Partners in Research

New program aims to support Manitoba scientists

By Bob Armstrong • Photography by Marianne Helm

The Manitoba Health Research Council has teamed up with five local health science research institutions to create a new partnership grant program to support research proposals with a potential to make a difference.

The MHRC Partnership Grant program is a joint effort with the University of Manitoba's Faculties of Medicine and Nursing, Manitoba Institute of Child Health, Health Sciences Centre and CancerCare Manitoba Foundation. It offers five partnership awards per year to researchers whose proposals were highly ranked by scientific peers, but did not receive federal funding.

Christina Weise, Executive Director of the MHRC, says the MHRC Partnership Grant is intended in part to provide recipients with an extra year of experimentation so that their proposals will be even stronger when future federal funding opportunities become available.

"It's absolutely critical to keep a project alive so that it can be an even stronger applicant next time," says Weise.

The MHRC is funded by the provincial government to support basic, clinical and applied research in the health sciences, and has a number of other funding programs, including operating and establishment grants for new and established researchers, as well as fellowships for graduate students and postdoctoral researchers.

This year's MHRC Partnership Grant recipients, along with a brief synopsis of their work, appear on the pages that follow.

Dr. Jim Davie — FIGURING OUT FIBROBLASTS

A better understanding of how our bodies respond to wounds may lead to new ways to prevent our defences from turning against us.

That's the goal behind the research Dr. Jim Davie is carrying out into the cascading chain reaction of genetic activity that stimulates cells known as fibroblasts to begin healing wounds.

Using the Manitoba Next Generation Sequencing Platform, which allows users to read the biochemical code in DNA samples, Davie will examine the fibroblasts from skin and various organs in order to better understand the healing process. It's a process in which one group of genes, known as "immediate early genes" are turned on in response to an injury.

"The immediate early genes are poised to fire," he notes. Once they are signaled by a protein to begin the process of turning on other genes, "this ultimately leads to cell proliferation and wound healing."

His goal is to identify which genes are involved and which proteins regulate these genes, as well as to understand how this process happens. The ultimate goal is to generate knowledge that can be used to develop treatments for use when this genetic chain reaction is out of control.

Davie notes that scientists have discovered that for some highly aggressive cancers this process is "running amok. ... We know that this particular process is deregulated in cancer cells. Once the process is deregulated, these genes don't turn off anymore."

Seeing exactly how the immediate early genes are turned on in wound healing may show which protein in particular to target in a cancer treatment. Developing a designer drug that only targets one specific protein could allow for treatments with fewer side effects for patients, Davie says.

"As we know more about these processes, we will gain valuable insights into designing novel therapeutic options."

A professor in the University of Manitoba's Department of Biochemistry and Medical Genetics since 1983, Davie is a scientist in the Manitoba Institute of Child Health, where his lab and research team are located, and a senior scientist at the Manitoba Institute of Cell Biology. His research, supported by an MHRC-Partnership Program grant, is an example of how fundamental research into the workings of the body can lead to applications in treatment.

"If you don't know what's going on normally, how can you tell what's going wrong in a disease state?"

Dr. Sachin Katyal — IMPROVING CANCER TREATMENTS

A Winnipeg researcher is trying to make chemo- and radiation therapy more effective – and easier – on patients.

Dr. Sachin Katyal is working to develop compounds that inhibit enzymes that counteract the damage that chemotherapy and radiation do to the DNA of tumours. The recent arrival to Manitoba, who received his PhD from the University of Alberta's Cross Cancer Institute, has received a CancerCare Manitoba-MHRC Foundation Partnership grant to further his research program here.

"Chemotherapy and radiation fight cancer by causing so many breaks in the DNA of tumour cells that they cannot make sufficient repairs," notes Katyal. Cancer treatment often targets tumour DNA while it is replicating. During this process, the DNA is vulnerable and chemotherapy or radiation can cause DNA breaks.

"The idea is to overwhelm the tumour's system with so much DNA damage that the cells die," he says. "The problem is that our good cells are also unfortunate casualties leading to pretty bad side-effects in patients undergoing cancer treatment."

In the usual DNA processing pathway, an enzyme called Topoisomerase-1 (TOP1) opens up DNA so that it can replicate or make proteins needed for cell function. "Many chemo- and radiation therapy strategies trap TOP1 and increase DNA breaks," he says.

Katyal has found that two proteins, TDP1 and ATM, together help to clear these trapped TOP1-DNA complexes, which can reduce the effectiveness of cancer therapies. "As a result, inhibiting these proteins could improve overall cancer treatment," says Katyal.

Katyal will use tumour cell lines derived from patients and grown in mice to develop drugs that inhibit TDP1 or ATM in tumours. Making tumour cells more vulnerable to treatment could have a big impact on the lives of cancer patients.

"These [chemo and radiation] are highly toxic treatments, and we want to improve quality of life," he says. "In finding a way to enhance the sensitivity to treatment of tumour cells, the idea is you could then reduce the dosage in chemo or radiation. This strategy has potential applications to wide variety of tumour types, many of which are common amongst Manitobans and Canadians."

An assistant professor in the Department of Pharmacology and Therapeutics at the University of Manitoba, as well as a senior scientist at the MICB within CancerCare Manitoba, Katyal's research is also supported by funding from the U of M, CancerCare Manitoba Foundation and an MHRC Establishment award.

Dr. Larry Jordan

EXPLORING SPINAL CORD INJURY

Many people know that serotonin is "the happiness molecule."

It's the substance, produced in the brain stem, involved in regulating mood and sleep, among other important functions.

Dr. Larry Jordan, a professor in the Department of Physiology and Pathophysiology at the University of Manitoba's Faculty of Medicine, is investigating ways in which serotonin could be the key to allowing recovery of movement after spinal cord injury.

With support from an MHRC/Faculty of Medicine Partnership Grant, Jordan is investigating the transplantation of neurons that produce serotonin into the spinal cord.

Serotonin, he explains, increases the excitability of neurons that create the rhythms involved in locomotor movements, as well as turning on the neurons involved in co-ordination. Movement, or to be more specific, locomotion, requires both a regular rhythm and co-ordination of flexor and extensor muscles around the joints, as well as coordination of the left and right lower limbs.

"A major effect of spinal cord injury is to interfere with co-ordinated activity," says Jordan. "You can have an absence of co-ordinated activity between the left and right side, or you can have the flexors and extensors going at the same time."

Animal models have shown that after a spinal cord injury, muscles may be rhythmically active but not co-ordinated. However, when serotonin is added, co-ordination returns, and the flexors and extensors as well as the left and right legs begin working at the correct time.

"There's plenty of indication that the human spinal cord contains a similar set of neurons that just have to be turned on."

The neurons that produce serotonin – called serotonergic neurons – are found in the brain stem and normally project to the spinal cord. In Jordan's experiments, serotonergic neurons from mice will be transplanted into the spinal cords of paraplegic rats, and then activated so that they release serotonin.

Jordan has been investigating the nervous system for more than four decades. After completing his PhD in neurophysiology at the University of Texas, Jordan came to Winnipeg in 1970 as a post-doctoral fellow. He was the founding director of the Health Sciences Centre/U of M Spinal Cord Research Centre.

In his current research he will collaborate with a colleague from Warsaw, Poland, as well as colleagues in Winnipeg.

"This will allow us to do the experiments to determine if activation of these neurons can make a difference," he says.

Dr. Alan Mutch

MEASURING CONCUSSION RECOVERY

Thanks to high-profile coverage of concussions in professional and amateur sport, millions of Canadians understand that recovery can be very gradual. What might surprise many is that there is still no quantifiable test for the lingering effects of a brain injury.

That's something Dr. Alan Mutch hopes to change, through research involving magnetic resonance imaging of patients breathing oxygen with an elevated concentration of carbon dioxide.

"The brain is exquisitely sensitive to carbon dioxide," he says. "What appears to happen is that when a patient is concussed, they don't respond to the stimulus (of breathing increased carbon dioxide) in the same way."

Using carbon dioxide in such a test can reveal areas where the brain is still healing.

Carbon dioxide is a vaso-dilator, meaning it increases the flow of blood through the brain. Using an MRI technology called BOLD imaging, it is possible to see differences in blood-oxygen levels in the brain. The result is extremely detailed, colour-coded images that divide the brain into 60,000 areas, known as voxels, with 300 to 500 individual images taken during a scan.

Mutch hopes his research can lead to a test for post-concussion syndrome that is similar to a cardiac stress test, in which placing the injured organ under stress allows doctors to see where it is at risk.

Current assessments of healing from concussion are symptom-based. A quantifiable test would allow doctors to see if a patient has fully healed after he or she has begun to feel better.

In order to prepare for this research, Mutch travelled to the University of Toronto and Cambridge University on sabbaticals funded by the University of Manitoba to learn the technology he uses to control the concentrations of gas and map the brain. He's bringing both new approaches to Winnipeg, where he collaborates with colleagues from Health Sciences Centre Winnipeg and the Pan Am Clinic and uses a new MRI at the Kleysen Institute for Advanced Medicine (KIAM). The research group has already conducted nearly 40 studies, with about half being healthy control subjects.

Mutch came to Winnipeg after graduating from Queen's University in 1977 and has been a neuro-anaesthetist for more than 30 years. He is now part of a group of approximately 40 clinicians and researchers involved in concussion testing, diagnosis and therapy who are looking to establish the Canada North Concussion Network in Winnipeg.

Dr. Michael Czubryt

THE HEART OF THE MATTER

The human heart needs a lot of reinforcement to endure expanding and contracting 100,000 times a day. But the same substance that allows the heart to withstand this exertion can also cause heart failure.

Dr. Michael Czubryt, a researcher at the Institute of Cardiovascular Sciences and the University of Manitoba's Faculty of Medicine, is investigating the causes of cardiac fibrosis, a stiffening of the heart that results from excessive collagen build-up. He hopes this can lead to a treatment that might prevent fibrosis, in the heart and elsewhere in the body.

He's one of this year's recipients of an MHRC – U of M Faculty of Medicine Partnership Grant for medical research.

If you've ever noticed a band of white, tough fibre running through a steak, you've been looking at collagen.

"The heart has a protein-rich skeleton of long collagen fibres that give it strength," says Czubryt. "Without them, your heart chambers would enlarge due to the pressure that builds up with each contraction."

Too much collagen in the heart causes it to stiffen and forces it to work harder. After a heart attack, cells in the heart, called fibroblasts, produce extra collagen to patch the damaged area. But once they start, they continue producing collagen all over the heart. This leads to cardiac fibrosis, which can result in heart failure.

"We've identified a player that seems to be involved in turning on the collagen," says Czubryt. That player is scleraxis, a "transcription factor" or protein that turns on the genes in the fibroblasts that encode collagen.

Ultimately, the goal is to develop a small molecule compound that inhibits collagen production by targeting scleraxis.

"One of the issues with fibrosis is that there are no drugs that target it. This is a huge gap in our arsenal for heart disease. We hope that if we can find a way to influence collagen in the heart we can influence collagen in the airway, the kidneys, the liver."

After earning his undergraduate and PhD degrees from the U of M, Czubryt spent three years at the University of Texas Southwestern Medical Center in Dallas, one of the top cardiovascular research facilities in the world. In 2013 he took up an appointment in the U of M's Department of Physiology and Pathophysiology. He directs a laboratory at the Institute of Cardiovascular Sciences at the St. Boniface Hospital Research Centre.

NEW MSAD Coming