



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 concept of using cell-based therapy to rebuild blood vessels in and around the heart is proving to be the next frontier in cardiac medicine. This landmark development clearly represents a major step forward in adding to our ability to cure heart failure.”

– Dr. Marc Ruel, Director,
Cardiac Surgery Laboratory, UOHI
(from *A “Smart” Way to Repair
Damaged Tissue*, pages 1–3)

“What we are trying to do is to figure out which genetic pathways are lost or activated as we age to see if that capacity for repair can be recreated in the adult heart.”

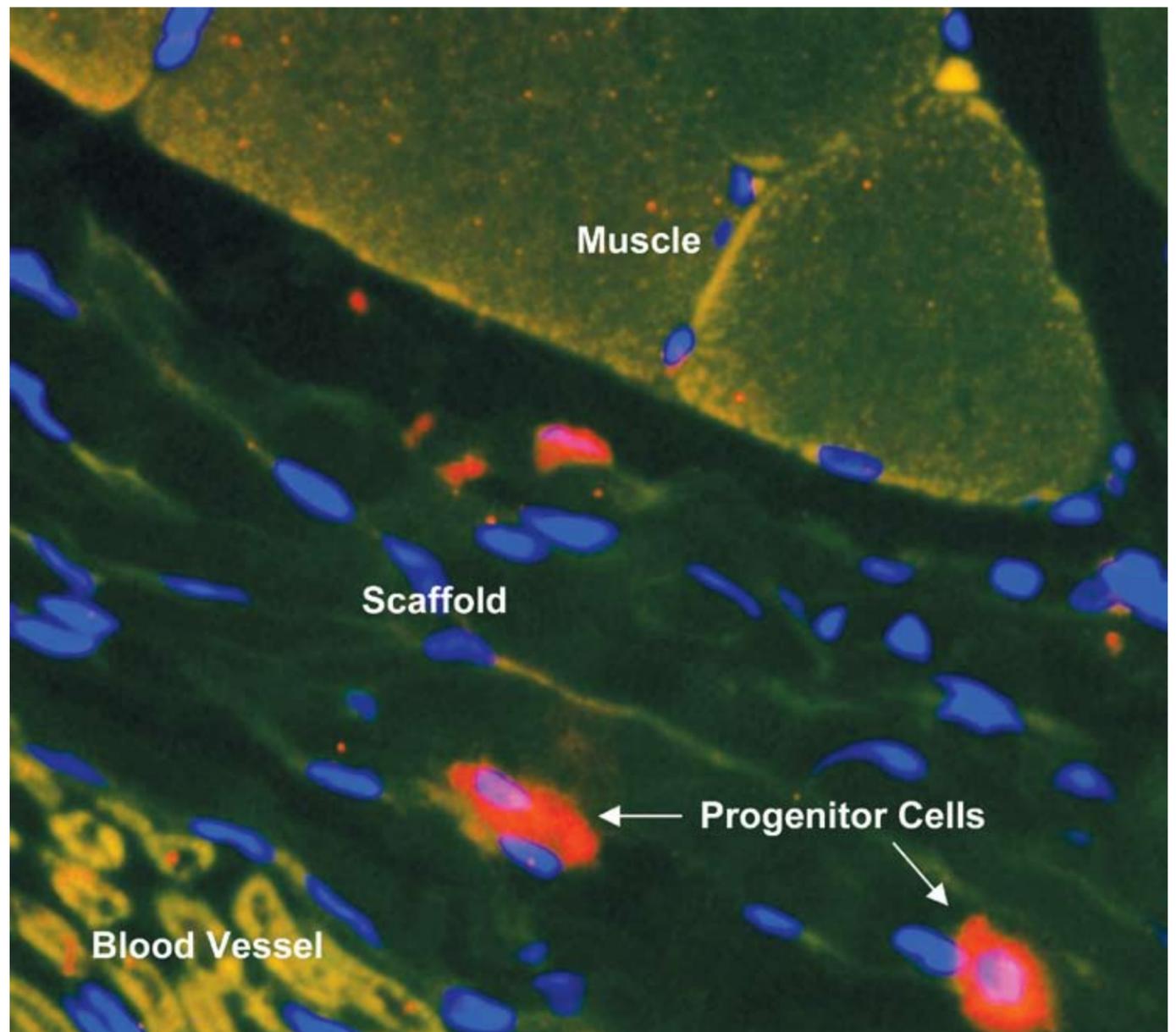
– Patrick Burgon, UOHI researcher
(from *Regenerative Medicine*, page 3)

The Heart Institute’s Ottawa Model for Smoking Cessation is considered the most advanced approach in Canada for identifying and treating tobacco addiction.

(from *Playing a Pivotal Role:
The Heart Institute Leads
New Approaches to Clinical Care*, page 3)

The electron microscopy expertise of the Stewart Whitman Histology Core Laboratory is generating a lot of outside interest and paying clients.

(from *Canada Beats a Path to Heart
Institute Core Pathology*, page 4)



Researchers at the University of Ottawa Heart Institute have developed a smart scaffold that one day may help repair damaged heart tissue following a heart attack. In this image of tissue from a rat’s hind limb, progenitor cells have been recruited to form new blood vessels to support the growth of muscle tissue.

A “Smart” Way to Repair Damaged Tissue

A heart attack is an emergency event, but once the immediate danger has passed, the damage can be long-lasting. Heart tissue may die, compromising cardiac function, while the scar tissue that forms as a result doesn’t conduct electrical signals the way healthy muscle does. This can lead to potentially dangerous arrhythmias. Researchers at the University of Ottawa Heart Institute have developed a smart biomaterial that promises to help the body repair tissue damaged by impaired blood flow associated with heart attacks and other conditions such as diabetes.

Let’s take a look, for a moment, inside the chest of a person with coronary artery disease. Among other things, we can see that there are yellowy patches in the arteries. These are plaque deposits that have accumulated in the artery walls over many years. As we watch, a piece of plaque breaks free from one of these deposits. It tumbles along in the bloodstream

carried towards the heart until it hits a narrowing in the artery. The plaque becomes lodged and, suddenly, the flow of oxygen-rich blood to the heart is blocked.

What we’ve just witnessed is the onset of a heart attack. The lack of oxygen, known as ischemia, damages the tissue normally

UOHI researchers have developed a way to support and enhance the heart’s innate capacity to regenerate itself.

fed by the blocked blood vessel. Muscle cells start to die and heart tissue can be permanently lost. The heart has a maintenance system for replacing cells that regularly die off, but the amount of damage caused by a heart attack overwhelms that system. Working with Dr. Marc Ruel, Director of the Cardiac

Surgery Laboratory, Erik Suuronen and his Heart Institute colleagues have developed a way to support and enhance the heart’s innate capacity to regenerate itself.

There are two aspects to regenerating lost tissue. One is to regrow muscle that will contract like normal heart tissue. But for

that to happen, you also need new blood vessels to feed that growing tissue. While research is underway to effectively regrow muscle, studies have shown that generating new blood vessels — a process known as revascularization — on its own helps

(continued on page 2)

IN THIS ISSUE

P. 1–3 A “Smart” Way to Repair Damaged Tissue

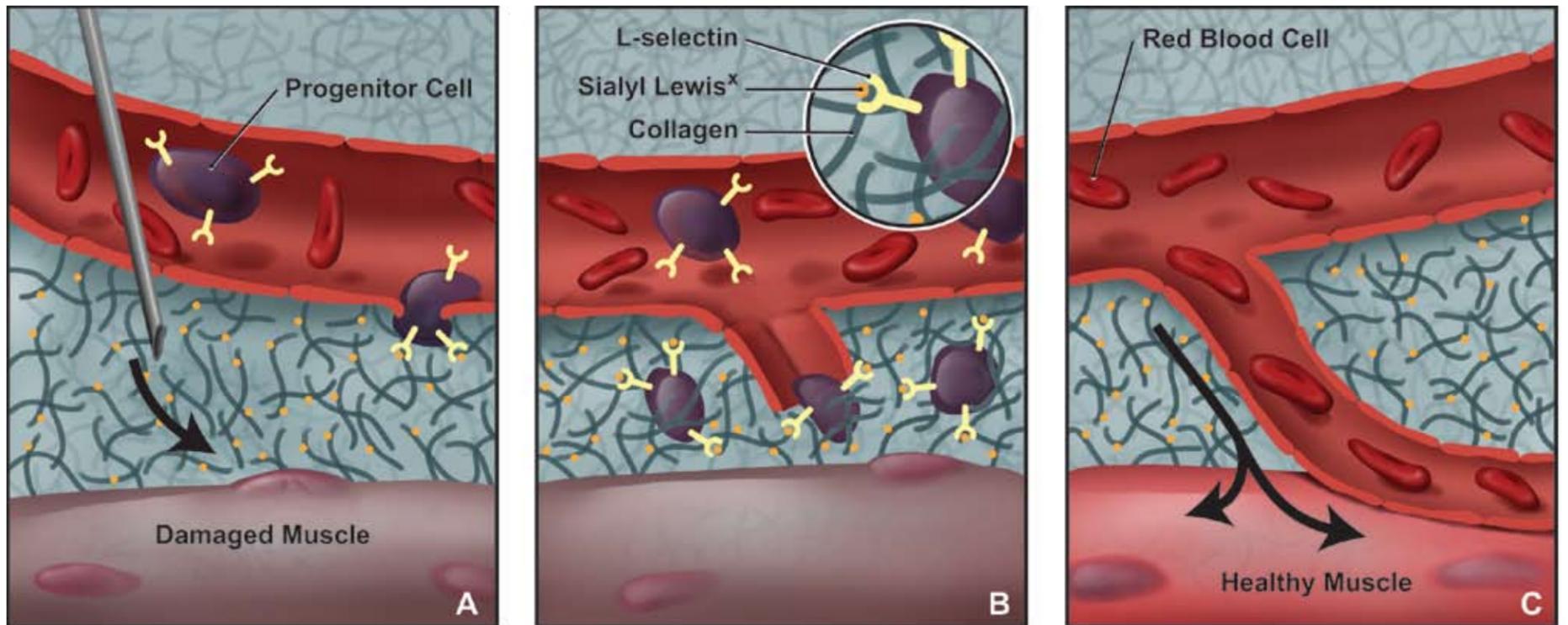
P. 3 Playing a Pivotal Role: The Heart Institute Leads New Approaches to Clinical Care

P. 4 Canada Beats a Path to Heart Institute Core Pathology

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

© 2009 University of Ottawa Heart Institute

The Beat is a trademark of the University of Ottawa Heart Institute.



Repairing Damaged Muscle: A) A collagen matrix containing sialyl Lewis^x is injected at the site of damaged muscle tissue, where it gels to form a smart scaffold. B) The presence of sialyl Lewis^x attracts progenitor cells to the site and binds with their L-selectin receptors. The progenitor cells take up residence in the scaffold, where they begin to differentiate and form new blood vessels. C) The new vessels provide oxygenated blood to growing muscle tissue, repairing the damage caused by ischemia.

(A "Smart" Way to Repair Damaged Tissue, continued)

restore cardiac function. Suuronen's work focuses on the revascularization process. The key, he has found, is helping progenitor cells do their job.

One of the cell types that replenish blood vessels is known as endothelial progenitor cells (EPCs). They are undifferentiated cells originating in bone marrow that the body calls on when damage occurs. Signals go out to attract EPCs to a damaged site. Once they arrive, the progenitor cells can become or stimulate the growth of new blood vessels, supplying oxygen to support new muscle growth. Unfortunately, EPCs are not abundant, so by itself, the body can accomplish only so much repair.

One hope of scientists has been to give the system a boost by externally introducing progenitor cells to increase their numbers. To date, the results of these cell therapies have been less successful than originally expected. Instead of introducing cells from the outside, the biomaterial developed by Suuronen's group expands the capacity of the body's own regenerative process. "Our goal," Suuronen explained, "is to develop safe and effective treatments for coronary artery disease by helping the body rebuild blood vessels and improve heart function."

Three things need to happen for EPCs to become new blood vessels. They need to be called into action and released into the bloodstream through cell signalling; they need to be recruited to and retained at the damaged site; and they need to be kept alive and active long enough to transform into new vascular tissue.

The new biomaterial addresses each of these issues. It consists of a collagen matrix that has been modified to increase its strength and longevity. Collagen is the main component of connective tissue in the body. The matrix provides a scaffold where EPCs can reside while they go through the process of differentiation.

A carbohydrate molecule known as sialyl Lewis^x puts the "smart" in the scaffold. This molecule binds and retains EPCs where they are needed. In turn, the progenitor cells then release protein messengers called cytokines that travel through the circulatory system and to the bone marrow. These act as homing signals that call other cells to join them in

the regeneration process. This combined effort greatly increases the extent of EPC mobilization. Sialyl Lewis^x also improves EPC survivability so the cells have more time to fully engraft and differentiate. The biomaterial is liquid when cool, making it easily injectable at the damaged site. It then gels at body temperature to form the stable scaffold.

To test their creation, the researchers induced ischemia in thigh muscle in the hind limbs of rats. They then treated some rats with the smart scaffold and gave others collagen alone. The results showed that the rats receiving the smart scaffold had a 90 per cent increase in blood flow to the damaged tissue compared with the collagen-only rats. The treated rats also had improved functioning after two weeks and showed no increase in inflammatory response. These results were published online in January by *The FASEB Journal* (Erik Suuronen et al., *FASEB J.* 2009 Jan 9. [Epub ahead of print]).

The success of this approach opens the door to a variety of applications. Because the smart scaffold enhances the body's natural regenerative process, it could be paired with several current and future interventional strategies to increase their impact. These include angioplasty, cell transplant therapies, and the transplantation of heart muscle tissue grafts.

"The concept of using cell-based therapy to rebuild blood vessels in and around the heart is proving to be the next frontier in cardiac medicine. This landmark development clearly represents a major step forward in adding to our ability to cure heart failure," said Dr. Ruel.

Added Suuronen, "We see this as a breakthrough that may also positively impact diseases such as diabetes, some disorders of the liver and chronic brain ischemia." This close collaboration between scientist and cardiac surgeon is indicative of the Heart Institute's integration of research and clinical practice. As this work progresses, the partnership will help translate successful research into patient therapies more quickly. 🌀

The results showed that the rats receiving the smart scaffold had a 90 per cent increase in blood flow to the damaged tissue compared with the collagen-only rats.



Erik Suuronen, PhD

"Our goal is to develop safe and effective treatments for coronary artery disease by helping the body rebuild blood vessels and improve heart function."

- Scientist, Division of Cardiac Surgery, University of Ottawa Heart Institute
- Research Investigator, Molecular Function & Imaging Program, University of Ottawa Heart Institute
- Associate Professor, Department of Surgery; cross-appointment with the Department of Cellular and Molecular Medicine, University of Ottawa
- Research interests: treatment of cardiac injury and disease using tissue engineering and cell-based approaches; stem cell response to heart tissue damage 🌀

Regenerative Medicine

If it were possible to shift the body's own repair mechanisms into high gear or to grow replacement tissues, we could avoid the risks of invasive surgeries or rejection issues and long waits on transplant lists. This is the promise of regenerative medicine, a rapidly expanding area of medical research.

The work of Erik Suuronen and Dr. Marc Ruel highlights one promising approach (see A "Smart" Way to Repair Damaged Tissue). Other University of Ottawa Heart Institute researchers are attacking the problem of tissue regeneration in different ways.

Patrick Burgon comes at regenerative medicine from a developmental perspective. "The heart of a newborn has a great capacity to repair itself, but this capacity is lost shortly after birth," he explained. This is why congenital defects of the heart are more frequently corrected today through *in utero* surgery. The fetus can heal with little or no scar tissue formation.

"What we are trying to do," he continued, "is to figure out which genetic pathways are lost or activated as we age to see if that capacity for repair can be recreated in the adult heart." Burgon and his graduate student, Lara Kouri, are currently in the process of identifying these genes and pathways.

Investigator Alexandre Stewart and his PhD student Alan Teng work in the Ruddy Canadian Cardiovascular Genetics Centre. They are exploring gene and cell therapies to treat the damage caused by heart attacks. It is recognized that patients recovering from a heart attack grow new blood vessels, but the mechanisms that govern this process are not understood. Many of the relevant genes have been identified, but not the various factors that turn them on and off.

Vascular endothelial growth factor (VEGF) is well known as a key player in influencing blood vessel formation. Stewart's group recently identified a novel factor that greatly increases production of the VEGF protein in the heart. This is the kind of groundwork that is essential for the development of new regenerative therapies in the future.

These and other groups at the Heart Institute, such as the positron emission tomography (PET) imaging group, are highly collaborative. They share expertise and interim findings to spur innovation and facilitate progress in this burgeoning area. This approach has proved to be remarkably productive. As Burgon puts it, "The interface of collaboration is where you get the greatest discoveries." 

Playing a Pivotal Role: The Heart Institute Leads New Approaches to Clinical Care

Two innovative conferences brought hundreds of physicians and nurses to the doorstep of the University of Ottawa Heart Institute early in 2009. Both events offered some dramatic new lessons in managing coronary artery disease.

In late 2007, the Heart Institute, working with The Ottawa Hospital, opened the first multidisciplinary Pulmonary Hypertension Clinic in Canada. The clinic provides patients with access to the Institute's full diagnostic, treatment and research resources. In January of this year, the country's leading physicians, researchers and health care professionals presented a day-long series of lectures at a national Pulmonary Hypertension Symposium organized and hosted by the Heart Institute.

Most of the speakers represented expertise from the clinic, including Dr. Lisa Mielniczuk, Medical Director of the Pulmonary Hypertension Program, and Dr. George Chandy, the program's Co-Director. Prominent invited guests included Dr. Richard N. Channick, Division of Pulmonary and Critical Care, University of California, San Diego Medical Center, and Dr. John T. Granton, Program Director, Critical Care Medicine, University of Toronto.

Pulmonary hypertension, a disease of the blood vessels that affects the lungs, carries a serious prognosis, particularly among young women. It generally claims the lives of patients within two years of diagnosis.

Researchers are not yet certain why young women are affected, noted Dr. Ross Davies, Administrative Director of the Heart Institute's Pulmonary Hypertension Program. Further, it is a complex illness that can be difficult to diagnose. The Heart Institute program delivers what Dr. Davies calls a "one-stop service" for patients, providing access to cardiologists, respirologists and nurses at the Institute and from The Ottawa Hospital. The clinic has served 265 patients since it opened, and the annual number of patients is expected to grow.

Another event organized by the Heart Institute early in 2009 was the First Ottawa Conference on Smoking Cessation, where top tobacco addiction experts from across North America came to advise physicians and other health professionals on preventive strategies.

The Heart Institute's own smoking cessation network has now grown to 50 Canadian hospitals and medical centres since the program began in 2004. Each has been mentored by Institute personnel in the Ottawa Model for Smoking Cessation. To date, some 6,000 Canadians are smoke-free after being identified and treated through the Heart Institute-developed Ottawa Model, which is considered the most advanced approach in Canada for identifying and treating tobacco addiction. Close to 50 per cent of participants remain smoke-free at the 12-month mark.

"Tobacco addiction is the most fundamental preventive health issue in Canada. Smokers understand why they shouldn't smoke and very much welcome assistance in quitting smoking," said Dr. Andrew Pipe, Medical Director of the Institute's Minto Prevention and Rehabilitation Centre. "Through our programs, we are developing a group of clinical leaders who will introduce a very successful smoking cessation program — the Ottawa Model — to hospitals across Canada. The conference was another demonstration of the Heart Institute's leadership in preventive medicine."

Just as important is how the Heart Institute is using its leadership to help other hospitals recast their role in preventive medicine. Robert Reid, Associate Director of the Prevention and Rehabilitation Centre, said, "The Heart Institute is playing a pivotal role in educating hospitals and clinicians on new approaches to medical care and research." Reid's research has resulted in several highly effective new programs in heart health education.

The Ottawa Model has received wide recognition as an efficient but personal approach to helping patients quit smoking.

Fourteen hospitals joined the Heart Institute's smoking cessation network in December alone.

These include hospitals within the River Valley Health Authority in New Brunswick, institutions within Vancouver Coastal Health (VCH) in British Columbia, St. Joseph's Healthcare in Hamilton, and six prominent hospitals in the Toronto area, such as St. Michael's Hospital and Sunnybrook Health Sciences Centre. Other recently partnered hospitals include Regina General Hospital in Saskatchewan, Moncton Hospital in New Brunswick, and Boundary Trails Health Centre in Winkler, Manitoba.

At the conference, Dr. Pipe, Canada's leading researcher on new approaches to the prevention of cardiovascular disease, repeated and refuted many of the common misconceptions about quitting smoking. Within the Ottawa Model, all nurses and physicians are trained about tobacco addiction, how to address patients about tobacco addiction, and how to use nicotine replacement therapy to help patients quit for good.

Dr. Richard Hurt, of the Mayo Clinic's Nicotine Dependence Center, and an internationally respected authority on issues of tobacco control and smoking cessation, provided a secondary viewpoint on smoking as a global epidemic. Tobacco companies, he said, are targeting the Asian market, and China is the world's largest producer of cigarettes. Dr. Hurt, an admitted three-pack-a-day smoker until he quit in 1975, is no stranger to the world of smoking addiction. He said about 60 per cent of Chinese men smoke. This means that the number of smokers in China is larger than the entire population of the United States.

Dr. John Hughes, a psychiatrist and Director of the Human Behavior Pharmacology Laboratory at the University of Vermont in Burlington, is a leading researcher on issues relating to mental health and tobacco addiction. Nicotine, he explained in his



Dr. Richard N. Channick, of the University of California, San Diego, was the keynote speaker at the Pulmonary Hypertension Symposium. He presented on "Classification, Diagnosis and Treatment of Pulmonary Hypertension: A Practical Approach for Clinicians."

talk, is becoming known as a renaissance drug thanks to various confusing studies that have shown that it improves concentration, decreases hunger, and can relieve depression and anger.

Further, nicotine offers the perfect reward to smokers because in many places and compared with other drugs, cigarettes are relatively acceptable, carry no immediate side effects, and are easily obtained. Dr. Hughes went on to discuss the clear biological mechanisms that kick in with smoking and how abstinence may cause a relapse of prior alcoholism and depression in a minority of smokers.

The Heart Institute continues to take a leadership role and expand its professional education activities. Other new symposia conducted in the past year include:

- Heart Failure;
- Small Animal Imaging; and
- Molecular Function and Imaging: Cardiovascular Metabolism. 

Canada Beats a Path to Heart Institute Core Pathology

Sample preparation and microscopic imaging are critical, if unglamorous, aspects of research. Consistency and precision are the hallmarks of good histology and microscopy. The Stewart Whitman Histopathology Core Laboratory was established as a shared resource to provide specialized equipment and expertise to researchers at the University of Ottawa Heart Institute. Over the years, the lab's reputation for excellent work has grown, and institutions from around Ottawa and across the country now line up for its services.

Histology is the study of the anatomy and structure of cells and tissues. In histology, tissue samples are prepared, thinly sliced, and mounted on glass slides for examination under a microscope. It is one of the workhorse processes for medical diagnostics and biological research. Preparing histological samples is a labour-intensive process. For immunohistochemistry-based tests (those that use antibodies to identify proteins in tissues), the samples are usually flash-frozen in liquid nitrogen and sectioned on a machine known as a cryostat, which keeps them cold throughout the procedure. For structural studies, tissue samples that have been chemically preserved are dehydrated in alcohol and ultimately impregnated with paraffin wax, solidifying them for cutting into sections only a few microns thick — far thinner than a human hair.

Standardization and quality control are essential in preparing histological samples. If the samples are handled incorrectly, molecular changes can occur and be mistaken for intrinsic properties of the tissue, obscuring or invalidating research results. The core facility has equipment to automate the entire preparation process, which greatly reduces the variability that can occur with manual sample preparation. "When I first came here, the equipment in individual labs was definitely in need of upgrading. The Core Lab offers the technical capabilities to support the histology needs of any of our researchers," said Peter Rippstein, Manager of the Histopathology Core Laboratory.

Previously the technical head of diagnostic electron microscopy (EM) and supervisor of the Histopathology Laboratory at The Ottawa Hospital (Civic campus), Rippstein was recruited by the Heart Institute to establish and manage an EM facility dedicated to research. That facility now resides within the Core Lab. It is Rippstein's EM expertise that is generating a lot of outside interest and paying clients from other research centres, such as the University of Ottawa, the Ontario Health Research Institute, McGill University, the University of Saskatchewan, Health Canada, and the National Research Council.

"Because of the variety and specificity of immunohistochemical methods [antibody staining or tagging] which became available in the early 1980s, EM became less popular, particularly as a diagnostic tool," explained Rippstein. "So over time EM training programs eroded, and now we find ourselves in a situation where it's difficult to find EM expertise." This shortage of electron microscopy specialists has placed the Heart Institute facility in great demand among Canadian scientists wishing to incorporate EM imaging into their research. In addition to processing and imaging EM samples, Rippstein provides investigators with assistance in interpreting results.

The electron microscope is still a vital piece of equipment for researchers studying the biological structures underlying cell function. The capability has certainly paid dividends for Institute researchers. For example, in 2008, Heidi McBride, a highly regarded expert in mitochondrial research, uncovered an unknown method that mitochondria use to transport waste products within cells. She credits Rippstein's EM expertise with making this significant discovery possible.

The origins of the Core Lab go back to 2001 when Stewart Whitman joined the Heart Institute as a vascular biology researcher. He brought with him a substantial young investigator equipment grant from the Canada Foundation for Innovation. The histology equipment he was able to purchase for his laboratory was very advanced and helpful to many of the Institute's scientists. Whitman decided that it should reside in a shared facility that anyone could access.

"The money to buy this equipment came from the Canadian taxpayers," said Whitman. "We wouldn't want them to think that we're hoarding it." He became the driving force behind establishing the Core Lab and training technicians from other Heart Institute laboratories in histological techniques, such as immunohistochemistry.

Whitman is an immunologist who works in the field of atherosclerosis. His research explores how the immune response to tiny cracks in blood vessel walls may contribute to atherosclerotic plaque formation. His presence has provided a perspective on heart disease that has influenced researchers throughout the Heart Institute. To honour his role as the founder and advocate of the core facility and his varied contributions to research at the institution, the Heart Institute recently dedicated the lab in his name as the Stewart Whitman Histopathology Core Laboratory.

For those interested in learning more about services available from the Core Lab, please contact Peter Rippstein at prippstein@ottawaheart.ca.

"The Core Lab offers the technical capabilities to support the histology needs of any of our researchers."

— Peter Rippstein, Manager, Stewart Whitman Histopathology Core Laboratory, UOHI



Peter Rippstein conducts the Heart Institute's highly sought-after electron microscopy services and manages the Stewart Whitman Histopathology Core Laboratory. He is seen here at the electron microscope.



Stewart Whitman, PhD

"The money to buy this equipment came from the Canadian taxpayers. We wouldn't want them to think that we're hoarding it."

- Co-Director, Vascular Biology Laboratory, University of Ottawa Heart Institute
- Associate Professor, Department of Pathology and Laboratory Medicine; cross-appointment with the Department of Cellular and Molecular Medicine, University of Ottawa
- Research interests: immunology and cardiovascular disease, specifically the inflammatory-immune system's effect on atherosclerosis; bacterial pathogens and their relationship to cardiovascular disease