2011 CNMSRS Abstracts

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University of Manitoba,
June 7-9th, 2011

Dispensing geographies: understanding the realities of distance, telehealth, and oncology pharmacy practices in northern British Columbia

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OBJECTIVES
Northern Health services about 300,000 people across a geographic region comprising almost two-thirds of BC. In September 2008, Northern Health began using telehealth to assist with chemotherapy preparation in locales equipped to deliver chemotherapy but lacking a pharmacist to perform checks of the chemotherapy preparations. Currently, seven sites participate in and contribute to telehealth oncology pharmacy services in northern BC. The objective of the present research was to evaluate the challenges and successes surrounding the growth of telehealth technologies in the area of oncology pharmacy services.

METHODS
In order to gather data on the challenges or successes of telehealth for oncology pharmacy services in BC, telephone interviews were conducted with 37 health care professionals providing oncology services. Interviews were conducted by two medical students during July 2009. The interviewees included one patient, one patient caregiver, sixteen pharmacy technicians (techs), seven pharmacists, nine registered nurses (RNs), and three general practitioner oncologists (GPOs).

RESULTS
Results suggest the health professionals and patients feel positively about telehealth, believing it allows patients to receive chemotherapy in their home communities. However, challenges around scheduling, delays, safety, and confidentiality were identified.

CONCLUSIONS
Telehealth oncology pharmacy services are clearly fulfilling a need in the Northern Health region. Patients receive chemotherapy in their home communities. If challenges identified are addressed, telepharmacy for oncology may become more streamlined and efficient. This would provide a valuable service to the Northern Health region population and enable health-care professionals caring for oncology patients to communicate easily with each other.

Bevacizumab and Ranibizumab for neovascular age-related macular degeneration: A treatment approach based on individual patient needs

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Supervisor: Marc Hébert, PhD

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OBJECTIVES:
In this retrospective study, the aim was to compare the visual acuity (VA) outcomes of Ranibizumab and Bevacizumab at 1 year with a treatment regimen based on patient needs. Patients have received an initial treatment of three monthly intravitreal injections of Ranibizumab or Bevacizumab and retreatment was individually considered for each patient on the basis of optic coherence tomography, angiography and clinical examination.

METHODS:
Data were collected at the Centre Oculaire de Québec between June 2006 and December 2009. All eyes with prior or additional treatment for AMD were excluded. Clinical data included VA at baseline and 12 months (Snellen chart), and number of injections received over 12 months. For analysis, Snellen VA was converted into logMar.

RESULTS:
In total, 50 eyes were treated with Ranibizumab and 142 eyes with Bevacizumab. Mean age at baseline was 76.9 ± 8 years and 76.4 ± 8 years in the Ranibizumab and Bevacizumab group respectively. At 12 months, mean logMar equivalent of VA improved from 0.69 to 0.55 in the Ranibizumab group (p value = 0.006) and 0.70 to 0.67 logMar in the Bevacizumab group (p value > 0.05). 92% of eyes treated with Ranibizumab had lost fewer than 0.3 logMar at one year, as compared with 83% in...
the Bevacizumab group. The Ranibizumab group received a mean of 4.92 injections vs 4.75 in the Bevacizumab group over 12 months. After the first three injections, 20% of patients in the Ranibizumab group and 26% in the Bevacizumab group never needed another injection.

CONCLUSION:
Although VA stabilization is obtained with Bevacizumab, Ranibizumab significantly improves vision with fewer injections than monthly treatment through 1 year. These findings suggest that an approach based on clinical onset and angiographies may provide benefit by reducing the risks of adverse events associated with intravitreal injections.

**Miscibility and stability of sterol/phospholipid bilayers are optimized by the double bond position in the sterol nucleus**

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**OBJECTIVES**
Understanding the variation in the strength, number and types of interactions between the sterol ring system and neighboring phospholipid molecules is important in understanding the structure and function of sterol-containing membranes. This has important implications in treating sterol-involved pathological processes such as Parkinson’s, Alzheimer’s and prion-associated diseases, as well as some cancers. In this study, we investigated how the presence, position, and conjugation of the carbon 5,6 double bond in ring B of cholesterol influences the thermotropic phase behavior of dipalmitoylphosphatidylcholine (DPPC, a model mammalian lipid)/sterol mixtures.

**METHODS**
Film casts of binary mixtures of DPPC and 0 to 50 mol% sterol were dispersed in aqueous media and subjected to differential scanning calorimetry and Fourier-transform infrared spectroscopy. Data collected was analyzed to determine changes to lipid phase transition behavior with respect to temperature, cooperativity, enthalpy, and organizational structure.

**RESULTS**
Being fully miscible in a DPPC bilayer, cholesterol stabilizes the gel phase and reduces the enthalpy and cooperativity of the DPPC gel/liquid crystalline phase transition, eliminating its enthalpy by 50 mol% sterol. None of the other sterols studied have these abilities. Generally, we see that an all-trans ring system is required to stabilize the gel phase, and presence of a single double bond within ring A or B to abolish the phase transition at high sterol levels. All sterols in this study (equatorially-orientated carbon 3β-alcohols) broaden the phase transition better than corresponding axially-orientated carbon 3α-alcohols and carbon 3-ketones. Further, a conjugated double-bond system may give rise to additional electronic properties that lead to an increased favorability in interactions between like-like (sterol) molecules over like-unlike (sterol-lipid) molecules, the latter being a necessary condition for optimal sterol/lipid miscibility and stability.

**CONCLUSIONS**
Given the differences in the thermodynamic parameters obtained from DPPC mixtures containing different sterol ring conformations and their associated changes in bilayer stability and miscibility, it is clear that sterol conformation has a significant effect on bilayer physical properties. Any sterol molecule whose ring structure deviates from that of cholesterol is unlikely to be fully miscible in the mammalian cell membrane.

**Survey study of primary health care usage and experience in the gay male population of Winnipeg**

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**OBJECTIVES:**
To explore primary health care experiences, realities and preferences of Winnipeg’s gay male population and to determine whether gay men’s health care needs would be better met through access to a gay male physician.

**METHODS:**
Gay male survey participants were recruited through healthcare clinics, social venues serving the gay population and per-
CONCLUSIONS: Although the gay male population does not seem marginalized with regard to primary health care services, it is likely that for a subset health care needs may be better met through access to gay male physician.

Cystathionine gamma-lyase and hypoxia: Implicating hydrogen sulfide in the hypoxic stress response

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Neelam Khaper, PhD Associate Professor, Medical Sciences Division

OBJECTIVES: Hydrogen sulfide (H\textsubscript{2}S) is a novel and important gasotransmitter for the cardiovascular system, where it is generated by cystathionine gamma-lyase (CSE). Indeed, mice genetically deficient in CSE exhibited increased blood pressure, decreased H\textsubscript{2}S level and compromised vasorelaxation (Yang et al., 2008). Using vascular smooth muscle cells (SMCs) isolated from this unique model, we have recently shown that over-proliferation of CSE-deficient (CSE-KO) SMCs contributes to the observed hypertension (Yang et al., 2010). In the present study, we characterize the responses of these CSE-KO SMCs to hypoxic stress, a hallmark of vascular pathologies. Specifically, we explore cellular viability, death, redox balance, and expression of hypoxia-inducible factor-1\(\alpha\) (HIF-1\(\alpha\)).

METHODS: A commercial hypoxia tissue culture chamber afforded 12h cell incubations at 1% \(\text{O}_2\). Cellular viability/proliferation and superoxide dismutase (SOD) activity were assessed via colorimetric assays. Intracellular reactive oxygen species (ROS) and apoptosis were determined via fluorescence flow cytometry assays. Expression of HIF-1\(\alpha\) was evaluated via quantitative real-time PCR.

RESULTS: Under basal conditions, CSE-KO cells featured significantly greater proliferation and ROS versus their WT counterparts (\(p < 0.01\)). Hypoxia stressed significantly decreased viability of CSE-KO (\(p < 0.01\)) but not WT cells, and significantly greater apoptosis of CSE-KO versus WT cells (\(p < 0.01\)). Hypoxia induced similar increases in SOD activity in CSE-WT and KO cells (\(p < 0.05\)), but only CSE-KO cells exhibited significantly higher ROS versus control (\(p < 0.01\)). Hypoxia elicited greatly increased expression of HIF-1\(\alpha\) in CSE-WT cells (\(p < 0.01\)), but only a modest increase in KO cells (\(p < 0.01\)) versus control.

CONCLUSIONS: Taken together, these data suggest that endogenous CSE/H\textsubscript{2}S pathway modulates redox status and is essential for SMC survival under hypoxic conditions. Moreover, the observation of blunted HIF-1\(\alpha\) expression in hypoxic CSE-KO cells indicates a potential connection between CSE/H\textsubscript{2}S pathway function and HIF-1\(\alpha\)-mediated signal transduction.

Reduced alzheimer's disease pathology in APP/PS1 mice treated with drug candidate MC-032

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OBJECTIVES: MC-032 is a small molecule that has been shown to inhibit the aggregation of amyloid-\(\beta\) (A\(\beta\)) and tau, two proteins whose self-assembly into soluble neurotoxic aggregates is implicated in Alzheimer’s disease (AD). The molecule was further shown to rescue long-term potentiation (LTP) in hippocampal slices.
taken from doubly transgenic APP/PSEN1 mice, an animal model of AD, and reduce memory deficits in the mice, as determined in the Radial Arm Water Maze and Morris Water Maze. The objective of this study was to evaluate brains of APP/PSEN1 mice treated with MC-032 to determine whether they had reduced AD pathology compared to controls. Specifically, the study aimed to determine whether treated mice had fewer Aβ plaques and/or reduced levels of soluble Aβ oligomers compared to mice receiving vehicle.

METHODS:
Doubly-transgenic APP/PS1 mice received, from age 6 weeks to sacrifice at 6 months, either MC-032 (25 mg/kg, ip, n=4) or vehicle (n=3). After sacrifice and brain harvest, immunohistochemical staining techniques were used to quantify Aβ plaque burden in 40 µm brain sections, while Aβ oligomers were quantified by dot blot analysis of brain homogenate using A11 antibody.

RESULTS:
Aβ plaque load in the cerebral cortex was reduced by 30% in mice receiving MC-032 compared to controls (p=0.024). No difference was found in hippocampal plaque load. Aβ oligomer levels were also decreased in brains of treated mice – mice receiving MC-032 were found to have a 41% reduction in oligomer level compared to untreated litter-mates (p=0.036).

CONCLUSIONS:
MC-032 reduced Aβ plaque load in the cerebral cortex of transgenic AD mice, while at the same time reducing total-brain levels of Aβ oligomers. These results are consistent with memory improvements seen in mice administered the compound, recommending further evaluation of MC-032 for its potential as a novel and effective treatment for Alzheimer’s disease.

Autoimmune skin disease: A potential cause of widespread pruritic rash in the elderly?
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 Supervisor: Dr. John F. Elliott

OBJECTIVE:
Elderly patients with persistent widespread pruritic rash are seen fairly often in the dermatology clinic, but they seldom receive a clear diagnosis. We hypothesized that in at least a subset of these patients, their rash is occurring due to autoimmune reactions to self-antigens found specifically in the skin.

METHODS:
To test this hypothesis, we collected sera from 35 elderly patients, which we examined for the presence of autoantibodies to the skin protein bullous pemphigoid 180 (BP180). We chose to screen for autoantibodies to BP180 in part because of its known association with the autoimmune skin disease bullous pemphigoid, but also because a diagnostic assay for a specific polypeptide region of BP180, the NC16A region, was commercially available.

RESULTS:
Initial screening revealed that 6 patients out of 35 had levels of autoantibodies to NC16A high enough to be considered indicative of BP, despite the fact that all patients lacked the bullae considered diagnostic for BP. We then established a more cost-effective and inclusive enzyme-linked immunosorbent assay (ELISA) to test for autoantibodies to the N-terminal intracellular region of BP180 and have begun screening patient samples.

CONCLUSIONS:
Overall, our preliminary data suggests that screening for autoimmune disease in elderly pruritic patients may be a viable option, and may help generate a more precise diagnosis for this subset of patients in the future.

Retention of specialist physicians in Newfoundland and Labrador*
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Supervisor: Dr. Maria Mathews

BACKGROUND:
Although specialist physicians comprise nearly half of the physician workforce in Newfoundland and Labrador (NL), relatively little is known about their retention patterns. We compared two cohorts of physicians who were initially licensed to practise in NL between 1993 and 1997, and between 2000 and
2004 to examine whether retention had changed over time. Additionally, we examined the retention of four groups of physicians in each cohort: 1) fully licensed Memorial University Medical Graduates (MMGs), 2) fully licensed Canadian Medical Graduates (CMGs), 3) provisionally licensed International Medical Graduates (IMG(Prov)), and 4) fully licensed IMGs (IMG(Full)). Provisional licenses allow physicians who have not received Canadian certification to practise while obtaining credentials. We hypothesized that fully licensed physicians (largely locally trained physicians) would remain in NL longer than provisionally licensed physicians (largely IMGs).

METHODS:
Using data from the provincial medical registrar and Memorial University’s Office of Post-Graduate Medical Education, we used survival analysis (Cox regression) to compare the retention of the two cohorts and the four groups of physicians within each cohort.

RESULTS:
After 48 months, roughly 60% of the 2000-04 cohort physicians and 45% of the 1993-97 cohort physicians remained in NL. MMG comprised 61/180 (33.9%) of the 2000-04 cohort and 38/211 (18.0%) of the 1993-97 cohort. The 2000-04 cohort physicians were 1.6 (1.23-2.08) times less likely to leave NL compared to the 1993-97 cohort physicians. In the 2000-04 cohort CMGs, IMGs(Prov), and IMGs(Full) were 3.19 (1.47-6.89), 1.85 (1.09-3.17), and 4.39 (1.91-10.10) times more likely to leave NL compared to MMGs. In the 1993-97 cohort, IMGProv were 2.16 (1.37-3.42) times more likely to leave NL compared to MMGs. There was no significant differences in retention between MMG and CMGs or IMGs(Full) in the 1993-97 cohort.

INTERPRETATION:
The improvement in the retention of specialist physicians in NL since the 1990s may be attributable to the increase in the relative proportion of MMGs. While provisional licensing enables IMGs to begin practice in the NL, it does not lead to long-term retention.

*The full manuscript for this project has been accepted for publication in a forthcoming issue of Open Medicine.

Injury patterns and discharge dispositions in BC motorcycle crash victims
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OBJECTIVES:
Motorcycle ridership is on the rise in Canada. Though the risks of motorcycling have been documented in studies in the United States, Europe and Asia, there is a notable paucity of Canadian studies. This study uses a retrospective chart review to provide a descriptive analysis of injury patterns in motorcycle crash victims and their relationship to discharge disposition and length of hospital stay.

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

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

Most riders were discharged home (N=403, 70.0%). This group had significantly fewer injuries (M=2.2) than those who remained in hospital or expired (M=4.4 injuries). The most common injuries experienced by those discharged home were tibial and forearm fractures (N=70, 17.4%, for each), and ankle and/or foot fractures (N=69, 17.1%). Those who remained in hospital were most likely to have sustained injuries to the pelvis (N=43, 29.3%), cervical spine (N=38, 25.9%), or thoracic spine (N=37, 25.2%). Among the 14 patients (2.5%) who expired, the most common injuries were intracranial haemorrhage, rib fracture, haemothorax, liver injury, and cervical spine fracture (N=5, 35.7% for each).
CONCLUSION:
The results provide a starting point to help physicians predict injuries in motorcycle crash victims and highlight potential health care costs associated with increasing motorcycle usage.

Primary health care needs assessment for Calgary’s homeless populations and the role of a student-run medical clinic
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Dr. Wilfreda Thurston

OBJECTIVES:
Significant barriers impede individuals experiencing homelessness from accessing health services, and there is a paucity in the research literature describing how Canadians experiencing homelessness access care. The focus of this study is on (1) the health needs of Calgary’s homeless populations, (2) barriers that hinder them from accessing primary healthcare services and (3) what the role of a student-run medical clinic should be in addressing these needs and barriers.

METHODS:
This study was a needs assessment and involved collecting data from stakeholders in the University of Calgary Student-Run Clinic. These included homeless clients, employees from several homeless healthcare agencies, faculty of medicine representatives and medical students. Data was collected via open-ended interviews (n=15) and focus groups (n=22). Interview transcripts were analyzed into themes using NVivo qualitative analysis software.

RESULTS:
Some of the primary health care needs which were identified by stakeholders included mental health, addictions, chronic disease management, urgent care, and care that addresses the social determinants of health. Stakeholders identified that the health care needs among Calgary’s homeless populations are complex, often describing the needs as overwhelming. Types of barriers to primary care included: financial, geographical, structural, emotional and educational barriers.

Stakeholders identified that the student-run clinic could facilitate communication between social agencies and health care professionals, provide after-hours care, help patients navigate through the health care system, and provide educational and emotional support to patients. Stakeholders also emphasized that educating medical students early on and providing population-specific training may encourage them to continue working with marginalized populations as physicians.

CONCLUSIONS:
Our findings highlight the diverse primary health care needs and barriers of Calgary’s homeless populations. A student run medical clinic has the potential to address some of these gaps in care and may encourage medical students to pursue careers that involve caring for socially marginalized populations.

Plasmodium falciparum histones induce endothelial pro-inflammatory response and barrier dysfunction
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OBJECTIVES:
Severe Plasmodium falciparum infection is associated with endothelial activation and permeability that are important determinants of the outcome of the infection. How endothelial cells become activated is not fully understood but is believed to be either a response to cytokines from leukocytes and/or a direct effect of parasite components. Here we explored the direct effect of parasite components on endothelial pro-inflammatory responses and barrier function.

METHODS:
Primary human dermal microvascular endothelial cells (HDMEC) were stimulated with purified extracts from clinical P. falciparum isolates. In vitro endothelial signaling, pro-inflammatory responses and barrier function were examined using Western blot, PCR, ELISA and transwell permeability models.

RESULTS:
In this study, we demonstrated that P. falciparum sonicates directly stimulated the production of IL-8 and other inflammatory mediators by HDMEC through a signalling pathway that involved the Src family kinase Lyn and p38 MAPK. The active parasite component was identified as acid soluble proteins of which histones were a major constituent.
The role of histones was confirmed by abrogation of the stimulatory effect of HCl-extracted histones (HeH) by histone-specific antibodies and the use of recombinant P. falciparum H3 (PfH3) and recombinant human H4. The release of nuclear contents upon IRBC rupture was captured by live cell imaging using the cell membrane impermeable DNA stain Sytox Green, and was confirmed by detecting nucleosomes in supernatants of parasite cultures. HeH and recombinant histones also induced endothelial permeability through a charge-dependent mechanism that resulted in disruption of junctional protein expression and cell death. Recombinant human activated protein C cleaved HeH and PfH3 and prevented IL-8 production and increased permeability. Circulating nucleosomes of both human and parasite origin were detected in the plasma of patients with falciparum malaria, and correlated positively with disease severity.

CONCLUSIONS:
These results strongly support a pathogenic role for both host- and pathogen-derived histones in P. falciparum malaria.

The nude mouse model of human hypertrophic scar

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OBJECTIVES:
Hypertrophic scar (HSc) is a poorly understood fibroproliferative disorder affecting the skin, which, develops following deep dermal injury. This disorder results in cosmetic as well as functional limitations for patients including a reduction in extremity range of motion, intense pruritus and heat intolerance. HSc responds slowly and incompletely to currently available therapies. One barrier towards improving our understanding of HSc and developing novel treatment options is the lack of a relevant animal model. The objective of this study is to demonstrate that grafting human skin onto the backs of nude mice results in scars with morphologic and histologic characteristics of human HSc.

METHODS:
Twenty nude (Foxn1nu/Foxn1nu) mice were grafted with split thickness human abdominal skin (human xenografts). Post-operatively, mice recovered and wounds were photographed weekly to document healing. Animals were euthanized in groups of five at 30, 60, 120, and 180 days post-operatively. Scar biopsies were harvested for histological analysis, including skin thickness measurements and relative expression of decorin.

RESULTS:
Macroscopically, 19/20 of mice developed red, shiny, firm, elevated scars, grossly resembling human HSc. The average human xenograft thickness was 541 ±2 μm and 157 ±3 μm for normal, uninjured mouse skin (paired t-test, p=0.0001). Histologically, human xenograft biopsies demonstrated thickened, disorganized collagen fibers, increased vascularity and hypercellularity all characteristic of human HSc. Relative expression of decorin, a small leucine-rich proteoglycan (SLRP), known to be decreased in HSc, was also decreased in human xenografts compared to normal human skin.

CONCLUSION:
Human skin grafted onto nude mice results in scars that are morphologically and histologically similar to human HSc. The nude mouse model therefore represents a promising research tool in the study of human HSc. Immunohistochemistry for biglycan (SLRP) and RT-qPCR for decorin are ongoing.

Assessment of delay of knee magnetic resonance imaging in 10-16 year olds who have undergone MRI for activity related injury

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OBJECTIVES:
To determine the time interval between injury and Magnetic Resonance Imaging (MRI) in 10-16 year olds with activity-related injuries and compare this with the perceived ideal time to image.

METHODS:
A search of patients between 10 and 16 years of age (mean = 14.9) imaged at our institution and a private clinic from July 2005 to July 2010 yielded 345 MR examinations of the knee. One hundred and seven were excluded for various reasons, leaving 238 included in this study. Information identifying the
patient or indicating time of injury was removed and the images and reports were presented to two orthopedic surgeons, who indicated if the MR study was necessary and when imaging should have occurred post-injury to allow for optimal management. This number was then compared with the actual interval from injury to imaging. For analysis the cases were grouped into three study cohorts based on the primary pathologic finding (cartilage, meniscal, and ligamentous injuries).

RESULTS:
MR imaging was considered necessary by surgeon 1 and/or surgeon 2 in 141 cases (59.2%). For these patients, the average wait time from injury to imaging was 47.3 days (range 0 to 178). The mean recommended time from injury to MRI (as determined by averaging the opinions of surgeon 1 and 2) for the overall study group was 18 days (IQR 7-28). We found a statistically significant delay in imaging when examined within various types of injuries (p<0.01) and all injuries combined (p<0.001). The median delay time in patients who required imaging is 21 days.

CONCLUSION:
Our data suggests that there is a significant delay in MR imaging for this demographic with knee injury regardless of injury type.

Impact of EC-IC bypass on cerebrovascular reactivity and clinical outcome of patients with symptomatic moyamoya vasculopathy
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OBJECTIVE:
To determine whether symptomatic Moyamoya patients with impaired cerebrovascular reactivity (CVR) benefit from cerebral revascularization.

METHODS:
Brain revascularization was performed using a direct superficial temporal artery to middle cerebral artery (STA-MCA) bypass or indirect Encephalo – Dural – Arterial Synangiosis (EDAS). CVR was measured pre- and 3 months post-operatively using BOLD-MRI imaging during iso-oxic hypercapnic changes in end-tidal carbon dioxide. Outcomes were assessed by MR imaging, clinical examination and mRS scores.

RESULTS:
55 hemispheres were revascularized in 39 patients (STA-MCA in 47, EDAS in 8). Surgery effectively reversed CVR impairment in 52 hemispheres (94.5%), and in 36 of 39 patients (92.3%; Fisher’s exact test, p<0.001), and this was predictive of a patent EC-IC bypass. New, clinically-silent perioperative hemorrhages, cortical foci of ischemia, or new white matter T2 hyperintensities were detected after 11 surgeries (20%), but no new lesions arose after 3 postoperative months. One patient suffered a clinical perioperative stroke (1.8%). In clinical follow-up, 37 of 39 patients (95%) had stable or improved MRS scores and 2 patients (5.1%) worsened. No patients with patent bypasses or CVR improvements exhibited new clinical symptoms but failure of CVR improvement corresponded to a poorer long-term outcome (Fisher’s exact test, p<0.001).

CONCLUSIONS:
Cerebral revascularization surgery is a safe and effective treatment for reversing preoperative CVR defects and preventing preoperative symptom recurrence. Moreover, CVR measurements may be useful in long-term follow up and for predicting bypass patency.

Cardiac dysfunction in the diabetic heart is associated with abnormal myocardial lipid metabolism
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Dr. Jason Dyck, Dr. Thomas Pulinilkunnil, Dr. Petra Kienesberger

OBJECTIVE:
Diabetic patients often exhibit cardiac dysfunction, which is associated with enhanced myocardial triacylglycerol (TAG) deposition. The objective of this study was to determine whether the dysregulation of triacylglycerol (TAG) catabolism results in elevated TAG levels and cardiac dysfunction in the diabetic heart.

METHODS:
To simulate a diabetic state, genetic (12 week old Akita mice) and pharmacological (4-week post intraperitoneal injection of 225 mg/kg Streptozotocin, STZ, in C57Bl6 mice) models
were utilized. In vivo cardiac function was assessed by transthoracic echocardiography. To determine the role of cardiac adipose triacylglycerol lipase (ATGL), the rate-limiting TAG hydrolyzing enzyme in diabetic cardiomyopathy, a mouse model with cardiac-restricted overexpression of ATGL driven by the alpha-myosin heavy chain promoter (MHC-ATGL) was utilized, in which diabetes was also induced by administering a single dose of streptozotocin (STZ, 185 mg/kg i.p.). At the end of the study, mice were euthanized and hearts were frozen in liquid nitrogen for biochemical analysis.

RESULTS:
Diabetes induced hyperglycemia, hyperlipidemia, body weight loss, and marked cardiac dysfunction in Akita and STZ-diabetic mice. Cardiac TAG content and ATGL expression were also increased in both models. To clarify whether this elevation in cardiac ATGL during diabetes is detrimental or protective for cardiac function, we studied four-week STZ-diabetic WT and MHC-ATGL mice. Hyperglycemia, hyperlipidemia, and body weight loss were comparable between genotypes. Echocardiographic and histological analysis revealed cardiac dysfunction in the diabetic WT mice, which was associated with increased myocardial TAG content. In addition, we observed enhanced expression of the FA transporter, CD36, and the lipid-binding protein, Oxpat, indicating increased FA uptake and oxidation in the diabetic heart. Diabetic MHC-ATGL mice did not exhibit cardiac dysfunction, lipid accumulation, or upregulation of proteins involved in fatty acid utilization.

CONCLUSIONS:
These findings suggest that upregulation of cardiac ATGL during diabetes is an adaptive, albeit insufficient, response to compensate for the increased accumulation of myocardial TAG and that overexpression of ATGL prevents TAG accumulation and diabetic cardiomyopathy.

ACKNOWLEDGEMENTS:
Alberta Innovative Health Solutions and Canadian Institute of Health Research

Lamin A/C expression is a prognostic indicator in stage 3 colorectal cancer, and a predictor for the development of distant metastasis

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OBJECTIVES:
Colorectal cancer lacks reliable biomarkers for individual patient prognosis. Lamin A/C expression in tumor nuclei has potential use as such a biomarker, we determined its utility in this role.

METHODS:
We collected demographic, molecular, pathological and clinical data from 391 patients with colorectal cancer, and developed a tissue microarray with their tumors. We performed immunohistochemistry with antibodies against lamin A/C, and assessed its value as a prognostic marker.

RESULTS:
Expression of lamin A/C in >25% of tumor cells was significantly associated with advanced clinical stage at diagnosis (P=0.01), with increased risk of disease-specific death (HR 1.59, P=0.02), and development of distant metastasis (HR 2.53, P=0.006). After multivariate adjustment, the independent risk of developing metastases was 2.5 fold greater for patients whose tumors expressed lamin A/C in >25% of cells compared to those whose tumors expressed lamin A/C ≤25% of cells (HR 2.55, P=0.006). These results were driven by outcomes in patients with stage 3 tumors. Patients with stage 3 tumors and high lamin A/C expression had a significant, independent, increased risk of disease-specific death (HR 4.14, P=0.01), and development of distant metastasis (HR 3.42, P=0.03). In stage 3 patients treated with chemotherapy this biomarker was an independent predictor of death from their disease (P=0.01).

CONCLUSIONS:
Lamin A/C expression in tumor nuclei is an independent, negative prognostic indicator for CRC patients diagnosed with stage 3 tumors. It is also a strong, independent predictor of developing distant metastasis, and a potential predictive marker for decreased response to standard adjuvant chemotherapy.
Drusen and pro-inflammatory proteins in the post-mortem human eye

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OBJECTIVE:
Earlier studies found components of drusen promote inflammation through the up-regulation of multiple pathways in RPE cells. In this study, we evaluated the association between increasing age/presence of drusen and levels of selected cytokines and proinflammatory mediators in the retina of the postmortem human eye.

METHODS:
Normal human eye tissues were sectioned and probed with antibodies against IL-1β, CFI, RSAD2, STAT3, and CXCL-11. Donors were characterized either by age groups (<57 years old verses ≥70 years old) or by size and presence of drusen independent of age.

RESULTS:
Level of IL-1β and activated form of STAT3 increase dramatically with both advanced age and presence of drusen. RSAD2 expression/accumulation appears to be independent of age but did increase significantly in donors with drusen deposits. Like RSAD2, CXCL-11 levels are also higher in donors with drusen deposits, independent of age. However, in retinal tissue, we only observed a significant increase in CFI with respect to age. Donors with drusen did not appear to express more CFI than those donors without drusen.

CONCLUSIONS:
We found that with increasing age and drusen accumulation, the environment of the eye tends to shift towards a pro-inflammatory state through either IL-1β and/or possibly INF-γ pathways. Little change is induced in CFI, a negative regulator of the complement system, suggesting that the complement system may not yet be affected in these normal donors. Furthermore, a novel accumulation pattern of CXCL-11 in younger donors with drusen highlights its possible role as a precursor to future disease.

The effect of personality on functional outcomes of patients diagnosed with mood disorders: The role of personality dimensions

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Supervisor: Dr. Roger S. McIntyre

OBJECTIVES:
The aim of this work is to determine whether normative personality dimensions predict personal and work functionality of patients with mood disorders.

METHODS:
Personality dimensions were measured with the NEO-Five Factor Inventory (NEO-FFI), and functionality with the Sheehan Disability Scale (SDS; Global and domain-specific [social life, family life and work impairment]) and Endicott Work Productivity Scale (EWPS; work productivity), in adults (age > 18) with DSM-IV-TR-defined MDD (N=400), BD (N=317) and any mood disorder (MDD and BD). Bivariate correlations and linear multiple regressions were performed.

RESULTS:
Global functional impairment was significantly predicted by lower conscientiousness in individuals with MDD (p=0.017), whereas social impairment was significantly predicted by lower extraversion in the any mood disorder (p=0.001) and BD (p=0.021) groups. Family impairment was significantly predicted by lower conscientiousness in individuals with any mood disorder (p=0.004), and lower work productivity was significantly predicted by lower conscientiousness in all mood disorder groups (Any mood disorder: p<0.001, MDD: p=0.002, BD: p=0.021).

CONCLUSIONS:
The results herein suggest that discrete personality dimensions predict functional outcomes in individuals with mood disorders. Personalizing disease management approaches in mood disorders with a particular emphasis on vocational rehabilitation should give consideration to measurement and intervention targeting personality in individuals with mood disorders.
Extended adjuvant temozolomide and cis-retinoic acid for glioblastoma multiforme patients in Manitoba: Molecular correlates to clinical outcomes
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University of Manitoba, Faculty of Medicine, UGME program
Dr. Marshall Pitz & Dr. David Eisenstat

OBJECTIVES:
Glioblastoma multiforme (GBM) cells paradoxically survive under hypoxic conditions, circumventing the normal action of Bcl-2 nineteen kDa interacting protein (BNIP3) and down-stream activation of apoptosis inducing factor (AIF). This study seeks to determine whether expression of these molecules correlates to survival outcomes.

METHODS:
All GBM patients at CancerCare Manitoba from 2002-2009 were assessed. Inclusion criteria: histologically confirmed GBM, age 18-70 years, receipt of chemoradiotherapy (CRT), and intention to treat with adjuvant temozolomide (TMZ) and concomitant cis-retinoic acid (CRA). Patients received up to 30 cycles of TMZ (150-200 mg/m² days 1-5/28 day cycle) concurrent with (CRA) (50 mg/m² BID) days 1-21. BNIP3 and AIF expression were determined on formalin-fixed paraﬃn-embedded (FFPE) section slides of patient tumours using immunohistochemistry. Correlation between BNIP3 and AIF expression and survival outcomes were examined.

RESULTS:
Eighty patients met inclusion criteria. Fifty-two tissue samples have been analyzed representing thirty-eight patients. Median overall survival (OS) for the cohort initiating adjuvant therapy was 18.9 months and median progression free survival (PFS) on TMZ was 9.6 months. Nuclear BNIP3 expression highly correlated with low AIF expression. Thirty-three of thirty-seven samples with nuclear expression of BNIP3 had minimal expression of AIF. Previously completed analysis of 29 patients did not demonstrate statistically significant survival advantage based on BNIP3 or AIF status.

CONCLUSIONS:
Nuclear BNIP3 expression and low AIF expression tended to be associated with poorer overall survival, though this was not statistically significant. Evaluation of tumour sections for the full cohort is ongoing.

Sub-cellular localization of Y-box protein 1 regulates proliferation, invasion, and increased mesenchymal phenotype in astrocytomas
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1
McGill university
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Supervisor: Dr. Nada Jabado.
Xiao-Yang Liu1, Damien Faury3, Caroline Sollier, Noha Gerges, Brian Meehan, Zhifeng Dong, Peter Siegel, Andrey Korshunov, Stefan Pfister, Janusz Rak and Nada Jabado1

OBJECTIVES:
Y-Box-Protein-1 (YB1) is a transcriptional/translational regulator implicated in cancer progression. We previously established elevated YB1 levels in pediatric Glioblastoma (GBM), possibly driving oncogenesis in this cancer. The purpose of this study is to investigate the role of YB1 in glioblastoma genesis and its possible association with poor prognosis.

METHODS:
We overexpressed or silenced YB1 protein in 2 GBM cell lines SF188&U87 and normal human astrocytes immortalized with H-Tert (NHA). Proliferation, migration, so agar colony formation assays were performed, accompanied by mice xenograft to assess the tumorigenic and metastatic ability of these cells. Meanwhile, tissue microarrays including 150 pediatric GBM and 70 Grade I Pilocytic Astrocytoma were stained immunohistochemically (IHC) with YB-1, to identify any association with patient prognosis and tumor grades.

RESULTS:
In all YB1 silenced clones, residual YB1 was nuclear, and cells showed increased proliferation. Ectopic expressed YB1 in GBM cell lines was predominantly cytoplasmic, similar to endogenous YB1. In NHA, silencing YB1 increased proliferation and decreased cell migration, while ectopic expression induced the reverse, in addition to the induction of marked mesenchymal features in these cells. Subcutaneous injection of YB1-overexpressing-U87 cells into SCID mice showed increased metastatic ability into the liver. IHC on tissue microarrays of patient tumors showed strong YB1 expression in 66% of pediatric GBM samples, but only 8% in Grade I astrocytoma, suggesting a role of YB1 in a more invasive tumor phenotype. In addition, we showed that nuclear YB1 expression indicated worse progression free survival compared to cytoplasmic YB1 expression in the 150 pediatric GBM tumor samples.
CONCLUSIONS:
YB1 modulates cellular proliferation and mesenchymal properties, including migration and metastasis, based on its subcellular localization. While ascertaining the role of nuclear YB1 in driving cell growth and its association with worse patient prognosis, our data argue for caution in targeting YB1 for therapeutic intervention.

Assessment of significant of blood oxygen level dependent (BOLD) imaging in patients with coronary artery disease – a validation study using fractional flow reserve
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University of Calgary

Supervisor: Dr. Matthias Friedrich
Judy Luu, Jodi Harker, Dominik Guensch, James Hare, and Matthias Friedrich

BACKGROUND/OBJECTIVES:
Blood oxygen level–dependent (BOLD) cardiac MRI (CMR) uses the signal generated by haemoglobin to directly measure tissue oxygenation and may represent a non-invasive method to assess myocardial ischemia in patients with coronary artery disease (CAD). The aim of this study was to validate whether BOLD CMR can detect and quantify alterations in myocardial oxygenation in CAD.

METHODS:
Oxygen-sensitive BOLD CMR scans were performed in patients who were scheduled for clinically-indicated coronary angiography. BOLD images were captured during rest and adenosine-induced coronary hyperemia. The mean BOLD signal intensity (SI) percent changes in segmental regions were calculated between rest and hyperemia and were compared to intracoronary fractional flow reserve (FFR) assessed on angiography. FFR is the current gold standard to assess the extent of coronary occlusion (FFR <0.80 indicates significant stenosis).

RESULTS:
Twenty-eight patients totaling 147 myocardial segments were available for analysis. 73 segments were excluded, with 66% of these being apical. The remaining 74 segments equated to 22 patients (60 +/- 9y, 19 males), eight of these had a normal FFR (± 0.80) and 14 had FFR values <0.80. Mean BOLD SI percent change was significantly less in patients with abnormal FFR values (-4.62 +/- 2.28% SEM), in comparison to patients with normal FFR values (8.54 +/- 3.08 % SEM); p=0.003. The Bland-Altman analysis indicated that the 95% limits of agreement between the two readers ranged from -23.6% to 27.8%, with a mean of 2.08%.

CONCLUSION:
This pilot study found that BOLD-sensitive CMR can detect changes in oxygenation in patients with CAD. Our preliminary data suggests that BOLD-sensitive CMR may allow for a non-invasive approach to directly assess myocardial ischemia in patients with coronary artery disease.

Chitosan/pVaxFGF18 promotes peri-implant bone formation through non-FGFR3 signaling in a murine model of osteopenia
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McGill University

E.J. Harvey, J.E. Henderson

OBJECTIVES:
The study is aimed at determining if a chitosan/Fibroblast Growth Factor-18 (chitosan/pVaxFGF-18) complex can effectively delivered down the femoral canal in a murine model and act locally to induce bone formation around implanted intramedullary titanium-coated rods.

METHODS:
The femoral canals of 5 FGFR3-/- and 4 FGFR3+/+ C3H mice were canalized and the chitosan/pVaxFGF18 solution was injected in the left femurs, saline solution in the right and smooth, titanium-coated nylon rods were bilaterally inserted. The animals were given 6 weeks to allow for bone formation to occur, then were euthanized and their femurs harvested. Femurs were fixed in 4% paraformaldehyde (PF) for 24 hours and washed twice in phosphate-buffered saline (PBS) over 48 hours. They then underwent Micro Computed Tomography (MicroCT) scanning and histological analysis. Further tests were conducted using fluorescent chitosan and chitosan/LacZ to determine if chitosan remains at the site of delivery and if the plasmid effectively transfected the targeted cells.
RESULTS:
In the wild-type mice, when comparing chitosan/pVaxFGF18-treated femurs with saline controls, no significant increase in bone formation was noted. Conversely, 2 out of the 4 wild-type animals exhibited markedly less peri-implant bone in the treated femurs. However, in FGFR3-/- osteopenic mice, peri-implant bone formation was consistently elevated in all chitosan/pVaxFGF18-treated femurs compared to controls. Furthermore, the trabecular pattern factor, which measures the relative convexity or concavity of bone and is therefore considered to be an inverse indicator of bone connectivity, was consistently lower in chitosan/pVaxFGF18-treated femurs. These findings indicate that in an FGFR3-/- genetic background, chitosan/pVaxFGF18 produces more, better connected peri-implant bone compared to controls.

CONCLUSION:
In a murine model of peri-implant bone formation, chitosan/pVaxFGF18 produces more, well-connected bone compared to saline controls in an FGFR3-/- background. Additional studies are needed to fully explain these findings.

Mitochondrial inhibition alters calcium handling in hippocampal neurons
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Dr. Stefan Kruger, Department of Physiology & Biophysics

OBJECTIVES
Ca^{2+} deregulation is centrally involved in the pathophysiology of stroke. Physiologically, neuronal Ca^{2+} homeostasis is tightly maintained through chelation by Ca^{2+} binding proteins, extrusion by the PMCA and the Na/Ca exchanger, and uptake into cellular Ca^{2+} stores. Mitochondria have a dual role: they are a source of ATP utilized by PMCA, and act as a Ca^{2+} store, acting as a transient Ca^{2+} sink during large Ca^{2+} transients. Ischemic stroke directly affects mitochondria, impairing both functions.
The objectives were the following: (1) can the genetically encoded Ca^{2+} indicator, GCaMP4, be used to sensitively measure Ca^{2+} transients in axons of cortical neurons? (2) what is the effect of mitochondrial inhibition on Ca^{2+} transients? (3) how does the arrest of mitochondrial respiration affect basal cytosolic Ca^{2+} concentrations?

METHODS
Calcium transients were measured in axons and presynaptic varicosities in a minimally invasive way – using a genetically encoded Ca^{2+} indicator named GCaMP4. Mitochondrial respiration was inhibited with antimycin A.

RESULTS
We found that following the inhibition of mitochondrial respiration, the recovery of action potential-evoked calcium transients was substantially prolonged but their amplitudes remained unchanged. Moreover, we observed apparently spontaneous, transient, localized calcium transients which may be of functional significance by increasing the frequency of spontaneous neurotransmitter release.

CONCLUSIONS
(1) The genetically encoded calcium sensor, GCaMP4, can be used to measure Ca^{2+} transients in axons and presynaptic varicosities in a minimally invasive manner. It leaves the linear range following ~20 action potentials (2) With cessation of mitochondrial respiration, evoked Ca^{2+} transients initially remain unaltered. After 10-15mins, however, the decay of the calcium transient is significantly delayed while the amplitude remains unchanged (3) After 10-15mins of mitochondrial inhibition, basal Ca^{2+} concentrations show transient regional elevations. This may have impact on spontaneous neurotransmitter release.

Attenuation of inflammatory responses from cystic fibrosis monocytes by an innate defence regulator (IDR) peptide
Matt Mayer
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Supervisor: Robert E. W. Hancock

OBJECTIVES:
In cystic fibrosis (CF), progressive respiratory failure occurs due to chronic, exaggerated inflammatory responses triggered by bacterial colonization of the lungs. Innate defence regulator peptides (IDRs) are synthetic derivatives of endogenous host defence peptides, and under investigation as anti-infective agents. IDRs lack effective direct antimicrobial activity; rather, they facilitate eradication of bacterial pathogens by increasing leukocyte recruitment to foci of infection. Immunomodulatory IDRs (such as IDR-1018) also limit bacterial-mediated in-
flammation *in vitro* and *in vivo*, counterbalancing toxic sequelae that accompany heightened innate immune responses. The aim of this study was to investigate the ability of IDR-1018 to attenuate exaggerated inflammatory responses exhibited by CF peripheral blood mononuclear cells (PBMCs).

**METHODS:**
Blood from clinically stable pediatric CF patients (n=5) or healthy donors (n=5) was used to isolate PBMCs. Cells were treated with inflammatory bacterial products (LPS or flagellin) +/- IDR-1018, and cytokine production was quantified by ELISA. RNA was isolated from the PBMCs, and analyzed using Illumina Gene Expression platforms. Network analysis of cellular transcriptional responses was carried out using open source bioinformatics tools InnateDB, MetaGEX, and Cytoscape.

**RESULTS:**
LPS and flagellin elicited exaggerated responses from CF PBMCs, including production of chemokines (MCP-1) and pro-inflammatory cytokines (TNFα, IL-6). IDR-1018 pretreatment normalized the responses between CF and control PBMCs by increasing MCP-1 production in healthy cells, and decreasing TNFα/IL-6 production in CF cells. Network analysis of transcriptional data from both groups revealed IDR-1018 altered cellular responses to LPS and flagellin through well integrated protein-level interaction networks with discrete “hubs”, including Src, Stat1, and Hnf4α.

**CONCLUSIONS:**
IDR-1018 attenuated the heightened innate immune responses of CF PBMCs to bacterial ligands, with network analysis providing preliminary insights affected cellular pathways. As both antibiotics and anti-inflammatory agents are efficacious in CF, further studies into therapeutics with both properties could lead to new translational bedside strategies.
Distinct responses to prostaglandin E2 in upper and lower segment human myometrial smooth muscle cells

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OBJECTIVES:
We have previously demonstrated that prostaglandin E2 (PGE2) can repress inflammatory chemokine output from cultured primary human myometrial smooth muscle (HMSM) cells isolated from the lower segment of the pregnant uterus. Using selective agonists for PGE2 receptor (EP) subtypes, this effect has been demonstrated to occur via EP2 and EP4, but not EP1 or EP3. As it has been suggested that there may be functional differences between regions of the pregnant uterus, we next sought to investigate whether PGE2 would elicit the same effect in HMSM cells isolated from the upper segment of the uterus.

METHODS:
Paired upper and lower segment myometrial biopsies were obtained from Caesarean section procedures at term, prior to labour onset (n=3) and utilized to isolate HMSM cells. Cells were treated with prostaglandin receptor agonists (10nM – 300pM) in the presence and absence of IL-1β (1ng/ml). IL-8 output was determined by ELISA.

RESULTS:
Treatment of HMSM cells with IL-1β resulted in a significant increase in IL-8 output compared to non-stimulated controls in both lower and upper segment. IL-8 output was greater in lower segment HMSM cells compared to upper segment HMSM cells. PGE2 significantly repressed IL-1β-induced IL-8 output from lower segment HMSM cells in a dose-dependent manner (Student's t test, p*<0.05 at 30nM); however, this effect was not observed in upper segment HMSM cells. Furthermore, selective EP2 and EP4 agonists repressed IL-1β-induced IL-8 output in lower segment HMSM cells but failed to do so in upper segment HMSM cells.

CONCLUSIONS:
We demonstrate that within the uterus, smooth muscle cells isolated from two distinct uterine sites are capable of producing unique responses. We intend to further characterize these cells in order to use them as a model to study different regions of the uterus and improve our understanding of prostaglandin signaling within the myometrium.

The role of three dimensional echocardiography in assessment of right ventricular dysfunction after a half marathon: comparison with cardiac magnetic resonance imaging

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Supervisor: Dr. Jassal

OBJECTIVE:
Although marathon running is associated with transient right ventricular (RV) systolic dysfunction as detected by 2D transthoracic echocardiography (TTE), quantitative assessment of the RV is difficult due to its complex geometry. Little is known about the use of real-time three-dimensional echocardiography (RT3DE) in the detection of cardiac dysfunction post marathon. The aim of this study was to assess the extent of cardiac dysfunction completion of a half marathon using cardiac biomarkers, RT3DE and cardiac MRI (CMR).

METHODS:
A prospective study was performed with 15 individuals in 2009 participating in the half arathon. Cardiac biomarkers (myoglobin, creatine kinase and cardiac troponin [cTnT]), RT3DE and CMR were performed one week prior to the race, immediately following the race and one week post marathon.

RESULTS:
At baseline, cardiac biomarkers and function were within normal limits. Immediately following the half marathon, all patients demonstrated elevated cTnT levels, with a median value of 0.37 ng/mL. Right ventricular ejection fraction (RVEF), as assessed by RT3DE, decreased from 59±4% at baseline to 45±5% immediately following the race (p<0.05).
On CMR, RV end diastolic volume increased after the half marathon and the RVEF was reduced, at 47±5% compared with 60±2% at baseline (p<0.05). There was a strong linear correlation between RVEF as assessed by RT3DE and CMR after the half marathon (r=0.93, p<0.01).

CONCLUSION:
As compared to CMR, RT3DE is a feasible and reproducible method of assessing transient RV dysfunction in athletes completing a half marathon run.

Unraveling the mystery of the progression of chronic myeloid leukemia: The role of a novel fusion gene NUP 98-HOXA9

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Supervisor: Dr. Connie Eaves

OBJECTIVE:
Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm characterized by three phases: a chronic phase, where a hematopoietic stem cell expressing the BCR-ABL fusion oncogene is formed whose progeny attains clonal dominance while suppressing the activity of residual normal stem cells, an accelerated phase in which clonal growth becomes difficult to control, and a terminal blast crisis phase, in which differentiation becomes blocked and non-functional blasts result. Blast crisis has been associated with additional genetic changes, including the acquisition of a NUP98-HOXA9 (NA9) fusion gene. Thus, the objective was to investigate the role that NA9 has in contributing to progression of CML.

METHODS:
Primitive CML cells from two patients were transduced with either an NA9-encoding or control vector and then grown in vitro to study effects on the growth kinetics, self-renewal, and differentiation of the cells, evaluated using phenotypic and functional endpoints. A fraction of the engineered CML cells were also transplanted into immunocompromised mice producing human growth factors to evaluate effects on CML progression in vivo.

RESULTS:
Cells transduced with NA9 yielded 93-fold more immature progeny and 239-fold more colony forming cells compared to control CML cells. The morphology and phenotype of the NA9-engineered cells showed marked changes in the erythroid and monocyte/macrophage lineages and the CFCs showed a much better serial replating ability. In vivo, NA9-transduced cells outcompeted an equal input of co-injected control-transduced cells with maintenance of an exclusive myeloid output for at least 8 weeks.

CONCLUSIONS:
Acquisition of the NA9 fusion gene by primitive CML cells deregulates their proliferative activity in vitro and in vivo and impairs their ability to produce normal mature blood cells. Taken together, these findings suggest that NA9 plays a direct role in the progression of chronic phase CML to blast crisis, and may reveal new diagnostic and/or therapeutic targets.

Does solid culture for tuberculosis influence clinical decision making in India?

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Supervisor: Dr. Michael John, Department of Immunology and Microbiology, The Schulich School of Medicine & Dentistry, The University of Western Ontario

OBJECTIVES:
To investigate the impact of solid culture on Löwenstein-Jensen medium on clinical decision making in the medical units at a tertiary referral hospital in Southern India.

METHODS:
In a retrospective review of 150 culture-positive and 150 culture-negative consecutively sampled tuberculosis (TB) suspects, treatment decisions were analysed at presentation, after the availability of culture detection results and after the availability of drug susceptibility testing (DST) culture results.

RESULTS:
A total of 124 (82.7%) culture-positive patients and 35 (23.3%) culture-negative patients started anti-tuberculosis
treatment prior to receiving their culture results; 101 patients (33.7%) returned for their results; two (1.3%) initiated treatment based on positive culture and no culture-negative patients discontinued treatment. DST was performed on 119 (79.3%) positive cultures: 30 (25.2%) showed any resistance, eight (6.7%) showed multidrug resistance and one (0.84%) showed extensively drug-resistant TB. Twenty-eight patients (23.5%) returned for their DST results. Based on DST, treatment was modified in four patients (3.4%).

CONCLUSIONS:
Using solid culture, 150 cultures need to be tested for one treatment modification and 30 for DST. The cost of the widespread application of culture will need to be balanced against its impact on treatment decisions in India.

Social support predicts outcomes following distal radius fractures across the lifespan

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Dr. Ruby Grewal

INTRODUCTION:
Distal radius fractures are the most common fracture and cause variable disability. This study examined the role of social support on patient-reported pain and disability at 1 year.

METHODS:
The Medical Outcomes Study (MOS) Social Support Survey was administered to a prospective cohort of 134 subjects with DRF at their baseline visit. Range of motion (ROM), grip strength, radiographic images, SF-12 scores and patient-reported outcomes were collected at baseline and after 3, 6, and 12 months. Pearson correlations and backward regression were used to identify predictors of the primary outcome: Patient Rated Wrist Evaluation (PRWE) 1-year post injury.

RESULTS:
Most injuries were low-energy (69.4%) DRF and were treated non-operatively (76.6%). Pearson correlation analysis revealed that higher reported social support (based on MOS survey) correlated with improved PRWE scores at 1 year ($r = -0.27, p < 0.05$). The impact of social support on patient rated outcomes was not related to age. The PRWE score at 1 year was also correlated with grip strength ($r = -0.36$), SF-12 mental ($r = -0.31$) and physical ($r = -0.49$) scores, and range of motion at 1 year. Higher social support also correlated with SF-12 physical ($r = 0.16, p < 0.05$) and mental ($r = 0.38, p < 0.05$) scores at 1 year.

CONCLUSION:
Lower social support at time of injury is correlated with more pain and disability one-year following DRF. To design more optimal recovery strategies, research should be directed at investigating the mechanisms by which social support affect outcomes.

Reassessment of anti-platelet therapy using an individualized strategy using a novel point-of-care genetic test for CYP2C19*2 loss-of-function allele – the rapid pilot study

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University of Ottawa

Dr. Derek So

OBJECTIVES:
Dual anti-platelet therapy with aspirin and clopidogrel is integral for post percutaneous coronary intervention (PCI) management. In patients after PCI, high on-clopidogrel platelet reactivity (unresponsiveness) is associated with major adverse clinical events (MACE). CYP2C19*2, a common variant allele, have been associated with high on-clopidogrel reactivity and MACE after PCI. We sought to assess the feasibility of a novel strategy to prospectively individualize anti-platelet treatment based on point-of-care genetic testing for CYP2C19*2 carrier status.

METHODS:
In this pilot proof of concept study, patients were randomized to: a) Personalized Treatment (PT) arm – patients underwent point-of-care genotyping, with carriers of the CYP2C19*2 allele receiving 75mg of clopidogrel BID while non-carriers continue with 75mg of clopidogrel once daily; vs. b) Standard-of-care (SC) arm – no genetic screening and continue with 75mg of clopidogrel daily. All patients underwent platelet function testing with the VerifyNow P2Y12 reactivity unit (PRU) assay at baseline and at follow-up on day 7. All patients had their genotype confirmed with direct DNA sequencing.
RESULTS:
Thirteen patients were enrolled: 6 in Personalized Treatment and 7 in the Standard-of-care arm. The baseline demographics, cardiac risk factors and concurrent medications were comparable between the two groups. The sensitivity and specificity of the point-of-care genetic system relative to direct genetic sequencing was 100%. In the PT arm, 3pts (50.0%) were *CYP2C19*’2 carriers vs. 2pts (28.6%) in the SC arm. In the PT arm there was an improvement in PRU by 8 units vs. a decrease in PRU of 17 units in the SC arm (p = 0.449) between time 0 and day 7.

CONCLUSIONS:
Our novel point-of-care *CYP2C19*’2 identification is sensitive and specific. Subsequent alteration of clopidogrel treatment based on genetics is feasible. RAPID PILOT is the first prospective study to evaluate individualized therapy based on rapid genetic testing.

Childhood trauma, family history of substance abuse and age of first drug injection

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V ancouver Fraser Medical Program, UBC

Supervisor: Dr. Michael Krausz, Professor of Psychiatry

OBJECTIVE:
To better understand the relationship between childhood abuse, family history of alcohol and drug abuse and injection drug use initiation in a cohort of chronic opioid users. The design used was a cross-sectional survey in two Canadian cities (Vancouver and Montreal).

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

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

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

High resolution rapid scanning X-ray fluorescence imaging to track superparamagnetic iron oxide labeled neural stem cells in an experimental stroke model

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University of Saskatchewan

Dr. Michael Kelly

OBJECTIVE:
Magnetic resonance imaging (MRI) of SPIO-labeled stem cells has become a widely used technique for in vivo cell imaging. The MRI signal obtained is however not specific for the SPIO-labeled stem cells and experimental paradigms rely on histological verification using Prussian Blue staining. Here we explored synchrotron XRF imaging using a hard X-ray microprobe in continuous rapid scanning mode to detect iron in SPIO-labeled stem cells after intravascular transplantation in an experimental stroke model.

METHODS:
Stroke was induced in NodScid mice using a hypoxia-ischemia model. Animals underwent unilateral temporary common carotid artery (CCA) occlusion followed by exposure to 8% O2 for 20 minutes and subsequent reperfusion. On day 3 after stroke 5x10⁵ SPIO-labeled human derived embryonic neural progenitor cells (hNPC) were injected into the ipsilateral CCA. Control animals received either stereotactic intraparenchymal injection of 5x10⁵ SPIO-labeled hNPC or saline. Animals were sacrificed 24-hours following hNPC implantation. MRI using a FIESTA sequence was then performed. 30µm whole brain sections were scanned at the Stanford Synchrotron Radiation Lightsource on beamline 2-3 with specific sub-regions imaged with 3µm spot size at 200 ms per point. Sections were then stained with Prussian Blue.

RESULTS:
Bioluminescence imaging and MRI demonstrated significant homing of hNPC to the ischemic hemisphere but not to the
contralateral hemisphere (p<0.01). XRF depicted distinct areas of Fe signal distributed in the ischemic hemisphere correlating with MRI findings. High-resolution scans depicted single cells in clusters with an average iron content of 7.0632 pg. Intraparenchymal cell grafts appeared as focal signal on MRI and XRF. Saline controls produced a needle shaped artifact on MRI, which correlated to a Fe signal on XRF very distinct from the cellular morphology of SPIO-labeled hNPC. Prussian blue staining correlated with XRF imaging.

CONCLUSION:
The synchrotron X-ray microprobe in rapid-scanning mode allows high-resolution quantitative Fe specific imaging of single cells. Here we demonstrate its application in a multimodality imaging paradigm to track SPIO-labeled hNPC in a stroke model. We found excellent correlation between MRI, XRF and histology.

An investigation of risk factors for childhood asthma in farming and non-farming environments

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Supervisor: Josh A Lawson

OBJECTIVE:
Farming environments have been associated with lower childhood asthma prevalence. However, the exposures responsible for this effect are unknown. The objective of this study was to investigate potential risk factors for childhood asthma and to assess whether these associations were consistent between farming and non-farming environments.

METHODS:
Parents of 898 children aged 6-12 years from central Saskatchewan participated. Cross-sectional questionnaires were completed between 2004 and 2006. Questionnaires included questions on health, environment, health behaviors, and home location. Home location was classified as farm, acreage or town. Asthma was considered present with a doctor’s diagnosis and at least one of the following in the preceding year: wheeze, medication use for asthma, or an ER/doctor’s visit for asthma.

RESULTS:
Asthma prevalence was highest in town (16.7%) followed by acreage (15.6%) and farm (14.0%). Personal characteristics including parental history of asthma and personal history of allergy, showed strong associations with asthma (odds ratios > 3; p<0.01) and were consistent across location of residence. Playing sports outside of school was associated with the presence of asthma (p<0.05). Significant interactions (p<0.05) were observed between home location and exposure to cleaning barns, and between sex and father’s history of smoking. Children who lived in town but spent time cleaning or playing in barns had reduced risk of current asthma, but this association was not seen in the other locations. Girls whose father smoked at home were at higher risk of having asthma. This association was not seen among boys.

CONCLUSION:
The association between personal characteristics and asthma are the strongest predictors of asthma and are consistent between locations. The association between environmental exposures, may differ between locations. Similarly, the response to the environment may differ between boys and girls.

Microwell culture of pre-implantation embryos and its applications

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Supervisor: Dr. Ri-Cheng Chian

OBJECTIVES:
Microwells, in addition to being useful for immobilizing embryos within the culture medium, has been shown to improve in vitro bovine embryo development compared to conventional flat-surface culture. Our primary objective was to assess the relative feasibilities of group culture in microwells versus single culture for the purpose of tracking individual mouse embryos as part of the methodology for another study. Secondly, we aimed to evaluate the potential of the microwell method to improve existing protocols for embryo culture in clinical assisted reproductive technologies (ART).

METHODS:
In vitro fertilized (IVF) CD1 strain mouse zygotes were distributed into three culture conditions: (1) flat-surface culture of one embryo in 7 µl of medium; (2) microwell culture of eight embryos in 56 µl of medium; and (3) flat-surface culture of eight embryos in 56 µl of medium as control. Another experiment using the same three conditions was performed with in...
in vivo fertilized zygotes collected from mated CD1 females. The percentage of 2-cell embryos developing to the blastocyst stage (blastocyst rate) was used to evaluate embryonic development.

RESULTS:
Single culture blastocyst rates for IVF and mated embryos were 5.8% and 23.3%, respectively, and are significantly lower than those observed in group flat-surface culture (48.0% IVF, 64.5% mated) and microwell culture (57.9% IVF, 75.9% mated). Microwell culture produced slightly higher blastocyst rates than the group flat-surface culture, but the differences are not statistically significant.

CONCLUSIONS:
Culturing mouse embryos in groups appears to be essential to maintain adequate development rates. The microwell culture system is suitable for tracking individual mouse embryos because it retains group culture conditions. As such, we have successfully integrated this method into our experimental protocol for our research in oocyte competence prediction. However, the possible developmental benefits of the well culture system and its potential to be applied in ART requires further investigation.

A pilot study of sleep and sensory characteristics of children with FASD
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Dr. Ana Hanlon-Dearman

OBJECTIVE:
The purpose of this study was to describe sleep patterns in children with FASD between 3 and 6 years of age, and investigate the relationship between sleep and sensory processing in these children.

METHODS:
Sleep data was gathered using Actigraphy, The Child Sleep Habits Questionnaire (CSHQ) and a Sleep Log. The Sensory Profile™, completed by caregivers was used to evaluate the child’s sensory processing ability. Sleep parameters in the FASD group (n=19) and control group (n=12) were compared using t-tests. Overall differences in sensory processing were correlated with actigraphic parameters measured in alcohol exposed and control groups using spearman’s correlations. Ethics approval was obtained from the Health Research Ethics Board at the University of Manitoba.

RESULTS:
Children with FASD had significantly more sleep disturbances than typically developing children, including bedtime resistance, sleep durations, sleep anxiety, night awakenings and parasomnias. Actigraphy revealed a significant difference between groups for sleep onset latency. Sensory processing abnormalities were shown to positively correlate with multiple sleep disorders, including sleep duration, night wakening, parasomnias, wake time and mean total activity. Sleep onset delay, night wakening, parasomnias and CSHQ total were found to correlate with behavioural outcomes of sensory processing indicating that these sleep disorders may be a result of abnormal sensory processing. Sedentary behaviour negatively correlated with percent wake, wake time, total activity and CSHQ total. This suggests that sleep disruption may contribute to hyperactivity, a core behavioural feature of FASD.

CONCLUSIONS:
The results from this study demonstrate that sleep is a significant problem for children with FASD and that sensory processing abnormalities contribute to these sleep disturbances. Therefore, children with FASD should be screened for sleep related disorders and would benefit from occupational therapy for sensory based treatment aimed at sleep regulation and consolidation.

The role of CHRNA6 in chronic pain
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Dr. Jeffrey Mogil

OBJECTIVES:
Chronic pain is an exceedingly prevalent and costly health problem. It is widely acknowledged that significant interindividual variability exists in an individual's propensity to experience chronic pain following similar insults. Since much of this variability is genetic, the identification of genes predisposing to severity of symptoms of chronic pain could be of great value in terms of early intervention and drug development.
METHODS:
To identify potential candidate genes that may account for the great interindividual variability, we conducted an expression genomics study, and observed strong correlations between dorsal root ganglion (DRG) *Chrna6* (cholinergic receptor, nicotinic, alpha 6 subunit) gene expression and neuropathic mechanical allodynia following spared nerve injury (SNI). *Chrna6* null mutant mice and gain-of-function mutant mice were tested for mechanical allodynia following SNI and intraplantar complete Freund’s adjuvant (CFA) injection to causally establish a role for *Chrna6* in chronic pain.

RESULTS:
Correlation analysis of SNI allodynia in 25 inbred mouse strains with basal DRG expression revealed that the top two correlations, genome-wide, were with two different probes for *Chrna6*. Subsequent RT-PCR experiments revealed that DRG *Chrna6* expression is >10-fold higher than whole brain expression and 2-fold greater than eye expression. Behavioural testing for both SNI and CFA revealed that *Chrna6* knockout mice displayed higher overall levels of allodynia as compared to wildtype mice, while *Chrna6* gain-of-function mutant mice displayed significantly less allodynia.

CONCLUSIONS:
The findings presented here demonstrate the protective role of *Chrna6* in chronic pain. Ultimately, by identifying and manipulating those genes responsible for inducing variable levels of chronic pain, such as *Chrna6*, novel therapeutic approaches and drugs can be developed that target the symptoms of debilitating chronic pain conditions.

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Effect of valproic acid on fludarabine activity in chronic lymphocytic leukemia

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Spencer B. Gibson

OBJECTIVES:
Valproic acid (VPA) is a first-generation anti-epileptic drug with histone deacetylase (HDAC) inhibition activity that has been shown to inhibit proliferation and induce apoptosis in various haematological malignancies, including chronic lymphocytic leukemia (CLL). The objectives are to assess the effect of the VPA and fludarabine combination (VF) on CLL and elucidate the mechanism of interaction *in vitro*.

METHODS:
The pharmacodynamic relationship between VPA and fludarabine was examined *in vitro* in human leukaemic cell lines and primary CLL cells. The impact of the combination on the levels and post-translational modifications of various proteins were examined by immunoblotting.

RESULTS:
VPA and fludarabine (VF) are synergistic *in vitro* in leukaemic cell lines and primary CLL cells. The synergistic actions of the VF combination induced cleavage of caspase-8, caspase-9, BID and caspase-3, implicating both the intrinsic and extrinsic pathways of apoptosis. This synergistic interaction was associated with enhanced hyper-acetylation of histones and induction of DNA damage compared to VPA and fludarabine single-drug treatments. The VF combination also induced greater degradation of the Inhibitor of κB-α (I-κB-α) protein, suggesting a greater liberation of the Nuclear Factor-κB (NF-κB) complex. This liberation of NF-κB appears to be necessary for the synergy, as inhibiting this step by the addition of Bay-11-7082 was sufficient to suppress the VF synergy. Interestingly, despite the greater reduction in I-κB-α protein levels, the VF combination reduced the levels of the NF-κB target proteins that inhibit apoptosis, including members of the Inhibitor of Apoptosis Proteins (IAPs).

CONCLUSIONS:
Presence of VPA enhances the action of fludarabine in a synergistic manner, through a mechanism triggering both the intrinsic and extrinsic apoptotic pathways. There was a concomitant down-regulation of the NF-κB target proteins that normally function to inhibit apoptosis. The exact role of NF-κB is under further study.