
TRAINEE SECTION

Ghadi Antoun, BSc^{1,3}
Jonathan Keow, MSc^{1,3}
Véronique D. Ram, PhD^{1,2}
Christina Thornton²
Xin Wang, BHSc^{1,4}
Ju-Yoon Yoon, MD, PhD^{1,5}

¹ CITAC/ACCFC Executive Committee

² MD/PhD Program, University of Calgary

³ MD/PhD Program, University of Ottawa

⁴ MD/PhD Program, University of Toronto

⁵ Department of Laboratory Medicine and Pathology, University of Toronto

Scientific overview: CSCI-CITAC Annual General Meeting and Young Investigator's Forum 2013

Abstract

The 2013 joint Canadian Society of Clinician Investigators (CSCI)–Clinical Investigator Trainee Association of Canada/Association des cliniciens-chercheurs en formation du Canada (CITAC/ACCFC) annual general meeting (AGM) was held in Ottawa, September 2013. The symposium focused on “Applications of the ‘omics’ to Clinical Practice”, with presentations from Drs. William T. Gibson (University of British Columbia), Julie Ho (University of Manitoba) and David Hwang (University of Toronto), discussing topics of genome, proteome and the microbiome, respectively.

Other highlights from the 2013 AGM include presentations by Dr. Salim Yusuf (McMaster University, 2013 CSCI-RCPSC Henry Friesen Award winner), Dr. Gary Lewis (University of Toronto, 2013 CSCI Distinguished Scientist Award winner) and Dr. Michael Taylor (University of Toronto, 2013 Joe Doupe Award winner). The CSCI/CITAC/Friends of CIHR Joint Symposium consisted of presentations from Drs. John Bell (University of Ottawa), Dan Drucker (University of Toronto) and Heather J. Dean (University of Manitoba). Finally, the meeting ended with the presentation “The Power of an Idea to Bring Ideas to Power” by Dr. Harvey V. Fineberg (President, U.S. Institute of Medicine), the winner of the 2013 Henry Friesen International Prize.

Also presented at the conference was research by clinician investigator (CI) trainees from across Canada; ie., those enrolled in MD/MSc, MD/PhD or Clinician Investigator Program (CIP) programs. Canadian trainees’ research extended beyond the pillar of biomedical research, covering the spectrum between basic and clinical research, with a focus on the causes of significant morbidity and mortality for Canadians, including cancers, infectious diseases and other maladies. It is this research that we have summarized in this review.

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The 2013 AGM showcased CI trainees' research in two different formats—oral and poster presentations. Six prizes in total were awarded, with three prizes in each format, and the prize-winning presentations are covered separately. The remaining abstracts are divided into four different categories: basic research, microbiology/infectious diseases, cancer research and clinical research.

2013 Winning Presentations

Oral Presentation Prize Winners:

Christina Thornton (University of Calgary)
Linda Vi (University of Toronto)
Cynthia Luk (University of Toronto)

The 2013 AGM was an exhibition of excellent research performed by CI trainees from across Canada, and the calibre of their work was evident in the platform presentations. Christina Thornton's presentation, titled "Harmless Commensal Microbial Neighbours Synergistically Trigger *Pseudomonas aeruginosa* Virulence Genes in Cystic Fibrosis", focused on the interaction between *P. aeruginosa* and other members of the oropharyngeal flora in cystic fibrosis patients. Interestingly, other species of the oro-pharyngeal flora, especially *Streptococcus* species, were found to induce up-regulation of virulence genes in *P. aeruginosa*, demonstrating a synergistic relationship and leading to enhanced virulence. Linda Vi, in her talk "Uncovering the Fountain of Youth: Rejuvenating Fracture Healing", demonstrated that transplantation of young bone marrow into old mice results in accelerated fracture repair in older mice. The main culprit of this enhanced repair was found to be the macrophages from the young bone marrow, and transplantation of the specific, isolated macrophages into the old mice was sufficient to improve fracture healing. The final prize-winning presentation "The Essential Role of Adipocyte FAK in Insulin Resistance and Adipose Tissue Remodelling" was by Cynthia Luk. In her talk, focal adhesion kinase (FAK) in adipocytes was shown to play a crucial role in diabetes, as adipocyte-specific FAK knockout mice were found to be insulin resistant. Her work demonstrates a new link between obesity and diabetes.

Poster Presentation Prize Winners:

Siddharth Nath (McMaster University)
Ram Anantha (Western University)
Jason Bau (University of Calgary)

Chosen as the top poster presented at the 2013 AGM, Siddharth Nath's work "Huntingtin Regulates Intracellular

Vesicular Trafficking in Response to Cell Stress" examined the role of huntingtin in endosome fusion during stress response. Ram Anantha presented his work "Th2-Polarized Invariant Natural Killer T Cells Reduce Disease Severity in Intra-abdominal Sepsis", which demonstrated that septic patients have an increased proportion of invariant natural killer T cells (iNKT) (*vs.* non-septic controls). In turn, polarization of the iNKT cells toward the anti-inflammatory phenotype resulted in significant reduction in severity in intra-abdominal sepsis. The final poster prize was awarded to Jason Bau for his work "Selective Inhibition of Topo II α by Salicylate Occurs through a Non-competitive Mechanism by Blocking DNA Cleavage". Bau examined a proposed role for a well-known anti-inflammatory agent, salicylate, which was demonstrated to decrease the ATPase activity of the enzyme topoisomerase II α , thus impacting the DNA topology.

Back to Basics

Basic science research continues to be an area of significant focus for MD+ trainees. The foundation of medicine relies on sound biological research that can be translated to benefit patients at the bedside; whether it be understanding the role of inflammation in diabetes or characterizing the role of early cardiac progenitor development, this basic research will significantly increase our understanding of the mysteries of our body during normal development and in response to disease.

For decades, the dogma of biology has been the linear progression of DNA to RNA to protein. The study of this progression has led to a significant increase in our knowledge of cell division and function. Recently, other classes of RNA have been identified that play significant roles in regulation gene expression; these include microRNAs and another class known as long non-coding RNAs. Man *et al.* (University of Toronto) attempt to show how lncRNAs contribute to endothelial cell gene expression. Their work identified *ENC-2* RNA as a potentially important lncRNA in the regulation of endothelial cell gene expression. In the area of cardiac progenitor development, Deshwar *et al.* (University of Toronto) are undertaking a study to explore the role of apelin receptors during early cardiac development. Using the powerful developmental model of the zebrafish, Deshwar observed how the loss of *MespAA*, part of the *Mesp* family of genes, results in the inability of progenitors to develop into cardiomyocytes. His work is the first to illustrate that the apelin receptor is critical to the activation of *Mesp* expression. In the field of obstetrics, Mosher *et al.* (University of Calgary) are leading a study to investigate the role of prostaglandin E2 pathway in the human myometrium. Their work demonstrates the regional differences in the mRNA ex-

pression of COX2 and EP3, which are important parts of the prostaglandin E pathway. This work has implications for the treatment of preterm labour, which continues to impact the safety of both the mother and baby.

Canadian CI trainees' fascination with stem cells was evident at the 2013 AGM, where stem cells and their derivatives were both the focus of rigorous research and tools for understanding diseases. The biological basis of autism spectrum disorder remains largely unknown and unexplored. Recent evidence has pointed to the role of *de novo* mutations in the scaffolding gene, *SHANK2*. Using human-induced pluripotent stem (iPS) cells derived from patients, Zaslavsky *et al.* (University of Toronto) characterized the functional role of *SHANK2* in neuronal function. Their work demonstrates the feasibility of using human iPS cells to study neuronal function. Together, these projects highlight the important work that is done in the field of basic cellular biology. Suen *et al.* (University of Ottawa) used endothelial progenitor cells (EPCs) derived from cryopreserved human mononuclear cells to improve pulmonary arterial hypertension in immune-deficient rats. In this pilot study, the authors established that xenotransplantation of human early EPCs may be effective in reducing experimental pulmonary arterial hypertension, suggesting that immune mismatch has a detrimental impact on efficacy. Wilcox *et al.* (University of Toronto) presented on spinal cord injury recovery following adult and embryonic stem cell transplantation. Grafted neural precursor cells migrated to damaged white matter and motor tracts, significantly improving white and gray matter lesions and improving gait following transplantation. These data warrant further work to improve this treatment paradigm for clinical translation. Two CI trainees focused on dermal stem cells, albeit in different contexts. Rahmani *et al.* (University of Calgary) characterized the dermal stem cells within adult hair follicles, uncovering them as a potential target for restoring hair growth and improving wound healing. Eslinger *et al.* (University of Calgary) examined the effect of human dermal stem cells on split-thickness skin grafts and showed that dermal stem cells can repopulate the dermis beneath the skin graft, thereby uncovering a new potential strategy to improve skin graft function.

Inflammation is now well understood to be a fundamental aspect of many diseases, and the topic was prominent at the 2013 AGM. Westwell-Roper *et al.* (University of British Columbia) focused their research on the role of interleukin-1 (IL-1) receptor antagonist (IL-1RA) on human islet amyloid polypeptide-induced islet dysfunction, and its effects on amyloid formation in a mouse model of type 2 diabetes with islet amyloid formation. Treatment with IL-1RA improved glucose

tolerance, with no effect on insulin sensitivity, providing evidence that IAPP-induced islet dysfunction in type 2 diabetes is mediated by IL-1, and suggesting that the protective effects of IL-1RA are associated with an altered inflammatory milieu. Woodsworth *et al.* (University of British Columbia) illustrated a biophysical model of T-cell toxicity by demonstrating, using mathematical models, that granzyme endosomes escape before pore formation occurs in the case of an open synapse. Due to the prediction of a high loss rate, these results challenge the dogma of a sealed immunological synapse. Ouyang *et al.* (University of Toronto) reported on the response of human coronary artery smooth muscle cells (hCASMCs) to monocyte signals. Their project focuses on the potential use of anovel degradable polyurethane as a synthetic artery, and on defining the role of synthetic biomaterial-monocyte interactions.

Other fascinating work from Ng *et al.* (University of Toronto) revealed the deleterious effects in habitual behavior formation with calcium sensor deficient mice, allowing further exploration of the role of synaptic plasticity in learning and memory. MacEachern *et al.* (University of Calgary) also presented a new study investigating the role of enteric glia. By inhibiting inducible nitric oxide synthase in experimental colitis, the electrogenic ion transport dysfunction, which can subsequently lead to epithelial barrier dysfunction in inflammatory bowel disease, was restored. Elsewhere, Antoun *et al.* (University of Ottawa) examined the role of prenyl diphosphate synthase subunit 1 (PDSS1) in obesity, which was identified as an important genetic locus related to the rate of weight loss in obese patients.

Examining the Small Things – Microbiology and Infectious Diseases

The human microbiome is complex and the number of microorganisms is more than a 100-fold greater than the number of genes within the human genome. How do these organisms contribute to human health? With recent insight into the role of microbiota in diseases ranging from obesity to autism, more researchers are looking into this ecosystem. The following studies focus on bacterial pathogenesis, host response and subsequent disease progression and highlight the complexity of infections. By elucidating these interactions, clinician scientists will be better positioned to develop treatments for a number of disease.

The presence of virulence factors, which are produced by bacteria to cause overt harm to the host, is a hallmark of pathogenic microorganisms. Bulir *et al.* (McMaster University) sought to investigate the function of translocator proteins essential to the Type III secretion system of *Chlamydia pneumo-*

niae. The translocation systems are used as a sensory mechanism to detect host cells and secrete proteins that aid in invasion. This group demonstrated that two proteins, CopB and CopD, not only behave as other known translocator proteins but also aid in the breakdown of red blood cells within the host.

An important aspect of pathogenesis is the host's response to microorganism invasion; a response that is essential for the establishment of infection. In some diseases, death can be caused by the host's response to a secondary infection; for example, the most common cause of death following influenza infection is a bacterial (e.g., *Staphylococcus aureus*; *S. aureus*) super-infection, which causes pneumonia. Armstrong *et al.* (University of Toronto) demonstrated that exposure to low doses of influenza virus was sufficient to prime the lung microvascular endothelium to leak upon subsequent exposure to *S. aureus*, an effect seen even days later. This may have important implications for the prevention of super-infections following influenza exposure. Cotton *et al.* (University of Calgary) showed the importance of the host inflammatory response by observing attenuation of neutrophil chemotaxis in cell-lines infected with *Giardia duodenalis*, facilitated by the production of cathepsin-like cysteine proteases. Elphinstone *et al.* (University of Toronto) have linked low levels of the host protein hemopexin, responsible for scavenging free heme, with increased mortality due to cerebral malaria. Mouse models showed increased susceptibility to cerebral malaria with decreased levels of hemopexin, but intriguingly heme levels were constant. They propose that exogenous administration of hemopexin may improve clinical outcomes in severe malaria.

How do we interact with the microorganisms in our environment and what occurs when there is dysregulation? Faria *et al.* (University of Calgary) sought to assess the microbial communities within septic patients using both molecular profiling and standard culturing methods, as often the blood cultures of patently septic patients return negative. The vast majority (95%) of septic samples were polymicrobial, as determined by molecular profiling, but 75% were negative, as determined by standard culturing techniques. Bacterial DNA could be detected up to 7 days post ICU-admission, despite being blood culture negative, suggesting a complex etiology. Gut epithelial barrier dysfunction is intricately linked to *Escherichia coli* (EHEC) 0157:H7 infection. Wu *et al.* (University of Toronto) pre-treated T84 epithelial cell monolayers with prebiotics and observed reduced induction of attaching-effacing lesions in response to EHEC infection. The modulation of epithelial barrier function may play an important role in the colonization of EHEC.

Continued Efforts to Better Understand and Treat Cancers

Reflecting the importance of cancers as a major cause of mortality and morbidity in Canada, cancers remain a major focus of study among many Canadian CI trainees, with 14 of the 63 abstracts directly related to cancers. A number of different cancers, from breast cancers to myeloma, are being studied by Canadian CI trainees who are examining various aspects of cancers, from pathophysiology to therapy.

Considering the heterogeneity of the different cancers with regards to their prognosis and sensitivity to treatment, the search for clinically practical biomarkers has been difficult. As we continue our quest to better understand cancers, novel biomarkers continue to be identified. Kuzyk *et al.* (University of Manitoba) examined changes in telomeric signals and copy number variations in aggressive neuroblastoma. Mesci *et al.* (University of Toronto) found that Pea3 expression levels form a spectrum in colorectal tissues; from lower levels in normal colon to adenoma and adenocarcinoma. Mesci *et al.* further characterized Pea3 to demonstrate its role in invasive behaviours seen with colorectal cancer cells. Pon *et al.* (University of British Columbia) characterized the MEF2 transcription factor, examining the impact of *MEF2B* mutations in Non-Hodgkin's lymphoma. Work done by Samuel *et al.* (University of Toronto) is the first to combine a large cohort of patient data, using copy number, gene expression and RNAi screens to identify putative driver genes in pancreatic ductal adenocarcinoma. Samuel's study uncovered several of these putative genes, of which ECT2 was found to play an oncogenic role in the disease process.

One of the most common malignancies that afflict children is medulloblastoma (MB), and this year a record number of trainees have made significant gains in the understanding of the pathogenesis of this disease. Advancements in treatment modalities for childhood MB have seen survival rates increase to more than 70%. Despite this, much of the mortality seen with advanced disease and treatment-induced morbidities continue to affect the survival and quality of life in patients. Two of the talks selected for oral presentations were studies done on MB. The first is the work of Manoranjan *et al.* (McMaster University) who studied the role of Sox2 in Shh subgroup MB, specifically the treatment-resistant population. This work has significant implications for the design of novel treatments to target this disease. In a Ptch+/- model of MB, Vanneret *et al.* (University of Toronto) investigated the role of Sox2 as a marker for quiescent medulloblastoma cells. Their data show that the Sox2+ population is chemo-resistant and is largely responsible for driving tumour growth *in vivo*. Another study,

by Aiken *et al.* (University of Manitoba), has demonstrated that CD271 is a selective marker for higher self-renewing cells in the Shh subgroup of MB. Finally, Wang *et al.* (University of Toronto) took a genomics approach to identify novel genes that maintain tumour progression. Together these studies have paved the way for novel therapeutics for MB patients.

Cancer therapy continues to be a prominent theme at the CSCI YIF. Rotin *et al.* (University of Toronto) screened a drug library and discovered a synergistic interaction between erlotinib and ethacridine in acute myeloid leukemia. Exploring the world of nanomedicine, Sindhwani *et al.* (University of Toronto) examined a novel nanoparticle system, with the goal of developing a system for sustained siRNA release. Aghaei *et al.* (University of Calgary) examined the effect of vascular disrupting agents in breast cancer cells, demonstrating that 5,6-dimethylxanthenone-4-acetic acid promoted necrosis of subcutaneous, but not osteolytic metastatic breast cancer cells. Cancer therapy generally presents a double-edged sword, and adverse effects of therapy are a common cause of morbidity among cancer patients. Interestingly, when Bernad *et al.* (McGill University) examined the amygdala and the hippocampus in small cell lung cancer patients treated with chemoradiation, they observed decreased volumes in both regions, and these decreased volumes were exacerbated with prophylactic cranial irradiation. These decreases may explain the previously observed finding that patients undergoing these therapies had poorer performance on some cognitive function tests.

In the Clinics

As the focus of the research landscape in Canada is quickly shifting towards patient-oriented research, it naturally follows that numerous projects presented at this year's meeting were of a strong clinical nature. With the ultimate goal of improving patient outcomes, many projects offered recommendations that could be used to guide policy makers in different areas.

Lane *et al.* (University of Toronto) summarized the cost-effectiveness of a Nurse Practitioner-led care transition program and discussed the program's ability to reduce readmission among high-risk seniors. Bailey *et al.* (Dalhousie University) presented their work on the impact of adverse events on healthcare costs for older adults undergoing non-elective abdominal surgery. Following similar trends in surgical studies, Hurton *et al.* (Dalhousie University) showed that resection rates and overall survival of pancreatic cancer patients in Nova Scotia are comparable to outcomes reported in the current scientific literature despite their apparent inferior access to adjuvant therapies. Dumaine *et al.* (University of Saskatchewan), on the other hand, focused on the inadequacy of renal biopsies

performed in Saskatchewan and suggested that alterations in practice, such as using a larger gauge biopsy needle, may improve various outcomes. Livingstone *et al.* (Western University) studied the effects of massive transfusions in pediatric trauma patients and its association with coagulopathy, severe injuries, long hospital visits and increased mortality. On the closely related subject of mortality, Roberts *et al.* (University of Calgary) validated an epilepsy specific risk adjustment index that could be used to improve mortality prediction. Elsewhere, Schmidt *et al.* (University of Calgary) examined the potential use of cardiovascular MRI (CMR) in diabetic patients. Using CMR, type 2 diabetic patients were observed to exhibit significantly different T1 values, which may reflect globally-increased collagen deposition in the diabetic myocardium.

Two studies were themed around pregnancy. Nowik *et al.* (Queen's University) demonstrated how patient characteristics, such as age, smoking, number of living children, diagnosis of severe preeclampsia and distance from hospital, predicted the rate of follow-up of patients at a maternal health clinic. Roy *et al.* (University of Calgary), on the other hand, showcased data from a longitudinal pregnancy cohort study that supported the idea that Aboriginal and other ethnic minority women scored higher on the Edinburgh Postnatal Depression Scale relative to White/Caucasian women.

On the theme of medical education in the clinical environment, Min *et al.* (University of British Columbia) presented their work on improving the assessment of physician competence and concluded that the halo effect may reflect true performance instead of rater error. Lastly, Murias *et al.* (University of Calgary) presented a systematic review of MRI abnormalities in children with developmental delays.

Concluding Remarks

Canadian CI trainees continue to display a wide depth and breadth of research, trainees focusing on topics of great importance to the well-being of Canadians, including cancers and infectious diseases. The CSCI-CITAC joint AGM continues to provide a forum for sharing of scientific ideas among the Canadian CI trainees, as well as providing the grounds for networking and career development.

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