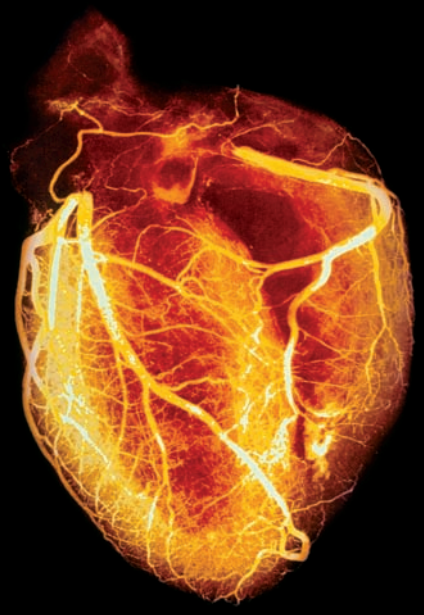
Peter Munk Cardiac Centre

CLINICAL AND RESEARCH REPORT

VOL. 9 NO.1 / SUMMER 2013



The road to regeneration

RESEARCH AT PMCC OPENS DOORS TO NEW HEART THERAPIES

Does the human heart have the ability to repair itself? This has long been one of the great mysteries facing researchers studying heart disease. In fact, it has generally been accepted that this self-repair function was restricted by the fact that heart cells, unlike many other human cells, are unable to regenerate. Now, breakthrough research at the Peter Munk Cardiac Centre is changing this perception – potentially unlocking exciting new approaches to the treatment of heart disease.

Dr. Phyllis Billia and her team of researchers at the Centre have presented direct evidence that regeneration of heart cells is possible. Their research also suggests that the ability of heart cells to regenerate is being suppressed by natural 'roadblocks'. And if these roadblocks can be removed, heart cells would be able to regenerate and multiply, providing a potential pathway to repair the damage caused by an insult or injury to the heart, such as that resulting from a heart attack.

Dr. Billia's practice is focused on the treatment of heart failure, hypertrophic cardiomyopathy, mechanical assist devices and transplantation. In addition, she is a partner within the Echocardiography Department at University Health Network.

Dr. Phyllis Billia's research is showing – for the first time - that heart cells do have the potential to regenerate and repair themselves.

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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

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Dr. Billia completed her PhD at the University of Toronto and went on to complete her medical degree, including her Internal Medicine and Cardiology training at the Faculty of Medicine, University of Toronto. She continued with sub-specialty training in echocardiography and completed a post-doctoral fellowship at the Campbell Family Institute for Cancer Research in Dr. Tak Mak's laboratory.

Finding clues in cancer

It was this experience in cancer research that played a significant role in the breakthrough in heart muscle cell regeneration. "Historically, we have not had a lot of success in trying to solve this problem," Dr. Billia notes. "Heart muscle cells are somehow prevented or suppressed from regenerating. So, if they are damaged, for example during a heart attack, the damage is irreversible. This suppression is a type of protective measure. It is a concept well known in the cancer world where tumour suppressor genes force the inability to regenerate and proliferate. These tumour suppressors help stop cancer from spreading."

By studying and manipulating tumour suppressor genes and refocusing them on damaged heart cells, Dr. Billia has been able to break new ground. "The genetic manipulations of tumour suppressor genes have provided us with an avenue to control heart regeneration," she states.

Through the establishment of a dedicated research lab at the Centre, Dr. Billia and her colleagues will be able to further explore the processes which are responsible for the heart's inability to regenerate muscle cells.

Dr. Billia's experience in cancer research has played a significant role in this exciting new breakthrough in heart cell regeneration.

Repairing from within

Dr. Billia's small team includes a technician, research assistant and summer lab assistant. They are able to utilize the latest techniques in molecular biology to study tumour suppressor gene function in the heart.

Her own research shows that heart-specific manipulation of these genes provides a potential mechanism that can be harnessed in patients to improve heart function. Therefore, Dr. Billia's work is now focused on the development of a clinical strategy to exploit the targeted manipulation of the processes responsible for this suppression in preclinical animal models. She expects that these investigations will identify potential drugs that can then be used to induce cardiac muscle cell division in patients. She believes that through this research, the removal of the roadblocks to cardiomyocyte regeneration is very possible, thus providing an exciting new opportunity for the heart to potentially repair itself after a damaging event.

Dr. Billia explains: "When it comes to damaged heart cells we've previously believed that the heart could not regenerate or recover function. In the case of a heart attack, when an artery closes there is little or no blood flow beyond that closure. Without nutrition the cardiomyocytes die, causing damage which we thought was permanent. Now we see a unique opportunity to repair that damage by regeneration of cardiomyoctyes in the affected part of the heart."

The potential long term implications of this work are very exciting. By developing ways to reverse damage done to the heart cells and permanently repair the heart from within, it may be possible to reduce or eliminate other existing therapies, such as long-term drug therapy and its association with side effects and negative impact on quality of life, or risky surgical interventions. Regeneration of resident cardiac muscle cells could potentially be used in all forms of heart disease associated with deterioration of function within the heart, with the exemption of genetically-derived heart disease.

Envisioning new therapies

Over the next few years Dr. Billia will continue her research with the ultimate goal of developing a new way of treating heart damage. "Right now we are still at the proof of concept stage, testing and identifying candidate compounds in established small animal models replicating the effects of a heart attack," she says. "After that we hope to move to pre-clinical trials in larger mammals, and testing our clinical approach to regenerating cells and repairing damage at the site of the injury. If all goes well, the next stage would be clinical trials to perfect the safety and efficacy of the treatment we currently envision to develop."

> "We see a unique opportunity to repair heart damage by the regeneration of cardiomyocytes."

Dr. Billia believes that the result of this work being conducted at the Peter Munk Cardiac Centre could be far reaching, impacting other important areas of medicine. The observation that the heart cells do have the ability to regenerate can be applied to other organ systems. In fact, Dr. Billia's laboratory already has seen examples of this occur in other organs. "Our ability to identify the processes needed to allow heart cells to regenerate can also conceptually be applied to other organs that do not naturally regenerate, such as the brain, kidney and pancreas, as well as the spinal cord. This could have exciting implications for treating other conditions, from diabetes to spinal cord injury."

MOLECULAR MEDICINE

Cardiovascular disease affects over 500,000 Canadians with 50,000 new cases diagnosed every year. In Canada alone, one person dies every seven minutes from heart disease or stroke. An increasing number of patients who survive heart attacks and other cardiac episodes often develop chronic problems and face even more complex cardiac conditions that are progressively leading to the epidemic of heart failure.

Heart failure is the leading cause of morbidity and mortality in North America and has been identified as the second leading cause of extended hospital stays. The quality of life and the prognosis for this group of patients remains poor with one-year survival rates of less than 40%. In addition, more than $1 billion of Canada's annual health budget is being spent for the care of patients with heart failure.

Alternatives to medical therapy are limited to transplantation or mechanical assist devices. These approaches are highly invasive and often have inherent risks. As such, it is exceedingly important to research and the development of alternate treatment strategies that will effectively help the heart repair itself.

Molecular medicine is a field of research that strives to understand the pathogenesis of diseases at the cellular and molecular level. Understanding the regulation of heart cell growth, production and death is the key to being able to prevent the development of heart failure. This research will open the door to the development of new, exciting therapies and treatments that will not only improve the quality of life for patients but also reduce the costs associated with patient care.

CARDIOVASCULAR SURGERY

Pocket controller makes life easier for patients

PMCC SELECTED FOR FIRST NORTH AMERICAN TRIAL

Patient care does not end with a medical intervention or procedure. The commitment to providing the most advanced care extends well beyond the walls of the Peter Munk Cardiac Centre, improving not only outcomes, but the patient's quality of life when they leave the hospital environment. The selection of the Centre as the first in North America to use a new state-of-the-art device – the *HeartMate II Pocket Controller* – for patients with left ventricular assistive devices is just the latest example of this commitment.

"Our selection as the first site in North America to use this device demonstrates the reputation that PMCC has within the industry for high quality clinical outcomes, research and education," notes Dr. Vivek Rao, Head, Division of Cardiovascular Surgery, PMCC Chair in Advanced Cardiac Therapeutics.

Left ventricular assist devices – or LVADs – are surgically implanted, battery-powered pumps designed to augment the pumping action of a heart that has become too weak, as a result of heart failure, to function effectively on its own. It is implanted inside the chest to help the patient's weakened heart ventricle pump blood efficiently throughout the body. Unlike an artificial mechanical heart, the LVAD doesn't replace the heart; it simply helps the heart to do its job more effectively. The procedure to implant a LVAD requires open-heart surgery and has some risks. However, a LVAD can be lifesaving for patients with severe heart failure (see sidebar).

Pierre Zurawicki, one of the first patients to try the new Pocket Controller, with Dr. Vivek Rao.

A lifesaving device

Surgeons at the Centre have implanted many LVADs over the years. The LVAD is surgically implanted just below the heart. One end is attached to the left ventricle, the chamber of the heart that pumps blood out of the lungs and into the body. The other end is attached to the aorta, the body's main artery. Blood flows from the ventricles into the LVAD. When the device's sensors indicate that it is full, the blood is pumped out, into the aorta and subsequently through the body.

The safety of LVADs has been greatly improved over the years, with many of these improvements being made because of work done here in Toronto.

The HeartMate II is the most widely used and extensively studied LVAD in the world. This device has proven to be highly durable, capable of long-term circulatory support. A number of controlled clinical trials have demonstrated significant improvement in patients' functional capacity. Overall, many patients report returning to active living, with meaningful improvements in their quality of life. To date, over 14,000 patients have been implanted with HeartMate II, including many at the Centre.

The device consists of the pump and its connections – which are implanted during open-heart surgery – a power pack, a reserve power pack and a computer controller that remains outside the body.

This controller is a key component, displaying the status of the system and issuing warnings if needed. It is an important interface and its ease of use and convenience to the patient are vital. It is a major advancement in controller technology, in the form of the *HeartMate II Pocket Controller,* that is now being used at the Peter Munk Cardiac Centre.

"This is the first site in North America where the Pocket Controller is being used, through special access from Health Canada," explains Stephen Harwood of Thoratec, the device's manufacturer. "We call this device the 'brains of the operation', and it's a vast improvement over previous LVAD controllers. It's smaller, lighter and ergonomically designed specifically for the patient, who can literally put it in their pocket. It has an intuitive user interface with enhanced information content. It has also been designed to promote patient safety, through features including prioritized visual alarms, on-screen instructions, and a backup battery, which can provide at least 15 minutes of full power during periods of inadvertent disconnections from power sources."

The deliberate patient focus of the new device is already scoring points with users. Pierre Zurawicki suffers from chronic heart failure. He was implanted with a HeartMate II LVAD at the Peter Munk Cardiac Centre in 2011. As one of the first patients to be switched to the Pocket Controller, Pierre is thrilled. "I think it's a fantastic improvement," he says. "It's a lot lighter. I can see the readings right on the controller's screen at the push of a button instead of having to plug it in to a monitor. The battery lasts longer and the battery status is easy to read. I love it."

Nurse Practitioner Jane MacIver helps familiarize Pierre with the features of the new controller.

Improving quality of life

Pierre's enthusiasm translates into clear benefits: an enhanced level of compliance through ease-of-use and an overall improved quality-of-life.

These QOL-related benefits are matched by clinical ones. "The new pocket controllers serve two purposes," states Dr. Rao. "One, in response to patient requests, the size and weight of the controller are significantly reduced compared to the previous version. Two, the pocket controller provides more interactive data (in multiple languages) for both patient and care provider. Instead of a yellow or red alarm, the new controller provides a text message indicating the nature of the alarm state."

Nurse practitioner Jane MacIver has been involved with Pierre's care since he was implanted with his LVAD two years ago. "It's great to see the progress Pierre has made," she says. "Before he received his implant, he had shortness of breath and was extremely restricted. Now he's able to do things he couldn't before and is back at work full time. This smaller, lighter controller will give him more freedom as well as peace-of-mind from its advanced safety features. His quality of life will get even better."

LEFT VENTRICULAR ASSISTIVE DEVICES:
Saving and improving lives

LVADs are typically used in three clinical situations:

Heart failure: Implantation of a LVAD device can allow a damaged left ventricle to "rest" and to repair itself. LVADs can help improve function for individuals with acute myocarditis, after cardiac surgical procedures, or following major acute heart attacks.

Transplantation support: LVADs can be used in patients with chronic heart failure who are waiting for a heart transplant, serving like a 'bridge to transplantation'.

Destination therapy: LVADs have a key role for individuals with severe end-stage heart failure who require support for their hearts, but are not candidates for transplantation (due to age, other medical conditions, etc.). In these patients, LVADs are often effective in increasing the heart's pumping ability and reducing the symptoms of heart failure, such as shortness of breath and severe weakness. In these cases LVAD therapy is usually permanent.

FOCUS ON RESEARCH

Solving the mysteries of MSNA

UNDERSTANDING THE SYMPATHETIC NERVOUS SYSTEM'S ROLE IN HEART HEALTH

The sympathetic nervous system plays a vital role in the everyday lives of human beings, including regulating arterial blood pressure. Sympathetic nerves innervate the heart and blood vessels, and when activated can increase heart rate and cause peripheral vasoconstriction. Learning more about the sympathetic neural control of the circulation is important in our understanding of a number of cardiovascular-related problems, including hypertension and heart failure, and how we can better manage these conditions.

The Peter Munk Cardiac Centre is leading the way in increasing our knowledge in this key area.

Important research in this area is ongoing in the labs of Dr. John Floras, Director, Cardiology Research and Canada Research Chair in Integrative Cardiovascular Biology. Dr. Floras was the first person in Canada to study the sympathetic nervous system by recording directly from muscle sympathetic nerves directed towards the calf muscle (muscle sympathetic nerve activity, or MSNA). One of the defining characteristics of MSNA in humans is that the sympathetic nerves exhibit spontaneous "bursts" of activity. These bursts represent the coordinated activity of several individual nerve fibers and their effects are numerous and complex. As sympathetic activity is elevated in many cardiovascular conditions, the direct measure of MSNA has opened the door to a greater understanding of neural circulatory control, but there are still many aspects to be explored and numerous questions remain.

The work currently being done on MSNA at the Centre is helping to provide answers in some key areas. Two particularly significant projects are being led by Dr. Catherine Notarius and Dr. Philip Millar respectively.

Dr. Catherine Notarius: MSNA response to leg exercise in heart failure

It has been known for some time that MSNA decreases in healthy individuals during leg cycling exercise performed at mild to moderate intensities. In a recent study, conducted as part of a larger collaboration with the Toronto Rehab Institute, Dr. Notarius and colleagues compared the MSNA response during leg exercise in subjects with heart failure (HF) to healthy individuals. The purpose was to test the hypothesis that, in contrast to the drop in MSNA shown in healthy people, MSNA would actually increase in individuals with HF.

The study confirmed the hypothesis and clearly showed, for the first time, an MSNA increase in HF subjects during leg exercise.

"Sympathetic nerve activity is known to most people as the 'fight or flight' response," explains Dr. Notarius. "It is measured directly by inserting a small recording electrode in a nerve and counting the number of 'bursts' per minute. Sympathetic activity is increased in heart failure patients to help compensate for low blood flow from the heart. This short-term benefit has a negative long-term effect, and leads to exercise intolerance and disease progression. We can now start looking at why these patients have a more reactive MSNA response during exercise than healthy individuals and whether regular exercise training, as in cardiac rehabilitation, can lower this response."

Dr. Philip Millar: MSNA response and statin medications

This study examined the effects of statins, a class of cholesterol medications, on hypertensive individuals – specifically their mechanisms beyond basic cholesterol lowering, and those effects possibly linked to MSNA.

"The clinical success of these drugs has been attributed largely to their lowering of total and LDL cholesterol," notes Dr. Millar. "We focused on any concurrent autonomic effects that may be independent of their primary action."

The results, recently published in the prestigious clinical journal *Heart*, showed that the lipophilic (i.e., with the ability to cross the blood-brain barrier) drug simvastatin did, among other things, lower MSNA. This was thought to be caused by an interaction with regions of the brain responsible for regulating central sympathetic outflow.

This knowledge could have clinical relevance for people with conditions characterized by high MSNA, including post-infarct patients, as well as hypertensive individuals with comorbidities, such as metabolic syndrome.

"The next step is to examine if this applies to all statins" Dr. Millar states. "These results suggest that statins have central autonomic effects which may contribute to their overall ability to reduce cardiovascular morbidity and mortality in high-risk populations."

Heart and Stroke funding boosts research

The Heart and Stroke Foundation has announced a $300 million initiative to support cutting-edge heart and stroke research at leading health institutions across the country, including the Peter Munk Cardiac Centre.

University Health Network, as a member of the Heart and Stroke Foundation Research Leadership Circle, will receive $25 million in research funding over the next 10 years . The funding initiative is the largest research commitment in the organization's 60-year history. It will accelerate the progress of the Heart and Stroke Foundation's goal of reducing Canadians' rate of death from heart disease and stroke by 25 per cent by 2020.

As part of the newly-formed Heart and Stroke Foundation Research Leadership Circle, UHN is one of 19 centres to benefit from this gift. The commitment will bolster the research of scientists and clinicians across UHN who are already pursuing research, teaching and clinical breakthroughs and innovation in stroke and cardiovascular health.

"The new commitment from the Heart and Stroke Foundation will provide UHN with a stable source of funding for cardiovascular research," says Dr. Michael Farkouh, Chair of the Peter Munk Centre of Excellence in Multinational Clinical Trials, Peter Munk Cardiac Centre, UHN. "This will allow us to build on our discoveries and ensure our research is translated into better health care outcomes for Canadians who are confronting the threat of heart disease and stroke."

Dr. Michael Farkouh believes the funding from the Heart and Stroke Foundation will allow the PMCC to build on its excellent record of scientific discovery.

PETER MUNK CARDIAC CENTRE - CLINICAL & RESEARCH REPORT

Acknowledgments

Dr. Phyllis Billia
Dr. Michael Farkouh
Dr. John Floras
Jane MacIver, RN-NP
Dr. Philip Millar
Dr. Catherine Notarius
Dr. Vivek Rao

In the news

Golf charity event benefits cardiac surgery

On June 24, 2013, Duff & Phelps, with the support of over 40 corporate sponsors and more than 100 individual golfers, raised more than $150,000 for the Peter Munk Cardiac Centre. Held at Beacon Hall Golf Club in Aurora, this was the Charity Golf Outing's 16th year.

A highlight of this year's tournament was PGA Tour golfer Erik Compton who hosted a golf clinic at the event. When he was nine, Compton was diagnosed with viral cardiomyopathy. This condition resulted in him undergoing two successful heart transplants.

Also lending their golf talents to the tournament were PMCC Medical Director Dr. Barry Rubin and PMCC Campaign Cabinet Chair and TGWHF Board Member Jeff Rubenstein, who was instrumental in linking Duff & Phelps with the PMCC.

PGA Tour Golfer and heart transplant recipient Erik Compton (second from right), with Robert Harlang, Richard Rubenstein and PMCC Campaign Chair Jeff Rubenstein at the Duff & Phelps Charity Golf Outing

"This year, our charity golf event will benefit the Peter Munk Cardiac Centre because more than five million Canadians suffer from various forms of heart disease today and the demand for expert cardiac, vascular and cardiovascular care will only increase," said Robert Harlang, Managing Director at Duff & Phelps and event co-chair. "The proceeds from the 2013 Duff & Phelps Charity Golf Outing will be used to assist in the recruitment of three cardiac surgeons and two vascular surgeons over the next two years and provide them the opportunity to establish their respective research laboratories. Their research will help to change the face of heart disease."

Duff & Phelps is a global financial advisor and investment banking firm with offices throughout North America, Europe and Asia.

The Peter Munk Cardiac Centre gratefully acknowledges the generosity of Judy and Peter Braaten and the Brompton Group for their generous sponsorship of this Clinical and Research Report.

For more information, please visit **www.petermunkcardiaccentre.ca**
To support the PMCC through a donation, please visit **www.inaheartbeat.ca** or call **416-340-4056**

Thank you – our donors – for your continued support of the Peter Munk Cardiac Centre.

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