapy and Rehabilitation, Aged and Allied Health at Flinders University.



Stroke in Cardiac Disease

Chief Investigator: Dr Mark Mackay

Co-Investigators: Dr Darren
Hutchinson, Dr Michael Cheung,
Dr Chris Barnes, Miss Belinda
Stojanovski, Dr Julia Gunn, Dr Rod
Hunt and Associate Professor Susan
Donath

Strokes are relatively frequent occurrences in children and babies compared to better publicized disorders. For example stroke is more common than brain tumours and it is the among the top ten causes of death in children. Heart disease is the second most common cause of stroke; accounting for almost one third of cases in recent studies. Stroke and other forms of brain injury are very common events in newborns with congenital heart defects. Recent studies have shown that at least one third of babies undergoing heart surgery have evidence of brain injury, including stroke, on brain scans and at least another third have evidence

of new brain injury after surgery. Children with heart disease are the most important target group for strategies to prevent stroke occurring because heart disease is usually known prior to the stroke.

This study will provide important insights into the nature, timing and outcome of stroke in children with heart disease. We have already identified 77 babies and children with heart disease and stroke and found that almost three quarters have complex heart defects and 53% were aged < one year old. 16% of children died and 84% of survivors have disabilities. We would now like to compare this group to other children with heart disease who have not had a stroke, to find out how the groups differ. This will allow us to identify factors that predispose children to stroke. We will explore the influence of age of the child, the type of heart defect and what happened in the periods during and after heart operations in the subgroup requiring surgery.

Better understanding of factors contributing to stroke in children has the potential to change practice with regard to recognition and management of children with cardiac disease. We expect publication of the findings to contribute to knowledge in this field.



2011 Research Grant Awards

Celebrating over 40 years of funding neurological research

The Bain Foundation's 2011 Research Grant Awards were made possible by:

Alma May George & Helynnne Annette Hoban Estate and Ami Olian Memorial Fund: Parkinson's Disease Award

Rosemary Palmer-Brown Estate: Amyotrophic Lateral Sclerosis Award

Marjorie Grace Lawn and Grace Admans Estates: Corticobasal Syndrome CBS Award

Paul Ainsworth Charitable Foundation: Dystonia Award

Christopher Hanavan Memorial Fund with sponsorship by The Caledonia Foundation: Neuro Vascular Disease Award

Brian Quilty Memorial Fund and Phyllis Edith Chard Estate: Brain Tumours Award

Clarence Verner Ellis and Bill Goodridge Estates and Brain Foundation North West Committee Estate: Paediatric Neurology Award

Michael Rogers Stirling Estate: Epilepsy Awards

Esther Nina Hennessey and Frank & Morphyn Young Estates: Spinal Cord Injury Award

Australian Equity Trustees and Allen & Patricia Coulson Estate: Spinal Cord Injury Award

Decima Strachan Charitable Trust and Edith Sweeney Estate: Traumatic Brain Injury Award

Colin Gordon Munro Estate: Traumatic Brain Injury Award

Rex Banks Estate: Alzheimer's Disease Award

Other Estate, Trusts and Funds Partly funding or accumulating: Gordon & Roy Hutchens Trust; Leslie Keller; Christopher Hollow; Constance Heidenreich; Kathleen Thompson; Edith May; Doreen Shaw; Lennox Smith; Lesley Sperry; Walter Hutcheson; Idelia Mary Jacque; Alice Margaret Jones; Annie Newstead; Gordon Robert Townsend; Allan Kenneth Williams; Linda Turner; Bruce Wall Trust Fund; Thomas McNight; Bruce Wall Trust; Leonard Grant; R W Harvey

Blood circulation in the brain after head injury

Chief Investigator: Dr Judith Bellapart

Co-Investigators: Associate Professor Robert Boots, Professor John Fraser, Professor Marc Maybauer and Dr Stephan Helps

Victims of traumatic brain injury often lose much blood resulting in dangerously low levels of oxygen reaching the brain. Optimal transfusion and subsequent oxygenation of the brain are therefore essential to both survival and successful recovery in these critically ill patients.

Studies have shown that blood transfusion benefits brain oxygenation and that the more anemic the patient, the greater the benefit of a blood transfusion. This implies that those trauma patients, who are at high risk of brain death due to loss of blood supply, would benefit the most from a blood transfusion. Although this is known, an understanding of how the small blood vessels circulate blood during injury and the best procedure for

transfusion in traumatic brain injury has not yet been determined.

The aim of this study is to compare the state of blood circulation between the injured hemisphere and the non-injured hemisphere during different degrees of anemia using an animal sheep model. This model simulates an injury very commonly found amongst head injury patients. Merino sheep will be put under deep anesthesia to avoid any suffering, before applying a humane non-penetrating stunner over the side of the head. This technique has already been used in previous studies and it is currently the accepted method for humane euthanasia of domestic livestock in Australia. Before and at various times after induced head injury, microspheres of different colours will be injected to assess the microcirculation over time. The various colours will help to distinguish changes in microcirculation at different times post injury.

For the analysis of the injury generated within the brain tissue, this study will use immunohistochemistry staining methods which are standard techniques used in all hospital



Prof Noel Dan accepting the award on behalf of Dr Judith Bellapart

laboratories. Finally, the combination of the tissue damage assessment and the circulation assessment will be compared, giving unique information of the microcirculation in brain post trauma, that has never before been reported. The results of this study will be used as the starting point for a series of studies within a PhD, over the next three years.

How do Anti-epileptic Drugs Work?

**Chief Investigator:
Dr Christopher French**

Co-Investigators: Dr Elisa Hill and Mr Zhen Zeng

Epilepsy is a common, immensely disruptive and occasionally fatal disorder affecting about one percent of the population. Drug therapy will prevent seizures in about 70% of patients, but about 30 % remain "refractory" to medication. Despite many years of use, we remain surprisingly ignorant of exactly how anti-epileptic drugs work.

There is therefore both a major deficit in effectiveness of these drugs, as well as a major deficit of knowledge.

Research from our lab has found that some of the most commonly used drugs seem to. This Brain Foundation grant will allow us to pursue these intriguing findings through a combination of electrophysiological, molecular biological and computational experiments with the aim of finding better drugs for epilepsy. It is possible that these findings may also apply to several other classes of drugs including cardiac antiarrhythmics, local anaesthetics and analgesic drugs.



This grant from the Australian Brain foundation will make a major difference to our research.

Electrical activity in a stem cell model of Friedreich Ataxia

Chief Investigator:
Dr Karina Needham

Co-Investigator: Dr Mirella Dottori

Friedreich's Ataxia (FA) is an inherited disorder that results in progressive degeneration of the nervous system and heart. The onset of symptoms of this debilitating condition occur in childhood or adolescence, and include loss of control of muscle movement, muscle wasting, deterioration of hearing, vision and speech, as well as heart disease and diabetes. The cause of this condition is a genetic mutation that leads to a disruption in the normal production of a cellular protein known as frataxin. In FA patients, the low levels of frataxin protein cause iron accumulation in cells leading to cellular toxicity. The cells which are particularly affected in FA include specific nerves within the brain and spinal cord as well as cardiac cells.

In order to develop effective treatments for FA, it would be tremendously useful to

have human diseased cells in culture so that we may be able to understand the disease mechanisms and develop suitable drugs to counteract cell degeneration. To achieve this objective, we recently generated a population of stem cells from skin cells taken from Friedreich Ataxia patients, and showed that these stem cells can become nerves in the culture dish. These nerves exhibit the cellular hallmarks of FA disease. The aim of this project is to now characterize the electrical properties of these nerves using a technique known as patch-clamp electrophysiology. This will allow us to examine how cellular stress in FA influences the communication of these nerves. In addition, we will examine whether increasing the level of frataxin protein in diseased nerves will restore their electrical functional properties. These studies are very important for developing cellular models of Friedreich ataxia to aid the progression of drug discoveries and well as cell replacement therapies.



Combined imaging in the diagnosis of early Corticobasal Syndrome

Chief Investigator:
Associate Professor John O'Sullivan

Co-Investigators:
Dr Andre Troiano, Ms Amy Jones,
Associate Professor Stephen Rose
and Dr David MacFarlane

Corticobasal degeneration (CBD) is an uncommon but devastating neurodegenerative condition. Patients develop progressive problems with movement and cognitive function, typically affecting one side of the body first. Many patients who appear to have the typical clinical features of CBD are found at post mortem to have pathological changes of different diseases such as Parkinson's disease (PD), frontotemporal dementia (FTD) and progressive supranuclear palsy (PSP). Conversely patients with CBD at post mortem may present with clinical features more suggestive of these other diseases. Because of this discrepancy, the clinical features are referred to as corticobasal syndrome (CBS) and CBD is reserved for those who have pathological confirmation. Providing accurate diagnosis and prognosis for patients with early symptoms of CBS is very difficult. Advanced brain imaging techniques

utilizing magnetic resonance imaging (MRI) and positron emission tomography (PET) reveal some differences between these conditions in established cases, but it is unclear if such techniques will help in the early differentiation of these conditions.

In this study, patients with early and inconclusive early features of CBS will be examined in detail and undergo MRI and PET imaging. After 3 years, the patients will be examined again, and with progression of the disease a more definitive clinical diagnosis will be possible. We will then determine whether changes on the original scan were helpful in determining the final diagnosis. We also hope to obtain a final pathological diagnosis in patients after death.

With research suggesting different treatments to help slow the progression of distinct neurodegenerative diseases, it will become critical to more accurately differentiate neurodegenerative diseases as early as possible to appropriately target therapy and to provide a more accurate prognosis. This results of this project will determine whether MRI and PET imaging will be useful in the early diagnosis of these conditions.



Prof Dominic Rowe accepting the award on behalf of Associate Professor John O'Sullivan

2011 Research Grant Awards

Cerebrovascular contributions to dementia

Chief Investigator: Dr Hannah Keage

**Co-Investigators: Dr Mark Kohler
and Dr Owen Churhes**

The Australian population is aging and with this comes increased prevalence and incidence of dementia. The prevalence of dementia in Australia was estimated at around a quarter of a million people in 2009 with late onset Alzheimer's Disease (AD) being the most common dementia. Currently we lack early diagnostic tools, intervention strategies and effective pharmaceutical treatments for late onset AD. We need to understand the underlying biology to address these gaps. This project will assess the functioning of the vascular system within the brain in AD and a prodromal stage, Mild Cognitive Impairment (MCI).

Since AD was first documented over 100 years ago, the majority of research has focused on problems with the structure

and function of brain cells. For example, how the accumulation of amyloid and tau proteins disrupt communication between cells. Little research has assessed how blood flow changes during the AD disease process, or how changes in blood flow contribute to the manifestation of the disorder. This is despite the first documented case of AD including vascular pathology. More recent evidence for a vascular contribution to AD includes reports from autopsy studies (the collection of the brain after death) that vascular pathologies are associated with cognitive impairment in dementia, over and above that related to cellular communication pathologies. Another line of evidence is that vascular conditions in midlife such as hypertension, obesity and diabetes, increase the risk of developing AD in late life.

This study will measure blood flow velocity in major arteries of the brain at rest and during cognitive tasks in groups



Dr Mark Kohler accepting the award on behalf of Dr Hannah Keage

of individuals with AD and MCI along with healthy aging controls. The study stands to make a valuable contribution to the biological understanding of AD and MCI. We thank the Brain Foundation for their invaluable support.

Limiting the damage in TBI

Chief Investigator: Dr Peter Crack

This project seeks to investigate a potential therapeutic antibody (MAR-1) that can limit the damage of traumatic brain injury.

Traumatic brain injury (TBI) represents the major cause of death in young individuals in industrialised countries. Despite the improvement of neurosurgical procedures as well as critical care management, morbidity and mortality are still high. Furthermore, approximately 25% of these patients remain with permanent disabilities with a high familial, social and economic burden for society. Over the past decade it has become clear that the central nervous system (CNS) can exhibit features of inflammation in response to TBI. TBI triggers acute inflammation, which exacerbates primary brain damage. It is important that ways are found to control this neuroinflammation as controlling the neuroinflammation will limit the damage the brain suffers after TBI.

In our laboratory we have been researching the effect of the interferon signaling system and neural injury. Interferon is a molecule that is released after an inflammatory event. It can be either beneficial or detrimental – depending on the stimulus that initiates its release. Our research into stroke has found that interferon plays a critical role in regulating neural injury and that mice that lack the receptor for interferon are protected

from neural injury induced from stroke. We have generated preliminary data that shows that these mice are also protected after TBI (Figure 1). We have also used a monoclonal antibody (called MAR-1) that blocks the interferon receptor and found that treating mice with this antibody reduces the damage seen after stroke (Figure 2). However a therapy can only be successful in TBI if it is applied after the initiation of injury. In a major advance we find that application of MAR-1 30 minutes after TBI leads to significant neuroprotection.

We feel that TBI represents an area where the MAR-1 therapeutic antibody can have a dramatic effect. Over 90% of all TBIs occur in areas where there is a rapid response from the ambulance service. This response is under 30 minutes in almost all reported cases of TBI. This means that there is a great opportunity to therapeutically intervene with a drug within a critical time window. The MAR-1 antibody is currently in third phase clinical trials for immune disorders so it has passed the clinical testing hurdles for safety. All that is needed is evidence that it can be valuable in treating TBI. Our data using it in a mouse model of stroke suggests that this is highly likely.

What we are proposing to do is test the neuroprotective ability of the MAR-1 antibody in a mouse model of TBI. Wild-type mice will be administered MAR-1 intravenously 30 minutes before the initiation of TBI surgery to



address the optimum dosage required eliciting neuroprotection. A dose response curve will be constructed comprising 0.1, 0.25, 0.5 and 1mg of MAR1. Initial infarct assessment will be carried out at 24 and 48hrs as described in aim 1. A crucial question in the search for a viable therapeutic in trauma is therapeutic window. Once the optimum concentration of MAR1 is defined, this concentration (and the next largest) will then be given to wild-type mice 0, 2 hours after the initiation of TBI and the brain damage assessed at 24 hours.

If successful this study will be the first of its kind to show that a monoclonal antibody that blocks interferon signaling can be a serious potential therapeutic for the treatment of traumatic brain injury.

Utilising plasticity of the neural axis to improve functional recovery after spinal cord injury

Chief Investigator: Dr Michael Lee

Co-investigator: Dr Cindy Lin

Spinal cord injury (SCI) is a catastrophic event which results in severe sensory, motor and autonomic impairment at and below the level of the injury. Given that muscle weakness is a common sequel of SCI and a major cause of poor functional recovery, therapies that improve muscle strength is justified and essential.

Recent studies from our laboratory have demonstrated profound peripheral nerve excitability changes after traumatic SCI. Changes in peripheral nerve function was

evident within one week of cord injury and the overall excitability changes were similar to in-vivo recordings from healthy nerves subjected to limb ischemia, an intervention known to impair function of the Na⁺/K⁺ pump. These recent studies provided new evidence that peripheral nerve function is affected by traumatic spinal cord injury. Therefore, it is possible that some motor impairment after the initial trauma to the spinal cord maybe secondary to peripheral nerve dysfunction superimposed on disconnection of lower motor neurons from upper motor neurons. The project funded by the Brain Foundation will specifically investigate the neuroprotective benefits of short-term electrical nerve



stimulation and resistance training on peripheral nerve function, plasticity and patient outcome post spinal cord injury. This research project will increase our understanding of the mechanisms and rehabilitation of spinal cord injury and will have major clinical implications for the management and rehabilitation of spinal cord injury.

Molecular imaging in brain AVMs

**Chief Investigator:
Dr Thi Thuy Hong Duong**

**Co-Investigator:
Professor Marcus Stoodley**

Arteriovenous malformations (AVMs) are congenital vascular anomalies of the brain that consist of complex connections between arteries and veins that lack the intervening capillary bed. They form a tangled collection of abnormal arteries and veins, known as the nidus of the AVM.

Gamma Knife Radiosurgery (GKS) is a current treatment option for people who have a brain AVM. However, has a failure rate of 20 – 30% and a delay to vessel occlusion of up to 2 – 3 years. Over 20,000 Australians are affected

by brain AVMs and over 90% of large lesions are either untreatable, or treatable only with unacceptably high risk.

This project utilises in vivo imaging to study the changes of endothelial membrane proteins of brain arteriovenous malformations (AVMs) in response to GKS, and identification of molecular targets localisation and level of expression to further enhance the development of a vascular targeting strategy to induce thrombosis in an animal model of human brain AVM. Our general hypothesis is that GKS can be used to alter AVM endothelium cell surface characteristics. Assessing these changes using in vivo imaging approach will enable our project to identify potential vascular targets to be used in order to promote thrombosis rapidly and specifically in AVM vessels.



The overall aim of this project is to develop a new treatment for brain arteriovenous malformations (AVMs) that is safer and more effective than the current methods of surgery and radiosurgery, using biological methods to promote intravascular thrombosis after radiosurgery.

Cortical hyperexcitability and ALS

**Chief Investigator: Associate Professor
Ostoja (Steve) Vucic**

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disorder of motor neurons in the spinal cord, brainstem, and motor cortex, for which there is no cure. In Australia, the prevalence of ALS is 4-6 per 100 000, with median survival of 3-5 years and one Australian dying from ALS every day. ALS results in rapid development of physical disability, thereby negatively impacting on quality of life, and placing tremendous strain on carers, families and the health care system. Unfortunately, very little is known about the underlying causes of ALS, in particular the site of disease onset. Such information would of course be of immense diagnostic and therapeutic significance, as for example, if stem cell therapy is shown to be effective,

then knowledge of where the disease begins will be crucial in directing the site of stem cell infusion. Currently, there is debate as to whether ALS begins centrally, namely in the brain, peripherally, in the muscles and nerves, or whether it is multifocal. Recent studies have suggested that ALS begins within the brain and that brain overactivity, also called cortical hyperexcitability, is linked to nerve loss. However, this issue has not been fully resolved with some arguing that such changes in brain overactivity represent cortical plasticity. As such, the current project aims to determine the site of ALS onset, and in particular whether brain overactivity or hyperexcitability, underlies the development of ALS, by combining novel threshold tracking transcranial magnetic stimulation (TMS) techniques for assessing cortical excitability, together with MRI and sensitive neurophysiological techniques for assessing peripheral nerve loss. It is



envisaged that this project will provide more conclusive evidence as to whether cortical hyperexcitability precedes the onset of lower motor neuron degeneration, and thereby confirm a central origin of ALS.

2011 Research Grant Awards

The long term experience of people with a new diagnosis of epilepsy

Chief Investigator: Dr Patrick Carney

**Co-Investigators: Dr Anne McIntosh,
Professor Samuel Berkovic,
Professor Terrence O'Brien,
Dr Mark Newton**

Epilepsy is a condition in which people experience recurrent seizures. The experience of seizures can have a significant impact on people both personally and professionally. Seizures may even lead to serious injury or death. The treatment of epilepsy requires the use of medications which can have significant side effects which further impact on people's life style. Epilepsy is a common condition affecting as many as 4 in 100 Australians. Twice as many Australians will have a single seizure but do not go on to develop epilepsy. Epilepsy can occur at any age and the experience of a first seizure is frightening and leads to uncertainty and fear about

the future and the risk of repeated seizures. Unfortunately the information we have to advise people about the likely outcome after a first seizure is limited as rigorous studies following large groups of patients have not been performed. At the Austin hospital we established the idea of a rapid access clinic to support the needs of patients with a new onset seizure in 1994. This clinic facilitates rapid diagnosis and management by a neurologist with expertise in epilepsy. A similar clinic has also been running at the Royal Melbourne Hospital (RMH) since 2001. A prospective database of all patients who have attended these clinics has been maintained. Using this information we are in a unique position to study the long term outcome of patients with their first ever seizure. We are able to classify patients at the time of their first presentation to clinic and then re-contact them to find out whether they have had subsequent seizures, whether they are requiring medications for treatment



and what complications they have had associated with their treatment. We believe this comprehensive assessment of over 4000 patients will provide the most thorough and informative study into the implications of a new diagnosis of epilepsy.

Vascular Biomarkers in Brain Cancer

Chief Investigator: Dr Iwan Bennett

**Co-Investigators:
Associate Professor Christopher
Hovens and Dr Andrew Morokoff**

It has become apparent that despite identical appearances under the microscope, braincancers designated as glioblastoma multiforme (GBMs) may have greatly varied clinicalcourses & responses to treatment. One recent example comes from a well-known study coined the Stupp trial, which identified a subgroup of GBM patients with significantly improved long-term survival despite identical diagnosis & therapy. A surrogate marker, MGMT-promotor methylation status, was found to be the strongest predictor of benefit from this therapy.

Surrogate markers of tumour vascularity are also likely to be useful in GBM. Not only is glioblastoma amongst the most vascular tumours known, but the progression & growth of these aggressive tumours is reliant on their ability to obtain & maintain an adequate bloodsupply. In fact, this is the rationale behind the introduction of some newer chemotherapy medications used in the treatment of GBM which target tumour blood vessel formation, a process called neovascularisation.

Vascular biomarkers are also expected to be of significant clinical value rather than

solely a research tool. Circulating cells involved in neovascularisation such as vascular endothelial cells & endothelial progenitor cells can be procured from blood tests. AdvancedMRI techniques have been developed which have been shown to correlate with tumour vascularity, & can be added to routine patient scans without significant addition to time & resources. As such, vascular biomarkers can be made easily available to treating doctors, at multiple time-points & in a relatively non-invasive fashion.

To determine the usefulness of these surrogate markers in GBM, the Vascular Biomarkers in Malignant Glioma project was initiated at the University of Melbourne via its Department of Surgery, & in close collaboration with the Neurosurgical Units of the Royal Melbourne Hospital & the Melbourne Private Hospital. Nineteen patients were enrolled into a pilot study assessing the pre- & post-operative levels of circulating endothelial cells in GBM patients. This study demonstrated that these cells could be reliably identified from peripheral blood samples, & that levels in GBM patients were elevated compared to normal subjects. A consistent post-operative decrease in circulating cell numbers was also uncovered.

With the aid of generous sponsors such as the Brain Foundation we have been able to continue this important research. Using research-specific software, pre- &



post-operativeMRI scans from pilot-study patients have been analysed & included in a submission for publication. New computing techniques have also been developed for the analysis of perfusion MRI scans, & analysis of the available data in pilot-study patients is being prepared for publication. These techniques will then be applied to a retrospective review of a 2-year database of glioblastoma patients imaged with perfusion MRI at the Royal Melbourne Hospital.

Ethics approval has also been obtained for the further enrollment of GBM patients into the Vascular Biomarkers in Malignant Glioma project. As with the initial pilot study, their pre- & post-operative blood test & MRI scan data are being recorded. This entire cohort of patients will be closely followed, & follow-up blood test & MRI scan data obtained to identify any significant correlates with ongoing treatment & disease progression. This 2 year project is expected to reach conclusion in early 2013.

Delivery of BDNF to motor neurons to promote axonal regeneration and recovery of motor function

Chief Investigator: Dr Renée Morris

Co-Investigators: Associate Professor Matthias Klugmann and Professor Ian Q. Whishaw

In Australia, 10,000 people are living with spinal cord injury, with health costs estimated to be \$ 2 billion dollars per year. Over recent decades, significant research efforts have been deployed to find ways to promote axonal regeneration. More recently, scientists have gathered evidence that BDNF, a protein that is essential for the maintenance of axonal connections, can promote growth and repair after a spinal cord injury. In the laboratory rat, for instance, it has been shown that cell implants that secrete BDNF, if placed in the injured spinal cord, can trigger axonal elongation. Unfortunately however, injured axons tend to dwell in the BDNF-secreting implants rather than to elongate enough to reconnect with motor neurons, a process that is essential for the recovery of motor

function. What stops the elongating axons from leaving the BDNF-rich implant? One may speculate that BDNF-secreting implants provide such an ideal environment for the injured axons that they prefer to stay within the implants' boundaries rather than to seek out for their lost motor neurons.

This research project seeks to overcome the limitations associated with BDNF-secreting cell implants. We propose to lure injured axons towards motor neurons. With the use of a deactivated virus, BDNF gradients will be created along the injured axons path. Injured axons will have to elongate to reach the first source of BDNF. They will need to elongate even more to get to the next source of BDNF, and so on and so forth, hence bringing them each time closer to their lost targets. This innovative gene therapy scenario, by encouraging axons to elongate enough to possibly reconnect with motor neurons, has the potential to overcome the poor outcomes obtained so far with static implants of genetically engineered cells,



therefore bringing gene therapy a step closer for human spinal cord injury.

Posterior subthalamic area deep brain stimulation for Parkinson's Disease

**Chief Investigator:
Professor Christopher Lind**

**Co-Investigators: Dr Rick Stell,
Associate Professor Sergio
Starkstein and Associate Professor
Jacqueline Alderson**

Deep Brain Stimulation of the subthalamic region is an effective treatment for advanced Parkinson's Disease but the exact best part of this area to stimulate is uncertain. Our group's early trial-based experience of stimulating a very specific part of this region, the posterior subthalamic area, has shown great promise at maximising beneficial effects while minimising side effects of the treatment.

Our group has been studying the posterior subthalamic region now for several years. We have shown excellent clinical results with few side effects in a group of people with Parkinson's disease. What we need to do now is measure the effects of stimulation of the region millimetre by millimetre. We can

so this by turning one of four electrodes on or off for a period of 6 months and then switching over to other settings for the following 6 months. At the end of each period we have detailed testing we can do with the individual to measure the control of Parkinson's disease. By temporarily hiding which electrode is being stimulated from both the investigators and participants and then revealing this at the end of the study we can work out which electrode contacts give the best results.

Subsequently to prove that one position is better than another position there needs to be a large scale multi-centre study but such a study will need to be based on data such as that which we are collecting now. In other words, we need to estimate the difference of effect between the two stimulation sites to know how many individuals would need to go into a multi-centre trial.

The important components of the funding of this application are for a research assistant who can change the stimulator settings and liaise with participants to organise the day to day running of the



study and also a PhD student working under supervision who can collect the detailed movement analysis data. This will then need specialist analysis supervised by the biomechanist in our study, Assoc Prof Alderson.

One exciting thing is that a study of this type in this part of the brain has not been performed anywhere to date and Australia will be the first.

Fundraising

Christmas came early to Tamworth

Our wonderful committee members in Tamworth know how to put on a great event, and this year was no different. The annual Christmas Fair on Saturday 19th November, was a crowd pleaser with something for everyone. Held at the Tamworth Race Course, there were market stalls and great entertainment. Many thanks to the committee headed by the indefatigable Pip Warner. The hard work from this committee is responsible for donating many thousands of dollars to brain research since the Christmas Fairs began.



Pictured enjoying the fair are organiser, Pip Warner, Gerald Edmunds and Brain Foundation Director, Val Gibson.

Fundraising for the Brain Foundation

Would you like to Fundraise for the Brain Foundation?

We welcome anyone who would like to raise funds for us. You are welcome to ring our office anytime Monday to Thursday or e mail us and we would be happy to support you in anyway we can. Alternatively, you may like to investigate one of the online fundraising sites that make it very easy for you:

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We look forward to hearing from you! Phone: Sydney (02) 9437 5967
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In Memoriam

The Brain Foundation would like to extend our very sincere thanks to the families of the following who supported us in a time of great sadness and loss.

Warren MILTON
David BARBERA
Frank MOORE
Alfred MELLOR
Pauline HOLLAND
Rhonda BIGNELL EDMUNDS
Christopher HANAVAN
Darryl WISEMAN
Ken JONES
Robyn RABBITT
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