
TRAINEE SECTION

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Scientific overview: CSCI-CITAC Annual General Meeting and Young Investigators' Forum 2014

Abstract

The Canadian Society of Clinician Investigators (CSCI) and Clinical Investigator Trainee Association of Canada/Association des cliniciens-chercheurs en formation du Canada (CITAC/ACCFC) annual general meeting (AGM) was held in Toronto during November 21-24, 2015 for the first time in conjunction with the University of Toronto Clinician-Investigator Program Research Day.

The overall theme for this year's meeting was the role of mentorship in career development, with presentations from Dr. Chaim Bell (University of Toronto), Dr. Shurjeel Choudhri (Bayer Healthcare), Dr. Ken Croitoru (University of Toronto), Dr. Astrid Guttman (University of Toronto), Dr. Prabhat Jha (University of Toronto) and Dr. Sheila Singh (McMaster University).

The keynote speakers of the 2014 AGM included Dr. Qutayba Hamid, who was presented with the Distinguished Scientist Award, Dr. Ravi Retnakaran, who was presented with the Joe Doupe Award, and Dr. Lorne Babiuk, who was the CSCI-RCPSC Henry Friesen Award winner.

The highlight of the conference was, once again, the outstanding scientific presentations from the numerous clinician investigator (CI) trainees from across the country who presented at the Young Investigators' Forum. Their research topics spanned the diverse fields of science and medicine, ranging from basic science to cutting-edge translational research, and their work has been summarized in this review.

Over 120 abstracts were presented at this year's meeting. This work was presented during two poster sessions, with the six most outstanding submitted abstracts presented in the form of oral presentations during the President's Forum.

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President's Forum oral presentations

Matthew Benesch (University of Alberta)
 Ayesh Seneviratne (University of Toronto)
 Nischal Ranganath (University of Ottawa)
 Alexandra Rogers (University of Calgary)
 Julie Lovshin (University of Toronto)
 Ryan Leigh (University of Calgary)

Matthew Benesch presented his work on breast malignancy inhibition. His group discovered that breast adipose tissue expresses >10,000-fold more autotaxin mRNA than 4T1 breast cancer cells, and that autotaxin inhibition delays breast tumour growth and metastasis and suppresses pro-inflammatory cytokine production in mice. Autotaxin inhibition provides a novel therapeutic strategy for breaking this vicious cycle of inflammatory cytokine and lysophosphatidate production, which drives breast tumour growth, treatment resistance and metastasis. Ayesh Seneviratne found that the islet-regenerative functions of ALDHhi UCB-derived hematopoietic progenitor cells remained intact following expansion in culture. This is key to their potential as an islet-regenerative therapy due to the low ALDHhi UCB cell fraction within peripheral blood mononuclear cells. Nischal Ranganath gave a presentation on the novel use of oncolytic Maraba virus (MG1) to selectively target and kill HIV-infected cells, including latently HIV-infected cells. As he had hypothesized, HIV-infected cells were more susceptible to MG1 infection and cytotoxic effects than uninfected cells, as demonstrated by a decrease in cell viability. Alexandra Rogers presented her work on the role of transcriptional repressor capicua (CIC) in neuronal progenitor cells. She showed that CIC regulated proliferation, migration and cell fate of oligodendrocytes. CIC ablation resulted in increased expression of glioblast markers in a mouse model. She concluded that loss of CIC may promote oligodendroglioma formation in vivo. Julie Lovshin presented a randomized, double-blinded, placebo-controlled crossover trial of liraglutide or placebo for 3 weeks to hypertensive subjects with type 2 diabetes. The results demonstrated that sustained liraglutide administration increased urinary sodium excretion and this was not associated with changes in ANP or blood pressure. Ryan Leigh investigated kinematic gait patterns in individuals with mild-to-moderate hip osteoarthritis. The researchers looked at 23 individuals with mild-to-moderate hip osteoarthritis and identified multiple gait abnormalities as compared with healthy control.

Community health

Studies on public health and community medicine are becoming increasingly important in the effective management and dispensation of equal healthcare to all. We had the pleasure of witnessing high quality research on the socioeconomic impact of healthcare at this year's AGM. Amrita Roy studied the various risk factors for and consequences of prenatal depression in aboriginal communities. Using the Edinburgh Postnatal Depression Scale (EPDS), Roy found that non-aboriginal women had significantly lower mean depressive symptom score and this was partially driven by socioeconomic factors. Andrea Jones investigated the role of marginal housing as a risk factor for mortality and substance use. Using the Framingham Risk Score, Jones found that substance use may be an indicator of mortality risk and could be an effective health care target. Natasha Lane investigated the role of socioeconomic status in moderating the effect of increasing chronic disease burden. The authors found that individuals with higher chronic disease burdens had significantly poorer survival. They suggest that targeting multimorbidity prevention efforts for patients with low socioeconomic status would reduce disparities in multimorbidity incidence. Kathleen Armstrong described the results of a study aimed at modelling cost-effective scenarios to replace conventional, in-person postoperative follow-up care with mobile follow-up care following ambulatory breast reconstruction. The effect was modelled based on RCT and prospective trial data comparing the effectiveness of in-person and mobile follow-up care. Preliminary modelling demonstrated that the replacement generated a societal and healthcare system incremental benefit of \$245 CAD and \$38 CAD, respectively, suggesting that mobile monitoring was safe and cost-effective for low-risk ambulatory patients. Lauren Lapointe-Shaw presented the results of a cost-effectiveness analysis aimed at identifying the optimal treatment strategy for recurrent *Clostridium difficile* infection (CDI). The lifetime costs and health effects of five strategies for a typical patient experiencing up to three recurrences were compared. Fidaxomicin and fecal transplantation by enema or nasogastric tube were found to be more cost-effective treatments for recurrent CDI, as compared with metronidazole.

Ashton Conner quantified the population-based prevalence of germline pancreatic ductal adenocarcinoma (PDAC) predisposition genes using the Ontario Pancreatic Cancer Study registry. Her findings indicated that the frequency of Lynch syndrome within PDAC was higher than previously estimated, suggesting a possible role for DNA mismatch repair deficiency testing for PDAC in at risk patients. Christopher Wallis analyzed data from a population-based retrospective

cohort study to identify risk factors for developing complications following radical prostatectomy. His findings suggested that complications are common following surgery. Furthermore, salvage or adjuvant radiation with surgery increased the rates of complications, but those rates were still lower than patients treated with radiation alone. Kevin Schwartz presented a study of the efficacy and cost-effectiveness of palivizumab (PMB) in the treatment of respiratory syncytial virus in infants with cystic fibrosis, using a Markov cohort model based on literature data. The results demonstrated that PMB was not generally cost-effective, but that clinicians may consider providing PMB to select CF infants given the potential long-term health benefits and relatively small budget impact.

Quality Assurance Research

In the field of medicine, we continue to look for ways of improving patient outcomes. Scores of applied research were presented at this year's AGM regarding healthcare management. Lauren Capozzi investigated the role of physical activity in managing symptoms and overall quality of life for head and neck cancer patients. They found that there was a relationship between physical activities and improved overall functioning and recommended physical activity for these patients. Dominique Mathieu evaluated the Quality of Life (QoL) and pulmonary function tests (PFTs) progression in patients with early stage non-small cell lung cancer (NSCLC) treated with stereotactic ablative radiotherapy (SABR). In the phase II prospective trial, SABR was found to be an effective therapy for medically inoperable NSCLC patients who may have achieved disease control while maintaining QoL and pulmonary function. Nicholas Light performed allele-specific analysis of gene expression and chromatin marks to investigate variants in cis-regulatory regions. Their findings related to the regulatory mechanisms, regional enrichment and epigenetic markers related to cis-regulatory SNPs, revealing allele-specific analysis as a useful variant mapping approach. Michael Zywiell investigated the health economic implications of perioperative delirium in elderly patients who underwent surgical treatment of fragility hip fractures. The authors found that nearly 50% of patients developed perioperative delirium and this led to a significant incremental in-hospital length of stay and its associated care costs. Natasha Seemann explored the relationship between physiologic and perceived stress as experienced by surgeons in the operating room. Six staff surgeons from varying specialties were studied for a minimum of three complete operations each. Intra-operative monitoring included heart rate, respiratory rate, sweat gland activity and salivary cortisol levels. The short-form State-Trait-Anxiety Inventory was used to as-

sess perceived stress. Seemann reported great variability in the physiologic manifestations and subjective experiences of stress.

Artuela Caku presented an open-label trial of lovastatin in 15 subjects for 3 months, assessing the impact on behavioral symptoms before and after treatment. The results demonstrated that lovastatin was safe and that a placebo-controlled trial in FXS is warranted. Nardin Samuel sought to determine if TP53 tumour suppressor gene variants correlated with the presence of TP53 mutations or influenced cancer risk in pre-menopausal breast cancer patients. TP53 polymorphism, rs1042522, was observed in a large proportion of patients in this study, and parallel studies of genome-wide methylation demonstrated methylation differences that are specific to TP53 germline mutation carriers in early-onset breast cancer. Emilie Belley-Côté performed a meta-analysis to determine whether vitamin K agonist (VKA) dosing informed by CYP2C9 and VKORC1 genotype significantly decreased adverse outcomes, using a random effects model that included 12 studies involving 3217 patients. They found that genotype-guided VKA dosing did not decrease a composite of death, thromboembolism, and major bleeding but appeared to improve time in therapeutic range. Gwyneth Zai studied 222 OCD patients using a SNP array in order to investigate genetic correlates with response to SSRIs and SRIs. They detected statistically significant associations with variants in the 5HT2A and 5HT1B genes, suggesting their potential roles in drug response.

Mino Mitri aimed to understand the context upon which a palliative care approach is taken in patients with chronic obstructive pulmonary disease (COPD). The authors took a qualitative approach to interviewing care takers to identify themes associated with palliative care and its role in the management of COPD. Egan Goligher explored the association between diaphragm inactivity during mechanical ventilation and the rate and magnitude of diaphragmatic atrophy. Seventy-two intubated ICU patients who were expected to continue receiving mechanical ventilation for at least 24 hours were enrolled within 72 hours of intubation. Among patients ventilated for at least 5 days, 63% lost more than 10% of baseline diaphragm thickness, with 26% losing more than 20% thickness, which was associated with worsening outcomes. This supports the hypothesis that diaphragmatic atrophy develops rapidly in many patients during mechanical ventilation. Victoria McCredie investigated palliative care in patients with severe traumatic brain injury. The authors performed a multicenter retrospective cohort study and looked at the timing of withdrawal of life support as it related to mortality. The authors concluded that centers rendering early decisions related to withdrawal of life-sustaining therapies do not have worse out-

comes than those making later decisions. Mehdi Tahiri's work centered on evaluating short and long term outcomes with Self-Expanding Metallic Stent (SEMS) insertion in palliative esophageal cancer patients. She conducted a retrospective review of all patients who underwent esophageal stenting for palliation of malignant dysphagia over a 24 month period. Results demonstrated that the procedure was indeed safe and effective, with no cases of stent migration and a low incidence of tumour overgrowth/undergrowth. In a multi-centre prospective study, Anick Nater examined prognostic factors for survival in cancer patients with Symptomatic Metastatic Epidural Spinal Cord Compression (MESCC). A multivariate Cox-regression analysis revealed that only spinal metastasis involving four or more vertebral bodies had a negative impact on survival. Kathleen Bingham presented a secondary analysis of a multi-center randomized trial that investigated the outcome of psychotic depression. She focused on the relationship between psychotic depression and vascular disease and concluded that vascular risk, as defined by the Framingham Stroke Score, is an independent negative predictor of depression severity.

Study Design and Execution

Clinical studies are a major aspect of medical research, and these studies form the underpinnings of our evidence-based approach to medicine. A number of rigorous and high quality clinical studies were presented at the AGM. Michael Richards presented a study on amblyopia, which is a developmental visual impairment resulting from an abnormal visual experience during early development. Using audiovisual integration, they tested a group of controls using a dark acoustic chamber and their next step will be to repeat the study on patients with amblyopia. Brett Shaw investigated the role of orthostatic hypotension as a risk factor for falling in elderly care home residents. Shaw and colleagues generated a frailty index and found a strong correlation with prospective falling. Paul Kudlow developed a novel cross-publisher content recommendation widget (TrendMD) to augment the reach and impact of online scientific, technical and medical (STM) publishers. They found that using this cross-publisher recommendation link improved visibility and reach of STM articles. Philip Jong investigated the validity of the Seattle Heart Failure Model (SHFM) as a prognostic tool when applied to a clinical practice setting. They followed patients to ascertain health outcomes and concluded that SFHM showed adequate prediction of event-free survival in patients with chronic heart failure. Rayzel Shulman evaluated how physicians value technology as it relates to reflective clinical practice. The authors conducted an open-ended, semi-

structured interview concerning pediatric insulin pump therapy. The authors found that technology adoption involved value judgments as well as effectiveness and cost. Sarah MacEachern used a questionnaire-based approach to characterize postictal symptoms to better understand how these symptoms impact the ability of children with epilepsy to perform their regular activities. Meera Rayar designed a study to explore the patient, disease and health care system factors that influence the choice of locus of care for Ontario adolescents with cancer. This study was driven by the observation that adolescents have not experienced the same improvements in cancer survival when compared with other age cohorts. This project has now completed the data collection phase and data analysis is ongoing.

Basic Science

Basic science research was a central focus of this year's meeting, with many CI projects focused on answering the fundamental questions of how biological systems work. The volume and quality of basic science research presented was immense, and the work is summarized by medical subspecialty.

Cardiology

Benjamin Steinberg presented an investigation of heart rate variability (HRV) as a biomarker of inflammatory status in adult mice. This study demonstrated that cardiac-based diagnoses may be beneficial in determining inflammatory status and affords advantages over invasive methods such as serological inflammatory biomarker measurements. Ashish Deshwar studied the role of the Apelin receptor (*Aplnr*) in early cardiac progenitor migration using morpholino anti-sense oligonucleotides to modify gene expression levels. They found that increased Nodal activity in *aplnr* mutants resulted in near complete rescue, suggesting that *aplnr* is key to enhancing Nodal function. Ilya Mukovozov studied the effect of Slit2, a neuronal chemotaxis inhibitor, on the recruitment and adhesion of monocytes in using BrdU pulse labelling in LDLR mutant mice. They observed that Slit2 inhibited monocyte endothelial adhesion in atherosclerotic regions of blood vessels. Jieun Kim created a novel *in vitro* high-throughput human myocardial infarction model by polarizing two key pro-inflammatory macrophage types with different cytokines. They found that these macrophage types induced cardiomyocyte injury.

Dermatology

Brian Keller optimized the use of oncolytic viruses as a therapeutic strategy in malignant melanoma. The preliminary findings demonstrated that vaccinia V (VacV) can be tailored for specific oncolytics. Sam Saibil investigated the role of PPAR-delta signalling in the control of cytotoxic T lymphocyte (CTL) metabolism in a murine model of melanoma and demonstrated that PPAR-delta agonists can be used to alter the metabolism of CTLs and enhance the clinical efficacy of adoptive cell therapy in melanoma.

Diagnostic Imaging

Cameron Kaye received a poster award for his research aimed at studying the properties of various contrast media for functional microwave imaging (a low-cost portable soft-tissue imaging modality). His preliminary findings highlighted the plausibility of incorporating contrast agents in microwave imaging. Patrick Steadman presented a surface-based analysis of the white-grey matter tissue boundary of the cerebellum in two separate mouse transgenic lines. They found that foliation differences in depth were found extensively across the white-grey matter boundary, showing that cerebellum morphology can differ markedly between transgenic lines.

Endocrinology

Synthia Luk investigated the role of adipocyte caspase 8 in weight gain and glucose intolerance in a mouse model. Luk found that caspase 8 played an important role in promoting obesity and glucose intolerance, which may have implications in treatment for type 2 diabetes. GhadiAntoun examined the physiology of skeletal muscle mitochondria in diabetic and non-diabetic obese individuals. Surgically excised human rectus abdominis muscle exhibited lower mitochondrial respiration across many respiratory states in diabetic patients, suggesting impaired skeletal muscle metabolism in patients with type 2 diabetes.

Gastroenterology

Tao Wang demonstrated that senescence fibroblasts disproportionately promote *in vitro* pancreatic cancer invasion, correlating with elevated levels of cytokines. Cytokine receptors on these senescence fibroblasts may, therefore, be potential targets for future therapies against pancreatic cancer. David Lim adapted a translational piglet model of neonatal short bowel syndrome and studied exogenously administered GLP-2 on small bowel length. Although no difference was observed in

small bowel length, jejunum and ileum villus height and permeability were increased following treatment. Menglin Yang investigated the potential for *Nepenthes* plant extracts to act as a celiac disease therapy by digesting gliadin. Carrying out enzyme digests and mass spectrometry, they determined that *Nepenthes* extracts digested gliadin better than pepsin and lowered the levels of immunogenic peptides.

Hematology

Jeffrey Man presented his work on long non-coding RNAs (lncRNAs), and their ability to regulate endothelial gene expression and function. They discovered that divergent transcription of long non-coding RNA at the GATA2 locus in human endothelial cells regulated genes implicated in hypoxia and angiogenesis. These results provided important new insights into gene regulation by divergent transcription of lncRNA produced from the GATA2 locus. Brent Williams studied the impact of monoclonal antibody (mAb) pretreatment, directed at NK-activating receptors, on the cytotoxicity of NK cell lines in patients with acute myeloid leukemia (AML). His findings showed a novel means to enhance cytotoxicity of KHYG-1 human malignant NK cell lines by pretreatment with mAbs against NKp30 and NKp44, which led to enhanced killing of AML primary blasts *in vitro*. Maria Georgescu presented a study of the role dexamethasone in reducing the FVIII immune response in a mouse model of hemophilia A, demonstrating that administration of dexamethasone during initial FVIII exposure reduced the anti-FVIII immune response. Lianne Rotin presented her work with Bruton's tyrosine kinase-inhibitor, ibrutinib. Her work showed that ibrutinib synergized with ROS-inducing agents, including daunorubicin, by inhibiting downstream targets, sensitizing acute myeloid leukemia cells to reactive oxygen species inducers. Michael Atkins used a mass spectrometry-based phospholipidomics approach to characterize and profile oncolytic virus-infected leukemia cells. Their results suggest that oncolytic virus infection did not significantly alter the phosphocholine-derivatized lipidome of infected cells. Erin Degelman investigated how hTERT mutations and telomere shortening impact disease progression and drug response in aplastic anemia, myelodysplastic syndrome, and acute myeloid leukemia. Using a leukemic cell line, they observed that hTERT mutant expression delayed G1/S transition, potentially impacting differentiation in hematopoiesis. They also found that these cells exhibited increased resistance to conventional therapy. Nick Holzapfel devised an approach to survey the regulatory impacts of MSI2 in leukemias. Using RNA-sequencing followed by cross-linking immunoprecipitation in

lentiviral mediated knockdown of MSI2 in human AML stem cells, they hope to generate an exhaustive list of RNA targets regulated by MSI2. Parker Jobin characterized the role of matrix metalloproteinases (MMPs) in processing tryptophanyl-tRNA synthase (WRS). They found that MMP7 and MMP12 produced N-terminal truncations in WRS processing, and may act as antiangiogenic targets in WRS.

Infectious disease

David Bulir presented a study of CopB and CopD proteins and their interactions with a cognate chaperone. The results demonstrated that mutated peptides blocked chlamydial infection and could represent a novel class of therapeutics. Gordon McSheffrey presented a study of the response of M1 and M2 macrophages to *N. gonorrhoeae*. The authors measured the secretion of several cytokines and chemokines and demonstrated that *N. gonorrhoeae* skewed macrophages towards the M1 phenotype and may contribute to gonococcal evasion of the immune response by suppression of an adaptive T-cell response. Paul Adamiak presented a study of variation in transferring binding protein B (TbpB) in the context of vaccine design and used X-ray crystallography to solve the isotype I TbpB structure. The study demonstrated an approach to mitigate TbpB vaccine escape using a protein subcomponent. Richard Xiang presented a study investigating the mechanistic role of Rac1 in microbial killing of *Cryptococcus neoformans* through natural killer (NK) cells, using cells lines from healthy donors. The results demonstrate that Rac1 was activated in response to *C. neoformans* and controls NK-mediated cryptococcal killing through the PI3K-Erk pathway. Robyn Elphinstone presented a study of increasing bioavailable nitric oxide (NO) to improve clinical outcomes in malaria in a mouse model. The results showed that loss of the enzyme that reduces S-nitroglutathione and, therefore, that amount of S-nitrosothiol, improved outcomes in an experimental model of cerebral murine malaria.

Neurology

Kevin Wang's project focused on the role of Sleeping Beauty (SB) and piggyBac (PB) transposon systems in medulloblastoma initiation and progression. His work, therefore, aims to create transgenic mouse lines carrying these mutations, and develop a penetrant model of medulloblastoma. This research will allow discrimination between shared maintenance genes from initiation genes and passenger events, and reveal potential therapeutic targets. Kirill Zaslavsky's work used induced pluripotent stem cell-derived neurons to explore the mechanisms by

which SHANK2 mutations, implicated in a small subset of autism spectrum disorder (ASD), affect neuronal function. Zaslavsky found that SHANK2-mutation neurons failed to extend neurites in response to KCl treatment in 12-week old neurons grown on astrocytes, demonstrating inconsistent differences between control and SHANK2 mutant neurons in synapse number and miniature excitatory postsynaptic potential (mEPSC) frequency. Together these results suggest IPSC-derived neurons can be used to study neuronal phenotypes resulting from ASD-linked mutations. Alexandra Kuzyk investigated the effect of N-myc amplification on telomere organization in patients with neuroblastoma (NB). Her findings concluded that N-myc amplified NBs had unbalanced 17q gain, and that alteration in telomere organization was dependent on the level of MYCN expression. Kyle Eastwood's work centered on investigating the biomechanics of hydraulic elastically deformable contractile McKibben actuators for the purpose of increasing articulation in neuroendoscopy. Pressure-displacement and pressure-contractile force curves for five different actuators were recorded. Preliminary work suggests that soft flexible actuators were indeed promising for expanding the reach of neuroendoscopy. Annie Drapeau examined the use of intra-arterial (IA) infusion of Temozolomide (TMZ), in conjunction with radiotherapy, for the treatment of glioblastoma. Annie concluded that method of TMZ administration impacted its CNS delivery, but a single dose of TMZ by IA infusion showed no additional benefit in rats. Enoch Ng examined the role of neuronal calcium sensor-1 (NCS-1) on behaviours that depend on intact striatal dopamine signalling in a gene knockout study using mice. He concluded that knockout of NCS-1 decreased motivation to work for a food reward without significantly impairing acquisition of operant responding. Jared Wilcox assessed the effects of neural progenitor cell transplantation in a rat model of traumatic cervical cord injury. The grafts showed long-term survival, even more than three months after implantation. The treated rats showed improved spinal cord function, especially forelimb function and grip strength. Joseph Catapano assessed nerve regeneration in response to N-acetyl cysteine and acetyl-L-carnitine in neonatal rats after sciatic nerve injury. He found that N-acetyl cysteine significantly improved motor neuron survival during the treatment period while acetyl-L-carnitine did not. Laura Sens won a prize for an outstanding poster presentation for her work on stress-induced cannabinoid receptor regulation. In vitro patch clamp recording in hypothalamic tissue slices from rats that had been stressed showed short-term plasticity of the cannabinoid type-1 receptor. She concluded that endocannabinoid signalling was labile and could be regulated by homo-

typic and novel stressors. Michael Keough presented his work on the use of chondroitin sulfate proteoglycan synthesis inhibitors to promote myelin regeneration and immunomodulation in experimental models of demyelination. *In vitro* and *in vivo* assays of murine oligodendrocyte precursors or astrocytes were assessed for their myelinating capability after exposure to chondroitin sulfate proteoglycans and an inhibitor, fluorosamine. They found that systemic treatment with fluorosamine promoted remyelination and reduced the proliferation of T cells *in vitro*. These results show promise for the development of the next generation of therapeutics, which would focus on the direct enhancement of remyelination, in addition to immunomodulation. Branavan Manoranjan investigated the role of pituitary adenoma stem cells (PASCs) in driving clonal growth of human pituitary adenomas by probing stem cell gene expression profiles of eight primary and matched-recurrent adenomas. They found that expression of the CD15 gene was the most predictive factor for increased proliferative and self-renewal capacity, which agreed with clinical/pathological correlates of adenoma onset and invasiveness. Michael Chen worked towards developing a MALDI-MS method to quantify 25OHD2 and found that although native D2 is undetectable on MALDI-MS, chemically derivatized D2 yielded quantifiable spectral peaks; providing a proof-of-concept for the potential of this assay. Holly Fan studied the impact of the Warburg effect on the clearance of amyloid- β in Alzheimer's Disease. They found that Warburg effect enzymes, PDK1 and LDHA, appeared to increase A β clearance, suggesting a potential mechanism for the Alzheimer's drug J147.

Oncology

Karineh Kazazian led a project to investigate the effect of over-expressing a putative oncogene, Plk4 in HeLa cells. This study discovered that Plk4 enhanced cancer cell spreading, polarity, migration and invasion; all features of highly aggressive cancer cells. Kim Tsoi presented a novel strategy to synthesize a versatile quantum dot conjugate platform capable of one-step functionalization with a variety of biological moieties. This technique addresses a current limitation to widespread use of this powerful technology, ideal for both *in vitro* and *in vivo* cell labelling applications. Mark Chandy studied the role of the c-Myb transcription factor in regulating the expression of the microRNA, miR-143/145. Using flow cytometry, sequencing, chromatin immunoprecipitation and site-directed mutagenesis, they found that c-Myb was necessary for miR-143/145 enhancer activity.

Orthopedics

Brandon Hisey built on previous work that contradicted the classical theory of muscle contraction by demonstrating higher active than passive forces of myofibril contraction beyond lengths of myofilament overlap. They showed that such differences diminished at higher levels of muscle organization, such as skinned fibres and whole muscle, and suggested that the effects of extracellular structural elements may mask the molecular factors modulating myofibril force at long sarcomere lengths. Linda Vi presented a study exploring the functions of macrophages during fracture repair and aging in a mouse model of tibial fractures, in the context of ablated macrophages. This study demonstrated that old animals retain the capacity for fracture healing and exposure to young macrophages can overcome age-related aberrant macrophage signaling. Marc-Olivier Deguise investigated the molecular pathways implicated in the reduction of muscle fiber size in mouse models of Spinal Muscular Atrophy (SMA). They found that the myogenic program was misregulated and delayed in two different mouse models of SMA, and that muscle atrophy appeared to be mediated through FoxO3 transcriptional regulation. These results strongly reinforce the idea that intrinsic muscle defects, in addition to atrophy, led to SMA muscle phenotype. Jeremiah Hadwen presented his work investigating the potential for a p38 pathway-dependent small molecule, Anisomycin, as therapeutic for Duchenne Muscular Dystrophy. They discovered that treatment with anisomycin caused an inhibition of the p38 pathway led to an induction loss of utrophin, a constitutively-expressed protein that restores sarcolemmal stability and alleviates symptoms in mice models of muscular dystrophy. Biochemical and behavioural tests are currently underway to confirm a systemic effect of anisomycin on the mouse phenotype. Anand Laknani presented work characterizing the anabolic effects of clodronate (a non-nitrogenous bisphosphonate) on cartilage. They found that clodronate induced a mild anabolic effect, which increased extracellular matrix accumulation and calcium ion signalling, suggesting transduction through the purigenic receptor pathway.

Respirology

Barbara Maciejewski presented a study of primary human bronchial epithelial cells cultured in human rhinovirus (HRV); alone or in combination with bacteria. The results demonstrated that HRV and bacteria synergistically induce CCL20 expression at the transcript and protein levels and identified a novel target for therapeutic intervention. Raidan Alyazidi presented a study investigating mast cell infection with RSV using

human cord blood-derived mast cells. The results demonstrate that human mast cells produced multiple mediators, in response to RSV, through type I interferons. John Soleas aimed to engineer an apicobasally-polarized respiratory epithelium, with planar alignment induced by microgrooved gelatin hydrogels. These cells were then assessed under microscopy and alignment and apicobasal polarization were observed. Neil Goldenberg investigated the role of TRPV4 in hypoxic pulmonary vasoconstriction. Wild type mice undergoing TRPV4 inhibition and *trpv4*^{-/-} mice. Knockout mice displayed reduced HPV, and TRPV4 inhibition blocked hypoxia-induced calcium flux.

Women's Health

Long Nguyen used an oncogene transduction strategy to produce human breast cancers *de novo*. They were able to create primary tumours that resembled ductal carcinomas, and secondary tumours were obtained after another 8 weeks that showed more advanced histological features. These findings showed that biologically diverse, serially transplantable polyclonal breast cancers can be efficiently and rapidly generated from different human mammary cell types transduced with a single oncogene. Vanessa Kay studied the effects of uterine natural killer, angiokines, on angiogenesis to assess their potential role in decidual angiogenesis of pregnancy. To this end, they developed a model for the study of decidual angiogenesis using the retinas of neonatal mice.

Applied Medical Research

As we acquire knowledge from the basic sciences, we, in turn, seek to apply this knowledge to positively influence patient outcomes. Many of this year's presentations showcased the bench-to bedside translation of knowledge. Nathan Kolla characterized changes in monoamine oxidase-A (MAO) distribution volume in impulsive, violent offenders with Antisocial Personality Disorder (ASPD) and high psychopathic traits using a Harmin Positron Emission Tomography study. His work demonstrated that a reduction of brain MAO-A levels was found in individuals with ASPD, and supports an important extension of preclinical models of impulsive aggression into human disease marked by pathological aggression and impulsivity. Sindy Magnan sought to evaluate the effectiveness and tolerability of androgen deprivation therapy for patients treated with external beam radiation therapy combined with a high-dose-rate brachytherapy boost for localized prostate cancer. They found that the addition of androgen deprivation therapy did not seem to yield to a significant increase in bio-

chemical recurrence-free survival, but was associated with greater sexual toxicities. Mai El Banna found that skin picking and nail biting are highly prevalent in patients with Tourette Syndrome, particularly when there is comorbid Obsessive Compulsive Disorder (OCD). These findings have clinical implications as they highlight habits that clinicians may consider in the assessment and management of Tourette Syndrome. Elia Abi-Jaoude investigated striatal dopamine receptors in Tourette Syndrome using positron emission tomography (PET). In his study, healthy controls and patients with Tourette Syndrome showed similar dopamine D2/D3 receptor availability measures, challenging the notion that striatal dopamine receptors play a major role in Tourette Syndrome. Jacob Cooley used diffusion tensor imaging (DTI) to assess brain white matter changes in patients with early psychosis who use cannabis. He described a decrease in fractional anisotropy in the left superior longitudinal fasciculus in patients relative to controls. Interestingly, he found evidence of increased white matter integrity in patients with heavier lifetime cannabis use within that same region. Jennie Pouget challenged the concept of schizophrenia being caused by aberrant activation of the immune system. Very large discovery and replication cohorts were analyzed using genome-wide association studies. She concluded that the few single-nucleotide polymorphisms in the major histocompatibility complex associated with schizophrenia were not the most significant variants in their respective genetic regions.

Siddarth Nath characterized a novel spinocerebellar ataxia variant involving the *ATXN7* gene. Whole exome sequencing was conducted in primary human skin fibroblasts sourced from patient 13CG990, as well as from his mother and father, to determine mutations. Researchers were able to demonstrate that ataxin-7 nuclear localization was enhanced, and that mitochondrial morphology was altered in the patient's cells. Victoria Baronas investigated the role of voltage-gated potassium channels in the developing nervous system, and the basis of their electrophysiology. Their observations suggested a unique role for voltage-gated potassium channels, and described a novel mechanism of channel regulation that influences channel activity during bursts of cellular electrical activity. Michael Tseng investigated the role of brain-derived neurotrophic factor expression, basal calcium levels and cell proliferation in an olfactory neural precursor study model of bipolar disorder. Using B-cell lymphoblast cell lines and olfactory neural precursor cells from patients with lithium-responsive bipolar disorder, they reported that lithium may affect neurogenesis due to its impact on cell proliferation. They also discovered that changes in cultured olfactory neural precursor cells demon-

strated dysregulated cell cycle dynamics, possibly also affecting neurogenesis. Aaron Springs presented about high frequency oscillations (80-250 Hz) on intracranial electroencephalograms (iEEG) as a way to detect the seizure onset zone in patients with epilepsy. Spike-associated high frequency oscillations identified the seizure onset zone with high specificity, underlining the potential of this technique to change clinical practice. Craig Beers sought to determine whether high frequency oscillations could be recorded with iEEG during functional MRI (fMRI) scanning. He found that this was not only possible, but also that high frequency oscillations and the fMRI activity associated with these events helped localize the seizure focus more accurately than epileptic spikes.

Anita Villani studied the relationship between PIN1 expression and cancer phenotype in patients with Li-Fraumeni syndrome (LFS) using quantitative PCR and Western blot techniques. Her results demonstrated that LFS patients with PIN1 (-)842 GG genotype had an earlier age of cancer onset. Christopher Aiken identified novel biomarkers for subtype specific medulloblastoma phenotypes using the BD Bioscience Lyoplate screening platform. His work highlights a new approach to screening for differentially expressed surface markers across matched samples. Kristine Woodward assessed motor networks in frontal lobe epilepsy using task-based and resting-state fMRI. Her studies revealed motor network disturbances in frontal lobe epilepsy, which was more pronounced in patients with a higher seizure burden; possibly explaining the motor deficits that were seen in those patients. Ian MacNairn conducted a review of the health implications of play on childhood development. The authors examined existing literature on the role of activity in natural spaces with health outcomes. They concluded that increased time spent in play and activity lowered morbidity both during childhood as well as adulthood.

Shari Manga conducted a systematic review of cardiac resynchronization therapy (CRT) and its readout of left ventricular reverse modelling as it relates to reduced mortality. Six electronic databases were searched and the pooled mean increase in left ventricular ejection fraction was 3.5%, which was associated with a lower risk of death. Ben Ouyang's research evaluated the feasibility of using focused ultrasound for image-guided non-invasive cardiac ablation. During simulation he found that after delivering energy for 1.9 seconds, a volume of 3x3x10mm was ablated, with peak temperature reaching 62°C. While preliminary, this simulation demonstrated that transthoracic focused ultrasound ablation is possible in targeting structures as deep as the cardiac ventricular wall. Amanda Murphy presented results of a preclinical study aimed at evalu-

ating the effect of losartan, an angiotensin receptor blocker (ARB), on hypertrophic scar development in rat model. She found that losartan was associated with decreased cutaneous scar formation in rats, with immunohistochemical analysis revealing decreased density of inflammatory cells and myofibroblasts in losartan-treated specimens relative to controls.

Adam Katchky explored the impact of two different types of total knee arthroplasty (TKA) implants (e.g., cruciate-retaining and posterior-stabilized) on balance recovery and knee joint biomechanics. He tested the hypothesis that patients receiving cruciate-retaining TKA will demonstrate better balance, as evidenced by a higher threshold for stepping and multiple stepping and joint mechanics more similar to controls, when compared with those receiving posterior-stabilized TKA. The aim of Kristen Barton's study was to characterize cartilage damage following idealized anterior cruciate ligament reconstruction (ACL-R) surgery after dexamethasone injection. Six skeletally-mature, female sheep were allocated into three groups: ACL-R + DEX (n=2), surgical sham (n=2) and non-operated controls (n=2). Preliminary results demonstrated that one injection of DEX immediately after ACL-R surgery mediated induction of cartilage damage at 2 weeks post-surgery. Christopher Walsh presented a clinical study of patients with ICU-acquired weakness (ICUAW) with percutaneous muscle biopsies of the vastuslateralis in 24 patients and eight control subjects and differential gene expression was determined. The results demonstrated differences in transcriptional networks between ICUAW and controls.

Alex Frolkis' research assessed the association between smoking status and the need for intestinal resection among patients with Crohn's Disease (CD). Results showed that the effect of smoking on the need for surgery was dependent on the age at diagnosis of CD: smoking only increased the risk of surgery for patients diagnosed after the age of 80, but not for those diagnosed from 17-40 years. Abdul Elkadri presented a study of SNP genotyping of 9478 patients from the iNternational Early Onset Pediatric IBD Cohort Study (NEOPICS) and NIDDK consortia. The results demonstrated that IBD SNPs identified in adult studies are distinct from the loci implicated in pediatric IBD, playing a lesser role in patients under the age of 6 years. Emily MacKay characterized fatty acid metabolite abundance in serum from individuals with colorectal cancer using gas and liquid chromatography-mass spectrometry. These findings suggested that circulating fatty acids are altered in colorectal cancer, due in part to increased expression of SREBP1c transcription factor modulating host-derived IGF-1. Helen Cheung presented a study on patients with colorectal liver metastases who have had a gadobutrol-enhanced

liver MRI (3T). These patients often present with hyperenhancement on delayed-phase -an imaging feature often used to exclude malignancy. This study found that hyperenhancement of colorectal liver metastases was a common finding, and may represent a diagnostic imaging pitfall to colorectal liver metastases identification. Dmitry Rozenberg presented a study of 169 lung transplant candidates, assessing the association of thoracic computed tomography (CT) muscle cross-sectional area (CSA) with exercise capacity, quality of life and clinical outcomes. The results demonstrated that thoracic muscle CSA may have some utility in predicting post-transplant outcomes, but further study is required. Monica Faria-Crowder presented a study of molecular analysis of bacterial DNA in whole blood to detect sepsis infections. The results demonstrated that bacterial DNA profiles were identified in the blood of septic patients both in the ICU and ED and showed that molecular profiling could complement routine blood culture analyses to identify bacterial DNA profiles. Eric Zhao investigated trends in BRCA1/2 mutation, cisplatin use and cisplatin response, with a BRCA signature exposure. Preliminary findings suggested that BRCA signature exposure may be predictive of cisplatin response, and this work may eventually improve methods for detecting effective BRCA1/2 status and thereby the capacity to guide therapy.

Medical Education

Medical education was a small but growing aspect of this year's AGM. Jonathan Keow presented about a discussion group held at the CFMS AGM seeking to establish the merits of including research as a mandatory curriculum requirement of undergraduate medical education. He explored whether this could improve the scientific competencies and skills of tomorrow's clinicians and foster innovation. Amanda Khan's poster highlighted her approach to developing stomach phantoms for surgical simulation of gastrointestinal stromal tumour (GIST) resection. A digital model was created, based on the CT scans of a patient with GIST, the mould was then 3D printed and filled with silicone rubber. Samples with varying ratios of silicone rubber to other additives continue to be tested for the degree to which they mimic real stomach tissue. Such research will contribute to the development of a phantom-based curriculum for the training of new surgical residents. Acya Toprak presented interim results of a case study investigating the validity of the Surgical Procedure Feedback Rubric (SPR); an assessment tool designed to document resident performance during single, directly-observed operative encounters:191 SPRs were completed across 15 General Surgery, 15 Orthopaedic

and five Obstetrics and Gynecology residents. Interim analysis revealed the utility of the SPR in distinguishing the intraoperative performance of junior and senior residents. Cynthia Min explored why physicians may not be engaging in self-directed performance improvement and why the design of physician performance review programs may not be conducive for quality improvement. Analysis revealed that motivational and knowledge-related factors were major contributors to the low impact of physician performance review programs on quality improvement in practice. Janelle Rekman described the results of a consensus group of five expert surgical staff and two surgical residents aimed at discussing essential elements of competency in surgical clinic. Using the nominal group technique to generate and prioritize ideas in consensus, 13 independent items were identified and used to develop a single patient encounter assessment tool that is currently being piloted at the Ottawa Hospital. Jonathan Fuller in his presentation argues for a more integrated role for biomedical science in models of knowledge translation (KT) and evidence-based treatment. Using a method called rational reconstruction, Fuller deconstructed the KT model. He described how basic science provides clinically-relevant knowledge, and not just pre-clinical data, and that clinician-scientists are well poised to integrate this knowledge into evidence-based treatment at various points in the KT model. Marisa Louridas aimed to identify components used in the selection process for general surgery residents across the country and establish a national consensus on the desired traits for candidates entering general surgery and the technical skills assessments that would be most helpful during selection. Delphi methodology was used to achieve consensus amongst program directors across Canada. The top five traits for success in general surgery training identified were work ethic, passion for surgery, teamwork, ability to assimilate information and sound decision-making. Performance on the one-handed tie and subcuticular suture were deemed the most appropriate technical skills for inclusion into the selection process. The objective of Peter Szasz's study was to outline a consensus on the operative procedures and tasks that are appropriate across all levels of general surgery training and outline a consensus on procedures where performance differences are commonly exhibited across general surgery training. Ultimately, a training framework including 101 unique procedures and tasks, both open and minimally-invasive, was generated. Such information will be valuable in informing the development of competency-based assessments.

Concluding Remarks

Clinician Investigator trainees are a small but growing field of medical trainees in today's world, and each brings with them a skill set that uniquely positions them to answer and ask the questions that are critical to advancing the field of medicine. The work presented at the CSCI-CITAC AGM demonstrates the trainees' commitment to high quality research and shows an extensive breadth of scope. As we look to the future, we can see that the Young Investigators' Forum will provide a unique place to share ideas and to sample an amazing cross-section of work, while continuing to provide a place for mentorship and career development.

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