February 2006, Volume 1, Issue 2

THE BEAT

A COMPENDIUM OF INFORMATION ABOUT THE UNIVERSITY OF OTTAWA HEART INSTITUTE

HIGHLIGHTS

UOHI has been working closely with engineering researchers at Carleton University for more than a decade to help improve and develop medical devices for the prevention, diagnosis and treatment of cardiovascular disease.

(from Research by Number, page 4)

"A set of robotic eyes could be programmed to scan the chest area within a certain trajectory. If undetected, a bleeding vessel would have serious consequences for a cardiac patient if the cavity were closed after surgery."

– Tofy Mussivand, FRSC, Director, Cardiovascular Devices Division, UOHI (from Automated Eyes Help Human Hands, page 4)

"There is tremendous potential for regeneration of the heart. We just have to understand the biology better. It could be five years or it could be 15 years. It's difficult to know how soon."

– Dr. Marc Ruel, Director of Cardiac Surgery Laboratory Research, UOHI (from Research Boldly Pursues 'Star Trek' Medicine, page 5)

Early data indicates that the UOHI may have been the first in the world to perform a triple MVST procedure that bypassed all territories of the heart, including the right coronary artery.

(from UOHI Team Pushes Surgical Boundaries, page 6)

IN THIS ISSUE

The Beat is published 9 times a year 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

University of Ottawa Heart Institute
Institut de cardiologie de l'Université d'Ottawa

Dr. Alex Stewart is spearheading work that examines the transcription of gene codes that trigger the development of cardiac disease.

Puzzling Out a Pictureless Puzzle

One of the newest weapons in the battle against the leading killer in North America is a mouse that exhibits traits linked with heart disease. The mouse is genetically modelled to develop an irregular heartbeat, which affects up to 10 per cent of people over age 65 and occurs in as many as half of patients undergoing cardiac surgery.

The mouse model was invented by Alex Stewart, now principal investigator at the Canadian Cardiovascular Genetics Centre™ at UOHI. Research in his 3rd floor laboratory is underway to study the mouse model right down to its proteins. The goal is to figure out why the mouse develops the irregular heartbeat or arrhythmia, how to arrest its development and possibly reverse it by exploring drug discovery platforms that would target selected genes.

A native of Ottawa, Stewart was recruited early in 2005 from the University of Pittsburgh's Cardiovascular Institute after carving out a niche in molecular cell biology and human genetics. His PhD is in organismal biology and anatomy from the University of Chicago. He was lured to UOHI to establish the country's dynamic new laboratory devoted to the genetics of heart disease.

Stewart works with genes and the encrypted information that passes between parts of the cell machinery – from DNA to the functional proteins. Most genes encode proteins. By understanding the transcription of genetic codes, researchers can investigate how the regulation or control of certain genes triggers the development of particular diseases. Stewart's interest lies in interrogating genes involved in heart disease – specifically transcription regulation. One of his jobs is to find the genes that cause Coronary Artery Disease (CAD).

The Canadian Cardiovascular Genetics Centre™, which opened in June 2005, is the only one of its kind in Canada dedicated to CAD. Stewart's lab is an integral part of the Centre, one of the few facilities in the world dedicated to exploring the genetic makeup of CAD. With his appointment,

(continued on page 2)

Research Leads to Better Patient Care

A Comment by Dr. Robert Roberts, President and CEO, UOHI

Welcome to a special edition of *The Beat* dedicated entirely to the topic of research. On the following pages, you will read about some of the exploratory work that – each and every day – aims to improve our understanding of the causes and effects of heart disease and motivates our team to find a cure for what still remains the number one killer of North Americans.

This issue will give you an appreciation for the broad range of research topics and thrusts that we undertake at UOHI. However, there is a fundamental issue that needs to be answered before delving into the intricacies of what we do here.

The issue is this: why is research so important to a clinical environment? Why don't we simply let someone else advance the boundaries of scientific knowledge and just implement new knowledge as it is derived? The answer to this lies in the quality of care we are able to provide our patients.

We are the University of Ottawa Heart Institute (UOHI) which means we are not a regional hospital. Nor are we a community hospital. We are an academic health centre. Academic health centres, by definition, have three obligations: patient care, education and research. In addition to fulfilling that definition of obligation is the crucial point that we pride ourselves as a centre dedicated to cardiovascular care of the highest order.

If we want our patients in the city of Ottawa, the Champlain region and elsewhere to really get the most advanced care at the time it is available, it is essential that we be part of the clinical and basic research community.

For example, we currently have upwards of fifty clinical trials ongoing at UOHI. This makes available to our patients the latest, most advanced drugs that are

(continued on page 3)

(Puzzling Out a Pictureless Puzzle continued)

Stewart sought out and equipped the laboratory with more than $2 million in advanced gene sequencing, DNA analysis and GeneChip™ technology. It was not a difficult task for a research scientist and professor who exudes an infectious enthusiasm for his work in uncloaking the mystery of life at its very core. Within months of his arrival, Stewart had secured $444,000 in funding over four years from the Canadian Institutes of Health Research.

"The appeal of my work is trying to figure out why some people get heart disease and why some people don't," says Stewart. "It's like a puzzle without a pattern. You have a puzzle but you don't have the box cover to know what you are working with. You start with the edges and move in. Here in this lab, we're starting with the edges."

Stewart has made significant contributions to the understanding of cardiac and skeletal muscle biology. He identified the TEF-1 family of transcription factors, which serve to turn on certain genes in the heart muscle during normal development. Stewart's transgenic mice were created with the ability to turn on the genes with one of the TEF factors called RTEF-1. Transgenic mice have long provided the tools for exploring biological questions and now they are key to identifying the controls that trip the on-and-off switches for various gene functions.

In particular, Stewart is examining certain adrenalin signalling pathways. These trigger the signal for the heart to speed up, pump harder and even enlarge when the human body is under stress. And this occurs naturally whether from running a marathon or through prolonged anxiety that can invite high blood pressure and other problems related to heart disease. But sedentary people, whose hearts are not accustomed to performing work such as shovelling the driveway, are at risk of sudden arrhythmia and heart attack.

"This TEF comes in different flavours," says Stewart. "It's a multi-gene family and one of the genes in this family of four seems to mediate this signalling. We figured out earlier where on the protein the signalling is modified. Then we made mice that over-expressed this transcription factor at slightly higher than normal levels."

The breadth of Stewart's research activities extends beyond the genetics of irregular heartbeats. "I wear several hats," says Stewart, who is also assistant professor in the Department of Medicine at the University of Ottawa. He is cross-appointed to the Department of Biochemistry, Microbiology, and Immunology and is a member of the university's Faculty of Graduate and Postdoctoral Studies. His pioneering research activities provide a unique opportunity for his graduate students.

Stewart is also involved with co-ordination of a major research project that will investigate genetic differences between patients who suffer CAD and people who do not. The initial pilot for the project is just getting underway as researchers are recruiting 2,000 people in the Ottawa region; 1,000 from each group. Dr. Ruth McPherson, Director of UOHI's Lipid Clinic and Lipid Research Laboratory, is principal investigator of the study. The preliminary research is expected to lead to a wider national project that will involve 8,000 Canadians.

"We're going to find out which genes may cause a person to be susceptible to CAD," says Stewart. The answer may well lie with a defective gene that may be spotted somewhere within the human genome among the patients with CAD and will occur at a much higher frequency in patients with CAD than in healthy people. "The pilot study will help us identify the major targets, then we will refine our search, customize our analysis to a restricted number of DNA sites and narrow it down so we can find out the genetic differences."

Stewart's end of the research is tied strictly to the laboratory technology. Blood samples taken from each group will yield the necessary DNA but that is only the beginning. Following DNA extraction, the encoded information in the DNA, is purified and the long encoded strings of DNA are analyzed. The Canadian Cardiovascular Genetics Centre™ is equipped with a special biorobot for processing the DNA. Stewart's lab is using the most advanced DNA microarray technology, in which robotic machines arrange thousands of gene sequences – the long strings of encoded DNA information – onto two microchips. UOHI employs the Affymetrix GeneChip™, which processes massive amounts of miniature arrays and identifies genes. This allows researchers to identify genetic differences that may account for disease. With the development of microarray technology, researchers can examine the activity of thousands of genes at the same time. Each microarray has 250,000 probes and the pair of microchips together enables the identification of 500,000 genetic markers. With development of the technology, researchers are also able to determine patterns of activity in genes.

"It's like a puzzle without a pattern. You have a puzzle but you don't have the box cover to know what you are working with."

- Principal Investigator, The Canadian Cardiovascular Genetics Centre™, appointed 2005
- Assistant Professor, Department of Medicine, University of Ottawa. Cross-appointed to Department of Biochemistry, Microbiology and Immunology, Faculty of Medicine, University of Ottawa.
- Former Assistant Professor, Department of Cell Biology and Physiology, University of Pittsburgh.
- Assistant Professor of Medicine, Division of Cardiology, Department of Medicine and the Cardiovascular Institute, University of Pittsburgh.
- PhD Organismal Biology and Anatomy, University of Chicago.
- Post-doctoral fellow, Department of Anatomy and Cardiovascular Research Institute, University of California, San Francisco.
- Research interests: identifying genes that predispose patients to heart disease, understanding the molecular mechanisms underlying heart disease using cultured cells and transgenic mice; understanding the mechanism of myogenic differentiation to improve stem-cell based therapies of cardiac and skeletal muscle diseases.

"Each GeneChip™ allow us to interrogate the human genome of individual patients and ask if there is a particular gene sequence that's different in Patient 1 versus Patient 2," says Stewart. "Basically, we're taking a particular approach to examine if we can see a specific profile. Once we identify these genes, we will put them in cells in culture and figure out what's wrong with them."

The goal is to identify the genes that are defective and which may predispose certain people to CAD. "Much later, we will want to show if a mouse with this defect develops the same disease as a human."

Another focus of research in Stewart's laboratory involves the genetics leading to muscle tissue development. He has identified the transcription factors that promote the process at the genetic level of differentiating skeletal muscle from stem cells – undeveloped cells that can be switched into any cell type.

"A lot of genes in the heart are also expressed in skeletal muscle," he says. "They have widely overlapping programs. Our idea was that if you identify transcription factors that are common to both cardiac and skeletal muscle, you can find out what drives differentiation of cells," he says. By understanding the cell machinery that goes into development of the heart muscle, scientists may someday find a means of learning how to rebuild the heart muscle – a process that may yet be decades away from reality, says Stewart.

With the nature of his genetic research and the advanced technology in his laboratory, Stewart sees a dramatic new frontier in advancing medical knowledge. "It's not just new, it's cutting edge and that's the excitement for me," says Stewart. "To be at the forefront and this is the forefront right here – it's like standing at the head of the nose cone on a rocket."

Dr. Stewart's mouse is genetically modeled to develop an irregular heartbeat, enabling UOHI researchers to explore ways to reduce or eliminate the problem.

Do Genes Really Matter?

Researchers know that heredity plays a role in determining the health of an individual. Just how large a role is the focus of a world-renowned study of 120 Quebec families who trace their ancestry back more than 300 years. Many of these families are direct descendants of Canada's earliest French settlers. Their geneological records dating to 1680 have been computerized. A team of researchers in the massive Canada-U.S. study is creating a genetic database that could someday improve diagnosis and treatment of high blood pressure, which affects about five million adult Canadians.

The 900 individuals involved in the 120 families were tested and researchers found 46 significant chromosomal areas associated with high blood pressure and its cardiovascular effects. The study, led by Centre hospitalier de l'Université de Montréal, includes Université du Québec à Chicoutimi, École Polytéchnique de Montréal, McGill University, and MIT with significant contribution from the Medical College of Wisconsin.

(Research Leads to Better Patient Care continued)

approved for human use. If we were not part of these clinical trials, it would be at least another 5-7 years before our patients would have access to these drugs.

We, as an institute, have reached a critical mass where we have the expertise and resources to pursue clinical and basic research. It is unacceptable for us to think that we can sit and wait for someone else to do it for us. Even if you were to accept the alien notion that you don't have an obligation to society to contribute through science, it would mean again that there would be a significant delay in any of this research reaching the bedside.

So, in short, doing clinical and basic research fuels the fastest and best way to improve the care we can provide to our patients. From that point of view, it is imperative that we undertake research. It's what is best for our patients.

"Snipping" Away at Heart Disease

Like a true stealth fighter, heart disease can strike men and women in the form of a heart attack without any apparent warning. Men and women under the age of 65 who have no pre-diagnosed risk factors or who don't seem to fit the typical profile with risk factors such as smoking habits, diabetes or high cholesterol levels can still fall prey to this silent killer.

Identifying a high-risk patient and choosing a suitable prevention strategy can be a tough call for any physician. A multi-million-dollar study now under way at UOHI aims to identify common genetic variations that differentiate healthy people from those who suffer early heart disease. The goal is to improve our ability to prevent and treat heart disease, says Dr. Ruth McPherson, who is one of the leaders of this study at UOHI. As director of the Institute's Lipid Research Laboratory, Dr. McPherson is also professor in the Departments of Medicine and Biochemistry at the University of Ottawa. "The point of doing this study more than anything else is to come up with better blood tests to assess future heart disease risk," says Dr. McPherson.

One problem in the fight against heart disease is how to identify a person who should be receiving preventive therapy. If a 40-year-old person has a borderline cholesterol problem, should he or she be treated with drugs or be left alone to carry on with a managed diet? "If we have better things to go on beyond just measuring cholesterol and evaluating known risk factors, we will be able to target preventive strategies to those who will benefit most."

Collaborative research in the first three years of this large project has already identified genetic variations that differ between the group with heart disease, and the group that was healthy, says Dr. McPherson. The first study was done in partnership with Dr. Jonathan Cohen at the University of Texas Southwestern Medical School. Results will soon be published.

Now with the Canadian Cardiovascular Genetics Centre™, which opened last summer at UOHI, Dr. McPherson and Dr. Roberts, CEO of the Heart Institute, are moving forward on a much larger research project. New GeneChip™ technology at the centre will enable identification of 500,000 genetic markers across the whole genome. "The study we have done so far, used only 100,000 markers," she says. "So the new chip provides a much more powerful approach with more markers and a much larger study population."

"If we have better things to go on beyond just measuring cholesterol and evaluating known risk factors, we will be able to target preventive strategies to those who will benefit most."

– Dr. Ruth McPherson

A total of 1,000 male and female patients with a diagnosis of premature coronary artery disease and a control group of 1,000 healthy elderly people are currently being studied. "We are rapidly expanding the study and over the course of the next five years, we hope to enroll several thousand individuals," says Dr. McPherson. "What the study is doing is comparing what we call extreme phenotypes – individuals who have developed definite coronary heart disease at an early age; men before the age of 55, and women before the age of 65. These include individuals who have had an angioplasty."

We are comparing the group of individuals with very early heart disease with a group of very healthy elderly subjects, that is, people over the age of 70 who have never had a whiff of angina, have no heart disease in their family and really have just been completely heart healthy.

Researchers are examining single nucleotide polymorphisms or SNPs (pronounced snips), which are common DNA sequence variations that occur when a single nucleotide in the genome sequence is altered. DNA is made up of repeating units of nucleotides and contains all of the genetic information that makes us who we are. Scientists believe that many common SNPs might predispose people to a particular disease or could influence their response to a particular drug. The UOHI research is scanning the entire genome – the complete set of genetic information including SNPs in coding and noncoding regions of known and unknown genes.

"We have already found some SNPs – common genetic variants that appear to differ between the two groups," says Dr. McPherson. "What we're actually doing in genetic studies of "complex diseases" such as heart disease is quite different from finding a gene for something like cystic fibrosis. When we think about heart disease, the predisposition is affected by common variations in many different genes. We hope to be able to develop a simple blood test to better identify individuals at increased risk for future heart problems based on a number of genetic markers across the whole genome."

The UOHI study is continuing to recruit research subjects, including those with early heart disease and healthy elderly individuals. A new web site has been established (www.heartstudy.ca) for this purpose.

"This is a very important area of study and we have strong support at UOHI. Genetics research is essential to better understand the causes of heart disease and to enable us to prevent and more effectively treat this number one killer," says Dr. McPherson.

(Editor: This issue of The Beat also contains a special insert detailing various research projects, including this one, for which research volunteers are needed. See the insert for additional contact details if you wish to volunteer for this project.)

Research by Number

Research into cardiac medicine usually evokes images of scientists in white lab coats armed with syringes and microscopes. Increasingly, advanced technologies using computer-generated graphics, mathematical modelling and signal processing are the power tools in medical research. These are the same research and development tools that helped transform telecommunications technology, which has delivered smaller, faster and cheaper communications and computer devices.

UOHI has been working closely with engineering researchers at Carleton University for more than a decade to help improve and develop medical devices for the prevention, diagnosis and treatment of cardiovascular disease. A letter of agreement between the university and the Institute took effect 12 years ago. Even before then, Carleton researchers from the Department of Mechanical and Aerospace Engineering were working with the Institute on ventricular assist control systems used in developing more effective artificial heart technology. Researchers work in collaboration with Tofy Mussivand, the pioneering director of the Cardiovascular Devices Division at the Heart Institute.

"When the Heart Institute was looking to develop innovative research programs they found a natural match with Carleton University. They all fell into the very aggressive research programs we have here," says Feridun Hamdullahpur, Carleton Vice-President (Research and International). "Carleton has a number of programs and is developing new ones to deal with health-related issues in science and engineering programs." These include a biomedical engineering program in co-operation with the University of Ottawa.

"When the Heart Institute was looking to develop innovative research programs they found a natural match with Carleton University. They all fell into the very aggressive research programs we have here."

– Feridun Hamdullahpur, Carleton Vice-President (Research and International).

Donald Russell is Associate Professor in Carleton's Department of Mechanical and Aerospace Engineering. His wide expertise includes the control and dynamics of artificial hearts. His list of research projects also includes a simulated human circulatory system created with the Heart Institute. The simulated circulatory system is developed from new mathematic models to evaluate artificial heart designs and improve their control devices.

"In order to understand the controllers for the artificial heart, we have to experiment with them on the computer and the only way to do that is to have a model of the circulatory system," says Russell. "The model is a computer simulation employing mathematical representations and algorithms. We will give it the parameters of a cardiovascular system and an artificial heart, and it will predict how the two will behave together."

Signal processing researchers from Carleton's Department of Systems and Computer Engineering are also working with the Ottawa Heart Institute. Signal processing tools are being applied to visual and video images to allow more accurate diagnosis. Cardiac positron emission tomography (PET) scanning, for example, measures the metabolic activity of cells and can help detect defects in the heart. The research involves applying mathematical models to test for the strongest, clearest visual images. These will aid in more accurate diagnosis of heart problems.

Automated Eyes Help Human Hands

The precision of robotics is gradually moving into the field of medicine to relieve medical teams of certain tedious tasks, leaving surgeons to perform the more complex handiwork for which they are highly skilled and valued.

Researchers at UOHI in collaboration with Ottawa's Carleton University are developing a robotic system that would use intelligent image processing tools to scan the chest cavity for ruptured blood vessels during open-heart surgery. The system would also be capable of automatically performing cauterization. The Vision-Based Autonomous and Semi-Autonomous Robotic Surgical Assistant would relieve the task of surgeons who remain vigilant for signs of unexpected bleeding or a rupture.

A set of robotic eyes could be programmed to scan the chest area within a certain trajectory. If undetected, a bleeding vessel would have serious consequences for a cardiac patient if the cavity were closed after surgery, says Tofy Mussivand, the pioneering director of the Cardiovascular Devices Division at the Heart Institute. Mussivand, who obtained Doctorates in medical engineering and medical sciences from the University of Akron and North Eastern Ohio University College of Medicine, is renowned for his research into clinical artificial hearts, bridge-to-heart transplantation and cardiac surgery devices. He holds the Medical Devices Chair at the University of Ottawa Heart Institute. The Chair is a collaborative initiative between the University's Faculties of Medicine and Engineering.

For this project, UHOI has teamed up with research partners that include Carleton University. Robotics in the operating room cannot be confused with the robots seen working the line at an automotive parts assembly plant, says John Hayes, assistant professor in the Department of Mechanical and Aerospace Engineering at Carleton. This kind of advanced technology combines intelligent systems and digital image processing with mechanical and aerospace engineering technology. Hayes is recruiting up to four university engineering researchers to work on the prototype for this collaborative project. His expertise lies in automated optical robot calibration systems, more in keeping with advanced technology used in space research. "Because of the multidisciplinary nature of the project, graduate students will have the opportunity to work with and learn from medical professionals ranging from surgeons to technical staff," says Hayes. "It's very rare for a mechanical engineer to have an opportunity to work with a heart surgeon."

The developed system will use intelligent digital image processing tools that would also serve as a camera to collect, analyze and store data for easy retrieval and review later, says Hayes. Funding for the project includes $100,000 over two years from Materials and Manufacturing Ontario.

If successful, the device could be applied to other surgical procedures, says Hayes. "For operations such as liver resections or things of that nature, there is a very well defined set of edges that we can isolate with image processing."

Tofy Mussivand, FRSC

- Fellow, Royal Society of Canada.
- Director, Cardiovascular Devices Division, UOHI.
- Chair, Medical Devices, UOHI.
- Professor, Department of Surgery, Faculty of Medicine, University of Ottawa, cross-appointed to School of Information Technology and Engineering, University of Ottawa.
- Adjust professor, Department of Mechanical and Aerospace Engineering, Carleton University.
- Research interests: biomedical engineering, medical devices, artificial heart, clinical engineering, virtual patient simulation, biotelemetry, biofluid dynamics, devices for heart failure, remote power transfer, telemedicine.
- 10 patents in Canada, U.S., Europe and Japan.

Research Boldly Pursues 'Star Trek' Medicine

Recruiting or transplanting a person's own cells, perhaps even using a single molecule, to repair the heart may someday replace complex cardiac surgery. Even a decade ago, medical researchers could not have imagined the possibility of rebuilding heart tissue. Now they are finding new hope for cardiac patients who have exhausted other treatments and face the possibility of heart failure.

Dr. Marc Ruel calls it Star Trek medicine. Dr. Ruel is Director of Cardiac Surgery Laboratory Research at UOHI, where he is studying innovative methods to improve blood flow to cardiac patients with severely compromised hearts. A cardiac surgeon, his expertise centres on minimally invasive and beating-heart bypass surgery. His laboratory work folds over into his clinical work and vice versa.

"The whole thing fits together," says Dr. Ruel, whose principal goal is researching new ways to treat coronary artery disease. Cell transplantation is the ultimate development – so far, he adds. "For those patients who have had extremely diseased arteries, where even bypass is not feasible or if they have had three or four bypasses in the past, what do these patients have as an option? We are working on how to use each patient's stem cells to create new arteries."

Stem cells – undeveloped cells in the body that can switch to many cell types – harvested from a blood sample could theoretically be used on the same patient to stimulate growth of new vessels and help repair an ailing heart. Research elsewhere has already shown positive results with stem-like cells taken from bone marrow to improve the pumping ability of the heart. Dr. Ruel is working with stem cells isolated from blood samples.

"Two things are certain," he says. "First, this is going to happen. And second, one day the real Star Trek medicine will be a patient who will have some of their cells isolated, hopefully from the blood and not from the bone marrow – and we will expand them in the lab, re-inject them and those cells will go where they are needed."

Tests have already been conducted on animals, where new blood vessels have been created using human cells, Dr. Ruel says. His research is also addressing the critical issue of survival since the cells do not live very long. "About 99 percent of those cells die right upon implantation. It's like mechanical trauma or spatial trauma because they just don't have the cell influences around them that tell them how to perform."

He is investigating a special biopolymer gel that can effectively protect the cells within the first days of implantation giving them better survival and function. But he is also exploring alternatives to cell replacement. Scientists have been examining the therapeutic value of other molecules such as L-selectin. L-selectin is a cell adhesion molecule, which helps capture the cells in tissue and blood as part of the defensive line set up to kick-start the immune system when the body comes under attack.

"Perhaps the solution won't be taking out cells to expand and reinject," says Dr. Ruel. "Perhaps instead, we will inject a special molecule that will stay in the area of the heart and attract stem cells over a period of weeks. Perhaps that's how regeneration will work."

While research at UOHI has involved regeneration of blood vessels, researchers elsewhere have been examining the potential for regenerating the heart muscle. "Regeneration of blood vessels is very close to being done in humans," adds Dr. Ruel. "It's already been shown that if you have this area in the heart where the muscle is dead, then regenerating the vessels may be the main mechanism in improving heart function. Just by regenerating the blood vessels, we may be able to recruit enough muscle cells from the bone marrow and from the blood for muscle generation to follow. Perhaps we just need to work on the blood vessels and whole thing will fall into place."

"Two things are certain. First, this is going to happen. And second, one day the real Star Trek medicine will be a patient who will have some of their cells isolated,..."

– Dr. Ruel, Director of Cardiac Surgery Laboratory Research at UOHI

Dr. Ruel's research has been supported by $1 million in funding from various sources including the Canadian Institutes of Health Research, the Canada Foundation for Innovation, and the Heart and Stroke Foundation.

"There is tremendous potential for regeneration of the heart," says Dr. Ruel. "We just have to understand the biology better. It could be five years or it could be 15 years. It's difficult to know how soon.".

"The real Star Trek medicine for treatment of coronary artery disease won't be a new stent and it won't be robotic surgery."

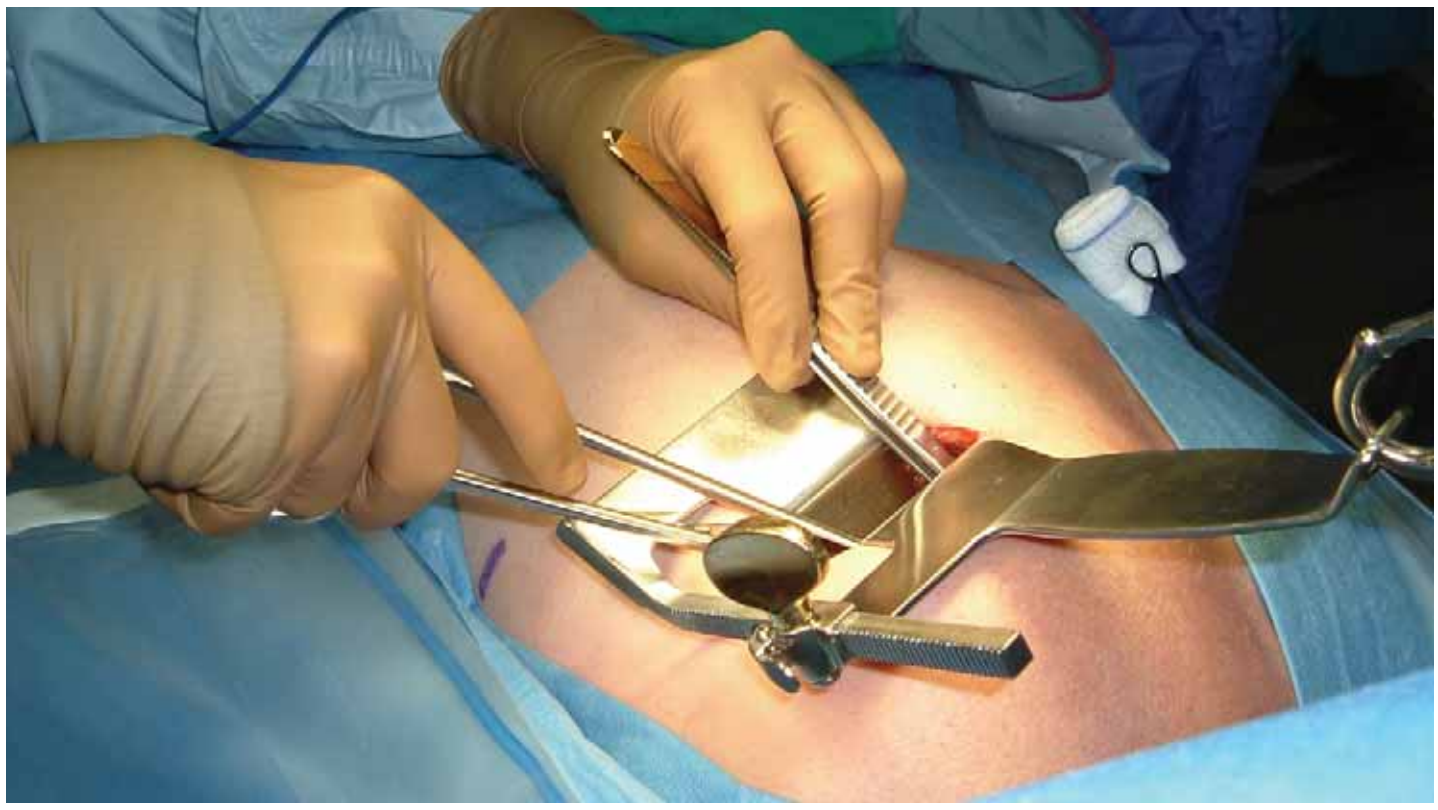
- Cardiac Surgeon
- Director of Laboratory Research, Division of Cardiac Surgery
- Associate Professor of Surgery, University of Ottawa
- Cross-appointed to Department of Cellular and Molecular Medicine, and Department of Epidemiology, University of Ottawa.
- Member, Canadian Cardiovascular Society, Canadian Society of Cardiac Surgeons, Society of Thoracic Surgeons, Cardiovascular Surgery Council of the American Heart Association, North American Vascular Biology Organization, Human Research Ethics Board at UOHI.
- Special interests: minimally invasive and beating heart bypass surgery, replacement of aortic valve, heart transplantation, research into cell transplantation, molecular research.

UOHI Team Pushes Surgical Boundaries

Cardiac surgeons at UOHI have peformed the first triple coronary bypass graft in Canada using a keyhole incision and on a beating heart. The technique proved so successful that the 65-year-old patient could have performed heavy physical labour within a month of surgery.

The surgical team performed the operation in September 2005 and has since accomplished at least four similar procedures. The Multi-Vessel Small Thoroctomy (MVST) is a revolutionary approach to Coronary Arterial Bypass Grafting (CABG) and, to date, is the least invasive surgical technique developed in this area. Standard bypass grafting involves fracturing the breast bone to open the chest cavity for multiple grafts of healthy vessels onto arteries to bypass clogged vessels and improve blood flow to the heart. Only a few centres in North America perform MVST, which requires an extremely high level of dexterity to maneuver the beating heart into position using specially designed precision tools. Early data indicates that the UOHI may have been the first in the world to perform a triple MVST procedure that bypassed all territories of the heart, including the right coronary artery.

In the case of the first UOHI patient, grafting was performed on three major arteries. The patient was released after four days; his progress, closely monitored. After one month, the incision had healed sufficiently to allow the patient to begin lifting heavier objects. "He could have gone back to a construction job," says Dr. Marc Ruel, who led the surgical team with Dr. Harry Lapierre. "The results of the other procedures have been like that as well."



Keyhole incisions are part of a revolutionary approach to bypass grafting. The method is the least invasive surgical technique developed to date in this area.

UOHI has enhanced its beating-heart coronary bypass program under Chief of Cardiac Surgery Dr. Thierry Mesana. UOHI has focused on innovative, less invasive procedures designed to help patients recover more quickly while reducing the risk of complications. Traditional coronary bypass employs a heart-lung machine, known as a 'pump,' which mechanically pumps oxygen and nutrients to the body while the heart is stopped. Recent advances in surgical techniques and medical devices have enabled the less invasive alternative Off-Pump or Beating Heart Bypass, referred to as OPCAB.

"The Multi-vessel Bypass is the logical continuation of the OPCAB," says Dr. Ruel. "With the MVST procedure, the surgeon can bypass all regions on the heart and it's done with the human hand so there is no robotics involved. It is a difficult technique. Coronary bypass surgery is a difficult operation to begin with, but surgeons do it everyday and they have become experts at it. The extra degree of difficulty and requirement for more dexterity in OPCAB is another level above that."

OPCAB involves breaking the sternum or breast bone to fully open the chest cavity. With MVST, the lateral incision – called a keyhole – is made without carving open the sternum or breaking a single rib. Several programs in the U.S. have initiated MVST using a robotic system. Dr. Mesana has said that robotics cannot always address complex surgical issues.

Beyond the issue of cost, Dr. Ruel adds that with the use of robotics, candidates for surgery are usually selected more carefully. "You need coronary vessels that are relatively healthy. With the MVST procedure that we perform, we can work with patients with very difficult coronary vessels."

Dr. Ruel says that Canadian surgeons are well positioned to develop an expertise in this area. "It is a much more difficult operation and there are exponential degrees of complexity over off-pump bypass, which goes beyond traditional coronary bypass."

The multi-vessel system technique could theoretically be performed by any surgeon who develops an expertise in OPCAB, and is ready to move to the next level. "This can all be done with the human hand and it involves a very small incision – a keyhole. It's the ultimate keyhole surgery. It is all done by direct vision through that small incision. This operation uses an integral port that displaces the heart inside the chest to bring the area inside the heart right into view of the keyhole."

The technique essentially uses a suction device on the apex of the heart, which allows the surgeon to manoeuvre the apex of the heart into position beneath the incision. "It is a very clever procedure," says Ruel.

New Trial May Lead to New Cardiac Treatments

An important international trial is underway to evaluate the effects of a heart hormone called BNP in the treatment of acutely decompensated heart failure. The trial is sponsored by Ortho Biotech (Johnson & Johnson). Dr. Adolfo de Bold, who is the Director of the Cardiovascular Endocrinology Laboratory at the Heart Institute, delivered the opening lecture at the trial investigator's meeting in Toronto on November 3, 2005. Dr. Haissam Haddad, Director of UOHI's Heart Failure Clinic is also a participant and design advisor. Other countries participating in the trial include Taiwan, Singapore, Korea and Mexico.

The trial stems from the discovery in the 1980's by Dr. de Bold that the heart possesses an endocrine function, producing and storing hormones that regulate other systems in the body. Dr. de Bold's discovery of a hormone called ANF (Atrial Natriuretic Factor) and the regulating function it serves has proven to be a landmark discovery that opened a new chapter in the history of medicine. Through ANF, the heart modulates blood pressure, blood volume and cardiovascular growth at multiple levels. For example, ANF induces the kidneys to increase salt output which in turn lowers blood pressure.

Dr. de Bold's discovery has triggered worldwide research on ANF. To date, more than 10,000 basic and clinical science papers on ANF have been published around the world since it was identified some 20 years ago.

More recently, another regulating hormone known as BNP (Brain Natriuretic Peptide) has been identified. BNP is produced in the brain (where it was discovered) but is produced most abundantly by the heart. BNP exhibits the same pharmacological properties as ANF but also appears to modulate the process of inflammation. Like ANF, BNP is relatively short-lived. The two hormones compete for the same receptor sites and have the same mechanisms for acting upon the body.

The new trial aims to explore the similarities – and differences – between ANF and BNP in the hopes that a better understanding of the role played by BNP in regulating cardiac functions will ultimately lead to another significant treatment for acute heart failure.