

The 6th Annual MUS-UBCMJ Research Forum Abstracts

Year 1

The role of nitric oxide and superoxide in vascular endothelial dysfunction in gestational diabetes

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Purpose: To investigate the changes in molecular physiology of endothelial cells in normal pregnancy and gestational diabetes mellitus (GDM).

Hypothesis: We hypothesize that endothelial function will be maintained or enhanced in normal pregnancy but impaired in GDM, resulting from a shift in the balance of vasodilatory and oxidative stress pathways.

Methods: Our model of GDM involves mice with a heterozygous mutation of the leptin receptor, resulting in the spontaneous development of diabetes during pregnancy. To study the endothelial function in non-pregnant mice and mice with a normal pregnancy or GDM, we measured nitric oxide (NO) and superoxide (O₂⁻) bioavailability through oxidative fluorescence microtopography on isolated mesenteric arteries. Using fluorescence immunohistochemistry, we measured the expression of NO synthase. As NO reacts with O₂⁻ to produce peroxynitrite, we also measured levels of nitrotyrosine (a marker of peroxynitrite formation), and superoxide dismutase by fluorescence immunohistochemistry.

Results: Vascular sensitivity to endothelium-dependent vasodilation has been shown to be increased in normal pregnancy compared to GDM. In our studies, NO bioavailability was increased in normal pregnancy over GDM ($p < 0.05$). However, the expression of all three NO synthase isoforms was down-regulated in both normal pregnancy and GDM compared to that of non-pregnant controls ($p < 0.05$). Concomitantly, O₂⁻ levels were significantly increased in GDM over normal pregnancy and non-pregnant controls, suggesting an increase in oxidative stress in GDM. Interestingly, nitrotyrosine levels of mesenteric arteries were reduced in both normal pregnancy and GDM compared to

non-pregnant controls ($p < 0.05$). Preliminary results also suggest a decrease in superoxide dismutase expression in GDM compared to normal pregnancy.

Conclusion: There exists an adaptation in the mesenteric endothelium during normal pregnancy that is absent in GDM. We postulate that this vascular adaptation involves an increase in NO synthase coupling, increasing NO production in spite of the reduced NO synthase expression during normal pregnancy. However, the lack of vascular adaptation in GDM results in NO synthase uncoupling, leading to reduced NO and increased O₂⁻ production. Vascular nitrotyrosine expression is limited by reduced O₂⁻ and NO levels in normal pregnancy and GDM, respectively. Our results highlight the differences in molecular physiology between normal pregnancy and GDM.

Transplantation of Reprogrammed Embryonic Stem Cells Improves Visual Function in a Mouse Model for Retinitis Pigmentosa

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Background: To study whether C57BL/6J-Tyrc-2j/J (C2J) mouse embryonic stem (ES) cells can differentiate into retinal pigment epithelial (RPE) cells in vitro and then restore retinal function in a model for retinitis pigmentosa:

Rpe65rd12/Rpe65rd12 C57BL6 mice.

Methods: Yellow fluorescent protein (YFP)-labeled C2J ES cells were induced to differentiate into RPE-like structures on PA6 feeders. RPE-specific markers are expressed from differentiated cells in vitro. After differentiation, ES cell-derived RPE-like cells were transplanted into the subretinal space of postnatal day 5 Rpe65rd12/Rpe65rd12 mice. Live imaging of YFP-labeled C2J ES cells demonstrated survival of the graft. Electroretinograms (ERGs) were performed on transplanted mice to evaluate the functional outcome of transplantation.

Results: RPE-like cells derived from ES cells sequentially express multiple RPE-specific markers. After transplantation, YFP-labeled cells can be tracked with live imaging for as long as 7 months. Although more than half of the mice were complicated with retinal detachments or tumor development, one fourth of the mice showed increased electroretinogram responses in the transplanted eyes. Rpe65rd12/Rpe65rd12 mice transplanted with RPE-like cells showed significant visual recovery during a 7-month period, whereas those injected with saline, PA6 feeders, or undifferentiated ES cells showed no rescue.

Conclusions: ES cells can differentiate, morphologically, and functionally, into RPE-like cells. Based on these findings, differentiated ES cells have the potential for the development of new therapeutic approaches for RPE-specific diseases such as certain forms of retinitis pigmentosa and macular degeneration. Nevertheless, stringent control of retinal detachment and teratoma development will be necessary before initiation of treatment trials.

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Safe Administration of Propofol in Children

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Introduction: Propofol is increasingly used in children. Its use in some settings remains controversial as respiratory depression is a significant risk (1). Slower administration of propofol will reduce the drug's peak concentration and may allow for the accumulation of carbon dioxide to offset central respiratory depression. This investigation aimed to increase the safety of propofol administration by developing a dosing schedule that would preserve spontaneous ventilation in at least 95% of subjects.

Methods: With REB approval and informed consent, we recruited 52 ASA 1 & 2 children aged 6-15 years presenting for upper or lower gastrointestinal endoscopy in the operating room. An intravenous loading dose (LD) of propofol (4 mg/kg) was administered at a rate determined by a randomization schedule.

Following the LD, propofol was infused at a rate of 200 mcg/kg/min for 5 min, or until a period of apnea was observed. The randomization schedule began with an initial rate of 1000 mcg/kg/min. The rate was sequentially increased by 100 mcg/kg/min until apnea was observed in three subjects. If apnea occurred, the rate for the subsequent subject was decreased by an increment of 100 mcg/kg/min. The next 33 subjects were randomized according to a Biased Coin Design principle (2): The time for infusion was increased by 20 s if apnea occurred, or decreased by 20 s 5% of the time if spontaneous ventilation was preserved. The maximum infusion rate that preserves spontaneous respiration was calculated using the pooled-adjacent-violators algorithm (PAVA) and bootstrap methods were used to compute 95% confidence limits.

Results: The analysis included 50 subjects, mean (SD) age 11.4 (2.5) years and weight 43.0 (14.9) kg. Infusion rates ranged from 1000 mcg/kg/min to 2300 mcg/kg/min. Seven subjects experienced apnea. The mean (SD) time to apnea was 104 (36) s and duration was 93 (51) s. A LD of propofol administered over 3.0 min maintained spontaneous ventilation in 95% of subjects (CI= 1.9 - 3.5).

Conclusion: A 4 mg/kg dose of propofol, administered as the sole anesthetic agent over 3 min, maintained spontaneous ventilation in 95% of subjects aged 6-15 years.

Phosphoinositide 3-kinase p110delta regulates natural antibody production, marginal zone and B-1 B cell function, and autoantibody responses

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B-1 and marginal zone (MZ) B cells produce natural antibodies, make antibody responses to microbial pathogens, and contribute to autoimmunity. Although the delta isoform of the phosphoinositide 3-kinase p110 catalytic subunit is essential for development of these innate-like B cells, its role in the localization, activation, and function of normal B-1 and MZ B cells is not known. Using IC87114, a highly selective inhibitor of p110delta enzymatic activity, we show that p110delta is important for murine B-1 and MZ B cells to respond to B cell receptor (BCR) clustering, the Toll-like receptor (TLR) ligands LPS and CpG DNA, and the chemoattractants CXCL13 and sphingosine 1-phosphate. In these innate-like B cells, p110delta activity mediates BCR-, TLR- and chemoattractant-induced activation of the Akt pro-survival

kinase, chemoattractant-induced migration, and TLR-induced proliferation. Moreover, we found that TLR-stimulated antibody responses by B-1 and MZ B cells, as well as the localization of MZ B cells in the spleen, depend on p110delta activity. Finally, we show that the in vivo production of natural antibodies requires p110delta and that p110delta inhibitors can reduce in vivo autoantibody responses. Thus targeting p110delta may be a novel approach for regulating innate-like B cells and for treating antibody-mediated autoimmune diseases.

The Biosynthesis of CMP-N,N'-Diacetyllegionaminic Acid from UDP-N,N'-Diacetylbaucillosamine in *Legionella pneumophila*

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Legionaminic acid is a nine carbon alpha-keto acid that is similar in structure to other members of the sialic acid family that include neuraminic acid and pseudaminic acid. It is found as a component of the lipopolysaccharide in several bacterial species, and is perhaps best known for its presence in the O-antigen of the causative agent of Legionnaires' disease, *Legionella pneumophila*. In this work, the enzymes responsible for the biosynthesis and activation of N,N'-diacetyllegionaminic acid are identified for the first time. A cluster of three *L. pneumophila* genes bearing homology to known sialic acid biosynthetic genes (*neuA,B,C*) were cloned and overexpressed in *Escherichia coli*. The *NeuC* homolog was found to be a hydrolyzing UDP-N,N'-diacetylbaucillosamine 2-epimerase that converts UDP-N,N'-diacetylbaucillosamine into 2,4-diacetamido-2,4,6-trideoxymannose and UDP. Stereochemical and isotopic labeling studies showed that the enzyme utilizes a mechanism involving an initial anti-elimination of UDP to form a glycol intermediate, and a subsequent syn-addition of water to generate product. The *NeuB* homolog was found to be a N,N'-diacetyllegionaminic acid synthase that condenses 2,4-diacetamido-2,4,6-trideoxymannose with phosphoenolpyruvate (PEP), although the in vitro activity of the recombinant enzyme (isolated as a MalE-fusion protein) was very low. The synthase activity was dependent on the presence of a divalent metal ion and the reaction proceeded via a C-O bond cleavage process, similar to the reactions catalyzed by the sialic acid and pseudaminic acid synthases. Finally, the *NeuA* homolog was shown to possess the CMP-N,N'-diacetyllegionaminic acid synthetase activity that generates the activated form of legionaminic acid used in lipopolysaccharide biosynthesis. Together, the three enzymes constitute a pathway that converts a UDP-linked baucillosamine derivative into a CMP-linked legionaminic acid derivative.

Identification of Cpn60.2 as a surface ligand of *Mycobacterium tuberculosis* that mediates bacterial binding to macrophages via CD43

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Mycobacterium tuberculosis bacilli initially contact host cells with elements of their outer cell wall, or capsule. We have shown that capsular proteins from the surface of *M. tuberculosis* competitively inhibit the non-opsonic binding of whole *M. tuberculosis* bacilli to macrophages in a dose-dependent manner that is not acting through a global inhibition of macrophage binding. CD43 is a large sialylated glycoprotein that is found on the surface of macrophages and has been shown in previous studies to be necessary for efficient macrophage binding and immunological responsiveness to *M. tuberculosis*. Using capsular proteins and recombinant CD43, we have employed affinity chromatography to show that Cpn60.2 (Hsp65, GroEL), and to a lesser extent DnaK, bind to CD43. We subsequently demonstrated that both Cpn60.2 and DnaK can be identified on the surface of *M. tuberculosis* bacilli. Furthermore, we performed recombinant protein competitive inhibition and polyclonal F(ab')₂ antibody-mediated epitope masking studies to show that Cpn60.2, but not DnaK, acts as a mycobacterial adhesin for macrophage binding. We then compared *M. tuberculosis* binding of CD43+/+ versus CD43-/- macrophages and found that the adhesin function of Cpn60.2 is CD43-dependent. Additionally, the binding between Cpn60.2 and CD43 can be saturated; however the binding affinity is comparatively weak in the micromolar range. We also showed that the ability of Cpn60.2 to competitively inhibit *M. tuberculosis* binding to macrophages is shared by the *Escherichia coli* homologue, GroEL, but not by the mouse and human Hsp60 homologues. These findings add to a growing field of research that implicates molecular chaperones as having extracellular functions, including bacterial adherence to host cells, distinct from their well-described protein folding activities within the cytosol.

Impact of an antimicrobial stewardship program on treatment of critically ill patients with Gram-positive bloodstream infections

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Introduction: Initial management of bacterial growth in blood cultures (BC) usually includes broad-spectrum antibiotics. Once speciation and an organism's susceptibility is available, antibiotic therapy should be adjusted. Physicians may be over-prescribing drugs active against methicillin-resistant *Staphylococcus aureus* (MRSA) such as vancomycin when drugs active against methicillin-sensitive *Staphylococcus aureus* (MSSA)-active would suffice. This practice may contribute to the emergence of drug-resistant bacterial strains. The objective of this study was to examine whether an antibiotic stewardship program (ASP) could change the usage of MRSA-active drugs for patients with gram-positive (GP) bloodstream infections in the ICU.

Methods: Data from patients with BCs drawn from a single tertiary centre ICU were analyzed. Positive blood cultures were identified from the laboratory information system (SoftLab, SCC Soft Computer, Clearwater FL). Patients were identified through ICU admission books; data was collected retrospectively, using patient paper files and electronic medical records. The analysis of antibiotic usage was from January 2008 to July 2009. Data analysis was performed using Student's t-test for continuous variables and chi-squared for dichotomous variables.

Results: A total of 103 and 43 episodes of GP infections were identified, pre-ASP and post-ASP, respectively. The two groups were similar in terms of demographics and severity of illness. Both pre- and post-ASP, 95% of all GP bloodstream isolates were due to coagulase-negative staphylococci. There was a 41% reduction in the duration of vancomycin and linezolid following introduction of the ASP. Overall usage of MRSA-active antibiotics was also significantly reduced post-ASP while infection rates remained the same. Central venous catheter dwell time was also reduced by a mean of 5.3 days.

Conclusions: The proportion of MRSA-positive cultures in the ICU when compared to other GP blood cultures does not justify the high use of MRSA-active drugs. Introduction of an antimicrobial stewardship program resulted in a 40% reduction in vancomycin and linezolid use. The relationship of central line dwell times to antibiotic use is unclear at present, but warrants further investigation.

been shown to significantly reduce the severity and occurrence of IDH, or its associated morbidity. Midodrine is frequently used at the hemodialysis unit at this institution for the treatment of IDH despite its unknown impact.

Objective: To evaluate midodrine use in the management of IDH at the hemodialysis unit. The primary objectives were to observe the impact of midodrine on BPs at various intervals during the HD sessions, and its usage pattern on the unit. The secondary objectives were to compare the patient characteristics and risk factors between the midodrine and non-midodrine (control) groups, while also determining the overall incidence of IDH and non-midodrine interventions made.

Methods: A prospective observational review was conducted to assess BPs, dosing and frequency of midodrine administration, and the number of IDH episodes during hemodialysis sessions in both midodrine and control groups. Patient characteristics and risk factors influencing IDH were also compared between the two groups. Descriptive statistics were used.

Results: Fifty-five midodrine patients and 53 non-midodrine patients were included. The midodrine patients entered their hemodialysis sessions with lower mean BPs than the control group (123/65 vs. 133/70 mm Hg, respectively). This trend continued during the hemodialysis sessions and may have increased the susceptibility of these patients to IDH as this group also had a higher rate of symptomatic IDH (12% vs. 4.8%). A mean midodrine dose of 7.5 mg was used per hemodialysis session, although the range was quite large. Patient characteristics were found to be similar between the two groups.

Conclusions: This study revealed that midodrine was used commonly for IDH at this hemodialysis unit despite a lack of well documented clinical benefits. The midodrine users had lower BP values throughout the hemodialysis sessions and experienced more symptomatic IDH despite the use of midodrine.

Assessment of Midodrine Use in the Management of Intradialytic Hypotension (AMUSING)

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Background: Intradialytic hypotension (IDH) occurs frequently in the hemodialysis setting and may increase morbidity and mortality within this population. With its α -1 receptor agonist action, midodrine is a potential treatment option for IDH. Although midodrine may improve blood pressure (BP) values, it has not

Year 2

Peak hip flexion during common physical activities: a review

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Aim: Repetitive flexion of the hip has been hypothesized to contribute to hip pain and hip osteoarthritis in individuals with a condition known as femoroacetabular impingement (FAI). This pilot study was designed to review the literature on peak hip flexion for selected physical activities in a healthy population.

Methods: A literature search was conducted to determine the degree of peak hip flexion in 10 physical activities and 55 recreational activities included in a previously developed Lifetime Physical Activity Questionnaire (jumping, kneeling, running, sitting, sitting cross-legged, sprinting, stair-climbing, standing, walking; aerobics, climbing, backpacking, hiking, badminton, baseball, basketball, cycling, bowling, boxing, broomball, canoeing, circuit-training, cricket, curling, fencing, field-hockey, floor-hockey, ultimate, football, golf, gymnastics, hunting, ice-hockey, martial-arts, equestrian, racquetball, rollerblading, rafting, rowing, rugby, sailing, skateboarding, skating, cross-country-skiing, alpine-skiing, sledding, snorkeling, snowshoeing, snowboarding, snowmobiling, soccer, squash, swimming, table-tennis, tai-chi, tennis, track-and-field, trampoline, volleyball, water-polo, water-volleyball, weight-lifting, wrestling). The search engine MEDLINE (OvidSP) was used with three subject headings: “hip joint”, “range of motion, articular” and “biomechanics”. These were combined with the keyword for the desired type of activity. The searches were limited to articles written in English and focusing on human subjects. For each activity, the mean peak hip flexion in each study was either taken directly from a data table or read from a graph and a mean and weighted mean across the studies were calculated. Information regarding the study population and methodology of the studies from which the data were extracted was compiled.

Results: The physical activity literature search produced 812 hits, of which 176 were reviewed and 29 were used to determine the results. Of these, squatting had the greatest degree of peak hip flexion - weighted mean of 90.6°. For the recreational activities, there were 158 hits, 69 were reviewed and 20 were included. 10 of the 55 activities had results, and gymnastics (157.5°) had the greatest peak hip flexion.

Conclusions: These data can now be used in conjunction with survey data obtained with the Lifetime Physical Activity Questionnaire to study the potential effects of the amount hip flexion over lifetime on the development of hip pain and hip osteoarthritis.

Fabricating durable silicone skin phantoms for laser speckle modelling

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Background: When skin is illuminated by a low coherence laser, the remitted laser speckle pattern contains information on surface roughness and intrinsic optical properties. Laser speckle technology could be useful for skin roughness evaluation and skin lesion differentiation. A suitable skin phantom with controllable surface roughness and intrinsic optical properties is thus needed for calibrating laser speckle devices.

Objective: Our study aim is to construct durable skin phantoms with known surface roughness, absorption and scattering coefficients.

Methods: Silica microspheres, which control the scattering of the phantom, were added to silicone resin and dispersed in a resin-hexane mix using an ultrasonic bath. The catalyst was added after hexane evaporation and air bubbles were removed using a vacuum. The microsphere-resin-catalyst mix was then cured on the bases of metal standards with varying roughness values. Pigmented powder was added during the process to adjust the absorption coefficients of the phantoms.

Results: We have successfully created silicone skin phantoms with embedded silica microspheres at specified concentrations and standardized surface roughness values. Using confocal microscopy we obtained images of the phantoms and were able to confirm that the silica microspheres were randomly disbursed. We are currently testing the detailed physical properties of the phantoms.

Clinical Significance and Knowledge Translation: This process of skin phantom fabrication produces phantoms that simulate the tissue properties desirable in laser speckle measurements, and potentially other imaging techniques. This would provide a potential new method for quality control in the technology currently used in medical practice for the imaging of tissues. It will also help to model the performance of novel optical equipment.

Creating a Quick Reference Pocket Guide to Preceptor Visits for Medical Students

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As part of the curriculum, first and second year University of

British Columbia (UBC) medical students participate in family practice office visits. Working with preceptors, students are exposed to a wide variety of clinical practice guidelines and common conditions. To assist the students with office visits, family medicine departments across Canada have created pocket cards and information sheets related to common medical topics. This project aimed to enhance UBC student experiences at preceptor offices by creating a reference booklet of the most common diagnoses in family practice. To identify booklet content, a focus group and literature review were conducted. The focus group was comprised of nine first-year UBC medical students and held in June 2009. Based on their own preceptor office visits, students identified the usefulness of including basic clinical guidelines (ex. immunization schedules, maternity guidelines) in addition to common diagnoses. A literature search failed to solidify a ranking list of diagnoses so a list of seven common patient complaints was constructed using focus group feedback, literature, the Canadian Shared Family Medicine Curriculum Core Objectives list and second year rural rotation data. Booklet information was gathered from curriculum resources, guideline authors and medical literature. The final product, "Quick Reference Pocket Guide to Preceptor Visits," was distributed to first and second year medical students in Fall 2009. The pocket guide contains basic clinic tools (ex. comprehensive history template, Rourke Records) and seven common patient complaints that students will likely encounter in preceptor offices. Differential diagnoses, focused history questions, and clinical information (definition, etiology, pathophysiology, signs and symptoms) for select diagnoses are provided for each complaint. Next steps for the guide include a year-end student evaluation and potential revisions based on feedback.

Implementing a sustainable health education curriculum for children of a remote community in the Indian Himalayas

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Background: UBC Global Health Initiative (GHI) is a student led group that has run health projects through a remote boarding school in the Indian Himalayas since 2007. In the past, the community approached GHI requesting a health curriculum to encourage practical applications of basic hygiene and health knowledge. In 2009, a sustainable curriculum was developed which built upon existing health initiatives in the community.

Methods: GHI students oversaw the design and implementation

of the health curriculum, which included lessons on hand washing, skin and oral hygiene, tobacco, and water. This required the identification of major health issues through health screens and observation along with collaboration with school and community leaders. Teaching materials (posters and lesson outlines) were provided to teachers and GHI students taught lessons from this curriculum. Sustainability was incorporated through the formation of a teaching partnership with local nursing students and engagement of senior students.

Results: In 2009, 420 students were provided lessons from the curriculum. Success has been measured by changes in hygiene, specifically an increase in frequency of hand washing and wound cleaning, and the use of more appropriate drinking water sources. By involving teachers, senior students and nursing students, GHI has empowered the community to take a more active role in health education. With a successful program in place, the school can act as a model for change for other schools in the Spiti Valley; additionally students can continue to build healthy habits long after GHI has left the community.

Legal Needs in Adult Survivors of Paediatric Malignancies

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Background: This study analyzes the efficacy of the BC Cancer Agency (BCCA) Late Effects Clinic for adult survivors of childhood cancers and the need for a legal resource center.

Methods: 77 adult survivors were approached with a mean age of 7.5 (SD 4.7) and 31.8 (SD 7.0) at the time of primary diagnosis and survey completion, respectively.

Results: 76 (98.7%) of respondents completed the survey. Central nervous system (CNS) tumors were the most common malignancy (34.2%), followed by leukemia (31.6%), sarcoma (15.8%), and lymphoma (11.8%). Legal problems were common overall (38.1%), though more prevalent in those with CNS versus non-CNS tumors (59.1% vs. 26.8%; $p = 0.016$). 93.3% of individuals with legal problems found it difficult to find legal help. Overall, 83.6% of respondents indicated it would be beneficial to have a legal help resource. In terms of care provided, 97.3% of survivors indicated that follow up at the BCCA had been beneficial. Family doctors were seen more frequently by CNS versus non CNS tumors survivors, (6.21 vs. 4.6; $p = 0.357$) though this was not statistically significant. The majority of patients (92%) preferred to be followed by BCCA and their family doctor.

Conclusions: These results suggest that a legal resource center would likely be beneficial for childhood cancer survivors (especially those with CNS tumors) due to their increased encounters with legal difficulties. Different ways to improve communication and co-ordinate patient care with family doctors should be further explored.

Applying CanMEDS Competencies to Surgical Training

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New knowledge, specialization and technical advances in general surgery, as well as changes in resident work hours, reductions in operating time and increasingly sophisticated therapeutic options in an environment of scarce resources, have created numerous challenges for surgical education. A comprehensive strategy including a rigorous approach to the delivery and evaluation of clinical and technical competencies, and sound approaches to developing communication, advocacy and professionalism, is urgently needed. The CanMEDS competencies can provide a framework for the initiation of novel initiatives in surgical education. Our objective was to develop a competencies-based curriculum in surgical residency training that fully integrates the concepts of CanMEDS. A stepwise consultative process was used to define rotation and level of training specific competencies in each of the CanMEDS spheres in a large Canadian general surgery program. The project employs a mixed methodology: qualitative methods were used to analyze survey and interview data with program directors, clinical service chiefs, teaching faculty and residents. Thematic analyses within and across data sources were performed to inform recommendations. Study results have informed the design of a new, transparent competency-based system of evaluation, whose effects are currently being measured.

Reduction of Diarrheal Disease Through Distribution of Portable Water Filters on Remba Island, Kenya

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Background: Remba Island, situated in Lake Victoria, Kenya, is a small fishing community with a population of approximately 4600 people. Remba has no health facility, public waste disposal, sewage system, or safe water source. Water from Lake Victoria, documented to be grossly contaminated, is the only source of drinking water on the island and as such, leads to very high rates of diarrhea among the residents of Remba. Of the potential safe water interventions for Remba Island, one promising option is the use of LifeStraw® filters, a new line of easy to use and low maintenance point-of-use water filters.

Methods: In collaboration with the Kenyan Ministry of Health, LifeStraw® filters were provided to 50 households (family filter)

and 108 fishermen (personal filter) as part of a pilot project. Baseline data and follow-up data was collected at 1, 2, and 3 months to gauge reduction of diarrheal rates and community perception of the filters.

Results: Pilot phase data demonstrated a noticeable reduction in diarrheal rates at the 3-month follow-up (65% to 33% and 10% among households and fishermen, respectively). LifeStraw® filter use was higher among fishermen (82%) compared to household use (62%).

Conclusions and Future Directions: Based upon promising preliminary reductions in diarrheal disease, there was a scale up of the project and LifeStraw® filters were provided to the entire population of Remba in July 2009. New baseline data will be compared to follow-up data at 4, 8, and 12 months from 500 randomly selected households and 500 randomly selected fishermen. The LifeStraw® intervention will elucidate the efficacy of these filters at providing safe water for communities in rural locations.

Lights, camera, surgery: evaluation of a pilot project for medical students to produce surgical education learning resources

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Purpose: The university has recently launched a distributed medical undergraduate program, doubling its class size in the last 4 years. This expansion has led to a necessary increase in the use of new educational resources to bridge learning at multiple sites. The application of modern technology can create valuable online resources which are accessible at all times. The Office of Pediatric Surgical Evaluation and Innovation (OPSEI) has launched a pilot project called, “Lights, Camera, Surgery” for medical students to design and produce instructional videos for teaching common surgical procedures.

Methods Used: A group of 13 medical students were given a leadership role in filming key surgical cases within the operating room setting in Pediatric Surgery. The students were mentored by faculty and by a professional videographer coach. At the end of the project, the students were surveyed using a 5-step Likert scale (strongly disagree, disagree, neutral, agree, or strongly agree). This scale was used to assess whether this pilot project allowed students to broaden access to clinical learning resources, explore careers within the surgical environment, develop skill sets necessary for creating online resources, and ignite student leadership in creating clinical learning resources.

Summary of Results: Eight of 13 surveyed students responded. All respondents indicated no previous experience filming, editing, narrating videos, or producing educational learning resources. All students reported that they agreed the overall project experience allowed them to assume a leadership role in the development of the project. All students either agreed or strongly agreed that

the project allowed them to create valuable educational learning resources. When asked if the project allowed them to explore careers in surgery, 62.5% agreed and 37.5% strongly agreed. All students agreed or strongly agreed that the project allowed them to gain valuable skills in video filming.

Conclusions: A total of 21 surgical videos were developed. The pilot project “Lights, Camera, Surgery” was a worthwhile learning experience and provided students specialized skills in the production of clinical education videos. This novel approach has served as a unique way to expose students to careers in surgery and to interact with surgical mentors.

The Live Renal Donor Experience

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Introduction and Objective: Last year 195 Canadians died on the organ transplant waiting list before they could receive a transplant. In Canada, there are currently 4,000 people on the waiting list; 75% of which are awaiting kidneys. In British Columbia, 106 living donor renal transplants occurred in 2007. The objective of this study was to suggest improvements in the transplant experience to facilitate the live donation process. This was done by analyzing positive and negative aspects of the renal donor transplantation experience from a donor’s point of view: during and following the donation process.

Methods: Ten renal transplant donors in BC were interviewed during a follow-up post-operative appointment. All surgeries were done by a single surgeon, with BC Transplant. Interview questions focused on donor experiences during laboratory work-up, on the surgery day, and up to several months post-surgery. Further information was elucidated through prompting questions pertaining to their health (physical health, mental/emotional health [pre- and post- donation]), relationships (personal and professional), and the overall donation process. Transcripts were read three times, and common trends and categories were identified via the grounded theory of inductive approach.

Result: Nine of the ten donors felt so strongly and positively about the importance of the donation process that they would do it again and/or recommend siblings or relatives to donate. Successful areas of support and services noted by donors included: flow and coordination of the donation process, Transplant Agency support, caring staff, finances, and employer social support. Areas of concern for the donors included: physical recipient-donor recovery reunion, pain control, management of expectations of post-surgical physical outcomes, and fatigue levels.

Conclusion: The results of this study can be applied as recommendations to improve the donation process by continuing the beneficial services, while addressing areas of concerns for donors. By modifying the recruitment process to improve the donor experience, this has the potential to alleviate the current need for live renal donors. Furthermore, these results have widespread application to all transplant societies, not necessarily just renal transplants, nor those confined to BC.

Cancer as an epigenetic disease: CpG island hypomethylation of Mdm4 in squamous cell lung cancer

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Aberrant DNA methylation patterns in an increasing number of tumor suppressor genes have been shown to determine carcinogenic transformation. The methylation state of a particular CpG island present near the transcription start site of the gene Mdm4 is of particular importance. A technique for rapid DNA methylation analysis, known as MSRE-PCR, was employed and its effectiveness is evaluated. The CpG island located near the transcription start site of Mdm4 was found to be unmethylated in all six pairs of normal and squamous cell lung cancer samples. This result corresponds to Mdm4 protein’s role as a p53 inhibitor and cancer-inducing protein but does not indicate methylation to be a contributor to cancer formation. MSRE-PCR was successful at determining the methylation state of CpG dinucleotides in a specific CpG island and it has proven to be an invaluable tool in determining the role of methylation in various types of carcinogenesis.

Prevalence of femoroacetabular impingement in individuals undergoing total hip replacement for osteoarthritis – a retrospective radiographic review

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Objective: Recently, femoroacetabular impingement (FAI) has been suggested as the major cause of primary hip osteoarthritis. We assessed the prevalence of FAI detected radiographically in a comparatively young cohort that underwent total hip replacement (THR) for primary hip osteoarthritis.

Methods: The Vancouver Coastal Health Authority Total Joint Replacement Service database was used to identify subjects aged < 55 years with pre-operative radiographs acquired prior to a THR procedure for primary hip osteoarthritis during the period 2007-2008. Exclusion criteria included hip fracture, rheumatoid arthritis, hip infection, osteonecrosis, congenital and other hip dysplasia, and other secondary causes of osteoarthritis. Eighty-two subjects were included in the study by random selection. Two radiologists reviewed together the classic radiographic FAI signs to form consensus for definitions, then independently assessed the retrospective pre-operative radiographs (AP pelvis

and lateral views) for each subject. Using a standardized scoring tool, subjects were categorized as: definite FAI, no FAI, and not possible to exclude FAI due to advanced osteoarthritis. In the event of disagreement between the radiologists for a given subject, consensus was achieved by discussion.

Results: Of 470 THR cases identified, 82 were randomly selected. Seven of the 82 subjects were subsequently excluded due to lack of pre-operative radiographs (N=3), readmission of subject already selected (N=3), and radiograph of inadequate diagnostic quality (N=1). Of 75 subjects, 49 (65%) were male. Mean age was 49.5 ± 4.7 . Definite FAI was present in 27 subjects (36%) and no FAI in 25 subjects (33%). In 23 subjects (31%), FAI could not be excluded due to advanced osteoarthritis. Thus, of those that could be adjudicated clearly, 27 of 52 (52%) had FAI. Of the 27 subjects with FAI, 5 cam-type, 13 pincer-type, and 9 mixed-type cases were identified. Consistent with previous studies, there was a male predominance in cam-type features and a female predominance in pincer-type features.

Conclusions: FAI is common in young subjects undergoing total hip replacement for primary osteoarthritis. Since other work proposes that it is FAI combined with specific physical activities that result in osteoarthritis, the findings suggest a potential for prevention of hip osteoarthritis in the future.

Cost-effectiveness of Ranibizumab (Lucentis) for the Treatment of Age-related Macular Degeneration

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Background: The objective of this study was to evaluate the cost-effectiveness of ranibizumab versus photodynamic therapy with verteporfin (PDT-V) and Standard Care (SC) for the treatment of all wet age-related macular degeneration (AMD) lesions (Predominantly Classic (PC), Minimally Classic (MC) and Occult (OC) lesions) in Canada.

Methods: A Markov model, with a 3-month cycle length and 10-year time horizon was adapted to the Canadian setting to simulate the evolution of visual acuity (VA) levels in patients with subfoveal wet AMD. Analyses were performed from the perspective of the Ontario Ministry of Health. The initial distribution of patients across VA levels followed the distribution observed in MARINA and ANCHOR at randomization. Transition probabilities were based on data from the same trials. Resource use was determined through a clinician questionnaire. Quality-of-life estimates attributed to visual acuity levels were obtained from a simulation study to elicit utilities in a sample of the UK general population. Outcomes were measured in terms of quality-adjusted-life-years (QALY). The incremental cost-effectiveness ratio (ICER) between interventions was calculated; one-way and probabilistic

sensitivity analyses were performed to capture variability and uncertainty around results.

Results: Ranibizumab demonstrated cost-effectiveness relative to PDT-V and SC in all lesion types assuming a \$50,000 threshold. The highest QALY gain was 0.36 relative to SC in OC lesions, while the lowest cost increment was \$826 relative to PDT-V in PC lesions. The ICER for PC lesions was \$4,167/QALY and \$21,857/QALY relative to PDT-V and SC respectively. For MC and OC lesions the ICER was \$37,363/QALY and \$38,151/QALY respectively relative to SC. Results were most sensitive to the estimate of cost of blindness.

Conclusions: Results from this economic analysis demonstrate that ranibizumab offers good value for money compared to the current standard treatments for all wet AMD lesion types.

The Roles of Wnt6 and Wnt4 in Intramembranous Bone Formation

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Objectives: Based on the requirement for epithelium to initiate bone formation in the face and on the epithelial expression of Wnt4 and Wnt6, I hypothesize that Wnt4 and Wnt6 promote the differentiation of intramembranous bone in facial mesenchyme.

Methods: Micromass cultures recapitulate the process of intramembranous bone formation, providing a window to study intramembranous bone formation at isolated stages. Micromass cultures containing mandibular mesenchymal tissue from chicken embryos were incubated for 8 days in a conditioned media containing either Wnt6 or Wnt4 protein. A dilution series using different ratios of conditioned media to regular media was also used to observe the dose-response effects of Wnt6. After the incubation period, the bone was stained with RedFast and Naphthol Blue, and cartilage was stained with Acid Alcian Blue respectfully. Adobe Photoshop was used to quantify the amount of bone and cartilage, as well as total culture size as measured in pixels. ANOVA statistical models were used to analyze the data recorded.

Results: Between stages 20-24, cultures grown in media containing Wnt6 were significantly smaller after the 8 day incubation period when compared to the control. Wnt6 blocks differentiation of bone and cartilage completely at 1:1 to 1:5 dilutions. At 1:8 cartilage recovers more than bone, followed by nearly normal bone at 1:12 dilution. Wnt4 had no effect on differentiation of cartilage and bone. There was also no significant change in total culture size between stages 20-24.

Conclusions: Instead of promoting differentiation, ectodermal Wnt6 in the face may act to inhibit bone and cartilage formation near the epithelium. Wnt4 has no effect on skeletal differentiation or the size of the cultures so this growth factor is less important for facial morphogenesis than Wnt6. In the future antagonizing Wnt6 signalling could help to increase intramembranous bone during wound healing in the face.

Acknowledgements: Funding for this project was provided by UBC Faculty of Dentistry, CIHR Health Professional Student Research Awards, and CIHR grants to JMR.

Diabetes in south Asians: etiology and the complexities of care

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Fifteen to twenty percent of south Asians will develop type 2 diabetes mellitus. This extremely high prevalence of diabetes is seen in both south Asians living in developed countries and in south Asians who are living in either urban or rural south Asia. South Asians have specific diabetic risk factors resulting from a tendency to develop metabolically active abdominal fat, resulting in a poor lipid profile even at a low body mass index. They are also particularly vulnerable to microvascular and macrovascular diabetic complications including renal and cardiac disease. The increased prevalence of diabetes in south Asians is likely due to a combination of biological and cultural factors. Targeting these factors is the only way to provide effective education, prevention, screening, and treatment to south Asians. Culturally focused community programs and interprofessional care teams are two health care paradigms that have been successful in helping them manage this chronic illness. Continuing culturally targeted care and education programs is necessary to reduce the prevalence and complications of diabetes in south Asian communities.

Dynamic Changes in Cranial and Facial Relations during Human Lip Development

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Introduction: Isolated cleft lip, a common human congenital craniofacial malformation, can be caused by deficient or delayed outgrowth of the facial prominences limiting their contact and fusion.

Objectives: The purpose of this study was to analyze spatial and temporal relations between key structures and potential signaling sites in serial sections and 3D models during development of the primary palate (PP; midface, nose and lip).

Methods: Transverse and coronal sections of human embryonic heads were reconstructed with the program “WinSURF” to illustrate relations between cranial and facial structures such as the brain, eyes and optic stalks, nasal pits and olfactory epithelium, the medial nasal prominence (MNP), developing adenohypophysis (AH), diencephalon floor (DF), trigeminal ganglia (TG) and the facial prominences (FP).

Results: During PP formation, lack of definitive boundaries between the face and brain permits close association between facial, cranial base and cranial tissues. In stage 16 and early

17 embryos, the DF lies within the MNP and extends to the roof of the oronasal cavity. In the midline, a large ectoderm thickening (developing AH) is present between the DF and the midbrain. Nasal pits and eyes are laterally positioned and large TG lie immediately behind the eyes. In advanced stage 17 and 18 embryos, the DF is elevated, the MNP narrows and increases in height, and maxillary prominences grow forward to contact the MNP. Closure of the PP must occur while epithelium is capable of fusion and before these growth patterns displace components. Analysis of an embryo with bilateral cleft lip revealed asymmetric and reduced growth of the DF and AH due to presence of a blood clot in the area.

Conclusions: Components of the developing face and developing brain are first closely associated and then separated. During lip formation, abnormal function of signaling sites could delay outgrowth of FPs and delay fusion.

The Effect of Breathing Port Design during Standard Eucapnic Voluntary Hyperpnoea Provocation Challenge

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The eucapnic voluntary hyperpnoea (EVH) challenge is a commonly used test to evaluate airway sensitivity and is designed to stimulate bronchoconstriction by elevating minute ventilation and thus evaporative water loss from the airways.

Purpose: The purpose of this investigation was to test the hypothesis that breathing through a mask rather than a mouthpiece during an EVH challenge would significantly reduce post challenge bronchoconstriction.

Methods: Eight young, physically active subjects with a history of exercise-induced asthma completed two standard EVH challenges in random order: 1) mouthpiece breathing (MO) and 2) mask breathing (MA). Each EVH challenge consisted of 6 minutes of hyperpnoea at a minute ventilation (VE) of 30 x individual baseline forced expiratory volume in one second (FEV1). Spirometry was performed at baseline, 3, 5, 10, 15, and 20 minutes postchallenge.

Results: There were no statistically significant differences in peak post challenge %fall in FEV1 (MO =9.93±8.4%, MA=11.63±10.76%), peak post challenge %fall in maximal forced expiratory flow (FEFmax) (MO=14.21±9.2L/min, MA=15.11±19.05L/min), or mean VE (MO =84.84±22.28L, MA=83.35±19.05L) between conditions.

Conclusions: These findings suggest that an EVH challenge with a mouthpiece and a mask result in similar postchallenge airway responses.

Mapping Dyslexia Susceptibility Genes

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As a specific reading disability with a neurobiological origin, developmental dyslexia is distinct from reading difficulties due to sensory impairments in vision or hearing. The disability is commonly attributed to a core deficit in phonological processing, the understanding of how phonemes, syllables and words are used in a language. Dyslexia is a complex genetic disorder with a strong genetic component; nine susceptibility loci (DYX1-9) have been identified with eight other dyslexia linkages lacking gene symbols also reported.

The statistical methods of linkage and association were employed to investigate the genetic susceptibility for phonological coding dyslexia (PCD), a common form of dyslexia characterized by difficulties in single word decoding and resulting from deficits in phonological processing. A genome-wide non-parametric linkage (NPL) study and four targeted fine-mapping family-based association studies were performed to locate the genes predisposing to PCD in 101 Canadian families with multiple affected members.

The NPL scan identified suggestive evidence for linkage with PCD at the two novel regions 16p12 and 4q12-q13, and provided independent confirmation of linkage to the well-replicated DYX3 locus (at 2p21). Some support for linkage was noted at a further five regions previously linked to dyslexia, while no linkage was detected at five other reportedly-linked regions, in particular, no linkage to DYX2 (6p22.2). Four regions (16p12, 2p21, 4q12-q13 and 6p22.2) were tested for association with PCD in 83 trios, a subset of the 101 families, using the transmission disequilibrium test (TDT) and the affected family-based controls (AFBAC) test. Association was detected in each of the three PCD-linked regions in the NPL scan; none of the tested marker alleles was associated with PCD in the 6p22.2 region. Four candidate genes were identified, two of which belong to the same gene family, with a possible role in the neurodevelopmental mechanisms underlying reading.

Fetal heart rate and Doppler blood flow velocity characteristics in pregnancies associated with SSRI antidepressant therapy compared to control pregnancies

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Introduction: Prenatal exposure to selective serotonin reuptake inhibitor (SSRI) antidepressants may increase risks for persistent pulmonary hypertension and poor neonatal adaptation. Whether there are fetal antecedents to these outcomes remains unclear. This study investigated the impact of prenatal SSRI exposure on third trimester fetal vascular flow/resistance indices and heart rate characteristics.

Methods: At 36 weeks gestation fetal heart rate (FHR) (50 min) (Sonicaid 8002), and Doppler middle cerebral artery (MCA) blood flow velocity waveforms (Aloka 5500) were obtained from SSRI exposed (EXP) (n=14) and non-exposed (NEXP) (n=27) fetuses during a morning (AM) (0800 hrs) and post SSRI dose afternoon (PM) (1230 hrs) (3.2 ± 0.4 hrs after SRI dose) session. Maternal mood was assessed at 36 weeks gestation.

Results: FHR accelerations were significantly less frequent in EXP fetuses compared with NEXP fetuses in AM (11.6 ± 3.8 vs 15.5 ± 5.7) and PM (12.7 ± 3.7 vs 18.3 ± 6.0) sessions. MCA resistance indices (PI, RI and S/D ratio) were significantly lower in the EXP fetuses in the AM, but not in the PM (p<0.05). EXP fetuses had decreased short and long term variation and episodes of high HR variability in the PM compared with the AM sessions (p<0.05). Group differences remained even after controlling for maternal mood.

Conclusion: Prenatal SSRI exposure reduces 3rd trimester FHR variability and MCA resistance or impedance, even when accounting for maternal mood. Acute SSRI pharmacologic and metabolic factors, as well as SSRI-related neurological and vascular alterations remain to be studied.

Cell-based gene therapy for pulmonary hypertension: Application of an established therapy in a neonatal model

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Pulmonary arterial hypertension is characterized by increased pulmonary vascular resistance secondary to a decrease in the caliber and number of pulmonary vascular channels. We hypothesized that the targeted overexpression of an angiogenic factor within the lung would potentially minimize the development and progression of pulmonary arterial hypertension in the animal model by preventing the loss of existing vessels or by inducing the development of new blood vessels within the lung.

We used a cell-based method of gene transfer to the pulmonary microvasculature by delivering syngeneic smooth muscle cells overexpressing vascular endothelial growth factor (VEGF)-A to inbred Fisher 344 rats in which pulmonary hypertension was induced with the pulmonary endothelial toxin monocrotaline. Four weeks after simultaneous endothelial injury and cell-based gene transfer, right ventricular (RV) hypertension and RV and

vascular hypertrophy were significantly decreased in the VEGF-treated animals. Four weeks after gene transfer, the plasmid VEGF transcript was still detectable in the pulmonary tissue of animals injected with VEGF-transfected cells, demonstrating survival of the transfected cells and persistent transgene expression. In addition, delay of cell-based gene transfer until after the development of pulmonary hypertension also resulted in a significant decrease in the progression of RV hypertension and hypertrophy.

These results indicate that cell-based VEGF gene transfer is an effective method of preventing the development and progression of pulmonary hypertension in the monocrotaline model and suggest a potential therapeutic role for angiogenic factors in the therapy of this devastating disease.

P16INK4A Immunoexpression – A Negative Predictive Marker for High-Risk HPV in Oral Precancers

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Studies have shown a strong correlation between high-risk HPVs (HPV-HR) and a subset of head and neck cancer with a better survival outcome. Currently there is no gold standard or “lab friendly” markers for HPV detection in head and neck cancers. Due to the availability and readiness, immunohistochemical detection of p16 has been used widely in pathology laboratories as a surrogate marker for the presence of HPV-HR in cervical cancer and precancers, but not for those at oral and oro-pharyngeal sites.

Objectives: 1) To explore the presence of HPV-HR in precancers of oral and oro-pharyngeal site using chromogenic in-situ hybridization (CISH) and 2) To correlate the presence of p16 and HPV-HR.

Methodology: A total of 205 oral mucosal lesions diagnosed as cancer, precancer, and normal (N=24) were analyzed for HPV-HR (Cocktail for types 16/18/31/33/35/39/45/51/52/56/58/59/68 and HPV16/18) using CISH and p16 using immunohistochemistry (IHC).

Results: Fourteen percent of cases showed the presence of HPV-HR with site predilection (28% soft palate complex vs. 13% anterior mouth, $P < 0.0001$). Half of the HPV-HR cases were positive for HPV16/18. Severe dysplasia/carcinoma in-situ (HGD) samples showed the highest rate (37%) of detection of HPV-HR, compared to 5% of low-grade dysplasia and 10% of invasive cancer. Of these HGD, 57% were located at the soft palate complex. Forty-five (25%) cases showed large patchy or diffuse cytoplasmic overexpression of p16. The sensitivity, specificity, positive predictive value and negative predictive value of using p16 as a surrogate marker for HPV-HR are 0.92, 0.92, 0.66 and 0.99, respectively.

Conclusion: This is the first and largest series of oral tissue

microarrays to detect the presence of HPV in oral dysplasia. The presence of HPV16/18 does not explain those without obvious risk factors in this study set. Patchy or diffuse patterns of p16 immunostaining can provide an easy, negative marker for the presence of HPV-HR.

Diarrhea education through water purification in a northern Himalayan community

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An estimated 3.5 billion episodes of diarrhea cause 1.8 million child deaths annually in the developing world, making diarrhea prevention campaigns essential components of most global health projects. At the Munsel-Ling boarding school in Northern India, we aimed to assess the burden of diarrhea and evaluate the feasibility of a water treatment program. A survey administered to 300 students suggested a disease burden of 5 weeks of diarrhea per 100 person weeks. This finding was supported by similar results obtained from tracking the number of diarrhea cases which presented to our clinic. Water quality analysis was performed with accepted field assays and it was found that the major measures of water quality were within the limits accepted by the Indian government. Microbial analysis, performed using commercially available culture trays and indicators, showed that the major sources of drinking water in the school had an average coliform load of 150/100mL, approximately 15 times the allowable limit. Although a hand washing program developed to reduce transmission increased the number of students washing their hands from 0 to about 500 per day, water disinfection is the best long term solution. Our group has designed and is currently testing a passive bleach injection system that will connect with the water conduction system already in place. Preliminary testing has shown the system to be reliable and we expect to install the system next year. Finally, we suggest that knowledge of water quality and disease burden is essential to developing water treatment and lobbying strategies.

Sharps handling practices among junior surgical residents - a video analysis

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Purpose: This study examines sharps handling practices of junior surgical residents and evaluates whether experience in performing a common surgical procedure correlates with a decrease in unsafe sharps behavior.

Methods Used: Junior residents (2nd year general surgery and 1st year plastic surgery) were videotaped performing indirect inguinal hernia repairs on pediatric patients as part of their technical surgical training during a 2 month rotation. For each procedure, the resident was the principal operator, with the attending surgeon assisting. Technical feedback was given by the attending surgeon to the resident by reviewing the videotape footage with them. A second video was taken of the resident performing the same procedure after the performance feedback session. Residents were not given specific feedback on their sharps handling technique. Assessment of safe and unsafe sharps handling was determined based on the Association of Perioperative Nurses and the American College of Surgeons guidelines. Resident safety performance was assessed in three areas: personal sharps tasks, passage of sharps and verbal notification regarding sharps. For residents with a second procedure video-taped, safety performance was compared between the 2 procedures. Descriptive statistics were employed.

Summary of Results: Data was collected from 19 surgical residents' videos: 4 plastic surgery and 15 general surgery. Residents safely performed sharps tasks, passed sharps and verbally notified about sharps an average of 66.3%, 91.5% and 10.6% of the time respectively. Eight residents had a second hernia repair videotaped. In comparing the second to the initial video, residents demonstrated a 10.5% increase in safe personal sharps tasks, a 3.9% increase in safe passing of sharps and a 16.6% decrease in verbal notification about sharps.

Conclusions: Junior surgical residents video taped performing an indirect inguinal hernia repair most consistently passed sharps safely. Personal sharps tasks were less likely to be performed safely and only a minority of residents verbally notified about sharps placement to the team. Review of the initial technical performance by video did not improve safety behavior for all categories of sharps-related activities.

Does the use of i>clicker increase student engagement in a distributed medical education program?

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Background: Engaging students in large classes, particularly in videoconferencing (VC) environments, is a challenge. i>clicker technology allows students to anonymously respond to questions posed during an educational session. The purpose of the study was to determine first year student opinion on the use of i>clicker technology in a VC environment in the UBC distributed medical program.

Methods: Medical and Dental students at the three distributed

sites utilized i>clicker during the weekly case wrap-up sessions over a 5 week period. In weeks 1, 3, and 5 quantitative data was collected using the i>clicker during the class. Qualitative data was collected by an online survey at the end of the block. Quantitative data was analyzed by a non parametric test to compare differences between sites and the Mann Whitney U test to compare results between the beginning and end of the study.

Results: Implementation of i>clicker technology in a VC environment was complex and intermittent difficulties resulted in some data loss and contributed to student frustration (<6%). Despite this, the use of i>clicker was felt by students to be an engaging teaching tool that improved their understanding (81%) and created focused class discussion (76%). Student opinion remained positive throughout the study (week 1 vs week 5 ($p > 0.05$)). There was no difference in student attitude between the three sites (week 1 ($p > 0.05$)). Students voiced a preference for the use of i>clicker in discussion/review sessions and not for didactic lectures.

Conclusion: i>clicker technology can be a useful tool in promoting student engagement in distributed programs. Technological problems and the session format should be considered when using the i>clicker.

Toll-like receptor 9 involvement in skin wound repair

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Background: Toll-like receptors (TLRs) have been implicated in microbial recognition and wound repair. Mice deficient in MyD88 (downstream adapter molecule common to all TLRs except for TLR3) have been shown to exhibit delayed and decreased skin wound repair. TLR-9 expression in keratinocytes has been found to be up-regulated after skin wounding, and it has been suggested that TLR-9 induces angiogenesis to promote skin wound repair. The involvement of TLR-9 in skin wound repair was examined in vivo.

Methods: Dorsal skin of C57BL/6 control ($n = 8$), MyD88 deficient ($n = 8$) and TLR-9 deficient ($n = 8$) mice was shaved and disinfected with Betadine. Two circular, 4-mm diameter, full-thickness wounds (one on each side of midline) were surgically induced by punch biopsy and covered with a transparent dressing (Tegaderm 3M). Wounds and a calibration scale were photographed using a digital camera for area quantitation (Image Pro 6) every other day over 10 days.

Results: No significant difference in the rate of skin wound closure was observed among the 3 experimental groups. This could be due to the use of small size wounds (4-mm diameter) which contracted rapidly, masking any actual differences in skin wound closure among the groups.

Conclusion: Further experiments that utilize larger size wounds and examine histological events in skin wound repair are needed to confirm the involvement of TLRs. Identification of receptors involved in tissue injury recognition offers potential therapeutic targets for intervention.

Year 3

A Cross-Sectional Survey of Immigrants' Health Care Access in Vancouver General Hospital Area

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Objective: Identification of the demographics of the immigrant and Canadian born population in access to primary health care.

Methods: A random sample of attendees at three community centres and ESL classes was surveyed. Responses were analyzed based on whether they were born in Canada. If not, based on year of arrival in Canada, immigrants were identified either as "recent immigrants" (living in Canada <3 years) or "long term immigrants" (living in Canada >3 years). Descriptive analyses were employed.

Results: Of the 167 responses used for analysis, 64 were recent immigrants; 59 were long-term immigrants. Finally, 44 responders were born in Canada. Recent immigrants reported lowest level of subjective health (3.76/5), while those born in Canada reported the highest level of perceived health (4.41/5). Thirty six percent of recent immigrants reported not having a family physician, citing use of walk-in clinics for accessing health care. In those who did have a family doctor, ability of the physician to speak their first language was crucial (34%). For long-term immigrants (31%) and those born in Canada (54%), level of comfort with the physician drove their choice. In all groups, referral through family or friends was the primary route for finding a family physician. Most patients in all groups were able to find a physician in less than 6 months. Rates of family physician visits in the past year were similar in all groups, although higher proportion of long term immigrants and Canadian born individuals, reported more frequent visits (5-9 times) to their physician (19% and 27% respectively, compared to 8% in recent immigrant population).

Conclusion: In our survey, recent immigrants reported having lower level of subjective health. Moreover, higher percentage did not have a family physician. On average fewer visits to a physician's office was noted in the population, although the statistical significance of these findings are unknown. It is hoped that our survey findings will guide future research in this field.

Mass Gathering Medicine Registry

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Introduction: Extensive medical planning is required for mass gathering events conducted throughout the world. At this current time, limited prospective research exists in the literature to guide medical planning. Our study aims to prospectively and retrospectively capture patient and event data at mass gathering events in British Columbia with the goal to derive evidence-based standards for planning and patient care.

Methods: A confidential, de-identified patient registry for mass gatherings using both retrospective and prospective data has been established. Patient information is collected using standardized encounter forms. Event and medical response capacity is collected using web-based survey tools and a semi-structured interview.

Individual patient encounters and individual "mass gathering events" are the units of analysis. Patient presentation rate (PPR), medical transfer rate (MTR) and ambulance transfer rate (ATR) will be calculated for each event, consistent with the existing literature. Multiple linear regression will be used to develop a prediction model with the dependent variable being the number of medical encounters or the number of transfers to hospital (separate models). Predictors (independent variables) will be the various patient and event characteristics recorded.

Results: By March 30, 2010, some data from 34 event days between LiveCity Yaletown and Downtown sites during the Vancouver 2010 Winter Olympics, in addition to 6 event days during the Paralympics will be analyzed.

Conclusions: The creation of a mass gathering medical registry immediately gives the ability to report PPR, MTR, and ATR for each event, and allows comparison between events. By cross referencing characteristics of different types of events (musical, athletic, multi-day, etc.) against the patterns of injuries and illnesses reported, recommendations for planning of facilities, personnel, equipment and policies will be derived. The Registry will provide us with the data to prospectively derive and subsequently validate evidence-based guidelines for minimum standards for planning and patient care at mass gathering events, which may ultimately decrease the medical transfer rate.

Prognosis associated with monosomies in complex AML karyotypes

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Introduction: Cytogenetic abnormalities have been reported in a wide range of cancers. More specifically, in acute myeloid leukemia (AML), they play an important role in the diagnosis, prognosis and follow-up of patients. Grimwade et al. have identified three prognostic groups: favourable (t(8;21), t(15;17), and inv(16)), intermediate (normal, abnormal 11q23, +8, +21, +22, del(9q), del(7q) and all other abnormalities) and adverse

(monosomy 5, monosomy 7, del(5q), abnormal 3q, and complex karyotypes). The poor disease outcome of patients with complex karyotypes have been described in many studies, but a recent study Breems et al. (2008) addressed the contribution of the different components of complex karyotypes and reported a poor prognosis in patients with any type of autosomal monosomy, and an even poorer prognosis of karyotypes with at least two autosomal monosomies or a single monosomy plus one or more structural cytogenetic abnormalities.

Methods: The initial cytogenetic reports of patients with AML between January 1, 1983 and June 30, 2005 were reviewed. The study determined the median and mean survival of patients based on the prognostic groups defined above. The same parameters were evaluated again for two different age groups (patients < 60 years old at diagnosis vs. patients >60 years old at diagnosis). Overall survival was calculated at 4 years for all patients and then for the different age groups. Median and mean survival was the calculated on patients with one or more monosomies.

Results: When dividing AML into the previously identified favourable, intermediate and adverse prognostic groups, the results are in keeping with previous reports: patients with “good prognosis” karyotypes have higher mean and median survivals and patients in the “poor prognosis” group demonstrate lower mean and median survivals. In this group, the lowest survival was observed for patients with monosomy 5.

Does Pre-biopsy Contrast Enema Delay the Diagnosis of Long Segment Hirschsprung’s Disease?

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Background/Purpose: The diagnosis of long segment Hirschsprung’s disease (LSHD) is frequently delayed. Our purpose was to: 1) evaluate utility of contrast enema (CE) by comparing LSHD patients managed with/without pre-biopsy CE, 2) summarize CE findings in patients with LSHD patients, and 3) evaluate the impact of initial CE reports on outcome.

Methods: All LSHD cases (transition zone {TZ} proximal to splenic flexure) treated between 1984 and 2009 were stratified by whether a pre-biopsy CE was done (Group 1), or not (Group 2). Group comparisons included elapsed days from admission to diagnostic rectal biopsy, first operation, and initial length of hospital stay (LOS). CEs were reviewed by a single pediatric radiologist, and the original reports were categorized as “helpful”, “non-specific”, or “misleading”.

Results: 29 patients (16 -Group 1; 13 -Group 2) were identified. Group 1 patients experienced a significant delay in time to biopsy ($p=0.047$), first operation ($p=0.005$), and showed a trend towards prolonged LOS. CE review revealed TZ in 7/16 (44%); and of these, 6 (86%) underestimated actual aganglionic segment length. 6/16 (38%) original CE reports were “misleading” and

those patients showed a trend towards a delay in rectal biopsy and experienced significantly longer lengths of stay. There was a significantly higher proportion of patients with small bowel aganglionosis in the group with misleading reports.

Conclusions: Pre-biopsy CE offers little to the diagnosis of LSHD and likely contributes to diagnosis/treatment delays. Even if a TZ is recognized in biopsy proven HD, the predicted aganglionic segment length should not guide operative planning.

A Web-based tool for family-initiated adverse event reporting: an end-user investigation of usability and reliability

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Objectives: To assess the usability and reliability of a web-based adverse event reporting tool designed for families of children admitted to hospital.

Introduction: Usability is a strong predictor of adoption of a new technology, and reliability is essential when making decisions based on information. Family reports of adverse events have been shown to be reliable and able to identify events not reported by health care providers. Through an iterative design process using previous publications, expert opinion, and family feedback, a web-based tool to allow families to report adverse events was developed.

Methods: Following Institutional Review board approval, 25 parents of pediatric patients consented to participate. Sample size was determined by qualitative needs and not statistical significance. Fifteen families used the web based tool to report on their child’s hospital stay and completed a validated usability questionnaire. Ten parents used the adverse event reporting tool to report 6 fictional adverse event scenarios, from which reliability was assessed.

Results: Average usability was 2.1 on a 7-point scale (1 = maximum, 7 = minimum score). High usability scores (<2.0) were achieved for simplicity, learnability, productivity, and understandability. However, only moderate usability scores (2.0-2.5) for ease of use, comfort, effectiveness, and recoverability were obtained, with lower usability scores (>2.5) for on-screen messages and likeability of using the tool. Examples of elements that were given low and high usability scores will be provided. Parents showed acceptable (80.2%), but imperfect reliability in classifying scenarios.

Conclusion: Good usability scores predict that parents will use the tool to report adverse events that occur in hospital, and acceptable reliability implies that the system will be acceptable to safety analysts.

The Effectiveness of Standard Pediatric Daycare Surgery Discharge Communication: A Quality Improvement Gap Analysis

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Background: The period after a patient is discharged from hospital is potentially dangerous. Post-discharge adverse events occur in approximately one in five patients within thirty days after discharge (*Jt Comm J Qual Patient Saf.* 2008;34(2):85-97). Communication failures are at the root of a significant fraction of adverse events (*Jt Comm J Qual Patient Saf.* 2008; 34(10):563-70). Understanding how to improve discharge communication to parents presents an opportunity to improve patient safety.

Methods: Survey development was performed using focus groups and safety domain modeling. The development included clinical sensibility and face validity testing. The survey was administered by telephone 24-72 hours after discharge from hospital. Results were analyzed according to percent problematic response rates in each safety domain.

Findings: Clinical sensibility and face validity results met acceptability criteria (*CMAJ.* 2008;179(3):245-52). Problematic responses indicating poor understanding of patient safety were frequent when parents answered questions about medication safety (52% problematic), surgical wound care (34% problematic), nausea and vomiting (34% problematic), quality of communication (15% problematic), and safety culture (6% problematic). Communication to parents may be improved by analyzing the discharge process via a theoretical model. Using this model, problematic responses can be classified as gaps in: institutional awareness of needed communication, communication content, communication form and gaps in safety culture. Special attention is warranted in improving communication for parents using post-discharge medications, the most problematic domain.

Conclusion: Patient safety may be enhanced by redesign of the hospital discharge process. Redesign should proceed according to the gaps identified in each of the communication model components. Emphasis should be placed on reducing problematic responses in the medication safety domain.

Identification of conditioning film components on indwelling ureteral stents and their role in bacterial adhesion

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Introduction & Objectives: A common problem with indwelling ureteral stents is adhesion of bacteria to the device surface. We believe that urinary proteins within a conditioning film form anchor points to which bacteria adhere. We sought to identify these proteins.

Methods: Polaris stents (Boston Scientific) and InLay stents (Bard) removed from patients were analyzed for adherent proteins. Stent biofilms were scraped using a sterile scalpel blade and re-suspended in protein solubilization buffer (7M urea, 2M thiourea, 25mM triethylammonium bicarbonate, 0.2% CHAPS and 0.2% SDS). Total protein was determined for each sample via Bradford Assay and 15µg were run on a 12% SDS-Polyacrylamide gel. Protein was extracted from gel pieces via gel trypsin digestion and analyzed using Quadrupole Time of Flight Mass Spectrometry.

Results: In total, 116 and 99 unique proteins were identified on the Polaris (n=24) and InLay (n=20) stents, respectively. The most common proteins found on both stents were the following, along with the percentage of stents containing them (InLay and Polaris respectively): Cytokeratin 1 90% , 91%; Serum Albumin 85% , 91%; Hemoglobin subunit beta 80% , 62%; Uromodulin 80%, 42%; Fibrinogen (gamma chain) 75%, 42%; Cytokeratin 10 75%, 66%; Cytokeratin 9 75%, 62%; Cytokeratin 2 70%, 75%; Protein S100A9 60%, 42%; Fibrinogen (alpha chain) 55%, 33%; Fibrinogen (beta chain) 55%, 46%; Hemoglobin (subunit alpha) 50%, 58%; Cytokeratin 19 40%, 50%; Vitronectin 40%, 42%; Apolipoprotein 35%, 17%; Cytokeratin 13 25%, 46%; Cytokeratin 8 25%, 46% and Cytokeratin 7 20%, 42%. Significantly less Polaris stents were found to contain Uromodulin (p=0.002) and Fibrinogen gamma chain (p=0.026) than InLay stents, while no significant differences were found for the remaining protein.

Conclusions: The majority of conditioning film components do not differ between different stents or between patients with the same stent type. Uromodulin normally inhibits bacterial colonization and calcium oxalate crystal formation by binding bacteria and calcium, but in this scenario, it may facilitate stent associated infection and encrustation. Furthermore, the presence of calcium binding proteins such as S100A9 may serve as a nidus for stent encrustation. Of the fifteen most commonly found proteins, the majority are known binding sites for bacteria. We believe that the key to preventing bacterial adhesion and biofilm formation to ureteral devices is preventing the deposition of these bacterial-anchoring proteins. We have taken the first step in identifying these protein.

The Learning Curve for Endoscopic Transsphenoidal Resection of Pituitary Tumors

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Background: The learning curve for acquiring surgical skills has important implications in the incorporation of new procedures, resident training, and surgical innovation. In this study, the learning curve for the endoscopic resection of pituitary tumors was determined by measuring patient outcomes with respect to complication rates.

Methods: Retrospective data on 120 consecutive patients treated by the same senior surgeon between October 2005 and November 2009 was collected and divided into four equal groups based on surgery date. Demographic information, surgery date, complications, length of stay (LOS), and length of follow-up were all noted.

Results: In the first group, 10 patients had CSF leaks (33%), 9 required lumbar drains (30%), and the average LOS was 4.1 days. In the second group, 3 patients had CSF leaks (10%), 1 required a lumbar drain (3%), and the average LOS was 3.6 days. In the last group, 2 patients had CSF leaks (7%), 2 required lumbar drains (7%), and the average length of stay was 3.1 days.

Conclusion: The number of CSF leaks and lumbar drain insertions decreased after the first 30 patients. The total number of complications decreased over the course of the four groups and the LOS declined over successive cases.

Development of urology-based PBL cases: leveling the learning field in UBC's distributed medical program

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The University of British Columbia (UBC) has expanded its medical undergraduate program to include primary clinical training at three sites across the province. As such, not all 256 students have the opportunity to experience a urology rotation. With an aim to promote equivalent learning experiences at all three sites, the department of Urologic Sciences has produced over 50 online problem-based learning (PBL) cases in the past three years. These cases also serve to ease the transition from pre-clinical medical school education to clerkship years, where the focus shifts from knowledge acquisition to knowledge integration. The PBL cases, written by medical students with supervision from faculty members, are based on real cases that represent a variety of urologic issues. They review clinical presentations, management plans and include quizzes that test learning objectives. The cases are published on the Diagnosis X server in conjunction with

McGill University and the Molson Medical Informatics Institute. The cases were successfully published online, creating an easily accessible resource for learners in the distributed medical program. In April 2008, FERGU block of 1st year medical curriculum, was augmented with 4 PBL online cases as supplemental material. Approximately 35% of the class accessed the cases and 40% of those individuals reported that they enhanced their understanding of the clinical approaches to urologic problems. In 2009, 24% of students completed the same survey at the end of the block with 41% saying the cases had a positive impact on their learning.

These online resources enable learners to improve their urologic knowledge and work through interesting cases that they may not be exposed to in their clinical training. Hopefully, this improves the equality of medical education in a large undergraduate class spread across BC. These resources also ease the transition from pre-clinical medical school years to clerkship years, as they expose learners to the practical management of real cases. There are future plans to further integrate Diagnosis X as a supplemental resource in FERGU while continuing to improve and enhance the diversity of the online cases. This integration will provide a valuable learning resource to medical professionals at all levels.

A novel online video learning resource to enhance urology medical education

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In order to meet growing healthcare demands in the province, the University of British Columbia (UBC) launched a distributed medical education program in 2004. This initiative doubled the undergraduate class size to 256 students while providing clinical training opportunities across the province. However, with the increased number of students, opportunities to complete a urology rotation during clerkship years have been significantly reduced. As a result, many students lack exposure to key urological procedures in the operative setting. Recently, the UBC Department of Urological Sciences, in partnership with the Office of Pediatric Surgical Excellence and Innovation, developed a novel online video educational resource to help increase medical students exposure to and understanding of key urological procedures without the restraints of teaching within the operative setting.

A team of UBC medical students was recruited to produce educational videos as a summer project under the guidance of Urology residents and faculty. Key urological procedures were identified and after patient consent was obtained, the procedures were recorded using an HD camcorder and direct endoscopic video. Each video was edited to last 6 to 8 minutes with the goal of highlighting the materials used, identifying the important anatomical landmarks, explaining the key surgical steps and discussing the indications, contraindications and potential

complications of each procedure. The videos were then published onto a secure external server to allow students from all distributed sites access to the videos at any time.

Ten videos that met the above criteria were produced and published online. These include ureteroscopy, cystoscopy, suprapubic catheterization, female catheterization, varicocele repair, circumcision, pyeloplasty, bilateral hydrocele repair, laparoscopic partial nephrectomy, and robotic-assisted radical prostatectomy. Furthermore, interest in the project from other specialties resulted in the production of Ten non-urological videos.

In conclusion, the collaboration between students and urology faculty can result in the successful production of educational videos outlining key urological procedures. Future plans include the continued expansion of the project, the formation of an educational synergy between each video to online Problem Based Learning urology cases developed at UBC, and the completion of a study to identify the usefulness of online video in medical education.

Natural History of Arachnoid Cysts in Pediatric Population

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Introduction: Pediatric arachnoid cysts can be diagnosed as an incidental finding in head imaging studies. The literature provides little to guide decision making regarding need for follow-up. Given the limited natural history studies for this condition, the current study aims to examine growth patterns over time, and to identify any factors that are associated with cyst growth.

Methods: A retrospective chart review of pediatric patients with a diagnosis of intracranial arachnoid cyst was performed, selecting patients who did not initially undergo surgical intervention. Using radiological reports on serial images, we determined whether asymptomatic arachnoid cysts in this population of patients change in size over time.

Results: 53 asymptomatic non-operated intracranial arachnoid cysts were identified. The majority of arachnoid cysts did not grow (n=40, 75%) on serial imaging, while 20% (n=10) increased in size and 6% (n=3) decreased. In patients diagnosed under 1 year of age, 9/18 showed growth of the cyst, while only 1/34 patients diagnosed over 1 year of age showed growth of the cyst (p<0.0001). The location and initial size of the cyst did not appear to correlate with cyst growth.

Conclusions: Age at diagnosis correlated with growth of the arachnoid cyst, with children diagnosed under one year of age having a high probability of growth. It may be that close serial imaging is justified in the younger child diagnosed with an asymptomatic arachnoid cyst, while less frequent imaging is indicated in the older child.

Matrix metalloproteinase-12 (MMP-12) may be a binding partner of NFκB

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Introduction: MMP-12 is well known for its ability to cleave extracellular substrate, but intracellular functions have never before been characterized. The function of the 35kDa nuclear MMP-12 active form is, as yet, unknown. The 35kDa MMP-12 activity may be related to anti-viral immunity as the presence of MMP-12 within the nucleus increases during viral infection. We have shown that MMP-12 binds the IκBα promoter, but whether it is acting alone or in conjunction with another transcription factor as part of a complex is unclear. NFκB is the best-characterized transcription factor responsible for expression of the IκBα promoter. In this study, we are investigating whether MMP-12 is interacting with NFκB as parts of a complex within a cell.

Methods: Sham-infected and respiratory syncytial virus infected HeLa cells are incubated for one hour then lysed. Positive control samples are collected at this time. The cellular contents are then immunoprecipitated with one of the following antibodies: mouse anti-NFκB; mouse anti-MMP-12; rabbit anti-NFκB; and rabbit anti-MMP-12. The immunoprecipitate products and the controls are analyzed via immunoblotting. The immunoblotting primary antibody is one of the four listed above and the secondary antibody is goat anti-rabbit or goat anti-mouse. The samples are imaged with ChemiGenius using the imaging reagent Super Signal West Femto Maximum Sensitivity Substrate by VectaStain.

Results: The nuclear 35kDa form of MMP-12 can be detected following immunoprecipitation of NFκB with a rabbit polyclonal anti-NFκB followed by immunoblotting with mouse anti-MMP-12 as the primary antibody.

Conclusions: Preliminary results suggest that MMP-12 is interacting with NFκB during viral infection. This might suggest that MMP-12 is acting with NFκB or that MMP-12 is using NFκB to gain access to the nucleus. This will have to be confirmed with further controls before any conclusions can be drawn.

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Schizophrenia patients show differences in activity of neural systems underlying associative memory encoding

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We sought to reveal functionally connected neural networks mediating associative memory encoding, and examine differences between schizophrenia patients and control subjects.

While undergoing functional magnetic resonance imaging, 26 schizophrenia patients and 26 control subjects completed 90 association tasks (i.e., they were provided a cue word, and were required to choose the more strongly associated of two companion words). Following scanning, subjects were asked to free-recall and cue-recall the word pairs viewed in the scanner. Using constrained principal component analysis with a finite impulse response basis set, three statistically significant components of neural activity emerged. Component 1 involved activity in left inferior parietal lobe, left superior temporal gyrus, bilateral visual cortices and dorsal anterior cingulate cortex (dACC). Component 2 showed activity in dACC/supplementary motor area, visual cortices, and left premotor cortex. Component 3 showed deactivation in medial prefrontal cortices and posterior cingulate/precuneus. For all components, encoding words that were later not recalled was associated with higher activation or deactivation than encoding free- or cue-recalled words; and encoding cue-recalled words showed higher activation or deactivation than encoding free-recalled words. For components 1 and 3, schizophrenia patients exhibited less activation or deactivation than control subjects when encoding cue-recalled words ($p < .05$). Greater activity when encoding non-recalled words, or those only recalled when cued, may reflect increased difficulty or interference at the encoding stage. The differences in activity of these components observed in schizophrenia patients may help elucidate the variations in associative memory function thought to underlie many characteristic features of this disease.

Are the Eyes the Windows to the Human Soul? Gaze Direction Study and its Effects on Attentional Orienting and Crossmodal Target Responses

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Objective: Human beings are highly social creatures who use verbal and body language to communicate. Eye contact is a powerful means of communication. The following 7 experiments attempt to determine the degree in which the eyes illicit reflexive responses in human senses from visual, auditory, and tactile responses; and hopes to answer the age-old question of whether the eyes are the windows to the soul.

Methodology: A schematic face was shown on a computer screen, with eyes that were either spatially informative (looked towards the target) or spatially uninformative (looked in the opposite direction of the target). Participants were instructed to press either the left or right button depending on where they thought the visual target appeared. To measure the effect of eye-gaze on auditory attention, sound, rather than a visual target, was used as the target. Again, the participants were asked to input where they thought the sound originated (left or right). To measure tactile response, the schematic face was replaced by 4 dots that flashed on the left or right of the screen. Participants were again asked to input on the response pad where they thought the sound originated (left or right). Response

times and accuracy were measured for all the experiments.

Results: Eye-gaze cuing produced a shift in visual attention, as supported by faster response times in the valid trials (when the eyes pointed towards the visual cues) than in the invalid trials (when the eyes did not point towards the visual cues) with a $p < 0.005$. No effect of validity or facilitated response times were seen in the experiments that used auditory targets instead of visual targets. A significant crossmodal orienting effect ($p < 0.005$) was seen when the schematic face was replaced with peripheral cues.

Conclusions: Eye-gaze orienting triggers a genuine shift in visual reflexive attention, as seen in the results of Experiment 1. Eye-gaze orienting does not result in shifts of auditory attention, as supported by 6 experiments using different target types. Crossmodal reflexive orienting was observed when peripheral cues are used instead of eye-gaze cues, as supported by the results in Experiment 6.

Blood pressure lowering efficacy of reserpine for primary hypertension

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Purpose: To investigate the dose-related effect of reserpine on blood pressure, heart rate and withdrawals due to adverse events. **Methods:** Systematic review of randomized controlled trials comparing reserpine to placebo in patients with primary hypertension. The databases CENTRAL, EMBASE, and MEDLINE were searched. We also traced citations in the reference sections of the retrieved studies.

Results: Of 242 studies, 4 trials met our inclusion criteria and were analyzed quantitatively. The results of this systematic review indicate that reserpine has a statistically significant hypotensive effect on systolic blood pressure as first-line agent (weighted mean difference -7.92, 95%CI -14.05, -1.78). It also lowers diastolic blood pressure (-4.15, 95% CI -9.19, 0.90), mean arterial pressure (-7.87, 95% CI -16.86, 1.11) and heart rate (-5.70, 95% CI -21.74, 10.34) but these results were not statistically significant. Rauwiloid, an alternative Rauwolfia serpentina alkaloid to reserpine, seemed to reduce diastolic blood pressure (-10.00, 95% CI -14.44, -5.56) and heart rate (-6.00, 95% CI 9.84, -2.16) with statistical significance. Withdrawals due to adverse effects were not reported in the included trials and as such could not be quantified. The dose-response data are weak and trials with more inclusive dosage range are lacking. As well, parallel placebo controlled data on the various Rauwolfia serpentina alkaloids and the whole root are also lacking to draw conclusive evidence.

Conclusions: The evidence shows that reserpine monotherapy is effective in reducing systolic blood pressure in primary hypertension. It also lowers diastolic blood pressure, mean arterial pressure and heart rate, but these results were not statistically significant compared to its systolic blood pressure lowering effect. However, we could not make definite conclusions as the sample size from these randomized controlled trials was small. For the same reason, a dose-response pattern could not be established.

A Sustainable, Community-driven Approach to Treating Anemia in the Indian Himalayas

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Since 2006, University of British Columbia Global Health Initiative has sent teams of medical, dental, nutritional science and engineering students to improve student health at Munselling boarding school in the Spiti Valley in rural Northern India. Annual hemoglobin screens since 2007 demonstrate that anemia remains an ongoing health issue. Childhood anemia is associated with poor health and impaired cognitive development, as well as reduced school achievement and work productivity in adulthood. Here we present a multifactorial approach to reduce the burden of this disease.

In 2007, 88.4% of students were anemic (mean Hb=130.4 g/L, n=379), decreasing to 78.9% in 2008 (mean Hb=134.6 g/L, n=382) and further decreasing to 71.2% in 2009 (mean Hb=141.1 g/L, n=413). Previous blood smear testing identifies a mixed, multifactorial cause. Accordingly, our approach to anemia includes: 1) Dietary analysis for nutritional deficiencies. 2) Improving general student health through dental care, deworming treatment, building infrastructure for sanitation, hygiene and water purification, along with education on nutrition, handwashing, basic personal hygiene and toothbrushing. 3) As iron deficiency is a common contributor to anemia, iron supplementation and increasing consumption of iron-rich green leafy vegetables through the construction of solar-powered greenhouses. Spiti Valley is isolated 7 months of the year due to snow-covered mountain passes, making year-long access to fresh vegetables difficult, but a greenhouse can provide vegetables for 10 months of the year. The decreasing prevalence of anemia shows that the various factors contributing to this disorder were diminished while maintaining a sustainable and community-driven approach.

Development of a Realtime Intraoperative Electrical Impedance Tomography Sensor for Cavernous Nerve Mapping for Radical Prostatectomy

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Introduction and Objective: Radical prostatectomy is a proven efficacious treatment locally confined prostate cancer, however

rates of post operative impotency continue to range between 10-30% in contemporary series. Thus, in addition to satisfactory cancer control, accurate localization of the cavernous nerves and the contributing plexus during resection is exceedingly important during radical prostatectomy. We have developed a realtime, intraoperative tissue impedance sensor for nerve localization based on electrical impedance tomography (EIT) technology, which will serve to reduce post prostatectomy impotence.

Methods: The prototype constructed consists of a probe with a needle array to interface with the tissue, and a signal generator and analysis system. The device cycles through each set of electrodes on the probe, and injects current while simultaneously computing the voltage change. Reconstruction algorithms determine nerve location based on tissue impedance properties.

The system was functionally validated in an in vitro model system and following further refinement, rat sciatic nerve identification. For each trial, the probe was placed on the tissue and the device sequentially injected 5mA sinusoidal current across each of its electrodes with the resulting voltages recorded.

Results: Each trial demonstrated the ability of the device to detect changes in impedance of different tissues. Electrodes closest to the wire in the in vitro model had the smallest voltage change, corresponding to a lower impedance value. $V=0.135V$ for the electrodes near the wire, compared to $V=0.256V$ for other electrodes. Localization of rat sciatic nerve was also successful demonstrating $V=0.294V$ for the electrodes near the nerve, compared to $V=0.467V$ for the remaining electrodes.

Conclusions: We have developed a realtime intraoperative tissue sensor prototype based on electrical impedance tomography which has demonstrated early proof of principle success in in vitro and small animal models of mixed tissue determination and nerve localization. With further refinements in both probe array fabrication and miniaturization as well as digital signal processing we believe this device may deliver significant benefit to procedures such as radical prostatectomy where nerve structures may be visually indeterminate but critical for preservation of function.

Comparing Complications of 952 Percutaneous Nephrolithotomies From a Single Centre

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Introduction: Urinary stone disease is a common problem, and more than 50% of stones require surgical intervention. Percutaneous nephrolithotomy (PCNL) and ureteroscopy have made it possible to treat stones without open surgery. PCNL is a minimally invasive procedure involving placement of a tract into the kidney through which instruments are inserted to disintegrate and remove renal stones.⁵⁻⁷ The Vancouver General Hospital Stone Center was opened in the fall of 2008, with dedicated staff and facility for performing PCNL. We analyzed and compared

the PCNL procedures performed prior to and after opening of the Stone Center.

Methods: 952 PCNL cases were analyzed retrospectively. Of these, 750 cases were done prior to opening of the Stone Center, from 2000 - July 2008, representing the first group. The second group had 202 cases and were done in the period from October 2008 - December 2009. Different complications including bleeding, pulmonary, cardiovascular, genitourinary, infection, and need for readmission to ER post-procedure, were compared and analyzed between the two groups.

Results: Records for 952 patients were available for analysis. The data was analyzed using INSTAT (Prism) statistical program using the p-value (significance: $p < 0.05$), odds ratio (OR), and 95% confidence interval (CI). The results showed that the major complication rate was lower in the second group (1% vs 8%, Stone Center vs prior to Stone Center, respectively; $p < 0.05$, OR=2.795, CI(95): 1.184 to 6.598) as well as bleeding rates (1% vs 10%; $p < 0.01$, OR=2.160, CI(95): 1.184 to 3.940), transfusion rates (0.5% vs 6%; $p < 0.001$, OR=129.25, CI(95): 17.501 to 954.54), and pulmonary complications (1% vs 6%, $p < 0.01$, OR=17.646, CI: 7.166 to 43.455). There was no practical difference between the stone free rates for the two groups. Infection rate, GU complications, readmission to emergency, and minor or no complications were not statistically different between the two groups.

Conclusion: At our institution, with a dedicated Stone Center unit, the complication rates fell significantly. Studies show that as centers gain more experience, complication rates tend to decrease. The use of dedicated staff and facilities allows for increased proficiency and competency in performing PCNL, which will continue to lower complication rates. The limitation of this analysis is that there was more data collected in the first group than the second group. We need to continue with data collection from the Stone Center to see if this will reveal other significant differences and improvements.

Year 4

Tuberculosis Management at the University Hospital of Northern British Columbia: A Retrospective Review 2001-2009

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Introduction: Mycobacterium tuberculosis infections remain a major cause of global morbidity and mortality. In Canada, British Columbia continues to have an above national average prevalence of tuberculosis infections. This retrospective review looks at the epidemiology of tuberculosis cases at the University Hospital of Northern British Columbia in Prince George (UHNBC).

Methods: A record review was conducted on all patients with a suspected or confirmed diagnosis of tuberculosis while in the UHNBC between the years of 2001 and 2009, inclusive.

Results: 25 cases of tuberculosis infection were identified, averaging 2.77 cases per year (annual rate of 0.91 per 100,000 population). 20 cases (80%) were male with a mean age of 52 years (SD = 15), female mean age was 51 (SD = 27). 22 cases (88%) were residents of northern British Columbia, 17 (68%) resided in Prince George. 14 cases (56%) had documented Aboriginal status. Hepatitis C infection was the most common comorbidity (44%). Respiratory symptoms were the most common presenting complaint (56%) followed by constitutional symptoms (40%). 18 cases (72%) were respiratory tuberculosis. The mean time to diagnosis was 5.61 days (SD = 8.57). 19 cases (76%) were placed in isolation with a mean times to isolation and in isolation of 5.25 days (SD = 9.10) and 20.74 days (SD = 21.09), respectively. Diagnosis was made by sputum culture in 15 cases (60%). A single isolate exhibited resistance to streptomycin and isoniazid. 16 patients were discharged to community care, 4 were transferred, 2 were readmitted for tuberculosis, 1 died, 1 left against medical advice and 1 remained in hospital at the conclusion of this data set.

Conclusion: Tuberculosis infection rates in British Columbia and the Northern Health Regions remain above national and provincial averages, respectively. The demographic trends of cases seen at UHNBC largely correspond with available provincial statistics. Although our hospital only diagnosed and primarily treated a fraction of the total cases in the Northern Health Regions these cases required substantial inpatient and isolation hospital days. This record review highlights the diverse manifestations of tuberculosis and the need for diagnostic vigilance to ensure safe and effective case management.

The Situation Creates the Action: Experiences of Earthquake Relief and Medical Care in Haiti

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A devastating earthquake struck Haiti on January 12, 2010, resulting in the death of over 200 000 people and displacement of millions more. A myriad of organizations have responded to the disaster and suffering that it has caused. This poster describes the experiences of Maxo Luma, a Vancouver-based physician from Haiti and Pouya Rezazadeh-Azar, a fourth year UBC medical student, both of whom provided medical care in Port-au-Prince in the month after the earthquake. The authors describe conditions on the ground, cases they encountered, and the plans of their respective organisations for ongoing work in the country. The authors also reflect on lessons learned and the significance of the earthquake as a pivotal moment in history for the revitalization of public health and improvement of the social determinants of health in Haiti.

High prevalence of childhood emotional, physical and sexual trauma in a cohort of HIV-seropositive illicit drug users

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Background: The psychosocial impacts of various types of childhood maltreatment on vulnerable illicit drug-using populations remains unclear. We examined the prevalence and correlates of antecedent emotional, physical and sexual abuse among a community-recruited cohort of adult HIV-seropositive illicit drug users.

Methods: We estimated the prevalence of childhood abuse at baseline using data from the Childhood Trauma Questionnaire, a 28-item validated instrument used to retrospectively assess childhood maltreatment. Multivariate modeling was used to estimate relationships between sub-types of childhood maltreatment with various social-demographic, drug-using and clinical characteristics.

Results: Overall, 233 HIV-positive injection drug users were included in the analysis, including 83 (35.6%) women. Of these, moderate or severe emotional childhood abuse was reported by 51.9% of participants; emotional neglect in 36.9%; physical abuse in 51.1%; physical neglect in 46.8%; and sexual abuse in 41.6%. Using multivariate models, emotional, physical and

sexual abuse were independently associated with greater odds of recent incarceration. Emotional abuse and neglect were independently associated with a score of ≥ 16 on the Centre for Epidemiologic Studies Depression Scale (CES-D). There was no association between any form of childhood maltreatment and clinical HIV variables including viral load, CD4 count and history of antiretroviral therapy use.

Conclusion: Given the substantial prevalence of childhood maltreatment among this population there is a need for evidence-based resources to address the deleterious effect it has on the social determinants of health. Of particular importance appears to be the need to provide support for those who have suffered from childhood emotional abuse which is significantly associated with both incarceration and depression in later life.

MD/PhD

Impaired neuronal structure and function in the dentate gyrus of a mouse model of Fragile X syndrome

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Fragile X syndrome (FXS) is the most common form of inherited intellectual disability. It is caused by transcriptional repression of the *Fmr1* gene. Surprisingly, a clear link between behaviors indicative of intellectual disability and neuronal abnormalities has been elusive in the mouse model of FXS (*Fmr1* knockout (KO) mice). Here we show that the dentate gyrus (DG) subregion of the hippocampus in the mammalian brain may be particularly affected by transcriptional repression of the *Fmr1* gene. We report abnormalities in the morphology of neurons in the DG as well as impairments in the degree of synaptic plasticity that these cells exhibit. Finally, we show that learning and memory dependent on the DG is impaired in *Fmr1* KO mice. These data implicate impaired neuronal structure and function in the DG in the pathophysiology of intellectual disability in FXS.

Electrostatics in the Stability and Misfolding of the Prion Protein

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Using a recently developed mesoscopic theory of protein dielectrics, we have calculated the salt bridge energies, total residue electrostatic potential energies, and transfer energies into a low dielectric amyloid-like phase for 12 species and mutants of the prion protein. Salt bridges and self energies play key roles in stabilizing secondary and tertiary structural elements of the prion protein. The total electrostatic potential energy of each residue was found to be invariably stabilizing. Residues frequently found to be mutated in familial prion disease were among those with the largest electrostatic energies. The large barrier to charged group desolvation imposes regional constraints on involvement of the prion protein in an amyloid aggregate, resulting in an electrostatic amyloid recruitment profile that favours regions of sequence between alpha helix 1 and beta strand 2, the middles of helices 2 and 3, and the region N-terminal to alpha helix 1. We found that the stabilization due to salt bridges is minimal among the proteins studied for disease-susceptible human mutants of prion protein.

Immunomodulatory peptides attenuate local and systemic inflammation in a murine DSS-colitis model

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Innate defence regulator (IDR) peptides are synthetic derivatives of endogenous host defence peptides (HDPs), 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. We hypothesized that IDRs might be efficacious in attenuating inflammation in a murine DSS colitis model, given that dysfunctional innate immune responses to gut microflora are believed to drive the etiopathogenesis of IBD. Two peptides, IDR-1002 and IDR-1018, were selected for their ability to modulate PBMC cytokine production, and enhance clearance of *Staphylococcus aureus* and *Escherichia coli* in murine infection models. Using a standard model of DSS-colitis, colonic inflammation was induced by daily addition of 2.75% DSS (w/v) to the drinking water C57BL/6 mice. Mice were randomized to receive IDR-1002 (IP) or IDR-1018 (IV or IP). Weights were recorded daily, and serum was collected for ELISA quantification of Serum Amyloid A. Colons were excised from cecum to rectum and homogenized for quantification of IL-12p70, IL-10, TNF- α , IL-6, and IFN- γ . Colonic myeloperoxidase (MPO) was quantified as a measure of neutrophil infiltration. Sections of the cecum and proximal, mid, and distal colons were formalin fixed, and H&E stained for histopathological scoring. Mice administered DSS showed progressive weight loss beginning on day 5. Both IDR-1002 and IDR-1018 slowed the weight loss trajectory. Relative to healthy controls, colitic animals showed a 4-fold reduction in tissue IL-10, however treatment with IDR-1018 restored IL-10 to healthy levels. Serum amyloid A, a systemic correlate of inflammation, was reduced by 3-4 fold in IDR-1002 and IDR-1018 treated mice. In contrast, tissue levels of MPO, a marker of PMN infiltration, was increased by both IDR-1002 and IDR-1018. IDR-1018 (IP) improved the histological appearance of colitis, predominately in the distal colon. When taken together, these data provide the first evidence that IDR peptides being developed as anti-infective agents might one day be used in the treatment of auto-inflammatory diseases. Further research is needed to determine if the effects of IDRs in DSS-colitis are due to enhanced immune killing of intestinal microbiota, attenuation of the inflammatory process, or both.

Complex patterns of spontaneous cortical activity reflect functional neural circuits

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Remarkably, most of the energy consumed by the brain is not used for ongoing sensorimotor tasks. Rather, it is used to fuel spontaneous oscillations of neuronal membrane potential, unrelated to current sensory input or motor output. Although the full purpose of this activity is unknown, it is suspected to be involved in consolidating memories and coordinating diverse brain regions.

To provide insight into this question, we sought to determine the extent to which neuronal oscillations are regional, dynamic events in local neural circuits as opposed to global changes in overall brain activity. We used voltage sensitive dye applied to large regions of the mouse cortex. This provides highly detailed representations of brain activity at very high temporal and spatial resolution.

We focused on delta, or slow-wave, activity, which in humans is typically reported as a global change in brain activity that slowly travels from anterior to posterior regions of the cortex. The higher spatial resolution provided by voltage sensitive dyes revealed that slow-wave activity is in fact highly dynamic, with multiple regions of activity traveling across the cortex in complex patterns. By comparing this activity to brain activity elicited by sensory stimulation, we next found that slow-wave activity uses the same functional connections as used by somatosensory stimulation. Finally, we found that the patterns of slow-wave activity can be changed by relatively brief periods of sensory inputs.

We interpret these findings to suggest that, in the mouse at least, slow-wave spontaneous activity is involved in shaping functional circuits and in processing previous sensory input, possibly for memory consolidation. These possibilities open further avenues for understanding more fully the role of spontaneous brain activity.

Charting the diversity of *Cenarchaeum symbiosum* symbionts within a marine sponge

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Recently a number of symbiotic relationships have been identified between species of Archaea and marine sponges, yet, at present, our understanding of the molecular exchanges that facilitate these mutualistic relationships is limited¹. The first of such relationships to be identified was that between *Cenarchaeum symbiosum* and a marine demosponge, *Axinella mexicana*². Given that *C. symbiosum* is the only archaeon harboured within *Axinella mexicana*, this relationship offers a model system for

functionally characterizing the molecular relationships between Archaea and their sponge hosts. Recent sequencing of the *C. symbiosum* genome has identified 5 putative serine protease inhibitors (serpins) harbored by *Cenarchaeum*. These may play a central role by allowing *Cenarchaeum* to circumvent sponge immune system activation, similarly to a mode of serpin-mediated innate immune regulation demonstrated in fruit flies³. In this study we used a cultivation independent approach to assess the level of *Cenarchaeum* diversity within a single California sponge sample. Gene sequencing of 16S ribosomal RNA suggests that in addition to the two previously identified *Cenarchaeum* strains our sample may possess a third, distinct but less abundant strain. In addition, sequencing experiments characterizing diversity at the level of serpin genes propose the existence of a novel clade of *Cenarchaeum* serpins. Kinetic assays to functionally characterize the activity of these serpin proteins are still in the beginning stages but could provide significant insight into serpin evolution. Furthermore by increasing our understanding of immune modulation in the sponge, this study may shed light on conserved mechanisms of innate immune modulation still important in humans.

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Role of CHOP in dysfunction of sub-optimal mass islet transplants

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Pancreatic islet transplantation offers improved glycemic control in type 1 diabetic patients, potentially decreasing macro- and microvascular complications of diabetes mellitus while obviating the need for insulin injections. Long-term success has been limited, however, with fewer than 10% of patients retaining insulin independence at two years post-transplantation. Up to 60% of transplanted graft mass is lost in the first week following transplantation. Excessive metabolic demand upon remaining beta cells greatly increases protein trafficking through the endoplasmic reticulum (ER). Elevated loads of unfolded proteins in the ER lumen activate ER stress responses to restore homeostasis; prolonged activation of these responses may activate the pro-apoptotic CCAAT/-enhancer-binding protein homologous protein (CHOP). Others have shown that CHOP expression in syngeneic islet grafts is elevated at 1, 3 and 7 days post-transplant. To study the role of CHOP in the early post-transplantation period, we performed syngeneic transplants of islets isolated from CHOP-deficient (CHOP^{-/-}) mice or wild-type (WT) C57Bl/6 controls into streptozotocin-diabetic C57Bl/6 recipients. Following transplantation of an optimal

mass of 300 WT or CHOP-/- islets, normoglycemia was restored immediately. Following transplantation of a marginal mass (100 islets), restoration of normoglycemia was delayed by 2-3 weeks in recipients of WT islet grafts, but was restored much earlier in recipients of CHOP-/- islets. At 1 week post-transplantation, 86% of WT islet grafts remained diabetic (blood glucose >12 mM) as compared to 53% of CHOP -/- islet grafts ($p < 0.05$). At 2 weeks post-transplantation, 57% of recipients of WT islet grafts remained diabetic as compared to 24% of recipients of CHOP-/- islet grafts ($p < 0.05$). No difference was seen between insulin-positive graft area between WT and CHOP-/- grafts. Thus absence of CHOP enhances function of sub-optimal islet grafts. We next compared CHOP mRNA levels by RT-PCR at 3 days post-transplantation in optimal (300 islets) versus sub-optimal (100 islets) grafts in syngeneic diabetic recipients. Glucose levels tended to be higher in recipients of sub-optimal grafts indicative of increased metabolic stress. CHOP mRNA levels were ~30% higher in sub-optimal grafts at 3 days post-transplant. These findings suggest that CHOP plays an important role in islet graft dysfunction in the early post-transplantation period, particularly when sub-optimal numbers of islets have been transplanted, and also raise the possibility that ER stress is an important contributor to graft failure.

Role of human islet amyloid polypeptide in pancreatic islet inflammation

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Background: Islet amyloid polypeptide (IAPP) is a 37-amino acid peptide co-secreted with insulin by pancreatic β -cells. Pathological IAPP aggregation occurs in type 2 diabetic and transplanted islets, both characterized by inflammation with macrophage infiltration. IAPP fibrils share a common β -sheet structure with other amyloids known to induce a potent inflammatory response. To determine whether IAPP promotes islet inflammation, we evaluated the effects of IAPP on monocyte recruitment to islets and on cytokine release by islets and macrophages.

Methods: Pro-inflammatory cytokines were measured in media from four-day cultures of human IAPP (hIAPP) transgenic mouse islets and from hIAPP-treated bone marrow-derived macrophages. Monocyte migration in response to supernatants from hIAPP-treated human islets was assessed by transwell assay. In vivo macrophage recruitment was evaluated by F4/80 staining of hIAPP transgenic islet grafts three months after transplantation into diabetic recipients.

Results: Cultured islets expressing hIAPP produced more macrophage chemoattractant protein-1 (MCP-1) than non-transgenic controls. Accordingly, conditioned media from hIAPP-treated human islets induced monocyte chemotaxis, and transgenic hIAPP grafts had more F4/80-positive cells than non-

transgenic grafts. Furthermore, hIAPP but not non-amyloidogenic rat IAPP significantly increased macrophage production of tumor necrosis factor- α (TNF- α), interleukin- (IL-) 6, MCP-1, and IL 1 β . Cultured islets expressing hIAPP produced more macrophage chemoattractant protein-1 (MCP-1) than non-transgenic controls. Accordingly, conditioned media from hIAPP-treated human islets induced monocyte chemotaxis, and transgenic hIAPP grafts had more F4/80-positive cells than non-

Conclusions: These data suggest that IAPP-induced chemokine production by islets promotes macrophage recruitment. Direct interaction of macrophages with IAPP may induce cytokines such as TNF- α and IL-1 β that promote β -cell apoptosis. Furthermore, IAPP fibril formation can induce MyD88 signalling and the MyD88-dependent IL-1 β receptor is at least partially required for TNF- α release. Thus, inhibition of IAPP aggregation may represent a novel mechanism for suppressing the innate immune response to islet transplantation and metabolic stress.