TRAINEE SECTION

Lindsey M. Logan BSc
Samuel K. Jensen BSc
Noreen Singh MD, PhD
Michael A. Peplowski MD, PhD
Doreen Rabi MD, MSc
Bryan G. Yipp MD, MSc
Morley D. Hollenberg D. Phil., MD
Paul L. Beck PhD, MD

Cumming School of Medicine
University of Calgary, Calgary AB

Proceedings from the 8th Annual University of Calgary Leaders in Medicine Research Symposium

Abstract

On November 14, 2016, the Leaders in Medicine (LIM) program at the Cumming School of Medicine, University of Calgary hosted its 8th Annual Research Symposium. Professor Stephen Sawcer, Professor of Neurological Genetics at the University of Cambridge and an Honorary Consultant Neurologist at Addenbrooke's Hospital, was the keynote speaker and presented a lecture entitled, "Multiple sclerosis genetics - prospects and pitfalls". This was not only a cutting edge address on genetics but also a thoughtful overview on Dr. Sawcer's career and career choices. We were extremely grateful for the opportunity to have Dr. Sawcer participate in our annual symposium.

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Correspondence to:

Dr. Paul L. Beck
Leaders in Medicine Program
Cumming School of Medicine, Health Sciences Centre, University of Calgary,
Calgary AB
E-mail: plbeck@ucalgary.ca

On November 14, 2016, the Leaders in Medicine (LIM) program at the Cumming School of Medicine, University of Calgary hosted its 8th Annual Research Symposium. Professor Stephen Sawcer, Professor of Neurological Genetics at the University of Cambridge and an Honorary Consultant Neurologist at Addenbrooke's Hospital, was the keynote speaker and presented a lecture entitled, "Multiple sclerosis genetics - prospects and pitfalls". This was not only a cutting edge address on genetics but also a thoughtful overview on Dr. Sawcer's career and career choices. We were extremely grateful for the opportunity to have Dr. Sawcer participate in our annual symposium.

The LIM Program at the University of Calgary was founded in 1997 with the mission of allowing undergraduate medical trainees to become leaders in health care by simultaneously pursuing medical and post-graduate degrees. The program has grown exponentially and, as of 2016, had over 150 students, including several students pursuing joint degrees, such as MD/MSc, MD/MA, MD/MBA or MD/PhD (known as joint degree students). The LIM program also includes MD students who have a background in research, having completed an MSc or PhD prior to medical school, or students who are pursuing research concurrently while completing their medical degree (known as affiliate members).

A major advantage of the LIM program, which makes it unlike any other program in Canada, is its flexibility. Trainees in the LIM program at the University of Calgary choose whether they want to complete their graduate training before or after they start their medical degree. We believe that the flexibility to pursue the research that interests students at the time that is most suitable for them allows them to build valuable research skills that they can then merge with their clinical training to become "bilingual" experts in the clinic, as well as in research, business or in whatever field they chose. The skills that these trainees develop allow them to be uniquely positioned to contribute to pursuing innovation in medicine and translating that innovation to the front-lines.

The LIM program is student-driven: all program events are planned and organized by the Student Executive Committee. These events include the annual symposium, monthly research in progress meetings and monthly journal club, as well as periodic social and professional development activities and visiting speakers. In 2016–2017, a new seminar series entitled, "Business in Medicine" was offered. This seminar series was developed and pioneered by Brad Prince, one of our MD/MBA students.

The LIM symposium provides a forum for both LIM and non-LIM medical students to present their research work, as

either oral or poster presentations. In 2016, there were a total of seven oral presentations and 74 posters presented (Figure 1). The objectives of the 8th Annual LIM Research Symposium were to (1) showcase the impressive variety of projects undertaken by LIM Program Students, LIM Program Affiliates and medical students at the University of Calgary, (2) promote medical student participation in research and special projects and involvement in the LIM Program at the University of Calgary, (3) highlight the diversity of opportunities and importance of pursuing research and special projects during medical school and beyond and (4) engage our many LIM Program alumni in continued involvement and interaction with current students and the program to foster future mentorship opportunities. The abstracts recorded

FIGURE 1. Attendees of the LIM symposium enjoying the poster session in the University of Calgary's Health Research and Innovation Centre atrium.

below are intended to portray the diversity of areas of investigation in our LIM programme, so as to enable a comparison with ongoing work in other joint degree and MD-PhD programmes across the country.

The following researchers gave oral presentations: Heather Leduc-Pessah, Lauren Galbraith, Chris Smith, Daniyil Svystonyuk, Amrita Roy, Dana Stewart and Anna Kovalchuk. Heather Leduc-Pessah was awarded the Best Oral Presentation Award.

The following students won the Best Poster Presentation Awards for their categories: Michael Keough, James Rogers, Jaye Platnich, Sultan Nelson, David Guzzardi, Daniela Keren, Graeme Prosperi-Porta, Lauren Capozzi, Christopher D. Powell, Zoe Polsky, Mackenzie Grisdale, Kelcie Lahey and Miles Hunter. The full abstracts of the oral presentation and award winners are given below, followed by titles of the remaining posters. For further authorship details and full abstracts please see the LIM website (<https://cumming.ucalgary.ca/lim/>).

We would like to acknowledge all of the individuals who volunteered their time to help with the symposium. In particular, we would like to thank the oral and poster competition judges: Drs. S Jarvis, J Lockyer, L Schmitt, K Moncrieff, T Schryvers, H Bassyouni, R DeVinney, A Metcalfe, V Wee Yong, J Moser, A Caprariello, J Deniset, B Yipp, T Chowdhury, E Lang, M Russell, M Hollenberg, P Ronksley, F Zemp, M Lee, P Beck, S Hirota and T Cluff.

We would also like to thank the departments and associations who generously provided funding, including the Cumming School of Medicine, Department of Physiology and Pharmacology, Department of Neuroscience, Office of the Vice President, Research, Medical Science Graduate Program, Department of Medicine, Arnie Charbonneau Cancer Institute, Graduate Students' Association, Students' Union, the Den and Black Lounge and the Bookstore. Other sponsors included the Alberta Medical Association and Alberta Health Services and the Timberline Café.

Best Oral Presentation Award: Heather Leduc-Pessah

Site-specific phosphorylation of the P2X7 receptor in response to morphine critically gates analgesic tolerance

H Leduc-Pessah, NL Weilinger, CY Fan, NE Burma, RJ Thompson, T Trang
Departments of Comparative Biology & Experimental Medicine and Physiology & Pharmacology, Hotchkiss Brain Institute, University of Calgary, Calgary AB

Introduction: One in five Canadians experience chronic pain, which has profound implications on quality of life. The potent opioid, morphine, is indispensable in the treatment of chronic pain; however, its use is limited by the development of analgesic tolerance. The ATP-gated P2X7 receptor (P2X7R) is a key locus mediating analgesic tolerance. In the present study, we examined the expression and function of P2X7Rs after repeated morphine treatment, and their role in the development of morphine analgesic tolerance.

Methods: Sprague Dawley rats were treated with morphine (15 mg/kg; IP) over seven days. Anti-nociception was assessed using thermal tail flick and mechanical paw pressure tests. Cultured BV2 microglial cells were treated with morphine (1 μ M) for five days. Changes in P2X7R protein expression were assessed by western blot, whereas modulation of P2X7R function was determined by whole cell patch clamp recordings and calcium imaging.

Results: Treatment with morphine over seven days caused a progressive decline in morphine anti-nociception and a loss in morphine analgesic potency. Morphine-tolerant animals displayed an up-regulation of P2X7R expression, which was concomitant with a potentiation of P2X7R ion channel function. We then tested whether receptor phosphorylation played a role in the potentiation of P2X7R function. We found an increase in P2X7R tyrosine phosphorylation with repeated morphine treatment. Daily co-administration of a tyrosine kinase inhibitor with morphine prevented the morphine-induced potentiation of BzATP-evoked calcium

influx and inward current. This demonstrated a critical role for morphine-mediated tyrosine phosphorylation of the P2X7R and, through this mechanism, a modulation of ion channel function. Using P2X7R-mimetic peptides and mutant P2X7R constructs, we identified the specific site of phosphorylation on the P2X7R that contributes to changes in function in response to morphine. By blocking this site-specific phosphorylation *in vivo* we were able to attenuate the development of morphine tolerance and preserve its analgesic potency.

Conclusion: Our findings demonstrate that morphine-mediated phosphorylation of microglial P2X7Rs critically gates the development of morphine analgesic tolerance, and that by blocking this site *in vivo*, morphine retained its analgesic potency. The critical mechanisms and specific site involved in the modulation of P2X7R function in response to morphine presents a potential therapeutic target in the management of morphine tolerance.

Oral Presentations

The CANN-NET Nurse- or Pharmacist-led Anemia Management Protocol: An effort to standardize anemia management in hemodialysis centres in Canada

L Galbraith, B Manns, S Brimble

Departments of Community Health Sciences and Medicine, University of Calgary, Calgary AB; Department of Medicine, McMaster University, Hamilton ON

Introduction: The Canadian KidNey KNowledge TraNslation and Generation NeTwork (CANN-NET) sought to operationalize recommendations from the Canadian Society of Nephrology for anemia management in patients with chronic kidney disease by developing a national nurse- or pharmacist-led anemia management protocol. This protocol aimed to standardize anemia management in patients with chronic kidney disease to improve patient outcomes, reduce the burden of anemia management on physicians and increase scope of practice for nurses.

Methods: A survey of renal program directors was used to determine practice patterns and interest in an anemia management protocol. Through an iterative process, a protocol was developed and approved by the CANN-NET Knowledge Users Committee, and piloted in eight hemodialysis units. The final protocol was advertised and disseminated across Canada. A mixed-methods evaluation was conducted using a pre-post study design, and included quantitative clinical outcomes and a qualitative thematic analysis.

Results: The national anemia survey obtained a response rate of 50%, of which 44% indicated their hemodialysis unit currently used an anemia protocol of some type. The majority of respondents (92.3%) were interested in using the CANN-NET anemia protocol. Following implementation of the protocol, the proportion of patients within the target TSAT range and the target hemoglobin range both increased (TSAT: 64.5% in 2014 versus 78.3% in 2015; Hgb: 47.5% in 2014 versus 51.2 in 2015). The proportion of patients on ESA or iron therapy did not change between 2014 and 2015 (ESA: 80.2% and 80.0%; Iron: 94.8% and 95.5%, respectively); however, while the amount of iron per patient decreased over this period (494.7 mg and 402.8 mg), the amount of ESA per patient did not change (373.5 mcg versus 374.6 mcg). Through qualitative interviewing, nursing staff expressed that

the anemia protocol improved patient care. Standardizing patient care was felt to be a key factor in improving job efficiency, in particular increasing the autonomy of managing anemia and reducing the frequency of notifying a physician of small changes covered by the protocol were important advantages of the protocol, which led to a more engaged team environment.

Conclusion: The CANN-NET Nurse- or Pharmacist-led Anemia Management Protocol successfully achieved implementation throughout Alberta, and in several centres in Ontario. Data suggest the use of a protocol is equivalent to standard care for patient safety and clinical outcomes. Most importantly, it may contribute to system-level improvements such as ensuring evidence-based anemia management and increasing job satisfaction. The protocol is free, available online, and has a comprehensive educational package.

A recurrent mutation in MYH14 causes autosomal dominant Charcot-Marie-Tooth Disease with suspected mitochondrial pathology

C Smith, T Shutt, G Pfeffer, RE Lamont, F Bernier, J Parboosingh, AM Innes, Care4Rare Canada Consortium
Department of Medical Genetics, Department of Biochemistry & Molecular Biology and Department of Clinical Neurosciences, University of Calgary, Calgary AB; Alberta Children's Hospital Research Institute, Calgary, Alberta AB

Introduction: Mutations in myosin heavy chain 14 (MYH14) are an established cause of autosomal dominant non-syndromic hearing loss (DFNA4A, OMIM: 600652); however, there are two literature reports of a NM_001077186.1 (MYH14): c.2822G>T (p.Arg941Leu) mutation being associated with Charcot-Marie-Tooth Disease (CMT) in addition to hearing loss (PNMHH, OMIM: 608568). Using exome sequencing we have identified a three generation family with CMT and hearing loss that also has the p.Arg941Leu mutation.

Methods: We have previously utilized exome sequencing to identify potentially causative genetic variants in a family with unexplained peripheral neuropathy and deafness. In order to better understand the pathogenesis of the disease, we attempted to characterize the role of MYH14 protein in cell culture (U2OS cells).

Results: Expression of a GFP-tagged protein showed localization to mitochondria. Moreover, MYH14 was observed at sites of mitochondrial fission, where it co-localized with the well-studied fission factor DRP1. Overexpression of MYH14 caused cells to take on a subtly more fragmented mitochondrial morphology, while cells overexpressing p.Arg941Leu mutant MYH14 were no different from cells containing an empty vector.

Conclusion: Based on these results, we suspect that MYH14 has a role in mitochondrial fission and that dysfunction in this role contributes to the pathogenesis of CMT and hearing loss. This is an attractive hypothesis because disruption of other genes involved in mitochondrial dynamics also cause CMT. Our experiments in cell culture further suggest a loss-of-function mechanism. Finally, the identification of a third family confirms the association between the p.Arg941Leu mutation and CMT with hearing loss.

Acellular matrix biomaterial promotes cardiac repair through an active bio-inductive mechanism

DA Svystonyuk, HE Mewhort, JD Turnbull, G Teng, DD Belke, DG Guzzardi, S Kang, DS Park, PWM Fedak
Cumming School of Medicine, University of Calgary, Calgary AB

Introduction: Use of extracellular matrix (ECM) biomaterials is an emerging therapeutic strategy to promote cardiac repair and prevent heart failure. We have shown that implantation of ECM biomaterials on the epicardial surface of infarcted tissue prevents cardiac remodelling and improves functional recovery that extended beyond the passive biomechanical effects of the material. In this study we explored the specific bio-mechanism through which ECM therapy enhances myocardial repair following ischemic injury.

Methods: Human cardiac fibroblasts (CF) were isolated from atrial appendage from patients undergoing cardiac surgery. The CF were seeded onto active or biologically inactive (glutaraldehyde-fixed) ECM-biomaterial. Conditioned media was collected from each group and analyzed using Luminex. To test *in vitro* angiogenic potential, active ECM-biomaterial was co-cultured with endothelial cells embedded in Matrigel. A rat model of myocardial infarction was used to compare ECM-biomaterial treatment against sham.

Results: The ECM-biomaterial was characterized and shown to contain FGF-2 that was released from the ECM upon hydration. The CF are the predominant heart cell type that maintain the ECM, thereby regulating surrounding cell behaviour and tissue remodeling processes. The CF cultured on active ECM biomaterial assumed a pro-angiogenic state, showing significantly increased expression of FGF-2, HGF and VEGF. Exogenous FGF-2 inhibition using 1 M PD 173074 attenuated the pro-angiogenic response, suggesting a paracrine role for FGF-2 as part of the ECM-biomaterial's bio-inductive mechanism. Relative to biomaterial-free and inactive-ECM biomaterial conditions, active ECM-biomaterial significantly increased endothelial tube formation and sprouting in an *in vitro* model of angiogenesis. Using a rat model of myocardial infarction (MI), active ECM-biomaterial was implanted over the epicardial surface of the infarct and compared against biologically inactive material and sham-treated animals. Post-treatment (14-weeks), animals receiving the active-ECM biomaterial showed enhanced vascularity (vessels per high powered field) in the infarcted myocardium relative to the inactive-ECM biomaterial group. Tissue samples of the infarcted myocardium revealed an increase in vasculogenic growth factors (FGF-2 and VEGF) relative to the inactive treatment group consistent with our observations *in vitro*. The enhanced vascularity was observed adjacent to structural and functional improvements of the heart post-MI.

Conclusion: These data suggest that an ECM biomaterial applied to the epicardium after ischemic injury can enhance myocardial repair through an FGF-2-dependent mechanism that stimulates vasculogenesis by host cell paracrine effects.

Improving services for pregnant Aboriginal women: Data from a constructivist grounded theory study in Calgary, Canada

A Roy, WE Thurston, SB Patten, S Tough, L Crowshoe
Department of Community Health Science, Cumming School of Medicine; LIM MD-PhD Program, Cumming School of Medicine; Department of Ecosystem and Public Health, Faculty of Veterinary Medicine; Department of Psychiatry, Cumming School of Medicine; Department of Pediatrics, Cumming School of Medicine; Department of Family Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB

Introduction: Aboriginal maternal-child health issues are pressing concerns. The ability of service systems to meet the needs of pregnant Aboriginal women depends on their accessibility, safety and responsiveness. This research sought to examine accessibility, utility and safety of health and social service systems used by pregnant Aboriginal women.

Methods: A community-based, qualitative constructivist grounded theory study was conducted in Calgary, Alberta, involving personal interviews with pregnant Aboriginal women (n=13) and service-providing professionals (n=12), along with focus groups with stakeholders (n=11). Data saturation was achieved through purposeful and theoretical sampling. Interviews were recorded, transcribed, and coded with the software NVivo 10.

Results: Some services were described as effective and meaningful. More Aboriginal-specific, culturally-appropriate services were requested, including group-based prenatal education programs that would facilitate positive mutual social support among women. Barriers to access include hours of operation, childcare and transportation constraints. Negative interactions involving judgmental or racist professionals discourage access, as does fear of child welfare authorities. Service-providing professionals expressed a need for better training and resources around creating safe, stigma-free service environments. Better networking between services, as well as integration between sectors, are warranted for care comprehensiveness and continuity.

Conclusion: Pregnancy offers a meaningful intervention point for health and social issues. Action is warranted to create barrier-free and culturally-safe services that meet the needs of pregnant Aboriginal women.

Funding: The Voices and PHACES study was funded by an Investigator-Driven Small Grant from the Alberta Centre for Child, Family and Community Research. Amrita Roy's doctoral work is funded by: Frederick Banting and Charles Best Canada Graduate Scholarship Doctoral Award, from the Canadian Institutes of Health Research (CIHR); Izaak Walton Killam Memorial Scholarship, from the Killam Trusts; MD-PhD Studentship, from Alberta Innovates-Health Solutions (AIHS); Scobey Hartley Doctoral Award, from the Alberta Centre for Child, Family and Community Research; Alberta Award for the Study of Canadian Human Rights and Multiculturalism, from the Government of Alberta; and

Achievers in Medical Science doctoral scholarships, from the University of Calgary.

Are EMS offload delay patients at increased risk of adverse outcomes?

D Stewart, D Wang, E Lang

Cumming School of Medicine, University of Calgary, Calgary AB

Introduction: Offload delay is the period of time considered to exceed what is necessary to complete the transfer of care between emergency medical services (EMS) and emergency department (ED) staff. It is a marker of hospital overcrowding and causes delays in care. It also prevents EMS crews from returning to their duties in the community, as large portions of the fleet can be held in hospital corridors while their patients await care in EMS park. Our objective was to determine if patients experience higher rates of negative outcomes following offload delay.

Methods: From July 2014 to June 2016, hospital administrative data were collected from four EDs in the Calgary Zone. Eligible patients were those triaged as Canadian Triage and acuity Scale (CTAS) level 2 who arrived to hospital by EMS transport. Exclusion criteria included patients who left the ED without being seen, or those whose disposition status was unknown. The primary outcome was ICU admission. Secondary outcomes included hospital admission rate, mortality in hospital, inpatient length of stay (LOS) and 7-day readmission rate.

Results: A total of 60,010 patients were included in the study and 41,578 patients experienced no offload delay or were in EMS park for <30 minutes. An offload delay of <30 minutes likely poses little harm to patients and results from a brief period of transition while a bed in the ED is prepared. Thus, patients waiting in EMS park for <30 minutes were added to the non-EMS park cohort. Furthermore, 7,155 patients waited in EMS-park for 30–60 minutes and 11,277 waited in EMS park for >1 hour. The average age of non-EMS park patients was 56.2 years and 53.6% male, compared to 59.6 years and 50% male in EMS park 30–60 minutes, and 60.9 years and 48.9% male for patients in EMS park >1 hour. Intensive care unit admission rates were 1.70% for non-EMS park, 1.36% for EMS park 30–60 minutes and 0.83% for EMS park >1 hour ($p<0.05$ for comparison of non-EMS park vs. EMS park >30 minutes, non-EMS park vs. EMS park 30–60 minutes and

non-EMS park vs. EMS park >1 hour). Hospital admission rates were 42.4%, 42.5%, and 41.7% in non-EMS park, EMS park 30–60 minutes, and EMS park >1 hour, respectively ($p=NS$ for all comparisons). Seven-day revisit admission rates were 3.57%, 3.97% and 3.46%, respectively ($p=NS$ for all comparisons). Average inpatient length of stay was 11.6 for non-EMS park, 12.3 days for EMS park 30–60 minutes and 13.6 days for EMS park >1 hour ($p<0.05$ for all comparisons). Mortality in hospital was 1.58%, 1.72% and 1.35% in non-EMS park, EMS park 30–60 minutes and EMS park >1 hour, respectively ($p=NS$ for all comparisons).

Conclusion: Offload delay imposes a significant strain on pre-hospital resources, with a large proportion of ED patients being cared for in these spaces as a result of access block in the ED and hospital. We have demonstrated an association between longer delays in EMS park and prolonged inpatient length of stay. Offload delay appears to represent a hazard for CTAS 2 patients, particularly those waiting for 30–60 minutes who had significant rates of intensive care unit admission, mortality and ED revisits resulting in admission.

Chemo brain: From mechanisms to prevention strategies

A Kovalchuk, Y Ilnytsky, S Shpileva, S Melnyk, A Katz, D Sidransky, O Kovalchuk and B Kolb

Department of Neuroscience and Department of Biological Sciences, University of Lethbridge, Lethbridge AB; Division of Biochemical Toxicology, National Center for Toxicological Research, FDA, Jefferson AR, USA; Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock AR, USA; Department of Oncology, Champions Oncology, Baltimore MD, USA

Introduction: An array of central nervous system complications, neurological deficits and cognitive impairments occur and persist as a result of cancer and cancer treatments. This condition is known as “chemo brain”. The molecular and cellular mechanisms of chemo brain are under-investigated. Based on our preliminary data, we propose a new epigenetic theory of chemo brain, whereby the mechanisms underlying the neurotoxic side effects of chemotherapy are epigenetic and linked to aberrant global gene expression.

Methods: Our analysis focuses on the hippocampus and prefrontal cortex (PFC) for their roles in memory, learning

and executive function, and on the published data showing these regions as key targets in chemo brain. We used well-established mouse TumorGraft™ models of triple negative (TRN) and progesterone receptor positive (PR+) breast cancer to profile the epigenetic, transcriptome and small RNAome changes in chemotherapy-treated tumor-bearing mice as compared with untreated and control mice.

Results: For the first time, we show that the presence of a tumor itself significantly affects the brain's molecular networks and causes oxidative stress that manifests as elevated levels of 8-oxodG, paralleled with the global loss of DNA methylation and the increase of DNA hydroxymethylation in the PFC of tumor-bearing animals as compared with intact controls. Extracranial tumor growth also leads to significant transcriptome changes, affecting the pathways involved in axonal guidance, neuroactive ligand signaling, apoptosis and other processes. Chemotherapy treatments (topotecan or crizotinib for PR+ and doxorubicin, paclitaxel, cyclophosphamide for TNT tumors) further exacerbate tumor-induced epigenetic and transcriptome changes. Both the tumor and the chemotherapy affect small RNAome and alter the levels of miRNAs, piRNAs, tRNAs, tRNA fragments and other molecules that are involved in the post-transcriptional regulation of gene expression. Amongst those, miRNA changes were the most pronounced, involving several miRNA families, such as the miR-200 family and the miR-183/96/182 cluster, which were deregulated in tumor-bearing and chemotherapy-treated animals. The miRNA deregulation was associated with altered levels of several key targets, such as brain-derived neurotrophic factors and several other proteins that play key parts in cognition and memory.

Conclusion: Our results show that the presence of the tumour itself influenced the brain's molecular processes and networks, and chemotherapy exposure further affected the changes. Upon completion, this project will delineate the molecular and cellular mechanisms of tumor brain and chemo brain that may underlie neuroanatomical changes and behavioral outcomes and define chemo brain and tumor brain biomarkers. The outcomes of our study may be used to design strategies to mitigate tumor brain and chemo brain.

Abstracts from Best Poster Presentation Awards

Gestational BPA exposure lowers the threshold for autoimmunity in a multiple sclerosis model

JA Rogers, MK Mishra, C Greene, R Yates, L Metz, V Wee Yong

Hotchkiss Brain Institute and the Department of Clinical Neurosciences, Cumming School of Medicine; Department of Comparative Biology and Experimental Medicine, Faculty of Veterinary Medicine; Department of Biochemistry and Molecular Biology, Cumming School of Medicine, University of Calgary, Calgary AB

Introduction: We determined whether bisphenol-A (BPA) exposure altered susceptibility to experimental autoimmune encephalomyelitis (EAE), an inflammatory model of multiple sclerosis (MS). Environmental factors have been implicated in dysregulation of immune responses in MS and BPA is a prominent environmental contaminant that has been shown to act on a variety of cell types. Furthermore, early life exposure is suggested as a time of increased susceptibility to lasting physiological changes.

Methods: The BPA was administered daily orally as either 3 mg/kg or 1 mg/kg in corn oil and 0.5% ethanol to pregnant female mice. Vehicle mice were administered corn oil and ethanol. Control mice were untreated. The EAE was induced when gestational exposed mice reached adulthood using myelin oligodendrocyte glycoprotein (MOG) and complete Freund's adjuvant (CFA) without the use of pertussis toxin. Mice were monitored and tissues were collected for *in vitro* experiments and PCR.

Results: Male mice, gestationally-exposed to BPA, had an increased susceptibility to EAE, but female mice did not. Increased inflammatory markers were observed in male macrophages following gestational BPA exposure and subsequent activation *in vitro*. Furthermore, the number of circulating neutrophils was increased in male mice gestationally-exposed to BPA, but not in females, and increased expression of granulocyte colony-stimulating factor (G-CSF) was observed in circulation following immunization. Examination of the marker CD11b demonstrated that neutrophils were also significantly more activated in male mice

gestationally-exposed to BPA following immunization with MOG in CFA without pertussis toxin. Furthermore, we were able to reverse the observed increased susceptibility in male mice by blocking G-CSF in adult animals using a function-blocking antibody.

Conclusion: Gestational exposure to BPA increased susceptibility to EAE in male, but not female mice, using sub-optimal immunization through innate immune alterations. The BPA is a potential environmental factor that increases the future risk of MS.

A mechanistic study of NLR protein activation: examining the role of a novel, conserved lid region overlying the ATP-binding pocket

JM Platnich, HJ Chung, NA Bondzi-Simpson, J Chun, DA Muruve
Cumming School of Medicine, University of Calgary, Calgary AB

Introduction: The Nod-like receptors (NLRs) are a family of immune receptors that have been associated with a variety of inflammatory diseases. The NLRs are mechanistically linked by their need to bind ATP and oligomerize in order to transduce downstream signals. We have identified a highly conserved region overlying the ATP binding pocket of NLRs. The objective of this study is to examine the importance of this putative lid region with regard to the function of NLR proteins.

Methods: Conserved amino acids in the putative lid region were targeted for ablation using site-directed mutagenesis. A co-immunoprecipitation assay was designed where oligomerization could be quantified based on the ability to pull down wild-type or mutant GFP-tagged NLRP3/6 using wild type FLAG-tagged NLRP3/6. An *in vitro* inflammasome reconstitution assay was employed to examine the functional activity of NLRP3.

Results: Structural modelling of the putative lid region revealed that it directly overlays the Walker A motif of both NLRP3 and NLRP6. Deletion of the entire region or mutations of select amino acids significantly abrogated the oligomerization of both NLRP3 and NLRP6. The greatest decreases in oligomerization were observed in the (D)403-430 ((D)379-406 in NLRP6) deletion mutant and the P412A (P388A in NLRP6) point mutant. The reduction in

oligomerization observed was comparable to that seen following the mutation of a known ATP binding motif (i.e., the Walker A site). Furthermore, the loss of oligomerization in NLRP3 was accompanied by impaired activity of the NLRP3 inflammasome, as denoted by decreased caspase-1 cleavage and IL-1 β secretion *in vitro*. The impact of these mutations on ATP binding and hydrolysis remains unknown.

Conclusion: Mutation of the putative lid region impairs the oligomerization and functional activities of NLR proteins. To parse the different roles of these processes in NLR activation and downstream function, ATP binding and hydrolysis assays are required. By understanding the fundamental mechanisms through which NLRs are activated, novel therapeutic agents can be developed to modulate the inflammatory effects of these proteins.

Vibrational profiling of brain tumors using atomic force microscopy

SL Nelson, DT Proctor, A Ghasemloonia, S Lama, K Zareinia, Y Ahn, MR Al-Saiedy, FHY Green, MW Amrein, GR Sutherland
Project neuroArm, Department of Clinical Neuroscience and the Hotchkiss Brain Institute, Department of Cell Biology and Anatomy, Department of Pediatrics, Alberta Children's Hospital Research Institute, Department of Pathology and Laboratory Medicine, University of Calgary, Calgary AB

Introduction: Brain tumor diagnoses that can be done during surgery are in demand. Here we present a novel atomic force microscopy (AFM) application in an attempt to offer a real-time diagnostic tool to differentiate tumorous from normal brain tissue. We tested the system using excised rat brain and demonstrated clinical application by vibrational profiling of surgically resected brain tissues and tumors. This technique could be used in tissue interrogation for intra-operative assessment of the tumor-brain interface.

Methods: We utilized high sensitivity AFM cantilever probes to detect nanoscale vibration patterns of cells and tissues. We also used a spectrum analyzer, which allowed real-time detection of a wide range of frequencies and directed attention to frequency bands of interest for post-signal processing.

Results: We have shown that newborn rat cultured neurons emit nano-scale vibration. Intensity of fluctuation measured in root mean square (RMS) is significantly greater than

background thermal fluctuation (baseline) and neurons treated with sodium azide, suggesting that living cells fluctuate and could be a function of metabolic activity.

These findings were expanded to study tissue excised from newborn rat brain, which exhibited higher RMS fluctuations than baseline. The RMS recordings were enhanced in depolarizing tissue, reduced when action potentials were inhibition and eliminated in PFA-fixed tissue. Next, assessing clinical application, we have shown that human malignant glioma cell line exhibited significantly higher RMS fluctuations than slow growing tumor cells or normal astrocytes. A similar trend was observed in the oxygen consumption rates, which suggests that RMS may be linked to metabolic activity.

Finally, fresh human tissues of human normal cortex as well as benign and malignant tumors were shown to have dominant frequency peaks, in addition to the higher RMS measured. We were also able to convert the vibrations recorded to audible signals in the human hearing range, thereby offering the potential for intra-operative use during brain surgery.

Conclusion: In conclusion, utilizing sensitive vibration detection technology we have obtained unique vibrational and metabolic signatures of brain tumor from cultured cells and tissues, and into the clinical setting. Across multiple levels of testing and validation of the set-up, we have, for the first time, provided an acoustic identity to glioma, meningioma and neocortex.

Proteoglycan 4 releasing in situ cross linking hyaluronic acid hydrogels for reducing postsurgical adhesions

G Proserpi-Porta, S Regmi and T Schmidt
Cumming School of Medicine and Faculty of Kinesiology,
University of Calgary, Calgary AB

Introduction: Postsurgical adhesions are a significant source of morbidity, causing bowel ischemia or obstruction after intraperitoneal surgery and female infertility or ectopic pregnancies after pelvic surgery. Proteoglycan 4 (PRG4) is a biologic interface lubricant found throughout the body. This work summarizes the synthesis and characterization of *in situ*-forming injectable hyaluronic acid hydrogels that can provide localized and sustained delivery of PRG4 to prevent

postsurgical adhesions.

Methods: Hyaluronic acid polymers of varying molecular weight (MW) were oxidized with sodium periodate to produce aldehyde groups and coupled with adipic acid dihydrazide using carbodiimide chemistry. Mixing these polymers results in a crosslinked hydrogel. Polymers were characterized by ¹H NMR and FTIR to determine chemical properties. Gelation rate, swelling ratio, degradation rate in saline +/- hyaluronidase, mechanical properties, rhPRG4 release and *in vitro* cell viability were examined.

Results: The three MWs of hyaluronic acid were modified to achieve a low and high degree of modification (17-20/33-35% oxidation and 57-58/71-75% ADH coupling determined by ¹H NMR). This allowed both the effects of MW and degree of theoretical crosslinking to be studied. The high modification materials gelled in <5 s of mixing while the low modification materials gelled in <10 s. The swelling ratio increased with MW in the low modification hydrogels, but the high modification hydrogels were not dependent on MW and had a comparatively lower swelling ratio. In physiologic saline the low modification materials showed 40%–60% degradation over four weeks compared with 21%–27% in the high modification materials. Within modification groups, higher molecular weight showed a trend of faster degradation. A similar relationship was found in the hyaluronidase degradation but occurring more rapidly in all materials. Young's and dynamic modulus showed a dependent relationship to both molecular weight and degree of modification. The PRG4 loading showed significant uptake within the hydrogel, and prolonged its release in a physiologic hyaluronidase solution. The PRG4 release was shown to be determined largely by the degradation rate of the material, rather than by diffusion from the hydrogel. When cultured with human synovial fibroblasts, modified polymers and hydrogels both showed excellent biocompatibility reinforcing the material's non-toxic properties and potential for application in the human body.

Conclusion: This work shows the potential of these hydrazide-aldehyde modified hyaluronic acid polymers to act as a physical cushion and provide sustained release of PRG4 at surgical sites to reduce the incidence of postsurgical complications that arise from adhesion formation. The ability to control the PRG4 release rate, hydrogel degradation rate, and mechanical properties suggests that these materials can be

tunable for various applications in cardiac, abdominal, gynecologic and tendon surgery.

Identifying specific health behavior differences in patients with human papillomavirus positive versus negative head and neck cancer

LC Capozzi, ML McNeely, H Lau, RA Reimer, J Giese-Davis, S Nicole Culos-Reed

Faculty of Kinesiology and Faculty of Medicine, University of Calgary; Department of Physical Therapy and Department of Oncology, Faculty of Medicine, University of Calgary & Tom Baker Cancer Centre; Department of Psychosocial Resources, Tom Baker Cancer Centre, Alberta Health Services, Calgary AB

Introduction: Growing evidence supports the role of physical activity (PA) in the rehabilitation of patients with head and neck cancer (HNC), but little is known about PA in patients with human papillomavirus (HPV) -positive versus HPV-negative HNC and associations with quality of life, depression and physical fitness. Since those with HPV-negative HNC generally participate in riskier health behaviours, it was hypothesized that they would also report lower PA and associated health outcomes.

Methods: A total of 60 newly diagnosed HNC patients were recruited to participate in a year-long randomized controlled trial examining the impact of progressive resistance training on body composition, fitness, psychosocial and metabolic outcomes. This study specifically examined baseline group differences, associations and regressions evaluating PA and health outcomes prior to radiation treatment and exercise intervention initiation.

Results: On average, only 25.4% of participants met the PA guidelines (of at least 150 minutes of moderate intensity activity per week) prior to radiation treatment, with HPV-positive patients achieving significantly more weekly PA minutes (253.5 ± 44.8 minutes) than HPV-negative patients (143.0 ± 140.2 minutes; $t = -2.089(48.74)$, $p = 0.042$). Total PA was positively correlated with physical fitness, including functional aerobic capacity ($r = 0.355$, $p < 0.01$) and grip strength ($r = 0.295$, $p < 0.05$). Physical activity was also associated with improved physical and functional wellbeing ($r = 0.378$, $p < 0.01$), as well as improved disease-related symptom management ($r = 0.472$, $p < 0.01$) and HNC-specific quality of life factors ($r = 0.469$, $p < 0.01$). Physical activity was

not significantly correlated with depression status.

Conclusion: Physical activity levels were low in patients with HNC, particularly among those with HPV-negative cancers. Given the health benefits of activity among this population, these results suggest that interventions tailored specifically to the PA experience levels of patients with distinct phenotypes (i.e., HPV-positive vs. -negative) are necessary. Beyond PA levels, ongoing analysis of the data from this randomized controlled trial is investigating whether HPV status predicts differing response to a PA intervention.

Cancer patients, emergency department visits and palliative care: The canary in the coal mine

Z Polsky, E Lang, I Rodin, A Sinnarajah, TS Fung, B Thomas
Faculty of Medicine, Department of Emergency Medicine, Division of Palliative Medicine, Department of Oncology, Research Computing Services, Information Technologies and Division of Psychosocial Oncology, Department of Oncology, University of Calgary, Calgary AB; Department of Psychosocial and Rehabilitation Oncology, Tom Baker Cancer Centre, Alberta Health Services, Calgary AB; Faculty of Science, McGill University, Montreal QC

Introduction: For cancer patients undergoing active treatment, visits to the Emergency Department (ED) act as an indicator of a breakdown in continuity, or poor quality of care. Palliative Care (PC), however, is an important resource for patients transitioning away from curative treatments. To prevent unnecessary visits, it is important to understand why cancer patients present to the ED. This study aims to describe ED utilization by cancer patients, examining if PC consults are protective against ED use.

Methods: Data were obtained from the Screening for Distress database at the Tom Baker Cancer Center, linked to PC and ED databases, and analyzed as a retrospective cohort study. ED data were obtained from SCM and REDIS and PC data were obtained from SCM, PallD, Paris, Physician Billings and Pathways databases. The diagnosis, gender, marital status, living arrangement, education, culture, First Nations, first language and income were analyzed using Univariate, Chi-Square and nominal logistic regression.

Results: Four actively-treated cancer patient cohorts were identified: 1) ED only users (n=1,091); 2) PC only users (n=294); 3) both ED and PC users (n=791); and 4) neither PC nor ED users (n=2,153). Univariate and Chi-Square analyses determined that gender ($p=0.157$) and the patient being First Nations ($p=0.899$) were not significant amongst the groups and were thus excluded from the nominal logistic regression. Compared to neither service, ED only use was associated with a prostate cancer diagnosis, being single, separated or an audible minority. Among new cancer diagnoses, gastrointestinal malignancy patients represent the highest users of the ED. Compared to neither service, PC only use was associated with a primary diagnosis of lung, breast, prostate and gastrointestinal cancer. Palliative Care only use was also associated with being single, separated, living alone, partial university completion, income less than \$50,000 and receiving social assistance. Compared to neither service, ED and PC use were associated with a diagnosis of lung, breast, prostate cancer and being separated.

Conclusion: A variety of sociodemographic factors contribute to the patient's use of the ED, the PC, both or neither. Primary diagnosis, marital status, and culture impact ED use, while primary diagnosis, marital status, living situation, education, and income impact PC use. Use of both was impacted by the primary diagnosis and marital status. ED complaints, and utilization patterns, should be analyzed to determine if initiating earlier PC consults in treatment can contribute to decreased ED utilization.

Distracted walking with mobile technology: Are Calgary high school students at risk?

P Quon, M Grisdale, K Lahey, B Hagel, A Elliott
Department of Pediatrics, Alberta Children's Hospital and
Cumming School of Medicine, University of Calgary, Calgary
AB

Introduction: A 2013 study found that 85% of grade 11 students own a cell phone, compared with 46% in a 2005 study. Internet use with a cell phone rises sharply in grades 9–11. As this age group has been shown to be at higher risk of pedestrian injury, determining whether these trends in mobile technology add further risk is important. This study aims to create a training module for observers so that prevalence estimates of distracted walking in Calgary high school students can inform traffic and pedestrian policy.

Methods: All 17 public high schools in Calgary were identified for a prospective observational study. Criteria were developed to classify types of distracted walking, as well as inclusion and exclusion parameters for data collection. Females and males talking or texting on a cell phone, using head phones or earbuds, or performing more than one of these behaviours while crossing the street were considered distracted. High school students walking across the street using the designated crosswalk were included in data collection. Those using transportation devices, not using the designated crosswalk, or engaging in other distractions not specified were excluded from data collection. Students engaging in distracted walking with mobile technology were observed at the most populous crosswalk following afternoon bell time at 4 high schools. Data were collected at Bowness, Forest Lawn, Crescent Heights and Sir Winston Churchill high schools. All 17 high schools are being observed at the end of the day to identify the busiest crosswalk.

Results: Preliminary observations showed an average of 15% of students engaged in one or more of the described distracted behaviours. Crescent Heights students engaged most in distracted walking, with 19% of students engaging in one or more of these behaviours. Use of earbuds or headphones was the most common distracted behaviour at three of the observed schools. The identified crosswalks will be used for the remainder of the study.

Conclusion: Preliminary data collection shows prevalence rates similar to previous studies, suggesting that distracted walking is a concern amongst Calgary high school students. Furthermore, the use of earbuds or headphones as the most common behaviour is consistent with previous studies looking at distracted pedestrian behaviour. Because of the potential for pedestrian accidents associated with these behaviours, further investigation is warranted. The described parameters will be used to develop a training module for data collection in the future. Determining the prevalence of distracted walking may contribute to the development of new traffic and pedestrian policies to prevent pedestrian injuries amongst adolescents, a population known to be at risk.

Systematic review of the management of lateral epicondylitis using transdermal nitroglycerin

M Hunter, A Bhargava, H Ganshorn, E Lang
Cumming School of Medicine; Health Sciences Library;
Department of Emergency Medicine, University of Calgary,
Calgary AB

Introduction: Lateral epicondylitis (LE), also known as tennis elbow, is an overuse-underuse tendinopathy originating from the forearm extensor tendons of the elbow. An emerging therapy for the treatment of LE is the use of transdermal nitroglycerin (NTG) patches for pain relief and improved function. Our systematic review assesses 18 to 65 year old patients with clinically-diagnosed LE to determine if transdermal NTG patches provide improved pain relief as well as improved function compared with placebo.

Methods: We included randomised controlled trials (RCTs) as well as prospective comparison studies of NTG patch use versus placebo for the treatment of LE. We performed a literature search using MEDLINE, EMBASE, SportDiscus and the Cochrane Database of Systematic Reviews. English language articles were retrieved for review up to November 2015. Risk of bias within the studies was assessed regarding randomisation, allocation sequence concealment, blinding and selective outcome reporting.

Results: Three RCTs were included that compared transdermal NTG patch (two studies with 1.25 mg/24 h and one study comparing 0.72, 1.44 and 3.6 mg/24 h) versus a placebo to treat LE. One prospective comparison study of five years duration was included as a follow-up to one of the included RCTs to assess pain and function five years after the discontinuation of therapy. Data were not pooled because of heterogeneity in study methods and outcomes. The use of transdermal NTG patches provided short term pain relief (2–6 weeks for dosing of 0.72 mg/24 h or 1.25 mg/24 h) compared with placebo as suggested by three RCTs. Long term pain relief was improved by NTG patch use compared with placebo at six months in one RCT, but not at five years in a prospective comparison study. Function improved in two different RCTs with NTG patch use at 0.72 mg/24 h and 1.25 mg/24 h when compared with placebo. Five years after cessation of treatment, there was no difference between NTG patch and placebo.

Conclusion: Overall, the included studies demonstrate that the use of NTG patches compared with placebo improved

short term and long term pain relief, as well as elbow function. However, more studies are required to bridge the gaps between the existing studies and to reduce heterogeneity between the study designs.

Wall shear stress mapping identifies diseased tissue in the ascending aorta of bicuspid aortic valve patients using 4D flow MRI

DG Guzzardi, AJ Barker, P van Ooij, SC Malaisrie, JJ Puthumana, DD Belke, HEM Mewhort, DA Svystonyuk, S Kang, D Park, S Verma, J Collins, J Carr, RO Bonow, M Markl, JD Thomas, PM McCarthy, PWM Fedak
Division of Cardiac Surgery, University of Calgary, Calgary AB; Department of Radiology, Division of Surgery-Cardiac Surgery, Department of Medicine-Cardiology and Department of Biomedical Engineering, Northwestern University; Evanston IL; Department of Radiology, Academic Medical Center Amsterdam, Amsterdam, Netherlands; Division of Cardiac Surgery, University of Toronto, Toronto ON

Abstract withheld as per the authors' wishes.

DNA methylation patterns in human hepatocellular carcinoma tissue samples compared with adjacent non-tumourous tissue samples, as analyzed using next-generation sequencing

D Keren, R Maciver, S Ramchandani, S Nanji, T Ozolins
Cumming School of Medicine, University of Calgary, Calgary AB; Department of Biomedical and Molecular Sciences, Department of Biomedical and Molecular Sciences, Department of Biomedical and Molecular Sciences, Department of Surgery, School of Medicine and Department of Biomedical and Molecular Sciences, Queen's University, Kingston ON

Abstract withheld as per the authors' wishes.

Enhancing central nervous system repair by removal of inhibitory scars with the novel protease ADAMTS4

MB Keough, NJ Michaels, SK Jensen, LW Lau, V Wee Yong
Hotchkiss Brain Institute, Department of Clinical
Neurosciences and Cumming School of Medicine, University
of Calgary, Calgary AB

Abstract withheld as per the authors' wishes.

Maternal diet and infant brain-sparing among Ngorongoro Maasai

CD Powell
Cell Biology & Anatomy, Cumming School of Medicine,
University of Calgary, Calgary AB

Abstract withheld as per the authors' wishes.

Abbreviated abstracts

The following are titles and authors of abstracts presented in poster format. Full details can be seen on our LIM website (<https://cumming.ucalgary.ca/lim/>).

CRITICAL success factors and unanticipated consequences from the implementation of a single-entry model of referral for total joint replacement surgery

Z Damani, G MacKean, E Bohm, T Noseworthy, J Meng
Han Wang, B DeMone, B Wright, DA Marshall
Department of Community Health Sciences, Cumming
School of Medicine, University of Calgary, Calgary AB; Public
Health Ontario; Department of Surgery; University of
Manitoba, Winnipeg MB; Manitoba Health, Healthy Living
and Seniors, Acute, Tertiary and Specialty Care / Regional
Policy and Programs; Winnipeg Regional Health Authority,
Winnipeg MB

Calreticulin promotes osteogenic differentiation and attenuates chondrogenic differentiation of embryonic stem cells by regulating Runx2 nuclear translocation

YH Yu, C Pilquil, L Al-Mansoori, M Opas
Department of Laboratory Medicine and Pathobiology,
University of Toronto, Toronto ON

Advancing pediatric cardiac care and characterizing the scope of congenital heart disease in Guyana

D Isaac, A Bell, **W Nagesh**
Cumming School of Medicine, University of Calgary, Calgary
AB

Genetics of trigeminal neuralgia: Insight from 15 families and whole exome sequencing

SJ Mosca, ZH Kiss, AM Innes
Cumming School of Medicine, University of Calgary;
Department of Clinical Neuroscience, Hotchkiss Brain
Institute, University of Calgary; Department of Medical
Genetics, University of Calgary; Alberta Children's Hospital
Research Institute, Calgary AB

Integrating choosing wisely Canada content and principles into medical school curriculum

N Enns, S Skinner

Cumming School of Medicine, University of Calgary, Calgary AB

Gonioscopy-assisted transluminal trabeculotomy (GATT): The western Canadian experience

S Cote, B Ford, P Gooi

Cumming School of Medicine and Division of Ophthalmology, University of Calgary, Calgary AB

Menopause status is associated with mortality in women on hemodialysis in Canada

S Ramesh, MT James, SB Wilton, JM Holroyd-Leduc, EW

Seely, M Tonelli, BR Hemmelgarn SB Ahme
Cumming School of Medicine, University of Calgary, Calgary AB; Libin Cardiovascular Institute of Alberta; Department of Community of Health Sciences, University of Calgary, Calgary AB; Alberta Kidney Disease Network; Brigham and Women's Hospital, Harvard University, Boston MA, USA

Disseminated tuberculosis in a woman presenting with intrapartum seizure

SM Crooks, GAE Jewett, B Meatherhall, R Kapadia

Faculty of Medicine; Department of Clinical Neurosciences, Division of Neurology; Department of Clinical Medicine, Division of Infectious Diseases, University of Calgary, Calgary AB

The use of mitochondrial protective agents to reverse general anesthetic-induced neurotoxicity

R Armstrong, F Xu, D Urrego, M Qazzaz, M Pehar, JN

Armstrong, NI Syed
Hotchkiss Brain Institute and Department of Anesthesia, Cumming School of Medicine, University of Calgary, Calgary AB

The GHSR and a novel, potentially protective mechanism in chronic corticosterone treatment

R Hay, M Smorenburg, T Rodrigues, A Edwards, M Klein, L

Hyland, H MacKay, I Karatosoreos, MN Hill, A Abizaid
Department of Neuroscience, Carleton University, Ottawa ON; Hotchkiss Brian Institute, University of Calgary, Calgary AB; Department of Integrative Physiology and Neuroscience, Washington State University, Pullman WA, USA; Institute of Biomedical Sciences, University of Sao Paulo, Sao Paulo, Brazil

Pioneering surgery in wartime and the effects on current civilian practice—an Albertan link

R Buttar

Cumming School of Medicine, University of Calgary, Calgary AB

Use of the Papanicolaou test in women under 25 years of age in southern Alberta

R Snodgrass, C Naugler

Department of Kinesiology and Physical Education, McGill University, Montreal QC; University of Calgary and Calgary Laboratory Services, Calgary AB

A provisional model of deference behaviour observed within pediatric resuscitation

N Delaloye, R Ellaway, E Oddone Paolucci, A Kassam, A

Deacon, T O'Neill, E Gilfoyle
Department of Community Health Sciences, Department of Psychology and Department of Paediatrics, University of Calgary, Calgary AB

Targeting DNA repair defective tumors

N Jette, C Wang, D Moussienko, SP Lees-Miller

Cumming School of Medicine, University of Calgary, Calgary AB

Prospecting microbe-microbe interactions to discover natural inhibitors of *Pseudomonas aeruginosa* c-di-GMP signaling and biofilm formation

NK McCartney, BR Borlee, MD Parkins, JM Conly, DJ Mahoney, D Derksen, JJ Harrison and The Bugs-to-Drugs Collaborative
Faculty of Science and Cumming School of Medicine, University of Calgary, Calgary AB; College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins CO, USA

When physicians choose less wisely: Determinants of CT head ordering for low-risk headache in the emergency department

M MacKenzie, R Hiranandani, D Wang, E Lang
Cumming School of Medicine and Department of Emergency Medicine, University of Calgary, Calgary AB

Assessment of patient care and educational outcomes of the University of Calgary's Student Run Clinic

A Jensen, M Smith, R Ellaway
Cumming School of Medicine, University of Calgary, Calgary AB

Mental health outcomes for young adults with high functioning Autism Spectrum Disorder following completion of social skill intervention

M Coret, K Murphy, A McCrimmon
Department of School and Applied Child Psychology, University of Calgary; Autism Spectrum Education, Research, and Training Lab (ASERT), Calgary AB

Mechanisms of early filling in the left ventricle

LM Burrowes, A Satriano, NG Shrive, JV Tyberg
Schulich School of Engineering and Cumming School of Medicine, University of Calgary, Calgary AB; Stephenson Cardiac Imaging Centre; Libin Cardiovascular Institute of Alberta.

A close look into Dectin-1-mediated phagocytosis

L Cadili, N Touret
Department of Biochemistry, University of Alberta, Edmonton AB

Combined gross morphological joint damage is progressive in a long term partial anterior cruciate ligament transection ovine model

KI Barton, BJ Heard, JL Seveck, M Chung, CR Martin, CB Frank, NG Shrive, DA Hart. McCaig Institute for Bone and Joint Health, University of Calgary, Calgary AB

Predicting short-term risk of arrhythmia among patients with syncope: The Canadian Syncope Arrhythmia Risk Score

K Kwong, V Thiruganasambandamoorthy, MLA Sivilotti, BH Rowe, M Mukarram, K Arcot, A McRae, IG Stiell, GA Wells, M Taljaard
Ottawa Hospital Research Institute, Ottawa ON; School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa ON; Department of Emergency Medicine, University of Ottawa, Ottawa ON; Department of Emergency Medicine, Queen's University, Kingston ON; Department of Biomedical and Molecular Sciences; Department of Emergency Medicine and School of Public Health, University of Alberta, Edmonton AB; Department of Emergency Medicine, University of Calgary, Calgary AB

Risk of blood transfusion during radical cystectomy

K Witiuk, M Spurrell, R Mallick, D Fergusson, C Morash, I Cagiannos, RH Breau
Cumming School of Medicine, University of Calgary, Calgary AB; Ottawa Hospital Research Institute and Division of Urology, Department of Surgery, The Ottawa Hospital, University of Ottawa, Ottawa ON

The role of rural community tours in undergraduate medical education

K Wilson, K Farrington, L Standerwick, D Myhre
Cumming School of Medicine and Distributed Learning and Rural Initiatives, Cumming School of Medicine, University of Calgary, Calgary AB

Establishing a continuous feedback system to improve patient reported outcome measures in the Post Anesthesia Care Unit (PACU)

J Nicholas, A Moazeni, C Fantuz, D Finegan, W Leung, J Davies
Cumming School of Medicine, University of Calgary, Calgary AB; Alberta Health Services

Factors associated with illicit substance use and cigarette smoking in people with epilepsy

JI Roberts, KM Fiest, SB Patten, S Wiebe, S Macrodimitri, AGM Bulloch, N Jetté
Department of Community Health Sciences and Institute for Public Health; Department of Clinical Neurosciences and Hotchkiss Brain Institute; Department of Critical Care Medicine; Department of Psychiatry and Mathison Centre for Mental Health Research & Education, University of Calgary, Calgary AB

Examining the role of NOD-like receptors in intestinal fibrosis

J Tjong, Y Li, PL Beck
Cumming School of Medicine, University of Calgary, Calgary AB

Lesion location is associated with kinaesthetic impairment post-stroke

JM Kenzie, JA Semrau, SE Findlater, JA Desai, TM Herter, MD Hill, SH Scott, SP Dukelow University of Calgary, Calgary AB; University of South Carolina, Columbia SC, USA; Queen's University, Kingston ON

Platin induced phosphorylation of ATM and ATM-deficiency as a predictive marker of platin sensitivity in non-small cell lung cancer

JT Moore, LF Petersen, AA Elegbede, DG Bebb
Cumming School of Medicine and Tom Baker Cancer Centre, University of Calgary, Calgary AB

Influenza vaccination knowledge, attitude and practice of university athletes

J Lautermilch, P Doyle-Baker
Faculty of Environmental Design, University of Calgary, Calgary AB

Characterizing the molecular components of lineage-specific transcription in developing *Caenorhabditis elegans*

J Feng, J McGhee
Cumming School of Medicine and Department of Biochemistry and Molecular Biology, University of Calgary, Calgary AB; Alberta Children's Hospital Research Institute, Calgary AB

Calibrated functional magnetic resonance imaging in multiple sclerosis

J Bird, E Mazerolle, W-M Luh, B Pike
Hotchkiss Brain Institute, University of Calgary, Calgary AB; Cornell MRI Facility, Cornell University; Ithaca NY, USA

Social cognition in people with bipolar disorder

J Bobyn, B Fonseka, S Hassel, G MacQueen
Cumming School of Medicine, University of Calgary, Calgary AB; School of Life and Health Sciences, Aston University, Birmingham UK

Identification of novel PAX6 genetic abnormalities in aniridia: Correlation with clinical presentation and in vivo imaging of foveal architecture

H Zakrzewski, N Sannan, CY Gregory-Evans, CJ Lyons, AM Lehman, S Langlois, SJ Warner, K Gregory-Evans
Cumming School of Medicine, University of Calgary, Calgary AB; Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver BC; Department of Ophthalmology, BC Children's Hospital, Vancouver BC; Department of Medical Genetics, University of British Columbia, Vancouver BC

An evaluation of Students for Health Innovation and Education (SHINE) in fostering CanMED roles in medical students

F D'souza, DT Senaratne
Cumming School of Medicine, University of Calgary, Calgary AB

Family Integrated Care (FICare) in Level II NICUs: An innovative program for Alberta

E Fridfinnson, A Lodha, K Benzies, K Aziz, V Shah
Cumming School of Medicine, Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary AB; Alberta Children's Hospital Research Institute; Faculty of Nursing, University of Calgary, Calgary AB; Department of Paediatrics, University of Alberta, Edmonton AB; Neonatal Research Unit, Royal Alexandra Hospital, Edmonton AB; Department of Paediatrics and Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto ON; Department of Paediatrics, Mount Sinai Hospital, Toronto ON

PDA ligation in pediatric patients: Recurrent laryngeal nerve damage and vocal fold immobility

E Holmes, W Yunker
Cumming School of Medicine; Department of Surgery, Divisions of Otolaryngology and Pediatric Surgery, Cumming School of Medicine, University of Calgary; Alberta Children's Hospital, Calgary AB

Is shiftwork harmful to your cardiovascular health? Findings from an updated systematic review

D Radomske, E Lang, E Pedersen
Cumming School of Medicine, University of Calgary, Calgary AB

Non-penetrance in cerebro-costo-mandibular syndrome

DC Lynch, AM Innes, RE Lamont, JS Parboosingh, FP Bernier
Department of Medical Genetics, Cumming School of Medicine, University of Calgary; Alberta Children's Hospital Research Institute, Calgary AB

Do cyclooxygenases play a role in labour? A review of the scientific evidence

D Urrego, A Liwa, S Pender, WC Cole, S Wood, DM Slater
Department of Physiology and Pharmacology, Department of Obstetrics and Gynaecology and Cumming School of Medicine, University of Calgary, Calgary AB; Institute of Allied Sciences, Catholic University of Health and Allied Sciences, Mwanza, Tanzania

Tumour thrombus of the inferior vena cava extending into the right atrium in the setting of colon cancer

D Meyers, NA Nixon, A Franko, D Ng, VC Tam
Cumming School of Medicine, University of Calgary, Calgary AB

DNA double-strand break repair in different neural cell lineages

ND Berger, S van Rooijen, AA Goodarzi, JA Chan
Cumming School of Medicine, University of Calgary, Calgary AB

Pediatric Ahmed glaucoma valves as a primary procedure for the surgical management of glaucoma in adults

C Mardinger, A Abbott, A Crichton

Faculty of Medicine and Department of Surgery, University of Calgary, Calgary AB

Rituximab use in a case of successfully treated anti-NMDA receptor encephalitis in Trinidad

A Panday, CA Beers

Faculty of Medical Sciences, University of the West Indies (St. Augustine) Trinidad and Tobago, West Indies; Cumming School of Medicine, University of Calgary, Calgary AB

Risk of recurrent spontaneous preterm birth: A systematic review and meta-analysis

C Phillips, Z Velji, C Hanly, A Metcalfe

Cumming School of Medicine, Faculty of Nursing, Department of Obstetrics and Gynecology, and Department of Community Health Sciences, University of Calgary, Calgary AB; School of Kinesiology, University of British Columbia, Vancouver BC

Impact of ketogenic feeding to O-GlcNAc modify key proteins governing mitochondrial dynamics in the BTBR^{tf/j} mouse model of autism

C Newell, V Johnsen, W Xu, D Hittel, Y Ahn, JM Rho, A Khan & J Shearer

Department of Medical Science, Faculty of Kinesiology, Department of Biomedical Engineering, Department of Pediatrics, Department of Medical Genetics, Department of Biochemistry & Molecular Biology, Cumming School of Medicine, University of Calgary, Calgary AB

STABILITY Study: A multicentre RCT comparing ACL reconstruction with and without lateral extraarticular tenodesis for individuals at high risk of graft failure

C Hewison, A Firth, D Bryant, R Litchfield, K Willits, R McCormack, M Heard, P MacDonald, T Spalding, P Verdonk, D Peterson, D Bardana, A Rezansoff, N Mohtadi, STABILITY Study Group, A Getgood
Fowler Kennedy Sport Medicine Clinic, London ON; Department of Surgery, Schulich School of Medicine and Dentistry, Western University, London ON; School of Physical Therapy, Western University, London ON; Department of Orthopaedics, University of British Columbia, Vancouver BC; New West Orthopaedic & Sports Medicine Centre; Department of Surgery, University of Calgary, Calgary AB; Banff Sport Medicine, Banff AB; Department of Surgery, University of Manitoba, Winnipeg MB; Pan Am Clinic; University Hospital Coventry and Warwickshire NHS Trust; Department of Physical Medicine and Orthopaedics, Ghent University; Antwerp Orthopaedic Center; Department of Surgery, McMaster University, Hamilton ON; Department of Surgery, Queen's University, Kingston ON; University of Calgary Sport Medicine Centre, Calgary AB

Induction of mucus transcription in intestinal epithelial cells is a compensatory mechanism against Giardia duodenalis mucolytic activity

CB Amat, J-P Motta, K Chadee, AG Buret

Department of Biological Sciences, Department of Microbiology, Immunology & Infectious Diseases, SERC CREATE Host-Parasite Interactions, Inflammation Research Network, University of Calgary, Calgary AB

The discordant effects of DMXAA on tumours arising in different anatomical locations is attributable to both density of infiltration and drug-induced repolarization of tumour-associated macrophages

C Blomquist, F Jirik

Department of Biochemistry and Molecular Biology, McCaig Institute for Bone and Joint Health, University of Calgary, Calgary AB

Microglia sever radial glia processes to influence the development of hypothalamic energy balance centers

CM Marsters, F Malik, L Adnani, N Klenin, R Dixit, C Schuurmans, QJ Pittman, DM Kurrasch
Department of Medical Genetics, Department of Biochemistry and Molecular Biology and Department of Pharmacology & Physiology, Cumming School of Medicine; Hotchkiss Brain Institute and Alberta Children's Hospital Research Institute, University of Calgary, Calgary AB

The use of sit-to-stand testing to measure orthostatic vital signs: What cut-off is appropriate to diagnose orthostatic hypotension?

BH Shaw, EM Garland, BK Black, SY Paranjape, CA Shibao, LE Okamoto, A Gamboa, A Diedrich, WD Plummer, WD Dupont, I Biaggioni, D Robertson, SR Raj
Department of Cardiac Sciences, Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary AB; Autonomic Dysfunction Center, Division of Clinical Pharmacology, Department of Medicine, Department of Biomedical Engineering, Department of Biostatistics, Department of Pharmacology and Department of Neurology, Vanderbilt University, Nashville TN, USA

A hierarchical examination of failure in skeletal muscle

B Hisey, W Herzog
Cumming School of Medicine; Human Performance Laboratory, Faculty of Kinesiology; Department of Biomedical Engineering, Schulich School of Engineering; Faculty of Veterinary Medicine, University of Calgary, Calgary AB

Evaluating the use of CEUS in the characterization of complex Type II Endoleaks in patients who underwent failed endoleak repairs

B Stebner, E Nzekwu, R Choo, D Bakshi, O Halliwell
Cumming School of Medicine, University of Calgary, Calgary AB; Faculty of Medicine, University of Alberta, Edmonton AB

Premature stroke mortality and disparities in the Americas

P Ordunez, **A Mirian**, R Martinez
Non-communicable Diseases and Mental Health Unit, Pan American Health Organization; Cumming School of Medicine, University of Calgary, Calgary AB

Systematic review of MRI abnormalities in children with developmental delay

A Moir, K Murias, I Liu, K Myers
University of Calgary; Pediatric Neurology, Alberta Children's Hospital, Calgary AB

Maternal mental health and child health in rural Nicaragua

A Rudkoski, G Brown, N Hoehn, B Piperata, K Schmeer, W Wilson
Department of Anthropology and Archaeology and Department of Community Health Sciences, University of Calgary, Calgary AB; Department of Anthropology and Department of Sociology, Ohio State University, Columbus OH, USA

Sexual education on reserve: Exploring inequities and barriers of partnership

A Marchak, Z Polsky, N Kloos
Cumming School of Medicine, University of Calgary, Calgary AB

Dose-dense paclitaxel with carboplatin vs intra-peritoneal cisplatin with paclitaxel for the treatment of advanced ovarian cancer: Is there a clear winner?

A Forsyth, S Glaze, G Nelson
Cumming School of Medicine, University of Calgary; Department of Gynecologic Oncology, Tom Baker Cancer Centre, Calgary AB

Prediction of early adverse events in emergency department patients with acute heart failure: A systematic review

A Michaud, S Parker, H Ganshoren, A McRae
Cumming School of Medicine, Faculty of Nursing, Health Sciences Library, Department of Emergency Medicine, University of Calgary, Calgary AB

20/20 vision after DSAEK and DMEK: Are they equal?

AA Amayem, DL DeMill, AF Mouser, CR Terry, ZM Mayko, M. Terry
Cumming School of Medicine, University of Calgary, Calgary AB; Dever's Eye Institute, Portland OR, USA

EEG localization of brain activity during walking: A case study

A Kline, D Pittman, B Goodyear, J Ronsky
Schulich School of Engineering, McCaig Institute for Joint Health, Cumming School of Medicine, University of Calgary, Calgary AB

Formally evaluating the variability and generalizability of visual HFO evaluations: A new semi-supervised framework

AM Spring, DJ Pittman, Y Aghakhani, J Jirsch, N Pillay, LE Bello-Espinosa, C Josephson, P Federico
Department of Clinical Neurosciences, Hotchkiss Brain Institute, Department of Paediatrics and Department of Radiology, University of Calgary, Calgary AB; Seaman Family MR Research Centre, Foothills Medical Centre, Calgary AB; Department of Medicine, University of Alberta, Edmonton AB