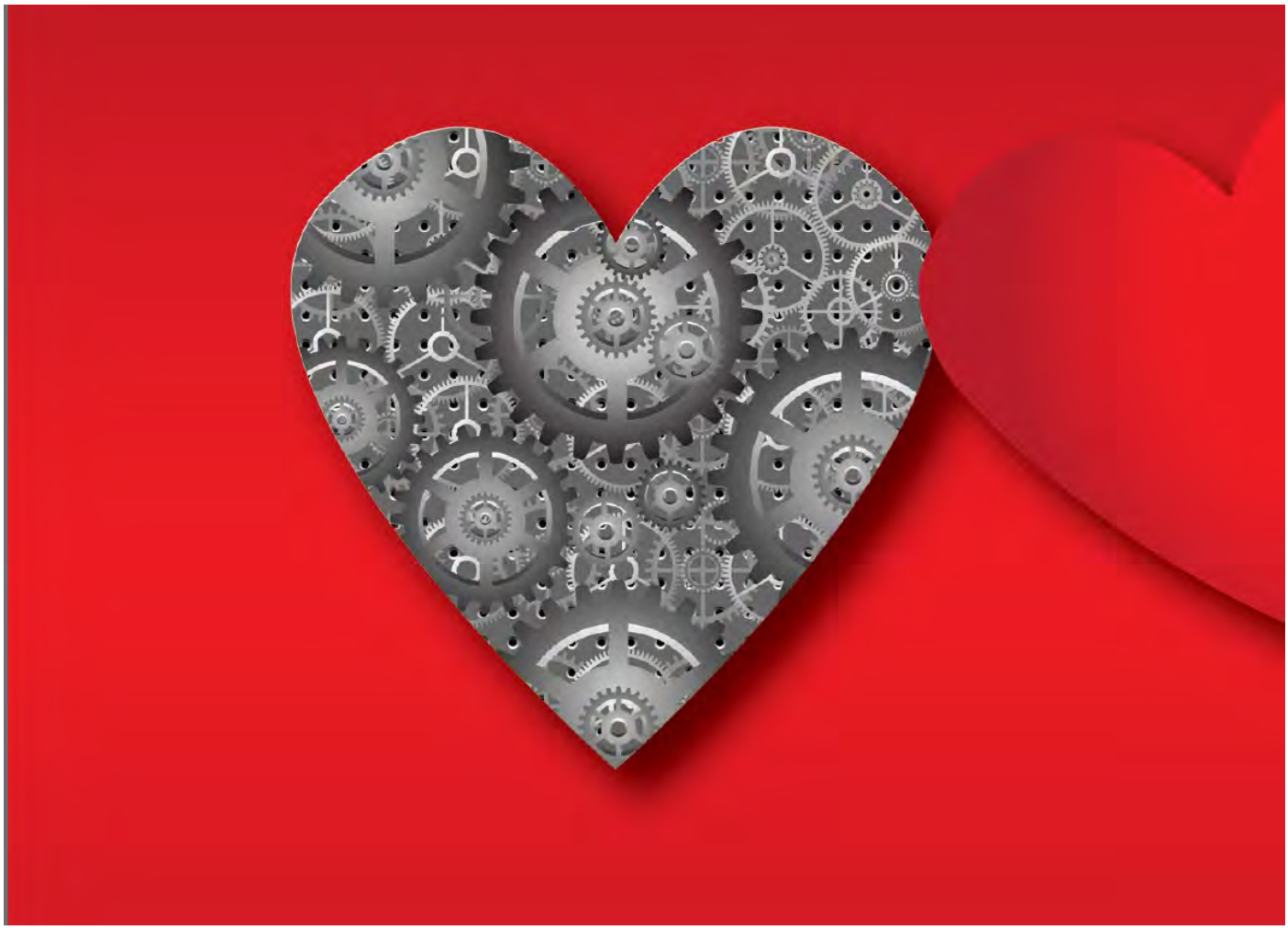
Heart & Stroke | Richard Lewar
Centre of Excellence in Cardiovascular Research

HSRLCE Self-Study Report
Period: 2017-2022

Departmental Review: April 29, 2022



Dr. Michael E. Farkouh, Director
Liz Thuo, Business & Communications Manager

6 Queens Park Crescent, Room 303, Toronto, ON M5S 3H2
T: 416-978-2351 **E:** hsrl.centre@utoronto.ca **W:** www.hsrlce.com

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

2017-2022 External Review
April 29, 2022

Table of Contents

APPENDICES

Appendix 1: **EDUCATION**

- Trainee Awards Recipients
- Distinguished Visiting Professor Lecture Listings
- Michael J. Sole Annual Cardiovascular Scientific Day Programs
- Case-Based Practical Continuing Medical Education Programs
- National & International Knowledge Exchange Seminars Programs

Appendix 2: **RESEARCH**

- Research Funding Data
- Research Global Ranking
- Research Productivity

HSRLCE INTRODUCTION

BACKGROUND:

In 1988, Dr. Michael Sole founded the Centre for Cardiovascular Research (CCR) as a joint venture between the Toronto General Hospital, Mount Sinai Hospital and the University of Toronto Faculty of Medicine to bring together interdisciplinary talent in the cardiovascular sciences. The CCR developed integrated bench-to-bedside programs in heart failure, atherosclerosis and arrhythmias and established a clinical trials unit. It offered start-up funds for new investigators and support programs for fellows and students. The CCR established an annual Cardiovascular Scientific Day and a Distinguished Visiting Professor Lecture Series to support cardiovascular education.

In 1999, with support from the Heart and Stroke Foundation and the Richard Lewar family, the Heart and Stroke/Richard Lewar Centre of Excellence in Cardiovascular Research (HSRLCE) was established to continue the CCR's success at a University-wide level and foster excellence in cardiovascular research and education at UofT. HSRLCE is a self-funded extra-departmental unit (EDU) of the Temerty Faculty of Medicine, University of Toronto. The HSRLCE expanded its collaborative infrastructure and brought together more than 137 researchers in basic science, clinical investigation and community health.

Today, the HSRLCE builds upon a solid foundation to strengthen its network and international impact. The Centre brings together a consortium of university and hospital research centres in the heart of the city to deliver a comprehensive research program that spans the entire cardiovascular system. With an increased commitment to education, in 2015, the HSRLCE brought the established Collaborative Cardiovascular Sciences Program (CSCP) under its umbrella to be the educational arm of HSRLCE; a partnership that lasted for five years. Looking abroad, the HSRLCE pursues an internationalization strategy to increase its impact by attracting global talent, ideas, research collaborations, funding and new academic and industrial partners.

Leadership
HSRLCE's inaugural Director was Dr. Peter Liu who served until 2006. Dr. Mansoor Husain succeeded him as Director and served from 2007 to 2012. Dr. Michael Farkouh was appointed Director of the Centre on a five-year term starting January 1, 2013. His appointment was renewed in 2018 for an additional 5 years.

Vision & Mission Statements
The Centre's mission is: *To foster a collaborative research and educational environment, locally and internationally, that transforms cardiovascular health.*

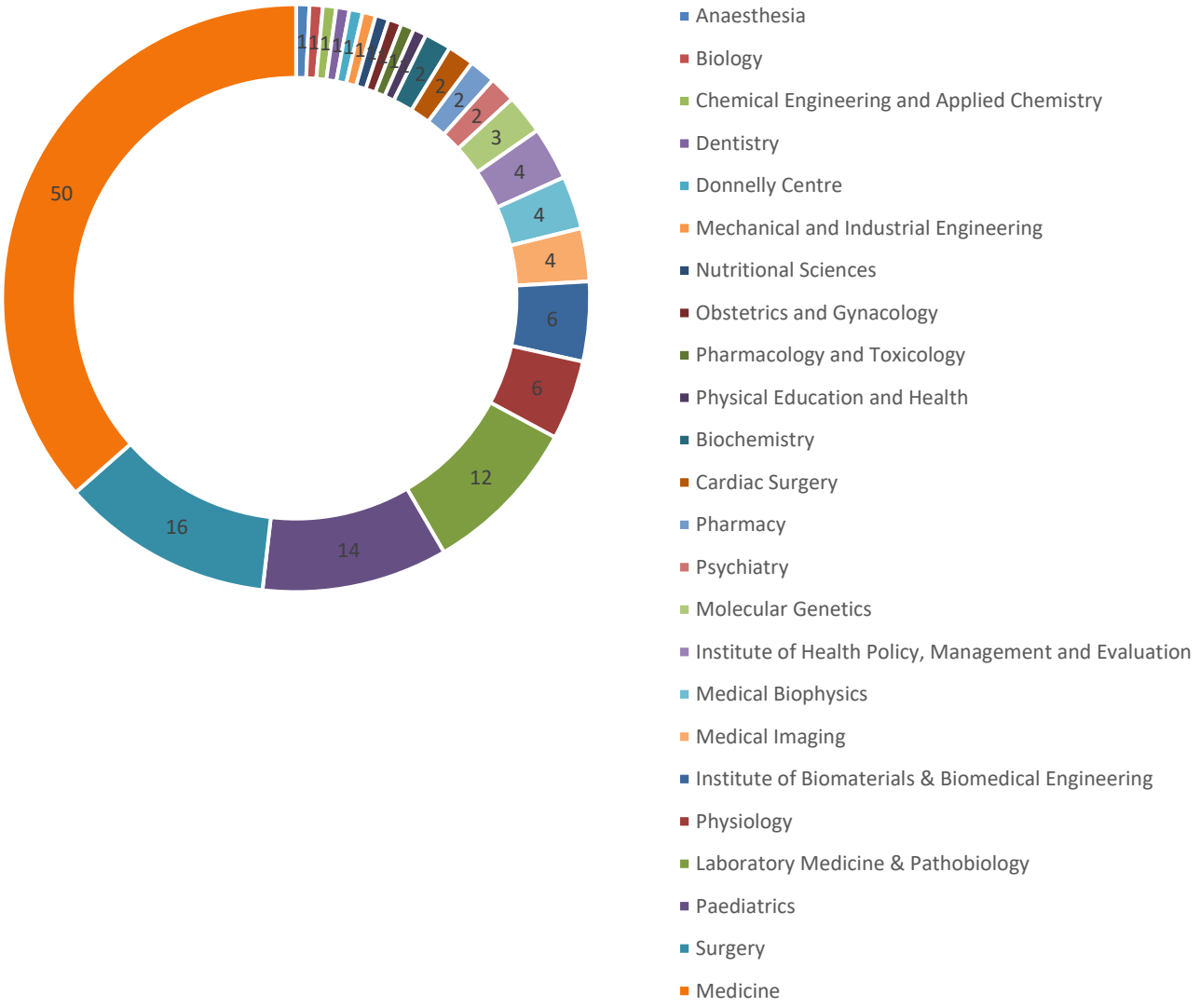
The Centre's vision is: *To conquer cardiovascular disease through research and education*.

The Centre's tagline is: *Leading the fight against cardiovascular disease.*

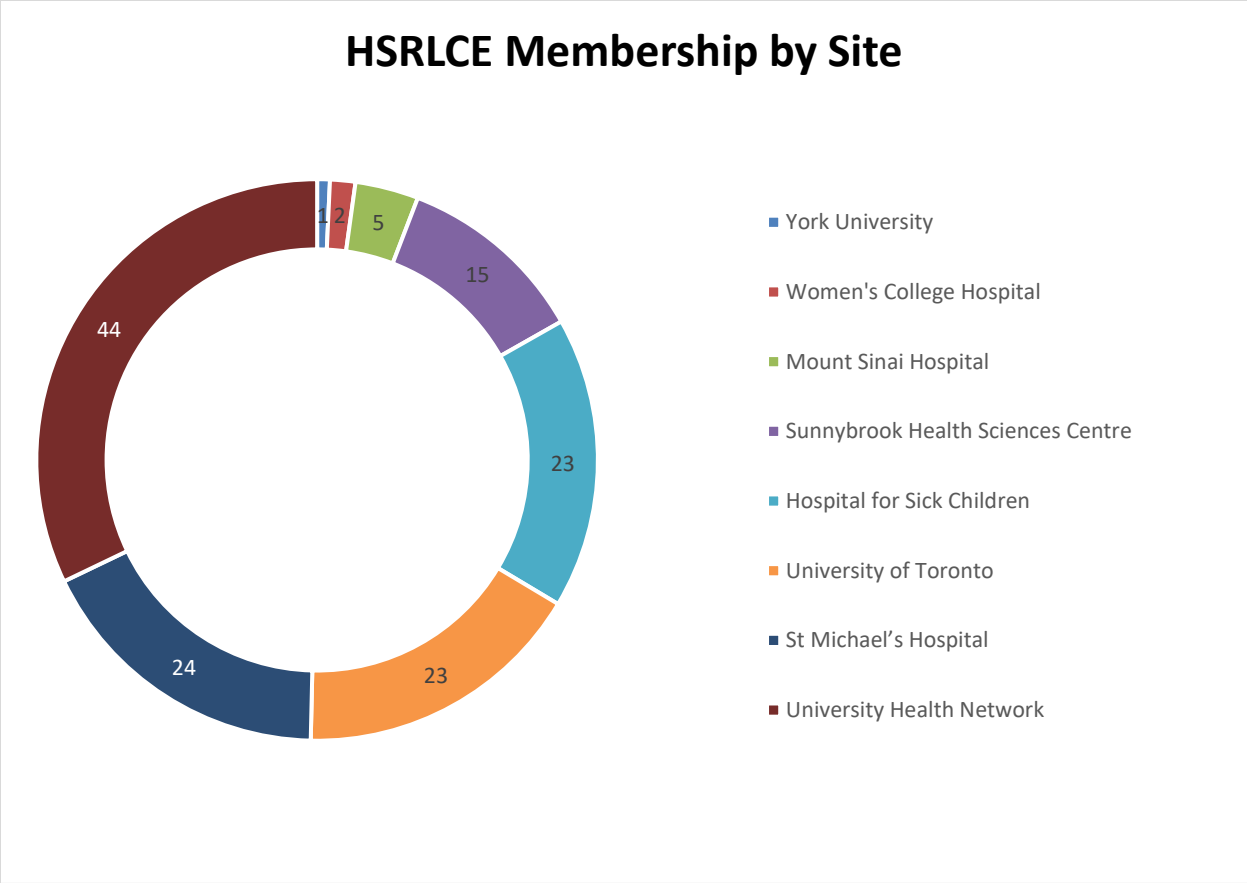
Membership

HSRLCE is a cross-departmental, multi-sited, inter-disciplinary academic unit that seeks to coordinate and accelerate cardiovascular research and training throughout our basic science and allied health campuses.

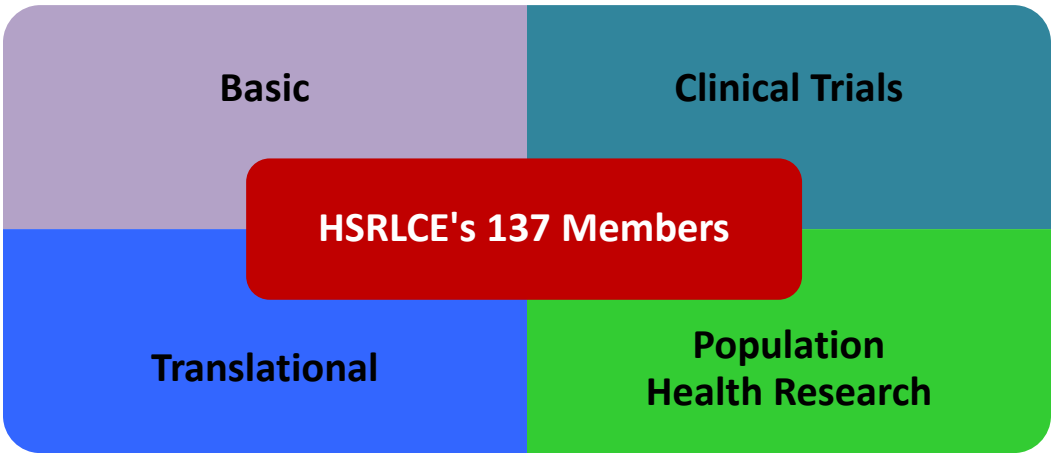
HSRLCE Membership by Department



HSRLCE currently has 137 members representing 24 departments and situated across seven campuses, including the Temerty Faculty of Medicine, University Health Network, Mount Sinai Hospital, Sunnybrook Health Sciences Centre, The Hospital for Sick Children, St. Michael's Hospital, and Women's College Hospital (WCH), with affiliate members from York University. The HSRLCE office is embedded within the Department of Medicine's office space at the C. David Naylor Building.



Our membership spans across four pillars: basic, clinical, translational and population health research.



The Centre's website is: http://hsrlce.utoronto.ca/

DIRECTOR'S REPORT

This report is provided as a high-level summary of the Centre's activities and accomplishments over the past five years. I invite you to refer to the entire self-study report for a complete picture.

The Heart and Stroke Richard Lewar Centre of Excellence in Cardiovascular Research (HSRLCE) at the University of Toronto was established as an extra departmental unit of the Faculty of Medicine in 1999 to foster collaborative cardiovascular research education across University of Toronto's affiliated hospitals. Prior to my appointment in 2013, HSRLCE was directed first by Dr. Peter Liu, who went on to become Vice-President of the Ottawa Heart Research Institute and then subsequently the centre was led by Dr. Mansoor Hussain who is now Executive Director of the Ted Rogers Centre for Heart Research. It has been my privilege to lead the HSRLCE over the last 9+ years during a period of extensive growth especially in the spheres of forging partnerships and collaborating on education and multi-disciplinary research locally, nationally and internationally.

The HSRLCE incorporates participation from more than 137 researchers in basic science, clinical investigation, and community health. This includes participation from multiple departments of the Temerty Faculty of Medicine, the Faculty of Applied Science and Engineering, the Dalla Lana School of Public Health, and from all University of Toronto teaching hospitals. We also pursue and welcome partnerships from allied organizations globally with whom we team up to further HSRLCE's mission to foster collaborative research in an educational environment locally and internationally to transform cardiovascular health.

When I assumed the directorship of the HSRLCE in January of 2013 I had a number of major goals which I believe we have achieved over the last 9+ years:

1. To support our fundamental key platforms and to encourage true collaboration between the basic and translational research community and our colleagues in clinical and implementation sciences research through Working Groups;
2. To foster partnerships locally, nationally and internationally with the goal of collaborating on research, education and training;
3. To bring the HSRLCE to the international stage through a collaborative research network (WNICER) with the goal of increasing the impact of our work;
4. To enhance our educational programs by supporting the Cardiovascular Sciences Collaborative Program (now named Cardiovascular Sciences Collaborative Specialization);
5. To work hand in hand with our member hospitals and their respective foundations and to encourage all partners to recognize that the HSRLCE is supportive of their needs and goals;
6. To sustain the centre for the next 10 years; and
7. To create a governance and oversight model that is transparent and inclusive of our constituents across the University.

RELATIONSHIPS AND COLLABORATIONS:

We place high value in forging partnerships and collaborating with other departments within the University, and with organizations nationally and across the globe. Our membership is cross-departmental, multi-sited, inter-disciplinary. We have very deep relationships with other University of Toronto extra departmental units (EDUs), particularly the Banting and Best Diabetes Centre. Together we launched a $1.5 million collaborative challenge grant for interdisciplinary research between diabetes and cardiovascular disease, and we have served as a principal investigator in the SPOR grant (Diabetes Action Canada) to evaluate diabetes and its complications. We also collaborate closely with the Ted Rogers Centre for Heart Research, holding joint Scientific and Research Days, and having our members also serve as members of TRCHR.

Since the last external review, we have added new strategic partners to our network; a move that has served to magnify our impact, broaden our reach, and multiply our investments in research and education. In 2017, in collaboration with six academic/teaching hospitals from the Toronto Central Local Health Integration Network (i.e. SHS, SHSC, SickKids, SMH, UHN, WCH) and the Translational Biology and Engineering Program, the HSRLCE developed a Cardiac and Vascular Collaborative Innovation Competition (later renamed The Dr. Michael R. Freeman Innovation Award) to spur innovation and collaboration between institutes with the aim of improving quality of care within cardiac and vascular programs. To-date, five awards totalling $580,000 have been presented to Toronto researchers. Building on this success, our Innovation Director, Dr. Bradley Strauss, expanded on the local innovation program to include partners across Canada and Israel, leading to the creation of a new initiative in 2021: the Canada-Israel Cardiovascular Innovation Forum. The CICI has 17 institutional partners and aims to: 1) encourage early-stage cardiovascular innovations in medical devices and digital health in Canada and Israel; 2) establish collaboration between Israel and Canada in developing and funding cardiovascular innovations through competitions; 3) grow a network of interested investors and provide a vehicle for joint funding of promising early-stage projects and companies; and 4) provide young innovators an education experience in early-stage company development. See https://www.cicvinnovation.com/ for more details.

In 2017, we entered into an agreement with the Heart and Stroke Foundation to collaborate on the program development, accreditation, and delivery of the Heart and Stroke Clinical Update Educational Program. Although HSF discontinued the program in 2019, we continue to have strong relationships with them in other areas: their leadership serves on our Due Diligence Committee, and our membership serves on various HSF grant and award review committees.

In 2018, in partnership with the Canadian VIGOUR Centre, the HSRLCE established the Canadian Cardiovascular Research Collaboratory (C^3), chaired by HSRLCE member Dr. Shaun Goodman. The C^3 is a virtual clinical research network comprised of more than 50 cardiovascular disease researchers affiliated with university-based research centres across Canada.

In 2018, we entered into agreement with Sunnybrook Hospital's ICES to provide support for the Cardiovascular Health in Ambulatory Care Research Team (CANHEART) SPOR initiative aimed at

leveraging big data to conduct innovative cardiovascular clinical trials. Our support for CANHEART includes providing studentship and fellowship awards to trainees so they can work alongside CANHEART investigators, sponsorship of visiting professors, and serving as principal investigators. We also continue to have a fruitful relationship with the Canadian Institutes for Health Research (CIHR), and with Dr. Brian Rowe who is the Director for the Institute for Circulatory and Respiratory Health.

In 2019 we invited the Canadian Cardiovascular Society to partner with us in our pre-existing Cardiometabolic Research Award program geared towards young investigators. To-date, 10 young investigators have received $205,000 to fund innovative ground-breaking clinical research projects in cardiometabolic disease, specifically exploring the link between cardiovascular disease and diabetes. In 2022, we also invited the CCS, as well as the Israel Heart Society, to partner with us in our Innovation initiative, the Canada-Israel Cardiovascular Innovation Program. The inaugural CICI award competition in 2021 received 31 applications, and the inaugural event had 170 registered participants from five countries.

On a global scale, our collaborative work in research and education with The Worldwide Network for Innovation in Clinical Education and Research (WNICER) continues to grow as we seek more areas of common interest.

The HSRLCE remains very active in public relations with regards to promoting cardiovascular research in Canada. Our membership continues to provide visiting professorships in institutions across Canada and internationally. We also continue to have a strong media presence in television and print through CBC, CTV and other news outlets. We continued to participate (pre-COVID) in all major local charity events (Ride for Heart as an example) that deal with cardiovascular awareness and prevention.

In May of 2021, we yet again led the cardiovascular stream of the International Conference on the prevention and treatment of chronic diseases at the Vatican (virtual). This 3-day event brought together the world's leading physicians, scientists, leaders of faith, patient advocates, and policymakers to engage in conversations on the latest breakthroughs in medicine, health care delivery, and prevention as well as the anthropological outcomes and the cultural impact of technological advances. The Conference explored the role of religion, faith and spirituality, and the interplay of mind, body and soul, and looked for areas of convergence between the humanities and the natural sciences. This event received broad media attention owing to the fact that Pope Francis gave an address, and the moderators were high-ranking media personalities from CNN, CBS, NBC, ABC, PBS, and the Dr. Oz Show. For more information on the Conference, please visit https://vaticanconference2021.org/

EDUCATION:

The HSRLCE has experienced great success in the area of Continuing Medical Education development. Starting in 2018, we launched a new learning stream aimed at providing practical tips that can be used in daily practice. These multi-disciplinary accredited programs aim to help physicians and specialists increase their confidence in the initiation and use of specific cardioprotective therapies. More than imparting knowledge and furthering our vision of conquering cardiovascular disease through research and education, these educational programs have been a great fundraising avenue for the Centre in the form of unrestricted grants from Industry. To-date we have held 5 such programs (35+ cross-Canada in-person and virtual sessions). These include: 'Diabetes and Cardiovascular Disease: A Practical Guide for Specialists Managing Patients With or At Risk for Cardiovascular Disease'; 'An Educational Debate on Optimal Cardiorenal Protection of Patients With or Without Diabetes'; 'Straight from the Heart – Insights on Optimal Cardioprotection'; 'The Heart, the Kidney and SGLT2 Inhibitors: From Clinical Trials to Patient Care'; and 'Diabetes Connect: A Practicum for Primary Care'. Plans are underway to develop additional programs, and offer more sessions on existing programming.

We also continue to offer educational programs on the world's stage by holding national and international knowledge exchange seminars at all major cardiology conferences (ACC, AHA, CCC, ESC). In the last five years we have held 16 seminars (70 talks). These seminars, with a multi-national audience, unpack the results of late-breaking clinical trials and explore what implications these findings have on daily practice.

The HSRLCE continues to be dedicated to educating tomorrow's research leaders. In 2015 we made a strategic decision to help sponsor the Cardiovascular Sciences Collaborative Program (CSCP – now known as Cardiovascular Sciences Collaborative Specialization) which was originally established in 1992 as a ground breaking program to promote exemplary linkages between cardiovascular teaching and research across the University's teaching centres. Under the leadership of Dr. Carin Wittnich, the CSCP is a cooperative interdisciplinary, intradepartmental graduate teaching program that brings together University departments and hospitals to provide strong curriculum and unique learning opportunities for our graduate students. This single decision brought over 80 graduate students to the HSRLCE family and helped us to participate in graduate courses in two major streams: cardiac and vascular. While we would have wanted the sponsorship to continue indefinitely, this agreement lasted for five years (until 2019) due to limited funding. The CSCS is now supported by the Translational Biology & Engineering Program.

We have continued to make important investments in education over the last five years:

1. We have continued to provide stipend awards (just under $400,000 since 2017) at the undergraduate, graduate and post-graduate levels.
2. Pre-COVID, we held our annual Michael J. Sole Cardiovascular Science Day every Spring. For two years we partnered with the Ted Rogers Centre for Heart Research to host one joint event. Over the past 3 years, this event has been very successful in recruiting international experts, national authorities and our own UofT research community in a

healthy knowledge exchange, which has included topics such as: Innovation in Devices, Research and Novel Partnerships; From Discovery to Clinical Trials; and Heart Failure. We also hosted 11 Visiting Professors to give lectures and meet with our UofT Faculty; an exercise that fosters collaborative research and has led to participation in multiple National Institutes of Health (NIH) and CIHR studies.

3. Pre-COVID, we also hosted international symposia at all the major international cardiovascular meetings including the European Society of Cardiology, the American Heart Association, and the American College of Cardiology sessions. This was done in collaboration with the WNICER network members institutions and researchers.

RESEARCH:

We have continued to make investments in research focused on the interaction between the cardiovascular system and diabetes and cardiometabolic disorder (with the Banting and Best Diabetes Centre); heart failure (with the Ted Rogers Center for Heart Research); and the brain (with the Toronto Stroke Network, and the Heart and Stroke Foundation).

Additionally, we added three new research platforms to our foci:

1) 'The Athlete and the Heart' - by supporting Sports Cardiology Toronto, which provides a unified, fully integrated, and cross-disciplinary program of research, advocacy, consultation, and education across the University. This research group examines the impact of intensive exercise training on cardiac health outcomes.
2) 'COVID-19 and the Heart' - by partnering with WNICER to present a series of educational events on the Long-term Effects of COVID-19; Acute and Chronic Cardiovascular Complications of COVID-19; and How the Use of Blood Thinners Can Impact COVID-19 Outcomes and Reduce the Need for Life Support.
3) 'Inflammation and the Heart' - by partnering with WNICER to host a multidisciplinary event 'Inflammation: Shared Pathways in Diverse Diseases' on September 24-25, 2021 in New York. This event united inflammation specialists from leading global institutions with the goal of better understanding inflammation in diverse diseases, providing a structured assessment for its evaluation, and improving therapeutic approaches to modulate inflammatory pathways and processes. See the Research Tab for more information.

We continue to make investments in research initiatives of young investigators, that is, clinical residents (PGY 4-6), and MDs or PhDs who are within the first five years of their first faculty appointment at a Canadian academic institution. As mentioned earlier, we recently invited the CCS to partner with us in this initiative – a move that saw us double the prize fund and triple the number of applications received across-Canada. Finalists are invited to present their research at the Canadian Cardiovascular Congress.

Establishment of the Canadian Cardiovascular Research Collaboratory (C^3) was a response to the need to strengthen synergies among Canadian researchers to expedite the discovery, evaluation, and application of emergent observational and clinical trial studies, and the application of

emergent therapies and strategies for cardiovascular disease. The C^3 jointly collaborates on the areas of population health, prevention, coronary artery disease, heart failure, and interventions/surgery. Working together means the larger group can combine efforts and combine funding to enhance the prevention, diagnosis, and treatment of cardiovascular disease.

Internationally we continue to collaborate on clinical trials with the members of the Worldwide Network for Innovation in Clinical Education and Research. A few to mention include: TAILOR-PCI (Tailored Antiplatelet Therapy Following PCI) – a 5,300-patient multinational study that was published in JAMA in August 2020; INVESTED (INfluenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure) – a 5,388-patient multinational study that was published in JAMA in December 2020;); ATTACC (Antithrombotic Therapy to Ameliorate Complications of COVID-19) – a 1,200 patient multinational study; and the FREEDOM COVID-19 Anticoagulation Strategy. WNICER has 60+ lead investigators from 10 countries representing 400+ team members, and a one billlion+ population base; a real asset in the conduct of multi-centre, multi-national clinical trials.

Since our last review, we have now finalized our financial commitment to the following initiatives:

Recruit Support:

- ***Dr. Husam Abdel-Qadir*** is an Assistant Professor and Clinician-Scientist at Women's College Hospital. His research focuses on cardio-oncology, specifically mitigating the adverse effects of chemotherapy by exploring the modifiable elements of the sociocultural environment, promoting mental well-being and enabling earlier detection of heart disease to arrest its progression.
- ***Dr. Brian Courtney*** is an Assistant Professor and Clinician-Scientist at the Sunnybrook Health Sciences Centre and a leader in the design and development of new medical devices including the first 3-D forward-looking intracardiac echo catheter imaging system. He develops new medical innovations, with a particular focus on imaging and therapeutic catheters for minimally invasive cardiovascular procedures.
- ***Dr. Slava Epelman*** is an Assistant Professor and Clinician-Scientist at the University Health Network. His work focuses on the understanding of the role of macrophages on cardiac tissue injury and regeneration. His lab explores therapies that enhance macrophage-mediated regeneration of cardiac tissue as a novel therapeutic avenue.
- ***Dr. Michael Laflamme*** is an Associate Professor and Scientist at the Toronto General Research Institute and a member of the Department of Laboratory Medicine and Pathobiology. Dr. Laflamme's research focuses on developing novel therapies for post-MI heart failure based on human pluripotent stem cells.
- ***Dr. Patrick Lawler*** is an Assistant Professor and Clinician-Scientist at the Peter Munk Cardiac Centre at University Health Network. His research, focused on inflammation and metabolism, aims to develop personalized medicine approaches for the prevention and treatment of cardiovascular disease and critical illness.
- ***Dr. Idan Roifman*** is an Assistant Professor and Clinician-Scientist at Sunnybrook Health Sciences Center and is an expert in outcomes research and cardiac imaging.

Research Platforms (these platforms serve(d) as core facilities for all members of the HSRLCE):

1. ***Cardiovascular Data Management Centre (CVDMC):*** The CVDMC served the cardiovascular disease community by forging linkages between databases, and by providing access to the data for researchers and clinicians, risk adjusted reports for clinical quality improvement initiatives, and statistical services to participants.
2. ***Large Animal Facility****:* Primary hub in Toronto that promotes the integration of large animal cardiovascular disease models with novel imaging modalities (X-ray, MRI, CT, ultrasound, and optical coherence tomography).
3. ***Transgenic Physiology Laboratory*****:** This was located in the Max Bell Research Building at UHN and was a core facility for integrating our translational research, primarily in heart failure.
4. ***Athletic Heart Laboratory (Now Sports Cardiology Toronto):*** A cross-disciplinary research group that examines the impact of intensive exercise training on cardiac health outcome.

Research Productivity

Productivity was measured from years 2016-2021 for this report and benchmarked against Harvard, UCLA, University College London, University of British Columbia, and McGill University. In the field of Cardiology and Cardiovascular Medicine, University of Toronto as a whole ranked second with 4,962 publications, 83,771 citations, and a field-weighted citation impact of 2.1.

In the period between 2016 to 2021, HSRLCE scientists specifically:

- Published 6,745 papers across multiple subject areas (not just cardiology), with 176,105 citations and a field-weighted citation impact of 3.05;
- Held 53 patents;
- Commercialized 14 inventions;
- Filed invention disclosures to commercialize an additional 44 inventions; and
- Secured over $496 million in peer-reviewed funding.

Overall, a US News and World Report powered by Clarivate ranked University of Toronto the 5th best university in the world (out of 250 universities) based on research performance in the field of Cardiac and Cardiovascular Systems.

***** *Further details are furnished in the 'Research' tab of this report.*

FINANCIAL OVERVIEW:

The HSRLCE received its initial investment of $13 million from the Heart & Stroke Foundation of Ontario and the Lewar family (Stephan and Sophie in memory of their son Richard) in 1999. The initial budget of the HSRLCE was originally planned for 10 years; but the Centre is now in its 23rd year of operation. Currently, our main sources of revenue include income from endowments and programmatic sponsorship in the form of unrestricted grants from Industry. Our main

expenditures are education, training, research support, and administration, currently averaging just under a million dollars a year. A snapshot of our finances is provided in the 'Financial Overview' tab of this report.

We are in the final stages of funding and have been taking innovative approaches to fundraising. We held a fundraising event dubbed "Closer to the Heart" on June 12, 2019. The event was attended by 200 guests and showcased the following research and education initiatives: The Sports Cardiology Institute (Athlete and the Heart Program); the Cardiovascular Sciences Collaborative Program; the Clinician -Scientist Training Program; and our international research arm – The Worldwide Network of Innovation in Clinical Education and Research. We were in the midst of cultivating relationships with would-be donors, with the help of UofT's Office of Advancement, when COVID hit, slowing down our progress. The prospects are still promising and we continue to pursue these relationships. In the interim, we have been very successful in fundraising for specific educational and research programming, and in collaborating with other entities to magnify our education and research investments – as highlighted earlier in this report.

IMPORTANT MILESTONES - 2017-2022:

These have been addressed throughout this report, but we wanted to take an opportunity to highlight a few:

1. Positioned the HSRLCE on the world stage through collaborations with the leading cardiovascular, diabetes, and innovation institutions worldwide – including participation in global events such as the Vatican Conference, the Global Inflammation Think Tank, and the Canada-Israel Cardiovascular Innovation Forum;
2. Magnified our investments by partnering with allied organizations in seven key research platforms: heart failure, diabetes and the heart, the brain and the heart, athlete and the heart, inflammation and the heart, COVID-19 and the heart, and innovation in cardiometabolic research;
3. Created a partnership with the CCS and the BI-Lilly Alliance to enhance and expand support for early career investigators;
4. Partnered with the Heart & Stroke Foundation to collaborate on the development , accreditation, and delivery of the Heart and Stroke Clinical Update Educational Program;
5. Established Sports Cardiology Toronto – a clinical care facility that will become operational by the Spring of 2022, and is already attracting referrals in need of unique expertise by sports cardiology experts;
6. Helped establish the Canadian Cardiovascular Research Collaboratory – a national virtual network that collaborates on the areas of population health, prevention, coronary artery disease, heart failure, and interventions/surgery;

7. Developed, created content, and implemented the roll out five new accredited case-based practical CME programming for physicians and specialists caring for patients with cardiovascular disease and other risk factors;
8. Led and organized 16 international knowledge exchange seminars with a multi-national audience to explore the practical implications of late-breaking clinical trial results;
9. Formalized and expanded the scope of the Worldwide Network for Innovation in Clinical Education and Research;
10. Created a new Innovation program that has 17 partner institutions in Canada and Israel (including, the CCS, the Israel Heart Society, and UofT's Sunnybrook Medventions Program, Health Innovation Hub, and the Translational Research Program); and
11. Supported other institutions / departments in their research and educational endeavours.

FUTURE DIRECTION:

We believe that the future of the Centre is bright and promising. We are fortunate to have a robust multi-disciplinary, highly productive, collaborative, research-minded membership at HSRLCE. We are a small but nimble department and thus we are easily able to actively pursue, and quickly react to partnership and collaboration opportunities that are presented to us; opportunities that are mutually-beneficial to our membership and magnify our impact locally, nationally and internationally.

We have also built a great mechanism for developing new practical and innovative Continuing Medical Education programs that can be easily repackaged for presentation to a national and international audience. We have created a network of experts in various cardiovascular and other chronic disease fields, and are often called upon nationally and internationally to provide Faculty to speak to various hot topics like the interrelationship of cardiovascular disease and diabetes, COVID-19, cancer, inflammation, stroke, and so on.

The creation of WNICER continues to be an investment that continually generates dividends especially in the area of clinical trials collaboration. The opportunity to collaborate internationally is extremely beneficial for patient recruitment, and it also opens up access to international clinical grants that might not otherwise be available to our membership. With institutions like The HUB (which encompasses CLEAR, AHRC and BreaKThrough); the Peter Munk Centre of Excellence in Multinational Clinical Trials; and ICES, the University of Toronto has the potential to become the Canadian clinical trials centre for NIH trials as they emerge outside of the United States.

We have identified annual funding avenues to assist our faculty and trainees in their research and education endeavors. To name a few … Undergraduate awards are made possible by an endowment from the HSBC; studentship awards are partially funded through matching funds from the Graduate Student Endowment Fund (GSEF); young investigator cardiometabolic awards are made possible through an unrestricted grant from the BI-Lilly Alliance; and innovation

investments are facilitated through the CICI Forum which creates opportunities to connect innovators with investors.

The primary issue facing the Centre is funding. HSRLCE was established in 1999 when the University received a donation of 13 million dollars from the Heart & Stroke Foundation of Ontario and the family of Richard Lewar. The gift was to last 10 years – but we have more than doubled the timeline and are currently in the 23rd year of operation. We have been able to raise additional funds through philanthropic gifts and through unrestricted educational grants from Industry. We have also been creative in our programming approach – rather than funding a program entirely on our own, we have been forging partnerships with other local, national or international entities to contribute towards funding of projects. But for the Centre to continue to live up to its full research, training and education potential, a cash injection is required to drive these important initiatives forward. Ideally the Centre should have an annual operational budget of $1.5 million, but due to the partnerships we have in place, and a lean staff of only 2 personnel, an annual budget of $1 million would still enable HSRLCE to continue its important mandate of transforming cardiovascular health locally, nationally and internationally.

We look forward to our review as a way to guide the Centre's future directions and to provide important insights into opportunities for growth on the international stage. With our collaborative and inclusive spirit, and the groundwork that has been done to forge strong collaborative relationships, we are very excited about the future of the HSRLCE.

Sincerely,

Michael E. Farkouh, MD, MSc, FRCPC, FACC, FAHA
Director, Heart & Stroke/Richard Lewar Centre of Excellence in Cardiovascular Research, University of Toronto
Vice-Chair, Research & Professor of Medicine, Department of Medicine, University of Toronto
Peter Munk Chair in Multinational Clinical Trials

EDUCATION

EDUCATION OVERVIEW:

HSRLCE invests in education by:

1. Providing **stipend awards** to its members' trainees at the undergraduate, graduate, and postdoctoral levels;

2. Hosting **Distinguished Visiting Professors** that meet with trainees and faculty and give a talk on the research projects they are involved in;

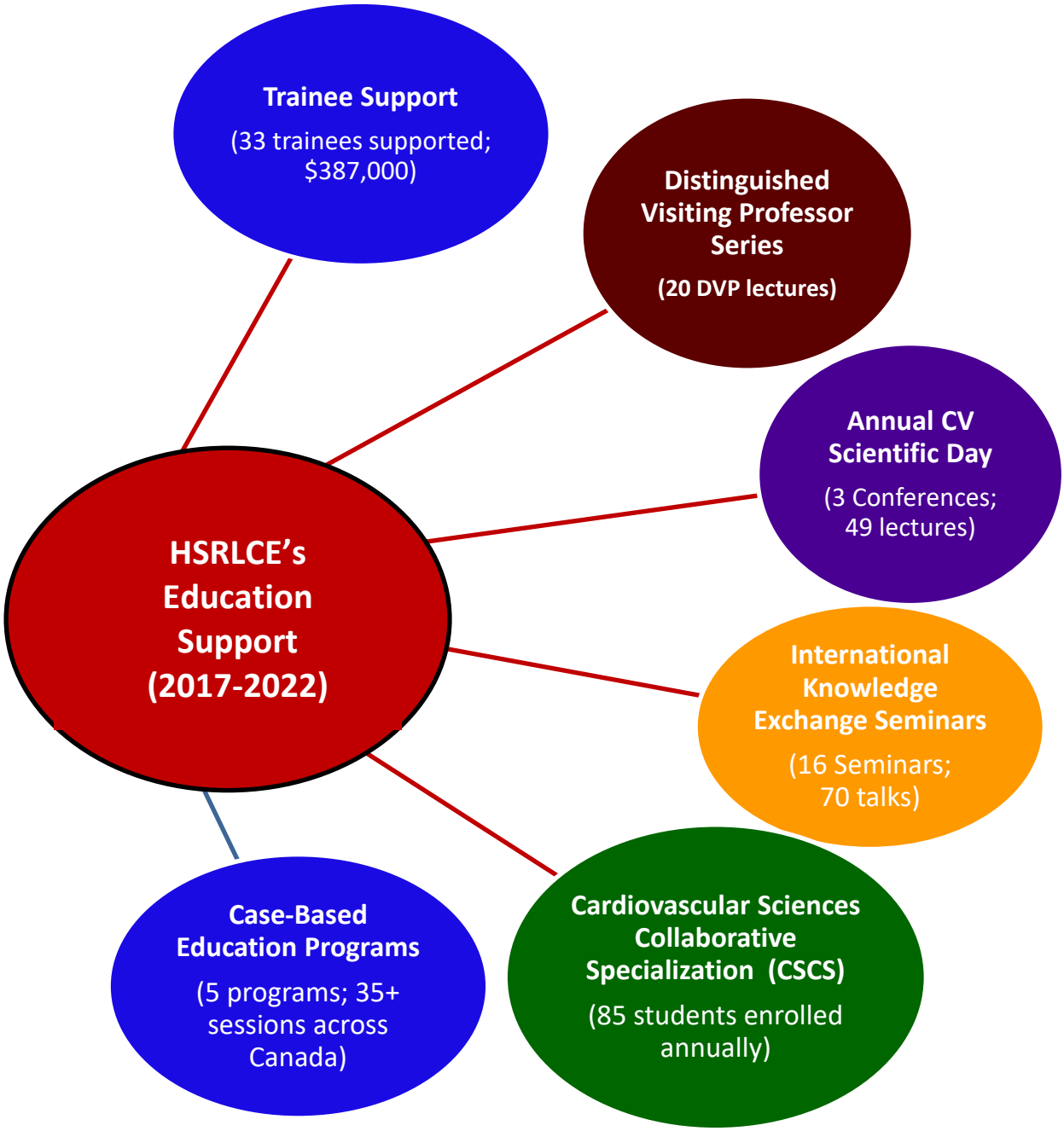
3. Organizing an annual **Cardiovascular Scientific Day** where international experts, local faculty and trainees engage in knowledge exchange;

4. Hosting one-day **knowledge exchange and clinical trials collaboration seminars** with its national and international partners. These seminars are held in conjunction with major cardiology conferences (CCC, AHA, ACC, & the ESC) – typically the meetings are held the day before the major conference commences. These seminars serve to advance HSRLCE's internationalization and collaboration strategies;

5. Holding multi-provincial **case-based Continuing Medical Educational programs** that offer practical tips that can be used in daily practice. These programs aim to help physicians and specialists increase confidence with the initiation and use of specific cardioprotective therapies; and

6. Partnering with the **Cardiovascular Sciences Collaborative Specialization** (CSCS) – which served as HSRLCE's education arm for 5 years until 2019. CSCS was established in 1992 and has developed into a popular program that promotes exemplary linkages between teaching and research at the University of Toronto. The CSCS is a co-operative, interdisciplinary and inter-departmental graduate teaching program that brings together university departments and partnering hospitals to offer a strong curriculum and a unique learning experience. CSCS's annual enrollment averages around 85 trainees – who benefit from $153,000 annually in scholarships, bursaries and awards.

Five-Year Educational Investment Snapshot (2017 - 2022)



1. TRAINEE AWARDS

Undergraduate Awards
In partnership with HSBC, HSRLCE offers two to three summer Undergraduate awards in the amount of $4,500 to enable students to work alongside scientists in cardiovascular research laboratories. This award program was established in 2013. To-date (2022) 26 students have been funded.

Studentship Awards
HSRLCE offers Studentship awards in the amount of $15,000. The awards are intended to support individuals in the initial phase of their training (MSc or PhD) who wish to pursue a career in cardiovascular science. To-date (2022) 94 students have been funded.

Fellowship Awards
HSRLCE offers Fellowship awards in the amount of $25,000. The awards are intended to support individuals pursuing a career in cardiovascular science who are still considered "in training" but have completed a PhD, MD, BM, DVM or equivalent degree. To-date (2022) 105 students have been funded.

***Award recipients*:** see the list of award recipients in the appendix section of this report.

2. HSRLCE DISTINGUISHED VISITING PROFESSOR SERIES

HSRLCE organizes a Distinguished Visiting Professors Series with sponsorship acquired through industry (Amgen, AstraZeneca, Merck, and Servier). Through this series, a forum is provided whereby external experts performing cutting edge research in priority areas are invited to speak and interact with Centre's members and in turn, the activities of the Centre are profiled to the world's opinion leaders. The Centre regularly collaborates with University of Toronto Departments and teaching hospitals. Faculty, clinicians, and students are encouraged to attend.

Visiting Professors: please see the list of professors and talk titles in the appendix section.

3. MICHAEL J. SOLE ANNUAL CARDIOVASCULAR SCIENTIFIC DAY (ACvSD)

Pre-COVID, the HSRLCE hosted the ACvSD every April/May; averaging around 220 delegates. Local, national and international experts share their knowledge with the Centre's trainees, faculty, industry, and other healthcare professionals. Each year we focus on a different theme. The Day also sees us host a trainee poster competition with three prizes (worth $1,000, $500 and $250) given to the top three students. We also have a lecture given by the Dr. Subhash C. Verma Young Investigator's Award recipient. The Award was established in 2006 by the HSRLCE. It is funded by the family of the late Dr. S. C. Verma. The award recognizes exceptional

achievement in the cardiovascular sciences and is open to HSRLCE members who have not been principal investigators for more than seven years. The themes in the past three years have been: Innovation in Devices, Research and Novel Partnerships; From Discovery to Clinical Trials; and Heart Failure (held in conjunction with the Ted Rogers Centre for Heart Research).

ACvSD details: please see the program details in the appendix section of this report.

4. NATIONAL & INTERNATIONAL KNOWLEDGE EXCHANGE SEMINARS

As part of HSRLCE's commitment to education as well as national and international collaboration, pre-COVID, the HSRLCE hosted one-day knowledge exchange and clinical trials collaboration seminars with its national and international partners. These seminars were held in conjunction with major cardiology conferences (CCC, AHA, ACC, & the ESC). Typically the meetings are held the day before the major conference commences.

We run two versions of these seminars:

1. **Canadian-centric seminars:**
   The seminars provide a forum for key experts from across Canada to share best practices and discuss clinical challenges in coronary syndromes. Data from clinical trials is presented and an opportunity to discuss and debate the implications of these data for clinical practice is provided. Seminars held in the last 5 years were:
   i. CCC Seminar – 2017 (Vancouver)
   ii. ACC Seminars – 2018 (Orlando); 2019 (New Orleans)
   iii. AHA Seminars – 2018 (Chicago); 2019 (Philadelphia)
   iv. ESC Seminars – 2017 (Barcelona); 2018 (Munich); 2019 (Paris)

2. **International-focused seminars:**
   In 2015, HSRLCE Director, Dr. Michael Farkouh founded the Worldwide Network for Innovation in Clinical Education and Research (WNICER); an ambitious initiative to connect and coordinate leading cardiologists and cardiovascular scientists on an international level by using the combined resources of its members. The consortium's goal is to facilitate the conduct of high quality clinical trials and translational research under the guidance and leadership of an international collaborative of world class cardiovascular clinical investigators from member institutions. WNICER's administration is handled by the HSRLCE office. In the past 5 years, the following WNICER knowledge-exchange seminar have been held:
   i. ACC Seminars – 2018 (Orlando); 2019 (New Orleans)
   ii. AHA Seminars – 2017 (Anaheim); 2018 (Chicago); 2019 (Philadelphia); 2021 (Virtual)
   iii. ESC Seminars – 2017 (Barcelona); 2018 (Munich); 2019 (Paris); 2020 (Virtual)

Seminar details: please see the program details in the appendix section of this report.

5. CASE-BASED PRACTICAL CONTINUING MEDICAL EDUCATION PROGRAMS

Starting in 2018, the HSRLCE launched a new learning stream aimed at providing practical tips that can be used in daily practice. These multi-disciplinary accredited programs aim to help physicians and specialists increase confidence with the initiation and use of specific cardioprotective therapies. To-date we have held 5 such programs (35+ cross-Canada in-person and virtual sessions, with plans to develop more).

I. ***Diabetes and Cardiovascular Disease: A Practical Guide for Specialists Managing Patients With or At Risk for Cardiovascular Disease***

Learning Objectives

- Outline the impact of T2DM upon CV morbidity and mortality
- Describe the role that approved anti-hyperglycemic therapies play in reducing CV risk
- Select appropriate anti-hyperglycemic agents in order to reduce CV risk in patients with T2DM
- Develop an integrated management plan in order to meet patient needs and reduce T2DM morbidity and mortality

II. ***BE IT RESOLVED THAT… An Educational Debate on Optimal Cardiorenal Protection of Patients With or Without Diabetes***

Learning Objectives

- Discuss the cardiorenal protective role of sodium glucose transport protein 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1-RA) in patients with and without diabetes.
- Compare different treatment sequencing options for SGLT2i and GLP1-RA in type 2 diabetes mellitus (T2DM), as well as in chronic kidney disease and heart failure populations with or without type 2 diabetes, based on recently published data.

III. ***Straight from the Heart – Insights on Optimal Cardioprotection***

Learning Objectives

- Recognize the importance of early initiation of cardioprotective therapies (SGLT2 inhibitors) in patients with heart failure with reduced ejection fraction (with or without diabetes)
- Recognize the importance of early initiation of cardioprotective therapies (SGLT2 inhibitors and GLP-1 receptor agonists) in patients with atherosclerotic cardiovascular disease and diabetes

- Initiate SGLT2 inhibitors and GLP-1 receptor agonists in appropriate patients using guideline-recommended strategies
- Advise patients on the safe use of SGLT2 inhibitors and GLP-1 receptor agonists

IV. ***The Heart, the Kidney and SGLT2 Inhibitors: From Clinical Trials to Patient Care***

Learning Objectives

- Describe the effects of SGLT2 inhibitors on HF-related outcomes – cardiologist perspective
- Interpret the evidence for SGLT2 inhibitors from clinical trials in patients with CKD with and without diabetes – nephrologist perspective
- Discuss practical considerations regarding the use of SGLT2 inhibitors – endocrinologist perspective

V. ***Diabetes Connect: A Practicum for Primary Care***

Learning Objectives

- Discuss the interplay between diabetes, cardiovascular and renal disease
- Investigate and manage cardiovascular and renal issues in patients with diabetes
- Apply evidence and guidelines recommendations to reduce cardiovascular and renal risk for patients with diabetes

6. CARDIOVASCULAR SCIENCES COLLABORATIVE SPECIALIZATION (CSCS)

Below is an excerpt from the 2017-2018 CSCP Annual Report (Director's message) highlighting the collaboration between CSCP and HSRLCE:

"Our partnership with the Heart & Stroke/Richard Lewar Centre of Excellence in Cardiovascular Research (HSRLCE) is now in its' fourth successful year and has resulted in continued high quality education experience for our trainees. Visiting professors brought in by the HSRLCE continue to be integrated into CSCP student opportunities to meet and hear world experts share their passion and knowledge - which is a valuable exposure for our students. In addition, a new initiative was added this year whereby, at the HSRLCE Michael J. Sole Annual Cardiovascular Scientific Day in April both our Phenix and Bigelow awardees from the previous year were prominently featured as keynote speakers. Both Emily Vecchiarelli as the Phenix Award winner and Cedric Manlhiot as the Bigelow award winner were warmly received. This is an important step in showing our trainees of their value and highlight beyond just the reaches of the CSCP their outstanding work to our general cardiovascular community."

Source: CSCS 2017-2018 Annual Report:
http://www.cscp.utoronto.ca/report/cscpAnnualReport2017-2018.pdf

For CSSC's activities in 2018-2019, please see their Annual Report:
http://www.cscp.utoronto.ca/report/cscpAnnualReport2018-2019.pdf

HSRLCE'S INVESTMENT IN RESEARCH

INVESTMENT IN YOUNG INVESTIGATORS

The HSRLCE in partnership with the Boehringer Ingelheim and EI Lilly Alliance founded the "HSRLCE/BI-Lilly-Cardiometabolic Research Award" in 2018. The goal of the program was to fund innovative ground-breaking clinical research projects in cardiometabolic disease, specifically the link between cardiovascular disease and diabetes.

Eligible applicants were qualified Canadian MDs or PhDs who were within the first five years of their first faculty appointment at a Canadian academic institution for a research project on any topic related to cardiometabolic disease. Top scoring finalists got a chance to present their project at a session at the Canadian Cardiovascular Congress in October.

In 2020, HSRLCE brought in the Canadian Cardiovascular Society as a partner, and the award was renamed "CCS/HSRLCE/BI-Lilly-Cardiometabolic Research Award.". Eligibility was expanded to also include Canadian clinical residents (PGY 4-6); and the prize fund was increased from $45,000 to $70,000.

To-date, the following young investigators have been supported (for a total of $205,000):

2021 Recipients:

Dr. Bahar Behrouzi, University of Toronto
PROJECT: Investigating viral respiratory infections (VRI) in real-world patients with/at risk of cardiovascular disease (CVD) using epidemiological techniques
Awarded $20,000

Dr. Vaibhav Patel, University of Calgary
PROJECT: Targeting mitochondrial dynamics and metabolism in aortic aneurysm
Awarded $20,000

Dr. Vinay Garg, University of Toronto
PROJECT: ADJUnctive use of SGLT2i Prior to Elective Cardioversion for Prevention of Atrial Fibrillation/Flutter Recurrence: A Pilot Study
Awarded $15,000

Dr. Husam Abdel-Qadir, University of Toronto
PROJECT: SGLT2 inhibitors for Patients with Atrial fibrillation and Diabetes
Awarded $15,000

2020 Recipients:

Dr. Marie-Eve Piché, University of Ottawa
PROJECT: Effects of Exercise and lifestyle intervention on subclinical cardiac function in adults with metabolic syndrome: a 16-week randomized study
Awarded $25,000

Dr. Mireille Ouimet, Laval University
PROJECT: Role of Lipophagy in Macrophage Polarization
Awarded $20,000

2019 Recipients:

Dr. Walter Swardfager, Sunnybrook Research Institute
PROJECT: Oxylipins in the Diabetic Microvascular Contributions Cognitive Impairment and Dementia
Awarded $25,000

Dr. Patrick Lawler, University Health Network
PROJECT: Plasma Metabolomic Alterations Accompanying Empagliflozin Therapy
Awarded $20,000

2018 Recipients:

Dr. Cynthia Luk, St. Michael's Hospital
PROJECT: The Role of Adipose Tissue Signaling in the Pathogenesis of Atherosclerosis
Awarded $25,000

Dr. Charles de Mestral, St. Michael's Hospital
PROJECT: Reducing Amputation from Diabetes and Peripheral Arterial Disease through Regional Foot Care and Amputation Prevention Pathways
Awarded $20,000

INVESTMENT IN RECRUITS TO UNIVERSITY OF TORONTO

The HSRLCE has played a major role in partnering with various University of Toronto Departments and University Hospitals to recruit cardiovascular investigators. In the last five years (2017 to 2022), HSRLCE has finalized its support of the recruitment of 6 researchers who were supported for a period of up to 3 years, for total funding of up to $75,000.

Husam Abdel-Qadir, MD, PhD, FRCPC, DABIM
Assistant Professor and Clinician-Scientist at Women's College Hospital

Dr. Abdel-Qadir's research tackles two large threats to the health of women (cancer and CV disease) at their intersection through his unique cardio-oncology research. He is addressing the challenges of providing the best possible care for these complex patients whose needs are not currently being met within our healthcare system. Dr. Abdel-Qadir recently received an early career Women's Heart and Brain Health Chair from the Heart & Stroke and the Canadian Institutes of Health Research to support his research on improving women's heart health focusing on health services, as well as the impact of social, cultural, and environmental factors. With the chair award, Dr. Abdel-Qadir will expand his research focus to address the cardiovascular concerns of older women with non-cardiovascular disease to enhance management of multiple conditions. By developing better pathways of care, he hopes to identify higher-risk women to address modifiable risks to improve their cardiovascular health, as well as lower-risk women to ensure they are spared unnecessary interventions and doctor visits.

Brian Courtney, MD, FRCPC, MSEE
Assistant Professor and Clinician-Scientist at Sunnybrook Health Sciences Centre

Dr. Courtney develops new medical innovations, with a particular focus on imaging and therapeutic catheters for minimally invasive cardiovascular procedures. His current research projects include:

- Intracardiac echocardiography catheters and systems that provide 3D imaging of structures in the heart, Doppler capability, 4D imaging (3D + time) and anatomical reconstruction. This technology is being developed to guide a number of procedures such as trans-septal punctures during atrial fibrillation procedures, revascularization of peripheral or central venous occlusion, valve repairs and endovascular aneurysm repair.
- Hybrid intravascular ultrasound and optical coherence tomography imaging catheters and systems for producing high-resolution cross-sectional images of coronary arteries. This technology is being developed to assess the extent of coronary plaque, identify plaque composition, assist with stent deployment and resolve ambiguities in coronary angiograms.
- Custom medical devices for patients with unique cardiovascular anatomy who would otherwise go untreated.
- Preclinical validation of medical devices and cardiovascular procedures in animal models.

Slava Epelman, MD, PhD, FRCPC
Assistant Professor and Clinician-Scientist at the University Health Network

Dr. Epelman has 2 major areas of ongoing investigation:

- Animal models of cardiac tissue injury and repair – his lab is focused on understanding the role myeloid cells (monocytes, macrophages and dendritic cells) play within the myocardium during steady state and following tissue injury. Using genetic and surgical mouse models, they are trying to understanding how individual myeloid subsets are activated, what factors regulate their entry, persistence and fate after entry into the myocardium. In addition, they are identifying the contribution of each myeloid subset to the process of cardiac regeneration. They use models of hemodynamic stress (hypertension), ischemic stress (myocardial infarction) and also infective injury (viral myocarditis) in order to study the role of macrophages in tissue damage and repair.
- Translational studies in patients with cardiovascular disease – They have several integrated translational projects that focus on the corresponding human myeloid subsets, how they are activated and how their activation state relates to myocardial function and myocardial recovery in patients following myocardial tissue injury (myocardial infarction). By focusing on how myeloid cells are activated in humans, they hope to identify pathological pathways that both identify patients who will be at high risk for developing severe cardiac dysfunction, and also identify new therapeutic targets.

Michael Laflamme, MD, PhD
Associate Professor and Scientist at the Toronto General Research Institute

Dr. Laflamme's laboratory is focused on developing novel therapies for post-MI heart failure based on human pluripotent stem cells (hPSCs) because hPSCs are the only stem cell type capable of differentiating into large quantities of phenotypically unambiguous cardiomyocytes. Our goal is to restore the electrical and contractile function of injured hearts by "remuscularizing" the infarct scar with hPSC-derived cardiomyocytes.

His laboratory has already made a number of important advances in this area, including the development of efficient protocols to guide hPSCs into cardiomyocytes and specialized cardiac subtypes, proof-of-concept

transplantation studies with hPSC-derived cardiomyocytes in rodent MI models, and the first direct demonstration that hPSC-derived cardiomyocytes can become electrically integrated and activate synchronously with host myocardium in injured hearts. Their ongoing work builds on these successes and is bringing them closer to a viable cell therapy. Current projects in the lab include 1) developing scalable approaches to promote the maturation of hPSC-derived cardiomyocytes in vitro, 2) creating and validating new tools to characterize the electrical behavior of hPSC-derived cardiac grafts in vivo, 3) exploring novel pharmacological and gene-engineering approaches to improve host-graft electromechanical integration and graft electrophysiological function, and 4) testing the efficacy and safety of hPSC-derived cardiomyocyte transplantation in highly relevant preclinical MI models.

Patrick Lawler, MD, PhD, FRCPC
Assistant Professor and Clinician-Scientist at the University Health Network

Dr. Lawler's research aims to develop personalized medicine approaches for the prevention and treatment of cardiovascular disease and critical illness. This work that has a strong scientific focus on inflammation and metabolism, is at the intersection between cardiovascular disease and sepsis, and leverages molecular epidemiology/systems medicine approaches in epidemiology and clinical trials.

He also has a focus on Bayesian adaptive/platform trials in critical care medicine, and serve on the International Trial Steering Committee of the REMAPCAP global adaptive platform trial (NCT02735707), on the Protocol Development/Leadership Committee for the NIH/NHLBI ACTIV-4 platform trial (NCT04505774), and as co-Principal Investigator of the ATTACC adaptive trial of anticoagulation in hospitalized patients with COVID-19 (NCT04372589) which completed enrollment of 1,204 patients at 62 hospitals in 4 countries. His research is funded by the Canadian Institutes of Health Research and the U.S. National Institutes of Health, among others.

Idan Roifman, MD, FRCPC, M.Sc
Assistant Professor and Clinician-Scientist at Sunnybrook Health Sciences Center

Dr. Roifman's research program focuses on two areas:

- Translational and clinical MRI research including the description and assessment of remodelling of the heart and tissue characterization after a heart attack. This research also includes clinical assessment of novel cardiac MRI sequences.
- The application of health services and clinical epidemiology principles and techniques to cardiac imaging including MRI, computed tomography and echocardiography to assess clinical outcomes related to imaging biomarkers, and to conduct comparative effectiveness and imaging-related resource utilization research.

INVESTMENT IN SPORTS CARDIOLOGY RESEARCH

Sports Cardiology Toronto (SCT) is a recent development of the HSRLCE, launched in 2019 thanks to a fund-raising initiative that enabled its development support of several research projects. Its mission is to "*Promote safe, healthful exercise for athletes at risk of, or diagnosed with cardiovascular disease, informed by a world-class multidisciplinary research team, and through a program of research, education, advocacy and the provision of clinical care and consultation, delivered by leading experts in sports cardiology and exercise physiology".*

A distinguishing feature of Sports Cardiology Toronto is the provision of a unified, fully integrated, and cross-disciplinary program of research, advocacy, consultation, education, and clinical care, all coordinated from within the HSRLCE and leveraging facilities across the University of Toronto landscape. The founding members of SCT are Drs. Jack Goodman (Faculty of Kinesiology and Physical Education), Kim Connelly (St. Michael's Hospital) and Paul Dorian (St. Michael's Hospital) and our team includes Drs. Susanna Mak and Andrew Yan, and a growing list of collaborators beyond the University of Toronto landscape.

The clinical care facility will become operational by the Spring of 2022 and the SCT is already attracting referrals in need of unique expertise by sports cardiology experts.

A key foundation of SCT is research. Our group continues to examine the impact of intensive exercise training on cardiac health outcomes. A large "Athlete's Heart Study" has been completed, examining the impact of long-term vigorous exercise on cardiac remodeling in aging endurance athletes. We have also leveraged novel wearable technology to conduct a field study to verify the relationship between the overall metabolic and cardiac burden of intensive training in middle-aged athletes, novel inflammatory biomarker signatures during exercise in athletes with atrial fibrillation (AF) and the impact of AF on cardiac function and exercise performance in middle-aged endurance athletes. A pilot study has begun to assess the utility of ventilatory patterns during exercise to predict cardiac reserve. The current "Rowers Study, will ascertain the relationship between lifetime exercise training burden and incidence of atrial fibrillation in active or retired world-class Canadian rowers, and a new pan-Canadian "Marathon Study" will survey the past and current training burden in aging marathon runners to determine the impact of exercise history on trajectories of cardiac health outcomes. Numerous trainees have contributed to our research, and they, along with a summary of publications arising from our group, are listed below.

Further fund-raising initiatives will aim to expand the scope and reach of Sports Cardiology Toronto and to further advance its mission.

Trainees (past and current, * now faculty members at U of T or collaborating institutions):
Laura Banks*, Robert Bentley*, Emily Vecchiarelli, Meghan Glibbery, Becky Laudros, David Dorian, Karen Konieczny*, Katharine Currie*, Deva, Saeed Al-Mousawy, MA Altaha, Wesseem Osman, Glen Katsnelson, Stephanie Nevison, Ryan Quinn.

Relevant Publications from the Sports Cardiology Toronto Team (Last 5 years):

1. Fanous Y, Dorian P. Wearables for cardiac monitoring in athletes: Precious metal or fool's gold. European Heart Journal – Digital Health (in press June 2021).
2. Snir AW, Connelly KA, Goodman JM, Dorian D and Dorian P. Exercise in hypertrophic cardiomyopathy: Restrict or rethink. *American Journal of Physiology - Heart and Circulatory Physiology*. 2021;320:H2101-H2111.
3. McKinney J, Connelly KA, Dorian P, Fournier A, Goodman JM, Grubic N, Isserow S, Moulson N, Philippon F, Pipe A, Poirier P, Taylor T, Thornton J, Wilkinson M and Johri AM. COVID-19–Myocarditis and Return to Play: Reflections and Recommendations From a Canadian Working Group. *Canadian Journal of Cardiology*. 2021;37:1165-1174.
4. Glibbery M, Banks L, Altaha MA, Bentley RF, Konieczny K, Yan AT, Dorian P, Deva DP, Goodman JM and Connelly KA. Atrial structure and function in middle-aged, physically-active males and females: A cardiac magnetic resonance study. *Clinical Cardiology*. 2021;44:1467-1474.
5. Dorian D, Chatterjee D, Connelly KA, Goodman JM, Yan AT, Bentley RF, Banks L, Hamilton RM and Dorian P. A Novel Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Biomarker—Anti-DSG2—Is Absent in Athletes With Right Ventricular Enlargement. *CJC Open*. 2021;3:1413-1418.
6. Banks L, Al-Mousawy S, Altaha MA, Konieczny KM, Osman W, Currie KD, Connelly KA, Yan AT, Sasson Z, Mak S, Goodman JM and Dorian P. Cardiac remodeling in middle-aged endurance athletes: relation between signal-averaged electrocardiogram and LV mass. *Am J Physiol Heart Circ Physiol*. 2021;320:H316-H322.
7. Banks L, Al-Mousawy S, Altaha MA, Konieczny KM, Osman W, Currie KD, Connelly KA, Yan AT, Sasson Z, Mak S, Goodman JM and Dorian P. Cardiac remodeling in middle-aged endurance athletes: Relation between signal-averaged electrocardiogram and LV mass. *American Journal of Physiology - Heart and Circulatory Physiology*. 2021;320:316-322.
8. Valle FH, Esfandiari S, Jang HJ, Fuchs FC, Wright SP, Granton J and Mak S. Contrasting haemodynamic effects of exercise and saline infusion in older adults with pulmonary arterial hypertension. *ERJ Open Res*. 2021;7.
9. Ton VK, Ramani G, Hsu S, Hopkins CD, Kaczorowski D, Madathil RJ, Mak S and Tedford RJ. High Right Ventricular Afterload Is Associated with Impaired Exercise Tolerance in Patients with Left Ventricular Assist Devices. *ASAIO J*. 2021;67:39-45.3.
10. Wright SP, Dawkins TG, Eves ND, Shave R, Tedford RJ and Mak S. Hemodynamic function of the right ventricular-pulmonary vascular-left atrial unit: normal responses to exercise in healthy adults. *Am J Physiol Heart Circ Physiol*. 2021;320:H923-H941.
11. Valle FH, Mohammed B, Wright SP, Bentley R, Fam NP and Mak S. Exercise Right Heart Catheterisation in Cardiovascular Diseases: A Guide to Interpretation and Considerations in the Management of Valvular Heart Disease. *Interv Cardiol*. 2020;16:e01.
12. Bentley RF, Barker M, Esfandiari S, Wright SP, Valle FH, Granton JT and Mak S. Normal and Abnormal Relationships of Pulmonary Artery to Wedge Pressure During Exercise. *J Am Heart Assoc*. 2020;9:e016339.
13. Dorian P, Goodman JM and Connelly KA. Policies to prevent sudden cardiac death in young athletes: Challenging, but more testing is not the answer. *Journal of the American Heart Association*. 2020;9.

14. Bentley RF, Vecchiarelli E, Banks L, Gonçalves PEO, Thomas SG and Goodman JM. Heart rate variability and recovery following maximal exercise in endurance athletes and physically active individuals. *Applied Physiology, Nutrition and Metabolism*. 2020;45:1138-1144.
15. Banks L, Bentley RF, Currie KD, Vecchiarelli E, Aslam A, Connelly KA, Yan AT, Konieczny KM, Dorian P, Mak S, Sasson Z and Goodman JM. Cardiac Remodeling in Middle-Aged Endurance Athletes and Recreationally Active Individuals: Challenges in Defining the "Athlete's Heart". *Journal of the American Society of Echocardiography*. 2020;33:247-249.
16. Moulson N, Dorian P, Krahn A, Virani A, Isserow S, McKinney J. Shared decision-making and the cardiovascular care of athletes: Is it time to get back in the game? Can J Cardiol 2020 Jun;36(6):941-944. Epub 2019 Oct 17. PMID: 32173054
17. Sequeira N, D'Souza D, Angaran P, Aves T, Dorian P. Common wearable devices demonstrate variable accuracy in measuring heart rate during supraventricular tachycardia. Heart Rhythm 2020 May;17(5 Pt B):854-859. PMID: 32354450
18. Landry CH, Fatah M, Connelly KA, Angaran P, Hamilton RM, Dorian P. Evaluating the 12-lead electrocardiogram for diagnosing ARVC in young populations: Implications for preparticipation screening of athletes. CJC Open 2020 Dec 18;3(4):498-503. PMID: 34027353
19. Banks L, Altaha MA, Yan AT, Dorian P, Konieczny K, Deva DP, La Gerche A, Akhavein F, Bentley RF, Connelly KIMA and Goodman JM. Left Ventricular Fibrosis in Middle-Age Athletes and Physically Active Adults. *Medicine and Science in Sports and Exercise*. 2020;52:2500-2507.
20. Wright SP, Opotowsky AR, Buchan TA, Esfandiari S, Granton JT, Goodman JM and Mak S. Flow-related right ventricular to pulmonary arterial pressure gradients during exercise. *Cardiovasc Res*. 2019;115:222-229.
21. McKinney J, Johri AM, Poirier P, Fournier A, Goodman JM, Moulson N, Pipe A, Philippon F, Taylor T, Connelly K and Dorian P. Canadian Cardiovascular Society Cardiovascular Screening of Competitive Athletes: The Utility of the Screening Electrocardiogram to Predict Sudden Cardiac Death. *Canadian Journal of Cardiology*. 2019;35:1557-1566.
22. Konieczny K, Banks L, Osman W, Glibbery M, Connelly KA, Yan AT, Goodman JM and Dorian P. Prolonged P wave duration is associated with right atrial dimensions, but not atrial arrhythmias, in middle-aged endurance athletes. *Journal of Electrocardiology*. 2019;56:115-120.
23. Johri AM, Poirier P, Dorian P, Fournier A, Goodman JM, McKinney J, Moulson N, Pipe A, Philippon F, Taylor T, Connelly K, Baggish AL, Krahn A and Sharma S. Canadian Cardiovascular Society/Canadian Heart Rhythm Society Joint Position Statement on the Cardiovascular Screening of Competitive Athletes. *Canadian Journal of Cardiology*. 2019;35:1-11.
24. Buchan TA, Wright SP, Esfandiari S, Fuchs FC, Gray T, Currie KD, Sasson S, Sasson Z, Mak S and Goodman JM. Pulmonary hemodynamic and right ventricular responses to brief and prolonged exercise in middle-aged endurance athletes. *Am J Physiol Heart Circ Physiol*. 2019;316:H326-H334.
25. Buchan TA, Wright SP, Esfandiari S, Fuchs FC, Gray T, Currie KD, Sasson S, Sasson Z, Mak S and Goodman JM. Pulmonary hemodynamic and right ventricular responses to brief and prolonged exercise in middle-aged endurance athletes. *American Journal of Physiology - Heart and Circulatory Physiology*. 2019;316:H326-H334.
26. Fanous Y, Dorian P. The prevention and management of sudden cardiac arrest in athletes. CMAJ 2019 Jul 15;191(28):E787-E791. PMID: 31308007

27. Goodman JM, Banks L, Connelly KA, Yan AT, Backx PH and Dorian P. Excessive exercise in endurance athletes: Is atrial fibrillation a possible consequence? *Applied Physiology, Nutrition and Metabolism*. 2018;43:973-976.
28. Landry CH, Allan KS, Connelly KA, Cunningham K, Morrison LJ, Dorian P, Rescu Investigators. Sudden cardiac arrest during participation in competitive sports. N Engl J Med 2017 Nov 16;377(20):1943-53. PMID: 29141175
29. Esfandiari S, Wright SP, Goodman JM, Sasson Z and Mak S. Pulmonary Artery Wedge Pressure Relative to Exercise Work Rate in Older Men and Women. *Med Sci Sports Exerc*. 2017;49:1297-1304.
30. Wright SP, Granton JT, Esfandiari S, Goodman JM and Mak S. The relationship of pulmonary vascular resistance and compliance to pulmonary artery wedge pressure during submaximal exercise in healthy older adults. *J Physiol*. 2016;594:3307-15.
31. Wright SP, Esfandiari S, Gray T, Fuchs FC, Chelvanathan A, Chan W, Sasson Z, Granton JT, Goodman JM and Mak S. The pulmonary artery wedge pressure response to sustained exercise is time-variant in healthy adults. *Heart*. 2016;102:438-43.

INVESTMENT IN RESEARCH COLLABORATIONS

Michael R. Freeman Innovation Award

In collaboration with the Heart and Stroke/Richard Lewar Centre of Excellence in Cardiovascular Research (HSRLCE), the academic/teaching hospitals from the Toronto Central Local Health Integration Network (i.e. Hospital for Sick Children, St. Michael's Hospital, Sinai Health Systems, Sunnybrook Health Sciences Centre, the Women's College Hospital, the University Health Network and University of Toronto's Translational Biology and Engineering Program) founded the Cardiac and Vascular Collaborative Innovation Competition in 2017 (which was later renamed "The Michael R. Freeman Innovation Award".)

The goal of the program is to spur innovation and collaboration between institutes with the aim of improving quality of care within cardiac and vascular programs. The purpose of the award is to provide seed funding for novel ideas aimed at cardiovascular disease management, emphasizing collaborative research and development at multiple sites within the TCLHIN. Available funding is up to $250,000 annually.

Criteria for selection are: *novelty of innovation; commercialization potential; cardiovascular disease target; and multi-site collaboration*.

2019 Recipient

PI:	**Dr. Robert Hamilton**
Co-Applicants:	Drs. Benedict Glover (Sunnybrook), Anthony Gramolini (UofT), Danna Spears (UHN)
Research Site:	The Hospital for Sick Children
Project:	Investigation of a Sensitive and Specific Biomarker Profile for Brugada Syndrome
Award:	$114,500

2019 Recipient

PI:	**Dr. Mitesh Badiwala**
Co-Applicants:	Dr. Yu Sun (UofT)
Research Site:	Peter Munk Cardiac Centre, Toronto General Hospital, University Health Network
Project:	Development of an ex vivo heart perfusion system with non-invasive heart functional assessment capability
Award:	$88,000

2018 Recipient

PI:	**Dr. Robert Hamilton**
Co-Applicants:	Drs. Danna Spears (UHN), Paul Dorian (SMH)
Research Site:	The Hospital for Sick Children
Project:	Validation and application of a biomarker identifying arrhythmogenic right ventricular cardiomyopathy (**see report highlighted)*
Award:	$112,500

2018 Recipient

PI:	**Dr. Paul Dorian**
Co-Applicants:	Drs. Sheldon Cheskes (Sunnybrook), Paul Angaran (SMH)
Research Site:	St. Michael's Hospital
Project:	The "AED on the way" project: Getting automated external defibrillators to the scene of cardiac arrest
Award:	$115,000

2017 Recipient

PI:	**Dr. Andrew Dueck**
Co-Applicants:	Drs. Graham Wright (Sunnybrook), Trisha Roy (UofT), Thomas Forbes (UHN), Mark Wheatcroft (SMH)
Research Site:	Sunnybrook Research Institute
Project:	Development of a novel image analysis software program to plan peripheral vascular interventions (PVI) for patients with peripheral arterial disease (PAD)
Award:	$150,000

SPOTLIGHT: Michael R. Freeman Innovation Award Report
Project: "Validation and Applications of a Biomarker Identifying Arrhythmogenic Right Ventricular Cardiomyopathy". PI: Dr. Robert Hamilton

Description of the project and results to date:
Arrhythmogenic Cardiomyopathy (ACM), still known as Arrhythmogenic Right ventricular Cardiomyopathy (ARVC) in Europe, is a heart muscle disorder in which arrhythmia is a major feature and is out of keeping with the degree of cardiomyopathy. Its clinical diagnostic features were characterized as Task Force criteria by the European Society of Cardiology in 1994, and modified in 2010. The majority of gene discovery for ARVC occurred between 2004 and 2006, and identified a common theme of desmosomal mutations in up to 60% of affected individuals.

Nevertheless, both the clinical and genetic diagnosis remain challenging with incomplete sensitivity for either.

In 2015, I proposed that anti-desmosomal antibodies might be present in ARVC, as they are known to be present and appear to be causative in pemphigus, a blistering disorder of skin, the other organ where desmosomes are important for cell adhesion. We identified that anti-desmoglein-2 antibodies were present in all individuals with Task Force criteria for definite ARVC, and absent in controls. This work was presented as late-breaking science to the European Society of Cardiology, and published in the European Heart Journal (with Dr. Spears as a coauthor). We further assessed athletes with right ventricular enlargement (but no other features of ARVC), and demonstrated that they do not have these antibodies.

Funding from the Freeman award has helped us to recruit additional patients from the Toronto Academic Health Science Network, demonstrating feasibility that has additionally led to Canadian Institutes of Health Research funding of an international multi-centred study to evaluate diagnostic, predictive and prognostic features of this biomarker.

In terms of translation, we have filed several patents around this invention:

- 2019: Method of Diagnosing Arrhythmogenic Right Ventricular Cardiomyopathy. Pending. Germany. Patent Number: H8313030EP.
- 2019: Method of Diagnosing Arrhythmogenic Right Ventricular Cardiomyopathy. Pending. Canada. Patent Number: 3049902.
- 2019: Method of Diagnosing Arrhythmogenic Right Ventricular Cardiomyopathy. Pending. United States. Patent Number: 16/477013.
- 2018: Method of Diagnosing Arrhythmogenic Right Ventricular Cardiomyopathy. Granted/Issued. United States. Patent Number: H8313030PCT.

We have enlisted a Canadian company, Diagnostic Biochem Canada (DBC), to manufacture the In Vitro Diagnostic Device (IVDD) for this test, which will be submitted to both Health Canada and the F.D.A. for regulatory approval. We have enlisted a national laboratory network, Dynacare, Inc., to provide clinical testing as a Laboratory-Developed Test (LDT), providing reports to Canadian heart rhythm specialists.

List of publications resulting from research related to the project:

1. Chatterjee D, Fatah M, Adkis D, Spears DA, Koopmann TT, Mittal K, et al. A Novel Serum Biomarker Identifying Arrhythmogenic Right Ventricular Cardiomyopathy. European Heart Journal. 2017;38(Supplement):1413-4.
2. Chatterjee D, Fatah M, Akdis D, Spears DA, Koopmann TT, Mittal K, et al. An autoantibody identifies arrhythmogenic right ventricular cardiomyopathy and participates in its pathogenesis. Eur Heart J. 2018;39(44):3932-44.
3. A Novel Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Biomarker Anti-DSG2 is Absent in Athletes with Right Ventricular Enlargement (submitted to Int. J. Cardiol.)

Canada-Israel Cardiovascular Innovation Forum (CICI)

The CICI, established in February 2021, is co-Chaired by Dr. Bradley Strauss (Sunnybrook), Dr. Michael Farkouh (HSRLCE) and Dr. Yair Feld (Rambam Healthcare Campus in Israel); and is administered by Liz Thuo at the HSRLCE. The CICI was inspired by the Michael R. Freeman Innovation Award program. We built on the innovation collaboration aspect and expanded the program to include multiple institutions across-Canada and internationally.

The aim of the CICI is:

1. Encouraging early-stage cardiovascular innovations in medical devices and digital health in Canada and Israel
2. Establishing collaboration between Israel and Canada in developing and funding cardiovascular innovations through competitions
3. Growing a network of interested investors and provide a vehicle for joint funding of promising early-stage projects and companies
4. Providing young innovators an education experience in early-stage company development

Below are the institutions that have partnered to make this program possible.

INSTITUTIONAL PARTNERS

Canadian Cardiovascular Society — Leadership. Knowledge. Community.

Hadassah University Hospital

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

Health Innovation Hub

האיגוד הקרדיולוגי בישראל ISRAEL HEART SOCIETY

MEDX xelerator

RABIN MEDICAL CENTER BEILINSON • HASHARON

RAMBAM Health Care Campus

SHEBA Tel HaShomer — The Leviev Cardiothoracic & Vascular Center

Sunnybrook MEDVENTIONS PROGRAM

translational research program

INDUSTRY PARTNERS

Baylis MEDICAL

BAYMED VENTURE PARTNERS — SOURCE · GUIDE · GROW

Integer®

RAMBAM MedTech — technology for health.

TORYS LLP

The inaugural CICI competition was held in March of 2021. We received 31 applications (17 from Canada and 14 from Israel). Of those, the top scoring 9 applicants were selected to present their innovation at an event that took place on April 15, 2021. 170 people registered to attend – including physicians, government officials, innovators, investors, faculty, trainees, and industry reps.

Canadian Presenters:	Israeli Presenters:
Stephanie Buryk-Iggers Company: **SPARKED** **Innovation:** Handheld, non-invasive device for early risk detection of cardiovascular disease	**Lihu Avitov** Company: **Revamp Medical** **Innovation:** The Doraya Catheter - a novel temporary intravenous flow regulator
Daniel Gelman Company: **Aufero Medical** **Innovation:** Device to stabilize contact force during radiofrequency catheter ablation therapy for atrial fibrillation	**Nitai Hanani** Company: **Paragate Medical Ltd.** **Innovation:** Implantable Peritoneal Ultrafiltration Device (IPUD) for continuous and active fluid decongestion in heart failure patients
Surath Gomis Company: **Arma Biosciences** **Innovation:** A handheld device for rapid, continuous remote monitoring of biochemical markers in patients with heart failure	**Elon Reshef** Company: **Invatin Technologies Ltd.** **Innovation:** A novel continuous stroke prevention device
Ali Tavallaei Company: **Magellan Biomedical Inc.** **Innovation:** A novel catheter allowing for accurate localized steering and tracking of endoluminal devices	**Ariel Weigler** Company: **Cuspa Ltd.** **Innovation:** Transcatheter artificial cusp for repair of valve insufficiency
Ryan Tennant Company: No named company **Innovation:** A novel re-entry device for angioplasty of coronary and peripheral chronic total occlusions	

For more information on the 2021 event, please visit the CICI website: https://www.cicvinnovation.com/.

The 2022 competition will close on March 15, 2022 – and an event to showcase the top applicants will take place on May 15, 2022.

Cardiovascular/Diabetes Grant

HSRLCE, Banting & Best Diabetes Centre, UofT Faculty of Medicine, and AstraZeneca partnered to fund a grant in cardiovascular/diabetes research. A total of $1.5 Million was raised to fund this initiative. The purpose of this funding program is to: foster bench to bedside translational research with a focus on innovation and first-in man clinical trials; foster the training of graduate students across disciplines and research institutes; establish the University of Toronto as an international leader in the study of diabetes and heart disease; and encourage collaboration between the BBDC and the HSRLCE. To-date, six awards of up to $250,000 have been given to researchers investigating diabetes and cardiovascular disease.

2018 Recipient

PI:	**Dr. Jason Fish, UHN (HSRLCE)**
Co-Applicants:	Dr. Sara S. Nunes de Vasconcelos (UHN)
Collaborators	Drs. David Cherney (UHN), Filio Billia (UHN)
Research Site:	Princess Margaret Cancer Research Tower, Toronto General Hospital Research Institute
Project:	Elucidating the Pleiotropic Cardioprotective Mechanisms of Empagliflozin on Heart Failure in Type 2 Diabetes Mellitus
Award:	$97,420

2017 Recipient

PI:	**Dr. David Cherney, UHN (HSRLCE/BBDC)**
Co-Applicants:	Drs. John Parker (MSH/UHN), Susanna Mak (MSH/UHN), Mansoor Husain (UHN), Bruce Perkins (MSH/UHN), John Floras (MSH/UHN), Jacob Udell (UHN/WCH), Daniel Drucker (MSH)
Research Site:	Toronto General Hospital, Renal Physiology Laboratory
Project:	iNcretin And TReatment with Inhibition of sodiUm-glucose cotRansportEr-2 combinaTion In Congestive Heart Failure Preserved Ejection Fraction Trial
Award:	$249,863

2016 Recipient

PI:	**Dr. Rulan Parekh, SickKids (HSRLCE)**
Co-Applicants:	Drs. Jason Fish (TGRI), David Cherney (UHN), Mansoor Husain (UHN)
Research Site:	Toronto General Research Institute/ SickKids/ UHN
Project:	Novel Biomarkers of Vascular Dysfunction in Diabetes and End-stage Renal Disease
Award:	$224,960

2015 Recipient

PIs:	**Drs. Graham A. Wright & Idan Roifman, Sunnybrook (HSRLCE)**
Co-Applicants:	Drs. Kim Connelly (St. Mike's), Michael Farkouh (UHN), Nilesh Ghugre (Sunnybrook), Andrew Crean, Harindra Wijeysundera (Sunnybrook), Anna Zavodni (Sunnybrook)
Research Site:	Sunnybrook Health Sciences Centre
Project:	The impact of Diabetic Microvascular Dysfunction on Late Major Adverse Cardiac Events Post Non-ST Elevation Acute Coronary Syndrome
Award:	$247,225

2014 Recipient:

PI:	**Dr. Ravi Retnakaran, Mount Sinai (BBDC)**
Co-Applicants:	Drs. Candice Silversides (UHN); Philip Connelly (St. Mike's)
Research Site:	Mount Sinal Hospital
Project:	A Randomized Controled Trail to Evaluate Exenatide and Insulin Glargine Combination Therapy for the Preservation of Pancreatic Beta-cell Funcation and Endothelial Function in Early Type-2 Diabetes
Award:	$249,340

2014 Recipient:

PI:	**Dr. Kim Connelly, St. Mike's (HSRLCE/BBDC)**
Co-Applicants:	Drs. Richard Gilbert (St. Mike's); Andrew Advani (St. Mike's); Howard Leong-Poi (St. Mike's); David Cherney (UHN); Darren Yuen (St. Mike's)
Research Site:	St. Michael's Hospital
Project:	CD34+ Cell Therapy for Diabetic Cardio-Renal Disease
Award:	$250,000

Collaboration in Heart Failure Research with the Ted Rogers Centre for Heart Research

In November 2014 the Ted Rogers Centre for Heart Research (TRCHR) was formed, enabled by an unprecedented gift from the Rogers family and jointly conceived by SickKids, UHN and UofT. The Centre represented a major investment in basic science, translational and clinical research, innovation, and education in regenerative medicine, genomics, and clinical care of pediatric and adult heart disease. TRCHR's mission is to transform and dramatically improve the future of heart health for children, adults and families across Canada and around the world, through an integrated program of outstanding research, education, and clinical care. Its vision is to provide the world with new diagnoses, treatments, and tools to help people prevent, manage, and survive the devastating consequences of heart failure; and to provide global leadership in the cardiac field and be a magnet for research and clinical talent.

HSRLCE has a collaborative relationship with the TRCHR in terms of personnel, educational programming, and research support. TRCHR's leadership and team members are also members of the HSRLCE. In terms of programming, where in the past the HSRLCE would have had heart failure-focused lectures and visiting professorships, we now partner with TRCHR and publicize their activities to our membership. Prior to COVID, the two Centres jointly held a combined Scientific Day to take advantage of our joint expertise to offer outstanding programming to our common stakeholders. The two Centres have also jointly supported key research programs such as the Cardiovascular Data Management Centre (CVDMC) and the Peter Munk Cardiac Centre Biobank; as well as the Cardiovascular Sciences Collaborative Specialization.

INVESTMENT IN CROSS-UNIVERSITY RESEARCH

HSRLCE is integrated with every teaching hospital engaged in cardiovascular research at University of Toronto. As part of its commitment to advancing collaborative cardiovascular research, the HSRLCE has invested more than $2 million over the last 10 years to support the following research initiatives across University of Toronto and the teaching hospitals:

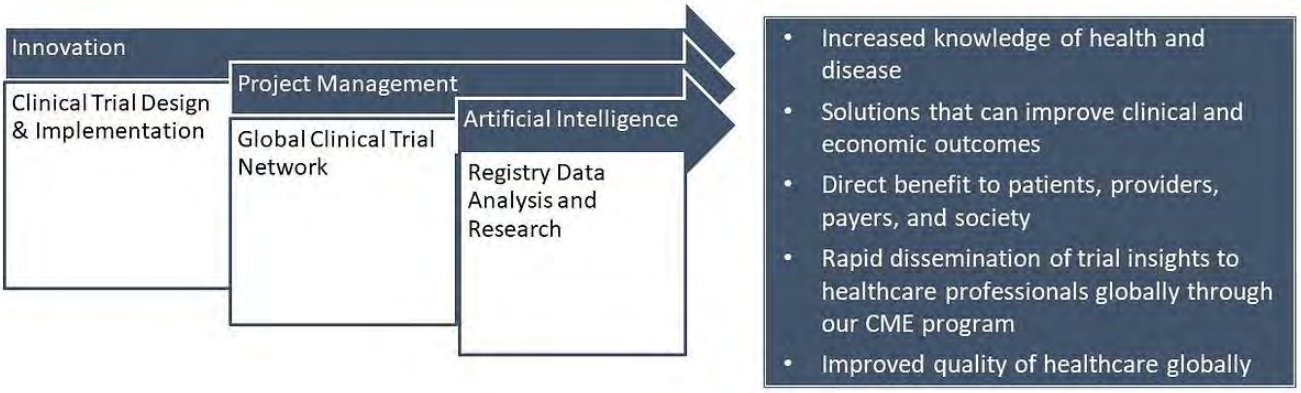
Initiative	**Support Amount**
Athlete's Heart Laboratory (Now Sports Cardiology Toronto) A cross-disciplinary research group that examines the impact of intensive exercise training on cardiac health outcome.	$45,000
Cardiovascular Biobank (UHN's PMCC) The PMCC CV Biobank was established at UHN with the support of the HSRLCE, with the ultimate goal of biobanking samples for every patient seen at the PMCC. The plan was to establish biobanking as a routine part of patient care. Mission: to establish and maintain a standardized approach to human specimen accrual, management, distribution and use for research purposes. Objective: to improve researchers' accessibility to blood and tissue specimens from patients suffering from cardiac and vascular disease and to create a framework that promotes appropriate standards of quality and security.	$255,000
Cardiovascular Data Management Centre (SickKids, St, Mike's, Sunnybrook, UHN) The CVDMC was founded in 2012 as an initiative of the Division of Cardiac Surgery in the Faculty of Medicine at the University of Toronto, and with support from HSRLCE. CVDMC was created to solve a highly prevalent and detrimental problem associated with the University of Toronto model, namely that patient populations are scattered across multiple University-affiliated hospitals, each being an independent legal entity with its own set of policies and procedures. The Centre served the cardiovascular disease community by forging linkages between databases, and by providing access to the data for researchers and clinicians, risk adjusted reports for clinical quality improvement initiatives, and statistical services to participants.	$465,000
Large Animal Models Facility (Sunnybrook) HSRLCE supported the establishment of the Large Animal Testing Facility (est. 2009) at SRI as the primary hub in Toronto to promote the integration of large animal cardiovascular disease models with novel imaging modalities (X-ray, MRI, CT, ultrasound, and optical coherence tomography). HSRLCE facilitated access to these incredible resources via support for technical staff, materials and coordination. New multidisciplinary projects emerged from this joint partnership resulting in several new funding mechanisms. Research at the clinic has included: reperfused cardiac infarction, chronic total occlusion, myocardial ischemia, intraplaque hemorrhage, aortic atherosclerotic plaques with hemorrhage, metabolic changes during heart failure, and breast cancer tumour ablation in porcine and rabbit models.	$360,000

Toronto Centre for Microvascular Medicine (UofT) TCMM combines basic science and clinical medicine to advance new microvascular knowledge and technologies with promising translational and clinical applications. With a multidisciplinary approach, the TCMM hopes to illuminate the microvascular system's importance and relevance to major health and disease states. In doing so, the TCMM will attract attention and resources to prioritize microvascular research in the cardiovascular sciences.	$250,000
Centre for Microvascular Medicine, Munich The CM³ was designed to extend the translational abilities of the Toronto Centre for Microvascular Medicine (TCMM) under the leadership of Dr. Steffen-Sebastian Bolz. In Munich, the CM³ was designed to take advantage of the high concentration of leading academic research institutions and biotech companies. Academically, it will advance international collaborations, strengthen ties between German and Canadian academic institutions, broaden the scope of discovery and training and provide a flexible means to model, test and evaluate new paradigms in research and education.	$364,000
Toronto Stroke Research Network (UHN, St. Mikes, and Sunnybrook) The Network combines the expertise, strengths and patient populations of 3 University of Toronto Stroke Centers (St. Michael's Hospital, Sunnybrook Health Sciences Centre, and University Health Network) and Stroke researchers across the Greater Toronto Area with the aim of becoming an international leader in stroke clinical practice, research and education.	$50,000
Transgenic Physiology Lab (UofT) The TPL platform is one of the original four core platforms developed by the HSRLCE at its inception in 2001. TPL's mandate is to provide mouse cardiac physiological assessment of mice, to generate mouse models of disease, and to allow acute genetic manipulation of mice as well as mouse tissues/cultures using viral-based gene transfer methods.	$237,000

INVESTMENT IN INTERNATIONAL RESEARCH

Worldwide Network for Innovation in Clinical Education and Research:

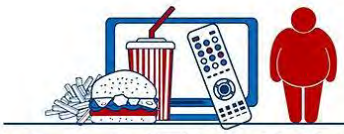
The Network for Innovation in Clinical Research (NICR) was birthed from a University of Toronto initiative to conduct single and multicentre trials under the leadership of the University's cardiovascular clinical investigators. This vision was then expanded to include international partners – and WNICER was formed (founded by Dr. Michael Farkouh). WNICER's membership includes biomedical researchers, clinician scientists, cardiologists, experts in diabetes and cardiometabolic disorders, nutritional scientists and epidemiologists. WNICER's mission is to improve human health through better understanding the interrelationship of chronic diseases. This is achieved through collaborative and innovative approaches to research, clinical trials, and education.



WNICER targets major global health issues and improves human health through better understanding the interrelationship of chronic diseases

OBESITY

- It is estimated that over **1.4 billion adults** over the age of 20 are overweight.
- **Obesity is a major risk factor** for developing diabetes & cardiovascular disease.



Almost 90% of people living with type 2 diabetes are overweight or obese.

DIABETES

- There are over **400 million people** with diabetes worldwide, with numbers estimated to rise to 600 million by 2030.
- The WHO projects that diabetes will be the **7th leading cause of death in the next 15 years.**

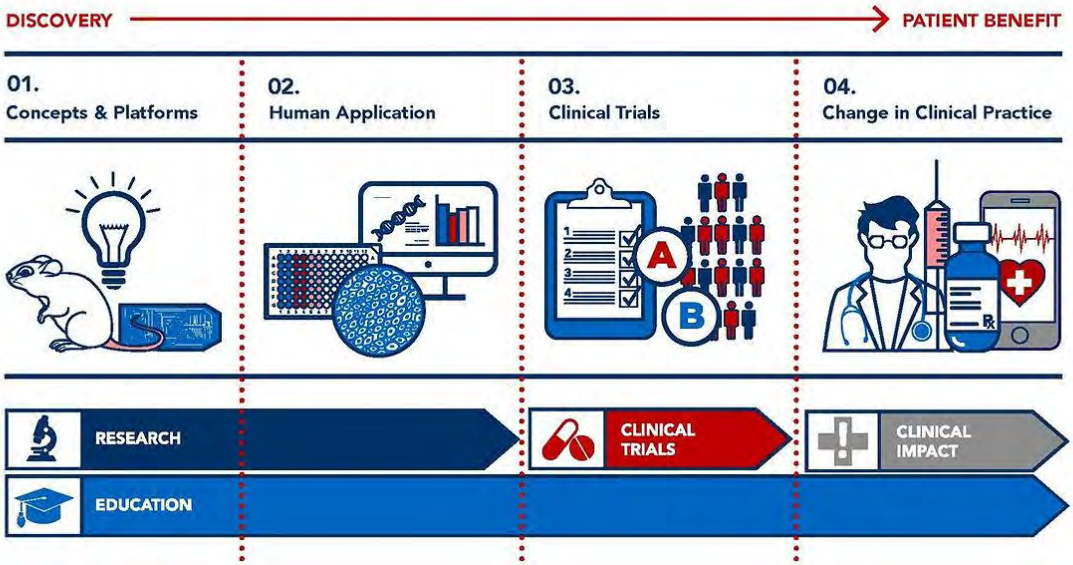
70% of diabetics 65 or older die from some form of heart disease.

CARDIOVASCULAR DISEASE

- Cardiovascular disease remains the **#1 cause of death worldwide** with **17.5 million deaths** each year (accounting to nearly half of all deaths caused by non-communicable diseases).

! Global costs of cardiovascular diseases are projected to reach **$1.04 trillion by 2030.**

WNICER implements programs that shorten the time from discovery to patient benefit:



OVERVIEW: RESEARCH PRODUCTIVITY

PERIOD ASSESSED: 2016- 2021

The research data below represents 141 HSRLCE members. It should be noted that HSRLCE membership does not include all investigators engaged in cardiovascular research at UofT or its allied teaching hospitals. There are many investigators in the Departments of Medicine, Surgery, Paediatrics, and other basic and applied science departments who directly or indirectly engage in cardiovascular research but are not members of the Centre. As such, the research productivity of the HSRLCE noted below under-represents the full breadth and depth of cardiovascular science at UofT.

Global Comparisons:

UofT's research productivity in cardiology and cardiovascular medicine was measured against that of five other academic institutions: Harvard University, University of California Los Angeles, University College London, University of British Columbia, and McGill University. UofT was ranked 2nd, after Harvard University. HSRLCE's (specifically) bibliometrics data is also provided.

Totals Global Comparisons 2016-2021					
Institution (Subject area: cardiology and CV medicine)	**Scholarly Output**	**Citation Count**	**Citations per Publication**	**Cited Pubs (%)**	**Field-Weighted Citation Impact**
Harvard University	12,861	240,683	18.7	83.2	2.18
University of Toronto	**4,962**	**83,771**	**16.9**	**80.3**	**2.1**
University of California Los Angeles	4,257	69,838	16.4	80.8	1.8
University College London	2,713	55,768	20.6	83.5	2.21
University of British Columbia	2,152	41,670	19.4	83.3	2.3
McGill University	1,389	27,973	20.1	82.9	2.08

Bibliometrics – HSRLCE Members (2016-2021):

Data is for publications in multiple fields and subject areas; not just cardiology/CV

- Scholarly Output: 6,745
- Times Cited: 176,105
- Citations per Publication: 26.1
- Percentage of Documents Cited: 85.1%
- Percentage of International Collaborations: 51.6%
- Field-Weighted Citation Impact: 3.05

HSRLCE Patents and Commercialization of Inventions:

For the 2016 to 2021 period, HSRLCE members:

- Held 53 patents;
- Commercialized 14 inventions; and
- Filed invention disclosures to commercialize an additional 44 inventions

*** Please see the appendix for more details*

OVERVIEW: RESEARCH FUNDING

PERIOD ASSESSED: 2015/16 – 2020/21

In the six-year period between 2015 and 2021, HSRLCE members received a total of 4,548 awards totaling $496 million.

Sponsor Type	Sponsor Subtype	Funding
Government, Other	Federal Government, Other	$ 20,475,767.96
	Networks of Centres of Excellence	$ 612,163.45
	Ontario Provincial Government	$ 17,443,548.47
	Provincial Centres of Excellence	$ 543,904.76
	United States Government	$ 8,066,027.56
	Government, Other Total (282 Grants)	**$ 47,141,412.20**
Not-for-Profit Sector	Internal	$ 54,892,704.91
	Not-for-Profit	$ 155,129,251.87
	Research and Academic Sector	$ 26,175,601.82
	Not-for-Profit Sector Total (2,531 Grants)	**$ 236,197,558.60**
Tri-Agency	CIHR	$ 116,495,771.32
	NSERC	$ 13,076,922.02
	SSHRC	$ 148,331.20
	Tri-Agency Institutional Program Secretariat	$ 23,869,666.19
	Tri-Agency Total (1,087 Grants)	**$ 153,590,690.73**
Private Sector & Industry	**Private Sector & Industry Total (648 Grants)**	**$ 59,159,100.89**

*** Please see the appendix for more details*

HSRLCE ADMINISTRATIVE/ORGANIZATION STRUCTURE

HSRLCE is an organization for the cardiovascular research community in Toronto, run by the cardiovascular research community of Toronto. The members of the Centre are faculty members within the research community in Toronto, holding appointments in various departments and working in different research areas. Members of the Centre occupy all the seats on the operational and advisory committees.

The Director of HSRLCE reports to the Vice Dean, Research & Innovation; and the Dean, Temerty Faculty of Medicine. The Director has one direct report: Business, Communications and Programs manager.

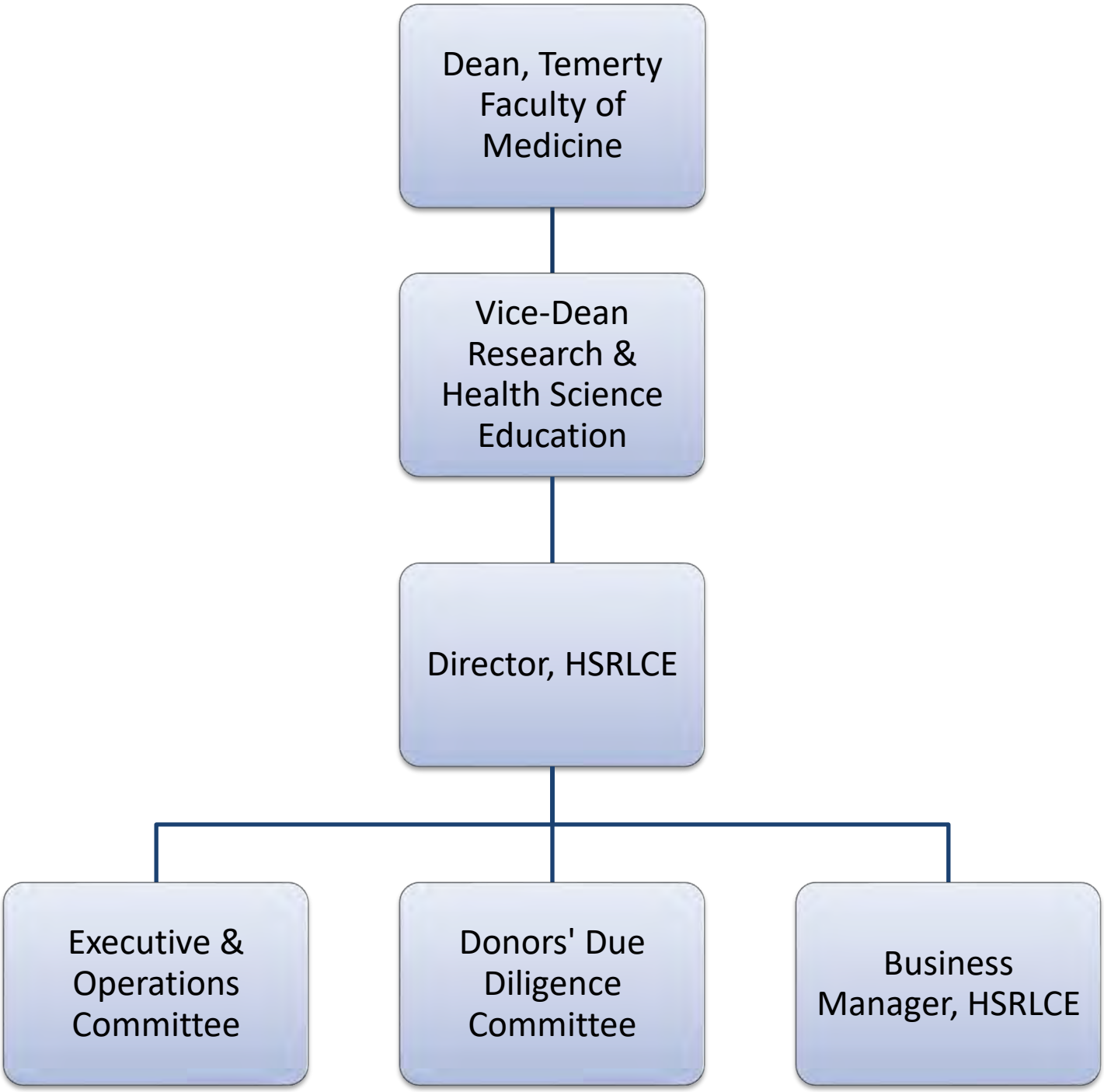
The Centre's main governing body, the Executive & Operations Committee, represents every constituency of the cardiovascular sciences community within the Toronto Academic Health Science Network (TAHSN). Their guidance has broadened the impact of the Centre and continues to facilitate the research priorities developed through the Centre's strategic planning. This Committee also serves as the Educational Activity Committee – whose purpose is to determine themes, propose talk topics, and identify potential speakers for HSRLCE's Annual Michael J. Sole Cardiovascular Scientific Day and Distinguished Visiting Professor Series.

The Director is also guided by the Donor's Due Diligence Committee comprised of representatives of the original Donors as well as representatives from the Temerty Faculty of Medicine.

HSRLCE STAFF

Name	Position	Role
Michael Farkouh, MD *(2013-Present)*	Director	Financially accountable, directs strategic direction, supervises personnel. Responsible for all academic aspects of HSRLCE and for the management of University resources.
Liz Thuo, MBA *(Jan. 2014 to Mar. 2015; and Feb 2016-present)*	Business, Communications & Program Officer	Oversees the administrative and financial operations for the HSRLCE. This role ensures the effective and efficient management of financial, administrative, human resources, communications, research, and educational activities, and initiatives in support of the strategic goals of the Centre.

GOVERNANCE & ADMINISTRATIVE STRUCTURE



COMMITTEES: MEMBERSHIP & MANDATE

EXECUTIVE & OPERATIONS COMMITTEE - Provides guidance to the Director on matters of strategic scientific and research-related direction. Makes operational and policy-related decisions including financial, administrative, research-related and educational-related issues of the Centre.	
Members:	**Dr. Michael Farkouh** Director, Heart & Stroke/Richard Lewar Centre of Excellence, University of Toronto Peter Munk Chair in Multinational Clinical Trials Vice-Chair Research, Department of Medicine, University of Toronto Professor of Medicine, University of Toronto **Dr. Justin Nodwell** Vice Dean, Research & Health Science Education Temerty Faculty of Medicine University of Toronto **Dr. Kim Connelly** Scientist and Cardiologist, St. Michael's Hospital Associate Professor, Department of Medicine, University of Toronto Executive Director, Keenan Research Centre for Biomedical Science **Dr. Myron Cybulsky** Research Division Head, Toronto General Hospital Research Institute Professor, Department of Laboratory Medicine & Pathobiology, University of Toronto **Dr. Shaun Goodman** Associate Head, Division of Cardiology, Department of Medicine, St. Michael's Hospital Professor and Heart & Stroke Foundation of Ontario (Polo) Chair Department of Medicine, University of Toronto **Dr. Peter Juni** Professor of Medicine and Epidemiology, IHPME, University of Toronto Director, Applied Health Research Centre, St. Michael's Hospital Scientific Director, Ontario COVID-19 Science Advisory Table **Dr. Dennis Ko** Director, Schulich Heart Research Program, Sunnybrook Research Institute Senior Scientist, ICES and Interventional Cardiologist, Sunnybrook Health Sciences Centre Associate Professor, Department of Medicine and IHPME, University of Toronto **Dr. Douglas Lee** Senior Core Scientist, ICES Professor, Department of Medicine and IHPME, University of Toronto Cardiologist, Peter Munk Cardiac Centre and University Health Network

	Dr. Seema Mital Head of Cardiovascular Research, Hospital for Sick Children Professor of Paediatrics, University of Toronto Scientific Lead, Ted Rogers Centre for Heart Research **Dr. Bradley Strauss** Staff Cardiologist, Sunnybrook Health Sciences Centre Reichmann Chair in Cardiovascular Research, Sunnybrook Health Sciences Centre Professor, Department of Laboratory Medicine & Pathobiology, University of Toronto

DUE DILIGENCE COMMITTEE- To fulfil stewardship and fiduciary responsibilities to founding donors; also acts as an external advisory committee.	
Members:	**Dr. Michael Farkouh** Director, Heart & Stroke/Richard Lewar Centre of Excellence, University of Toronto Peter Munk Chair in Multinational Clinical Trials Vice-Chair Research, Department of Medicine, University of Toronto Professor of Medicine, University of Toronto **Dr. Justin Nodwell** Vice Dean, Research & Health Science Education Temerty Faculty of Medicine University of Toronto **Justice Kathryn Feldman** *(representative of the Richard Lewar Family)* Justice of the Court of Appeal for Ontario **Natalie Gierman** Sr Manager, Health Systems and Research – Heart & Stroke Foundation **Avril Goffredo** Executive Vice President – ON & NU – Heart & Stroke Foundation An Advancement Officer from the Office of Advancement, University of Toronto

FINANCIAL OVERVIEW

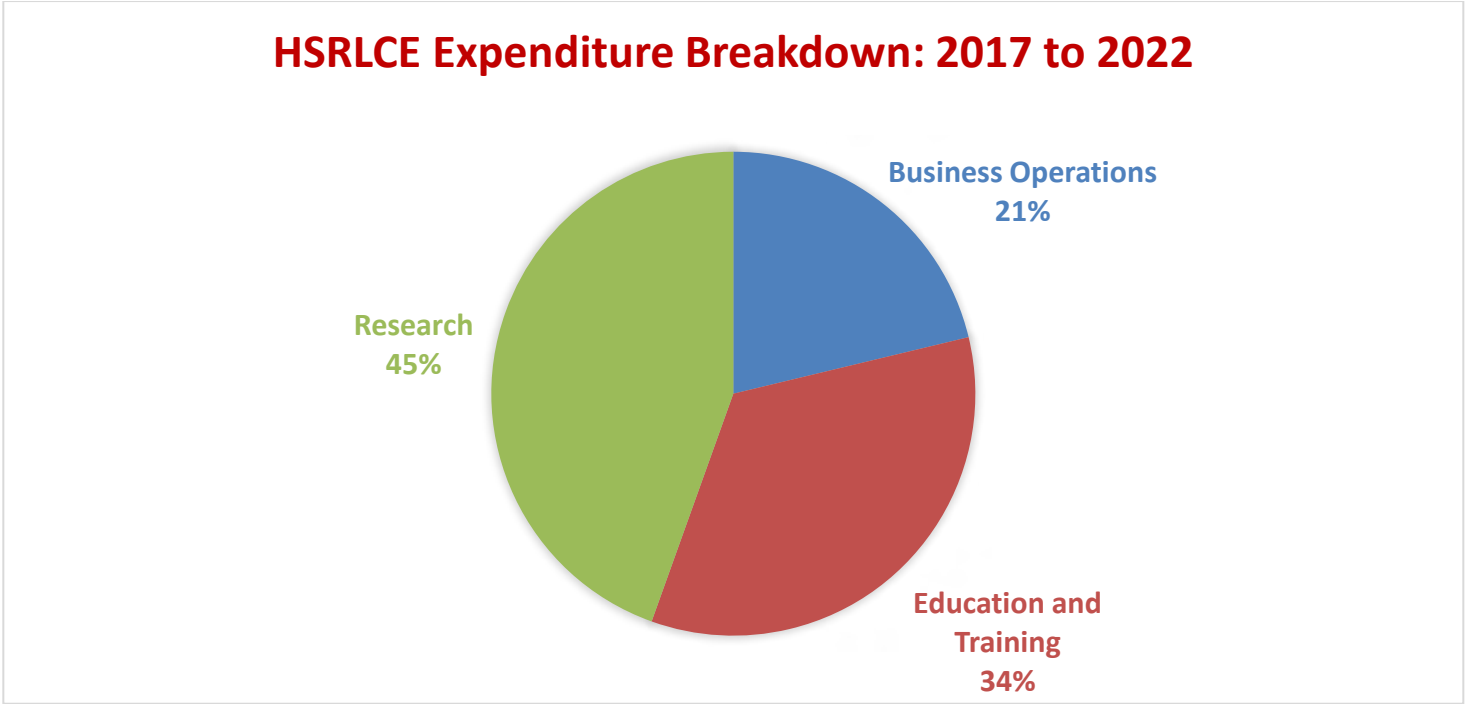
Over the past five years (2017 - 2022)….

- HSRLCE had an average annual expenditure of around $911,000. The main spending categories are: administration, education, training, and research.
- HSRLCE's annual average revenue was $675,000; $3.04 million over the last 5 years. Sources of revenue are: investment income from short-term investments, income from endowments, and programmatic sponsorship (unrestricted grants) from industry.

HSRLCE EXPENDITURE SNAPSHOT FOR 2017 TO 2022

		Five Year Totals	Average Per Year
Operations	Compensation, Office Operations, Meetings, Fundraising	$ 967,914	$ 193,583
Education	CSCP, DVP Lectures, Science Day, National & Intl. Seminars	$ 1,112,150	$ 222,410
Training	Student Awards (Undergrad, Graduate, Fellows)	$ 447,750	$ 89,550
Research	Collaboration with Other Institutes, Programs	$ 277,004	$ 55,400
Research	Initiatives (CVDMC, TCMM, TPL, Large Animal Facility)	$ 227,958	$ 45,592
Research	Platforms (Diabetes, Brain, Innovation, Athletes)	$ 1,058,400	$ 211,680
Research	International Collaborations (Research, Initiatives)	$ 107,228	$ 21,446
Research	New Recruits' Salary Support & Young Investigator Awards	$ 357,573	$ 71,515

TOTALS:	Business Operations	$ 967,914	$ 193,583
	Education and Training	$ 1,559,900	$ 311,980
	Research	$ 2,028,162	$ 405,633
	Totals	**$ 4,555,976**	**$ 911,195**



REPORT OF MEMBERS

HSRLCE members' views and visions have been addressed in other sections of this report; some of the members whose research we have supported have written reports concerning their research and what impact HSRLCE's support has had on their work.

REPORT OF LEARNERS

This section shares exit reports from trainees written in the year they were awarded. This section speaks to the impact receiving a HSRLCE award has had on their education journey. Below are a few of the testimonials:

Trainee: **Steve Botts,** MD/PhD Student
Supervisor: **Dr. Kathryn Howe,** University Health Network
Project: **Extracellular vesicles: Novel biomarkers for abdominal aortic aneurysm progression**

2019/20 Recipient

I would like to offer my sincere thank you for the *HSRLCE/HSBC Future Research Leaders Internships Award*. I am currently in my third year of the combined Doctor of Medicine and Doctor of Philosophy (MD/PhD) program at the University of Toronto.

Prior to beginning this program, I studied therapeutic strategies for necrotizing enterocolitis, a devastating intestinal disease associated with reduced blood flow and high mortality in premature babies, at The Hospital for Sick Children (8 co-authored publications and several national/international conference presentations). After exploring potential specialities in my first year of medical training, I am similarly drawn to vascular surgery (focusing on diseases of the vascular system – arteries, veins, and lymphatics) as a future career. I began my PhD in vascular disease this September, where I currently investigate potential treatment strategies for abdominal aortic aneurysms by targeting the cells which compose diseased blood vessels.

Outside of my studies, I serve as VP Publications on the University of Toronto's Medical Society and Director of Toronto Medical Student Publications Inc., where I oversee the University of Toronto Medical Journal (UTMJ), our arts and culture magazine (Palette) and various other published materials. I was also on the coordinating team for our 2020 Medical Student Research Day, a 1-day conference that showcases research projects undertaken by University of Toronto medical students, and now serve as the co--Lead for the 2021 Surgical Exploration and Discovery Program (SEAD), a two-week program which exposes medical students to surgical specialities through observerships and hands-on workshops. In my spare time, I enjoy training and competing in powerlifting (a strength sport) and listening to podcasts concerning medicine, fitness, philosophy, and everything in between.

Sincerely,
Steven Botts

Trainee: **Kimberly Lau,** MD Candidate, Year 3
Supervisor: **Dr. Ana Carolina Alba,** University Health Network
Project: **Validation of the Accuracy of Venus 2000 to Measure Central Venous Pressure**

2018/19 Recipient

My name is Kimberley Lau and I am currently entering my third year of medical school at the University of Toronto. Before medicine, I graduated from the Bachelor of Health Sciences (Honours) Program at McMaster University. Studying medicine and conducting medical research has been a dream of mine for a long time. Growing up, I witnessed many of my close relatives suffer and pass away from illness. As a child, I dreamt that one day I would be able to provide the help I could not provide for my own loved ones, whether that be through a career in medicine and/or a career in medical research.

From the bottom of my heart, thank you for the *HSRLCE/HSBC Future Research Leaders Internships Award*. It is difficult for many medical students, like me, to keep up with our studies while finding ways to keep up with the costs of school, while also pursuing other interests such as in research.

Going forward, I aspire to become a cardiologist as well as a heart failure researcher. This summer, I worked in heart failure research at Toronto General Hospital and my passion towards quality of care research has grown. When planning my summer, I considered many different jobs and research opportunities. I was not too concerned about the financial compensation of each job when deciding between opportunities. Instead, I considered my own interests, which aligned most closely with the cardiology research position I was offered at Toronto General Hospital. I had a wonderful summer learning about heart failure and cardiology research and interacting with patients in clinics under the guidance of many intelligent mentors at a world-renowned institution. Thank you for making this possible!

Sincerely,
Kimberley Lau

Trainee: **Madeleine Rudolph,** MD Candidate, Year 3
Supervisor: **Dr. Michael Farkouh,** University Health Network
Project: **HERMES: Modelling symptom expression according to gender in order to predict CAD**

2017/18 Recipient

Thank you from the bottom of my heart for your generous support. This funding enabled me to spend my summer in one of the top cardiology research centres in the world, under the careful and supportive mentorship of current leaders in the field. The value of this experience cannot be overstated: I learned an incredible amount about the clinical research process, from the inception and design of a study to the process of outlining and preparing a manuscript. I was able to gain experience in literature review, chart review, and an understanding of research ethics.

Beyond my own personal growth, I also feel that I was able to make real contributions to furthering our understanding of the symptomatology of coronary artery disease in women. The hope is that this in turn might help physicians reverse the worrying trend of these diseases going underrecognized and undertreated in their female patients. This is an issue that I care about deeply as a woman studying medicine, and the support of this funding removed financial barriers that made it possible for me to dedicate myself to this fulfilling and important work.

Moving forward into my career as a physician, I know that the skills, experiences, and professional connections that this internship allowed me to foster will open doors, enable me to continue to contribute the field of cardiology research, and ultimately benefit my future patients. Thank you again for making this opportunity possible.

Sincerely,
Madeleine Rudolph

As mentioned earlier, HSRLCE provides support (trainee awards) for the CANHEART SPOR initiative aimed at leveraging big data to conduct innovative cardiovascular clinical trials. Below are exit reports from two of the awardees under this program:

Trainee: **Neda Pirouzmand**
Supervisor: **Dr. Dennis Ko**, Sunnybrook Health Sciences Centre
Project: **A systematic review on the effectiveness of using e-health technologies to improve outcomes in patients with cardiovascular disease**

SUMMER RESEARCH BACKGROUND

I focused on two projects over the summer period. The first project involved developing text messages as an intervention to improve transitions in care for patients after a hospitalization with acute coronary syndrome. As an example, the simplest text message might say, "Have you remembered to take you medications today?" This first project was completed, and a bank of text messages has been sent to a Research Ethics Board for approval. When the study is carried out, the effectiveness of the text messages will be evaluated against medical compliance, mortality, and readmission after one year follow-up. The second project was a systematic review of studies evaluating e-health technologies in the secondary prevention of cardiovascular disease. E-health involves using the Internet to record data that is transmitted, stored, and retrieved electronically for healthcare. Electronic medical records, wearable sensors, and mobile apps are e-health technologies. As an example, wearable (and sometimes wireless) electrocardiogram (ECG) monitors can measure an ECG and send readings to a patient's healthcare practitioner for potential change in management or urgent treatment.

DETAILS OF SUMMER RESEARCH

Beginning in the month of June, I familiarized myself with the available literature on e-health interventions in cardiovascular disease. A significant proportion of this time was spent on texting trial interventions (most were randomized controlled trials). Drawing on paper protocols, I learned from the text trial design process of experienced researchers who had written highly cited papers with low risk of bias1,2. I noticed these protocols were often driven by psychological theories of behaviour such as Icek Ajen's Theory of Planned Behaviour and Albert Bandura's Theory of Human Agency3,4. Takeaways from various theories were compiled, along with more modern commentaries, critiques, and updates to them. In addition to protocols, I looked at pilot studies or focus groups conducted in preparation for larger trails5,6. This part of the process revealed strategies to improve participants' engagements with texts, such as addressing participants by their first name (for e.g., the earlier text message may say, "Hi Bob, have you remembered to take your medications today?").
In July, I was given the initial drafts of ~50 text messages that I edited using the research mentioned above. A key challenge was balancing brevity with content. Longer text messages were more likely to lose patient engagement. By mid-July, I had also begun working on my second project. The first step of the second project was to explore systematic reviews in the cardiovascular e-health space. The purpose of this was to get an idea of research questions that had already been asked and identify potential opportunities for my own review.

During the month of August, I built on the database from July. I compiled the texting trials from earlier in the summer into a database. Next, I added e-health studies from other categories such as wearables and phone applications (most were RCTs). I carefully evaluated each study for risk of bias using a systematic framework. At this point, I had not conducted a systematic search. The purpose was to explore the literature and investigate citations from papers that I had read previously. After multiple meetings with Dr. Ko during which I pitched research opportunities from my own brainstorming, it became clear that e-health research was quite saturated. Many of my ideas would not be able to stand as their own paper or project. Eventually, we devised a potential opportunity that I am continuing to work on.

NEXT STEPS

Thank you for this summer studentship opportunity. Coming from a predominant wet lab background, this was my first in depth experience with clinical research. While I am in school, I have spent September building on the August database and a systematic review project. A protocol has almost been completed for submission to PROSPERO in order to begin a systematic review on cardiovascular e-health trials and their reporting methods.

THANK YOU NOTE

Thank you to those at CANHEART who took the time to provide feedback on my initial proposal. I am grateful to have had the opportunity to work with and learn from Dr. Ko under this studentship.

REFERENCES

1. Bermon A, Uribe-Rodríguez AF, Pérez-Rivero PF, et al. Evaluation of the efficacy and safety of text messages targeting adherence to cardiovascular medications in secondary prevention: the txt2heart Colombia randomised controlled trial protocol. BMJ Open. 2019;9:e028017. doi: 10.1136/bmjopen-2018-028017
2. Klimis H, Thiagalingam A, Chow CK. Text messages for primary prevention of cardiovascular disease: the TextMe2 randomised controlled trial protocol. BMJ Open. 2020;10:e036767. doi: 10.1136/bmjopen-2020-036767
3. Ajzen, I. The Theory of Planned Behaviour. Organization Behaviour and Human Decision Processes. 1991;50: 179-211. Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.317.9673&rep=rep1&type=pdf
4. Bandura, A. Human Agency in Social Cognitive Theory. American Psychologist. 1989. Available from: https://www.uky.edu/~eushe2/Bandura/Bandura1989AP.pdf
5. Ross ES, Sakakibara BM, Mackay MH, Whitehurst DGT, Singer J, Toma M, Corbett KK, Van Spall HGC, Rutherford K, Gheorghiu B, Code J, Lear SA. The Use of SMS Text Messaging to Improve the Hospital-to-Community Transition in Patients With Acute Coronary Syndrome (Txt2Prevent): Results From a Pilot Randomized Controlled Trial. JMIR Mhealth Uhealth. 2021;9(5):e24530. doi: 10.2196/24530.
6. Redfern J, Thiagalingam A, Jan S, Whittaker R, Hackett ML, Mooney J, De Keizer L, Hillis GS, Chow CK. Development of a set of mobile phone text messages designed for prevention of recurrent cardiovascular events. Eur J Prev Cardiol. 2014 Apr;21(4):492-9. doi: 10.1177/2047487312449416.

Trainee: **Hifza Buhari**
Supervisor: **Husam Abdel-Qadir,** Women's College Hospital
Project: **Does Sex increase the Risk of Stroke in Patients with Atrial Fibrillation?**

INTRODUCTION

Atrial fibrillation (AF) is the most common irregular heart rhythm1. A severe complication of AF is development of thromboembolism and stroke; those with AF are five times more likely to develop a stroke than the general population2. Therefore, for patients diagnosed with AF, an important consideration is if anticoagulative therapy is warranted. To determine the optimum balance between stroke mitigation and hemorrhagic risk, several risk prediction models were developed; the more famous model being the CHA2DS2VASc score3. The CHA2DS2VASc score assigns one point each to congestive heart failure, hypertension, diabetes mellitus, vascular disease, age >65, and female sex, and two points for age ≥75, or for a previous stroke or transient ischemic attack4. It has a modest predictive value with a c-statistic <0.653.

A large controversy surrounding the CHA2DS2VASc score is if female sex is an independent risk factor for developing stroke. A systematic review published in 2015 by Chapa et al. found 9 articles which provided evidence for increased stroke risk in females with AF while seven articles found no or reduced association5. A meta-analysis from 2018 pooled results of 44 studies (993,603 patients) and found females at an increased risk of stroke with a hazard ratio (HR) of 1.24 (95% confidence intervals [CIs]: 1.14-1.36)6. We reviewed the literature and identified several potential explanations for the contention. Recently, a paper published by Nielson et al. in 2018 proposed female sex as a risk modifier rather than a risk factor10. They found that while there was no difference in thromboembolic risk in males versus females when the CHA2DS2VA was 0 (i.e. no other risk factors), as the CHA2DS2VA scores increased (1 through 6 excluding 3), females had a higher risk of stroke than men10. Hence female sex may interact with other risk factors to accentuate the risk of stroke in atrial fibrillation.

Secondly, females live longer than males on average, and tend to develop cardiovascular disease at an older age than men11. As old age is a risk factor for stroke, studies which do not account for age as a continuous variable and instead as a categorical variable could miss the interaction between age and sex6,12. Third, we hypothesize that there are sex-based differences in the medical treatment of comorbid conditions when women are compared to men.

RESEARCH DESIGN

We conducted a retrospective cohort study of community-dwelling individuals (i.e. not residing in long-term care facilities) who were newly diagnosed with AF in Ontario between April 2007 and March 2019 and for who we had LDL data available 1 year before AF diagnosis. As Ontario residents receive universal health coverage through the Ontario Health Insurance Plan, data was collected through administrative datasets linked using unique encoded identifiers and analyzed at ICES. The data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act which does not require review by a research ethics board.

This base cohort was developed for a previous research study. For each patient, a new diagnosis of AF will be identified using a validated algorithm using hospital discharge records or four physician billing claims within 365 days for AF. The key exposures are sex, age, congestive heart failure, hypertension, previous stroke or TIA, vascular disease, and medications including antihypertensives such as angiotensin-converting enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARBs), Calcium Channel Blockers (CCBs), statins, and hypoglycemic agents. The primary outcome will be stroke (hemorrhagic or ischemic) with death as a competing risk. Cause-specific hazard regression was used to study the association of sex with stroke rate **within** one year with progressively increasing list of covariates in four models. Model 1 only included CHA2DS2- VASc factors as predictors and analyzed age as a categorical variable where as Model 2 modelled age as a continuous variable. Model 3 further added differences in stroke risk factor treatment such as LDL levels, treatment with statin , P2Y12 and ACE inhibitors. Finally, Model 4 further accounted for location of AF diagnosis (ED, hospital, or outpatient) and neighbourhood marginalization index (measure of regional socioeconomic status).

RESULTS

Our cohort consisted of 183,909 community-dwelling individuals aged ≥66 years diagnosed with AF between April 2007 - March 2019 who met study inclusion criteria. The median age was 77 (IQR 72-83), Female 79; IQR 73-84), Male 76 (IQR 71-82). Women were older and less likely to be diagnosed in an outpatient setting. Women with AF were more likely to be of lower SES (deprivation quintiles; higher quintiles equal greater deprivation). Women had higher cholesterol (Mean ± SD; 4.43 ± 1.13 vs. 3.86 ± 1.0, p<0.001), LDL (2.33 ± 0.94 vs. 2.06 ± 0.86, p<0.001), and triglyceride levels (1.40 ± 0.67 vs. 1.33 ± 0.69, p<0.001) at baseline, but more men were on statin therapy (68.0% vs 58.5%, p<0.001). Women were more likely to be seen by a GP, but less likely to be seen by a cardiologist at baseline.

Crude Outcomes

Of the 183,909 individuals followed over 365 days, there were 2,810 (1.5%) strokes (2,491 (1.4%) ischemic, 147 (0.2%) hemorrhagic). The crude risk of ischemic stroke was higher in women (1.6% vs. 1.2%, p<0.001). There were 23,230 (12.6%) deaths (10,071 (11.9%) female, 13,159 (13.3%) male). One year after diagnosis of AF, men were more likely to be on full-dose anticoagulation (24.6% vs 22.9%, p<0.0001) whereas women were treated with sub-therapeutic doses of anticoagulation (18.7% vs 14.1%, p<0.0001). Men continued to have higher statin exposure compared to women (71% compared to 61.6%, p<0.0001).

Association of Stroke Risk Factors and Their Management with Female Sex

Female sex conferred a 14% increased risk of stroke in Model 1 (hazard ratio [HR] 1.14; 95% CI 1.06 – 1.23, p= 0.0005). Age as a categorical variable, hypertension, previous stroke/TIA, and diabetes were also associated with higher stroke incidence. In Model 2, in addition to CHA2DS2-VASc risk factors age was further assessed as a continuous variable rather than a categorical variable, which reduced risk of stroke by 3% (HR 1.11; 95% CI 1.03 – 1.20), p<0.01). Adjusting for treatment differences (Model 3), including anti-platelets, anticoagulants, statins, ACE-I/ARBs and LDL values further reduced stroke risk in women further (HR 1.08; 95% CI 1.00 – 1.17,

p<0.05). Model 4 which further accounted for location of diagnosis (in-patient vs hospital) and SES status did not translate to a significant change in stroke risk (HR 1.06; 95% CI 0.99 – 1.15, n.s).

DISCUSSION

Female sex was associated with higher crude stroke rates, older age, lower SES, more diagnosis in the ED, and less treatment of stroke risk factors. When adjusting for these baseline differences, female sex was not independently associated with stroke rate in people with incident AF. Higher stroke rates for women than men with AF may be due to risk factor undertreatment, suggesting that sex-based disparities in stroke risk in AF may be ameliorated by equitable risk factor treatment