Peter Munk Cardiac Centre

CLINICAL AND RESEARCH REPORT

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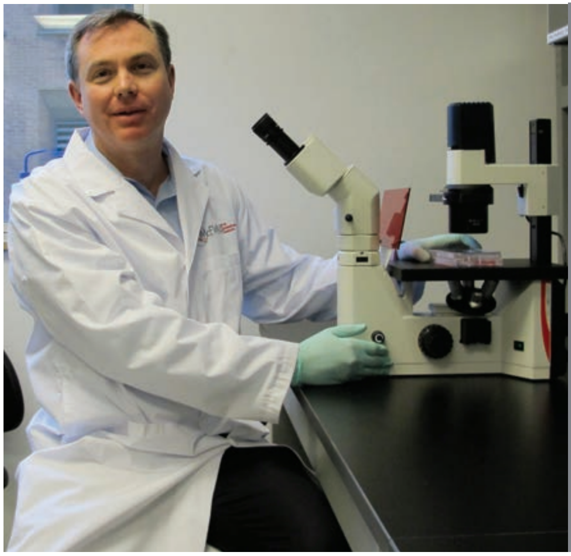
CARDIOVASCULAR REGENERATIVE MEDICINE

Providing the fuel for groundbreaking discovery

WILL STEM CELL RESEARCH MAKE IT POSSIBLE TO REGENERATE DAMAGED HEART MUSCLE IN PATIENTS WITH HEART DISEASE?

Despite many breakthroughs in cardiovascular medicine, heart attacks and congestive heart failure remain among the most prominent global health challenges of our time. Unlike most organs in our body, the heart is very poor at repairing itself after sustaining injury. What if scientists could use a special kind of stem cell to produce new heart muscle and inject those new cells into a patient's heart as a fix?

"It's one of the most promising and exciting fields in medical research," says Dr. Michael Laflamme, the newly recruited Robert R. McEwen Chair in



Dr. Michael Laflamme's laboratory has ongoing work focused on promoting the maturation of human stem cell-derived cardiomyocytes, understanding and improving their electrical function after transplantation into injured hearts, and ultimately translating these advances into safe, effective therapies for heart failure patients.

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ABOUT THE PETER MUNK CARDIAC CENTRE

The Peter Munk Cardiac Centre is the premier cardiac centre in Canada. Since it opened in 1997, the Centre has saved and improved the lives of cardiac and vascular patients from around the world. Each year, approximately 55,000 patients receive innovative and compassionate care from multidisciplinary teams in the Centre. The Centre trains more cardiologists, cardiovascular surgeons and vascular surgeons than any other hospital in Canada. It is based at the Toronto General Hospital and the Toronto Western Hospital, members of University Health Network, which also includes the Princess Margaret Cancer Centre and Toronto Rehabilitation Institute. All four sites are research hospitals affiliated with the University of Toronto. For more information please visit www.petermunkcardiaccentre.ca

…Providing the fuel for groundbreaking discovery continued.

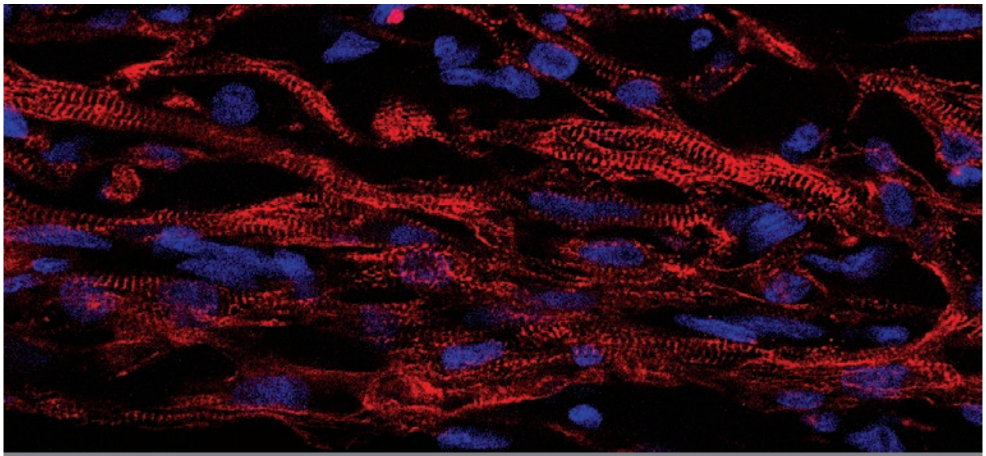
Cardiac Regenerative Medicine in the McEwen Centre for Regenerative Medicine at University Health Network. "The ability of stem cells to become any cell type in the body means that they have the potential to be used to treat, and perhaps cure, devastating and costly illnesses such as heart disease."

Simply put, the goal of stem cell therapy is to replace the damaged tissue with new heart cells and restore the failing heart to normal function. The process involved in getting there can be quite complex.

When Laflamme first started working with different stem cell types over a decade ago, he tried everything to push bone marrow cells and other cells types that people claimed could differentiate into heart muscle cells, or cardiomyocytes. A watershed moment came when he was effectively able to create beating heart muscle cells in a petri dish derived from human embryonic stem cells, offering a potential solution to create large numbers of cells to facilitate repair of the damaged heart.

"The first time we had beating heart muscle cells in a dish, I was sold from that moment on," recalls Laflamme. "It was amazing, the realization that we could basically produce these cells in virtually limitless quantities."

In 2007, Laflamme and collaborators at the University of Washington restored the damage heart muscle of rats and guinea pigs by transplanting these cells, and they later provided the first direct evidence that stem cell-based grafts could electrically couple with adjacent normal cells in the heart and



Research conducted by Dr. Michael Laflamme shows human stem cell-derived heart muscle that was implanted and engrafted in an animal heart. The red depicts a cardiomyocyte (heart muscle cell) marker called alpha-actinin. The blue objects are nuclei. (Image credit: Dr. Michael Laflamme)

contract in unison with host heart muscle cells in previously injured hearts. More recently, their team performed a proof-of-concept study in which they showed that similar grafts could be formed in injured primate hearts, a model that is much closer in size and structure to humans.

"Although we were successful in producing and grafting new heart tissue, it was not without significant hurdles," explains Laflamme. "It was very labour intensive to produce the large number (approximately one billion) of heart muscle cells needed in flasks for transplantation. The cell recipients also tended to develop irregular heart beat patterns, probably in part because our cell therapy needed further refinement."

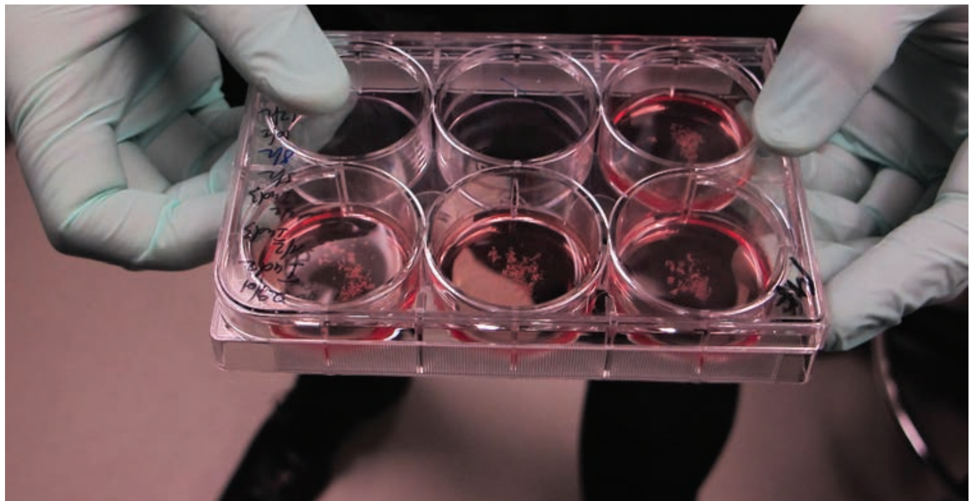
Enter the McEwen Centre for Regenerative Medicine

To solve these challenges, Laflamme looked north of the border to where Dr. Gordon Keller, a world leader in the growth and application of embryonic stem cells, and the expertise housed within the McEwen Centre for Regenerative Medicine, were discovering how to make different types of heart muscle cells from human embryonic stem cells. For Laflamme, Toronto represented a synergy of world-renowned researchers and clinicians working collaboratively to make advances in heart research; the opportunity to define the future of cardiovascular therapy inspired his move.

"Studies conducted in the Keller Laboratory have established the protocols required to transform human embryonic stem cells into different types of electrically active cells in the heart," explains Laflamme. "This represents enormous potential as it provides a population of more pure cells better suited for specific heart diseases."

These include sinoatrial node-like cells, which could be potentially used in a biological pacemaker (thereby replacing conventional electronic pacemakers), and ventricular cells, which are the cell type lost during a myocardial infarction (also known as a "heart attack"). Laflamme's earlier transplantation experiments employed a mixture of these two cell types, which may have contributed to the rhythm disturbances in the cell recipients.

With the goal to eventually submit an application for a world-first human clinical trial in the coming years, Laflamme also needs the requisite technology to efficiently reproduce a critical mass of heart muscle cells at a standard high enough for clinical use. A partnership with the Centre for Commercialization of Regenerative Medicine (CCRM) and the McEwen Centre will enable the mass production of heart muscle cells through the use of bioreactors.



Dr. Michael Laflamme holds beating heart muscle cells grown in laboratories at the McEwen Centre for Regenerative Medicine.

Bioreactors housed at the CCRM will enable the robust and scalable production of heart muscle cells needed for cell therapy applications. (Image credit: CCRM)

"These unique capabilities in stem cell biology and cell manufacturing make Toronto well positioned for this work," says Laflamme. "The bioreactors will allow us to produce the quantities of heart muscle cells that will be needed for cell therapy applications as well as drug screening and disease modelling."

Collaboration with the Peter Munk Cardiac Centre

"The medical advances and innovations happening at the Peter Munk Cardiac Centre are world-class," says Laflamme. "The PMCC embodies all the hallmarks that make Toronto the most promising place to fundamentally alter the course of heart disease: strong leadership, support and investment for innovation, state-of-the-art equipment, and a culture of discovery that encourages risk-taking and teamwork. Many things that would have seemed like science fiction a mere decade ago are in fact routine activity now because of the novel research being funded at the PMCC."

Much work remains to be done before this promising approach can advance to human trials. The next step for Laflamme is testing these laboratory-grown heart muscle cells in larger animals and developing what is known as "preclinical proof of concept." To do this, Laflamme has formed an active working group of PMCC experts, including: Drs. Phyllis Billia, Michael Gollob, Ren-Ke Li, Barry Rubin, Richard Weisel and Terry Yau. Ongoing cell therapy trials being conducted by Drs. Yau and Weisel provide precedent and serve as a model for how Laflamme's own eventual trials will be structured.

"We're uniquely positioned here to be able to develop breakthrough technologies in cardiovascular regenerative stem cell medicine," says Laflamme. "I'm confident that we have the resources in place to harness the power of stem cells and define the next frontier of cardiac care."

VASCULAR SURGERY

Celebrating a decade of excellence

DR. THOMAS LINDSAY DISCUSSES THE TRANSFORMATION OF VASCULAR SURGERY CARE ACROSS ONTARIO

The automotive pioneer Henry Ford is credited with saying: "Coming together is a beginning, staying together is progress, and working together is success."

This is the journey that Dr. Thomas Lindsay, Head of the Division of Vascular Surgery, has travelled during his 24-year career at the Peter Munk Cardiac Centre.

A complex, resource-intensive specialty, vascular surgery involves the repair of aneurysms (ballooning) and blockages in the arteries that slow or stop the flow of blood to the brain, vital organs or limbs. Without proper treatment, these problems can lead to loss of limbs, kidney failure, strokes or other, potentially fatal, complications.

When Dr. Lindsay began his term as the incoming Chair of the Department of Vascular Surgery at University of Toronto in 2003, he noticed an alarming decline in the number of vascular surgery residents in the city. At the same time, vascular surgery procedures were declining across Ontario as hospitals faced budget-cutting and cost savings pressures.

Dr. Lindsay and his colleagues began to feel that vascular surgery was just not a priority for Toronto hospitals, though the need for these life-saving treatments was obviously there.

"It was very frustrating because we had the expertise," he recalls. "What we didn't have was access to the latest technology, which is a key motivator for recruiting top talent. So we're losing surgeons to other centres."

At the time, surgeons at Toronto General were using the traditional way of repairing aneurysms, by cutting open the patient's abdomen, despite the fact that studies were indicating a newer, less invasive method was resulting in better outcomes, including shorter hospital stays, fewer complications and better survival rates in older, high-risk patients. A few patients who could benefit most from the method were being referred to the London Health Sciences Centre, site of a pilot program on the new technique.

The University of Toronto's Department of Vascular Surgery, in collaboration with Dr. Bob Howard at St. Michael's Hospital (SMH) and the Ontario Ministry of Health and Long-Term Care developed a new model for consolidated vascular surgical care. The Centre of Excellence ensured that Toronto patients with life or limb-threatening vascular surgical problems, such as a ruptured aorta or an acutely blocked leg artery, were treated in a timely and efficient manner utilizing the best expertise and resources available.

Since the model was implemented in 2006, the Vascular Surgery centres at PMCC and SMH have become provincial resources.

One of the most exciting ramifications of the PMCC's designation as a Centre of Excellence for vascular surgical care at the time was the Ministry of Health initiative to fund aortic stent grafts. Stent grafting allows surgeons to treat aneurysms in a less invasive manner, often with only local anesthesia. Rather than making a large incision in the abdomen, a small incision is made in the groin, and a synthetic stent graft is passed from an artery in the groin up into the aorta. Using x-ray imaging in the operating room, the vascular surgeon guides the stent graft to the enlarged part of the aorta. Once in position, the stent graft is deployed, and blood flows through the stent graft instead of into the aneurysm.

Dr. Thomas Lindsay, Head of the Division of Vascular Surgery, Peter Munk Cardiac Centre.

"This was a big win for academic vascular surgery," comments Dr. Lindsay. "It injected new energy into the specialty and created a sense of excitement for the team. It was also transformative for vascular surgery in Toronto and, subsequently, across Ontario."

Today, the Division of Vascular Surgery at the PMCC has evolved into a world-class tertiary academic referral unit renowned for delivering care to highly complex cases through advanced diagnostic and surgical interventions. The division currently treats approximately 6,000 vascular patients and performs more than 800 major vascular reconstructions each year.

Dr. Lindsay credits the hard work of his colleagues, such as PMCC Chair and Program Medical Director Dr. Barry Rubin, Dr. K. Wayne Johnston and their counterparts at SMH in achieving a shared vision to deliver integrated state-of-the-art surgical, radiological and medical care to patients who need the best vascular surgery care.

"Our collaboration with St. Mike's provided one of the first successful examples of collaboration and centralization in the province's healthcare system," Dr. Lindsay states. "With the proper resources in place, vascular surgery had the tools to flourish in this rich academic environment."

Specialists in the Division of Vascular Surgery work in complementary multidisciplinary teams on complex cases to ensure patients receive optimal care.

MILESTONES FOR THE DIVISION OF VASCULAR SURGERY OVER LAST 10 YEARS:

- Recruitment of 4 new vascular surgeons
- Development of Multi-Purpose Operating Room
- Adoption of the Advanced Practice Nursing Initiative
- Successful integration of EVAR (Endovascular Aneurysm Repair) technology
- Canadian Society of Vascular Nursing confers honours to vascular nurses
- Site of clinical trial for stem cells to treat limb ischemia
- Integrated practice with Interventional Radiology to both groups' benefit
- Black Family Fellowship in Vascular Surgery-Interventional Radiology established

FOCUS ON RESEARCH

Unravelling the mysteries of macrophages

DR. SLAVA EPELMAN EXAMINES THE ROLE OF PRIMITIVE IMMUNE CELLS IN OVERCOMING HEART INJURY

When the heart suffers an injury, such as from a heart attack or viral infection, the body activates immune cells to repair the damaged tissues. However, these immune cells can themselves cause tissue damage. Why and how this occurs are among the questions Dr. Slava Epelman hopes to unravel through his ground breaking research at the Peter Munk Cardiac Centre.

The answers, according to Dr. Epelman may be found in a type of primitive immune cell.

"It is unclear how immune cells could possess such opposing roles," says Dr. Epelman. "Our work has already shown that a subset of primitive immune cells, called macrophages, enter the heart as early as gestation and remain there during adulthood."

It is already known that versions of these macrophages play a role in cell regeneration in other species. "Think of a salamander," notes Dr. Epelman. "If you cut off its arm, it will regenerate. These macrophages play a major role in that regeneration."

Now, with the aid of Dr. Epelman and his colleagues, these primitive macrophages have been shown to help experimental animals regenerate heart tissue after injury following both a heart attack, and after infection with viruses which cause heart damage. These findings represent a major advance in the field.

In contrast, however, adult macrophages have been shown to promote inflammatory tissue damage in the heart.

Enhancing healing function

Dr. Epelman's research will use genetic animal models and human patient samples to understand how these different macrophage populations (primitive and adult) are related to heart disease in animals and humans. The hope is to enhance the healing functions of the primitive macrophages as a means to improve the ability of heart tissue to regenerate after injury.

"These primitive macrophages, which can be so beneficial in the developing heart still exist in the adult heart, so what happens?" queries Dr. Epelman. "Something occurs to stop them or inhibit them from continuing to work in the same way. We are trying to figure out what happens and why. And try to get them to continue to do what they were originally intended to do – that is aid in growth."

Although he is relatively new to the Peter Munk Cardiac Centre, arriving only at the beginning of 2015, Dr. Epelman is already an internationally-recognized leader in the field of the role of the immune system in heart disease. He earned his PhD and his MD at the University of Calgary, and subsequently spent ten years in the United States at leading institutions including the Cleveland Clinic, Baylor College of Medicine and Washington University.

In his new role as a clinician/scientist at University Health Network, he will devote 80% of his time to research, where he runs his own independent and active research laboratory. The remaining 20% of his time will be spent as a cardiologist treating patients

Dr. Slava Epelman hopes to enhance the healing functions of the primitive macrophages as a means to improve the ability of heart tissue to regenerate.

with the very cardiovascular diseases he studies in the lab. This dual complimentary role will provide Dr. Epelman with a unique ability to translate his studies directly into improved patient care.

With grants from the Heart & Stroke Foundation, the March of Dimes and the Ontario Institutes of Regenerative Medicine, among others, Dr. Epelman will look at a variety of possible connections between macrophages and heart disease.

Dr. Epelman describes some of the areas being investigated.

1. Manipulating cardiac macrophages after myocardial infarction in order to improve cardiac regeneration: "We have observed significant changes in cardiac macrophage composition in

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INNOVATIVE PARTNERSHIP

Improving patient safety at the PMCC

PMCC-BOSTON SCIENTIFIC COLLABORATION TO FOSTER A NEW ERA IN HIGH-RELIABILITY CARE

A newly forged partnership between the Peter Munk Cardiac Centre and Boston Scientific Corporation will aim to optimize and improve the care that is delivered to cardiac and vascular patients.

"This unique collaboration is about using proven techniques and tools to create capacity within our current structure at the PMCC to ensure both excellence in patient care and efficiency in our daily workflows," says Dr. Barry Rubin, Chair and Program Medical Director of the PMCC. "Importantly, it moves our program forward significantly towards UHN's vision of becoming a high-reliability organization – which has a goal to reduce preventable patient harm to zero."

The Boston Scientific team will be embedded on-site over the next several months to gain an in-depth understanding of the PMCC and to share international best practices and proven support tools to work in tandem with staff in specific focus areas to identify improvement opportunities, and to develop and implement solutions.

"Boston Scientific has a record of success with this type of initiative in thirty hospitals across eight countries both in the U.S. and internationally, and we will be the first Canadian site to realize this type of important partnership," says Dr. Rubin.

Using known best practices, collaborative teams, smart technology and innovative processes are all integral components to creating patient-focused solutions for healthcare delivery. As the PMCC continues to explore new and exciting ways of enriching the patient experience, their voices will be critical in guiding this process.

"Thinking about our patients as partners is one more way to push our thinking, actions, and commitment to them and their families to the next level," says Dr. Rubin. "The Boston Scientific team that will be joining us has extensive consultative experience in similar healthcare environments and that experience will be a huge asset."

PETER MUNK CARDIAC CENTRE - CLINICAL & RESEARCH REPORT

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Dr. Terrence Yau

In the news

First international cardiac tumour conference

With a view to sharing knowledge and better understanding the role of multidisciplinary medical and surgical teams involved in the care of patients with cardiac tumours, the inaugural Toronto Cardiac Tumour Conference was held on January 21st, 2016.

"I thought it would be good to bring experts from around the globe to Toronto to talk about this very rare topic that really has never been discussed in an organized way before," says cardiac surgeon and conference organizer, Dr. Robert Cusimano.

Considered a "rare" medical occurrence, cardiac tumours are abnormal growths that either develop in the heart or heart valves (primary tumour), or spread to the heart from another part of the body (secondary tumour), already afflicted with cancer. While most cardiac tumours are benign, they can prove to be challenging to treat depending on their size and position in the heart.

"We've been fortunate to have people send us patients with cardiac tumours because we are such a highly-specialized care centre," says Dr. Cusimano. "With really rare conditions, it's important to send them to somebody who has a lot of experience."

The inaugural Toronto Cardiac Tumour Conference focused on the evaluation and treatment of tumours of the heart.

...Unravelling the mysteries of macrophages continued

the injured area following a myocardial infarction, or heart attack. We hypothesize that a certain macrophage subset promotes repair after myocardial infarction, and our focus is to enhance the function of this reparative macrophage subset."

2. Determine the role of cardiac macrophage subsets in protection against viral myocarditis and cardiac tissue injury: "Viral myocarditis is an important contributor to the development of cardiomyopathy in children and adults—a condition for which we have few effective treatment options. Although it is known that macrophages play an important role in the progression of cardiomyopathy, the cells that mediate host protection against the viral infection and/or by-stander injury remain poorly defined."

3. Perform translational studies examining human cardiac macrophages in patient tissue samples: "In parallel to animal studies, we will perform translational studies on human tissues. This may help us to advance our understanding of a number of areas, including isolating macrophages and understanding their lineage, and finding ways to predict recovery patterns."

"Altogether, our research program combines a number of innovative elements," Dr. Epelman concludes. "These include both the discovery of macrophages that regenerate heart tissues and the development of strategies to improve their function following a heart attack, as well as understanding how macrophages prevent viral infections that cause heart injury."