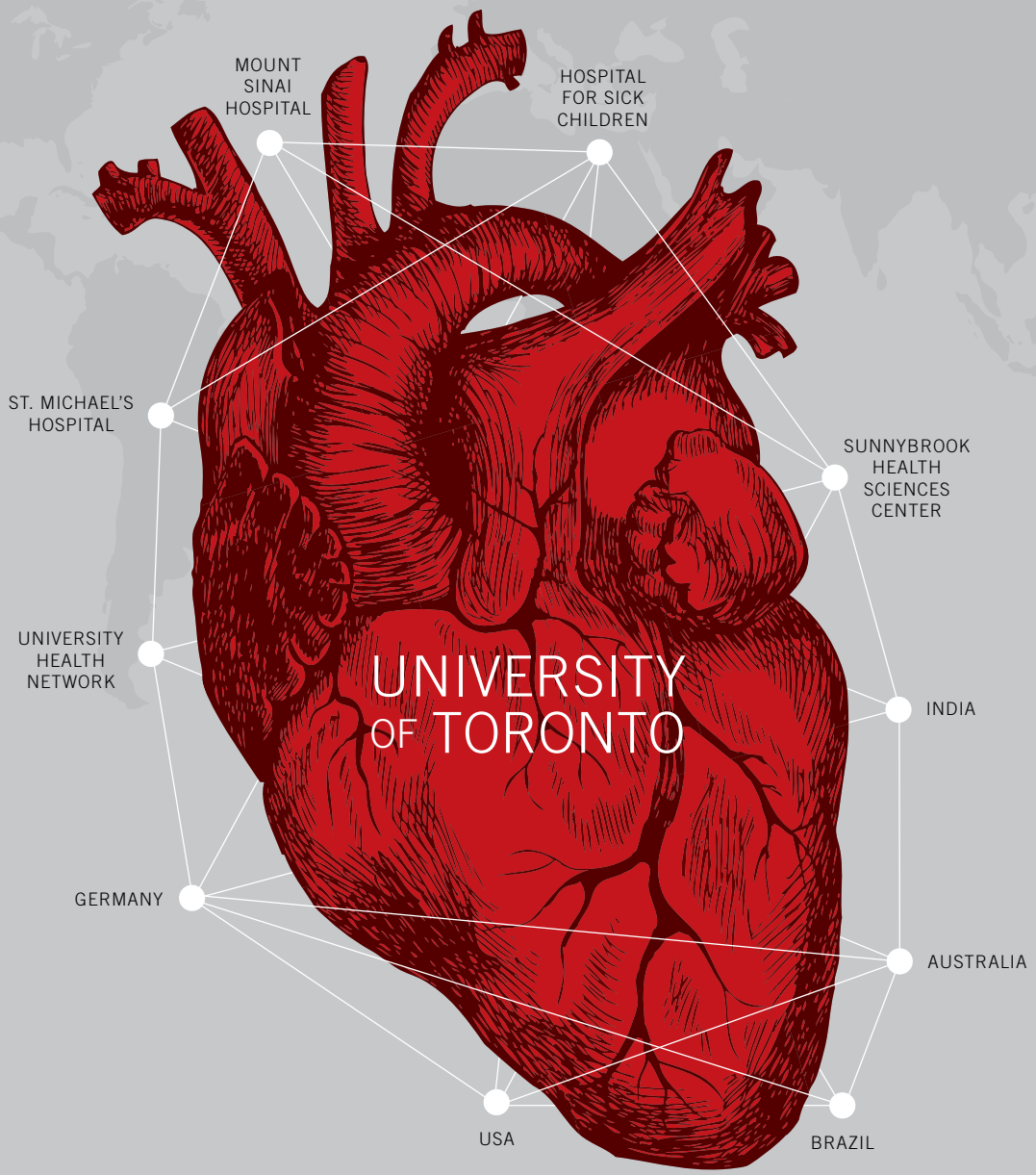


HEART & STROKE / RICHARD LEWAR

CENTRE OF EXCELLENCE

BIENNIAL REPORT
2013–2014

CONTENTS

THE HEART & STROKE / RICHARD LEWAR CENTRE OF EXCELLENCE IN CARDIOVASCULAR RESEARCH

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

DIRECTOR'S MESSAGE

MICHAEL FARKOUH

PHOTO: ROB WAYMEN

It is my pleasure to provide an update on the progress of the Heart and Stroke Richard/Lewar Centre of Excellence in Cardiovascular Research (HSRLCE) at the University of Toronto. The past two years have seen a number of changes, with expansion in our membership, our involvement on the global level and our investment in education initiatives.

For over 15 years the HSRLCE has established and developed strong relationships with all of our partnering institutions. A large animal facility at the Sunnybrook Health Sciences Centre is thriving, our microvascular laboratory at St. Michael's Hospital has expanded to Munich and the transgenic physiology laboratory is moving into an exciting new phase in its development. We have seen exciting developments with the cardiovascular surgical outcomes database across the University of Toronto, the CVDMC. Our university-wide clinical trials unit, the Network for Innovation in Clinical Research (NICR), has launched three multicentre trials with the support of the Applied Health Research Centre at the Li Ka Shing Knowledge Institute. Through these core facilities and the strong support of all of our member institutions we are poised to strike on the world stage. This has allowed us to develop a programmatic approach to addressing the most pressing research questions.

These programs have now developed on two new major fronts. The first is diabetes and heart disease. Through our collaboration with the Banting and Best Diabetes Centre and the Faculty of Medicine, we have developed grant proposals for translational research across institutions. Our program in heart arrhythmias, particularly atrial fibrillation, has been received with a spirit of collaboration across all institutions and across the four major pillars.

One of the most exciting developments in the past two years has been the evolution of our Annual Science Day. This is very much mirrored our programmatic approach to cardiovascular translational research. In 2014, we decided to name the Annual Science Day after one of the Centre's founders, Dr. Michael J. Sole. Honouring Michael with this distinction was one of the highlights of 2014.

Another outstanding development has been our collaboration with the Cardiovascular Sciences Collaborative Program. This exciting program affords the opportunity for our trainees and graduate students to learn across different departments and institutions and to develop their careers in cardiovascular research. We believe that this relationship will bring the best minds forward to tackle the epidemic of cardiovascular disease. We hope that this will help to distinguish us as not only a centre of research but also a centre of education.

Perhaps the greatest distinction that can be given to the Centre is our emergence on the world stage, through collaborations in multiple countries including the United States (Mayo Clinic and Harvard School of Medicine), Brazil (University of São Paulo) and Australia (the George Institute). We have long recognized that our collaborations on the international front led to the highest impact work in scientific literature. This has made these collaborations more important and has led to exciting new initiatives. Our ability to work across different national levels allows us to take advantage of opportunities for funding beyond Canada and in their respective countries.

This leaves a most exciting development for the HSRLCE. This is our development of a microvascular research centre in Munich, Germany. Our Associate Director, Dr. Steffen-Sebastian Bolz, has taken the leadership in developing the U of T Centre for Microvascular Medicine Munich. This will include a drug centre to evaluate new therapies and will act as a hub for our European clinical trials network. Having a footprint in Europe will give us a great advantage in terms of accessing European Union funds and working collaboratively across a number of European countries. We are most grateful for the vision that Steffen-Sebastian has demonstrated in reaching out beyond the walls of the University of Toronto and bringing our brand in research and education across the pond.

Overall, we have made some strategic decisions to be programmatic, supportive of young investigators and to distinguish ourselves on the world stage. These exciting times will require new and innovative ways to approach cardiovascular research. The collaboration of cardiovascular scientists and educators across the University of Toronto is a work in evolution. Over the past 16 years, the HSRLCE has sought to be a collaborative force in tackling the most pressing questions in cardiovascular medicine. I am pleased to inform you that we are now in a position to reach out beyond the University of Toronto and to collaborate seamlessly with our international colleagues. I have no doubt that the members of the HSRLCE are up for the challenge and will exceed our expectations.

> Through core facilities and the strong support of all of our member institutions we are poised to strike on the world stage

MICHAEL E. FARKOUH, MD, MSC.
Director, HSRLCE
2013 – present

LEADING THE FIGHT AGAINST CARDIOVASCULAR DISEASE

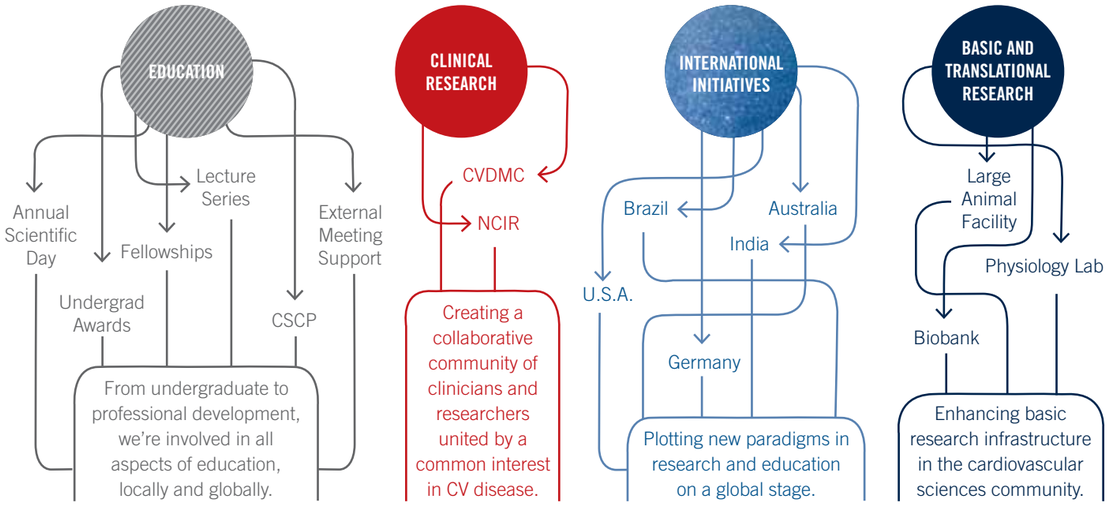
LOCAL & INTERNATIONAL COLLABORATIONS

Together we can defeat cardiovascular disease by fostering a collaborative research and educational environment, locally and internationally, that transforms cardiovascular health.

LOCAL
TORONTO

INTERNATIONAL

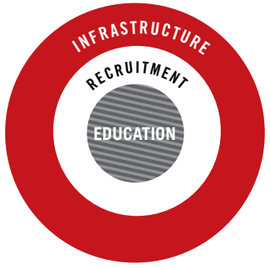
FLOW OF FUNDS



OUR IMPACT

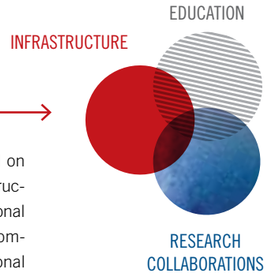
PAST

Initially the Centre focused its efforts on providing an outstanding infrastructure for research.



PRESENT

Our priorities are now focused on expanding a collaborative infrastructure, supporting basic, translational and clinical research and a commitment to supporting educational programs on all levels.



FUTURE

Our future impact will reach a broader global community through our continued commitment to the highest level of education, research and international collaborative initiatives.

CONQUERING CARDIOVASCULAR DISEASE THROUGH RESEARCH AND EDUCATION

Dr. Michael E. Farkouh (L), Dr. Alison Buchan (C) and Dr. Steffen-Sebastian Bolz (R)

PHOTO: ROB WAYMEN

REACHING

BEYOND BORDERS

THE Heart and Stroke/Richard Lewar Centre of Excellence's evolution and growth have been dramatic since its inception 15 years ago. Having recently entered a new growth phase, over the past two years, the Centre has successfully launched an international expansion strategy.

"By stepping onto the world stage, we are extending our research network capacity and reach, embracing research and education opportunities in multiple countries and forming international alliances with some of the world's leading medical institutions," explains Dr. Michael E. Farkouh, HSRLCE Director.

The Centre's global footprint is already in countries such as the United States, where members are actively engaged in NIH-funded genomics research in partnership with the Mayo Clinic; ongoing education and research initiatives in Brazil; and in Germany, where HSRLCE's Associate Director, Dr. Steffen-Sebastian Bolz, has led the establishment of the newly minted University of Toronto Centre for Microvascular Medicine Munich.

"Global expansion has granted us opportunities for rich collaboration and clinical trial involvement we would never have had without our willingness to reach out," says Dr. Farkouh. Through its international alliances, the Centre has been able to achieve some of its highest impact research. It has also gained access to new funding channels facilitated through partnerships in other countries that boast strategic ties to academia, industry and government. Moreover, the Centre has been able to leverage strengths from its partners' complementary areas of expertise, and gain "out-of-the-box" perspectives to help address the most urgent research questions.

As part of the University of Toronto's larger globalization strategy, we are working closely with Dr. Alison Buchan, the Vice-Dean of Research & International Relations. The main goal is to share our innovations and expertise worldwide through strategic partnering that maximizes our research endeavours, optimizes our ongoing collaborations and ultimately advances our global health and international relations agenda.

While the Centre's international exploration began recently, the plan to reach beyond Canadian borders was seeded much earlier, in cultivating its internal leadership and strengthening its ties with partnering institutions, locally and nationally. Growing the internal collaboration network will remain a priority for the Centre, in order to maintain a strong leadership base across different disciplines, which will provide a solid foundation for launching new international collaborative efforts. Matching members with international partners across all four of its research pillars—basic science, translational research, clinical trials and outcomes research—the Centre is truly carrying forth its bench-to-bedside approach to international programming.

> "Sharing innovations and expertise worldwide maximizes our research endeavours, optimizes our collaborations and advances our global health and international relations agenda"

Thrilled to showcase and broaden the Centre's success story of transforming cardiovascular science, Dr. Farkouh predicts that the momentum will only continue to build on a global platform. Says Dr. Farkouh: "In the future, we will increasingly have the ability to make important discoveries, innovations and novel therapies here in Toronto, expand them worldwide, increase our scope and impact, and bring new discoveries here from our international partners—all in the name of better patient care."

TESTING PROMISING THERAPIES WITH NOVEL

CARDIAC IMAGING TECHNOLOGY

Given heart failure's high morbidity and mortality rates, there is a pressing need to better understand the molecular underpinnings of this disease, as well as to develop more targeted preventive and interventional therapies that can ultimately improve patient prognosis. HSRLCE's Dr. Kim Connelly, a non-invasive cardiologist at St. Michael's Hospital, is exploring the use of advanced cardiac imaging techniques to more accurately assess heart damage, such as fibrosis and hypertrophy, as well as test promising gene and stem cell–based therapies.

One of his key collaborators is Dr. Graham Wright, Canada Research Chair in Imaging for Cardiovascular Therapeutics and a senior scientist at the Sunnybrook Research Institute, whose work is focused on advances in cardiac imaging modalities, including optimizing the use of real-time cardiac MRI. The imaging work is not just to develop better diagnostic tools but to guide decision-making about interventions. "We're using novel imaging technology to identify molecular signatures of disease and aiming to develop novel therapeutic strategies," explains Dr. Connelly. They also use cardiac imaging to monitor an experimental or existing therapy in a non-invasive way to see if it is actually working.

They are currently involved in two pre-clinical trials, one of which is the Enhanced Angiogenic Cell Therapy - Acute Myocardial Infarction Trial (ENACT-AMI) in collaboration with the Ottawa Heart Research Institute. The multicentre trial consists of "supercharging" patients' own stem cells with a gene called endothelial nitric oxide synthase (eNOS), then putting the treated cells back into patients after a heart attack to see if improves cardiac function. "We're using MRI to look at tissue damage to see if heart function improves and if remodelling is reduced in that experimental group," explains Dr. Connelly. The study marks the world's first trial to use a combination of gene and cell therapies to treat cardiac disease.

Dr. Connelly is also working on a two-year pilot study that will launch later in 2015 called the Diabetic Renal Disease and Cell-based Therapy (DIRECT) study. Funded by the Banting & Best Diabetes Centre and the HSRLCE, it will examine whether stem cell therapy can reduce fibrosis and improve heart and kidney function in diabetes and cardio-renal disease. Another research project will look at how to improve the function of stem cells by treating them with an anti-aging drug known as an SRT activator before delivering them back into patients. The ultimate prize is to develop a drug that works and that can advance to clinical trials and benefit patients, says Dr. Connelly.

> "There is a pressing need to better understand the molecular underpinnings of this disease and to develop targeted therapies that can ultimately improve patient prognosis"

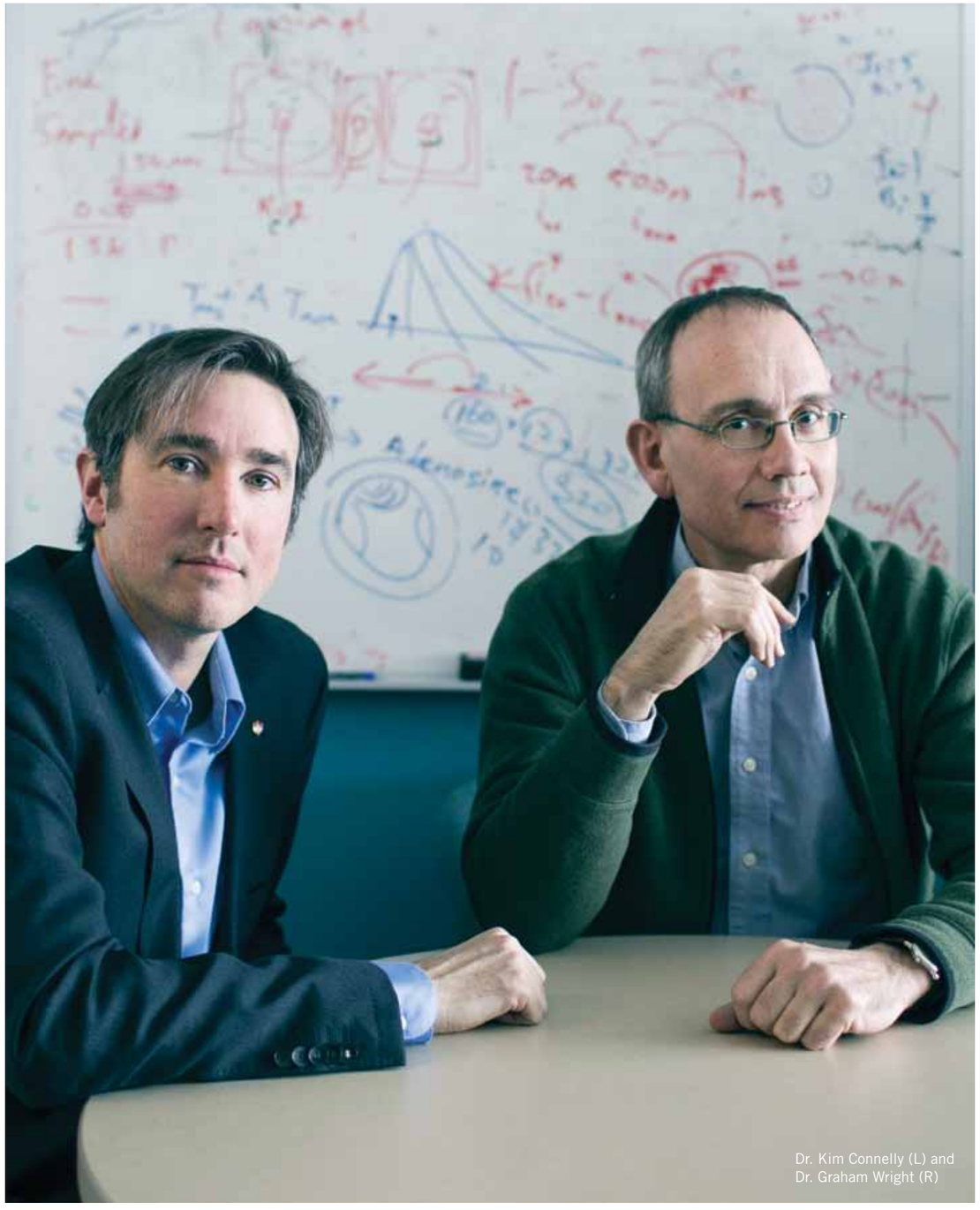


PHOTO: CHRISTOPHER WAHL

Dr. Kim Connelly (L) and Dr. Graham Wright (R)

Dr. Jay Udell (L) and
Dr. Muhammad Mamdani (R)

PHOTO: ROB WAYMEN

FIGHTING CVD

WITH FLU VACCINE

Seasonal influenza results in up to 20,000 hospitalizations and claims about 4,000 lives in Canada each year. But it likely causes a lot more morbidity and mortality related to cardiovascular disease (CVD) than we think, suggests Dr. Jay Udell, an HSRLCE member and staff cardiologist at Women's College Hospital and the Toronto General Hospital, as well as a clinician-scientist at the University of Toronto.

In response, Dr. Udell and Dr. Michael Farkouh, HSRLCE's Director, are exploring whether a flu vaccine could serve as a cardioprotective measure—essentially, a cardiovascular disease vaccine.

Heart attack and stroke risk are acutely elevated for a few days after flu infection. Evidence suggests that the flu has pro-inflammatory and pro-thrombotic effects, which can produce unstable plaque and blockages and lead to serious cardiovascular events. The flu vaccine triggers antibodies that may have a stabilizing—cardioprotective—effect, says Dr. Udell.

Dr. Udell's quest to determine whether the flu vaccine would protect high-risk individuals began with a systematic review of six randomized clinical trials of flu vaccine with CV outcomes as endpoint. The findings, published in the *Journal of the American Medical Association*, were positive. "People who got treated with flu vaccine had a lower risk of major adverse CV events such as heart attacks and stroke for the next year," Udell reports. The greatest benefit was seen among the highest-risk patients with more active coronary disease.

Now the HSRLCE team is launching a large North American clinical trial to investigate whether the flu vaccine's benefits perhaps extend beyond infection control to cardiovascular protection. The collaboration spans the University of Toronto in cardiovascular medicine and infectious disease and involves all teaching hospitals in Toronto, plus 60 hospitals and clinics across Canada and another 120 in the United States.

The ambitious project also involves HSRLCE member Dr. Muhammad Mamdani's team at the HUB, a U of T–affiliated organization that manages the logistical end of clinical trials. Recruitment for the study will start in 2016, aiming for 9,300 patients and running for three flu seasons (over three years), with a minimum of one year of follow-up.

> "Exploring whether a flu vaccine could serve as a cardioprotective measure — essentially, a cardiovascular disease vaccine"

While Dr. Udell's team awaits Canadian and U.S. National Institutes of Health funding, it is embarking on a pilot study that compares a more potent flu shot with the regular shot in patients with heart attacks or congestive heart failure. "We want to see if we can do a better job of mounting an immune response to the flu and preventing bad clinical outcomes," says Dr. Udell. "The Holy Grail will be looking at whether we have a CV disease vaccine on our hands."

DECODING THE UNDERLYING PATHOLOGY OF EXERCISE-INDUCED

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is an increasingly common heart arrhythmia that is reaching epidemic proportions in Canada, mainly affecting those over 65 and tripling the risk of stroke. Two HSRLCE members have largely devoted their work to deciphering and addressing heart arrhythmias and, more specifically, the molecular underpinnings of exercise-induced AF.

For the past two decades, Dr. Paul Dorian, a scientist in the Keenan Research Centre of the Li Ka Shing Knowledge Institute and department director, Division of Cardiology, University of Toronto, and Dr. Peter Backx, director of HSRLCE's Transgenic Physiology Lab, have been studying cardiac arrhythmias. Bringing their combined expertise in cardiology, clinical pharmacology, molecular biology and animal physiology to bear on key emerging knowledge about exercise and AF, over the past two years the pair has been exploring the effects of intense exercise on cardiac remodelling using animal models of atrial fibrillation.

While exercise is generally viewed as a heart-healthy proposition, intense exercise has been shown to raise the risk of this heart rhythm disturbance in former athletes and current competitive middle-aged athletes. "Exercise is almost always protective on the heart's ventricles," explains Dr. Dorian. "However, there is a volume of exercise beyond which it starts to result in maladaptive remodelling of the atria, and is likely to lead to atrial fibrillation, at least in animal experiments." Their current investigation focuses on finding ways to better define the molecular mechanisms underlying this maladaptive change, and developing strategies to reverse it either by preventing inflammation and scarring or addressing them once they occur.

Dr. Backx and Dr. Dorian recently led a pivotal study examining how intense exercise leads to cardiac remodelling, which identified the role of tumor necrosis factor (TNF-alpha), an inflammatory cytokine in AF that seems to be activated by intense exercise. They subsequently co-authored and published their findings in the journal *Nature Communications*. This research has been instrumental in shedding new light on the mechanisms of maladaptive changes in the heart, and suggests a new therapeutic target as well as a possible role for TNF-inhibitors to prevent atrial structural remodelling while preserving the physiological benefits of exercise.

They are also embarking on exciting new research that involves the testing of antiarrhythmic drugs in combination in a brand new model using atrial stem cells and tissue. Dr. Dorian says that this area has not been well investigated to date, and that using human cardiac stem cells should yield some very useful insights.

> "Two HSRLCE members, Drs. Paul Dorian and Peter Backx, have largely devoted their work to deciphering and addressing heart arrhythmias and, more specifically, the molecular underpinnings of exercise-induced AF"

PHOTO: CHRISTOPHER WAHL

Dr. Paul Dorian

Dr. Milica Radisic (L) and
Dr. Sara Nunes de Vasconcelos (R)

PHOTO: CHRISTOPHER WAHL

REPAIRING DAMAGED HEARTS AND DEVELOPING SAFER DRUGS WITH

BIOWIRE TECHNOLOGY

THE newest brainchild of cardiac tissue engineering is to make possible the regeneration of heart tissue, and two HSRLCE members plan to turn that prospect into reality.

Dr. Milica Radisic, a scientist at the Institute of Biomaterials and Biomedical Engineering (IBBME), and Dr. Sara Nunes de Vasconcelos, an assistant scientist at the Toronto General Research Institute (TGRI), are pioneering a heart "patch kit" using human pluripotent stem cell–derived cardiomyocytes (hPSC-CMs) and coaxing them into becoming living, implantable cardiac tissue that can help to repair heart damage.

The work is a major triumph, since it addresses an inherent challenge in using stem cell–derived cardiac cells, in that they reflect very early human development. Dr. Radisic's team figured out how to make the cells mature so they act more like adult cells, findings that they reported in the journal *Nature Methods* in 2013. Other collaborators included stem cell scientist Dr. Gordon Keller (McEwan Centre for Regenerative Medicine) and Dr. Peter Backx, director of HSRLCE's Transgenic Physiology Lab.

The team developed an in vitro platform called biowires (because they are wire shaped and propagate electrical impulses) to create an optimal environment, using 3D cell culture that mimics the physiological and electrical cues of a real heart. After two to three weeks, the cells emerge as fully mature and functional adult cardiac cells.

The timing was right for this endeavour, suggests Dr. Radisic: "Ten or 15 years ago it wasn't possible to get human cardiomyocytes or develop these models in the labs, since post-natal human cardiomyocytes are terminally differentiated and it is not possible to propagate them. Using human pluripotent stem cells and differentiating cardiomyocytes from them enabled us to achieve this goal."

Dr. Nunes de Vasconcelos is now focusing on how to vascularize the cardiac tissue, which includes addressing the high cell death that typically occurs immediately after cell transplantation. Her lab is using an innovative technology to accelerate vascularization, using ready-made vessels obtained from fat tissue that can connect with host vessels and start carrying blood within the first days post-transplantation. Preliminary findings show significantly improved survival of the transplanted cardiac cells. Vascularization will also aid in generating more complex tissues for in vitro use such as drug screening.

> "Offering new ways to repair or replace damaged heart tissue"

Ultimately, biowires will offer new ways to repair or replace damaged heart tissue. The more immediate goal is using the novel technology as an in vitro drug-screening tool to assess cardiotoxicity before drugs reach the market. Using the bioengineered human heart tissue will offer more accurate information than animal models have offered to date. The Radisic lab is developing the proprietary drug-testing platform with U.S. partners at Columbia University and MIT through a start-up company called Tara Biosystems.

BUILDING SUCCESS IN

FIGHTING HEART FAILURE

As many as one in five Canadians die of heart failure. That dismal figure is unacceptable to HSRLCE scientists Dr. Anthony Gramolini, a scientist at the Toronto General Research Institute (TGRI), Canada Research Chair in Cardiovascular Proteomics and Molecular Therapeutics and associate professor in the Department of Physiology at the University of Toronto, and Dr. Thomas Kislinger, an associate professor in the Department of Medical Biophysics at the University of Toronto. They are joining efforts to unravel the cellular pathways and molecular changes that underlie heart failure to facilitate earlier diagnosis and better patient outcomes. With the incidence of heart failure quickly reaching epidemic proportions, theirs is an urgent task. "National data suggests that once heart failure is diagnosed, the five-year mortality rate is more than 50 percent. Our focus is delaying disease progression," says Dr. Gramolini.

The Gramolini and Kislinger labs have been collaborating for over a decade, seeking novel methods to investigate general events in cardiac development and disease progression in cardiomyopathies using proteomic analyses of mouse models of cardiac disease. Joining their complementary expertise, Dr. Gramolini is focused on identifying novel proteins and signalling pathways in cardiac tissue involved in heart pathologies. Meanwhile, Dr. Kislinger uses methodologies in proteomics and informatics to analyze the large proteomic data sets generated.

The idea is that "obtaining novel insights into disease mechanisms will help to identify potential blood based biomarkers," Dr. Kislinger explains. They have been making significant strides already, as evidenced by a recent licensing agreement struck with Roche Diagnostics for a patented biomarker called biglycan. The vital discovery stems from research supported by a 2010 Genome Canada grant, led by fellow HSRLCE scientist Dr. Peter Liu. The project used mass spectrometry as a tool to identify and quantify novel cardiac membrane proteins to find blood-based early markers of heart disease.

The biomarker assay and platform for assessing heart failure will be made commercially available as a clinical tool in hospitals to help diagnose and manage heart failure patients. While earlier diagnosis and intervention are the ultimate aim, the biomarker's current indication is to measure therapeutic response and prognostic monitoring. "With such high mortality, current therapies are moderate, but there are always new opportunities to identify patients who are responding to therapy compared to those who are not," says Dr. Gramolini. Coming later this year are licences for two more biomarkers that are likely to predict early disease, as well as outcome, which are two important factors in managing heart failure.

> "Joining efforts to unravel the cellular pathways and molecular changes that underlie heart failure to facilitate earlier diagnosis and better patient outcomes"

PHOTO: ROB WAYMEN

Dr. Thomas Kislinger (L)
and Dr. Anthony Gramolini (R)

Dr. Darren Yuen (L) and Dr. Lisa Robinson (R)

PHOTO: CHRISTOPHER WAHL

TURNING DOWN INFLAMMATION IN

VASCULAR INJURY

Vascular injury is a common and complicating factor in renal disease. During injury, inflammation signals the recruitment of leukocytes (white blood cells) to the affected site to help. However, since leukocytes also release pro-inflammatory chemicals, excessive migration can compound the damage.

For nearly a decade, HSRLCE member Dr. Lisa Robinson, Canada Research Chair in Leukocyte Migration in Inflammation and Injury and head of Nephrology at the Hospital for Sick Children, has been examining the problem of massive white blood cell traffic, and searching for an "anti-migration" signal in the body. Specifically, she has been shedding new light on the role of a protein known as Slit2 (and its receptor, Robo) and demonstrating that it can reduce white blood cell migration, thus stemming progressive injury.

Known for its involvement in neurodevelopment, Slit2's role in regulating vascular inflammation has only emerged recently. Dr. Robinson's research has also shown that Slit2 boasts anti-platelet activity (prevents clots) and inhibits vascular smooth muscle cell migration (which causes progressive narrowing of blood vessels). "People have looked at individually targeting these different events that occur in cardiovascular disease. But we found that Slit2 can address all those things at once, which makes it a potential therapy for preventing progressive disease," says Dr. Robinson.

Dr. Robinson has also been investigating the role of Slit2 in renal ischemia-reperfusion injury (IRI). Dr. Darren Yuen, a nephrologist and scientist in the Keenan Research Centre of the Li Ka Shing Knowledge Institute of St. Michael's Hospital, has been collaborating with Dr. Robinson on this research. They co-authored two papers published in 2013 in *Current Opinion in Nephrology and Hypertension* and the *Journal of the American Society of Nephrology*, reporting on Slit2's signalling function in vascular injury and its specific role in IRI, respectively. More recently, they have been examining the progressive scarring that follows acute vascular injury. "Slit2 is the only agent to date that can slow that scarring process and injury progression," suggests Dr. Robinson.

Their next goal is to address vascular injury in diabetes kidney disease by targeting the overgrowth of blood vessels that occurs early in the disease process. "Possessing both pro- and anti-angiogenic effects, Slit2 may be able to block this early diabetes-induced blood vessel growth that leads to kidney damage later," explains Dr. Yuen.

> "Helping to illuminate the pathophysiology of vascular injury in renal disease, and proposing a new therapeutic target"

Their work to date has helped to illuminate the pathophysiology of vascular injury in renal disease, and propose new therapeutic targets, including Slit 2 or a Slit2-based therapy, which may help to attenuate organ damage in kidney, heart and other forms of vascular disease.

MEET SOME OF THE

CENTRE'S TRAINEES

The Centre prioritizes the importance of training the next generation of research leaders. The Centre supports research and education on the prevention and cure of cardiovascular diseases with its own fellowship, graduate and undergraduate 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.

MARK BLASER

UNCOVERING CAUSES OF AND TREATMENTS FOR AORTIC VALVE DISEASE

Calcific aortic valve disease (CAVD) is a common and deadly cardiovascular pathology with no pharmacological treatment available. Instead, surgical replacement is required when the valve leaflets become fibrotic and calcified, leading to serious cardiac complications. As a sixth-year PhD candidate in Dr. Craig Simmons' lab at the University of Toronto's Institute of Biomaterials and Biomedical Engineering, I investigate the intricate molecular and biomechanical signaling at play in the aortic valve and the factors which initiate CAVD.

The overall goal of my work is to examine the in vivo importance of a putative protective molecule that could be given before an untreatable burden of calcification develops. Using a variety of genetic and dietary mouse models, we have demonstrated that one of the natriuretic peptides is essential to proper valvular development and homeostasis. Mice lacking the receptor for this protein are more likely to suffer from disease-prone bicuspid malformations and also acquire impaired valvular function, fibrosis and calcification. Ongoing research will identify whether therapeutic delivery of this peptide can indeed slow the progression of CAVD.

The trainee support I receive through the HSRLCE has been invaluable to both the progress of my research and to my growth as a scientist. Along with funding, it has enabled our successful collaborations with other HSRLCE members such as Dr. Scott Heximer, and allows us access to world-class facilities and expertise throughout UofT.

In the future, I hope to pursue a post-doctoral fellowship in cardiovascular biomedical engineering. My ultimate goal is to become a primary investigator who combines engineering and biological principles in order to further our understanding of cardiovascular pathobiology.

XIAOHONG (RUBY) XU

NOVEL MECHANISMS TO PREVENT AND TREAT CARDIOVASCUALR DISEASES

I obtained my MD in China in 2011 and am currently a second-year M.Sc graduate student in Dr. Heyu Ni's lab in the Department of Laboratory Medicine and Pathobiology, University of Toronto.

Since 2012 I have been trained intensively by Dr. Ni to investigate novel mechanisms of thrombosis, which is the major cause of heart attacks and stroke, and to develop new anti-thrombotic therapies. My thesis project is to study the role of apolipoprotein A-IV (apoA-IV), a lipid binding plasma protein, on platelets and in thrombosis. In this study, apoA-IV is identified as a novel ligand of platelet IIb 3 integrin and an endogenous thrombotic inhibitor, which establishes a new link between lipoprotein metabolism and platelets, both critical factors in cardiovascular diseases. The manuscript of my project is currently under consideration by the journal *Nature*.

Dr. Ni is not only a leading scientist in the field but also an outstanding supervisor. He and the senior lab members have created an environment for trainees to actively present, discuss and debate our proposals and data, through which my critical thinking, presentation and writing skills have been greatly improved.

As an international graduate student, it was very challenging since we have very limited external funding. The HSRLCE studentship provides me with great support, which is critical for my research and further developing my knowledge and skills in the field of cardiovascular diseases and stroke. Being a trainee of the HSRLCE, I also have the opportunity to learn from other excellent scientists and network with peers.

I would like to continue my research in cardiovascular diseases and I also would like to apply my findings to clinical medicine, which may be eventually beneficial to patients.

JEFF KROETSCH

CIRCADIAN RHYTHMICITY OF THE MYOGENIC RESPONSE IN HEALTH AND CARDIOVASCULAR DISEASE

I am fascinated by the interconnected nature of the cardiovascular system; how the heart and blood vessels work harmoniously to preserve normal function, and how dissonance results in pathologic dysfunctions.

As a doctoral student supervised by Dr. Steffen-Sebastian Bolz, I investigated the role of the cytokine TNFa in the regulation of small artery responses to pressure, termed myogenic responsiveness. We found that TNFa promotes greater myogenic responsiveness in diverse cardiovascular pathologies and we hypothesized that this TNFa mechanism may also operate under healthy conditions. Indeed, we found that many species, from mice to humans, require TNFa to maintain normal myogenic responsiveness and to preserve healthy blood pressures. Surprisingly, TNFa is most important in maintaining blood pressure during sleep time. This implies that (i) there is a daily rhythm to myogenic responsiveness with strongest responses in sleep time and (ii) that blood vessels and the heart work in a complementary way to maintain normal blood pressure.

Now, as a post-doctoral fellow with Dr. Bolz, I will investigate the circadian rhythm of myogenic responsiveness, and its implication to cardiovascular health. This project is generously supported by a joint fellowship between the HSRLCE and the CIHR-funded Sleep and Biological Rhythms Program. For this study, we have partnered with Dr. Tami Martino at the University of Guelph, an expert in cardiac circadian rhythms. Our collaborative project aims to (i) identify the molecular pathway that regulates the circadian rhythmicity of myogenic responsiveness and (ii) extend this investigation into cardiovascular pathologies where myogenic responsiveness may be uncoupled from its normal circadian rhythm. This work will help explain the progression of cardiovascular disease and may lead to optimal timing of clinical treatments.

MARK BLASER

XIAOHONG (RUBY) XU

JEFF KROETSCH

MICHAEL J. SOLE

ANNUAL CARDIOVASCULAR SCIENTIFIC DAY

THURSDAY, APRIL 16, 2015, TORONTO REFERENCE LIBRARY, BRAM & BLUMA APPEL SALON

8 AM — REGISTRATION, CONTINENTAL BREAKFAST, POSTER SET-UP

8:30 — **WELCOME & OPENING REMARKS**
Dr. Michael Farkouh, HSRLCE Director, and **Dr. Alison Buchan**, Vice-Dean Research and International Relations, University of Toronto

8:45 — REMARKS FROM DR. MICHAEL J. SOLE

9 AM — **CEREBROVASCULAR DISEASE** CHAIR: ALAN MOODY

9:05 — DR. SANDRA BLACK
Senior Scientist and Director, Hurvitz Brain Sciences Research Program at Sunnybrook Health Sciences Centre; Professor, Department of Medicine (Neurology), University of Toronto
Translational

RICHARD LEWAR PLENARY LECTURE

9:25 — DR. CHERYL JAIGOBIN
Clinical Researcher, Toronto General Research Institute; Associate Professor, Department of Medicine (Neurology), University of Toronto
Clinical

9:45 — DR. R. LOCH MACDONALD
Neurosurgery Division Head, St. Michael's Hospital; Scientist, Keenan Research Centre of the Li Ka Shing Knowledge Institute of St. Michael's Hospital; Professor, Departments of Surgery/Neurosurgery, University of Toronto
Basic

10:05 — Session Overview & Active Discussion

10:25 — Refreshment Break

10:55 — **VASCULAR MEDICINE & DIABETES** CHAIR: SUBODH VERMA

11 AM — DR. MANSOOR HUSAIN
Director, Toronto General Research Institute, Professor, Departments of Medicine, Physiology and Laboratory Medicine and Pathobiology, University of Toronto
Basic

11:20 — DR. RICHARD GILBERT
Scientist, Keenan Research Centre of the Li Ka Shing Knowledge Institute of St. Michael's Hospital; Professor, Departments of Medicine/Endocrinology, University of Toronto
Translational

11:40 — DR. DAVID CHERNEY
Associate Professor of Medicine, University of Toronto; Clinician Scientist, Division of Nephrology and Director, Renal Physiology Laboratory, UHN
Clinical

12 PM — Session Overview & Active Discussion

12:20 — Lunch & Poster Sessions

2:20 — **VASCULAR MEDICINE** CHAIR: MYRON CYBULSKY

2:25 — **HEART & STROKE KEYNOTE LECTURE**
DR. DUNCAN J. STEWART
CEO and Scientific Director, the Ottawa Hospital Research Institute; Vice-President, Research, The Ottawa Hospital; Professor, Department of Medicine, University of Ottawa
Clinical

2:45 — DR. JASON FISH
Assistant Professor, Department of Laboratory Medicine and Pathobiology, University of Toronto; Canada Research Chair in Vascular Cell and Molecular Biology
Basic

3:05 — DR. PHIL MARSDEN
Scientist, Keenan Research Centre of the Li Ka Shing Knowledge Institute of St. Michael's Hospital; Professor and Vice-Chair of Research, Department of Medicine, University of Toronto
Translational

3:25 — Session Overview & Active Discussion

3:45 — Refreshment Break

4:15 — **DR. SUBHASH C. VERMA AWARD LECTURE**
DR. KIM CONNELLY
Scientist in the Keenan Research Centre for Biomedical Sciences at St. Michael's Hospital and Assistant Professor, Department of Medicine, University of Toronto

5 PM — **PRESENTATION OF POSTER AWARDS**

5:30

DISTINGUISHED VISITING

PROFESSORS

DUNCAN STEWART

DAVID ALAN KASS

PAUL ARMSTRONG

2013

DENISA WAGNER, PHD: Department of Pathology, Harvard Medical School
NETs: Linking Inflammation and Thrombosis
January 14, 2013

DAVID HOOD, PHD: Professor, York University
Molecular Mechanisms of Mitochondrial Adaptations in Aged Skeletal Muscle
February 11, 2013

KAI C. WOLLERT: Professor of Molecular and Translational Cardiology, Hans-Borst Center for Heart & Stem Cell Research
Paracrine Signaling in the Heart: Novel Players and Emerging Clinical Applications
March 4, 2013

PIETER DE TOMBE, PHD: James R. DePauw Professor of Cell and Molecular Physiology, Co-Director, Cardiovascular Research Institute, Loyola University
Myocardial Sarcomere Dynamics in Health and Disease
April 3, 2013

PAUL ARMSTRONG, MD: Professor of Medicine, University of Alberta
Lessons Learned and Roads Untraveled; Perspectives of a Clinical Investigator
April 29, 2013

KEITH A FOX, MD: Professor of Medicine, University of Edinburgh
Acute Coronary Syndrome: Have We Reached the Limits?
May 6, 2013

ARIE HOROWITZ, D.SC.: Assistant Professor, Department of Molecular Cardiology Lerner Research Institute, Cleveland Clinic Foundation
Exploiting Membrane Traffic for Targeting Angiogenesis
June 10, 2013

DUNCAN STEWART, MD: CEO and Scientific Director of the Ottawa Hospital Research Institute, Vice-President of Research at the Ottawa Hospital and Professor of Medicine at the University of Ottawa
Cell Therapies for Cardiovascular Disease – Version 2.0
September 30, 2013

NAVEEN PEREIRA, MDL: Assistant Professor of Medicine; Division of Cardiovascular Diseases, Mayo Clinic
Clopidogrel Pharmacogenetics: Can We Impact Clinical Practice?
October 15, 2013

DAVID ALAN KASS, MD: Director of the Johns Hopkins Center for Molecular Cardiovascular Biology and Professor of Medicine, Biomedical Engineering and Cellular and Molecular Medicine, John Hopkins University
Reverse Engineering Cardiac Resynchronization
November 4, 2013

MANSOOR HUSAIN, MD: Director of the Toronto General Research Institute, Professor of Medicine, Physiology, and Laboratory Medicine and Pathiobiology and former Director of the Heart & Stroke/Richard Lewar Centre of Excellence.
Molecular Studies of Cardiovascular Disease: Toronto-Style
December 16, 2013

2014

JOAO LIMA, MD: Professor of Medicine and Radiology, Director of Cardiovascular Imaging at Johns Hopkins Hospital
Myocardial Fibrosis in Incident Heart Failure in the US: Lessons from MESA
January 13, 2014

JUSTIN EZEKOWITZ, MD: Associate Professor of Medicine in the Division of Cardiology at the University of Alberta
Acute Heart Failure: Risk and Endpoints
January 27, 2014

DEEPAK BHATT MD, MPH: Professor of Medicine at Harvard Medical School
Advances in Antiplatelet Therapy
February 20, 2014

ROBERT GIUGLIANO, MD: Senior Investigator at TIMI Study Group; and Associate Professor of Medicine at Harvard Medical School
Target Specific Oral Anticoagulants for Atrial Fibrillation
March 25, 2014

EUAN ASHLEY, MD: Associate Professor of Medicine (Cardiovascular), of Genetics and of Pathology at the Stanford University Medical Center
Six Degrees: Networks, Systems and Therapeutics in Cardiovascular Biology
April 28, 2014

STEFAN D. ANKER, MD: Professor of Innovative Clinical Trials (Cardiology & Cachexia Research) University Medical Center Göttingen (UMG), Göttingen, Germany
Co-morbidities in Heart Failure: Update on Cachexia & Iron Deficiency
November 12, 2014

VIVEK RAO, MD: Chief of Cardiovascular Surgery, Munk Professor in Advanced Cardiac Therapeutics at Peter Munk Cardiac Centre, and Professor of Surgery at the University of Toronto
Translational Concepts in Regenerative Medicine: Pitfalls with Innovation
December 1, 2014

THANK YOU TO OUR 2013-2014 DISTINGUISHED VISITING PROFESSORS. YOU BRING A WEALTH OF INFORMATION TO OUR MEMBERS.

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Denise Belsham
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