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 heart-beat 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)
The breadth of Stewart’s research activities extends beyond the genetics of irregular heartbeats. “I wear several hats,” says Stewart, who is also assis-
tant 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 1,000 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 deficiency 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 biochip 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.

“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.

Dr. Alexandre 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.”

• Principal Investigator, The Canadian Cardiovascular Genetics Centre™, appointed 2003
• 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, distinguishing 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.

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.” 00

Stewart sought out and equipped the laboratory with more than $1 million in advanced gene sequencing, DNA analysis and GeneChip™ technology. It was not a difficult task for a research scientist and professor with boundless enthusiasm for his work in unclocking 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 genes with one of the TEF factors called RTF-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 heart 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 arrhythmias 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 stems to mediate this signalling. We figured out earlier where on the protein the signalling mechanism of myogenic differentiation to improve stem-cell based therapies of cardiac and skeletal muscle diseases.

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 Québec families who trace their ancestry back more than 300 years. Many of these families are direct descendants of Canada’s earliest French settlers. Their genealogical 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 Polytechnique de Montréal, McGill University, and MIT with significant contribution from the Medical College of Wisconsin.

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 healthier lifestyle? “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 100,000 genetic markers across the whole genome. “The study we have established (www.heartstudy.ca) for this purpose.

“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 had no heart attack or other 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.

“If 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.

(Research Leads to Better Patient Care continued)
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.

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 mathematical models to evaluate artificial heart designs and improve their control devices.

“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 Ontario University College of Medicine, is renowned for his research into clinical artificial hearts, bridge-to-bridge transplantation, artificial heart 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 Faculty 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.

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“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.”

– Perioud Hamdullahpur, Carleton Vice-President (Research and International).
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 couldn’t 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 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.”

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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.”
Cardiac surgeons at UOHI have performed 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-Thoracotomy (MVST) is a revolutionary approach to Coronary Artery 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. Ruel. The patient, who works as an NP in the Ambulatory setting with Dr. Harry Lapiere. “The results of the other procedures have been like that as well.”

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.

“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.