HEART & STROKE
RICHARD LEWAR
CENTRE OF EXCELLENCE
2010–12 BIENNIAL REPORT

CONTENTS

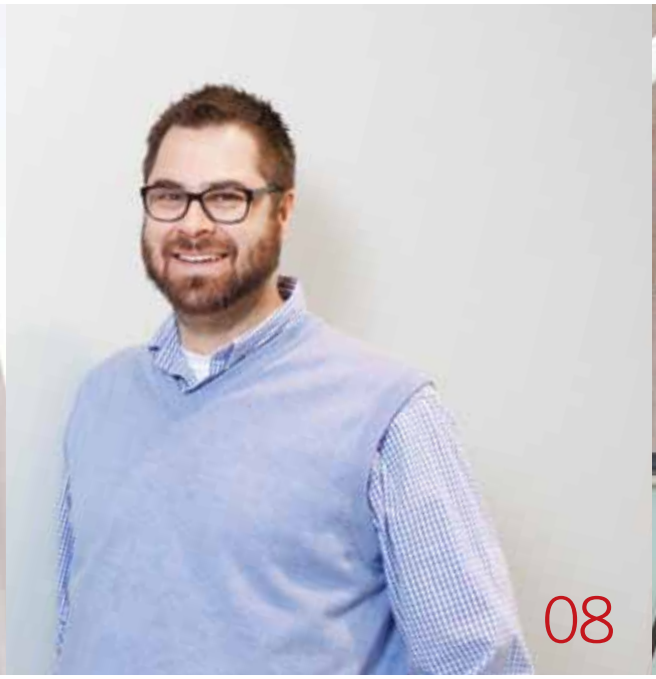
THE HEART & STROKE / RICHARD LEWAR CENTRE

MISSION

The Heart & Stroke / Richard Lewar Centre of Excellence in Cardiovascular Research (HSRLCE) supports research and education on the prevention and cure of cardiovascular diseases. From these efforts will evolve diagnostic and therapeutic innovations that impact the health of all Canadians.

VISION

Through innovations in science, collaboration of minds and recruitment of the brightest leaders, the HSRLCE aims to become an internationally renowned institution of cardiovascular research and training.



Heart & Stroke/Richard Lewar Centre of Excellence in Cardiovascular Research

OF EXCELLENCE IN CARDIOVASCULAR RESEARCH

2010–12 BIENNIAL REPORT

MANSOOR **HUSAIN** MESSAGE

I am delighted to add my words of welcome to this edition of our Biennial Report. As the outgoing Director of the HSRLCE, I am very proud of our accomplishments and extremely grateful for the support I have received from the Dean, the Centre's staff, steering committee, faculty and trainees.

My goal as Director of the HSRLCE has been to broaden participation of our Centre throughout UofT and its allied research institutes. This has been achieved by establishing support nodes in (a) small animal models on campus, (b) large animal models at Sunnybrook, (c) microvascular research at St. Michael's Hospital, (d) a cardiovascular surgery database at SickKids, and (e) human molecular and cellular diagnostics and therapeutics at the University Health Network (UHN), and in helping to recruit the next generation of scientists and leaders.

The Centre has become relevant to almost every teaching hospital engaged in cardiovascular research at UofT, broadened its impact beyond basic biomedical science, and positioned itself to launch and foster first-in-man translational research projects right through to clinical trials. Cardiovascular care is on the threshold of personalized health initiatives, and the HSRLCE is poised to facilitate this. The Centre's support of a cardiovascular biobank at UHN is now operational, and holds much promise in this regard. I am tremendously excited by the Centre's future, and delighted by the selection of Dr. Michael Farkouh as my successor. I have every confidence in his ability to take the HSRLCE to the next level of international prominence.

It has been my privilege to serve as Director of the HSRLCE, and to witness first-hand how faculty and trainees have worked together to make the whole of cardiovascular research in our community greater than the sum of its parts. My parting request is that you all join me in supporting Dr. Farkouh in his efforts to further strengthen the recognition and reputation of the HSRLCE as a key catalyst of cardiovascular research and education at our University and beyond.

Mansoor Husain, MD
Director, HSRLCE
2008 – 2012

MICHAEL **FARKOUH** MESSAGE

AS the incoming Director of the HSRLCE, I am pleased to present the activities for the 2010-2012 Biennial Report. My predecessor, Dr. Mansoor Husain, provided outstanding leadership over the past five years. Dr. Husain has provided his own reflections on the Centre in this report. We are very pleased with the course we have taken at the HSRLCE and are very optimistic about our future to continue to facilitate our translational approach from the bench to the bedside.

In the past two years, we have continued to support three strong centres of research related to the HSRLCE including the Large Animal Facility at Sunnybrook Hospital, a Microvascular Laboratory at St. Michael's Hospital and the Transgenic Physiology Laboratory. In addition, we have funded some exciting new initiatives, including the clinical outcomes database for the Department of Cardiovascular Surgery at the University of Toronto and the support of a Cardiovascular Biobank and Human Molecular Physiology Laboratory at UHN. We have provided strong support in the recruitment and assistance of outstanding young scientists to our Centre and have actively supported trainee stipends. Our goals in the years to come are to develop our brand, integrate our resources across the University and provide the best training programs for our undergraduate and graduate students.

We are also very proud of our Annual Science Day activities, which included, in 2011, *Cardiovascular Imaging: Seeing the Future,* and in 2012, *Atrial Fibrillation*. Our Distinguished Visiting Professor series has been a tremendous success and attracted internationally renowned investigators.

Overall, we believe the activities of the HSRLCE in research and education have continued to bring international distinction to the University of Toronto and we are looking forward to building on this strong foundation in the next several years.

Michael E. Farkouh, MD
Director, HSRLCE
2013 – present

PUBLICATION ACTIVITY

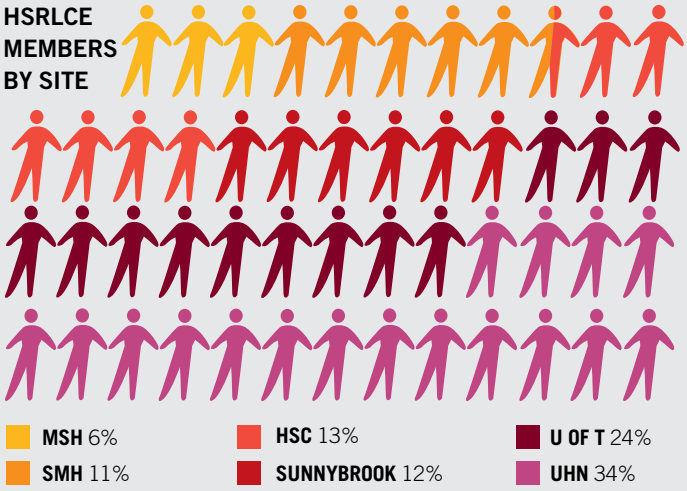
PUBLICATION ACTIVITY

In an effort to quantitatively assess the scientific impact and measure the research activity of our membership, the Centre had an extensive bibliometric analysis prepared in 2011, analyzing publications, citations and journal impact factor for the period of 2006-2010.

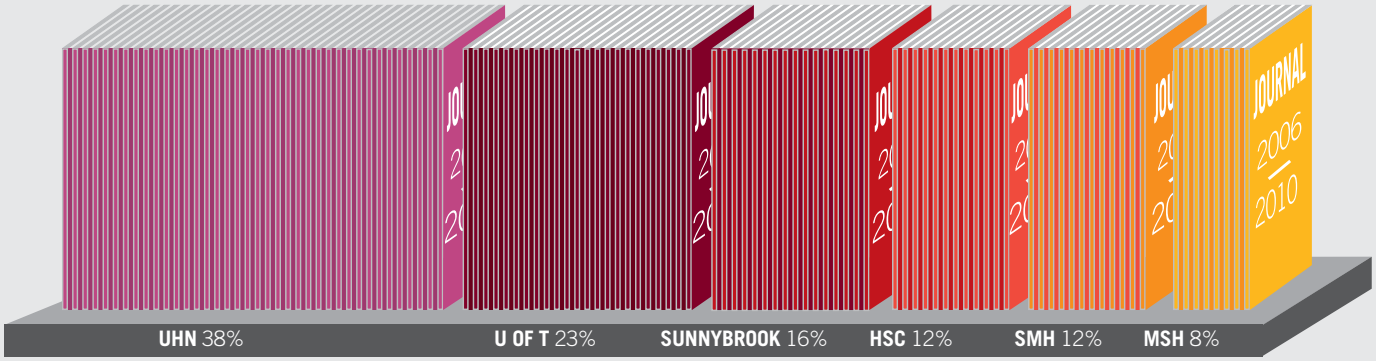
Overview

The HSRLCE had a total of 1920 papers averaging 5 papers per PI annually. These papers were cited a total of roughly 34,000 times or 18 cites per paper. The mean journal impact factor for all papers was 5.85.

*Publication data reflects articles and reviews published by HSRLCE investigators between 2006 and 2010 in journals indexed by Thomson Reuters. Publications in non-indexed journals and group author papers not clearly attributable to a member are excluded.
*Publications stemming from more than 1 institution were attributed to each group equally. This accounts for the Papers by Site analysis summing to 109%



HSRLCE PAPERS BY SITE



JOURNAL IMPACT FACTOR

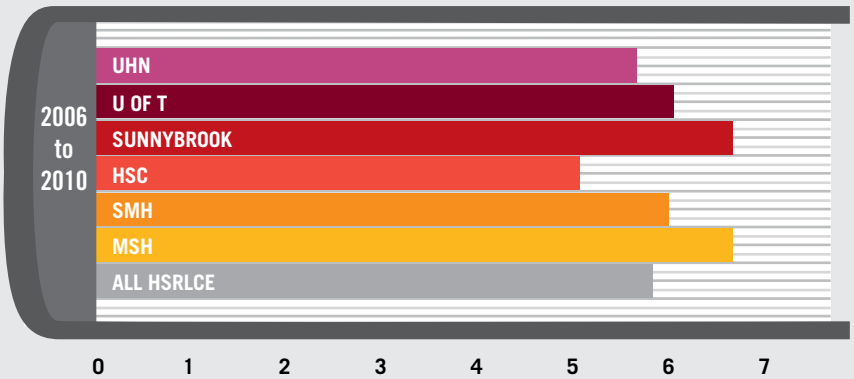
Journal impact has been used as an indicator of author or group success in having publications in prestigious journals.

Overview

HSRLCE publications achieved journal impact scores that were notably stable year over year. Almost 15% of HSRLCE papers appeared in Top Journals (journals with an impact of 10 or more, which represent < 2% of all journals).

* Journal Impact Factor (JIF) represents the average citation count of articles published in the journal.

MEAN JOURNAL IMPACT FACTOR SCORES BY SITE



CITATION IMPACT

Citations are the bibliographic acknowledgement of the contribution of one work to another. The number of times a work is referenced by others indicates its impact on a body of knowledge, although citations take time to accumulate and often vary by field and journal.

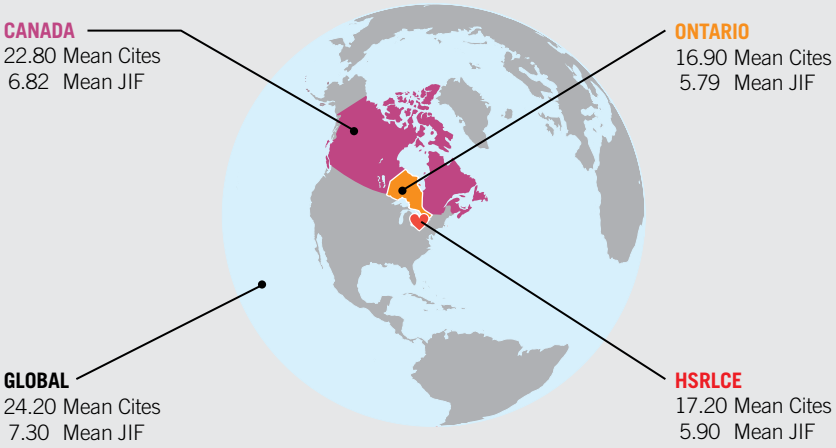
Overview

HSRLCE publications were cited 34,000 times. Almost 13% of cited papers appeared in high impact journals and were cited an average of 60 times. Analysis of the top 20% most-cited HSRLCE papers show nearly ¾ of these top papers were considered highly cited for Major Field (achieved when a paper's citation count places it amongst the top 10% of papers published in the year and major field).

*Citations: Counts were current as of Sept. 2011. Citation rates vary considerably by publication age and field.

JOURNAL IMPACT FACTOR SCORE	PROPORTIONAL CONTRIBUTION		
	OF TOTAL PAPERS	OF TOTAL CITES	MEAN CITES
GREATER THAN 10	12.8%	43.9%	60.7
5-10	24.7%	25.7%	18.4
2.5-5	37.8%	20.6%	9.6
LESS THAN 2.5	24.7%	9.8%	7.1

PUBLICATION IMPACT



COLLABORATION

Analysis of patterns of collaboration can be useful for identifying areas of strategic opportunity and networks of strength.

Overview

Of the total HSRLCE papers, 40% represent collaborations with peers from 47 different countries. These global collaborative papers have been cited more than 18,000 times. Almost 22% of these collaborations appeared in top journals and 31% were considered highly cited for their field.

* Ontario – Papers with at least one address affiliation outside the Greater Toronto Area. Canada – Paper with at least one address affiliation outside Ontario. Global – Papers with at least one address affiliation outside Canada.

ANALYSIS BY CIHR PILLAR

Analysis of publications based on CIHR Pillar is used to describe HSRLCE publication intensity and citation impact of each area, as well as the extent to which HSRLCE investigators papers involve multiple research foci (as per CIHR Pillar).

Overview

Almost ⅔ of all HSRLCE papers were attributed to the Biomedical pillar. These papers were cited over 20,000 times and 15% of these appeared in Top Journals.

CIHR PILLAR	HSRLCE 2006-2010 PUBLICATIONS			
	PAPERS (% OF TOTAL)	CITES (PER PAPER)	MEAN JIF	IN TOP JOURNALS
BIOMEDICAL (N=56)	1184 (61.6%)	21608 (18.3)	5.944	14.7%
CLINICAL (N=23)	650 (33.87%)	10429 (16.0)	5.685	14.8%
OTHER (N=4)	187 (9.7%)	3026 (16.3)	6.472	14.4%

UNDERSTANDING IMMUNE RESPONSE IN ATHEROSCLEROSIS

New HSRLCE Recruit Dr. Clinton Robbins from Harvard Medical School brings his interest in innate immune responses to research that examines atherosclerosis. Being part of the HSRLCE allows him to integrate with other cardiovascular disciplines while staying rooted in immunology. Over the last three years, he has concentrated his efforts on cardiovascular immunology, which has yielded vital insights into the inflammatory response in atherosclerotic lesions.

Primarily interested in uncovering the origins of the myeloid and monocyte-macrophage responses, both in health and disease, atherosclerosis seemed a natural fit with his research focus in cardiovascular immunology. "Atherosclerosis is a nice platform from which to study innate biology and myeloid responses," explains Dr. Robbins.

Moreover, the evolution of our understanding of atherosclerosis has made an immunological perspective an increasingly relevant piece of the puzzle. Two decades ago, atherosclerosis was thought to be the accumulation of lipids within the arterial wall, whereas now it is known to be an inflammatory response. In fact, macrophages are the dominant inflammatory cell type in the arterial plaque.

Dr. Robbins' work attempts to decipher how these immunological responses develop, contributing to the growing knowledge of how monocytes and macrophages accumulate within arterial lesions. His research has been published in several high-impact journals, including *Science* and *Nature*. A recently published study in *Circulation* added clarity to where the macrophages that infiltrate atherosclerotic plaque originate. Findings demonstrated that hematopoietic monocytes, previously thought to be generated exclusively in the bone marrow, are also produced in peripheral tissues, and that cells made in these niches can participate in the atherosclerotic response. Another paper, published in *Nature*, unequivocally proved a long-held but unproven clinical observation, namely that myocardial infarction accelerates atherosclerotic progression. Findings also showed that accelerated disease in the post-MI period is associated with increased monocyte recruitment.

> ATHEROSCLEROSIS IS A NICE PLATFORM FROM WHICH TO STUDY INNATE BIOLOGY AND MYELOID RESPONSE

Dr. Robbins is currently working on other research that will examine how inflammation is more closely linked with the proliferation of fully differentiated cells, or macrophages, than the influx of precursor monocytes. Pinning down the immune-modulated inflammatory responses in arterial lesions will help to harness new therapeutic strategies to quell the process and mitigate heart damage.

HIGHER HOSPITAL SPENDING & BETTER PATIENT OUTCOMES

Soaring health care costs and increased demands on a universal access system have made fiscal restraint a common mantra among Canadian hospitals. While higher spending may equate with better health outcomes, no one had examined that proposition until recently.

Dr. Douglas Lee, a HSRLCE scientist and an Associate Professor of Medicine at the University of Toronto, co-authored a study that examined whether increased hospital spending in Ontario yielded better outcomes for acute care patients, including lower mortality and readmission rates.

Lee and colleagues, including HSRLCE's Dr. Dennis Ko, Associate Professor of Medicine and Scientist at the Sunnybrook Research Institute, looked at 30-day and one-year mortality and readmission and major cardiac events for acute myocardial infarction (AMI) and congestive heart failure (CHF). They found that higher spending did indeed translate into better patient outcomes. The study involved nearly 400,000 Ontario adults with a first admission for AMI, CHF, hip fracture or colon cancer during 1998–2008, with follow up to one year.

The concept of higher spending to produce better patient outcomes, and ultimately reduce overall health care spending, has been debated due to inconsistent findings. Higher spending, says Dr. Lee, may be reflected in technological advances in diagnostic and treatment modalities, which tend to incur more resources.

What was most striking about the current findings, says Dr. Lee, is that they were in contrast to data from the U.S., which has found the opposite—that higher spending was associated with worse health outcomes. Data indicate that U.S. hospital spending is approximately four times higher than in Ontario.

"It suggests we're doing something right in Ontario," says Dr. Lee. "Perhaps it speaks to our efficient use of resources. Despite having one of the smallest numbers of hospital beds per capita, the outcomes are good, albeit better in the higher-spending hospitals."

> HIGHER SPENDING MAY BE REFLECTED IN TECHNOLOGICAL ADVANCES IN DIAGNOSTIC AND TREATMENT MODALITIES

Dr. Lee also leads a research program that has explored containing hospital spending while improving patient outcomes. He recently led a CIHR-funded study to develop a simple, low-cost clinical decision support system to stratify risk of heart-failure patients in the emergency department, helping clinicians better determine whether to admit or discharge patients.

With a focus on health services research, cardiac care and outcomes, and clinical epidemiology, Dr. Lee will continue to play a key role with the HSRLCE in developing advanced and cost-effective solutions to meet growing health care demands.

STEPPING UP
STEM CELL PRODUCTION

Canada Research Chair in Stem Cell Bioengineering Dr. Peter Zandstra has worked tirelessly to understand the language of stem cells, which has provided invaluable insights into what determines stem cell differentiation and self-renewal.

Over the last two years, Dr. Zandstra has found that signals stem cells receive from their differentiated progeny are incredibly important in modifying or regulating stem cell fate. A study led by his PhD student, Elizabeth Csaszar, recently published in *Cell Stem Cell,* involved the use of blood stem cells as a model system to understand how that feedback signalling from different populations of cells might control stem cell growth or differentiation.

Using a bioengineering approach, they developed a mathematical model to establish how this interaction might work and determined that it was the net effect of positive or negative molecules, not just a single molecule, which controlled stem cell fate. To address this emerging complexity, the team designed a bioreactor that controlled the rate at which the media around the stem cells was diluted in an automated manner. Dynamically changing their environment tricked stem cells into thinking they were still in a stimulatory environment in which stem cells keep multiplying but don't diversify yet.

This novel dynamic approach with a bioreactor allowed them to grow blood stem cells to higher levels than previously possible. Findings showed that they were able to rapidly generate an 11-fold increase in human cord blood cells over a 12-day period.

Growing stem cells in sufficient batches, and quickly enough, for therapeutic use in adults has long challenged researchers and clinicians. "The ability to generate ever-increasing yields of stem cells is incredibly important since cells and their progenitors are strongly correlated with clinical outcomes in blood stem cell transplantation," explains Dr. Zandstra.

> THE PRINCIPLE OF INTERCELLULAR SIGNALLING TO CONTROL STEM CELL FATE COULD BE IMPLEMENTED FOR UNDERSTANDING CARDIAC DEVELOPMENT AND TREATMENT

The Zandstra Lab's current research, aimed at using the expanded blood stem cells to treat adult leukemia, is a collaborative effort with researchers and clinicians across Canada, including the Sauvageau Lab at the University of Montreal.

While the recent findings explore potential applications for treating blood cancers, there are some shared insights and implications for cardiac disease as well. The general principle of intercellular signalling to control stem cell fate is equally relevant in cardiac medicine and could be implemented for both understanding cardiac development and treatment of cardiac disease.

NEW TARGETS, NEW HOPE

FOR TREATING HEART FAILURE

The HSRLCE is known for being an incubator of cutting-edge research, as exemplified by the work of Dr. Steffen-Sebastian Bolz, whose research promises to shift the perspective on the molecular underpinnings of vascular resistance in heart failure and identify novel therapeutic targets.

Bolz's research, which has focused on resistance artery physiology, recently explored the neurological fallout of heart failure, namely cognitive deficits that result from cerebral vascular resistance. This new work sheds light on how this collateral damage occurs and suggests a viable treatment to restore blood flow in the brain.

Bolz and colleagues published two papers that have elucidated the mechanism by which sphingosine-1-phosphate (S1P), a bioactive lipid mediator, increases vascular resistance in heart failure, as well as identifying three new potential therapeutic targets for restoring cerebrovascular blood flow.

Earlier research confirmed S1P's involvement in regulating vascular tone, but the underlying mechanism remained a mystery—until now. Published last year in the journal *Circulation*, one of Bolz's studies demonstrated how this happens: tumour necrosis factor (TNFα), a pro-inflammatory protein, regulates the tone in the small arteries. One way in which TNFα does this is by activating S1P signalling, thus leading to artery constriction. These findings suggest the candidacy of the TNFα/S1P signalling pathway as a potential therapeutic target to improve cognitive function in heart failure. The paper went a step further by testing a treatment, a TNF-antagonist called etanercept, in mice and showing it works by interrupting TNFα /S1P signalling and restoring blood flow in the brain.

The second paper, also published in *Circulation*, examined how TNFα affects microarteries. It found that TNFα down-regulates another protein called the cystic fibrosis transmembrane conductance regulator (CFTR), which activates S1P signalling and increases microvascular tone. Using etanercept helped to restore the expression of CFTR, which decreased S1P signalling and normalized blood flow. CFTR therefore represents another potential novel therapeutic target.

> DRAWING ON THE ORGANIZATION'S MULTIDISCIPLINARY STRENGTHS, BOLZ COLLABORATED ON STUDIES WITH TWO OTHER HSRLCE MEMBERS: DRS. SCOTT HEXIMER AND MANSOOR HUSAIN

Drawing on the organization's multidisciplinary strengths, Bolz collaborated on these studies with two other HSRLCE members: Dr. Scott Heximer, Canada Research Chair in Cardiovascular Physiology, who brings his molecular expertise to the table, and Dr. Mansoor Husain, Director and Senior Scientist at the Toronto General Research Institute (TGRI), who enabled the molecular findings to be carried into disease models and animals.

"Our latest research creates a new perspective," says Dr. Bolz. "Since the heart has to pump against peripheral resistance, having in our hands a target to reduce that vasoconstriction—thus making it easier for the heart to pump the blood volume it needs—is very useful."

HARNESSING THE POTENTIAL OF A DIABETES DRUG FOR CARDIOVASCULAR DISEASE

Cardiologist Dr. Mansoor Husain and endocrinologist Dr. Dan Drucker are an inspiring example of what interdisciplinary collaboration can achieve. Together, the HSRLCE scientists have been investigating the potentially cardiovascular protective effects of a class of drugs indicated for type 2 diabetes known as GLP-1 receptor agonists. The clinical implications may be significant for both the treatment of diabetes and cardiovascular disease.

A world-renowned diabetes treatment expert, Dr. Drucker has made major contributions to the development of new drugs for the treatment of type 2 diabetes. His current focus as a Senior Investigator at the Samuel Lunenfeld Research Institute of Mount Sinai Hospital is on understanding the biology of glucagon-like peptides (GLP).

Meanwhile, Dr. Husain, Director of the Toronto General Hospital Research Institute, examines the pathophysiology of cardiovascular diseases such as hypertension, atherosclerosis and heart failure using transgenic mouse models he has developed. His translational research holds the ultimate hope of identifying new therapeutic targets. Working alongside Dr. Drucker, Dr. Husain's lab succeeded in demonstrating in animal models that GLP-1 agonists are cardio-protective.

To date, diabetes medications have been solely aimed at blood glucose control while co-therapies such as cholesterol-lowering and antihypertensive drugs help to manage cardiovascular risk factors and complications of the disease. However, diabetes medications themselves have not shown cardioprotective properties and, in some cases, they may even negatively impact heart health. Given that over two-thirds of patients with diabetes die from cardiovascular disease, the search for treatments that safeguard the heart and brain has been ongoing.

Moving towards that goal, the HSRLCE researchers will lead a national clinical trial, expected to begin later this year, which will examine the cardioprotective potential of a GLP-1 analog in about 200 heart attack patients from 10 centres across Canada. Earlier, smaller studies have shown that when diabetes patients take GLP-1 agonists, their cardiovascular health measures improve, including their lipid profile, blood pressure and even weight. The researchers hope that clinical trial results will offer definitive proof that these drugs are also beneficial in patients with heart disease, regardless of whether or not they have diabetes.

> AN INSPIRING EXAMPLE OF WHAT INTERDISCIPLINARY COLLABORATION CAN ACHIEVE

FREEDOM TRIAL

SETTLING THE SURGERY VS. MEDICAL THERAPY DEBATE

Rising diabetes rates worldwide make it imperative to find treatments that rein in diabetes and its complications. At the HSRLCE, researchers are developing innovative, evidence-based approaches that will ultimately improve the prognosis of diabetes patients with multi-vessel disease.

Atherosclerosis commonly develops in people with diabetes, predisposing them to the risk of coronary artery disease, myocardial infarction and death. Atherosclerosis often progresses to the extent that patients need revascularization, a procedure that restores normal blood flow. Treatment options are typically either percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG), but the choice has been debated.

Some studies have pointed to CABG as the preferred treatment for patients with diabetes and multi-vessel disease. But now, clinicians and surgeons have unequivocal evidence to recommend CABG as the optimal strategy. These findings will dramatically change guidelines for diabetes and, ultimately, for clinical practice.

Dr. Michael Farkouh, HSRLCE's new director, was co-principal investigator on a pivotal study called FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease). It brought together 140 clinical centres in North America, Europe, South America, India, Australia and New Zealand. The effort bridged the expertise of five HSRLCE and university-affiliated centres and included interventional cardiologists, surgeons and diabetes specialists.

The large-scale trial randomized 1,900 patients with diabetes and multi-vessel coronary artery disease to either PCI with drug-eluting stenting or CABG (standard of care), then followed them for five years. The study found that CABG was superior to PCI, significantly reducing rates of death and myocardial infarction but with a higher rate of stroke.

Dr. Farkouh is eager to build on these findings: "The Lewar Centre will be focusing on one of its major platforms – diabetes and heart disease – which will allow us to bring interested parties together to develop the next set of studies and trials." This includes evaluating the impact of having well-controlled patients (through optimizing medical therapy, such as statins, anti-hypertensives and diabetes medications) on the success of PCI and CABG.

> THESE FINDINGS WILL DRAMATICALLY CHANGE GUIDELINES FOR DIABETES AND, ULTIMATELY, FOR CLINICAL PRACTICE

Research will also explore newer ways of performing revascularization procedures. There is particular interest in assessing how combining PCI and CABG, known as hybrid revascularization, would work.

As the prevalence of diabetes continues to grow globally, the international medical community will look increasingly to the HSRLCE, where scientists will leverage findings from the FREEDOM trial to develop leading-edge interventions for managing high-risk patients.

NOVEL DRUG THERAPY OFFERS NEW HOPE FOR BLOCKED ARTERIES

Chief of the Schulich Heart Centre and HSRLCE scientist, Dr. Bradley Strauss' research efforts are aimed at deciphering the pathophysiology of chronic total occlusions (CTO) and developing minimally invasive therapeutic strategies to treat them.

Recently, Dr. Strauss developed a novel drug therapy that makes it possible to successfully perform angioplasty in patients with CTO, which may turn the tables on current common practices for managing patients with blocked arteries.

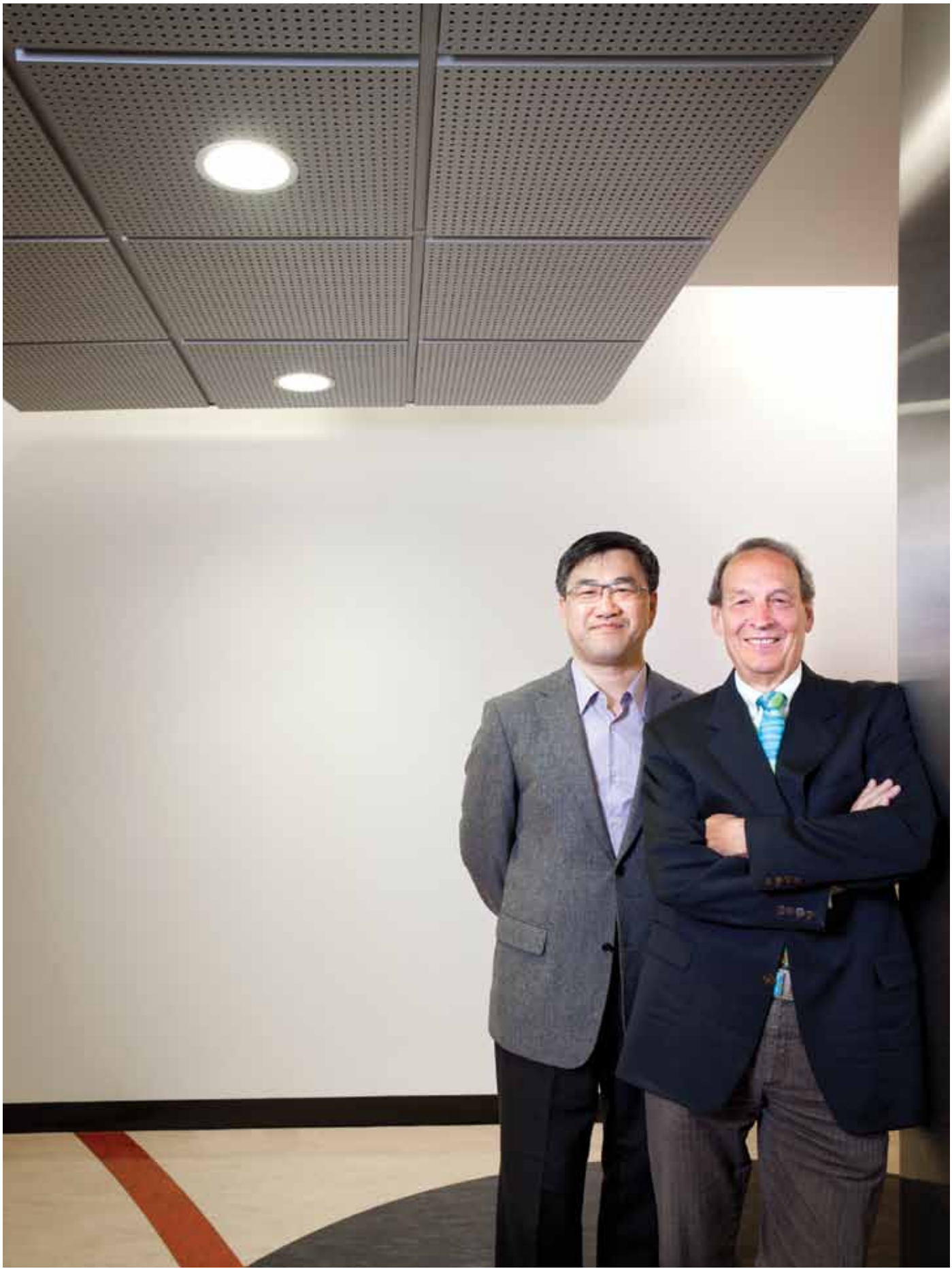
Patients with total occlusions often get relegated to more invasive procedures and treatments, which may not fully address symptoms such as shortness of breath and angina. Treatment options generally exclude angioplasty for such patients due to the difficulty of penetrating blocked arteries with the guidewires required to perform the procedure. The success rate is fairly high (95 percent or more) when angioplasty is performed in non-occluded arteries, but much lower (about 50 to 70 percent) when attempted in patients with total occlusion.

Dr. Strauss has been working with an investigational drug, known as MZ-004, a collagenase or enzyme that breaks down collagen. As total occlusions become older, they fill up with a fibrous tissue called collagen. Injecting the collagenase into blocked arteries degrades the built-up collagen, which enables angioplasty operators to insert soft-tipped guidewires (rather than hard wires) into blocked arteries. This increases both the ease of the procedure and the success rate.

According to study findings Dr. Strauss and colleagues published in the journal *Circulation*, using MZ-004 enabled three-quarters of patients (15 out of 20) to successfully undergo angioplasty. Next, the study will enter a phase-3 trial with over 400 patients and involving 30 sites across Canada and the US. Consistent clinical trial findings would reassure clinicians and surgeons that angioplasty is a viable option for many more patients with coronary artery disease, even those with total occlusions.

> TURNING THE TABLES ON CURRENT COMMON PRACTICES FOR MANAGING PATIENTS WITH BLOCKED ARTERIES

Currently, approximately 10 percent of CTO cases are ever attempted, 25 percent go to bypass surgery and the rest are treated medically. The use of a novel technique such as collagenase could double the proportion of patients with CTO receiving angioplasty and full relief of their symptoms.



YOUNG AT HEART

REJUVENATING AGED STEM CELLS

While cell therapy has been the Holy Grail of regenerative medicine over the last decade, it has not been without its glitches, and aging seems to be a leading culprit. The groundbreaking research of HSRLCE members Drs. Ren-Ke Li and Richard Weisel, both Senior Scientists at the Toronto General Research Institute, has shown that the deleterious effects of aging—a major cause of death and disability in industrialized nations—extend to stem cells as well.

In 1996, the team demonstrated that healthy stem cells could be transplanted into cardiac tissue. The clinical results of this promising therapy, however, were not as encouraging as pre-clinical testing had suggested. Focusing on troubleshooting the problem, the researchers made a vital discovery: aging impairs stem cells in both number and function, which impairs cardiac healing.

Examining isolated cells from old animals revealed several defects that contribute to the cells' limited capacity for regeneration. Also, by studying bone marrow stem cells removed from patients undergoing cardiac surgery, they found that limited stem cell function correlated linearly with patient age.

The end result is that older patients respond poorly to cardiac stem cell therapy. So the researchers asked: What if stem cells could be rejuvenated to act more like younger cells? For several years now, the team has focused on developing new methods to rejuvenate endogenous stem cells and restore their ability for self-renewal and regeneration.

"At the cellular level, we introduced functional genes; at the protein or tissue level, we introduced growth factors; and at the systemic level, we added stem cells from young donors," explains Dr. Li. Using these strategies, the researchers have been able to rejuvenate stem cells from older patients, restoring their capacity for proliferation and myogenic differentiation, which permitted them to return ventricular function towards normal.

> OUR GOAL IS TO TRANSLATE OUR FINDINGS FROM BENCH TO BEDSIDE

Ultimately, the researchers aim to maximize the therapeutic benefit of cardiac stem cell therapy in older patients. "Our goal is to translate our findings from bench to bedside, to provide new approaches for treating aged patients, enhance their recovery from cardiac injury, improve their quality of life and hopefully increase their lifespan," says Dr. Weisel.


KNOWLEDGE

IMAGING & GENE THERAPY

ADVANCES FOR HEART DISEASE

AT a new facility at the University of Toronto, Drs. Howard Leong-Poi and Kim Connelly are using state-of-the-art ultrasound imaging and hemodynamics to study in detail how the heart works and exploring novel methods of delivering and monitoring non-invasive therapies for heart disease, including gene and cell-based therapies.

The Cardiac Imaging and Hemodynamic Core Facility for Translational Research, which is funded by the Canadian Foundation for Innovation (CFI), embraces a "molecules to medicine" approach, producing new findings at the basic science level and pushing the knowledge through preclinical model and clinical trial stages, ultimately to the patient bedside.

Dr. Leong-Poi, a scientist in the Keenan Research Centre of the Li Ka Shing Knowledge Institute of St. Michael's Hospital leads a research program focused on novel diagnostic and therapeutic applications for contrast ultrasound and ultrasound-targeted gene- and cell-based regenerative therapies. Dr. Connelly is another clinician scientist at St. Michael's Hospital whose work is devoted to developing novel therapies for diastolic heart failure and cardiac imaging techniques.

Functional and molecular ultrasound imaging and hemodynamic quantification enable the HSRLCE researchers to look at the heart at a physiological and tissue level, which offers useful insights to clinicians examining post-MI remodelling and scar tissue. The advanced imaging technology also helps to optimize ultrasound-mediated gene delivery.

Whereas current gene therapies typically involve viruses or invasive procedures and pose side effects (due to widespread or remote transfection), ultrasound-mediated gene therapy with microbubbles is a fairly non-invasive method with several advantages. Microbubbles are smaller than red blood cells and are given intravenously, then targeted where genes will be delivered. Ultrasound destroys the microbubbles, causing genes on the surface of the bubbles to penetrate into the vasculature, which results in targeted transfection within the organ. It is also a more precise method since intravascular gene delivery "preferentially targets the inner surface of the vessels, referred to as the vascular endothelium," explains Dr. Leong-Poi.

> ULTRASOUND IMAGING AND HEMODYNAMIC QUANTIFICATION ENABLE HSRLCE RESEARCHERS TO LOOK AT THE HEART AT A PHYSIOLOGICAL AND TISSUE LEVEL

Dr. Leong-Poi says their team is also exploring the use of multi-gene therapies—gene combinations "delivered sequentially in a pattern that is most effective in growing new vessels that are actually more functional and last longer."

Both clinician scientists are actively involved in phase 2 clinical trials getting underway this year that use CFI-funded ultrasound imaging and hemodynamic equipment. One will assess the effects of a new treatment in patients with diabetes and heart disease, while another examines the use of genetically enhanced progenitor cells to improve function after a large myocardial infarction.

MEET SOME OF THE CENTRE'S TRAINEES

The Centre continuously supports research and education on the prevention and cure of cardiovascular diseases and supports its trainees in cardiovascular science with its fellowship and graduate funding programs. These awards aim to enrich the productive research enterprise in Toronto, and we expect these trainees to become the scientific leaders of tomorrow. Currently the Centre supports 6 graduate trainees and 3 post-doctoral fellows.

KAUSTABH (BUNTY) SINGH

DEVELOPING STRATEGIES TO IMPROVE OUTCOMES IN CARDIAC DYSFUNCTION

I am currently a third-year PhD student in Dr. Ren-Ke Li's lab in the Department of Laboratory Medicine and Pathobiology at the University of Toronto.

My PhD dissertation revolves around studying basic molecular pathways regulating cardiac remodelling following an infarction. One of these is the WNT/β-catenin signalling pathway. My project focuses on its regulation by employing genetic mouse models that target the disruption of this pathway in cardiomyocytes. The overall goal is to better understand how this pathway affects cardiac dysfunction following injury, and then work towards developing therapeutic strategies to improve outcomes that can be translated in the clinic.

Through the UofT and UHN I am provided with the opportunity to work with some of the leading researchers in the cardiovascular field in Toronto. I am also privy to being mentored by an esteemed research supervisor, Dr. Ren-Ke Li, who is able to teach me how to ask the right research questions and conduct an effective project.

In addition, being a trainee of the HSRLCE has provided me with the added benefit of funding, close collaborations and other resources through networking for my research and training. I would not be able to find such opportunity in other places.

I would like to continue my training in cardiovascular-related pathobiology by pursuing a post-doc. Eventually I would like to work on improving basic research in the cardiovascular platform and aid in translating it to clinical practices.

ALLEN TENG

POTENTIAL THERAPY TO PATIENTS WITH HEART FAILURE

I have always been fascinated by human cardiovascular biology and enjoy asking related questions in life. For example, why wouldn't our heart repair itself like skeletal muscles when damaged? What happens to our heart when suffering trauma? How do genetic mutations translate into heart failure? These simple questions prompted me to pursue research in the field and I begin my journey here at the University of Toronto. Uof T has a strong tradition in medical research, there are many high-calibre, talented and passionate scientists with whom I can share my vision, including my current supervisor Dr. Anthony Gramolini.

My specific project is focused on understanding how mutant phospholamban proteins are degraded or mislocated in heart cells and thus cause heart failure. Knowing how phospholamban degradation is modulated in heart cells provides a key answer to normal heart contractility. By the same token, these studies are indispensible for comprehending how a heart responds to stress at a critical state by modulating phospholamban functions and levels. This ongoing research may also provide a potential therapy to patients with heart failure.

I hope that many years of research training will help me understand human cardiovascular biology better so I can develop novel scientific findings. I plan to become a physician-scientist so I can pass these findings on to my fellow Canadians.

MARK ROUFAIEL

REDUCING THE RISK OF HEART DISEASE

I am a fourth-year PhD student in Dr. Myron Cybulsky's lab at the Department of Laboratory Medicine and Pathobiology, University of Toronto.

My thesis project studies the reverse transmigration of arterial intimal dendritic cells. Dendritic cells (DCs), a specialized class of white blood cells that are critical to the body's immune system, are found in the inner artery wall of healthy humans and animals. We have found that DCs are particularly abundant in atherosclerosis-predisposed areas of normal mice (resident intimal DCs or RIDCs). When blood cholesterol is high, RIDCs take up lipid and transform into lipid-loaded foam cells, which is the first step in the formation of atherosclerosis. RIDCs exit the normal artery wall, but lipid accumulation in RIDCs as a result of high blood cholesterol blocks their exit.

Our goal is to elucidate the mechanisms underlying RIDC exit from normal arteries, and to determine how accumulated lipid inhibits exit. We anticipate that information gained from the proposed studies will enable us to overcome the inhibitory mechanisms in lipid-loaded RIDCs in the future, so that lipid can be removed from the artery wall by exiting lipid-loaded RIDCs.

I am passionate about this field as cardiovascular diseases are currently the number-one killer of people in Canada and North America. I hope that my research will have an impact on reducing the risk of heart disease or work on novel therapies.

My future plan is to carry on with my graduate studies followed by post-doctoral training to prepare for a career in the cardiovascular field as an independent investigator.

ANNUAL CARDIOVASCULAR SCIENTIFIC DAY

Bringing together faculty and trainees to facilitate collaborative research. Providing knowledge on the frontiers of cardiovascular science on all research themes, from basic biomedical to clinical and outcomes. Promoting cross-fertilization of ideas and research direction.

APRIL 21 2011

CARDIOVASCULAR IMAGING: SEEING THE FUTURE

8:30 – 8:45 AM
Opening Remarks
David Sculthorpe, CEO HSFO
Avrum Gotleib & Mansoor Husain

8:45 – 9:30 AM
Heart & Stroke keynote lecture
Gary Lopaschuk, PhD
Treating Heart Failure by Optimizing Cardiac Energy Metabolism

9:30 – 10:00 AM
Craig Simmons, PhD
Mechanics-Based Insights into Aortic Valve Pathobiology

10:45 – 11:15 AM
Charles Cunningham, PhD
Metabolic Imaging in the Heart using Hyperpolarized 13C

11:15-11:45 AM
Howard Leong-Poi, MD
Beyond Imaging: Therapeutic Applications of Contrast Ultrasound

IMAGING CARDIAC ENERGETICS

11:20 – 1:30 PM
Poster Judging, Discussion

2:00 – 2:45 PM
Richard Lewar Plenary Lecture
Jonathan R. Lindner, MD
Molecular Imaging of Endothelial Phenotype in Cardiovascular Disease: Potential Clinical Applications

2:45 – 3:15 PM
Michelle Bendeck, PhD
Imaging Extracellular Matrix Remodelling in Vascular Disease

3:15 – 3:45 PM
Bradley Strauss, MD, PhD
Biologic Modification of Chronic Total Occlusions: Lessons from Preclinical Models and the Clinic

4:00 – 4:30 PM
Dr. Subash C. Verma Award Lecture
Anthony Gramolini, PhD

4:30 – 5:00 PM
Presention of poster award

APRIL 19 2012

ATRIAL FIBRILLATION SYMPOSIUM

8:15 – 8:30 AM
Welcome and Opening Remarks
Mansoor Husain

8:30 – 9:10 AM
Richard Lewar Plenary Lecture
Sanjiv Narayan, MD, PhD
The Mechanism of Sustained Human AF and Electrogram-based Ablation Strategy

9:10 – 9:50 AM
Heart & Stroke keynote lecture
Allan Skanes, MD
Electrogram-based Ablation of Atrial Fibrillation: Is it useful and practical?

10:20 – 11:00 AM
Science Day Visiting Lecture
Michael Gollob, MD
Heritable Factors in Atrial Fibrillation

11:00 – 11:30 PM
Scott Heximer, PhD
Increased Susceptibility to Parasympathetic Signalling and Atrial Arrhythmias in RGS4KO Mice

11:30 – 12:00 PM
Peter Backx, PhD
Atrial Fibrillation-induced Exercise: What every high-performance athlete should know

12:00 – 2:15 PM
Poster Session and Discussion

BREAKOUT SESSIONS

SESSIONS #1
Diabetic Heart Disease

SESSIONS #2
Atrial Fibrillation: Where to go from here?

SESSIONS #3
Human Pluripotent Stem Cells for Cardiovascular Disease-modelling and Regeneration

4:00 – 4:30PM
Dr. Subash C. Verma Award Lecture
Dennis Ko, MD

4:30 – 5:00 PM
Presention of poster award

APRIL 18 2013
DIABETES AND HEART DISEASE

8:30 – 8:45 AM
Welcome and Opening Remarks
Michael Farkouh

EPIDEMIOLOGY AND OPTIMIZING THERAPY

8:50 – 9:35 AM
Richard Lewar Plenary Lecture
Robert S. Rosenson, MD
Heart Disease and Diabetes: What is the next frontier?

9:35 – 10:05 AM
UofT Spotlight on Incretin
Mansoor Husain, MD

UofT Spotlight on Revascularization

10:30 – 10:50 AM
Michael Farkouh, MD
FREEDOM Trial

10:50 – 11:10 AM
Vlad Dzavik, MD
EMPRESS Trial

11:20 – 1:30 PM
Poster Session and Discussion

IMAGING AND NOVEL INSIGHTS

1:35 – 2:20 PM
Heart & Stroke Keynote Lecture
James HF Rudd, MD, PhD
Can we predict heart attack using imaging? An approach using PET/CT

2:20 – 3:05 PM
Annual Cardiovascular Science Day Visiting Lecture
Peter Light, PhD
Sulfonylurea Molecular Pharmacology and Clinical Cardiotoxicity: From molecule to malady

APRIL 17 2014

4:30 – 5:00 PM
Presention of poster award

4:00 – 4:30 PM
Dr. Subash C. Verma Award Lecture
TBA

3:30 – 4:00 PM
UofT Spotlight on Microvascular Research
Steffen-Sebastian Bolz, PhD

DISTINGUISHED VISITING **PROFESSORS**

Our Distinguished Visiting Professor series is a forum for external experts to present their cutting-edge research and to interact with our members and trainees. It also provides an opportunity for our members to highlight the Centre's activities to international opinion leaders.

"**PIVOTAL ROLE** OF HEART RATE IN **ATHEROSCLEROSIS**"

JEAN-CLAUDE TARDIF, MD
Director, MHI Research Centre
Professor of Medicine, Université de Montréal

"**NEW INSIGHTS** INTO THE MECHANISMS AND TREATMENT OF **AORTIC VALVE DISEASE**"

PHILIPPE PIBAROT, DVM, PhD, FACC, FAHA, FASE, FESC
Director of the Research Group in Valvular Heart Diseases, Quebec Heart & Lung Institute
Professor of Medicine, Laval University

"PROTEIN KINASES IN THE HEART: **TARGETS OLD** AND **NEW REGULATING INJURY** AND **REPAIR"**

THOMAS FORCE, MD
Clinical Director, Center for Translational Medicine, Jefferson Medical College
Professor of Medicine, Thomas Jefferson University

"**PROTEOTOXICITY** AND CARDIAC DISEASE"

JEFFREY ROBBINS, PhD, FAHA
Director of the Division of Molecular Cardiovascular Biology
Professor of Pediatrics, Cincinnati Children's Hospital Medical Center

"BLOOD GLUCOSE IN ACUTE MI: **TRIALS, TRIBULATIONS** AND **FUTURE DIRECTIONS**"

MIKHAIL KOSIBOROD, MD, FACC, FAHA
Associate Professor, University of Missouri, Kansas City School of Medicine

"VASCULAR BED-SPECIFIC REGULATION OF **VON WILLEBRAND FACTOR**"

WILLIAM AIRD, MD
Director of the Center for Vascular Biology Research and Chief of Molecular and Vascular Medicine, Beth Israel Deaconess Medical Center
Professor of Medicine, Harvard Medical School

"CELL- AND GENE-BASED APPROACHES FOR ENGINEERING BIO-ARTIFICIAL HUMAN HEART CELLS AND TISSUES: **HOW CLOSE ARE WE?**"

RONALD LI, PhD
Director, Stem Cell and Regenerative Medicine Consortium Li Ka Shing Faculty of Medicine, University of Hong Kong
Professor of Medicine and Physiology, University of Hong Kong

"PLURIPOTENT STEM CELL ENGRAFTMENT TO **ENHANCE VENTRICULAR FUNCTION**"

PHILIPPE MENASCHE, MD, PhD
Director, Heart Failure Surgical Unit, Hôpital Européen Georges Pompidou
Professor of Thoracic and Cardiovascular Surgery, University Paris Descartes

MEMBERS & COMMITTEE

"PROTEINASE SYSTEMS AND THORACIC AORTIC **ANEURYSM PROGRESSION**"

JOHN S. IKONOMIDIS, MD, PhD, FRCS(C), FACS, FAHA, FACC
Chief of the Division of Cardiothoracic Surgery and Director of the South Carolina Heart Valve Center
Professor of Surgery, Medical University of South Carolina

"IMAGING IN HEART FAILURE: **THE BIG PICTURE**"

ROBERT BEANLANDS, MD
Chief of Cardiac Imaging, Director of the Cardiac PET Centre, Ottawa Heart Institute
Professor of Medicine, University of Ottawa

"STIMULATING **MYOCARDIAL GROWTH AND REGENERATION** TO TREAT HEART DISEASE"

BERNHARD KUHN, MD
Assistant Professor of Pediatrics, Harvard Medical School

"HOW OBESITY GOES TO OUR HEADS: **UNIQUE ASPECTS OF CNS REGULATION** OF FOOD INTAKE AND BODY WEIGHT"

RANDY SEELEY, PhD
Director of the Cincinnati Diabetes and Obesity Center
Professor of Medicine, University of Cincinnati College of Medicine

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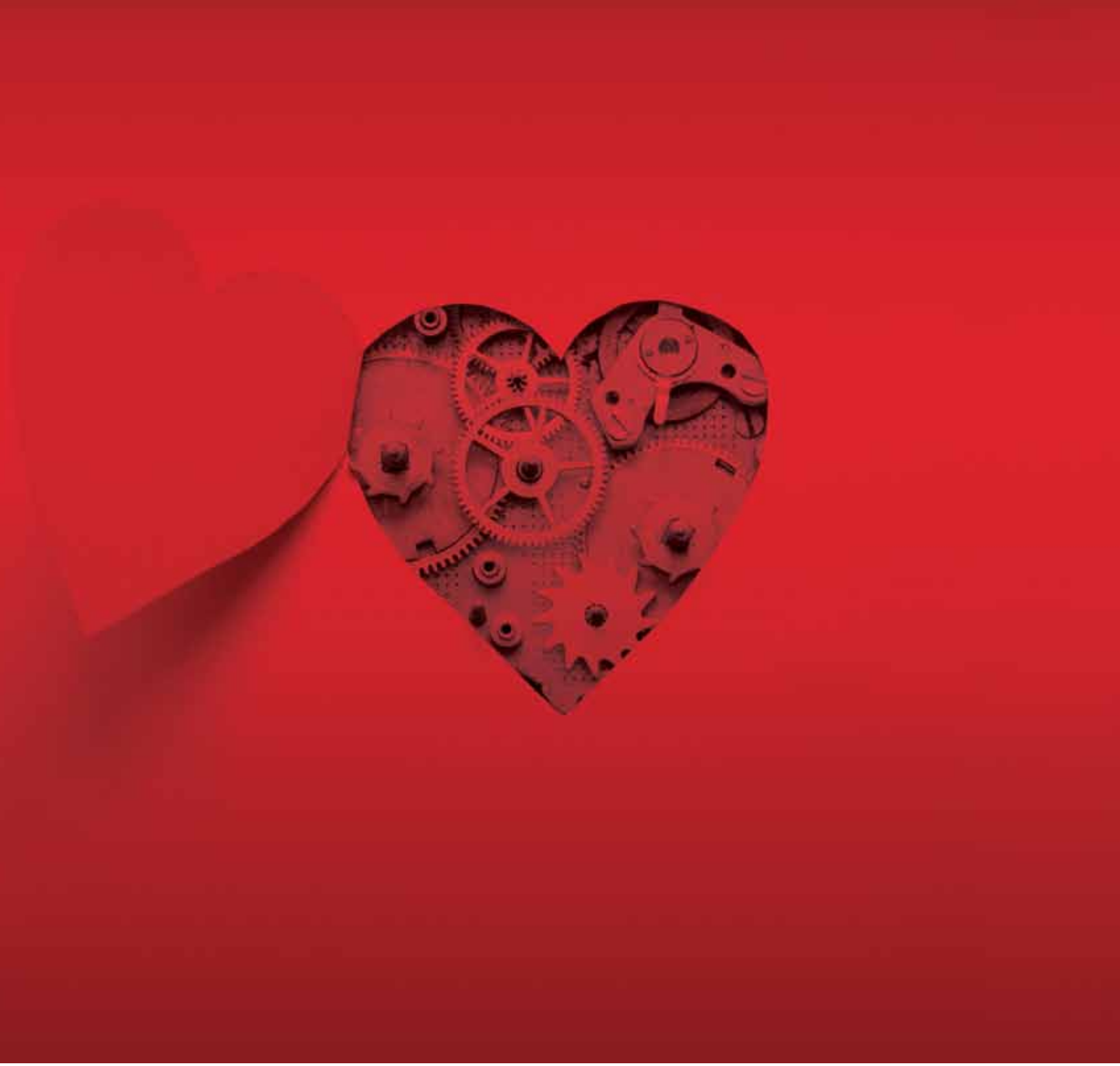
Dr. Richard Hegele, Department of Laboratory Medicine and Pathobiology
Dr. Stephen Matthews, Department of Physiology



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