TRAINEE SECTION

Ghadi Antoun, BSc^{1,4}
Véronique D. Ram, PhD^{1,2}
Xin Wang, BHSc^{1,3}
Jared T. Wilcox, MSc^{1,3}
Ju-Yoon Yoon, MSc^{1,5}

¹ CITAC Executive

² MD/PhD Program, University of Calgary

³ MD/PhD Program, University of Toronto

⁴ MD/PhD Program, University of Ottawa

⁵ MD/PhD Program, University of Manitoba

Scientific overview: CSCI – CITAC Annual General Meeting and Young Investigator's Forum 2012

Abstract

In 2012, the Annual General Meeting of the Clinical Investigator Trainee Association of Canada – Association des cliniciens-chercheurs en formation du Canada (CITAC – ACCFC) and the Canadian Society of Clinician Investigators (CSCI) was held 19-21 September in Ottawa. Several globally-renowned scientists, including 2012 Friesen International Prize recipient, Dr. Marc Tessier-Lavigne, the CSCI/Royal College Henry Friesen Award recipient, Dr. Morley Hollenberg, and the recipient of the Joe Doupe Young Investigator Award, Dr. Phillip Awadalla, presented on a range of topics on research in basic and translational science in medicine.

This year's CITAC Symposium featured presentations by Dr. Alain Beaudet, Dr. Michael Strong and Dr. Vivek Goel on the Role of Physician Scientists in Public Health and Policy, which was followed by a lively discussion on the role of basic science and clinical research in patient-oriented policy development.

This scientific overview highlights the research presented by trainees at both the oral plenary and poster presentation sessions. As at previous meetings, research questions investigated by this year's trainees span multiple medical disciplines; from basic science to clinical research to medical education. Below is a summary of the presentations showcased at the Young Investigator's Forum.

Clin Invest Med 2013; 36 (5): E248-E252.

Correspondence to:

Veronique D. Ram
Faculty of Medicine, Health Sciences Centre
Foothills Campus, University of Calgary
3330 Hospital Drive NW
Calgary, Alberta, T2N 4N1
E-mail: vram@ucalgary.ca

Clinician scientists and trainees from across Canada attended the 2012 Young Investigator's Forum to present their research as well as partake in networking and mentoring opportunities. The scientific overview section of the forum highlighted the research presented by trainees at both the oral plenary and poster presentation sessions. Research questions investigated by this year's trainees spanned medical disciplines; from basic science to clinical research to medical education.

In this scientific overview, the winners of the oral and poster presentations will be showcased for their solid contributions to investigative medical research. The remaining research has been divided into the following categories: a. basic science research, b. clinical research, anatomy and surgery, c. cellular and genetic research, d. imaging, and lastly e. public health, quality assurance and medical education.

2012 Winning Presentations

Oral Presentation Winners:

1. Clara Westwell-Roper, University of British Columbia
2. Jared Wilcox, University of Toronto
3. Ju-Yoon Yoon, University of Manitoba

The winners of this year's oral presentations illustrate the foundational significance of basic science research. Clara Westwell-Roper's presentation "Macrophages mediate islet dysfunction in response to human islet amyloid polypeptide" outlined the contribution of islet macrophages to IAPP-induced islet inflammation and beta cell dysfunction. Her data suggests that islet macrophages are the major source of IAPP-induced pro-inflammatory cytokines, and that diverse amyloidogenic peptides act as endogenous stimuli for TLR2; thus, manipulation of macrophage activation or blockade of TLR2 may limit IAPP-induced islet inflammation and beta cell dysfunction in type 2 diabetes and islet transplantation.

Jared Wilcox presented on the "transplantation of adult and embryonic stem cell (ESC)-derived neural precursor cells" to preserve tissue and improve "neurobehavioural function in a rat contusion-compression model of cervical spinal cord injury." He concluded that an injury at the mid-to-high cervical (C5, C6 vertebral level) is needed in models designed to study cervical spinal cord injury. The C6 clip paradigm appropriately models neurobehavioural recovery and spasticity of cervical SCI, which is ameliorated in tissue preservation and neurobehavioural function to the forelimb following adult and ESC-derived NPC transplantation.

Ju-Yoon Yoon presented on his research project, which hypothesized that the addition of valproic acid (VPA), an in-

hibitor of histone deacetylases (HDACs), can improve fludarabine-based therapy. He concluded that a novel mechanism was discovered through which VPA interacts with fludarabine synergistically by enhancing the activity of cathepsin B. The resulting enhancement in caspase activation was associated with reduction in Mcl-1 and XIAP levels. The combination also proved effective for relapsed CLL patients.

Poster Presentation Prize Winners:

1. Christina Thornton, University of Calgary
2. Jillian Belrose, University of Western Ontario
3. Kyla Huebner, University of Calgary

Christina Thornton's poster outlined her doctoral research entitled "The streptococcus antibiotic resistance of adult cystic fibrosis (CF) patients results from mutation and horizontal gene transfer." She concluded that the prevalence, species distribution and influence of therapy on resistance profiles suggest that complex ecological interactions among the streptococci in the airways of CF patients with the mutation, rather than solely horizontal gene transfer, is a significant mechanism of acquired antibiotic resistance in some species within this patient population.

Jillian Belrose's poster examined how TRPM2 is implicated in cellular senescence and A β -mediated toxicity in hippocampal neurons. Her results implicated TRPM2 in the calcium dysregulation and neurodegeneration associated with Alzheimer's disease, and suggested that pharmacological manipulation of the TRPM2 channel may have therapeutic potential.

Kyla Huebner's poster illustrated how osteoarthritis (OA) develops in an anatomically ideal ovine anterior cruciate ligament (ACL) autograft. She concluded that although this model simulates a number of features of human ACL reconstructive surgery and eliminates some confounding factors, such as variation in graft attachment site, they were unable to restore normal gait kinematics and prevent the development of osteoarthritis. Further work is necessary to confirm and identify the association between the kinematic abnormalities and the initiation of OA in this model, and to evaluate the biological contributors to disease.

In the Lab: Basic Science Research

This year's basic science presentations demonstrate how current research already reflects the changing face of CIHR's funding model: research that focusses on patient-oriented results. Although united by their basic science focus and methodology,

these patient-oriented research project subjects ranged from investigation of heart disease to neuroscience, obesity, embryonic development and immunology.

Many novel therapeutic targets were identified for the potential treatment of a plethora of diseases. On the cardiac research front, Bracey *et al.* outlined the function of Nlrp3 in the development of cardiac fibrosis and myofibroblast differentiation. Kim *et al.* presented their work on myocardial infarction and the early interaction between the immune system and cardiac tissue. Desnoyers *et al.* spoke of the role of oxytocin in improving the therapeutic potential of stem cells and its possible application in the treatment of cardiovascular disease.

A few projects also touched on genomics, genetics and epigenetic phenomena and their impact in the development and prevention of disease. Antoun *et al.* summarized the potential role of PDSS1 in mitochondrial bioenergetics and in the development and treatment of obesity. Velker *et al.* also studied metabolic activity but in a developmental context and with a focus on genomic imprinting, concluding that preimplantation embryos that maintain low levels of metabolic activity might be better adapted to the suboptimal culture environments and result in healthier offspring. Wang *et al.* introduced the epigenetic effects of diabetes on the sperm of diabetic male mice and their transgenerational repercussions.

In addition, many projects were related to the field of neuroscience. Li *et al.* presented their studies relating to potential Parkinson's disease treatments; specifically, regarding the effects of PGC-1 α on toxicity induced by alpha-synuclein in mice. Magown *et al.* concluded that stem cell-derived motoneurons display comparable electrophysiological characteristics when cultured on fast and slow myotubes. Zhang *et al.* demonstrated that antipsychotic drugs might promote the differentiation of certain oligodendrocytes *in vitro*, which could prove to be a novel therapeutic target for future antipsychotic drugs. Ng *et al.* presented work on a neuronal calcium sensor-1 (Ncs-1) knockout mouse line that suggests, from an initial behavioral screen, that the global knockout does not have any obvious impact on locomotion, anxiety, levels of "despair," working memory, or fear memory in mice.

The last few works in this section focused on immunology and the roles played by different effectors in the immune system's response to various disease states. Armstrong *et al.* focused on the effects of influenza on the pulmonary microvasculature and possible treatment options. Mukovozov *et al.* presented their work on vascular inflammation and specifically on the role of Slit2/robo-1 signaling in monocyte recruitment and adhesion proposing the use of Slit2 as a novel anti-inflammatory therapy.

It is evident that, despite the wide variety of basic science research projects, the patient-oriented focus sought by the CHIR is already omnipresent among the clinician investigator trainees. Despite the fact that much work is yet to be done to bring some of these studies to the clinical realm, results so far are promising and great things should be expected from the MD/PhD trainees working in the basic sciences.

In the Clinic: Clinical Research

Strides in clinical investigations underscore the progress of research from basic laboratory science to clinical application. A broad range of topics was presented, ranging from repair of multiple ligament injuries of the knees to treatment of obstructive sleep apnoea. A limited number of abstracts in clinical research focused on disease processes. Examination of perceptual processing in schizophrenic population showed measurable differences in certain aspects of visual processing.

Novel diagnostic means were also presented at the meeting, and there was an obvious focus on imaging tools. Blood oxygen level-dependant cardiovascular magnetic resonance (BOLD-CMR) was found to be a sensitive tool to examine myocardial oxygenation and coronary artery stenosis. In another study, pre-operative magnetic resonance imaging of the hip joint and the whole organ MRI score (WORM) algorithm were refined to better predict post-operative hip function.

Many of abstracts in clinical research focused on therapy, and the study size varied from case reports to comparative clinical trials. Arthrofibrosis was found to be problematic after arthroscopic bi-cruciate reconstruction of multiple ligament injured knees (MLIKs), leading the Calgary group to hypothesize that repair of MLIKs, complemented with aggressive physiotherapy, could minimize arthrofibrosis. Prophylactic nasal continuous positive airway pressure (nCPAP) was found to improve post-operative pulmonary gas exchange, suggesting that nCPAP may be helpful in preventing post-operative respiratory complications. In obstructive sleep apnoea (OSA), CPAP treatment was found to result in reduced activation of the renin angiotensin system (RAS), which supports of the role of CPAP in preventing the progress of cardiovascular diseases in OSA patients. Deep inferior epigastric perforator (DIEP) and superficial inferior epigastric artery (SIEA) flap methods for breast reconstruction were compared and the analysis of preliminary data from an ongoing clinical trial suggested SIEA may be associated with higher rate of complications. In another therapy-focused study, the implication of discontinued government funding of ranibizumab was examined on the outcome of centre-involving diabetic macular edema (C-DME) and macular edema following retinal vein occlusions (ME-

RVO). The retrospective study suggested that ranibizumab was the superior therapy in C-DME compared to alternative therapy.

In the Body: 3D Modeling, Anatomy and Surgery

Research focused on anatomical and surgical study was clearly emphasized in this year's proceedings. These studies all showcased the powerhouse that is the researchers at the Agur Laboratory (Division of Anatomy) in conjunction with the Departments of Physical Therapy and Psychiatry (University of Toronto, ON), and their colleagues at Mercer University (Atlanta, GA) and Duquesne University (Pittsburgh, PA). Three-dimensional (3D) modelling from digitization of images from cadaveric dissections was the overarching technique used by these researchers. These models include the volume, angulation and spatial relation of all bony and soft tissues. Each author used the reconstructions generated in each population to evaluate the potential mechanism of injury through aberrant neuromuscular spatial arrangement or during surgical intervention.

Davies and Chang reported on 3D studies of nerve branchings and the distribution of the fronto-temporal branch of the facial nerve (FTN) and the subscapular nerve. Both of these nerves are vulnerable to damage during surgical intervention and better knowledge of their spatial course could reduce nerve injury and subsequent denervation and atrophy. Davies provides the first study using 3D mapping of the FTN, allowing for annotation of fixed references that may replace the current method that uses variable soft tissue landmarking. These 3D reconstructions, published in "Clinical Anatomy", provide directly quantified measurements of the branching position and branch angle of the FTN superimposed on detailed and high-quality imagery of the skull topology. Next, Chang presented a reconstruction of the innervation and compartmentalization of the subscapularis. Preservation and avoidance of the infra-clavicular and subscapular nerves is essential during open shoulder repair of the compromised rotator cuff. First, extra- and intra-muscular innervation patterns were determined. Chang and colleagues were then able to discern four spatial patterns of subscapular nerve innervation based solely on the extra-muscular branching at subscapularis. This subdivided the subscapularis into superior, middle and inferior muscle bellies. These results describe and predict the atrophy following denervation due to unfavourable surgical intervention.

Parente and Scallan offered new insight into proving the mechanism and anatomical basis of sciatica and piriformis syndrome (PS). These painful syndromic conditions have been assumed to be due to aberrant muscular impingement if no

spinal involvement is found; however, this hypothesis had been largely unsupported anatomically. A set of in-depth musculo-tendinous models of the sacral roots (L4-S3), piriformis muscle, sciatic nerve, and associated aponeuroses and neighbouring bony attachments were generated. This approach identified two potential anatomical bases of sciatica and PS. Results demonstrated that the sciatic nerve is in direct contact with the piriformis aponeurosis and bony ischial spine, leaving the nerve vulnerable as it exits the pelvis. Prior to joining the sciatic nerve, the sacral roots must pass by the/through the piriformis, and it was found that the positioning of the S2 root is intramuscularly in three of the seven subjects observed, causing a significant angular deviation of 21° in one subject. These features provide possible mechanisms of sciatica and PS; however, confirmation with *in vivo* imaging and disease findings are now needed to determine the predictive value of these measures for sciatic-related pain. These anatomical reconstructions made possible by such software platforms provide new and powerful tools for researchers who look to improve the pre-surgical mapping of vulnerable structures, to elucidate the mechanism of syndromic pain and to improve medical education.

In Cells: Cancer and Genetics

The understanding of the role of genetics as a major player in disease pathogenesis has led to the development of several drugs that target the resultant aberrant phenotypes. This is especially the case in the context of cancer. Worldwide, cancer has and will continue to claim the lives of millions: it is, thus, pressing that clinician-scientists to collaborate with pure scientists to understand the disease and find novel therapeutic avenues.

Although most of the cancers have been catalogued and studied histologically, the mechanisms that led to the initiation and progression of neoplasms are largely unknown. Kwong *et al.* investigated the role of miRNAs in non-melanoma skin cancer; the most common form of cancer worldwide. miRNAs play a pivotal role in normal development, but its deregulation can sometimes result in tumorigenesis. Kwong *et al.* were able to show that the exogenous expression of miR-125b induces loss of cellular differentiation, a hallmark of invasive cancer.

In epithelioid sarcoma, a soft tissue cancer that targets younger populations, Jamshidi *et al.* reported the cause of the loss of SMARCB1 expression in this disease. SMARCB1 is a well-described tumour suppressor gene implicated in the pathogenesis of several pediatric tumours. This group demonstrated that SMARCB1 inactivation in epithelioid sarcoma is due to gene rearrangements and this understanding could drastically change our understanding of the pathogenic process of

this disease. In other pediatric neoplasms, Wang *et al.* are aiming to establish a novel immune-competent animal model of medulloblastoma to screen for maintenance genes. Over the course of cancer development, the majority of mutations are passenger mutations and a goal for cancer geneticists is to be able to identify the handful of genes that actually contribute to tumorigenesis and that target these specific mutations. Wang *et al.* are hoping to accomplish this feat using a novel Sleeping Beauty insertional mutagenesis screen. The burden of cancer treatment on our health care system is immense; as such, the search for new cancer therapeutics will be pivotal to the sustainability of Canada's health care system.

Clinician-scientist trainees around Canada have also been busy looking at the pathogenesis of other diseases spanning from Alzheimer's disease to gonorrhea. Belrose *et al.* investigated the role of TRPM2 channel and found that TRPM2 may be involved in calcium dysregulation and neurodegeneration associated with Alzheimer's disease. The group postulated that targeted therapeutics aimed at modulating the TRPM2 channel may provide patients with Alzheimer's disease new hope. *Neisseria gonorrhoeae* causes over 90 million new infections annually and with the recent rise of multi-resistant strains of the bacteria, the race is on to find novel treatment avenues. McSheffrey *et al.* have accepted this challenge. The research group investigated the immune response to *N. gonorrhoeae* after infection; specifically the resident macrophages. The researchers found that strains expressing the outer membrane Opa protein interact with adhesion molecule CEACAM1 and suppresses the secretion of proinflammatory mediators by macrophages.

The efforts by clinician-scientist trainees in the field of genetics and cancer are already beginning to clarify our basic understanding of disease pathogenesis. Only by understanding how diseases progress, evade immune detection and develop pharmacological resistance can we begin to find cures.

In Imaging: Radiology

The majority of this year's presentation relating to radiological research employed ultrasound technologies for methodological purposes. One group observed how ultrasonography reveals a significant increase in anterior compartment richness in chronic exertional compartment syndrome (CECS) patients compared with controls, suggesting that further studies are warranted to investigate the potential role of using ultrasound to diagnose CECS. Another group determined that contrast enhanced ultrasound (CEUS) can be used to determine the disease activity in irritable bowel disease (IBD) patients for whom baseline prediction with colour Doppler imaging (CDI)

and traditional ultrasound was indeterminate. One study evaluated the use of DTI, a novel magnetic resonance imaging technique that can image specific fiber tracts *in vivo* to monitor disease progression and stability in multiple sclerosis patients with chord lesions. Two studies looked at chest radiographs: one that reported on the limited clinical history provided on radiographic requisitions of the chest from the emergency room while the other observed that the development of an automated radiographic TB detection system is warranted.

In Practice: Public Health, Quality Assurance and Medical Education

There was also a focus on projects relating to public health, medical charts and quality assurance, as well as medical education in order to optimize patient care. Ranging from prenatal depression in Aboriginal women to surgeon responses to wait times for hip and knee replacements, multiple studies employed interviews with patients and physicians to assess current practices and the impact of such practices on patient care. Interestingly, one study considered physician self-monitoring of uncertainty in order to optimize patient care. The findings indicated how the accuracy of self-monitoring was not influenced by the opportunity to review possible responses prior to judging the likelihood of being able to provide an accurate answer. Lastly, one poster presentation outlined the growing interest in the incorporation of the study of humanities in medical education and highlighted the current trend of narrative medicine in the US and Canada, which offers a theoretically complex avenue to examine physician practices and medical ethics. This poster provided data on medical programs in Canada that currently require some level of narrative training, as well as offered potential avenues for expansion of such programming options.

Concluding Remarks

The 2012 forum highlights the quality and the wide variety of research presented by MD and trainees across the country. The CSCI-CITAC annual meeting remains an effective collaborative platform for trainees and we look forward to future meetings and to the resultant enhanced research networks and trainee initiatives.

Acknowledgments

CITAC-ACCFC acknowledges CIHR and the Burroughs Wellcome Fund for financial support.