PRESS RELEASE

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NEUROLOGICAL FOUNDATION OF NEW ZEALAND
PROGRESS THROUGH RESEARCH

THE NEUROLOGICAL FOUNDATION ANNOUNCES JULY 2016 GRANT ROUND RECIPIENTS

The Neurological Foundation launches its Annual Appeal week with a commitment of over $1.3 million to brain research funding in the July grant round.

The Neurological Foundation is pleased to announce that funding of $1,340,602 for neurological research projects, a clinical research fellowship, a repatriation fellowship and travel grants has been approved in its July 2016 grant round. The Neurological Foundation is the primary non-government sponsor of neurological research in New Zealand, and Annual Appeal week runs from Sunday 3 July through to Saturday 9 July.

Neurological Foundation Executive Director Max Ritchie says "This grant round illustrates the breadth of brain research in New Zealand as it continues to contribute to and progress global knowledge of neurological disorders. Many of the projects in this round involve collaborations of New Zealand's brain research leaders; being able to fund highly innovative research is both gratifying and exciting, and we thank our donors for their continued commitment as we work towards improving outcomes for the hundreds of thousands of people living with neurological disorders in New Zealand. We would be very grateful for additional support from the public during our Annual Appeal week.

In this round, young New Zealand neurologist Dr Jenny Taylor has been awarded the 2016 Neurological Foundation V J Chapman Clinical Research Fellowship to study autoantibodies in autoimmune encephalitis at John Radcliffe Hospital in Oxford. Dr Taylor will return to New Zealand after her research year.

The 2016 Neurological Foundation Repatriation Fellowship will bring neuroscientist Dr Juliette Cheyne home to the University of Auckland to investigate how auditory cortex development affects Autism Spectrum Disorders. Dr Cheyne is currently a postdoctoral fellow at the Netherlands Institute for Neuroscience.

The July grants allocated include the funding of the following projects which will be carried out at the University of Auckland, the University of Otago Christchurch and the University of Otago:

- Epilepsy: A proof-of-principle study of a tailor-made, intranasal anti-convulsant drug carrier system
- Fragile X Syndrome: Developing an authentic research model of Fragile X Syndrome using an innovative New Zealand-developed technology
- Multiple sclerosis: Can a new drug-delivery system specifically target lesions in a model of multiple sclerosis to improve brain function?

Continued over…

- Parkinson's disease: Investigating the role of sub-thalamic nucleus activity in impulsivity in a model using optogenetic technology
- Alzheimer's disease: The investigation of a neuroprotective protein's potential to rescue memory function
- Epilepsy: A laboratory based study to determine reliable methods for examining the effect of cannabidiol in epilepsy
- Brain function: Investigating the mechanisms of proteins in oxidative stress in brain disorders
- Stroke: Investigating a new approach to brain stimulation in a model of stroke to optimise recovery
- Traumatic brain injury: Development of a skin/skull/brain model to measure impact forces to the head and brain-injury mechanisms
- Schizophrenia and ADHD-like hyperactivity: Measuring changes in brain circuitry to increase knowledge of the anatomical basis of schizophrenia and ADHD-like hyperactivity

All grant details follow.

For further information, please contact:

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The Neurological Foundation would like to acknowledge the remarkable support of Mitre 10 staff and customers nationally and record that this year marks a 25-year partnership. Thank you Mitre 10!

Donations to the Neurological Foundation's Annual Appeal can be made at www.brain.org.nz

NEUROLOGICAL FOUNDATION RESEARCH APPROVED JULY 2016

Grants totalling $1,340,602 were approved by the Neurological Foundation Council on 1 July 2016. Educational travel grants were awarded in addition to the below.

NEUROLOGICAL FOUNDATION V J CHAPMAN RESEARCH FELLOWSHIP

The Neurological Foundation V J Chapman Research Fellowship is awarded to a medical graduate committed to a career in neurology, to give him or her the opportunity of spending a period in clinical or biomedical research. This may be combined with advanced clinical training in neurology, but the research component should be at least 50%, and is designed to provide a unique training experience to clinicians with an interest in a career in clinical investigation.

Dr Jennifer Taylor
(Australia New Zealand Association of Neurologists) ANZAN Fellow in Neurology
John Radcliffe Hospital
Oxford University Hospital NHS Trust

$126,314

The Neurological Foundation V J Chapman Research Fellowship will enable Dr Young to undertake this one-year research project under the supervision of Oxford University Hospital Head of Neuroimmunology within the Clinical Neuroimmunology service at John Radcliffe Hospital. This laboratory is an international referral centre for the measurement of antibodies in neurologic disease, and the largest clinical neuroimmunology laboratory in the United Kingdom. Samples from New Zealand are routinely referred to this laboratory.

Dr Young plans to return to New Zealand following her clinical research year and intends to work as a clinical neurologist, and will seek an appointment to a position in Wellington. She is interested in contributing to neurological research in New Zealand during her clinical career.

Detection of known and novel autoantibodies in patients with encephalitis (Optimising early diagnosis of autoimmune encephalitis with sophisticated testing)

Autoimmune encephalitis is a recently discovered complex disease of the central nervous system. Clinicians from multiple medical disciplines are often required for effective diagnosis and treatment because of the complexity of the condition. Detection of specific auto-antibodies in patients through sophisticated testing leads to a swifter diagnosis. Importantly, with rapid diagnosis, autoimmune encephalitis can be treated early with improved outcomes for the patient. This study will compare different methods in antibody detection with the goal of optimising auto-antibody testing. In addition, patients with evidence of autoimmune encephalitis, without an antibody identified, will be tested looking for new antibody targets. This study has the potential to improve clinicians' ability to diagnose patients with this severe but treatable disease.

NEUROLOGICAL FOUNDATION REPATRIATION FELLOWSHIP

Repatriation Fellowships are intended to support the repatriation of outstanding young researchers who have recently completed postdoctoral studies outside New Zealand and who propose to return to New Zealand and conduct research in scientific fields of relevance to the Neurological Foundation.

Dr Juliette Cheyne
Postdoctoral Fellow
Netherlands Institute for Neuroscience

$66,599

This Neurological Foundation Repatriation Fellowship award will enable Dr Cheyne to return to New Zealand to the Department of Physiology at the University of Auckland. Dr Cheyne's supervisors will be Associate Professor Johanna Montgomery and Professor Peter Thorne.

Measuring* in vivo *activity in the auditory cortex of a model and its link to Autism Spectrum Disorders
(How is auditory cortex development affected in Autism Spectrum Disorders?)

Autism Spectrum Disorders (ASD) are defined by learning difficulties, sensory changes, communication difficulties, social deficits and stereotyped behaviours. Because ASD symptoms appear during infancy, it is crucial to examine how brain development is altered, as this may underlie behavioural deficits. The communication and social difficulties in ASD are likely due to abnormal sound processing, which impairs language ability. Dr Cheyne hypothesises that impaired sound processing is due to connections between brain cells in the auditory cortex forming incorrectly during development. She will utilise state-of-the-art cellular recording techniques in a model to examine how auditory cortex development is affected in ASD. Dr Cheyne's experiments will lead to future research examining how, in a similar model, auditory processing and plasticity are altered in ASD and ultimately how this affects behaviour.

PROJECT GRANTS

Dr Shakila RIzwan
School of Pharmacy
University of Otago

$12,000

A novel intranasal mucoadhesive carrier for delivering anticonvulsant drugs to attenuate seizures in a model
(A proof-of-principle study of a tailor-made, intranasal anti-convulsant drug carrier system)

It has been estimated that 20-40% of epilepsy patients become resistant to available antiepileptic drugs (AEDs) over time, leading to a lack of seizure control. The underlying causes of this resistance are complex and multifactorial. Dr Rizwan and her team's long-term goal is

to develop a new non-invasive treatment strategy for delivering AEDs to suppress drug-resistant seizures. They aim to achieve this by packaging AEDs inside very small drug carriers administered via the nose. The nasal cavity is a site for direct absorption of drugs into the brain; however it is important that the compound stays in the cavity long enough for effective delivery. In this proof-of principle study, they will test, in a model, if their tailor-made, adhesive drug carrier system can deliver sufficient AED to the brain to stop seizures. Proof of efficacy in this model will be the first step towards testing this technology in drug-resistant models of epilepsy and progress re-clinical development

Dr Rizwan will collaborate on this project with Associate Professor Nigel Jones from the Royal Melbourne Hospital. Dr Jones is a specialist in epilepsy modelling.

Associate Professor Bronwen Connor
Department of Pharmacology and Clinical Pharmacology
University of Auckland

$192,944

Modelling the neurodevelopmental disorder Fragile X Syndrome by direct cell reprogramming
(Developing an authentic research model of Fragile X Syndrome using an innovative New Zealand-developed technology)

Fragile X syndrome (FXS) is the most common known genetic cause of intellectual disability and autism, and is thought to be due to impairment in the development and function of neurons. However inaccessibility to live developing human neurons is a major barrier to studying FXS. To overcome this, Associate Professor Bronwen Connor, and Associate Professor Johanna Montgomery from the Department of Physiology (an expert in electrophysiology and cell biology),will use innovative direct reprogramming technology, developed by Dr Connor, to turn skin cells from FXS patients into immature brain cells (neural precursor cells). They will then study the development of FXS neural precursor cells to mature neurons and investigate whether neurons generated from the skin cells of FXS patients exhibit changes in the expression of genes and protein associated with neuronal development, and differences in function compared to normal neurons. The outcome of this project will establish a human model of FXS with the potential to enhance the understanding and treatment of this disorder and enable future research in this area.

In the Neurological Foundation's edition of *Headlines* volume 108, Associate Professor discussed her career research work, much of it funded by the Foundation, and said "We can now take skin biopsies from normal people and people with Huntington's or Parkinson's disease. We can grow disease-induced neural precursor cells and subsequently generate mature diseased neurons. We can then compare the diseased neurons with neurons from a normal person. This gives us this beautiful strength of being able to compare living diseased human neurons with normal human neurons to better understand disease mechanisms – something we cannot do with post-mortem

tissue. The ideal outcome of this work is the identification of potential new drug treatments.

This study builds on the large body of cell-reprogramming research work that Associate Professor Bronwen Connor's laboratory is internationally well-regarded for.

Dr Justin Dean
Department of Physiology
University of Auckland

$11,806

Targeted drug delivery to white matter lesions in a model of multiple sclerosis
(Can a new drug-delivery system specifically target lesions in a model of multiple sclerosis to improve brain function?)

Multiple sclerosis is a common autoimmune disorder of the nervous system that causes a wide range of physical, mental, and psychiatric problems. Patients with MS show lesions in the brain and spinal cord that exhibit loss of insulating material called myelin, a molecule important for normal brain signalling. If this loss of myelin can be prevented or restored, this could promote brain function and reduce the symptoms of MS. In this study Dr Dean, and Dr Zimei Wu, an expert in the development of drug-delivery systems based at the university's School of Pharmacy, will test whether their novel drug-delivery system can specifically target the demyelinated lesions in a model of MS, to deliver drugs to promote myelination and improve brain function. This research has the potential to provide targeted drug-delivery to patients with MS, which will ultimately improve treatment efficacy and reduce drug side effects in these patients.

Professor Neil McNaughton
Department of Psychology
University of Otago

$199,605

Investigating the role of sub-thalamic nucleus activity in impulsivity in a model using optogenetic technology
(Using innovative technology to investigate brain activity involved in impulsivity, a common side effect of treatments used in Parkinson's disease)

Deep brain stimulation (DBS) is an important alternative or supplement to pharmacological treatment for many disorders. In particular it treats the debilitating motor (movement) symptoms in Parkinson's disease (PD). The sub-thalamic nucleus (STN) is the most frequently targeted brain structure for DBS in PD. Despite highly efficacious therapeutic effects, DBS into a part of the brain known as the sub-thalamic nucleus (known as STN-DBS surgery) has been linked to various cognitive, emotional and behavioural side-effects. Particularly, deficits in impulse control have been reported as a consequence of STN-DBS in PD. Conversely, improvements in impulse control

have been reported with STN-DBS in obsessive compulsive disorder (OCD). Professor McNaughton and his team including leading optogenetics researcher Dr Louise Parr-Brownlie will address the role of sub-thalamic nucleus activity in impulsivity by dissecting brain network activity with an innovative technology called optogenetic stimulation, and use high-density neurophysiological recordings. The team will modulate STN activity in a model at different frequencies and test for selective changes among key areas in the brain and in different aspects of motor inhibition. The results will improve the understanding of how normal and pathological activity are related in disorders such as PD and OCD; and will determine if different patterns of STN-DBS can selectively mediate its therapeutic and off-target effects at a single site – providing a basis for improved DBS treatment outcomes across a range of disorders.

Professor Cliff Abraham
Department of Psychology
University of Otago

$180,342

Stimulation of neurogenesis by a potential therapeutic protein
(The investigation of a neuroprotective protein's potential to rescue memory function)

Lead investigator Professor Cliff Abraham, one of New Zealand's top Alzheimer's disease researchers, and co-investigators from the University of Otago's Department of Biochemistry, Dr Stephanie Hughes and Professor Warren Tate, aim to investigate the ability of a neuroprotective protein called secreted amyloid precursor protein-alpha (sAPPα) to enhance the birth of new nerve cells in the adult brain. Then, in an animal model of Alzheimer's disease, they will attempt to rescue this neurogenesis capability through an innovative gene therapy approach. Finally, the team will determine in these animals whether restoring the birth of new neurons correlates with the rescue of spatial memory abilities, something that is severely impaired in Alzheimer's patients. The discovery of a neurogenic protein/peptide that can be administered non-invasively will be an important step in the development of therapeutic approaches for Alzheimer's disease. sAPPα's therapeutic potential may also extend to traumatic brain injury and stroke.

Dr John Ashton
Department of Pharmacology and Toxicology
University of Otago

$7,012

Finding tools to investigate the anti-epileptic effects of cannabidiol
(A laboratory based study to determine reliable methods for examining the effect of cannabidiol in epilepsy)

One third of epilepsy patients are resistant to therapy. This is particularly true for childhood epilepsy, leading some parents in the USA to try using an atypical cannabinoid drug,

cannabidiol (CBD). Some reports suggest children gain relief from treatment with oral CBD oil. However, this is anecdotal, low quality evidence, and although early trials on adults appeared positive, these were again of low quality with a high risk of bias, highlighting the need for high quality randomise controlled trials. A recently completed placebo controlled trial however has reported promising results, with CBD reducing seizures significantly compared to patients receiving placebo. *How* CBD reduces seizures is not known. Answering this question could help the development of other drugs for epilepsy. A first step is to find experimental methods that can be used to study the effect of CBD on epileptic-like activity in the laboratory, and this is the aim of Dr Ashton's project. Any positive results will be followed with investigations into mechanisms in subsequent research.

Professor Mark Hampton
Department of Pathology
University of Otago Christchurch

$117,983

Regulation of neurite formation and growth by oxidative stress
(Investigating the mechanisms of proteins in oxidative stress in brain disorders)

Brain function depends on the ability of neurons to transfer information via a network of axons and dendrites (neurites). Disruption of these networks can occur during development and during the course of several neurological diseases. Oxidative stress has been previously linked to neurological disease through the destruction of neurons. Professor Hampton and co-investigators Dr Paul Pace and Professor Christine Winterbourn from the Department of Anatomy at the University of Otago Christchurch, and Associate Professor Christine Jasoni from the Department of Anatomy at the University of Otago, propose that oxidative stress has more subtle effects through interfering with neurite structure. The team has preliminary evidence for a critical interaction between two proteins that triggers neurite collapse, and will investigate whether this collapse can be prevented by a peptide that separates the two proteins. If the team can confirm a specific pathway that relies on a selective protein interaction, it will provide a new and feasible opportunity for therapeutic intervention.

Associate Professor John Reynolds
Department of Anatomy
University of Otago

$192,307

Harnessing metaplasticity for stroke recovery using transcranial magnetic stimulation
(Investigating a new approach to brain stimulation in a model of stroke to optimise recovery)

Stroke is the leading cause of adult disability in New Zealand. Aside from the devastating effects on the individual, stroke-induced disability places a heavy social and financial burden on New Zealand society. Treatments that accelerate and enhance maximal recovery would therefore provide significant benefit to the individual and community. Repetitive transcranial magnetic stimulation (rTMS) uses an externally placed magnetic coil to repeatedly non-invasively stimulate the brain, and has been recognised as a therapy with the potential to induce lasting changes in brain function. Unfortunately, despite intensive investigation, using TMS to facilitate the strengthening of neural circuits to compensate for lost function has not shown sustained enhancement for stroke recovery. Associate Professor Reynolds and his team have preliminary scientific evidence indicating a different way of applying TMS that may achieve this aim. This approach is grounded in cellular neuroscience, and they will apply this approach to a model of stroke to determine if neural circuits can be similarly strengthened, and will use recording techniques that allow the recording of brain cells during the application of TMS. This work may point towards a rethink as to how rTMS should be applied in terms of protocols and how intensity of stimulation is set.

Associate Professor Neil Waddell
Department of Oral Rehabilitation
University of Otago

$12,000

Development of a skin/skull/brain model to measure impact forces to the head and brain-injury mechanisms

In professional contact sports and martial arts, there are increasing reports linking mild traumatic brain injuries (concussion and subconcussion) to early onset dementia and chronic traumatic encephalopathy. Subconcussive brain injury is defined as cranial impact that does not show obvious symptoms and is therefore not diagnosed as a clinical concussion. Associate Professor Neil Waddell and colleagues including Professor Darryl Tong (whose research interests include maxillofacial research, trauma and reconstruction as well as subconcussion in sports) wish to study subconcussive brain injury because it is very difficult to diagnose clinically as no minimum threshold has yet been established. When the human head is subjected to impact, kinetic energy is transmitted to the brain. The literature describing various animal head models cannot be realistically compared to the human head, yet obtaining *in vivo* data from cranial impact in humans is unethical. Instead, an accurate biomechanical model of the human head would be preferable for impact testing. The aim of this research is to develop a skin/skull/brain model to measure impact forces to the head and brain, (by subjecting the prototype to impact testing with a bamboo sword in the martial art of kendo, where head strikes are routine) to help in the understanding of the biomechanics of brain injury in concussion and subconcussion. A range of impact forces will be used to calculate the degradation of energy transfer through the skin/skull/brain system. The knowledge from this study will also be translational to fall injuries, the design of industrial personal protective equipment, and the detection of physical abuse.

Associate Professor Dorothy Oorschot
Department of Anatomy
University of Otago

$190,383

Opposite changes in midbrain dopamine circuitry in schizophrenia versus ADHD-like hyperactivity
(Measuring changes in brain circuitry to increase knowledge of the anatomical basis of schizophrenia and ADHD-like hyperactivity)

The relation between the anatomy of brain cell circuits and their functions is central to understanding information processing in the brain. A wealth of information exists about the brain disorders schizophrenia and attention deficit hyperactivity disorder (ADHD), yet little is known about the microscopic changes in neural circuits that may contribute to the manifestations of each disorder.

Associate Professor Dorothy Oorschot and colleagues including Professor David Bilkey, Dr Louise Parr-Brownlie and Dr Stephanie Hughes, hypothesise that a major causal factor in both disorders is altered synaptic input onto specific midbrain dopamine neurons resulting in excessive or diminished release of the neurotransmitter dopamine. (Neurons in the brain receive thousands of synaptic inputs from other neurons). The team will combine a cutting edge technology to selectively label inhibitory input neurons, and electron microscopy to identify excitatory inputs, onto midbrain dopamine neurons. This will enable the measure of the number of structural changes that potentially underlie long-term changes in synaptic input. An understanding of these structural alterations and relationships, should they exist, will significantly increase knowledge on the anatomical basis of schizophrenia and of ADHD-like hyperactivity, and will provide a marked step forward in understanding the core biology and thus allow for a mechanism-driven approach to new opportunities for treatment.

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