TRAINEE SECTION

Scientific Overview of the CSCI-CITAC 2009 Conference

Stephan Ong Tone^{1,7,*}

Sagar Dugani^{2,6,*}

Harry Marshall^{3,7,*}

Mohammed Farid Shamji^{4,7,*}

Jean-Christophe Murray^{5,7,*}

Dominick Bossé^{5,7,*}

**Note: These authors contributed equally to the work*

¹ MD-PhD Program, McGill University,

² MD-PhD Program, University of Toronto

³ MD-PhD, University of Western Ontario

⁴ CIP and Division of Neurosurgery, University of Ottawa

⁵ MD-MSc Program, Université de Sherbrooke

⁶ Chair, CIM Trainee Committee

⁷ CIM Trainee Committee

Clin Invest Med 2010; 33 (1): E69-E72.

From September 21st-23rd 2009, the Clinical Investigator Trainee Association of Canada – Association des cliniciens-chercheurs en formation du Canada (CITAC-ACCFC) and the Canadian Society for Clinician Investigators (CSCI), held their annual conference in Ottawa. Participants included clinician investigators and trainees from across the country.

The conference featured many excellent guest speakers including this year's recipient of the Henry G. Friesen International Prize in Health Research, Sir John Bell. There were several forums focusing on professional development, with topics such as "sustaining the clinician investigator in Canada", "succeeding as a clinician investigator", and "collaborating internationally with MD+ trainees", alongside networking opportunities to help establish relationships with potential mentors and collaborators. Further, the CSCI-CITAC annual conference featured some of the cutting edge research that MD+ trainees throughout Canada are engaged in. Trainees presented their research either at the Young Investigators Forum poster session or at the

oral plenary.

This scientific overview aims to highlight some of the research presented by trainees at the annual conference. The broad themes of scientific interest included topics from both basic science and clinical research. In this article, we summarize some of the major research questions that are being investigated by clinician-investigator trainees in the following areas: neurological sciences, cell biology, medicine, immunology, obstetrics, gynecology, neonatology, orthopedics, rheumatology, and public health.

Neurological Sciences

The vast knowledge gained during "The Decade of the Brain" has provided great understanding about neurotransmission and functional neuroanatomy. This has now led to many neuroscientific investigations aimed at characterizing neuronal tissue response to injury. Trainees investigated how both membrane and cytoplasmic proteins modulate neuronal response to

trauma, stroke, and other neurodegenerative diseases. Additionally, the modifiable extracellular microenvironment was also revealed to have importance in neuronal protein translation and neurite outgrowth. Indeed, astrocytic signaling through connexin channels has the potential to dampen calcium-based toxicity in occlusion models of stroke. This finding may lead to therapeutic strategies that target glial cells to improve functional recovery following neuronal injury. Other work examined the ability of skin-derived precursor based Schwann cells to promote recovery in two discrete models of injury. Electrophysiological and functional recovery was accompanied by biochemical changes including heightened matrixolytic enzyme expression with possible impediment to developing obstructive gliosis.

Translation of neurophysiology into neurosurgical intervention formed the basis of a study that sought to understand cognitive signaling in the primate brain with the goal of eventually interfacing with external robotic devices. Using microelectrodes implanted in supplementary eye fields and dorsolateral prefrontal cortex, behavior tasks could be understood at the level of animal intent. This exciting research has potential in the field of neuroprosthetic development.

Accurate neuroimaging is a requisite to support medical and surgical intervention. One group investigated the ability of diffusion tensor imaging based magnetic resonance imaging (MRI) tractography to accurately assess the white matter spinal cord tracts following spinal cord injury. Although current spatial resolution limits clear delineation of functional tissue around pathology, this imaging technique could have surgical implications in defining unsafe areas for spinal cord incision.

Cost effectiveness of MRI and computerized tomography (CT) in the setting of suspected acute ischemic stroke was also examined in a population-based, retrospective study using a Registry of the Canadian Stroke Network. The results showed shorter hospital stay and reduced in-hospital mortality among those screened with MRI, although this represented

only a small fraction of all suspected stroke patients, and the demographic and clinical similarities between the two groups remains unclear. Nevertheless, the hypotheses generated concerning the early sensitivity and cost-effectiveness of MRI screening support further work in this field.

Cell Biology

The field of cell biology was rich in studies concerning oncogenesis. One set of experiments showed that integrin-linked kinase's (ILK) function as an oncogene or tumor suppressor in the pediatric skeletal muscle tumor rhabdomyosarcoma depends on the expression of a novel target, JNK1, thereby identifying a potential biomarker of ILK neoplastic function.

The molecular mechanisms of brain tumour development were explored by another group who observed that decreased cyclin-dependent kinase 5 (CDK5) activity in knockout mice predisposed them to develop medulloblastoma. Normal cell cycle regulation by the p53 signaling pathway is modulated by CDK5, and tumorigenesis may ensue when this pathway is dysregulated. Another study showed that p63, a protein related to p53, regulates survival of embryonic neural precursors, and that p63 collaborates with the third member, p73, to regulate survival of newly-generated neurons. Finally, a novel anti-cancer protein, GIFT-21, was identified and shown to induce macrophage production of cytokines, which then in turn recruit lymphocytes to assist in killing cancer cells. These studies highlight the importance of identifying aberrant signaling pathways involved in oncogenesis, which will guide the development of novel therapeutics for the treatment of cancer.

Medicine and Immunology

The topic of type 1 diabetes was a recurring theme among medical investigators. Insulin was observed to reduce PAR2 (protease activated receptor 2)-induced inflammation, leukocyte trafficking, and calcium signaling in endothelial cells. Given that PAR2-induced

inflammation is enhanced in murine models of type 1 diabetes, diminishing these effects in diabetes may be of clinical relevance. Related to this, a study on pancreatic islet transplantation showed that CEBP (CCAAT/Enhancer binding protein)-homologous protein (CHOP) plays an important role in islet graft dysfunction with possible contributions from endoplasmic reticulum stress. Another group used a phenotype-driven approach to identify genes important for renal disease; they found two novel heritable mutations with reproducible phenotypes of glomerulocytic changes and glucosuria. These models can be used to study end-organ damage in diabetes.

As for immunological research, one group used a mouse model of *in vivo* cytotoxic T-cell lymphocyte induction to identify factors that regulate dendritic cell maturation. Related to this study, another group showed that the Src-like Adaptor Protein, SLAP2, regulates dendritic cell maturation, while another group used *N. gonorrhoeae* and T-cells to show that the tyrosine phosphatase SHIP-1 (SH2-containing inositol phosphatase-1) contributes to neisserial inhibition of T-cells.

Obstetrics, Gynecology and Neonatology

From the disciplines of obstetrics, gynecology and neonatology, there were three studies with topics ranging from conception to the care of neonates. Using a rodent model, the role of placental lactogen in pregnancy, a hormone detectable past mid-gestation, was described. By comparing the characteristics of inseminated female mice with the prolactin or prolactin receptor genes knocked-out, they concluded that placental lactogen may establish or maintain pregnancy. Furthermore, it was found that prolactin deficiency may be associated with delays in fetal development.

Another group explored the biochemical pathways involved in delivery. Phosphorylation of myosin light chain (MLC) is an important biochemical step in the initiation of uterine contractions. MLC is phosphorylated by MLC kinase, but another enzyme called Rho

associated kinase (ROCK) may play a role by phosphorylating and inhibiting MLC phosphatase. By exposing myometrial cell cultures to various contractile stimulants and ROCK inhibitors, the authors observed that ROCK accounts for about half of all baseline phosphorylated MLC, identifying an important role for ROCK in uterine contractions.

Continuing through development, one group examined the treatment of neonates in cardiogenic shock. Currently, high-dose dopamine is an important component in the standard of care. To test if the addition of other inotropes is beneficial, a controlled study on forty-six neonatal piglets with hypoxia induced cardiogenic shock was carried out. The authors concluded that adding milrenone, epinephrine, or dobutamine to high-dose dopamine provided no improvement in any of a number of systemic and pulmonary hemodynamic measures over high-dose dopamine used in isolation.

Orthopedics and Rheumatology

Three studies were designed to evaluate different methods to accelerate fracture healing. The first study introduced a novel apparatus to apply intermittent cyclic hydrostatic pressure (ICHP) to cells *in vitro*. They determined that the *in vitro* environment modulates the responsiveness of osteoblast-like cells to ICHP, suggesting that appropriately timed and administered mechanical loading could positively influence recovery from fractures. The second study compared the effects of two stem/progenitor cells, endothelial progenitor cells (EPCs) and mesenchymal stem cells (MSCs), on the healing of critical sized bone defects in a rat model. They suggest that EPCs are effective for therapeutic angiogenesis and osteogenesis in fracture healing, based on radiographic evidence of early healing of bone defects in EPCs treated rats. Finally, the third group outlined their plan to investigate the ability of the recently identified osteogenic factor, FGF18, to accelerate bone regeneration and prevent non-union. They will model non-union using a seg-

mental defect in the rat femur fixed internally with a polyethylene plate and K-wires. This study will also assess chitosan-mediated delivery of FGF18 and its ability to expedite bone repair.

Two studies were designed to evaluate the progression of arthritis. One investigated how osteoclastogenesis was modulated in the pathology of rheumatoid arthritis (RA). The authors assessed osteoclasts from patients with or without RA and determined that osteoclastogenesis was increased in patients with RA. This finding might help clinicians better assess the severity of the disease in patients with RA. The other study examined the requirement of transforming growth factor alpha (TGF α) in the progression of osteoarthritis (OA) in an animal model. TGF α appeared to play an important role in OA since TGF α null mice experience delayed OA progression compared to heterozygous littermates.

Although most studies focused on basic science research, one group designed an experiment to optimize the clinical outcome of patients with Achilles tendinopathy. They performed a triple blinded randomized controlled trial evaluating the ability of sclerotherapy with a dextrose/lidocaine solution to decrease pain and increase function in patients with Achilles tendinopathy who failed a standardized physical therapy regimen. Their results suggest that sclerotherapy with a solution of 25% dextrose is a successful treatment option for patients with chronic Achilles tendinopathy.

Public Health

Although most research this year was at the basic science or pre-clinical level, two studies addressed public health issues. One study took advantage of extensive epidemiological data to correlate four anthropomorphic measures of adiposity with three vascular parameters that, in turn, can be used to predict cardiovascular risk. They found that all measures of obesity

(body mass index, waist circumference, waist-to-hip ratio, and waist-to-height ratio) were related to two of the three vascular parameters (hyperaemic velocity time integral and hyperaemic shear stress), but not the third (flow-mediated dilation). These results may help direct the design of improved models to predict atherosclerotic burden.

The other study examined the ethics of expanding anti-retroviral treatments in Vancouver's inner city by analyzing fifteen months of observational data, life histories, and semi-structured interviews. The authors identified that although emphasizing "rights" in the context of HIV/AIDS and treatment has beneficial functions, rights-based discourse also has associated deficiencies that can further marginalize the most disadvantaged.

This year's CSCI-CITAC conference provided MD+ trainees with an opportunity to share their research with their peers as well as established clinician investigators. We are optimistic about the future of Canadian health research, and we are hopeful to see many of these early research findings translate into clinically-relevant research.

Acknowledgments

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

Correspondence to:

Stephan Ong Tone
Department of Neurology and Neurosurgery
Montreal Neurological Institute
3801 Rue University
Montreal, Quebec
H3A 2B4
Email: stephan.ongtone@mail.mcgill.ca