SHARPMINDS:SKILLEDHANDS

Department of Surgery
45th GALLIE DAY - FRIDAY MAY 3, 2019

SYMPOSIUM: Advances in Cancer Research: From Cell to the Clinic
Chair: Michael G. Fehlings, Vice Chair Research

♦ **Peter Dirks**, MD, PhD, FRCSC;
"Brain cancer's pervasive developmental hierarchies"

♦ **J. Andrea McCart**, MD, MSc, FRCSC
Gastro-intestinal Surgical Oncology & Peritoneal Malignancy
"A window into the tumour microenvironment of oncolytic virus therapy"

♦ **Jay S. Wunder**, MD, MSc, FRCSC
Surgeon-in-Chief, Rubinoff-Gross Chair in Orthopaedic Oncology, Mount Sinai Hospital
"Improving sarcoma outcomes: From genetic to immune-based therapies"

♦ **Cari Whyne,** PhD FIOR, Susanne and William Holland Chair in Musculoskeletal Research; Research Director, Holland Bone & Joint Program, Sunnybrook Research Institute
"Multimodal treatments for spinal metastases"

PETER DIRKS, MD, PhD, FRCSC

Dr. Peter Dirks is a professor of neurosurgery and molecular genetics at the University of Toronto and a senior scientist in the Developmental and Stem Cell Biology Program at the Hospital for Sick Children. His research focus is on the biology of brain tumours of children and adults, with a primary aim to understand how the molecular programs in normal neural stem cells become perturbed to cause and sustain the growth of these hard-to-treat cancers. In addition, he is interested in brain tumour heterogeneity and how the diverse cell types that comprise these tumours contribute to tumour maintenance and therapeutic resistance.

His group was the first prospectively identified cancer stem cells (CSCs) in human brain tumours (Nature 2004), the second such description in a solid human cancer. They subsequently identified new methods for culturing patient-derived glioblastoma (GBM) stem cells (Cell Stem Cell 2009), which directly led to chemical and genetic screening capacities. Recently they have used single cell cloning approaches with human GBM to understand the functional and genetic heterogeneity at a single clone level (PNAS 2015). They have also identified CSCs in brain tumours arising in genetically engineered mice (Cancer Res. 2009), particularly using lineage tracing approaches (Cancer Cell 2014), which point to rare quiescent and treatment resistant stem cells at the apex of the cancer hierarchy. Together with collaborators, they published one of the first chemical biology screens on normal neural stem cells (Nature Chem. Biol 2007), unexpectedly uncovering hits in neurotransmission pathways, which led to a recent discovery that blocking dopamine signaling through its DRD4 receptor could be a neurochemical strategy for GBM treatment (Cancer Cell, 2016).

More recently, they have shown that increasing ASCL1 levels in GBM stem cells can restore neuronal lineage potential and can promote terminal differentiation (Cell Stem Cell 2017). Directing GSCs toward terminal differentiation may provide therapeutic applications for a subset of GBM patients and strongly supports efforts to restore differentiation potential in GBM. Finally, in a study of the clonal dynamics of barcoded fresh primary GBM cells, they showed that tumors of diverse genetic background follow a similar growth program that resembles a developmental hierarchy, suggesting that therapies that exploit cell programs may be applicable to tumors of diverse genotypes (Nature 2017).

His clinical interests lie with the entire spectrum of paediatric neurosurgical practice, with emphasis on the surgical treatment of childhood brain tumours and brain vascular malformations.

Title: "Brain cancer's pervasive developmental hierarchies"

J. ANDREA MCCART, MD, MSc, FRCSC
Gastro-intestinal Surgical Oncology & Peritoneal Malignancy
Dr. Andrea McCart completed medical school and General Surgery training at the University of Western Ontario. During residency she undertook research training and obtained her MSc in cancer research. Following residency, she completed a surgical oncology fellowship focused on regional therapies of cancer at the National Cancer Institute in Bethesda Maryland. While there she also did post-doctoral research in the laboratory of Dr. David Bartlett, investigating gene and viral therapies for cancer. Dr. McCart moved to Toronto following her fellowship where she is currently an Associate Professor in the Department of Surgery and a Scientist at the Toronto General Hospital Research Institute. Dr. McCart is a surgical oncologist at Mount Sinai Hospital and Princess Margaret Cancer Centre where she started the Peritoneal Malignancy Program in 2011. Her clinical interests include the treatment of peritoneal malignancies and other gastrointestinal cancer. Her research laboratory is developing novel viral-based therapeutics for peritoneal and other malignancies.

Title: "A window into the tumour microenvironment of oncolytic virus therapy"

CARI WHYNE, PhD, FIOR
Dr. Cari Whyne is a Senior Scientist and the Director of the Holland Bone and Joint Research Program at Sunnybrook Research Institute, and holds the Susanne and William Holland Chair in Musculoskeletal Research at Sunnybrook Health Sciences Centre. She is a Professor in the Department of Surgery, Institute of Biomaterials and Biomedical Engineering and Institute of Medical Sciences at the University of Toronto. Dr. Whyne received her BScEng from the Queen's University in Mechanical Engineering and her PhD from the University of California Berkeley / University of California San Francisco in Bioengineering. The focus of her work within the Orthopaedic Biomechanics Laboratory is clinically translational bioengineering research. Dr Whyne's research integrates biomechanical analyses with basic science and preclinical investigations, including extensive work in computational image analysis, micro-imaging and finite element modeling techniques. Her work also incorporates design, simulation, evaluation and clinical translation of novel less/minimally invasive surgical techniques and devices. The primary foci of Dr Whyne's research are cancer in bone, spinal/lower extremity/thin bone biomechanics and fracture fixation/healing.

Title: "Multimodal treatments for spinal metastases"

JAY S. WUNDER, MD, MSc, FRCSC
Surgeon-in-Chief, Rubinoff-Gross Chair in Orthopaedic Oncology, Mount Sinai Hospital
Dr. Jay Wunder is an orthopaedic surgeon, specializing in the care of patients with bone and soft tissue sarcomas at Mount Sinai Hospital and Princess Margaret Cancer Centre. Jay is a graduate of the Surgeon Scientist Training Program in the Dept of Surgery at UofT. He holds the Rubinoff/Gross Chair in Orthopaedic Oncology, is Surgeon-in-Chief at Mount Sinai Hospital and a Professor at UofT. He is known to be an excellent educator and has won numerous undergraduate and postgraduate teaching awards. Jay co-leads a sought after orthopaedic oncology fellowship training program, and is involved in a multifaceted research program focused on musculoskeletal oncology, including development of a surgical navigation system for bone sarcomas, prospective database for clinical and functional outcomes and for validating new surgical techniques, and a translational research program in sarcoma biology. He developed an extensive sarcoma tumor bank to facilitate developmental biology and molecular epidemiological studies in order to better understand sarcoma biology and develop novel patient treatments.

Title: "Improving sarcoma outcomes: From genetic to immune-based therapies"

E-POSTER PRESENTATIONS

1. Mitchell Adamson, Roberto Ribeiro, Frank Yu, Julieta Lazarte, Kyle Runeckles, Cedric Manlhiot, Vivek Rao, Diego Delgado: **HLA-G 14BP polymorphism donor/recipient matching protects against development of post-transplant malignancy following heart transplantation**

2. Christopher Ahuja (SSTP), Mohamad Khazaei, Yao Yao, Ali Hasan, Vjura Senthilnathan, Inaara Walji, Nayaab Punjani, Sohanthen Udayashankar, Zijian Lou, William Luong, Alex Post, Gokce Ozdemir, Edward Robinson, Priscilla Chan, Jian Wang, Michael G. Fehlings: **Self-assembling peptide biomaterial to optimize human neural stem cell-mediated regeneration of the injured spinal cord**

3. Karen J Aitken, Martin Sidler, Darius J Bagli: **Murine partial outlet obstruction induces macrophage-dependent changes in cytokine, ECM and AKT pathway expression coordinate with bladder function and pathology**

4. **(TR)** Mashriq Alganabi, Haitao Zhu, Maarten Janssen Lok, Joshua S O'Connell, George Biouss, Edoardo Bindi, Bo Li, Agostino Pierro: **Involvement of calcium/calmodulin-dependent protein kinase IV (CAMKIV) in experimental necrotizing enterocolitis**

5. Ikran Ali, Charles Godbout, Hening Sun, Emil Schemitsch, Aaron Nauth: **Characterizing the effects of locally applied vancomycin powder on bone healing and infection in an animal model**

6. Lina Antounians, Huayun Hou, Cadia Chan, Areti Tzanetakis, Louise Montalva, Augusto Zani: **RNA cargo of amniotic fluid stem cell extracellular vesicles epigenetically regulates fetal lung epithelial cells in experimental congenital diaphragmatic hernia**

7. **(TR)** Christopher Auger, Osai Samadi, Abdikarim Abdullahi, Alexandra Parousis, Marc G. Jeschke: **Metformin induces the phenotypic switch of beige fat to white fat in adipose tissue post-burn (oral presentation)**

8. **(TR)** Dalia Barayan, Christopher Auger, Carly Knuth, Roohi Vinaik, Abdilkarim Abdullahi, Marc G. Jeschke: **Reduction of PKA-mediated lipolysis with acipimox improves mitochondrial coupling in adipose tissue following burn injury**

9. George Biouss, Joshua S O'Connell, Lina Antounians, Agostino Pierro, Augusto Zani: **Neuroinflammation secondary to necrotizing enterocolitis**

10. David Burns (SSTP), Robin Richards, Cari Whyne: **Intra-operative verification of the glenoid implant position with structured light imaging in total shoulder arthroplasty**

11. **(TR)** Katelyn Chan, Marina Manoraj, Jenny Cheung, Jennifer Zhang, Tessa Gordon, Gregory H Borschel: **A nerve wrap for the localized delivery of FK506 to enhance peripheral nerve regeneration**

12. **(TR)** Priscilla Chan, Christopher S Ahuja (SSTP), Mohamad Khazaei, Alexander Velumian, Michael G Fehlings: **Self-tracing human neural stem cells to map transplant integration**

13. Douglas Cheung (SSTP), Hala Muaddi (SSTP), Antonio Finelli, Paul Karanicolas, John De Almeida: **Cost utility analysis of prophylactic incisional negative pressure wound dressing compared to conventional dressing to reduce surgical site infection in elective open colectomy**

14. **(TR)** William Chu Kwan (SSTP), Adam C Waspe, Unni Narayanan, James M Drake: **Biomechanical changes in porcine tendion following high-intensity focused ultrasound**

E-POSTER PRESENTATIONS

15. Karen Chung (SSTP), George Ho, Aysegul Erman, Joanna M Bielecki, Christopher Forrest, Beate Sander: **The cost-effectiveness of cleft lip and/or palate surgery in low- and middle- income countries: A systematic review**

16. Allison Clement, Cari Whyne, Margarete Akens, Phoenix Wilkie, Albert Yee, Michael Hardisty: **Radiomic features used to differentiate between osteoblastic and healthy tissue in metastatically involved vertebrae**

17. David P Cyr (SSTP), Paul Savage, Evangelia Theodosopoulos, Tyler R Chesney, Carol J Swallow: **Outcomes of salvage surgery for anal squamous cell carcinoma: A systematic review and meta-analysis**

18. **(TR)** Alexa Desimone, Jetan Badhiwala (SSTP), Michael G Fehlings: **The role of apolipoprotein e4 in the pathophysiology and clinical outcomes of degenerative cervical myelopathy**

19. **(TR)** Gertraud Eylert, Richard Cheng, Sijin He, Jean-Michel Gariepy, Axel Guenther, Marc G Jeschke: **Burn skin tissue regeneration with a novel intraoperatively bio-printer**

20. Niloofar Ganji, Yuhki Koike, Bo Li, Hiromu Miyake, Carol Lee, Agostino Pierro: **Remote ischemic conditioning improves nec-induced intestinal injury by improving structure and microvascular density of the intesinal villi**

21. Bruno de M Gomes, Rafalela Ribeiro, Khaled Ramadan, Marcos Galasso, Aadil Ali,Yui Watanabe, Emanuela Paradiso, Massimiliano Meineri, Harley Chan, Yu Zhang, David Hwang, Arthur Slutsky, Eddy Fan, Mingyao Liu, Shaf Keshavjee, Marcelo Cypel, Lorenzo Del Sorbo: **Evaluating the influence of peep-induced alveolar recruitment on lung injury during VV-ECMO for ARDS**

22. Vaibhav Gupta (SSTP), Paul Carroll, Jordan Levy (SSTP), Gail Darling, Natalie Coburn: **Utilization, safety, and efficacy of hybrid esophagectomy in Ontario (withdrew)**

23. John R Han, John Tran, Philip W.H. Peng, Anne M.R. Agur: **Sensory innervation of the ankle joint: Implications for nerve block and radiofrequency ablation**

24. Amanda Hird (SSTP), Douglas Cheung (SSTP), Diana Magee (SSTP), Rano Matta (SSTP), Girish S Kulkarni, Robert K Nam: **Abiraterone versus docetaxel for metastatic hormone sensitive prostate cancer: A MARKOV microsimulation model**

25. George Ho, Kaitlyn Beyfuss, Sten Myrehaug, David L Chan, Victoria Zuk, Calvin HL Law, Alyson Mahar, Julie Hallet: **Prediction of survival for pancreatic neuroendocrine tumours: A systematic review of clinical tools**

26. Tiffany Yun-Yee Ho, Lili Li, David Francis Stojdl, Judith Andrea McCart: **Vaccinia virus deletion mutants are potent oncolytic viruses against mesothelioma**

27. Maarten Janssen Lok, Michael Maalouf, Niloofar Ganji, Hiromu Miyake, Agostino Pierro: **Remote ischemic conditioning with limited ischemia time reduces intestinal injury in experimental NEC**

28. Nefateri Jeffrey, Annette Schroder, Aliza Siebenaller, Martin Sidler, Karen J Aitken, Paul Delgado-Olguin, Darius J Bägli: **Rapamycin restores core clock genes after release of obstruction coordinate with discrete physiology changes**

29. Yunni Jeong (SSTP), Julie Hallet, Alyson Mahar, Nicole Mittmann, Vaibhav Gupta (SSTP), Lev Bubis (SSTP), Natalie Coburn: **Clinical and economic outcomes for gastric cancer patients treated with gastrectomy at centres with and without cancer surgery centre designation**

E-POSTER PRESENTATIONS

30. Mai-Lan Johnston, Ellis Kelly, Zhi Li, Nancy McKee, Anne Agur: **Musculoaponeurotic architecture of the flexor digitorum superficialis: A 3D modelling study of intramuscular aponeuroses and fibre bundle morphology**

31. Graham Kasper, Sunit Das: **Identifying the burden of depression and anxiety in patients with intracranial meningiomas: A combined qualitative and quantitative approach**

32. **(TR)** Carly M Knuth, Chris Auger, Marc G Jeschke: **Unraveling the unique burn-induced temporal alterations in adipose tissue metabolism**

33. Jason Koppert, Noami Eisenberg, Maral Ouzounian, Jacob Udell, Kong Teng Tan, John Byrne: **Restrospective analysis of incidental and symptomatic penetrating aortic ulcers and their associated outcomes**

34. **(TR)** Carol Lee, Bo Li, Yuhki Koike, Hiromu Miyake, Agostino Pierro: **Disrupted tight junctions in injured intestinal organoids**

35. Jordan Levy (SSTP), Vaibhav Gupta (SSTP), Catherine Allen-Ayodabo, Elmira Amirazodi, Naheed Jivraj, Qing Li, Alyson Mahar, Olli Saarela, Charles de Mestral, Natalie Coburn: **Textbook outcomes and survival in patients with stomach cancer: An analysis of the Population Registry of Esophageal and Stomach Tumours of Ontario (PRESTO) (withdrew)**

36. **(TR)** Bo Li, Carol Lee, Marissa Cadete, Andrea Zito, Richard Wu, Agostino Pierro: **High mobility group AT-hook 1 is important for intestinal epithelium proliferation**

37. **(TR)** Zijian Lou, Mohamed Khazaei, Christopher S Ahuja (SSTP), Michael G Fehlings: **Tripotent neurogenic NPCS for repair and regeneration of the injured spinal cord**

38. **(TR)** William Luong, Christopher S Ahuja (SSTP), Mohamad Khazaei, Michael G Fehlings: **Genome engineering human neural precursor cells for closed-loop delivery of chondroitinase ABC**

39. **(TR)** Shelly Luu (SSTP), Karineh Kazazian, James Conner, Jossie Swett-Cosentino, Karina Pacholczyk, Deanna Ng, Savtaj Brar, Anand Govindarajan, Carol Swallow: **Expression of the plk4 inhibitor fam46c predicts better survival following resection of gastric adenocarcinoma (GCA)**

40. Diana E Magee (SSTP), Amanda E Hird (SSTP), Beate Sander, Srikala S Sridhar, Robert K Nam, Girish S Kulkarni: **Peri-operative chemotherapy for upper tract urothelial carcinoma: A microsimulation Markov model**

41. Ahmad Makhdoum, Seleman Reza, Emilie Belley-Cote, Kevin Teoh, Waleed Alhazzani, Andre Lamy, Bobby Yanagawa, Richard Whitlock: **A survey of cardiac surgeons to evaluate the use of sutureless aortic valve replacement in Canada**

42. Dave Mealiea (SSTP), Lili Li, Emilie Boudreau, Jason Fish, J Andrea McCart: **A window into oncolytic virotherapy: Using a novel zebrafish model to quantify the anti-tumor effects of vaccinia virus in colon cancer**

43. Kumi Mesaki, Orli Silverberg, Zehong Guan, Xiao-hui Bai, Stephen Juvet, Tereza Martinu, Marcelo Cypel, Thomas Waddell, Mingyao Liu, Shaf Keshavjee: **CRISPR-mediated IL-10 gene activation as a novel gene therapeutic strategy in lung transplantation**

44. May-Anh Nguyen, Basheer Elsolh, Dee Naidu, Ashlie Nadler: **Timing of ct for adhesive small bowel obstructions (SBO)**

E-POSTER PRESENTATIONS

45. **(TR)** Joshua S O'Connell, Carol Lee, Bo Li, Agostino Pierro: **Conditioned media from human derived amniotic fluid stem cells: A novel treatment of necrotizing enterocolitMis**

46. Gokce Ozdemir, Mohamad Khazaei, Michael G. Fehlings: **The effect of synaptic activity on integration of transplanted neural progenitor cells and functional recovery after spinal cord injury**

47. **(TR)** Alexander Post, Mohammad Khazaei, Michael G. Fehlings: **The effect of conditional GDNF expression in IPSC-NPCS using cell state-specific promoters following spinal cord injuries**

48. Sneha Raju, Naomi Eisenberg, Janice Montbriand, Graham Roche-Nagle: **Preoperative anemia has gender based differences in Immediate postoperative mortality**

49. **(TR)** Rafaela V. Pinto Ribeiro, Terrance Ku, Victor H. Ferreira, Sajad Moshkelgosha, Marcos Galasso, Bruno M. Gomes, Aadil Ali, Vinicius Michaelsen, Khaled Ramadan, Aizhou Wang, Shaf Keshavjee, Atul Humar, Marcelo Cypel: **Targeting latent cytomegalovirus (CMV) with a novel fusion toxin protein using *ex vivo* lung perfusion (EVLP) as a platform**

50. Mélissa Roy (SSTP), Stephanie Sebastiampillai, Toni Zhong, Stefan O P Hofer, Anne C O'Neill: **Synergistic interaction between risk factors increases complication rates following microvascular breast reconstruction**

51. Kate Rzadki, Sunit Das: **Identifying barriers to completion of adjuvant therapy in patients with newly diagnosed glioblastoma multiforme**

52. **(TR)** Justin Saddlemyre, Hamid Ebrahimi, Sebastian Tomescu, Cari Whyne: **Orthopaedic alignment tools for guidewire and screw insertion: Path to clinical testing**

53. Omar Selim (SSTP), Andrew Dueck, Catharine Walsh, Ryan Brydges, Mahan Kulasegaram, Allan Okrainec: **The development and evaluation of a tool to assess competence in wound management**

54. Qiang Shen, Kiichi Murakami, Pamela S. Ohashi, Michael Reedijk: **Notch-inhibition: A novel strategy to reverse the immunosuppression in basal-like breast cancer**

55. Mikaela L. Stiver, Dinesh Kumbhare, Anne M.R. Agur: **Musculoapoeneurotic junctions and myofascial trigger points in the human trapezius**

56. Hening Sun, Charles Godbout, Gareth Ryan, Ikran Ali, Emil Schemitsch, Aaron Nauth: **The induced membrane technique: Effects of antibiotic-impregnated spacers on healing of a critical-size femoral defect in a rat model**

57. John Tran, Philip Peng, Anne Agur: **3D anatomy of the articular branches supplying the glenohumeral joint: Implications for nerve block and radiofrequency ablation**

58. Stephanie Tung, Natalie Coburn, Laura Davis, Alyson Mahar, Sten Myrehaug, Haoyu Zhao, Craig Earle, Avery Nathens, Julie Hallet: **Management of high patient-reported pain scores in non-curative pancreatic adenocarcinoma: A population-based analysis**

59. Sergio Vega, Aodhnait Fahy, Karolina Piorkowska, Adam Waspe, Mandolin Bartling, James M Drake, J. Ted Gerstle: **Bowel safety margins with MRgHIFU thermal ablation in a preclinical porcine model**

60. Tomas Vilde, Allen Duong, Valera Castanov, Anne Agur: **A dynamic in vivo ultrasound study of the superior, middle, and inferior parts of infraspinatus**

E-POSTER PRESENTATIONS

61. **(TR)** Roohi Vinaik, Abdikarim Abdullahi, Marc G. Jeschke: **Inhibition of NLRP3 inflammasome post-burn impairs wound healing**

62. Jinyuru (Donna) Yang, Silviu Agotici, Catherine Amara, Kei Masani, Paul B. Yoo, Anne Agur: **A three-dimensional architectural analysis of the innervation of tibialis anterior muscle**

63. Elliott Yee, Natalie Coburn, Laura Davis, Alyson Mahar, Ying Liu, Julie Hallet: **Geographic disparities in care and outcomes for non-curative pancreatic adenocarcinoma: A population-based study**

64. Lu Yin, Wey-Liang Leong, Nicole Look Hong: **The role of metformin in breast cancer genetics (withdrew)**

65. Frank Yu, Juglans Alvarez, Roberto Ribeiro, Mitchell Adamson, Juan Posada, Terry Yau, Robert Cusimano, Filio Billia, Ana Alba, Mitesh Badiwala, Vivek Rao: **Does left atrial appendage occlusion in lvad patients impact outcomes: a single centre study**

66. Mohammad Zavvarian, James Hong, Mohamad Khazaei, Jian Wang, Michael G. Fehlings: **Systemic protein kinase inhibition reduces local inflammation after cervical spinal cord injury**

67. **(TR)** Haitao Zhu, Shanshan Deng, Bo Li, Shan Zheng, Chun Shen, Agostino Pierro: **Downregulation of PTEN expression provide intestinal protection against experimental necrotizing enterocolitis**

68. Helene Retrouvey (SSTP), Beate Sander, Herbert P. von Schroeder, Paul Binhammer, Heather L. Baltzer: **Cost-effectiveness analysis of motion preserving surgeries for wrist arthritis**

69. Jetan H. Badhiwala (SSTP), Michael G. Fehlings: **Development of a clinical prediction model for central cord syndrome: an evaluation of motor recovery and the effectiveness of early surgery**

70. Jenna Belitzky, Emily Ho, Lisa Isaac, Jennifer Stinson, Howard Clarke, Kristen Davidge: **Pain in children with brachial plexus birth injuries**

71. **(TR)** Jonathon Chon Teng Chio, Jian Wang, Anna Badner, James Hong, Vithushan Surendran, Michael G. Fehlings: **The Effects Of Human Immunoglobulin G On Enhancing Tissue Protection And Neurobehavioral Recovery After Traumatic Cervical Spinal Cord Injury Are Mediated Through The Neurovascular Unit**

72. **(TR)** Adam Di Palma, Azusa Maeda, Timothy Jackson, Allan Okrainec: **Risk factors for recurrent and chronic marginal ulcers requiring surgical treatment following Roux-en-Y gastric bypass**

73. **(TR**) Zachary Fishman, Jeff A Fialkov, Cari M Whyne: Fixing the face and its foundation: a novel treatment planning workflow for craniomaxillofacial soft tissue and skeletal reconstruction

74. Sahil Gupta, Song Hui Jia, Kevin Ho, Claudia dos Santos, Andras Kapus, Ori D. Rotstein, John Marshall: Tyrosine phosphorylation of caspase-8 regulates toll like receptor 4 dependent signaling during clinical sepsis

75. Hetshree Joshi, Jetan Badhiwala, Michael G. Fehlings: **Surgical outcomes in mild, moderate, and severe patients with degenerative cervical myelopathy**

76. Omar Khan, Jetan Badhiwala (SSTP), Michael G. Fehlings: **Machine learning models predict functional outcomes after traumatic spinal cord injury with excellent performance**

E-POSTER PRESENTATIONS

77. Ann Mansur, Megan A. Hird, Alexa Desimone, Sara Vaughan, Iryna Pyshonyak, Tom A. Schweizer , Sunit Das: **To drive or not to drive, that is still the question: Determining fitness to drive in patients with brain tumours**

78. **(TR)** Nina Noskovicova, Sander Van Putten, Anne Koehler, Stellar Boo, David Griggs, Peter Ruminski, Ruud Bank, Boris Hinz: **Inhibiting fibrotic encapsulation of body implants by targeting mechanical activation of profibrotic TGF-β1**

79. **(TR)** Ahsan Rai, Sultan Al-Shaqsi, John Phillips, Christopher Forrest: **Public perception of a normal head shape in children with sagittal craniosynostosis**

80. Roberto VP Ribeiro, Vivek Rao, Mitesh V Badiwala**: DCD hearts reconditioned using normothermic regional perfusion can be successfully transplanted following an extended period of static storage**

81. **(TR)** Joan Miguel Romero, Barbara Grünwald, Ashton Connor, Gun Ho Jang, Prashant Bavi, Aaditeya Jhaveri, Mehdi Masoomian, Sandra Fischer, Amy Zhang, Robert E. Denroche, Tracy McGaha, Faiyaz Notta, Pamela Ohashi, Grainne O'Kane, Julie Wilson, Jennifer Knox, Steven Gallinger: **Mediators of cd8+ cytotoxic t lymphocyte infiltration in pancreatic cancer**

82. Tomas J Saun (SSTP), Teodor Grantcharov: **Objective and subjective assessment of a prototype camera system for intraoperative video recording of open surgery**

83. Christine Schemitsch, Jas Chahal, Milena Vicente, Lauren Nowak, Patrick Henry, Aaron Nauth: **Surgical repair versus conservative treatment and subacromial decompression for the treatment of rotator cuff tears: A meta-analysis of randomized trials**

84. Daniella C. Terenzi, Justin Z. Trac, David A. Hess, Subodh Verma: **A novel role for SGLT2 inhibitors to increase circulating proangiogenic progenitor cells in patients with type 2 diabetes and cardiovascular disease**

85. Justin Z. Trac, Daniella C. Terenzi, Hwee Teoh, Adrian Quan, Ori D. Rotstein, Stephen A. Glazer, David A. Hess, Subodh Verma: **Impact of bariatric surgery on circulating inflammatory and pro-vascular progenitor cell content**

86. **(TR)** Jamie RF Wilson, Jetan H Badhiwala, Fan Jiang, Jeff R Wilson, Branko Kopjar, Alexander Vaccaro, Michael G Fehlings: **The impact of older age on functional recovery after surgical decompression for degenerative cervical myelopathy: Results from an international, multicentre, prospective dataset in 757 patients**

87. David Zhang (SSTP), Jess Sussman, Fahima Dossa (SSTP), Maria Cusimano, Anuj Aurora, Naheed Jivraj, Brittany Speller, Arlinda Ruco, Tari Little, Sav Brar, Karim Ladha, Duminda Wijeysundera, Andrea Tricco, Hance Clarke, Nancy Baxter: **Opioid prescribing at discharge after abdominal-pelvic surgery: identifying existing guidance and strategies to improve practice**

HLA-G 14BP POLYMORPHISM DONOR/RECIPIENT MATCHING PROTECTS AGAINST DEVELOPMENT OF POST-TRANSPLANT MALIGNANCY FOLLOWING HEART TRANSPLANTATION

Mitchell Adamson, Roberto Ribeiro, Frank Yu, Julieta Lazarte, Kyle Runeckles, Cedric Manlhiot, Vivek Rao, Diego Delgado
Division of Cardiovascular Surgery, University Health Network and University of Toronto

Hypothesis/Purpose: Post-transplant malignancy (PTM) is the leading cause of morbidity and mortality 5 years post-heart transplant. Human leukocyte antigen-G (HLA-G) is an immune checkpoint that reduces allograft rejection by dampening the host immune response. Reports suggest that tumor cells utilize HLA-G to evade the immune system and promote cancer development. We hypothesize that HLA-G donor/recipient genotype matching influences the development of PTM. **Methods:** Recipients (n=251) and corresponding donors (n=196) were genotyped to identify relevant HLA-G polymorphisms in the 5'regulatory region (SNP -725, -201), 3'untranslated region (SNP +3197, +3187, +3142, 14BP INDEL) and coding region (haplotypes 1-6). Association between donor/recipient polymorphism matching and the development of PTM was assessed with parametric hazard regression models. **Results**: Recipient and donor median (IQR) age were 50(16) and 35(24) years, respectively. Mean follow-up was 7.2±4.6 years. Overall, 42 recipients had a de novo diagnosis of PTM (17%). Donor/recipient matching for the 14BP polymorphism significantly reduced the proportion of cancer, suggesting a protective effect (p=0.017). Further, 14BP unmatched cohort had a greater number of individuals with 2 or more independent types of cancer compared to the matched group (unmatched: 8%, matched: 1%; p=0.03). No differences were seen between the 14BP matched vs unmatched cohort regarding donor/recipient pre- and post-transplant characteristics. No other polymorphisms showed significant effects. **Conclusion**: We identified 14BP donor/recipient polymorphism matching as a protective factor against PTM. HLA-G may have a role in therapeutic and diagnostic strategies against cancer. Identifying relevant HLA-G polymorphisms may warrant alterations in immunotherapy in order to reduce PTM risk.

2

SELF-ASSEMBLING PEPTIDE BIOMATERIAL TO OPTIMIZE HUMAN NEURAL STEM CELL-MEDIATED REGENERATION OF THE INJURED SPINAL CORD

Christopher Ahuja (SSTP), Mohamad Khazaei, Yao Yao, Ali Hasan, Vjura Senthilnathan, Inaara Walji, Nayaab Punjani, Sohanthen Udayashankar, Zijian Lou, William Luong, Alex Post, Gokce Ozdemir, Edward Robinson, Priscilla Chan, Jian Wang, Michael G. Fehlings

Genetics and Development, Krembil Research Institute, University Health Network
Division of Neurosurgery, Department of Surgery, University of Toronto

Hypothesis and Purpose: Human induced pluripotent stem cell-derived neural stem cells (hiPS-NSCs) are a promising therapeutic approach for spinal cord injury (SCI). Unfortunately, the harsh post-injury microenvironment hinders regeneration. QL6 is a novel, pH-neutral, biodegradable peptide capable of self-assembling into an extracellular matrix-like lattice *in vivo*. Early evidence suggests it may facilitate endogenous and exogenous cell-based CNS regeneration. We hypothesize that QL6 will support the proliferation and integration of translationally-relevant hiPS-NSCs to enhance regeneration after chronic SCI.

Methods: hiPS-NSCs were grown on QL6 versus Geltrex control. qPCR and an EDTA assay were used to determine mechanisms of cell adhesion. hNSC survival, proliferation, and neurosphere formation was extensively characterized *in vitro*. T-cell deficient rats underwent a clinically-relevant C6-7 clip-contusion injury. In the chronic phase, animals received: (1) vehicle, (2) hiPS-NSC transplant, (3) QL6, (4) QL6+hiPS-NSCs. All rats received daily rehabilitation.

Results: hiPS-NSCs proliferated robustly on QL6 versus geltrex control as demonstrated by $Ki67^+$ labelling (29 vs 6%; $p<0.01$). EDTA assay suggested that human NSC-QL6 binding is largely Ca^{2+}-independent. hNSCs cultured on QL6 downregulated apoptosis markers, upregulated pro-neuronal markers and select Ca-independent cell adhesion molecules. QL6 also promoted adherent neurosphere formation, the native conformation of NSCs. Analyses of blinded rat sensorimotor data, immunohistochemistry, and RNA sequencing are ongoing.

Conclusions: This work provides key proof-of-concept data that engineered QL6 self-assembling peptide biomaterial can support translationally-relevant human iPS-NSCs for CNS regeneration.

MURINE PARTIAL OUTLET OBSTRUCTION INDUCES MACROPHAGE-DEPENDENT CHANGES IN CYTOKINE, ECM AND AKT PATHWAY EXPRESSION COORDINATE WITH BLADDER FUNCTION AND PATHOLOGY

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Partial bladder outlet obstruction (PBO) can induce inflammation and remodeling in the detrusor. Macrophages infiltrating to sites of tissue damage are a major source of inflammation, and affect extracellular matrix (ECM) tissue remodeling. *We **hypothesize*** that macrophages aggravate inflammation and distort ECM remodeling to alter the pathophysiology of PBO. **Purpose**: to investigate the role of macrophages in process of production of inflammatory cytokines, remodeling and related functional changes during obstruction. **Methods:** Using our chronic obstruction model, 18-21 g female C57bl/6 mice were anaesthetized and 5-0 non-absorbable suture tied around a 26-gauge needle and the mid-urethra. The suture was then tied, and needle removed. In shams, the urethra was exposed and suture passed behind the urethra. Mouse numbers included: n=11 shams, n= 15 sham plus Clodronate, a macrophage depleting drug, n=16 obstruction, n=25 obstruction plus clodronate. Cytokine protein, RNA expression, cell numbers + bioinformatics were analysed by Cytokine Array, RNAseq, CyTOF mass cytometry and DAVID 6.8, respectively. **Results**: Macrophage infiltration during PBO vs. sham increased 4.9-fold, which was depleted 2.5-fold by Clodronate. During PBO, Clodronate vs. vehicle reduced IL-1a protein, hyperactive voiding ($p<0.01$) and residual volumes ($p<0.05$ by 1-tailed test). RNAseq revealed 276 differentially expressed genes (DEG) between obstruction and sham. DEG correlated in <u>all</u> mouse groups with >1 pathophysiologic endpoint by Pearson's correlations, and were enriched for ECM-integrin + PI3K/AKT pathways. **Conclusion**: PBO induces macrophage-dependent inflammation and ECM signaling, altering pathophysiology.

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INVOLVEMENT OF CALCIUM/CALMODULIN-DEPENDENT PROTEIN KINASE IV (CAMKIV) IN EXPERIMENTAL NECROTIZING ENTEROCOLITIS

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Hypothesis and Purpose: Calcium/Calmodulin-dependent protein kinase IV (CAMKIV) has been studied in several autoimmune and intestinal diseases. CAMKIV activation has been shown to increase intestinal injury and inhibit epithelial cell proliferation in DSS-colitis mice. However, the role of CAMKIV in necrotizing enterocolitis (NEC) is unknown. We aim to study the expression and activation of CAMKIV in experimental NEC.

Methods: Following ethical approval, NEC (n=5) was induced in C57BL/6 mouse pups by hypoxia, gavage hyperosmolar formula feeding and lipopolysaccharide from postnatal days P5-9. Breastfed pups served as control (n=5). Mouse pups were sacrificed on P9 and the ilea were harvested. NEC injury was scored blindly by 3 independent investigators. CAMKIV gene and protein expression were assessed and the data compared using Mann-Whitney U test. $P<0.05$ was considered significant.

Results: Intestinal injury was induced in the NEC mice ($p<0.05$). *CAMKIV* and its downstream target genes of *RoRγT, CREM,* and *IL17* were all significantly elevated in NEC mice relative to control. Similarly, phosphorylated-CAMKIV (pCAMKIV), the active form of CAMKIV, was more notably expressed in the NEC group relative to control.

Conclusion: CAMKIV expression and activation are upregulated in experimental NEC suggesting a potential contributing factor in the pathogenesis of NEC. Further investigations are planned to elucidate the mechanism of CAMKIV activation in NEC.

CHARACTERIZING THE EFFECTS OF LOCALLY APPLIED VANCOMYCIN POWDER ON BONE HEALING AND INFECTION IN AN ANIMAL MODEL

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Purpose and Hypothesis: The purpose of this study is to investigate the effects of local antibiotics, specifically vancomycin, on the prophylactic prevention of infection and on fracture healing. We hypothesize that the application of local intra-wound antibiotics will be effective in preventing the development of surgical-site infection (SSI) without having a negative effect on fracture healing in an animal model.

Methods: Male Sprague Dawley rats are assigned to one of four groups: 1) no antibiotics, 2) local intra-wound vancomycin powder, 3) systemic cefazolin, or 4) both local and systemic antibiotics. Animals from each group either receive an inoculum of methicillin-sensitive *Staphylococcus aureus* or a control solution at their fracture site, creating a total of eight groups. The fracture is surgically created by performing a mid-diaphysis osteotomy in the right femur of all rats, followed by stabilization with plate and screws. Local intra-wound vancomycin powder is administered at the fracture site before incision closure based on the treatment group. Biweekly radiographs of the operated leg are taken to monitor healing progression. All animals are euthanized 10 weeks after surgery. Samples of soft tissue are collected from the surroundings of the fracture site, along with fixation material, and processed for microbiological detection.

Results and Conclusion: In our preliminary studies, we were able to obtain an ideal bacterial concentration, and therefore we have established a consistent infection in our animal model. We are currently taking biweekly radiographs of the operated leg and will follow up with post-mortem analyses. The results will help to clarify the role of local intra-wound antibiotics for SSI prevention in orthopaedic trauma and ultimately help promote excellence in trauma patient care.

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RNA CARGO OF AMNIOTIC FLUID STEM CELL EXTRACELLULAR VESICLES EPIGENETICALLY REGULATES FETAL LUNG EPITHELIAL CELLS IN EXPERIMENTAL CONGENITAL DIAPHRAGMATIC HERNIA

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Hypothesis and Purpose: The severity of pulmonary hypoplasia (PH) is a main determinant for poor outcome for neonates with congenital diaphragmatic hernia (CDH). We previously showed that PH can be rescued by administration of extracellular vesicles secreted from amniotic fluid stem cells (AFSC-EVs) in experimental CDH. Herein, we investigated the RNA species responsible for these beneficial effects.

Methods: AFSC-EVs were isolated from conditioned medium of AFSC using ultracentrifugation, characterized for size, morphology, and expression of EV markers. E14.5 lung epithelial cells were isolated from fetuses of dams that received nitrofen to induce fetal PH at E9.5. Cells were treated with either medium alone or AFSC-EVs. Fetal lungs and epithelial cells from untreated dams served as control. To identify the mediators of AFSC-EV effects on PH lungs, we used DESeq (FDR<0.01) to differentially analyze RNA from: i) ASFC-EV cargo, ii) lung epithelial cells from normal lungs, nitrofen exposed lungs treated with vehicle, or nitrofen-exposed lungs treated with AFSC-EVs.

Results: AFSC-EVs contained miRNA that are critical for lung development, such as microRNA17~92 that controls lung branching morphogenesis. When we investigated AFSC-EV microRNA epigenetic effects on lung cells, we found 13 microRNA-mRNA interactions.

Conclusions: AFSC-EVs contain many RNA species in their cargo, but microRNAs are the main effectors of their beneficial effect on lung maturation in experimental CDH. Further studies are underway to identify the critical microRNAs that may be used for clinical application.

METFORMIN INDUCES THE PHENOTYPIC SWITCH OF BEIGE FAT TO WHITE FAT IN ADIPOSE TISSUE POST-BURN

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Hypothesis and Purpose: For hypermetabolism stemming from burn trauma, the browning of white adipose tissue (WAT) is thought to contribute to energy wasting and supraphysiological nutritional requirements. Reversal of the browning process is hypothesized to greatly improve patient outcomes.

Methods: Here, we use both a 30% total body surface area murine burn model and adipose from burn patients to determine if metformin has anti-lipolytic effects which would preserve adipose depots post-burn. Metformin's cellular effects are elucidated via Western blotting, immunoprecipitation of protein phosphatase 2A (PP2A), transmission electron microscopy and Seahorse XF96 analysis.

Results: Our results demonstrate that treatment with metformin lowers lipolysis and mitochondrial uncoupling in beige fat by inducing PP2A independently of AMPK activation and insulin signaling. Increased PP2A activity catalyzes the dephosphorylation of acetyl-CoA carboxylase (ACC; Ser 79) and hormone sensitive lipase (HSL; Ser 660), thus promoting fat storage and the "whitening" of otherwise lipolytic beige adipocytes. Additionally, we show that metformin does not activate this pathway in the WAT of control mice and that the AMPK activator AICAR potentiates the browning of white adipose, offering further evidence that metformin acts independently of this cellular energy sensor.

Conclusion: The data herein demonstrate that metformin exerts an AMPK-independent anti-lipolytic role in beige adipose tissue via the activation of PP2A. The subsequent dephosphorylation of ACC and HSL decreases β-oxidation and lipolysis, respectively, thus preserving this fat depot during hypercatabolic states.

REDUCTION OF PKA-MEDIATED LIPOLYSIS WITH ACIPIMOX IMPROVES MITOCHONDRIAL COUPLING IN ADIPOSE TISSUE FOLLOWING BURN INJURY

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Hypothesis and Purpose: Following severe burn injury, the systemic increase in plasma free fatty acids (FFA) may culminate in multiple organ dysfunction, sepsis, and ultimately death. Thus, reducing the lipolysis of white adipose tissue (WAT) to diminish FFA mobilization may render an effective means to improve organ function post-burn. Here, we investigated the long-term effects of Acipimox (APX), a clinically approved drug that suppresses lipolysis via inhibition of hormone-sensitive lipase (HSL), in a murine model of thermal injury.

Methods: Adult (9 week) C57BL/6 mice received a 30% total body surface area dorsal (98°C, 10 sec) and ventral (98°C, 2 sec) scald burn. Select mice were then given daily intraperitoneal injections of APX (50 mg/Kg). On day 7 post-burn, the liver and adipose tissue depots (inguinal, epididymal) were harvested for histological analyses. Oil Red O staining was used to assess fat infiltration, and select proteins were analyzed via western blot.

Results: APX administration significantly decreased whole body ($p<0.001$) and liver ($p<0.05$) weight. While no change in adipose content was observed, APX reduced total HSL ($p<0.01$) and ATGL ($p<0.05$) protein levels in the iWAT. This was accompanied by increased mitochondrial coupling, reflected by the decrease in UCP-1 ($p<0.05$) and PGC-1 ($p<0.01$) levels relative to the iWAT of untreated burn mice. The anti-lipolytic action of APX appeared to be mediated by PKA, which consequently lowered the phosphorylation of HSL at serine 660, thereby inhibiting its enzymatic activity ($p<0.01$).

Conclusion: Acipimox effectively suppressed PKA-mediated lipolysis and improved mitochondrial coupling in adipose tissue of burn mice. Importantly, long term treatment significantly reduced liver weight, suggesting it may also mitigate ectopic fat deposition. Our data validate the pharmacological inhibition of HSL as a potentially powerful therapeutic strategy to counteract the detrimental metabolic effects induced by burn.

NEUROINFLAMMATION SECONDARY TO NECROTIZING ENTEROCOLITIS

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Hypothesis and Purpose: The pathogenesis of neurodevelopmental delay in neonates with necrotizing enterocolitis (NEC) remains poorly understood. We previously reported that neonatal mice with NEC develop neuroinflammation in specific brain regions. Herein, we aimed to investigate whether the gut-brain axis was implicated in the development of neuroinflammation in our neonatal NEC model.

Methods: NEC was induced in 5-day-old mice using hypoxia, gavage feeding (hyperosmolar formula), and oral lipopolysaccharide (4mg/kg). Breastfed pups served as control. Brain and ileum (most affected gut segment) from the same pup were harvested on postnatal day 9 and assessed for IL-6 and TNFα levels via RT-qPCR and ELISA. Pearson test was used to correlate cytokine levels between brain and ileum, and the severity of gut damage (0= no damage; 2= severe damage) with the degree of neuroinflammation in hippocampus (Iba1+ activated microglia; GFAP+ astrocytes).

Results: Compared to control, NEC pups had higher IL-6 and TNFα levels in both brain and ileum. A positive correlation was found between the severity of brain and gut inflammation, and between gut damage and the number of activated microglia and astrocytes.

Conclusions: This study shows for the first time that the degree of inflammation caused by NEC in the intestine is proportional to the inflammatory response occurring in the brain. Our results implicate that the gut-brain axis is involved in the pathogenesis of neuroinflammation secondary to NEC and that it could be a potential target for the prevention of cerebral damage in NEC.

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INTRA-OPERATIVE VERIFICATION OF THE GLENOID IMPLANT POSITION WITH STRUCTURED LIGHT IMAGING IN TOTAL SHOULDER ARTHROPLASTY

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Hypothesis and Purpose: Positioning of the glenoid component is one of the most challenging steps in total shoulder arthroplasty. Prosthetic longevity and functional outcomes are considered highly dependent on accurate positioning. Currently, there are no adequate means to verify the position of the glenoid component intra-operatively which is a significant impediment to accurate positioning. We hypothesize that our computer vision system (Bullseye) utilizing a hand-held structured light sensor can verify the 3D position of the glenoid vault guide pin prior to preparation of the glenoid for component implantation. **Methods:** The Bullseye system was evaluated for measuring the position of the glenoid vault guide pin on 10 Sawbone and 6 cadaveric procedures. The scapulae were instrumented with a 3.2 mm threaded guide pin. The Bullseye optical tracker was positioned over the guide pin against the glenoid articular surface. A single optical color surface image of the surgical field was obtained using a hand-held structured light sensor. The position of the glenoid guide pin with respect to the scapula was registered from the pre-operative CT scan and the intra-operative optical surface image. The accuracy of the Bullseye system for measuring the glenoid vault guide pin position was validated against a post-operative CT scan. **Results:** All 16 imaging procedures were carried out successfully. For the sawbone procedures, the Bullseye glenoid vault guide pin position measurement was accurate to 0.37 ± 0.28 mm for the start point, and 0.92 ± 0.40 degrees for the trajectory. For the cadaveric procedures, the accuracy was 0.54 ± 0.49 mm for start-point, and 1.72 ± 0.95 degrees for trajectory. **Conclusions:** Optical surface structured light imaging can be used to accurately evaluate the 3D position of the glenoid vault guide pin for total shoulder arthroplasty in-vitro and ex-vivo. The Bullseye imaging system permits shoulder surgeons to verify and readjust the glenoid vault guide pin as necessary to achieve accurate implantation of the glenoid component in total shoulder arthroplasty. Future work will involve Phase 1 validation of the Bullseye system in the setting of a clinical trial, and demonstration of improved glenoid component positioning outcomes with its use.

A NERVE WRAP FOR THE LOCALIZED DELIVERY OF FK506 TO ENHANCE PERIPHERAL NERVE REGENERATION

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Hypothesis and Purpose: FK506, an FDA-approved drug, encapsulated in biodegradable microspheres and hydrogel, enhances peripheral nerve regeneration in rats. Though effective, this process is not user-friendly enough for human surgical use. We hypothesize that incorporating FK506 in a nerve wrap will be a simpler and more clinically-feasible method to locally deliver FK506 and improve regeneration following microsurgical repair. We aim to develop an implantable FK506 delivery nerve wrap with suitable properties for clinical application, to sustain bioactive release of FK506, and be biocompatible and biodegradable.

Methods: Nerve wraps were fabricated using electrospinning, a one-step process to create fibrous mats. Polycarbonate urethane (PCNU), a biodegradable synthetic polymer, was electrospun with FK506. Fiber diameter and porosity were determined using scanning electron microscopy. Tensile tests were conducted to measure the dry elastic modulus, and mass spectrometry was used to determine the encapsulation efficiency.

Results: The means ± standard deviation of the fiber diameter and porosity were 320 ± 70 nm and 40 ± 10%, respectively, and of the dry elastic modulus, 2.38 ± 1.05 MPa. The physical properties of the nerve wrap indicate a longer degradation rate to prolong FK506 delivery and high tensile strength to withstand surgical forces. The FK506 encapsulation efficiency was 92 ± 14%, indicating complete availability of FK506 to encourage peripheral nerve regeneration following implantation of the nerve wrap.

Conclusion: The electrospun PCNU and FK506 fibers have the potential to form clinically useful and feasible nerve wraps that enhance peripheral nerve regeneration due to their simplicity and ideal physical properties. Future work is being conducted to extend the FK506 release profile and quantify biocompatibility and bioactivity of FK506 following encapsulation.

SELF-TRACING HUMAN NEURAL STEM CELLS TO MAP TRANSPLANT INTEGRATION

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HYPOTHESIS AND PURPOSE: While previous studies have shown that human induced pluripotent stem cell-derived neural stem cells (hiPSC-NSCs) can promote functional recovery after spinal cord injury (SCI), few have been able to demonstrate graft-host integration. This is largely attributed to unreliable conventional tracing methods. Here, we aimed to engineer hiPSC-NSCs to express both trans-synaptic tracers to effectively map transplant integration.

METHODS: A bicistronic vector encoding ANTERO-mCherry and GFP-RETRO was non-virally integrated into hiPSC-NSCs and sorted into monoclonal lines. The resultant self-tracing NSCs (stNSCs) were characterized for self-renewal, proliferation, and pluripotency. stNSCs-derived neurons were co-cultured with wild-type neurons and monitored to assess the extent of tracing. Functional connectivity of the self-tracing neurons was determined by whole-cell recording. To assess tracing i*n vivo*, RNU rats with a chronic C6/7 SCI were randomized to receive (1) stNSCs, or (2) GFP-hiPSC-NSCs followed by viral tracing.

RESULTS: stNSCs retained typical NSC properties compared to a control line. ANTERO-mCherry was successfully detected in primary rat neurons 2 weeks post-co-culture. During patch clamp recordings, large INa^+, IK^+, and action potential firing were observed, confirming functional differentiation of the stNSCs. *In vivo*, stNSCs retained transgene expression 12 weeks post-transplant and were found along the corticospinal tract in the dorsal white matter.

CONCLUSION: This exciting proof-of-concept data demonstrates how stNSCs can be used to delineate synaptically integrated sensorimotor pathways involved in stem-cell mediated recovery.

COST UTILITY ANALYSIS OF PROPHYLACTIC INCISIONAL NEGATIVE PRESSURE WOUND DRESSING COMPARED TO CONVENTIONAL DRESSING TO REDUCE SURGICAL SITE INFECTION IN ELECTIVE OPEN COLECTOMY

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Purpose and Hypothesis: Surgical site infection (SSI) is associated with increased cost related to prolonged hospitalization, fascial dehiscence and incisional hernia. Recent evidence demonstrates benefit in the application of prophylactic post-operative negative pressure wound therapy (NPWT) over closed abdominal laparotomy incisions to prevent SSI after elective colectomy. However, this is met with hesitancy due to its additional cost and efficacy concerns.

Method: A cost-utility analysis comparing prophylactic NPWT versus conventional dressing was completed with a Markov microsimulation model. The Ministry-of-Health payer perspective was adopted across a lifetime horizon. The base case was a standardized patient undergoing elective open colectomy and the primary outcomes of interest were SSI rates, total costs, and QALYs gained. Secondary outcomes included ER presentation, hospital re-admission, home-care utilization, fascial dehiscence and incisional hernia rate, and non-SSI-related complications.

Results: Standardized to 1,000 patients, we demonstrate that NPWT prevented 104 SSIs, 107 home-care referrals, 6 fascial dehiscences, 18 incisional hernias, 46 ER presentations, and 12 hospital re-admissions. This result in an average cost-saving of $284.51 and 0.12 QALYs per patient. This dominated conventional dressing with lower costs, improved outcomes, and QALYs. In further analysis across 50,000 micro-simulations, NPWT cost less in 10.2% of patients where a large cost or complication could be avoided, and with a nominal investment in the remainder (89.8%). Our model was sensitive to the efficacy of NPWT (threshold: OR 0.39) and the baseline rate of SSI (threshold: 4.3%).

Conclusion: The use of NPWT dominated conventional dressing in open colectomy with lower costs, improved efficacy and better outcomes. This was mediated by a large effect on patients who would have developed SSI.

*Translational Research

BIOMECHANICAL CHANGES IN PORCINE TENDION FOLLOWING HIGH-INTENSITY FOCUSED ULTRASOUND

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Background: Musculotendinous contractures are associated with musculoskeletal and neuromuscular disorders, spinal cord injury, and dementia. They can be corrected with surgical resection of tendons. Magnetic Resonance-guided Focused Ultrasound (MRgFUS) is a transcutaneous non-invasive ablation technique that could provide an incisionless treatment for these conditions, decreasing the comorbidities of anesthesia and surgery. Our study aims to perform a quantitative biomechanical analysis of changes in tendons after MRgFUS ablation.

Materials and Methods: Four agar phantoms, each with 4 pairs of porcine deep digital flexor tendons, were prepared. For each pair of control and treatment tendons, temperature, length, and diameter were verified for consistency. Ablation was performed using a V1 Sonalleve (Profound Medical) MRgFUS. The treated tendons were randomly assigned to one of four different ablation parameters. Group 1 did not receive any treatment. Group 2 had 1 treatment of 50W for 20 seconds. Group 3 had 1 treatment of 100W for 20 seconds. Group 4 had 2 treatments of 100W for 20 seconds each. Following ablation, the tendon biomechanical properties were analyzed using an Instron MicroTester, yielding the Young's modulus and maximum tensile stress.

Results: There was a decrease in Young's modulus as more power was used to ablate the tendon. The tendons in Group 2 had a decrease of 16.07% in Young's modulus and no tendon rupture. The tendons in Group 3 had a decrease of 41.97% in Young's modulus and a maximum tensile stress of 6.59 MPa when ruptured. Finally, the tendons in Group 4 had a decrease of 73.01% in Young's modulus and a maximum tensile stress of 4.48 MPa when ruptured.

Conclusions: Our results demonstrate that MRgFUS ablation decreases the Young's modulus and its elasticity. As more power is delivered, the maximum tensile stress required to rupture the tendon decreased. This demonstrates that MRgFUS ablation could be a feasible intervention for non-invasive tendon transection for many conditions.

THE COST-EFFECTIVENESS OF CLEFT LIP AND/OR PALATE SURGERY IN LOW- AND MIDDLE- INCOME COUNTRIES: A SYSTEMATIC REVIEW

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Purpose: Cleft lip and/or palate (CLP) is the most common craniofacial anomaly. Yet, there are still untreated children in low- and middle-income countries (LMICs) who experience extreme social stigma, poor health, and speech deficiencies. Unfortunately, CLP is not a priority due to scarce healthcare resources. We conducted a systematic review that summarizes the cost-effectiveness of a primary CLP surgical repair, compared to no repair in LMICs.

Methods: We followed PRISMA guidelines. We searched eleven electronic databases for articles from 2000 to January 2019, including Ovid MEDLINE, Ovid EMBASE and Global Index Medicus. We included all English CLP primary cost-effectiveness analyses in LMICs. Two reviewers independently screened results, extracted data and conducted quality appraisal using the Joanna Briggs Institute (JBI) checklist. Costs were adjusted to 2019 International Dollars.

Results: We screened 459 citations and included 9 articles. All economic evaluations were conducted by charities working in Africa (n=3) and Asia (n= 6). One study met over 70% of JBI criteria. All but two studies used disability weights from the Global Burden of Disease Study to evaluate health outcomes, discounted at 3%. CLP repair was cost-effective at $37.3 to $547.6 per DALY averted, depending on the country. All estimates were below the “very cost-effective threshold” recommended by the World Health Organization.

Conclusions: Primary CLP repair is cost-effective in LMICs. To date, all assessments are from charities, which may be subject to bias. Other perspectives could help inform decisions at the government level. Collaborations in economic assessments with local hospitals may stimulate government involvement towards comprehensive care for CLP patients.

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RADIOMIC FEATURES USED TO DIFFERENTIATE BETWEEN OSTEOBLASTIC AND HEALTHY TISSUE IN METASTATICALLY INVOLVED VERTEBRAE

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Purpose: Skeletal metastasis affects bone quality, which can be visualized in preclinical models as changes in trabecular bone texture on μCT imaging. This investigation aims to develop an automated method to segment spinal osteoblastic metastases in μCT images using radiomic-based feature extraction. We hypothesize that radiomics will be sensitive to changes in osteoblastic bone texture and that these changes will be useful for automating segmentation.

Methods: Osteoblastic metastases were generated via intracardiac injection of human ZR-75-1 breast cancer cells into a preclinical athymic rat model (n=3). Four months post inoculation, ex-vivo μCT images (34μm, μCT100, Scanco) were acquired of the third lumbar vertebrae (L3). Trabecular bone within each vertebra was isolated using an atlas and level-set based approach. Pyradiomics was used to calculate 3D features for each voxel. Osteoblastic lesion isolation was accomplished through thresholding of Radiomic features. Segmentation accuracy was evaluated on randomly selected 2D slices (n=6). A Random Forest Classifier was used to combine multiple feature maps. Randomly selected 2D slices were used for training (n=6) and test data (n=3) and compared to manual segmentations via Dice Similarity Coefficients (DSC).

Results: The radiomic based features that best segmented osteoblastic tissue while optimizing computational time were derived from the Neighbouring Gray Tone Difference Matrix (NGTDM). Coarseness yielded the best agreement with manual segmentations (DSC=70±7%) followed by contrast, strength and complexity (DSC=65±13%, 54±28%, and 48±26%, respectively). Combining these features using machine learning based classification improved segmentation performance, in the training set (DSC=99±.2%, n=6) and test data (DSC=74±14%, n=3).

Conclusion: This pilot study using a radiomic based approach demonstrates the utility of the NGTDM features combined with Random Forest Classification for segmentation of vertebral osteoblastic lesions, with potential for improvement with additional training data.

OUTCOMES OF SALVAGE SURGERY FOR ANAL SQUAMOUS CELL CARCINOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Hypothesis and Purpose: Following definitive chemoradiotherapy for primary squamous cell carcinoma of the anal canal (A-SCCa), 10-30% of patients develop persistent or recurrent cancer. Both persistent and recurrent A-SCCa may be amenable to salvage surgery, which is typically quite resource intensive. Because only small case series have been reported, we synthesized the evidence for salvage surgery to gain an understanding of expected outcomes. **Methods:** A systematic search of MEDLINE, Embase, and the Cochrane Library (up to 11/1018) identified 39 retrospective, uncontrolled cohort studies reporting on oncologic and/or postoperative outcomes following salvage surgery for persistent or recurrent A-SCCa in 1388 patients. Overall survival (OS) and disease-free survival (DFS) were pooled using two approaches: survival curve meta-analysis, and exact binomial likelihood random-effects model for survival probabilities. **Results:** Pooled 5-year OS was 45.5% (95% CI 40.6 to 49.9; 33 studies; 1,308 patients), and did not differ in patients resected for recurrent (259 patients) vs. persistent (238 patients; 14 studies) disease. Pooled 5-year DFS was 38.3% (95% CI 31.4 - 43.9; 14 studies; 554 patients). Pooled 30-day complication rate was 65.3% (95% CI 50.2 - 77.9; 17 studies; 720 patients): major complications (Clavien-Dindo grade ≥3) 27.7% (95% CI 22.3 - 33.8), reoperations 12.7% (95% CI 8.7 - 18.2), and mortality 1.7% (95% CI 1.1 - 2.6%). **Conclusion:** Salvage surgery for recurrent/persistent A-SCCa offers 5-year OS of ~45% and DFS of ~40%. Although postoperative mortality is rare, major complications are very common. Comparative effectiveness studies comparing surgery to other treatments are warranted.

THE ROLE OF APOLIPOPROTEIN E4 IN THE PATHOPHYSIOLOGY AND CLINICAL OUTCOMES OF DEGENERATIVE CERVICAL MYELOPATHY

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Hypothesis and Purpose*:** We intend to evaluate the role of apolipoprotein E4 (ApoE4) as a prognostic biomarker of neurological outcomes in patients with degenerative cervical myelopathy (DCM). DCM is the progressive compression of the spinal cord resulting in neurological dysfunction. The standard treatment for DCM is surgical decompression, yet many patients suffer from residual disability, and 7-11% may deteriorate neurologically. ApoE4 is a candidate protein which merits closer study considering its crucial role in Alzheimer's disease and association with poorer outcomes following traumatic brain injury. It is hypothesized that ApoE4 is a marker of poor neurological outcomes following surgical decompression in DCM patients. ***Materials and Methods*:** One-hundred DCM patients undergoing surgical intervention will be prospectively enrolled. At time of DCM diagnosis, venous blood samples will be obtained and clinical outcomes assessed by the modified Japanese Orthopaedic Association (mJOA), Nurick grade, Neck Disability Index, and SF-36. Presence of the ApoE2, E3, and E4 alleles will be evaluated by allele-specific quantitative polymerase chain reaction. At 1-year post-surgery, clinical outcomes will be reassessed. ***Preliminary Results: We have found ApoE4 to be associated with neurological decline following surgical decompression for DCM. In a prospective cohort of 66 patients with DCM, 33% of patients with the ApoE4 allele deteriorated 2 points in the mJOA score at 1-year post-surgery, compared to 0% of patients with the ApoE3 allele. With our expanded cohort, we expect to see similar results. ***Conclusion*:** This study represents an important step towards personalized medicine for DCM. Our exciting preliminary data indicates ApoE4 as a potential prognostic biomarker will serve to individualize treatment strategies. This study sits on the translational front, with the potential of integrating investigation in rodent models of DCM to complement clinical evaluation in human DCM patients.

BURN SKIN TISSUE REGENERATION WITH A NOVEL INTRAOPERATIVELY BIO-PRINTER

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Background: Full thickness burns have a devastating impact on patients and must be treated. Bio-Printing is a promising delivery strategy and is evolving in all disciplines in medicine including printing skin scaffolds and cells for skin regeneration. Mesenchymal Stem Cells (MSCs) are known to promote wound healing and tissue regeneration but delivery of these cells remains a challenge.

Hypothesis: We printed MSC from umbilical cord with a novel hand-held intraoperatively usable bio-printer embedded in an extracellular matrix in an experimental large burn porcine animal study and investigated wound healing and tissue regeneration.

Purpose: Investigation of the applicability of a novel intraoperatively usable bio-printer for stem cell application in burn treatment.

Results: Our data (day 28) show accelerated wound healing after stem cell application, with significantly increased collagen regeneration (<p=0.05, ANOVA) compared to controls, as well as increased neovascularization (<p=0.05, T-Test) and less contracture formation (<p=0.01, T-Test) compared to acellular control.

Conclusions: This novel hand-bio-printer deposits stem cells directly onto burn wounds which has significant potential for burn patients to enhance skin regeneration investigated in our translational research study.

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REMOTE ISCHEMIC CONDITIONING IMPROVES NEC-INDUCED INTESTINAL INJURY BY IMPROVING STRUCTURE AND MICROVASCULAR DENSITY OF THE INTESINAL VILLI

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Hypothesis and Purpose: We have previously shown that Remote Ischemic Conditioning (RIC) promotes resolution of experimental necrotizing enterocolitis (NEC) by improving intestinal morphology, reducing inflammation, and enhancing survival. We hypothesize that the mechanism of action of RIC is preservation of normal microvasculature and structure of the intestinal villi.

Methods: After Ethics approval (no. 32238), NEC was induced via gavage feeding with hyperosmolar formula, hypoxia and oral administration of LPS (postnatal day P5-9). RIC was administered to Tie2-CRE/mTmG NEC-induced mice (n=10) before NEC induction (P5 and P7) via intermittent occlusion of the hind limb in 4 cycles of 5 minutes occlusion followed by 5 minutes reperfusion. Breastfed (n=4) and NEC-induced mice not receiving RIC (n=10) served as controls. Two-photon laser scanning microscopy (TPLSM) was used to assess intravital ileal microcirculation in terms of intra-villi microvascular density and arteriole height, arterial diameter (µm), and arterial velocity (µm/s) on P9. Flow volume [(µm)3/s] in ileal submucosa was calculated from arterial velocity and diameter. We also used Sytox Green to evaluate necrosis in the villi. Data was reported as mean ± SD and groups were compared using Mann-Whitney test.

Results: The villi perfusion index, height of intra-villi arterioles, as well as arterial blood diameter, velocity, and flow volume were significantly decreased after NEC induction. RIC significantly rescued these derangements and also reduced NEC-induced necrosis in the villi.

Conclusions: This study shows that derangements in intra-villi microvasculature and intestinal microcirculation during experimental NEC are improved following administration of RIC. RIC is a non-invasive maneuver applicable in clinical setting and could represent a novel treatment strategy for neonates with NEC.

EVALUATING THE INFLUENCE OF PEEP-INDUCED ALVEOLAR RECRUITMENT ON LUNG INJURY DURING VV-ECMO FOR ARDS

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Hypothesis and Purpose: In a large animal model of ARDS supported with VV-ECMO to maintain adequate gas exchange we investigated whether PEEP-induced alveolar recruitment reduces lung injury in comparison to atelectatic lungs.

Methods: Lung injury was induced by two serial bronchoscopic instillations of gastric juice to achieve a P/F ratio <100mmHg in anesthetized pigs supported with mechanical ventilation and VV-ECMO. The animals were then randomized to receive PEEP 20 cmH2O (n=4 HP) or 5 cmH2O (n=5 LP), with 5 cmH2O of driving pressure. Lung and cardiac function were monitored for 5 hours. Lung injury was assessed by W/D ratio and histology.

Results: During VV-ECMO, gas exchange and hemodynamic parameters remained stable and comparable in the two groups, despite the very low tidal volume delivered (HP 54 ml ±; LP 41 ml ±11). Lung volume was higher in the HP compared with the LP group and remained unchanged after 5 hours. At the end of the experiment, in the dependent lung the W/D was significantly higher in the HP compared to LP group (HP 11.1, 95%CI:10.5-11.7; LP 9.2, 95%CI:8.2-10.3); in the non-dependent lung the W/D was significantly higher in the LP compared to HP group (LP 6.3, 95%CI:5.6-6.9; HP 5.3, 95%CI:4.9-5.8). Histological lung injury score was significantly higher in the dependent lung compared to the non-dependent lung but similar in the two groups.

Conclusions: During VV-ECMO for ARDS mechanical ventilation with low PEEP results in a more homogeneous distribution of edema compared to high PEEP, suggesting a more homogenous distribution of lung perfusion. Further analysis is required to assess the impact of these findings on lung injury.

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UTILIZATION, SAFETY, AND EFFICACY OF HYBRID ESOPHAGECTOMY IN ONTARIO

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Hypothesis and Purpose: Population-based data on the postoperative mortality, resource utilization, and long-term survival of minimally-invasive or hybrid (MIE) versus open (OE) esophagectomy are needed to determine utilization and efficacy. Our objective was to compare short and long-term outcomes following these two procedures.

Methods: This population-based study included adults undergoing esophagectomy in Ontario, Canada from 2009-2014 for cancer. Patients undergoing a laparoscopic and/or thoracoscopic approach were classified as hybrid esophagectomy and compared to patients undergoing open esophagectomy. The primary analysis compared the two groups in the whole cohort, and the secondary analysis compared the two groups in a propensity score matched cohort.

Results: Of 1467 included patients, 1003 underwent open and 464 underwent hybrid esophagectomy. Patient characteristics were similar except hybrid patients underwent surgery more recently. For 850 patients with pathology data available, tumour size, T and N stage, and grade were similar. The proportion of patients undergoing hybrid surgery increased from 14% in 2009 to 43% in 2014 ($p<0.001$). Lymph node yield was equivalent in the hybrid (median 17, IQR 11-26) and open groups (median 17, IQR 11-24; $p=0.69$). Hybrid patients had shorter hospital stay (median 10 days [IQR 8-15] vs 12 days [IQR 9-19, $p<.001$). Ninety-day readmission was higher in the hybrid group (31 vs 24%, $p=0.002$). There was no difference in 90-day mortality (6.5 vs 6.9%, $p=0.77$) or median overall survival (23 mo. [IQR 12-43] vs 25 mo. [IQR 11-48]) between the two groups. Propensity score matching achieved balance for 464 patients in each group and confirmed findings from the primary analysis.

Conclusion: This large population-based study demonstrates safety of hybrid esophagectomy in real-world practice, with shorter length of stay, higher readmission, and equivalent oncologic and mortality outcomes compared to open surgery.

SENSORY INNERVATION OF THE ANKLE JOINT: IMPLICATIONS FOR NERVE BLOCK AND RADIOFREQUENCY ABLATION

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Purpose and Hypothesis: The purpose of this cadaveric study was to determine the pattern of sensory innervation of the ankle joint and to identify bony and soft tissue landmarks visible with image-guidance to localize the articular branches. It is hypothesized that all nerves that supply the leg give rise to articular branches that innervate the ankle joint.

Methods: Three formalin embalmed specimens were used in this pilot study. The course of the saphenous (SAN), tibial (TN), sural (SUN), superficial fibular (SFN), and deep fibular (DFN) nerves and their articular branches supplying the joint capsule were digitized (Microscribe® G2X Digitizer) relative to anatomical landmarks and reconstructed in 3D using Autodesk® Maya®.

Results: The ankle joint received innervation from articular branches from the TN, SUN, SAN, and DFN: the posteromedial capsule was innervated by articular branches of TN that coursed through the fat pad deep to the calcaneal tendon; posterolateral and lateral capsule by articular branches of SUN located just inferior to the lateral malleolus; medial capsule by articular branches of SAN which coursed over the medial malleolus; and anterior aspect by articular branches by DFN just inferior to the middle third of the inferior margin of the tibia.

Conclusions: The results of this pilot study provide 3D data of the innervation to the ankle joint and relationship to bony and soft tissue landmarks visible with image-guidance. This provides the anatomical basis to propose novel clinical nerve block/ablation techniques.

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ABIRATERONE VERSUS DOCETAXEL FOR METASTATIC HORMONE SENSITIVE PROSTATE CANCER: A MARKOV MICROSIMULATION MODEL

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Purpose: In the setting of metastatic castrate sensitive prostate cancer (mCSPC), androgen deprivation therapy (ADT) has traditionally been the standard of care; however, the introduction of early docetaxel chemotherapy (DC) and anti-androgen agents (abiraterone with prednisone [AA]) have resulted in significant improvements in overall survival (OS). While these two alternative regimens have shown to be efficacious, they have not been compared head-to-head. Our aim was to determine whether ADT with AA or ADT with DC resulted in improved quality adjusted life months (QALMs) among men with de novo mCSPC.

Methods: A Markov microsimulation model was constructed employing two-dimensional Monte Carlo simulation (Figure 1). A lifetime horizon was used. Our primary outcome was QALMs. Secondary outcomes included rates of second- and third-line therapy, OS, and adverse events. A systematic literature review was used to generate probabilities and utilities to populate the model. The base case was a 65-year-old patient with de-novo mCSPC.

Results: 100,000 microsimulations were generated. AA resulted in a gain of 1.1 QALMs compared to DC (37.0 versus 35.9 QALMs, respectively). Median crude OS was 45 months with AA and 42 months with DC. Overall, 45.2% and 45.6% of patients received second line therapy and 8.5% and 8.3% patients received third line therapy in the AA and DC groups, respectively. Grade 3/4 adverse events were experienced in 57.9% and 26.3% of patients, respectively.

Conclusion: This study suggests that AA results in a higher QALM and crude OS compared to DC. Until robust randomized trials can be completed, the results of this study may help to guide treatment. However, the ultimate choice should be based on patient and tumor factors. In the next phase of this project, cost data will be added to the model to determine the incremental cost effectiveness of AA over DC.

PREDICTION OF SURVIVAL FOR PANCREATIC NEUROENDOCRINE TUMOURS; A SYSTEMATIC REVIEW OF CLINICAL TOOLS

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Hypothesis and Purpose: Individual prognostication can support the management of pancreas neuroendocrine tumours (PNETs). Little is known about PNETs prediction tools' accuracy and utility. We sought to evaluate the quality of prediction tools in PNETs.

Methods: We systematically searched the literature for studies reporting development or validation of tools predicting survival for PNETs. We evaluated the tools using the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies guidelines and the American Joint Committee on Cancer (AJCC) acceptance criteria for risk models.

Results: We identified 7 tools to predict survival in PNETs that all addressed resected tumours. All were developed on patients diagnosed back to 1980-90s. They included 2 to 5 prognostic factors; the majority excluded key factors such as age and sex. Tumour grade was most commonly included. Five tools were designed to predict overall survival, and two for both disease-specific and recurrence-free survival. Two tools underwent bootstrapping internal validation with one showing "good" discrimination (C-statistic: 0.74). Two tools were externally validated: calibration was evaluated with inspection of survival curves and estimates, but discrimination was not assessed. Validation samples relied on unknown or small (<100) number of events. No tool met AJCC acceptability criteria for risk models.

Conclusion: Existing tools cannot be confidently used for PNETs prognostication in current clinical practice. Patient-level and non-pathologic disease factors should be included for more personalized prognostication. Better quality tools should be developed and validated following best methodology practices for predictive tools development and validation.

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VACCINIA VIRUS DELETION MUTANTS ARE POTENT ONCOLYTIC VIRUSES AGAINST MESOTHELIOMA

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Introduction/Objectives:

Engineered gene deletions in oncolytic vaccinia virus (VV), vvDD, enhance wild-type Western Reserve (WR) VV tumour-specificity based on cell proliferation rates, but alternate strategies of tumour-selectivity could yield an equally safe but more potent VV. Previously, a panel of WR VVs with single deletions of redundant VV immunomodulatory genes (ΔN1L, ΔK1L, ΔK3L, ΔA46R, or ΔA52R VV) demonstrated safety and superior potency against colon and ovarian cancer. In this study, we evaluated the oncolytic potency of the panel of candidate VVs against mesothelioma.

Methods: The viral replication and cell cytotoxicity of candidate VVs and vvDD were compared in human mesothelioma cell lines AB12 and AC29 using plaque assays and MTS cell viability assays, respectively. Viral spread was measured with fluorescent microscopy in monolayer culture and tumour spheroids.

Results: Compared to vvDD, all candidate VVs demonstrated equal or enhanced viral spread in monolayer and tumor spheroids. At 48 hours post-infection, candidate VVs spread to an area up to 2 times larger compared to vvDD in both AC29 and AB12 monolayer cultures. All candidate VVs also demonstrated equal or enhanced viral replication compared to vvDD wherein the highest fold change in viral load was observed at 48h after infection with ΔK1L VV in monolayers of both mesothelioma cell lines. Some VVs also exhibited superior tumour cell cytotoxicity. Notably, ΔN1L and ΔA52R VVs were consistently more cytotoxic than vvDD.

Conclusions: Novel tumour-selection strategies for VV can generate promising oncolytic viruses and may result in new clinical candidates.

REMOTE ISCHEMIC CONDITIONING WITH LIMITED ISCHEMIA TIME REDUCES INTESTINAL INJURY IN EXPERIMENTAL NEC

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Hypothesis and Purpose: We have previously shown that Remote Ischemic Conditioning (RIC), with 4 cycles of 5 minutes ischemia and 5 minutes reperfusion in a limb, reduces intestinal injury and inflammation in experimental Necrotizing Enterocolitis (NEC). The purpose was to evaluate the efficacy of RIC in NEC when the duration of ischemia and reperfusion is minimized, to enhance the translational applicability of RIC to preterm neonates. We hypothesized a decrease of intestinal injury in the RIC treated mice with NEC.

Methods: Four groups of mice (7-10 animals per group) were included: control, NEC, NEC with "extended" RIC (4 cycles/5 minutes) and NEC with "limited" RIC (4 cycles/3 minutes). NEC was induced from postnatal day 5 (p5) to p9 by gavage feeding (formula), hypoxia and Lipopolysaccharide. RIC was performed after NEC induction on p6 and p8. Terminal ileum was harvested on P9 for analysis. NEC was confirmed when histological NEC-severity score was ≥2. Statistical analysis was performed using one-way ANOVA for histology and TNF-α (inflammatory cytokine) gene expression.

Results: All animals exposed to NEC induction developed intestinal injury similar to NEC. However, NEC was present in 43% of extended RIC and 25% of limited RIC (Fig. A). TNF-α relative gene expression was significantly decreased in both RIC groups (Fig. B).

Conclusion: Ischemic conditioning of a limb is beneficial to an injured distant organ such as the intestine. In experimental NEC, RIC seems to be effective even if the duration of remote ischemic conditioning is limited. These results are important for the clinical application of RIC as a novel treatment for NEC.

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RAPAMYCIN RESTORES CORE CLOCK GENES AFTER RELEASE OF OBSTRUCTION COORDINATE WITH SOME PHYSIOLOGY CHANGES

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Rapamycin restores bladder smooth muscle cell (SMC) phenotype and gene expression patterns that are lost during stretch and partial bladder obstruction (PBO), but we do not know if it restores lost function or phenotype in the clinically more relevant model of persistent disease after release of the obstructing suture (Chronic Obstructive Bladder Disease, COBD).

PURPOSE: to test if and how our model of COBD responds to rapamycin. ***Hypothesis:*** Rapamycin im-proves COBD pathophysiology and gene expression. **METHODS:** Sprague-Dawley female rats underwent PBO by suturing around the proximal urethra and a 0.9mm steel rod; the rod is then removed leaving the suture in place. Animals were randomized to 6 week PBO or 6 week COBD (PBO plus release). COBD rats were randomized to vehicle (saline) or rapamycin 1mg/kg/day for 6 weeks. High-throughput and regular QPCR, and bladder voiding function analysis were performed. Pharmaco-inhibition was used to assess signaling pathway function in mechanically stimulated SMCs. **RESULTS**: IGFBP7, BMP2, and SOD3 expression correlated with physiologic improvements in COBD+rapamycin vs. COBD+vehicle. *In silico* sites of transcriptional regulation of these 3 genes identified a core clock gene E-box. PBO and COBD showed persistent upregulation of core clock genes CLOCK, NPAS2 and CRY2. Rapamycin blocked expression of all 6 genes above, $p<0.01$. The core clock protein NR1D1 inhibitor SR9009 (vs. vehicle) lowered mechanical stretch-induced +/- basal expression of all 6 genes, $p<0.01$, while increasing SMC differentiation marker Myh11 expression. **CONCLUSION: COBD dysregulates** core clock gene transcription which is reversible by rapamycin. MTOR and NR1D1 both regulate clock gene expression and smooth muscle cell phenotype.

CLINICAL AND ECONOMIC OUTCOMES FOR GASTRIC CANCER PATIENTS TREATED WITH GASTRECTOMY AT CENTRES WITH AND WITHOUT CANCER SURGERY CENTRE DESIGNATION

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Hypothesis and Purpose

We conducted an evaluation of clinical and economic outcomes for gastric cancer (GC) patients treated with gastrectomy at centres with and without cancer surgery centre designation (CSCD). We hypothesized CSCD would be associated with lower 90-day mortality, higher overall survival, and higher healthcare costs.

Methods

A retrospective cohort study was performed using linked administrative data on patients with GC treated with gastrectomy. Multivariable logistic regression, Cox proportional hazards analysis, and linear regression with log-transformed costs were used to derive parameter estimates with 95% confidence intervals. Costs were inflated to 2016 Canadian dollars.

Results

A total of 2,930 patients with GC were treated with gastrectomy (CSCD n=1,436; non-CSCD n=1,494). CSCD was associated with lower 90-day mortality (OR 0.70, 95% CI 0.52-0.94, p=0.02), and no difference in overall survival (HR 0.94, 95% CI 0.85-1.04, p=0.24), or health care costs with adjusted mean monthly care costs of $3,310 (95% CI $2,384-$4,595) for the CSCD group, and $3,430 (95% CI $2,469-$4,765) for the non-CSCD group (p=0.36).

Conclusions

GC surgical care at institutions with CSCD may result in lower 90-day mortality, and similar overall survival, with no difference in healthcare costs compared to treatment at institutions without cancer surgery centre designation.

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MUSCULOAPONEUROTIC ARCHITECTURE OF THE FLEXOR DIGITORUM SUPERFICIALIS: A 3D MODELLING STUDY OF INTRAMUSCULAR APONEUROSES AND FIBRE BUNDLE MORPHOLOGY

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Hypothesis and Purpose: The purpose of this cadaveric study was to investigate the 3D musculoaponeurotic architecture of flexor digitorum superficialis (FDS) to determine the location and extent of aponeuroses, tendons, and fibre bundle attachment sites for each muscle belly.

Hypothesis: The muscle bellies of FDS have unique aponeurotic cores.

Methods: The musculotendinous elements of FDS were serially dissected and digitized (MicroScribe® Digitizer) in 7 embalmed specimens. The data were reconstructed into 3D models (Autodesk® Maya®) that were used to visualize, document, and compare the spatial relationships of the aponeuroses and fibre bundle attachment sites of the bellies of FDS.

Results: FDS consisted of 4 digital bellies and a proximal belly. The muscle bellies originated from intramuscular aponeuroses: 1. a triangular proximal aponeurosis extending from the medial epicondyle into the superior 1/3 of the forearm, providing attachment for the proximal belly; 2. a distal aponeurosis on the deep surface of the 3rd digital belly, continuous with the tendon of the 3rd digit; 3. a long, slender aponeurosis on the medial aspect of the 2nd digital belly spanning from the medial epicondyle proximally and continuous distally with the digital tendon. The 4th digital belly was most superficial, attaching to aponeuroses 1 and 3 proximally, and to the 4th digital tendon distally. The fibre bundles of the 5th digital belly originated from aponeurosis 3, distal to the 4th digital belly.

Conclusion: The results of this pilot study suggest that each of the bellies of FDS has a unique, complex musculoaponeurotic core for fibre bundle attachment. Functionally, aponeuroses are an important component of force transmission to terminal tendons, however their location and role is poorly understood and requires further investigation.

IDENTIFYING THE BURDEN OF DEPRESSION AND ANXIETY IN PATIENTS WITH INTRACRANIAL MENINGIOMAS: A COMBINED QUALITATIVE AND QUANTITATIVE APPROACH

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Purpose: Meningiomas comprise 10-15% of all intracranial tumours and are typically benign in nature. Coping with the diagnosis of an intracranial tumour is associated with increased psychosocial and emotional burden; however, this relationship is founded on evidence focusing on high-grade tumours, and thus is poorly understood in the context of meningiomas. This study aimed to identify the prevalence and burden of symptoms of depression and anxiety in patients with meningiomas. **Methods:** The Hospital Anxiety and Depression Scale (HADS) was administered to each participant. Summary statistics were computed and 2-tailed t-tests were performed to assess significance between post-operative and non-surgical patients' HADS scores. Semi-structured interviews were carried out on a subset of patients. Thematic analysis of interviews was performed to identify emerging themes. **Results:** We included 30 patients with intracranial meningiomas in the study, with 14 patients having undergone surgical resection and 16 patients being followed with serial imagining. Symptoms of anxiety appear more prevalent than symptoms of depression, with 23.3% of participants demonstrating symptoms suggestive of anxiety, as compared to 3.3% for depression. Emerging themes from the 8 completed interviews include the importance of personal resilience throughout the patient experience, the presence of acute stress while waiting for diagnostic and follow-up test results, the desire for comprehensive formal supports such as support groups, and the positive influence of reassuring medical experts. **Conclusion:** The prevalence of symptoms of anxiety in patients with meningiomas appears higher than that of the Canadian general population. Importantly, combined quantitative analysis and qualitative reporting indicate that patients who do not meet HADS thresholds for clinical suspicion of depression or anxiety may still experience a significant mental health burden, illustrating the need for patient-centred care focusing on the psychosocial and emotional aspects of health.

UNRAVELING THE UNIQUE BURN-INDUCED TEMPORAL ALTERATIONS IN ADIPOSE TISSUE METABOLISM

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Hypothesis and Purpose: A severe burn elicits a systemic hypermetabolic response that substantially alters the function of multiple organs including white adipose tissue (WAT), which converts from an energy storing to an energy dissipating state in a process termed browning. Rodent models are commonly used to provide mechanistic insight towards the progression of burn injury, which can then be translated to a clinical setting. However, a comprehensive characterization of the acute and long-term pathophysiological responses to burns has yet to be determined. Therefore, we aimed to clarify the time-dependent changes to adipose tissue metabolism that occur post-burn. **Methods:** 9 wk old male mice were subjected to either a burn encompassing 30% total body surface area or were denoted sham, for which mice underwent identical procedures excluding burn. Cohorts of mice were sacrificed at 6hrs, 1, 3, 5, 7, 14 and 30d post-burn and epididymal (eWAT) and inguinal WAT (iWAT) and brown adipose tissue (BAT) was collected. **Results:** Burn mice lost significantly more weight at 3 and 5d post-burn while maintaining a similar food intake in comparison to their sham counterparts. There was a marked decrease in eWAT mass at 1, 3 and 5d, and significant increases in BAT mass at 7d post-burn. While iWAT mass remained unchanged, the protein content of UCP1 and PGC1α, the master regulators of browning and mitochondrial biogenesis, respectively, were significantly upregulated at days 3 and 5; UCP1 remained elevated until day 7 post-burn. Concomitantly, the presence of multilocular clusters, indicative of WAT browning, was most pronounced at 1 and 3d post-burn. **Conclusion:** Consistent with the temporal remodelling that occurs following cold exposure, a severe burn elicits a dynamic hypermetabolic response. Our preliminary results demonstrate a unique pattern, whereby burn injury causes alterations at the whole-body, tissue and protein level in a time-dependent manner with most notable differences at 3 days post-burn.

RESTROSPECTIVE ANALYSIS OF INCIDENTAL AND SYMPTOMATIC PENETRATING AORTIC ULCERS AND THEIR ASSOCIATED OUTCOMES

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Hypothesis and Purpose: Our hypothesis is that incidental and symptomatic PAUs have different clinical courses. Analysis of this population should allow better understanding of appropriate management.

Methods: Montage radiology software was used to query the term 'PAU' and synonyms in scans done through the Joint Department of Medical Imaging at UHN. CT or MRI scans of PAUs were analyzed and measured for individual patients and charts were also reviewed.

Results: A total of 389 patients with 545 PAUs were identified with a mean age of 74±9.5 years. Follow up data was available for 341 patients. Of the 341 patients in our review with follow up data, 131 (38.4%) presented with symptoms of acute aortic syndrome and 210 (61.5%) patients were asymptomatic, incidental findings. Surgical treatment occurred in 32 (24.4%) of symptomatic and 22 (10.4%) of incidental. Median survival was similar in incidental and symptomatic patients at 97 and 101 months respectively (p=0.16). 5 patients (2.3%) in the symptomatic group and 4 patients (3.1%) in the incidental group died due to aortic complications. Additionally, 132 patients (34%) had current or prior malignancy.

Conclusion: The population of patients presenting with a PAU is a highly comorbid population. A large portion, 28% (109), were deceased from pathologies other than PAU. Our cohort of incidentally diagnosed patients had a median survival similar to those presenting with Acute Aortic Syndrome.

DISRUPTED TIGHT JUNCTIONS IN INJURED INTESTINAL ORGANOIDS

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Hypothesis and Purpose: Using intestinal organoids, we hypothesize that injured intestinal organoids permeability is increased and that this increase is due to the change in the tight junctions which can be reversed by AFSC.

Methods: Following ethical approval (#32238), mouse intestinal organoids were established using ileal crypts. To induce injury, organoids were treated with lipopolysaccharide (LPS) (200µg/ml) and hypoxia for 48 hours. AFSC were used as treatment. Organoids permeability was investigated using FITC-dextran, 4kDa (FD4) and tight junction markers were assessed by immunofluorescence staining.

Results: Translocation of FD4 was not observed in control organoids, increased in injured organoids, and not observed in organoids treated with AFSC. Immunofluorescence staining shows that tight junction ZO-1 was lower in injured organoids compared to control and administration of AFSC restored ZO-1 expression. Pore-forming claudin 2 was upregulated in injured organoids while claudin 3 and claudin 4 were deranged in injured organoids compared to control and administration of AFSC prevented these changes.

Conclusions: Intestinal organoid permeability was impaired and tight junctions were altered by hypoxia and LPS. This damage can be reversed by AFSC administration. These findings indicate that AFSC play an important role in restoration of intestinal permeability.

TEXTBOOK OUTCOMES AND SURVIVAL IN PATIENTS WITH STOMACH CANCER: AN ANALYSIS OF THE POPULATION REGISTRY OF ESOPHAGEAL AND STOMACH TUMOURS OF ONTARIO (PRESTO)

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Background: Textbook Outcomes (TO): a composite of eight surgical and post-operative parameters which exemplify high quality surgery, may represent a new benchmark in gastric cancer surgery. The objectives of this study were to describe the survival of patients with and without Textbook Outcomes and measure the association between Textbook Outcomes and time-to all-cause-mortality.

Methods: This study is a population-based retrospective analysis of all adult patients with gastric adenocarcinoma undergoing gastrectomy between 2004 and 2016 in Ontario. Post-operative outcomes were analyzed, and patients were assigned to TO vs. non-TO groups. Median and 5-year survival rates were estimated using the Kaplan Meier method. A marginal cox proportional hazards model accounting for clustering and regressed on patient confounders was used to assess the association between TO and overall survival.

Results: In total, 2,399 patients were deemed eligible and Textbook Outcomes were achieved in 20% of patients (n=489). Median survival was greater in TO patients (155 months vs. 39 months, Log Rank $p<0.001$). Following adjustments for covariates and clustering by hospital, TO was associated with a 38% decrease in the relative rate of death (HR 0.62 [95%CI 0.52, 0.73]).

Conclusions: TO is a rare outcome in most patients, which is all the more significant given its strong association with improved survival. Textbook Outcomes should be considered the new benchmark in gastric cancer surgery.

HIGH MOBILITY GROUP AT-HOOK 1 IS IMPORTANT FOR INTESTINAL EPITHELIUM PROLIFERATION

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Hypothesis and purpose: High mobility group AT-hook 1 or Hmga1 is an epigenetic regulator shown to be involved in intestinal stem cell (ISC) expansion and epithelial proliferation. Hmga1 is confirmed to be downregulated in both human and murine experimental necrotizing enterocolitis (NEC), though its specific role has not been investigated. The purpose of this study is to determine the role of HMGA1 on intestinal epithelium homeostasis impairment in vitro.

Methods: IEC-18 intestinal epithelial cells were treated with 50 & 100pmol of Hmga1 siRNA via lipofectamine transfection. Scrambled (Scr) siRNA was used as a negative control. Immunofluorescence staining and western blotting were used to confirm HMGA1 knockdown. ISC activation (Lgr5) and cell proliferation (Ki67) were analyzed through immunofluorescence staining and RT-qPCR.

Results: Immunofluorescence staining and western blot analysis confirmed Hmga1 knockdown. Compared to control, IEC-18 treated with Hmga1 siRNA exhibited down-regulation of ISC Lgr5 ($p<0.05$) indicating lack of stem cells and decreased Ki67 staining indicating impairment of proliferation.

Conclusions: Hmga1 knockdown IEC-18 exhibited decreased cell proliferation and ISC activation. This study shows that Hmga1 is an important regulator of intestinal ISC maintenance and epithelial cell proliferation in the presence of intestinal injury. Hmga1 has the potential to be a novel therapeutic target for infants with acute intestinal injury.

TRIPOTENT NEUROGENIC NPCS FOR REPAIR AND REGENERATION OF THE INJURED SPINAL CORD

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Hypothesis and Purpose: We are investigating what is the optimal ratio of neuron, oligodendrocyte, and astrocyte differentiation in transplanted tripotent neural precursor cells (NPCs) for promoting neurobehavioral recovery in SCI. In addition, we will screen for cell surface markers that target synapse formation with specific neuron subsets of the host neural network to enhance effects of NPC transplantation.

Materials and Methods: Detailed *in vitro* characterization of the neurogenic neural precursor cell (nNPC) line will be done through morphological analyses, immunostaining, qPCR, and RNA sequencing to determine genetic identity and differentiation profile. Oligodendrocyte biased NPCs (oNPC), nNPCs, and conventional NPCs will be transplanted into rats 2-weeks post cervical spine injury. The rats will undergo rehabilitation along with behavior analysis over 12 weeks. Differentiation and viability of transplanted NPCs will be analyzed using neuron tracing, FACS, and patch clamp.

Results: Preliminary *in vitro* data has shown that nNPCs differentiate in an approximately 40:40:20 ratio of astrocytes, neurons, and oligodendrocytes. qPCR analysis has shown that the nNPCs over express neuronal markers such as NEUROD1 and ASCL1 and under express astrocyte markers such as GFAP and NF1A compared conventional NPCs.

Conclusion: Optimizing the differentiation profile for NPC grafts into the injured spinal cord will allow for sufficient replacement of lost neurons, remyelination of denuded axons, and trophic support, and targeted synaptic formation will allow for an increased proportion of newly differentiated neurons to form synapses with functionally relevant neurons.

GENOME ENGINEERING HUMAN NEURAL PRECURSOR CELLS FOR CLOSED-LOOP DELIVERY OF CHONDROITINASE ABC

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Hypothesis and Purpose:

Engineered neural precursor cells (NPCs) that deliver chondroitinase ABC in a closed-loop feedback system will degrade inhibitory chondroitin sulfate proteoglycans (CSPGs) that are increased after spinal cord injury.

Methods:

Human induced pluripotent stem cell-derived NPCs were exposed to varying levels of CSPGs. RNA was extracted from the cells and analyzed by RNA-sequencing and qRT-PCR to find differentially expressed genes. Candidate genes will be selected based on fold-change in expression between physiological and injury levels of CSPGs. The promoter of the candidate gene will be cloned into a CRISPR/Cas9 plasmid construct with chondroitinase ABC and red fluorescent protein. The plasmid will be stably transfected into hiPS-NPCs by electroporation and sorted to generate a monoclonal cell line expressing chondroitinase ABC. The engineered cells will be characterized for their chondroitinase ABC secretion and CSPG responsiveness.

Results:

In qRT- PCR experiments, NPCs show increased expression of AKT1, GSK3B, RHOA and ROCK1 after exposure to higher levels of CSPGs. Further analysis of the RNA will narrow down candidate genes for selection of an optimal closed-loop system promoter.

Conclusions:

NPCs respond to CSPG in a concentration-dependent manner. These transcriptional responses will be used to design a gene circuit in NPCs for delivery of chondroitinase ABC. Ultimately, these findings further the development of a more effective therapy to regenerate the spinal cord after chronic injury.

EXPRESSION OF THE PLK4 INHIBITOR FAM46C PREDICTS BETTER SURVIVAL FOLLOWING RESECTION OF GASTRIC ADENOCARCINOMA (GCA)

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Hypothesis and Purpose: Despite improvements in surgical technique and perioperative adjuvant therapy for GCa, ≈40% of Western patients die of recurrent disease. Novel molecular markers and targets are urgently needed. We are investigating the role of the oncogene Plk4 and a 61-gene panel of BioID-defined Plk4 interactors (*Cancer Res 2017*) in GCa progression. **Methods:** Patients who underwent curative-intent resection for GCa from 2006-2016 were identified in our institutional database. Banked primary tumour (T) and paired normal mucosa (NM) samples were microdissected, RNA extracted, and the Plk4 interactome interrogated using qPCR. Pattern of recurrence was categorized as locoregional, peritoneal or distant. Survival was estimated by Kaplan-Meier method and comparisons made by log-rank analysis. **Results:** From 84 consecutive patients, Plk4 interactome expression analysis was informative in 77 cases (median age=69 yrs, F:M 30:47). At median follow-up time of 47 mos (IQR 29-75), 33 patients had died of GCa, 5 had died of other causes, and 39 were alive with no evidence of disease. Plk4 was modestly overexpressed in GCa tumour tissue (median T/NM 1.45, IQR 0.59-3.0), but not prognostic of overall survival (OS) or disease-specific survival (DSS). The Plk4 inhibitory interactor FAM46C was depleted (T/NM<1) in 93% of cases. Median FAM46C T/NM was 0.29 (IQR 0.13-0.51). Retention of FAM46C expression (defined as T/NM≥0.35, n=27) was associated with superior 5-yr OS (69% vs 35%, p=0.02) and 5-yr DSS (76% vs 38%, p=0.01). The prognostic significance of FAM46C persisted in the node positive subgroup of patients (n=49, OS p=0.03; DSS p=0.04). Loss of FAM46C in the resected tumor tissue predicted distant recurrence (12/50 vs 1/27, p=0.03, Fisher's). **Conclusions:** Retention of FAM46C expression was associated with a better prognosis following curative-intent resection of GCa. FAM46C may be protective through its inhibition of Plk4, reducing the risk of distant metastasis.

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PERI-OPERATIVE CHEMOTHERAPY FOR UPPER TRACT UROTHELIAL CARCINOMA: A MICROSIMULATION MARKOV MODEL

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Hypothesis and Purpose: Upper tract urothelial carcinoma (UTUC) is rare and clinically understudied. As a result there are no definitive recommendations regarding the use and timing of peri-operative chemotherapy. The objective of this study was to create a decision model comparing three treatment pathways in UTUC: nephroureterectomy (NU) alone, neoadjuvant chemotherapy (NAC), and adjuvant chemotherapy (AC).

***Methods*:** A Markov microsimulation model was constructed using TreeAge Pro to compare treatment strategies for patients with newly diagnosed UTUC. Our primary outcome was quality adjusted life expectancy (QALE). Secondary outcomes included rates of adverse chemotherapy events, bladder cancer diagnoses, and crude survival. Markov cycle length was 3 months. A systematic literature review was conducted to populate the model with appropriate probabilities. The base case was a 70-year-old patient with a radiographically localized upper tract tumor.

***Results*:** A total of 100,000 microsimulations were generated. NAC was preferred with an estimated QALE of 7.52 years versus 6.80 years with NU alone and 7.20 years with AC. A total of 37.5% of patients in the NAC group experienced an adverse chemotherapy event compared to 15.1% of patients in the AC group. Bladder cancer recurrence rates were 64.9%, 66.0%, and 67.1% over the patient's lifetime in the NU, NAC, and AC groups, respectively.

***Conclusion*:** This study provides evidence to support the increased use of NAC in UTUC until robust randomized trials can be completed. While the use of NAC in this population appears favourable, the ultimate decision rests with the clinician and should be based on patient and tumor factors.

A SURVEY OF CARDIAC SURGEONS TO EVALUATE THE USE OF SUTURELESS AORTIC VALVE REPLACEMENT IN CANADA

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HYPOTHESIS AND PURPOSE:

We sought to establish practice patterns and perceptions regarding SuAVR of cardiac surgeons in Canada.

METHODS/RESULTS:

A surgeon survey was developed by established content experts, including cardiac surgeons, cardiologists and methodologists. The survey was administered electronically. Five Clinicians piloted the survey for clarity and length. The questionnaire examined several domains including respondent characteristics, factors influencing the decision to implant a SuAVR, barriers to SuAVR use, and interest in participating in a trial. We surveyed 56 of 79 surgeons (71% response rate) from 18 hospitals across Canada with at least 1 SuAVR implantation. Respondents were in independent practice for median of 15 (9-20) years. 54% performed SuAVRs, while 32% performed SuAVR and TAVR; 14% did not perform SuAVR routinely. Factors that guided the decision to perform SuAVR included "hostile root" (73%), small annular size (58%), high STS score (42%), older age (41%), minimally invasive approach (26%), and Redo-operation (19%). Reported factors against implanting SuAVR involved young age (71%), low STS score (40%), and large annular size (31%).

CONCLUSION:

Surgeons reported being more likely to use a SuAVR in patients with high surgical risk, older age, hostile root, redo-operations, and a small annulus.

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A WINDOW INTO ONCOLYTIC VIROTHERAPY: USING A NOVEL ZEBRAFISH MODEL TO QUANTIFY THE ANTI-TUMOR EFFECTS OF VACCINIA VIRUS IN COLON CANCER

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Purpose and hypothesis: The use of oncolytic viruses (OVs) in the treatment of solid tumors represents an area of intense current research, with clinical successes for colorectal cancer remaining modest to date. As the ability of OVs to act as immunotherapeutic agents is increasingly recognized, and they are integrated into combination therapies in cancer management, novel approaches to model the therapeutic efficacy of these strategies are needed. We hypothesized that a tumor xenograft model of colorectal cancer in zebrafish embyros would be an ideal system to allow for in vivo quantification of OV, tumor, and immune cell interactions throughout the course of virotherapy.

Methods: Zebrafish embryos were injected with mammalian colon cancer cells 48 hours post-fertilization. Oncolytic vaccinia virus or control injections were administered 24 hours later, following a period of initial tumor xenograft development and angiogenesis. Confocal fluorescent imaging was then used to quantify fluorescently-labelled virus, tumor, and immune cell dynamics, as well as anti-tumor response.

Results: We found that xenografts successfully recapitulated early colorectal tumor development and enabled real-time quantification of immune cell/OV/tumor dynamics. Using our model, we have demonstrated a significant anti-tumor response in vaccinia-treated zebrafish compared to controls, with a reduction in tumor volume as well as complete tumor regression in a proportion of treated fish.

Conclusions: Our protocol offers a powerful new approach to OV modeling. Potential future applications include evaluating the anti-tumor and immunotherapeutic capabilities of novel oncolytic viruses, alone and in combination with other therapeutic agents, in a high-throughput manner.

CRISPR-MEDIATED IL-10 GENE ACTIVATION AS A NOVEL GENE THERAPEUTIC STRATEGY IN LUNG TRANSPLANTATION

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Hypothesis & Purpose: Lung transplantation (LTx) is a life-saving treatment for end-stage respiratory failure. Inflammation and alloimmune response are main mechanisms underlying post-transplant complications which limit the outcome of LTx. We hypothesize that the upregulation of the IL-10 gene, an anti-inflammatory and immune down-regulating cytokine, in the whole lung utilizing CRISPR-based technology will improve the outcome of LTx. The purpose of this study is to achieve CRISPR-mediated targeted IL-10 gene activation in vitro and to generate a viral vector for future whole organ studies.

Methods: Seven guide RNAs (gRNA) were designed to target the promoter region of IL-10 gene of the rat genome. First, each gRNA was expressed together with Cas9 activator by plasmid transfection in rat lung cell lines to validate activation activity. Second, recombinant adenovirus, which expresses both the determined gRNA and Cas9 activator, were generated and used for gene delivery. For the assessment of IL-10 gene activation, the expression of rat IL-10 gene and the production of rat IL-10 protein are measured by qPCR and ELISA respectively.

Results: Both lung epithelial and macrophage cell lines demonstrated enhanced IL-10 gene expression when transfected with Cas9 activator and one of designed gRNAs at 48h. Using a recombinant adenovirus, gRNA-expressing group showed over 10000-fold increase of endogenous IL-10 gene expression and significantly high IL-10 protein level in supernatant compared to no-gRNA group (702±42 pg/μl vs undetectable, mean±SEM) in epithelial cells at 48h.

Conclusion: Targeted IL-10 gene activation was achieved in both epithelial and macrophage cell lines. CRISPR-mediated IL-10 gene activation of the lung holds considerable promise as a potential gene therapy strategy.

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TIMING OF CT FOR ADHESIVE SMALL BOWEL OBSTRUCTIONS (SBO)

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Hypothesis and Purpose:

Small bowel obstruction management strategies vary widely between practitioners. The aim of this study was to assess the timing of computed tomography (CT) scan from emergency department (ED) presentation on outcomes for SBO patients to guide the development of an evidence-based clinical pathway.

Methods:

A single institution retrospective chart review to establish pre-pathway implementation performance metrics was performed on SBO patients for 2016 and 2018. SBO was confirmed by CT in all patients. Non-adhesive causes were excluded. The calculated median time to CT was used to identify 2 groups: patients undergoing CT in 0-6 hours from ED presentation (early CT) and those undergoing CT after 6 hours (late CT). Groups were compared using Chi-square.

Results:

299 SBO patients were identified. The median time to CT from ED presentation was 6.2 hours. 149 patients had adhesive SBOs of which 68 had an early CT and 81 had a late CT. The median length of stay was 3 days in the early CT group and 4 days in the late CT group. There was no difference in the red flags identified by CT in either group (10% vs. 18.5%). In the early CT group, 5% required surgery after failure of conservative management versus 12% in the late CT group ($p=0.072$). Of the patients who required immediate surgery, 4.4% of the early CT group required a bowel resection while 9.9% of the late CT group did ($p=0.056$).

Conclusion:

This data suggests that early CT may result in improved care by reducing bowel resections in patients with adhesive SBO.

CONDITIONED MEDIA FROM HUMAN DERIVED AMNIOTIC FLUID STEM CELLS: A NOVEL TREATMENT OF NECROTIZING ENTEROCOLITIS

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AUB Approval: #44032

Hypothesis and Proposal: Necrotizing enterocolitis (NEC) is a devastating gastrointestinal emergency affecting preterm neonates. In the past, amniotic fluid stem cells (AFSC) improved intestinal injury related to experimental NEC but are difficult to administer. We evaluated whether conditioned medium (CM) derived from ***human*** AFSC have similar effects.

Methods: C57BL/6 mice were divided into (1) control (breast fed; n=11); (2) NEC (NEC + phosphate buffered saline [PBS] administration; n=10); and (3) CM (NEC+CM administration; n=10). Experimental NEC was induced from post-natal day (P) 5-9 by gavage feeding of hyperosmolar formula four times daily, hypoxia for 10 minutes prior to all feeds, and lipopolysaccharide administration. Intraperitoneal injections of PBS or CM were given on P6 and P7. Ileum was harvested on P9. Data were analyzed by ANOVA with mean ± SEM.

Results: Histological scores revealed that CM administration during NEC induction reduced the incidence of intestinal injury back to control levels. In addition, inflammatory markers *IL-6* and *TNF-α* (elevated during NEC induction) were recovered after CM administration. Lastly, significant rises in intestinal stem cell (*Lgr5*) and proliferation (*Ki67* by immunofluorescence) markers indicated recovery from injury after CM administration.

Conclusion: Administration of CM derived from ***human*** AFSC in experimental NEC is associated with reduced intestinal injury, reduced inflammation, increased stem cell expression, and enterocyte proliferation. This provides first evidence of the usefulness of human AFSC products in NEC.

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THE EFFECT OF SYNAPTIC ACTIVITY ON INTEGRATION OF TRANSPLANTED NEURAL PROGENITOR CELLS AND FUNCTIONAL RECOVERY AFTER SPINAL CORD INJURY

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Hypothesis and Purpose: Using a clinically relevant rat model of C6/C7 level spinal cord injury (SCI), the purpose of this project is investigating the role of synaptic activity on improved forelimb function observed in this model upon transplanting glial derived neurotrophic factor (GDNF)-expressing neural progenitor cells, derived from human induced pluripotent stem cells (hiPSC-NPCs), in the sub-acute phase of a clip-compression injury. We hypothesize that synaptic activity of hiPSC-NPCs is important for their differentiation, integration into local network, and functional recovery; and this effect can be interrogated by blocking neurotransmission with tetanus toxin light chain (TeTxLC). **Methods:** GFP^{+}GDNF-hiPSC-NPCs will be genetically modified using a *PiggyBac* transposon with a TetON system and a human synaptophysin 1 (hSYN1) promoter for neuron-specific expression of TeTxLC. Upon *in vitro* characterization of TeTxLC expressing cells by immunocytochemistry and whole-cell patch clamping, the *in vivo* effect of synaptic activity will be elucidated by transplanting immunodeficient Rowett Nude (RNU) rats with TetON-hSYN1::TeTxLC NPCs 2 weeks after a C6/7 SCI. During the 8 weeks after transplantation, animals will undergo neurobehavioral tests and motor evoked potential measurements, followed by sacrifice for *ex vivo* patch clamping, immunohistochemistry, and immune-transmission electron microscopy. **Results:** It is expected that even though TeTxLC neurons will be able to project appropriately, they will fail to maintain synaptic connections, resulting in reduced number of neurons, integration, and functional recovery. **Conclusion:** This project will highlight the importance of synaptic activity on recovery independent of other proposed stem-cell mediated repair mechanisms like remyelination, trophic support, tissue sparing, and immunomodulation.

THE EFFECT OF CONDITIONAL GDNF EXPRESSION IN IPSC-NPCS USING CELL STATE-SPECIFIC PROMOTERS FOLLOWING SPINAL CORD INJURIES

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Hypothesis and Purpose: Recent findings from our lab show that glial-derived neurotrophic factor (GDNF) expression in neural progenitor cells (NPC) enhances differentiation to neurons; increases synapse formation; and, promotes graft survival following transplantation. However, the ramifications of indefinite GDNF expression are unclear. To circumvent these ramifications, we are genetically modifying NPCs for progenitor state-specific GDNF expression. By limiting GDNF expression to the cell stages where it is most beneficial, we hypothesize that GDNF expression under a progenitor state-specific promoter will enhance functional recovery while mitigating deleterious effects. **Materials and Methods:** GFP^+hiPSC-NPCs will be genetically modified using a third-generation lentiviral system for neural progenitor-specific expression of GDNF under one of the following stem cell promoters: Nestin, Pax6, DCX, or Sox2. Upon the creation of a stable monoclonal cell line, we will perform *in vitro* characterization of GDNF expressing cells by qPCR, immunocytochemistry and whole-cell patch clamping. To validate the genetically modified GFP^+hiPSC-NPCs *in* vivo, we will perform cellular spinal transplants of cell-state specific or constitutive GDNF expressing cell lines into our labs established spinal cord injury model of RNU rats (n=6) and immunodeficient NOD-SCID mice. We will euthanize a rat weekly for 6 weeks to evaluate promoter strength and efficacy; and, euthanize mice 9 months post-transplant for assessment of tumour formation. **Expected Results:** hiPSC-NPC expression of GDNF under a progenitor state-specific promoter minimizes off-target effects and reduce the tumorigenic potential of transplanted cells while maximizing the neuroregenerative capabilities of hiPSC-NPCs. **Conclusion:** An in-depth analysis of conditional GDNF expression under several stem cell state-specific promoters will highlight the safety and ideal level of GDNF expression in NPCs after SCI. These insights will help to determine if future cell therapies should include GDNF, and if so for what duration.

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PREOPERATIVE ANEMIA HAS GENDER BASED DIFFERENCES IN IMMEDIATE POSTOPERATIVE MORTALITY

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Objective: The objective of the present study was to assess hemoglobin thresholds to prevent short-term mortality, adverse cardiac events, and immediate post-operative complications.

Methods: Data was extracted from the Vascular Quality Initiatives Database (VQI) at our institution from January 2010 to December 2017. After testing for differences in key baseline demographics, logistic regression analyses were running with hemoglobin and necessary covariates predicting outcomes. Anemia was defined as <135 g/L (<13.5 g/dL) in men, and <120 g/L (< 12.0 g/dL) in women. Predictive probabilities were saved from these models to create ROC curves. When appropriate, cut-offs were created for the ROC curves using Youden's index.

Results: There were a total of 1682 patients, with 1274 (76%) males (M) and 408 (24%) females (F). There were 249 carotid endarterectomies, 498 EVARs, 308 infrainguinal repairs, 213 open AAA repairs, 233 suprainguinal repairs, and 181 TEVARs. 38% (n=639) of the study population was anemic (Hb<135 in M, 120 in F). The average preoperative hemoglobin was 133 g/L. Preoperative hemoglobin was associated with in-hospital mortality (F $p < 0.0001$; M $p < .0001$), adverse cardiac events (M $p < 0.0001$; F $p < .02$) and post-operative complications (M $p < 0.001$; F $p = 0.008$). COPD played an important role in predicting in-hospital mortality (F $p = 0.008$; M $p = .01$), with a higher expected mortality in those with COPD. Predicted hemoblogin cutoffs were 130 g/L with COPD and 116 g/L without COPD in females and 127 g/L with COPD and 148g/L without COPD in males.

Conclusions: Preoperative anemia is a powerful predictor of immediate mortality, adverse cardiac events and postoperative complications. There are important gender differences in risk of adverse events and preoperative anemia should be aggressively treated in vascular surgery patients.

TARGETING LATENT CYTOMEGALOVIRUS (CMV) WITH A NOVEL FUSION TOXIN PROTEIN USING *EX VIVO* LUNG PERFUSION (EVLP) AS A PLATFORM

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Hypothesis and Purpose: Donor to recipient CMV mismatch leads to high incidence of CMV infection post lung transplant causing devastating impacts in patient outcomes. EVLP is a potential platform to modify grafts prior to transplantation. We hypothesized that EVLP delivery of F49A-FTP, a fusion toxin protein that targets with ultra-high affinity cells expressing the latent CMV protein *US28*, may safely clear latent CMV from donor lungs, thus attenuating viral reactivation post transplant. **Methods:** Human donor lungs rejected for transplantation were placed on EVLP alone (n=2) or EVLP with 1mg/L of F49A-FTP (n=2) for 6 hours. Lung viral burden was quantified through RT-qPCR measurements of US28 and since F49A-FTP induces apoptosis of the cells expressing US28 (CD34+ stem cells and CD14+ monocytes), flow cytometry was used to quantify the proportion of these cells in lung tissue collected pre- and post-perfusion. **Results:** F49A-FTP was delivered through vasculature of the lung on EVLP and no evident physiological adverse events were noticed. Regarding viral burden, a 5-fold decrease in US28 levels was observed in the F49A-FTP group compared to only a 0.4-fold in control group. The ratio of post to pre perfusion live and apoptotic CD34 and CD14 cells was used to assess the efficacy of F49A-FTP to kill infected cells. Lungs perfused with F49A-FTP demonstrated lower live CD34+ and higher apoptotic CD34+ cell frequency after perfusion vs control lungs (mean ratio live cells = 0.65 vs 1.08; apoptotic cells = 2.87 vs 1.00). Same trend was not noticed in CD14+ cells. **Conclusion:** Initial results from our study shows that F49A-FTP has the capacity to decrease CMV latent burden in donor lungs using EVLP with no evident acute toxic effects.

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SYNERGISTIC INTERACTION BETWEEN RISK FACTORS INCREASES COMPLICATION RATES FOLLOWING MICROVASCULAR BREAST RECONSTRUCTION

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Purpose: Microvascular breast reconstruction is a complex procedure that can be associated with high complication rates. While a number of individual predictors of peri-operative complications have been identified, few studies have explored interaction between risk factors. Understanding the synergistic effects of multiple risk factors is central to accurate and personalized pre-operative risk prediction.

Methods: We conducted a retrospective cohort study of patients who underwent microvascular breast reconstruction at our institution between 2009 and 2017. All intra- and post-operative complications were recorded. A multivariable logistic regression exploratory model identified independent predictors of complications. Interactions between individual variables were then assessed using the Relative Excess Risk Index (RERI) and Synergy Index (SI).

Results: Nine hundred and twelve patients were included in the study and 26.1% experienced at least one post-operative complication. Obesity (OR1.54, p=0.009), immediate reconstruction (OR1.49, p=0.028), and comorbidities (OR1.43, p=0.033) were identified as independent predictors of complications. Obesity and comorbidities had significant synergistic interactions with immediate reconstruction (RERI 0.86, SI 2.35, p=0.0002; RERI 0.54, SI 1.78, p=0.001), bilateral reconstruction (RERI 0.12, SI 1.15, p=0.002; RERI 0.59, SI 3.16, p=0.005) and previous radiotherapy (RERI 0.62, SI 4.43, p=0.01; RERI 0.11, SI 1.23, p=0.040). Patients undergoing immediate breast reconstruction who were both obese and smokers had a 12-fold increase in complication rates (OR 12.68, 95% CI 1.36-118.46, p=0.026) with a very strong synergistic interaction between variables (RERI 10.55, SI 10.33).

Conclusions: Patient and treatment related variables interact in a synergistic manner to increase the risk of complications following microvascular breast reconstruction.

IDENTIFYING BARRIERS TO COMPLETION OF ADJUVANT THERAPY IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME

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Hypothesis and purpose: This study aims to identify the key factors that are influencing one third of medically eligible newly diagnosed glioblastoma (GBM) patients diagnosed at St. Michael's Hospital to choose to decline or withdraw from the recommended regimen of chemoradiation, the Stupp protocol. We hypothesize that there are underlying factors that influence a GBM patient's decision to decline or withdraw from the Stupp protocol, other than those related to the disease itself, and that these factors fall within Kim et al.'s (2018)* Conceptual Framework for Individual and Family End-of-Life Decision Making. **Methods**: In this mixed methods study, data will be collected from two sources: medical chart review and semi-structured interviews. During the chart review of newly diagnosed GBM patients (n=150), factors that are common amongst patients who have not completed treatment will be analyzed in order to identify profiles of those at risk of decline or withdrawal from care. Next, semi-structured interviews will be conducted with three groups: newly diagnosed GBM patients who have declined or withdrawn from treatment (n=20), caregivers (n=20), and healthcare providers (n=10). Data collected from the interviews will be analyzed to identify common themes or factors related to the decision to decline or discontinue treatment and the decision-making process. **Results:** Data collection is underway and we anticipate that analysis will be completed by May. **Conclusion**: The results of this study may be used to inform practitioners by identifying barriers to completion of chemoradiation which in turn, may lead to the identification of patient profiles at risk of withdrawing from care. Identifying these risk factors may help in the development of tailored resources that can be used to better support GBM patients in the treatment and decision-making process. The findings from the analysis will also offer supporting or non-supporting evidence to Kim et al.'s framework.

*Kim, K., Heinze, K., Xu, J., Kurtz, M., Park, H., Foradori, M., & Nolan, M. T. (2018). Theories of Health Care Decision Making at the End of Life: A Meta-Ethnography. Western Journal of Nursing Research, 40(12), 1861–1884. https://doi.org/10.1177/0193945917723010

ORTHOPAEDIC ALIGNMENT TOOLS FOR GUIDEWIRE AND SCREW INSERTION: PATH TO CLINICAL TESTING

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Introduction: In femoral intramedullary nailing (IMN) procedures, guidewire alignment achieved under fluoroscopy in one plane is often lost while adjusting the alignment in the orthogonal plane. A novel surgical tool, Femoral Antegrade Staring Tool (FAST), was created to facilitate entry point selection and alignment of the guidewire. Sawbone and cadaveric testing demonstrated positive results and the next step in the path to clinical translation of this technology is in vivo evaluation focused on ease of use and workflow.

Aim: To prepare the FAST technology to enable an observational in vivo clinical evaluation.

Approach: The FAST prototype had to be advanced to clinical readiness. Analysis of the tool, its' materials and manufacturing methods resulted in redesign for better integration with cleaning, sterilization and OR assembly. Minimization of parts and utilization of press fits rather than screws reduced cleaning and OR assembly requirements. Further changes were required to ensure compatibility with reaming. Using titanium k-wires provided sufficient flexibility to accommodate the curvature of FAST at a diameter matched to IM reamers. Training materials were developed for surgeons, nurses and research staff. Creating a protocol and getting ethics and Sunnybrook approval required consultations with surgeons, the Research Ethics Board, OR Services, the Medical Device Reprocessing Centre, and research teams.

Results and Conclusion: The redesigned FAST device has gained approval from the REB, OR Services and the MDRC to be used in first in human trials. Pilot clinical testing (N=10 patients) will commence in April, 2019 and will support a larger clinical study to evaluate the device's efficacy. The success and clinical interest in FAST thus far have motivated expansion of this technology into a similar tool redesigned for screw insertion during pelvic surgery.

THE DEVELOPMENT AND EVALUATION OF A TOOL TO ASSESS COMPETENCE IN WOUND MANAGEMENT

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Background: Diabetic foot wounds comprise a third of diabetes-related healthcare expenditures, and are the primary cause of amputation in Canada. Few studies focus on how to teach and assess wound management. Given the importance of 'assessment for learning' in Competence by Design, we aimed to develop, and examine specific sources of validity evidence for, an assessment tool of wound management competencies.

Method: We organized our tool development and validation process using Kane's framework. Using a nominal group process involving 9 Canadian experts in diabetic wound management, we developed the tool items, and two 10-minute simulation-based testing scenarios. We then assessed 74 participants' (61 physicians, 13 non-physicians) performance during the two scenarios. Reliability was evaluated using Generalizability Theory. Test-retest reliability was measured with intraclass correlation coefficient (ICC) comparing raters' scores across scenarios. We also compared performance scores across the three levels of experience.

Results: Internal consistency was excellent (Cronbach's alpha = 0.953). Test-retest reliability was excellent (ICC=0.971, CI 0.954, 0.982, average measures). Pooled inter-rater reliability was good (ICC=0.827 CI 0.806, 0.845, average measures). Scores differed significantly ($p<0.01$) between novice clinicians and intermediate and expert clinicians (latter two did not differ). Our Generalizability coefficient was 0.871.

Conclusion: The accumulated validity evidence suggests our tool can be used to assess novice clinicians' competence in diabetic wound management during simulated cases. We plan to continue establishing validity evidence for use in other settings.

NOTCH-INHIBITION: A NOVEL STRATEGY TO REVERSE IMMUNOSUPPRESSION IN BASAL-LIKE BREAST CANCER

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Background: Basal-like breast cancer (BLBC) is an aggressive malignancy with poor prognosis and without effective targeted treatment. BLBCs are heavily infiltrated by tumor-associated macrophages (TAM) and cytotoxic-T-lymphocytes (CTL) and both are strongly correlated with outcome. We have shown that activation of the Notch pathway drives BLBC and more recently have discovered that Notch regulates the expression of pro-inflammatory cytokines, IL1β and CCL2, that promote TAM recruitment to the tumor microenvironment and tumor progression. Recent clinical trials have demonstrated immune checkpoint blockade (ICB) as a strategy to prevent cancer cells from silencing CTL-mediated attack. However, CTLs can be inactivated by TAMs, producing ICB resistance. We **hypothesize** that through TAM recruitment, Notch suppresses CTL anti-tumor immunity, producing ICB-insensitive tumors. This project will explore novel anti-Notch and anti-TAM immunotherapeutic strategies to increase CTL:TAM ratios in Notch-activated BLBC, making them susceptible to ICB. **Methods and Results**: Murine basal-like mammary tumor 4T1 cells were grafted into mammary fat pads of BALB/c mice. These mice were subjected to Notch inhibition (LY411575), ICB (anti-PD1; RMP1-14), or control treatments for 12-days. Then, each treatment group was randomly allocated to continue the same treatments or switch to either Notch inhibition or anti-PD1 to complete treatment for a further 12-days. As a control, clodronate liposome was used for macrophage depletion in the tumor microenvironment, followed by or combined with anti-PD1 treatment. Compared to the control (mono therapies) we found a synergistic therapeutic effect with Notch inhibition followed by anti-PD1 treatment. **Conclusion**: These pre-clinical data support sequential Notch inhibition and anti-PD1 treatment as a promising therapeutic strategy in BLBC.

MUSCULOAPOENEUROTIC JUNCTIONS AND MYOFASCIAL TRIGGER POINTS IN THE HUMAN TRAPEZIUS

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Hypothesis and Purpose: The purpose of this study was to quantify and compare the 3D musculoaponeurotic architecture of trapezius to patterns of myofascial trigger points (MTrPs) using digitized data from cadaveric specimens. We hypothesized that there would be a correlation between MTrP patterns and musculoaponeurotic junctions in trapezius.

Methods: The connective and contractile tissue elements of trapezius in 4 embalmed specimens were meticulously dissected, serially digitized at the fibre bundle (FB) level (MicroScribe® G digitizer), quantified, and modelled (Autodesk® Maya®). The connections between connective and contractile elements (musculoaponeurotic junctions) were mapped on the 3D models and compared to established patterns of MTrP presentation in trapezius. Architectural parameters were also computed for the entire muscle and partitions thereof.

Results: FBs throughout the muscle volume span between independent medial and lateral aponeuroses, resulting in large areas of musculoaponeurotic junction. The 3D approach employed in this study revealed that aponeurotic tissue in trapezius is far more extensive than apparent from the superficial surface of the muscle. These deep and/or intramuscular aponeurotic projections visually correlate with the MTrP patterns of prevalence published by Travell and Simons – the current 'gold standard' for myofascial pain diagnosis and treatment.

Conclusion: This study revealed that there is a close relationship between musculoaponeurotic junctions and MTrPs in trapezius. Additional imaging and clinical studies are warranted to further investigate how these regions may be related to MTrP etiology and/or pathophysiology.

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THE INDUCED MEMBRANE TECHNIQUE: EFFECTS OF ANTIBIOTIC-IMPREGNATED SPACERS ON HEALING OF A CRITICAL-SIZE FEMORAL DEFECT IN A RAT MODEL

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Purpose and Hypothesis: This study seeks to evaluate the effect of adding antibiotics to the polymethylmethacrylate (PMMA) spacer, as part of the induced membrane technique (IMT), on bone healing in a rat model of segmental defect. We hypothesize that the presence of antibiotics, at both high and low doses, will have no significant impact on healing outcomes.

Methodology: Male Fischer 344 rats are randomly divided into three groups (n=10) according to the spacer used during the first stage of the IMT: **1)** Control (PMMA alone), **2)** Low-dose antibiotics (1.2 g tobramycin + 1.0 g vancomycin per 40 g of PMMA), **3)** High-dose antibiotics (3.6 g tobramycin + 3.0 g vancomycin per 40 g of PMMA). We create a 5-mm defect in the femoral diaphysis of each rat. The bone is then stabilized with a plate and screws followed by spacer insertion into the defect. Four weeks later, we carefully replace the spacer with bone graft through an incision in the membrane that has formed around the defect. Radiographs are then taken biweekly and scored by two orthopedic surgeons in a blinded fashion to quantify the extent of bone healing. Twelve weeks after grafting, we euthanize the rats and collect the femora. The bone volume and the bone volume fraction at the defect site will be quantified by micro-computed tomography imaging and analysis. Biomechanical testing in torsion will be performed to determine the yield point, maximum torque, and maximum stiffness.

Results: We were able to develop a consistent and effective model of the IMT in Fischer 344 rats. The bone graft was standardized to contain a morselized mixture of vertebral bodies, femora and tibiae. Reliable union rates were seen at 12 weeks post bone graft. We are currently analyzing radiographic data and will proceed to post-mortem analysis.

Conclusion: Our study may offer assurance to continue combining antibiotics with PMMA or support the need for re-evaluation of this method of infection treatment and/or prophylaxis.

3D ANATOMY OF THE ARTICULAR BRANCHES SUPPLYING THE GLENOHUMERAL JOINT: IMPLICATIONS FOR NERVE BLOCK AND RADIOFREQUENCY ABLATION

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Purpose and Hypothesis: In this cadaveric study we investigated the 3D innervation patterns of the glenohumeral joint (GHJ) and identified the key ultrasound (US) landmarks for image-guided radiofrequency ablation (RFA). It is hypothesized that sensory nerves supplying the GHJ can be localized and targeted in 3D space by using anatomical landmarks visible with US.

Methods: Fifteen specimens were serially dissected. The muscle volumes, nerves, and bony surfaces associated with the GHJ were digitized with a Microscribe™ G2X Digitizer and reconstructed in 3D using Autodesk® Maya®.

Results: The GHJ was found to be innervated by articular branches of the suprascapular nerve (SSN), axillary nerve (AN), and nerves to subscapularis (NS). The SSN provided a significant contribution to the superior-posterior aspect of the capsule providing 4-6 branches. The AN supplied the anterior-inferior and posterior-inferior aspects of the capsule. The AN provided 1-2 branches anteriorly and after coursing through the quadrangular space gave off an additional 1-3 branches posteriorly. The superior-anterior capsule was innervated by 1-2 branches of the NS. Landmarks to localize the articular branches innervating the GHJ included the spinoglenoid notch (SSN), superior border of the quadrangular space (AN), and inferior border of the coracoid process (NS).

Conclusion: Based on these findings the spinoglenoid notch, superior border of the quadrangular space, and inferior border of the coracoid process could be used as clinical landmarks to capture the nerves innervating the GHJ. To assess the feasibility of these landmarks a cadaveric needling study will follow.

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MANAGEMENT OF HIGH PATIENT-REPORTED PAIN SCORES IN NON-CURATIVE PANCREATIC ADENOCARCINOMA: A POPULATION-BASED ANALYSIS

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Hypothesis and Purpose: Pain is a common debilitating symptom in pancreas adenocarcinoma (PA). Multi-disciplinary pain management for patients reporting high pain scores (HPS) is suspected to be related to certain patient factors, but data is lacking. We examined the use of, and factors associated with, pain-directed interventions for HPS in non-curative PA.

Methods: We linked administrative databases and identified non-resected PA patients diagnosed in 2010-2016 reporting ≥1 patient-reported Edmonton Symptom Assessment System (ESAS) score. HPS was defined as ESAS ≥4 out of 10. Outcomes were pain-directed interventions: opiates (assessed in patients ≥65 years old with universal drug coverage), nerve-block, and radiation therapy around the time of HPS. We also examined reduction in pain score (≥1 point) following pain-directed intervention. Modified Poisson regression examined factors associated with use of opiates and other pain-directed intervention.

Results: Of 2,623 patients, 1,621 had HPS at a median of 38 days (inter-quartile range: 21-69) post-diagnosis. Of those with HPS, 75.6% received opiates, 13.5% radiation, and 1.2% nerve-block. The pain score decreased in 62.2% after opiates, 73.8% after radiation, and 100% after nerve-block. On multivariable analysis, no patient factor was associated with receipt of non-opiate pain-directed intervention for HPS. In patients ≥65 years old, more advanced age was associated with lower odds of opiate use.

Conclusion: Opiates are the most common pain-directed intervention for non-curative PA. Despite effectiveness in reducing high pain score, radiation therapy and nerve-blocks are seldomly used. The lack of association of pain-directed interventions with patient factors points toward decision-making dependent on established practice patterns. This data should encourage more consideration of non-opiate interventions.

BOWEL SAFETY MARGINS WITH MRGHIFU THERMAL ABLATION IN A PRECLINICAL PORCINE MODEL

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Hypothesis and purpose: To minimize the risk of injury to the bowel, current protocols for HIFU recommend maintaining a margin of 4 cm. However, this margin has not been scientifically delineated. The objective of this study was to create an *in vivo* porcine model to refine bowel safety margins for thermal ablation using MRgHIFU as a proof of concept.

Materials and Methods: Pigs (n=2, mean weight 22 kg) underwent a laparotomy. A 4cm gel marker (Aquaflex®, Parker Labs) was placed in a pocket within the retroperitoneal muscle. A 10 cm segment of small bowel was fixed to the retroperitoneal wall with a Penrose drain through the mesentery. Pigs were imaged with a 3T MRI (Philips Achieva, Best, Netherlands) which enabled localization of the gel markers. HIFU treatment was performed on a Sonalleve V1 HIFU table (Profound Medical, Toronto, Canada) using a soft tissue ablation protocol (acoustic power100 W, sonication duration 20s at 1.2MHz). Sonications on the gel marker within the muscular layer was 1.0 cm and 1.5 cm from the nearest bowel. Afterwards, bowel segments were collected for histological analysis.

Results: The Penrose drain allowed stable but not restrictive fixation of small bowel near to the fiducial marker. The distance from the fiducial and sonication to the bowel wall was measured with MRI. This simulated the naturally fixed duodenum, which could not be used due to its proximity to ribcage. Immediate necrosis of bowel occurred at both 1.0 and 1.5 cm distance from HIFU therapy.

Conclusions: This porcine model enables reproducible positioning of fixed bowel in relation to the abdominal wall, which will help to determine a safety margin to bowel with thermal ablation using MRgHIFU.

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A DYNAMIC IN VIVO ULTRASOUND STUDY OF THE SUPERIOR, MIDDLE, AND INFERIOR PARTS OF INFRASPINATUS

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Hypothesis and Purpose: In this *in vivo* ultrasound (US) study of the superior (SP), middle (MP), and inferior (IP) parts of infraspinatus, changes in muscle architecture were investigated in 4 positions: relaxed, 90º abduction (AB), 90º abduction/ maximum external rotation (ER) and 90º abduction/maximum internal rotation (IR). It is hypothesized that there will be significant differential changes in muscle architecture of SP, MP, and IP between the 4 positions.

Methods: The SP, MP, and IP were scanned bilaterally in 20 participants with no previous history of shoulder injuries. The US protocol was standardized using anatomical landmarks. Each part was scanned in the four study positions. Mean muscle thickness (MT), cross-sectional area (CSA), fibre bundle length (FBL), and pennation angle (PA) of each part were quantified and compared (one way ANOVA, followed by independent samples t tests) to asses functional activation patterns.

Results: In SP: 1) mean PA, MT, and CSA of AB, ER, and IR were significantly different from the relaxed position; 2) no significant difference between IR and ER. In MP: 1) Mean CSA and MT were significantly greater on ER compared to IR. 2) 90º AB was significantly greater than the relaxed position, and significantly less than ER. In IP: 1) mean FBL on IR was significantly less than the relaxed position. 2) mean CSA and MT were significantly greater on IR than in the relaxed position.

Conclusion: The patterns of relative architectural changes in each part of infraspinatus suggest that SP may have a greater role as an arm abductor, while MP may be activated more in abduction and external rotation, and IP in abduction and internal rotation.

INHIBITION OF NLRP3 INFLAMMASOME POST-BURN IMPAIRS WOUND HEALING

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Hypothesis and Purpose: Survival of burn patients is contingent on effective wound healing, a complex process that requires coordinated responses of myeloid cells and inflammatory pathways. NLRP3, which serves as a platform for secretion of pro-inflammatory cytokines, is implicated as a central regulator of wound healing. However, its role during the acute dermal and epidermal regeneration in the context of burns is unknown.

Methods: Wild-type (WT) and NLRP3$^{-/-}$ knockout were exposed to a 30% TBSA scald burn. Mice were sacrificed at 3 and 7 days post-burn. Gene expression was conducted via RT-PCR. Trichrome staining assessed collagen deposition and granulation tissue formation. F4/80 staining compared macrophage infiltration. Flow cytometric analysis characterized macrophage distribution and profile.

Results: NLRP3, IL1□□□□□□□□□□ expression was upregulated in skin post-burn, and these changes were non-existent in NLRP3$^{-/-}$. NLRP3$^{-/-}$ skin demonstrated significantly less macrophage infiltration and higher expression of M2 anti-inflammatory macrophage markers Arg1 and Fizz1 compared to WT. Trichrome staining of NLRP3$^{-/-}$ skin showed decreased collagen deposition.

Conclusion: NLRP3$^{-/-}$ demonstrate impaired wound healing, indicating that NLRP3 is protective in burn wounds via production of inflammatory mediators, macrophage recruitment and polarization to M1 pro-inflammatory phenotype. Post-burn activation of NLRP3 in skin plays a central role in mediating inflammatory processes leading to improved wound healing.

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A THREE-DIMENSIONAL ARCHITECTURAL ANALYSIS OF THE INNERVATION OF TIBIALIS ANTERIOR MUSCLE

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Hypothesis and Purpose:

The purpose of this pilot study was to document the intramuscular innervation pattern of TA volumetrically to improve Spatially Distributed Sequential Stimulation (SDSS) techniques. It is hypothesized that TA is neuromuscularly partitioned.

Methods:

One formalin embalmed TA muscle (88-year-old male) without any evidence of surgery/pathology was serially dissected, digitized, and modelled in 3D. The intramuscular innervation pattern was analyzed and incorporated into the SDSS by our collaborator.

Results:

To innervate TA, the deep fibular nerve gives off two secondary nerve branches: a superior and inferior branch, which ramify intramuscularly to supply the proximal third of TA, the largest part of the muscle belly. The inferior branch also gives off a long lateral branch that courses along the posterior border of TA, superficial to the interosseous membrane with the anterior tibial artery. The lateral branch was found to give off 11 small nerves that entered the middle third of TA, and 2 branches that supplied the distal third of TA. Overlapping innervation was only observed in the middle third.

Conclusion:

This is the first study to provide cartesian coordinate data to construct volumetric models of the intramuscular innervation of TA, as in situ. This will enable a better understanding of TA electrode placement for FES therapy to reduce rapid fatiguing by stimulating individual sub-components of the muscle and provide a clinical map of nerve regeneration following trauma.

GEOGRAPHIC DISPARITIES IN CARE AND OUTCOMES FOR NON-CURATIVE PANCREATIC ADENOCARCINOMA: A POPULATION-BASED STUDY

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Hypothesis and Purpose:

Access to care and its impact on outcomes is unknown for non-curative pancreatic adenocarcinoma (PA). We examined whether care delivery and survival for PA is related to geographic distribution of cancer-care-centres across Ontario.

Methods:

A population-based analysis identified non-resected PA (2005-2017). Outcomes were medical oncology consultation, care by high-volume medical oncology provider, cancer-directed therapy (CDT), and survival. Geographic information system analysis was used to map outcomes across census-divisions. Multivariate models examined the adjusted effect of cancer-care-centre density by km^2 on outcomes.

Results:

Of 15,970 patients surviving a median of 3.3 months (IQR: 1.2-8.6), 38.5% received CDT, 65.6% had medical oncology consultation, and 17.1% saw a high-volume provider. Regions of comparable survival and care delivery were clustered throughout Ontario. Cancer-care-centres were distributed unevenly, with higher levels in Southern Ontario. Higher-level care centres clustered in regions with higher rates of consultation, CDT, and survival. Lower cancer-care-centre density was independently associated with lower likelihood of consultation and inferior survival, but not with CDT and care by high-volume providers.

Conclusion:

The majority of patients with non-curative PA did not receive CDT. Care delivery and survival exhibited high geographic variability. Cancer-care-centre density influenced access to medical oncology assessment and survival, but not high-volume provider care or CDT.

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THE ROLE OF METFORMIN IN BREAST CANCER GENETICS

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Hypothesis and purpose: Both *in vivo* and *in vitro* studies have demonstrated that metformin has a greater effect on cell proliferation in triple negative breast cancer. However, there have not been studies focusing on the effect of metformin on triple negative breast cancer (ER-/PR-/Her2) in patients. We hypothesis that metformin is associated with a reduced incidence of triple negative breast cancer.

Methods: We conducted a retrospective case-controlled study of a cohort of patients who underwent surgical interventions for their primary breast cancer between 2010-2015 at Princess Margaret Hospital (Toronto, ON) and Sunnybrook Health Sciences Centre (Toronto, ON). A chart review of operative room reports, pathology reports, and consults notes to determine past medical history and medications has been performed.

Results: We have reviewed 1020 charts. The proportion of triple negative breast cancers patient who are taking metformin versus not taking metformin will be compared to the corresponding groups who are not triple negative using a Chi-square analysis. A univariate and a multi-variate analysis will be performed to assess the correlation between medication use and the incidence of breast cancer. (Statistical analysis ongoing)

Conclusion: We aim to identify pharmacologic agents, such as metformin, that may be associated with a decreased incidence of triple negative breast cancer.

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DOES LEFT ATRIAL APPENDAGE OCCLUSION IN LVAD PATIENTS IMPACT OUTCOMES: A SINGLE CENTRE STUDY

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Hypothesis/Purpose: The use of left atrial appendage occlusion (LAAO) for stroke prevention following cardiac surgery remains contradictory. No data has been presented on the outcomes of LAAO during left ventricular assist device (LVAD) implant. Therefore, we studied the effects of LAAO during LVAD implantation on postoperative risk of stroke and mortality. We hypothesize that patients undergoing LVAD implant with concurrent LAAO will have a lower risk of stroke post operation. **Methods**: This single-centre retrospective cohort study included patients who underwent LVAD implantation between October 2004 and April 2018. We performed a univariate Cox regression analysis to assess the effect of LAAO on the risk of post-operative stroke and mortality. **Results**: Among 156 patients who underwent LVAD implantation (mean age, 52.5 [SD 12.8] years, 34 [21.8%] females), 14 (9.0%) underwent concurrent LAAO. There were no significant differences in baseline characteristics except for gender (p=0.039). There were no significant differences in intraoperative identification of thrombus, stroke, or embolism between groups. Patients who received LAAO had longer bypass time (p=0.035), ICU stay (p=0.006), and days hospitalized (p=0.019) compared to those without LAAO. Median follow-up was 7 months [range 0-92]. A total of 23 strokes and 48 deaths were identified in our cohort and LAAO was not associated with a reduced risk of stroke (HR 1.014 [0.233-4.419]; p=0.985) or mortality (HR 1.209 [0.432-3.384]; p=0.718). **Conclusion**: Among patients undergoing LVAD implantation, concurrent surgical LAAO was independently associated with a clinically irrelevant increase in bypass time and clinically relevant increase in ICU and hospital length of stay. Furthermore, LAAO was not associated with a reduced risk of subsequent stroke and all-cause mortality. Further research including data from large registries is required to definitively determine the role of surgical LAAO during LVAD implantation.

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SYSTEMIC PROTEIN KINASE INHIBITION REDUCES LOCAL INFLAMMATION AFTER CERVICAL SPINAL CORD INJURY

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Purpose and Hypothesis: The disruption of blood-spinal cord barrier (BSCB) by the physical trauma is a major challenge in spinal cord injury (SCI), as it results in the infiltration of reactive immune cells that cause further secondary damage to the spinal cord. Therapeutic stabilization of BSCB can potentially attenuate the immune cells migration and improve SCI recovery. The purpose of this study is to examine the effects of systemic protein kinase inhibition on BSCB integrity, and to determine its efficacy as a treatment for SCI. It is hypothesized that midostaurin—a clinically approved protein kinase inhibitor—mitigates the secondary SCI pathogenesis by reducing immune cells migration.

Methods: SCI was induced in female Wistar rats using the clip-compression injury model at C6-7. All subjects were sacrificed at 24-hours post-operation, and the total RNA and protein were extracted from the spinal cord to evaluate the molecular changes.

Results: Administration of 25 mg/kg midostaurin reduced the phosphorylated GSK3 and STAT3 at the injury epicenter (1-day post-injury). The transcriptional analysis reveals downregulation of adhesive and migratory genes including JAM2, THY1, and ITGB1. This ultimately leads to the mitigation of pro-inflammatory markers, such as fractalkine, IL-1a, and IL-5 at 1-day post-injury.

Conclusions: This study demonstrates that systemic protein kinase inhibition is an effective strategy for preventing secondary SCI damage, which can have a significant impact on the enhancement of neuroprotective regime applied upon traumatic SCI.

DOWNREGULATION OF PTEN EXPRESSION PROVIDE INTESTINAL PROTECTION AGAINST EXPERIMENTAL NECROTIZING ENTEROCOLITIS

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Hypothesis and Purpose: Downregulation of phosphatase and tensin homolog (PTEN) in intestinal epithelial cells has been previously shown to protect against intestinal ischemia-reperfusion injury. We hypothesize that PTEN inhibition can decrease the intestinal injury associated with experimental necrotizing enterocolitis (NEC).

Methods: NEC was induced in C57BL/6 mice by hypoxia, gavage feeding of hyperosmolar formula and lipopolysaccharide administration between postnatal days 5 and 9. NEC mice received daily intraperitoneal injection of either phosphate buffered saline (PBS; n=10) or the inhibitor of PTEN bisperoxovanadium (bpv; 0.1 μM; n=10). Breast fed pups were used as control and were not exposed to bpv (n=10). Clinical status was assessed on P9 using a clinical sickness score. Distal ileum was harvested and analyzed for PTEN gene expression, mucosal injury (score 3 = maximal damage), inflammation and intestinal stem cell (ISC) survival/proliferation. Groups were compared using one-way ANOVA with a Bonferroni post test.

Results: Compared to control, NEC+PBS mice had poorer clinical status, higher NEC scores, enhanced IEC apoptosis and autophagy, reduced IEC migration activity, decreased ISC proliferation, increased expression of PTEN mRNA, as well as increased expression of IL-6, TNF-α and Lgr5. Administration of bpv significantly decreased these NEC-induced deleterious effects.

Conclusion: PTEN inhibition protects the intestine from the epithelial damage and inflammation caused by NEC. This study contributes to our understanding of NEC pathophysiology and indicates that PTEN is a potential target for NEC therapy.

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COST-EFFECTIVENESS ANALYSIS OF MOTION PRESERVING SURGERIES FOR WRIST ARTHRITIS

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Purpose: Proximal row carpectomy (PRC) and four corner fusion (FCF) have been widely compared as motion-preserving strategies to treat wrist osteoarthritis (OA). With the recent introduction of the improved total wrist arthroplasty (TWA), it is important to compare it to previous options. We conducted a cost-effectiveness analysis to answer the question: "Which motion preserving surgical strategy, 1) FCF, 2) PRC, 3) TWA, used for the treatment of wrist OA is the most cost-effective?" Hypothesis: PRC is the most cost-effective surgical procedure for wrist OA.

Methods: A simulation model was created to model a hypothetical cohort of wrist OA patients (mean age of 45 years old) presenting with painful wrist and having failed conservative management. Three initial surgical treatment strategies 1) FCF, 2) PRC, or 3) TWA were compared from a hospital perspective. Outcomes included clinical outcomes and cost-effectiveness outcomes (quality-adjusted life years (QALYs) and cost) over a lifetime.

Results: The highest complication rates were seen in the FCF cohort: 27.1% compared to 20.9% for TWA and 17.4% for PRC. Secondary surgery was common for all procedures; 87% for FCF, 56% for PRC and 46.5% for TWA. PRC generated the highest QALYs (30.5) over the lifetime time horizon, compared to 30.3 for TWA and 30.2 for FCF. PRC was the least costly; the mean expected lifetime cost for patients starting with PRC was $4,285, compared to $5,301 for TWA and $8,033 for FCF.

Conclusions: Our study supports the use of PRC as the initial surgical interventions to treat patients with SNAC or SLAC wrist OA having failed non-surgical management; however, when PRC was contraindicated, this model supports TWA as the preferred strategy.

DEVELOPMENT *of a* CLINICAL PREDICTION MODEL *for* CENTRAL CORD SYNDROME: *an* EVALUATION *of* MOTOR RECOVERY *and the* EFFECTIVENESS *of* EARLY SURGERY

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HYPOTHESIS & PURPOSE: In patients with acute central cord syndrome (CCS), we sought to: 1) develop a clinical prediction model for neurological outcome; and 2) evaluate the effect of early surgery (< 24 hrs) on neurological recovery. We hypothesized: 1) it is feasible to predict motor recovery following CCS; and 2) early surgical decompression may be associated with improved motor recovery in patients with CCS, particularly those with more severe injury.

METHODS: Patients with CCS, defined by AIS grade C or D and ASIA LEMS–UEMS ≥ 5, were identified from two prospective, multi-center SCI datasets (NACTN, STASCIS). A clinical prediction model was developed by multiple linear regression; the outcome was change in ASIA motor score (AMS) at 1-year. Covariates for model construction were chosen a priori: 1) age; 2) baseline AMS; 3) baseline AIS grade (C vs. D); 4) time to surgery (early [< 24 hrs] vs. late [≥ 24 hrs]); and 5) time to surgery × AIS grade. Effect sizes were summarized by β coefficients. Multicollinearity was assessed by VIF. Internal validation was performed by bootstrapping (R=200). The model was externally validated in a cohort of patients from the NASCIS III trial.

RESULTS: A total of 211 patients were eligible. β coefficients were significant for all variables in the model: age (-0.12, P=0.04); baseline AMS (-0.71, P<0.01); AIS grade (9.69, P=0.01); time to surgery (12.67, P<0.01); AIS grade × time to surgery (-13.18, P<0.01). There were no concerns relating to collinearity. The mean R^2 value across bootstrap replications was 0.66 (95% CI 0.65 to 0.67). In patients with AIS C injury, early surgery resulted in significantly improved motor recovery (marginal mean: +12.7, 95% CI 5.8 to 19.6); there was no significant difference in recovery with early surgery in patients with AIS D injury (marginal mean: -0.5, 95% CI -4.4 to 3.3). The model showed good external validity, with R^2 = 0.65 in the validation cohort (N = 38).

CONCLUSION: Motor recovery after CCS may be predicted by age, AMS, AIS grade, and time to surgery. Early surgery improves recovery, particularly in patients with more severe injury.

PAIN IN CHILDREN WITH BRACHIAL PLEXUS BIRTH INJURIES

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Hypothesis and Purpose: Chronic pain following brachial plexus birth palsy (BPBI) remains poorly understood. The onset of pain following BPBI is atypical for a nerve injury in that it is delayed, typically occurring in late childhood or adolescence; as such, it has been vastly under-recognized. The goal of this study was to establish the prevalence of pain in children and adolescents with BPBI. **Methods:** A cross-sectional survey of children with BPBI was conducted to determine the point prevalence of pain in children 8 to 18 years. Eligible patients were identified from our prospective research database (1993-present; 98.5% population inclusion). The self-report survey included the Faces Pain Scale-Revised (FPS-R) and two questions regarding presence/absence of altered sensation and prior discomfort in either upper limb. Point prevalence of pain was determined by the proportion of patients with an FPS-R score greater than 0. Survey implementation followed the modified Dillman Tailor Design Method. **Results:** 684 children with BPBI were identified as eligible for study inclusion. Preliminary data from 202 respondents (63% female; mean age 15.1 $\pm$ 3.1 years) demonstrates a point prevalence of pain of 42% (n=76) in the affected upper limb. Among those reporting pain on the FPS-R, the scores ranged from 2-10: score 2 (n=45), 4 (n=22), 6 (n=15), 8 (n=1), 10 (n=1). 70% of patients reported altered sensations in their affected upper limb, and utilized a variety of musculoskeletal and neuropathic pain descriptors to qualify these sensations. When asked about prior pain in their affected upper limb, 60% reported pain. In the unaffected limb, current pain was reported by 4% and prior pain by 15% of children with BPBI. **Conclusion**: This study provides evidence that pain is common in older children and adolescents with BPBI, with a preliminary prevalence estimate of 42%. Children reporting pain on this survey are currently undergoing a more in-depth assessment of pain characteristics and pain interference to further clarify the pain experience in BPBI.

DRUG REPURPOSING: HIGH DOSE HUMAN IMMUNOGLOBULIN G FOR TREATENT OF TRAUMATIC CERVICAL SPINAL CORD INJURY

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Purpose and hypothesis: Neuroinflammation exacerbate damage caused by initial trauma from spinal cord injury (**SCI**). Severity of neuroinflammation depends on integrity of the blood-spinal cord-barrier (**BSCB**), as a compromised BSCB enhances neuroinflammation by facilitating immune cell infiltration. By targeting neuroinflammation, immunosuppressants are used to treat SCI patients. However, as patients experience immune suppression, immunomodulation is more effective than immunosuppression. Human Immunoglobulin G (**hIgG**) is used in clinic as an immunomodulatory treatment for inflammatory disorders. Although we have shown that administration of hIgG (0.4g/kg) is beneficial after SCI, the optimal dose and mechanism of hIgG are unknown. It is hypothesized that hIgG stabilizes the BSCB; reducing leukocyte infiltration, yielding long-term functional recovery and tissue preservation.

Methods: With a clinically-relevant rat model of SCI, hIgG (0.02, 0.2, 0.4, 1, 2g/kg), methylprednisolone (0.03g//kg) or vehicle was administered intravenously at 15 minutes post-SCI. Spinal cord and serum were collected to evaluate hIgG's short and long-term effects.

Results: hIgG co-localized with BSCB. At 24 hours post-SCI, relative to hIgG (0.4g/kg) and vehicle control, hIgG (2g/kg) significantly enhanced BSCB integrity. This was associated with reduced spinal cord neuroinflammation. Intriguingly, hIgG (2g/kg) increased serum levels of inflammatory cytokines, antagonized binding ligands that facilitate immune cell infiltration into spinal cord and directed these cells to the spleen. Short term benefits of hIgG (2g/kg) correlate with enhanced tissue preservation, blood flow and functional recovery at six weeks post-injury.

Conclusion: As a clinically-relevant immunomodulatory treatment, hIgG (2g/kg) can improve health of patients. hIgG alleviates neuroinflammation without increasing immune suppression.

RISK FACTORS FOR RECURRENT AND CHRONIC MARGINAL ULCERS REQUIRING SURGICAL TREATMENT FOLLOWING ROUX-EN-Y GASTRIC BYPASS

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HYPOTHESIS AND PURPOSE Marginal ulcer (MU) formation is a known complication following Roux-en-Y gastric bypass (RYGB) for weight loss. Although most respond to medical treatment, many patients have recurrent or chronic MU, with some requiring surgical revision. Although non-steroidal anti-inflammatory drug (NSAID) use, smoking and *H. pylori* infection have been proposed as risk factors for MU, little is known about what increases the likelihood of developing recalcitrant ulcers. The goal of this study was to identify potential risk factors for recurrent or chronic MU, including those requiring surgical revision.

METHODS All patients undergoing RYGB between 2011 and 2017 at an academic centre in Toronto, Ontario were included. Patients with a post-operative diagnosis of MU were identified from the institution's bariatric database and had their medical records reviewed. Patient characteristics, operative data and surgical outcomes were collected for statistical analysis.

RESULTS A total of 2 830 RYGB were performed during the study period. The incidence of MU was 6.9% with 4.5% having a single episode, 1.4% developing recurrent but medically-responsive MU and 1% undergoing revisional surgery. Patients requiring revision were significantly younger than patients with a single episode of MU or recurrent medically-responsive MU (39.2 vs. 44.5 and 41.8 years, p=0.027). However, only smoking history (OR 7.98, 95% CI 2.35-27.09) and immunosuppression (OR 11.6, 95% CI 1.18-114.07) emerged as risk factors for MU requiring surgery when a multivariate logistic regression model was applied. NSAID use and *H. pylori* infection did not predict recalcitrant MU requiring surgical treatment.

CONCLUSIONS Patients with a history of smoking and patients on immunosuppressive medication were at significantly higher risk of developing a MU requiring surgical revision. Further studies are needed to validate these findings and determine how they can inform perioperative management of the bariatric patient.

A NOVEL TREATMENT PLANNING WORKFLOW: DEVELOPING FOREHEAD FLAP TEMPLATES FOR NASAL RECONSTRUCTION FROM 2D AND 3D IMAGES

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Hypothesis: Computational computer-vision and manufacturing algorithms can form the foundation for a clinically relevant workflow to facilitate treatment planning for surgical reconstruction and improved accuracy of severe cranio-facial soft tissue injury/pathology. **Purpose:** The face is a complex three-dimensional (3D) structure that is important to function and an individual's self-perception. Facial anatomy can be impacted by trauma (i.e. car accidents, sporting and military injuries) or pathology (i.e. cancer or congenital disease). After a traumatic injury or pathologic change to the face, an individual's primary desire is to return to their original state both in terms of function and their appearance. However, there is generally insufficient information regarding the shape of an individual's pre-injury/pathology face and especially the nose shape from front view photographs. This makes accurate restoration of appearance through surgery extremely challenging, with much of the work of a plastic surgeon dependent on their experience and 3D spatial visualization abilities. **Methods:** This case report highlights the pre-operative planning of forehead flap template with a CAD and CAM process. Planning was performed for five cases, of which three examples are provided to demonstrate a unilateral rhinectomy with design from 3D scan mirroring, a partial bilateral rhinectomy from a 3D scan with aesthetic subunit labelling, and a complete bilateral rhinectomy with nose design from a 3D morphable model. The 3D nose designs of the missing nasal surface were then flattened with digital unwrapping tools to generate a 2D forehead flap template. The 2D design is translated into a physical traceable template via a 1:1 scale paper print-out for a rapid and low-cost CAM tool, which is then transferred to sterilizable metal foil. **Results:** Intra-operative photos for two cases are presented showing the template applied by tracing it on the forehead as the first stage of nasal soft tissue reconstructions. This digital forehead flap planning and fabrication presents a new patient-specific workflow for plastic surgeons to compliment current their existing experience and practice. **Conclusions:** These computer vision-based technologies are being integrated into a cohesive 2D to 3D surgical planning pipeline for traumatic facial reconstruction. The novel approach exploits the ubiquity of face photos and combines repurposed and optimized existing non-clinical software with new algorithms and digital/physical templates to improve the ability (speed and accuracy) of surgeons to restore pre-injury/pathology facial soft tissue.

TYROSINE PHOSPHORYLATION OF CASPASE-8 INDUCES CELL ACTIVATION THROUGH TLR4 DEPENDENT SIGNALING IN SEPTIC NEUTROPHILS

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Hypothesis and purpose: Using healthy control and septic patient neutrophils (PMNs) we tested the hypothesis that tyrosine phosphorylated caspase-8 interacts Toll-Like Receptor 4 (TLR4) to commit the PMN towards activation and thereby prevent apoptosis.

Methods: Healthy control and septic patient PMNs were harvested by density centrifugation. Control PMNs were treated with LPS to activate TLR-4. Confocal microscopy assessed protein localization and immunoblot detected caspase-8 and TLR-4 protein. Apoptosis was quantified on FACS (ANN V/PI^+). siRNA directed at caspase-8 was transfected into septic PMN, and downstream gene expression (IL-1β and IL-6) was measured by RT-qPCR. For *in vitro* studies, c-myc tagged caspase-8 phospho-mimetic (Y380E) and deficient (Y380F) constructs were generated and transfected into human leukemia (HL) 60 cells. Protein binding was assessed by immunoprecipitation. Protein complex stability was analyzed *in silico* using PyMOL Edu software.

Results: In LPS treated control PMNs, tyrosine phosphorylated caspase-8 colocalized and bound to TLR-4 (n=3), leading to NF-κB nuclear translocation to increase IL-1β (n=13; $p<0.0001$) and IL-6 (n=5; p=0.008) transcription; apoptosis was lower in comparison to unstimulated healthy control PMN (1.5±1.2% vs. 9±3.8%; n=7; $P<0.01$). In septic PMNs transfected with caspase-8 siRNA versus scramble control siRNA, both interaction between TLR-4 and MyD88 (n=3) and IL-1β (n=6; p=0.01) but not IL-6 (n=5) transcription was reduced. In comparison to HL-60 transfections with Y380F, HL-60 cells transfected with Y380E demonstrated significantly lower rates of apoptosis, and greater interactions between tyrosine phosphorylated caspase-8, TLR-4 and PI3-K (n=3) in an anti-apoptotic protein complex we term the *survivalsome*. *In silico*, the Y380E:TLR-4:PI3-K complex is more stable when compared to WT or Y380F (10-fold lower ΔG and K_d).

Conclusion: Tyrosine phosphorylated caspase-8 interacts with TLR-4 to induce MyD88 receptor-mediated dependent signaling, enhancing PMN activation and preventing apoptosis.

SURGICAL OUTCOMES IN MILD, MODERATE, AND SEVERE PATIENTS WITH DEGENERATIVE CERVICAL MYELOPATHY

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Hypothesis and Purpose: Degenerative cervical myelopathy (DCM) is one of the most common causes of non-traumatic spinal cord injuries leading to significant impairments in quality of life (QOL). Current management strategies indicate surgery for patients with moderate and severe DCM, whereas they are more controversial for patients with mild DCM. With the hypothesis that surgery may be equally beneficial in mild patients compared to moderate and severe patients, the objective of this study was to comparatively evaluate neurological outcomes and QOL in DCM.

Methods: Two prospective, multi-center cohort studies (AOSpine CSM North America and International) were used. Outcomes were evaluated pre-operatively at baseline and at 6 months, 1 year, and 2 years after surgery using the Neck Disability Index (NDI), mJOA, Short Form 36 (SF36), and Short Form 6D (SF6D). A normalized recovery index (NRI) was evaluated by ANOVA.

Results: A total of 735 patients were enrolled and baseline characteristics for each group were assessed. Significantly greater improvement was seen with mild DCM in the sensory upper limbs domain of the mJOA however, the total score was significantly lower in mild DCM compared to that of moderate and severe DCM. NDI scores showed significantly better outcomes in personal care, driving, and concentration in mild DCM ($p<0.05$). The bodily pain component of SF36 score showed a significantly greater improvement in mild DCM but physical component scores were worse in mild DCM compared to moderate and severe DCM($p<0.05$). SF6D scores showed the greatest improvement in mild DCM compared to moderate and severe DCM($p<0.05$).

Conclusions: This is the largest study comparing surgical outcomes in mild, moderate, and severe DCM patients using prospective data. Sensory improvements, specifically in pain, seen in patients with mild DCM may account for many improvements observed in this study. Overall, this study shows neurological and QOL improvements supporting surgical treatment in mild DCM.

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MACHINE LEARNING MODELS PREDICT FUNCTIONAL OUTCOMES AFTER TRAUMATIC SPINAL CORD INJURY WITH EXCELLENT PERFORMANCE

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Hypothesis and Purpose: Traumatic Spinal Cord Injury (SCI) results in devastating physical, occupational, and psychosocial consequences for over 13000 North Americans every year. Given these wide-ranging implications, accurate determination of SCI prognosis in multiple functional areas can be enormously beneficial. We hypothesize that machine learning (ML) can be used to accurately predict clinical outcomes and identify prognostic factors in SCI.

Methods: This is a retrospective analysis of a large, prospective 1119-patient SCI dataset. Multiple demographic and clinical variables (e.g. age, sex, neurological scores) are evaluated at initial presentation. 14 functional outcomes of interest (e.g. eating, grooming, walking) are also evaluated 1-year post-injury. Via nested cross-validation, ML models (e.g. random forests, support vector machines) relating the functional outcomes at 1 year to predictor variables are developed. In addition, the model predicting independent bladder function is externally validated against a 1250-patient European Multicenter SCI dataset.

Results: ML models showed excellent discrimination against out-of-fold testing data, with areas under the ROC curves (AUCs) ranging from 0.90-0.93 for the 14 outcomes. Moreover, the ML model for bladder function exhibited excellent external validity on the European SCI dataset (AUC = 0.90). Our models found that higher lower extremity motor scores were associated with a favorable prognosis for independent walking and stair climbing at 1 year, while advanced age was a negative predictor of overall functional independence.

Conclusion: Using data from only patient history and physical examination findings, ML models with excellent predictive power were developed. Our results demonstrated that machine learning can be a valuable tool for clinicians in making prognoses, forming treatment plans, and counselling patients with traumatic SCI.

TO DRIVE OR NOT TO DRIVE, THAT IS STILL THE QUESTION: DETERMINING FITNESS TO DRIVE IN PATIENTS WITH BRAIN TUMOURS

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Hypothesis and Purpose: Driving is a complex task that can be impaired in patients with brain tumours. The purpose of this study was two-fold: (1) to understand the reporting practices of physicians throughout Ontario on driving safety in patients with brain tumours, and (2) to determine driving habits/behaviours of patients with brain tumours in order to better inform discussions around driving safety in this population. **Methods:** A questionnaire was sent to 126 physicians who take care of patients with brain tumours in Ontario to determine their understanding of driving legislation, their reporting practices and how they determine fitness to drive. A questionnaire was administered to patients with brain tumours about their driving habits. Thirteen patients and age/sex-matched healthy controls participated in cognitive testing and driving simulation in order to determine driving performance. **Results:** Less than 10% of healthcare professionals said they could reliably determine fitness to drive, less than a quarter felt that current guidelines are sufficient in this endeavor, and 70% felt that cognitive/emotional deficits were relevant in driving. Patients with brain tumours engaged in a variety of driving scenarios with little subjective difficulty. However, 40% had at least one collision since their diagnosis. Patients had more speed exceedances and had greater variability in their speed of driving compared to controls. Performance on the selective attention component of the UFOV was significantly associated with greater total errors in the Bus Following tasks in the patient cohort. **Conclusion:** We found that while patients self-report good driving skills, they do sustain numerous collisions and engage in riskier driving habits compared to healthy controls and have more issues with sustained attention that have direct implications for complex driving. Comprehensive driving assessments are needed to identify patients with driving behaviours that put themselves and others at risk on the road.

INHIBITING FIBROTIC ENCAPSULATION OF BODY IMPLANTS BY TARGETING MECHANICAL ACTIVATION OF PROFIBROTIC TGF-β1

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Hypothesis and Purpose: The clinical performance of reconstructive silicone implants is compromised by foreign body reactions (FBRs). FBRs culminate in formation of fibrotic collagen tissue by α-SMA-expressing myofibroblasts contributing to implant failure. TGF-β1 is a key driver of fibrosis and secreted into the matrix in complex with the latent TGF-β1 peptide (LAP). Cell pulling on LAP via αv integrins mechanically activates TGF-β1 in context of a resistant matrix. The mechanisms and integrins activating TGF-β1 in FBRs are unknown. We hypothesized that the stiff surface of silicone implants enhances activation of αv integrin and TGF-β1.

Methods: Silicone implants and osmotic pumps releasing the αv integrin-specific inhibitor CWHM12 were implanted subcutaneously in transgenic mice. Implants were excised, and fibrotic capsules analyzed for thickness, collagen, and myofibroblasts recruitment using immunohistochemistry. Stiffness-tunable implant silicones were coated with recombinant LAP and used as substrates for fibroblasts *in vitro*. Integrin recruitment to these surfaces was quantified as a function of stiffness.

Results: Blocking αv integrins with CWHM12 significantly reduced fibrotic capsule thickness, collagen deposition, and myofibroblast accumulation *in vivo* and reduced force transmission to LAP and TGF-β1 activation *in vitro*. Reducing extracellular and intracellular stress resulted in the decreased recruitment of the latent TGF-β1-activating integrin αvβ1 to the implant material.

Conclusion: Mechanical activation by stiffness silicone bio-implants enhances integrin αv binding to and activation of latent TGF-β1. Active TGF-β1 drives implant encapsulation by stiff scar tissue, amplifying the process.

PUBLIC PERCEPTION OF A NORMAL HEAD SHAPE IN CHILDREN WITH SAGITTAL CRANIOSYNOSTOSIS

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Hypothesis and Purpose: The application of crowdsourcing in healthcare allows studies to garner large sample sizes while decreasing costs and saving time. Ratings from the general public provide assessments of how children with craniofacial differences are viewed. A survey on the attractiveness of children with single suture craniosynostosis yielded lower ratings in comparison to their normal counterparts. This rating did not improve with post-surgical intervention (Collett et al., 2013): highlighting the divide between public perception and objective surgical outcomes. A question that remains unanswered is at what level of surgical correction does the public perceive a head shape to be “normal”? The purpose of this cross-sectional pilot study is to determine the average “acceptable” head shape of sagittal craniosynostosis perceived by laypersons. The null hypothesis in this study is that there is no difference between a normocephalic and subjectively normal head shape (as deemed by the survey participants).

Method: A 3D image of a patient with severe sagittal craniosynostosis (based on cephalic index (CI)) was used as the index case representing extreme deformity in the diagnosis. An age and gender matched normative infant skull was the desired result for surgical correction. Using a step-wise wrap/unwrap method, 11 still images of lateral and top down views were generated with 10% incremental changes from the extreme abnormal to normal head shape. Participants were recruited via the Sickkids Twitter channel and completed an online survey, indicating their perception of the head shape as “normal” or “abnormal”.

Results: Subjective public perception of a normocephalic head shape was quantified and comparatively assessed alongside the patient’s CI.

Conclusions: Crowdsourced public ratings data is essential in supplementing outcome variables and the clinician’s perspectives on objective reconstructive goals.

DCD HEARTS RECONDITIONED USING NORMOTHERMIC REGIONAL PERFUSION CAN BE SUCCESSFULLY TRANSPLANTED FOLLOWING AN EXTENDED PERIOD OF STATIC STORAGE

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Purpose: Normothermic regional perfusion (NRP) allows *in situ* assessment of hearts donated after circulatory death (DCD), allowing only acceptable organs to be procured. We sought to determine if extended cold storage was possible for DCD hearts following NRP and to compare hearts stored using standard cold storage (HTK) with a novel cardioprotective solution (SOM).

Methods: Donor pigs underwent hypoxic cardiac arrest followed by 15min of warm ischemia and resuscitation on NRP. They were then randomly assigned to static storage with HTK at 4˚C (n=5) or SOM solution at 21˚C (n=5). Beating-heart donations were used as controls (n=4).

Results: 14 transplants were successfully performed. HTK hearts showed initial dysfunction following reperfusion; however, they demonstrated significant recovery up to 3 hours post-transplant. No significant differences were seen between HTK and control hearts post-transplantation (Cardiac index - CI: Control 49.5±6%, HTK 48.5±5% of baseline; p=ns). SOM improved myocardial recovery; hearts showed stable contractility after transplantation (SOM CI: 113.0±43% of NRP function; p=ns vs baseline) and improved diastolic function compared to HTK. SOM also improved coronary endothelial function compared to HTK and significantly reduced proinflammatory cytokine production and release following transplantation.

Conclusion: DCD hearts stored in cold storage demonstrated comparable post-transplantation myocardial function to controls. Thus, short periods of cold storage following successful NRP and documented adequate function is an acceptable strategy for DCD hearts. Preservation in Somah at room temperature is feasible and can improve cardiac recovery by minimizing endothelial dysfunction and tissue injury. Further testing is still needed to determine which post-NRP functional parameters better predict cardiac performance and investigate if longer periods of storage are feasible.

MEDIATORS OF CD8+ T CELL INFILTRATION IN PANCREATIC CANCER

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Hypothesis and Purpose: In a bioinformatics-driven approach, we investigated the role of chemokines in $CD8^+$ infiltration in pancreatic cancer. We hypothesize $CD8^+$ infiltrated tumours harbour distinct chemokine signatures, and segregation of patients based on signatures identifies differences in metrics of antitumour immunity.

Methods: We analyzed 74 primary resections for associations between $CD8^+$ tumour infiltrating lymphocyte (TIL) counts by IHC with chemokine expression by RNAseq. We segregated 120 samples into $chemokine^{hi}$ and $chemokine^{lo}$ groups based on chemokines strongly associated with TILs. Metrics of antitumor immunity were compared using RNAseq data. Two independent cohorts were assessed, including 182 primary tumors from TCGA and 62 liver metastases.

Results: CCL4, CCL5, CXCL9 and CXCL10 were most strongly associated with $CD8^+$ TIL counts ($p < 0.001$). $Chemokine^{hi}$ patients had increased expression of pathways involved with antitumor immunity, including Batf3+ dendritic cells, T cell activity, and immune exhaustion genes ($p < 0.05$). Results were recapitulated in 62 liver metastases, suggesting an underlying immunobiology between primary and metastatic tumors.

Conclusion: This study is the first unbiased RNASeq gene expression analysis to uncover associations between chemokines and $CD8^+$ T cell infiltrate in pancreatic cancer, identifying a subset of patients with increased antitumour immune response potentially through a $Batf3^+$ dendric cell/chemokine-mediated homing axis. Understanding mediators driving cytotoxic T cell infiltration may help stratify patients amenable to current and novel immunotherapies dependent on effector T cell responses.

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OBJECTIVE AND SUBJECTIVE ASSESSMENT OF A PROTOTYPE CAMERA SYSTEM FOR INTRAOPERATIVE VIDEO RECORDING OF OPEN SURGERY

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Hypothesis and Purpose: Intraoperative video recording has become a fundamental technology in modern-day surgery however the technology for routine video capture in open surgery is limited. The objectives of this study were to compare a shoulder-mounted prototype open capture system to the commonly used head-mounted GoPro.

Methods: *Objective Assessment* - Surgeons were outfitted with both cameras and performed repeated skin procedures in a simulated OR setting. A custom-made Inertial Measurement Unit (IMU) was affixed to each camera to measure the position of each device in 3D space. The videos were objectively analyzed based on the key deficiencies identified in our literature review: motion, obstruction, brightness, and sharpness. This was done in a modular fashion using a series of computer algorithms. *Subjective Assessment* - A modified Delphi method was used to develop 2 evaluation instruments: the i) User Experience (UX) Survey and the ii) Video Quality Evaluation (VQE) Survey. Surgeon's performing open surgery were then recruited to subjectively evaluate the camera devices and the video they produced during their surgical cases.

Results: 12 skin procedures were performed in a simulated OR setting. The IMU sensor detected significantly less angular displacement from the prototype compared to the head-mounted GoPro when analyzed as quaternions (130±56 vs. 253±31, $p<0.001$). Video data were then processed through the objective evaluation algorithms. The mean motion score calculated was significantly lower in the prototype camera videos compared to the head-mounted GoPro video (33.9±23.9 vs. 82.67±27.4, $p<0.001$).

Conclusions: This study presents a camera system for open surgery and benchmarks it against existing technology. In a simulated OR setting, the prototype camera system demonstrated less movement compared to a head-mounted GoPro.

SURGICAL REPAIR VERSUS CONSERVATIVE TREATMENT AND SUBACROMIAL DECOMPRESSION FOR THE TREATMENT OF ROTATOR CUFF TEARS: A META-ANALYSIS

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Hypothesis and Purpose: The purpose of this study was to compare the effectiveness of surgical repair to conservative treatment and subacromial decompression for the treatment of rotator cuff tears. We hypothesized that surgical repair would result in a significant improvement in functional outcomes when compared to conservative treatment or subacromial decompression.

Methods: PubMed, Cochrane database, and Medline were searched for randomized controlled trials published until March 2018. Included studies were assessed for methodological quality and data were extracted for statistical analysis.

Results: Six studies were included in this review. A meta-analysis of the Constant Murley Score (CMS) one year following surgical repair showed that surgical repair resulted in significantly improved scores compared with conservative treatment (mean difference = 6.15, P=0.002). A meta-analysis of the CMS one year following surgical repair also showed that surgical repair yielded significantly improved scores as compared to subacromial decompression (mean difference = 5.81, P= 0.0004). In the conservatively treated group, 11.9% (16/134) of patients eventually crossed over to surgical repair following unsatisfactory results. Four studies assessed rotator cuff integrity following surgical repair. The overall “re-tear” rate was 32.9% (55/167).

Conclusion: The results of this review show that surgical repair results in significantly improved outcomes when compared to either conservative treatment or subacromial decompression alone for degenerative rotator cuff tears in older patients. However, the magnitude of the difference in outcomes between surgery and conservative treatment may be small and the “success rate” of conservative treatment may be high, allowing surgeons to be judicious in choosing those patients who are most likely to benefit from surgery.

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A NOVEL ROLE FOR SGLT2 INHIBITORS TO INCREASE CIRCULATING PROGENTOR CELLS IN PATIENTS WITH TYPE 2 DIABETES AND CARDIOVASCULAR DISEASE

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Purpose and Hypothesis: Chronic hyperglycemia and inflammation during type 2 diabetes (T2D) contribute to ischemic cardiovascular complications. The use of sodium glucose co-transporter-2 inhibitors (SGLT2i's) has been associated with decreased major adverse cardiovascular events in patients with T2D. We hypothesized that alongside improved glucose levels, SGLT2i will increase circulating cell types that co-ordinate blood vessel repair.

Methods: This was a sub-study of the EMPA-HEART randomized controlled trial that enrolled patients with T2D with a history of coronary artery disease. Participants were randomly allocated empagliflozin (EMPA) 10mg QD or placebo for 6 months. Peripheral blood was collected at randomization and at ~6-months (N=26) and analyzed for regenerative cell content by multi-parametric flow cytometry. Regenerative cell phenotype was evaluated by elevated aldehyde dehydrogenase (ALDH)-activity, an enzyme that protects progenitor cells from oxidative damage, with co-expression of primitive cell and M1/M2 macrophage surface markers.

Results: Following a ~6-month intervention, samples from patients allocated EMPA showed a two-fold, but non-significant (P=0.61) decrease in $ALDH^{hi}SSC^{hi}$ cells, suggesting a reduction in circulating pro-inflammatory granulocyte precursors after EMPA treatment. The prevalence of pro-angiogenic monocytes with "M2" polarization was significantly increased in patients allocated EMPA. Importantly, circulating pro-vascular $ALDH^{hi}SSC^{low}$ myeloid progenitor cells ($P<0.01$) with CD133 co-expression ($P<0.05$) was increased in patients allocated EMPA.

Conculsions: We have established that circulating pro-vascular progenitor cells with early myeloid phenotype and anti-inflammatory M2 macrophages were increased in patients allocated EMPA, indicating a partial reversal of the "regenerative cell exhaustion" phenotype associated with chronic T2D. Functional assessments of protective and destructive enzyme activity is warranted to elucidate a mechanism of cellular revitalization in this patient population.

IMPACT OF BARIATRIC SURGERY ON CIRCULATING INFLAMMATORY AND PRO-VASCULAR PROGENITOR CELL CONTENT

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Purpose and Hypothesis: Obesity represents a growing concern globally with more than 2 billion adults affected by unhealthy weight gain. Given that chronic inflammation and metabolic insufficiency are intimately associated with obesity, excessive weight gain can dramatically elevate the risk of type 2 diabetes (T2D) and related ischemic complications. Since bariatric surgery is associated with sustained metabolic and vascular improvements, we hypothesized that individuals who have undergone bariatric surgery will demonstrate increased circulating pro-angiogenic progenitor cell content and reduction in inflammatory cell burden.

Methods: Peripheral blood was collected from 20 individuals prior to and 3 months after gastric bypass (Roux-en-Y) surgery. Progenitor cells were assessed by multi-parametric flow cytometry for elevated aldehyde dehydrogenase (ALDH)-activity, a self-protection enzyme in vascular progenitor cells, and co-expression of pro-angiogenic progenitor cell surface markers.

Results: Following bariatric surgery, there was a 2-fold reduction in circulating $ALDH^{hi}SSC^{hi}$ inflammatory granulocyte content ($P<0.05$). Circulating $ALDH^{hi}SSC^{mid}$ cells, representing macrophage/monocyte precursors, were significantly increased following bariatric surgery ($P<0.05$). Within this $ALDH^{hi}SSC^{mid}$ cell population, we observed that the frequency of circulating angiogenic monocytes (CD68+/CD14+, $P<0.01$) were significantly increased following bariatric surgery. Unexpectedly, $ALDH^{hi}SSC^{low}$ cells, consistent with rare circulating early myeloid progenitor cells, were significantly reduced following bariatric surgery ($P<0.001$). However, the frequency of $ALDH^{hi}SSC^{low}$ cells, co-expressing primitive cell surface markers (CD133+/CD34+, $P<0.01$) previously associated with vasculogenic function were significantly increased.

Conclusion: Bariatric surgery reduced circulating inflammatory cells and increased circulating pro-angiogenic monocyte content, suggesting that increased vascular regenerative potential may improve cardiovascular outcomes in obese patients after bariatric surgery.

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THE IMPACT OF OLDER AGE ON FUNCTIONAL RECOVERY AFTER SURGICAL DECOMPRESSION FOR DEGENERATIVE CERVICAL MYELOPATHY: RESULTS FROM AN INTERNATIONAL, MULTICENTRE, PROSPECTIVE DATASET IN 757 PATIENTS

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Hypothesis and Purpose: Surgical decompression has been shown to improve long-term function, disability, and quality of life (QOL) in degenerative cervical myelopathy (DCM); however, the role of surgery, and the effect on the outcomes in elderly patients is controversial.

Methods: Of 757 patients enrolled in the AOSpine CSM-North America and International studies, 107 were identified as elderly (≥70 years). Functional and quality of life (QOL) outcomes were assessed at 6, 12 and 24 months, between young adult and elderly groups through unadjusted univariate analyses and regression analysis adjusting for age-related variables.

Results: The baseline functional assessment in the elderly group was worse compared to the younger group with mJOA (11.0 vs 12.9; $p<0.01$) and Nurick grade (3.80 vs 3.15; $p>0.01$). The change in mJOA scores were similar for both groups at all intervals, but after adjustment, the coefficient for change in the elderly group was worse. The result for Nurick grade was equivalent. With QOL outcomes, the younger cohort demonstrated greater improvement in the SF-36 physical component after surgery, yet both groups had a similar degree of improvement in the SF-36 mental component scores.

Conclusion: In this combined dataset from 2 large prospectively collected multi-centre studies on DCM surgery, the group aged 70 or greater demonstrated significantly worse functional and QOL recovery when compared to the younger cohort after adjusting for the effect of age-related co-morbidities and baseline impairment. Elderly patients undergoing surgery for DCM should therefore be counseled appropriately regarding expectations of surgery.

A SYSTEMATIC REVIEW OF BEHAVIORAL INTERVENTIONS TO IMPROVE OPIOID PRESCRIBING AFTER SURGERY

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Hypothesis and Purpose: Current practices for the prescription of opioids at discharge after surgery are highly variable and often excessive. We conducted a systematic review to identify behavioral interventions designed to improve these practices.

Methods: We searched MEDLINE, EMBASE, CINAHL and PsycINFO until December 14th 2018 to identify studies of behavioral interventions designed to decrease opioid prescribing at discharge among adults undergoing surgery. Behavioral interventions were defined according to the Cochrane Effective Practice and Organisation of Care (EPOC) taxonomy. We assessed the risk of bias of included studies using criteria suggested by Cochrane EPOC and the Newcastle-Ottawa scale.

Results: Of 8,048 citations that were screened, 24 studies were included in our review. Six types of behavioral interventions were identified: local consensus-based processes (18 studies), patient-mediated interventions (2 studies), clinical practice guidelines (1 study), educational meetings (1 study), inter-professional education (1 study) and clinician reminder (1 study). All but one study reported a statistically significant decrease in the amount of opioid prescribed at discharge after surgery, and only two studies reported evidence of increased pain intensity. Reductions in prescribed opioids ranged from 34.4 to 212.3 milligram morphine equivalents. All studies were found to have medium-to-high risks of bias.

Conclusion: We identified six types of behavioral strategies to decrease opioid prescription at discharge after surgery. Despite the risk of bias, almost all types of intervention appeared effective in reducing opioid prescriptions at discharge after surgery without negatively impacting pain control.