TRAINEE SECTION

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Proceedings from the 5th Annual University of Calgary Leaders in Medicine Research Symposium

On November 8, 2013, the Leaders in Medicine (LIM) program hosted the 5th Annual Research Symposium. Dr. Jerrold Ellner, Chief of the Infectious Diseases section at Boston Medical Centre and Professor of Medicine at Boston University School of Medicine, was the keynote speaker and presented his lecture entitled "Tuberculosis – Past, Present and Future". The LIM symposium gives a forum for LIM as well as non-LIM medical students to present their research work as either an oral or poster presentation. There were a total of 53 abstracts presented and five oral presentations. The symposium was attended by over 100 students and more than 30 staff members.

The oral presentations included

- Amrita Roy, Aboriginal identity, ethnic minority status, and prenatal depressive symptoms in a longitudinal pregnancy cohort study in Alberta.
- David Nicholl, Obstructive sleep apnea treatment with continuous positive airway pressure decreases intraglomerular pressure and alters renal sensitivity to angiotensin.
- James Cotton, An assemblage A *Giardia* cathepsin B protease degrades interleukin-8 and attenuates neutrophil chemotaxis.
- Krystyna Ediger, Alexander Arnold and Emily Shelton, Rebuilding the Calgary Student Run Clinic: A Model for Sustainability.
- Sarah MacEachern, Inhibiting inducible nitric oxide synthase restores electrogenic ion transport in experimental IBD: a novel role for enteric glia.

See the article on the University of Calgary Leaders in Medicine Program, "*A Prescription that Addresses the Decline of Basic Science Education in Medical School*" in this same issue of CIM for more details on the program. In short, the LIM Research Symposium has the following objectives: (1) to showcase the impressive variety of projects undertaken by students in the LIM Program as well as U of C medical students; (2) to encourage medical student participation in research and special projects; and, (3) to inform students and faculty about the diversity of opportunities available for research and special projects during medical school and beyond.

The following abstracts are those that were put forward for publication.

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Every Body is a Story: Introducing Narrative Medicine

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Background/Purpose: Current international literature demonstrates that physicians and with exposure to the humanities improve their critical thinking skills and bring enhanced sensitivity and analysis to diagnostic reasoning. Medical programs, particularly in the United States, incorporate “narrative medicine” into the curriculum to enhance training in communication skills, strengthen knowledge translation aptitudes, provide more creative thinking tools and to alter public perception of physician practices. Existing studies illustrate that this thriving area of research can highlight the importance of biomedical narrative forms and promote the balance of treatment options between belief systems, patient history, and the technological possibilities offered by medical science.

Research Questions: What are Canadian programs doing to keep up with this trend? Which studies clarify the principles of “narrative medicine” and how can we expand on the benefits that narrative medicine holds for clinical practice?

Methods: A review (as of June 2012) of Canadian and American medical program curriculums and a literature search (Medline, UpToDate, MLA Bibliography, ERIC) were performed.

Results: The programming survey shows substantial support for narrative medicine in the United States, and a growing interest at Canadian institutions (Alberta, Toronto, Dalhousie, Calgary and McGill). There is a wealth of research on the defining characteristics of narrative medicine and the benefits of integrating the study of narratives into medical schools; however, there is a lack of research on physician “stories” (for example, the clinical chart) as narrative medicine.

Conclusion: The current trend of narrative medicine offers a theoretically complex and intellectual new avenue to examine physician practices. More clinically focused projects, however, are needed to research the benefits of narrative medicine beyond medical education and physician health to consider clinical charts and physician documents as narratives themselves. Only through the analysis and data collection of both sides of the story can narrative medicine actually prove beneficial to the patient-physician relationship.

Examining the Role of Pre-departure Training across Canadian Medical Schools for Global Health Electives

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Background: The rising interest from Canadian medical students in participating in international medical electives demands an emphasis on structured Pre-departure Training (PDT) to prepare and optimize the student learning experience. At the core of PDT are five competencies: personal health, travel safety, cultural competence, language competence and ethics. This study examines the completeness and effectiveness of PDT among Canadian medical schools.

Methods: A survey examining various components of PDT – core competencies, assessment of students’ preparedness, length of PDT training, post-return debrief – was sent to one faculty member and one student representative at every Canadian medical school. The survey is an extension of similar surveys conducted in 2008 and 2010.

Results: Of the five core competencies of PDT, four (personal health, travel safety, cultural competence and ethics) were covered by 100% of medical schools. Language competence was addressed by 93% of schools, which is a major improvement from 63% in 2010. Students’ preparedness was assessed in the form of interviews, tests/assignments and modules in 36% of medical schools.

In addition to PDT, 70% of schools reported that students received supplemental training and orientation at the site of their electives. Upon return from international electives, 93% of medical schools provided post-return debriefing activities.

Conclusion: While it is not possible to predict and prepare for every potential scenario that students might face, effective PDT enhances the international learning experience and equips students with tools to become responsible global citizens and professional representatives of the Canadian medical education system.

Support for Early Treatment of Major Depressive Disorder in Recovering Alcohol Dependency: Improved Mood and Prolonged Abstinence

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Objectives/Introduction: Alcohol dependency and Major Depressive Disorder (MDD) are prevalent and highly comorbid presentations in the community. Each condition worsens the course of the other creating greater impairment than either condition alone. This is true even when the patient is newly abstinent from alcohol; the presence of untreated MDD can hinder recovery efforts reducing the time to relapse. Traditionally, MDD was not treated in alcohol-dependent patients until 4-12 weeks of abstinence had passed; however, recent data supports the conclusion that the early treatment of MDD in patients with substance dependency offers subjective and clinical improvements in mood that can enhance recovery efforts. Further, when antidepressants are combined with an opioid-antagonist medication, the benefit of prolonged abstinence and reduced relapse are noted in addition to improved mood.

Methods: A literature review and analysis were undertaken to assess the clinical evidence for treatment of MDD in patients with alcohol dependency with consideration to the primary outcomes of improved mood and prolonged abstinence from alcohol.

Results: Three studies assessing the clinical effect of antidepressants on MDD in patients with substance use disorders were reviewed. The studies included one meta-analysis and two randomized control trials and each demonstrated improved mood in patients with comorbid MDD and alcohol dependency (NNT=9, $p=0.021$). The combination of an SSRI and an opioid-antagonist medication demonstrated greater abstinence and prolonged time to relapse than either medication achieved alone ($p=0.001$ and $p=0.003$, respectively).

Conclusion: Antidepressants are effective in the early treatment of MDD in newly abstinent patients with alcohol dependency. The addition of an opioid-antagonist to an antidepressant prolongs abstinence when compared to either monotherapy alone.

Is Housing First an appropriate model for community-based solutions that encourage connection with the homeless? A preliminary analysis of Calgary's Project Homeless Connect

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Objective: Project Homeless Connect (PHC) is a one-day event where homeless can connect with community services at one location with reduced barriers (e.g., multiple travel or stigmatization). While non-housing services (e.g., hair cuts and medical appointments) are offered, PHC's primary goal is to connect people with housing services. Guided by a Housing First model, the Calgary Homeless Foundation (CHF) has decided to discontinue PHC after finding most clients were drawn to the event for basic needs rather than housing support. This study aimed to gain a preliminary understanding of PHC's impact on housing service connection and personal empowerment among participants who sought medical care.

Methods: This cross-sectional study design asked participants receiving medical care to complete a post-appointment survey adapted from Denver's Guest Evaluation Survey PHC-7. Tool pre-testing was limited by short notice of PHC's discontinuation. SPSS was used for data analysis.

Results: Of 50 medical clinic participants, 20 completed the survey. Fifteen did not indicate "housing" as their primary purpose of attending PHC. Instead, reported purposes were: "personal needs" (60%), "food" (20%) and "employment assistance" (20%); however, 13.3% had used or planned to use housing services that day. Benefits on empowerment were also reported: decreased feelings of isolation from the rest of the community (33%), improved confidence in ability to take control over homeless situation (20%) and knowledge gained on how to change their homeless situation (46.7%). **Conclusion:** While the primary purpose of PHC attendance may not be "housing", the event may still offer other benefits such as service connection and self-empowerment. By focusing PHC on a Housing First model, we may be overlooking an important barrier: community disconnect. Rather than removing basic services for un-conforming behaviour, perhaps a harm reduction model, where the community can meet homeless people where they are would be more appropriate. Further research is warranted due to the limited methods and small sample size of this study.

Increasing Rate Of Fluoroquinolone-Resistant *Escherichia coli* And Incidence of Infectious Complications Following TRUS-Guided Prostate Needle Biopsy in Calgary, Alberta, Canada – A Retrospective Population-Based Analysis

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Introduction: Increasing risk of infectious complications associated with colonic *Escherichia coli* (*E.coli*) following transrectal ultrasound guided prostate biopsy (TRUS-PB) has been observed across North America and Europe. Fluoroquinolone (FQ) antibiotics are used as the first line prophylaxis prior to TRUS-PB. We sought to evaluate whether the increased *E.coli* antibiotic resistance correlates with increased incidence of infectious complications following TRUS-PB at our institution.

Methods: Retrospective chart and electronic health record reviews were conducted on 927 patients who underwent TRUS-PB between January and July 2012 in Calgary, Alberta, Canada. The variables collected prospectively included age, pre-biopsy prostate specific antigen (PSA) and date of biopsy. Presentations to an emergency department (ED) within 30 days of TRUS-PB for infectious and non-infectious complications were documented.

Results: Overall, 58 patients (6.3%) were admitted to the ED due to post TRUS-PB complications within 30 days post-biopsy. The most common infectious complications observed were sepsis in 21 (2.2%), followed by urinary tract infection (UTI) in nine (0.9%) and prostatitis in four patients (0.4%) – 83% of the septic episodes and 66.6% of the UTIs were attributed to ciprofloxacin-resistant *E.coli*. The incidence of non-infectious complications was as follows: urinary retention in 12 (1.2%); hematuria in nine (0.9%); and, rectal bleeding in eight patients (0.8%).

Conclusion: Our results suggest increased incidence of infectious complications caused by FQ-resistant organisms following TRUS-PB. This finding could be attributed to increasing community resistance to ciprofloxacin. The current antimicrobial prophylactic regimen needs to be re-evaluated, and novel alternative approaches will be considered at our institution.

Obstructive sleep apnea treatment with continuous positive airway pressure decreases intraglomerular pressure and alters renal sensitivity to angiotensin II

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Background: Obstructive sleep apnea (OSA) has been associated with the progression of chronic kidney disease. The underlying mechanism may be related to changes in the renin angiotensin system (RAS). The effect of continuous positive airway pressure (CPAP) on renal hemodynamics was investigated at baseline and in response to Angiotensin II (AngII) infusion in OSA patients.

Methods: Twenty normotensive, non-diabetic, newly diagnosed OSA subjects (15 men, five women; age 50±2 years; respiratory disturbance index [RDI]>15 hr⁻¹) with nocturnal hypoxia (oxyhemoglobin saturation [SaO₂] <90% for >12% of night) were studied in high-salt balance pre- and post-CPAP therapy (>4 hr CPAP use/night for one month). Glomerular filtration rate (GFR), renal plasma flow (RPF) and filtration fraction (FF), a surrogate for intraglomerular pressure, were measured pre- and post-CPAP therapy using inulin and para-aminohippurate clearance technique at baseline and in response to graded AngII infusion (3 ng/kg/min-30 min, 6 ng/kg/min-30 min).

Results: CPAP-corrected OSA and nocturnal hypoxia (RDI: 42±4 *vs.* 4±1 hr⁻¹, p<0.001; duration SaO₂<90%: 36±5 *vs.* 6±2%, p<0.001; all values pre- *vs.* post-CPAP). Post-CPAP treatment, there was a reduction in baseline GFR (124±8 *vs.* 110±6 mL/min, p=0.014) and an increase in baseline RPF (692±36 *vs.* 749±40 mL/min, p=0.059), which resulted in reduced baseline FF (18.9±1.6 *vs.* 15.3±1.0%, p=0.004).

Post-CPAP therapy there was a blunted GFR response (-9 ± 3 *vs.* -2 ± 2 mL/min, $p=0.033$) to the low dose of AngII, while there was an augmented RPF response (-182 ± 22 *vs.* -219 ± 25 mL/min, $p=0.024$) to the high dose of AngII. The FF response to AngII was maintained ($p=0.4$). CPAP therapy also reduced baseline mean arterial pressure (94 ± 2 *vs.* 89 ± 2 mmHg, $p=0.002$), urinary protein excretion ($61[39, 341]$ *vs.* $56[22, 204]$ mg/day, $p=0.003$), and plasma aldosterone (149 ± 18 *vs.* 109 ± 10 pmol/L, $p=0.003$).

Conclusions: CPAP treatment decreased intraglomerular pressure and improved renal hemodynamic sensitivity to AngII in OSA patients, supporting a role for the RAS in mediating OSA-associated hypertension and kidney disease.

Ethics in surgical innovation: Lessons of the intravaginal slingplasty

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Background: Innovation in surgical medicine provokes important ethical questions. Development of new surgical treatments often occurs outside the context of RCTs and follows a trajectory that highlights ethical issues concerning medical innovation. This paper asks what ethical considerations arise in the context of surgical innovation, and what the implications of those considerations are for innovators and for practicing surgeons. **Methods:** A case study of the development of the intravaginal slingplasty (IVS) procedure, the precursor to the highly successful tension-free vaginal tape surgery for female stress urinary incontinence, was used to demonstrate ethical issues that can arise in response to surgical innovation. Historical documents constituted the data of this paper.

Results: The IVS was developed largely through a process of trial-and-error. The developers of the IVS learned from the mistakes they made on their early patients; these mistakes iteratively contributed to the shape of subsequent versions of the IVS. These mistakes are inevitable and necessary for surgical innovation; however, they provoke questions regarding patient safety and how to balance the need for innovation with the need to protect patients from harm. Additionally, some choices in the series of studies leading up to the IVS and vagaries in published material conflict with standard norms of scientific

rigour, calling into question whether the burden of risk carried by patients was justified.

Conclusions: Innovation is central to advancing medicine and improving patient care. There are, however, key ethical issues to consider when engaging in innovative medicine. The trial and error process through which medical devices develop necessitate errors that can cause negative outcomes for whole cohorts of patients, causing us question how to control harm to patients while encouraging surgical innovation. The IVS case also shows how choices about study design are ethical choices – in order to justify the risk inherent in experimental studies, high quality study design and communication is paramount.

Dopamine Prevents Form-Deprivation Myopia via Nitric Oxide Relay

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Purpose: Myopia (nearsightedness) is due to excessive elongation of the growing eye, which causes images of distant objects to be out of focus without optical correction. Form-deprivation myopia (FDM), an established experimental model for human myopia, was induced in young chickens with translucent diffusers. It is known that dopamine (DA) and nitric oxide (NO) prevent FDM by acting in series, because an antagonist to either agent alone blocks FDM rescue by brief goggle-removal. In this study, the hypothesis that NO prevents FDM in chickens through a DA-D2-receptor pathway was tested.

Methods: A series of dose response experiments was performed to determine the optimal doses of a

NO-donor, SNAP to prevent FDM, and a DA-D2R-antagonist, spiperone, to block the effect of 2-hr goggle-removal. Male chickens (1-10 day old) were maintained on a 12:12 hour light:dark cycle. One eye was goggled with a diffuser, while the fellow eye remained ungoggled as an internal control. Predetermined doses of SNAP (dissolved in 1% DMSO) and spiperone were administered separately and together in goggled eyes; control animals (injected with vehicle) had goggles on or off permanently. The drug was injected into the vitreous cavity of the goggled eye and 1x PBS vehicle into the ungoggled fellow eye, every second day for one week, under O₂-N₂O-isoflurane anesthesia. The day after the third treat-

ment, refractive error and eye size and weight were measured. Optimal doses of a DA-agonist, ADTN, and a NOS-inhibitor, L-NIO, were also determined, and the reverse hypothesis that the DA-D2-receptor acts via NOS to prevent FDM was tested similarly. The protocol was approved by the University of Calgary Animal Care Committee, and the study was supported by an NSERC Discovery Grant (W.K.S.) and O'Brien Centre Summer Studentships (P.M., E.C.)

Results: The optimal doses (weight/injection) were: spiperone, 5 nmol; SNAP, 500 nmol; ADTN, 3 mM; L-NIO, 20 μ M. SNAP or ADTN inhibited FDM, and spiperone or L-NIO alone blocked myopia-prevention by diffuser-removal. The inhibition of FDM by SNAP was not diminished by spiperone, but preliminary results indicated that the effect of ADTN was diminished by L-NIO.

Conclusions: Spiperone did not block the effect of SNAP, indicating that the inhibition of FDM by NO does not require downstream activation of DA-D2. L-NIO, however, did block the effect of ADTN, indicating that the inhibition of FDM by dopamine may require downstream activation of NOS. These findings enhance our understanding of the mechanisms underlying emmetropia and myopia and may lead to novel anti-myopia drug therapies.

Infection site evolution in *Trichomonads*

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Introduction: *Trichomonads* are an important group of anaerobic protists in both human and animal medicine. The Parabasalia phylum is a diverse group that encompass pathogens and commensals in numerous hosts that include mammals, birds, reptiles, amphibians and many others. There is sparse research in the area of comparative infection site specificity for this group. The focus of this paper is to examine host site evolution in this group.

Methods: A GenBank search was used to locate all trichomonad species with archived rRNA sequences for the gene ITS-1/5.8S/ITS-2. Data was collected on the infection host and site through the original or additional articles. A phylogenetic tree with 48 final data points on infection sites was constructed using the MEGA5 computer program and host site evolution patterns were inferred through ancestral character state reconstruction using Mesquite V.2.75.

Results: Among the taxons included in this study, use of a genitourinary infection site appears to have evolved independently five times, lung infection site twice and a free-living state twice.

Conclusions: As a group, trichomonads appear to have evolved from infecting only the gastrointestinal tract to other anatomic sites via a series of independent evolutionary events. The limitations of this study include 1) using only a single gene to derive the phylogeny and 2) not all species were included due to missing information. As recent studies have suggested that the ITS gene used may not be the most suitable one to use for the study of this phylum so future studies could investigate a multigene phylogenetic tree. Additional species, pathogenicity, protein evolution and function and host evolution could also be examined.

Nano-structured Brain Stimulating Electrodes: The Future of Neural Prosthetics?

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Introduction: The exceptionally promising field of neural interfaces and neural prosthetics relies on the successful electrical stimulation of nervous tissue through the use of electrodes. Current electrical stimulation therapies for various neurological disorders (i.e., deep brain stimulation for Parkinson's disease and cochlear implants for hearing loss) utilize these neural interfacing devices. A principal problem with current neural electrodes is their lack of stimulus selectivity due to large electrode size relative to the targeted neuronal population; however, as bulk electrode size is reduced, charge density increases, which may cause irreversible damage to both the electrode and the stimulated tissue. In an effort to find a balance between electrode size and charge density, our objective was to develop a novel iridium-nickel oxide bimetallic coating that could intrinsically offer high charge injection. Secondly, we attempted to nanostructure the surface of these coatings to create a higher surface/volume ratio, which would result in a higher extrinsic charge storage capacity than currently used stimulating electrodes.

Methods: Thermal decomposition was used to fabricate iridium oxide, nickel oxide, titanium oxide and bimetallic iridium-nickel oxide coatings on titanium substrate electrodes. Each

sample was investigated using cyclic voltammetry (CV), electrochemical impedance spectroscopy (EIS) and scanning electron microscopy (SEM).

Results: Experiments showed that specific iridium-nickel oxide coatings offered a significantly higher true, electrochemically-active surface area (i.e., higher roughness) than the currently used state-of-the art, iridium oxide coatings. These iridium-nickel oxide bimetallic coatings were also capable of delivering significantly more charge than the iridium oxide control, both from the intrinsic and extrinsic point of view.

Conclusion: Nano-structuring the surface of stimulating electrodes with a high surface area coating will assist in the miniaturization of neural electrodes. This will ultimately improve charge injection specificity and narrow the cyclization potential limits, decreasing the negative effect of the electrodes on surrounding tissue.

Does abdominal ultrasound show equivalence to Computed Tomography and Magnetic Resonance Enterography in predicting active Crohn disease and its complications?

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Background/Purpose: Crohn disease (CD) is an inflammatory disease of the bowel that requires imaging for diagnosis and surveillance. Ultrasound (US) is a radiation-free, cost-effective, and readily available modality that provides realtime assessment of the bowel in routine and emergent cases. Given the accuracy and safety of US, our objective was to demonstrate equivalence of US with computed tomography (CT) and magnetic resonance enterography (MRE) in detecting disease activity and complications in patients with established and suspected CD. We hypothesize that US can be used as a first-line investigative tool for routine diagnosis, surveillance and detection of complications in those with acute symptoms.

Methods: We analyzed 308 patients with known or suspected CD who had a positive bowel US exam with CT, CTE and/or MRE scans from May 2010-June 2013. Two reviewers, blinded to the pathology, evaluated the US images for active disease/

complications. Disease was assessed with color Doppler or contrast-enhanced US (CEUS). Concordance was determined by the percentage of cases that showed agreement on US and the gold standard modality.

Results: US and gold standard concordance for disease activity were as follows: wall thickness-98.05%, blood flow-96.69% and inflammatory fat-87.13%. US correctly ruled in 84/86(97.67%) strictures, 53/54(98.14%) fistulae, 28/29(96.5%) perforations, 43/44(97.7%) phlegmon and 18/20(90%) abscesses. Real time US scanning identified dysfunctional peristalsis, fixed luminal apposition and bowel angulation strictures and partial bowel obstructions. Spatial resolution of US was superior in identifying perforations with phlegmon. MR was superior in predicting bowel wall edema and mucosal ulceration; insignificant difference between MR and US noted when determining active disease. Inflamed or perforated appendices were better visualized with US and but had 100% concordance to other modalities.

Conclusion: In patients with CD, our study shows that US is equal and occasionally superior to CT/CTE/MRE in its ability to predict disease activity and intestinal complications for routine evaluation, monitoring or acute presentations.

Treating donor site pain in burn victims that have undergone autologous split-thickness skin grafting: A review of the literature

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Introduction: Current standard of treatment for deep burn injuries is split-thickness skin grafting (STSG). STSGs are harvested from a remote area of healthy skin creating a new wound, which is referred to as the donor site. Pain, caused by harvest, is reported to be one of the most distressing symptoms following STSG. Resultant pain can affect early mobilization, sleep and the need for analgesics post-operatively. Although donor site pain presents a significant problem, there are no evidence-based guidelines concerning its treatment. The purpose of this literature review was to gather information on current practices for managing donor site pain and to determine whether further investigation of donor site pain management is warranted.

Methods: Ovid MEDLINE was searched using the terms 'burn', 'donor site', 'pain' and 'split-thickness skin graft' from 2003–2013. Only human studies were included in the review. Non-English language articles were excluded from the review.

Results: The literature review identified five techniques used in minimizing donor site pain. One technique initiated treatment prior to STSG harvest by infiltrating the pre-harvest site with a combined anesthetic/tumescent solution. Four techniques initiated treatment immediately following STSG harvest: 1) continuous subcutaneous local anesthetic infusion (CSLA); 2) subcutaneous injection of anesthetic; 3) application of topical anesthetic gels; and, 4) the use of ice packs. All studies measured pain using a visual analog scale (VAS). In a majority of these studies, subjects gave anecdotal reports of decreased pain at the donor site regardless of the technique used to treat pain. Few studies showed that the use of a particular technique significantly decreased VAS scores.

Conclusion: Although donor site pain is of chief concern for both the patient and the physician, its treatment is scantily addressed. This review highlights the need to design and carry out more rigorous and effective studies in order to work towards standardizing care and improving the patients' pain experience following STSG harvest.

Controlling inflammation to prevent the development of osteoarthritis following reconstruction anterior cruciate ligament and drill hole surgery

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Introduction: Severe injury to the knee joint, such as anterior cruciate ligament (ACL) tears and/or menisci damage, often results in accelerated development of osteoarthritis (OA). It is thought that there may be an injury-induced, mechanical abnormality of the injured joint and subsequent interplay between altered mechanics and/or biological changes, such as inflammation, which may lead to cartilage damage. Dexamethasone (DEX) is a synthetic steroid with anti-inflammatory properties that could be a possible treatment

strategy for controlling inflammation. The purpose of this study was to characterize inflammation and joint mechanics following idealized ACL reconstruction (ACL-R) surgery after DEX injection.

Methods: A small pilot study was conducted in untrained sheep (n=2 ACL-R, n=2 controls). Surgeries involved an arthrotomy to the right stifle joint, with the left joint serving as the control. DEX was given immediately after ACL-R by an intra-articular injection (0.5 mg/kg body weight). Animals were sacrificed 2 weeks after surgery and tissues, synovial fluid and blood were collected. Gross morphological grading was conducted for gross cartilage defects, osteophyte formation, and meniscal damage. Histology of synovium was evaluated for microscopic changes with Hematoxylin and Eosin staining.

This pilot study is the start of a large-scale project: 20 sheep divided into three groups: ACL-R+DEX (n=8); ACL-R (n=8); and, controls (n=8). Furthermore, an *in vivo* motion analysis system (instrumented spatial linkage) will measure kinematics. mRNA expression of inflammatory cytokines will be measured by real-time polymerase chain reaction.

Results: Combined gross morphological score in the ACL-R+DEX group was lower than that of the control for cartilage damage/defects, osteophyte formation, and meniscal damage. Mean aggregate synovitis score consisting of sub-intimal fibrosis, intimal hyperplasia, and cell infiltration in the ACL-R+DEX group was similar to that of the control group.

Conclusion: Preliminary results demonstrate that even one injection of DEX immediately after ACL-R surgery is sufficient to completely block induction of cartilage damage and synovitis in this experimental animal model.

Characterizing hypoxic vascular lesions using susceptibility weighted MRI in a model of multiple sclerosis

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Introduction: Multiple sclerosis (MS) is an inflammatory and demyelinating neurological condition. Susceptibility weighted imaging (SWI) is a magnetic resonance imaging (MRI)

method that is sensitive to iron in hemosiderin, ferritin and deoxyhemoglobin (dHb) and that has detected lesions not seen with conventional MRI in MS patients. Previously, SWI has been used in the experimental autoimmune encephalomyelitis (EAE) mouse model of MS where two types of lesions were detected: 1) vascular lesions (or hypointensities), due to dHb; and, 2) parenchymal white matter lesions, due to iron deposition/demyelination. Here, we aimed to determine if vascular and parenchymal lesions could be differentiated using SWI by increasing the inspired oxygen to reduce dHb in the blood. Vascular lesions would alter in appearance with high oxygen, whereas parenchymal lesions would not.

Methods: Control and EAE mice were imaged at 9.4 T using 3D gradient echo with flow compensation (for SWI) with 30% O₂/70% N₂ then 100% O₂. A subset of mice were imaged with these gases and then after perfusion (to remove blood). Lesions were counted and compared between control and EAE mice, and the number of lesions seen with 30% O₂ was compared with the number that remained unchanged with 100% O₂. Iron deposition was assessed using DAB-enhanced Perl's staining.

Results: Most lesions (hypointensities) seen with 30% O₂ altered in appearance with 100% O₂ in control ($p < 0.001$) and EAE mice ($p < 0.01$). Hypointensities that changed in appearance with 100% O₂ also disappeared after perfusion, supporting that they are due to dHb. Parenchymal white matter lesions appeared dark in MRI and did not change in appearance with high oxygen.

Conclusions: Changing the inspired oxygen concentration differentiates between vascular and parenchymal lesions in the EAE model *in vivo*. This method can be applied in MS patients, paving the way to investigate the pathophysiology of venous hypoxia and iron deposition in MS.

Rebuilding the Calgary Student Run Clinic: A model for sustainability

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Introduction: Since May 2012, The University of Calgary Student Run Clinic (SRC) has been rebuilding and restructuring its programs in order to create a sustainable and diverse

clinic model. The goal of the clinic is to provide high quality, accessible health care to low income, marginalized and/or homeless clients, as well as to provide educational opportunities and clinical exposure to medical students. **Methods:** Through an "umbrella" model, the SRC aims to act as a platform organization facilitating student involvement at multiple clinic sites. Each site offers services to a specific marginalized population, including children at a family emergency shelter, new Canadians at a refugee clinic, and older male patients experiencing addictions and homelessness on board a mobile clinic. Methods for sustainability include securing multiple sites, preceptors and funding sources. **Results:** Today's SRC utilizes a two-pronged approach to delivery of care, focusing on inter-professional collaboration to provide primary care to its patients in various clinic settings, as well as engaging in health promotion initiatives in the community. With respect to health promotion, the SRC has developed a literacy program, a child care program at the family shelter site, a health education series, a community services night for low income women, and is an active participant in a health and community fair for Calgary's homeless population. **Conclusions:** The SRC umbrella model has provided a framework for sustainability, both for its target population and for medical students and health professionals, where it provides a professional, engaging clinical experience. As a result, there has been a marked increase in capacity, with student participants growing from twelve to thirty. The number of permanent preceptors has increased from one to four, and the number of clinic sites has increased from one to three. This model has strengthened partnerships with the community and has led to increased opportunities for funding and expansion.

Viscosity of Lubricin: Effects of Concentration, Structure and Interaction with Hyaluronan

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Introduction: The viscosity (resistance to flow) of synovial fluid (SF) is essential for its ability to provide lubrication and cushioning to articular joints. Hyaluronan (HA) is a large gly-

cosaminoglycan that contributes significantly to the viscosity of SF. HA also works synergistically with lubricin (a mucin-like glycoprotein) to provide SFs lubricating ability. HA is currently used as an intra-articular treatment for pain relief of osteoarthritis (OA), a painful and debilitating disease affecting 13% of Canadians. Lubricin has demonstrated ability to slow cartilage degradation in animal injury models of OA; however, the viscosity of lubricin alone and lubricin+HA solutions are unknown. The objective of this study was to measure the viscosity of 1) lubricin alone, 2) lubricin with its naturally-occurring disulfide bonded multimers broken by reduction and alkylation (R/A), and 3) lubricin+HA solutions.

Methods: Viscosity analyses of lubricin±R/A, HA, and lubricin+HA solutions were performed with high molecular weight HA and lubricin purified from media conditioned by bovine cartilage explants.

Results: Lubricin, at physiologically normal concentrations, demonstrated concentration- and multimer-dependent shear thinning behaviour (decreasing viscosity with increasing rate of deformation, like paint); however, lubricin at low concentration and lubricin+R/A viscosities were similar to that of water. When lubricin was added to low concentrations of HA, viscosity increased in a manner independent of lubricin concentration but dependent on multimeric structure. Viscosities for lubricin+R/A and lubricin+HA were similar to those of HA alone.

Conclusions: These results demonstrate that the disulfide bonded structure of lubricin is essential in the unknown mechanism of lubricin+HA interaction. They suggest that intra-articular treatment with lubricin might increase the viscosity of diseased SF; this is the objective of current HA treatments. Characterization of the viscosity of lubricin+HA solutions will contribute to the understanding of SF function in health and disease, and will be necessary for new lubricin±HA biotherapeutic treatments.

Harmless Commensal Microbial Neighbours Synergistically Trigger *Pseudomonas aeruginosa* Virulence Genes in Cystic Fibrosis

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Rationale: Cystic fibrosis (CF) is the most common lethal genetic disease among Caucasians: 90% of CF patients succumb to pulmonary failure from chronic respiratory infections. Traditionally, research has focused on a narrow spectrum of microorganisms as principal pathogens, such as *Pseudomonas aeruginosa* (PA). The oropharyngeal flora (OF) have been implicated in enhancing pathogenesis of PA while acting as benign commensals, otherwise known as “synergens”. These interactions may skew the balance between clinical stability and acute pulmonary exacerbation, leading to hospitalization. The objectives here were to evaluate these interactions and construct synergen mutants to identify the pathway(s) involved.

Methods: Seven oropharyngeal-derived microbes were isolated from sputum of adult CF patients (*Streptococcus*. sp, *Rothia*. sp and *Actinomyces*. sp) and screened *in vitro* for affecting PA virulence gene expression in co-cultures. The ability of these benign microbe synergens to stimulate PA virulence genes was evaluated using transformed PA reporters harboring luciferase constructs for known virulence gene promoters. The luciferase light production caused by the co-culture *vs.* monoculture of PA was monitored to quantify synergen activity by measuring changes in light production. Transposon libraries in the synergens were constructed with 8000 mutants screened.

Results: Up-regulation of PA virulence gene expression was seen for all seven synergens tested. The virulence pathways affected were for quorum sensing or bacterial communication. The highest up-regulation was by *Streptococcus*. sp, with 1800-fold increased virulence gene expression in co-culture as compared with PA alone. From 8000 synergen mutants, 526 were isolated as hits involved in co-culture. Sixty one of these mutants were conserved in all PA reporters, suggesting common interaction pathway(s) triggered by the synergens. Thirty five mutants displayed 10-fold or greater activation in co-culture as compared to the wild-type, demonstrating a gain-of-function mutation.

Conclusion: Seemingly harmless non-pathogenic oropharyngeal synergen microbes can trigger virulence genes in PA found in CF patients. The production of secondary signaling molecules have been shown to influence pathogen virulence profiles

by modulating bacterial cell-cell communication pathways. Understanding the way in which commensal microbes synergistically trigger virulence will lead to better treatment and management of CF.

Characterization of the aspartic protease, nepenthesin, as a therapeutic for the treatment of celiac disease

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Background: Celiac disease (CD) is a highly prevalent autoimmune disorder that is triggered by the incomplete digestion of immune stimulatory peptides in the gliadin fraction of dietary gluten. The basis for gliadin resistance to digestion is due to the abundance of P (~15%) and Q (~30%) residues in its protein sequence. Currently, no therapeutic product for CD exists but oral proteases aimed at efficiently digesting gliadin throughout the gastrointestinal tract have shown promise in advanced clinical trials. In this study, the potential of a novel aspartic protease from *Nepenthes* plant extracts, nepenthesin, whose properties appear suited for an oral protease therapeutic for CD was evaluated.

Methods: Both isoforms of nepenthesin (I and II) were recombinantly expressed in *E. coli* and purified from inclusion bodies. Functionality was assayed by comparing cleavage specificities of recombinant nepenthesins to native plant extracts. Gliadin was digested *in vitro* with various concentrations of recombinant nepenthesins under simulated stomach-like conditions and analyzed by LC-MS/MS. Digestion of an immunodominant 33-mer peptide was quantified by indirect ELISA.

Results: The cleavage specificities of native plant extracts vs. recombinant nepenthesins showed that cleavage N- and C-terminal to all residues are retained except cleavage C-terminal to proline. *In vitro* digestions of gliadin showed that the average length of peptides, including all immunogenic epitopes, decreased in a dose-dependent manner at clinically relevant nepenthesin doses as compared with leading clinical oral protease candidates. Quantification by indirect ELISA showed that the immunodominant 33-mer peptide within gliadin extracts was digested by nepenthesin in a dose-dependent manner. In addition, digestion maps show cleavage within all known immunogenic epitopes, including the 33-mer peptide.

Conclusions: Preliminary results from the identification and initial characterization of the first aspartic protease, which appears to efficiently process gliadin in all known immunogenic regions and act optimally in the stomach, supports nepenthesins potential as an effective oral therapeutic candidate for CD.

A model for chronic consequences of acute enteric infection: the role of pathogen-mediated disruptions in the intestinal microbiota

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Introduction: *Giardia duodenalis* (*G. duodenalis*) is a leading cause of water-borne infectious dysentery that is encountered worldwide. Following a number of recent outbreaks, the symptomology profile of giardiasis has been extended to include the development of both chronic and long-term gastrointestinal complications characteristic of post-infectious irritable bowel syndrome (PI-IBS). Despite its occurrence in upwards of 40% of individuals who have experienced previous enteric infection, the mechanisms underlying the generation of PI-IBS remain obscure. Disruptions in the normal species distribution of the intestinal microbiota in IBS patients have been observed, but remain incompletely characterized. Moreover, novel insights into the ability of enteropathogens to modify the phenotype of the mucosa-associated microflora, normally existing as a series of biofilm communities, must be expanded in order to fulfill an all-encompassing view of the poly-microbial interplay that can elicit gastrointestinal disease.

Objective: This study measured the presence of *G. duodenalis* in colonic biopsies to examine the impact of an acute enteropathogen on the structure, species composition, and resulting pathogenic profile of human mucosal biofilm communities.

Methods: Representative intestinal mucosal biofilms were cultivated from human colonic mucosal biopsy samples collected during routine colonoscopy procedures.

Results: *Giardia*-exposure results in a loss in diversity in the species composition of microflora biofilms, when compared to

control-communities. Additionally, *Giardia* promotes a phenotypic switch from the normal biofilm mode of bacterial growth, to planktonic growth in microflora biofilms via a disruption in normal extracellular matrix production, characteristic of biofilm communities. Finally, *Giardia*-exposed biofilm communities induce higher levels of enterocyte apoptosis, and promote changes in Caco2 monolayer permeability.

Conclusion: Human mucosal biofilm communities exposed to *Giardia* exhibit an alteration in the normal biofilm phenotype, as well as species composition. Furthermore, the detrimental effects of *Giardia*-exposed mucosal biofilms on enterocyte homeostasis outlines the potential consequences that complex poly-microbial interplay may have in initiating functional gastrointestinal disorders, such as PI-IBS.

The role of NCX in the regulation of endothelial-dependent flow-mediated dilation

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Introduction: Appropriate release of nitric oxide (NO) from the endothelium is critical for normal physiological functioning of the cardiovascular system. Although changes in intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) due to Ca^{2+} influx are thought to lead to activation of nitric oxide synthase (eNOS) and the release of NO, the molecular mechanism(s) underlying endothelial Ca^{2+} influx is (are) poorly understood. Transient receptor potential (TRP) channel proteins are widely viewed as molecular candidates for the Ca^{2+} entry pathway; however, the non-selective nature of TRP channels for cations indicates that TRP channels can also act as a Na^+ entry pathway. Na^+ accumulation under the plasma membrane could then facilitate sodium-calcium exchanger (NCX) activity in the reverse, Ca^{2+} entry mode. Although NCX has been implicated as a Ca^{2+} influx pathway, its role in endothelial cells, specifically flow-mediated dilation (FMD) has not been elucidated. Here, the molecular mechanisms responsible for regulating endothelial $[\text{Ca}^{2+}]_i$ and their role in controlling NO production and release during FMD were characterized.

Methods: The effect of flow on arterial diameter was studied using pressurized myography in endothelium-intact rat cerebral arteries (RCAs). Co-localization of proteins was assessed using

proximity ligation assay (PLA). A three-step method of western blotting was utilized to detect eNOS phosphorylation at Ser1177.

Results: The eNOS inhibitor, L-NAME, significantly reduced the magnitude of FMD, suggesting a role for NO in FMD. Inhibition of endothelial NCX by intraluminal perfusion of KB-R7943 or 6H2 NCX antibody also significantly reduced FMD. Moreover, FMD was associated with the phosphorylation of eNOS at serine 1179, which was inhibited in the presence of NCX blockers. PLA data indicated the presence of TRPV4/C1-NCX1 co-localization in intact RCA endothelium.

Conclusions: Our findings provide unique insight concerning the molecular mechanisms underlying regulation of endothelial $[\text{Ca}^{2+}]_i$ and FMD. The data suggest that a TRP-NCX signaling complex mediates Ca^{2+} influx, leading to a rise in $[\text{Ca}^{2+}]_i$, activation of NOS and release of NO to evoke cerebral arterial FMD.

Psychosocial stress partially mediates the association between race and prenatal depressive symptoms in a sample of pregnant women in Alberta

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Introduction: Prenatal depression is a serious maternal-child health concern and risk factors and health consequences appear to be more prevalent in Aboriginal communities and among ethnic minority groups; however, research on these populations is limited. The following research questions were examined: A) How do pregnant Aboriginal women, ethnic minority women and white/Caucasian women compare on levels of depressive symptoms, and on major risk and protective factors? B) Is non-dominant race associated with higher de-

pressive symptoms? C) Through what pathways does race operate to contribute to depressive symptoms?

Methods: Data were from the *All Our Babies* study (n=3354 pregnant women from Alberta recruited between 2008-2011). Depressive symptoms were measured with the Edinburgh Postnatal Depression Scale (EPDS). Descriptive statistics and multivariable regression methods were used to assess the following hypotheses: Aboriginal and ethnic minority women would have significantly higher mean EPDS score estimates relative to white/Caucasian women. The association between race and EPDS score was hypothesized to be partially mediated by risk factors such as social and economic factors, health background, negative life experiences, including discrimination and domestic violence, and psychosocial stress. Potential confounders were age, marital status and parity. Protective factors (diet, social support and optimism) were hypothesized as buffers between stress and depressive symptoms.

Results: White/Caucasian women appeared to have higher incomes, better employment, higher social support and higher levels of optimism, and have significantly lower depressive symptoms. The association between race and depressive symptoms appeared to be partially mediated by socioeconomic factors and psychosocial stress; the attenuation with addition of stress in the model, in particular, was quite striking. Race remained highly statistically significant as a predictor.

Conclusion: Mental health inequities between pregnant white/Caucasian women and other women are driven by social inequities. A better understanding of the determinants of prenatal depression in specific populations may facilitate more effective public health and clinical interventions.

Kawasaki disease disguised as retropharyngeal abscess

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Introduction: Kawasaki disease is an acute and self-limited inflammatory vascular condition of undetermined etiology that primarily affects young children and infants. Cardiac complications of the disease can be severe and life threatening; however, the risk of the most severe cardiac complication, coronary artery aneurysm, can be significantly reduced by treatment with intravenous immunoglobulin (IVIG) within a 10-day window of fever onset. A prompt diagnosis is essential in ensuring good outcomes. In order to diagnose Kawasaki dis-

ease, clinicians rely on a classic pattern of symptoms; however, many children present with non-specific findings or symptoms that mimic other disease processes. In these cases, erroneous diagnoses may lead to delay in treatment of Kawasaki disease.

Case Description: A 3-year-old unimmunized boy presented to hospital with four days of fever, irritability, and neck pain. On physical exam, the child was febrile, had a rigid neck and bilateral non-purulent conjunctivitis. Laboratory and radiological findings were consistent with retropharyngeal abscess and the patient was started on intravenous antibiotic therapy. Despite 48 hours of intravenous antibiotics, the patient remained febrile. His symptoms slowly began to evolve - he developed prominent right anterior cervical chain lymphadenopathy, bilateral edema of the hands and a polymorphous rash. A diagnosis of Kawasaki disease was made. While the patient had a normal echocardiogram and a positive treatment outcome, appropriate high-dose aspirin and IVIG therapy was delayed by four days because of the atypical presentation.

Conclusion: Unusual clinical symptoms and radiographic findings in Kawasaki disease can be misleading and may contribute to delayed diagnosis and treatment. By recognizing that Kawasaki disease can initially present with specific head and neck manifestations such as retropharyngeal abscess, physicians may consider the diagnosis sooner, ultimately reducing the risk of cardiac sequelae in affected children.

Frontal Lobe Epilepsy Alters Functional Connections Within the Brain's Motor Network: A Resting-state fMRI Study

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Introduction: Patients with frontal lobe epilepsy (FLE) often experience motor deficits. Previous studies have associated impairments in patients with epilepsy with changes in resting-state connectivity; a technique that examines temporally-correlated brain regions at rest using modalities such as functional magnetic resonance imaging (fMRI). It is not known whether patients with FLE have altered motor networks, and if such alterations could contribute to functional motor deficits; therefore, resting-state motor networks were examined in participants with FLE using fMRI.

Methods: Thirteen patients (seven right FLE, six left FLE) and ten control participants were examined. While in the MR scanner, participants concentrated on a fixation cross for five minutes. fMRI data was analyzed using FSL. First, the left and right sensorimotor cortices were identified as regions of interest (ROI). The average BOLD signal from voxels in the ROI was compared to every voxel in the brain to determine the temporal correlation between BOLD signals. Mean maps were generated for each group and compared to determine voxels exhibiting a significant difference ($Z > 2.3$, corrected cluster significance $p = 0.05$). Laterality indices from resting-state maps were calculated for each patient and correlated with years since diagnosis, lifetime seizures, seizures in past year, and months since last seizure to determine significant relationships.

Results: Patients with FLE had significantly decreased connectivity between the left and right sensorimotor cortices compared with controls ($Z > 2.3$). Laterality indices were significantly correlated to total lifetime seizures (left FLE: $r_s = 0.89$, right FLE: $r_s = 1.00$). As patients experienced more seizures, the healthy hemisphere sensorimotor cortex became less connected to the epileptic hemisphere sensorimotor cortex.

Conclusions: Resting-state motor networks are altered in patients with FLE compared with controls, and differences become more pronounced when patients had experienced more lifetime seizures. These results have important implications for understanding the mechanisms behind daily motor deficits experienced by patients with FLE.

Evaluation of haptic controller dexterity with regards to driving surgical performance in teleoperated robotic-assisted surgery

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Introduction: In robotic-assisted surgery, the surgeon's interface is the component connecting the surgeon to their tools and environment. The interface is required to be responsive, intuitive, and ergonomic in order to optimize the advantages of robotic systems, and streamline transition from conventional surgical techniques. It can represent a significant bottleneck if

not designed appropriately, which would correlate negatively for patient outcomes. Surgeons require precision hand controllers that provide kinesthetic and in some cases tactile feedback, which also feature a wide range of motion and ergonomic considerations. Robotic systems without the sense of touch (haptics), have been recently introduced into medicine (e.g., da Vinci, Intuitive Surgical Ltd). The lack of haptic interaction has been identified as a major drawback of most current robotic-assisted surgical systems, and a satisfactory solution has yet to be developed. The purpose of this study was to evaluate existing haptic devices and drive design considerations for the development of a new surgical interface created specifically to enable robotic-assisted surgery.

Methods: Seven commercially available haptic hand controllers were procured for this study. Previous literature and experience within the neuroArm team identified dexterity as a key metric of haptic controller performance. Study design and performance metrics are also outlined for a future trial involving surgeons from numerous surgical disciplines immersed in simulation-based (virtual reality) surgical skill-testing scenarios. The project consists of several components: quantitative analysis, where dextrous workspace analysis of each hand controller was conducted; empirical study, via performance evaluation through simulation-based test-cases performed by surgeons from multiple surgical disciplines; subjective assessment, in which qualitative assessment of user-perceived performance was considered. We assessed performance based on several metrics: task completion time, errors (e.g., excessive force and slip), clutching frequency, path deviation from optimal trajectory and total traveled trajectory.

Results: Results included dexterity quantification in the form of isodexterity mapping and global conditioning indices, which showed that the hand controllers with greater ranges of motion also had lower values of GCI.

Conclusion: Further study will investigate how this correlates with performance in surgical scenarios.

Giardia cathepsin B proteases degrade interleukin-8 and attenuate neutrophil chemotaxis.

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Introduction: During acute inflammatory responses, the secretion of interleukin-8 (CXCL8) by intestinal epithelial cells (IECs) recruits extravasated neutrophils (PMN) to the basolateral membrane of the intestinal epithelium. Several parasitic organisms modulate aspects of their host's acute inflammatory immune response. *Giardia duodenalis* is a non-invasive protozoan parasite of the upper small intestine of many animals including humans. During *Giardia* infections, the small intestinal mucosa is devoid of signs of overt inflammation despite trophozoite numbers exceeding 10^6 per centimetre of intestine. Moreover, infections have been associated with decreased intestinal inflammatory responses via unknown mechanisms. The *Giardia* genome contains genes for 23 cathepsin-like cysteine proteases, most of which have no known function. The purpose of this study was to determine if *Giardia* cathepsin-like cysteine proteases modulate CXCL8 secretion from IECs and attenuate CXCL8-induced PMN chemotaxis.

Methods: *Giardia* trophozoites (assemblage A: NF, WB or assemblage B: GS/M) were co-incubated *ex vivo* with small intestinal mucosal biopsy tissues or *in vitro* with Caco-2 monolayers. After 2 hours, groups were administered recombinant interleukin-1 β (IL-1 β) (1.0 ng/ml), CXCL8 (1.0 ng/ml), or *Salmonella typhimurium* (MOI 100:1). Samples were processed for various assays, western blotting, qPCR, and PMN chemotaxis assays.

Results: Co-incubation of assemblage A *Giardia* trophozoites with small intestinal mucosal biopsy tissues or *in vitro* Caco-2 monolayers resulted in attenuation of IL-1 β -induced CXCL8 secretion; similar results were obtained when Caco-2 monolayers were apically administered *S. typhimurium*. *Giardia* assemblage A trophozoites decreased levels of recombinant CXCL8 administered to supernatants in the presence or absence of Caco-2 monolayers, while *Giardia* assemblage B trophozoites did not. Inhibition of cathepsin B proteases prevented assemblage A trophozoites from degrading CXCL8. Supernatants from the co-incubation of *Giardia* assemblage A trophozoites and Caco-2 monolayers with CXCL8 significantly attenuated CXCL8-induced PMN chemotaxis; these effects were reversed when cathepsin B activity was inhibited in *Giardia* trophozoites.

Conclusion: *Giardia* assemblage A cathepsin B-like proteases degrade CXCL8 and attenuate CXCL8-induced PMN chemotaxis.

Exploiting the Immunomodulatory Capacity of the Rat Tapeworm *Hymenolepis diminuta* to Treat Colitis

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Background: Epidemiological and proof-of-principle data support the concept of helminth therapy for several autoimmune disorders prevalent in Westernized societies. One goal is to isolate and characterize immunomodulatory molecules from parasitic helminths for drug development. We utilized the *Hymenolepis diminuta* (*H. diminuta*)-mouse model system to explore novel anti-inflammatory possibilities. We hypothesize that one or more anticolic molecules can be isolated from *H. diminuta*. To test this, mice are infected with *H. diminuta*, or injected with a crude extract thereof (HdAg), and the impact on dinitrobenzene sulphonic acid (DNBS)-induced colitis assessed.

Methods: Male Balb/C mice (n=7-8/group) were treated as follows: (1) infected with 1, 3 or 5 cysticercoids of *H. diminuta* and colitis induced 8 days later with DNBS (3 mg in 100 μ L 50% ethanol, i.r.); (2) given one injection (ip., sc. or im.) of 1 mg of PBS-soluble HdAg 6 h after DNBS; or, (3) given 10 μ g, 100 μ g or 1 mg of HdAg ip. 6 h after DNBS. Mice were monitored daily for 3 days, then necropsied and colitis assessed.

Results: Infection with even one *H. diminuta* protected mice from DNBS-induced colitis. This anticolic effect was accompanied by increased IL-4, IL-5 and IL-10, typical of the mammalian helminth infection response. Moreover, a single ip. or sc. (but not im.) injection of HdAg was as effective as a prophylactic as viable 5 cysticercoid infection of *H. diminuta* at inhibiting DNBS-induced colitis. A threshold dose of 100 μ g HdAg was needed for significant colitis inhibition.

Conclusion: The rat tapeworm, *H. diminuta*, is identified as a remarkably potent anticolic stimulus of DNBS colitis. We conclude that (a) infection with viable *H. diminuta* could be developed as a therapy for IBD, and (b) that *H. diminuta* has at least one effective anti-colic molecule, the isolation and purification of which could result in a novel therapeutic immunomodulator.

Multimodal Quantitative MR Imaging in Acute Ischemic Stroke: Mapping Tissue Fate

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Introduction: Stroke therapies are available within a “time window” (4.5 hours) of stroke onset with concerns about hemorrhagic transformation. We hypothesized that quantitative (q) implementations of conventional T1- and T2-mapping with magnetic resonance (MR) imaging could provide a more accurate depiction of tissue at risk of dying. Prediction of tissue fate is a step towards a “tissue window” paradigm of therapy where response to treatment is stratified by the “tissue properties” of ischemic brain.

Methods: Acute ischemic stroke patients were imaged within 6 hours of symptom onset and at 24 hours with a 3 T MR scanner. T1 mapping was performed with a 3D-GRE-LL sequence (22 phases) or a DESPOT1 sequence (two spoiled-gradient acquisitions). T2 mapping was performed using a CPMG sequence with 8 echoes (30 ms intervals) or 16 echoes (15 ms intervals). Typical diffusion-weighted imaging was also performed to provide apparent-diffusion coefficient (ADC) maps. Volumetric and absolute value analysis of the infarct core was conducted on the ADC, T1 and T2 maps.

Results: Fourteen patients were included with a median time from onset to first MR exam of 228 min. Eleven had detectable ADC lesions; median infarct volume on ADC increased from 13 ml at baseline to 29 ml at 24 hours. Nine patients had visible qT2 changes. Eight patients showed early qT1 changes. Distinct differences in ADC, qT1 and qT2 evolution were observed: qT1 reversal occurred in three patients; qT2 changes increased in all patients by 24 hours; qT1 and qT2 depicted changes in different areas of the suspected ischemia compared to ADC.

Conclusion: Distinct qT1 and qT2 changes occur in response to acute ischemic stroke. The presence of qT2 concurrent with reduced ADC suggests a more complicated process than cytotoxic edema, with the influence of blood-brain barrier compromise. These findings suggest qMR can define ischemic tissue properties, and may help in determining tissue fate.

A comprehensive case study of an orthopaedic surgery referral service in the Winnipeg Regional Health Authority: A single-entry model to manage waiting times for total joint replacement surgery of the hip and knee.

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Introduction: Single-entry is a wait time management strategy that consolidates multiple queues into one. When used for surgery, patients are referred to see the next-available surgeon. Gaining popularity across Canada, single-entry models (SEMs) have been shown to reduce wait times and improve patient experience but it is not clear how this model affects other aspects of quality of care such as acceptability, appropriateness and safety.

Methods: The Winnipeg Central Intake Service (WCIS; a SEM for hip and knee replacement) will be evaluated using a pre/post case study approach. Semi-structured telephone interviews will be conducted with multiple stakeholders: patients; family physicians; surgeons; surgical office assistants; and, those who designed the WCIS. Regression analysis will be applied to administrative data to measure changes in quality of care. This will be based on six dimensions of quality - acceptability, accessibility, appropriateness, effectiveness, efficiency and safety - and 20 quality of care indicators. Subsequent interviews (Round 2) and data analysis in 2014 will provide greater insight into the uptake, acceptability and performance of the model.

Results: Seventy stakeholder interviews have been completed (Round 1). Policy-makers and patients are in favour of the model because of reduced wait times and better availability of information related to patient care (appointment dates, preparation for surgery, etc.). Family physicians and surgeons appreciate the streamlined referral process but remain concerned about loss of autonomy and question the model's ability to permanently improve access. Surgical office assistants were initially opposed and faced an increase in administrative workload, but with ongoing support from the WCIS team and simplified processes, they are optimistic. Greater emphasis on assessment of capacity for change and readiness would have improved initial uptake and awareness among stakeholders.

Conclusion: Stakeholder expectations have been divergent and acceptance of SEMs has been conditional not universal. Continual improvement based on stakeholder feedback will be critical for sustained success.

Should pollution be considered when identifying human and animal populations at high risk for emerging infectious disease?

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Objectives/Introduction: Emerging infectious diseases (EID) have important impacts on human health and animal conservation and productivity. Most recent human EIDs are of animal origin. Organizations worldwide are focussed on predicting high risk areas of disease emergence to enable preparedness for EIDs before clinical and population impacts. Although it is known that exposure to chemical pollutants can cause immunomodulation in both humans and animals, little effort has been focussed on determining if pollution is a shared environmental exposure for EID risk.

Methods: A scoping literature review was undertaken to determine whether data and experiences in human and veterinary medicine supported the hypothesis that variation in environmental contaminants could affect vulnerability to EIDs. We also took a more in-depth look at the body of knowledge surrounding four cases.

Results: (1) Synergies and/or associations between rates of infectious diseases and levels of patient contamination could be found in both the veterinary and medical literature; (2) these trends could be found for multiple different species, exposure routes, diseases, and pollutants; (3) some associations could be found for the same contaminant in both people and animals;

(4) biologically plausible and demonstrable mechanisms for these associations were present in the literature; and, (5) pollution patterns are not homogenous globally and some of the more highly polluted regions have experienced EID events.

Conclusions: The literature supported our hypothesis and suggested that pollution tracking and control should be managed in concert with medical and veterinary programs intended to predict EID risk globally and reduce the impacts of infectious diseases.

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Role of Serine Protease Inhibitor (SERPINB3) in Radiation Response in Squamous Cell Carcinoma of the Cervix

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Introduction: Cervical cancer remains a significant global health problem: it is the second leading cause of cancer death in women worldwide. Currently, the primary treatment for patients with locally advanced disease (FIGO IB2-IVA) is high dose radiotherapy (RT), with chemotherapy. Unfortunately, a subset of patients are not cured, likely due to radiation resistance. There is an urgent need to develop better prognostic and predictive information for response to RT, in an effort to improve patient outcomes and reduce toxicities. The aim of this project is to identify and validate the candidate radiation response tumour biomarker SERPINB3 (a serine protease inhibitor found to protect tumors from apoptosis) in clinical specimens, and determine its role in clinical outcome in patients treated with RT.

Methods: Patients treated with radical RT for locally advanced cervical cancer were identified from a retrospective database; pre-treatment formalin-fixed paraffin-embedded tumour biopsies were retrieved. Cervical cancer specimens that passed GeneChip and Data QC were further tested: eleven non-responder samples (patients with cervical cancers that did not respond to RT) were evaluated versus twelve responder samples (patients with cervical cancers that responded to

radiation). These raw scores were analyzed with SERPINB3 probe sets in SPSS statistical software. Parametric and non-parametric analyses of these scores were correlated with histological, overall survival (OS) and progression-free survival (PFS). Finally, real time PCR analysis on ten cervical cancer specimens and normal cervix (control) were used to verify microarray dataset.

Results: Our microarray dataset demonstrates SERPINB3 levels were upregulated in responders and down-regulated in non-responders. This data was further supported by statistical analysis in which higher levels of SERPINB3 was correlated significantly ($p=0.033$) with responders. Furthermore, patients with higher levels of SERPINB3 (6.77-362.43) demonstrated significantly ($p=0.000$) better overall and progression-free survival ($p=0.001$). Real-time PCR results on ten blind cervical cancer specimens demonstrate similar results when compared with normal cervix data.

Conclusion: In this pilot study, we found that SERPINB3 was upregulated in responders and was associated with better clinical outcome. Follow-up with a larger dataset will be required to confirm these findings. In addition, further studies are required to determine the molecular role of SERPINB3 in response to RT.

A Systematic Literature Review of the Trail-Making Test and its Effectiveness in Identifying Cognitively Impaired Drivers

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Introduction: The medical community is well-placed to identify cognitively-impaired drivers who may no longer be safe to drive; however, the validity of commonly used screening tools for identification of cognitive impairment for *decisions about driving* is not well established. The primary objective of this research was to examine the accuracy of the Trail Making Test (Parts A and B) [TMT] for determination of driving competency.

Methodology: Using established systematic review methodology, a search of six electronic databases was conducted, with studies from database inception to June 2011 included. Key terms to identify studies using the TMT as a predictor variable for driving performance were used, with pre-defined

inclusionary/exclusionary criteria used for study selection. Rigorous full-text review with data extraction was conducted by both investigators blinded to each other's results.

Results: From an initial sample of 4,441 studies, 30 articles met the inclusionary/exclusionary criteria and were included in the systematic review. The results from the 30 empirical studies yielded 46 unique data points. The majority ($n = 36$) of data points had on-road evaluation as the outcome measure, with 10 data points having crashes ($n = 5$) or simulator results ($n = 5$) as the outcome measure. The vast majority of studies relied on correlational analyses, with only four studies using cutpoints. Only one of the four studies using cutpoints examined sensitivity and specificity, with a reported sensitivity of 45% and a specificity of 86%.

Conclusion: The results from the 30 empirical studies reveal that TMT-A and -B scores are *associated* with driving outcomes; however, knowledge of that association provides little in the way of information for decision making on driving competency in the clinical setting. Without the aid of empirically determined cut points, the use of the TMT for decision making on medical fitness to drive is questionable.

Does Land-Based Exercise Decrease Pain and Improve Function in Hip Osteoarthritis Patients? A Systematic Review and Meta-Analysis

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Introduction: Therapeutic exercise is commonly prescribed as treatment modality in the management of lower extremity osteoarthritis (OA). To date, however, there is conflicting evidence as to whether exercise is effective in reducing pain and improving function in hip OA patients. Given the disparate findings, the purpose of the present study was two-fold: 1) to determine whether land-based exercise is an effective intervention for decreasing pain and improving function in individuals with hip OA; and, 2) to determine whether semi- tailored exercise programs are more efficacious than generic exercise interventions with respect to pain and function outcomes.

Methods: Systematic review and meta-analysis of randomized controlled trials (RCTs) compared land-based exercise to a control intervention in people with hip OA not awaiting surgery. Group means, standard deviations and sample sizes were extracted from each study. From these data, mean differences, standardized mean differences (SMD = mean difference divided by the pooled standard deviation) and their 95% confidence intervals were calculated. When ≥ 2 studies measured the same outcome at time points within 6 weeks of each other, meta-analyses of their SMDs were performed. Confidence intervals that included zero were interpreted as having no effect. The PEDro quality index scale was used to determine the quality of the evidence.

Results: Eight RCTs involving 570 participants with hip OA were identified and included in the review. The eight identified RCTs scored an average of 7.5/10 on the PEDro quality index score indicating sound methodological quality. Pooled data revealed that exercise interventions had no effect on pain outcomes (SMD = -0.15 (-0.60 to 0.29) post-intervention or at follow-up (SMD = -0.15 (-0.55 to 0.25)) when compared with controls and no effect on self-reported function post intervention (SMD = -0.10 (-0.41 to 0.22), at 6-months (SMD = -0.13 (-0.43 to 0.18) or 10-12 months follow-up (SMD = -0.15 (0.55 to 0.26) and no effect on performance-based physical function. When only those studies that prescribed a semi-tailored exercise program were considered, data pooling of three studies revealed that exercise resulted in moderate improvements in pain (SMD = -0.78 (-1.21 to -0.35)) immediately post-intervention.

Conclusions: Low risk of bias studies provided no evidence of an effect of land-based exercise on pain and function (both self-reported and performance-based) post-intervention; however, exercise that is based on patient assessment findings (semi-tailored) does appear to impart a moderate beneficial effect on pain post-intervention and should be considered an important component of exercise based interventions in hip OA populations.

Dynamic Link Between Communication and Computation in an *in vitro* model of the human temporal neocortex.

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Objectives/Introduction: The role of theta frequency inter-laminar oscillations of the human neocortex and their role in the coordination of communication and computation is not well understood. We hypothesized that the requisite circuitry for both local computation and long-range communication should overlap and be related in a dynamic and functional way.

Methods: Electrical activity was measured from dual electrophysiological recordings from the deep and superficial lamina of human temporal neocortical slices resected during surgery for epilepsy. Cross frequency coupling (CFC), which is thought to represent a neural code implicated in local neuronal computation, and a variety of behavioural and cognitive correlates such as spatial awareness, sensation and memory were measured. Inter-regional oscillatory coherence is thought to be marker for long-range communication, and is encapsulated in what is known as the communication through coherence (CTC) hypothesis. Phase-dependent power correlations (PDPC), which was generated from the CTC hypothesis, were measured..

Results: There is a strong correlation between the strength of CFC and CTC between trials of oscillatory activity at theta (4-15 Hz) frequency. This correlation was particularly marked between CFC in the deep cortical layers and CTC between layers, indicating that deep layers may play a preferential role in driving inter-laminar communication.

Conclusions: For the first time, a quantitative correlation has been demonstrated between local computation and long-range communication. This result supports further research into an integrative approach to studying brain activity, whether *in vivo*, *in vitro* or *in silico*. Furthermore, such communication occurs at theta frequency, a frequency well known to be involved in both interlaminar and cortical-subcortical communication processes.