MESSAGE FROM THE CHIEF SCIENTIFIC OFFICER

2015-16 has been a sensational year for research at the University of Ottawa Heart Institute! Our success rate at the Canadian Institutes of Health Research\(^1\) was 40%, far higher than the national average. We were awarded funding for state-of-the-art infrastructure and equipment from the Ontario Ministry of Research, Innovation and Science. Internationally acclaimed researchers joined our Institute and are setting up their leading-edge laboratories within our walls.

Our Institute model places our integrated research program as a core priority, mindful of the role it will play in tomorrow’s treatment for our large volumes of patients and for patients globally. This year, we identified additional directions to enhance our global research impact as a priority in the Institute’s 2015-19 strategic plan\(^2\).

I would like to thank our researchers, the research staff, trainees and the supporting administration for their unwavering commitment and hard work.

Peter Liu

PEER-REVIEWED\(^3\) RESEARCH FUNDING HIGHLIGHTS

In 2015-16, researchers at the Institute were awarded almost $13 million in external peer-reviewed funds to undertake cutting-edge discovery and clinical research.

Success rates for peer-reviewed grants at the Canadian Institutes of Health Research (CIHR) was head-and-shoulders above the competition. A whopping 40% of our applications to CIHR open competitions were funded. Compare this to the national average (everyone else applying) of 15%. At CIHR, six operating grants and four salary awards were awarded to the Institute ($2.7 million in total).

The Institute was awarded $5.8 million from the Ontario Research Fund—Large Infrastructure initiative for the Centre for Original Medical Target Evaluation & Translation (COMET-\(\alpha\)) project. This large-scale infrastructure grant, which includes support from 18 industry partners, will enable the Institute to transform research space to fast track first-in-human research and invest in more state-of-the-art equipment.

\(^1\) Government of Canada’s health research investment agency
\(^2\) Peer review is the internationally accepted benchmark for ensuring quality and excellence in scientific research and ensures that only the highest quality scientific proposals receive funding.
\(^3\) Under the leadership of Dr. Frans Leenen, the Institute runs a rigorous internal grant review program, where grants are reviewed, vetted and approved prior to submission to external agencies. We regard this program as key to our ever-increasing success at the funding agencies.

INSTITUTE RESEARCH TEAM AWARDED $5.8 MILLION FOR NEW STATE-OF-THE-ART RESEARCH INFRASTRUCTURE

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Dr. Peter Liu, Chief Scientific Officer & lead of the COMET-\(\alpha\) team

Ontario Ministry of Research, Innovation and Science
National Research Council Canada
National Sciences Engineering and Research Council
National Institutes of Health (USA)
National Institute ofevity (UK)
Ontario Research Chair
Other
Canadian Institutes of Health Research
Heart and Stroke Foundation

NATIONAL AVERAGE
UOHI

CIHR OPERATING GRANT SUCCESS RATE

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OCEAN CLINICAL TRIAL
Dr. David Birnie, MD, in collaboration with Dr. Atul Verma, MD, (an affiliate researcher at the Institute with primary appointment at Southlake Regional Health Centre), developed the protocol entitled “The Optimal Anticoagulation for Enhanced Risk Patients Post-AF Ablation (OCEAN) Trial.” Dr. Birnie succeeded in obtaining over $5 million in grant funding from two industry partners as well as a CIHR network grant to conduct this investigator-initiated trial. This is Dr. Birnie’s third large-scale multi-centre investigator-initiated trial in the last five years.

This trial, which is enrolling over 1,400 patients in Canada and internationally, is comparing medical approaches for stroke prevention in people who have atrial fibrillation (AF) and have undergone a successful procedure called ablation to eliminate or substantially reduce the arrhythmia. AF is normally associated with an increased risk of stroke which, in many patients, can be presented with appropriate blood thinner therapy. This trial will compare a strategy of oral anticoagulant therapy after successful ablation to therapy with an aspirin per day.

RESEARCH
BY THE NUMBERS
• 250 research staff, including 69 scientists and clinician investigators
• $12.8 million awarded in peer reviewed grants
• 246 published research articles including 32% with international collaborations
• Over 100 international speaking engagements
• 7 cutting-edge core facilities, including the Ruddy Canadian Cardiovascular Genetics Centre
• Hosted 3 international conferences, including the Ottawa Heart Research Conference, the Conference on Smoking, Cessation and the Women’s Heart Health Summit
• 248 active clinical research studies
• 50% success rate for Heart and Stroke Foundation funding competition, compared to 20% national average

INSTITUTE RESEARCHER PLACES FIRST IN CIHR CLINICIAN SCIENTIST AWARD COMPETITION!
Dr. Darryl Davis, MD, succeeded in obtaining a CIHR Clinician Scientist Phase 2 award as career support for his application on “Strategies to enhance cardiac repair of advanced ischemic cardiomyopathy by autologous cardiac-derived cells.” The application was ranked #1 in the competition and the award represents a renewal, as testament to the tremendous progress made by Dr. Davis and his team in the field of cardiac stem cell research.

A LITTLE ABOUT THE RESEARCH…
Dr. Davis’s team in the Cardiac Translational Research Lab is exploring new ways to Repair damaged hearts using stem cells. Patients with damaged and failing hearts are a growing epidemic and many do not survive for long. Although the human heart has natural stem cells, they are infrequent and unable to repair hearts after a large heart attack. The team has developed methods to extract and grow these stem cells from small pieces of heart tissue. The stem cells are then encapsulated into an artificial cocoon and are transplanted back into damaged hearts where they stimulate the heart to repair itself and grow into new working heart tissue. The process of encapsulation increases the number of transplanted cells retained in the heart. The ultimate aim is to grow new heart tissue to heal damaged hearts. The team hopes to provide a new way to treat these very sick patients with very few remaining options.

INSTITUTE RISING STAR
Dr. Thais Coutinho, MD, a clinician scientist and staff cardiologist, was recruited to the Institute in 2013, following training in Internal Medicine, Cardiology, Vascular Medicine, advanced Echocardiography and research at the Mayo Clinic, Rochester, MN.

Dr. Coutinho’s research program focuses on arterial health, with a special emphasis on arterial stiffness and its role on the pathogenesis of cardiovascular diseases. She focuses on sex differences in arterial aging, and how it may help explain sex differences in cardiovascular diseases.

In two short years, as an independent principal investigator at the Institute, Dr. Coutinho has been awarded a number of grants to pursue her research program. These include both an Early Research Leaders grant and Grant-in-Aid from the Heart and Stroke Foundation (HSF) of Canada, and a career support award from HSF Ontario. This year, she was invited to give a plenary lecture at the American Heart Association conference and she received the Young Investigator Award from the Canadian Cardiovascular Society. Dr. Coutinho publishes her research findings in high-impact manuscripts in the field of cardiovascular diseases and collaborates internationally, notably with the British Heart Foundation and the University of Glasgow.
In 2015-16, Institute scientists and investigators published 246 research articles. Many of these represented global collaborations. Below are five highlights:

**ABOUT THE FINDINGS:**
A landmark collaborative study led by three groups, including scientists in the Ruddy Canadian Cardiovascular Genetics Centre, was published in the prestigious journal *Nature Genetics*. The study described a comprehensive survey of the fine genetic architecture of cardiovascular disease, showing that genetic susceptibility to heart disease is largely determined by the cumulative effects of numerous small genetic variants.

This study represented a collaboration within the international CARDIOGRAMplusC4D Consortium and was led by researchers at the University of Oxford in the UK, the Broad Institute of MIT and Harvard University and the Ottawa Heart Institute and involved a total of 48 centres around the world including more than 185,000 individuals.

**ABOUT THE FINDINGS:**
A milestone study led by Institute researchers and published in *Science* in 2007 identified the first genetic region associated with risk for heart disease. However, the mechanism by which this genetic region on chromosome 9 (9p21.3) confers risk for disease development has remained unknown. Significant progress has now been made to answer this question in this notable study by the Institute’s Laboratory of Translational Genomics led by Dr. Alex Stewart. The research team showed that genetic variants at position 9p21.3 increase the risk of heart disease by preventing the TEAD proteins from binding to DNA and turning on nearby genes required to prevent smooth muscle cells from growing. The findings indicate that the resulting increased growth of the smooth muscle cells causes narrowing of the arteries that supply the heart and eventually leads to a heart attack.

**9p21.3 coronary artery disease risk variants disrupt TEAD transcription factor-dependent TGFbeta regulation of p16 expression in human aortic smooth muscle cells**
Senior author: Dr. Alexandre A. F. Stewart
First author: Dr. Naif Almontashiri (PhD student at the time of publication)
Journal: *Circulation* (Impact factor: 15)
Date: November 2015

In 2015, the BRUISE CONTROL trial (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial) demonstrated that continuing warfarin use during cardiac implantable device surgery was safe and reduced the incidence of having a clinically significant postoperative hematoma (C SH) at the device site (Birnie et al, New England Journal of Medicine, 2013). Published in 2016, the BRUISE CONTROL INFECTION study followed 659 patients for one year after their device surgery to see who developed a device-related infection (such as an infection of the device site pocket, bloodstream infection or infection within the heart or on a heart valve) and to see if there was an association with this infection and having a C SH. The study found that the risk of serious infection requiring hospitalization increased by more than sevenfold at one year if the patient had a C SH after implantable device surgery. This is the first study to observe and make a clear-cut association between hematoma and subsequent serious infections. Previously, C SH has been considered as a minor complication of device surgery. However, not all but this novel data suggests they are more serious, with a major increase in risk of infection. The key clinical message from this research finding to physicians is to make every effort to reduce rates of C SH.

ABOUT THE FINDINGS:
Severe aortic valve disease results in reduced heart function, heart failure and ultimately death, if left untreated. The most common treatment is surgical replacement of the aortic valve, which usually improves heart function. However, not all patients will improve and, currently, it is difficult to predict which patients will not improve following this surgical intervention. This study asked the question: what are the factors that correlate with incidence of death and heart failure after aortic valve replacement? The study, the largest series of patients ever followed for size and function of the heart muscle after aortic valve replacement, showed that left ventricular heart function recovery following surgery led to better long-term clinical outcomes in including better survival and quality of life. Furthermore, patients that underwent surgery before their heart became bigger (hypertrophy) or before they developed symptoms were far more likely to have a positive clinical outcome. By contrast, there was more mortality when there was incomplete left ventricular recovery, when the surgically-placed prosthetic valve had a size mismatch with the patient’s body, or when the pressure gap was low across the aortic valve prior to surgery.

The study findings will help surgeons and cardiologists refine the indications, timing, prognostication and follow-up of patients before and after aortic valve surgery.

Clinical impact of changes in left ventricular function after aortic valve replacement: Analysis from 3112 patients.

Senior author: Dr. Marc Ruel
First author: Dr. Dai Unu, Fellow in Cardiac Surgery
Journal: Circulation (Impact Factor: 15)
Date: August 2015

ABOUT THE FINDINGS:
In 2015-16, he had a year to talk about! Here are some highlights:

• He co-authored seven original articles in 2015-2016, seven review/commentary articles, and two chapters in prominent cardiac surgery textbooks.

• In October 2015 at the Canadian Cardiovascular Congress in Toronto, he presented on the Hybrid coronary revascularization in diabetes (HYCARDS) randomized controlled trial and won the Bayer/Canadian Cardiovascular Society Resident Vascular Research Award ($7,500). The presentation was part of the Vascular Forum: Advancing Research Excellence for the Next Generation of Canadian Leaders.

• He received an American Association of Thoracic Surgery (AATS) Resident Critical Care Scholarship.

Dr. Hadi Toeg is Cardiac Surgery Chief Resident and a recent Masters in Public Health (Quantitative Methods) graduate from Harvard University. He also works on optimizing aortic valve repair using left heart simulation and long-term outcomes following cardiac surgery.

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In 2015-16, our researchers had over 100 international speaking engagements. The highlights include:

**Dr. Frans Leenen**: gave two international keynote lectures including at the 3rd Premium Hypertension Conference, in Tokyo, Japan on “Brain Mechanisms contributing to chronic sympathetic hyperactivity and hypertension: Critical role of brain MR-AT1R signaling.”

**Dr. Katey Rayner**: gave an invited lecture on “Innovative Inflammatory Mechanisms That Drive Plaque Vulnerability” at the Atherosclerosis, Thrombosis, and Vascular Biology Scientific Session in San Francisco.

**Dr. Ben Chow**: participated in “Great Debates in Imaging: Cardiac CT. Stable patients with suspected CAD should be required to undergo CT prior to Cath” at the American College of Cardiology Scientific Session.

**Dr. Rob deKemp**: gave an invited lecture on “What’s New in Nuclear Cardiology” at the American College of Cardiology Conference in Chicago.

**Dr. Andrew Pipe**: spoke about “The Ottawa Model for Smoking Cessation: Doing Ordinary Things Extraordinarily Well” at Stanford University and the University of California Center for Tobacco Control Research & Education, and the University of Ulm in Germany.

**Dr. Ruth McPherson**: gave an invited lecture on “Novel Biological Insights Derived from GWA Studies of CAD” at the Gordon Conference on Atherosclerosis.

**Dr. Thierry Mesana**: chaired the “Ask the Experts – Update on Valve Repair Technique” at the American Heart Association Scientific Meeting. Dr. Mesana also presented “An update on Mitral Clip” at the Canadian Cardiovascular Congress.

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**INSTITUTE RESEARCH MAKING IMPRESSIONS ON THE INTERNATIONAL SCENE**

UOHI investigators have a great presence on the international scene! Here are some highlights from 2015:

- **Dr. Munir Boodhwani**, cardiac surgeon, co-hosted a very successful 1st North American Aortic Valve Repair Symposium in Philadelphia in May 2015, in collaboration with the University of Pennsylvania.
- **Dr. Emilio Alarcon** received a Wellcome Burroughs Fund to collaborate with the Wellman Center for Photomedicine at Harvard University.
- **Dr. Katey Rayner’s** collaboration with New York University researchers resulted in funding of a grant from the US National Institutes of Health. The total project budget is US$2.5 million.
Dr. Wenbin Liang, MD, PhD, won the Gordon K. Moe Young Investigator Award at the American Heart Association Northeast Affiliate Cardiac Electrophysiology Society Meeting.

Dr. Rob Beanlands, MD, FRCP, received the Canadian Cardiovascular Society Research Achievement Award, in recognition of his important contributions to cardiovascular research throughout his career. He is an international expert in cardiac imaging and a leader in establishing positron emission tomography (PET) imaging as an accepted tool in the diagnosis and management of heart disease.

Dr. Thais Coutinho, MD received the Canadian Cardiovascular Society Young Investigator Award for her achievements in clinical research. (See box for more information on Dr. Coutinho)

This award recognizes a Heart Institute investigator who demonstrated significant research achievements in the past year.

Dr. Wells’s research interests are in the design and analysis of multicentre clinical trials, methodology related to health care delivery, systematic reviews and network meta-analysis, economic evaluations, health technology assessment, and the development and assessment of decision support technologies for patients and clinicians.

Recent successes culminating in this award include:

• In 2014, Dr. Wells was successful in securing his largest peer-reviewed funding to date of $26 million over five years as a co-principal investigator on the Canadian Arrhythmia Network (CANet), a Network of Centres of Excellence, in collaboration with colleagues at the UOHI and Dr. Anthony Tang at Western University.
• Canadian Medical Association Journal Top Achievement in Health Research in 2011
• University of Ottawa Excellence in Research Award in 2014
• Dr. Wells was recognized as one of the 400 most influential medical researchers from the period of 1996-2011 (Boyack et al, European Journal of Clinical Investigation, Vol 43 (12): 1359-1365).

Dr. George Wells, PhD
Director, Cardiovascular Research Methods Centre, University of Ottawa Heart Institute
Professor, School of Epidemiology, Public Health and Preventive Medicine & Professor, Department of Medicine, University of Ottawa

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The The Roberts Award recognizes an Institute investigator who published in the preceding year a peer-reviewed, original research paper that has a high impact on cardiovascular science.

Dr. Marc Ruel and colleagues discovered that an anti-clotting drug called clopidogrel can lessen the worsening of heart disease after coronary artery bypass grafting (CABG). CABG is commonly used to improve blood flow to the heart by grafting a healthy artery or vein to the heart in such a way that it allows blood to bypass a blocked artery.

As part of the CASCADE trail, patients in this study were randomized to receive aspirin plus clopidogrel or aspirin plus placebo for one year after CABG. The study, published in Circulation, showed that the addition of clopidogrel to aspirin correlates with better angiographic outcomes for patients and brings a detailed understanding of the evolution of native coronary artery disease after bypass surgery.

These findings are changing practice around the world and they have already been incorporated into a recently-published treatment paper that has a high impact on cardiovascular science.

Dr. Dr. Michel Le May is a tour-de-force in STEMI management. Dr. Le May’s work has brought on innovative changes to the way STEMI’s are treated worldwide. This STEMI model of care was originally published in the prestigious New England Journal of Medicine and has been adopted widely throughout North America, Europe, and beyond. Dr. Le May is currently helping to set up STEMI programs in India and Southeast Asia.

Dr. Le May has carried this leadership further and is developing programs for patients who have undergone cardiac arrest and have recovery of spontaneous circulation. Dr. Le May is currently leading a Canada-wide initiative that will enhance care, establish training standards and complex care models required in Cardiac Intensive Care Units.

Dr. Le May has received numerous awards for his leadership and impact, including the CIHR/CMIA Top Canadian Achievement in Health Research Award. Most recently in 2014, Dr. Le May was presented the Lumen Global Achievement Award. Most recently in 2014, Dr. Le May was presented the Lumen Global Achievement Award.

Dr. Michel Ruel, MD, MPH, FRSC
Chief, Cardiac Surgery, University of Ottawa Heart Institute;
Professor and Chair, Department of Cardiovascular Surgery;
Cross-appointments, Department of Cellular and Molecular Medicine & Department of Epidemiology.

Dr. Ruth McPherson has had a strong presence and influence on the global research stage for decades. She is a world leader in cholesterol and genetics research and has made significant contributions to our understanding of human cholesterol metabolism. Dr. McPherson has made major discoveries in human genetics, most notably the 2007 discovery of the chromosome 9p21 risk locus for coronary artery disease. Most recently, as a lead investigator in the international CARDIOGRAMPlusC4D Consortium, Dr. McPherson, et. al., published in a landmark paper, leveraging data from 1,000 Genomes and highlighting that the genetic basis of heart disease is primarily related to multiple common genetic variants of small effect size.

Dr. McPherson has been recognized with numerous awards, including the Queen’s Golden Jubilee Medal for Research Excellence in 2002; the AHA Council on Arteriosclerosis, Thrombosis & Vascular Biology Special Recognition Award in 2011; and the Canadian Society of Atherosclerosis, Thrombosis & Vascular Biology Scientific Excellence Award in 2012. Dr. McPherson was inducted as a Fellow of the Royal Society of Canada in 2014.
SELECT RESEARCHER AND RESEARCH GROUP PROFILES

Over 65 translational and clinical researchers head up their own independent research programs at the Heart Institute. Most of these researchers also have an active clinical role at the Institute, while some are dedicated full time to research. Select research groups are highlighted below.

**DR. KATEY RAYNER AND THE CARDIOMETABOLIC MICRORNA LABORATORY**

Directed by Dr. Katey Rayner, PhD, the research team focuses on how microRNAs control multiple aspects of the risk factors that drive both atherosclerosis and obesity, namely inflammation, dysregulated energy metabolism and how microRNAs may be used as therapeutics in the future to treat these cardiometabolic diseases. This innovative research has led the Institute to seek intellectual property protection for the team’s discoveries.

**DR. ERIK SUURONEN AND THE CARDIOVASCULAR TISSUE ENGINEERING LABORATORY**

Directed by Dr. Erik Suuronen, PhD, the team’s interests focus on the use of tissue engineering and cell-based approaches to develop new therapies for the treatment of cardiac injury and disease. This includes the investigation of biomaterial scaffolds and stem/progenitor cell transplantation for promoting angiogenesis within the heart to restore blood flow to damaged tissue and improve its function. The team is also investigating how the body’s own stem cells respond when the heart is damaged and how to enhance this response. Another area of interest for the laboratory is the investigation of cardiovascular complications associated with diabetes.

**CROSS-DISCIPLINARY TEAM WORK IN ACTION**

Dr. Marc Ruel, MD, MPH, Dr. Erik Suuronen, PhD, and Dr. Emilio Alarcon, PhD, have collaborated extensively over the last year. The team is developing new regenerative therapies to improve cardiac tissue and other damaged tissues and organs. The team has discovered multiple technologies that, although early-stage, have the potential to significantly impact the field of cardiac surgery. The Institute is working with the team to facilitate development of these technologies and exploring collaborations with current and new industry partners with the aim of commercialization.
DR. LOUISE SUN
Dr. Louise Sun, MD, is a staff anesthesiologist and clinician investigator. Dr. Sun’s research interests include:
• Establishing an integrated approach to prediction and early treatment of perioperative RV failure and HFpEF using novel biomarkers, hemodynamic markers and echocardiography
• Health services utilization and patient outcomes relating to major cardiac surgery and intensive care medicine
• Interaction of perioperative hemodynamic parameters in prediction and prevention of major perioperative morbidity and mortality
• Advanced statistical modeling

DR. LISA MIELNICZUK
Dr. Lisa Mielniczuk, MD, is a cardiologist and clinician investigator. Dr. Mielniczuk is a heart failure specialist with a specific interest in evaluating metabolic adaptation in right heart failure and pulmonary hypertension. Dr. Mielniczuk’s research interests include clinical outcomes related to heart failure and pulmonary hypertension and the evaluation of myocardial energetics in right heart failure.

DR. VINCENT CHAN
Dr. Vincent Chan, MD, is a cardiac surgeon and clinician investigator. Dr. Chan’s research interests include mitral valve repair and replacement, minimally invasive surgery (including minimally invasive coronary artery bypass grafts), heart valve bioprostheses and mechanical valves.

To deliver on our strategic plan priority themes, our Innovation Clusters are working on a number of pilot projects that address major gaps and unmet needs in the knowledgebase that can potentially transform the field. An Innovation Cluster is the foundation of and has the potential to grow into a Centre of Excellence. A list of eight Innovation Clusters is provided below:

1. Atrial Fibrillation: Led by Dr. David Birnie
2. Behavioural and Environmental Interventions for Personal and Community Cardiovascular Health Research Group: Led by Dr. Bob Reid and co-led by Dr. Doug Manual (Ottawa Hospital Research Institute)
3. Heart Failure: Led by Dr. Lisa Mielniczuk and co-led by Dr. Balwant Tuana (University of Ottawa)
4. Non-invasive Cardiovascular Imaging Research Cluster (CIRC): Led by Dr. Benjamin Chow and co-led by Drs. Ghish Dwivedi and Rob de Kemp
5. Cardiovascular Percutaneous Intervention Trial (CAPITAL): Led by Dr. Derek So
6. Personalized Innovative peri/openActive Care and Long-Term outcomes (Research (PINNACLE): Led by Dr. Marc Raud and co-led by Drs. Munir Boodhwani, David Glineur, Bernard McDonald, Louise Sun and Diem Tran
7. Transplant and Pumps (TAPS): Led by Dr. Sharon Chih and co-led by Drs. Todd Fairhead (The Ottawa Hospital) and Rob Beanlands
8. Vascular Inflammation and Metabolism: From Bedside to Bench and Back: Led by Dr. Katelyn Rayner and co-led by Dr. Ruth McPherson