Volume 2, Issue 4 2007

UNIVERSITY OF OTTAWA HEART INSTITUTE
INSTITUT DE CARDIOLOGIE DE L'UNIVERSITÉ D'OTTAWA

# THE BEAT

A COMPENDIUM OF INFORMATION ABOUT THE UNIVERSITY OF OTTAWA HEART INSTITUTE

## HIGHLIGHTS

"The imaging technology is the glue that allows us to transition into the molecular level in studying information about humans."

*– Dr. Rob Beanlands, UOHI Chief of Cardiac Imaging (from Molecular Medicine: A Revolution in Heart Health, pages 1–2)*

"There is tremendous potential for regeneration of the heart, but so much remains to be understood and we are still just scratching the surface. This work helps us comprehend what we need to achieve a bit better."

*– Dr. Marc Ruel, UOHI Director of Cardiac Surgery Laboratory Research (from Mending Hearts with Regenerated Blood Vessels, pages 1 and 3)*

Dr. Marc Ruel, one of the Heart Institute's most promising cardiac surgeons, has been honoured with the Royal College Medal Award in Surgery for 2007 in recognition of research excellence. The medal is considered by the medical community to be one of the most prestigious awards in Canada.

*(from UOHI Surgeon-Scientist-Scholar Takes Top Canadian Medal, page 3)*

"This is a leading institute in the world in terms of cardiovascular research and a very attractive place to be right now."

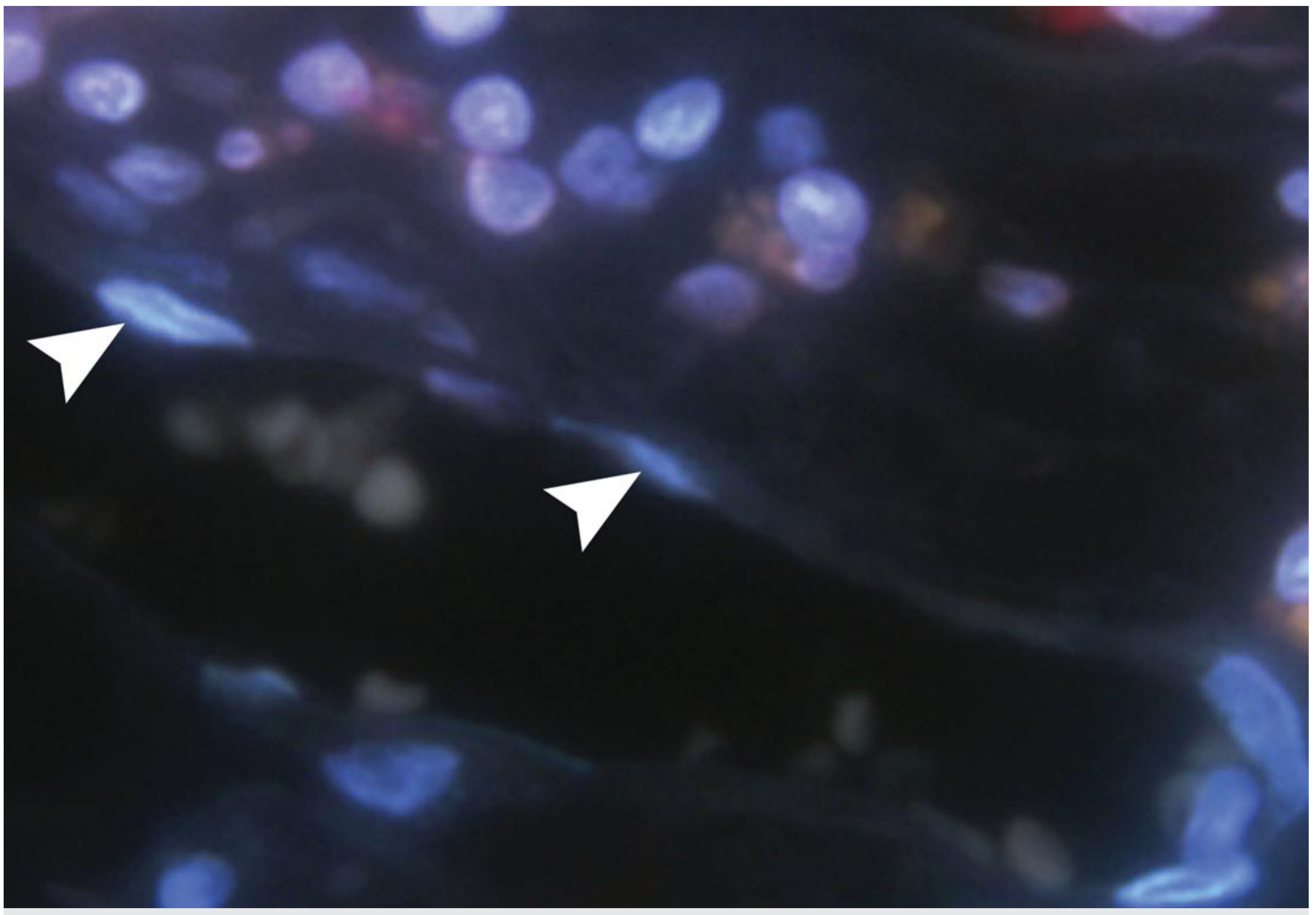
*– Dr. Pinchuang Zhang, Cardiac Surgeon (from Learning to Build Blood Vessels, page 4)*

## IN THIS ISSUE



*The Beat* is published by the University of Ottawa Heart Institute (UOHI). Comments or questions about *The Beat* should be directed to Jacques Guerette, Vice President, Communications at 613-761-4850 or jguerette@ottawaheart.ca. For more information about UOHI, please visit www.ottawaheart.ca.





The photo shows transplanted adult stem cells dyed blue. The arrows point to two cells that have merged into the lining of a blood vessel and have helped in its regrowth.

# Molecular Medicine: A Revolution in Heart Health

Someday physicians will be able to diagnose and treat heart disease even before symptoms appear. Cardiovascular medicine is undergoing a revolutionary change. Now researchers are hunting inside the body's cells and molecules to find better treatments for heart disease. The University of Ottawa Heart Institute (UOHI) sees the promise that this new era of medicine brings and has developed a large program in cellular and molecular imaging research.

Seven principal investigators at the Heart Institute have begun projects that are both diverse and extraordinary. Support came partly from the Heart and Stroke Foundation, which provided a prestigious program grant for the purpose of building a team of researchers – from surgeons and cardiologists to physicists and chemists. The team includes an elite corps of 35 'students' – some of whom have come from around the world as scientific experts in their own right – chosen to train at Heart Institute laboratories in molecular function.

"This program grant is geared to two very unique features," says Dr. Rob Beanlands, Chief of Cardiac Imaging at UOHI. "One is the actual translational research in molecular function and molecular imaging. The second is a very new kind of training – transdisciplinary training." Dr. Beanlands is also founding Director of the National Cardiac PET Centre at the Heart Institute, where a large portion of the molecular research will take place. Cardiac PET (Positron Emission Tomography) measures the activity of cells in, around and leading to the heart.

*(continued on page 2)*

# Mending Hearts with Regenerated Blood Vessels

Can the body's own cells be coaxed into mending a damaged heart? Scientists at the University of Ottawa Heart Institute are developing techniques to rebuild blood vessels, improve heart function and perhaps someday spare the need for heart transplantation. Led by cardiac surgeon Dr. Marc Ruel and scientist Erik Suuronen, PhD, the cardiac surgery research group is the only such team in Canada involved in clinical angiogenesis and vascular regeneration of the heart. Angiogenesis involves the growth of new blood vessels from existing vessels.

The concept of using cell therapy to rebuild heart tissue may prove to be the next frontier in cardiac treatment. Dr. Ruel, Director of Cardiac Surgery Laboratory Research at the Institute, and a research team led by Suuronen, a scientist in the Division of Cardiac Surgery, will have the results of their work published later this year. Their research suggests that transplanting cells, called endothelial progenitor cells, from the bloodstream might effectively treat patients who have suffered a heart attack.

"There is tremendous potential for regeneration of the heart, but so much

*(continued on page 3)*

*(Molecular Medicine: A Revolution in Health, continued)*

Translational research allows scientists to find new treatments and get them more quickly to patients. With the right structure in place, scientists and physicians work together to 'translate' new knowledge from the laboratory to the medical clinic and back again to the laboratory.

In most laboratories across the country, scientists with different disciplines work alongside each other. The cross-talk and exchange of ideas provides a very rich atmosphere for learning. What's unusual in the Heart Institute program is how medical and science students are being trained. Students not only have more than one supervisor but the co-supervisors have completely different backgrounds.

"Transdisciplinary training means they are not just focused in their silos but a cardiology resident will be getting some biochemistry, adding physics or working on biochemistry, but with a cardiac surgeon who is studying how to use cells to rebuild heart vessels," says Dr. Beanlands. The goal is to expand the training process, especially for post-doctoral and medical students, by providing dramatically different opportunities to learn science and clinical research.

"This is a large, diverse group that is coming together under a common theme, which is looking at molecular cell function and alterations as a result of heart disease," says Dr. Beanlands. Most of the work is in the lab but the Heart Institute is home to a highly advanced Canadian cardiac imaging centre that includes multi-slice Computerized Tomography (CT). This new multi-disciplinary research program was built around PET imaging, which allows physicians to watch the function of blood flow right to the heart in both animal models and humans.

"The imaging technology is the glue that allows us to transition into the molecular level in studying information about humans," Dr. Beanlands adds. "The Heart Institute has been moving like a bullet train in the area of genetics. Molecular imaging is what we have been doing all along and now we can advance research further."

The $1.25 million program grant from the Heart and Stroke Foundation is one of several grants that supports this program. Others include a $3.3 million award by the Canada Foundation for Innovation to help set up the molecular imaging program. The research themes being pursued are as follows:

> "This is a large, diverse group that is coming together under a common theme, which is looking at molecular cell function and alterations as a result of heart disease."
>
> – Dr. Rob Beanlands, UOHI, Chief of Cardiac Imaging

- **Dr. Rob Beanlands,** Cardiologist, Chief of Cardiac Imaging

The team, with 10 students including six medical residents and two cardiologists, is looking at metabolism, energetics, blood flow and cell function.

One study involves sleep apnea, also known as obstructive sleep disorder, which is often associated with loud snoring. The combination of heart failure and sleep apnea are commonly seen. Researchers are looking at whether the use of continuous positive airway pressure (CPAP) – a prescribed treatment for sleep apnea – can improve the heart's performance.

Other studies are investigating cardiac energetics – how energy production is regulated in the heart. An enlarged heart and diabetes may be complicated by changes in energy consumption of the heart. Energy in the heart is affected by the flow of blood and oxygen. And blockages in vessels, for example, limit the amount of oxygen and blood flowing to the heart.

- **Dr. Michael Gollob,** Cardiac Electrophysiologist

With five students, this team is working with diseased human and animal models to investigate cardiovascular genetics related to issues such as metabolic cardiomyopathy. Metabolic cardiomyopathy is weakness of the heart muscle due to chemical and physical risk factors such as high blood pressure, obesity, and blood glucose problems like diabetes. As cardiomyopathy worsens, the heart becomes weaker and less able to pump blood through the body. This can lead to heart failure and arrhythmias, which are abnormal heart rhythms. Evidence through groundbreaking research by Dr. Gollob indicates a genetic association.

- **Dr. Marc Ruel,** Cardiac Surgeon, Epidemiologist, Director, Laboratory Research
- **Erik Suuronen,** PhD Cellular and Molecular Medicine

A total of 11 students on these two teams are investigating cellular and molecular medicine as a means of rebuilding blood vessels and repairing a damaged heart through regenerative therapy. Techniques include cell transplantation, tissue engineering and cellular revascularization. Dr. Ruel is looking at growing new blood vessels from cells collected from a patient's own body. And he is working closely with Erik Suuronen on tissue engineering.

Tissue engineering allows human tissue to be grown in the laboratory from cells removed from the patient. This has proved useful in other areas of medicine where scientists have grown cells within a porous material and cut them to make a new jaw or limbs, replacing damaged parts after an accident.

Research at the Heart Institute is applying a similar but much more complex technique to help rebuild damaged heart material. Suuronen laid the groundwork for tissue engineering research at the Heart Institute. Among his specialties is the development of matrices designed to promote tissue rebuilding. Imagine a small piece of webbing that can hold moist plaster to repair a hole in the wall. But in human tissue, a matrix will be biodegradable and eventually dissolve once new tissue has grown and taken hold.

- **Jean DaSilva,** PhD Chemistry and Pharmacology, Head, Radiochemistry and Biotesting Laboratory

This team produces and analyzes traditional tracers in the Heart Institute Radiochemistry Laboratory. Tracers are labelled molecules, which are detected by the PET scanner. PET measures metabolic activity or receptor density at a site in the body. PET is useful in diagnosing cardiovascular disease because the imaging highlights areas with higher, lower or no metabolic activity or receptors – and can more precisely locate problems, help to study progression of disease and direct therapy.

The researchers are investigating novel tracers that would allow imaging of different, even more precise systems in the heart. One of DaSilva's specialties is developing tracers whose signals reveal diagnostic information about heart failure. A total of 14 students with backgrounds ranging from pharmacology and chemistry to cardiology comprise the team.

- **Robert deKemp,** PhD Physics, Head Imaging Physicist, Director, Small Animal Imaging Facility

Six students will be tutored in PET imaging physics and engineering. The Heart Institute is also equipped with a micro-PET, suitable for small animals so scientists can observe and measure blood flow, tissue growth and other organic functions in non-invasive environments. This area of research is especially suited to translational research because it allows scientists to use these measurements and observe differences and similarities between animal models and humans.

- **Mary-Ellen Harper,** PhD Biochemistry, Mitochondrial Bioenergetics Laboratory, University of Ottawa

Nine students will be involved with metabolic and functional changes in the body and how these relate to heart disease. Harper's work revolves around the mitochondria, the energy chargers for cells, which in turn have their own set of DNA. Recent research has shown that changes in mitochondrial DNA increase with age and are likely the cause of aging.

With reduced mitochondrial function now seen as a factor in aging, Harper's research will also examine how heart disease is involved in these functional changes.

## Watching PET in Motion

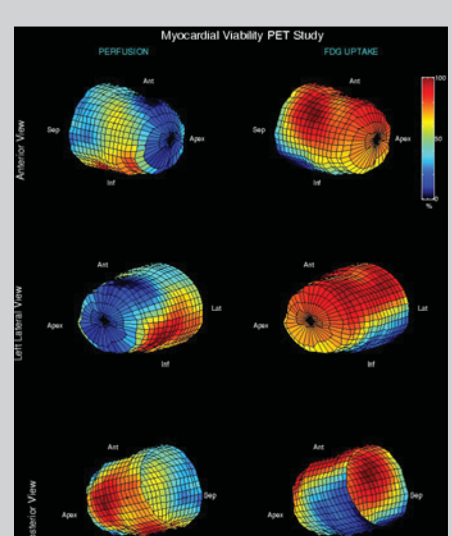
Cardiac imaging by Positron Emission Tomography has proven useful to understanding normal heart function. The University of Ottawa Heart Institute is conducting the first large patient study of its kind to use PET to measure how well the heart uses sugar. The study will help determine the best therapies and treatment for patients with poor heart function.

Oxygen and nutrients such as sugars and fatty acids work as fuel, providing the heart muscle with the necessary energy to pump. But abnormalities can distort how the energy is used. In some cases there is a reduced efficiency and this is a sign of reduced heart function.

The force of a heart's pumping action is controlled through stimulation at the heart cell surface by adrenalin and other hormones. Adrenalin molecules, for example, bind to proteins on the surface called receptors. These receptors stimulate chemical reactions inside the cell, ultimately leading to an increase in the force of contraction and thus a stronger heart beat. A diseased heart may alter the message from the adrenalin (or other hormones) and treatments sometimes focus on improving this messaging to improve the heart's function.

Research at the University of Ottawa Heart Institute is applying various evaluation methods using PET scanning to measure how the heart uses fuel and energy, and how the cells send the messages. PET will be used to characterize new compounds for measuring different heart cell receptors.

PET scans can measure the flow of trace amounts of substances. Measuring C-11-acetate, for instance, indicates how well the heart uses oxygen. The sugar-like compound F-18-FDG is used to measure how well the heart uses sugar, and C-11-hydroxy-ephedrine (HED) is used to measure the nerve function in the heart.




This Positron Emission Tomography (PET) image shows whether there is living tissue in the heart despite the patient's poor blood flow. The image emphasizes how PET can answer specific clinical questions.

# In Translation: From Science to the Bedside

Translational research is easy to understand but extremely complex to achieve. In a hospital, scientific discoveries are 'translated' into practical applications to help improve human health.

The most common image is a researcher in a white coat in the laboratory. This is basic research, which mostly takes place in the laboratory where scientists study cells and molecules. Their work at the 'bench' leads to tools such as vaccines or other therapies for patients attending a medical clinic or in a hospital bed. This approach is called 'bench to bedside' research.

Sometimes research starts at the other end – in a clinic or at the bedside where physicians observe patients and the process of a disease, such as the link between obese people and diabetes. This is clinical research.

Traditionally, basic research and clinical research have not crossed paths. There have been some unlikely but notable exceptions, for example Dr. (Sir) Frederick Banting, the co-discoverer of insulin. To further the cause of science and military medicine during the Second World War, Dr. Banting conducted experiments and exposed himself to mustard gas, test flights without cabin pressure and many other risks.

Dr. Banting conducted experiments and exposed himself to mustard gas, test flights without cabin pressure and many other risks.

Over the years, the separate domains of basic and clinical science have gradually merged. The combined efforts of pure scientists and physicians are in evidence at prestigious centres across North America, such as Duke University, Mayo Clinic College of Medicine and Rockefeller University. This is also true at the University of Ottawa Heart Institute (UOHI), where cardiologists and surgeons spend at least part of their time conducting clinical research and, increasingly, carrying out basic science.

Among them is cardiologist Dr. Ruth McPherson, who is translating new knowledge to the bedside from the bench and back again.

Dr. McPherson is Director of the Heart Institute's Lipid Clinic and a Canadian leader in cholesterol management and research. She is also Director of the UOHI Lipid Research Laboratory and among her projects is a study to identify the genes responsible for regulating weight gain. Her 'Thin Gene Study' is aimed at some of the most common risk factors for heart disease: obesity, which is a major cause of adult onset diabetes; and diabetes, which in turn is one of the strongest factors for developing heart disease.

Cardiac surgeon Dr. Marc Ruel (left) and scientist Erik Suuronen, PhD, lead the cardiac surgery research group that is developing techniques to rebuild blood vessels and improve heart function.

*(Mending Hearts with Regenerated Blood Vessels, continued)*

remains to be understood and we are still just scratching the surface. This work helps us comprehend what we need to achieve a bit better," says Dr. Ruel. Many laboratories around the world have focused on rebuilding the heart muscle using different cell groups to regenerate and restore heart function.

Suuronen says their new evidence shows that many positive effects of cell therapy are from secondary mechanisms, such as the restoration of blood supply rather than the muscle tissue. "Newly generated muscle tissue is often unable to function co-operatively with the host tissue. Our work demonstrates that using cells known for their ability to regenerate blood vessels is more effective than using cells once assumed to have muscle regenerative abilities. Until muscle regeneration options are better understood, the treatment of myocardial infarction (heart attack) may benefit more from blood vessel-forming cells than from muscle-forming cells."

The new technique imitates the natural process of blood vessel formation in the growing and developing body, and might someday work best by using a patient's own cells from bone marrow or blood.

The Ruel-Suuronen research shows that transplanted endothelial cells from the circulation system appear to preserve heart function better and tend to increase the growth of blood vessels.

It may be too early to see circulating endothelial cells as a cure for heart failure. But angiogenesis clearly holds the promise for a dramatically new approach to handling heart failure and provides a strong new weapon in the battle against heart disease.

# UOHI Surgeon-Scientist-Scholar Takes Top Canadian Medal

Dr. Marc Ruel, one of the Heart Institute's most promising cardiac surgeons, has been honoured with the Royal College Medal Award in Surgery for 2007 in recognition of research excellence. The medal is considered by the medical community to be one of the most prestigious awards in Canada.

Dr. Ruel has forged new techniques in heart surgery, such as bypass grafting through a keyhole incision on a beating heart. His work in the operating room has received acclaim but his additional roles as both a scientist and teacher have also gained high praise and wide interest. As an independent laboratory researcher, Dr. Ruel's key areas lie in vascular biology and regenerative medicine.

He is part of a new research program in cardiovascular molecular medicine that is also strongly geared to mentoring the next generation of medical scientists. An Associate Professor at the University of Ottawa's Faculty of Medicine, Dr. Ruel is also supervising students in the laboratory at the Heart Institute. Among his students is Dr. Pingchuan Zhang, a cardiac surgeon from China who was recently awarded a research fellowship to work with Dr. Ruel.

Dr. Ruel obtained his medical degree from the University of Ottawa, where he also completed his cardiac training. He left Canada in 2000 to accept a post-graduate fellowship at the Harvard University School of Public Health. He was also a research fellow at Beth Israel Deaconess Medical Center, a Harvard University hospital in Boston. He returned to Ottawa in 2002 to join the Heart Institute and is currently Director of Cardiac Surgery Laboratory Research.

"Dr. Ruel is one of the Heart Institute's shining examples of a new breed of physician, one who is skilled in clinical care, advanced research and teaching excellence. He is a pioneer in his field and is helping to transform cardiovascular medicine. Dr. Ruel has distinguished himself as a talented scientist dedicated to discovering new treatments for heart disease," said Dr. Robert Roberts, CEO and President of the Heart Institute.

"Dr. Ruel is seen as a rising star whose contributions in the laboratory underscore his potential as an independent researcher of international stature," said Dr. Éric Poulin, Chair of the Department of Surgery at the University of Ottawa.

The Medal Award is one of the College's longest standing awards. The first was awarded in 1949. Dr. Ruel is the first cardiac surgeon to receive the award.

# Learning to Build Blood Vessels

Dr. Pingchuan Zhang came to Canada to train with a new breed of surgeons who are as comfortable in a laboratory as they are in an operating room. A cardiac surgeon from Beijing, Dr. Zhang is among 35 students who have joined the University of Ottawa Heart Institute's new program in cardiovascular molecular imaging research.

Dr. Zhang was recently awarded the Lawrence Soloway Research Fellowship in Cardiac Surgery. His research interest lies in engineering the growth of new tissue around the heart. Dr. Zhang came to the Heart Institute specifically to help develop new techniques in regenerative medicine that may someday enable a damaged heart to repair itself. He will spend two years conducting research at the Heart Institute under the supervision of cardiac surgeon Dr. Marc Ruel and scientist Erik Suuronen, PhD.

Heart disease and stroke are now among the leading killers of middle-aged people in China, where high blood pressure and smoking have forced China into severe health transition. Today, the chronic diseases that afflict the West are prevalent in China. "The situation in China is very similar to what is happening here and in other western countries where cardiovascular diseases are common, and where mortality and morbidity are high," said Dr. Zhang.

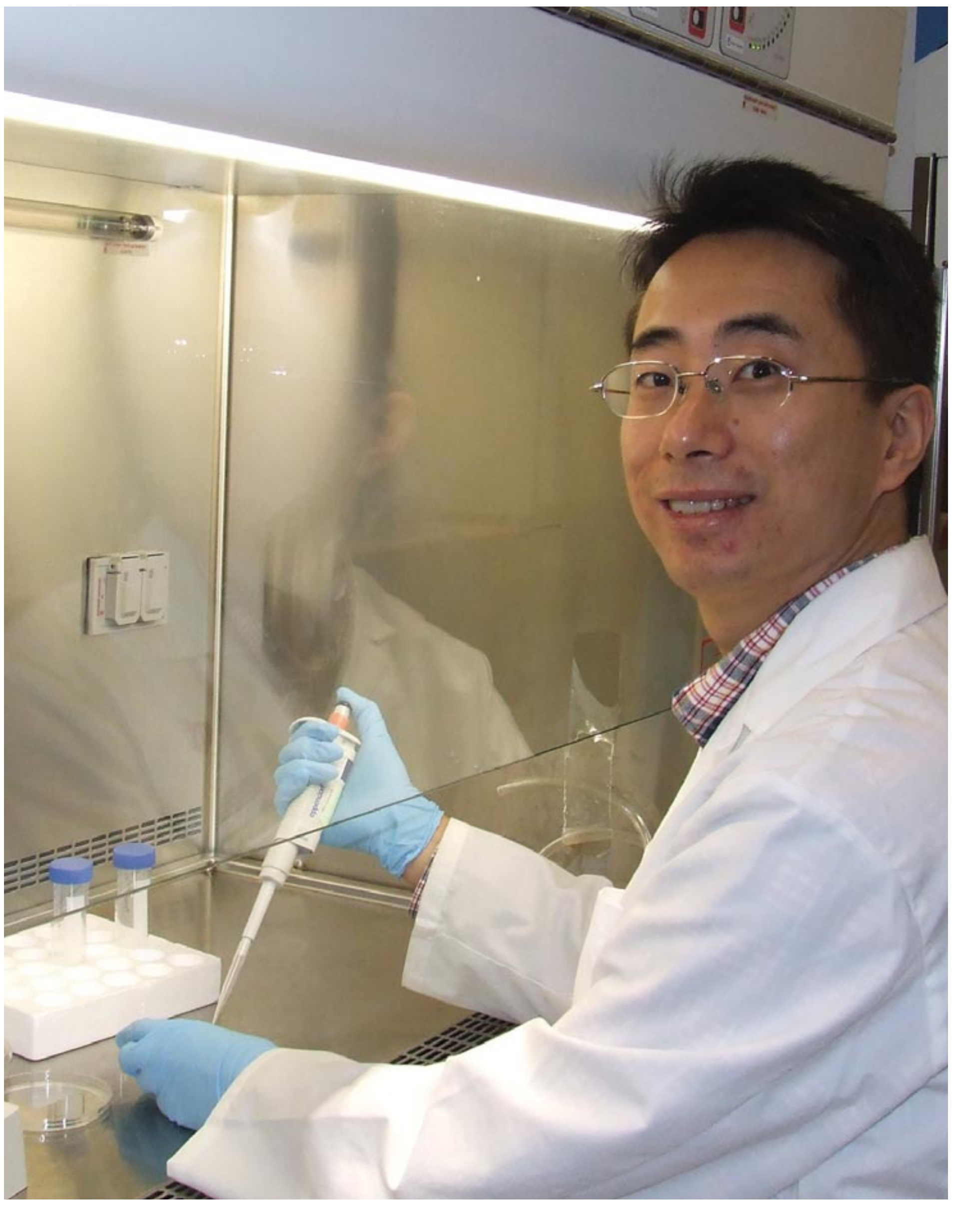
For a young researcher, the Heart Institute was the only place he wanted to be. "This is a leading institute in the world in terms of cardiovascular research and a very attractive place to be right now," said Dr. Zhang.

He arrived in Ottawa in January 2007 – in the dead of winter, the coldest month in what is considered one of the world's coldest national capital cities. Adjusting to the change of life was not easy, but the adjustment was softened significantly in mid-summer when his wife and daughter arrived.

His goals are twofold: to work in the laboratory with Dr. Ruel and Suuronen, and to perform cardiac surgery alongside Dr. Ruel in the operating room. Dr. Zhang's application for certification to perform surgery in the OR has been approved and he is on his way to clearing the next hurdle. Meantime, he is continuing to work in the area of molecular research with the goal of building new blood vessels by growing heart cells – in a field called molecular revascularization.

Heart cells – or cardiomyocites – are unusual. "The cardiomyocites around the coronary artery cannot regenerate, so the heart cannot fix itself," said Dr. Zhang. "In the last decade, researchers around the world have been searching to find certain stem cells to regenerate the heart. They inject these cells inside the heart but it is difficult for them to stay there."

Dr. Zhang's main research project is to develop a material that will serve as a magnet or natural homing device to attract the cells and enable them to stay and grow. "We are trying to understand what kind of cells will 'home' to our artificial material."



Dr. Pinchuang Zhang, a cardiac surgeon from China, chose the Heart Institute to learn new surgical techniques and pursue research in molecular medicine alongside surgeon Dr. Marc Ruel and scientist Erik Suuronen, PhD.

Dr. Wilbert Keon, the founding president and former chief of cardiac surgery at UOHI, has been honoured for his lifetime achievement in Canadian medicine.

# UOHI Founder Honoured for a Lifetime of Work

Dr. Wilbert Keon, the founding president and former chief of cardiac surgery of the UOHI, has been accorded honours by both the Canadian Medical Hall of Fame and the Canadian Medical Association.

To date, 66 laureates have been named to the Canadian Medical Hall of Fame, which is dedicated to the remarkable achievements of Canada's leaders in medicine. Dr. Keon, who was director general of the Heart Institute until 2004, retired from his academic appointments in 2001. He was at the Harvard Medical Center in the late 1960s when he was approached to establish a heart institute in Ottawa.

By the early 1970s, the doors had opened to a facility dedicated to the exclusive treatment of heart disease. In 1984, Dr. Keon performed the first heart transplant at the Heart Institute and, two years later, made Canadian history by performing the first artificial heart implant.

The Canadian Medical Association presented Dr. Keon with its highest honour, the Frederic Newton Gisborne Starr Award. He is the 42nd recipient, awarded in recognition of Dr. Keon's outstanding lifetime contribution to medicine.

"Dr. Keon laid the foundation for excellent care in the Ottawa area and helped establish promising directions in education and research. A surgeon, teacher and visionary, Dr. Keon set the stage that enabled the Heart Institute to pioneer a new era in heart health and to stand today as a world leader in care, education and research," said Dr. Robert Roberts, President and CEO of UOHI.