Cardiovascular Sciences Collaborative Program
17th Annual Student Research Day

The 17th Annual Cardiovascular Sciences Collaborative Program (CSCP) Student Research Day was held on Wednesday, April 13, 2016. Each year the Research Day provides trainees an opportunity to present their research to their peers in a welcoming environment promoting discussion and the free flow of ideas. The event provides a platform for expression of scientific ideas and inspiration for the mind, pushing the boundaries of current scientific paradigms in the field of cardiovascular research. Dr. Carin Wittnich, CSCP Director, led the day with opening remarks highlighting the excellence and diversity of the CSCP with Alan Lam, Chair of the Organizing Committee, briefing the audience on the events of the day. This year, the Organizing committee offered "lightning talks" in addition to the standard presentations to the students. The morning continued with the students sharing their research aimed at improving the treatment and prevention of cardiovascular disease, followed by inspiring presentations from our guest speakers, Professors Tara Moriarty, Faculty of Dentistry, and Scott Heximer, Faculty of Medicine. Awards were presented to students receiving the "Bigelow Book Prize" and the "Lorne Phenix Graduate Award". As well, certificates were handed out to students who had completed their CSCP training. The afternoon continued with more excellent student presentations concerning molecular mechanisms, exercise for a healthy heart, and imaging. Awards were also presented to students who were judged by their peers to have given the best oral presentation and most innovative presentations.

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STUDENT PRESENTATIONS

As part of the CSCP requirements, all students must present their research once during their graduate training. This presentation consists of either a 10-minute talk followed by a 3-5 minute question period or offered this year a 7-minute talk followed by a 3-5 minutes question period. This year students were grouped into four sessions – seen below – with excellent and innovative presentations given throughout.

Session I: Molecular Mechanisms of Cardiovascular Disease-Part 1 (Chair: Alan Lam)
Jillian Macklin, MSc/LMP
Distinct Cardiac Macrophage Populations and Their Role in Ischemic Injury
Shanna Stanley-Hasnain, MSc/IMS
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Control of Cardiomyocyte Proliferation Through p53/Mdm2-Regulated microRNAs
Diana Buchsbaum, MSc/PSL
Identifying the Functional Role of Ventricle Protein Tmem65 at the Intercalated Disc of Cardiomyocytes
Marianne Wauchop, MSc/PSL
Modelling Atrial Fibrillation in Human Embryonic Stem Cell-Derived Atrial Cardiomyocytes

The talks in this session demonstrated the important role basic molecular research plays in understanding cardiovascular disease. The first speaker described how cardiac macrophages are not a homogenous population and how their different origins result in different behavior post-myocardial infarction. The next three speakers investigated cardiomyocytes. p53 and Mdm2 are known to inhibit cardiomyocyte proliferation and one speaker discovered 11 miRNAs that regulate p53/Mdm2 expression allowing control of cardiomyocyte cell cycle inhibition. Another speaker presented work looking at how Tmem65 interacts with electrical and gap junction behavior of cardiomyocytes. The final talk revealed an *in vitro* platform of atrial cardiomyocytes able to recreate atrial fibrillation behavior with the potential to be used for drug testing.

(Session I: L-R): Jillian Macklin, Marianne Wauchop, Diana Buchsbaum, Shanna Stanley-Hasnain, Alan Lam

<u>Session II: Exercise for a Healthy Heart (Chair: Antoinette Bugyei-Twum)</u>
Ryan Sless, MSc/EXS
Physiologic Mechanisms of Exaggerated Blood Pressure Response to Exercise in Middle-Aged Endurance Trained Athletes
Yena Oh, MSc/PSL
Genome-Wide Analysis of Exercise-Induced Atrial Remodeling
Robert Lakin, PhD/EXS
Exercise-Induced Right Ventricular Dysfunction and Increased Arrhythmia Susceptibility in Mice

Appropriated titled “Exercise for a Healthy Heart”, Session II focused on the effect of long-term intensive exercise on cardiac structure and function in humans and experimental models. The first speaker examined the impact of prolonged, long-term exercise training on vascular function and blood pressure regulation in middle-aged endurance athletes while the second speaker focused on a common clinical problem often associated with intense endurance exercise training—atrial fibrillation. Using a genome-wide analysis approach, the second speaker’s studies revealed that intense endurance training in mice (90-minute swim, twice daily for 2

consecutive weeks) induced susceptibility to atrial fibrillation in association with fibrosis and inflammation that may be mediated by the pro-inflammatory cytokine TNF-alpha. The third speaker of the session investigated the impact of acute, prolonged intensive endurance exercise on right ventricular function and arrhythmia susceptibility in mice. Using invasive pressure-volume loops to assessment of cardiac function, the speaker's studies revealed that prolonged, intensive endurance exercise was associated with significant remodeling of the right ventricle. Increased right ventricular arrhythmia was also noted; to which the speaker alluded to a possible mechanistic link between right ventricular remodeling and arrhythmia susceptibility in prolonged, repetitive bouts of exercise.

Overall, the presentations of all three speakers in this session were well received and brought to our attention that although it is well known that moderate exercise can improve cardiovascular health, the impact of prolonged, intensive exercise on cardiac structure and function is not quite clear and requires further study.

(Session II: L-R): Yena Oh, Ryan Sless, Robert Lakin, Antoinette Bugyei-Twum

Session III: Molecular Mechanisms of Cardiovascular Disease - Part 2
(Chair: Roberto Ribeiro)

Kangbin Zhou, PhD/PCL
Studies Concerning Glyceryl Trinitrate (Nitroglycerin): Potential Mechanisms of Action
Mathew Wong, MSc/PSL
Statin-Mediated Modulation of Rhoa/ROCK Signalling in Experimental Chronic Neonatal Pulmonary Hypertension
Ustina Huh, MSc/PSL
Caveolin1 Modulates ACE by the Midkine-Notch2 Receptor Complex in Human Lung Epithelial Cells
Antoinette Bugyei-Twum, PhD/IMS
Theracurmin Improves Cardiac Function in a Rodent Model of Chronic Kidney Disease—Role of the Nlrp3 Inflammasome

This session continues on the theme of basic research investigating the mechanisms of various cardiovascular diseases. Starting with the investigation of novel pharmacologic mechanisms of action of nitroglycerin and moving on through potentially new target pathways for disease modulation and treatment and novel potential cardioprotective therapeutic agents. The session also included a presentation on the investigation of novel chronic neonatal pulmonary

hypertension disease pathway modulation by statins, as well as an excellent presentation in the shorter 5 minute Lightning Talk format on the cardioprotective role of Theracurmin.

(Session III: L-R): Kangbin Zhou, Mathew Wong, Antoinette Bugyei-Twum, Ustina Huh, Roberto Ribeiro

Session IV: Cardiovascular Imaging (Chair: Navneet Singh)

Angela Duan, MSc/IMS
Preliminary Investigation of the Utility of MRI for Measuring the Hematocrit in Fetal Anemia
Mathew Mathew, MSc/IMS
Hemorheological Profiles of Coronary Artery Aneurysms after Kawasaki Disease
Jessie Mei Lim, MSc/PSL
Cerebral Hemodynamics in Newborns with Congenital Heart Disease

The Cardiovascular Imaging session covered topics in pediatric cardiovascular MRI and computational fluid dynamics. Talks by Angela Duan and Jessie Lim revealed the potential of MRI to guide clinical care and provided insights into pediatric disorders including fetal anemia and congenital heart disease. Mathew Mathew shared plans on a study leveraging a North American Kawasaki Disease Registry to understand fluid dynamics associated with poor prognosis in coronary aneurysms. The session generated significant interest in the use of advanced Medical Imaging techniques for investigating the pathophysiology of a spectrum of cardiovascular disease.

(Session IV: L-R): Navneet Singh, Angela Duan, Mathew Mathew, Jessie Lim

SESSION PRESENTATION AWARD WINNERS

Each presenter was evaluated for the best oral presentation and most innovative research by the student body. Criteria, which was objectively scored, included content (quality of research, research knowledge), visuals (clarity, readability), delivery (voice level, pacing), translational potential of research, data interpretation and analysis (research techniques), ability to answer questions and overall impression. Certificates and gifts were presented to the winners by a member of the Organizing Committee, Alan Lam.

Congratulations to Robert Lakin for receiving the Most Innovated Research Award and Jessie Mei Lim for receiving the Best Oral Presentation Award. The presentations were judged by fellow CSCP students and the awards were given to the presenter with the highest overall score. The Most Innovative Research was awarded to the presenter with the highest overall score for the best research, technical, and analytical skills and the translational potential of their research.

Robert Lakin is a PhD student from the Department of Exercise Science and his research focuses on exercise-induced right ventricular dysfunction and increased arrhythmia susceptibility in mice. The Best Oral Presentation Award was awarded to the speaker that was able to communicate their research, objective, and hypothesis clearly and was able to answer questions effectively.

Jessie Mei Lim is a Master's student in the physiology department and she was one of the speakers who chose to do a lightning (5 min) presentation which was introduced this year. She captured the audience's attention with her presentation titled cerebral hemodynamics in newborns with congenital heart disease.

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GUEST SPEAKERS

This year the CSCP welcomed guest speakers Professor Tara Moriarty, an Assistant Professor in the Matrix Dynamics Group, Faculty of Dentistry, and Department of Laboratory Medicine & Pathobiology, Faculty of Medicine and Professor Scott Heximer, an Associate Professor in the Department of Physiology, Cardiovascular and Respiratory Platform, Faculty of Medicine. This was a unique opportunity for CSCP students to participate in informal discussion with professors on research, career paths, insights, and advice. Dr. Moriarty shared her moving story of the major successes and failures in her life that brought her to where she is today. In a complimentary narrative, Dr. Heximer discussed the various experiences in his life that helped him to make milestone decisions. These presentations created an engaging and insightful environment for discussion and the entire experiences was well received by the students.

We greatly thank Dr. Moriarty and Dr. Heximer for sharing their personal stories with the CSCP student body.

(L-R): Tara Moriarty, Rachel Adams, Scott Heximer

Tara Moriarty, is an assistant professor in the Matrix Dynamics Group, Faculty of Dentistry, and is cross-appointed to the Faculty of Medicine, Department of Laboratory Medicine and Pathobiology. The goal of research in the Moriarty lab is to decipher the largely uncharacterized mechanisms underlying dissemination of invasive bacteria (especially the Lyme disease spirochete *Borrelia burgdorferi*), in an effort to develop alternative therapeutic approaches for treating bacterial infection. Infectious diseases are responsible for one of every three deaths worldwide. Disseminated, invasive disease is responsible for most of the mortality associated with bacterial infections. The dissemination mechanisms of many pathogens are not yet well understood. The Moriarty lab studies multiple features of dissemination, using a wide range of techniques from genetics, molecular and cell biology, biochemistry, biophysics and physiology, as well as powerful live cell imaging approaches for investigating the molecular basis of dissemination in vivo. Specific projects in the lab are: 1) Vascular adhesion mechanisms of blood borne microbes; 2) Mechanisms coordinating vascular adhesion and motility in disseminating spirochetes; 3) Roles of chemotaxis and motility in Borrelia dissemination; 4) Role of diet-induced obesity in enhanced host susceptibility to disseminated Lyme disease; 5) Development of intravital imaging methods for studying periodontal disease and its association with cardiovascular disease. Research in the Moriarty lab is supported by funding from CFI,

CIHR and NSERC, and Dr. Moriarty is a recipient of the CIHR Bhagirath Singh Early Career Award in Infection and Immunity.

Scott Heximer was jointly recruited by the Department of Physiology, Faculty of Medicine, and the Heart & Stroke/Richard Lewar Centre of Excellence in 2002. Since establishing his laboratory at the University of Toronto, Dr. Heximer has focused on the physiologic processes that control blood pressure regulation and the mechanisms of heterotrimeric G protein signaling, and subsequently defining the roles of G proteins and their regulators in the cardiovascular system. Understanding how blood vessels interpret physiological signals to control blood pressure homeostasis may lead to new treatment possibilities for high blood pressure and atherosclerosis. Dr. Heximer's work strives to define the function of RGS proteins – potent inhibitors of heterotrimeric G protein signaling in the regulation of cardiovascular function at the level of the heart and blood vessels – in the cardiovascular system. RGS proteins normally "turn off" molecular switches that are activated by hormones and neurotransmitters, which cause blood vessels to constrict. The malfunction of RGS proteins may lead to persistent vessel constriction and high blood pressure. If RGS protein activity can be regulated by genetic or pharmaceutical means, researchers may be able to find new ways of controlling high blood pressure, thus reducing the incidence of heart and blood vessel disease.

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CERTIFICATES/AWARDS

Dr. Wittnich presented certificates to students who successfully completed the Cardiovascular Sciences Collaborative Program over the past year:

MSc
Ji Dong (Karen) Bai, IMS (Supervisor: X-Y. Wen)
Stephanie Beadman, PSL (Supervisor: S. Heximer)
Robert Civitarese, IMS (Supervisor: K. Connelly)
Danny Dinh, PSL (Supervisor: S-S. Bolz)
Mehroz Ehsan, IMS (Supervisor: S. Verma)
Zachary Laksman, IMS (Supervisor: P. Backx)
Julieta Lazarte, IMS (Supervisor: V. Rao)
Tina Binesh Marvasti, IMS (Supervisor: A. Moody)
Shira Sasson, PCL (Supervisors: J. Goodman/P. Dorian)
Joobin Sattar, PSL (Supervisor: S. Heximer)
Travis Wilder, IMS (C. Caldarone)

PhD
Katherine Allan, IMS (Supervisor: P. Dorian)
Danielle Bentley, EXS (Supervisor: S. Thomas)
Lee-Anne Khuu, IMS (Supervisor: C. Hudson)
Cedric Manlhiot, IMS (Supervisor: B. McCrindle)

Congratulations to all the students that successfully completed the CSCP. We wish them success in their future career endeavours which include medical school, continuing on to PhD training, post-doctoral training, cardiac electrophysiologist, and training related industry careers!
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Continuing the spirit of success and achievement, Dr. Wittnich continued with the annual CSCP student awards and presented:

2016 Bigelow Book Prize Recipient – Cedric Manlhiot

The CSCP congratulates Cedric Manlhiot (shown here with Dr. Wittnich), PhD, Institute of Medical Science, supervised by Dr. B. McCrindle, who was presented with the 2016 Bigelow Book Prize for his continued and sustained academic scientific excellence.

Many commonly used medications have been introduced in clinical care with a simple dosing regimen whereby all patients are treated with the same dose or, in the minority of cases, a simple dosing algorithm. Unfortunately, for the majority of drugs, this approach ignores important variations in individual patients' physiologies which can severely affect the dosing requirements or the drug's efficacy and safety profile. With an improvement in our understanding of the clinical, physiological and pharmacological factors associated with drug response in a specific patient population, we can create algorithms that can be used to individualize treatment regimens to maximize efficacy and reduce risks of adverse effects.

The case of heparin use in children undergoing cardiac surgery is particularly interesting in this regard. Currently, the dose of heparin in these patients is calculated with the assumption that 1 unit of heparin will produce 1 unit of anticoagulation. Unfortunately, in children 1 unit of heparin can produce anywhere from 0.5 to 4.0 units of anticoagulation. Too low anticoagulation and these patients can develop thrombosis, too high anticoagulation and they bleed. Either of those complications can be life threatening. My research specifically investigates the complex factors associated with heparin response in children and develops new models that can be used to predict the correct dose of heparin any individual patient needs. In the next few years, the algorithm we developed to individualize heparin dosing will be tested in clinical care and the methodology we developed will be adapted for the many other clinical situations facing a similar predicament.

2015-16 Lorne Phenix Graduate Award Recipient – Mathew Wong

The CSCP congratulates Mathew Wong, a Masters candidate in the Department of Physiology, supervised by Dr. R. Jankov, who was presented with the 2015-16 Lorne Phenix Graduate Award for his continued and sustained academic scientific excellence. Mathew is shown here with Margaret Rand, Kathryn Phenix and her daughter Ava.
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Statin-Mediated Modulation of RhoA/ROCK Signaling in Experimental Chronic Neonatal Pulmonary Hypertension

Chronic pulmonary arterial hypertension (PAH) is a debilitating and lethal disease in newborns. It is characterized by high pulmonary vascular resistance (PVR) in the lungs causing low oxygen levels and heart failure. Despite available treatments, progression of PAH is currently inevitable, leading to an early death (One-year 60% mortality rate).

Rho-kinase (ROCK) is critical to the progression of chronic PAH. Our laboratory's work has demonstrated that ROCK inhibitors can prevent and reverse experimental PAH, at the cost of stunted growth and systemic hypotension. Statins have a clinically proven safety profile and published evidence for cholesterol-independent ROCK inhibition.

Results to-date for chronic hypoxia-exposed (CH) newborn rats shows a trend for greater elevation of PVR in females, and a greater reduction in PVR with simvastatin treatment than males. Medial wall area (MWA) and degree of muscularization are markers of pulmonary arterial remodeling in PAH. Arterial MWA in CH females is significantly increased ($P<0.05$) and appear to have more muscularized arteries compared to males. All pups treated with simvastatin significantly attenuated ($P<0.001$) both markers of remodeling, with females trending towards a greater improvement. Rescue protocol treatment had similar results with reversing pulmonary arterial remodeling ($P<0.01$) and trending towards significance in sex differences.

Following the awards presentations, students socialized and networked during the complimentary lunch.

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CLOSING

The Student Research Day was a success and would not have been possible without the combined efforts of several individuals. Thank you to the Organizing Committee, Alan Lam (Chair), Antoinette Bugyei-Twum, Aileen Zhong, Rachel Adams and Roberto Ribeiro (Committee members) for all their hard work; Victoria Simpson for her support and knowledge in making this day successful, Professors Moriarty and Heximer for their outstanding and inspiring presentations, and the Sessions Chairs, Antoinette Bugyei-Twum, Roberto Ribeiro, Navneet Singh and Alan Lam for keeping the sessions running smoothly.
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(L-R): Antoinette Bugyei-Twum, Aileen Zhong, Alan Lam, Roberto Ribeiro, Rachel Adams

We are also grateful to the generous donation from the Heart & Stroke Foundation of Ontario for the Session Award prizes, the Phenix family, the Bigelow family, and the contributions from our participating units.

HEART & STROKE FOUNDATION

Thank you to all the CSCP students and to all involved in making the 17th Annual CSCP Student Research Day a great success!