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**Hypothesis and Purpose:** The coexistence of coronary artery disease (CAD) and peripheral artery disease (PAD) cannot be overstated. Yet, major societal guidelines discourage screening peripheral artery disease patients with intermittent claudication for cardiovascular risk in the absence of cardiac symptoms. The aim of this study is to assess the status of N-terminal pro-BNP levels in PAD patients with Rutherford class I-III in the absence of CAD symptoms.

**Methods:** We conducted a cross-sectional study of 505 participants. Patients were stratified on the basis of their clinical history and ankle-brachial index into non-PAD patients or PAD patients with ABI in the mild, moderate or severe range. Enzyme-linked immunosorbent assay was used to measure Nt-proBNP.

**Results:** The study cohort compromised of 391 (77.4%) PAD patients and 114 (22.6%) non-PAD controls. Nt-proBNP levels were significantly higher in in patients with severe PAD compared to patients without PAD (median = 374.3; IQR = 423.6; p-value < 0.001). We found significant association between levels of NT-pro BNP and severe (OR: 2.77; 95% CI: 1.99 – 6.55) and moderate (OR: 1.69; 95% CI, 1.06 – 2.69) PAD groups when compared with non-PAD controls. Age, smoking and CAD where significantly correlated with higher NT-pro BNP concentrations (p-value = 0.001, 0.015 and 0.042), respectively. However, in subgroup analysis of patients with severe PAD, this correlation became statistically insignificant.

**Conclusions:** Nt-pro BNP are elevated in patients with PAD (Rutherford class I-III) in whom ABI was the severe range. This correlation may have future implications in further intensifying risk reduction therapy in this patient group and further cardiovascular risk stratification prior to vascular intervention.
Hypothesis and Purpose: Antenatal cell-based therapies are currently considered invasive for the fetus. A promising cell-free strategy that holds great regenerative potential for several organs is the administration of stem cell derived EVs, whose cargo contains bioactive molecules that epigenetically regulate target cells. Herein, we aimed to 1) assess the ability of EVs to reach fetal organs when administered to the mother intravenously or intra-amniotically; 2) compare these administration routes on normal fetuses and fetuses with a congenital anomaly.

Methods: EVs were isolated from rat amniotic fluid stem cell conditioned medium using ultracentrifugation. EVs were assessed for size (nanoparticle tracking analysis), morphology (TEM), and expression of CD63, Hsp70, Flo-1, and TSG101 (Western). We injected rat dams with EVs stained by ExoGlow™-Vivo or saline (control) via maternal tail vein (IV) or intra-amniotically (IA) at E20.5. IA and IV injections were performed on dams carrying normal fetuses or fetuses exposed to nitrofen to induce congenital diaphragmatic hernia. After 24h, dams and pups were sacrificed. 3D high-sensitivity optical reconstructions of whole fetuses or micro-dissected fetal organs were imaged using the IVIS® Spectrum imaging system. EV fluorescence signal was compared between normal (n=27) and nitrofen-exposed (n=45) fetuses.

Results: Both IV and IA injection routes delivered EVs to fetal organs. No fluorescent signal was detected in saline only control. EVs reached more organs with IA than IV injections, and were detected in the lungs, gastrointestinal, and urinary tract of normal and nitrofen-exposed fetuses.

Conclusions: This proof of concept study shows that antenatal administration of stem cell EVs is feasible with different routes. Although maternally administered EVs cross the placenta, IA injection is more effective at reaching fetal organs. Further studies are underway to reproduce these findings in experimental models of various congenital anomalies.
SERUM METABOLOMICS SIGNATURE OF CRITICAL LIMB-THREATENING ISCHEMIA

Sandi Azab¹, Philip Britz-Mckibbin¹, Abdelrahman Zamzam², Muzammil H. Syed ², Rawand Abdin², Mohammad Qadura²

¹Department of Chemistry and Chemical Biology, McMaster University, Hamilton, ON
²Division of Vascular Surgery, Department of Surgery, St. Michael’s Hospital, Toronto, ON

Hypothesis and Purpose: Peripheral artery disease (PAD) is often undiagnosed, resulting in the disease progression of some patients to end-stage critical limb-threatening ischemia (CLTI). However, the metabolomics profile of this patient population has not been fully understood. Therefore, we sought to characterize PAD and CLTI at the metabolites level using comprehensive metabolites’ profiling (i.e. metabolomics).

Methods: A total of 60 patients were recruited and stratified into CLTI (n=20), intermittent claudication (IC) (n=20), and non-PAD (n=20) groups, based on the Rutherford Classification. Patients with diabetes, history of cancer, deep vein thrombosis, and acute coronary syndrome were excluded. Non-targeted metabolite screening of serum was conducted using three operation modes of multisegment injection-capillary electrophoresis-mass spectrometry (MSI-CE-MS) with full-scan data acquisition, where a total of 85 authentic metabolites were consistently detected after a stringent process of data filtering and quality control.

Results: Compared to controls, PAD patients had lower serum concentrations of a panel of six metabolites associated with elevated oxidative stress, atherosclerosis and aberrant energy metabolism within skeletal muscle ($p < 0.05$). Compared to IC, CLTI cases exhibited significantly higher serum levels of four additional metabolites along with lower concentrations of several circulating fatty acids; all of which satisfied a false discovery rate adjustment ($q < 0.05$). Most serum metabolites associated with PAD progression were also correlated with ABI ($a = \pm 0.24-0.51; p = 0.05-0.001$), whereas two top-ranked serum biomarker ratios differentiated CLTI from IC with good accuracy (AUC = 0.870, $p = 4.0 \times 10^{-5}$).

Conclusion: This work provides novel biochemical insights into the pathophysiology of CLTI and sheds new light on possible metabolic markers that can be used for PAD and CLTI screening.
UPFRONT SMALL BOWEL RESECTION FOR SMALL BOWEL NEUROENDOCRINE TUMORS WITH SYNCHRONOUS METASTASES: A PROPENSITY MATCHED COMPARATIVE POPULATION-BASED ANALYSIS

Sean Bennett (Surgical Oncology Fellow), Julie Hallet (Supervisor)
Division of General Surgery, Sunnybrook Health Sciences Centre, and University of Toronto

Hypothesis and Purpose: Resecting the primary tumor in metastatic small bowel neuroendocrine (SB-NET) remains controversial. We hypothesized that upfront small bowel resection (USBR) would decrease long-term healthcare utilization, compared to non-operative management (NOM).

Methods: We conducted a population-based analysis of patients with SB-NET metastatic at diagnosis between 2001-2017 in Ontario. USBR was defined as resection within 6 months of diagnosis. Primary outcomes were subsequent unplanned admissions and small bowel surgery. Secondary outcome was overall survival (OS). USBR and NOM patients were matched 2:1 using a propensity-score. We used time-to-event analyses with cumulative incidence functions and Andersen-Gill regression for primary outcomes, and Kaplan-Meier methods with Cox regression for OS. E-value methods assessed for residual confounding.

Results: Of 1000 patients identified, 785 (78.5%) had USBR. The matched cohort included 348 patients with USBR and 174 with NOM. Matched groups were well balanced with standardized mean differences <10% for matched variables. Patients with USBR had lower 3-year risk of subsequent admissions (72.6% vs 86.4%, p<0.001) than those with NOM, with hazard ratio (HR) 0.72 (95%CI 0.57-0.91). USBR was associated with lower risk of subsequent small bowel related surgery (15.4% vs 40.3%, p<0.001), with HR 0.44 (95%CI 0.29-0.67). E-values indicated that it is unlikely that these risk estimates could be explained by an unmeasured confounder. Both groups had prolonged survival, with a median of 12.44 years for the entire cohort.

Conclusion: USBR should be considered for metastatic SB-NETs to decrease subsequent admissions and surgery and improve patient outcomes and experience.
PHYSIOTHERAPY ACTIVITY OUT-OF-DISTRIBUTION DETECTION
Phil Boyer, David Burns (SSTP), Cari Whyne
Sunnybrook Research Institute and University of Toronto

Hypothesis and Purpose: Training a Machine Learning (ML) algorithm on all possible human actions for activity recognition is impractical, but supervised ML algorithms do not accurately classify Out-of-Distribution (OOD) activities. This is of particular importance to tracking at-home physiotherapy exercise adherence in “real-world” patient scenarios where subjects may perform unrelated activities (e.g. taking a drink) in addition to their prescribed exercises. Methods to address the OOD problem exist for image classification, but have not yet been applied to time series activity recognition. We hypothesize that OOD samples can be accurately detected in a physiotherapy activity dataset using ML (AUROC ≥ 0.95).

Methods: Our team has collected a novel dataset (SPARS9x) consisting of inertial data captured by smart watches worn by 20 healthy subjects as they performed supervised shoulder physiotherapy exercises (in-distribution), followed by a minimum three hours of data as they engaged in unstructured activities (OOD). The dataset was analyzed using “classical” algorithms on engineered features (One-Class State Vector Machine (OCSVM), K-Nearest Neighbour (KNN), and K-Means), and deep learning approaches (thresholding based on SoftMax “confidence”; confidence calibration via entropy regularization; confidence calibration via temperature scaling and input perturbations (ODIN); and extending the SoftMax layer for prediction of an unknown class (OpenMax)). OOD techniques were also tested on two publicly-available motion tracking datasets, SPARS and MHEALTH.

Results: KNN OOD prediction based on the nearest neighbour distance performed best in cross-validation on the test set for each of the three datasets, achieving mean Areas under the Receiver Operating Characteristic Curve (AUROC) of 0.97 (SPARS9x), 0.93 (SPARS) and 0.88 (MHEALTH). Conclusion: An AUROC of greater than 0.95 was found to be achievable for OOD detection on the SPARS9x physiotherapy activity inertial dataset. Simple and rapid OOD-detection techniques based on classical algorithms, such as KNN using engineered features, were found to outperform deep learning techniques on this time series dataset of physiotherapy exercise inertial data.
A RANDOMIZED SURGICAL TRIAL OF MITRAL VALVE REPAIR WITH LEAFLET RESECTION VERSUS LEAFLET PRESERVATION ON FUNCTIONAL MITRAL STENOSIS: PRIMARY RESULTS OF THE CAMRA CARDIOLINK-2 TRIAL

Vincent Chan¹, Aleksander Dokollari², C. David Mazer⁵, Thierry Mesana¹, Makoto Hibino², Benoît E. de Varennes⁷, Alexander J. Gregory⁶, Denis Bouchard⁸, Fei Zuo⁶, Faeez Mohamad Ali³, Wendy Tsang³, Deepak L. Bhatt¹⁰, David A. Latter², Peter Jüni⁶, Hwee Teoh²,4, Adrian Quan², Howard Leong-Poi³, Subodh Verma²
¹Division of Cardiac Surgery, University of Ottawa Heart Institute, Ottawa, ON; Divisions of ²Cardiac Surgery, ³Cardiology, and ⁴Endocrinology and Metabolism, ⁵Department of Anesthesia, ⁶Applied Health Research Centre, St. Michael’s Hospital, University of Toronto, Toronto, ON; ⁷Division of Cardiac Surgery, McGill University, Montréal, QC; ⁸Department of Anesthesiology, Perioperative, and Pain Medicine, University of Calgary, Calgary, AB; ⁹Department of Cardiac Surgery, Université de Montréal, Montréal, QC; ¹⁰Brigham and Women’s Hospital, Harvard Medical School, Boston, MA

Purpose: The gold standard treatment for mitral valve regurgitation due to prolapse involves surgery with annuloplasty and either leaflet resection (LR) or leaflet preservation (LP), with placement of artificial neochordae. It has been suggested that LR may be prone to functional mitral stenosis, whereby a patient may have a higher mitral gradient at peak exercise compared to a LP strategy. Both techniques are widely used but there has been no prospective comparative study, particularly in regard to functional mitral stenosis. Methods: 104 patients with posterior leaflet prolapse were randomized to undergo mitral repair with either LR (N=54) or LP (N=50) at 7 Canadian cardiac centers. Patient age, proportion of females, and mean Society of Thoracic Surgeons risk score was 63.9±10.4 years, 19%, and 1.4% for the LR group, and 66.3±10.8 years, 16%, and 1.9% for the LP group. The primary endpoint was the mean trans-mitral repair gradient at peak exercise 12-months after repair. Results: Baseline characteristics were similar between the groups. At 12-months, the mean trans-mitral repair gradient at peak exercise in patients who underwent LR and LP was 9.1±5.2 and 8.3±3.3 mmHg (P=0.4), respectively. Mean mitral valve gradient at rest was comparably (3.2±1.9 mmHg post-LR and 3.1±1.1 mmHg post-LP). There was no between-group difference for the 6-minute walk distance (451±147 m and 481± 95 m for the LR and LP groups, respectively). Conclusion: We report the first prospective surgical randomized trial to evaluate commonly used mitral valve repair strategies for posterior leaflet prolapse. Both LR and LP strategies yield acceptable results with no difference in postoperative valve gradient and functional status 12-months after surgical mitral valve repair.
Hypothesis and Purpose: Management protocols for displaced patella fractures in elderly (≥65 years) patients are lacking and there is relative controversy with respect to surgical indications. In young patients, surgery is recommended for all displaced fractures. It is unclear if this algorithm is applicable to older patients; many of whom have lower functional demands and numerous co-morbidities. Perceptions of orthopaedic surgeons play an important role in determining treatment provided. This study explored current management practices and surgeon considerations when treating patella fractures in older patients.

Methods: A 37-item electronic survey inquired about preferences for managing different fracture patterns, treatment indications, and complication rates. Questions were generated from the literature and incorporated feedback from orthopaedic surgeons. We anonymously surveyed members of the Orthopaedic Trauma Association and Canadian Orthopaedic Association.

Results: Of the 115 surgeons who participated in the survey, 82% practised in Canada. There was general consensus that non/minimally-displaced fractures should be conservatively (80%) managed, while displaced fractures require surgery (85%). Surgeons with fellowship training in lower extremity or trauma and younger surgeons (≤40 years) were less likely to select surgery for displaced fractures (p<0.05 for all). There was a lack of consensus on the degree of displacement warranting operative management: with 25% selecting <5mm, 37% selecting 5-10mm, 27% selecting >11mm, and 10% selecting ‘other’. The estimated complication rate was <20%. 70% of respondents indicated a need for future high level studies comparing treatments.

Conclusion: There remains a substantial lack of agreement surrounding the degree of displacement warranting operative management for patella fractures in elderly patients. Surgeon demographics and training often influence the treatment provided. Future studies are needed to establish standards of care.
Hypothesis: Diffusion Tensor Tractography Imaging (DTI) is an effective tool for monitoring tendon ablation treatment with Magnetic Resonance-guided Focused Ultrasound (MRgFUS).

Purpose: This study aims to evaluate DTI diffusivity parameters and tractography as quantitative, directional, and visual assessment of tendon tract integrity following MRgFUS ablation, which could be a viable modality to transcutaneously precisely release a tendon contracture for patients with musculotendinous contracture disorders, such as spinal cord injury or cerebral palsy.

Methods: Ex-vivo porcine flexor tendons underwent pre- and post-ablation imaging in a Bruker BioSpin 7T MRI with a specific DTI protocol. Diffusion tractography was constructed and DTI diffusivity parameters, fractional anisotropy (FA) and apparent diffusion coefficient (ADC), were statistically analyzed pre- and post- MRgFUS ablation.

Results: FA and ADC values for pre-ablated, compared to post-ablated tendons, were found to be significantly different; FA pre-ablation = 0.61±0.07 and post-ablation = 0.27±0.10 (p<0.005), ADC pre-ablation = 0.65±0.16x10^{-3} \text{ mm}^2/\text{s}, and post-ablation = 0.98±0.06 (p<0.05). With tractography, visual tendon disruption at the level of treatment was confirmed in all tendons (Fig1).

Conclusion: This is the first study that investigated changes in diffusivity parameters and tendon tractography following MRgFUS ablation. The decrease in FA and increase in ADC within the treatment volume following MRgFUS ablation were consistent with changes in anisotropy after disruption of tendon fascicles and loss of microstructural integrity. Additionally, diffusion tractography visually demonstrated the discontinuation of tendon fascicles at the level of ablation.
ASSESSING THE HEALTH BURDEN OF CLEFT LIP AND/OR PALATE IN ETHIOPIA: PRELIMINARY RESULTS FROM THE PATIENT AND SOCIETAL PERSPECTIVE.

Karen Chung (SSTP), Gebremedhin Gebretekle, Mekonen Eshete, Andrew Howard, Eleanor Pullenayegum, Beate Sander, Christopher Forrest
The Division of Plastic and Reconstructive Surgery, The Hospital for Sick Children and University of Toronto; and Addis Ababa University

Purpose: Current cleft lip and/or palate (CLP) economic evaluations for low-and middle-income countries (LMICs) use outdated health outcome values from high income countries. Primary health-outcome data from LMIC patient and societal perspectives can inform local clinical and policy decisions. This is the first study to elicit CLP utilities from an LMIC.

Methodology: A six-month cross-sectional study was conducted until December 20, 2019 at two Ethiopian hospitals. Multi-site ethics approval was obtained. Eligible patient-proxy participants included non-syndromic CLP patients < 18 years old and their proxies. Ethiopian societal participants included adults > 18 years old. Validated direct utility instruments (Visual Analogue Scale (VAS), Time-Trade-Off (TTO, Standard Gamble (SG)) and) were used. Patient-proxies (PP) evaluated their own health status. Each societal participant (SP) evaluated three of the following vignettes: untreated/treated cleft lip (CL), untreated/treated cleft palate (CP), untreated/treated CLP, and speech care (SC), where treatment refers to primary surgery.

Results: Data from 440 participants is reported. Differences between untreated and treated PPs were patient age (years, 1.2 vs 5.9, p<0.0001), living in a rural area (72 % vs 43%, p<0.0001) and monthly income (birr, 3490.5 vs 5932.4, p=0.0003).

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<th>Untreated (VAS, TTO, SG)</th>
<th>Treated (VAS, TTO, SG)</th>
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<tr>
<td>CL</td>
<td>PP n=73 (0.70, 0.73, 0.62)</td>
<td>PP n=23 (0.80, 0.84, 0.77)</td>
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<td>SP n=47 (0.59, 0.67, 0.80)</td>
<td>SP n=47 (0.79, 0.84, 0.90)</td>
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<td>CP</td>
<td>PP n=23 (0.64, 0.73, 0.62)</td>
<td>PP n=13 (0.77, 0.94, 0.70)</td>
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<td>SP n=38 (0.58, 0.60, 0.76)</td>
<td>SP n=38 (0.81, 0.83, 0.91)</td>
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<tr>
<td>CLP</td>
<td>PP n=78 (0.57, 0.70, 0.61)</td>
<td>PP n=53 (0.78, 0.81, 0.66)</td>
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<td>SP n=45 (0.35, 0.44, 0.55)</td>
<td>SP n=45 (0.64, 0.66, 0.75)</td>
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<tr>
<td>SC</td>
<td>PP n=47 (0.80, 0.82, 0.65)</td>
<td>SP n=38 (0.92, 0.95, 0.97)</td>
</tr>
</tbody>
</table>

Conclusions: This study lends evidence to inequalities within Ethiopia and suggests that CLP utility values from Ethiopia are more severe than previously cited values from high income settings. The implications in the delivery of cleft care in LMICs will be highlighted.
INADEQUACY OF AJCC 8th EDITION IN PREDICTING SURVIVAL OF COLORECTAL CANCER (CRC) PATIENTS TREATED IN A HIGH-VOLUME CANADIAN CENTRE

David P Cyr (SSTP)1,2,3,4, Amanpreet Brar1,2, Sameer Shivji5, Aysegul Akder5, Siham Zerhouni1,2, Mantaj Brar1, Robert Gryfe1,2, Helen MacRae1, Erin D Kennedy1,2,6, James Conner4,5, Richard Kirsch4,5, Carol J Swallow1,2,3,4

1Division of General Surgery, Dept Surgery, 2Surgical Oncology, Princess Margaret Cancer Centre, 3Institute of Medical Science, 4Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital. (MSH), 5Dept LMP, Mount Sinai Hospital, 6IHPME; University of Toronto

Hypothesis and Purpose: The 8th edition of the American Joint Committee on Cancer (AJCC 8th) TNM staging system was intended to incrementally enhance the accuracy of survival prediction for CRC patients, facilitating more strategic use of adjuvant therapies. We explored the validity of AJCC 8th in our setting, comparing it to a contemporaneous experience in an Asian centre. Methods. The MSH cohort (n=552) represents an observational study of consecutive patients (310M, 242F) who had resection of primary CRC between 01/2011 and 12/2016, with a minimum follow-up of 36 months (median 57 months). Overall and disease-specific survival (OS, DSS) were estimated by the Kaplan-Meier method. Results. 5-year OS in patients categorized as AJCC Stage III or IV was notably superior in the MSH vs. the Huzhang cohorts (Table). In the MSH cohort, neither OS nor DSS were different for Stage I vs. Stage II disease (Table).

<table>
<thead>
<tr>
<th>Centre, Survival type (5-year)</th>
<th>AJCC 8th Stage I</th>
<th>AJCC 8th Stage II</th>
<th>AJCC 8th Stage III</th>
<th>AJCC 8th Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSH, DSS</td>
<td>96% (92-100)*</td>
<td>91% (86-95)</td>
<td>80% (73-86)</td>
<td>23% (15-36)</td>
</tr>
<tr>
<td>[n=107]</td>
<td>[n=185]</td>
<td>[n=180]</td>
<td>[n=80]</td>
<td></td>
</tr>
<tr>
<td>MSH, OS</td>
<td>99% (84-96)</td>
<td>84% (78-90)</td>
<td>70% (63-78)</td>
<td>23% (15-36)</td>
</tr>
<tr>
<td>[n=131]</td>
<td>[n=194]</td>
<td>[n=663]</td>
<td>[n=55]</td>
<td></td>
</tr>
<tr>
<td>Huzhang#, OS</td>
<td>99% (84-96)</td>
<td>80% (78-90)</td>
<td>60% (63-78)</td>
<td>5% (15-36)</td>
</tr>
<tr>
<td>[n=131]</td>
<td>[n=194]</td>
<td>[n=663]</td>
<td>[n=55]</td>
<td></td>
</tr>
</tbody>
</table>

*95% Confidence Interval; #Tong et al, 2018

Given these inaccuracies, we sought additional histopathologic prognostic features in our cohort. Inferior DSS was predicted by: positive margin of resection, emergency surgery, high ASA score, and high preop neutrophil-to-lymphocyte ratio. Conclusions. The AJCC 8th edition TNM staging system was inadequate in predicting survival in our cohort of primary CRC patients. We will study additional advanced histopathologic features to refine a predictive model to inform individualized decision-making regarding adjuvant therapy and appropriate duration of follow-up.
MIDTERM OUTCOMES OF TRANSCATHETER VALVE IN VALVE IMPLANTATION VERSUS REDO SURGICAL AORTIC VALVE REPLACEMENT FOR AORTIC BIOPROSTHETIC VALVE DEGENERATION

Michaelis Demosthenous¹, Makoto Hibino¹, Didar-Karan S Kalra¹, Subodh Verma¹, Daniel Bonneau¹, Bobby Yanagawa¹, Rodolfo V Rocha², David Latter¹, Aleksander Dokollari¹

¹St. Michael's Hospital, Toronto, ON, Canada, and ²University of Toronto, Toronto, ON, Canada

Purpose: To compare the early and midterm outcomes of valve-in-valve (ViV) and redo surgical aortic valve replacement (re-SAVR) for aortic bioprosthetic valve degeneration.

Methods: Patients who underwent ViV and re-SAVR for aortic bioprosthetic valve degeneration between January 2010 and October 2018 were retrospectively analyzed. Patients with prosthetic valve endocarditis were excluded from the study. Mean follow-up was 3.0 years.

Results: 88 patients were included in the analysis, with 31 (37.3%) ViV and 57 (62.7%) re-SAVR. In the ViV group, patients were older (79.1 ± 7.4 vs 67.2 ± 14.1, p<0.01) and had an increased incidence of chronic kidney disease (54.8% vs 28.8%, p<0.01). Mean logistic EuroScore II for the ViV and re-SAVR groups were 9.5 ± 7.3 vs 11.1 ± 9.3, p=0.42. Postoperative prosthetic valve leakage (more than mild) was more frequent in the ViV group (48.4% vs 0%, p<0.01). In-hospital mortality was 0% and 7% for ViV and re-SAVR, respectively (p=0.30). There was no difference in in-hospital permanent pacemaker implantation (3.2% vs 8.8%, p=0.58), stroke (3.2% vs 7%, p=0.80), perioperative myocardial infarction (0% vs 10.5%, p=0.15), acute kidney injury (9.7% vs 15.8%, p=0.63), all cause infections (0% vs 8.8%, p=0.22), between ViV and re-SAVR groups. At 5-years, there was no difference in reintervention (3.2% vs 0%, p=0.86) and survival (78.3% vs 92.7%, p=0.10) between ViV and re-SAVR groups (Figure 1).

Conclusions: ViV and re-SAVR have a comparable short and midterm outcomes except for the incidence of paravalvular leakage.
Hypothesis and Purpose: The handover of patient information from paramedics to the receiving trauma team is vulnerable to communication errors such as interruptions, parallel conversations, repetition of information, and misinformation, which may negatively impact patient management and quality of care. The goal of this project is to introduce a structured protocol into an emergency clinical setting by implementing the previously validated handover tool, IMIST-AMBO, in a Canadian Level One Trauma Centre.

Methods: An educational video exemplifying the IMIST-AMBO tool was developed and will be disseminated to the Toronto Paramedic Services and Ornge. Implementation of the tool during the handover will be formally observed and recorded using a standardized data collection form by a trained observer over an eight-week period. Primary outcomes include handover metrics such as duration, adherence to protocol structure, number of parallel conversations, interruptions, and repetitions. Secondary outcome measures including perceived satisfaction with elements of the handover from the paramedics and trauma team.

Anticipated Results: We expect to reduce the frequency of interruptions, parallel conversations, informal handovers, and repetition of information. Furthermore, we anticipate increased completeness and efficiency of the handover, decreasing total handover duration. We expect perceived success and improved handover satisfaction amongst paramedics and the trauma team.

Conclusion: Improved handover procedures and enhanced interdisciplinary team performance may increase patient safety and quality of care. If successful adoption of the IMIST-AMBO protocol is displayed, this tool may be applied to other medical settings and implemented in multiple trauma centres across Canada.
ASSESSMENT OF EFFICACY AND SAFETY OF OSIMERTINIB FOR PATIENTS WITH INTRACRANIAL METASTATIC DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Anders W. Erickson¹, Priscilla K. Brastianos², Sunit Das³
¹Faculty of Medicine, University of Toronto, ²Division of Hematology/Oncology, Dana Farber/Harvard Cancer Center, Harvard Medical School, ³Division of Neurosurgery, St. Michael’s Hospital, University of Toronto

Hypothesis and Purpose: Osimertinib—a mutant epidermal growth factor receptor (EGFR) inhibitor that can penetrate the blood-brain barrier and inhibit tumor cell survival and proliferation in patients with non-small cell lung cancer (NSCLC) with specific EGFR mutations—may occupy a role in the treatment of patients with EGFR-mutant NSCLC and intracranial metastatic disease (IMD). The purpose of this study is to assess the efficacy and safety of osimertinib in the management of IMD.

Methods: Studies reporting intracranial outcomes for patients with EGFR-mutant NSCLC and IMD treated with osimertinib were included. Among 271 records identified in MEDLINE and EMBASE, 15 studies fulfilled eligibility criteria. Outcomes were pooled using a random-effects model. Risk of bias was assessed using the Cochrane Risk of Bias tool and modified Newcastle-Ottawa scale. Information extracted included study characteristics, intracranial efficacy measures, and safety measures. Meta-analyses were conducted to pool applicable outcomes.

Results: 15 studies reporting on 324 patients were included in the analysis. Combined CNS ORR and CNS DCR were calculated to be 64% (95% CI, 53–76%; n = 195), and 90% (95% CI, 85–93%; n = 246). Risk ratios for CNS ORR and CNS DCR were calculated to be 1.44 (95% CI, 1.06–1.96; n = 52) and 1.13 (95% CI, 0.96–1.33; n = 52). Included studies reported complete intracranial response rates of 7–23%, median best decrease in intracranial lesion size of 40–64%, and grade 3+ adverse event rates of 19–39%.

Conclusions: Findings reported here support a potential role for osimertinib for patients with EGFR-mutant NSCLC and IMD. Clinical decision-makers would benefit from the inclusion of patients with IMD in future trials to identify factors that predict responses to targeted therapy.
**GHRELIN, A NOVEL GROWTH HORMONE-RELEASING PEPTIDE, INHIBITS INFLAMMATORY RESPONSE AND APOPTOSIS DURING ISCHEMIA REPERFUSION INJURY DURING MURINE HEART TRANSPLANTATION**

Naoto Fukunaga, Roberto V. P. Ribeiro, Ved Bissoondath, Filio Billia, Mitesh V. Badiwala, Vivek Rao

Institute: Division of Cardiovascular Surgery and Cardiology, Peter Munk Cardiac Centre, University Health Network, and University of Toronto

**Purpose:** Ghrelin, a novel growth hormone-releasing peptide, has both anti-inflammatory and anti-apoptotic effects on human endothelial cells. Ischemia reperfusion injury (IRI) is an important risk factor for cardiac allograft vasculopathy. We evaluated the protective effects of ghrelin against IRI following murine heterotopic cervical heart transplantation (HCHT).

**Methods:** Donor hearts of C57BL/6J mice were heterotopically transplanted into C57BL/6J recipients. A day prior to HCHT, donor animals received ghrelin 300 nmol/kg intraperitoneally or saline (0.3ml). Upon reperfusion and on postoperative day 1, ghrelin or saline was administered. Donor hearts were procured on postoperative day 2.

**Results:** TUNEL-positive cells were significantly decreased in the ghrelin groups (0.38±0.21% vs. 5.74±3.68%; p = 0.0004). NF-kB p65 nuclear translocation was also reduced in the ghrelin groups compared to the control (3.17±1.84% vs. 19.28±13.14%; p = 0.0095). VCAM-1 (p = 0.0322), ICAM-1 (p = 0.0484) and NF-kB (p = 0.0130) levels were also significantly reduced in ghrelin-treated groups. No significant difference was observed in 8-isoprostane production between groups (47.67±13.14 pg/mg vs. 95.39±28.90 pg/mg; p = 0.1267).

**Conclusions:** Ghrelin inhibits the inflammatory response and apoptosis during transplant-related IRI. This study demonstrates the protective effects of ghrelin in IRI.
MINIMALLY INVASIVE SURGICAL APPROACHES ARE SAFE AND APPROPRIATE IN N2 COLORECTAL CANCER

Keegan Guidolin (SSTP)\textsuperscript{1}, Richard Spence\textsuperscript{1}, Sami Chadi\textsuperscript{1,2}, Fayez Quereshy\textsuperscript{1,2}

\textsuperscript{1}Division of General Surgery, University of Toronto, Toronto, ON
\textsuperscript{2}Division of General Surgery, University Health Network, Toronto, ON

Hypothesis and Purpose: The oncological safety of minimally invasive approaches (MIS) for advanced colorectal disease have been evaluated in the past. There is emerging evidence of oncological safety in T4 disease, however, such supportive data are lacking in N2 disease.

Methods: A retrospective cohort study was conducted using the American College of Surgeons National Surgical Quality Improvement Program’s generic and targeted colectomy datasets from 2014 to 2018 to compare nodal harvest (primary outcome) and perioperative complications of patients with pathological N2 disease treated with elective open and MIS resections. Patients were stratified by operative approach and compared using univariate and multivariate analysis.

Results: During the study period, 1,837 (31.9\%) patients underwent open and 3,907 patients underwent MIS colectomies for colorectal cancer (n=5,744). The median nodal yield was 20 (IQR 15-27) in the open and 21 (IQR 16-28) in the MIS resections (p<0.0001). Controlling for age, ASA, BMI, side of resection, and T and M Stage, the nodal harvest between the two groups in a Poisson regression analysis, was not significantly different. Perioperative complications were significantly higher upon univariate analysis in the open surgery group, with respect to key outcomes such as surgical site infection, anastomotic leak, post-operative ileus, and death (p<0.001). In the multivariate analysis, a composite of any complication was reduced by nearly half in the MIS group.

Conclusion: MIS approaches to colorectal cancer with N2 disease result in equivalent nodal harvests compared with open approaches, as well as lowering the rates of post-operative complications significantly. Our group supports the use of a minimally invasive approach in advanced nodal stage colorectal cancer in the appropriately selected patient.
EARLY ACUTE KIDNEY INJURY (AKI) FOLLOWING MAJOR BURNS

George Ho, Alan Rogers, Robert Cartotto
Division of Plastic and Reconstructive Surgery, Ross Tilley Burn Centre, Sunnybrook Health Sciences Centre, University of Toronto

Hypothesis and Purpose: AKI is a major complication of burn injury. The purpose of this study was to examine AKI that develops early (within 7 days) of burn injury.

Methods: Retrospective review of adults with burns ≥20% total body surface area (TBSA) admitted within 24 hours of injury to an adult American Burn Association verified burn center between 11/11/15 and 07/01/19. AKI was defined using the Kidney Disease: Improving Global Outcomes (KDIGO) urine and serum creatinine (sCr) criteria. Patients who developed AKI in the first seven days post burn (early AKI group) were compared to patients that did not develop AKI in the first seven days post burn (NoAKI group). Values are presented as median (1st-3rd IQR).

Results: We included 85 patients with age 46 (32-57) yrs, and %TBSA burn of 30 (24-47). Early AKI occurred in 53 (62%) of these patients. Patients who developed early AKI were significantly older [50 (41-61) yrs vs 38 (27-47) yrs], and significantly more were intubated in the first 24 hours post burn (91% vs 59%) compared to NoAKI patients. Resuscitation with high dose vitamin C (HDVC) was independently associated with a higher likelihood of developing early AKI (OR 5.5, 95% CI: 1.2, 24.9). HDVC (OR 5.5, 95% CI: 1.3, 24.9) and older age (OR: 1.0, 95% CI: 1.0, 1.1) were associated with very early AKI (onset day 0 or 1 post burn). Patients with early AKI had significantly higher in-hospital mortality than NoAKI patients (38% vs 9%). Development of stage 3 AKI (OR 11.0, 95% CI: 1.7, 72.4), along with older age (OR 1.1, 95% CI: 1.0, 1.2), and larger burn size (OR 1.1, 95% CI: 1.0, 1.1), were independently associated with higher mortality.

Conclusion: Early AKI is highly prevalent after major burn injury. Patients developing early AKI had significantly higher in-hospital mortality, greater age and larger burn size. HDVC resuscitation was independently associated with development of early AKI.
Degenerative cervical myelopathy (DCM) is caused by progressive compression of the cervical spinal cord. Surgical decompression (DEC), while effective in most cases, results in ischemia reperfusion injury (IRI) and hinders a return to baseline function. Remote ischemic preconditioning (RIPC) is a non-invasive intervention that uses transient ischemia distal to the site of injury to protect the host from ischemic insult. In this study, we posit that RIPC prior to DEC will enhance neurological recovery through the amelioration of DEC-induced IRI. DCM was induced in mice and at 12-weeks they either underwent: 1) hindlimb RIPC prior to DEC; or 2) DEC alone (n = 50, respectively). Acute (24h post-DEC) and chronic (5wk post-DEC) cohorts were subjected to molecular and behavioral analysis. Acutely, RIPC resulted in a significant decrease of nearly all proinflammatory markers relative to DEC alone (p < 0.05). Chronically, RIPC animals significantly outperformed both DEC and DCM groups in gait metrics including body speed, stride length, cadence, and swing speed (p < 0.05). In conclusion, RIPC when performed prior to DEC, reduces neuroinflammation and confers robust long-term neurological recovery relative to DEC alone. As a non-invasive procedure, RIPC can complement DEC for rapid translation into the clinic.
INCORPORATION OF DIALYSIS INTO EX-VIVO LUNG PERFUSION SYSTEM MAINTAINS HOMEOSTASIS AND STABILITY OF PORCINE DONOR LUNGS: A PILOT STUDY

Olivia Hough, Xinliang Gao, Chengliang Yang, Mamoru Takahashi, Andrea Mariscal, Antti Nykanen, Bruno Gomes, Aadil Ali, Marcelo Cypel, Christopher Chan, Shaf Keshavjee, Mingyao Liu
Latner Thoracic Surgery Research Laboratories, Toronto General Hospital Research Institute, and University of Toronto

Hypothesis and Purpose: Ex-vivo lung perfusion (EVLP) maintains marginal donor lungs at body temperature with ventilation and circulating perfusate, allowing for functional assessment prior to transplantation. Prolonged EVLP would allow for advanced time-dependent therapies for donor lung repair and reconditioning. We hypothesized that the addition of a dialysis machine to the EVLP circuit would maintain homeostasis of the donor lung and prolong EVLP duration.

Methods: Porcine donor lungs (n=3) were extracted and placed on the EVLP platform for 36 hours or until termination criteria (dynamic compliance < 15ml/cmH2O) was reached. Lungs were perfused with an acellular solution and closed atrium, according to the Toronto protocol. A dialysis machine was incorporated into the EVLP circuit with a custom-designed dialysate to continuously dialyze perfusate using continuous venovenous hemodialysis. Physiological function, electrolytes and inflammatory mediators in EVLP perfusate were measured hourly. In this pilot study, dialysis cases were compared to historical controls with similar protocol.

Results: Dialysis successfully prevented an increase in electrolyte levels and maintained glucose and lactate levels at baseline. EVLP was prolonged in the dialysis group (dEVLP) with a mean duration of EVLP reaching 32±6.93 h in the dEVLP group compared to 18.67±3.27 h in the historical control group. Percent lung survival at 24h of perfusion was 100% in the dEVLP group, while only 20% was seen in historical controls. Both lungs which survived to 36h of EVLP presented excellent lung function based on assessment by EVLP.

Conclusions: Dialysis may preserve lung function and length of EVLP by maintaining homeostasis of the lung. Following the results of this encouraging pilot study, a formal blinded experiment is being performed and is underway.
EXPRESSION OF PROGRAMMED CELL DEATH LIGAND (PD-L1) IN MENINGIOMA: CLINICAL UTILITY FOR PREDICTION OF TUMOR RECURRENCE AND ASSOCIATION WITH HYPOXIC RESPONSE AND NFKB2 ACTIVATION

Shirin Karimi, Sheila Mansouri, Yasin Mamatjan, Jeff Liu, Farshad Nassiri (SSTP), Suganth Suppiah (SSTP), Olivia Singh, Kenneth Aldape, Gelareh Zadeh

Background: Tumor recurrence is one of the most important clinical challenges in the management of meningioma patients. Prognostic significance of PD-L1 as a driver for immunosuppressive response and predictor for tumor growth has been demonstrated in several malignancies. **Hypothesis and purpose:** We studied the prognostic role of PD-L1 expression for tumor recurrence in meningioma and explored underlying activation mechanisms. **Method:** We analyzed a total of 93 meningioma cases diagnosed between 1998 and 2016 at University Health Network: F/M ratio 58/35; WHO grades I (43), II (42), III (9) with 47% recurrence rate and median follow up 6.97 years. **Results:** Immuno-histochemical (IHC) analysis showed PD-L1 expression in 33 (35%) cases with distinctive patchy distribution. Univariate and multivariate analyses confirmed that PD-L1 expression is an independent prognostic marker for recurrence free survival (RFS) after adjusting for extent of resection, WHO grade, and maximum tumor diameter (p<0.0001). Additionally, we performed Gen Set Enriched Analysis (GSEA) on RNA-seq data from 88 meningiomas using HUVEC hypoxia Dataset GSE89831 as reference to calculate the hypoxia score. PD-L1 expression was significantly higher in hypoxic meningiomas. Furthermore, analysis of PD-L1 in 3 different meningioma cell lines under normoxic and hypoxia by real-time RT-PCR indicated that in addition to the expected HIF1a target genes, PD-L1 mRNA level increased in hypoxia. Analysis of RNA-seq data from two GEO meningioma studies demonstrated prominent NFKB2 activation associated with PD-L1 mRNA expression. IHC analysis confirmed expression of NFKB2 protein in 26 (30%) cases, which correlated with PD-L1 expression. **Conclusions:** Our data strongly suggest the clinical utility of PD-L1 expression for prediction of tumor recurrence and a potential link between hypoxia and anti-cancer immunity in meningioma patients. These results also provide a rationale for a potential therapeutic role for PD-L1 inhibitors in clinically aggressive meningiomas.
CLINICAL UTILITY OF DNA METHYLATION PROFILING DIAGNOSTICALLY CHALLENGING CNS TUMORS

Shirin Karimi, Jeff Zuccato (SSTP), Sheila Mansouri, Yasin Mamatjan, Farshad Nasiri (SSTP), Suganth Suppiah (SSTP), Phedias Diamandis, David Munoz, Kenneth Aldape, Gelareh Zadeh
MacFeeter Hamilton Center for Neuro-oncology Research, Princess Margaret Cancer Center

Hypothesis and purpose: The development of DNA methylation-based classification represents a critical step in the molecular diagnosis of CNS tumors.

Methods and results: We report our experience on 55 CNS tumors enriched for primary challenging brain tumors. The methylation profiling was performed using the online DKFZ classifier. Of the 55 cases, 2 (4%) cases showed misleading profiles and the original pathology diagnosis of 15 (27%), cases were confirmed. Molecular integrated diagnosis of 38 (69%) cases were revised due to establishment of a new diagnostic entity in 24 (44%), determination of IDH (non-canonical) mutation status in 11 (20%), and final determination of 1p/19q co-deletion in three (5%) diffuse glioma cases. Methylation analysis had a dramatic impact on WHO grading; 12 (23%) upgraded and four (7%) downgraded. The molecular subtypes of medulloblastoma, ependymoma, and glioblastoma subclasses were determined in 36 (65%) cases. The copy number variation (CNV) analysis contributed to the final diagnosis in 40 (72%) cases. The MGMT promoter methylation status was determined in 17 of 20 (85%) glioblastoma cases. Of the initial 55 cases, 85% resulted in confirmation of initial diagnosis or change in molecular diagnosis, had Calibration score (CS) > 0.5, among which 51% had a CS >0.9. Furthermore, we observed higher CS in glioma IDH-mutant tumors in comparison to glioblastoma IDH-wild type cases (p=0.04). Methylation profiling resulted in the establishment of new diagnosis in 44% of the cases.

Conclusion: Our findings are in line with the recent studies that demonstrated clinical value of methylation profiling in both diagnostic decisions and estimation of prognosis in primary brain tumors. Our experience underscores clinical utility of methylation profiling of brain tumors as a reliable ancillary diagnostic tool in routine neuropathology practice.
REDUCED ATGL-MEDIATED ADIPOSE TISSUE LIPOLYSIS PROTECTS AGAINST HYPERMETABOLIC RESPONSE POST-BURN

Supreet Kaur, Priyal Shah, Christopher Auger, Marc G. Jeschke
Ross Tilley Burn Centre, Sunnybrook Health Sciences Centre, and University of Toronto

Hypothesis and Purpose: Accumulation of fat in white adipose tissue (WAT) is an evolutionarily conserved mechanism to aid our survival during high energy demand. A modern sedentary lifestyle has triggered many obesity-associated metabolic disorders. As a result, drugs triggering WAT lipolysis and browning have gained wide interest to combat metabolic disorders. However, hypermetabolic conditions, arising from burn injury or cancer, are thought to enhance the WAT lipolysis and browning that disturbs the energy balance and results in metabolic disease-associated complications. Here, we hypothesize that targeting ATGL lipase [using adipose-specific ATGL knockout mice and Atglistatin (ATGL inhibitor)] can reduce adipose tissue lipolysis and associated complications after burn injury.

Methods: This study has employed the adipose-specific ATGL knockout mice and C57Bl/6 mice model to assess the metabolic effects of ATGL lipase and Atglistatin treatment post 7 days of burn injury. Atglistatin (2mM/kg) treatment was initiated post one day of burn injury and was continued for 7 days.

Results: No effect was observed in food intake behavior and reduction in body weight was comparable in test versus control burn mice. ATGL knockout and Atglistatin treated mice resulted in reducing WAT lipolysis markers (such as ATGL and HSL) in inguinal WAT but no effect on lipolysis markers was observed in the liver. In addition, targeting ATGL lipase resulted in reducing systemic triglyceride and free fatty acid levels in burn-treated mice.

Conclusion: This work highlights the impact of targeting ATGL lipase using adipose-specific knockout mice and Atglistatin treatment on adipose tissue lipolysis and hepatic fat infiltration post-burn injury. However, the mechanistic changes induced by targeting ATGL lipase post-burn injury are still under investigation.
PLATELET WORKS AS A POINT OF CARE TEST FOR ASPIRIN RESISTANCE

Hamzah Khan, Muzammil Syed, Mohammed Al-Omran, Margaret Rand, Mohammad Qadura
Division of Vascular Surgery, St. Michael’s Hospital, and University of Toronto

Hypothesis & Purpose: Aspirin (ASA) is the first line antiplatelet medication prescribed to patients with peripheral arterial disease (PAD) and carotid artery stenosis (CAS). It has been reported that up to 30% of patients are “ASA Resistant”, having a lower than normal ability to inhibit platelet aggregation after standard dosing. Using Light Transmission Aggregometry (LTA) as a gold standard, we tested the hypothesis that Platelet Works, a point-of-care in vitro platelet function test could be used to diagnose ASA resistance. Methods: In this exploratory study, PAD and CAS patients presenting to St. Michael’s Hospital ambulatory clinics were recruited. Platelet Works was used to determine platelet activation in response to ADP, Collagen, and Arachidonic Acid (AA). Patients were considered resistant to ASA therapy if there was ≥ 20% light transmittance after AA induced platelet aggregation using LTA. Results: A total of 58 patients were recruited to this study (39 patients on 81mg ASA and patients not on ASA). First, ASA sensitivity was established using LTA. Our data demonstrated that 12 of the 39 patients on ASA were found to be resistant to their therapy. Analysis of the ASA resistant patients using Platelet Works demonstrated that these patients had 18% and 9% greater platelet activation in response to AA (p=0.002), and Collagen (p=0.046) respectively. Receiver Operating Characteristics (ROC) analysis demonstrated <51% platelet activity with AA to be a cut-off point for Platelet Works, to distinguish sensitive patients with a specificity of 95% and sensitivity of 64% (AUC=0.922, p<0.001). Conclusions: In conclusion, Platelet Works is a good candidate as a point-of-care test to investigate ASA sensitivity in patients taking 81 mg ASA. We have demonstrated that a cut-off of 51% of platelet activity can be used to distinguish ASA sensitive patients.
Hypotheses and Purpose: Proper documentation of burn injuries is essential as it can alter burn management. To ensure standardization across all major burn centres, the American Burn Association (ABA) has developed a list of mandatory information that must be collected upon admission in the emergency department (ED). The available literature has shown that ED documentation is often poor. At present, few studies have assessed the accuracy and completeness of ED documentation of burns. This study involves an audit and review of medical charts of patients that presented to the SickKids ED over a one-year period, with the aim to investigate the completeness and accuracy of documentation of burn injuries. We expect to find poor and inaccurate documentation in keeping with current literature.

Methods: A retrospective audit of 255 electronic medical records in Epic from burn patients seen in the ED between June 1, 2018 and June 1, 2019 was conducted with assessment for completeness and accuracy of documentation. The data collected was the standard information required by the ABA and data deemed important according to expert opinion and the SickKids burn team. Completeness was defined as the proportion of data elements completed. Accuracy was defined as the percent agreement between the size of burn reported in the ED note and that reported in the plastic surgeon’s consult note.

Results: Only 10% (n=38) of records were deemed complete. The elements most often found to be missing were dressing type and size of burn. There was an interclass correlation (ICC) of 0.68 (0.60-0.73) between the ED note and the plastic surgery consult note regarding burn size.

Conclusions: Burn documentation completeness was low overall and accuracy was moderate. This study demonstrates the need for more in-service education and a standardized template for proper burn documentation in the ED.
PURPOSE: Previous studies have linked physician burnout to inferior patient care and higher rates of medical error. American and French national-level studies have identified concerning levels of burnout (32% and 40%, respectively) amongst orthopaedic residents. The purpose of this study was to assess the mental quality of life (QOL) of orthopaedic residents within the largest Canadian training program and identify areas for program-led improvements.

METHODS: A 43-question anonymous survey was devised using a combination of the validated Physician Well-Being Index (PWBI, MedEd Web Solutions) and questions developed based on previously reported characteristics of training programs associated with increased risk of burnout (financial pressures, sleep deprivation, harassment, lack of free time, time at work, and daily microstressors). Statistical analysis was completed using paired T-test and ordinary least square regression model.

RESULTS: The response rate was 69%. Using the PWBI validated threshold, nearly two thirds (62%) of respondents demonstrated low mental QOL while nearly a third of respondents (30%) believe wellness is unachievable in residency. Trainee-level correlated positively and significantly with increasing PWBI scores (p-value <0.02). Half of the respondents wished they had pursued a career outside of medicine; a trend that positively increased as residents progressed through their training. There was no significant correlation between PWBI scores and gender, ethnicity, dependent-status.

CONCLUSION: A greater percentage of local orthopaedic residents demonstrated high risk for burnout compared to previously reported international cohorts. Findings suggest an accumulation of emotional exhaustion during residency and acquired job dissatisfaction.
HEMODYNAMIC VARIATIONS INDUCED BY FENESTRATED ENDOVASCULAR ANEURYSM REPAIR

Wei-Chih Patrick Lin¹, Matthew G. Doyle¹,², Cristina H. Amon¹,³, Thomas L. Forbes²
¹Department of Mechanical and Industrial Engineering, University of Toronto
²Division of Vascular Surgery, Department of Surgery, University Health Network & University of Toronto
³Institute of Biomaterials and Biomedical Engineering, University of Toronto

Hypothesis/Purpose: The purpose of this study is to determine whether hemodynamic indicators in post-operative fenestrated endovascular aneurysm repair (FEVAR) cases differ significantly from the corresponding pre-operative cases.

Methods: Computational fluid dynamics (CFD) simulations were conducted in SimVascular to simulate blood flow in patient-specific geometries. Pre-operative and post-operative computed tomography (CT) angiography images were obtained and segmented using VMTK. The inlet boundary condition was based on a literature-derived descending aorta flow waveform while 3-element Windkessel models were imposed on all branch outlets. CFD simulations were performed for one set of pre/post-operative patient-specific geometries.

Results: Post-operative results show that the peak pressure in the hepatic artery was ~4 mmHg higher than in the pre-operative case, with a mean pressure difference of 2 mmHg. Mean flow rate in the hepatic artery however did not change significantly (pre-operative 5.06 cc/s vs post-operative 5.14 cc/s). The post-operative peak pressure in the left renal artery was approximately 2 mmHg lower than the pre-operative case, but the mean pressure and flow rate did not change significantly. Oscillatory shear index (OSI) patterns were also different between the pre- and post-operative cases especially in the repaired aneurysm region.

Conclusions: Pressure and flow rate behaviours are slightly altered in select visceral branch vessels following FEVAR repair. The hepatic and left renal arteries exhibited the most change in the transient behaviour. Additionally, qualitative differences in OSI were observed. Further simulations and post-processing are in progress to affirm these results and their significance.
COMPUTATIONAL FLUID DYNAMICS IN TETRALOGY OF FALLOT REPAIR: SENSITIVITY OF ENERGY EFFICIENCY CALCULATIONS TO BOUNDARY CONDITIONS

Leslie Louvelle¹, Matthew Doyle², Glen Van Arsdell³, Osami Honjo⁴, Cristina Amon¹,²
¹Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario
²Department of Mechanical and Industrial Engineering, University of Toronto, Toronto, Ontario
³Division of Cardiac Surgery, University of California Los Angeles, Los Angeles, USA
⁴Division of Cardiac Surgery, Department of Surgery, University of Toronto, Toronto, Ontario

Purpose: Surgical repair of Tetralogy of Fallot (TOF) can produce a variety of potential postoperative geometries, some of which may be hemodynamically superior to, or more energy efficient than, others. Energy efficiency can be estimated using computational fluid dynamics (CFD) simulations of the postoperative geometries, however, the accuracy of these simulations is dependent on the boundary conditions imposed on the geometry’s inlet(s) and outlet(s). The purpose of this work is to investigate the sensitivity of the calculated energy efficiency to changes in the boundary conditions.

Methods: 16 postoperative TOF patient geometries were segmented from cardiac magnetic resonance angiography imaging to produce volumes of interest encompassing the right ventricular outflow tract and left and right pulmonary arteries. CFD simulations were completed in SimVascular with a range of inlet flow rates and outlet resistances, to reflect potential variability in cardiac output or downstream pulmonary vascular resistance. Energy efficiency was calculated for each case.

Results: Changes of ±30% in the flow rate resulted in an approximately ±2.5% change to the efficiency across all patients, with increased flow rates associated with reduced efficiency. Modification of the outlet resistances had a more significant effect on some patients than others. For those geometries sensitive to the flow resistance changes, energy efficiency ranged maximally 20% across the resistance values tested.

Conclusions: These results suggest that downstream pulmonary vascular resistance, and the subsequent effect on flow splitting at the pulmonary artery bifurcation, is a significant factor for some geometries in determining energy efficiency from CFD calculations.
NEUROPROTECTIVE EFFECTS OF A NOVEL, ANTI-INFLAMMATORY COMPOUND AD-16 IN NEONATAL HYPOXIC-ISCHEMIC BRAIN INJURY AND ADULT ISCHEMIC STROKE

Zhengwei Luo, Zhihua Huang, Zhong-Ping Feng, Hong-Shuo Sun
Department of Surgery, Department of Physiology, University of Toronto

Hypoxia-ischemia (HI) brain injury in newborn infants is one of the most common causes of acute mortality and chronic neurologic morbidity worldwide. Ischemic stroke is the second most common cause of death in adults. Both HI and ischemic stroke induce neuroinflammation that can aggravate brain damage.

**Hypothesis:** Inhibition of neuroinflammation exerts protective effects in both HI and ischemic stroke.

**Purpose:** To assess inhibition of neuroinflammation as a potential therapeutic approach by evaluating AD-16, a novel, potent anti-inflammatory compound.

**Methods and Results:** We investigated the *in vivo* neuroprotective effects in both the neonatal hypoxic-ischemic (HI) brain injury model and adult permanent middle cerebral artery occlusion (MCAO) model in mice. We showed that administration of AD-16, either prior to or after injury onset reduced brain infarction volume and preserved neurobehavioral outcomes in the neonate, but not in the adult. With Western immunoblots, we found that AD-16 inhibited the caspase-3 and STAT-3 signaling, which could potentially be the underlying mechanism for its neuroprotection.

**Conclusion:** Our study establishes the role of neuroinflammation in HI and suggests that targeting neuroinflammation is a potential therapeutic strategy for reducing HI-related brain damage.
THE EFFECT OF ENDOTHELIAL PROGENITOR CELLS AND LOCAL ANTIBIOTICS ON LOW-GRADE INFECTION OUTCOMES IN A CRITICAL SIZE BONE DEFECT MODEL

Richard Magony, Aaron Nauth, Emil Schemitsch, Stephane Gagnon
Keenan Research Centre for Biomedical Science, University of Toronto

Hypothesis and Purpose: We expect that endothelial progenitor cells (EPCs) will promote infection eradication, and that the addition of local vancomycin and rifampicin will further facilitate this outcome. We aim to evaluate the effect of EPC-based therapy on infection outcomes in the context of a low-grade infected fracture non-union, and to investigate how the presence of local antibiotics affects these EPC-induced infection outcomes.

Methods: A 5-mm critical-size mid-diaphyseal defect is established in the right femur of 250-300g male Fischer 344 inbred rats (n = 20) and stabilized with a mini-plate and screws. A gelatin scaffold contaminated with $10^3$ CFUs of methicillin-sensitive *staphylococcus epidermidis* is then placed in the defect site. Two weeks later, a second surgery is performed to insert a scaffold with one of four treatments: 1) control (empty), 2) EPCs, 3) vancomycin + rifampicin, and 4) EPCs + vancomycin + rifampicin. The EPCs are isolated from syngeneic donor rats and cultured over eight days prior to the second surgery. The dosages used are $2\times10^6$ EPCs and 25 mg/kg each of vancomycin and rifampicin. The primary outcome measure is microbiological analysis of cultured tissue samples taken during the second surgery and after animal sacrifice, and radiographic and serological analysis are treated as secondary outcome measures. Statistical analyses will be performed using one-way ANOVA and Tukey’s post-hoc test.

Results: Thus far, seven animals have been sacrificed and EPC- (n = 2) and vancomycin + rifampicin-treated (n = 2) groups have shown the highest levels of infection eradication in terms of culture results. More results are to come from the remaining rats in the upcoming weeks.

Conclusions: The study is ongoing and it is too early to draw any definitive conclusions, but data collection is in progress and we expect to have final results by early April.
LONG-TERM FOLLOW-UP FOLLOWING ADVANCED ENDOVASCULAR THORACOABDOMINAL AORTIC ANEURYSM REPAIR: A SINGLE-CENTRE EXPERIENCE

Daniyal N Mahmood, Rodolfo Rocha, Maral Ouzounian, Kong Teng Tan, Thomas F Lindsay
Division of Cardiac and Vascular Surgery, Toronto General Hospital, University of Toronto, Toronto, ON

Purpose: We reviewed outcomes of patients with thoracoabdominal aortic aneurysms (TAAA) repaired using branched or fenestrated endovascular devices for complications and long-term survival. Methods: Data was collected both prospectively and retrospectively with institutional ethics approval. Results: Seventy-eight consecutive patients underwent endovascular TAAA repair using B/FEVAR stent-grafts at our institution from June 2008 to July 2019 (47 male; mean age 74 ± 7 years) with a median follow-up for 5.43 years. Graft deployment was successful in all patients. Target vessel revascularization was successful in 276 of 290 (95.2%) vessels: 57 of 65 celiac arteries, 76 of 76 superior mesenteric arteries, 74 of 76 right renal arteries, and 69 of 73 left renal arteries. Seventeen branches over sixteen (20.5%) patients required reintervention for occlusion, endoleaks, and/or target vessel realignment during their hospital stay. Thirty-day mortality was observed in 8 (10.3%) patients. In the surviving patients, 13 (18.6%) developed perioperative spinal cord ischemia. Postoperative stroke occurred in 5 (6.4%) patients, acute myocardial infarction in 6 (7.7%) patients, 1 (1.3%) patient suffered renal failure requiring permanent dialysis at discharge, and 3 (3.8%) patients suffered bowel ischemia requiring reintervention. At 5 and 9 years, freedom from all-cause mortality was 54% (95% CI, 0.42-0.70) and 29.3% (95% CI, 0.16-0.53), respectively (Fig 1). There were no deaths related to aneurysm rupture. Conclusion: Endovascular repair of TAAAs was associated with a high rate of technical success and prevented rupture. While the rate of early mortality and morbidity is low, secondary reintervention rates indicate the need for further improvements and continuous patient follow-up.
Objective: Meningiomas would display risk of early tumor recurrence, but the inter-observer variability among pathologists for grading and some indistinguishable features of meningioma under the microscope prevent accurate prediction of recurrence risk that critically limits appropriate treatment and management of patients who may benefit from adjuvant radiation therapy. Our goal is to develop clinical machine-learning tool to predict early recurrence risk in each meningioma patient using DNA methylation signatures and prognostic clinical factors.

Method: The predictor is based on (1) GBM (generalized boosting machine) classification model to calculate the probability of recurrence over a time cut-off, and (2) continuous survival random-forest modelling to calculate the probabilities of a recurrence over various time frames. We processed over 500 meningioma samples using our machine-learning model that predicts probability of tumor recurrence based on methylation data. We used recurrence as a binary outcome (yes/no) and developed a predictor to predict the probability of recurrence at 5 years.

Result: We validated the predictor using independent external datasets using the selected probes and model developed based on the original discovery dataset. Methylation-based predictor distinguishes clear risk groups in each independent validation cohort. We found that methylation based predictor has potential to identify risk while determining the choice of adjuvant treatment (radiation vs. observation) in patients with grade II meningiomas. The genomic predictor also more reliably predicts 5-year recurrence free survival compared to a grade-based model.

Conclusion: This novel predictor outperformed established standard diagnostic tests. This predictor could be used to individualize decisions in the clinic regarding whether to treat patients with adjuvant radiation therapy versus observation alone.
Hypothesis and Purpose: Impaired fetal lung development is the recognized cause of poor outcome for babies with congenital diaphragmatic hernia (CDH). We showed that administration of extracellular vesicles derived from amniotic fluid stem cells (AFSC-EVs) restores lung branching morphogenesis in fetal rats with CDH. Herein, evaluated whether AFSC-EV administration could promote maturation of hypoplastic fetal lungs in experimental CDH.

Methods: AFSC-EVs were isolated from conditioned medium by ultracentrifugation and characterized for size, morphology, and canonical protein markers. AFSC-EV RNA cargo was isolated (SeraMir) and sequenced (NextSeq). Lung explants were harvested at E14.5 from fetuses of dams that received nitrofen at E9.5. Explants were treated with vehicle (nitrofen group) or AFSC-EVs (nitrofen+AFSC-EV group) for 72h. Explants were compared for cell proliferation (EdU) and distal lung progenitor cells (Sox9). Lung epithelial cells were isolated from both groups and sequenced (NextSeq).

Results: Nitrofen exposed lungs treated with AFSC-EVs had more proliferating cells than lungs treated with vehicle. The latter had more Sox9+ cells compared to AFSC-EV treated lungs. Most proliferating cells in AFSC-EV treated lungs were differentiated epithelium, contrarily to untreated lungs whose proliferating cells were Sox9+. AFSC-EV cargo was abundant in mir-17~92 cluster that controls lung cell proliferation and differentiation.

Conclusions: In experimental CDH, nitrofen exposure retains fetal lungs at an immature state. Conversely, AFSC-EV administration stimulates epithelial proliferation and differentiation, possibly through a miRNA-mediated mechanism. AFSC-EVs contain microRNA that are essential for normal fetal lung development.
Hypothesis & purpose: Only 10% of patients with pancreatic adenocarcinoma (PAC) undergo curative-intent resection, however many may have a non-therapeutic operation. This may lead to worse oncologic outcomes and add burdens to patients and the healthcare system.

Methods: We conducted a population-based analysis of operations for patients with PAC in Ontario between 2004 and 2017 by linking provincial administrative datasets. Non-therapeutic operations included diagnostic laparoscopy (DL), exploratory laparotomy (EL), biliary-enteric bypass (BP), and other operation (OO). Clinical outcomes and healthcare cost were analyzed.

Results: Of 19,874 patients with PAC, 3,867 underwent an operation, and 1,002 were non-therapeutic: 75 had DL, 118 EL, 579 BP and 230 OO. The median length of stay was 1 (DL), 8 (EL), 16 (BP), and 11 (OO) days (p<0.001). The median overall survival was 5 (DL), 3.8 (EL), 3.7 (BP), and 4.2 (OO) months (p=0.013). Few patients made it to systemic chemotherapy: 57% (DL), 42% (EL), 37% (BP), and 36% (OO) (p=0.005). The interval between operation and systemic chemotherapy was variable: median of 37 (DL), 42 (EL), 49 (BP), and 50 (OO) days (p=0.002). The median cost of the index admission was $5,793 (DL), $11,868 (EL), $25,575 (BP), and $16,853 (OO; p<0.001).

Conclusion: A significant number of patients undergo non-therapeutic operations for PAC, with poor outcomes, and a high cost to the system. Further research should investigate how this burden to patients and the healthcare system can be reduced.
Background: Neural stem cell (NSC) therapy shows promise as a regenerative therapy of Central Nervous System (CNS) damage. However, transplanted NSCs into the CNS often do not sufficiently integrate with endogenous tissue, resulting in suboptimal regeneration. Recently, researchers discovered that more successful transplant attempts were observed in NSC grafts that were derived from the same region they were transplanted into.

Purpose & Hypothesis: To characterize regional identity of spinal and brain-derived NSCs throughout the transplant process. NSCs will retain their identity following expansion, differentiation, and transplantation.

Methods: Rat embryos were isolated and brain and spinal cord-identity NSCs were dissected. Following this, NSCs were expanded into neurospheres, further differentiated into mature cells, and eventually will be transplanted in vivo into either matching or discordant environments. RT-qPCR of regional identity homeobox (Hox) gene markers will be used to confirm NSC identity.

Results: After expansion, differentiation, and RT-qPCR, spinal-derived NPCs exhibited Hox paralog expression HoxA4 through HoxD10. Cortically-derived NPCs do not express paralog groups 4-12, but rather exhibit enhanced expression of brain Hox markers, such as Otx2.

Conclusion & Future Directions: These results will further support idea that NSCs derived from different regions of the CNS retain their identity in a variety of conditions. As such, future co-culturing experiments and in vivo transplants may confer that regional identity of NSCs are maintained, and that matching cell identity to a transplant environment can facilitate optimal transplantation.
CRISPR/CAS9-MEDIATED EPIGENOME EDITING OF THE IL-10 GENE IN THE DONOR LUNG FOR TRANSPLANTATION

Kumi Mesaki, Stephen Juvet, Zehong Guan, Tereza Martinu, Marcelo Cypel, Mingyao Liu, Shaf Keshavjee
Latner Thoracic Laboratories, University Health Network, and University of Toronto

Objective: Inflammatory injury related to donor lung preservation and ischemia reperfusion is a major challenge in lung transplantation (LTx) that leads to low utilization of donor lungs and primary graft dysfunction. We propose to develop CRISPR/Cas9-based gene therapy to modify donor lungs prior to implantation. As a proof of concept, we aim to achieve CRISPR/Cas9-mediated targeted activation of the IL-10 gene, a potent anti-inflammatory cytokine, in rat lungs via trans-airway administration of adenoviral vectors.

Methods: An adenoviral vector expressing a Cas9 activator (dSaCas9-VPR) and either one or two effective guide RNAs (single gRNA group and two gRNAs group, respectively), were generated and administered to rat lungs via airway at a dose of 1E8 PFU/rat with immunosuppression similar to that received by transplant recipients (cyclosporine, prednisone and azathioprine). Treated lungs were analyzed after 72 hours for endogenous IL-10 gene activation and lung condition in comparison with the control group, which received the diluent without virus.

Results: The two gRNA group demonstrated significantly higher expression of the rat IL-10 gene compared to the single gRNA group (relative expression: 19.0±10.76 vs 2.89±0.78, p=0.026) and the control group (1.28±1.18, p=0.028). There was no significant increase in the expression of inflammatory cytokines TNFα, IL-6, and IL-1β in the two gRNA group compared to the control group. Lungs in all groups demonstrated good lung function and minimal signs of vector-related inflammation considered acceptable for transplant.

Conclusion: We have achieved targeted activation of the IL-10 gene using CRISPR/Cas9 in rat lungs. This strategy will provide a framework for our goal of creating epigenetically modified donor organs to optimize donor lung utilization and outcomes after LTx.
Hypothesis and Purpose: Microbial infection in donor lungs decreases organ utilization in transplantation. Previous in vitro studies have demonstrated high-dose gaseous Nitric Oxide (gNO) to be effective against bacteria, however, this concept has not been studied in the context of lung transplantation. The present study explores the antimicrobial effects in vitro and the ex vivo safety of continuously inhaled high-dose (iNO).

Methods: Effects of 200 ppm of gNO for 6h on clinical relevant strains of bacteria were performed in vitro. Safety of continuous high-dose iNO was studied in a porcine EVLP model. Donor lungs with minimal cold ischemia (2h) were randomized into control (medical air + O2 21%) and treatment (medical air + O2 21% + iNO 200 ppm), n=4 each. Physiologic and biologic measures were monitored over 12h of EVLP.

Results: gNO significantly reduced all strains of bacteria in Log10 CFU/mL when compared to controls (n=3 per group): P. aeruginosa (5.8 ± 1.27 vs 9.2 ± 0.4, p= 0.01), S. aureus (5.6 ± 0.65 vs 9.1 ± 0.66, p= 0.002), E. coli (5.3 ± 1.20 vs 9.4 ± 0.47, p= 0.005) and Burkholderia cepacia (7.0 ± 0.51 vs 8.9 ± 0.57, p= 0.01). No significant adverse effects in lung function during EVLP were observed in the treated group. Inflammatory cytokines (IL-1b, IL-6 and IL-8) at 1, 6 and 12h were similar between control and treatment. High levels of nitric dioxide (NO2) would lead to toxic effects. For all the treatment cases the levels of NO2 were < 2.8 ppm, considered safe.

Conclusion: Continuous high dose gNO is effective in reducing common respiratory pathogens in vitro. iNO appears to be safe during an extended time on the EVLP platform based on physiologic and inflammatory assesments. We are further exploring the efficacy of this approach using human lungs declined for transplantation. If successful, high-dose iNO could be a part of EVLP clinical protocols.
A NOVEL EX VIVO HUMAN PERITONEAL MODEL REVEALS PLK4-DEPENDENCE OF PERITONEAL METASTASIS IN GASTRIC ADENOCARCINOMA (GCa) CELLS

Deanna Ng, Aiman Ali, Denise Eymael, Marco Magalhaes, Carol J Swallow
University of Toronto

Hypothesis and Purpose: Spread within the peritoneal cavity renders gastric cancer (GCa) patients incurable, and causes intractable symptoms. We seek to understand the underlying mechanisms of peritoneal metastasis in GCa. In breast cancer xenografts, the oncogene Plk4 promotes cancer cell migration and invasion. We hypothesize that Plk4 facilitates GCa peritoneal metastasis by driving invasion through the mesothelial cell layer. Here, we test the effect of Plk4 using human peritoneal explants to recapitulate the microenvironment of GCa peritoneal metastasis. Methods: Fresh peritoneal tissue samples taken from patients undergoing abdominal surgery were suspended above a monolayer of red fluorescent stained AGS GCa cells and cultured for 10d. En face images were captured by confocal microscopy and tissue cross-sections taken for H&E staining q24h. Motility of AGS cells within the ex vivo peritoneal tissue (day 1), interaction with the mesothelial layer (day 7), and depth of invasion (day 7) were assessed. Mesothelial cell clearance by AGS cells was measured in an in vitro model. Results: Depletion of Plk4 to 35% of shGFP control was achieved by shPlk4 in AGS cells. Plk4-depleted cells displayed reduced motility, as well as impaired interaction with and invasion into peritoneal tissue; mesothelial cell clearance by AGS cells was also suppressed by Plk4 depletion (n=3 independent experiments, *p<0.001, Table).

<table>
<thead>
<tr>
<th>AGS cells</th>
<th>AGS cell motility within peritoneum, microns/sec, median (IQR)</th>
<th>Interaction with mesothelium, AGS cell #/HPF, median (IQR)</th>
<th>Invasion into peritoneum, total microns, median (IQR)</th>
<th>Mesothelial cell clearance, FITC intensity vs. time 0 (%) median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>shGFP (control)</td>
<td>0.038 (0.020-0.045)</td>
<td>133 (90-190)</td>
<td>26 (20-34)</td>
<td>59 (38-93)</td>
</tr>
<tr>
<td>shPlk4</td>
<td>0.014 (0.006-0.022)*</td>
<td>47 (32-59)*</td>
<td>12 (12-14)*</td>
<td>90 (75-100)*</td>
</tr>
</tbody>
</table>

Conclusion: In a human peritoneal explant model, Plk4 drives peritoneal invasion by GCa cells. Targeted Plk4 inhibition could contribute to quantity and quality of life in GCa patients who are at high risk of peritoneal metastasis.
BIASING MURINE NEURAL PROGENITOR CELLS TOWARD AN OLIGODENDROGENIC FATE

Katarzyna Pieczonka, Mohamed Khazaei, Michael G. Fehlings
Genetics and Development, Krembil Research Institute, University Health Network
Division of Neurosurgery, Department of Surgery, University of Toronto

Background: Myelin structure is particularly susceptible to dysregulation after spinal cord injury (SCI), ultimately contributing to impaired signal conductivity in the central nervous system (CNS). Neural progenitor cell (NPC) transplantation represents a potential regenerative approach for promoting remyelination, however the injury microenvironment predominantly directs NPC differentiation into astrocytes as opposed to oligodendrocytes.

Purpose and Hypothesis: Our lab has successfully developed a protocol for priming human neural progenitor cells (NPCs) toward an oligodendrogenic (oNPC) fate. Transplanted human oNPCs effectively differentiate into a greater ratio of oligodendrocytes and promote myelination and functional recovery in the immunocompromised RNU rat. Moving forward, we aim to bias murine NPCs toward oNPCs for transplantation into the mouse, in order to avoid the need for immunosuppression.

Methods: Murine induced pluripotent stem cells will be differentiated into NPCs. They will subsequently be exposed to culture conditions adapted from our human oNPC protocol that mimic oligodendrogenic developmental cues. Briefly, the cells will be caudalized using B27 and N2 supplements, retinoic acid and EGF, followed by ventralization using the sonic hedgehog agonist, Purmorphamine. The cell differentiation will then be characterized using immunohistochemistry and RT-qPCR.

Results: It is expected that this protocol will bias murine NPCs toward a pro-oligodendrogenic fate.

Conclusion: Murine oNPCs will be a safer alternative than human oNPCs and will allow us to study demyelination and remyelination in mice without immunorejection.
IN VIVO ISOLATED LUNG PERFUSION (IVLP) FOR DELIVERY OF HIGH DOSE CHEMOTHERAPY FOR THE TREATMENT OF COLORECTAL LUNG METASTASES

Khaled Ramadan (SSTP), Bruno Gomes, Arnaud Mbadjeu Hondjieu, Aizhou Wang, Rafaela Ribeiro, Anajara Gazzalle, Aadi Ali, Shaf Keshavjee, Thomas Waddell, Marcelo Cypel
Latner Thoracic Research Laboratories, University Health Network, University of Toronto

Hypothesis and Purpose: Lung metastases occur in 15-20% of patients with colorectal carcinoma. Despite optimal therapy, including complete metastatectomy when possible with or without systemic chemotherapy, survival remains poor. Residual micrometastatic disease, not resected during metastatectomy, is inadequately treated by chemotherapy as doses are limited by systemic toxicities. In Vivo Lung Perfusion (IVLP) can deliver targeted high-dose chemotherapy to the lungs while avoiding systemic toxicities. Our primary objective was to determine the dose-limiting pulmonary toxicity of oxaliplatin chemotherapy delivered by IVLP.

Methods: 12 Yorkshire male pigs were used. Left lung IVLP was performed for 3 hours. An accelerated titration dose-escalation study design was employed whereby oxaliplatin doses were sequentially doubled if no clinically significant toxicity was observed, defined as a PaO2/FiO2 ratio < 300mmHg or severe acute lung injury on biopsy. At 72-hours post-op, CT imaging of lungs was performed prior to sacrifice. Lung physiology, airway dynamics, gross appearance and histology were assessed before and during IVLP, at reperfusion, and at sacrifice.

Results: After an initial training phase, no mortality, systemic toxicity, or adverse events related to the procedure were observed. There was no lung injury at the time of IVLP for any case. At sacrifice, clinically significant lung injury was observed at 80 mg/L of oxaliplatin, with a PaO2/FiO2 ratio of 112 mmHg. Mild and subclinical lung injury was observed at 40 mg/L, with this dose being repeated to confirm safety.

Conclusion: A stable and reproducible porcine 3-day IVLP survival model was established. Oxaliplatin delivered by IVLP showed delayed-onset toxicity that was not apparent at the time of reperfusion, with a maximal-tolerated dose of 40mg/L. This information will inform initiation of a clinical trial examining IVLP delivery of oxaliplatin at our institution.
Purpose: Immediate breast reconstruction has many advantages but is associated with higher complication rates than delayed reconstruction. Complications can delay the delivery of adjuvant cancer treatments. This study aimed to develop and validate a risk stratification model for the prediction of peri-operative complications in immediate microvascular breast reconstruction.

Methods: The association between patient and treatment variables and peri-operative complications was evaluated in a retrospective cohort of 351 women undergoing immediate breast reconstruction using free deep inferior epigastric artery perforator (DIEP) flaps. Multivariable logistic regression was used to determine the strength of association and weighted scores were assigned. Using cumulative risk scores, patients were stratified into low, intermediate and high-risk groups. The model was then validated in a prospective cohort of 100 consecutive patients.

Results: Obesity, smoking, prior radiation and comorbidities were important predictors and incorporated into the risk model. Complications occurred in 23.5% of low-risk (95%CI:17.7–29.2), 38.4% of intermediate-risk (95%CI:29.2-47.5) and 53.9% of high-risk (95%CI:33.3–74.4) patients. Validation confirmed a linear relationship between the risk stratification categories and complications in a model with good predictive power (c-statistic=0.7, 95%CI:0.6–0.8).

Conclusions: A simple risk score, based on known pre-operative variables, provides accurate risk stratification for patients considering immediate microvascular breast reconstruction.
GENERAL HEALTH OUTCOMES FOLLOWING DISTAL CLAVICLE FRACTURES: RESULTS FROM A PREVIOUS RANDOMIZED CONTROLLED TRIAL

Christine Schemitsch, Aaron Nauth, Jeremy Hall
Division of Orthopaedic Surgery, St. Michael’s Hospital, University of Toronto

Purpose: The decision whether to operate or to treat distal clavicle fractures conservatively remains controversial. The purpose of this study was to examine general health outcomes in patients who were randomized to operative or non-operative treatment for distal clavicle fractures.

Methods: The SF-36 scores from a previous randomized controlled trial were analyzed. Patients who had sustained a displaced, type II distal clavicle fracture were randomized to either conservative treatment or surgical intervention. Patients completed the SF-36 at baseline, 6 weeks, 3 months, 6 months, 12 months, and 24 months. Both the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were calculated from the SF-36. A linear mixed model was used to predict the PCS and MCS scores over time and between groups.

Results: Fifty-seven patients were randomized; twenty-seven patients to the operative group and 30 to the non-operative group. There were no significant differences in the baseline characteristics between the two groups. Analysis of the PCS scores demonstrated no difference between the operative and non-operative groups at any time point (P = 0.773). By two years, PCS scores in the conservative group were similar to pre-injury levels (mean difference = 2.42, 95% CI = -5.23 to 0.39). In the operative group, PCS scores at two years were lower than pre-injury levels (mean difference = 4.89, 95% CI 1.86 to 7.92). Analysis of the MCS scores demonstrated that there were no significant differences between the two groups at any time point (P = 0.35). In both groups, MCS scores at 2 years were similar to pre-injury scores (conservative group: mean difference = 1.25, 95% CI -2.78 to 5.29; operative group: mean difference = -3.04, 95% CI -7.41 to 1.31).

Conclusion: The results of this study demonstrated that there was no difference in general health outcomes between operative and non-operative groups for distal clavicle fractures at 1 and 2 years. Our findings suggest surgical intervention for distal clavicle injuries appears to have uncertain benefits.
PREDICTION OF BIRD-BEAK CONFIGURATION FORMATION USING FINITE ELEMENT SIMULATIONS OF THORACIC ENDOVACULAR AORTIC REPAIR

Negin Shahbazian\textsuperscript{1}, Matthew G Doyle\textsuperscript{1,2}, Cristina H Amon\textsuperscript{1,3}, Thomas L Forbes\textsuperscript{2}

\textsuperscript{1}Department of Mechanical and Industrial Engineering, University of Toronto, Toronto, Ontario
\textsuperscript{2}Division of Vascular Surgery, Department of Surgery, University of Toronto, Toronto, Ontario
\textsuperscript{3}Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario

Purpose and Hypothesis: During thoracic endovascular aortic repair (TEVAR), a wedge shape gap at the proximal stent graft (SG) attachment site, called a bird-beak configuration (BB), can form due to poor wall apposition, leading to complications, such as type Ia endoleaks. The hypothesis is that the proximal landing position and SG design parameters contribute to BB formation. The purpose of this work is to assess and quantify the impact of these factors on the occurrence of BB using realistic computation models of TEVAR.

Methods: Realistic computational models of the aorta and two commercial SGs with 0\% and 5.5\% oversizing were developed. SG deployment simulations were performed for different proximal landing positions and the BB length and angle were measured for each simulation.

Results: Thirteen simulations were performed using the two SGs in landing zones 0-3. The average BB length and angle were reduced for 5.5\% oversizing compared to 0\%. The average length and angle for 0\% and 5.5\% oversizing was 7.5 mm vs. 3.6 mm and 25.6° vs. 9.5°, respectively. The largest BB length of 11.5 mm in zone 1 and the largest BB angle of 39.7° in zone 0 were found for 0\% oversizing. There was a direct correlation between the BB angle and the slope of the centerline in the proximal landing position. There was a direct correlation between the length of the BB and the absolute value of the centerline slope at the proximal landing site.

Conclusions: Previous studies have indicated that BB length and angle are directly correlated with type Ia endoleaks. These results suggest that computational simulations of TEVAR may be useful in predicting the impact of SG selection and TEVAR landing position on the risk of BB related type Ia endoleaks. Validation of the simulation results will be carried out using patient-specific geometries and clinical information.
MECHANICAL PRIMING ON SKIN-SOFT CULTURE SURFACES ENHANCES THE WOUND HEALING POTENTIAL OF HUMAN MESENCHYMAL STROMAL CELLS

Dong Ok (Donna) Son\textsuperscript{1,2}, Marielle Walraven\textsuperscript{1,2}, Michelle Im\textsuperscript{1,2}, Akosua Vilaysane\textsuperscript{1,2}, John E Davies\textsuperscript{1}, Boris Hinz\textsuperscript{1,2}

\textsuperscript{1}Laboratory of Tissue Repair and Regeneration, \textsuperscript{2}Faculty of Dentistry, University of Toronto, Toronto, Ontario, Canada

RATIONALE: Production of mesenchymal stromal cells (MSCs) for skin burns transplant therapy requires culture expansion. We published that prolonged culture on skin-soft silicone elastomer substrates suppresses rat MSC fibrogenesis observed on stiff culture surfaces. Delivery of soft-primed rat MSCs improves healing of rat wounds whereas stiff-primed MSCs induces scarring.

HYPOTHESIS AND PURPOSE: Expansion on skin-soft culture substrates produces human MSCs that support scarless wound healing. We aim to uncover the mechanisms and features mediating anti-scarring actions of soft-primed MSCs in a rat transplantation model.

METHODS: Human umbilical cord-derived MSCs were mechanically primed on skin-soft and scar-stiff culture substrates. Prior to transplantation to splinted rat full-thickness skin wounds, MSCs were profiled for fibrotic activation, secreted factors, differentiation and regeneration potential. Wound tissue was assessed after 2-9 d for MSC grafting, activation, and wound cell populations.

RESULTS: Soft-primed MSCs retained stem cell markers CD44+/CD90+, differentiation potential, and low expression of scar marker alpha smooth muscle actin (α-SMA). Transplanted soft-primed MSCs grafted for 4 d in the wound granulation tissue that was characterized by earlier recruitment of CD68+ macrophages, and enhanced vascularization. Conversely, the amounts of host scar fibroblasts and mature matrix were lower than in wounds receiving stiff-primed MSCs. Cytokine analysis revealed profound effects of mechanical priming on the MSC secretome.

CONCLUSION: Soft priming generates human MSCs that suppress scarring and improve wound healing by enhancing macrophage recruitment, likely through trophic effects.
SYSTEMATIC REVIEW AND NONINFERIORITY META-ANALYSIS OF EARLY URINARY CATHETER REMOVAL AFTER RECTAL SURGERY

Colin Sue-Chue-Lam (SSTP), Matthew Castelo (SSTP), Teruko Kishibe, Sergio A Acuna, Nancy N Baxter
Li Ka Shing Knowledge Institute, St. Michael's Hospital, and University of Toronto

Background and rationale: Urinary catheters are placed after rectal surgery to prevent urinary retention, but prolonged use may increase urinary tract infection risk. We conducted a systematic review to evaluate whether early urinary catheter removal is noninferior to late catheter removal for acute urinary retention risk after rectal surgery in adults.

Methods: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched from January 1980 – February 2019. Randomized controlled trials comparing early versus late catheter removal after rectal surgery were eligible. The primary outcomes were acute urinary retention and urinary tract infection; the secondary outcome was length of stay. Early catheter removal occurred up to postoperative day 2. Late removal occurred after day 2. We used the noninferiority margin from an included trial for the analysis of urinary retention ($\Delta NI = 15\%$). Pooled estimates of risk differences were derived from random-effects models.

Results: Four trials were included, consisting of 409 patients. We found insufficient evidence to conclude noninferiority of early catheter removal to late removal for acute urinary retention (RD 9\%, 90\% CI -1\% to 19\%). Early catheter removal was superior for urinary tract infection (RD -9\%, 95\% CI -16\% to -1\%). Results for length of stay were mixed.

Conclusion: The existing literature is inconclusive for noninferiority of early urinary catheter removal to late removal for acute urinary retention. Early catheter removal is superior for urinary tract infection.
THE INDUCED MEMBRANE TECHNIQUE: EFFECTS OF ANTIBIOTIC-IMPREGNATED SPACERS ON HEALING OF A CRITICAL-SIZE FEMORAL DEFECT IN A RAT MODEL

Hening Sun¹, Charles Godbout¹, Gareth Ryan¹, Ikran Ali¹, Emil Schemitsch², Aaron Nauth¹
¹Keenan Research Centre for Biomedical Science, St. Michael’s Hospital, University of Toronto, Toronto ON Canada; ²London Health Sciences Centre, London ON Canada

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 created a 5-mm defect in the femoral diaphysis of each rat. The bone was then stabilized with a plate and screws followed by spacer insertion into the defect. Four weeks later, we carefully replaced the spacer with bone graft. Radiographs were taken biweekly until 12 weeks post graft and were scored to quantify the extent of bone healing. The bone volume at the defect site was 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: Radiographs at 12 weeks following grafting demonstrated complete union in 83.3% (10/12) of control animals, 100% (13/13) of low-dose animals and 66.7% (8/12) of high-dose animals. Micro-CT demonstrated higher BV in the control (37.49 mm³ ± 11.39 standard deviation) and low dose (36.58 mm³ ± 5.90) groups relative to the high-dose group (28.37 mm³ ± 8.75). These differences were statistically significant comparing control and high-dose (p=0.0436), but not statistically significant comparing high-dose to low dose (p=0.0684).

Conclusion: In the context of the IMT, our results suggest that high doses of antibiotics in PMMA may negatively impact bone healing. Further investigation is needed to determine the optimal antibiotic dosage and the extent to which antibiotics impact functional bone healing.
Purpose and Hypothesis: Lower-limb amputation is a catastrophic complication of diabetes. Despite the seriousness of the complication, amputation prevention efforts are severely fragmented within this patient population. Therefore, we sought to develop a multidisciplinary foot care and amputation prevention pathway at St. Michael’s Hospital.

Methods: We developed an integrated foot care pathway that coordinates the expertise of chiropody, vascular surgery and general internal medicine with support from plastic surgery, orthopaedic surgery and other medical subspecialties when required. All patients presenting to the emergency room (ER) with a lower-extremity diabetic foot ulcer (DFU) are triaged by chiropody during daytime hours and by the ER physician and medicine service after hours. Admission, if necessary, is under general internal medicine with input from chiropody and vascular surgery and guaranteed within 1 working day of presentation. Patients are then treated via surgical management, nonsurgical management, or supportive management. Rehab and outpatient clinics are integrated into the end-to-end care pathway.

Results: Since November 2018, a total of 96 visits (61 unique patients) have been managed through this pathway, of which 46 (75%) were males and 15 (25%) females. Patients admitted to internal medicine were mostly referred to surgical interventions (63%), with the remaining referred to nonsurgical management (37%). On average, these patients had a length of hospital stay of 9.3 days, mean admission to intervention time of 2.5 days, and a readmission rate of 18%. With regards to disposition, the majority of patients were discharged home (74%), followed by rehabilitation (15%), another hospital (9%), and Community Care Access Centers (2%).

Conclusion: Chiropody-led multidisciplinary DFU pathway expedited patient management and disposition planning.
TARGETING MITOCHONDRIAL FISSION: THE ACHILLES' HEEL OF GLIOBLASTOMA

Michael STaccone (SSTP),1,2,3 Asish Das Gupta,4 Kuang-Hueih Chen,4 Stephen Archer,4,5 James Rutka3,6

1Surgeon-Scientist Training Program, Division of Neurosurgery, Department of Surgery, University of Toronto.
2Division of Neurosurgery, Department of Surgery, University of Ottawa
3Department of Laboratory Medicine & Pathobiology, Faculty of Medicine, University of Toronto.
4Queen’s Cardio-Pulmonary Unit, Faculty of Health Sciences, Queen’s University.
5Division of Cardiology, Department of Medicine, Faculty of Medicine, Queen’s University.
6Division of Neurosurgery, The Hospital for Sick Children, University of Toronto.

Purpose: Glioblastoma (GBM) is the most common and lethal primary malignant brain tumour with an overall survival of 10-14 months despite aggressive treatment. In an era where kinase inhibitors, growth factor antagonists, and cell-cycle blockades are failing in clinical trials, susceptibilities in cancer metabolism have emerged as a potential Achilles’ heel of GBM. Cell-cycle progression, generation of ATP, reactive oxygen species, apoptosis, mitophagy and oxygen sensing are tightly regulated by the mitochondrial dynamic processes fission and fusion. Previous work has shown that fission drives proliferation in lung cancer, prostate cancer, hepatocellular carcinoma, melanoma and glioma.

Hypothesis: GBM is highly reliant on mitochondrial fission to fuel proliferation and therapeutic targeting of fission mediators will lead to the inhibition of tumour growth.

Methods: Basal level of mitochondrial fission in GBM cell lines was determined via live imaging of tetramethylrhodamine stained cells using super resolution live fluorescence confocal microscopy. The mitochondrial fission coefficient (MFC) was calculated using our machine-learning algorithm. Cell lines were treated with our patented fission inhibitor dripitor. Cell viability and apoptosis was measured using Edu staining followed by flow cytometry/FACS sorting.

Results: In GBM cell lines, compared to baseline controls, dripitor treatment was associated with an overall lower MFC (p<0.05). Additionally, in vitro assessment of dripitor revealed a dose-dependent antiproliferative effect in GBM cell lines (p<0.05).

Conclusions: Targeting of mitochondrial fission represents a promising therapeutic strategy for GBM. In addition, as this novel therapeutic strategy aims to exploit a common metabolic pathway, this work has broader applicability to multiple cancers.
THE MICRORNA PROFILE OF PATIENTS WITH CHRONIC LIMB THREATENING ISCHEMIA

Drishti Thakkar*, Muzammil H Syed, Abdelrahman Zamzam, Hamzah Khan, Jason Valencia, Rawand Abdin, Mohammad Qadura
Division of Vascular Surgery, St. Michael’s Hospital and University of Toronto, Toronto, Ontario

Hypothesis and Purpose: Chronic limb threatening ischemia (CLTI) is the most severe form of peripheral arterial disease (PAD) affecting up to 5% of PAD patients. Despite the known burden of the disease, the microRNA (miRNA) profile of CLTI patients has been insufficiently studied. It was hypothesized CLTI may be associated with specific miRNAs, hence a genome-wide plasma miRNA sequencing study to identify miRNAs associated with CLTI was conducted.

Methods: Discovery Study (n = 23): Next generation sequencing (NGS) was used to identify microRNAs circulating in the blood plasma of CLTI patients (n=13) compared to non-PAD controls (n=10). Confirmatory Study (n = 52): miRNAs identified from the discovery phase underwent further investigation in a secondary cohort of non-PAD (n = 20) and CTLI (n = 32) patients using qRT-PCR. Validation Study (n = 28): Plasma levels identified during the confirmatory study were validated via qRT-PCR in a third cohort of CLTI patients (n = 10) matched to non-PAD controls (n = 10). A fold change of >2 (upregulated or downregulated) was considered significant in each experimental study.

Results: Discovery Study: Two down regulated miRNAs (miRNA-6843-3p and miRNA-6766-5p) and three upregulated miRNAs (miRNA-1827, miRNA-320 and miRNA-98-3p) were identified. Confirmatory study: miRNA1827 was statistically upregulated in the CLTI group relative to non-PAD controls. Validation study: miRNA1827 plasma levels of CLTI patients were matched to non-PAD controls and was found to be statistically elevated in the CLTI cohort. In matched cases and controls, Ingenuity Pathway Analysis (IPA) associated CLTI to 22 genes targets of miRNA 1827.

Conclusion: Our data demonstrates that miRNA-1827 is significantly associated with CLTI. Further studies need to be conducted to discover the exact mechanism behind miRNA-1827 upregulation in CLTI patients.
ASSOCIATION BETWEEN CENTRAL DIFFUSIVITY METRICS AND SURGICAL RESPONSE ACROSS SUBTYPES OF TRIGEMINAL NEURALGIA

Sarasa Tohyama¹, Jia Y Zhang², Joshua C Cheng³, Matthew R Walker², Mojgan Hodaie¹,²
¹University of Toronto; ²Krembil Brain Institute; ³Stony Brook University

Purpose: Trigeminal neuralgia (TN) is a chronic neuropathic facial pain condition. To aid in diagnosis and treatment, TN is often classified into different subtypes, including classical TN (CTN), TN secondary to multiple sclerosis (MS-TN), and TN associated with solitary pontine lesion (SPL-TN). While the differing treatment response rates across the subtypes of TN is well-established, the rationale behind this spectrum is not well understood. In this comparative study, we aimed to determine whether the degree of brainstem trigeminal fiber microstructural alterations predicts the likelihood of surgical response across subtypes of TN. Methods: We retrospectively studied 101 patients with TN (41 males and 60 females, mean age ± SD: 59.2 ± 14.5 years), consisting of 65 CTN (43 responders, 22 nonresponders), 26 MS-TN (11 responders, 15 nonresponders), and 10 SPL-TN (all nonresponders) patients. Each patient underwent a MRI session before treatment to acquire anatomical and diffusion-weighted images. Diffusivity metrics of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were extracted from the proximal pontine segment of the affected trigeminal pathway. The contralateral, unaffected side served as the control. Results: There was a statistically significant difference between the subtypes of TN nonresponders for FA, MD, and RD on the affected side. SPL-TN patients demonstrated the greatest degree of microstructural alterations, characterized by lower FA, and higher MD and RD, followed by MS-TN patients, and, lastly, CTN patients. No significant diffusivity differences were observed for the responder subgroups of CTN and MS-TN. Conclusions: We find that the degree of brainstem trigeminal fiber microstructural alterations before treatment predicts the likelihood of surgical response across subtypes of TN. Thus, the clinical response spectrum across the subtypes of TN may be associated with the extent of microstructural disruption of the central trigeminal pathway.
EFFECT OF REHABILITATION TRAINING ON THE FUNCTIONAL INTEGRATION OF TRANSPLANTED STEM CELLS FOR TREATMENT OF CERVICAL SPINAL CORD INJURY

Amirali Toossi1, Damian Ascanio Hecker1, Mohamad Khazaei1, Kazuya Yokota1, Christopher Ahuja (SSTP)1,2, Anuka Hirimuthugoda1, Keith Fenrich3, Karim Fouad3, Michael Fehlings1,2

1Krembil Research Institute, University Health Network, Toronto, Ontario, Canada
2Department of Surgery, University of Toronto, Toronto, Ontario, Canada
3Department of Physical Therapy, University of Alberta, Edmonton, Alberta, Canada

The overall goal of this study is to develop a combinatorial treatment for spinal cord injury (SCI) involving neural stem cell (NSC) transplantation and intense motor rehabilitation. One of the promising strategies to treat SCIs and restore lost functions is to transplant stem cells into the injured cord to replace the lost cells and promote regeneration. The objective of this study is to investigate whether skilled motor training of the affected neural networks will enhance the integration of NSCs transplanted into the damaged cord and influence their fate and function.

Experiments were carried out in a clinically relevant clip-compression model of cervical SCI (C6-7) in Rowett Nude rats. NSCs used in this study were human induced pluripotent NSCs that were genetically modified to express pro-survival and pro-neuronal glial derived neurotrophic factor (GDNF). Prior to injury, animals were trained for 10 minutes daily for 14 weeks to acquire the motor skill needed for precise reaching and grasping of sugar pellets (i.e. single pellet reaching task). This motor skill is the basis of the study's intense rehabilitative training protocol for the affected forelimbs. Prior to injury, animals were trained to reach for an average of 139.8 pellets in each 10-minute training session with an average of 50% success rate in their retrieval. This level of reaching performance is categorized as high intensity training for rats (Torres et al, 2019). To investigate the effect of this combinatorial treatment, animals were divided into 5 groups: Sham, SCI+Vehicle, SCI+NSC, SCI+Vehicle+Rehab, and SCI+NSC+Rehab. NSCs were transplanted in the subacute phase (14-days post-SCI) at the lesion and perilesional sites (5 sites). This work is currently ongoing and will continue for 15 weeks to investigate treatment effects. Results of this study will have implications for clinical translation of NSC treatments for SCI and provide further insights into the functional contribution of the grafted cells.
EARLY SPICA CASTING FOR DIAPHYSEAL FEMUR FRACTURES IN YOUNG CHILDREN IS SAFE AND HAS A LOW INCIDENCE OF SECONDARY INTERVENTION

Eliane Rioux Trottier, Leah Hatcher, Jessica Feng, Mark Camp, Maryse Bouchard
Division of Orthopedic Surgery, The Hospital for Sick Children, and University of Toronto

Purpose: Children between 6 months and 5 years old with diaphyseal femur fractures are typically treated with spica cast application per AAOS Clinical Practice Guidelines. Risk of early spica application ($\leq$3 days from injury) is loss of reduction leading to malunion or shortening. This study aims to determine the incidence of early and late secondary interventions following early spica casting.

Methods: This is a retrospective cohort study of patients aged 0-6 years with diaphyseal femur fractures treated with early spica casting at our institution between January 2005 and May 2015.

Results: Two hundred and forty-six patients were included. Nine (3.7%) required secondary interventions before fracture union (8 cast wedges, 1 cast change). At last follow up, 51 (20.7%) had a clinically measurable limb length discrepancy (LLD) (mean 9.42 mm [3-25mm]) and 1 had mild valgus deformity on examination. LLD was associated with older age, increased patient weight, increased shortening and angulation on initial anteroposterior radiographs (all $p<0.05$). No patient required late secondary interventions to address residual deformity.

Conclusion: Early spica casting for diaphyseal femoral fractures in children $\leq$6 years old is safe and has a low complication rate. Despite 20% residual LLD, secondary intervention is seldom required after fracture union.
ACCESS TO CARE AND OUTCOMES FOR NON-CURATIVE ESOPHAGOGRASTRIC CANCER: A POPULATION-BASED GEOGRAPHIC STUDY

Elliott Yee, Natalie G. Coburn, Victoria Zuk, Laura E. Davis, Alyson L. Mahar, Ying Liu, Vaibhav Gupta (SSTP), Gail Darling, Julie Hallet

Division of General Surgery, Sunnybrook Health Sciences Centre, University of Toronto

Hypothesis and Purpose: Esophagogastric cancer (EGC) carries a heavy mortality burden owing largely to high rates of unresectable disease at diagnosis. Among patients not undergoing curative-intent therapy, access to care may vary. For non-curative EGC, we sought to examine whether distance to cancer centres (CCs) influences care access and survival, and to describe the geographic distribution of care delivery across a province.

Methods: We conducted a population-based analysis of adults with non-curative EGC from 2005-2017 using linked administrative healthcare datasets. Outcomes were medical oncology consultation, receipt of chemotherapy, and overall survival (OS). We used geographic information system analysis to map locations of CCs and outcomes across census divisions. Regions of discordance between care use and OS were identified with bivariate choropleth maps. Multivariable modified Poisson models assessed the relationship between distance to the nearest CC and outcomes, adjusting for demographic, clinical, and socioeconomic factors.

Results: Of 10,228 patients surviving a median of 5.1 months (IQR: 2.0-12.0), 68.6% had medical oncology consultation and 32.2% received chemotherapy. CCs providing higher-level care were distributed unevenly throughout the province and were concentrated in regions with higher oncology consultation, chemotherapy use, and OS. Compared to residence ≤10 km from the nearest CC, greater distances were associated with lower likelihood of seeing medical oncology and receiving chemotherapy, and inferior OS.

Conclusion: Location of residence influenced access to care and OS, with inferior outcomes for those living further from a CC. These findings are important for designing interventions and policies to reduce disparities in access to care and outcomes for non-curative EGC.
ALTERED COAGULATION PROFILE IN PERIPHERAL ARTERY DISEASE PATIENTS

Abdelrahman Zamzam¹; Muzammil H Syed¹; Margaret L Rand²; Hamzah Khan³; Rawand Abdin⁴; Mohammad Qadura¹,³

¹St. Michael’s Hospital; ²University of Toronto; ³Keenan Research Centre for Biomedical Science; ⁴McMaster University

Hypothesis and Purpose: Peripheral artery disease (PAD) patients have shown to be more susceptible to thrombotic events compared to non-PAD patients. The aim of this study was to investigate the coagulation profile in PAD patients with chronic limb threatening ischemia (CLTI), moderate PAD patients with claudication, and non-PAD controls.

Methods: CLTI patients were matched to PAD patients with claudication and non-PAD controls in a 1:1:1 ratio. Each patient had their cytokines, markers of thrombin generation, coagulation factors, natural anti-coagulants, fibrinolysis, and endothelial injury markers assessed.

Results: A total of 60 subjects were recruited (CLTI, n = 20; moderate PAD, n = 20; non-PAD, n =20). Markers of thrombin activation, thrombin Fragments F1+2 (Frag 1+2), and thrombin-anti-thrombin complex (TAT), were found to be significantly elevated in CLTI patients relative to PAD and non-PAD controls. Similarly, inflammatory markers including c-reactive protein (CRP), soluble platelet factor 4 (sPF4), and neutrophil gelatinase-associated lipocalin (NGAL) were also found to be significantly upregulated in severe CLTI patients, but not in moderate PAD patients. Finally, decreases in natural anti-coagulants (protein C and protein S) and coagulation factors FIX, FXI, and FXII were observed in CLTI patients when compared with PAD and non-PAD controls.

Conclusion: Our data suggest that CLTI patients are more hypercoagulable in relation to PAD patients who suffer from claudication and non-PAD controls, whereas PAD patients with claudication appear to have similar levels of circulating procoagulant markers as non-PAD patients. This may explain the increased risk of thrombotic events observed in CLTI patients.
THE APPLICATION OF EARLY INTRATHECAL KCC2 GENE THERAPY IN TRAUMATIC CERVICAL SPINAL CORD INJURY

Mohammad Zavvarian1,2, Bo Chen4,5, Miao He4,5, Mohamad Khazaeei1,2, Christopher Ahuja (SSTP)1,2, James Hong1,2, Zhigang He4,5, Michael G Fehlings1,2,3

1Toronto Western Hospital, University Health Network
2Institute of Medical Science, Faculty of Medicine, University of Toronto
3Department of Surgery, Faculty of Medicine, University of Toronto
4Harvard Medical School, Harvard University
5Boston Children’s Hospital

Purpose and Hypothesis: Traumatic spinal cord injury (SCI) impairs local neuronal conductance and induces a subsequent synaptic remodeling cascade, expanding into the rostro-caudal perilesional zone. Potassium-chloride transporter member 5 (KCC2) is a differentially expressed ligand-gated channels, which is pivotal for signal propagation in GABAergic synapses. Reduced KCC2 activity post-SCI intensifies inhibitory transmission in GABAergic interneurons and blocks the relay of signals in the spinal cord. KCC2 agonists are capable of improving functional recovery in the staggered double hemisection model. However, the continued daily administration of the agonist, in addition to the potential off-target effects, hinders its clinic translation. Gene therapy is a promising technique to alter the transcriptional profile of a cell. The aim of this study to examine the ability of gene therapy to induce KCC2 in a clinically relevant cervical SCI rodent model.

Methods: AAV9s were injected to injured rats via intrathecal administration. The rats were sacrificed 7 days following injection. The extracted spinal cords were prepared for RNA and protein analysis.

Results: KCC2 is significantly downregulated at transcriptional and protein level. AAV9 vectors are capable of transducing neurons and glial cells with high efficiency.

Conclusions: This study validates the downregulation of KCC2 following clip-compression injury and demonstrate the efficacy of intrathecal AAV9 administration to induce KCC2 expression.
DECLINING USE OF RED BLOOD CELL TRANSFUSIONS FOR GASTROINTESTINAL CANCER SURGERY IN ONTARIO BETWEEN 2007 AND 2018: A POPULATION-BASED ANALYSIS

Jesse Zuckerman¹ (SSTP), Natalie Coburn¹,², Jeannie Callum³, Alyson L Mahar⁴, Julie Hallet¹,²
¹Division of General Surgery, Department of Surgery, University of Toronto
²Division of General Surgery, Sunnybrook Health Sciences Centre
³Department of Laboratory Medicine, Sunnybrook Health Sciences Centre
⁴Department of Community Health Sciences, University of Manitoba

Hypothesis and Purpose: Perioperative anemia is common in gastrointestinal (GI) cancer surgery patients and is often treated with red blood cell transfusion (RBCT), which carries risks for inferior oncologic outcomes. Though transfusion guidelines exist, almost half of GI cancer patients receive unnecessary transfusions. Examining population-level RBCT use is necessary to support system-level efforts to improve surgical quality. We evaluated temporal trends in RBCT use in GI cancer surgery patients. Methods: We retrospectively studied perioperative RBCT use in patients undergoing GI cancer resection between 2007 and 2018 using administrative health datasets in Ontario. Temporal trends were analyzed with Cochran-Armitage tests. Poisson regression assessed trends while controlling for potential confounders. Results: Of 79,764 patients who underwent GI cancer resection, mean age was 68.2 ± 12.7 years old and 55.5% were male. The most frequent procedure was colorectal (n=60,456, 75.8%). 23% of patients received RBCT. The proportion of patients transfused decreased from 26.5% in 2007 to 18.9% in 2018 (p<0.001). This trend remained consistent when stratified by sex, type of surgery, surgical approach, and institution teaching status. After adjusting for patient, procedure and hospital factors, patients in the late time period (2015-2018) had a reduced risk of receiving RBCT relative to the middle time period (2011-2014) [RR 0.86 (95% CI: 0.83-0.89)]. Conclusions: Over 11 years, we observed decreasing RBCT use. This may reflect clinical guideline dissemination and patient blood management implementation. Institutional variation in this population should be evaluated to help identify and target opportunities for improvement.
MANIPULATION OF ORGAN TEMPERATURE AND METABOLISM PROTECTS MITOCHONDRIAL HEALTH AND ALLOWS FOR THE SUBSTANTIAL EXTENSION OF DONOR LUNG PRESERVATION TIMES

Aadil Ali, Marcelo Cypel
Latner Thoracic Surgery Research Laboratories, Toronto, ON, Canada.

**Hypothesis and Purpose:** Despite remote reports indicating 10ºC to be the optimal temperature for cold static organ preservation (CSP), preservation of lungs in an ice cooler at 4ºC remains the standard strategy in clinical transplantation. Here, we used a device that can keep a donor lung at 10ºC conveniently and compared 10ºC vs. 4ºC during a prolonged period of CSP followed by functional and biological assessment of lung grafts. **Methods:** Lungs were procured from Yorkshire pigs (28-35kg) using clinical protocols, flushed with a low-potassium dextran solution and randomized into two groups (n=5 each): CSP at 4ºC vs. CSP at 10ºC (MyTemp Mini Incubator, Benchmark Scientific). After 36h of CSP, lungs were subjected to 12h of normothermic ex vivo lung perfusion (EVLP) with hourly functional assessments. Lung biopsies and perfusate samples were taken for biological and metabolic evaluation. **Results:** During 12h of EVLP, lungs stored at 10ºC presented superior physiological parameters compared to 4ºC marked by a higher lung compliance (p = <0.0001), lower peak airway pressures (p = <0.0001) and reduced edema formation (30 ± 34.1 vs. 201 ± 33.2 g, p = 0.0159) during EVLP. Global metabolomic analysis revealed higher differential expression of mitochondrial protective metabolites (Itaconate, N-Glutamine, Glutamate) during CSP. Further biological examination showed significantly better mitochondrial protection in the 10ºC group in comparison to 4ºC based on lower circulating cell-free mtDNA within the EVLP perfusate (p = <0.0001), and lower mitochondrial oxidation rates (p = 0.056). **Conclusion:** With simple controllable refrigerators, 10ºC preservation is easily achievable and provides significantly superior static cold lung preservation in comparison to conventional 4ºC storage. Moreover, we identify protection of lung mitochondria as a potentially crucial feature of lung preservation, warranting further exploration. These results may potentially remarkably extend the clinical and transportation logistics in lung transplantation.
Hypothesis and Purpose: In response to burn trauma, white adipose tissue (WAT) adopts brown adipose-like characteristics in a process termed ‘browning’. This switch, driven by the activation of anti-inflammatory (M2) macrophages, is associated with hypermetabolism and poor outcomes. Recent evidence suggests that macrophages are regulated by the metabolic environment. Given that M2 macrophages rely on fatty acid oxidation to fuel their metabolism, we hypothesize that burn promotes M2 macrophage activation via increased FFA mobilization. Therefore, reducing WAT lipolysis may render an effective means to limit substrate availability for M2 macrophages thereby improving post burn WAT browning. To test this, we investigated the metabolic effects of the clinically approved lipolysis inhibitor, Acipimox (APX) in a murine model of burn injury.

Methods: Adult C57BL/6 mice received a 30% full-thickness scald burn. Select mice received daily intraperitoneal injections of APX (50 mg/Kg). On day 7 post-burn, the inguinal adipose tissue depots (iWAT) was harvested for histological analyses. Flow cytometry was used to assess adipose macrophage distribution and profile.

Results: APX reduced total HSL (p<0.01) and ATGL (p<0.05) protein levels in the iWAT. This was accompanied by a decrease in UCP-1 (p<0.05) and PGC-1α (p<0.01) levels. F4/80 immunostaining of iWAT demonstrated decreased macrophage recruitment in APX treated mice at 7 days post-injury (p<0.05), which was further confirmed via flow cytometric analysis (p<0.05). Additionally, iWAT from APX treated mice demonstrated a pro-inflammatory profile, indicated by a greater distribution of TLR4+ macrophages (p<0.05).

Conclusion: Here, we show that inhibition of lipolysis not only suppresses post burn browning, but also impairs WAT macrophage recruitment and polarization. While lipolysis was previously regarded as a by-product of browning, these findings suggest that liberated FFAs in turn can promote browning via M2 macrophage polarization.
THAT'S JUST THE PRICE YOU PAY: WOMEN WHO ARE HIGH-RISK NON-MUTATION CARRIERS ENROLLED IN THE HIGH-RISK ONTARIO BREAST SCREENING PROGRAM HAVE SUBSTANTIAL RATES OF CALL BACKS AND BIOPSIES

Matthew Castelo¹⁴, Zachary Brown⁵, Andrea Eisen⁶, Derek Muradali⁷, Adena S Scheer¹⁴

¹Division of General Surgery, Department of Surgery, University of Toronto, Toronto, Ontario, Canada
²Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
³Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada
⁴Department of Surgery, St. Michael's Hospital, Toronto, Ontario, Canada
⁵Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
⁶Odette Cancer Center, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
⁷Department of Medical Imaging, St. Michael's Hospital, Toronto, Ontario, Canada

INTRODUCTION: The Ontario Breast Screening Program was expanded in 2011 to offer annual MRI and mammography to women with high-risk genetic mutations (e.g. BRCA1/2) as well as women with strong family histories and ≥ 25% estimated lifetime risk of breast cancer. Data to support high risk screening is less clear in the non-mutation carrier group and there is no data that shows an impact on survival. The potential unintended consequences may be significant and need to be explored. We aimed to describe the frequency of call backs and biopsies as well as the demographics of non-mutation carriers undergoing high risk breast cancer screening. METHODS: This was a retrospective cross-sectional chart review study conducted at two tertiary care hospitals in Toronto, Ontario. Demographic surveys and chart review consent was sent to a sample of 441 individuals. Chart review was undertaken for clinicopathologic data. The cancer detection rate (invasive or in situ lesions/1000 screening episodes) was calculated. RESULTS: 169 non-mutation carriers were included. The majority were Caucasian, employed, highly educated, and high-earners. The median IBIS lifetime risk of breast cancer was 28.0% (range 24.5% - 89.0%). 108 individuals (64%) experienced at least 1 call back and 13 (8%) had 3 or more over a median 3 years of screening (range 1-6). Of 55 biopsies, 3 (5.5%) were malignant. The cancer detection rate was 8.4/1000 screens (95% CI 3.2-22.4). DISCUSSION: An MRI-based screening program for non-mutation carriers was effective at diagnosing breast cancer. However, this population experienced a high rate of call backs and intervention. Further research is needed to both improve the performance of MRI-based screening in these women and assess the psychological impact of call backs.
LONG TERM COMPARATIVE OUTCOMES FOLLOWING LUMBAR DISK ARTHROPLASTY: A CANADIAN SPINE OUTCOMES RESEARCH NETWORK (CSORN) STUDY

Tan Chen1, Sean Christie2, Charles Fisher3, Peter Jarzem4, Jean-Francois Roy5, Jacques Bouchard6, Albert Yee1

1Division of Spine Surgery, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
2Division of Neurosurgery, Dalhousie University, Nova Scotia, Canada
3Division of Spine Surgery, Vancouver General Hospital, Vancouver, BC, Canada
4Division of Orthopaedic Surgery, McGill University, Montreal, Quebec, Canada
5Département de Chirurgie, Université Laval, Quebec, Canada
6Division of Orthopaedic Surgery, University of Calgary, Alberta, Canada

OBJECTIVES: There is a paucity of published Canadian literature investigating long-term patient-reported outcomes following lumbar disc arthroplasty (LDA) and comparisons against fusion procedures in degenerative spondylosis. METHODS: Multicenter review of prospectively collected data on patients enrolled by CSORN who underwent LDA for symptomatic degenerative disk disease. LDA patients were matched to fusion patients included with a diagnosis of degenerative spondylosis, complaint of back pain, and underwent fusion irrespective of technique. Outcome scores and satisfaction were assessed. RESULTS: A total of 97 LDA and 94 fusion patients were collected. In the LDA cohort at 2-year follow-up (76%), numerical back pain improved from 7.21 to 3.25 and ODI improved from 45.7 to 23.9 (p<0.0001), with significance in all subgroups. A negative impact on preoperative work-status was found to correlate with lower satisfaction (r = -0.523, p<0.001), lower ODI improvement (r = -0.280, p<0.05), and less improvement in back and leg pain. Compared to fusions at 2-year follow-up, no differences were found in ODI improvement (LDA-20.32pts, Fusion-17.02pts, p=0.36), back-pain improvement (LDA-3.5pts, Fusion-3.06pts, p=0.40), leg-pain improvement (LDA-1.67pts, Fusion-1.87pts, p=0.76), and Health-Scale (LDA-17.12, Fusion-10.73, p=0.20). Similar findings were found in matched subgroups. Satisfaction rate was 86.7% and 82.4% for LDA and fusion patients respectively. CONCLUSIONS: Our outcomes confirm positive and comparable results to international literature. Following LDA, improvements exceeding minimum clinically important differences were observed in outcome scores and maintained through 2 years alongside high satisfaction rates. In optimizing patient selection, a negative impact to employment status is predictive of poor satisfaction. Compared against fusions, LDA demonstrated no differences in outcomes or satisfaction. LDA is an effective motion-preserving treatment option in clinically appropriate patients with debilitating degenerative disk disease.
Hypothesis and Purpose: Neuroinflammation exacerbates 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 targeting neuroinflammation, immunosuppressants are used to treat SCI patients. However, as patients experience immune suppression, immunomodulation is more effective than immune-suppression. Human Immunoglobulin G (hIgG) is used in clinic as an immunomodulatory treatment for inflammation. Although we have shown that administration of hIgG (2g/kg) is beneficial after SCI, the optimal time window of administration and mechanism of hIgG are unknown. We hypothesize that hIgG is beneficial when administered at extended time points.

Methods: With a clinically relevant rat model of SCI, a single bolus of hIgG (2g/kg) or control buffer was administered intravenously at 15 minutes, 1 hours or 4 hours post-SCI. Spinal cord, serum and spleens were collected to evaluate hIgG’s effects.

Results: hIgG co-localized with BSCB. At 24 hours post-SCI, relative to control buffer, hIgG (2g/kg) significantly enhanced BSCB integrity when administered at delayed time points. This was associated with reduced spinal cord neuroinflammation. hIgG (2g/kg) increased serum levels of inflammatory cytokines, reduced neutrophil counts in blood and resulted in spleens with greater amounts of neutrophils. Short term benefits of delayed hIgG (2g/kg) administration correlate with enhanced tissue preservation and functional recovery at eight weeks post-injury.

Conclusion: As a clinically relevant immunomodulatory treatment, hIgG (2g/kg) can improve recovery after SCI when administered in delayed fashion. hIgG alleviates neuroinflammation without increasing immune suppression.
MAGNETIC RESONANCE-GUIDED FOCUSED ULTRASOUND CAPSULOTOMY
FOR REFRACTORY OBSESSIVE COMPULSIVE DISORDER AND
MAJOR DEPRESSIVE DISORDER

Benjamin Davidson (SSTP), Clement Hamani, Ying Meng (SSTP), Peter Giacobbe,
Nir Lipsman
Harquail Center for Neuromodulation, Sunnybrook Research Institute

Background: Magnetic resonance guided focused ultrasound (MRgFUS) is a novel surgical
technique permitting incisionless ablative neurosurgery. In the past, patients with treatment
resistant obsessive compulsive disorder (OCD) and major depressive disorder (MDD) have
benefited from an ablative neurosurgical procedure known as anterior capsulotomy (AC).

Hypothesis: MRgFUS-AC is safe and effective in patients with refractory OCD and MDD.
Functional neuroimaging can be used to detect correlates of the procedure, and preoperative
predictors of response.

Purpose: Perform two phase-1 clinical trials treating patients with refractory OCD and MDD using
MRgFUS-capsulotomy in order to determine safety, efficacy, and neuroimaging correaltes

Methods: The safety profile and clinical response after MRgFUS-AC was tracked in 12 patients
(6 OCD, 6 MDD). Positron emission tomography (PET) and functional magnetic resonance
imaging (fMRI) was performed at baseline and followup.

Results: There were no serious adverse events. The response rate was 4/6 and 2/6 in the OCD
and MDD cohorts respectively. PET analysis revealed widespread decreases in metabolism
bilaterally in the cerebral hemispheres at 6 months post-treatment, as well as in the right
hippocampus, amygdala, and putamen. A pre-treatment seed-to-voxel resting-state functional
magnetic resonance imaging (rs-fMRI) analysis revealed three clusters significantly associated
with eventual clinical response.

Conclusion: MRgFUS capsulotomy is safe, and according to these initial results, may be an
important treatment option for patients with refractory OCD and MDD. MRgFUS capsulotomy
results in targeted and widespread changes in neural activity, and with larger samples is an ideal
environment for rs-fMRI prediction of outcome.
Background: Optimal repair during the first cardiopulmonary bypass (CPB) run is ideal. Intraoperative revisions (IR) may alleviate risk associated with residual lesions (RL) but increase perioperative risk. Evidence for ideal management of RL is lacking.

Purpose: We aimed to quantify, characterize, and assess the risk of additional CPB episodes, and specifically the decision to re-institute CPB for the purpose of intraoperatively revising RL, in congenital heart surgery.

Methods: We examined baseline, procedural, and early postoperative data in all children ≤18 years undergoing cardiac surgery with CPB at the Hospital for Sick Children (2014-2016, n=1040). The cohort was stratified on the basis of need for more than one CPB run and/or IR requiring CPB. Continuous variables are presented as mean ± SD and compared with Student’s T or Wilcoxon rank-sum tests, as appropriate. Categorical variables are presented as proportions (%) and compared with the Chi-square test or Fisher’s exact test.

Results: Mean age was 2.9 ± 4.5 years; 54% of patients were male. Both CPB>1 for any reason and IR were associated with increased risk of perioperative complications. CPB>1 was associated with increased in-hospital mortality (5% vs 2% p=0.05), however, IR was not. Most IR (77%) were “essential” to leaving OR. IR was associated with higher postoperative revision. Overall in-hospital mortality was 3% (n=30) and mean hospital stay was 18±36 days.

Conclusions: CPB>1 is generally associated with higher perioperative mortality, but not when IR is the indication. Most IR is for essential RL, may not prevent postoperative revisions, and should be considered in patients who are likely to tolerate a complicated postoperative course.
ALIVE AND AT HOME: 5-YEAR OUTCOMES IN OLDER ADULTS FOLLOWING EMERGENCY GENERAL SURGERY

Matthew P Guttman (SSTP)¹,², Bourke W Tillmann¹,³, Avery B Nathens¹,²,⁴, Refik Saskin⁶, Susan Bronskill⁶, Anjie Huang⁶, Barbara Haas¹,⁴
¹Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario; ²Department of Surgery, University of Toronto, Toronto, Ontario; ³Interdepartmental Division of Critical Care Medicine, Department of Medicine, University of Toronto, Toronto, Ontario; ⁴Sunnybrook Research Institute, Toronto, Ontario; ⁵American College of Surgeons, Chicago, IL; ⁶ICES, Toronto, Ontario

Background: While the short-term risks of emergency general surgery (EGS) admission among older adults (age≥65) have been studied, little is known about long-term functional outcomes in this population. Our objective was to evaluate the relationship between EGS admission and the probability of an older adult being alive and living in their own home 5 years later, and the extent to which specific EGS diagnoses, need for surgery, and frailty modified this relationship. Methods: We performed a population-based, retrospective cohort study of community dwelling older adults (age≥65) admitted to hospital for 1 of 8 EGS diagnoses (appendicitis, cholecystitis, diverticulitis, strangulated hernia, bowel obstruction, peptic ulcer disease, intestinal ischemia, or perforated viscus) between 2006-2018 in a large regional health system. Cases were matched to controls from the general population. Time spent alive and at home (measured as time to nursing home admission or death) was compared between cases and controls using Kaplan-Meier analysis and Cox proportional hazard models. Results: A total of 90,245 older adults admitted with an EGS diagnosis were identified and matched with controls. In the 5 years following their EGS admission, cases experienced significantly fewer months alive and at home compared to controls (mean time 43 vs. 50 months, p<0.001). Other than patients operated on for appendicitis or cholecystitis, all patient subgroups, regardless of diagnosis, operative status or frailty, experienced reduced time alive and at home compared to controls (p<0.001). Cases remained at elevated risk compared to controls for the entirety of the 5-year follow up (HR 1.17-5.11). Conclusion: Older adults who require hospitalization for an EGS diagnosis are at increased risk for death or admission to a nursing home for at least 5 years following admission. However, most patients remain alive and living in their own home for several years following admission.
HYPOTHESIS AND PURPOSE: The evidence basis for non-operative expectant management of traumatic intimal tear (IT) of the thoracic aorta remains weak. Our goal was to describe contemporary management and in-hospital mortality associated with blunt thoracic aortic IT within the American College of Surgeons Trauma Quality Improvement Program.

METHODS: All adult patients who sustained a thoracic aortic IT following blunt trauma from 2010 to 2017 were captured. For each patient, we extracted demographics, injury characteristics, the timing and approach of thoracic aortic repair and, in-hospital mortality. Mortality attributable to IT was calculated by comparing IT patients to a propensity-score matched control cohort of severely injured blunt trauma patients without aortic injury.

RESULTS: There were 2,230 IT patients across 330 facilities. Injury most often resulted from motor vehicle collision (75%). At total of 763 patients (34%) underwent operative management, with 94% (N=714) of repairs performed via an endovascular approach. The frequency of operative management was higher in patients without traumatic brain injury (TBI) (35%, n=679) compared with those with TBI (28%, n=84) (p=0.017). Median time to surgery was 11 hours (IQR 4-40). Compared to controls, IT was not associated with additional in-hospital mortality (10.8% for IT vs. 11.0% for no IT, absolute risk difference: -0.3%, 95%CI: -2.1% to 1.6%).

CONCLUSION: The majority of blunt thoracic IT are managed non-operatively and do not confer additional in-hospital mortality risk. Future studies should focus on the risk of injury progression.
Hypothesis and Purpose: Traumatic central cord syndrome (TCCS) refers to a cervical spinal cord injury (SCI), often as a result of a hyperextension injury in the elderly, characterized by greater impairment in upper compared to lower extremities, bladder dysfunction, and a varying degree of sensory loss below the level of the injury. Given the increasing prevalence, the objective of this study is to evaluate and identify factors that better predict functional recovery in TCCS.

Methods: Three large, international, prospective datasets of SCI (NACTN, STASCIS, NASCIS II) were merged in order to derive data for this study. Early surgery was defined as <24 h, and late surgery was defined as >= 24 h from the time of injury. Functional outcomes were measured by the Functional Independence Measure (FIM) scale at baseline and 1-year post-injury. Descriptive and regression analyses was used to correlate individual factors and functional outcomes.

Results: A total 170 patients with TCCS met eligibility criteria and baseline characteristics were assessed. In the motor subscale of FIM, only 11.2% of patients were completely independent while in the cognitive subscale 82.2% patients were completely independent indicating a greater effect of this syndrome on motor functionality. On a univariate regression analysis, baseline AMS (p<0.001), presence of fracture (p=0.012), time to surgery from injury (p=0.045), initial AIS grade (p=0.001), and initial GCS score (p=0.021) were significant negative predictors of FIM motor score at 1 year. The multivariate regression, age and time to surgery were negatively correlated with FIM motor score (p=0.015, p=0.027 respectively) while baseline FIM total scores were positively correlated with 1-year FIM motor scores (p<0.001). Presence of fractures was also not significantly correlated with functional outcomes measured by the FIM motor subscale.

Conclusion: Our findings are consistent with other studies and suggest that age, initial FIM motor score, and time to surgery all play a significant role with regards to recovery in TCCS patients with the only modifiable predictor being time to surgery.
ESTABLISHMENT OF THE NOVEL EX VIVO HEART PERFUSION IN RATS

Sachiko Kadowaki, Junko Kobayashi, Christoph Haller, Osami Honjo
Division of Cardiovascular Surgery, The Hospital for Sick Children, and University of Toronto,
Toronto, ON Canada

Hypothesis and Purpose: In the setting of langendorff technique of isolated rat heart perfusion, inevitable limitations are recognized such as the low oxygen-carrying capacity of crystalline solution, and the low oncotic pressure affecting the heart edema and functional availability. The present study aimed to confirm the feasibility of the novel ex-vivo heart perfusion (EVHP) system for a rat DCD heart with more similar way to a clinical setting than the conventional langendorff technique. Methods: Under general anesthesia, 350-400g rats were undergone circulatory arrest after clamping an endotracheal tube. Then, they were left at rest for 0, 15, and 30 minutes (n=5-9 per each group). After each ischemic time, the heart was injected cardioplegia and harvested, and then reperfused by blood based perfusate on the EVHP for two hours. The hemodynamic function was measured by intraventricular balloon technique. Result: The 15- and 30-minute ischemic groups were compared to the sham group. There was significant difference at the oxygen consumption (sham vs. 15 min; p<0.001, sham vs. 30 min: p<0.001). However, the lactate metabolism, the gain rate of the heart weight, and the maximum and minimum first derivative of left ventricular pressure didn’t show significant difference. Conclusion: the novel EVHP could distinguish the heart with different periods of ischemia in metabolic and hemodynamic aspects.
ROBOTIC BIPOLAR CAUTERY INSTRUMENT FOR TREATMENT OF HYDROCEPHALUS USING CHOROID PLEXUS CAUTERIZATION

Claudia Lutfallah, Thomas Looi, James Drake
Centre for Image Guided Innovation and Therapeutic Intervention, The Hospital for Sick Children, and University of Toronto

Purpose: A treatment option for hydrocephalus is endoscopic third ventriculostomy with choroid plexus cauterization (ETV/CPC). This is a relatively new treatment technique and as a result, there is a lack of instruments that can reach the complex structures of the ventricles to effectively perform the procedure. Hypothesis: A flexible, robotic, bipolar cautery instrument can be developed to reach the small, complex anatomies of the brain for the robot-assisted neuroendoscopic treatment of hydrocephalus by ETV/CPC. Methods: The instrument was designed to resemble grasping forceps to give surgeons control of the tissue they seek to cauterize. It is 1.9 mm in diameter and it is 3D printed with a photopolymer resin which offers electrical insulation between each forcep and the instrument’s shaft. The electrodes are made of stainless steel wire which also function as the actuating cables – pushing the cables forward opens the tips and pulling them back closes the tips. Finally, the instrument can achieve 6 degrees of freedom (DOF) by attaching to a concentric tube surgical robot. Results: The linear displacement of the wires required to open the tips to a certain jaw angle was found to be 0.06 mm of linear displacement for every 1° of jaw opening. The tool’s efficacy as a bipolar cautery instrument was tested on a porcine brain specimen, during which we observed a ‘sizzle’ noise when the tool was activated while underwater, the accumulation of charred tissue on the tips, and the thermal spread through the tissue as the setting on the electrosurgical unit (ESU) increased. Finally, the forces exerted by the tool on tissue were measured and show an average maximum force of 0.15 N per forcep. Conclusion: Overall, the instrument successfully cauterizes tissue, fits within the desired endoscopic channel, enables control of tissue without applying too much force, and can achieve 6 DOF to successfully reach complex anatomies within the brain. Further prototyping and clinical testing are required before bringing this instrument to market.
CURRENT ISSUES IN CONDUCT AND REPORTING OF NONINFERIORITY RANDOMIZED CONTROLLED TRIALS IN THE SURGICAL MANAGEMENT OF CANCER PATIENTS

Wanda Marini (SSTP)¹,a, Armen Parsyan²,a, Rouhi Fazelzad³, David Moher⁴,⁵, David McCready¹

¹ Department of Surgery, University Health Network, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada.
² Department of Surgery and Oncology, Western University, London Regional Cancer Program, St Joseph’s Health Care and London Health Sciences Centre, London, Ontario, Canada.
³ Library and Information Services, University Health Network, Princess Margaret Cancer Centre, Toronto, Ontario, Canada.
⁴ Centre for Journalology, Ottawa Hospital Research Institute.
⁵ School of Epidemiology and Public Health, University of Ottawa, Ontario, Canada.
a Authors contributed equally to this work

Hypothesis and Purpose: Serious concerns regarding the quality of noninferiority trials (NITs) have been raised. Systematic analysis of surgical NITs is critical given their potential clinical impact. We aimed to assess the quality of conduct, reporting and interpretation of NITs dealing with surgical management of cancer patients.

Methods: A cross-sectional analysis of papers identified through a comprehensive literature search was performed. Forty papers employing Phase III, noninferiority (NI), randomized trial design studying the effects of surgical methodology/sequencing in patients with solid cancers were included. Papers were assessed for type of analysis, noninferiority margin (NIM) justification, consistency of type I error with confidence intervals (CI), ability to achieve predefined sample size, and interpretations regarding noninferiority.

Results: Overall, 52.5% of the papers were deemed poor/fair quality. Only 50% used both intention-to-treat and per protocol analysis; 62.5% provided no/poor justification for the NIM; 42.5% showed inconsistency of the type I error with CIs; and 60.0% did not achieve predefined sample size. One fifth provided interpretation of the NI hypothesis that was discordant with CONSORT guidelines.

Conclusion: The quality of conduct, reporting and interpretation of surgical NITs is suboptimal, requiring further improvements through adherence to specific guidelines and rigorous assessment at the stages of study approval, funding and peer-review process.
Background: The blood-brain barrier (BBB) is a major obstacle for the effective therapeutic delivery to the brain in neurodegenerative disorders. MR-guided focused ultrasound (MRgFUS) is an emerging non-invasive technology to transiently disrupt the BBB for drug delivery. FUS has been shown to enhance immunotherapies and gene therapy among others in diseased animal models. BBB opening alone in amyloidosis models also reduced plaque burden and triggered neurogenesis possibly by inducing glymphatic clearance and microglial activation. We conducted pilot studies to investigate the safety and feasibility of MRgFUS BBBD in patients with Alzheimer’s disease (AD) and amyotrophic lateral sclerosis (ALS, NCT02986932, NCT03321487). Methods: 5 patients with mild-to-moderate AD and 4 with ALS and severe limb weakness were enrolled. The sonication target was the right prefrontal cortex in AD, which has heavy amyloid burden, and the primary motor cortex in ALS. FUS was delivered using a 220 kHz clinical-prototype under MRI thermometry and acoustic monitoring to brain regions measuring ~10x5x7 mm³. Subjects were followed for 60 days post-procedure. The primary outcome was safety – described by procedure-related adverse events – and feasibility – measured by contrast enhancement on MRI. Results: MRgFUS BBBD was successful and well-tolerated in all nine subjects. Gadolinium leakage was evident at the sonication target immediately after sonications and resolved in 24 hours. No significant temperature elevation was detected. Sonications of the eloquent primary motor cortex did not elicit any neurological symptoms. All procedure related AEs were transient, and mild-to-moderate (grade 1-2), the most common being headache (n = 6), scalp pain localized to the pin sites (n = 3), presyncope related to placement of the stereotactic frame (n = 2), nausea likely secondary to sedation (n = 3), and back pain from prolonged MRI (n = 2). Finally, we did not find any clinically significant change in neuropsychological tests, motor assessments, laboratory or electrophysiology assays after MRgFUS BBBD procedures. Conclusions: Therapeutic access to degenerating neurons and glial cells of eloquent and non-eloquent is essential in developing disease-modifying treatments for AD and ALS. We have taken the initial step in translating MRgFUS as a drug delivery platform.
THE IMPACT OF EMPAGLIFLOZIN ON KIDNEY INJURY MOLECULE-1: 
A SUB-ANALYSIS OF THE EMPA-HEART CARDIOLINK-6 TRIAL

Erika Opingari, Richard E. Gilbert, David Z. I. Cherney, Subodh Verma 
Divisions of Cardiac Surgery and Endocrinology & Metabolism, St Michael’s Hospital; 
Division of Nephrology, Toronto General Hospital; and University of Toronto

Hypothesis and Purpose: To better define the potential mechanisms that contribute to renal protection observed with sodium-glucose cotransporter 2 (SGLT2) inhibitors in type 2 diabetes (T2D), we assessed changes in urinary biomarkers, sodium and glucose excretion, in a prespecified sub-analysis of the EMPA-HEART CardioLink-6 trial.

Methods: Ninety-seven subjects with T2D (HbA1c 6.5-10.0%), established atherosclerotic cardiovascular disease, and estimated glomerular filtration rate (eGFR) >60 mL/min/1.73m², were randomized to receive either empagliflozin 10 mg once daily or matching placebo in addition to standard of care over a 6-month period. Random urine samples were collected at the randomization and 6-month visits. Analysis of covariance (ANCOVA) was performed to determine the mean percentage difference between groups at month 6, adjusting for baseline values.

Results: Data for 78 study participants (n=40 empagliflozin; n=38 placebo), for whom renal laboratory values were available, were included in the renal sub-analysis. Following 6 months of treatment, empagliflozin reduced levels of urinary kidney injury molecule-1 (KIM-1) by 34% (95% CI: -65% to-3%; P=0.03) compared with placebo. Urinary glucose excretion increased by 299% (95% CI: 202% to 396%; P<0.001) with empagliflozin compared with placebo. No between groups differences were observed in the other measured kidney injury markers that included the urine albumin-to-creatinine ratio, eGFR, and sodium excretion over the same period.

Conclusion: In a cohort of individuals at relatively low risk of diabetic kidney disease progression, empagliflozin treatment for 6 months reduced urinary KIM-1 excretion, suggesting that SGLT2 inhibitors may protect the proximal tubule, a major site of diabetes-related kidney injury.
TARGETING HUMAN CYTOMEGALOVIRUS IN DONOR LUNGS WITH A NOVEL FUSION TOXIN PROTEIN DURING EX VIVO LUNG PERFUSION PREVENTS VIRAL REACTIVATION

Rafaela VP Ribeiro¹, Terrance Ku², Victor H. Ferreira², Marcos Galasso¹, Sajad Moshkelgosha¹, Vinicius Michaelsen¹, Aizhou Wang¹, Aadil Ali¹, Khaled Ramadan¹, Bruno M. Gomes¹, Layla Pires¹, Hemant Gokhale¹, Anajara Gazzalle¹, John Sinclair³, Thomas Kledal³, Mingyao Liu¹, Shaf Keshavjee¹,², Atul Humar², Marcelo Cypel¹,²
¹Latner Thoracic Surgery Laboratories, Toronto General Research Institute, University Health Network, and University of Toronto;
²Multi-Organ Transplant Program, University Health Network, and University of Toronto;
³Department of Medicine, Addenbrooke’s Hospital, University of Cambridge

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: 12 human lungs rejected for transplantation were randomly placed on EVLP alone or EVLP+1mg/L of F49A-FTP for 6 hours. Biopsies pre and post perfusion were collected to evaluate in vitro viral reactivation. Since US28 has 38% homology to the human CX3CR1 chemokine receptor, potential off-target effects of the toxin were studied using flow cytometry for cell death assessment of CD34+ and CD14+ cells. Lung function on EVLP was evaluated as a safety endpoint. Results: F49A-FTP was delivered through the pulmonary artery on EVLP with no acute toxic events based on physiological parameters. Samples obtained from control EVLPs demonstrated a median increase from baseline of 32% (Range -16% to +112.5%) in viral reactivation, while samples from treated EVLPs demonstrated a median reduction of 76% (Range -15% to -99.9%), p=0.0087. We did not observe any measurable differences in apoptosis between treated lungs and control confirming the absence of off-target treatment related apoptosis.

Conclusions: Our study demonstrates that ex vivo F49A-FTP treatment of human lungs on EVLP markedly attenuates CMV reactivation. Additional in vivo studies to confirm the results are being planned prior to designing a safety clinical trial.
Aberrant activation of the Notch developmental signaling pathway is a defining feature of poor-prognosis basal-like breast cancer (BLBC). Our recent work shows that by regulating the expression of pro-inflammatory cytokines IL1β and CCL2, Notch promotes recruitment of tumor-associated macrophages (TAM) to the tumor microenvironment (TME). TAMs can suppress cytotoxic T lymphocyte (CTL) function and number, producing an immunosuppressive TME. This may explain the poor response rate of immune checkpoint blockade (ICB) therapy in BLBC, a subtype highly infiltrated by TAMs. We hypothesize that by reducing TAMs, Notch inhibition will reboot CTL activity and sensitize BLBC to ICB.

Methods: Murine basal-like mammary tumor 4T1 cells were grafted into mammary fat pads of BALB/c mice. Mice were then randomly allocated to different treatment groups including Notch (LY411575) or IL1β (Kineret) inhibition, ICB (anti-PD1), or vehicle treatments for 12 days. Mice in each group were then randomly assigned to continue treatment, or switch to another treatment for a further 12 days. At treatment completion primary tumor size, tumor-infiltrating immune cells, and lung metastasis were analyzed.

Results: A striking therapeutic effect was observed on the primary tumor and lung metastases when Notch inhibition was followed by anti-PD1 treatment. This regimen resulted in almost complete abolition of lung metastases. Supporting our hypothesis, TAMs were decreased in the primary tumor and a significant increase in tumor infiltrating CD8 T cells was observed in both primary tumor and metastases.

Conclusion: These findings suggest that Notch inhibition followed by ICB is a promising immunotherapeutic strategy in BLBC.
COMPREHENSIVE GENOMIC AND EPIGENOMIC CHARACTERIZATION OF THE SPECTRUM OF PERIPHERAL NERVE SHEATH TUMORS ASSOCIATED WITH NF1 IDENTIFIES TWO DISTINCT MPNST SUBTYPES

Suganth Suppiah, Sheila Mansouri, Jeff Liu, Mamatjan Yasin, Farshad Nassiri, Nazanin Ijiad, Neda Pirouzmand, Shirin Karimi, Ken Aldape, Gelareh Zadeh
Division of Neurosurgery, Department of Surgery, University of Toronto, Toronto, Ontario, Canada

Introduction: Neurofibromatosis type 1 (NF-1) is a tumor predisposition syndrome that results in the development of innumerable peripheral nerve sheath tumors. These tumors fall within a spectrum of benign, premalignant and malignant tumors. Here, we provide an integrated molecular characterization of the spectrum of peripheral nerve sheath tumors and identify two novel molecular subtypes of MPNSTs that are driven by SHH or WNT pathway activation. Methods: We investigated the DNA methylation patterns of a spectrum of peripheral nerve sheath tumors (N=108). The methylation classes were further characterized by WES and RNA sequencing on a subset of tumors. In addition, functional validation of identified pathways was performed using CRISPR/cas9 knockout in immortalized neurofibroma cell lines.

Results: Unsupervised consensus hierarchical clustering yielded seven stable and robust subgroups that are clinically relevant. The high-grade MPNSTs formed two distinct methylation-based clusters (MPNST-G1 and MPNST-G2). PTCH1 loss was prevalent in MPNST-G1 compared to MPNST-G2 (75% vs 12.5%, p < 0.05). Transcriptome profiling recapitulated the two distinct MPNST subgroups. Gene set enrichment analysis (GSEA) demonstrated that RB1 and PRC2 signaling pathways are aberrant in both MPNST-G1 and MPNST-G2. However, SHH pathway activation is observed in MPNST-G1, while WNT and CCND1 pathway activation is observed in MPNST-G2. To determine if SHH pathway activation is sufficient for malignant transformation, we knocked out PTCH1 in immortalized neurofibroma cells lines and observed induction of a malignant phenotype, with increased cellular proliferation and invasion.

Conclusions: Our integrative genomics approach to a large cohort of the spectrum of peripheral nerve sheath tumors identified two novel MPNST subgroups. The MPNST subgroups can be reliably assigned to subgroups through methylome and transcriptome signatures. Future research on MPNSTs and the development of clinical trials should take into consideration these two distinct types of MPNSTs to target these pathways as a novel therapeutic approach.
BARIATRIC SURGERY REDUCES INFLAMMATORY CELL BURDEN AND INCREASES PRO-VASCULAR PROGENITOR CELL CONTENT

Justin Z. Trac1,5, Daniella C. Terenzi1,6, Hwee Teoh1,2, Adrian Quan1, Mohammed Al-Omran3,5,6,7 Ori D. Rotstein4,6,7, Stephen A. Glazer8,9, David A. Hess3,5,10,11, Subodh Verma1,5,6,7

Divisions of 1Cardiac Surgery, 2Endocrinology and Metabolism, 3Vascular Surgery, 4General Surgery and Keenan Research Centre for Biomedical Science and the Li Ka Shing Knowledge Institute of Unity Health Toronto, Toronto, ON; 5Department of Pharmacology and Toxicology, 6Institute of Medical Science and 7Department of Surgery, University of Toronto, Toronto, ON; 8Department of Internal Medicine, Humber River Hospital, Toronto, ON; 9Division of Endocrinology & Metabolism, Queen’s University, Kingston, ON; 10Robarts Research Institute and 11Department of Physiology and Pharmacology, Western University, London, ON

Purpose and Hypothesis: Obesity represents a growing concern globally with >2 billion adults currently affected by an unhealthy weight. Chronic inflammation and metabolic insufficiency are associated with obesity, and excessive weight gain can dramatically elevate the risk of type 2 diabetes and ischemic complications. Since bariatric surgery has been associated with sustained metabolic and vascular improvements, we hypothesized that bariatric surgery will result in increased circulating pro-angiogenic progenitor cell content and reduced inflammatory cell burden.

Methods: Peripheral blood was collected from 20 individuals prior to and 3 months after gastric bypass (Roux-en-Y) surgery. Multi-parametric flow cytometry was used to identify 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 ALDHhiSSC^hi inflammatory granulocyte precursors (P<0.05) and a significant increase in circulating ALDHhiSSC^mid monocyte/macrophage precursors (P<0.01). Within the latter, surgery was also associated with a rise in circulating angiogenic monocytes (CD14+, P<0.001). Unexpectedly, the population of ALDHhiSSC^low cells, consistent with rare circulating early myeloid progenitor cells, was reduced following surgery (P<0.001). However, the frequency of ALDHhiSSC^low cells that co-expressed primitive cell surface markers (CD133+/CD34+), and which were previously associated with vasculogenic function, increased significantly (P<0.01). Conclusion: Bariatric surgery is associated with reduced circulating inflammatory cells and increased circulating pro-angiogenic monocyte content. This suggests that increased vascular regenerative potential may improve cardiovascular outcomes after bariatric surgery.
MITOCHONDRIAL METABOLISM IS PRESERVED FOLLOWING NORMOTHERMIC EX-VIVO KIDNEY PERFUSION OF GRAFTS PROCURED FOLLOWING CARDIAC DEATH

Peter Urbanellis (SSTP), Markus Selzner
Toronto General Hospital Research Institute and Division of General Surgery, Department of Surgery, University of Toronto

Purpose and Hypothesis: Normothermic ex-vivo kidney perfusion (NEVKP) preservation is a novel donor kidney storage method that has demonstrated superior graft outcomes for kidneys procured following donation-after-cardiac death (DCD) over static cold storage (SCS). To determine the mechanisms for this advantage, we compared the transcriptome from both groups through an unbiased genome-wide microarray analysis.

Methods: Kidneys from 30kg Yorkshire pigs were subjected to 30min of warm ischemia and then 8hrs of pressure-controlled NEVKP or SCS prior to heterotopic autotransplantation. Renal biopsies were collected on POD3 and RNA transcript expression was determined utilizing the Affymetrix GeneChip® Porcine Gene 1.0 ST Array platform examining over 23,000 transcripts.

Results: Graft function was significantly improved with NEVKP compared to SCS following transplantation with lower peak serum creatinine (POD1:4.0+/−1.15mg/dL vs POD3:12.0+/−0.78mg/dL,n=5,p<0.01) and higher creatinine clearance on POD3 (39.6+/−11.8mL/min vs 2.6+/−0.9ml/min,n=5,p<0.01). Gene set enrichment analysis demonstrated 12 Hallmark Gene Sets enriched in NEVKP compared to SCS including sets associated with fatty-acid metabolism and oxidative phosphorylation, while 10 Gene Sets were enriched in SCS compared to NEVKP (FDR-value<0.25,p<0.05). Gene ontology analysis demonstrated pathways associated with lipid oxidation/metabolism, the Krebs cycle, and pyruvate metabolism enriched in NEVKP vs SCS (FDR-value<0.05)

Conclusions: NEVKP maintained or enriched transcripts of key mitochondrial metabolic pathways compared to SCS in grafts procured following DCD, likely accounting for the improved post-transplant graft function.
REGULATION OF GLYCOLYSIS AND THE WARBURG EFFECT IN WOUND HEALING

Roohi Vinaik¹, Dalia Barayan¹, Abdikarim Abdullahi¹, Marc G. Jeschke¹,²,³
¹Sunnybrook Research Institute, Toronto, Canada
²Division of Plastic Surgery Department of Surgery, University of Toronto, Canada
³Ross Tilley Burn Centre, Sunnybrook Health Sciences Centre, Toronto, Canada

Purpose & Hypothesis: Abnormal scarring such as keloids is one of the most significant adverse post-burn responses. Perturbations in inflammation and glycolysis hinder normal healing and predispose certain patients to keloids. Therefore, we proposed that patients who develop keloids exhibit early evidence of altered immunometabolic responses at the site of injury, which interferes with healing and portends keloid development.

Methods: We enrolled 32 burn patients (38.9% ± 3.8% TBSA) for the non-keloid group and 10 burn patients that developed keloids within 2 years post-injury (43.4% ± 11.4% TBSA) for the keloid group. Skin was treated with shikonin and gene and protein expression of inflammatory and glycolytic markers were assessed. Trichrome and Glut1 staining was performed. For our murine studies, mice were subjected to a severe scald burn and sacrificed at 7 days.

Results: Keloids demonstrate NLRP3 activation (cleavage of caspase-1 (p<0.05) and IL1β (p<0.05)) and upregulation in Glut1 (p<0.001) and glycolytic enzymes. Burn skin similarly displayed enhanced glycolysis and Glut1 expression (p<0.01). Glut1 expression was significantly higher (>2 standard deviations) in keloid compared to non-keloid burn patients. Targeting aberrant glucose metabolism with shikonin, a pyruvate kinase M2 (PKM2) inhibitor, dampened NLRP3-mediated inflammation (decreased caspase-1 (p<0.05) and IL1β (p<0.01) cleavage) and improved healing in vivo.

Conclusion: Burn skin exhibited evidence of Warburg-like metabolism, similar to keloids. Targeting altered glucose metabolism with anti-glycolytic agents could change the trajectory towards normal scarring. This indicates the clinical possibility of shikonin treatment in burn patients for abnormal scar prevention.
Hypothesis & Purpose: The survival benefit of surgery for recurrent GBM in the current literature is variable, and often attributed to improvements in surgical technique over time. The purpose of our study was first to determine if surgery for recurrent GBM confers a survival benefit compared to patients not undergoing repeat surgery. The second goal of our study was to investigate the effect of known prognostic factors on survival for patients undergoing repeat surgery for GBM. In patients that have surgery for recurrent GBM, does a second surgery improve survival, and do any known prognostic factors further improve survival?

Methods: We analyzed our brain tumour bank database from 1992 to 2018 for all adult patients that underwent repeat surgery for primary recurrent GBM. This cohort was compared to publicly available data from The Cancer Genome Atlas (TCGA) on patients that did not undergo repeat surgery. Survival and prognostic factors were compared within and between groups.

Results: A total of 676 patients were analyzed (surgery cohort = 91, non-surgery cohort = 585). The surgery group had a lower age at diagnosis (50.6 vs 58.2 years old, p = <0.001) and higher Karnofsky Performance Status (KPS) (81.4 vs 77.5, p = 0.002) than the non-surgery group. Previously described prognostic factors were balanced between the groups. Overall survival was higher in the surgery group than the non-surgery group (28.8 months vs 14.8 months, p = <0.0001). Within the surgery group, prognostic factors including age, sex, KPS, extent of resection, tumour location, time to recurrence, and known biomarkers were not associated with improved survival.

Conclusion: Surgery for recurrent GBM improves survival independent of prognostic factors.
MAGNETIC RESONANCE GUIDED HIGH INTENSITY FOCUSED ULTRASOUND IN COMBINATION WITH THERMOSENSITIVE LIPOSOMAL DOXORUBICIN AS A NOVEL TREATMENT FOR RHABDOMYOSARCOMA

Claire Wunker, Karolina Piorkowska, Ben Keunen, Adam Waspe, Yael Babichev, Warren Foltz, Maximilian Regenold, Michael Dunne, Maryam Siddiqui, Christine Allen, Samuel Pichardo, Justin T. Gerstle, Rebecca A. Gladdy
Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, and University of Toronto

Hypothesis and Purpose: Rhabdomyosarcoma (RMS) is a common pediatric tumor. Current treatment includes vincristine-based chemotherapy, radiation and/or surgery. In cases of relapsed or metastatic RMS chemotherapies include doxorubicin which is cardiotoxic. An alternate form of doxorubicin is encapsulated in a thermosensitive liposome (TLD) which is released when heated. Magnetic resonance guided high intensity focused ultrasound (MRgHIFU) is a therapy that combines MRI imaging with ultrasound generating localized hyperthermia. We hypothesize that MRgHIFU with TLD will slow tumor growth, prolong survival, and reduce systemic drug toxicity.

Methods: Mosaic mouse model of RMS developed in our laboratory were used to optimize local delivery of heat to the tumors by MRgHIFU. High-performance liquid chromatography (HPLC) was completed to determine the amount of doxorubicin found in the tumors and plasma. Currently we are performing survival studies of mice with and without hyperthermia comparing: TLD, non-liposomal doxorubicin, vincristine, and saline. Drug accumulation in the heart, liver, and kidneys will be analyzed by HPLC and related to toxicity in long-term survival.

Results: Significantly higher concentrations of TLD were found in heated vs non-heated tumors ($P = 0.0163$). We found no statistical difference in the tumor accumulation of drug between TLD and non-liposomal doxorubicin for 10- or 20-minute durations of hyperthermia ($P >0.05$). Non-heated TLD remained in the plasma and was significantly higher than non-liposomal doxorubicin in the plasma at all time points ($P = 0.0020$). There was no correlation between tumor size and either plasma or tumor drug amounts ($r(59)= 0.11$ $P = 0.42$, $r(60)= -0.14$ $P = 0.30$).

Conclusions: This preclinical project forms the basis for the translation of MRgHIFU and TLD treatment into the pediatric oncology clinic, offering a novel treatment for RMS.
LOCAL FK506 DRUG DELIVERY ENHANCES NERVE REGENERATION THROUGH UNPROCESSED FRESH NERVE ALLOGRAFTS

Kevin J. Zuo,1 Golsa Shafa,1 Katelyn Chan,1 Jennifer Zhang1, Cynthia Hawkins,2 Kasra Tajdaran,1 Tessa Gordon,1 Gregory H. Borschel1

1Division of Plastic & Reconstructive Surgery, Hospital for Sick Children, and University of Toronto, Toronto, ON, Canada
2Department of Laboratory Medicine & Pathobiology, Hospital for Sick Children, and University of Toronto, ON, Canada

HYPOTHESIS & PURPOSE: Despite good outcomes, fresh nerve allografts are rarely used clinically due to the need for systemic immunosuppression. A local drug delivery system for FK506, an FDA-approved immunosuppressant, provides sustained release of FK506 without systemic effects. The study objective was to investigate the effects of local FK506 delivery to enhance nerve regeneration in a rodent model of nerve gap reconstruction using fresh nerve allografts. METHODS: In male Lewis rats, a hindlimb common peroneal (CP) nerve gap (10 mm) was reconstructed with 20 mm nerve isografts from donor Lewis rats or fresh nerve allografts from genetically mismatched donor ACI rats. Rats with allografts received either systemic FK506, local FK506, or no treatment. After 4 weeks, nerve regeneration was evaluated using: (1) retrograde labeling of regenerated neurons, (2) quantitative histomorphometry, and (3) serum cytokine profile. RESULTS: Rats with isografts or fresh allografts with systemic FK506 demonstrated significantly greater nerve regeneration compared to untreated fresh allografts (p<0.001). Allografts with local FK506 demonstrated robust regeneration of myelinated axons from motor and sensory neurons, which was significantly better than untreated allografts (p<0.001) and no different than nerve isografts or allografts treated with systemic FK506 (p>0.05). Serum concentrations of pro-inflammatory IL-12 were lower in rats treated with both local FK506 and systemic FK506 (p<0.05); however, local FK506 rats had undetectable serum levels of FK506 unlike rats treated with systemic FK506. CONCLUSION: Local FK506 drug delivery enhances nerve regeneration through fresh nerve allografts comparable to nerve isografts or allografts with systemic immunosuppression. Local FK506 does not result in systemic FK506 toxicity. In the future, local FK506 delivery may enable clinical nerve allotransplantation without systemic FK506 toxicity.