Faculty of Medicine Annual Grant Writing Workshop

Hosted by the Office of the Vice Dean, Research & Innovation

AGENDA

9:10am	**Overview of Services, Office of the Vice Dean, Research & Innovation**
9:15am	**A Reviewer's Perspective on Grant Review Panels and Funding Success** **Professor Brenda Andrews**, Director, Donnelly Centre
10:15am-10:40am	*Refreshment Break—25 Minutes* *(Food and Drink are not permitted in the lecture hall.)*
10:40am-11:00pm	**Core Facilities and Services in the Faculty of Medicine** **Natasha Christie-Holmes, PhD,** Research Operations Officer, Faculty of Medicine
11:00-12:00pm	**Grant Fundamentals and Tips to Improve Your Research Proposals** **Daniel Harney, PhD,** Grants & Awards Editor, Faculty of Medicine

Office of the Vice Dean, Research & Innovation

Dr. Richard Hegele, Vice Dean, Research & Innovation

- **Researcher Support & Authorization**
  - Authorizes funding applications, coordinates internal allocations & competitions (CRC, CFI), disseminates funding opportunities ("What's New?" e-newsletter)
- **Grant Application Facilitation & Development**
  - Proposal editing, budgetary reviews, and awards & honours nominations
- **Core Facilities & Services**
  - Oversees and manages the CSS, CL3, DCM, and MIL facilities
- **Research Metrics**
  - Provides research funding and bibliometric data to stakeholders and external partners
- **Health Innovation Hub (H2I)**
  - Educates and facilitates trainee-initiated commercialization of health matters

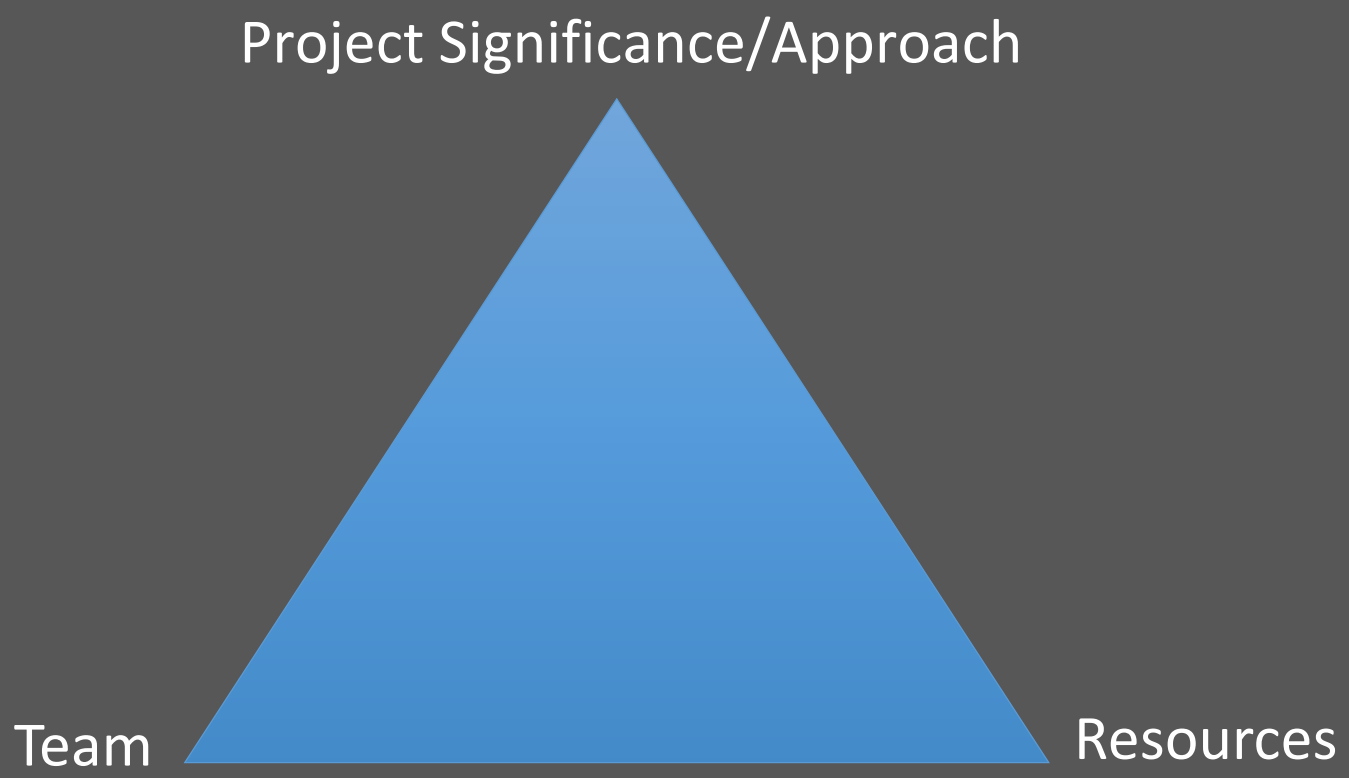
UNIVERSITY OF TORONTO
FACULTY OF MEDICINE

GRANT FUNDAMENTALS AND TIPS TO IMPROVE YOUR RESEARCH PROPOSALS

Daniel Harney, PhD
Grants and Awards Editor
Office of the Vice Dean, Research & Innovation

Takeaways for Today:

- **Principle 1: Grant Writing is a genre:**
  - Reviewers' expect you to make specific, pre-conceived "moves."
  - Strong grant writing can be learned.
  - Good grant writing is strategic storytelling that leverages data and emotions
- **Principle 2: Strong grant writers cater to their reviewers:**
  - Good grant writing persuades reviewers to become *advocates* of the proposed research
  - style/formatting elements draw *multidisciplinary* reviewers' eyes to key elements of the proposal and improve the reading experience.



The Proposal Triangle

Proposal Timeline:

- **3 Months**: Write the Overall Goal and Each Specific Aim; Gather accompanying documents; Convene Internal Scientific Review Panel.
- **2 Months:** begin writing body of grant proposal.
- **3 Weeks:** Provide draft to Internal Review Panel
- **2 Weeks:** Meet with Internal Peer Review Panel and submit to Editorial Review.

Write your Objectives First.

Weak Objective:

We aim to:

1. Better understand the effects of family, environment, and language skills on preparedness for kindergarten.

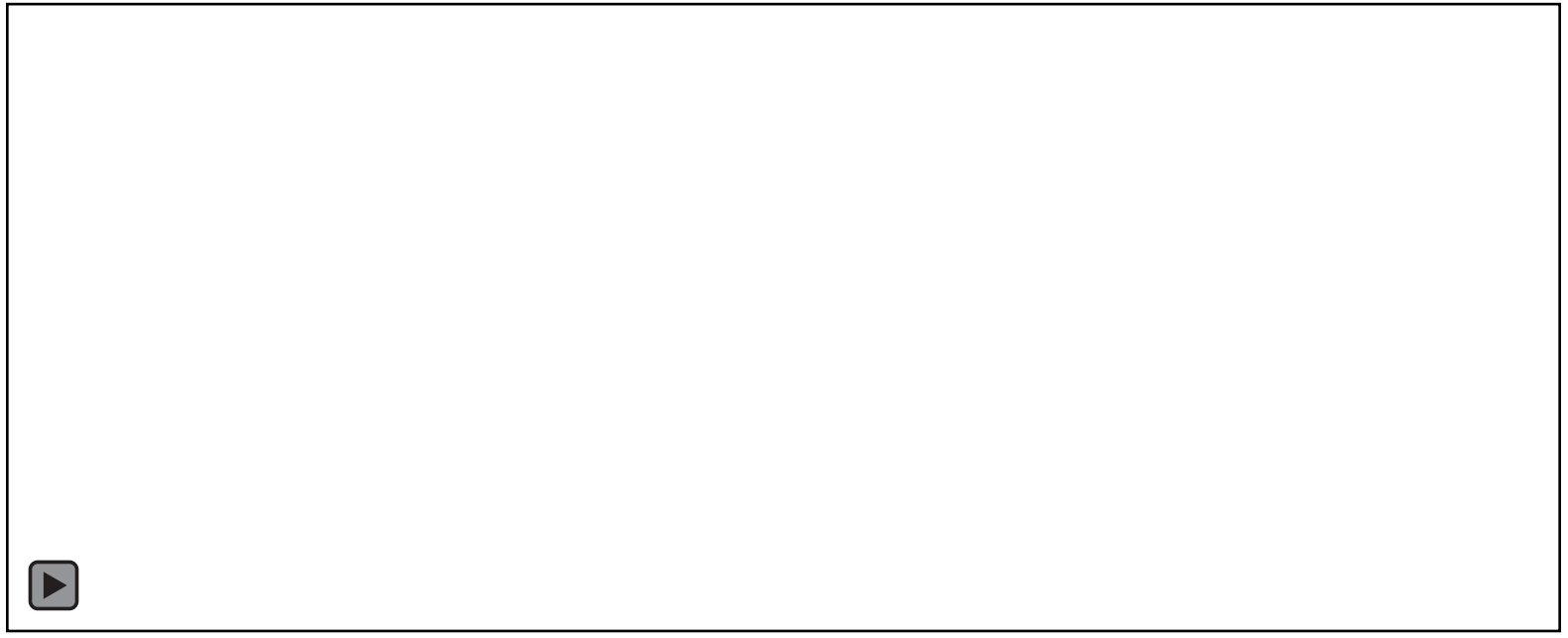
Strong Objective:

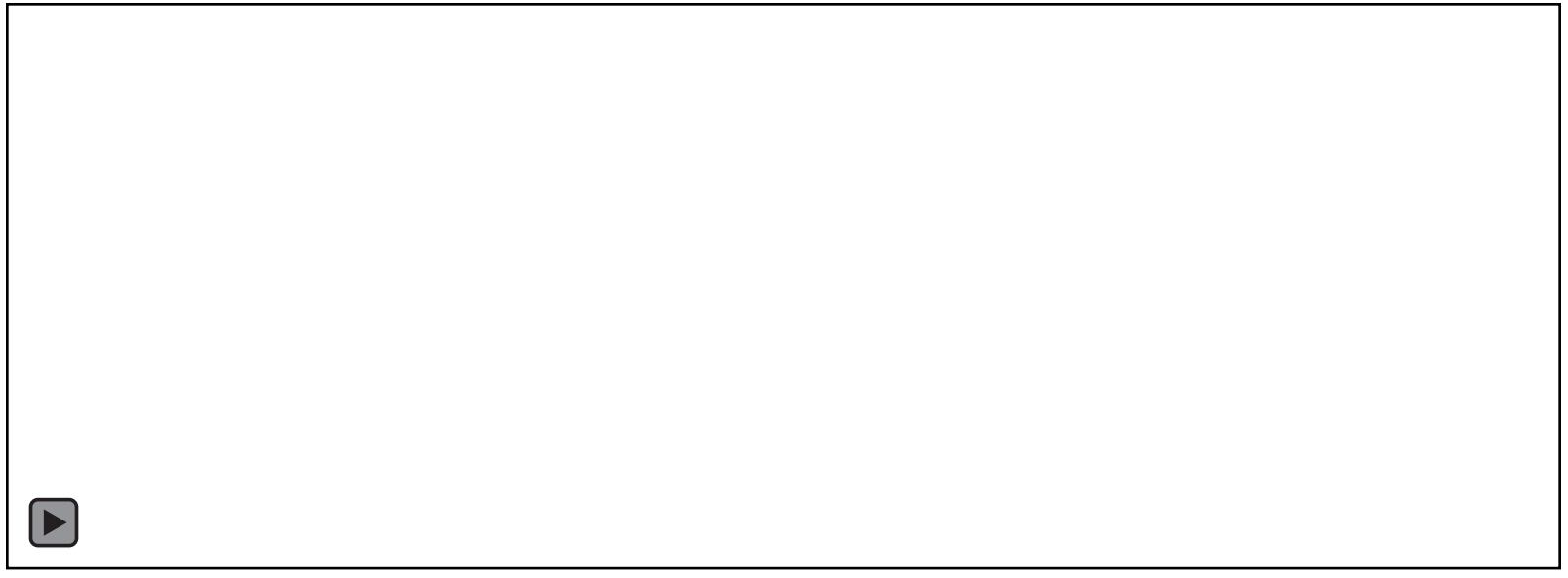
We aim to:

1. Determine the key factors that predict success or failure in transition from preschool to kindergarten. (Years 1-2)

Avoid Indeterminate Objectives:

- To explore the reasons for…
- To study the effects of…
- To better understand why…
- To improve our understanding of…

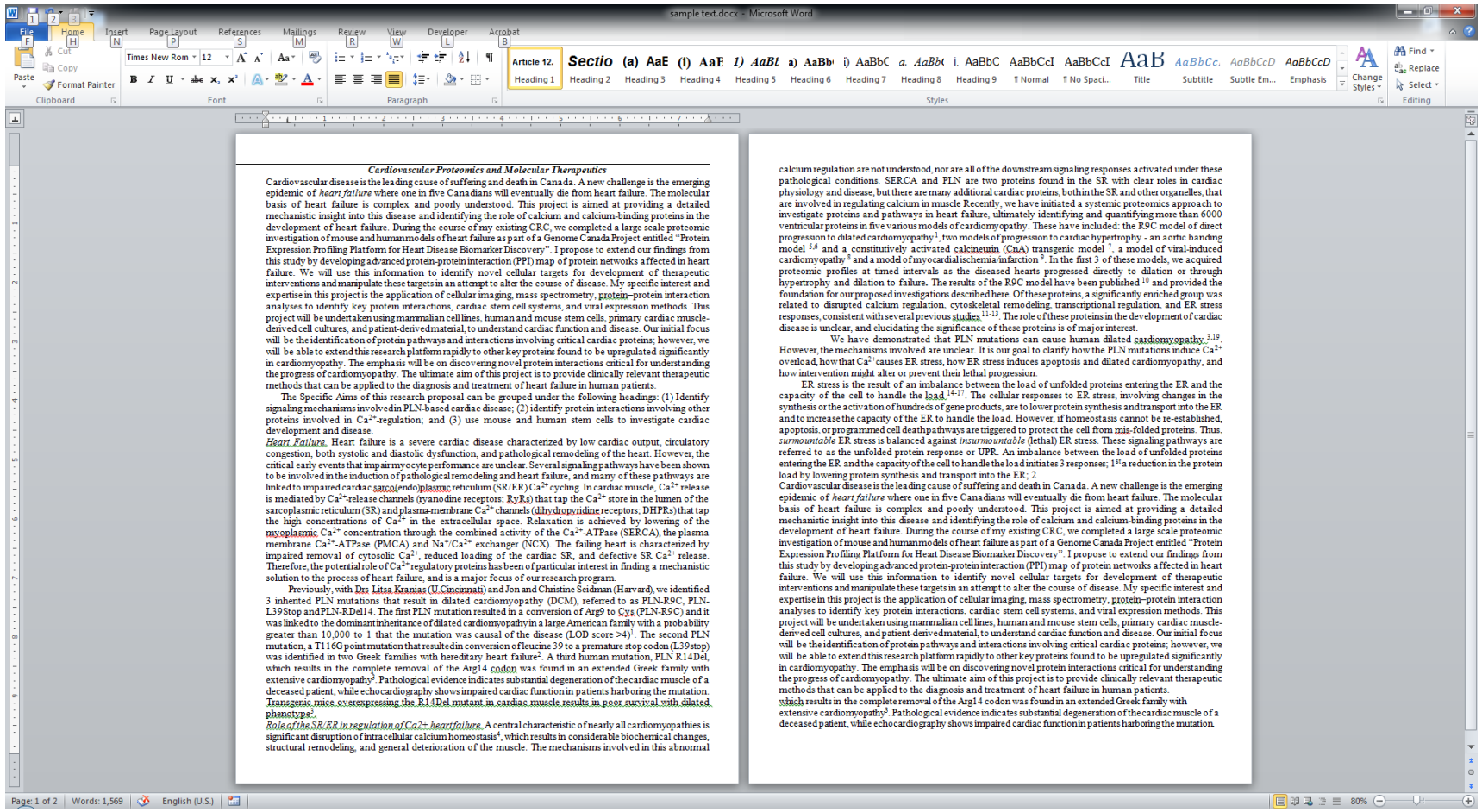




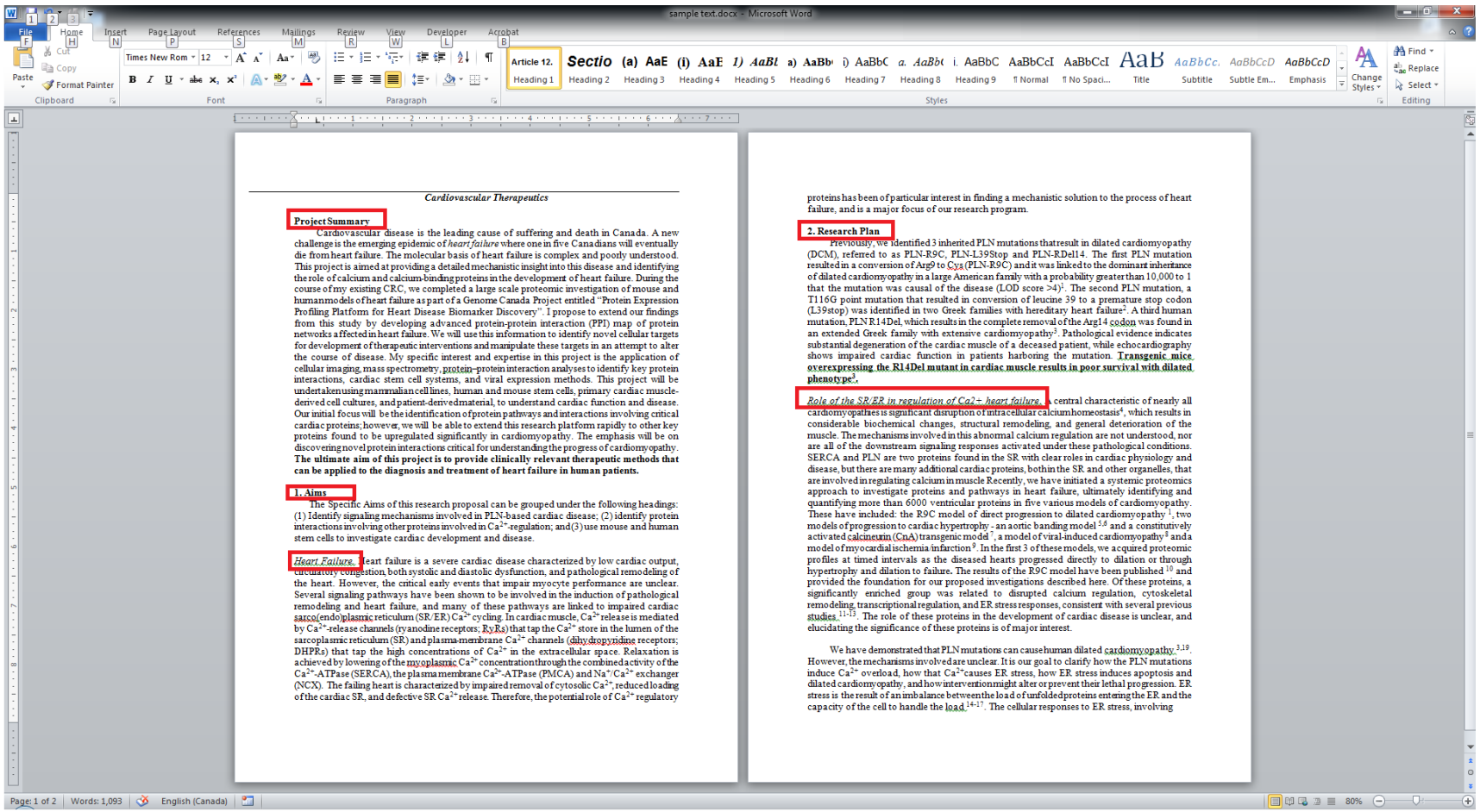
Case Study 1: Lay Summary

- What is the problem?
- Why is it significant?
- What is the gap in the existing knowledge?
- Why should we know more?
- Why do you think your approach will have better outcomes?
- What's new/original/creative about it?
- What will the impact of this research be?

Formatting Matters



Formatting Matters



Cardiovascular Therapeutics

Project Summary

Cardiovascular disease is the leading cause of suffering and death in Canada. A new challenge is the emerging epidemic of *heart failure* where one in five Canadians will eventually die from heart failure. The molecular basis of heart failure is complex and poorly understood. This project is aimed at providing a detailed mechanistic insight into this disease and identifying the role of calcium and calcium-binding proteins in the development of heart failure. During the course of my existing CRC, we completed a large scale proteomic investigation of mouse and human models of heart failure as part of a Genome Canada Project entitled "Protein Expression Profiling Platform for Heart Disease Biomarker Discovery". I propose to extend our findings from this study by developing advanced protein-protein interaction (PPI) map of protein networks affected in heart failure. We will use this information to identify novel cellular targets for development of therapeutic interventions and manipulate these targets in an attempt to alter the course of disease. My specific interest and expertise in this project is the application of cellular imaging, mass spectrometry, protein–protein interaction analyses to identify key protein interactions, cardiac stem cell systems, and viral expression methods. This project will be undertaken using mammalian cell lines, human and mouse stem cells, primary cardiac muscle-derived cell cultures, and patient-derived material, to understand cardiac function and disease. Our initial focus will be the identification of protein pathways and interactions involving critical cardiac proteins; however, we will be able to extend this research platform rapidly to other key proteins found to be upregulated significantly in cardiomyopathy. The emphasis will be on discovering novel protein interactions critical for understanding the progress of cardiomyopathy. **The ultimate aim of this project is to provide clinically relevant therapeutic methods that can be applied to the diagnosis and treatment of heart failure in human patients.**

1. Aims

The Specific Aims of this research proposal can be grouped under the following headings: (1) Identify signaling mechanisms involved in PLN-based cardiac disease; (2) identify protein interactions involving other proteins involved in Ca^{2+}-regulation; and (3) use mouse and human stem cells to investigate cardiac development and disease.

Heart Failure. Heart failure is a severe cardiac disease characterized by low cardiac output, circulatory congestion, both systolic and diastolic dysfunction, and pathological remodeling of the heart. However, the critical early events that impair myocyte performance are unclear. Several signaling pathways have been shown to be involved in the induction of pathological remodeling and heart failure, and many of these pathways are linked to impaired cardiac sarco(endo)plasmic reticulum (SR/ER) Ca^{2+} cycling. In cardiac muscle, Ca^{2+} release is mediated by Ca^{2+}-release channels (ryanodine receptors; RyRs) that tap the Ca^{2+} store in the lumen of the sarcoplasmic reticulum (SR) and plasma-membrane Ca^{2+} channels (dihydropyridine receptors; DHPRs) that tap the high concentrations of Ca^{2+} in the extracellular space. Relaxation is achieved by lowering of the myoplasmic Ca^{2+} concentration through the combined activity of the Ca^{2+}-ATPase (SERCA), the plasma membrane Ca^{2+}-ATPase (PMCA) and Na^+/Ca^{2+} exchanger (NCX). The failing heart is characterized by impaired removal of cytosolic Ca^{2+}, reduced loading of the cardiac SR, and defective SR Ca^{2+} release. Therefore, the potential role of Ca^{2+} regulatory proteins has been of particular interest in finding a mechanistic solution to the process of heart failure, and is a major focus of our research program.

2. Research Plan

Previously, we identified 3 inherited PLN mutations that result in dilated cardiomyopathy (DCM), referred to as PLN-R9C, PLN-L39Stop and PLN-RDel14. The first PLN mutation resulted in a conversion of Arg9 to Cys (PLN-R9C) and it was linked to the dominant inheritance of dilated cardiomyopathy in a large American family with a probability greater than 10,000 to 1 that the mutation was causal of the disease (LOD score >4)[1]. The second PLN mutation, a T116G point mutation that resulted in conversion of leucine 39 to a premature stop codon (L39stop) was identified in two Greek families with hereditary heart failure[2]. A third human mutation, PLNR14Del, which results in the complete removal of the Arg14 codon was found in an extended Greek family with extensive cardiomyopathy[3]. Pathological evidence indicates substantial degeneration of the cardiac muscle of a deceased patient, while echocardiography shows impaired cardiac function in patients harboring the mutation. **Transgenic mice overexpressing the R14Del mutant in cardiac muscle results in poor survival with dilated phenotype[3].**

Role of the SR/ER in regulation of Ca2+ heart failure. A central characteristic of nearly all cardiomyopathies is significant disruption of intracellular calcium homeostasis[4], which results in considerable biochemical changes, structural remodeling, and general deterioration of the muscle. The mechanisms involved in this abnormal calcium regulation are not understood, nor are all of the downstream signaling responses activated under these pathological conditions. SERCA and PLN are two proteins found in the SR with clear roles in cardiac physiology and disease, but there are many additional cardiac proteins, both in the SR and other organelles, that are involved in regulating calcium in muscle. Recently, we have initiated a systemic proteomics approach to investigate proteins and pathways in heart failure, ultimately identifying and quantifying more than 6000 ventricular proteins in five various models of cardiomyopathy. These have included: the R9C model of direct progression to dilated cardiomyopathy [1], two models of progression to cardiac hypertrophy - an aortic banding model [5,6] and a constitutively activated calcineurin (CnA) transgenic model [7], a model of viral-induced cardiomyopathy [8] and a model of myocardial ischemia/infarction [9]. In the first 3 of these models, we acquired proteomic profiles at timed intervals as the diseased hearts progressed directly to dilation or through hypertrophy and dilation to failure. The results of the R9C model have been published [10] and provided the foundation for our proposed investigations described here. Of these proteins, a significantly enriched group was related to disrupted calcium regulation, cytoskeletal remodeling, transcriptional regulation, and ER stress responses, consistent with several previous studies.[11-13]. The role of these proteins in the development of cardiac disease is unclear, and elucidating the significance of these proteins is of major interest.

We have demonstrated that PLN mutations can cause human dilated cardiomyopathy.[3,19]. However, the mechanisms involved are unclear. It is our goal to clarify how the PLN mutations induce Ca^{2+} overload, how that Ca^{2+} causes ER stress, how ER stress induces apoptosis and dilated cardiomyopathy, and how intervention might alter or prevent their lethal progression. ER stress is the result of an imbalance between the load of unfolded proteins entering the ER and the capacity of the cell to handle the load.[14-17]. The cellular responses to ER stress, involving

Case Study 2: Proposal Introduction

"Introduction: This project will test if artificially induced venous return during 70° head-up tilt with functional electrical stimulation can be used in incomplete sub-acute (< 3 months) individuals with SCI as a therapeutic intervention to help them cope with orthostatic stress. Individuals who had SCI at the L4 neurological level or higher are likely to have difficulties activating a venous pump due to partial or complete lower limb paralysis."

Tip #1: Situate multidisciplinary reviewers within the health, social and economic context of your research.

"<u>Introduction:</u> SCI affect approximately 86,000 Canadians and not only have a devastating impact on the quality of life of individuals and their caretakers, but also pose an estimated $2.7B economic burden on the Canadian economy.

Tip #2: State the problem you're proposing to solve.

"Introduction: SCI affect approximately 86,000 Canadians and not only have a devastating impact on the quality of life of individuals and their caretakers, but also pose an estimated $2.7B economic burden on the Canadian economy. **Following spinal cord injury, many patients are unable to upregulate their blood pressure.**

Tip #3: Define your terms. "Your reviewer is not as familiar as you are."

"Introduction: **Spinal cord injuries (SCI)** affect approximately 86,000 Canadians and not only have a devastating impact on the quality of life of individuals and their caretakers, but also pose an estimated $2.7B economic burden on the Canadian economy. Following spinal cord injury, many patients are unable to upregulate their blood pressure. **When patients are transferred from a supine position into an upright sitting or standing posture, they experience lightheadedness and may lose consciousness. These are typical symptoms of orthostatic stress.**

Tip #4: Answer: So what?

"Introduction: Spinal cord injuries (SCI) affect approximately 86,000 Canadians and not only have a devastating impact on the quality of life of individuals and their caretakers, but also pose an estimated $2.7B economic burden on the Canadian economy. Following spinal cord injury, many patients are unable to upregulate their blood pressure. When patients are transferred from a supine position into an upright sitting or standing posture, they experience lightheadedness and may lose consciousness. These are typical symptoms of orthostatic stress. **Inadequate treatment options for this condition currently result in delayed rehabilitation for SCI patients.**

Tip #5: Present preliminary data and expertise that will enable you to execute the project.

"Introduction: Spinal cord injuries (SCI) affect approximately 86,000 Canadians and not only have a devastating impact on the quality of life of individuals and their caretakers, but also pose an estimated $2.7B economic burden on the Canadian economy. Following spinal cord injury, many patients are unable to upregulate their blood pressure. When patients are transferred from a supine position into an upright sitting or standing posture, they experience lightheadedness and may lose consciousness. These are typical symptoms of orthostatic stress. Inadequate treatment options for this condition currently result in delayed rehabilitation for SCI patients. **We recently demonstrated an artificially reactivated venous pump by combining electrically induced muscle contractions in the legs with passive leg movements.**

Tip #6: Explicitly connect your preliminary data to your proposed project.

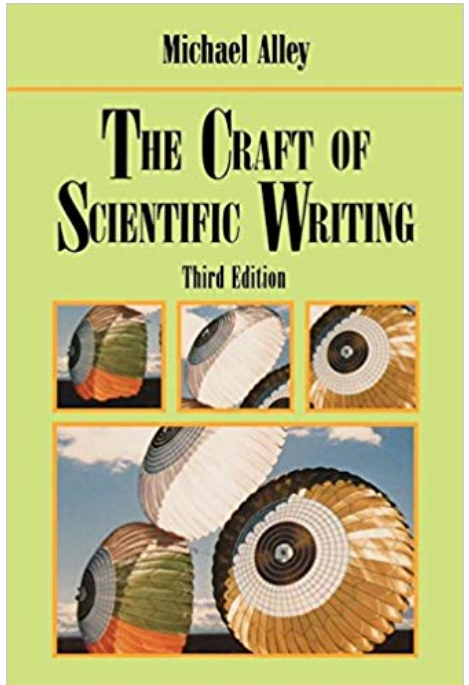
"Introduction: Spinal cord injuries (SCI) affect approximately 86,000 Canadians and not only have a devastating impact on the quality of life of individuals and their caretakers, but also pose an estimated $2.7B economic burden on the Canadian economy. Following spinal cord injury, many patients are unable to upregulate their blood pressure. When patients are transferred from a supine position into an upright sitting or standing posture, they experience lightheadedness and may lose consciousness. These are typical symptoms of orthostatic stress. Inadequate treatment options for this condition currently result in delayed rehabilitation for SCI patients. We recently demonstrated an artificially reactivated venous pump by combining electrically induced muscle contractions in the legs with passive leg movements. **We propose to test this therapeutic intervention during 70° head-up tilt with functional electrical stimulation with incomplete sub-acute (<3 months) SCI individuals.**

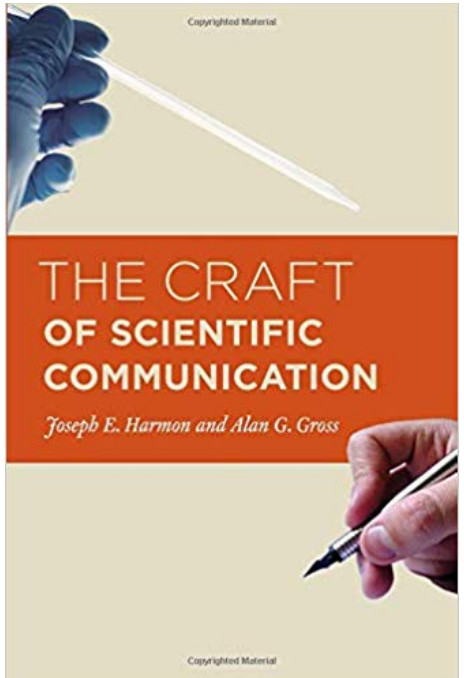
Tip #7: Describe concrete outcomes and impact.

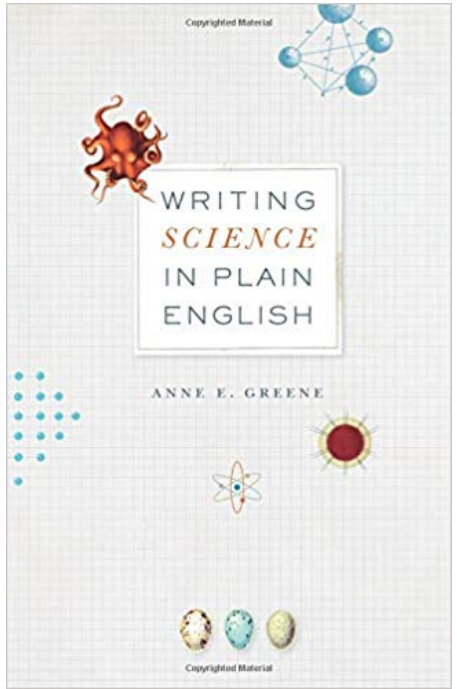
"Introduction: Spinal cord injuries (SCI) affect approximately 86,000 Canadians and not only have a devastating impact on the quality of life of individuals and their caretakers, but also pose an estimated $2.7B economic burden on the Canadian economy. Following spinal cord injury, many patients are unable to upregulate their blood pressure. When patients are transferred from a supine position into an upright sitting or standing posture, they experience lightheadedness and may lose consciousness. These are typical symptoms of orthostatic stress. Inadequate treatment options for this condition currently result in delayed rehabilitation for SCI patients. We recently demonstrated an artificially reactivated venous pump by combining electrically induced muscle contractions in the legs with passive leg movements. We propose to test this therapeutic intervention during 70° head-up tilt with functional electrical stimulation with incomplete sub-acute (<3 months) SCI individuals. **The intervention will enable this patient population to participate sooner and more successfully in their activities of daily living and in their rehabilitation programs, thereby improving patient outcomes and lowering healthcare expenses."**

Contextualize and engender enthusiasm for your project through storytelling.

"Consider a patient admitted to the hospital with a stab wound who suddenly loses blood pressure. Currently, clinical staff must guess as to whether they are responding to the stab wound, bacteria on the knife, or treatments that they themselves have administered. Most interventions have potentially harmful side-effects, and many established treatments are not associated with improved outcomes in randomized controlled trials. Often, clinical staff compare a given patient to their prior cases and find the most similar case using a mental model. However, parameters for similarity will vary by staff experience and seniority, and even the most experienced clinicians may not take into account all the ways that patients may respond differently to treatment. It is therefore critical to develop representations or health phenotypes that are robust representations of patient state."







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Core Facilities and Services in the Faculty of Medicine

Natasha Christie-Holmes

Research Operations Officer, Faculty of Medicine

natasha.christie@utoronto.ca

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- Dedicated management teams to provide specific technical expertise, training and protocol development assistance for research personnel

- Maximizing the impact of funding success to propel research at a Faculty-wide level and support future grant applications

- Supported through cost-recovery structures and strategic planning of grant-associated operational funding

https://medicine.utoronto.ca/core-facilities-services

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Division of Comparative Medicine (DCM)

- Director: Kate Banks
- Associate Director: Karen Parisien
- http://www.dcm.utoronto.ca/
- Federally and Provincially accredited Animal Care program at the Faculty of Medicine
- Preeminent veterinary technical staff including 5 Masters level animal technicians
- Over 60, 000 ft^2 dedicated to *in vivo* research, including germfree, gnotobiotics and SPF+ exclusion
- Multiple full animal imaging modalities on-site supported by dedicated technical expert

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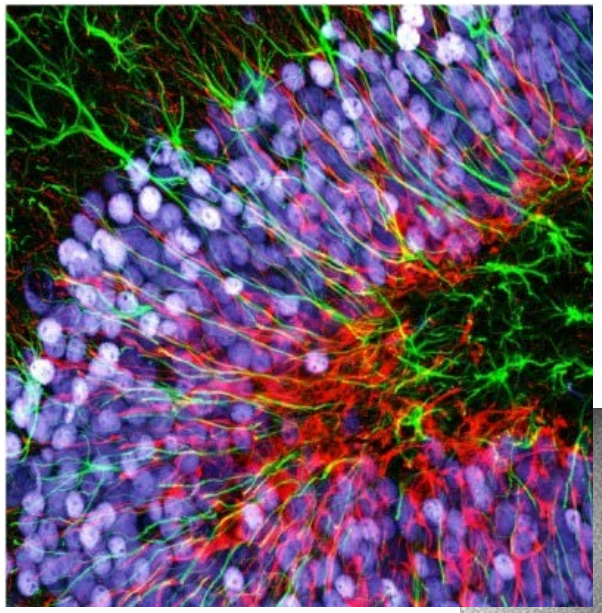
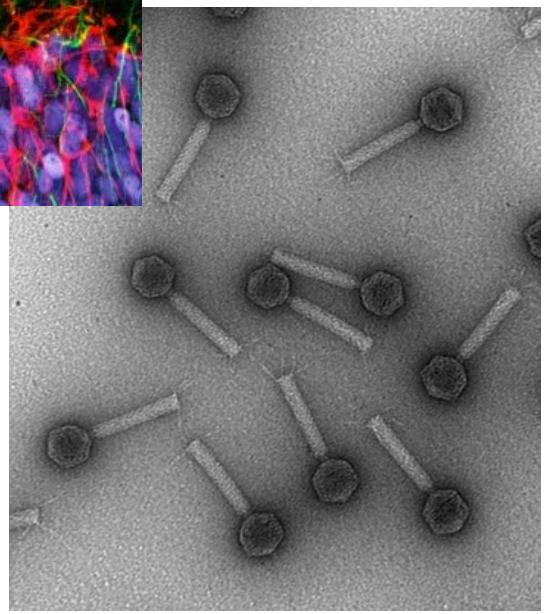
Microscopy Imaging Lab (MIL)

- Director: Stephen Girardin, PhD
- Manager: Lindsey Fiddes, PhD
- Consolidated microscopy core including confocal, fluorescence, scanning (SEM) and transmission (TEM) electron microscopes
- Expert technical team trains research personnel in microscopy techniques and development of protocols
- Dedicated preparatory lab for SEM/TEM samples, Equipped for Cryo-TEM prepration
- Providing full-service microscopy (prep and scanning)





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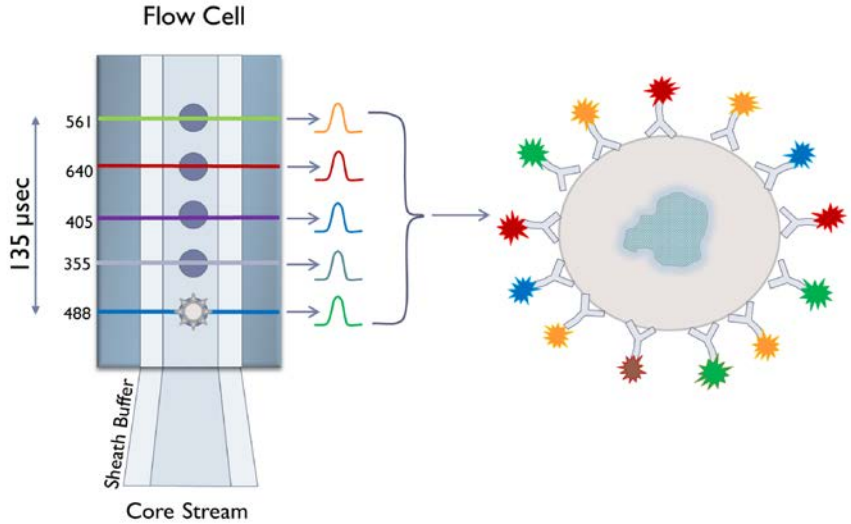
Flow Cytometry Facility

- Director: Tania Watts, PhD
- Manager: Dionne White
- http://flowcytometry.utoronto.ca/
- Equipped with 7 analyzers (3 to 5 laser each; up to 18 colour acquisition) and 3 cell sorters allowing for large multiparameter analysis
- Supported by dedicated operators with extensive FCM knowledge and over 20 years of experience
- Comprehensive training program partnership with Expert Cytometry(ExCyte™) and SickKids Hospital for research personnel



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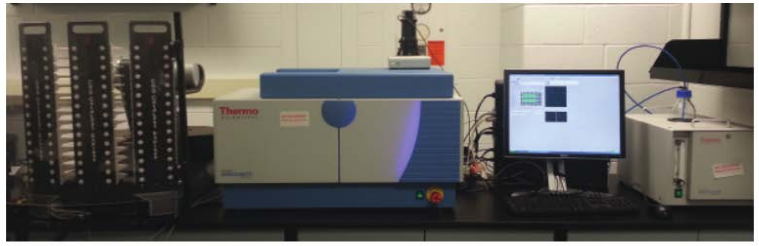
Diet, Digestive tract and Disease (3D) facility

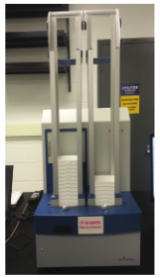
- Director: Herb Gaisano, PhD
- Manager: Alexandre Hardy, PhD
- Multiple analytic platforms to facilitate molecular investigations
- Various imaging platforms from molecular level to full small animal scans
- Partnership with DCM to provide technical expertise in animal imaging

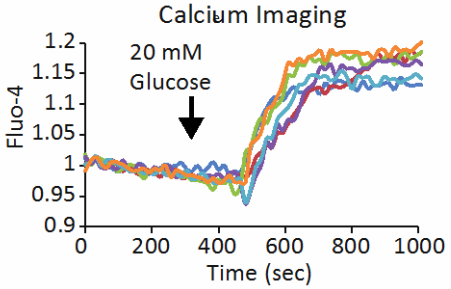
High capacity & fully automated single cell fluorescent microscopy platform



BMG PHERAstar FS

Versatile & FRET compliant plate reader





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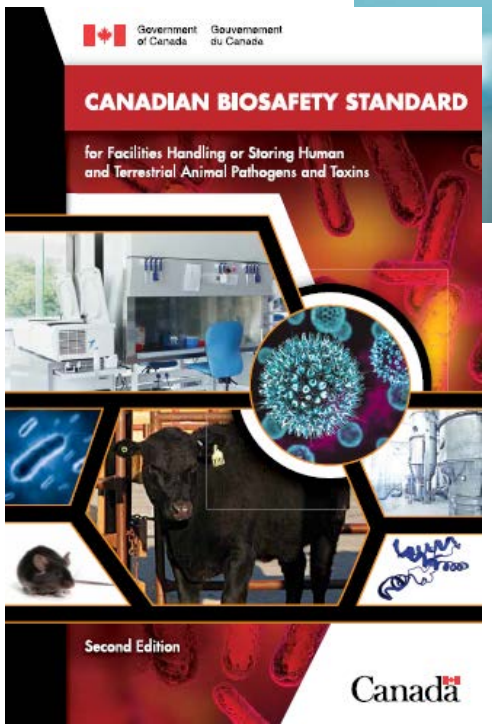
Combined Containment Level 3 (C-CL3) Unit

- Director: Scott Gray-Owen, PhD
- Manager: Natasha Christie-Holmes, PhD
- Federally licensed facilities for research involving RG3 pathogens
- Dedicated regulatory team providing guidance, validation and oversight
- Facilities for small animal *in vivo* studies and molecular *in vitro* research



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Central Sterilization Service (CSS)

- Providing glass-washing, laundry and sterilization services
- Centralized stock of glass and plasticware for all MSB researchers to access
- Multiple sterilization cycles daily allowing flexibility for lab schedules
- After-hours autoclaves available to trained users

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MedStore and MedPRINT

http://www.uoftmedstore.com/

https://uoftmedprint.com/

- Research materials store with UofT preferred pricing from vendors
- 3D printing service specializing in research applications
- Conveniently located in the Medical Sciences Building