



UBC Medical Journal  
By Students, For the World



UBC Medicine Research Forum  
March 15, 2011  
Life Sciences Centre, UBC

**Abstract Book**

# Table of Contents

## Clinical Research

Authors	Title	Page	Poster
Christopher J.D. Wallis, Hilary L. Nelson, Peter J. Pommerville	Testosterone deficiency syndrome and cardiovascular health: an assessment of beliefs, knowledge and practice patterns of general practitioners and cardiologists in Victoria, BC.	6	22
Kristin DeGirolamo, Stephen Chung	Focal Nodular Hyperplasia: A Case Report of Rare Multiple Ruptures of a Common Liver Tumour in a Single Patient	7	37
Michelle Lai, Ipek Oruc, Jason Barton	Facial age after-effects show partial identity invariance and transfer from hands to faces	8	49
Antonia Johnson, Paul Freund, Jaspreet Garcha, Yves Sauvé	Compensatory changes in retina function during early stages of age-related macular degeneration	9	8
Nancy Liu, Carlo Marra, Jamie Thomas	Falling through the Cracks: A multi-disciplinary Strategy to Improve DMARD use in Rheumatoid Arthritis	10	53
Aravind Ganesh, Rup Pandya, Scott Patten	The Case for Vitamin D Supplementation in Relapsing-Remitting Multiple Sclerosis (RRMS)	11	9
Tessa Chaworth-Musters, Elaine Fernandes, Ariane Alimenti, Evelyn Maan, Helene Cote, Deborah Money, John Forbes	Adverse Health Outcomes in HIV Exposed Uninfected Children (HEU) in British Columbia	12	69
Simon Bow, Jason Yap	Screening Abdominal Ultrasounds in Children with Chronic Viral Hepatitis	13	66
Tyler BM Hickey, Patrick Tang	Genetic investigation of isoniazid resistance in an ongoing tuberculosis outbreak in British Columbia.	14	72
Monica Lau, Jeff Brubacher, Herb Chan	Cannabis and Motor Vehicle Crashes	15	51
Pedro Lourenco, Afsaneh Shirani, Jameelah Saeedi, Joel Oger, William Schreiber, Helen Tremlett	Oligoclonal banding and csf markers in multiple sclerosis: associations with disease course and progression	16	58
Christopher C. Cheung, Demetrios J. Kutsogiannis	Central Line Infection and Non-Infectious Complications in a Canadian Intensive Care Unit	17	13
Andrew Wong, Mansoor Foroughi, Paul Steinbok, Ash Singhal, Michael Sargent, Douglas Cochrane	Third ventricular shape: a predictor of endoscopic third ventriculostomy success	18	6
Tonia Berg, Margaret Zhang, Billy Ashaba, Wayne Choi, Alex Kasangaki, Norman Musinguzi, Caitlin Meredith, Jackie Nambatya, Sara Nyairo, Wendy Cannon, Andrew Macnab	Brighter Smiles: a comparison of growth in rural Ugandan children to WHO standards	19	70
Margaret Zhang, Wayne Choi, Billy Ashaba, Mattias Berg, Tonia Berg, Caitlin Meredith, Norman Musinguzi, Jackie Nambatya, Sara Nyairo, Wendy Cannon, Alex Kasangaki, Andrew Macnab	Brighter Smiles Uganda: Key elements for successful global health education electives	20	41
Anne Lambert, Ann Wong, Louis D. Wadsworth, Nicholas Au, Ross MacGillivray	Molecular Analysis of alpha globin gene mutations in BC Families	21	7

## Clinical Research (continued)

Authors	Title	Page	Poster
Jeremy Neufeld, Donald Greisdale, Dale Dhillon, Jennifer Joo, Supna Sandhu, Frank Swinnton, Peter Choi	Risk factors for urinary retention after hip or knee replacement	22	18
Kiley Cindrich, Jim Potts, Stella Cockett, Derek G Human	Cost comparison and program growth characteristics of an established interdisciplinary pediatric cardiology outreach program in British Columbia	23	36
Cheryl Lane, Alyson Wong, Jane Burns, Don Sin, Stephan F van Eeden	Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD): ECG changes and Cardiovascular work-up.	24	12
Bains-Dahia S, Gauldie J, Häkkinen L, Larjava H	Role of Transforming Growth Factor-Beta Signaling Modulators in Periodontal Disease	25	67
M. Michiko Maruyama, Winnie Lei, Jenna Hill, Celia Ching	Designing for Bariatric Care: Toilet Aid Design	26	40
Noah Alexander, Sarah Foster, Shawna Mann, Marcio Penner, Erika Penner, Murray Penner	Injury Patterns and Discharge Dispositions in Motorcycle Crash Victims	27	65
Megan M. J. Burns, Vesna Sossi, Burkhard Madler, Alex MacKay, Katie Dinelle, Salma Jivan, Tom J. Ruth, Roy Ma, Richard Shaffer, Michael McKenzie, Alan Nichol, Montgomery Martin, Stefan Reinsberg	Multimodal Characterization of Vestibular Schwannoma with Magnetic Resonance Imaging and L-11C-Methionine Positron Emission Tomography	28	46

## Basic Sciences

Authors	Title	Page	Poster
Robert Dale, Elnaz Atabakhsh, Victoria Fell, Caroline Schild-Poulter	Characterization of RanBPM sequence components that regulate its subcellular localization.	29	60
Min-Han Michael Yang, Igor Shevelev, Igor Stagljar	Mapping protein-protein interactions of yeast xenobiotic efflux pump Pdr5p using the Integrated Membrane Yeast-Two Hybrid System: Pdr5p-Erg4p interaction important for Pdr5p function	30	50
Christopher E. Uy, K-Lynn N. Hogh, Robert Baker, Ali Asadi, Jordie Fraser, Michael Riedel, Timothy J. Kieffer, Sarah L. Gray	Overexpression of PPAR $\gamma$ in pancreatic $\beta$ -cells exacerbates glucose intolerance in diet-induced obese mice	31	14
Joshua Lai, Alison Boyd, Omar Ahmed, Mayank Mehta	The Relationship between Single Unit activity and Neocortical Gamma Rhythms during Behavior	32	29
Kelvin S.K. Kwan, M. Yat Tse, Stephen C. Pang	Characterization of the Intra-renal Vasculature in Atrial Natriuretic Peptide Gene-disrupted (ANP $-/-$ ) and Wild-type (ANP $+/+$ ) Mice	33	35
Michael A. Benusic, Georgina Macintyre, and Diane W. Cox	Functional analysis of variants of the Wilson disease copper transporter, ATP7B	34	47
Andrew Kwasnica	NMDA Receptor Subunit Expression in Male and Female Rat Hippocampus following Voluntary Exercise	35	5
Ranita H. Manocha, Megan K. MacGillivray, Bonita J. Sawatzky	The biomechanics of swing-through gait in lower-limb amputees: A comparison of the SideStix <sup>TM</sup> sports forearm crutch versus standard crutch designs	36	59
Matthew G.K. Benesch, David A. Mannock, Ruthven N.A.H. Lewis, Ronald N. McElhanev	Miscibility and Stability of Sterol/Phospholipid Bilayers are Optimized by the Double Bond Position in the Sterol Nucleus	37	44
Andre Isaac, Wen Fu, Jack H. Jhamandas	Expression and characterization of the human amylin receptor AMY3 in the mammalian cell-line RK13 (rabbit kidney cells) as a cellular model for Amyloid beta neurotoxicity in Alzheimer's Disease	38	4
H Kim, M Hemida, X Ye, M Zhang, DC Yang	Cleavage of Translation Factor NAT1/DAP5/p97 During CoxsackievirusB3 Infection by a Cellular Serine-like Protease	39	23
Julia Pon, Lisa Davies, Georgina Macintyre, Diane Cox	Functional Testing of Wilson Disease Patient Variants in the ATP Binding Domain and C-Terminus of ATP7B	40	31
Wan Kim, Cody Crick, Sang-Eun Kim, Christine Law, Sean Maurice, Paul John Winwood	Matrix Remodeling in Liver Fibrosis	41	73
B Ajami, J Bennett, D Mahdavian, K McNagny, F Rossi	Infiltration of Blood-Derived Monocytes is required for Disease Progress in Experimental Autoimmune Encephalomyelitis (EAE)	42	21
DC Brownrigg, VM Diewert	3D Modeling of Brain-Face Relations During Development of Kyoto and Carnegie Human Embryos	43	19
Sanam Verma, Mohamed A. Omar, Alexander S. Clanachan	Signalling mechanisms underlying adenosine-mediated inhibition of myocardial glycolysis	44	64
Norah-Faye Matthies, Adetola Adesida, Nadr Jomha	Extracellular matrix of meniscal cartilage is enhanced by co-culture of meniscus and stem cells under low oxygen tension	45	56
Julie Man, Yuexin Li, Paul Man, Don Sin	The Effect of Inhaled Steroids on PARC/CCL18 in COPD Patients	46	32

## Clinical Research (continued)

Authors	Title	Page	Poster
Joshua Lai, Mike Butterfield, Andrew Giles, Catharine Rankin	The role of slo-1 in short and long term habituation in <i>C. elegans</i>	47	30
Maryam Dosani, Raika Pancaroglu, Ipek Oruç, Jason J S Barton	Inter-feature transfer of aftereffects: evidence of adaptation in whole face representations	48	43
M. Haiducu, K. Fitzpatrick	Dmel/Gfat2 is an essential gene in <i>D. melanogaster</i> embryonic development	49	42
Jonathan Y. Chi, Ian M. MacDonald, Stacey Hume	Linking Genetic Duplications to Choroideremia Pathology	50	27
Caylib A. Durand, Martin Richer, Marc Horwitz, Marcia Graves, Kamal D. Puri, and Michael R. Gold	Selective Pharmacological Inhibition of Phosphoinositide 3-Kinase p110delta Inhibits Marginal Zone B-cell Function and Abrogates the Development of Autoimmune Diabetes in NOD Mice	51	11
Sesath Hewapathirane, Simon Chen, Wesley Yen, Shay Neufeld, Kurt Haas	Early-life seizures inhibit dendrite growth through synaptotropic mechanisms	52	17
Jaspreet Dhillon, Arezoo Astanehe, Abbas Fotovati, Kaiji Hu, Sandra Dunn	The expression of activated Y-box binding protein-1 serine 102 mediates trastuzumab resistance in breast cancer cells by increasing CD44+ cells.	53	25
ML Mayer, CJ Blohmke, CD Fjell, SE Turvey, REW Hancock	Systems Biology Identification of the AMPK-AKT-GSK3 $\beta$ Axis in Mediating Dysregulated Responses of Cystic Fibrosis Airway Cells to IDR-1018, an Immunomodulatory Peptide	54	45
David Mcvea, Majid Mohajerani, Tim Murphy	Slow cortical oscillations and limb twitches in the neonatal rat	55	20
Long V. Nguyen, Nagarajan Kannan, Pawan Pandoh, Peter Eirew, Maisam Makarem, Michelle Moksa, Kane Tse, Thomas Zeng, Martin Hirst, Marco Marra, Connie J. Eaves	Development of a lentiviral-based cellular barcoding strategy for clonal tracking of normal and malignant human mammary epithelial cells in a xenotransplant model	56	39
Josephine H. Y. Lee, Yulia Artemenko, Jane Borleis, Stacey Willard, and Peter N. Devreotes	A Novel Protein Kinase Involved in Chemotaxis, Development, and Substrate Adhesion in <i>Dictyostelium discoideum</i>	57	28
Clara Westwell-Roper, D.L. Dai, G.S. Soukhatcheva, J.A. Ehses, and C.B. Verchere	Blockade of IL-1 signalling improves human islet amyloid polypeptide-induced islet graft dysfunction	58	16
Michael Copley, David Kent, Stefan Woehrer, Keegan Rowe, and Connie Eaves	Evidence that High-Mobility Group A2 (Hmga2) Expression Contributes to the Ontogeny-Dependent Properties of Fetal Hematopoietic Stem Cells	59	48
Potter K, Cheng J, Werner, Chen Y, Park, Westwell-Roper C, Warnock GL, Oberholzer J, Fraser PE, CB Verchere	Heparin induces amyloid formation in cultured human islets and promotes graft failure following transplantation	60	34
Will Guest	Modelling Photosensitivity in the Visual Cortex	61	74
Kristen F Gorman, Julian K Christians, Jennifer Parent, Roozbeh Ahmadi, Detlef Weigel, Christine Dreyer, Felix Breden	A major QTL controls susceptibility to spinal curvature in the curveback guppy	62	61

## Case Reports

Authors	Title	Page	Poster
Julie Wilson, Ali Qazalbash, Dalpat Mistry	Zopiclone and Complex Sleep-related Behaviours	63	33
Amandeep Ghuman, Rick Schreiber, Manraj Heran, and Sonia Butterworth	Spontaneous rupture of hepatic hemangioma in a neonate - survival with non-operative management	64	2
Ida Molavi, Chris Wallis, John Masterson	Laparoscopic Management of Mixed Gonadal Dysgenesis with 45,X/46,XringY/46,XY Karyotype	65	24
Nima Kashani, Yashar Tashakkor, David Tso, Savvas Nicolaou	Imaging of the Craniocervical Junction in the Trauma Setting	66	55

## Population Health and Education

Authors	Title	Page	Poster
C. Taplin, V. Strehlau, I.Torchalla, K. Li, M. Schechter, M. Krausz	Childhood Trauma, family history of alcohol and drug abuse and age of first drug injection	67	15
Thomas L Perry, Blair Fulton, Billy Lin, Pedro Lourenco, Pavel Glaze, Peter Birks, Matthew Cooper, Wesley Jang, Sarah Mark, Bez Toosi	Patient videos to teach clinical pharmacology	68	10
Rui Chen, Anne Marie Jekyll, Elmine Satham, WG Cannon, Jean-Paul Collet	The development of a web-based multimedia educational resource for the learning of pediatric clinical skills	69	62
Jody Morita, Nicolas Bilbey, Sarah Yager	Health Status Classification in Primary Care: Empowering physicians and patients in Cuba	70	26
Michael David Cusimano, Wilson Polung Luong, Ahmed Faress, Timothy Leroux	Evaluation of a Novel Ski and Snowboard Injury Prevention Program	71	75
T Tan, B Buchan, I Janjua, M Trudeau, SK Yeong, D Dressier, E Kennah, J Scharf, D Kuk, F To, L Bornn, V Kapoor	Evaluation of Anemia among a Population of Children Living in the Indian Himalayas and the Role of Iron Supplementation	72	71
Amir Yashar Tashakkor, Ali Moghaddamjou, Peter Birks, Winson Y. Cheung	Identifying clinical factors associated with an increased risk of Diabetes Mellitus among cancer survivors.	73	3
Taylor Swanson, Alex Butskiy, Maryam Dosani, Kristy Williams, Disha Mehta	The Healthy Young Minds Project: Focus Groups about Mental Health	74	68
Pamela Verma, Kristin DeGirolamo, Sheila Wijayasinghe, Susan Dallin O'Grady, Dr. Andrea Cant, Deborah Hellyer	The Federation of Medical Women of Canada Smear Campaign and the Fight Against Cervical Cancer in Canada	75	57
Nathan Wong, Jessica Macleod, Ryan Truant, Kali Romano, Trent Kellock	Assessment of the Vancouver Native Health Youth Initiative	76	54
Rui Chen, Merry Gong, Celeste Loewe, Ying Yao	Assessment of Barriers to Bone Marrow Stem Cell Donation in Chinese-Canadian Young Adults	77	63
Naila Karim, Genevieve Tam, Tonia Timperley Berg	Engaging the Next Generation: Sustainable Solutions for Global Health Inequities	78	52
Lindsay McRae, Jennifer Campbell, Quynh Doan, Niranjana Kissoon, Abdullah AlQahtani	Body Mass Index and Acute Injury Risk in Children	79	38

**TESTOSTERONE DEFICIENCY SYNDROME AND CARDIOVASCULAR HEALTH:  
AN ASSESSMENT OF BELIEFS, KNOWLEDGE AND PRACTICE PATTERNS OF GENERAL  
PRACTITIONERS AND CARDIOLOGISTS IN VICTORIA, BC.**

Christopher J.D. Wallis (1), Hilary L. Nelson (2), Peter J. Pommerville (3)

*(1) MSI4, University of British Columbia Island Medical Program (2) MSI3, University of British Columbia Island Medical Program (3) UBC Dept of Urological Sciences*

Testosterone deficiency syndrome (TDS) or late-onset hypogonadism is a clinical syndrome marked by symptoms including a reduction in muscle mass and increase in adiposity, decreased sexual function, depressed mood, hot flushes, and fatigue, most often in association with laboratory evidence of decreased testosterone. There is an emerging body of evidence that TDS is an independent cardiovascular risk factor in addition to being a predisposing factor for the development of the metabolic syndrome, dyslipidemia, insulin resistance and type 2 diabetes, hypertension, atherosclerosis, and vascular dysfunction. We sought to assess the knowledge, beliefs and practice patterns of a cohort of general practitioners and cardiologists in Victoria BC with respect to TDS and cardiac health.

A questionnaire was distributed to all 20 cardiologists and a cohort of 120 family practitioners in Victoria BC. Of the 13 questions, 10 assessed their knowledge and beliefs with respect to TDS and 3 assessed their current practice patterns. Appropriate statistical analysis was undertaken.

Most respondents believed that TDS was medical condition and could have an adverse affect on body composition but a similar majority was unsure to whether it was a cardiac risk factor. While most believed that testosterone replacement therapy (TRT) could improve exercise tolerance, the majority were unsure as to if it was beneficial in patients with congestive heart failure, following myocardial infarction, or to improve myocardial perfusion. Cardiologists were statistically significantly more likely to believe that TRT was not beneficial in preventing recurrent myocardial infarction and improving myocardial perfusion ( $p = 0.0133, 0.00186$ , respectively). The vast majority (88%) did not screen male cardiac patients for TDS. If a patient was identified as having TDS, only 10% of those surveyed would refer to a urologist.

Despite being remarkably common in cardiac patients, both general practitioners and cardiologists lack knowledge as to the significant deleterious cardiovascular effects of testosterone deficiency. In their role as men's health advocates, urologists should consider promoting continuing medical education seminars to inform other relevant medical specialists regarding the correlation between TDS and cardiovascular mortality and risk factors.

## **Focal Nodular Hyperplasia: A Case Report of Rare Multiple Ruptures of a Common Liver Tumour in a Single Patient**

Kristin DeGirolamo (2), Stephen Chung (1,2)

*(1) Department of Surgery, University of British Columbia (2) Faculty of Medicine, University of British Columbia*

Focal nodular hyperplasia (FNH) is one of the three most common benign solid liver tumours along with hemangiomas and adenomas. (1) FNH is considered a vascular abnormality that usually follows an uneventful course after accidental discovery on CT or MRI for an unrelated medical problem and rarely requires any treatment. (1) These lesions are stable in nature with minimal risk of rupture and essentially no risk for malignant degeneration. (1) The general recommendations for an asymptomatic FNH are observation only, regardless of size of the mass. (1) However, the consequences of a ruptured liver mass can be very serious as abdominal bleeding may be catastrophic so accurate diagnosis is essential. (1) Here we present the only known case of a patient with multiple FNH nodules who ruptured two of her lesions, the first treated with a left hepatectomy and the second with embolization. A discussion of the management of her ruptured tumours follows and highlights how little evidence is available for the treatment of multiple ruptures of FNH or how to properly risk stratify patients.

1. Choi B and Nguyen M. The Diagnosis and Management of Benign Hepatic Tumors. *Journal of Clinical Gastroenterology* 2005 May/June: 39(5): 401-12.

Clinical Research (Short-term Project)

## **Facial age after-effects show partial identity invariance and transfer from hands to faces**

Michelle Lai , Ipek Oruc, Jason Barton

*Departments of Medicine (Neurology), Ophthalmology and Visual Science, University of British Columbia, Vancouver, British Columbia, Canada*

Age imparts long-term dynamic changes to faces: how these are represented in the human visual system has seldom been investigated. We investigated facial age after-effects using a perceptual bias paradigm, and studied the ability of adaptation to transfer across face identity, visual stimuli and sensory modality, as has been done for the short-term dynamic changes of facial expression. Age after-effects were reduced but still significant when the identity of the face was changed between the adapting and test stimuli, as we had found for expression after-effects, suggesting identity-specific and identity-invariant components of age after-effects. Although body silhouettes and greyscale body images failed to generate age after-effects in faces, we did find cross-stimulus transfer of age adaptation from hands to faces. There was no cross-modal transfer of after-effects from voices to faces. These findings confirm that face adaptation has components that cannot be explained by low-level image-based effects but involve high-level representations that may be influenced by related visual semantic information.

## **COMPENSATORY CHANGES IN RETINA FUNCTION DURING EARLY STAGES OF AGE-RELATED MACULAR DEGENERATION**

Antonia Johnson (1), Paul Freund (1), Jaspreet Garcha (1), Yves Sauvé (1)

*(1) Department of Ophthalmology, Faculty of Medicine & Dentistry, University of Alberta*

Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly of the Western world. One in four Canadians over 75 years of age has AMD. In order to find a cure for AMD it is essential to consider the baseline age-related retinal changes on top of which pathophysiological events take place.

We undertook a detailed study of retina function (using the electroretinogram, ERG) in five subjects ( $76 \pm 10$ y) afflicted by the early (dry) and late (wet) forms of AMD in either eye. Results were compared between both eyes and with healthy eyes of subjects from three age groups: 20-39y ( $n=27$ ; mean age  $25 \pm 5$ y), 40-59y ( $n=20$ ; mean age  $53 \pm 5$ y), and 60y+ ( $n=18$ ; mean age  $68 \pm 5$ y).

Changes in ERG properties were found in the oldest group when compared to the two younger groups: 1) a less pronounced photopic hill, reflecting changes in the OFF-bipolar system; 2) the slowing of implicit times, suggesting the occurrence of biochemical changes in rod and cone photoreceptors; 3) the selective amplitude reduction of maximal dark-adapted a-wave (reduced rod activity) and not b-wave (maintained post-synaptic activity from rod ON-bipolar cells) could be linked to post-synaptic compensation. Recordings from early AMD eyes showed an exacerbation of the changes seen in age-matched subjects with healthy eyes: 1) lack of any hill effect; 2) severely delayed responses; 3) further reductions in a-wave amplitudes (indicative of more pronounced photoreceptor dysfunction) while b-wave amplitudes were still unchanged, pointing to the occurrence of post-synaptic compensation despite pathological photoreceptor dysfunction. In contrast, late AMD eyes lacked any signs of such compensatory changes: there was a generalized loss of responsiveness in all ERG components (decreased amplitudes and delayed responses for all ERG components).

Clinical Research (Short-term Project)

## **Falling through the Cracks: A multi-disciplinary Strategy to Improve DMARD use in Rheumatoid Arthritis**

Nancy Liu , Carlo Marra, Jamie Thomas

*Collaboration for Outcomes Research and Evaluation, University of British Columbia*

**Aim of study:** The purpose of the study is for pharmacists to identify patients with rheumatoid arthritis who are not currently receiving DMARD therapy and to initiate a multi-disciplinary approach to improve disease management that includes the pharmacist, a physiotherapist and the patient's family physician.

**Methods:** Patients are recruited in pharmacies via posted advertisements and through pharmacist identification of eligible participants during normal pharmacists-patient interactions. Using a standardized questionnaire and medication review, the pharmacist will conduct a pharmacy-based assessment to determine the likelihood of RA and establish contact with the family physician to confirm the diagnosis. Patients who meet the eligibility criteria are referred to a physiotherapist, who will conduct assessment for joint inflammation. Pharmacists will then provide the results of the pharmacist and PT assessments to the patient's family physician with an emphasis on the role of DMARD Therapy.

**Results:** Study outcomes include the number of patients recruited through pharmacies who are assessed as likely having RA, the proportion of these patients who are prescribed a DMARD and/or those who are referred to a rheumatologist within 3 months of their PT assessment. In addition, changes in health status, RA symptoms and quality of life are assessed 3 and 6 months after the study enrollment. It was found that one of the biggest barriers to patient recruitment by pharmacists in the pilot phase include pharmacist being too busy. The full launch of the study in Vancouver, Victoria and Edmonton is currently taking place and result will soon be available in spring of 2011.

**Conclusion:** The study is ongoing so no conclusion can be drawn at this time. If successful, the study could provide a model that would inform healthcare policies that encourage interdisciplinary collaboration to improve RA outcomes. It could also be a model for other provinces to increase the use of DMARDs.

Clinical Research (Short-term Project)

## **The Case for Vitamin D Supplementation in Relapsing-Remitting Multiple Sclerosis (RRMS)**

Aravind Ganesh (1), Rup Pandya (2), Scott Patten (2)

*(1) MD candidate, University of Calgary Faculty of Medicine (2) Department of Psychiatry, University of Calgary Faculty of Medicine*

**Background:** Given that vitamin D has a role in immunomodulation, and its levels appear to correlate with the development of Multiple Sclerosis (MS), it is conceivable that vitamin D may also influence disease activity in MS patients. In this regard, we conducted a systematic review investigating the evidence for the role of vitamin D in disease activity in MS, in the context of the Bradford-Hill criteria of causation, and for the therapeutic supplementation of vitamin D in Relapsing-Remitting MS (RRMS).

**Methods:** A Medline search combining the MeSH terms 'Multiple Sclerosis' with 'Vitamin D' or 'Vitamin D Deficiency' yielded 146 results. These were then limited by clinical trials, giving 7 articles suitable for appraisal, the bibliographies of which were searched, giving one additional article for review.

**Results/Interpretation:** Overall, the current literature suggests that vitamin D plays an important role in disease activity in MS, with both cross-sectional and longitudinal studies demonstrating a strong positive correlation between vitamin D deficiency and the incidence of relapse and/or disability in patients with RRMS. As well, there appears to be a negative correlation between vitamin D levels and inflammatory markers in MS patients, suggesting that vitamin D modifies serum cytokines to a more anti-inflammatory profile, thus providing a plausible model for vitamin D immunomodulation in MS. However, as the Bradford-Hill criteria of temporality, dose-response, and reversibility are yet to be met, the current evidence does not permit inference of a causal relationship between vitamin D deficiency and disease activity in RRMS.

As for therapeutic supplementation, high-dose vitamin D supplementation (>10,000 IU/day) appears to be safe and well tolerated by RRMS patients, with preliminary evidence suggesting that this can help them remain relapse free. We calculated the number of patients that would need to be treated (NNT) to prevent one patient from relapsing over a year, giving a remarkably small NNT (unweighted) of 3.37, making vitamin D supplementation a promising new treatment option for MS patients that is worthy of further exploration. Nonetheless, owing to the paucity of longitudinal, placebo-controlled studies on the subject, the evidence for vitamin D supplementation in MS is not definitive.

Clinical Research (Short-term Project)

## **Adverse Health Outcomes in HIV Exposed Uninfected Children (HEU) in British Columbia**

Tessa Chaworth-Musters (1,2), Elaine Fernandes (2), Ariane Alimenti (1,2), Evelyn Maan (1,2), Helene Cote (2), Deborah Money (1,2,3), John Forbes (1,2)

*(1) University of British Columbia (2) Oak Tree Clinic, Children's and Women's Hospital (3) Women's Health Research Institute*

Background: Researchers in Europe /Africa have reported increased rates of severe infections in HEUs, prompting questions about underlying risk factors in this population. Little has been reported on the accessibility and health of HEUs in Canada.

Objective: To assess the rate of adverse health outcomes in a pilot population of HEUs in BC.

Methods: The pilot study was conducted at Oak Tree Clinic, the tertiary referral centre for HIV+ pregnant women and children in BC. Families were offered participation in-person or by mail with follow up phone call. Interviews included living situation, school experiences and health outcomes. Demographic, pregnancy, neonatal, and hospital visit data were extracted from clinical charts.

Results: 103 HEUs were enrolled from 7/09-3/10. Participants, mean age 5.4 (0.6-19.6) years, were ethnically diverse (45.6% caucasian, 21.3% aboriginal, 19.4% black). 36.9% had prenatal exposure to drugs/alcohol, with 10% experiencing neonatal abstinence syndrome requiring therapy. 92% had in utero exposure to ARVs for a mean of 21.5 (2-41) weeks. 23.3% were born premature. 14.6% had ever lived in foster care, and 16.5% required a classroom aide. 21 HEUs (20%) reported outcomes that were of a serious nature or required hospital admission. Severe infant infections in 11 children (10.7%) included meningococcal meningitis and severe RSV infection. Five children have severe developmental problems (autism, oppositional defiant disorder). Other problems included seizure disorder, complications of prematurity, renal cell carcinoma, congenital heart disease and idiopathic arthritis.

Discussion: This vulnerable cohort of HEU children reported high proportion of health problems requiring hospitalization, with infections being the most common. Factors that make this cohort vulnerable include prematurity, narcotic exposure, need for foster care, development and behaviour problems. Enrollment bias is towards families accessing care and morbidities may be underrepresented. These indicators inform the need for more comprehensive study of the entire cohort through provincial population data.

## **Screening Abdominal Ultrasounds in Children with Chronic Viral Hepatitis**

Simon Bow, Jason Yap

*Department of Pediatrics, University of Alberta*

**INTRODUCTION:** Surveillance for hepatocellular carcinoma is recommended in at risk adults with chronic viral hepatitis. The suggested modality is abdominal ultrasound (USS) with or without serum alpha fetoprotein. However, no recommendations exist in children. The choice of modality, frequency and timing are derived empirically or extrapolated from the adult literature. This study aims to assess the utility of screening and surveillance USS in children with chronic viral hepatitis.

**METHODS:** A retrospective chart review of all pediatric patients diagnosed with chronic hepatitis B and C, from 1995 to 2009 (inclusive) was conducted. Inclusion criteria were chronic HBV or HCV infection for at least 6 months and age < 18 years.

**RESULTS:** Forty three children were included into the study; 33 chronic hepatitis B infection (HBV), 9 chronic hepatitis C (HCV), and 1 HBV/HCV co-infection. The mean age at presentation was 9.8 years (95% CI: 7.1-11.2) with an average follow-up of 32 months. Vertical transmission accounted for 53% percent of all cases; whereas only 1 of 10 HCV infections was horizontally acquired. The majority (88%) of HBV cases were immigrants from endemic regions. The median ALT at presentation was 31 (IQR: 21-53). Screening USS were performed on 51% of children, while 79% of children received at least one USS during their care. Seventy two percent of screening USS were normal. Abnormal hepatic echotexture was the most common abnormality identified. Surveillance USS did not identify any hepatic malignancies. Incidental findings were noted in 13% of children during surveillance USS. Although 45% of patients had some findings on screening and surveillance USS, these findings did not influence management. No children received treatment for their chronic viral hepatitis.

**CONCLUSIONS:** In this cohort of children with chronic viral hepatitis, screening and surveillance USS did not significantly alter clinical management. There were inconsistent practices at our institution in requesting USS for children with chronic viral hepatitis.

Clinical Research (Short-term Project)

**Genetic investigation of isoniazid resistance in an ongoing tuberculosis outbreak in British Columbia.**

Tyler BM Hickey (1), Patrick Tang (1,2)

*(1) Faculty of Medicine, University of British Columbia (2) British Columbia Centre for Disease Control.*

**OBJECTIVE:** Beginning in 2008, an outbreak of tuberculosis (TB) that spread between two BC communities was identified. The *Mycobacterium tuberculosis* isolates were identical based on MIRU-VNTR genotyping. However, of the 20 cases of active TB identified, nine cases showed low level resistance to the antibiotic isoniazid (INH) whereas the others were fully susceptible to all first line anti-TB drugs. The *M. tuberculosis* from the index case acquired INH resistance during treatment in 2007 and the patient subsequently left hospital against medical advice. In order to understand the transmission dynamics within the outbreak and the evolution of INH resistance, we sought to determine the genetic mechanism of INH resistance.

**METHODS:** Genomic DNA from the *M. tuberculosis* isolates was used for PCR and sequencing of several genes associated with INH resistance: *katG*, *mabA*, *inhA*, *ndh*, *kasA*, and *oxyR-ahpC*. The genetic sequences of the isolates were compared against one another, as well as against multiple reference sequences of *M. tuberculosis*.

**RESULTS:** Sequence alignments of INH-susceptible and INH-resistant *M. tuberculosis* clinical isolates revealed identical sequences within the genes analyzed. In addition, there were no non-synonymous mutations between the sequences from the clinical isolates and those from reference strains known to INH-susceptible.

**CONCLUSIONS:** We were unable to identify the mutation conferring INH resistance in this TB outbreak. Either the mutation is occurring in a gene that was not addressed in this study or there may exist a mixed population of both INH-resistant and INH-susceptible bacterial populations within individual patients in this outbreak group and the methods used in this study lacked the sensitivity to identify the INH-resistant populations. High throughput second generation sequencing is one methodology that may be able to address these limitations in future studies.

Clinical Research (Short-term Project)

## **Cannabis and Motor Vehicle Crashes**

Monica Lau, Jeff Brubacher, Herb Chan

*Department of Emergency Medicine, University of British Columbia*

**Hypothesis:** Marijuana use is a road safety issue. We hypothesize that 10% of drivers treated in hospital for injuries sustained in a car crash will have biochemical evidence of recent marijuana use and that marijuana-using drivers are more likely to have caused the crash.

**Background and Experimental Research:** Cannabis is the most commonly used illicit drug in Canada and many drivers, especially young adults, report driving after using cannabis. Although there is abundant experimental evidence that cannabis, either alone or in combination with alcohol, impairs the psychomotor skills required for safe driving, epidemiological data on the contribution of cannabis to car crashes is mixed. This uncertainty hinders the ability of traffic safety policy makers to develop effective, evidence-based, traffic laws or road safety campaigns targeting people who drive while impaired by cannabis. The primary objective of the study proposed here is to determine whether injured drivers who used cannabis before a motor vehicle crash (MVC) are more likely to have caused the crash than those who did not. Our aim is to improve traffic safety by providing current North American data that can be used to inform the development of evidence based road safety policy targeting people who drive while impaired by cannabis.

Drivers treated in the Emergency Departments (ED) at five trauma centers throughout BC will be identified by chart review. Excess blood remaining after clinical use will be analyzed to determine the presence and concentration of cannabis, alcohol and other drugs that could impair driving ability.

**Anticipated Results:** We anticipate collecting blood samples from 3000 patients over the next five years. Of these, we anticipate that 10% of injured drivers will be positive for marijuana, and 30% for alcohol. These results will be linked to motor vehicle crash reports to determine culpability. Results will have traffic safety policy implications.

## **OLIGOCLONAL BANDING AND CSF MARKERS IN MULTIPLE SCLEROSIS: ASSOCIATIONS WITH DISEASE COURSE AND PROGRESSION**

Pedro Lourenco (1), Afsaneh Shirani (1), Jameelah Saeedi (1), Joel Oger (1), William Schreiber (2, 3), Helen Tremlett (1)

*(1) Neurology, University of British Columbia, Vancouver, BC, Canada (2) Vancouver General Hospital, Vancouver, BC, Canada (3) Pathology & Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada*

**Background:** Oligoclonal bands (OCBs) and CSF markers are useful in the diagnosis of MS. However, their role in disease course determination and prognosis is poorly defined. Here, we studied the association of OCB status and CSF markers with disease-course and progression. We also examined the impact of ethnicity and selection bias on our findings.

**Methods:** In a cohort of definite MS patients (Poser or McDonald criteria), registered at BC MS Clinics between 1982-2010, we retrospectively investigated the association between OCB status, IgG-index, IgG-synthesis rate, total CSF IgG, total CSF protein, disease course (relapsing-onset (RO) vs. primary-progressive (PP)) and disability progression. Disability outcomes included time to sustained Expanded Disability Status Scale (EDSS) 6 from MS onset and birth; the proportion of patients to reach EDSS 6 within 10 years after onset; and the progression index. Analysis was repeated in Caucasians only. Selection bias was examined by comparing the characteristics of those tested vs. those not tested.

**Results:** Of the 6935 patients with definite MS, 1,120 had CSF testing, of which 957 were tested for OCBs. A total of 694/957 (72.5%) patients had detectable OCBs. OCB positivity was marginally higher in PP (107/134; 79.8%) compared to RO (587/823; 71.3%) patients ( $p=0.047$ ); this association was stronger when Caucasians only were examined (69/79; 87.3% in PP vs. 346/481; 71.9% in RO;  $p=0.003$ ). Total CSF IgG ( $64.1\pm 44.6$  vs.  $52.0\pm 37.4$  mg/L) and total protein ( $502\pm 276$  vs.  $418\pm 174$  mg/L) levels were higher in PPMS compared to RO patients, respectively ( $p<0.001$ ). Other CSF markers were not associated with disease course. Disease progression outcomes were independent of OCB status. Patients tested were significantly more likely to be male (32.4 vs. 27.1%,  $p<0.001$ ), older at onset ( $35.0\pm 10.9$  vs.  $31.5\pm 10.0$  years,  $p<0.001$ ) and have a PPMS (14.2 vs. 8.8%,  $p<0.001$ ) than those not tested.

**Conclusions:** Presence of OCBs was higher among PP compared to RO patients; this association was stronger in Caucasians. Higher total CSF protein and IgG levels were associated with a PPMS, suggesting different immunological etiologies for RO and PPMS. Disease progression was not associated with OCB status. However, a selection bias was observed, warranting caution when comparing different OCB studies.

## **Central Line Infection and Non-Infectious Complications in a Canadian Intensive Care Unit**

Christopher C. Cheung (1), Demetrios J. Kutsogiannis (2)

*(1) University of British Columbia, (2) Critical Care Medicine, Royal Alexandra Hospital*

**INTRODUCTION:** Central lines (CL) are routinely placed in critically ill patients in the Intensive Care Unit (ICU) for the intravenous administration of fluids, nutrition, and medication. However, CL can predispose a patient to complications, with reported CL-related infection rates up to 10%. We examined the incidence and risk factors for developing CL-related infections and non-infectious complications.

**METHODS:** In this prospective observational study from 2008-2009, CL progress reports were reviewed for 1362 line insertions at the ICU at the Royal Alexandra Hospital in Edmonton, AB. Population statistics, univariate and multivariate logistic regression analysis were used.

**RESULTS:** There were 995 CL established on first insertion, 262 on second insertion, and 103 lines requiring >2 insertions, in patients with APACHE-II scores of 24.6+/-7.73 (mean+/-SD). CL were inserted by residents (45%), nurse practitioners (12%), anaesthesiologists (8%), radiologists (3%), attending physicians (2%), and unknown (30%); in the ICU (60%), ER (17%), OR (8%), other hospitals (6%), wards (2%), and other locations (7%). CL insertion bundles were used for all patients (>98%). There were CL-related infections (n=12, 0.88%) and non-infectious complications (n=38, 2.79%): of the 38 non-infectious complications, there were arterial cannulations (47%), pneumothoraxes (16%), failed attempts at other sites (16%), bleeding (11%), and others (10%). Univariate analysis revealed no association between complications and line administrator or use of total parenteral nutrition (TPN), but significant association between infection and APACHE-II score (p<0.05). Multivariate regression including line administrator, use of TPN, insertion site, location, and APACHE-II identified APACHE-II score as an independent predictor of infection (OR=1.10, p=0.01).

**CONCLUSIONS:** We demonstrate a low infection and non-infectious complication rate in CL, below that reported in literature, in a Canadian ICU. These results suggest increasing APACHE-II score to be a strong independent predictor for CL-related infection.

### **Third ventricular shape: a predictor of endoscopic third ventriculostomy success**

Andrew Wong (1), Mansoor Foroughi (2), Paul Steinbok (2), Ash Singhal (2), Michael Sargent (3), Douglas Cochrane (2)

*(1) University of British Columbia (2) Division of Pediatric Neurosurgery, BC Children's Hospital (3) Department of Diagnostic Imaging, BC Children's Hospital*

**INTRODUCTION:** Two main surgical treatments for hydrocephalus exist: endoscopic third ventriculostomy (ETV) and ventriculoperitoneal shunting. ETV is favorable as it is minimally invasive as well as provides for a decreased risk of infection, blockage and over-drainage. To date, however, the criteria for identifying good ETV candidates preoperatively, and assessment of success postoperatively remains in evolution.

**OBJECTIVES:** Preoperatively, does displacement of the third ventricle floor (TVF) inferiorly and lamina terminalis (LT) anteriorly predict clinical success? Postoperatively, does resolution of such displacements correlate with success?

**METHODS:** MR imaging of 39 consecutive patients treated at BC Children's Hospital between 2004 and 2010 was reviewed to assess displacement of the TVF and LT prior to and following ETV. Displacements of the TVF and LT were judged qualitatively and quantitatively, using a new index, the Third Ventricular Morphology Index (TVMI). The association between morphological features and clinical success of ETV was analyzed.

**RESULTS:** Patients with displacement of both the TVF and LT pre-operatively underwent a successful ETV ninety-six percent of the time. The TVMI correlated with the qualitative assessments of displacement. Postoperative decrease in the TVMI occurred in all successfully treated patients. Further, changes in TVMI preceded and were of greater magnitude than those of the current best index, the Frontal and Occipital Horn Ratio (FOHR).

**CONCLUSIONS:** Assessment of TVF and LT morphology is useful in predicting clinical success of ETV and in the follow up of patients so treated. The TVMI provides a quantitative assessment of the 3rd ventricular morphology which may prove useful in equivocal cases for the management of hydrocephalic patients.

## **BRIGHTER SMILES: A COMPARISON OF GROWTH IN RURAL UGANDAN CHILDREN TO WHO STANDARDS**

Tonia Berg (1), Margaret Zhang (1), Billy Ashaba (2), Wayne Choi (1), Alex Kasangaki (2), Norman Musinguzi (2), Caitlin Meredith (1), Jackie Nambatya (2), Sara Nyairo (2), Wendy Cannon (3), Andrew Macnab (3)

*(1) University of British Columbia Faculty of Medicine and Dentistry (2) BC Children's Hospital (3) Makerere University, Kampala, Uganda*

**Purpose of Study:** The current nutritional and environmental status of a nation determine child growth patterns and can predict the health of future generations.

**Methods Used:** Children enrolled in “Brighter Smiles”, a collaborative health-promotion program, were evaluated for parameters of growth. Height, weight, head circumference and health data via questionnaire were obtained for children at a primary school in rural Uganda to compare their status to the WHO Child Growth Standard (2006). The WHO Standard uses multiethnic sampling (over 8000 children from 6 countries) to capture the genetic variability among continents to generate a single international growth standard. This growth chart uses the breast fed infant as the new standard of growth and ties physical growth to developmental milestones, allowing for a robust tool against which to measure the world’s children. This standard is intended to underscore that differences in nurture, rather than nature, determine disparities in physical growth, and provide a basis for appropriate healthcare policy and intervention.

**Summary of Results:** 233 children (105 males, 128 females), aged between 5-13 years, were evaluated. Amongst the girls 91% were below the 50th centile for height and 90% for weight. Similarly, amongst the boys 89% and 88% were below the 50th centile for height and weight respectively. A high proportion of these children come from single parent or child-headed families (this community was the epicentre for the AIDS epidemic) and poverty, borderline nutrition, malaria, diarrheal disease and parasitic infections are prevalent. Prior research here has also documented that cultural and religious beliefs lead to restricted intake of essential foods, inadequate intake of vitamins and minerals, and infectious diseases commonly exacerbate protein-calorie malnutrition.

**Conclusions:** The finding that such a high percentage of our cohort’s children had height and weight below the 50th centile most probably reflects the impact of local social circumstances, sub-optimal nutrition and infectious disease, and indicates the value and potential for the WHO standards to identify where children’s growth patterns would benefit from interventions to promote appropriate nurture, and improve health and growth potential.

Clinical Research (Short-term Project)

## **BRIGHTER SMILES UGANDA: KEY ELEMENTS FOR SUCCESSFUL GLOBAL HEALTH EDUCATION ELECTIVES**

Margaret Zhang (1), Wayne Choi (1), Billy Ashaba (2), Mattias Berg (1), Tonia Berg (1), Caitlin Meredith (1), Norman Musinguzi (2), Jackie Nambatya (2), Sara Nyairo (2), Wendy Cannon (3), Alex Kasangaki (2), Andrew Macnab (3)

*(1) University of British Columbia Faculty of Medicine and Dentistry (2) BC Children's Hospital (3) Makerere University, Kampala, Uganda*

**Purpose of Study:** Global health electives have the potential to foster opportunities for service learning and create a platform to educate students on the key determinants of health, and cultural competencies and logistics necessary for successful program delivery. To be effective and relevant to the host country such electives require structure.

**Methods Used:** We describe the key elements (identified via annual evaluation) central to success of a five year global-health partnership (Brighter Smiles) between the University of British Columbia and Makerere University in Uganda.

**Summary of Results:** SERVICE DELIVERY - School-based health promotion is an effective model endorsed by WHO. Giving interactive workshops provides knowledge and skills for healthy practices and promotes change in school health culture. This informs and empowers the next generation on a broad range of health and social issues. COMMUNITY-BASED LEARNING - Clinical opportunities and collaborative research/evaluation provide new knowledge. Students learn the priorities and realities of medical care, prevention and social and cultural practices, establish the effectiveness of service delivery programs, and provide feedback and future direction to participating individuals and communities. COLLABORATION - Partnership of teams from different universities with local community leaders during project delivery and workshops generates invaluable dialogue and learning opportunities. Insights into realities and opportunities are gained, and essential skills learned re team-work, communication, and cultural sensitivity. MENTORSHIP - Passion and experience shared by local and visiting faculty is infectious and invaluable. This is an essential component to ensure safe, culturally-relevant and sustainable student experiences.

**Conclusions:** Global health electives based on the 'Brighter Smiles' template should prove to be relevant, and offer effective and appropriate learning for university students.

Clinical Research (Short-term Project)

## **Molecular Analysis of alpha globin gene mutations in BC Families**

Anne Lambert (1), Ann Wong (2), Louis D. Wadsworth (3), Nicholas Au (3), Ross MacGillivray (1,2)

*(1) Faculty of Medicine, University of British Columbia (2) Centre for Blood Research and Department of Biochemistry & Molecular Biology (3) Department of Pathology & Laboratory Medicine, University of British Columbia, and B.C. Children's Hospital, Vancouver, B.C., Canada*

**Introduction and Objective:** Mutations in hemoglobin can lead to structural changes which hinder its ability to transport oxygen throughout the body and can lead to anemia. Hemoglobin in humans consists of four globin chains - the vast majority of these tetramers being made up of two alpha chains and two beta chains. The alpha globin gene is present at two loci on chromosome 16. These duplicated alpha globin genes have identical coding sequences and a high GC content which complicates their ability to be amplified separately via Polymerase Chain Reaction (PCR). This study aims to individually amplify  $\alpha 1$  (HBA1) and  $\alpha 2$  (HBA2) in order to sequence the genes to look for single nucleotide polymorphisms (SNPs) or deletions.

**Methods:** Blood samples of patients that showed abnormalities in the alpha globin with HPLC analysis were obtained from B.C. Children's and Women's Hospital. The HBA1 and HBA2 genes were amplified separately using PCR. The resulting product was subjected to automated DNA sequence analysis.

**Results:** PCR amplification with alpha globin primers produced an 880bp product for HBA2 and an 887bp product for HBA1. Further sequential analyses of the amplified product produced 2 cases of note: Alpha hemoglobin PCR on a patient presenting with mild microcytic anemia revealed that she has both  $-\alpha 3.7$  and  $-\alpha 4.2$  deletions. HPLC produced an unknown peak indicating the presence of a hemoglobin variant and sequencing revealed an Asp74His amino acid change. This combination has been described only once previously as a double heterozygote for Hb Q-Thailand and  $\alpha^+$ -thalassemia ( $-\alpha QT/-\alpha 3.7$ ). On routine screening for common alpha thalassemia deletions, a mother and son were found to have a deletion of 204bp in one allele of HBA2. Sequential analysis led to the discovery of the break points and the conclusion that exon 3 of HBA2 had been deleted.

**Conclusion:** HBA1 and HBA2 can be amplified separately in order to locate a variety of SNPs or deletions in patients screened for alpha globin abnormalities. Significant findings include a rare double heterozygote mutation for Hb Q-Thailand and  $\alpha^+$ -thalassemia ( $-\alpha QT/-\alpha 3.7$ ) and the discovery of an uncharacterized 204bp deletion in HBA2.

## **RISK FACTORS FOR URINARY RETENTION AFTER HIP OR KNEE REPLACEMENT**

Jeremy Neufeld (1), Donald Greisdale(1), Dale Dhillon (1), Jennifer Joo (1), Supna Sandhu (1), Frank Swinnton (1), Peter Choi (1)

*(1) Department of Anesthesiology, Pharmacology and Therapeutics (2) Faculty of Medicine*

**INTRODUCTION:** Hip and knee replacements are two of the most commonly performed surgical procedures in developed countries. The rates of these procedures have increased with the aging of the Canadian population but wait times continue to be long. In 2006, our provincial government initiated a program to reduce wait times by referring elective patients to a single tertiary-care centre. This program provided an opportunity to identify risk factors for common perioperative complications as part of a continuing quality improvement project. We report the incidence rate of postoperative urinary retention after hip and knee replacements and the risk factors associated with this complication.

**METHODS:** After local Research Ethics Board approval, data were abstracted from a random sample of charts of patients who underwent elective primary unilateral total hip replacement (THR) or total knee replacement (TKR) surgery in the first 13 months of the program. When patients underwent more than one joint replacement during the study period, we collected data from the first procedure only. Variables included demographics, comorbid conditions, medications, anesthetic details, times, and postoperative complications in the first 24 h after surgery. We defined postoperative urinary retention as urinary catheterization due to inability to void or ultrasound evidence of bladder distention after unsuccessful attempts to void. Stata release 10 (StataCorp, Texas, USA) was used for data analysis. Normally distributed and skewed data were described by means (standard deviation [SD]) and median (interquartile range [IQR]) respectively. Risk factors were identified using multivariable logistic regression. Risks were expressed as odds ratios [OR] (95% confidence intervals [CI]). A p-value of <0.05 was considered to be significant.

**RESULTS:** From April 1, 2006 to May 31, 2007, 1440 patients underwent 1515 elective THR or TKR. We abstracted data from 1031 (71.3%) patients [age 62 y (IQR 55-70); 53.7% female; 605 THR, 426 TKR]. Procedures were performed under spinal anesthesia (n=844, 81.8%), general anesthesia (n=105, 10.2%), or combined spinal and general anesthesia (n=82, 8.0%). Patients spent 100 min (IQR 90-114 min) in the operating room and 3 days (IQR 3-4 days) in hospital. The 24-h incidence of postoperative urinary retention was 43.3% (446/1031). Male sex (OR 3.9, 95% CI 3.0-5.2) and intrathecal morphine [ $\leq$ 100 mcg (OR 3.7, 95% CI 2.2-6.3); 101-150 mcg (OR 5.5, 95% CI 3.1-10.0); >150 mcg (OR 4.0, 95% CI 2.0-8.0)] were risk factors for urinary retention (all p<0.001).

**DISCUSSION:** Postoperative urinary retention is a common complication after THR or TKR, especially amongst men and patients receiving intrathecal morphine. Intraoperative urinary catheterization should be considered to prevent this complication.

Clinical Research (Short-term Project)

**Cost comparison and program growth characteristics of an established interdisciplinary pediatric cardiology outreach program in British Columbia**

Kiley Cindrich (1, 2), Jim Potts (1), Stella Cockett (1), Derek G Human (1)

*(1) Department of Cardiology, BC Children's Hospital and BC Women's Hospital and Health Centre, Vancouver, British Columbia (2) VFMP 2013, Faculty of Medicine, University of British Columbia, Vancouver, BC*

**BACKGROUND:** Each year there are approximately 350-500 children in British Columbia who are diagnosed with congenital heart disease. Traditionally, these children and their families have travelled to the provincial tertiary care centre, British Columbia Children's Hospital (BCCH) in Vancouver, BC, to receive non-acute specialized medical care. Travelling adds a high financial and emotional cost to families. Thus, the Division of Cardiology at BCCH implemented interdisciplinary outreach clinics with partnered BC communities with no nearby pediatric cardiology service. We evaluated the cost and growth of this Pediatric Cardiology Partnership Program (PCPP).

**METHODS:** A retrospective chart review was completed. Historical data from the initial year of the PCPP were examined and internal patient databases, budget records, and staff communications were reviewed. Data was collected on any patient who was followed by the PCPP from April 1, 2005 to March 31, 2010.

**RESULTS:** The PCPP has grown from 45 clinic days and 620 patient appointments in the 2005-6 fiscal year to 55 clinic days and 728 patient visits in the 2009-10 fiscal year. Patients travel between 17-216km round trip to attend a PCPP clinic which is less than the 164-3906km to attend a clinic at BCCH. After their PCPP appointment, 81% of patients are not referred for appointments in the Vancouver area and thus do not need to travel to tertiary care centres for future visits. The cost of the program per patient is less than the cost of the patient's family travelling to Vancouver.

**INTERPRETATION:** The interdisciplinary PCPP through BCCH has been successful in caring for non-acute patients in rural BC health care settings and preventing their need to travel to tertiary care centres.

Clinical Research (Short-term Project)

## **Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD): ECG changes and Cardiovascular work-up.**

Cheryl Lane, Alyson Wong, Jane Burns, Don Sin, Stephan F van Eeden

*Pacific Lung Health Centre and James Hogg iCAPTURE Centre, University of British Columbia; St. Paul's Hospital, Vancouver, British Columbia*

**PURPOSE:** Risk factors for and cardiovascular disease (CVD) are common in subjects with Chronic Obstructive Pulmonary Disease (COPD) and predicts morbidity and all-cause mortality in COPD patients. Here we determine how patients are investigated for exacerbation of CVD in subjects admitted with AECOPD.

**METHODS:** Retrospective data review of subjects admitted to two tertiary care facilities during a 12 month period with AECOPD. GOLD criteria were used to verify underlying COPD and Anthonisen criteria to classify AECOPD.

**RESULTS:** We studied 163 admissions (82 patients), age  $65\pm 11$  years, mean GOLD stage  $3.4\pm 0.8$ , mean FEV1  $30.3\pm 1.1\%$ . Risk factors for CVD (excluding smoking) were present in 37% of subjects and documented underlying CVD in 49%. On admission, 85% of subjects received an ECG, of which 56.4% had abnormalities and 39.3% had new abnormalities. Subjects with ECG abnormalities had lower FEV1 ( $33.5\pm 1.5$  vs  $27.7\pm 1.4$ ,  $p<0.004$ ). Within 24hrs of admission, 47.1% of subjects had troponins, of which 9.3% were  $>0.05$  ng/mL, but only 19.6% had repeat troponins. Of those with new ECG abnormalities, 37.5% did not receive troponins within 24hrs. Subjects with new ECG abnormalities have more CV risk factors ( $p<0.044$ ), and are more likely to receive troponins ( $p<0.032$ ). New ECG changes and age predict CV work-up. There was a trend for subjects with an abnormal ECG to have longer LOS ( $9.9\pm 0.9$  vs  $13.2\pm 1.5$  days,  $p=NS$ ) but subjects with a history of IHD or ECG suggestive of ischemia, had significantly longer LOS ( $10.2\pm 0.8$  vs  $16.2\pm 2.5$  days,  $p<0.01$ ).

**CONCLUSIONS:** Underlying cardiovascular disease is prevalent in subjects admitted to hospital with AECOPD and exacerbation of CVD is poorly studied as an etiology for dyspnea despite evidence that CVD causes significant morbidity and mortality in this population. A larger prospective study is necessary to determine the impact of full cardiac work-up on morbidity and mortality of AECOPD.

**CLINICAL IMPLICATIONS:** Multiple CV risk factors, new ECG changes and signs of new/old ischemia on the ECG should prompt cardiovascular work-up in subject admitted for AECOPD to optimize management of CVD in this patient population.

Clinical Research (Short-term Project)

## **Role of Transforming Growth Factor-Beta Signaling Modulators in Periodontal Disease**

S Bains-Dahia (1), J Gauldie (2), L Häkkinen (1), H Larjava (1)

*(1) Laboratory of Periodontal Biology, Faculty of Dentistry, University of British Columbia, Vancouver, Canada (2) Centre for Gene Therapeutics, McMaster University, Hamilton, Canada*

Transforming growth factor beta 1 (TGF- $\beta$ 1) plays a crucial role in protection of many organs from inflammation. TGF- $\beta$ 1 is expressed as a latent cytokine and needs to be activated for function. Epithelial integrin  $\alpha\beta$ 6 and thrombospondin-1 (TSP-1) serve as activators of TGF- $\beta$ 1. Mice deficient of  $\beta$ 6 integrin ( $\beta$ 6<sup>-/-</sup>) develop periodontal disease with apical migration of junctional epithelium, inflammation and bone loss. The aim of the present investigation was to find out whether TSP-1 jointly with  $\alpha\beta$ 6 integrin participates in TGF- $\beta$ 1 activation and protection of periodontium from inflammation. In addition, we hypothesized that the TGF- $\beta$ 1-mediated immunoprotection is mediated via Smad3, a key signalling molecule in the TGF- $\beta$ 1 pathway.

Clinical Research (Short-term Project)

## **Designing for Bariatric Care: Toilet Aid Design**

M. Michiko Maruyama (1), Winnie Lei (2), Jenna Hill (1) and Celia Ching (2)

*(1) Department of Art and Design, University of Alberta (2) Department of Occupational Therapy, University of Alberta*

As described by the World Health Organization, “Obesity is a complex condition, one with serious social and psychological dimensions, that affects virtually all age and socioeconomic groups and threatens to overwhelm both developed and developing countries.” In order to better understand the social and psychological circumstances faced by the bariatrics community, our design team reached out and communicated with individuals through online obesity support groups. With their input and the clinical experience of the occupational therapists on the design team, we were able to identify a need within the bariatric community. Individuals stressed the need for a portable peri-anal care device that can be used outside the home or hospital environment to help them feel more independent. The quotes below were gathered from members of the online support group, [www.dailystrength.org](http://www.dailystrength.org):

“For some people, the inability to reach, a simple yet essential task, might very well be the pivot point between being a functionally mobile obese person versus Gilbert Grapes’ mother. The people stuck in their beds did not purposely lay down one day and just never got up. They stop leaving their houses first... And they continued to gain weight.”

“I try not to drink any liquids because I do not want someone to help me when I need to use the washroom.”

Current toilet aid devices are large and bulky making them unsuitable for portability. The user must wrap a large amount of toilet paper around the device. In public washrooms, the toilet paper may not be appropriate for current toilet aids. Also, cleaning the toilet aid in public or at home might be difficult for some users. To address this design problem, the team developed the Flushable Toilet Aid, a disposable personal care device designed to assist those with limited range of motion in performing peri-anal hygiene. The team researched various material choices and took into consideration ergonomics and portable functionality throughout the design process.

## **Injury Patterns and Discharge Dispositions in Motorcycle Crash Victims**

Noah Alexander, Sarah Foster, Shawna Mann, Marcio Penner, Erika Penner, Murray Penner

*Department of Orthopaedics, University of British Columbia*

**Background:** Increasing gas prices and urban congestion are causing more Canadians to consider motorcycling as an alternative mode of transport. The risks of motorcycling have been documented in studies in the United States, Europe, and Asia but there is a notable paucity of Canadian studies. Because of differences in helmet and traffic regulations Canadian motorcyclists' injury patterns cannot be assumed to parallel those in other countries. This study uses a retrospective chart review to analyze injury patterns in motorcycle crash victims and their relationship to discharge disposition and length of hospital stay.

**Methods:** All patients involved in a motorcycle crash and admitted to the Vancouver General Hospital between April 2001 and December 2009 (N = 567) were included in the study. Data was extracted from the ICD-10 coded Discharge Abstract Database.

**Results:** Riders tended to be male (89.2%) and had a mean age of 37.2. The average length of stay was 14.4 days, although patients with head/facial injuries,  $t(564)=6.23$ ,  $p<.01$ , and spinal injuries,  $t(564)=7.25$ ,  $p<001$ , were more likely to have extended stays. Overall, the most common injuries were tibial fractures (N = 108, 19% of cases), forearm fractures (N = 105, 18.5%), rib fractures (N=92%, 16.2%) and ankle and/or foot fractures (N = 91, 16.0%).

Most riders were discharged home (N=403, 70.0%). This group had significantly fewer injuries (M=2.2) than those who remained in hospital or expired (M=4.4 injuries). The most common injuries experienced by those discharged home were tibial and forearm fractures (N=70, 17.4%, for each), and ankle and/or foot fractures (N=69, 17.1%). In contrast, those who remained in hospital were most likely to have sustained injuries to the pelvis (N=43, 29.3%), cervical spine (N=38, 25.9%), or thoracic spine (N=37, 25.2%). Among the 14 patients (2.5%) who expired, the most common injuries were intracranial haemorrhage, rib fracture, haemothorax, liver injury, and cervical spine fracture (N=5, 35.7% for each).

**Conclusion:** The results provide a starting point to help physicians predict injuries in motorcycle crash victims and highlight areas where rider armor is most valuable. Finally they call attention to the potential health care costs with increasing motorcycle usage.

Clinical Research (Graduate Research)

## **Multimodal Characterization of Vestibular Schwannoma with Magnetic Resonance Imaging and L-11C-Methionine Positron Emission Tomography**

Megan M. J. Burns (1), Vesna Sossi (1), Burkhard Madler (2), Alex MacKay (1), Katie Dinelle (1), Salma Jivan (3), Tom J. Ruth (3), Roy Ma (4), Richard Shaffer (4), Michael McKenzie (4), Alan Nichol (4), Montgomery Martin (4), Stefan Reinsberg (1)

*(1) Department of Physics and Astronomy, University of British Columbia, Vancouver, BC, V6T 1Z1, (2) Philips Medical Systems, University of British Columbia, Vancouver, BC, Canada, V6T 2B5, (3) Department of Medicine/Neurology and UBC/TRIUMF PET Program, University of British Columbia, Vancouver, BC, (4) Departments of Radiation Oncology and Radiology, British Columbia Cancer Agency*

**Purpose:** A pilot study was designed to test the utility of functional magnetic resonance imaging (MRI) and L-11C-Methionine PET (MET-PET) imaging techniques as predictors of vestibular schwannoma response to radiotherapy.

**Methods:** Patients selected for radiotherapy with previously diagnosed vestibular schwannoma were scanned within eight weeks prior to receiving radiotherapy. Patients were scanned using diffusion tensor imaging (DTI) and dynamic contrast-enhanced MRI (DCE-MRI). MET-PET scans were acquired dynamically for 60 minutes.

**Results:** Population means for mean diffusivity and fractional anisotropy of tumours, excluding visibly cystic tumour regions ( $n = 12$ ) were  $1.43 \times 10^{-3} \text{ mm}^2/\text{s}$  and 0.526, respectively. Mean  $K_{\text{trans}}$ ,  $v_e$ , and  $\text{IAUC}_{60}$  for tumour population ( $n=12$ ) using individually-derived arterial input functions and a 2-parameter pharmacokinetic model were 0.132/min, 0.144, and 8.75  $\text{Mm}^* \text{s}$ , respectively. Different tumour regions were observed to enhance under MET-PET and post-contrast T1-weighted MRI. All tumours showed enhancement under MET-PET as compared to contra-lateral region.

**Conclusions:** DTI, DCE-MRI, and MET-PET show promise as investigatory tools for characterizing vestibular schwannoma and evaluating response to treatment. Quantitative parameters derived from DTI and DCE-MRI may aid in understanding the pathological progression of vestibular schwannoma by serving as surrogate markers of functional tissue properties. MET-PET appears to be sensitive to the metabolic activity of vestibular schwannoma.

**Characterization of RanBPM sequence components that regulate its subcellular localization.**

Robert Dale, Elnaz Atabakhsh, Victoria Fell, and Caroline Schild-Poulter

*Department of Cell Biology, Johns Hopkins University School of Medicine*

Ran-binding protein M (RanBPM) is a 90 kDa nucleocytoplasmic protein that has been implicated as a pro-apoptotic factor. In addition, it has been found to translocate out of the nucleus and into the cytoplasm following ionizing radiation (IR) treatment. Thus, RanBPM's subcellular localization may play a role in regulating its pro-apoptotic function. Since RanBPM is over the 50 kDa passive diffusion size limit for a nuclear pore complex, it must be actively transported across the nuclear membrane. The purpose of this study was to determine which regions of RanBPM are responsible for regulating its subcellular localization. HeLa cells stably expressing siRNA targeted against endogenous RanBPM were transfected with RanBPM constructs containing various point mutations and deletions. Constructs also contained point mutations in the C-terminal to make them resistant to siRNA-mediated knockdown. An HA tag was fused to each construct to enable visualization using indirect immunofluorescence microscopy. The N-terminal region (residues 1-251) was found to be important for subcellular localization. Specifically, residues 1-101 were found to promote nuclear retention whereas the N-terminal putative NES was found to facilitate nuclear export. In addition, deletion of RanBPM's SPRY domain localized RanBPM to the cytoplasm and caused significant aggregation. This suggests the SPRY domain may be important for cytoplasmic maintenance and solubility.

## **Mapping protein-protein interactions of yeast xenobiotic efflux pump Pdr5p using the Integrated Membrane Yeast-Two Hybrid System: Pdr5p-Erg4p interaction important for Pdr5p function**

Min-Han Michael Yang (1), Igor Shevelev (1), Igor Stagljar (1)

*(1) Department of Biochemistry & Department of Molecular Genetics, University of Toronto*

**Background:** Pdr5p is an ABC transporter protein in the pleiotropic drug resistance (PDR) family in *Saccharomyces cerevisiae*, which is homologous to the human P-glycoprotein important in cancer multi-drug resistance. Proteins like P-glycoprotein rarely exert their function alone, instead they are in constant dynamic interaction with other proteins and complexes that can modulate and influence their activity. However, it is difficult to study protein-protein interactions in human cells in a high-throughput manner. Using yeast as a model organism, this investigation aims to identify as many protein interactors of Pdr5p as possible using the Integrated Split-Ubiquitin Membrane-Yeast-Two Hybrid (iMYTH) System. Identifying Pdr5p's interactors in yeast will give clues as how to manage chemoresistance in cancers due to P-glycoprotein in human.

**Methods:** Pdr5p's ORF is endogenously tagged with Cub-TF by homologous recombination. Sequencing and genetic testing were performed to confirm the PDR5 gene was inserted in-frame. The tagged cell were then subjected to a large scale transformation using plasmids containing yeast genomic library with NubG fused to the N-terminal side and plated onto -WAH plates. The clones were then subjected to plasmid isolation, and then transformed into MC1061 bacterial cells to obtain sufficient plasmid for sequencing. The sequence results were ran through BLAST on the "Saccharomyces Genome Database" to identify the prey proteins. False positive interactors were identified by performing a Bait-Dependency test by increasing concentrations of 3-amino-1,2,4 triazole. In the Bait Dependency test, the prey containing plasmids were transformed into the Pdr5p-Cub-TF, Ste24p-Cub-TF and Ycf1p-Cub-TF yeast strains. Lastly, drug sensitivity tests were performed on knock-out mutants of potential interactors of Pdr5p by plating on cycloheximide containing plates.

**Results:** The iMYTH system yielded 18 unique protein interactors of Pdr5p of which 12 were confirmed using the Bait Dependency Test. Among the 12 true interactors of Pdr5p, Erg4p was confirmed to be in the same functional pathway as Pdr5p by using the cycloheximide drug sensitivity test.

**Conclusion:** 12 true protein interactors of Pdr5p were identified of which Erg4p was shown to be important to the xenobiotic efflux pump activity of Pdr5p.

**Overexpression of PPAR $\gamma$  in pancreatic  $\beta$ -cells exacerbates glucose intolerance in diet-induced obese mice**

Christopher E. Uy (1), K-Lynn N. Hogh (1), Robert Baker (2), Ali Asadi (2), Jordie Fraser (1), Michael Riedel (2), Timothy J. Kieffer (2), Sarah L. Gray (1)

*(1) Northern Medical Program, University of Northern British Columbia, Prince George, BC, Canada (2) Department of Cellular and Physiological Sciences and Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada*

Lipotoxicity is one mechanism implicated in beta-cell dysfunction during the development of obesity-induced type 2 diabetes (T2D). Peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) is a transcription factor involved in lipid uptake and storage. We hypothesize that localized overexpression of lipogenic PPAR gamma in pancreatic beta-cells will aggravate the effects of obesity induced lipotoxicity and impair glucose homeostasis.

In MIN6 cells, we have successfully overexpressed PPAR gamma utilizing an adeno-associated viral vector (dsAAV8) and have shown induction in PPAR gamma target genes. Additionally, we have overexpressed PPAR gamma in the pancreatic beta-cells of obese (16wks HFD) C57B/6 mice using the dsAAV8 virus. Changes in carbohydrate metabolism were monitored regularly through bi-weekly measurement of 4-hour fasted blood glucose and monthly measurement of oral glucose tolerance (OGTT), insulin tolerance (ITT), glucose-stimulated insulin secretion (GSIS), and plasma insulin levels. Islet morphology was also assessed at the end of the study. In vivo, pancreatic beta-cell specific overexpression of PPAR gamma impairs glucose tolerance compared to obese controls. This disruption in glucose homeostasis is not associated with changes in insulin sensitivity, and instead may be associated with reduced beta-cell mass. This study demonstrates that targeted delivery of PPAR gamma to the beta-cell specifically aggravates the lipotoxic effects of obesity on beta-cell function providing a useful in vivo model to elucidate the mechanisms involved in beta-cell lipotoxicity in obesity-induced T2D.

## **The Relationship between Single Unit activity and Neocortical Gamma Rhythms during Behavior**

Joshua Lai (1), Alison Boyd (2), Omar Ahmed (3), Mayank Mehta (4)

*(1) Department of Medicine, University of British Columbia (2) Department of Neurosciences, University of California, San Diego, (3) Department of Neurosciences, Brown University (4) Departments of Physics and Astronomy, University of California, Los Angeles*

Network activity facilitates information storage, transfer, and integration between neuronal populations for sensory, motor, and cognitive processing. Characterizing the vast array of neural networks, however, is a work in progress. Neocortical gamma rhythms have come to increasing attention as a possible method of communicating and binding information encoded by distinct neuronal populations across brain regions. Gamma rhythms are seen in primary sensory cortices, higher order association areas, hippocampus, and various subcortical structures. If gamma rhythms are intimately involved in integrative processing, they might have particular significance in association areas of neocortex such as the prefrontal and parietal cortices. Electroencephalogram (EEG) studies, functional MRI, and electrophysiological techniques have corroborated the role of gamma rhythms in these regions for sensorimotor integration, working memory, attention, and decision making in both animal models and humans.

The precise relationships between single unit activity and gamma rhythms, however, are poorly explored. Analyzing when neurons fire and how much they fire in relation to gamma rhythms can begin to clarify how neuronal populations interact to perform complex cognitive tasks. To this end, we used in-vivo recordings from two freely behaving rats to investigate how spike timing and spike rate related to simultaneously recorded gamma oscillations in the local field potential. We compared the results of these analyses across the prefrontal cortex and posterior parietal cortices. We show that the majority of cells in both regions are phase locked to gamma oscillations. We also find surprisingly strong relationships between the firing rates of individual cells and the precise frequency of gamma oscillations. However, even neighboring cells can show opposite relationships to gamma frequency, suggesting that gamma oscillations differentially regulate neuronal populations, even at the same anatomical location.

## **Characterization of the Intra-renal Vasculature in Atrial Natriuretic Peptide Gene-disrupted (ANP<sup>-/-</sup>) and Wild-type (ANP<sup>+/+</sup>) Mice**

Kelvin S.K. Kwan, M. Yat Tse, Stephen C. Pang

*Department of Anatomy and Cell Biology, Queen's University, Kingston, ON*

**PURPOSE:** Studies of the ProANP gene-disrupted (ANP<sup>-/-</sup>) mouse model have established that atrial natriuretic peptide (ANP) plays an important role in maintaining blood pressure homeostasis. Recently, ANP<sup>-/-</sup> mice have been found to have elevated sympathetic activity in the kidney, which could have a profound impact on renal development. The aim of this study was to develop a method for examining the intra-renal vasculature of ANP<sup>-/-</sup> and wild-type (ANP<sup>+/+</sup>) mice and to determine any morphological differences between these two genotypes.

**MATERIALS AND METHODS:** Fluorescent staining using antibodies targeting  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA), immunohistochemistry, fluorescent microscopy, and a novel method of graphical morphometric analysis were used to quantify and characterize the intra-renal vasculature of ANP<sup>-/-</sup> and ANP<sup>+/+</sup> mice. **RESULTS:** Preliminary results indicate a trend in which ANP<sup>-/-</sup> mice have a larger proportion of intra-renal blood vessels characterized by a smaller wall-thickness-to-lumen-diameter ratio, and in which ANP<sup>+/+</sup> mice have a larger proportion of intra-renal blood vessels characterized by a larger wall-thickness-to-lumen-diameter ratio.

**DISCUSSION:** The trends observed in the preliminary results for ANP<sup>-/-</sup> mice could be related to the structural development of intra-renal vasculature in the absence of ANP.

**CONCLUSION:** It is possible to characterize blood vessels of mice kidneys using fluorescent-linked antibodies targeting  $\alpha$ -SMA and the graphical morphometric analysis method developed in this study. Trends observed in the preliminary results provided new directions that could potentially explain the role of ANP on the morphology of the intra-renal vasculature in the ANP<sup>-/-</sup> mouse model.

Basic Sciences (Undergraduate Research)

## **Functional analysis of variants of the Wilson disease copper transporter, ATP7B**

Michael A. Benusic (1), Georgina Macintyre (2), Diane W. Cox (2)

*(1) Vancouver Fraser Medical Program 2014, Faculty of Medicine, University of British Columbia (2) Department of Medical Genetics, Faculty of Medicine & Dentistry, University of Alberta*

Copper is an essential trace element, acting as a cofactor for numerous enzymes that catalyze a multitude of biological processes. However, copper is toxic in excess. Wilson disease (WND) is an autosomal recessive disorder of copper homeostasis characterized by impaired biliary copper efflux. Copper accumulates in the liver, brain, and kidney, damaging these organs. Phenotypic manifestations of WND are highly variable, hampering many clinical and biochemical diagnostic methods. The WND gene, ATP7B, encodes a membrane ATPase which functions in transporting copper to apo-enzymes and trafficking excess copper out of cells. More than 500 variants have been identified in patients; functional analysis is crucial in determining if these are in fact disease-causing as opposed to rare normal variants.

We use several assays to analyze the consequences of ATP7B variants: a transport assay within yeast, and trafficking and viability assays within a mammalian cell model. Ccc2p, a yeast homologue of ATP7B, delivers copper to Fet3p which is essential for growth under iron-limited conditions.

## **NMDA Receptor Subunit Expression in Male and Female Rat Hippocampus following Voluntary Exercise**

Andrew Kwasnica

*University of Victoria, Division of Medical Sciences*

Voluntary exercise (VEx) can have robust structural and functional effects on the hippocampus, a region involved with learning and memory. Specifically, VEx can enhance neurogenesis, long-term potentiation (LTP), and differentially upregulate the expression of mRNA for specific subunits of the N-methyl D-aspartate receptor (NMDAR) in the dentate gyrus (DG; a subregion of the hippocampus) of male rats. Although previous studies have shown LTP and neurogenesis to differ between males and females, the effects of VEx on NMDAR subunit expression in the hippocampus has yet to be investigated in females. Juvenile (P22) male and female rats were group housed by sex in one of two housing conditions: VEx: unlimited access to a running wheel or sedentary (SED): no access to a running wheel. Between P30-35, hippocampi were isolated and subregions were rapidly dissected on ice and stored in a protease inhibiting cocktail at -80 Centigrade until assayed for NR2A, NR2B and NR1 subunits of the NMDA receptor by western blot. There was not a significant difference in the amount of running between males and females, and both males and females ran most during the dark phase of the light cycle. VEx did not increase protein levels of NR1 or NR2B levels in the DG of either males or females, but there was a trend toward more NR2A protein in the DG of both males and females following VEx. Interestingly, males have more NR2B protein than females, regardless of housing condition. These data indicate that both gender and housing conditions can have an effect on NMDAR subunit expression in the rat DG.

Further investigations into the nature of the differences between the sexes is warranted, to determine if, for example, NMDARs differentially contribute to LTP and neurogenesis in males and females.

## **The biomechanics of swing-through gait in lower-limb amputees: A comparison of the SideStix™ sports forearm crutch versus standard crutch designs**

Ranita H. Manocha (1), Megan K. MacGillivray (2,3), Bonita J. Sawatzky (3,4)

*(1) M.D. Candidate, Faculty of Medicine, University of British Columbia, Vancouver, Canada (2) Ph.D. Student, Department of Rehabilitation Sciences, University of British Columbia, Vancouver, Canada (3) International Collaboration on Repair Discoveries (ICORD), Vancouver, Canada (4) Associate Professor, Department of Orthopaedics, University of British Columbia, Vancouver, Canada*

Overuse injuries affecting the shoulder, elbow and wrist are prevalent amongst forearm crutch users. The SideStix™ sports forearm crutch is designed to reduce the physical impact of crutch walking, but this has yet to be validated experimentally. This crutch features a spring-like urethane polymer in the shaft and a ball-and-socket joint in the foot. We aimed to compare the biomechanics of swing-through gait in amputees using this sports crutch versus a traditional non-dynamic forearm crutch. As a result of the aforementioned modifications in the SideStix™ crutch, we hypothesized that this crutch would: a) reduce peak elbow extension; b) decrease peak wrist extension; c) decrease peak ground reaction force; d) increase propulsive force; and e) decrease braking force.

Phase I of our study aimed to develop a biomechanical model and protocol to analyze upper extremity kinematics and kinetics with forearm crutch use. Our model employed an optical tracking system and force plates to quantify joint angles and crutch ground reaction forces during swing-through gait for a 25-year-old able-bodied female with no previous forearm crutch experience. Data from 5 trials for a single crutch type were filtered, averaged, and processed for each 1% of crutch stance phase using custom Matlab™ programs.

Phase I demonstrated that SideStix™ crutches decreased the peak braking and propulsive forces, when compared to standard forearm crutches. This is potentially beneficial as loading in these directions threatens shoulder integrity. The SideStix™ also decreased elbow extension, which could prevent ulnar nerve compression. These findings demonstrated the model's potential effectiveness in the characterization of swing-through crutch gait. As a result, the model and protocol developed in Phase I will be applied to a wider sample of ten individuals with lower-limb amputations during Phase II of our research. The outcome of Phase II will improve our understanding of the biomechanics of swing-through gait in a clinical population and may demonstrate key opportunities for improving crutch design to reduce injury.

## **Miscibility and Stability of Sterol/Phospholipid Bilayers are Optimized by the Double Bond Position in the Sterol Nucleus**

Matthew G.K. Benesch, David A. Mannock, Ruthven N.A.H. Lewis, Ronald N. McElhaney

*Department of Biochemistry, School of Molecular and Systems Medicine, Faculty of Medicine & Dentistry, University of Alberta*

Understanding the variation in the strength, number and types of interactions between the sterol ring system and neighboring phospholipid molecules is important in understanding the structure and function of sterol-containing membranes. This has important implications in treating sterol-involved pathological processes such as Parkinson's, Alzheimer's and prion-associated diseases, as well as some cancers. In this study, we investigated how the presence, position and conjugation of the carbon 5,6 double bond in ring B of cholesterol influences the thermotropic phase behavior of binary dipalmitoylphosphatidylcholine (DPPC, a model mammalian lipid)/sterol mixtures using differential scanning calorimetry and Fourier-transform infrared spectroscopy. Being fully miscible in a DPPC bilayer, cholesterol stabilizes the gel phase and reduces the enthalpy and cooperativity of the DPPC gel/liquid crystalline phase transition, eliminating its enthalpy by 50 mol% sterol. None of the other sterols studied have all these abilities. Generally, we see that an all-trans ring system is required to stabilize the gel phase, and the presence of a single double bond within ring A or B to abolish the phase transition at high sterol levels. All sterols in this study (equatorially-orientated carbon 3 $\beta$ -alcohols) broaden and the phase transition better than corresponding axially-orientated carbon 3 $\alpha$ -alcohols and carbon 3-ketones. Further, a conjugated double-bond system may give rise to additional electronic properties that lead to an increased favorability in interactions between like-like (sterol) molecules over like-unlike (sterol-lipid) molecules, the latter being a necessary condition for optimal sterol/lipid miscibility and stability. Given the differences in the thermodynamic parameters obtained from DPPC mixtures containing different sterol ring conformations and their associated changes in bilayer stability and miscibility, it is clear that sterol conformation has a significant effect on bilayer physical properties. Any sterol molecule whose ring structure deviates from that of cholesterol is unlikely to be fully miscible in the mammalian cell membrane.

**Expression and characterization of the human amylin receptor AMY3 in the mammalian cell-line RK13 (rabbit kidney cells) as a cellular model for Amyloid beta neurotoxicity in Alzheimer's Disease**

Andre Isaac (1), Wen Fu (2), Jack H. Jhamandas (2)

*(1) Faculty of Medicine and Dentistry, University of Alberta (2) Division of Neurology, Department of Medicine, School of Internal Medicine, University of Alberta*

The neurotoxic effects of amyloid  $\beta$  protein ( $A\beta$ ) have been well documented as a key pathological process in Alzheimer's Disease (AD) (Hardy et al., Science, 2002). Although no receptor has been explicitly identified for  $A\beta$ , recent studies from our laboratory have demonstrated that  $A\beta$  may express its toxicity through the human amylin receptor, which is composed of the human calcitonin receptor (CTR) and a receptor-associated membrane protein (RAMP 3) (Jhamandas et al., Neuroscience, 2004). There is also evidence to suggest that activation of human amylin receptor complex elicits signal transduction effects via the  $G\alpha s$ -cAMP pathway (Morfis et al., Endocrinology, 2008). However, it is difficult to isolate the pharmacological and molecular aspects of the amylin receptor activation in neurons due to the complexity of such cell systems. We introduced the gene fragments necessary to express the human amylin receptor in a mammalian cell-line (rabbit kidney cells - RK13) in order to produce a simple cellular model, which is a necessary step to unequivocally establish the human amylin receptor as a target for  $A\beta$ . Both CTR and RAMP3 cDNA were inserted into a modified pBud-CE4 vector with GFP tag and transfected into RK13 cells. Transfection was confirmed by fluorescent tagging with GFP expression. A stable cell-line was developed by using zeocin antibiotic selection. Transfected cells were exposed to human amylin, and the resultant cAMP signal was detected via immunohistochemistry and compared to that for non-transfected, wild-type cells. Electrophysiological patch clamp recordings also suggested a link between the transfected amylin receptor and potassium ion conductances when the cells were exposed to human amylin. These data indicate that the transfected RK13 model can be used to express the human amylin receptor, and this system will be essential for future research into the cellular effects of  $A\beta$ , and its involvement in AD pathogenesis.

Basic Sciences (Short-term Project)

## **Cleavage of Translation Factor NAT1/DAP5/p97 During CoxsackievirusB3 Infection by a Cellular Serine-like Protease**

H Kim (1), M Hemida (2), X Ye (2), M Zhang (2), DC Yang (2)

*(1) Faculty of Medicine, The University of British Columbia (2) The James Hogg iCAPTURE Centre, Providence of Heart + Lung Institute, St. Paul's Hospital and Department of Pathology and Laboratory Medicine, University British Columbia*

NAT1, also named death –associated protein 5 (DAP5) and p97, is one of the host translation initiation factors. Although there have been ongoing debates about its role, recent studies have suggested that it has a role in up-regulating cap-independent translation, thus favoring translation of CVB3 RNA.

In this project, we previously identified that NAT1 protein is cleaved into two smaller fragments by a serine like protease using protease inhibitor assay. We also found that the protease is neither of the well known viral proteases 2A or 3C, nor the caspase-3. Our goal is to identify the cellular protease responsible for this cleavage as well as the specific cleavage site through site-directed mutagenesis.

Our working hypothesis is that a serine like cellular protease cleaves NAT1 at a region between the 380th and 435th amino acids during CVB3 infection, producing two peptides of 44 kDa and 53 kDa.

We have successfully created a mutation with a 26-amino acid deletion and the transfection, infection and protein analyses are in the process currently.

## **Functional Testing of Wilson Disease Patient Variants in the ATP Binding Domain and C-Terminus of ATP7B**

Julia Pon , Lisa Davies, Georgina Macintyre, Diane Cox

*Department of Medical Genetics, University of Alberta*

Wilson disease (WND) is an autosomal recessive disorder characterized by liver and neurological symptoms. WND results from copper accumulation due to mutations in the copper transporting ATPase, ATP7B. The clinical presentation of WND is variable and more than 580 variants have been identified in WND patients. Molecular analyses to distinguish disease-causing mutations from normal variants are essential. To determine whether eleven WND patient missense variants in the ATP binding domain and C-terminus are disease causing mutations, full length ATP7B variant cDNAs were stably transfected into Chinese Hamster Ovary (CHO) cells, and confirmed by ATP7B cDNA sequencing. Insertion location and expression were verified by  $\beta$ -galactosidase assays and RT-PCR.

As functional ATP7B protects CHO cells from copper toxicity by exporting copper, cell lines were assayed for copper resistance. G1149A and L1371P conferred no protection from copper. In contrast, A1250G and D1407E exhibited normal levels of protection. P1052L, I1184T, V1262F, P1273Q, L1305P, Y1331S and I1336T showed intermediate copper protection. Similar results were found at a lower ATP7B induction level. Wildtype ATP7B traffics between the Golgi and cytoplasmic vesicles in response to excess copper. Trafficking defects were observed for P1052L, G1149A, I1184T, V1262F, L1350P, I1336T, and L1371P. On western blots, variants with trafficking defects were undetectable, while the other variants appeared similar to wildtype. A1250G and D1407E are suspected non-disease causing variants, while the other nine variants likely contribute to the Wilson disease phenotype. Our identification of amino acids required for copper transport and ATP7B trafficking advances our understanding of ATP7B structure and function.

### **Matrix Remodeling in Liver Fibrosis**

Wan Kim (1), Cody Crick (1), Sang-Eun Kim (1), Christine Law (1), Sean Maurice (1), Paul John Winwood (2)

*(1) Cellular & Physiological Sciences, Northern Medical Program, UBC (2) Division of Gastroenterology, Department of Medicine, UBC*

The liver responds to injury in the same way most other tissues in the body do, by going through the processes of inflammation, tissue remodeling and wound healing. Recent evidence indicates that these processes are orchestrated by hepatic stellate cells (HSCs) which normally reside in the space of Dissé. Once HSCs are activated, they show similar characteristics to fibroblasts in other connective tissues as they begin to proliferate, reorganize cytoskeletal elements, and synthesize ECM components, particularly fibrillar collagens and proteoglycans (Moreira, 2007). Animal models have shown that once the damaging insult has been removed the liver restores itself to its original structure and function. However, in chronic liver fibrosis, it is thought that the altered structure of liver parenchyma and stroma is irreversible due to an ongoing insult resulting in molecular changes in its extracellular matrix (ECM). It is currently unknown what molecular changes direct the progression to chronic liver fibrosis versus structural restoration. One hypothesis that is being tested is that the increase in the levels of proteoglycans (PGs) and changes in the expression of ADAMTS enzymes are crucial in initiating HSC activation and influencing them to promote chronic fibrosis during persistent liver damage. In other tissues, PGs including versican are key components of fibrotic matrix that modulate cellular functions. The ADAMTS enzymes are now known to cleave versican and other proteoglycans in a manner previously ascribed to the matrix metalloproteinases. Hence, using activated hepatic stellate cells cultured in vitro and using mouse model of reversible liver fibrosis, we are investigating changes in the expression of versican and other candidate ECM proteoglycans as well as ADAMTS enzymes. Preliminary histological sections show that the liver fibrosis is reversible in our mouse model. Analysis of mRNA and protein expression levels of ECM proteins and ADAMTS enzymes are still on going in both our mouse model and in cultured HSCs in vitro.

**Infiltration of Blood-Derived Monocytes is required for Disease Progress in Experimental Autoimmune Encephalomyelitis (EAE)**

B Ajami (1), J Bennett (1), D Mahdavian (1-2), K McNagny (1), F Rossi (1)

*(1) The Biomedical Research Centre, University of British Columbia, Vancouver, BC (2) Faculty of Science, University of British Columbia, Vancouver, BC*

**Introduction:** Microglia, the principal immune cells of the Central Nervous System (CNS), are exquisitely sensitive to CNS injury and disease, fueling a reactive state called microgliosis. We have used parabiosis, a surgical procedure that allows the creation of peripheral blood chimeras without transplantation, to show that unlike most other tissue-resident macrophages that rely on circulating blood-borne precursors for their replacement, microglia are capable of self-renewal within the CNS. In contrast, certain inflammatory pathological conditions such as multiple sclerosis and its murine model, experimental autoimmune encephalomyelitis (EAE), are known to lead to the recruitment of inflammatory monocytes to the CNS. Is the entry of these cells, normally excluded from the CNS, a causal factor in disease progression?

**Methods:** To address this question we developed a new experimental model, based on parabiosis and differential bone marrow irradiation, which allows the precise distinction between peripheral blood-derived monocyte/macrophages and resident microglia, thus enabling us to investigate the kinetics of microglia activation, blood born monocytes entry in the CNS and their differentiation into macrophages during EAE progression.

**Results:** Our data reveals a dynamic interplay between macrophages and microglia and strongly supports a causal link between myelomonocytic cell invasion and disease progression. In summary, our data identified the invasion of circulating monocytes into the CNS parenchyma as a major adverse event in EAE progression, supporting therapeutic strategies specifically aimed at inhibiting the migration of myelomonocytic cells rather than that of leukocytes in general.

Basic Sciences (Short-term Project)

### **3D Modeling of Brain-Face Relations During Development of Kyoto and Carnegie Human Embryos**

DC Brownrigg , VM Diewert

*Department of Oral Health Sciences, Faculty of Dentistry, The University of British Columbia, Vancouver, Canada*

**Objectives:** As the face develops, the forebrain not only acts as a supportive structural framework but may also exert an influence from several potential signaling sites for facial morphogenesis such as ectodermal placodes. The purpose of this study was to produce 3D ribbon models and measurements to illustrate the dynamic spatial and morphologic relationships between potential signaling sites and features of the developing face in stage 16 to 18 Kyoto (Japanese) and Carnegie (Caucasian) embryos.

**Methods:** Photographs of normal transverse serial sections of stage 16 to 18 Carnegie and Kyoto embryos were reconstructed into 3D ribbon models using WinSURF software. ImageJ software was then used to take linear measurements of important areas of change and their relationships. Potential signaling sites in facial morphogenesis, including the adenohipophysis, olfactory epithelium, and trigeminal ganglia, were represented in reconstructions of coronally-sectioned embryos.

**Results:** Models and measurements showed advanced brain development but delayed primary palate and upper lip development in Kyoto embryos as compared to Carnegie embryos that may be related to the greater prevalence of Cleft Lip in the Japanese population. In both embryos, the maxillary prominences grew forward to contact and fuse with the medial nasal region that simultaneously narrowed and elongated. We also showed the forward movement of the face beneath the prosencephalon at the time of telencephalon outpocketing. Representation of potential signaling sites demonstrated the large volume occupied by ectodermal placodes in the developing embryo.

**Conclusions:** 3D ribbon models illustrate the complex relationships between the brain and face during primary palate development. These can also be measured to quantitatively analyze relationships that may be important in normal formation of the primary palate and upper lip.

**Acknowledgements:** Supported by CIHR Health Professional Student Research Award to DCB and MRC grant 4543 to VMD for collection of materials.

## **Signalling mechanisms underlying adenosine-mediated inhibition of myocardial glycolysis**

Sanam Verma, Mohamed A. Omar, Alexander S. Clanachan

*Department of Pharmacology, Cardiovascular Research Center, Mazankowski Heart Institute, University of Alberta*

**Introduction:** Adenosine (ADO) enhances post-ischemic left ventricular (LV) mechanical function, possibly due to inhibition of glycolysis that limits proton (H<sup>+</sup>) production and Ca<sup>2+</sup> overload, but the intracellular signalling mechanisms have not been identified. We tested the hypothesis that the ADO-induced inhibition of glycolysis and cardioprotection is mediated by inhibition of the stress-activated kinases, 5'-AMP-activated protein kinase (AMPK) and/or p38 mitogen-activated protein kinase (p38MAPK). As AMPK functions as a metabolic sensor, the roles of these kinases were assessed under conditions of high or low energy substrate availability. **Methods:** Isolated rat hearts were perfused in the working mode (80 mm Hg afterload, 11.5 mm Hg preload, paced at 5 Hz) with Krebs-Henseleit solution containing either 11 mM [3H/14C]glucose, 100 μUnits/mL insulin, and 1.2 mM palmitate as energy substrates (GIP condition, high energy availability), or 11 mM [3H/14C]glucose only (G-only condition, low energy availability). Hearts were perfused for 45 min, followed by 17 min global ischemia and 30 min reperfusion. LV minute work and rates of glycolysis were measured throughout perfusion; afterwards hearts were frozen for assays of glycogen content and enzyme activity indices (phosphorylation by immunoblotting).

**Results:** In GIP perfusions, ADO inhibited glycolysis and H<sup>+</sup> production by 44% and 51%, respectively, and improved recovery of post-ischemic LV work (56%, n=12, relative to 29% in untreated hearts, n=13). ADO also inhibited p38MAPK, AMPK, and PFK-2 by 74%, 90%, and 30%, respectively. ADO had no effect on LKB1. Furthermore, ADO decreased phosphorylation of glycogen synthase kinase-3β by 34% and increased phosphorylation of glycogen synthase by 249%. In G-only perfusions, ADO did not alter rates of glycolysis, but trended to inhibit H<sup>+</sup> production and improved recovery of post-ischemic LV work (43%, n=3, relative to 2.4% in untreated hearts, n=4). ADO also inhibited AMPK but had no effects on LKB1 or p38MAPK.

**Discussion:** These data indicate that ADO-mediated cardioprotection and inhibition of glycolysis occurs via a mechanism that involves inhibition of p38MAPK, AMPK, and PFK-2. However, as these effects were not evident under G-only conditions, our data demonstrate that energy availability influences phosphorylation status and activity of signalling molecules and affects recovery of post-ischemic LV work.

## **Extracellular matrix of meniscal cartilage is enhanced by co-culture of meniscus and stem cells under low oxygen tension**

Norah-Faye Matthies, Adetola Adesida, Nadr Jomha

*Department of Orthopaedic Surgery, University of Alberta*

**Background:** Meniscus is a fibrocartilaginous tissue in the knee joint where it protects articular cartilage, distributes load, provides shock absorption and joint stability. Meniscus injury can lead to poor biomechanical function and degenerative joint changes such as osteoarthritis. The avascular area of the tissue limits its reparative capacity. Cell-based tissue engineering can aid meniscus repair. Meniscus' biomechanical role is due to its extra-cellular matrix (ECM); mainly composed of proteoglycans, collagens I and II. ECM formation is influenced by many factors; we hypothesized that co-culture of meniscus cells (MEN) and mesenchymal stem cells will enhance ECM formation and that matrix formation will be further enhanced by a low O<sub>2</sub> tension due to meniscus' avascular nature and low O<sub>2</sub> tension within the knee joint.

**Methods:** Tissue specimens of bone marrow (BMSC) and menisci were obtained, digested, expanded (BMSC only) and mixed at MEN/BMSC ratios of 5/95, 10/90, and 25/75, respectively. Controls were pure BMSC or MEN. Cells were spun to form spherical pellets and cultured for 3 weeks at 37°C in a humidified chamber at either 21% (normoxia) or 3% (hypoxia) O<sub>2</sub> tension. At least two independent pellets from each group were processed for DNA, glycosaminoglycans (GAG), histochemical/immunohistochemistry (IHC) analysis for Alcian blue staining of sulphated GAG, collagens I and II, and qRT-PCR for aggrecan, collagens I and II.

**Results:** Co-cultures of MEN and BMSCs had higher GAG contents than all controls, regardless of O<sub>2</sub> tension. Alcian blue staining correlated with GAG data. With a few exceptions, hypoxia potentiated ECM formation that was greater than in normoxia. Hypoxia-generated co-cultures showed both increased total GAG content and GAG per cell (GAG/DNA). IHC and qRT-PCR showed higher gene expression of aggrecan, collagens I and II in co-cultures relative to controls; hypoxia further enhanced this phenotype.

**Conclusions:** Our results demonstrated that co-culture of MEN and BMSCs is an effective way of inducing ECM formation for cell-based meniscus tissue engineering; this process is further potentiated by low O<sub>2</sub> tension. Clinical application of these results suggests that co-delivery of MEN and BMSCs on scaffolds may result in the generation of functional meniscus grafts with improved biomechanical properties.

## **The Effect of Inhaled Steroids on PARC/CCL18 in COPD Patients**

Julie Man (1), Yuexin Li (2), Paul Man (3), Don Sin (4)

*(1) University of British Columbia, (2) Providence Heart and Lung Institute at St. Paul's Hospital, (3) Department of Medicine, University of British Columbia, (4) UBC James Hogg Research Center & Providence Heart and Lung Institute at St. Paul's Hospital.*

Background: Pulmonary and activation-regulated chemokine (PARC), also known as CC chemokine ligand 18 (CCL18), is an indicator of lung inflammation in humans. Produced by alveolar macrophages and dendritic cells, PARC is involved in the chemotaxis of immature dendritic cells, fibroblasts, T lymphocytes and B lymphocytes. PARC is lung-specific; it shows high expression in lungs and low in other parts of the body. This cytokine is elevated in people with COPD and related to accelerated lung decline. Certain steroid drugs, which are used to treat inflammation, have been shown to reduce PARC levels when given orally at high doses. We investigated the effect of inhaled fluticasone, a more commonly used steroid, on PARC levels in patients with COPD.

Hypothesis: Inhaled steroids reduce serum PARC levels in COPD patients.

Methods: We used serum samples from 220 patients with COPD. These patients included men and women, active smokers and ex-smokers, with a mean age of 69 years and mean body mass index (BMI) of 28. The subjects were randomly sorted into three treatment groups for a 4-week period: placebo, fluticasone, or drug combination (fluticasone and salmeterol). Serum was obtained before and after treatment, and PARC concentrations were measured using an enzyme-linked immunosorbent assay (ELISA). This data was analyzed and compared to various other patient characteristics.

Results: No significant difference was observed in PARC concentrations between treatment groups. There was also no difference in mean PARC levels before and after the treatment. PARC was significantly related to subject age, BMI and levels of C-reactive protein (CRP), a marker of systemic inflammation. The relationship between PARC and CRP was strongest in the active smokers.

Conclusion: Treatment with an inhaled steroid over a 4-week period does not modify serum PARC concentrations of COPD patients. Serum PARC is related to CRP levels, which may indicate a link between inflammation of the lungs and systemic inflammation.

## **The role of slo-1 in short and long term habituation in *C. elegans***

Joshua Lai (1), Mike Butterfield (1), Andrew Giles (2), Catharine Rankin (2)

*(1) Department of Medicine, University of British Columbia (2) Department of Psychology, University of British Columbia*

BK channels are large conductance, voltage-gated, calcium-activated potassium channels that modulate smooth muscle tone and neuronal excitability. The *C. elegans* homolog, SLO-1, is an important regulator of neurotransmitter release. *C. elegans* habituates to mechanical stimulation (tap) differentially at short and long interstimulus intervals (ISIs). We asked if deletion of *slo-1* in *C. elegans* changes the rate or degree of habituation, whether this effect is ISI dependent, and whether this deletion disrupts long-term memory for habituation. We characterize habituation behaviour in *slo-1* (*js118*) deletion mutants, and attempt to localize its effects to either presynaptic sensory neurons, or postsynaptic interneurons within the tap habituation circuit.

We found that at shorter ISIs (10s and 30s), *slo-1* deletion mutants did not differ from wild-type, but at 60s ISI, exhibited an impaired pattern of habituation. Mutations in *slo-1* that result in increased calcium sensitivity of the channel (strain *ky389gf*) showed decreased responses to stimulation, but did not differ from a wild-type pattern of habituation. *slo-1* deletion mutants also failed to show long term memory for habituation training. Selective rescue of *slo-1* expression in the nervous system restored wild-type patterns of habituation at 60s ISI, and rescued long term memory. We conclude that SLO-1 is necessary for normal patterns of short term habituation at 60s ISI, as well as for formation of long term memory for tap. At shorter ISIs, absence of SLO-1 does not appear to affect habituation. We have localized *slo-1*'s effects to identified neurons in the neural circuit for tap. We are currently testing rescues in specific subsets of neurons to determine the locus of *slo-1*'s effect on short and long term habituation.

## **INTER-FEATURE TRANSFER OF AFTEREFFECTS: EVIDENCE OF ADAPTATION IN WHOLE FACE REPRESENTATIONS**

Maryam Dosani (1), Raika Pancaroglu (1), Ipek Oruç (1), Jason J S Barton (1,2)

*(1) Human Vision and Eye Movement Laboratory, Departments of Medicine (Neurology) and Ophthalmology and Visual Sciences, University of British Columbia (2) Department of Psychology, University of British Columbia*

**Background:** It is hypothesized that upright faces are represented holistically in the human visual system, with only local part-based feature representations for inverted faces. To test this, we used a novel inter-feature adaptation transfer technique to determine if face aftereffects resulted from adaptation in whole-face representations.

**Method:** We divided face images into upper and lower halves, and examined first if each half created aftereffects for its own perception (within-feature adaptation), and second if each half created aftereffects for perception of the other half (inter-feature transfer). This was done for upright face identity, inverted face identity, and expression judgments for upright happy versus sad faces.

**Results:** Inter-feature transfer of adaptation was significant for upright face identity, and equivalent in magnitude to within-feature adaptation. No significant inter-feature transfer was found for inverted identity aftereffects. For upright facial expression, we found robust within-feature adaptation but no inter-feature transfer.

**Conclusions:** Most, if not all, identity aftereffects of upright faces may be generated in integrated whole-face representations, but not for inverted identities, consistent with hypotheses of an orientation-dependent expert holistic mechanism. However, our findings for expression suggest that happy/sad features in upright faces may be processed at a featural level.

## **Dmel/Gfat2 is an essential gene in D. melanogaster embryonic development**

M. Haiducu (1) and K. Fitzpatrick (2)

*(1) Faculty of Medicine, University of British Columbia (2) Department of Molecular Biology and Biochemistry, Simon Fraser University*

Glutamine:fructose-6-phosphate aminotransferase (Gfat) functions as the rate-limiting enzyme in the hexosamine biosynthesis pathway. There are two Gfat-encoding genes and, thus, two discrete enzymes, Gfat1 and Gfat2, in humans and other metazoans, including *Drosophila melanogaster*. Thus, the functional characterization of fly orthologues should help to elucidate the roles of the human enzymes in developmental processes and metabolic diseases. Particularly, since increased flow of glucose through the hexosamine pathway has been associated with the development of insulin resistance, the Gfat enzyme may serve as a key therapeutic target in the treatment of type 2 diabetes in humans. In *Drosophila*, mutations in Gfat1 are lethal, and the mutants are defective in formation of the embryonic cuticle. However, there are no known mutant alleles of Gfat2 and, thus, the requirements for this form of the enzyme are essentially undefined. Therefore, the objective of the current study was to identify and characterize putative P-element-induced lethal excisions that affect the Gfat2 gene. From 81 such excisions, we have identified 16 that are lethal in combination with known deficiencies for the Gfat2 genomic region (i.e. these deletions remove Gfat2 and varying numbers of adjacent loci). Through a combination of genetic crosses and molecular methods, we have confirmed that 14 of these mutant chromosomes contain intact *larp* and *moca-cyp* genes (the two genes that immediately flank Gfat2 on the *Drosophila* genomic map). Further studies on four of these excision chromosomes have confirmed at least partial deletion of the Gfat2 gene and the absence of second-site mutations. These four Gfat2- lesions were shown to have an embryonic lethal phase, thereby indicating that the Dmel/Gfat2 gene is essential for embryonic development.

## **Linking Genetic Duplications to Choroideremia Pathology**

Jonathan Y. Chi (1), Ian M. MacDonald (2), Stacey Hume (3)

*(1) MD Undergraduate Program, University of British Columbia (2) Department of Ophthalmology, University of Alberta (3) Department of Medical Genetics, University of Alberta*

**Introduction.** Choroideremia is an X-linked progressive chorioretinal degenerative disease that affects 1 in 50,000 males. Clinically, patients with choroideremia present with nightblindness and progressive loss of peripheral vision; however, typically central vision and colour vision is maintained.

Choroideremia arises from a dysfunctional Rab escort protein-1 (REP-1) which is encoded by the CHM gene. The absence of REP-1 in the eye, results in the gradual degeneration of the retina, retinal pigment epithelium, and choroid causing the ocular manifestations common in affected individuals. The exact pathogenesis, however, has yet to be determined. Through genetic studies, we have determined that choroideremia can arise from deletions in the CHM gene but deletions alone do not account for all cases of choroideremia. Our study delves into the biochemical genetics of the CHM gene to determine whether other genetic mutations such as copy number variants play a role in choroideremia pathogenesis.

**Methods.** We designed a multiplex ligation-dependent probe amplification (MLPA) assay kit for the detection of copy number variants in the CHM gene. Using our MLPA assay kit, we tested the DNA of several choroideremia patients that screened negative for genetic deletions in their CHM gene. Results. A duplication of several consecutive exons of the CHM gene was determined in one particular patient DNA sample. **Discussion.** Prior to this study, only deletions in the CHM gene have been linked to choroideremia pathology. The duplication in the CHM gene observed in this study represents a novel pathological mutation and potentially a novel mechanism of pathogenesis. We hope that this discovery will help us further understand the pathogenesis of choroideremia.

**Selective Pharmacological Inhibition of Phosphoinositide 3-Kinase p110delta Inhibits Marginal Zone B-cell Function and Abrogates the Development of Autoimmune Diabetes in NOD Mice**

Caylib A. Durand (1), Martin Richer (1), Marc Horwitz (1), Marcia Graves (1), Kamal D. Puri (2), and Michael R. Gold (1)

*(1) Department of Microbiology and Immunology, Infection, Inflammation, and Immunity (I3) and CELL Research Groups, Life Sciences Institute, University of British Columbia, Vancouver, British Columbia, Canada (2) Calistoga Pharmaceuticals Inc., Seattle, WA, USA*

In non-obese diabetic (NOD) mice, B-lymphocytes promote the development of type 1 diabetes (T1D) by acting as antigen-presenting cells (APCs) for T cells that mediate the destruction of insulin-producing pancreatic beta cells. Splenic marginal zone (MZ) B cells, which have been associated with multiple autoimmune diseases, are potent APCs that can take up blood-borne antigens, including beta-cell antigens released during the islet destruction in T1D. Recent work has shown that MZ B cells migrate to, and accumulate in, the pancreatic lymph nodes of NOD mice prior to the development of frank diabetes and that they can act as APCs that promote diabetogenic T cell proliferation. Thus modulating MZ B cell function may be a novel approach for preventing the progression of T1D.

We have shown (*J. Immunol.* 183:5673, 2009) that the catalytic activity of p110delta is important for the migration, activation, function, and in vivo localization of MZ B cells. We now show that treating NOD mice with IC87114, a p110delta-selective inhibitor, prevents the expansion of splenic MZ B cells and delays the onset of T1D. We found that a short-term 4 week treatment or a longer-term 10-week treatment with IC87114 reduced the incidence and caused a significant delay in the development of diabetes in NOD mice. Diabetes developed in >80% of vehicle-treated NOD mice by 20 weeks of age but in only 40% of IC87114-treated animals. Histopathological evaluation demonstrated that p110delta inhibitor decreased the infiltration of inflammatory cells into pancreatic islets. We also observed that once blood glucose levels were >300 mg/dL, they rapidly increased from 300 to >500 mg/dl within 7 days in vehicle-treated NOD mice. By contrast, administering IC87114 immediately after blood glucose levels were >300 mg/dl substantially delayed disease progression in more than one-third of mice. The data indicate that IC87114 can slow disease progression. Current studies are aimed at identifying the immunological and metabolic processes in NOD mice that are inhibited by IC87114 in order to better understand the drug's mode of action and to further characterize its potential as a therapeutic agent to prevent the progression of T1D.

### **Early-life seizures inhibit dendrite growth through synaptotropic mechanisms**

D. Sesath Hewapathirane (1-3), Simon Chen (1-3), Wesley Yen (2), Shay Neufeld (2), Kurt Haas (1-3)

*(1) Graduate Program in Neuroscience (2) Brain Research Centre (3) Department of Cellular and Physiological Sciences, University of British Columbia, Vancouver, BC Canada*

The effects of highly prevalent early-life seizures on neuronal activity-dependent developmental programs within the immature brain remain unclear. To address this issue, the present work examined the acute and persistent effects of early-life seizures on neuronal dendritogenesis, a key activity-dependent component of neural circuit development. A novel experimental model system of early-life seizures, based on the albino *Xenopus laevis* tadpole, was developed for these studies. The transparency of this organism allows in vivo imaging of neuronal growth and activity within the intact developing brain. Additionally, immobilization of tadpoles using reversible paralytics and immersion in agar, for electrophysiological or imaging experiments, allows examination of seizure activity and seizure-induced effects on neuronal growth for the first time within the unanaesthetized and awake brain. Chemoconvulsant-induced seizures in tadpoles were extensively characterized using behavioural assessment, measures of cell death, and in vivo examination of neural activity during seizures through electrophysiological recordings and imaging of intracellular calcium dynamics. Rapid and long-interval time-lapse in vivo two-photon imaging of individual fluorescently labelled growing optic tectal neurons within the intact tadpole brain revealed that seizures inhibit dendritic arbor growth, that these effects are mediated cell-autonomously by excessive AMPA-receptor mediated excitatory activity, and that a single seizure episode persistently stunts subsequent arbor growth. Reduced dendritic growth is a result of decreased branch elongation, increased branch elimination, and loss of dendritic filopodia. Seizures also persistently reduced the density of immunostained excitatory synaptic markers within the tectal neuropil. Rapid time lapse imaging at 5 minute intervals for 5 hours reveals selective effects on filopodial growth dynamics, characterized by rapid increase in the rate of elimination of pre-existing filopodia within minutes of seizure onset, followed by hyper-stabilization of filopodia generated during seizures. These data suggest that seizures interfere with neural circuit development by acutely destabilizing filopodia present prior to seizure induction and hyper-stabilizing filopodia formed during seizures, leading to a persistent inhibition of continued arbor elaboration and growth. This is the first examination of the effects of common early-life seizures on dendritic morphogenesis within the intact and awake brain, and these findings identify a potential morphological correlate of persistent seizure-induced neural dysfunction.

**The expression of activated Y-box binding protein-1 serine 102 mediates trastuzumab resistance in breast cancer cells by increasing CD44+ cells.**

Jaspreet Dhillon (1), Arezoo Astanehe (1), Abbas Fotovati (2), Kaiji Hu (2), Sandra Dunn (1,2)

*(1) Department of Medicine, University of British Columbia, Vancouver, British Columbia (2) Department of Pediatrics, Child and Family Research Institute, Vancouver, British Columbia.*

The development of acquired resistance to trastuzumab remains a prevalent challenge in the treatment of patients whose tumors express HER2. We previously reported that HER2 over-expressing breast cancers are dependent on Y-box binding protein-1 (YB-1) for growth and survival. Since YB-1 is also linked to drug resistance in other types of cancer, we address its possible role in trastuzumab insensitivity. Employing an in vivo model of acquired resistance, we demonstrate that resistant cell lines have elevated levels of P-YB-1 S102 and its activating kinase P-RSK and these levels are sustained following trastuzumab treatment. Further, to demonstrate the importance of YB-1 in mediating drug resistance, the expression of the active mutant YB-1 S102D rendered the BT474 cell line insensitive to trastuzumab. Questioning the role of tumor initiating cells (TIC) and their ability to escape cancer therapies, we investigated YB-1's role in inducing the cancer stem cell marker CD44. Notably, the resistant cells expressed more CD44 mRNA and protein compared to BT474 cells, which correlated with increased mammosphere formation. Expression of YB-1 S102D in the BT474 cells increased CD44 protein levels, resulting in enhanced mammosphere formation. Further, exposing BT474 cells to trastuzumab selected for a resistant subpopulation enriched for CD44. Conversely, siRNA inhibition of CD44 restored trastuzumab sensitivity in the resistant cell lines. Our findings provide insight on a novel mechanism employed by tumor cells to acquire the ability to escape the effects of trastuzumab and suggest that targeting YB-1 may overcome resistance by eliminating the unresponsive TIC population, rendering the cancer sensitive to therapy.

## **Systems Biology Identification of the AMPK-AKT-GSK3 $\beta$ Axis in Mediating Dysregulated Responses of Cystic Fibrosis Airway Cells to IDR-1018, an Immunomodulatory Peptide**

ML Mayer (1,2,3) CJ Blohmke (3,4), CD Fjell (1,2), SE Turvey (2,3,4), REW Hancock (1,2)

*(1) Centre for Microbial Disease and Immunity Research, University of British Columbia (2) Department of Microbiology and Immunology, University of British Columbia (3) Faculty of Medicine, University of British Columbia (4) Child and Family Research Institute, BC Children's Hospital*

**BACKGROUND:** Innate defence regulator (IDR) peptides are synthetic derivatives of endogenous host defence peptides, and are currently under investigation as novel anti-infective agents. IDRs lack effective antimicrobial activity; rather, they enhance bacterial clearance by increasing leukocyte recruitment to infection sites while simultaneously suppressing harmful inflammation. As cystic fibrosis (CF) pathology arises from chronic bacterial infections which in turn drive chronic lung inflammation, we sought to investigate the ability of a lead IDR (IDR-1018) to modulate human bronchial epithelial (HBE) cell responses to pro-inflammatory stimuli.

**METHODS:** Primary normal HBE cells, CF HBE cell lines (IB3-1, CuFi) or control cells (C38, NuLi, 16HBE) were stimulated for 24 hr with flagellin or heat-killed *Pseudomonas aeruginosa*, with or without 1 hr pretreatment with IDR-1018, and ELISA was used to measure IL-6 and IL-8 production. For microarray experiments, IB3-1 and C38 were stimulated with for 2 hr with flagellin, with or without 1 hr pretreatment with IDR-1018. RNA was harvested, converted to cDNA, and hybridized to Illumina HumanHT-12 chips. Systems biology and network analyses were carried out using our new systems biology platforms: InnateDB, Cerebral (Cytoscape) and MetaGEX.

**RESULTS:** IDR-1018 was found to enhance IL-6 and IL-8 secretion induced by heat-killed *P. aeruginosa* or flagellin in normal cell lines but in contrast had an inhibitory effect on cytokine secretion in CF cell lines. Cytokine modulation by IDR-1018 was not observed in cells stimulated with PAK  $\Delta$ fliC, suggesting a flagellin-dependent effect. Systems biology and network analyses identified multiple dysregulated genes mediating the differences between normal and CF cells, including the AMPK-Akt-GSK-3 $\beta$  axis. Pretreating IB3-1 cells with metformin (AMPK activator) or inhibitors of Akt or GSK-3 $\beta$  had negligible or subtle inhibitory effects on flagellin-specific responses, but completely reversed the ability of IDR-1018 to inhibit airway cell cytokine secretion.

**CONCLUSION:** Taken together, these data implicate the AMPK-Akt-GSK-3 $\beta$  axis in mediating dysfunctional responses of CF cells to immunomodulatory therapeutics, and validate the utility of systems biology in identifying signalling pathways which underlie abnormal pro-inflammatory cytokine secretion by CF cells.

## **Slow cortical oscillations and limb twitches in the neonatal rat**

David Mcvea (1,2), Majid Mohajerani (1), Tim Murphy (1)

*(1) MD/PhD Program, University of British Columbia (2) Department of Psychiatry, University of British Columbia*

The developing cerebral cortex is active well before it is functional. This activity manifests as patterns of synchronized membrane depolarization assumed to promote the formation of appropriate afferent inputs as well as integrative cortico-cortico connections. Here, we focus on the role of this activity in the maturation of the sensorimotor cortex by using voltage-sensitive dye (VSD) imaging to study cortical activity in the developing rodent cortex in vivo. Working with postnatal day 5-6 (P5-6) rats, we exposed the cortex via a large (50 mm<sup>2</sup>) craniotomy. We collected spontaneous changes in VSD fluorescence which reflect underlying membrane potential changes. To determine how peripheral limb twitches affect activity across the cortex, we also collected video signals of peripheral movements. Initially we focused our efforts on the dominant pattern of activity in the developing cortex, the spindle burst. Consisting of a fast (~20 Hz) oscillation atop a slower (~3 Hz) burst, this pattern generally follows afferent input caused by peripheral twitches. We found that VSD imaging provides high-resolution signals of the slow component of spindle bursts (the fast component was poorly reflected in the VSD signal). In the limb somatosensory cortices, this activity followed contralateral limb twitches, while the tail cortex was activated bilaterally by tail twitches. Taking advantage of the wide-imaging area provided by our techniques, we also found that dynamic bursts occasionally moved rapidly across the cortex independently of peripheral twitches.

We next examined slower components of the VSD signal, focusing on the infraslow (0.01-0.1 Hz) band. We found that VSD signals were effective at capturing infraslow activity, and that this activity preceded peripheral limb twitches. The coexistence of this slow activity with the subsequent fast, sensory-driven cortical bursts may be a system for calibrating and connecting the sensorimotor system during development.

**Development of a lentiviral-based cellular barcoding strategy for clonal tracking of normal and malignant human mammary epithelial cells in a xenotransplant model**

Long V. Nguyen (1), Nagarajan Kannan (1), Pawan Pandoh (2), Peter Eirew (1), Maisam Makarem (1), Michelle Moksa (2), Kane Tse (2), Thomas Zeng (2), Martin Hirst (2), Marco Marra (2), Connie J. Eaves (1)

*(1) Terry Fox Laboratory (2) Genome Science Centre, BC Cancer Agency, Vancouver, BC, CANADA*

Although it is known that breast cancers are a heterogeneous collection of diseases, the extensive heterogeneity within individual tumours has yet to be characterized in terms of phenotype and functional activity. Recent studies demonstrate that there is a phenotypically distinct rare subset of tumour-initiating cells (TICs) in primary human breast tumours that are characterized by their unique ability to produce tumours in xenografted immunodeficient mice. Further investigation into the genetic evolution of these cells and their predominance over time will help to ascertain how their frequency and growth potential, growth rate, treatment response and metastatic ability are related. To enable the clonal progeny of individual TICs (and normal human mammary stem cells) to be monitored in vivo (and in vitro) under different conditions, we are developing a lentiviral-based strategy for "marking" these with integrated noncoding variable 'barcode' sequences. Sequencing results from a first set of 230 individual clones within a larger barcode lentiviral library has demonstrated a diversity of the library in which <1% of the clones lack the barcode sequence. To validate a non-invasive technique for monitoring in vivo tumour growth, highly immunodeficient mice, NOD/SCID/IL-2R $\gamma$ -null, were transplanted orthotopically or heterotopically with transduced malignant breast cell lines that had been selected for stable expression of luciferase. As few as 625 transplanted cells could be detected at both sites 24 hours post-transplant. Also, although transplants of fewer than 250 cells could be imaged and monitored for tumour growth, the amplitude of the signal detected varied between individual host mice. Future experiments will aim to apply our cellular barcoding strategy to track the clonal evolution of human breast TICs and their relative contributions to individual tumour landscapes while concurrently monitoring their in vivo growth activity, metastatic properties, and responsiveness to anti-cancer therapies.

## **A Novel Protein Kinase Involved in Chemotaxis, Development, and Substrate Adhesion in *Dictyostelium discoideum***

Josephine H. Y. Lee , Yulia Artemenko, Jane Borleis , Stacey Willard, and Peter N. Devreotes

*Department of Cell Biology, Johns Hopkins University School of Medicine*

Chemotaxis, or directed cell migration in response to chemical concentration gradients in the environment, has wide biological applications. This process is important for tissue formation during embryonic development and leukocyte migration towards chemokines during immune response. Aberrant chemotaxis has been shown to participate in the progression of various inflammatory diseases, angiogenesis, and tumor invasion. By examining the molecular mechanism of directional sensing and cell migration, we can develop a greater understanding of these important biological processes and diseases.

The regulation of chemotaxis has been studied extensively in a social amoeba, *Dictyostelium discoideum*. This organism serves as an excellent model for chemotaxis, due to the accessibility of genetic manipulation and analysis. Pseudopod extension and many key signaling molecules in *D. discoideum* chemotaxis are conserved among mammalian neutrophils.

Recently, restriction endonuclease-mediated integration has been used to generate a library of mutant strains of *D. discoideum*, one of which is analyzed in the present study. In this strain, the insertional mutation occurred upstream of the gene *krsB*, which resulted in low levels of KrsB expression in the mutant strain. The mutant experiences a delay in the developmental program, possibly due to decreased motility speed in response to chemoattractant. The mutant also appears to adhere to substrate surfaces more strongly than wild-type cells.

KrsB is a member of the Ste20-like family of kinases, and the function of KrsB is studied here for the first time. Transformation of a vector overexpressing KrsB into the mutant strain rescues its phenotype. Overexpression of KrsB with an inactive kinase domain fails to rescue these phenotypes. Four C-terminal calpain III-like domains in KrsB appear to be essential for KrsB function in motility speed, but not in developmental timing or substrate adhesion. These results suggest that KrsB kinase activity plays an important role in chemotaxis and/or substrate adhesion in *D. discoideum*, and may be regulated by its C-terminal domains.

## **Blockade of IL-1 signalling improves human islet amyloid polypeptide-induced islet graft dysfunction**

Clara Westwell-Roper (1), Derek L. Dai (1), Galina S. Soukhatcheva (1), Jan A. Ehses (2), and C. Bruce Verchere (1,2)

*(1) Department of Pathology and Laboratory Medicine (2) Department of Surgery, University of British Columbia, Vancouver, BC, Canada*

Human islet amyloid polypeptide (hIAPP) is a 37-amino acid hormone co-secreted with insulin by pancreatic beta-cells. Pathological hIAPP aggregation occurs in type 2 diabetic and transplanted islets, both characterized by macrophage infiltration and increased expression of pro-inflammatory cytokines. hIAPP aggregates share a common cross beta-sheet structure with other amyloids known to interact with both Toll-like receptors (TLRs) and the NLRP3 inflammasome, providing two distinct signals required for secretion of IL-1 $\beta$ . To determine whether hIAPP can promote islet inflammation, we first evaluated the effects of hIAPP on cytokine release by isolated islets and macrophages. Transgenic islets expressing hIAPP produced more IL-6, CCL2, CXCL1, and CXCL2 than wild-type control islets. hIAPP but not non-amyloidogenic rat IAPP also induced release of IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$ , CCL2, CCL3, CCL4, CCL5, CXCL1, and CXCL2 from bone marrow-derived macrophages. A significant reduction in cytokine release was observed in MyD88- but not TLR2- or TLR4-deficient macrophages, and in cells treated with IL-1 receptor antagonist (IL-1Ra). To determine whether hIAPP-induced IL-1 mediates islet inflammation and graft dysfunction in vivo, we implanted 11-week-old male streptozotocin-induced diabetic NOD/SCID mice with mini-osmotic pumps containing IL-1Ra (50 mg/kg/d) or PBS. One day following pump implantation, we transplanted these mice with islets from hemizygous hIAPP transgenic or wild-type littermate control FVB donors. Recipients of transgenic grafts displayed impaired glucose tolerance eight weeks following transplantation (AUC=1940 $\pm$ 80 vs. 1260 $\pm$ 60, p<0.001). hIAPP-expressing grafts exhibited widespread amyloid deposition and contained 2.5-fold more F4/80-positive macrophages than wild-type grafts. Administration of IL-1Ra significantly improved graft function in recipients of transgenic grafts (AUC=1470 $\pm$ 160 vs. 1940 $\pm$ 80, p<0.005) but not wild-type grafts (AUC = 1370 $\pm$ 50 vs. 1260 $\pm$ 60, p=ns). These findings suggest that anti-IL-1 therapy may improve hIAPP-induced graft dysfunction by inhibiting the inflammatory response to hIAPP and/or by attenuating islet amyloid formation.

## **Evidence that High-Mobility Group A2 (Hmga2) Expression Contributes to the Ontogeny-Dependent Properties of Fetal Hematopoietic Stem Cells**

Michael Copley, David Kent, Stefan Woehrer, Keegan Rowe, and Connie Eaves

*Terry Fox Laboratory, BC Cancer Agency, Vancouver, BC, Canada*

Fetal and early neonatal hematopoietic stem cells (HSCs) are distinct from their adult counterparts by their rapid turnover and expansion rates *in vivo*. However, the mechanisms underlying the regulation of these properties are poorly understood. In an initial screen for regulators of the fetal versus adult HSC program, 2 genes (Hmga2 and Smarcc1) showed significant differences ( $p < .05$ ) in expression between fetal and adult HSCs and one of these (Hmga2) maintained this differential expression when the same cells were stimulated to divide for 48 hrs *in vitro*. To test the hypothesis that high expression of Hmga2 is a necessary and sufficient factor in determining the fetal HSC self-renewal program, purified adult HSCs were transduced with Hmga2-overexpressing or control lentiviruses and the kinetics of transduced vs untransduced hematopoietic cells in a congenic serial-transplantation model were then analyzed. Six weeks after transplantation of an estimated 20 HSCs infected with either control or Hmga2-overexpressing virus, the percentage of transduced donor-derived BM cells (%Y/GFP<sup>+</sup> of donor-type cells) was measured and found to be higher in the control (Experiment 1: 30%; Experiment 2: 33%) vs Hmga2-overexpressing animals (Experiment 1: 15%; Experiment 2: 6%) and likely representative of a higher infection efficiency for the control cells. Interestingly, when BM cells from the primary repopulated mice were transplanted into secondary animals and the peripheral blood was analyzed for donor-type %Y/GFP chimerism, the Hmga2-overexpressing cells were observed to have a competitive advantage and exhibited an ~6-fold expansion relative to the untransduced cells. In contrast, the control virus-infected BM cells were found to be equally competitive. These findings support the hypothesis that high expression of Hmga2 may be a critical mediator of the high self-renewal program of fetal HSCs.

## **Heparin induces amyloid formation in cultured human islets and promotes graft failure following transplantation**

K Potter (1,2), J Cheng (2), I Werner (2), Y Chen (5), K Park (2), C Westwell-Roper (1,2), GL Warnock (3), J Oberholzer (4), PE Fraser (5), CB Verchere (2,3)

*(1) MD/PhD Program, University of British Columbia, Vancouver, BC (2) Departments of Pathology and Laboratory Medicine and (3) Surgery, Child and Family Research Institute, University of British Columbia (4) Division of Transplantation, Department of Surgery, University of Illinois at Chicago (5) Department of Medical Biophysics and Centre for Research in Neurodegenerative Diseases, University of Toronto*

The long-term success of pancreatic islet transplantation is limited. Immune and non-immune factors may contribute to long-term graft dysfunction. Islet amyloid is an important non-immune contributing factor. It is typically known as a pathologic lesion of the islet in type 2 diabetes that contributes to the progressive loss of  $\beta$  cells in that disease and that has been shown to form rapidly in human islets transplanted into NOD.scid mice. Amyloid deposits are composed primarily of the  $\beta$  cell secretory product islet amyloid polypeptide (IAPP), are cytotoxic, and develop in environments in which  $\beta$  cells are stressed. Heparin sulfate is used as an anti-coagulant in clinical islet transplantation and to prevent the instant blood-mediated inflammatory reaction (IBMIR). However, it may stimulate amyloid formation. We cultured isolated human islets  $\pm$  heparin for 2 weeks in 11.1 mM glucose. Histological assessment of sections of cultured islets for the presence of amyloid revealed a marked, concentration-dependent increase in amyloid deposition following culture in the presence of heparin. We confirmed a similar trend by a non-histological method that we developed. To affirm that heparin can stimulate IAPP fibrillogenesis and enhance IAPP toxicity, we incubated synthetic human IAPP in the presence of heparin and measured amyloid formation in real time by thioflavin T fluorescence, and cell toxicity by Alamar blue viability assay in transformed rat (INS-1)  $\beta$ -cell cultures. Heparin stimulated IAPP fibril formation and increased death of INS-1 cells exposed to IAPP, suggesting that heparin stimulates IAPP aggregation and toxicity. Heparin also accelerated the onset of IAPP toxicity and hastened the disappearance of toxic IAPP species. Remarkably, preliminary assessment of human islets cultured in heparin did not show increased islet cell death by TUNEL staining or loss of insulin immunostaining. Following transplantation, however, human islets pre-cultured with heparin failed sooner ( $p < 0.05$ ). In summary, heparin increases amyloid formation in cultured human islets and pre-incubation with heparin may accelerate graft failure following islet transplantation. We speculate that heparin-induced amyloid formation may contribute to graft dysfunction and that caution should be used in the clinical application of this drug in islet transplantation.

Basic Sciences (Graduate Research)

## **Modelling Photosensitivity in the Visual Cortex**

Will Guest

*Brain Research Centre, University of British Columbia*

Certain visual stimuli, including bright flashing lights and high-contrast static patterns, are capable of inducing large-amplitude uncontrolled electrical activity in the visual cortices of susceptible individuals. To better understand this condition, a simplified mathematical model of the human visual system was designed to include the effects of retinal image processing, mapping onto the primary visual cortex, and excitation/inhibition balance within the cortex itself. The model was able to reproduce many of the known features of photosensitive epilepsy, including frequency, stimulus amplitude, and spatial pattern sensitivity. As well, the model demonstrates a mechanism of secondary generalization of seizure activity to brain regions outside the primary visual cortex. The ability of a simple model to recapitulate many aspects of photosensitive epilepsy suggests that such behavior is a fundamental property of excitable neural networks.

Basic Sciences (Other)

### **A major QTL controls susceptibility to spinal curvature in the curveback guppy**

Kristen F Gorman, Julian K Christians , Jennifer Parent , Roozbeh Ahmadi , Detlef Weigel , Christine Dreyer and Felix Breden

*Department of Biological Sciences, Simon Fraser University*

Understanding the genetic basis of heritable spinal curvature would benefit medicine and aquaculture. Heritable spinal curvature among otherwise healthy children (i.e. Idiopathic Scoliosis and Scheuermann kyphosis) accounts for more than 80% of all spinal curvatures and imposes a substantial healthcare cost through bracing, hospitalizations, surgery, and chronic back pain. In aquaculture, the prevalence of heritable spinal curvature can reach as high as 80% of a stock, and thus imposes a substantial cost through production losses. The genetic basis of heritable spinal curvature is unknown and so the objective of this work is to identify quantitative trait loci (QTL) affecting heritable spinal curvature in the curveback guppy. Prior work with curveback has demonstrated phenotypic parallels to human idiopathic-type scoliosis, suggesting shared biological pathways for the deformity.

## **Zopiclone and Complex Sleep-related Behaviours**

Julie Wilson (1), Ali Qazalbash (1), Dalpat Mistry (2)

*(1) Psychiatry, Lakeridge Health Oshawa (2) UBC Faculty of Medicine (2) Queen's University School of Medicine*

Complex sleep-related behaviours are uncommon side effects of certain sedative hypnotics. Though in recent years the U.S. FDA and Health Canada have issued warnings on multiple sleep aid medications, many of these advisements were created on theoretical grounds without evidence of published case reports. In our manuscript we describe a patient with zopiclone-induced complex sleep-related behaviours that include sleep eating, sleep driving, sleep conversations, and object manipulation during sleep. The patient's symptoms began after zopiclone initiation and ended immediately after discontinuation. A review of literature reveals only one prior case report in 1996 of a zopiclone-induced amnestic syndrome that exhibited symptoms similar to complex sleep-related behaviours. This is, to our knowledge, the first case report of a diagnosis of zopiclone-induced complex sleep-related behaviours. Zopiclone is a widely prescribed sleep aid in Canada and is used throughout the world. Evidence and characterization of this uncommon side effect of zopiclone is important for physicians prescribing this sedative hypnotic to create increased awareness of adverse events and information for diagnosis. In our manuscript we provide evidence based information describing complex sleep behaviours, prevalence, diagnosis, management, and risk factors.

**SPONTANEOUS RUPTURE OF HEPATIC HEMANGIOMA IN A NEONATE - SURVIVAL WITH NON-OPERATIVE MANAGEMENT**

Amandeep Ghuman (1), Rick Schreiber (2,1), Manraj Heran (1,3), and Sonia Butterworth (1,4)

*(1) University of British Columbia, Vancouver, BC, Canada (2) Division Gastroenterology, BC Children's Hospital, Vancouver, BC, Canada (3) Division of Radiology, BC Children's Hospital, Vancouver, BC, Canada (4) Division of Pediatric General Surgery, BC Children's Hospital, Vancouver, BC, Canada*

**BACKGROUND:** Hepatic hemangioma is the most common benign pediatric tumor of the liver. Spontaneous rupture of these tumors leading to hemoperitoneum is rare and has serious clinical implications with a high mortality rate.

**CASE REPORT:** 7 day old term male infant presented to the Emergency Room with jaundice, lethargy, increased work of breathing, distended and firm abdomen and in severe hypovolemic shock. On admission his hemoglobin was noted to be incredibly low at 27 for which he received a blood transfusion. He was also intubated as he was in respiratory distress and then admitted to the PICU for further investigations. An abdominal ultrasound was performed which showed a hepatic subcapsular bleed and numerous round vascular lesions in his liver. An abdominal CT scan was also done the same day and showed similar lesions and a preliminary diagnosis of hemangioendothelioma was established. Patient was placed on high dose tapering scale of I.V. steroids and had a fairly uncomplicated course in the PICU. Repeat ultrasound was performed 7 days later and noted that the hemoperitoneum had resolved. The subcapsular lesion was still present, but had decreased in size and no shunting was noted. Fifteen days after presenting to the hospital, Interventional Radiology performed an embolization of the right hepatic artery and 2 weeks later patient was discharged from hospital in stable condition.

**CONCLUSION:** We present a rare case in which a patient with spontaneous rupture of a hepatic hemangioma survives and is thriving today with no immediate surgical intervention. Literature reviews document cases of various successful and unsuccessful interventions for hepatic hemangiomas ranging from conservative therapy to liver transplants, but no single treatment has prevailed as treatment of choice.

## Case Report

### **Laparoscopic Management of Mixed Gonadal Dysgenesis with 45,X/46,XringY/46,XY Karyotype**

Ida Molavi (1,2), Chris Wallis (1), John Masterson (1,3)

*(1) University of British Columbia, Vancouver, BC, Canada (2) Office of Pediatric Surgical Evaluation and Innovation, Vancouver, BC, Canada (3) BC Children's Hospital, Vancouver, BC, Canada*

We report the case of a 5 month old boy who presented to the pediatric urology clinic with bilateral undescended testes and was subsequently found to have Mixed Gonadal Dysgenesis with karyotype 45,X/46,XringY/46,XY. Pre-operative MRI revealed a left intra-abdominal gonad in the iliac fossa, no right sided gonad and suggested the presence of a cervix with a small uterine structure at the superior aspect. Laparoscopy subsequently found a hemi-uterus with a fallopian tube and streak gonad on the right side and a left testicle just proximal to the internal ring of the inguinal canal for which a stage I Fowler-Stephens orchidopexy procedure was performed. It is essential to emphasize the importance of current diagnostic tools in treating and managing patients with sexual development disorders such as Mixed Gonadal Dysgenesis. Laparoscopic management not only provides minimally invasive surgery, but it also enables all necessary procedures, including evaluation, biopsy, and gonadectomy, for diagnosis and treatment.

## Case Report

### **Imaging of the Craniocervical Junction in the Trauma Setting**

Nima Kashani, Yashar Tashakkor, David Tso, Savvas Nicolaou

*Department of Radiology, University of British Columbia*

The educational exhibit will highlight the anatomy of this complex and commonly injured region with focus on common fracture patterns seen in the emergency setting. Indicators for determining the stability of the injury will be put forth and the implications in patient management and care will be discussed. The poster will highlight the basic anatomy of the ligaments, bones, neural elements and vascular supply of the craniocervical junction. It will discuss imaging techniques used in evaluating the region with emphasis on MDCT and MRI as the most definitive imaging modalities. Focus will be placed on occipital condyle fractures, atlanto-occipital dislocation, and trauma to the first and second cervical vertebrae.

## **Childhood Trauma, family history of alcohol and drug abuse and age of first drug injection**

C Taplin (1), V Strehlau (1), I Torchalla (1), K Li (1), M Schechter (2), M Krausz (1)

*(1) Centre for Health Evaluation & Outcome Sciences / Providence Health Care-University of British Columbia, Vancouver, BC, Canada (2) School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada*

**Aim:** To better understand the relationship between childhood abuse, family history of alcohol and drug abuse and injection drug use initiation in a cohort of chronic opioid users.

**Design:** Cross-sectional survey in two Canadian cities (Vancouver and Montreal).

**Methods:** A sub-sample (n=87) of long-term and difficult to treat intravenous opiate users of the North American Opiate Medication Initiative (NAOMI) cohort with the following demographic characteristics: 41.4% female, 14.9% First Nations, mean age of 38 years completed the Childhood Trauma Questionnaire (CTQ) and the Addiction Severity Index (ASI).

**Findings:** Maternal alcohol and drug use was significantly associated with childhood sexual abuse, emotional abuse and physical neglect. Paternal alcohol and drug use was significantly associated with physical abuse during childhood. Lastly, increased severity of all types of childhood trauma was related to an earlier age of first injection.

**Conclusion:** Family history of drug and alcohol use is strongly associated with childhood trauma that in turn can lead to an earlier initiation to the dangerous route of drug injection.

## **Patient videos to teach clinical pharmacology**

Thomas L Perry (1), Blair Fulton (2), Billy Lin (2), Pedro Lourenco (2), Pavel Glaze (2), Peter Birks (2), Matthew Cooper (2), Wesley Jang (2), Sarah Mark (2), Bez Toosi (2)

*(1) Department of Medicine, Anesthesiology, Pharmacology & Therapeutics Department (2) UBC Medical Students*

The University of British Columbia medical school relies mostly on lectures and problem based learning tutorials (PBL) in the first two years of its undergraduate medical program. While PBL exposes students to clinical scenarios, most students do not acquire experience with patients until their clerkships in 3rd and 4th year. Introduction of PBL starting in 1997 resulted in curtailment of some aspects of the former curriculum, notably basic and clinical pharmacology. Graduating medical students across Canada recognize this deficiency.

Canadian medical schools make an abrupt transition between the classroom-based years and clerkship years. The shift from classroom to bedside is often difficult for students. By 2nd year many students are weary of PBL and eager to be part of a medical team, while in 3rd year many students find the change of learning environment extremely stressful. We felt that short educational videos could help bridge this transition, by exposing first and second year students to the stories of real patients, told in their own words.

During summer 2010, 30 videos were prepared by 9 undergraduate medical students, under the direction of Dr. Thomas Perry (Internal Medicine and Clinical Pharmacology).

The videos are edited from patient interviews and physical examinations. The videos range from 2-7 minutes in length, and demonstrate:

- common and classical (but uncommon) conditions (e.g. diabetes, adrenal failure)
- the use of drugs to solve clinical problems (e.g. intravenous opioids for acute pain)
- pathophysiologically important medical phenomena (e.g. idiopathic orthostatic hypotension, symptoms of adrenal insufficiency)
- the importance of the doctor-patient relationship (e.g. a man dying of metastatic lung cancer who experienced neglectful treatment)
- routine hospital procedures (eg. the process of converting a urine sample into useful information)

Many of the videos are currently being introduced across the first two years of the undergraduate curriculum, particularly during “PBL case wrap-up” lectures to illustrate how the principles learned from the week’s PBL case can be applied to similar cases in clinical practice.

## **The development of a web-based multimedia educational resource for the learning of pediatric clinical skills**

Rui Chen, Dr. Anne Marie Jekyll, Dr. Elmine Statham, WG Cannon, Dr. Jean-Paul Collet

*Department of Pediatrics, UBC, BC Children's Hospital*

Few non-profit online resources currently exist for teaching medical students pediatric clinical skills. Increasing medical school sizes has resulted in many students training at sites distant from major teaching centres. Computer-based education is effective at teaching medical interviewing and physical examination in addition to being cost-effective. The Department of Pediatrics is developing a comprehensive interactive web-based educational resource for undergraduate medical trainees learning pediatric clinical skills.

"Learn Pediatrics" is an educational tool aimed at UBC medical undergraduate curriculum and distributed sites. In this project, we have created a free, online resource containing written material, videos and other multimedia formats to assist medical students with learning pediatric clinical skills and approaches to common pediatric presentations. The long-term goal for the Learn Pediatrics is to create and maintain an open domain, not-for profit website that will enhance the learning of medical students at our university at distributed learning sites as well as serve as a resource for students nationally and internationally

It involves a team of medical students, pediatric residents, faculty and videographers. The website consists of ten modules including general pediatrics, respiratory, cardiovascular, gastrointestinal, newborn, genitourinary, neurology, musculoskeletal, hematology/oncology, and endocrinology. Seven of these modules will contain physical exam teaching videos. Medical students write content on a voluntary basis and receive credit for their contributions. Pediatric residents involved with Learn Pediatrics then edit the articles for content and clarity. Video scripts are written by pediatric residents, in consultation with attending staff. All actors involved in the videos are volunteers. UBC Media Production records the narrations, films the clinical teaching videos and performs final edits with a pediatric resident or staff physician. Final written and multi-media materials are posted to the site by students employed by the faculty in work-study arrangements. The students have also aided in the website transfer to the UBC domain.

Overall Objectives: 1) To create a comprehensive web-based resource for medical students learning pediatric clinical skills. 2) To incorporate multimedia elements including video material as learning aids. 3) To evaluate the effectiveness of student learning through the use of pre and post testing.

## **Health Status Classification in Primary Care: Empowering physicians and patients in Cuba**

Jody Morita, Nicolas Bilbey, Sarah Yager

*School of Population and Public Health, Faculty of Medicine, University of British Columbia*

It is often said that "Cubans live like the poor but die like the rich". With Cuba's success at controlling infectious diseases despite low economic resources, chronic disease has emerged as a primary cause of death. The major goals of the current project were to 1) examine how the Cuban medical system has approached the emerging problem with chronic diseases within their country and 2) assess whether any of their approaches could be translated to a Canadian context.

In order to address these questions, six Canadian medical students spent 3 weeks in Santa Clara, Cuba, immersed within the Cuban primary care system. The students performed informal interviews with primary care doctors, specialists, and public health officials and gathered information about the structure of the system and the chronic disease prevention/management tools utilized within it.

We found that the Cuban medical system has actively sought to address the prevention, management and treatment of chronic diseases by creating an extensive network of primary care clinics staffed by physician-nurse teams. Primary care physicians classify each Cuban within a simple risk stratification model that we believe improves health outcomes by 1) increasing the effectiveness of family physicians in preventing and managing chronic disease 2) increasing patient awareness of their own health status 3) allowing for close monitoring of population health status and appropriate allocation of resources. We believe that this risk stratification model is directly translatable to the Canadian context and has the potential to improve health outcomes and patient care.

## **Evaluation of a Novel Ski and Snowboard Injury Prevention Program**

Michael David Cusimano (1,2), Wilson Polung Luong (1,3), Ahmed Faress (1,2), Timothy Leroux (1,2)

*(1) St. Michael's Hospital, Toronto, Ontario, Canada (2) University of Toronto, Toronto, Ontario, Canada (3) University of British Columbia, Vancouver, British Columbia*

**Background:** Skiing and snowboarding are enjoyed by millions, however, 4-8 injuries per 1000 skier-days occur. Many of these injuries occur in novices and children as a result of poor decisions and behavior, and so are preventable. The effectiveness of a video, A Little Respect: ThinkFirst! in educating the target population about safety and in preventing injuries was evaluated.

**Methods:** Pre-test/post-test analyses and a four-day observation of behaviors and injuries were documented. Sixty-nine Grade 7 students (ages 11-12) were randomized into control (n=34) and intervention (n=35) groups. Both groups completed a pre-test and post-test safety questionnaire. However, only the intervention group participated in the injury prevention program A Little Respect: ThinkFirst! prior to the post-test survey.

**Results:** The intervention group had twice the improvement in knowledge than the control group (gain scores  $3.06 \pm 2.85$  versus  $1.47 \pm 3.24$ ;  $p = 0.035$ ).

**Conclusions:** An educational video aimed at youth skiers and snowboarders was effective in improving knowledge of skiing and snowboarding safety. Large scale multisite studies with multiple interventions would be necessary to determine if injuries can be prevented.

## **Evaluation of Anemia among a Population of Children Living in the Indian Himalayas and the Role of Iron Supplementation**

T Tan, B Buchan, I Janjua, M Trudeau, SK Yeong, D Dressler, E Kennah, J Scharf, D Kuk, F To, L Bornn, V Kapoor.

*Faculty of Medicine, University of British Columbia*

Since 2007 the University of British Columbia Global Health Initiative, a student-led organization, has collaborated with local leaders in Spiti Valley of the Indian Himalayas to determine and address their major health concerns. The objective of this study was to determine the prevalence and etiology of anemia and observe the effects of iron supplementation. Hemoglobin levels of children in Spiti were measured annually with a b-hemoglobin photometer and results were adjusted for altitude, age and gender based on CDC recommendations. In 2007, there was a high prevalence of anemia at 88.4% (n=379) and thus yearly iron supplementation for 3 months was implemented in 2007 and 2008 based on WHO guidelines. Anemia levels dropped in 2008 to 78.3% (n=384) and to 71.3% (n=416) in 2009. Iron supplementation was not administered in 2009 and as such hemoglobin levels rose back to 89.5% in 2010. Peripheral blood smears obtained in 2008 revealed 57% of cases were normocytic normochromic RBCs, which could be attributed to mixed nutritional deficiencies and/or early iron deficiency and 11% showing hypochromic anisocytic RBCs, which is likely due to iron deficiency. Nutritional deficiencies can be attributed to minimal meat consumption and lack of fruits and vegetables during the winter months. Diarrheal diseases caused by intestinal pathogens due to poor water sanitation and hygiene may also contribute to the anemia burden. Anemia remains highly prevalent and results demonstrate the potential benefits of continuing iron supplementation and the need for more nutrient-dense food, water sanitation interventions and hygiene education to eliminate anemia.

**Identifying clinical factors associated with an increased risk of Diabetes Mellitus among cancer survivors.**

Amir Yashar Tashakkor (1), Ali Moghaddamjou (2), Peter Birks (1), Winson Y. Cheung (3)

*(1) VFMP 2013, University of British Columbia (2) University of British Columbia (3) British Columbia Cancer Agency.*

Background: In order to ensure that the survival gains from cancer advances are not lost because of competing health risks, quality preventive care should be an essential aspect during the routine follow-up of cancer survivors (CS). The ability to identify CS who are most at risk for potentially modifiable conditions, such as diabetes mellitus (DM), can help to streamline preventive efforts. Our objectives were to 1) identify clinical factors associated with an increased risk of DM among CS and 2) develop a stratification system to predict DM risk in CS.

Methods: Using the US National Health and Nutrition Examination Survey, we identified 26,206 patients: 2,374 CS and 23,832 non-cancer controls (NCC). Multivariate logistic regression models were developed to determine demographic characteristics and clinical parameters that were independently correlated with an elevated relative risk (RR) of DM. By assigning a score of 1 for each diabetic risk factor identified, a stratification system was constructed that estimated the prevalence of DM based on the risk score.

Results: In the entire cohort, mean age of 45.0 years (SD 17.4), 51.9 % were female, and 88.6% were White. Baseline characteristics were comparable between CS and NCC. DM was significantly more prevalent in CS when compared to NCC (13.2% of CS vs. 6.9% of NCC,  $p < 0.01$ ). Multivariate analyses revealed the following risk factors for DM: age  $\geq 60$  (RR 2.19, 95% CI 1.78-2.70); racial minorities (RR 1.65, 95% CI 1.16-2.33); less than high school education (RR 1.87, 95% CI 1.33-2.64); obesity (RR 5.90, 95% CI 4.88-7.14); history of ischemic heart disease (RR 2.20, 95% CI 1.45-3.33); history of congestive heart failure (RR 2.95, 95% CI 1.51-5.77); systolic blood pressure  $\geq 120$  mmHg (RR 1.66, 95% CI 1.22-2.26); and triglyceride level  $\geq 150$  mg/dL (RR 1.49, 95% CI 1.10-2.03). A stratification schema for DM in CS was devised (see Table). Conclusions: Through the identification of risk factors for DM, a simple stratification schema was developed, allowing for the identification of CS who may benefit most from appropriate DM preventive care.

Table: Risk of Diabetes in Cancer Survivors Stratified by Score

Prevalence of Diabetes (%): Risk Score

4.3%	≤1
10.8%	2
17.2%	3
32.4%	4
45.6%	5
67.8%	6+

## **The Healthy Young Minds Project: Focus Groups about Mental Health**

Taylor Swanson (1), Alex Butskiy (1), Maryam Dosani (1), Kristy Williams (1), Disha Mehta (1)

*(1) Faculty of Medicine, University of British Columbia*

**Introduction:** The Healthy Young Minds Project aims to create and deliver workshops to engage youth in the discussion of mental health (MH) with the goals of reducing stigma and facilitating access to care. The project has two Phases: Phase 1 involves focus groups with youth on the topic of MH, ensuring that the project is informed by their personal and collective experiences. In phase 2, a pilot version of the workshop will be created by integrating focus group results with expert knowledge.

**Methods:** This project was approved by UBC's BREB and the Vancouver School Board. At one Vancouver high school, school guidance counsellors recruited 36 students (grades 9 to 12) into 4 focus groups. Each group contained 8-10 students and was facilitated by 1-2 medical students under the supervision of a counsellor. Activities included: identifying terms used to describe people with mental illnesses, creating mind-maps, answering questions regarding a fictional student exhibiting signs of mental illness and discussing methods of self-care. Focus groups were recorded. An anonymous feedback and opinion form was circulated. Key themes were identified and classified into three categories (1) What youth know, (2) What misconceptions exist, and (3) What youth want to know about MH.

**Results:** These youth are aware that mental illness can affect anybody regardless of race or socioeconomic class. They can recognize concerning behaviour in peers and identify community supports including friends, family members, religious leaders, guidance counsellors, and family doctors. They are unsure about the etiology of mental illness and would like to know more about common mental illnesses, specifically depression and anxiety. Misconceptions exist regarding prevalence and prognoses for mental illnesses. Having MH workshops in high schools is important to 83% of students, and 67% of students are interested in learning more about MH.

**Discussion and Conclusion:** The results may be biased by the selection of participants by counsellors. Most participants want to learn more about MH. Next, a pilot workshop will be created and evaluated.

**Acknowledgements:** We thank Dr. Dharamsi and Ms. Allow for their guidance. Funding was provided by the BCMA and the CFMS.

## **The Federation of Medical Women of Canada Smear Campaign and the Fight Against Cervical Cancer in Canada**

Pamela Verma (1, 3), Kristin DeGirolamo (2, 3), Sheila Wijayasinghe (3,4), Susan Dallin O'Grady (3), Andrea Canty (5), Dr. Deborah Hellyer (6).

*(1) Faculty of Medicine, University of British Columbia, Class of 2012 (2) Faculty of Medicine, University of British Columbia, Class of 2013 (3) Federation of Medical Women of Canada (4) Past Chair of the National Pap Test Campaign Committee (5) Federation of Medical Women of Canada Past President (6) Federation of Medical Women of Canada President*

Elucidating cervical cancer's etiology and developing a detection and prevention strategy is an incredible accomplishment in women's health in our lifetime. Globally, 500,000 women are diagnosed with cervical cancer annually, and 274,000 women die from this disease[1]. In developing countries, cervical cancer is the largest cause of life-years lost to cancer[2]. The Human Papillomavirus (HPV) is responsible for 70% of cervical cancers[3] and is the most common sexually transmitted infection worldwide<sup>1</sup>. The landmark FUTURE I and II studies demonstrated an effective vaccination against HPV[4]. To further combat cervical cancers, FMWC launched an annual "Smear Campaign" to promote Pap smears for early detection, still necessary despite the vaccine. The campaign was started in 2008 and in 2010, 153 clinics participated which helped achieve the primary objective of the campaign, to increase access for women who face barriers to screening. Next year's campaign will focus on earlier media promotion and strategies to strengthen existing organizational partnerships.

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## **Assessment of the Vancouver Native Health Youth Initiative**

Nathan Wong, Jessica Macleod, Ryan Truant, Kali Romano, Trent Kellock

*Faculty of Medicine, University of British Columbia*

Individuals aged 29 years or less comprise 29.8% of the population of Vancouver's Downtown Eastside, yet preliminary data collected at the Vancouver Native Health (VNH) clinic, one of three major providers for DTES residents, showed that only 7.3% of this population were accessing the clinic (1). UBC Medical students founded the Vancouver Native Health Youth Initiative (VNHYI) to address this discrepancy by holding a youth drop-in on Wednesday evenings at the VNH Clinic. Although preliminary data and physician's observations confirm an increased number of youth utilizing the clinic since the VNHYI began, the demographic information and success of the VNHYI in decreasing barriers to health care faced by youth has not been formally assessed. Participants were recruited using research posters displayed at the drop-in and multiple choice surveys were utilized to collect information. Youth were asked to rate statements regarding the effectiveness of the Initiative in overcoming various barriers to health care on a scale of strongly disagree to strongly agree. Demographic information was compared to Census data from the Government of BC and the survey answers were compiled and analyzed. Our results demonstrate that the youth accessing our services are overwhelmingly Caucasian and Aboriginal, while there is an under representation of Asian and Black ethnicities relative to their population. Younger teenagers were not as represented as youth in their twenties. The majority of youth felt that the drop-in alleviated previously identified barriers to health care such as a judgemental attitude, lack of access, and safety. This work increases our understanding of which youth are accessing, why youth are accessing, and what has been helpful to them. We will use the demographic data to target our advertising and promotional materials to younger teens and other ethnicities in order to increase their awareness and access to services. The role of the VNHYI in decreasing barriers to health care and increasing the access of the DTES youth population demonstrates that the youth drop-in is a necessary and beneficial intervention.

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## **Assessment of Barriers to Bone Marrow Stem Cell Donation in Chinese-Canadian Young Adults**

Rui Chen (1), Merry Gong (1), Celeste Loewe (1), Ying Yao (1)

*(1) Department of Medicine, MD Undergraduate Education, University of British Columbia; DPAS 420 - Self-Directed Project Option*

Various life-threatening disorders (e.g. leukemia, lymphoma, etc.) can be treated with allogeneic hematopoietic stem cell transplants, which involve transplanting the donor's healthy stem cells to the patient's bone marrow to replaced diseased cells. Allogeneic donors and recipients must share compatible tissue markers (HLA) to minimize complications such as graft-versus-host disease. Over 70% of patients are unable to find a match within their families and must rely on the OneMatch Stem Cell and Marrow Network to search for an unrelated donor. A patient's best chance of finding a match is within the same ethnic group.

People of Chinese ethnicity are highly underrepresented in the global stem cell registry (<4%). Chinese patients only have a 10% chance of finding an unrelated donor compared to an 80% chance for Caucasian patients. Furthermore, young adults, whose stem cells are healthiest and most suitable for donation, have relatively low registration rates in the OneMatch Stem Cell and Marrow Network.

This project consists of three phases. During the first phase, UBC Chinese students aged 19-30 are surveyed to investigate common barriers or misconceptions that help to explain why Chinese-Canadian young adults are underrepresented in the OneMatch Stem Cell and Marrow Network. Phase two involves hosting two workshops to raise awareness and educate UBC students regarding hematopoietic stem cell transplants. Finally, phase three will conclude with two on-campus stem cell drives to increase donor registration in this age group.

Preliminary results from the survey show that there is generally a lack of understanding of the process involved in hematopoietic stem cell transplants. For example, even among the 10% of respondents who are already registered as potential donors, over 70% of them were not aware that hematopoietic stem cells can be collected from peripheral blood. Many respondents expressed willingness to register, but the most common barrier is lack of understanding of the process. It is hoped that the results of this project will be a valuable resource to contribute to the success of future stem cell campaigns and the recruitment of potential donors.

## **Engaging the Next Generation: Sustainable Solutions for Global Health Inequities**

Naila Karim (1), Genevieve Tam (2), Tonia Timperley Berg (1)

*(1) University of British Columbia (2) University of Ottawa*

Today's world demands a global perspective in every subject and every classroom. As leaders of tomorrow, we believe in giving our future generation the right knowledge, skills and perspectives to look beyond their borders. In doing so, they become responsible global citizens and engage in finding solutions for global crisis. Teaching global health and responsibilities is an opportunity to advance educational objectives by making subjects more engaging, relevant, and solutions-oriented. As such, several school boards across Canada have incorporated social responsibility as part of their curricula through primary and secondary grades. This project addresses aspects of the curriculum devoted to a very important right that defines Canada: every citizen's right to health care.

In both Vancouver and Ottawa, two medical students and a medical resident have come together to deliver engaging and interactive presentations on "Health and Human Rights." The goal of this project is to raise awareness among high school students of health inequities in the world and instill in the future generation an understanding of the need for shared global responsibility to help bring an end to such social injustices and a looming humanitarian crisis.

Each presentation was allocated one hour to focus on the defense of human rights and health inequities. We are choosing to raise awareness through an interactive presentation and skit to demonstrate United Nations Millennium Development Goal (MDG) # 5 on Maternal Health, which is the furthest from being realized of the eight 2015 MDG targets, even though pregnancy-related complications are largely preventable. Through these presentations, students will have the opportunity to act out a scenario surrounding maternal mortality in order to effectively appreciate both the direct and indirect causes of global inequities.

It is our hope that this work will serve to inspire and engage secondary school students to increase their knowledge regarding global health issues, foster their critical thinking skills, instill in them that they can make a difference in both their local and global community and as a result, provide them with the necessary confidence to take action in their own communities.

## **Body Mass Index and Acute Injury Risk in Children**

Lindsay McRae (1), Jennifer Campbell (3), Quynh Doan (2), Niranjana Kissoon (2), Abdullah AlQahtani (2)

*(1) Faculty of Medicine UBC (2) BC Children's Hospital (3) School of Population and Public Health UBC*

**Objective:** To evaluate the relationship between body mass index (BMI) and acute injury risk in children.

### **Methods & Materials:**

**Design:** Case based, case control study.

**Population:** Children age 5-17 years presenting to BC Children's Hospital Emergency Department. Five hundred patients were screened and 414 patients were enrolled.

**Analytical strategy:** Multivariate logistic regression to estimate the odds of injury occurrence by BMI categories (obese, overweight, and neither) adjusting for potential confounders.

**Results:** Chi-squared analysis revealed that the mild association between obesity and injury occurrence in our descriptive statistics was most likely due to chance ( $P=0.96$ ). Logistical regression, after adjusting the odds ratio for age, sex, activity level and socioeconomic status (SES), did not reveal an increased risk of acute injury in overweight and obese children (OR=0.08 [0.41, 1.55] for overweight and OR=1.16 [0.58, 2.31] for obesity). Analysis of secondary outcomes failed to show an increased risk of fracture in overweight and obese children after the final model was adjusted for age, sex, activity level and SES (OR=0.151 [0.019, 1.234] for overweight and OR=0.984 [0.298, 3.244] for obesity).

**Conclusions:** Our study did not find increasing BMI to be associated with an increased risk of acute injury in children.

**Future Directions:** We will continue to further analyze the data by focusing on the types of activities and the mechanisms of injury. A large scale, multi-site study investigating the relationship between obesity and risk of fracture will begin in the summer of 2011.



UBC Medical Journal  
By Students, For the World



# Research Forum Program

5-9pm March 15, 2011  
Life Sciences Centre, UBC

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|---------------|--|
| 5:00-5:30 PM  | Guest registration   |
| 5:30-5:35 PM  | Opening remarks  |
| 5:35-5:45 PM  | UBC Medical Journal Reveal   |
| 5:45-6:45 PM  | Poster session #1  |
| 6:45- 7:05 PM | Dr. Anita Palepu MD, MPH, FRCPC<br>Professor, Division of Internal Medicine, UBC |
| 7:05-8:00 PM  | Poster session #2  |
| 8:00-8:20 PM  | Dr. Matthew Farrer PhD<br>Professor, Dept of Medical Genetics, UBC               |
| 8:20- 8:30 PM | Faculty comments   |
| 8:30-8:45 PM  | Award presentations  |