BRAINwaves

The Newsletter of the Brain Foundation Summer 2007-2008

2007 RESEARCH GRANT AWARDS

The highlight of the Brain Foundation's year is the occasion when research awards are formally presented. This edition of Brainwaves is providing a showcase for the successful individuals and their projects **because this is why we ask you to donate**. These projects were selected from a competitive national pool based on the potential of each one to make a difference and advance treatment of sufferers in the areas under investigation.

This year the Awards were presented in The Great Hall at Sydney University by the Governor of NSW, Her Excellency Professor Marie Bashir AC CVO. The evening had a resounding opening with a recital by renowned International Concert Pianist, Ambre Hammond. She has kindly nominated the Brain Foundation as a Charity that she supports in her promotional material. Disks of her performances are available through this office and Ambre generously shares the proceeds with the Brain Foundation.

The total amount provided to research this year by the Foundation's State Branches and Committees was over $400,000 including a special, three year Doctoral Scholarship in Parkinson's Disease.

An integral part of the Awards process is the National Scientific Advisory Committee. The members show great dedication to helping select the applications with the greatest potential to advance understanding and techniques in neurosurgery, neurology and neuroscience. The committee had to evaluate a record 115 applications this year and deserve appreciation and special thanks for their voluntary efforts. The members of the committee are:

- Professor Nicholas Dorsch, Sydney,
- Associate Professor Richard Gerraty, Melbourne
- Professor Michael Halmagyi – Convenor, Sydney
- Professor Pamela McCombe, Brisbane
- Professor John O Willoughby, Adelaide
- Associate Professor Stephen Robinson, Melbourne
- Professor Elsdon Storey, Melbourne.

It is also important to note that these Awards are only possible because of the funds that you, our readers, generously donate and the support of our corporate sponsors.

AWARD WINNERS AND PROJECTS

Professor Philip M Beart, Brain Injury & Repair, Howard Florey Institute, University of Melbourne.

Co-Investigators: Dr Julie Atkin and Dr Ross O'Shea

A new hypothesis of Motoneuron Disease: astrocytes are the non-neuronal neighbours inducing motoneuron injury.

Her Excellency Professor Marie Bashir AC CVO & Professor Philip Beart

Motor Neurone Disease is a neurodegenerative condition, progressing to paralysis in 1-5 years, and killing 100,000 every year world-wide. We seek to understand its pathogenesis by investigating the underlying mechanisms, which involve different neighbouring cells contributing to the injury of motoneurons. Ongoing work from our laboratory reveals that a population of glial cells, astrocytes, which are intimately associated with motoneurons, profoundly affect their function and existence. We believe that changes to the chemistry and shape of astrocytes initiate a neurotoxic milieu, and that dissection of their roles will provide new clues for management of Motor Neurone Disease.

Dr Ostoja (Steve) Vucic, Conjoint Senior Lecturer, University of Sydney, Department of Neurology, Westmead Hospital.

Co-Investigators: Associate Professor Matthew C Kiernan.

Pathophysiological processes underlying familial Motor Neuron Disease.

To determine the pathophysiological processes underlying neurodegeneration in familial motor neuron disease and thereby

Her Excellency Professor Marie Bashir AC CVO & Dr Ostoja (Steve) Vucic

determine the site of origin and subsequent patterns of neuronal death in familial motor neuron disease. Advancing earlier studies that have explored the basis for neurological symptoms in sporadic motor neuron disease. This may result in the development of a sensitive diagnostic test for upper motor neuron involvement in motor neuron disease, thereby resulting in early diagnosis.

Providing new knowledge about the pathogenesis of motor neuron disease, potentially impacting on the future management of motor neuron disease patients. This may lead to the development of a new monitoring tool to assess the efficacy of future therapies in motor neuron disease patients.

Dr Cathryn Louise Haigh, Senior Research Officer, Department of Pathology, University of Melbourne.

Co-Investigators: Associate Professor Steven Collins, Dr Victoria Lawson, Ms Victoria Lewis (PhD Student)

Early oxiodative changes in live cells following infection with the neurodegenerative disease associated prion protein.

Brooke Lumicisi, Jeremy Welton, Cathryn Haigh, Steven Collins, Victoria Lewis & Marcus Brazier.

Prion diseases are a group of degenerative brain diseases affecting both humans and animals. The disease can be hereditary, with human examples including Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia, and some cases of Creutzfeldt Jakob disease (CJD); sporadic (accounting for most CJD cases); or caused by infection with the transmissible prion agent from sources such as infected foodstuffs or contaminated blood products. Variant CJD is an example of the last category as it is now widely associated with eating beef prepared from cattle with bovine spongiform encephalopathy (BSE). The prion agent is an abnormal form of the cellular prion protein. The role of the prion protein is as yet unknown but an increasing body of work has linked it with reactive oxygen species (ROS). ROS are often byproducts of normal cellular metabolism, but can be toxic to cells if not efficiently removed. Evidence for aberrant levels of ROS in terminal prion disease is convincing. However credible data supporting the role of ROS in pre and early disease has previously been lacking.

Our research has focused on these early events using a cell based model of prion infection. By means of microtitre plate based assays, we have measured a rapid and pronounced increase in ROS in cell populations during the initial phase of prion infection. We now wish to extend these findings to look at individual living cells from seconds to hours to days post inoculation with preparations of infectious prions. The Brain Foundation research grant has provided us with the funding needed to purchase a fluorescence microscope. This will allow the monitoring of fluorescent ROS probes inside single cells with the aim of visualizing the specific location within the cell where the early change in ROS levels occurs and to determine whether this is a cause or effect of disease initiation. Ultimately, an understanding of the earliest events in disease establishment will help us find effective treatments and develop prophylactic regimes.

Dr Janetta G Culvenor, Department of Pathology and Centre for Neuroscience, The University of Melbourne.

Co-Investigators: Associate Professor Heung-Chin Cheng, Dr Terrence D Mulhern, Dr Nicholas A Williamson

Deciphering the biochemical properties of parkinson's disease-associated leucine-rich repeat kinase 2.

This project will investigate biochemical features of the kinase domain of the Leucine-rich repeat kinase 2 (LRRK2). LRRK2 is a large complex brain protein (2527 amino acids) encoded by the gene most frequently mutated in genetically inherited autosomal dominant Parkinson's disease (Paisan-Ruiz et al. 2004). Very little is known about the cellular function of this recently identified key protein. Phosphorylation of molecules acts as a switch to turn many enzymes on or off. Thus LRRK2 as a kinase (phosphorylating enzyme) can regulate the function

or activity of other proteins. LRRK2 can also phosphorylate itself and thereby regulate its own activity in response to various stimuli thus the autophosphorylation is very important as it may cause a change in the activity of LRRK2 and eventually affect a large number of downstream events. We are currently studying recombinant LRRK2 regions by expression and purification in insect cell culture as utilised also for the study of the Parkinson's associated PINK1 kinase. We have established that purified truncated recombinant LRRK2 kinase enzyme can phosphorylate the artificial substrate, myelin basic protein and that our purified LRRK2 shows strong autophosphorylation. We have demonstrated that artificial substrate and autophosphorylation is enhanced by the most common Parkinson's disease mutation G2019S.

We hypothesize that: LRRK2 exerts its Parkinson's pathogenic effect by phosphorylation of a critical protein which increases neuronal cell death and that autophosphorylation activates LRRK2 and enhances its pathogenic effect.

In this project the major aim is: To identify the autophosphorylation site for LRRK2, analyse how autophosphorylation modulates LRRK2 kinase activity, and generate a phosphospecific antibody for detection and monitoring of the phosphorylation and activation status of LRRK2 in cells and samples from Parkinson's disease patients.

Once the autophosphorylation site is identified, we will perform site-directed mutagenesis to mutate the site to alanine. The kinase activity of the mutant and the autophosphorylated wild type enzyme will be compared. The study will reveal how autophosphorylation modulates LRRK2 kinase activity and the LRRK2 protein's interaction in known biochemical pathways causing Parkinson's Disease.

Dr Janetta Culvenor, Her Excellency Professor Marie Bashir AC CVO & Associate Professor Heung-Chin Cheng

Associate Professor Chris Levi, Department of Neurology, John Hunter Hospital.

Co-Investigators: Dr Mark Parsons, Dr Neil Spratt.

A randomised controlled trial of mild hypothermia in acute ischaemic stroke.

Her Excellency Professor Marie Bashir AC CVO & Associate Professor Chris Levi

Brain injury from stroke is one of the leading causes of long term disability in Australia. Strategies to protect the integrity and function of the brain have been a major focus of stroke research over the past two decades, however, despite numerous pharmacotherapeutic agents showing promise in animal models of brain ischaemia, none have translated into an effective therapy in human stroke. The likely reasons for failure of translation are numerous, however, among these are concerns about limited potency related to narrow therapeutic targeting of single pathways within the complex process of the biochemical ischaemic cascade.

Hypothermia is one of the most potent neuroprotectants in experimental stroke models and has been proven beneficial in human global brain ischaemic following cardiac arrest. Cooling results in attenuation of multiple potentially deleterious pathways in the ischaemic brain and can be considered a "multimodal" neuroprotectant.

The Stroke Research Program within the Centre for Brain & Mental Health Research, Hunter Medical Research Institute (HMRI) has conducted a successful pilot feasibility study in acute stroke patients using the technique of intravascular cooling. Intravascular cooling catheters are placed in the inferior vena cava producing cooling of the circulating blood and thereby brain cooling via a heat transfer mechanism. The technique can be deployed in the awake patient and in the acute stroke unit setting.

The group now plan a phase 2 randomised trial of intravascular cooling assessing the safety of the technique and the potential for the technique to reduce the amount of brain tissue progressing to infarction using advanced CT imaging techniques. The researchers anticipate completion of this phase of the work in two years and if positive, proceeding to larger scale trials examining clinical benefit of hypothermic therapy.

Dr Russell C Dale & Her Excellency Professor Marie Bashir AC CVO

Dr Russell C Dale, Senior Lecturer, Senior Research Fellow and Consultant Paediatric Neurologist, Academic Department of Child Health, Westmead Hospital.

Co-Investigator: Dr Fabienne Brilot.

Brain demyelination in Children: Development of a novel autoantibody method to detect antibodies against cell surface proteins.

Brain Demyelination is an important cause of morbidity in adults and children. In adults, a first episode of demyelination frequently represents the onset of a chronic relapsing demyelinating disease such as multiple sclerosis (MS). In young children however, monophasic brain demyelination is common (named acute disseminated encephalomyelitis-ADEM). Patients with ADEM usually have sudden onset post-infectious brain disease with encephalopathy, and respond quickly to steroid therapy.

ADEM patients rarely progress to MS. Alternatively, children can suffer a 'clinically isolated syndrome' (CIS) without encephalopathy and have a higher incidence of progression to multiple sclerosis. Although the white matter is predominantly involved in ADEM lesions, the cortical grey and deep grey matter is also frequently involved. It is hypothesised that different ADEM phenotypes have differing immune mechanisms, and therefore may require different treatment approaches. For example, some patients fail to respond to steroid therapy and require intravenous immunoglobulin.

Most investigators agree that acute onset demyelination is secondary to immune-mediated mechanisms. The immunology of multiple sclerosis has been extensively investigated, and involves both cellular and humoural (antibody) mechanisms. Despite ADEM being an excellent opportunity to investigate hyperacute demyelination, there has been little investigation of ADEM to date.

I have recently been part of a multi-centre study that found children with ADEM (but not MS) had autoantibodies against myelin oligodendrocyte glycoprotein (MOG). This study was important because they used a technique that maintained MOG in its natural conformational state, as exists in vivo. In other human autoimmune diseases, it is well established that autoantibodies recognise conformational epitopes of self antigens (such as acetylcholine receptor in myasthenia gravis).

Autoantibody assays are vulnerable to methodological variables. If the candidate protein is significantly altered or unfolded (such as in Western blotting), the antibody assay is unlikely to represent a 'physiological' system. We will develop a more physiological model using neuronal cells that express cell surface proteins with normal conformation and structure.

We aim to develop an antibody technique to measure autoantibodies against cell surface proteins using a 'physiological' cell system. Specifically we will use different cell lines to compare brain regions: oligodendrocyte-like, neuronal or astrocyte. We aim to compare the presence of these autoantibodies in ADEM patients with CIS and MS. We will semi-quantify these findings using FACS (fluorescent automated cell sorting). If this pilot data yields positive information, we will test specific protein hypotheses using transfected cell lines.

Dr David Ziegler, Children's Cancer Institute, Australia and Sydney Children's Hospital, Randwick.

Co-Investigators: Professor Michelle Haber,

Targeting Apoptotic Pathways in Medullobastomas

Our primary aim is to develop new targeted therapies to improve the outcome for children with medulloblastomas. We seek to achieve this by investigating agents that target the apoptotic pathway in medulloblastoma cells. Our hypothesis is that by rationally combining pro-apoptotic agents with other treatment modalities, including other targeted therapies or

Her Excellency Professor Marie Bashir AC CVO & Dr David Ziegler

standard-of-care cytotoxic therapies, it will be possible to overcome chemo- and radio-resistance, increase tumour treatment responses, decrease toxicities, and ultimately improve patient outcomes. Our aim is to evaluate these combinatorial strategies in vitro and in vivo and rapidly translate the most favorable therapeutic combinations to clinical trial.

New therapies for medulloblastomas are urgently needed. Medulloblastomas remain the most common malignant brain tumour of childhood, accounting for 20% of all primary paediatric CNS tumours. Whilst in recent years the survival rates for many patients have improved, the outcomes for infants and those with metastatic or high-risk tumours remains poor. Furthermore, current treatment regimens are highly toxic and often lead to devastating late effects. Targeting the apoptotic pathways in medulloblastomas offers a unique opportunity to develop novel therapeutic strategies that overcome tumour resistance, reduce the toxicity of conventional therapies and ultimately improve patient outcomes.

Apoptosis is the specific, ubiquitous mechanism by which cells undergo a programmed and highly regulated death. Activation of the apoptosis pathway is also a key mechanism by which cytotoxic drugs and radiation kill tumor cells. Overexpression of anti-apoptotic molecules in malignant cells has been shown to confer them with resistance to radiotherapy and chemotherapy and contribute to cancer progression.

In the second specific aim, we plan to investigate the potential synergy of the Inhibitor of Apoptosis Proteins (IAP) in conjunction with standard cytotoxic therapies. Our hypothesis is that overcoming the anti-apoptotic effect of IAPs may lead to the same synergistic effect as seen with targeted therapies, and thereby facilitate a reduction in the dose intensity and the subsequent morbidity and mortality incurred with current treatment modalities, particularly radiation therapy. Our laboratory expertise in apoptosis, and translational research, our successful studies with malignant gliomas, as well as our access to small molecule IAP inhibitors in late development, offer a unique opportunity to identify effective novel treatment strategies that can rapidly be translated to the clinic.

Her Excellency Professor Marie Bashir AC CVO & Dr Geoffrey A Lambert

Dr Geoffrey A Lambert, Department of Neurology, Division of Medicine, University of NSW

Investigating the cause of migraine.

In this project we hope to discover the cause of migraine headache. Many "triggers" lead to migraine, but we do not know how. We believe the triggers produce a defect in pain control by the brainstem, which normally keeps sensation from the head below the pain threshold. In migraine, trigger factors originating in the cortex open this "pain control gate", producing a migraine headache. If we can prove this, we can develop therapies that will prevent migraine before it starts.

Dr Gabrielle Todd

Dr Gabrielle Todd, Discipline of Physiology, School of Molecular and Biomedical Science, University of Adelaide.

Co-Investigators: Professor Timothy S Miles and Associate Professor Michael A Nordstrom

Tremor and Human Motor Cortex

The aim of this research project is to investigate the role of human motor cortex in normal physiological tremor and in a pathological condition known as 'essential tremor'. In addition, we will investigate the role of normal physiological tremor during movement. This research will enhance our understanding of the mechanisms that contribute to physiological tremor and may provide the basis for developing interventions to improve the rehabilitation of patients with essential tremor. Essential tremor has a debilitating effect on activities of daily living and is one of the most common neurological disorders among adults affecting ~ 4% of individuals over the age of 40 years. Approximately 60% of sufferers are unemployed due to disabling shaking.

Tremor is characterised by involuntary rapid and repetitive back-and-forth movement of a body part. The phenomenon is found in healthy individuals and can also appear as a pathological symptom. From as early as 1886, electrophysiological investigations have shown that voluntary muscle contractions are accompanied by an 8-12 Hz physiological tremor. Since then, tremor has been studied under numerous conditions. This has prompted the subdivision of physiological tremor into six categories: resting tremor, action tremor, postural tremor, tremor in isometric contractions, tremor in compliant contractions, and higher amplitude tremors.

The origin of physiological tremor has been hotly debated over the past century. Five sources are thought to contribute to physiological tremor. These include motor unit discharge properties (motor units commence firing at 8-10 Hz), synchronised motor unit discharge (the discharge of different motor units can become synchronised so that they tend to fire together at a particular rhythm), mechanical resonance (the

natural frequency at which a body part vibrates as the result of its intrinsic mechanical properties), activity in the muscle stretch reflex pathway, and central oscillations in brain activity. The six categories of physiological tremor involve a different contribution from central and peripheral mechanisms.

Pathological tremors can also arise through a variety of mechanisms. Pathological tremors are usually categorised on the basis of the frequency of tremor. Parkinsonian tremor and cerebellar kinetic tremor occur at a frequency of 3-6 Hz whereas essential tremor and enhanced physiological tremor occur at 6-12 Hz. Essential tremor is characterised by an abnormally large action tremor and postural tremor that leads to tremor-related disability. The incidence of essential tremor increases with age and population studies show that ~75-90% of essential tremor sufferers are undiagnosed and untreated. Little is known about the pathophysiology of essential tremor although abnormal activation of the midbrain, cerebellum, and peripheral reflex loop has been proposed. There is no cure for essential tremor and pharmacological treatments are only effective in some patients. In the current project, we will investigate the role of human motor cortex in the generation of action tremor in healthy individuals and patients with essential tremor.

The current project involves two studies. In the first study, we will determine whether the human motor cortex is involved in the generation of action tremor and whether action tremor plays an important role in learning new motor skills in healthy individuals. In the second study, we will extend our investigation to determine the role of human motor cortex in essential tremor.

Tulip Foundation Doctoral Scholarship Award

Miss Danni Cheng, Prince of Wales Medical Research Institute, Randwick.

Transcriptional regulation of the Parkinson's Disease protein α-synuclein.

This project was selected because it is seen to have the potential to reveal a major novel pathway regulating α-synuclein levels in the brain. It is very clear that important advances in the understanding of the causes and therefore potential treatment options for the neurodegeneration associated with Parkinson's disease can be made once the mechanism of α-synuclein can be revealed. Danni's PhD research will directly address this crucial issue.

Miss Danni Cheng & Her Excellency Professor Marie Bashir AC CVO

IN MEMORIAM

The President, Directors and Staff pass on their condolences and gratefully acknowledge gifts in memory of the following since the last Brainwaves Newsletter.

Kath Howick
Peter Whelan
Klaus Dieter Nauendorf
Joyce Parker (nee Jarrett)
Megan Lloyd
Stan O'Brien
Sheila Cammidge
Thomas Wolfe
Neville Churchill
Veronica Brogan

We continue to revere the memory of those for whom gifts have already been made and especially those who kindly made bequests to the Brain Foundation. If you are kind enough to consider a bequest to the Brain Foundation, please contact us on 1300 886 660 for a special bequest brochure that shows the format necessary to ensure that your wishes are carried out. Alternatively, a copy of the brochure is available in the bequest section of our website, www.brainaustralia.org.au.

Would you also kindly consider nominating a donation to the Brain Foundation as an additional or preferred tribute for your loved ones? We have personalised forms to facilitate such arrangements.

Other Gifts

The President, Directors and Staff gratefully recognise the celebration and acknowledgement gifts since the last Brainwaves Newsletter:

In Celebration:

- Dr David Rail – donated in celebration of his birthday.

In Acknowledgement:

- Gemma & team @ Next Byte – Broadway;
- Macquarie Bank Foundation; and
- All of our readers who regularly donate, some giving thousands or more and others giving smaller amounts within their means. When asked, these very kind people preferred not to have any further recognition.

FROM THE PRESIDENT - Professor Philip Thompson

It is pleasing to advise that, with your support, the Brain Foundation continues to grow and is able to meet its prime objective to increase the amount available for independent biomedical and neuroscientific research. As noted in the report about this year's Awards, the amount made available this year exceeded $400,000. The Board has set a target to increase that amount by 15% a year so I would be grateful if you could consider how you could increase your level of support to help the Brain Foundation's research programme pursue the goals of achieving earlier diagnosis of neurological disorders so that more effective and efficient treatments can be applied. Ultimately, we aspire to minimise or prevent the onset of such disorders once an early diagnosis is made.

We have also launched an initiative to attract as many as possible of the millions who suffer Chronic Headache and Migraine to enlist on the National Information Base that the Brain Foundation is establishing through its Division, Headache Australia. If you know anyone who is a sufferer, please refer them to the web site to become active in the struggle for better treatment.

I would like to wish all our readers my very best wishes for Christmas and the New Year.

Professor Philip Thompson

HEADACHE AND MIGRAINE

The World Headache Alliance (WHA) presented the 5th WHA Global Convention "Networks for Knowledge" in Stockholm earlier this year. Janssen – Cilag very kindly supported the National Executive Director, Gerald Edmunds' attendance at that conference. It was an opportunity to compare notes with headache organisations from around the world.

Of particular interest was the launch by the World Health Organisation (WHO) of their publication, NEUROLOGICAL DISORDERS – Public Health Challenges. This book is important because it includes and acknowledges Headache and Migraine as significant neurological disorders and, while acknowledging them as nonfatal, incorporating them because the burden can be quantified on the internationally standardised and accepted index called "the disability-adjusted life year". This allows a measure of the reduction in health status caused by these intermittent, chronic disorders.

WHO noted in the chapter dealing with headache disorders that, collectively, headache disorders are amongst the most common disorders of the nervous system, causing a substantial disability in populations throughout the world. The conclusions reached, which follow, clearly point to the task ahead for policymakers and for those organisations such as Headache Australia to provide information to advise the policymakers. The nine specific recommendations are:

1. Headache disorders are common and ubiquitous. They have a neurological basis, but headache does not usually signal serious underlying illness. The huge public health importance of headache disorders arises from the causal association with personal and societal burdens of pain, disability, damaged quality of life and financial cost.

2. Headache disorders have many types and subtypes, but a very small number of them impose almost all of these burdens. They are diagnosed clinically, requiring no special investigations in most of the cases.

3. Although headache disorders can be treated effectively, globally they are not, because health-care systems fail to make treatment available.

4. Management of headache disorders everywhere in the world has low priority, which abjectly fails to match headache related health-care provision and delivery to people's needs.

5. Effective management of headache disorders can be provided in primary care for all but a very small minority of patients. Nurses and pharmacists can complement the delivery of health care by primary care physicians.

6. Good management, at whatever level, requires education of doctors and of people affected by headache disorders. Mismanagement, and over use of medications to treat acute headache, are major risk factors for disease aggravation.

7. Every government should acknowledge the humanitarian arguments for effective health care for headache disorders.

8. Every government should be aware of the financial cost to the country of headache disorders in its population. Costs of illness studies will create awareness of the potential savings that better health care for headache disorders may achieve through mitigated productivity losses.

9. Partnerships between health policy makers, health-care providers and people affected by headache disorders and their advocacy groups may be the best vehicle for determining, and of bringing about, the changes that people with headache need.

Readers will remember that a Survey Form to register on Headache Australia's National Information Base was included with the last Brainwaves. This initiative was of great interest to those at the World Headache Alliance conference and led to an agreement to standardise information collection. Allowing a communication link to be established with those suffering Chronic Headache and Migraine and keeping them informed about the latest developments in treatment and prevention. This will provide a valuable source of information for researchers for more specific research based surveys or studies. It is the first major step to achieve a better result but it requires those affected to come forward so that with sufficient numbers, Headache Australia can help.

PERIPHERAL ISOPRENOID CHANGES IN PARKINSON'S DISEASE

Dr Kay Double, Prince of Wales Medical Research Institute, Sydney

Parkinson's disease is a progressive brain disorder that significantly affects mobility and quality of life. Research evidence from our group, and other research groups, suggests that certain fats (lipids) are changed in Parkinson's disease. We have recently demonstrated a change in the levels of a group of lipids called isoprenoids in brain cells which die in Parkinson's disease. These lipids, the most well known of which is cholesterol, are involved in the pathways resulting in brain cell death in this disorder. This suggests that changes in these lipids may play a causal role in Parkinson's disease. While these lipids appear to be changed in the brain in this disorder it is unclear if these lipid pathways are also altered in the periphery. This project is investigating changes in the concentrations and production pathways of these lipids in blood, and also in cells grown from the nose, collected from Parkinson's disease patients and healthy individuals of the same age. Analysis of blood samples collected to date indicates that blood dolichol levels increase with age. Further, cholesterol levels are lower in Parkinson's disease patients but blood concentrations of dolichol are unchanged in this disorder. Results from this project will assist our understanding of changes which cause particular brain cells to die in Parkinson's disease.

Dr Michael Hayes, Dr Kay Double and Mr Ian Ng

NEW THERAPIES FOR NEUROLOGICAL INJURIES & DISEASES BASED ON NEURAL STEM CELLS

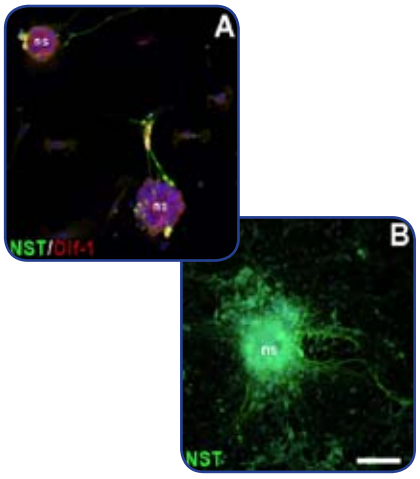
Professor Anne Cunningham

Consultant Neurologist & Director of Research, Sydney Children's Hospital & Professor of Pediatrics, School of Women's and Children's Health, UNSW

Background to the research project: Our experiments had two broad long term goals. Firstly, to develop ways of grafting adult neural stem cells into brain and spinal cord to replace damaged neurones; and secondly, to potentially use this knowledge to activate the dormant repair mechanisms of brain and spinal cord in order to promote self-recovery, i.e., we hope we may be able to teach the nervous system how to self-repair.

A key question was whether the neural stem cells we are studying, which are harvested from the olfactory region, are committed to the olfactory lineage or, alternatively, have the potential to reconstitute neurones of many different phenotypes, e.g. dopaminergic neurones, cerebellar Purkinje cells or spinal motor neurones. In the first phase of this project, we focussed on comparing neural stem cells from the olfactory system to central neural stem cells harvested from subventricular region of forebrain, regarding their growth factor requirements, pluripotentiality and progeny. These experiments indicated that the olfactory neural stem cells appeared committed to becoming cells of the olfactory lineage, under all the conditions tested to date. We have exciting new data about their expression of growth factors and growth factor receptors, which we will now apply experimentally to modify their growth and differentiation. A manuscript based on this work "A pluripotent progenitor cell capable of generating neurospheres isolated from olfactory neuroepithelium" by Wojciech Marlicz and Anne M. Cunningham will be submitted for publication.

Outlook summary: We are optimistic that the outcomes of the basic research described in this project will have relevance to the development of new therapies for brain and spinal cord injury, both traumatic and non-traumatic, and so ultimately benefit patients.



Pictured Right - NEURAL STEM CELLS GROWING AS NEUROSPHERE COLONIES A, Olfactory neurospheres produce neurones committed to the olfactory lineage, distinguished by nuclear Olf-1 expression. Relatively simple neurones are shown emanating from neurospheres (ns) labelled with an antibody to neuron-specific tubulin (NST) (green) and an antibody to Olf-1 (red), an olfactory neurone-specific marker. All nuclei are labelled with DAPI (blue). B, In contrast central neurospheres are relatively massive and generate a complex network of neurones as progeny (green). Nuclei are labelled with DAPI (blue). Scale bar in B, 40μm in A, 80μm in B.

NATIONAL DIRECTORY

National
Gerald Edmunds
National Executive Director
Suite 21 37-44 Alexander Street
Crows Nest, NSW 2065
PO Box 579, Crows Nest NSW 1585
Phone: 1300 886 660
Fax: 02 9437 5978
Email: info@brainaustralia.org.au

Victoria
Associate Professor Stephen Robinson
President, Brain Foundation, Victoria
Phone: 1300 886 660
Email: info@brainaustralia.org.au

South Australia
Lisa Taplin, Executive Director
Phone: 08 8223 3758
Email: brainfdn@tpg.com.au

Tasmania
Connie Diglois, Manager
Phone: 03 6231 4424
Email: connie@brainaustralia.org.au

Other States
Phone: 1300 886 660