Stroke

The challenge to regenerate the brain to improve stroke recovery
Table of Contents

1 Building a better future
2 The facts
3 A way forward
4 Building recovery
5 The project
6 The solution
7 Research directions
8 Project team
9 Where to from here?
The University of Queensland (UQ) is a leading research intensive university with world-class facilities and expertise.

UQ is championing neuroscience research, with the primary aim of understanding the fundamental mechanisms of brain function at all levels, from development to function and disease. At UQ, this is being addressed by researchers at a number of research centres including the Queensland Brain Institute (QBI), which houses dedicated research facilities focused on understanding brain function through a multifaceted approach.

QBI is a world leader in neuroscience working to understand the fundamental mechanisms, circuits, and functions in both the healthy and diseased brain. Through collaborations with clinicians and commercial partners, basic research findings are applied to develop new therapeutic approaches to combat diseases in which brain function has failed or is compromised. Currently, this includes the creation of the Stroke Recovery Laboratories Project.

QBI’s excellence in the field of neuroscience played a key role in UQ attaining the highest possible score of 5, well above world standard, in the 2010, 2012 and 2015 Excellence in Research for Australia (ERA) reviews. UQ is one of only two universities in Australia to achieve this.

One of QBI’s priorities is investigating treatments to maximize recovery for stroke survivors, which will have far-reaching social, economic, and health impacts.

QBI’s high calibre facilities and world class stroke researchers are building solid foundations for discovery in the area of neuroplasticity.

QBI has developed the Stroke Recovery Laboratories to focus on various components of neuroplasticity, neuroprotection, neurogenesis, neuroinflammation and neuroimaging.

The pieces of the puzzle have been identified and the journey is underway. Research to date is highly promising, and the risk of non-delivery of results is low, but the impact of making a huge difference to stroke survivors’ lives is significant.

Here’s why QBI is inviting your organisation to be part of this incredible journey of discovery...
The Future of Stroke Recovery

Globally, the World Health Organisation estimates that there are at least 62 million stroke survivors. Disability-adjusted life years (DALYs) are used as an estimate of the number of years of healthy life that are lost as a direct result of a disease and it has been calculated that stroke costs a staggering 49 million DALYs annually on a global scale.

In Australia, 50,000 people suffer a stroke each year, leaving them with physical and mental disabilities that create an enormous emotional, social, and financial burden on families and our community.

Currently, there are nearly half a million stroke survivors in this country who, through key research, could have an improved long-term outlook and quality of life, reducing the load on their carers and families.

The physical and mental consequences of stroke include paralysis and motor function deficits, problems with language and speech, vision loss, memory and cognitive impairments, social isolation, dependency, job loss, and depression.

The cost to the healthcare system is substantial, with an estimated $54 billion (in 2012) including direct financial costs, lost productivity, welfare payments and loss of tax revenue.

Stroke is common, is not always preventable and can happen to anyone at anytime. It is not just a disease of the older generation. One third of all stroke survivors in Australia are under the age of 65.

Valuable research into possible new treatments for stroke are not reaching their full potential as stroke research has attracted less than 4% of the highly competitive funding available through the National Health and Medical Research Council (NHMRC) in recent years.

Addressing the growing problem of stroke, and supporting the crucial research at QBI’s Stroke Recovery Laboratories, will create a more positive and worthwhile future for not only Australian stroke survivors, but also the 62 million stroke survivors around the world.
A great deal of the current stroke research that has been successfully applied to humans has been primarily focused on studying and understanding why strokes happen and how to prevent them.

The Stroke Recovery Laboratories will hone in on QBI’s expertise in investigating ways to limit the extent of damage at the time of stroke, and enhance the level of cognitive and physical recovery to improve quality of life after a stroke has occurred.

QBI is taking an innovative and team-based approach to unlocking the mysteries of stroke recovery by building on the work of Professor Perry Bartlett, inaugural Director of QBI and Foundation Chair of Molecular Neuroscience. Twenty years ago, Professor Bartlett discovered stem cells in the adult brain and their ability to make new brain cells, which resulted in the greatest paradigm shift in the neurosciences over the last 100 years. This meant acceptance of the reality of neurogenesis, or the production of entirely new brain cells in the adult brain – a form of neuroplasticity.

Professor Bartlett was the first to demonstrate conclusively that stem cells exist in the embryonic forebrain, before going on to demonstrate the existence of similar activity in the forebrain of adult mice. This second influential discovery provided definitive evidence for the presence of stem cells in the adult mammalian brain and the ongoing production of new brain cells. This discovery was one of the most important breakthroughs in the study of the adult brain in past decades.

Since then, he has gone on to reveal the presence of a latent hippocampal stem cell population, a major finding which underpins the current concept of functional stem cells in the adult brain and the burgeoning interest in activating these originating stem cells to repair the aged, damaged or diseased central nervous system.

Because of the impact of these major findings in the field, in 2015, Professor Bartlett was awarded two of Australia’s most esteemed biomedical science prizes – the CSL Florey Medal as well as the Research Australia Lifetime Achievement Award.

Building on Professor Bartlett’s discoveries, vital research into brain plasticity, and the brain’s natural ability to form new connections to compensate for injury, has resulted in strong evidence suggesting this holds the key to progressing and advancing recovery in stroke survivors.
The driving focus of QBI’s Stroke Recovery Laboratories will be to investigate treatments that stimulate neuroplasticity – the capacity of neurons and neural networks in the brain to change their connections and behaviour – to enable functional recovery after stroke. Professor Bartlett will provide oversight across the research to be undertaken at the Stroke Recovery Laboratories.

Improved recovery for stroke survivors will be achieved by focusing on four main areas of research related to neuroplasticity following stroke:

- **Neuroprotection** – investigating mechanisms and strategies to protect against neuronal injury or degeneration and as a result limiting the effects of stroke and facilitating effective recovery
- **Neurogenesis** – stimulating the growth and development of neurons (brain cells) to improve learning
- **Neuroinflammation** – altering the brain’s environment to promote plasticity
- **Neuroimaging and attention** – investigating a new brain imaging approach to better understand the brain systems involved in attention and to develop an effective treatment for attention deficits after stroke in the long term.

*“As a three-year old child, my very first memory was waiting outside the hospital for my mother after she had suffered a stroke. Most children start producing memories with a snapshot of their father’s face, or their favourite toy. I started with an image of an IV drip in my mother’s hand. As my first memories began, my mother’s started to fail.”*

— Zoe McDonald
daughter of stroke survivor and stroke researcher, Dr Lavinia Codd
The Queensland Brain Institute (QBI) has a strong track record and global reputation in neuroscience. QBI is a dedicated brain research institute with over 450 researchers and support staff and 38 laboratories. Many of the discoveries underpinning the work of the Stroke Recovery Laboratories have been made by QBI scientists in the course of understanding the mechanisms regulating brain function in health and disease. This type of cutting-edge knowledge led to the establishment of The Clem Jones Centre for Ageing Dementia Research (CJCADR) in 2012.

In 2015, CJCADR experienced a major breakthrough demonstrating that Alzheimer’s disease may be treatable with non-invasive ultrasound to restore memory deficits (Leinenga and Goetz, 2015). Further research will identify whether this work may also be effective in stroke-related dementia.

Professor Perry Bartlett’s work will underpin the stroke research initiative. Professor Bartlett is currently working towards reversing cognitive loss after stroke by generating more neurons in the damaged brain. Professor Bartlett has previously investigated the possibility of reversing age-related cognitive decline by stimulating neurogenesis. His results have been so promising in animal models that he is poised to start recruiting for human trials. Initial results from stroke models in rodents suggest that neurogenesis can also be stimulated following stroke and this is associated with improvements in recovery in learning and memory.

QBI also has a world-leading humane animal handling facility, well-equipped surgical suites, extensive behavioural testing facilities, advanced microscopic technologies and unparalleled access to the world’s best array of human and animal imaging technology, at the neighbouring Centre for Advanced Imaging.
Stroke survivors need and deserve effective new therapies, which QBI is working towards by substantially increasing its current research capacity.

To address this urgent need, QBI has established a Stroke Research Fund to raise money to support the Stroke Recovery Laboratories. This will enable QBI to expand its stroke research devoted to improving recovery and facilitate the recruitment of more world-leading investigators.

Funding has been kick-started through a generous five-year, $2.5 million grant from the Stafford Fox Foundation. As a result, QBI has recruited the outstanding young researcher, Dr Steven Zuryn, who is focusing on new ways to provide protection to damaged neurons, or brain cells, after a stroke.

“Recovery from stroke is difficult not only because of the physical barriers, but the emotional. For a long time, my mother was a different person. Stroke isolates its victims and because of her difficulty with names and directions, it was very hard for her to do the simplest things, like meeting other mums from school, because she could never remember who they were. Before I left for kindergarten, she would always memorise what I was wearing in case she didn’t recognise my face when she picked me up in the afternoon.”

— Zoe McDonald
daughter of stroke survivor and stroke researcher, Dr Lavinia Codd
The Stroke Recovery Laboratories provide a unique opportunity for members of the corporate community to join with QBI to be part of the solution in helping stroke survivors lead a full and worthwhile life. QBI researchers will focus on the following research targets to develop a way forward for recovery.

1. **Neuroprotection** – investigating mechanisms and strategies to protect against neuronal injury or degeneration, limiting the extent of brain damage following stroke and facilitating effective recovery

   Stroke deprives a region of the brain of a good blood supply. Blood transports oxygen from the lungs into the brain to allow brain cells to live. Stroke, therefore, puts brain cells at risk of dying, but the number of individual cells lost appears to be variable.

   Indeed, some of these brain cells can survive if adequate blood flow is re-established quickly after a stroke. For recovering optimal brain function, it is critical to keep the maximum number of brain cells alive for as long as possible after a stroke, especially in conjunction with treatment with clot-busting reagents like tissue plasminogen activator (tPA) or surgical clot retrieval.

   Dr Zuryn, the recipient of the Stafford Fox Foundation Grant, aims to build on his recent discoveries published in the journal *Science* to find an answer. He has uncovered mechanisms deep within the DNA of individual brain cells that prevent them from being adversely affected by environmental changes like lowered oxygen. Pharmaceuticals that can replicate the effect of these DNA mechanisms may increase neuronal survival and have enormous potential in minimising the effects of stroke.

2. **Neurogenesis** – stimulating the production and development of neurons to improve learning and promote recovery following stroke

   The hippocampus is a region of the brain crucial to learning and memory. The majority of stroke survivors display decreased hippocampal volume and significant impairment to cognition. The proposed new laboratories will build on the pioneering work of Professor Bartlett’s group, including Dr Codd, and Professor Bartlett’s exceptional career in neurogenesis. Researchers have found that stimulating the production of new neurons in the hippocampus in animal models of stroke can result in almost complete recovery from learning and memory deficits. Recent discoveries have shown that exercise is an effective way to stimulate neuronal production and recovery in animals that have had a stroke. A potential molecular mechanism underlying this effect has been identified and is currently being investigated further.

   The aim is to develop both physical and pharmacological therapeutic approaches for use in humans who have suffered a stroke.

“The culmination of my mother’s determination to recover happened in a single moment with a life-changing realisation. While performing tissue culture experiments with brain stem cells, my mother looked down the microscope and saw new brain cells growing in a petri dish, right in front of her. It was in that moment she realised that if the brain could grow new cells in a petri dish, what stopped that from eventually translating to regrowth in the human brain – even her own? Now her aim is to improve the future for stroke survivors so their journey is not a dead end but is one of hope and possibility.”

— Zoe McDonald

daughter of stroke survivor and stroke researcher, Dr Lavinia Codd
3. Neuroinflammation – regulating the inflammatory process to reduce the incidence and effects of stroke

There is mounting evidence to suggest that inflammation may be a risk factor for stroke and may also influence the degree of damage and recovery afterwards. Identifying the role inflammation plays will help to significantly change stroke outcomes. Professor Bartlett has previously established that a particular inflammatory cell in the brain modulates the neurogenic effect of exercise in the aged brain. The Stroke Recovery Laboratories will address this issue and determine if these particular cells also modulate the impact of exercise on neurogenesis and recovery following stroke, in a bid to develop new treatments and maximise recovery.

4. Neuroimaging and Attention – understanding the disruption to attentional circuits following stroke and the impact this has on recovery

The deficits arising from having a stroke can range from paralysis and sensory loss to cognitive problems, and depend on the extent and location of the brain damage. One particularly devastating form of impairment, referred to as neglect, involves a loss of attention – losing the ability to focus on relevant information in the environment, and to filter out distractions. This leaves individuals unable to return to independent living. Often the presence of attention deficits after stroke is an early indicator of a poor long-term prognosis for recovery. There is currently no medical treatment for this debilitating condition, and sufferers often end up in high-dependency homes. Researchers in the Cognitive Neuroscience Laboratory at QBI, led by Professor Jason Mattingley, are developing new approaches to tackling such devastating functional losses in stroke patients. Crucial research is needed to investigate a new brain imaging approach, aimed at better understanding the brain systems involved, which is critical in developing an effective treatment for attention deficits after stroke in the long term.

The different research approaches taken by the Stroke Recovery Laboratories will complement each other and converge to improve the long-term outlook for stroke survivors. Improving neuroprotection will preserve brain cells until blood flow is restored. Investigations into stimulating neurogenesis will discover and refine treatments to bring about neuroplasticity to boost recovery from stroke. Modulating the inflammatory effect of stroke will optimise the brain environment to be conducive for neuroplasticity.

Finally, given the impact that attention has on recovery following stroke in the human population, increasing our understanding of stroke-induced changes to attentional processes and investigating the brain circuits involved in attention will help in the application of our findings to human stroke survivors. Improving recovery will reduce ongoing medical costs, improve the quality of life for stroke survivors and reduce the load borne by their carers. Returning younger stroke survivors to work will also benefit society at large. Understanding all of these processes in the stroked brain will lead to treatments that can potentially be applied in many neurological disorders such as Parkinson’s and Alzheimer’s.
QBI has recruited an experienced team of professionals to investigate the cognitive and cellular effects of stroke and improve quality of life for stroke survivors into the future.

This qualified team, including Dr Steven Zuryn, Dr Lavinia Codd and Professor Jason Mattingley, are investigating stroke recovery using a building block approach. Dr Steven Zuryn targets the first area of the Stroke Recovery Laboratories research of neuroprotection, which focuses on the fundamental cellular level and looks at how individual brain cells can be made more resistant to the effects of stroke. Dr Lavinia Codd’s work builds on this by focusing on the next two research areas of neurogenesis and neuroinflammation, using various methods to stimulate the growth of new neurons in animal models. Investigating the role of neuroinflammation in modulating these benefits will refine the success of this technique. Professor Jason Mattingley’s focus is on the last of the Stroke Recovery Laboratories research areas of neuroimaging and attention, aiming to understand neural circuits that control selective attention which can be adversely affected by stroke.
NEUROPROTECTION

Dr Steven Zuryn
Stafford Fox Senior Research Fellow

Dr Zuryn is investigating the cellular mechanisms that allow brain cells to survive sub-optimal conditions, and how they can be made more resistant to the effects of stroke.

For as long as he can remember, Dr Zuryn has always been interested in understanding how the natural world works; this curiosity led him down a biology pathway, because for him, life is the most complex natural part of our world.

To understand how life functions, Dr Zuryn became focused on the enormous array of tiny molecular machines that work, like a clock, inside each cell. Unfortunately, these little machines are not perfect and often make mistakes that can lead to disease and ageing.

Dr Zuryn's curiosity for discovering the mysteries of life led him to study genetics and in 2008, he received his PhD from The University of Queensland for his work investigating mitochondrial (a structure in cells that produce energy) mechanisms of toxicity and ageing. In 2009, he moved to the Institute of Genetics and Molecular Biology, Strasbourg, France to undertake postdoctoral work in mapping DNA mutations and unlocking the cellular mechanisms that allow neurons to develop and grow. In September 2015, Dr Zuryn was appointed as the Stafford Fox Senior Research Fellow and a Group Leader at the Queensland Brain Institute. His laboratory looks at the fundamental processes that individual neurons use to protect themselves from being injured when a person has a stroke or dementia. He is working on enhancing these natural mechanisms so that the neurons are protected before damage is done.

Dr Zuryn's area of research deals with the ways in which brain cells counteract mistakes when they occur, such as when brain cells are starved of oxygen, which happens during stroke. He hopes to discover what cellular mechanisms allow brain cells to survive sub-optimal conditions and how they can be made more resistant to the effects of stroke.

Dr Zuryn's ultimate goal is to prolong neuronal function in the face of disease, including stroke, so that normal life can be preserved as much as possible.

The simple neural model organism C. elegans has been used to discover fundamental cellular mechanisms, resulting in three Nobel prizes in the last 20 years. Stroke causes mitochondrial dysfunction and neuron death, which led the Zuryn lab to create this fluorescent C. elegans to locate genes (green and red) indicative of mitochondrial dysfunction. This technique will be used to discover new molecular pathways that protect neurons during stroke.
NEUROGENESIS AND NEUROINFLAMMATION

Dr Lavinia Codd
Postdoctoral Research Fellow

Dr Codd is using a variety of techniques to stimulate the production of new neurons (neurogenesis) in an animal model of stroke and evaluate the resulting improvements in spatial learning, or an animal’s ability to memorise various locations and their spatial relationships.

Stroke research is intensely personal for Dr Codd; after suffering a stroke and becoming a stroke survivor, she is now a Postdoctoral Research Fellow at QBI, in Professor Perry Bartlett’s laboratory.

Dr Codd began her working life at PricewaterhouseCoopers (PwC), where she became a member of the Institute of Chartered Accountants. She worked in both the Brisbane and South London offices of PwC, as well as the London office of the Swiss Bank Corporation, and The Walt Disney Company (Australia) in Melbourne. However, after the birth of her first child, Dr Codd embarked on a career change and returned to UQ to study science.

Mid-way through her studies, aged just 31 and with two young children, Dr Codd suffered a stroke.

The nature of Dr Codd’s deficits meant that options for appropriate rehabilitation were limited, so she resumed her Bachelor of Science to drive her cognitive recovery, going on to complete her PhD in Professor Bartlett’s laboratory. It was during this time that Dr Codd developed a technique for inducing a small stroke that only affected an animal’s ability to form new spatial memories whilst not affecting motor function. This meant that cognitive function could be tested far more easily than with traditional stroke models.

Stem cell transplants are being heavily investigated around the world. However, the identification by Professor Bartlett’s group of different populations of latent hippocampal stem cells that can be activated by distinct pathways may make the need to obtain stem cells from an alternative source redundant. Dr Codd has built on the extensive findings from her colleagues, in Professor Bartlett’s laboratory, regarding activation of the different hippocampal stem cell populations in the normal and the aged brain.

She is examining what effect activating various hippocampal stem cells has on neurogenesis in an animal model of stroke and is currently determining the impact of this on cognitive recovery following stroke. Excitingly, initial results indicate that if a stroke survivor receives certain treatments, then they may be able to exploit the brain’s own natural ability to increase neurogenesis to compensate for stroke-induced deficits. Dr Codd and Professor Bartlett will also examine if there is an interaction between neuroinflammation and neurogenesis following stroke and how such relationships may impact on cognitive recovery.

Dr Codd’s ultimate aim is to translate positive laboratory findings into new behavioural and pharmacological approaches to restore cognitive functions in human stroke survivors. To spearhead this initiative, Dr Codd has established the Stroke Advisory Board, which was formed to promote ongoing stroke research and its potential to improve recovery outcomes for stroke survivors, as well as to raise funds to substantially increase QBI’s research capacity into stroke.

Dr Codd is also active in raising awareness of stroke and from her personal experiences advocates the position that recovery happens over the course of an entire lifetime and is not restricted to the immediate post-stroke years.
NEUROIMAGING AND ATTENTION

Professor Jason Mattingley
Foundation Chair in Cognitive Neuroscience

Professor Mattingley’s research is directed toward understanding the neural and cognitive mechanisms that underlie selective attention and the prioritising of sensory inputs, cognitive operations, and motor responses, which can be adversely affected following stroke.

As a child, Professor Jason Mattingley was fascinated by how things worked and liked to build things from odds and ends around the house. He got hooked on science in secondary school with Biology as his favourite subject. His innate curiosity and love of discovery led him to study science at university, with a focus on zoology and psychology. These subjects ignited his interest in how biological systems support and regulate behaviour, from basic sensory and perceptual processes through to attention, decision-making and higher cognitive reasoning. He was also fortunate to work with several wonderful mentors who taught him the value of combining studies of behaviour with measures of underlying brain processes.

Driven by the raw thrill of discovery, and also by the knowledge that what he is working on might one day have an impact on people’s lives, he completed a Bachelor of Science Degree with Honours at Monash University (1988), a Master of Science Degree in Clinical Neuropsychology at the University of Melbourne (1990), and a PhD in Psychology at Monash University (1995). In 1994, he was awarded an NHMRC Neil Hamilton Fairley Post-Doctoral Fellowship, which he took to the University of Cambridge. While in Cambridge he was elected a Fellow of King’s College.

Upon returning to Australia, Professor Mattingley was appointed as Senior Research Fellow (later Principal Research Fellow) at the University of Melbourne, where he was Director of the Cognitive Neuroscience Laboratory within the School of Behavioural Science (2000–2006). He was elected a Fellow of the Academy of Social Sciences in Australia in 2007.

Professor Mattingley was appointed as Foundation Chair in Cognitive Neuroscience at The University of Queensland in January 2007, a joint appointment between the Queensland Brain Institute and the School of Psychology. In 2012, Professor Mattingley was awarded an Australian Laureate Fellowship by the Australian Research Council.

Increasingly these days, he is also driven by the bright young people – students and research fellows – whom he mentors, who challenge him to think about problems in new ways, and whose boundless enthusiasm is infectious.

In his laboratory, Professor Mattingley is trying to understand the neural processes involved in regulating attention. By investigating these mechanisms in healthy volunteers, using behavioural measures, brain imaging and brain stimulation, Professor Mattingley is discovering how these processes break down in neurological and psychiatric disease and may be adversely affected by stroke.
QBI is perfectly positioned to advance our understanding of stroke and make huge inroads into how well survivors recover from stroke. QBI has a robust plan of specifically selected research areas to optimise results and maximise the success of the project. The key is to create conditions conducive to repair and use the brain’s own regenerative capacity by focusing on neuroplasticity. The co-ordinated team of QBI’s high-calibre researchers, in conjunction with state-of-the-art facilities and inspiring leadership, provides a strong approach based on good science. This is your organisation’s opportunity to play a role in making change happen and invest in quality medical research that has strong potential for improving future outcomes for stroke survivors based on results to date.

To discuss how your organisation can be part of improving the future for stroke survivors, we would appreciate the opportunity to expand on this proposal at a convenient time. Dr Codd is available to come and share her story and let you know how to take the next step on this exciting journey.

Visit the Queensland Brain Institute: www.qbi.uq.edu.au or donate here: www.qbi.uq.edu.au/how-support-qbi

For more information, please contact:
Mikaeli Costello
Director of Advancement and Communications
Queensland Brain Institute
0401 580 685
Mikaeli.Costello@uq.edu.au