Neuroscientist Professor Cindi Morshead is applying her research in stem cell biology and neural regeneration to a major problem in medicine – stroke repair. Here, she explains the importance of the problem at hand, the combined expertise of her team, and her solutions to the universal problem of funding.

**What inspired you to investigate stroke and the role of neural stem cell activation and rehabilitation in this neurological disability?**

My lab has a longstanding interest in using endogenous neural repair strategies for the injured brain. We became interested in stroke for a number of compelling reasons. It affects over 50,000 individuals every year and is a leading cause of permanent disability in Canada. Other than rehabilitation, there are no medical therapies for restoring brain function following stroke, making it an ideal candidate disorder for stem cell therapy.

We had already demonstrated success in sensory-motor recovery using endogenous repair strategies and were excited about applying this to cognitive function. Cognitive impairments following stroke are common and often more devastating than sensory-motor impairments. It was clear that the next step was to examine strategies to restore cognitive impairments using our promising, clinically relevant strategies.

**Where do your academic and professional skills lie? Which experiences have guided your research?**

Throughout my undergraduate studies I was unsure which research path to take, so I went through a process of elimination, scratching off the list what I least enjoyed. My main passion was the brain and decided I would continue investigating this area until I lost interest – which I never did. My PhD identified the niche for neural stem cells in the adult brain and I have been studying their biology and role in neural regeneration ever since. Finding ways to use neural stem cells to repair the brain holds great promise for the future and we want to be part of that.

**There are currently no effective medical therapies for alleviating the chronic functional impairments following stroke. How might your research change this?**

There is no single magic bullet that will repair the damaged brain. Our team came together because we have similar goals, but diverse approaches that together will advance the field of neural repair. Importantly, we are focused on developing relevant strategies that will allow for translation to a clinical setting. Developing novel, safe and effective drug delivery systems for clinically relevant molecules, to harness the potential of neural precursor cells and promote self-repair of the brain – and combine this with rehabilitation strategies – we are well positioned to achieve success.

**What benefits are brought by the different members of your team?**

The best characteristic of our team is the breadth of expertise. Dr Molly Shoichet’s expertise in material chemistry and biomaterials has led to the development of drug delivery systems that are crucial for the success we have achieved to date. Dr Dale Corbett’s knowledge in stroke and behaviour is the backbone for exploiting the plasticity of the brain and studying clinically relevant rehabilitation paradigms. Dale’s studies reveal that there are more effective rehabilitation strategies that can be used to help patients recover.

**One hypothesis of your lab is that endogenous stimulation of neural precursor cells may lead to neurogenesis and tissue repair. Have you managed to prove this?**

Our models show that growth factors and small molecules administered following stroke can activate resident neural precursor cells, inducing their expansion and migration to the injury site. Working with Molly’s group we have used drug delivery systems that permit the local and temporally-defined release of these drugs directly to the brain, thereby avoiding any negative, systemic effects. We have built on the rehabilitation strategies developed in Dale’s lab to enhance brain plasticity and have shown that the combination of growth factors and rehabilitation improves recovery more than either drugs or rehabilitation alone. We are now expanding our studies to include aged animals and models of stroke that lead to cognitive impairments.

**Has your team faced any obstacles during the research, and if so, how were they overcome?**

One of the biggest challenges we face, common to all researchers, is acquiring funding. We are thrilled to have support from the Canadian Institutes of Health Research (CIHR), Heart and Stroke Foundation and Canadian Program for Stroke Recovery for our adult stroke work. In our studies, the costs of doing research in aged animals is an impediment. We work to overcome these challenges by ensuring we have excellent trainees working in our labs, by critically evaluating our work on an ongoing basis, keeping in mind the goal of clinical application and, most importantly, and by not being afraid to pursue the important questions.
Stem cells for stroke

A forward-looking research group based at the University of Toronto is applying innovative strategies to aid recovery following stroke. Using novel animal models and treatment paradigms, this work has the potential to return independence to stroke victims.

STROKE IS THE leading cause of neurological disability in adults. Although mortality rates are in decline due to early recognition and advances in treatment, cognitive impairments following stroke remain a major problem, leaving patients with difficulties in learning, memory and communication. In Canada, there are over 50,000 new cases of stroke every year. Although many will survive their stroke, two-thirds are left with problems that impact on daily living.

Despite its prevalence and damage to quality of life, there remain no medical therapies able to alleviate chronic functional impairments after stroke. The identification of neural stem cells in the adult mammalian brain led to new hope. With their progeny, together termed neural precursor cells (NPCs), these cells have generated huge interest in the potential for stem cell therapy to treat neurological injury and disease. However, activating these cells in the brain has proven insufficient to promote repair, and small molecules are necessary to augment the process. In a similar way, rehabilitation – the major treatment for stroke recovery – can bring significant improvements, but not enough to achieve total repair.

Professor Cindi Morshead believes the solution may lie in combining both of these – alone insufficient – approaches to tackle stroke more effectively. Leading a research team at the Universities of Toronto and Ottawa, she is exploring the ability of combining NPC activation and rehabilitation to repair the injured brain after stroke.

THE AGEING BRAIN

Despite its consequences, particularly loss of independence for patients, little research has been conducted in how to repair cognitive impairment following stroke. Furthermore, although over 70 per cent of all strokes occur in those over 65, almost all studies are performed in young animals.

To meet these twin research needs, Morshead’s team will test approaches to repair cognitive function in both young and old animals. Indeed, clinical relevance is a key theme throughout their research: “Though logical to start with, proof of principal experiments in young adult animals when developing repair strategies, this is not sufficient and success will not necessarily translate into the aged brain,” Morshead explains. “The neural stem cell niche is different in the ageing brain and there is reduced plasticity, so it is critical to examine this population to make the work clinically relevant.”

However, this is not as simple as it sounds. There are several limiting features found in the aged brain, including impediments to stem cell activation. Furthermore, older animals are fragile and thus more expensive to work with. As a result, they are one of the only groups examining the potential of this repair strategy in the aged population.

INTERLINKED RESEARCH

In their efforts to test whether the combination of NPC activation and rehabilitation will promote cognitive recovery after stroke, the researchers are pursuing a number of experimental avenues.

The first is focused on the stem cells themselves, and whether their stimulation within the brain leads to the growth of new nervous tissue (neurogenesis) and repair of the existing damaged tissue. Having previously shown that NPC activation aids tissue repair and behavioural recovery in a sensory-motor model of stroke, the team will now activate cells in a cognitively impaired model. They will achieve this via the combined use of a small molecule called cyclosporin A (CSA) and a growth factor called erythropoietin (EPO), which activate NPC expansion and neurogenesis respectively. Measuring NPC activation, tissue repair and cognitive recovery, the team will be able to find the most effective method of activation.

Crucial to the success and clinical relevance of this work is a system that can deliver drugs directly into the brain, bypassing the blood-brain barrier. To this end, the researchers have engineered a novel system that can activate stem cells in a manner that is minimally
innovative strategies for tissue repair, which comprises a combination of physical exercise and cognitive rehabilitation paradigm, which is gradually becoming clear that no single therapy can successfully regenerate neurons and recover function following stroke. Thus, the group hopes to promote cognitive recovery in the final element of Morshead’s work, her group is uniquely positioned to develop next-generation approaches to promote brain tissue repair and cognitive recovery after stroke, and has far-reaching plans for the future, as Morshead underlines: “We are always planning for the future. Each experimental result leads us to a new question. This is the most exciting part of doing research – asking how we can make the brain work better and wanting to understand the fundamental biology underlying this success”.

The lab is collaborating with a number of prominent groups in this field, exploring the effects of endogenous repair strategies and childhood models of brain injury. For children, stroke and brain injury is an even greater tragedy. They are left with motor and cognitive deficits at a young age that in most cases will persist for a lifetime. “We feel our work to date in adult stroke has enormous implications for this population and are excited with this new direction,” she enthusiastically concludes.

**OBJECTIVES**

- To develop safe and clinically relevant therapeutic interventions to treat the physical and cognitive impairments that result following stroke
- To achieve this we will combine synergistic strategies of endogenous stem cell activation with rehabilitation, in young and aged animals, using novel drug delivery systems to deliver therapeutically relevant molecules to the injured brain to augment self-repair.

**KEY COLLABORATORS/PARTNERS**

Dr Molly Shoichet, University of Toronto
Dr Dale Corbett, University of Ottawa

**FUNDING**

Canadian Institutes of Health Research
Heart and Stroke Foundation

**CONTACT**

Dr Cindi M Morshead
Lead Principle Investigator
University of Toronto
Donnelly Centre
160 College Street
Room 1006
Toronto, Ontario
M5S 3E1, Canada
T +1 416 946 5575
C cindi.morshead@utoronto.ca

**INTELLIGENCE**

**PROMOTING COGNITIVE RECOVERY USING ENDOGENOUS NEURAL STEM CELL ACTIVATION AND REHABILITATION FOLLOWING STROKE**

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**FOLLOWING STROKE**

**AND REHABILITATION**

**NEURAL STEM CELL ACTIVATION**

**PROMOTING COGNITIVE INTELLIGENCE**

**LOOKING FOWARDS**

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