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SMART HUMAN NEURAL STEM CELLS TO DEGRADE CSPG SCAR AND OPTIMIZE REGENERATION AFTER TRAUMATIC SPINAL CORD INJURY

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Purpose and Hypothesis: Human induced pluripotent stem cell-derived neural stem cells (hiPS-NSCs) represent an exciting therapeutic approach to regenerate the traumatically injured spinal cord (SCI). Unfortunately, most patients develop a dense perilesional chondroitin sulfate proteoglycan (CSPG) scar which significantly hinders neurite outgrowth. CSPG-degrading enzymes are known to enhance NSC-mediated recovery, however, nonspecific administration via intrathecal catheters can cause off-target effects. We aimed to generate a novel genetically-modified line of hiPS-NSCs expressing a scar-degrading enzyme to enhance recovery.

Methods: A scar-degrading enzyme was non-virally transfected into hiPS-NSCs. A monoclonal line was generated by FACS (SMaRT cells). Enzyme expression and activity was extensively characterized \textit{in vitro} by biochemical and cell culture assays. T-cell deficient rats (N=60) with chronic C6-7 SCIs were randomized to (1) SMaRT cells, (2) naive hiPS-NSCs, (3) vehicle, or (4) sham surgery (laminectomy alone). Weekly behavioural tests are ongoing up to 32 weeks.

Results: Scar-degrading enzyme is expressed by transgenic SMaRT cells. The expressed enzyme appropriately degrades human CSPGs and allows neurons to extend into CSPG-rich regions \textit{in vitro}. Conditioned SMaRT cell media also degrades rodent CSPGs in \textit{ex vivo} injured cord cryosections. While blinded behavioural assessments are ongoing, an interim histologic analysis of several animals shows that grafted human cells are extending long (centimeter-scale) axons through rodent white matter.

Conclusions: This work provides exciting proof-of-concept data that genetically-engineered SMaRT cells can degrade CSPGs \textit{in vitro} and that human NSC transplants can generate long axons in chronic cervical SCI.
RISK OF INTRACRANIAL HEMORRHAGE FOLLOWING CAROTID ENDARTRECTOMY VS. STENTING: POPULATION-BASED STUDY

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Hypothesis and Purpose: Although multiple randomized controlled trials examined the relative efficacy of carotid revascularization procedures; they do not offer adequate power to examine rare complications such as intracranial hemorrhage (ICH). The objective of this study was to compare the rates of ICH following carotid stenting (CAS) versus endarterectomy (CEA).

Methods: This was a retrospective population-based cohort study of patients who underwent carotid revascularization in Ontario over the period of 2002-2015. 90-day ICH risk and 180-day mortality following ICH were compared using propensity scores methods and inverse-probability-weighting to adjust for selection bias. In sensitivity analyses, we excluded patients who had post-procedure ischemic stroke, and examined the subgroup of patients ≥66 years old to account for medication use. Results: Among 16,688 patients who underwent carotid revascularization (14% were CAS, 86% were CEA), 80 (0.48%) patients developed ICH and 40 (50%) died following ICH. Patients with more comorbid illnesses, history of symptomatic carotid stenosis, cardiac disease, and on antiplatelets or warfarin preoperatively were more likely to undergo CAS. In the adjusted analysis, CAS patients were more likely to have ICH (OR: 1.77; 95% CI: 1.32-2.36). The 180-day mortality following ICH was similar in CAS and CEA groups (OR: 0.73; 95% CI: 0.41-1.30). The results were consistent after excluding patients who developed post-procedure ischemic strokes (OR for ICH: 1.90; 95% CI: 1.41-2.56) and among the subgroup of patients ≥66 years old (OR for ICH: 1.53; 95% CI: 1.05-2.24). Conclusions: CAS is associated with rare but higher risk of ICH relative to CEA. Future research is needed to devise strategies that minimize the risk of this serious complication following CAS.
Hypothesis: Severe burn injuries are characterized by alterations in mitochondrial dynamics which coincide with the ‘ebb’ and ‘flow’ phase of metabolic progression following trauma. The elderly, in particular, are susceptible to poor outcomes after burns, due primarily to a scarcity of knowledge on the biomolecular effects of trauma in this population. Here, we investigated mitochondrial bioenergetics in the livers of adult and elderly mice following a severe burn to characterize age-dependent differences and determine if metformin, an antidiabetic agent which limits stress-induced hyperglycemia, can provide benefits.

Methods: Both 8 week (adult) and 50 week (elderly) old C57BL/6 mice received a 30% total body surface area dorsal (98°C for 10 sec) and ventral (98°C for 2 sec) scald burn. Select mice received daily intraperitoneal injections post-burn of metformin (100 mg/kg). At day 7, mice were sacrificed and livers were collected for functional mitochondrial studies. Respirometry was performed on freshly isolated samples using a Seahorse Xf96 analyzer, and these data were complemented by in-gel activity assays for complexes of the electron transport chain.

Results: At 7 days post-burn, adult liver bioenergetics were significantly higher than their sham counterparts, indicative that this group had entered the hypermetabolic period following trauma. The elderly, however, had significantly lower respiration in the burned cohort compared to shams, implying that these mice fail to recover from burn trauma at the mitochondrial level. Metformin treatment appears to normalize both types of mitochondrial dysfunction.

Conclusions: It appears as though an underlying factor for the increased susceptibility of the elderly to thermal trauma is a failure of hepatic bioenergetics to recover at the same rate as their adult counterparts. Interestingly, the administration of metformin in the elderly cohort bolsters the recovery of mitochondria, despite it lowering the respiration rate in the adult population, thus normalizing mitochondrial bioenergetics post-burn.
EXOSOMES ENRICHED IN THE ACELLULAR WHARTON’S JELLY OF THE HUMAN UMBILICAL CORD ENHANCES SKIN WOUND HEALING

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We recently reported that acellular gelatinous Wharton’s jelly (AGWJ) from the human umbilical cord enhances wound healing in-vitro and in-vivo. However, the active ingredient(s) of AGWJ is not known. **Hypothesis:** There are extracellular factors in the AGWJ which are beneficial for wound healing. **Purpose:** Investigate the active ingredient(s) in the jelly and establish the mechanism of action. **Methods:** Isolated and fractionated acellular WJ. Mass spectrometry on AGWJ to identify proteins, then isolated exosomes from AGWJ. In-vivo, 6mm punch biopsies on the backs of BALb/c male mice were performed; wounds were treated with control matrigel, matrigel with AGWJ and matrigel with exosomes from AGWJ. Mice were sacrificed on day 7, histology was performed on wounds. **Results:** AGWJ significantly enhanced fibroblast migration and changed morphology to a myofibroblastic phenotype, confirmed by upregulation of alpha smooth muscle actin (αSMA). In-vivo, a smaller wound length in the AGWJ treated mice were observed, with greater αSMA expression. Interestingly, the number of F4/80+ve macrophages were significantly higher in the AGWJ group compared to controls, suggesting that AGWJ enhance macrophage accumulation which upregulates αSMA and causes faster contraction. Mass spectrometry on AGWJ revealed a protein characteristic of exosomes. In murines, wounds treated with only exosomes isolated from AGWJ were the smallest in length compared to total AGWJ and controls, suggesting that exosomes in AGWJ are the main enhancing factor. Western blot analysis revealed an enrichment of TGF-β protein in exosomes. **Conclusion:** Data suggests that exosomes in AGWJ enhances wound healing through an increase in the number of myofibroblasts in granulation tissue, partly through the activation of TGF-β pathway.
EARLY DEVELOPMENT OF OSTEOSARCOMA AFTER BENIGN GIANT CELL TUMOR OR ANEURYSMAL BONE CYST. A CASE REPORT

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**Purpose:** To describe two cases in which patients developed malignant osteosarcoma in the early phase following treatment for a benign bone tumor.

**Hypothesis:** It is possible for malignant bone tumors to present in the site of recently treated benign giant cell tumor (GCT) or aneurysmal bone cyst (ABC).

**Methods:** Clinical charts including full radiographic and histology reports were reviewed for 2 patients who presented with malignant osteosarcoma after treatment for GCT and ABC respectively.

**Results:** We describe 2 unique cases, one ABC and one GCT, where aggressive local recurrence was found to be high grade osteosarcoma just months after definitive benign pathology reports. In both cases the histology slides from the initial resection were re-examined and showed no evidence of malignancy.

**Conclusion:** Benign bone tumors such as aneurysmal bone cysts (ABC) and giant cell tumors (GCT) may display aggressive features. However histologically these tumors most commonly remain benign and only rarely undergo malignant transformation. Malignant change, in the absence of radiation, usually occurs years after resection of the primary lesion with an average interval for GCT of 10 years and for ABC of 7 years. Although benign recurrence of ABC and GCT is relatively common, it is imperative that any short-term florid recurrence of a benign lesion be questioned as possible malignant transformation. We recommend that any rapidly progressive recurrence demonstrating bone destruction or any other aggressive features should be re-staged and worked-up as a new lesion in order to avoid missing these rare cases of malignancy.
LAPAROSCOPIC SURGERY FOR SMALL BOWEL OBSTRUCTION IS ASSOCIATED WITH A HIGHER RISK OF BOWEL INJURY: A POPULATION BASED ANALYSIS

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Objective: Laparoscopic lysis of adhesions for small bowel obstruction (SBO) is becoming more common yet might increase the risk of bowel injury given the distended and/or potentially compromised small bowel. To explore this possibility, we set out to compare the incidence of bowel repair and/or resection in a large cohort of patients with adhesive SBO (aSBO) managed operatively.

Methods: We used administrative discharge data to identify patients who underwent surgery for their first episode of aSBO over 2005-14 in Ontario. Procedure codes were used to determine the exposure: either an open approach or a laparoscopic approach (including procedures converted to open). The primary outcome was incidence of bowel intervention, defined as intraoperative enterotomy, suture repair of intestine, or bowel resection.

Results: 8,584 patients underwent operation for aSBO. Patients undergoing laparoscopic procedures were younger with fewer comorbid conditions. The incidence of bowel intervention was 53.5% vs 43.4% in laparoscopic vs open procedures (p<0.0001). After adjustment for potential confounders, the odds of bowel intervention among patients treated laparoscopically versus open was 1.6 (95%CI: 1.4-1.9).

Conclusions: Laparoscopic procedures for aSBO are associated with a greater likelihood of need for intervention for bowel injury and/or repair. This increase might be due to challenges inherent with laparoscopic approaches in patients with distended small bowel. Laparoscopic approaches in this patient population should be accompanied by considerable caution.
PLK4 REGULATES CANCER CELL MOTILITY THROUGH RHOA GEF ARHGEF1

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Background: Polo-like kinase 4 (Plk4) expression is increased in colorectal, pancreas and breast cancers, and predicts inferior survival. Our laboratory showed that Plk4 promotes migration and invasion of cancer cells. We previously identified a cytokinesis defect in Plk4+/- murine embryonic fibroblasts (MEFs) which is due to failure to phosphorylate the Rho GEF Ect2, impairing RhoA activation at the equatorial cortex. This finding led us to hypothesize that Plk4 regulates cell motility by altering activation of RhoGTPases.

Methods and Results: To identify potential mediators of the regulation of RhoGTPases by Plk4, we scanned a library of 149 GEFs and GAPs and identified 12 potential Plk4 substrates (all GEFs) that contain the Plk4 consensus phosphorylation motif. Since RhoA depletion by siRNA results in decreased wound healing, similar to Plk4 we chose RhoA GEFs for further examination. Co-transfection and co-immunoprecipitation (Co-IP) from HeLa cells show that Plk4 physically interacts with the RhoA GEF Arhgef1. In addition, Co-IP with truncation mutants of Plk4 showed that ARHGEF1 interacts with kinase domain and polo-boxes 1-2 of Plk4. Co-IP with truncation mutants of Arhgef1 showed that Plk4 interacts with DH/PH and L-DH/PH domains of Arhgef1. Plk4 phosphorylates full length Arhgef1 and L-DH/PH domain in *in vitro* kinase assays. To functionally validate these interactions, we examined scratch wound-healing in U2OS cells that overexpress YFP-Plk4 upon addition of tetracycline. Depletion of Arhgef1 decreases cell migration, similar to depletion of Plk4, with and without addition of tetracycline, suggesting that Plk4 may act through Arhgef1 to affect cell motility. The effect of Plk4 overexpression in cells depleted of Arhgef1 on RhoA activation is being examined. Conclusions: Our results indicate that activation of RhoA may mediate the stimulation of cancer cell motility by Plk4 through Arhgef1. Regulation of cancer cell motility via RhoGTPase pathways may contribute to promotion of metastasis and therapeutic resistance by Plk4.
CHARACTERIZING TAU HYPERPHOSPHORYLATION FOLLOWING TRAUMATIC SPINAL CORD INJURY: A POTENTIAL HISTOLOGICAL MARKER OF AXONAL INJURY

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Tau is a microtubule-associated protein primarily located within the axonal compartment of normal neurons, responsible for promoting the formation of microtubules and stabilizing their structure. Experimental trauma to the brain (TBI) has revealed that tau becomes hyperphosphorylated within injured axons. Due to the lack of hyperphosphorylated tau (p-tau) protein within uninjured axons, experimental research on TBI has utilized p-tau as a histological biomarker of axonal injury post-TBI. However, the field of spinal cord injury (SCI) has not examined the potential of p-tau to serve as a histological biomarker of axonal-injury. Therefore, this study will attempt to detect p-tau within injured axons post-experimental SCI, characterize the anatomical and temporal distribution of p-tau immuno-reactive axons, and compare the characterization profile of p-tau with the characterization profile of β-amyloid precursor protein (β-APP), an established histological biomarker of axonal injury. Female Wistar rats were subjected to a severe 35 gram impact clip-compression SCI and were sacrificed at 4 hours, 1, 3, 5, 7, and 30 days post-SCI. Both parasagittal and cross-sections were cut from formalin perfused spinal cord tissue and analyzed for p-tau using pS396 and pT205 antibodies as well as an antibody for β-APP. Work is still in progress, however, current results demonstrate that p-tau is present within injured axons as early as 4h post-SCI and as late as 7 days post-SCI. In addition, the highest amount of p-tau immunoreactive axons is observed 1 day post-SCI and over all time points examined the highest level of p-tau containing axons is observed between 2000-4000µm rostral and caudal to the injury epicentre. To date we have concluded that, compared to controls, p-tau antibodies are capable of identifying injured axons post-SCI, and the differential degree of p-tau containing axons from 4 hours to 7 days may be indicative of axonal degeneration.
Hypothesis and purpose: Lung hypoplasia plays a major role in the outcome of neonates with congenital diaphragmatic hernia (CDH). Recently, amniotic fluid stem cells (AFSC) were shown to rescue lung hypoplasia via an undetermined paracrine effect. We aimed to investigate whether this beneficial effect was due primarily to AFSC exosomes. Methods: AFSC exosomes were isolated via ultracentrifugation from AFSC conditioned medium (CM). In-vitro: primary epithelial cells were harvested from E14.5 fetal lungs whose dams received nitrofen (100mg) at E9.5 to induce lung hypoplasia. EpCAM+ cells were isolated, cultured for 5 days, and treated with: i. growth medium alone; ii. AFSC-exosomes (200ug/mL); iii. AFSC-CM; iv. AFSC-exosome-free CM. Lungs from fetuses not exposed to nitrofen served as control. Groups were compared for proliferation (5’EdU) and apoptosis (live/dead assay) using one-way ANOVA (Tukey post-test). Protein and RNA cargo was labelled with Exo-Glow™, added to epithelial cells, and tracked under microscopy. Ex-vivo: E14.5 lungs were harvested and treated for 72h as described above (i-iv). Results: In-vitro: We found that the detrimental effect on cell proliferation and apoptosis was rescued by AFSC-exosomes and AFSC-CM, but not by AFSC-exosome-free CM. AFSC-exosome RNA was endocytosed within 15min, whereas exosome proteins within 1h. Ex-vivo: Nitrofen administration resulted in severe lung hypoplasia. Lungs treated with either AFSC-CM or AFSC-exosomes had terminal bud density and surface area similar to normal control. Conversely, explants treated with AFSC-exosome-free CM failed to rescue lung hypoplasia. Exo-Glow™ stained AFSC-exosomes migrated into the explant as visualized by two-photon excitation microscopy. Conclusions: This study shows for the first time that AFSC-exosomes are able to rescue lung hypoplasia in fetal rats. Stem cell secreted vesicles could represent a promising cell-free therapy for babies with CDH.
PULLULAN/GELATIN SCAFFOLD: AN IDEAL NICHE FOR SKIN REGENERATION

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The World Health Organization (WHO) estimates that over 300,000 deaths are due to burn injuries and millions more are suffering from burn-related physical and emotional consequences annually. Wound healing and its complications is the major underlying reason for morbidity and mortality of patients. Therefore, developing assistant materials to promote wound healing is crucial. Due to good biocompatibility, excellent supportive capability on cell growth, and especially anti-oxidant property, pullulan/gelatin (PG) scaffold with physically cross-linked pullulan and chemically cross-linked gelatin can be a good candidate as an assistant material.

**Purpose**: We fabricated the second generation of PG scaffold (PG2) with improved mechanical property and biocompatibility. We compared PG2 to clinically used Integra® dermal regeneration template (Integra®) from aspects of material properties and *in vitro* cell study.

**Methods**: Material characterization of PG2 and Integra, such as morphology, porosity, water retention, swelling behaviour, mechanical strength, and anti-oxidant property, was evaluated. Their ability to support cell survival and cell proliferation, as well as extend cell penetration was investigated by incorporation of human skin fibroblasts.

**Results**: Salt-leaching method is been used to fabricate PG2. PG2 shows heterogeneous interconnected round-shaped porous structure; the pore size is 20-200um; the porosity is around 74%. PG2 shows a unique anti-oxidant property to protect incorporated cells from reactive oxidant species. *In vitro* cell study demonstrates that cells on PG2 have a comparable viability (86-90%), penetration capability (164-201um), and proliferation capacity (27%) to Integra®, especially in a clinically available low cell seeding density (4000 cells per cm$^2$).

**Conclusion**: Novel PG2 scaffold is a promising and affordable wound healing assistant material.
COST-UTILITY ANALYSIS OF HOME-BASED POST-OPERATIVE RECOVERY FOLLOWING TOTAL KNEE REPLACEMENT

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Hypothesis: We propose that home-based post-operative management of knee replacement recovery and its rehabilitation presents an opportunity for reducing costs and improving the quality of care within the Canadian healthcare system. Approximately 64,000 total knee replacements (TKR) occur in Ontario each year. Redefining TKR procedures as ambulatory surgeries is one proposed mechanism of reducing health system costs. An important distinction of the proposed home-based intervention in this study is that it aims to support self-efficacy, and thus build the capacity of patients and families in support of self-management.

Design and Purpose: We performed a cost-utility analysis. A Markov Monte Carlo microsimulation model with a life-long time horizon was created to compare quality-adjusted life years (QALYs) and the cost between the two post-operative recovery strategies from the perspective of the public healthcare payer.

Interventions: We compared two acute post-operative recovery strategies: outpatient post-operative telecare (OutPT) and in-hospital ward care.

Measurement and Main Results: Effectiveness was measured in quality-adjusted life years and costs were measured in Canadian dollars. OutPT was associated with an average gain of 0.0056 quality-adjusted life years relative to in-hospital ward care and an average cost-savings of $4,269 per case.

Conclusions: OutPT for post-operative recovery of knee replacement patients resulted in greater quality adjusted life expectancy over in-hospital ward care. The ICER between Outpatient Post-operative Telehealth in-hospital standard care is -$764,442.89/QALY, with 58.8% of cases being cost-effective according to probabilistic sensitivity analysis.
TEN-YEAR SURVIVAL OUTCOMES FOLLOWING RESECTION OF
LOCALLY RECURRENT RECTAL CANCER

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Hypothesis and Purpose. The international ‘Beyond TME’ Collaborative identified Locally Recurrent Rectal Cancer (LRRC) as a complex problem requiring multidisciplinary consultation and specialized surgical care. Aggressive en bloc resection has been associated with 5-year survival rates of 25-50%. However, skepticism persists that LRRC can be “cured” given the lack of published longer-term survival data. We investigated the oncologic outcomes at 10 years following resection of LRRC and sought relevant clinicopathologic prognostic factors.

Methods. The study cohort consists of 52 consecutive patients (31M, 21F) who underwent LRRC resection at our centre between 09/1997 and 08/2005. Patients were followed with history & physical and CT-Chest-Abdo-Pelvis q4mos X2y, q6mos X3y, then annually.

Results. At last follow-up (f/u), 32 patients had died of rectal cancer, 1 died of other causes, 4 were alive with rectal cancer, and 15 (29%) were alive cancer-free. For the entire cohort, overall survival (OS) was 42% at 5y and 37% at 10y, with a median OS of 43mos. Prognostic variables for OS in univariate analysis included: distant metastasis at the time of LRRC resection, resection margin status, receipt of systemic chemotherapy, and receipt of radiotherapy. All patients who had M1 disease at the time of LRRC resection died of recurrent cancer at a median of 21mos (4-46). In patients who had R0 resection (n=41), OS was 51% at 5y, 45% at 10y, median 72mos. Preoperative concurrent chemoradiation therapy prior to resection of LRRC (n=20) was associated with significantly improved prognosis (p = 0.04).

Conclusions. Complete resection of LRRC was associated with durable survival in approximately 40% of patients with plateauing of survival curves after 5 years. Neoadjuvant therapy before resection of LRRC may improve survival.
NON-ADHESIVE WOUND DRESSINGS FOR ENHANCED WOUND HEALING

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The mortality rate of burn patients remains at a substantial plateau due to infections, sepsis, and the hypermetabolic-catabolic response, which occurs when effective wound healing cannot take place. In patients with full thickness burns, the damage zone extends to the dermal and subdermal layers. Full-thickness burns normally do not heal, or heal over a prolonged period resulting in a devastating scar. A fundamental limitation of wound healing is the lack of available healthy tissues or cells, particularly for big wounds. Conventional wound dressings are not actively involved in the wound repair process, and cannot dynamically adapt their properties in any way. Herein we report on a novel wound dressing which acts as a device to actively and dynamically participate in the wound repair process. Hypothesis: We hypothesize that our prototype of a non-adhesive silicone-based dressing can enhance rates of wound repair, and avoid damage to the underlying tissue upon dressing removal. Methods: A flexible wound dressing has been manufactured from polydimethylsiloxane (PDMS), with perforations and an absorbent backing layer that allows exudate absorbency. We have measured the proliferation rate of fibroblast cells and evaluated the non-adhesive properties of the dressing. Results: In vitro data showed that the cells are not adhering to the dressing when compared with the commercial dressing products. This allowed for superior proliferation and differentiation, depending on the used cell type. Conclusions: This design offers active control of tissue healing at the wound site, by using different cell types delivered at a controllable rate to dynamically optimize the rate of tissue and wound repair.
AGE, SEX, MECHANISM OF INJURY, AND NUMBER OF PREVIOUS CONCUSSIONS: PREDICTORS OF DEPRESSION AND ANXIETY IN POSTCONCUSSION SYNDROME?

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Patients typically recover from concussion within 30 days of injury, however if recovery is not observed within this time, the patient is diagnosed with postconcussion syndrome (PCS). PCS can persist for months, years, or indefinitely. Patients are often unresponsive to cognitive, behavioural, and/or pharmaceutical therapies, leaving them hopeless and often suicidal. Our objective was to understand whether sex, age, mechanism of injury, and number of previous concussions are predictors of PCS related symptoms of depression and anxiety. If these variables can identify patients at risk for symptoms of depression ± anxiety, then they can be utilized to target vulnerable patients to implement interventional therapies. A retrospective cohort study was conducted by clinical chart review of 541 patients diagnosed with PCS by specialist Dr. Charles H. Tator. The patient population was divided into 4 cohorts: patients reporting depression (n=64), anxiety (n=86), anxiety ± depression (n=72), or neither (n=319). Within each cohort patient age, sex, mechanism of injury, and number of previous concussions was evaluated. XLSTAT was utilized to perform statistical analysis. PCS symptoms of depression ± anxiety were most commonly observed in patients who acquired a concussion through sports and recreation. The risk of developing symptoms of anxiety ± depression decreased with age, with young adults (10-20 yrs.) reporting anxiety ± depression most frequently. Interestingly, symptoms of anxiety increased in concordance with number of previous concussions. However, number of previous concussions was not a significant predictor of depression, or depression ± anxiety. A strong correlation exists between age, mechanism of injury and PCS related depression ± anxiety, and should be further evaluated. Future research will monitor this population to examine the effectiveness of prescribed therapies in symptom resolution and determine if they can be implemented as interventional treatments.
WATCH & WAIT APPROACH FOR RECTAL CANCER WITH COMPLETE RESPONSE TO NEOADJUVANT CHEMORADIATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: A watch and wait (W&W) approach for patients with clinical complete response (cCR) to neoadjuvant chemoradiation (nCRT) can potentially avoid the morbidity of conventional surgery for rectal cancer. However, the safety of this approach remains unclear. Purpose: This review aims to synthesize the evidence for W&W as a treatment for rectal cancer. Methods: We systematically searched MEDLINE, EMBASE, and the grey literature (up to June 28, 2016) to identify studies of patients with rectal adenocarcinoma treated by W&W after cCR to nCRT. We determined the proportion of 2-year local regrowth following W&W. For studies comparing groups undergoing W&W to radical surgery after cCR or to patients with pathologic complete response (pCR), we compared non-regrowth recurrence (NRR), cancer-specific mortality (CSM), disease-free survival (DFS), and overall survival (OS) between groups. Findings: We identified 23 studies including 867 patients. Pooled 2-year local regrowth was 15.7% (95% CI: 11.8-20.1%); 95.4% of patients with regrowth underwent salvage therapies (95% CI: 89.6-99.3%). As compared to patients with pCR, those treated by W&W had comparable rates of NRR (RR 1.46; 95% CI: 0.70-3.05), CSM (RR 0.87; 95% CI 0.38-1.99), and OS (HR 0.73; 95% CI: 0.35-1.51), but poorer DFS (HR 0.47; 95% CI: 0.28-0.78). When compared to patients with cCR managed by surgery, there were no statistically significant differences in rates of NRR (RR 0.58; 95%CI: 0.18-1.90), CSM (RR 0.58; 95% CI: 0.06-5.84), DFS (HR 0.56; 95%CI: 0.20-1.60), or OS (HR 3.91; 95%CI 0.57-26.72). Conclusions: The majority of patients treated by W&W successfully avoid radical surgery and in those who experience regrowth almost all have salvage therapy. Although we did not identify differences in non-regrowth cancer recurrence or overall survival in patients treated by W&W vs. surgery, the number of patients reported in the literature is small and additional prospective studies are needed to confirm long-term safety.
UTILITY OF MRI, CT, AND ULTRASOUND FOR ASSESSMENT OF CHRONIC WRIST PAIN

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Purpose: Individuals with wrist pain often undergo specialized diagnostic imaging (magnetic resonance imaging (MRI), computed tomography (CT) scan, or ultrasound) prior to being assessed by a hand specialist. The purpose of this study was to investigate whether these pre-emptive investigations have an impact on final diagnosis and management.

Hypothesis: MRI, CT, and ultrasound is often unnecessary to assess chronic wrist pain.

Methods: 115 patients were included based on the following criteria: referred to a tertiary level hand centre for subacute/chronic wrist pain & assessed by a hand surgeon (Jan. 2015 – Oct. 2016). Data collection included patient demographics and referral diagnosis/specialty. At initial consultation, clinical diagnosis and additional imaging requirements (beyond routine X-rays) were recorded. Previously performed MRI, CT and/or US results were reviewed. The final clinical diagnosis was compared to the initial referral diagnosis. Pre-consultation imaging was categorized as (1) no value for diagnosis/management (2) some value, or (3) high value.

Results: 82 patients had additional imaging completed prior to referral (69 MRIs, 11 CTs, and 16 ultrasounds). 77% of the MRIs performed were deemed non-contributory to final diagnosis or management. None of the ultrasounds performed provided any additional value in diagnosis or treatment. Of all the additional imaging performed, 2 CT scans were thought to be highly valuable aids in clinical management (scaphoid non-union detail). The majority of additional imaging (73%) was classified as unnecessary. Six patients required further imaging after consultation.

Conclusions: Clinical assessment and x-rays alone are usually sufficient to arrive at a diagnosis. Few patients require additional imaging with MRI, CT scan, or ultrasound. Future studies can be directed at referring physicians to identify how imaging can be used effectively to decrease utilization of this resource.
DEVELOPMENT OF A FLEXIBLE COOLING SYSTEM FOR PHOTOTHERMAL ABLATION OF PERIPHERAL LUNG TUMORS

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**Purpose:** The purpose of this project is to develop a flexible cooling catheter that can eliminate excess heat related problems, such as necrosis of surrounding tissue and damage to the optical fibre, that occur during endoscopic photothermal therapy (PTT) of peripheral lung nodules.

**Hypothesis:** If we can exchange coolant fluid near the tip of the optical fibre at a flow rate to dissipate 400 joules of energy per second (as generated by the current optical fibre used in Dr. Yasufuku's lab), then we can reduce or eliminate the heat related issues, and greatly improve the efficacy of PTT as a viable treatment for peripheral lung nodules.

**Methods:** The first aim of this project is to design and develop a functional prototype of the cooling system, to allow us to test the impact that it will have on reducing the heat related damage that accompanies PTT treatment. The second aim is to test this device using a phantom that will mimic the coagulation of human tissue, to allow us to gauge the device's performance, and modify the design to further improve its effectiveness. The third aim is to test the design in a perfused, ex-vivo human lung, to allow for further confidence that the testing done in the lab will yield a high rate of translation to the clinical setting.

**Results:** A prototype has been manufactured and tested for functionality. A polyacrylamide phantom is in development, and will be used to validate that the temperature increase remains below 10°C outside of the target area, and that there is no charring of the optical fibre.

**Conclusion:** The successful implementation of this cooling system will allow for improved efficacy of PTT, and validate it as a viable treatment for currently inoperable cases of peripheral lung nodules. Its use can also be spread to other treatment tools, such as radiofrequency ablation, which are accompanied by concerns over heat related harm that can be caused to the patient.
MICRORNA-34A: ROLE IN THE DEVELOPMENT OF OSTEOARTHRITIS DURING OBESITY

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\textbf{OBJECTIVE:} Mice fed a high-fat diet (HFD) exhibit an accelerated surgically-induced osteoarthritis (OA) phenotype compared to lean diet (LD) fed mice. Recent studies have shown that microRNA-34a is elevated in obesity. Despite the strong association between obesity and OA, no studies have examined the role of miR-34a in the development of OA during obesity. \textbf{We hypothesize that during obesity expression of miR-34a is elevated and contributes to OA pathophysiology.}

\textbf{METHODS:} Mouse blood was collected at 9 weeks of age (baseline) and at the end of a HFD or LD course. Human plasma was taken at preadmission from end-stage OA patients undergoing total knee replacement (TKR) surgery. Chondrocytes and synovial fibroblasts (SF) were plated in replicates and transfected with 100nM miR-34a mimic.

\textbf{RESULTS:} Plasma miR-34a levels were significantly up-regulated in HFD mice compared to baseline mice and LD controls. Human plasma miR-34a levels were up-regulated in obese end-stage OA patients compared to non-obese patients. In-situ hybridization shows HFD mouse knee joints express significantly higher levels of miR-34a than LD mouse knees and localized to cartilage and synovial membrane. Mir-34a mimic-treated chondrocytes showed significantly increased expression of MMP13 and reduced expression of SIRT1, Aggrecan, and autophagy markers (ATG5 and ULK1). Mir-34a-treated SFs show significantly increased Type I collagen (mRNA and protein), TNF-\(\alpha\), TGF-\(\beta\), IL-6, ULK1, ATG5 and ATG3.

\textbf{CONCLUSIONS:} This study will be the first to elucidate a mechanistic role for miR-34a in the development of OA during obesity and its potential as a therapeutic target.
TECHNICAL PERFORMANCE PREDICTS COMPLICATIONS IN LAPAROSCOPIC GASTRIC CANCER SURGERY: ANOTHER PIECE OF THE PUZZLE

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**Hypothesis:** Surgical skills predict short term outcomes in laparoscopic gastrectomies.

**Purpose:** The purpose of this study was to evaluate the relationship between intraoperative technical performance and patient outcomes in laparoscopic gastric cancer surgery.

**Methods:** A retrospective video and chart review was performed for all patients who underwent laparoscopic gastrectomy for cancer at three teaching institutions between January 1st 2009 and December 31st 2015. Patients with unedited video files were included in the study. Video files were rated using OSATS (Objective Structured Assessments of Technical Skills) and GERT (Generic Error Rating Tool) instruments. The main outcome variable was short-term complications. The effect of technical performance on patient outcomes was assessed using logistic regression analysis with backward selection strategy.

**Results:** Sixty-one patients were included in the study. The overall complication rate was 29.5%. The mortality rate was 8.2%. The mean Charlson Comorbidity Index (CCI), type of procedure and the global OSATS score were kept in the final model. Lower performance score (OSATS≤29) remained an independent predictor for short-term outcomes [Odds Ratio (OR): 6.49], while adjusting for comorbidities and type of procedure.

**Conclusions:** Intraoperative technical performance predicts short-term complications in laparoscopic gastrectomy for cancer. Ongoing assessment and enhancement of surgical skills, using modern strategies as structured feedback, deliberate practice, coaching etc., might improve patient outcomes. Future work should focus on developing and studying the effectiveness of such interventions in laparoscopic gastric cancer surgery.
EVALUATING THE EFFECT OF EX VIVO LUNG PERFUSION (EVLP) IN LUNGS FROM HEPATITIS C DONORS

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Hypothesis and Purpose: Hepatitis C (HCV) is a prevalent disease in potential donors. Due to a high risk of transmission for the recipient, HCV+ donors are not offered for lung transplantation. Although the effect of EVLP into bacterial infection in donor lungs has been studied, the impact into chronic virus diseases is unknown. We hypothesized that the EVLP is a realistic platform to treat HCV+ donor lungs. The aim of this study was to investigate the effect of EVLP-associated treatments into HCV virus loads. Methods: Rejected lungs from 8 HCV+ donors were used. Double lung blocks were separated and placed in 2 independent EVLP circuits for 9 hours. One lung was used as the control lung (standard EVLP protocol), whereas the other lung was subjected to different treatment conditions: 1: Intense lung wash (replacement of perfusate solution and circuit after 3h of EVLP); 2: Ultra Violet C (UVC) light applied to circuit using a specifically design device. The effect of UVC light into virus load was also evaluated in specifically designed EVLP mini-circuit (circuit without the lungs) using different virus quantities. Virus load was measured at different time points in lung and perfusate using Abbott RealTime HCV assay. Results: In 2 out of 8 donors, no HCV virus was detected in the lungs during EVLP, and this was associated with low donor viremia. For the remaining 6 donors, lung wash was the most effective treatment to decrease HCV titres: 85.8% (±2.83; n=3) in the wash group vs. 57.6% (±6.78; n=2) in UVC group vs. 19.78% (±25.73; n=07) in control group. UVC irradiation was very effective in the mini EVLP circuit at different HCV doses. After 180 minutes of UVC irradiation on the mini EVLP, the viral load decreased 95.7% (±4.3; n=3) from the initial load. In two cases, an undetectable viral load was reached. Conclusion: EVLP can be a platform to significantly decrease HCV quantities from donor lungs. Adjunct treatment strategies such as UVC may yield complete elimination of HCV in donor lungs. If this strategy succeeds, new donors could be included to the pool, increasing lung offer to the waiting list patients.
Remote Ischemic Conditioning Prevents the Development of Necrotizing Enterocolitis

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Hypothesis and purpose: Remote ischemic pre-conditioning (RIC) protects the heart from ischemic events. We hypothesized that RIC induction can prevent the development of necrotizing enterocolitis (NEC).

Methods: 3 groups of C57BL/6 mice were studied: (i) breastfeeding (BF, n=4); (ii) NEC (n=10); (iii) NEC + RIC (n=10): RIC was performed before and after induction of NEC on Postnatal day 5 (P5) and P7. Pups were euthanized on P9 and distal ileum was harvested and analyzed for severity of bowel injury (hematoxylin and eosin), inflammation (quantitative PCR for IL-6 and TNF-α, and myeloperoxidase, MPO).

Results: Intestinal injury was more severe in NEC mice compared to BF mice (NEC vs. BF: 2.0±0.66 vs. 0.25±0.5) whereas RIC prevented mucosal injury (0.5±0.53). Inflammatory cytokines IL-6 and TNF-α and MPO were higher in NEC mice compared to control BF mice (NEC vs. BF: 5.36±5.08 vs.0.39±0.16, 2.98±2.55 vs.0.25±0.21, 82.1±31.4 vs.57.3±9.12, respectively). RIC was associated with control level of inflammation markers (IL-6: 0.56±0.49, TNF-α: 0.46±0.6, MPO: 56.3±11.1).

Conclusion: RIC prevents the development of intestinal injury and inflammation during experimental NEC. This study proves the principle that RIC can be a novel therapeutic option to prevent the development of NEC in neonates at risk.
Purpose and Hypothesis: We sought to adapt the Generic Error Rating Tool (GERT) for use in open and robotic radical nephrectomy (OPN and RPN) and, second, examine the frequency and types of errors in OPN and RPN. We hypothesize that OPN and RPN will differ in the number and type of errors.

Methods: This prospective, multi-center, observational study collected intra-operative video feed from open and robotic partial nephrectomies starting in February 2016. Using the existing GERT, procedural steps and error types were modified to include those unique to open and robotic surgery. Videos were rated by blinded reviewers using the Objective Structures Assessment Tool (OSAT) and the new modified GERT using Studiocode© (Vigital). Studiocode timelines were analyzed to identify the total number and types of errors.

Results: Of a planned sample of 70, 67 surgical videos have been collected. Seven videos (RPN=5, OPN=2) from 6 different surgeons have been rated using the modified GERT. For both surgical modalities, bleeding was the most common event resulting from an error. Overall, RPN had a fewer average number of errors (n=153) and longer average procedure time (177min) than OPN (n=157 and 132min respectively). OPN had greater number of severe bleeding episodes (both OPN had 2 episodes/case) than RPN (1 case had 1 severe bleeding episode).

Conclusion: Preliminary data suggest that GERT assessment may be feasible to quantify errors in open and robotic partial nephrectomy. The preliminary data is underpowered to determine differences in errors between OPN and RPN and analysis of remaining cases will continue.
Hypothesis & Purpose: There is limited, yet compelling evidence supporting the role of surgeon technical skill in influencing patient outcomes. This concept has not yet been tested in urologic surgery. We hypothesized that a surgeon’s technical performance plays a role in predicting an early return to continence after robotic-assisted radical prostatectomy (RARP).

Methods: We conducted a retrospective, matched case-control analysis of prospectively collected unedited RARP endoscopic videos performed by a single surgeon. A blinded observer with expertise in intraoperative video analysis evaluated clinically relevant steps of RARP using the Global Evaluative Assessment of Robotic Skill (GEARS) and the Generic Error Rating Tool (GERT). The primary outcome was continence status at 3 months post-operatively. Mann-Whitney U tests were done to examine differences in predictor variables between cases and controls, and multivariate analysis was conducted using binary logistic regression models.

Results: 24 patients deemed to be incontinent at 3 months were matched across relevant patient predictors. No statistically significant difference in errors between groups was observed using the GERT, but a trend to significance for the bladder neck dissection step was observed ($p = .07$). On multivariate analysis, overall case GEARS score was independently predictive of three-month continence status ($OR = .55$, 95% CI .33-.91), as were urethrovesical anastomosis ($OR = .70$, 95% CI .50-.97) and bladder neck GEARS scores ($OR = .69$, 95% CI .51-.94).

Conclusions: Our study generates the hypothesis that there may be a link between surgeon technical performance and functional outcomes in RARP. A multi-institutional prospective study is underway to test this hypothesis.
OPTICAL TOPOGRAPHIC IMAGING FOR INTRA-OPERATIVE THREE-DIMENSIONAL NAVIGATION IN THE CERVICAL SPINE: ACCURACY VALIDATION AND INITIAL CLINICAL FEASIBILITY

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Introduction: Computer-assisted three-dimensional navigation may guide spinal instrumentation. Current systems are hampered by cumbersome registration and inability to account for intra-operative tissue movement. Here, we validate the accuracy of a novel optical topographic imaging (OTI) system, developed for craniospinal neuronavigation, in the mobile cervical spine.

Methods: Validation was performed initially in 4 human cadavers, and subsequently 6 clinical patients. Intra-operative registration was performed to thin-slice preoperative CT. A tracked drill guide navigated screw tracts at all levels. Lateral mass screws were placed at C1 and C3-6, pars screws at C2, and pedicle screws at C7. Navigation data were compared to screw positions on postoperative CT imaging, and the absolute translational and angular deviations computed.

Results: 53 cadaveric screws were analyzed; 5 lateral mass screws at C1 and 32 at C3-6, 8 pars screws at C2, and 8 pedicle screws at C7. (Mean±SD) translational and angular errors were (1.66±1.18mm)/(4.11±3.79°) and (2.08±2.21mm)/(6.96±5.40°) in the axial and sagittal planes, respectively. 22 clinical screws were analyzed; 2 pars screws at C2, 14 lateral mass screws at C3-5, and 6 pedicle screws at C7. (Mean±SD) translational and angular errors were (1.52±1.32mm)/(3.69±2.63°) and (1.06±0.97mm)/(2.83±2.65°) in the axial and sagittal planes, respectively. There were no differences in errors between levels, nor clinical complications.

Conclusions: Optical machine-vision is a novel navigation technique allowing efficient initial and repeat registration. Accuracy even in the more-mobile cervical spine is comparable to current spinal neuronavigation systems.
TYROSINE PHOSPHORYLATED CASPASE-8 REGULATES TOLL-LIKE RECEPTOR 4 ACTIVATION IN INFLAMMATORY SEPTIC NEUTROPHILS

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Background: Regulation of timely neutrophil (PMN) activation and termination (apoptosis) is critical for patient survival during infection, as prolonged PMN activation promotes multiple organ injury through a dysregulated inflammatory host response. We show that caspase-8 – the apical enzyme in the extrinsic cell death pathway - can promote divergent effects of apoptosis or enhanced activation, contingent on its dynamic phosphorylation state. Due to bacterial secretion of endotoxin (LPS) during sepsis, we hypothesized the LPS receptor, Toll-Like-Receptor-4 (TLR-4) interacts with phosphorylated caspase-8 to promote pro-inflammatory TLR-4 signaling.

Methods: PMNs from septic patients or healthy controls were isolated, and caspase-8 was genetically silenced using siRNA. Apoptosis was detected by flow cytometry (PI uptake) and by caspase-3 cleavage. Caspase-8 phospho-mimetic (Y→E) and deficient (Y→F) mutants were transfected into HEK293 cells. mRNA transcript synthesis was measured through qRT-PCR.

Results: Percentage of apoptotic septic PMN was reduced compared to healthy control PMN (8.809 ± 1.181 n=12 vs. 23.20 ± 2.703 n=6, p=0.0018). In contrast to healthy control, caspase-8 immunoprecipitation in septic PMN showed that caspase-8 is tyrosine-phosphorylated and bound to TLR-4, and interacts with intracellular adaptor proteins (TIRAP) to promote NF-kB signaling (n=5). Caspase-8 knockdown in septic PMN prevents TLR-4 engagement with TIRAP, downstream NF-kB activation, and decreases transcriptional synthesis of the following pro-survival genes: NAIP, Survivin, c-IAP-1 and 2, XIAP, and P-BEF (n=2). These findings were replicated in HEK293 by transfecting caspase-8 phospho-mimetic and deficient mutants (n=4).

Conclusion: Caspase-8 occupies a critical role in regulating the commitment of the PMN towards apoptotic death or sustained TLR-4 dependent activation. These studies indicate a novel protein candidate to regulate the onset and termination of inflammation in septic patients.
ADJUVANT CHEMOTHERAPY FOLLOWING RESECTION OF COLORECTAL LIVER METASTASES: A COST-EFFECTIVENESS ANALYSIS

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Background: The role of adjuvant systemic chemotherapy following upfront curative-intent resection for colorectal cancer liver metastases (CRCLM) is controversial. Clinical trials have not demonstrated clear survival benefit, although there is evidence of improved disease-free survival; this uncertainty has led to practice pattern variation in its use. A cost-effectiveness analysis of adjuvant chemotherapy versus surveillance-alone would provide important information for practitioners and policymakers. Methods: Cost-effectiveness analysis from the single-payer Ontario health system perspective was performed on two strategies for management of patients following curative hepatectomy for CRCLM: (A) six months of adjuvant systemic chemotherapy with 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX; $2,103/month) and (B) surveillance-alone. A Markov model was developed to simulate clinical care following hepatectomy over a lifetime horizon. Probabilities and costs were derived from focused literature review. Effectiveness was measured in life-years (LY), costs were adjusted to 2016 Canadian dollars, both were discounted 5% and used to calculate the incremental cost-effectiveness ratio (ICER). We utilized a willingness-to-pay (WTP) threshold of $50,000/LY.

Results: Adjuvant chemotherapy was more effective than surveillance-alone (4.7 vs. 4.3 LY) at a cost of $111,836 vs. $105,181 (ICER: $14,843/LY). The model was sensitive to probabilities of recurrence in each strategy and cost of adjuvant chemotherapy. Adjuvant FOLFOX remained cost-effective if the probability of recurrence at three years was 4.3% lower than with surveillance-alone (OR 0.83), and when its cost remained under $5,804/month. Conclusions: Adjuvant FOLFOX may be cost-effective versus surveillance-alone following resection of CRCLM. Uncertainty regarding the effectiveness of adjuvant chemotherapy significantly limits the strength of our findings; further evidence is needed.
GOBLET CELL ACTIVITY AND ENDOPLASMIC RETICULUM FUNCTION ARE ENHANCED IN HUMAN COLONIC EPITHELIAL CELLS BY MILK-DERIVED EXOSOMES

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Purpose: Exosomes are cell-derived vesicles containing microRNA, mRNA and proteins. We recently showed that milk exosomes promote intestinal cell viability, proliferation, and stem cell activity, but whether they impact mucus barrier is unknown. We aimed to investigate the effects of bovine milk exosomes on goblet cell function and delineate potential mechanisms of action.

Methods: Exosomes were isolated from bovine milk by ultracentrifugation. LS174T human colonic cells were cultured and exposed to exosome treatment (0.1 μg/μl) or control (PBS treated). To measure mucin production, we used Periodic-Acid Schiff (PAS) staining, and immunofluorescence (IF) staining for MUC2 and glucose-regulated protein (GRP94). In addition, goblet cell and endoplasmic reticulum (ER) functions were assessed by RT-qPCR.

Results: Exosomes promoted goblet cell function, as demonstrated by increased mucin production (Fig. A) and relative expression levels of goblet cell function markers MUC2 (p<0.05; Fig. B), TFF3, RETLNB, AGR2 and SPDEF. In addition, exosome treatment enhanced the expression of GRP94 (p<0.05; Fig. C and D), an ER chaperone protein responsible for binding to misfolded proteins and targeting them for degradation, thereby reducing ER stress.

Conclusions: The administration of bovine milk-derived exosomes promotes goblet cell function. This mechanism is related to the regulation of endoplasmic reticulum function.
A POPULATION-BASED ECONOMIC EVALUATION OF LAPAROSCOPIC VERSUS OPEN GASTRECTOMY FOR GASTRIC CANCER PATIENTS

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Hypothesis: Laparoscopic gastrectomy results in less cost than open gastrectomy.

Purpose: Assess health care system costs for laparoscopic gastrectomy (LG) versus open gastrectomy (OG) to compare costs of treatment with LG versus OG.

Methods: A population-based, retrospective, person-level costing study of patients diagnosed with gastric cancer between 2005 and 2008 was performed. A cost-minimization analysis from a health system perspective was conducted with a one-year time horizon. Costs associated with index admission, re-admissions, surgery, physician billings, drug benefits, homecare, and emergency department visits were derived from administrative data. The incremental equipment cost for LG was derived from a multi-center investigation of procedural costs. Mean net costs were derived and adjusted for length of stay. Costs were inflated to 2016 Canadian dollars.

Results: A total of 894 patients were analyzed. LG was conducted in 83 patients and OG in 811 patients. The difference between mean net costs for LG and OG was significant. Cost per patient per thirty days of use was $7,791 (Standard Deviation: $16,009) for LG and $9,796 (Standard Deviation: $21,227) for OG (p=0.03), representing savings of $2,005 per patient per thirty days of use with LG.

Conclusions: LG for gastric cancer results in lower costs than OG. Savings from LG adoption could be directed toward training and education in this minimally invasive technique. However, future economic evaluations using randomized controlled data are necessary to confirm our findings.
IMPACT ON PATIENT OUTCOME AFTER LIVE DONOR LIVER TRANSPLANTATION USING GRAFTS WITH ≥2 BILE DUCTS

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Hypothesis: The use of live donor (LD) liver grafts with multiple bile ducts (BD) does not increase the risk of BD related complications after live donor liver transplantation (LDLT).

Purpose: To evaluate the impact of multiple BD in right lobe LDLT.

Methods: Between 2000-2015, 510 right lobe LDLT were performed at our institution. Outcome parameters of patients receiving a LDLT using grafts with ≥2 BD (n=190) and patients receiving a LD graft with one BD (n=320) were compared.

Results: Demographic variables and disease severity were similar between both groups. Roux-y-reconstruction was significantly more common in the ≥2 BD group (≥2 BD: 148 (78%) vs. 1 BD: 123 (39%), p<0.001). There was no difference in biliary complication rates after LDLT between both groups (1 BD: 75 (23.4%) vs. ≥2 BD: 43 (22.6%), p=0.914). In the ≥2 BD group 98/190 (52%) patients were reconstructed with ≥2 anastomoses. The number of anastomoses did not impact on the biliary complication rates. Recipients’ major complication (Clavien≥3b) rate was not different between both groups (1 BD: 41.6% vs. ≥2 BD: 44.7%; p=0.517). In addition, the 1-(90% vs. 91%), 5-(82% vs. 78%), and 10-year (70% vs. 68%) graft survival was comparable between both groups (p=0.588). Nevertheless, from those patients who developed a biliary leak (n=53), the ≥2 BD group (n=20) showed significantly worse graft survival when compared to the single BD group (n=33) (10-year graft survival 89.6% vs. 68.4%, p=0.024).

Conclusion. This study demonstrated that selected LD grafts with multiple BD can be used safely and without negatively impacting on biliary complication rates and graft-survival.
ROLE OF CLUB CELLS IN THE DEVELOPMENT OF OBLITERATIVE BRONCHIOLITIS IN MURINE TRANSPLANTED LUNGS

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Purpose: Obliterative bronchiolitis (OB) is a primary contributor to the poor long-term survival of lung transplant recipients. OB manifests as fibroproliferative obliteration of small airways, suggesting that inadequate epithelial repair may contribute to the pathobiology. We hypothesized that insufficiency in the epithelial repair by club cells results in OB. We performed murine lung transplantations with club cell-depleted grafts using the club cell-specific naphthalene (NA) injury and assessed the prevalence of OB.

Methods: 1) We performed minor mismatched (C57BL/6(B6) to C57BL/10(B10)) or syngeneic (B6 to B6) murine single lung transplants (n=10 each). Recipients were euthanized on post-op day 28. HE, Masson trichrome and immunostaining for club cell secretory protein (CCSP) were performed. 2) We injected NA to donors two days before lung transplants and compared the prevalence of OB on post-op day 28 between NA-treated (n=5) and control (vehicle, n=3) groups for both syngeneic (B6 to B6) and allogeneic (B6 to B10) transplants. Donor club cell depletion was confirmed by CCSP immunostaining and by PCR for CCSP mRNA.

Results: 1) Without Naphthalene, 2/10 allografts (20%) and 0/10 isografts (0%) exhibited OB. CCSP expression was lower in allografts compared to syngeneic grafts at day 28. 2) Naphthalene club cell-depletion of the donor lung increased the rate of OB in both isografts and allografts to 100%.

Conclusion: Transplantation of club cell-depleted grafts results in OB even in the absence of alloimmunity. Since NA treatment alone does not cause OB, we conclude that the combination of club cell depletion and transplantation-associated lung injury, are required for OB development. These results suggest that club cell dysfunction or injury likely plays an important role in the development of OB after lung transplantation.
NECROTIZING ENTEROCOLITIS INTESTINAL PERMEABILITY IS RESTORED BY AMNIOTIC FLUID STEM CELLS

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Hypothesis and purpose: Amniotic fluid stem cells (AFSC) have been shown to improve survival, clinical status, gut structure and function in experimental necrotizing enterocolitis (NEC). We hypothesize that AFSC could restore intestinal permeability in experimental NEC.

Methods: Following ethical approval (license no. 32238), NEC was induced in C57BL/6 mouse pups using hypoxia, lipopolysaccharide and gavage feeding of hyperosmolar formula. Breastfed (BF) pups served as controls. To study the effect of AFSC on NEC, AFSC was administered intraperitoneal on postnatal day 6 and 7. Tissue permeability was measured ex vivo by Ussing chamber. Tight junction marker Claudin7 was stained and gene expression was quantified using real time PCR. Data were compared using one-way ANOVA with Bonferroni post-test.

Results: NEC was associated with an increase in transcellular intestinal permeability compared with BF. AFSC significantly decreased both transcellular and paracellular permeability in NEC. During NEC, AFSC administration increased both gene and protein expression of tight junction marker Claudin7 back to control level.

Conclusions: Intestinal epithelium in NEC is damaged as indicated by increased permeability and decreased cell-cell tight junction protein. These alterations can be reversed by administration of AFSC.
FEASIBILITY OF REMOTE ISCHEMIC CONDITIONING IN POSTTRAUMATIC HEMORRHAGIC SHOCK PATIENTS: A PHASE II RANDOMISED CONTROLLED TRIAL

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Background: Resuscitated trauma patients are susceptible to late morbidity due to the development of systemic inflammation and organ dysfunction. Remote ischemic conditioning (RIC) is a non-invasive intervention comprising transient limb ischemia-reperfusion that mitigates organ injury and inflammation in animal models of resuscitated hemorrhagic shock. The present phase II randomised controlled single-centre trial was designed to evaluate the feasibility of administering RIC post-injury in hemorrhagic shock patients upon arrival to the trauma centre.

Methods: Eligible patients admitted to St. Michael’s Hospital with blunt or penetrating trauma in hemorrhagic shock (systolic BP < 90mmHG) were randomised in a 1:1 ratio to receive either sham intervention (0 mmHg) or RIC (4 cycles of 5-min thigh cuff inflation at 250 mmHg followed by 5-min deflation using a pneumatic tourniquet). Feasibility was determined by whether RIC was administered and completed within 4 h of injury.

Results: 1447 patients were screened for eligibility between May, 2015 and Oct, 2016. 50 of 72 eligible patients with a median injury severity score of 17 were enrolled. 43 patients had completed either the sham (n=23) or RIC (n=20) intervention. The majority of patients received the intervention in the trauma bay (n = 17), followed by CT room (n = 11), operating room (n = 10), emergency department (n=3), and ICU (n=2). Of the patients who did not complete the intervention, 2 were from the RIC group. Peripheral blood samples were obtained at admission, 1 h, 3 h, and 24 h after RIC for immuno-inflammatory biomarker analyses.

Conclusions: Administration of RIC in the trauma bay was not always feasible as the patients were transferred before initiation or completion of the RIC cycles. However, implementation of RIC to initiate in other departments improved feasibility. Subsequent analysis of blood samples from these patients will provide insight on the potential immunomodulatory effects of RIC. RIC represents a potential intervention to improve the outcome in trauma patients.
HUMAN MILK OLIGOSACCHARIDES PREVENT EXPERIMENTAL NECROTIZING ENTEROCOLITIS

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Introduction: Necrotizing enterocolitis (NEC) is a leading cause of death in preterm infants. Breastfed neonates have a lower risk of NEC than those who are formula-fed, but the mechanism underlying this protection remains unclear. Human milk oligosaccharides (HMO) are a component of breast milk capable of suppressing inflammatory processes. The objective of our study was to investigate the effects of HMO on the intestinal epithelium during NEC.

Methods: NEC was induced in 5-day old neonatal mice using hypoxia, oral lipopolysaccharide and gavage feeding of hyperosmolar formula with PBS (n=10) or HMO (20 mg/ml, n=10). Breastfed pups served as controls (n=10). Mucosal injury in the distal ileum was scored blindly, with NEC diagnosed when the score was ≥2. Using immunofluorescence staining, the intestinal epithelium was assessed for proliferation (Ki67), differentiation (goblet cells, Muc2) and apoptosis (cleaved caspase-3, CC3). Data is reported as mean ± SD and groups are compared using one-way ANOVA with Bonferroni post-test.

Results: HMO reduced mucosal injury and NEC incidence. Epithelial cell proliferation and differentiation decreased during NEC, but increased with the administration of HMO. Apoptosis increased during NEC and HMO rescued apoptosis to normal levels.

Conclusions: This present study demonstrated that HMO administration prevented the development of NEC, promoted epithelial proliferation and differentiation, and reduced epithelial cell apoptosis in this experimental mouse model. HMO administration is a potential novel treatment for infants at risk of developing NEC.
ROLE OF SWELLING-INDUCED CHLORIDE CURRENT IN HYPOXIC-ISCHEMIC BRAIN INJURY

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Purpose: Neonatal hypoxic-ischemic brain injury leads to hypoxic-ischemic encephalopathy, which is a major cause of acute mortality and chronic neurological morbidity in neonates. In this study, we investigated the effects of swelling-induced chloride current $I_{Cl,swell}$ in hypoxic-ischemic brain injury using 4-(2-Butyl-6,7-dichloro-2-cyclopentylindan-1-on-5-yl) oxybutyric acid (DCPIB), a selective blocker of swelling-induced chloride current $I_{Cl,swell}$.

Methods: DCPIB was injected intraperitoneally to postnatal seven-day-old (P7) CD1 mouse pups of either sex and a modified hypoxic-ischemic (HI) brain injury model was performed. The outcomes were evaluated using 2,3,5-triphenyl-2H-tetrazolium chloride (TTC) staining, cresyl violet (Nissl) staining and whole brain imaging. Neurobehavioral tests were also used to assess the sensorimotor and vestibular recovery outcomes of the HI.

Results: DCPIB attenuates the infarction volume of HI injury in vivo, and improves neurobehavioral performance after HI.

Conclusions: Our results indicate that DCPIB has neuroprotective effect on neonatal HI brain injury.
COMPUTATIONAL FLUID DYNAMICS TO PREDICT RIGHT HEART MECHANICAL EFFICIENCY FOR PATIENTS WITH TETRALOGY OF FALLOT

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Right ventricular outflow tract (RVOT) repair is required for Tetralogy of Fallot (TOF) patients soon after birth. Multiple repair techniques exist, which may have variable success rates due to significant patient-to-patient variation in RVOT anatomy. There may be an optimal surgical strategy for a given patient, however, this is currently unknown. The purpose of this work is to develop an understanding of the relationship between right heart anatomy and patient outcomes. It is hypothesized that computational fluid dynamics (CFD) simulations can be used to identify: (i) the sensitivity of the right heart hemodynamics to changes in several key geometric variables, and (ii) the RVOT geometry with the highest mechanical efficiency.

An idealized model of the RVOT was developed in ANSYS Design Modeler (ANSYS Inc., Canonsburg, PA, USA). The radii of the infundibulum, valve annulus, sinotubular (ST) junction, and main pulmonary artery (MPA) were parameterized to allow for systematic adjustment and generation of 75 possible anatomical configurations (5x1x5x5 permutations of the parameters, with some configurations removed due to parameter relational constraints). A CFD simulation of blood flow through the each of the geometries was generated with ANSYS Fluent. The mechanical efficiency for each geometry was calculated.

For a given initial geometry, percentage decrease in the infundibular radius was strongly correlated with percentage increase in mechanical efficiency ($R^2 > 0.99$). ST junction size was insignificant. Interestingly, configurations combining a large MPA radius with moderately-sized infundibular radius were also mechanically efficient, suggesting a compensatory mechanism of the MPA. Simulation refinement is ongoing to validate the integrity of the results. However, these findings suggest that a planned, personalized surgical approach for each patient can improve postoperative mechanical efficiency thus potentially impacting long-term ventricular health.
IDENTIFICATION OF TUMOR OUTLIERS USING MULTIPLE GENOMIC PLATFORMS

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Rational and purpose: Classification and accurate characterization of tumour types and tumour subtypes are essential for appropriate diagnosis which then determines the treatment and management of the cancer. Current methods based on histopathology and morphology can in specific cases yield inconclusive findings and diagnostic discrepancies by pathologists. While histologic interpretation is subject to inter-observer variability, identification of misclassified samples (outliers) can contribute to reduce diagnostic errors or can be a quality-check in the clinic. Molecular platforms such as profiling by mRNA expression, DNA methylation, mutations, copy number variation, miRNA expression and protein expression may provide complementary information that complements histologically-based methods. **Method:** To characterize the potential utility of specific omics platforms as practical tumor classifiers, we investigated 2 platforms such as mRNA, methylation and their different integrations. Using spectral clustering in similarity network fusion (SNF) on 6216 TCGA tumour samples representing 19 cancer types (including glioma and head-neck cancers), we present data which demonstrates single or a multiplatform approach for classification with a specific interest in the characterization of tumor outliers. **Results:** Our SNF analysis showed high degree of classification accuracy (approximately 95% for both mRNA and methylation platforms). The combination of methylation and mRNA was slightly more accurate in identifying tumor outliers and reducing false positive rate. To gain further insights into these concordant outliers we performed Random Forest (RF) based classification analysis and hierarchical clustering (HC). Those outliers were concordantly identified by both methylation and mRNA platforms using all SNF, HC and RF methods. **Conclusion:** The comparative analysis of mRNA and methylation platforms can identify outliers and biologically distinct groups that can reduce diagnostic errors and has potential to help (e.g., as a quality check) in cases where the histology or the morphology of the tumour is ambiguous.
EVALUATING THE FEASIBILITY AND SPECIFICITY OF PIMONIDAZOLE AS A MARKER OF HYPOXIA IN MALIGNANT GLIOMAS

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Malignant gliomas are the most frequent primary brain tumor in adults and are also the most aggressive. Despite recent therapeutic advances, malignant gliomas are resistant to treatment and the survival time of patients is between 3-8 years for low-grade gliomas, and 6-12 month for glioblastoma (grade IV). Increasing malignancy of gliomas correlates with an increase in cellularity and a poorly organized tumour vasculature leading to insufficient blood supply, hypoxic areas, and ultimately to the formation of necrosis. Hypoxia is a predominant feature of malignant glioma microenvironment, and it is associated with the tumor growth, progression, and resistance to conventional chemotherapy and radiation. Hypoxia induces direct or indirect changes in the biology of a tumour and its microenvironment through the activation of specific transcription factors, leading to increased aggressiveness and tumour resistance to chemotherapy and radiation. Current clinic-pathological markers are insufficient to identify patients at risk of treatment failure. Therefore, a hypoxia biomarker would be of value for clinical decision-making.

The exogenous hypoxia marker pimonidazole is a 2-nitroimidazole compound, which forms covalent bonds with cellular macromolecules at oxygen levels below 1.3% and demonstrates poorly oxygenated regions in histological sections from tumours. In the present study, we have investigated the feasibility and specificity of pimonidazole as a specific marker of hypoxia in higher-grade glioma patients treated with pimonidazole preoperatively. We have quantified the extent of pimonidazole staining in tumor sections and determined its correlation with presence of other hypoxia markers such as carbonyl anhydrase IX. We have also determined the characteristics of tumor vasculature and its association with extent of pimonidazole staining.
30-DAY AND LONG-TERM MORBIDITY OF PARTIAL WRIST FUSIONS WITH K-WIRES VERSUS INTERNAL FIXATION

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Introduction: Partial wrist fusion (PWF) has become a widely accepted option for treating wrist arthritis and/or instability. Fusion is traditionally achieved using K-wires, however, internal fixation devices, such as screws and staples, have gained popularity. The early (30-day) and long-term morbidity comparing K-wires and internal fixation remains unknown.

Methods: A retrospective study of all patients that underwent PWFs from 1999 to July 2011 at a single institution was performed. Data on demographics, method of fixation, 30-day morbidity and healthcare utilization, and long-term outcomes was extracted. T-test, Mann-Whitney U, Chi-squared and Fischer’s exact tests were performed to compare 30-day and long-term outcomes.

Results: There were 150 PWFs performed, 69 (46%) using K-wires and 81 (54%) using internal fixation (77 screws, 4 staples). No significant differences were noted in the operative time, 30-day postoperative emergency and unscheduled clinic visits. In the K-wire group, 3 (4.3%) patients had infections within 30-days (p=0.095), with 2 requiring re-admissions and one requiring a return to the operating room for a total length of stay of 6 days. Looking at long-term data, patients in the internal fixation group required a total of 46 revision surgeries (14 revisions in the K-wire group) (p=0.000). Specifically, internal fixation led to a higher number of revision PWFs (p=0.007), total wrist fusion (p=0.001), and hardware removal due to irritation/impingement (p=0.019). Indications for aforementioned revisions included a higher incidence of hardware irritation/impingement (p=0.003), nonunion (p=0.048) and chronic pain and instability (p=0.006).

Conclusions: This series identified that patients undergoing fusion with K-wires versus internal fixation devices did not have significantly different 30-day morbidity, but internal fixation patients were more likely to have long-term complications requiring revision surgeries.
FEMALE-TO-MALE GENDER AFFIRMING TOP SURGERY: A SINGLE SURGEON’S 15-YEAR RETROSPECTIVE REVIEW & TREATMENT ALGORITHM

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Hypothesis: Safe and aesthetically good results can be obtained using a simplified algorithm in Female-to-male (FTM) Top Surgery.

Purpose: Mastectomy, referred to here as “Top Surgery”, is an important surgical step for FTM transgender patients. The goal is to excise breast tissue and create a masculine chest contour. Debate exists regarding selection of the most appropriate surgical technique to achieve optimal aesthetic outcomes safely. We propose to determine the safety profile and aesthetic outcome of one surgeon’s FTM top surgery experience.

Methods: A retrospective chart review was performed on 679 FTM patients (1358 mastectomies) undergoing Top Surgery from October 2001 to July 2016. Our Top Surgery algorithm utilizes two techniques, “Keyhole” and “Double Incision Free Nipple Graft (DIFNG)”, based on breast ptosis, inferior vertical skin pinch, and skin elasticity. Demographic data, operative details, complications, and reoperations reasons were collected and analyzed.

Results: There were 679 patients found in the study period, 15.3% underwent Keyhole and the remaining 84.7% underwent DIFNG procedure. The total complication rate was 18.1% and the total reoperation rate was 11.2% and these rates were found to decrease over time. The two techniques differed significantly (p <0.001) in operating time (136 vs. 102 min), breast weight excised (215 vs 638g), and complication rate (33 vs. 16%). The aesthetic rating of results was 4.6/5 for Keyhole and 3.7/5 for DIFNG on a 5-point Likert scale.

Conclusions: We describe the largest FTM Top Surgery series published to date. Safe and aesthetically pleasing results were achieved using a simplified algorithm. Experience with FTM techniques can decrease complication and reoperation rates over time.
CHARACTERIZING HIPPOCAMPUS CA1 ENSEMBLES DURING CONDITIONED PLACE PREFERENCE WITH IN VIVO CALCIUM FLUORESCENT IMAGING

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Introduction: An emerging technique using genetically encoded calcium activity indicators (GCaMP) and head-mounted fluorescent microscope allows visualization of hundreds of firing neurons in a moving animal over months. Other existing recording modalities are limited by experimental setups unsuitable for many behavioral and learning paradigms. Objective: We propose to characterize the spatiotemporal dynamics of hippocampus CA1 neurons during conditioned place preference (CPP) with cocaine. Method: In accordance to SickKids LAS regulations, GCaMP6f transgenic mice were anesthetized for surgical implantation of the lens over CA1. On day 1, animals were habituated with access to two different chambers (white versus stripped room). During the next 4 training days, the animals received cocaine i.p. before one context and saline the other for a total of two pairings. Contexts were counterbalanced. On day 6, the animals had access to both chambers to test for preference. CA1 neurons were imaged for the first five minutes of each session. After segmentation using independent component analysis and signal extraction, a graph network was constructed with neurons as nodes and Pearson correlation coefficient (> 0.3) as edges. Graph theory analysis was used to identify ensembles and changes in components and connectivity over training period. Results: Preliminary analysis showed association of a context to cocaine did not increase CA1 neuron mean activity. The number of graph components increased during testing versus training.

Conclusion: In vivo calcium recording during CPP is feasible and reproducible. We found that training changes the connectivity of CA1 neurons forming ensembles and will explore how salience changes other network properties. The mini-microscope will be a valuable tool in understanding the neural substrates of behavior and disease such as drug addiction.
GLIOMA-ASSOCIATED MACROPHAGES PROMOTE ENDOTHELIAL ACTIVATION

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One of the most prominent features of glioblastoma (GBM) is hyper-vascularization, characterized by abnormal hyper-dilated, distorted, leaky vessels and increased thrombosis. Bone marrow-derived macrophages are an important host cell population that are actively recruited to the tumour, associate closely with blood vessels, and are thought to provide a supportive role in tumour neo-vascularization. The objective of this study was to investigate the unknown molecular mechanisms of how GAMs alter the structure and/or function of ECs to promote tumour angiogenesis. Here we examined the effect of conditioned-medium (CM) from GAMs on the expression of angiogenesis genes in human umbilical vein endothelial cells (HUVECs). Strikingly, CM from GAMs produced a substantial upregulation of genes involved in endothelial activation including VCAM-1, ICAM-1, CXCL5, CXCL10, and VEGFA in comparison to CM from normal human astrocyte (NHA)-associated macrophages. We show that GAMs secrete high levels of TNFα compared to NHA-conditioned macrophages and inhibition of TNFα with a neutralizing antibody was sufficient to block GAM-induced EC activation in vitro. These findings suggest that TNFα is secreted from GAMs, which acts on nearby endothelial cells to promote endothelial activation. We propose that the pro-inflammatory state of activated glioma-associated ECs may promote pro-thrombic properties and vascular leakage that characterize and promote GBM neo-vascularization.
LONG-TERM OUTCOMES OF RESECTION FOR LOCOREGIONALLY RECURRENT COLON CANCER: A MULTICENTERED RETROSPECTIVE DESCRIPTIVE COHORT STUDY

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Purpose Local recurrence (LR) of colon cancer (CC) is less common than for rectal cancer; oncologic outcomes of resection of LRCC are not clear. The morbidity and mortality of resection are poorly documented in the limited literature available. We evaluate the short- and long-term outcomes of resection for LRCC at the University of Toronto. Method All patients undergoing curative-intent resection for LRCC were identified from prospective databases (1993-2016). Follow-up included serial clinical visits, colonoscopy, CEA level, and cross-sectional imaging. Primary outcomes were overall survival (OS) and time to re-recurrence estimated using the Kaplan-Meier method and cumulative incidence function. The effect of resection margin on OS was estimated using Cox proportional hazards model. Mean value imputation was used for missing data: 0% OS, 2.7% re-recurrence. Results 72 patients met inclusion criteria; 29 (40%), median age 63 (IQR:55-72) years. Half of patients (n=37) underwent multivisceral resection, and microscopically negative (R0) resection margins were achieved in 82% (59/72) of cases. There were no postoperative deaths, but complications occurred frequently (30/72, 42%). Median follow-up was 36.3 months (IQR:23.2-61.2). OS at 5 years was 64% (95%CI:49-78%). R0 resection was associated with improved OS compared with margin positive resection (74% vs 27%, HR 3.37, 95%CI:1.35-8.41). Re-recurrence of cancer following R0 resection of LRCC occurred in 56% of patients within 5 years. The use of chemotherapy and radiotherapy was limited. Conclusion In a cohort of consecutive patients selected for curative-intent management, R0 resection was achieved in the majority and overall survival was over 60%. These results compare favorably with the limited outcomes literature in LRCC. Morbidity was high. Outcomes may be further improved by application of multimodality therapy.
ENDOGENOUSLY PRODUCED OMEGA-3 FATTY ACIDS CAN PREVENT THE DEVELOPMENT OF NECROTIZING ENTEROCOLITIS IN NEONATAL MICE

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Hypothesis and purpose: Omega-3 polyunsaturated fatty acids (PUFAs) are known to reduce inflammatory response in various diseases. To elucidate the action of omega-3 PUFAs in necrotizing enterocolitis (NEC), we studied fat-1 transgenic mice who convert omega-6 to omega-3 PUFAs. We hypothesized that fat-1 neonatal mice are protected from NEC development.

Methods: We bred mice with two different genetic backgrounds with omega-6 PUFAs enriched diet: (i) wild type (WT); (ii) fat-1. On postnatal day 5 (P5) pups were randomly assigned to control breast feeding or NEC induction. From P5 to P9, NEC was induced by hypoxia, gavage formula feeding and lipopolysaccharide. On P9, the pups were sacrificed and the ileum was harvested to evaluate severity of mucosal injury (hematoxylin/eosin stain) and inflammation (IL-6 mRNA expression). NEC was considered as injury score 2 or more.

Results: As expected in WT mice, NEC induction was associated with higher mucosal injury. However, in fat-1 mice the mucosal injury was lower (Figure A). The incidence of NEC was significantly lower in fat-1 (25%) than in WT (88%) (p<0.05. Figure B). Similarly, IL-6 mRNA expression was significantly lower in fat-1 NEC compared to C57BL/6 NEC (p<0.05. Figure C).

Conclusions: Our results indicate that endogenously produced omega-3 PUFAS lead to reduction of NEC incidence, lower mucosal injury and attenuation of inflammation in the intestine.
LIVER TRANSPLANTATION TO SALVAGE PATIENTS WITH HCC RECURRENCE FOLLOWING CURATIVE TREATMENTS

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**Purpose and Hypothesis:** Liver resection (LR) and radiofrequency ablation (RFA) are curative therapies for early stage hepatocellular carcinoma (HCC). If HCC reoccurs, salvage liver transplant (SLT) may constitute a treatment option. We aimed to compare the outcomes of patients transplanted for recurrent HCC after curative-intent therapies to those transplanted as initial therapy.

**Methods:** We conducted a matched-control (1:1) cohort study comparing patients with HCC treated with primary liver transplant (PLT) to SLT after HCC recurrence. Matching was performed according to the size and number of viable tumours at explant pathology following liver transplant.

**Results:** Between Nov 1999 to Dec 2014, 559 patients with HCC were transplanted at our Institution. 193 patients were treated with PLT and 50 patients were treated with SLT for HCC recurrence after primary treatment with LR (n=25) or RFA (n=25). Median length of follow-up from transplant was 66 (0.5-195) months. The median time from curative-intent treatment of HCC with RFA or LR to recurrence was 11 (1-36) and 20 (3-143) months, respectively (p=0.09). The matched-cohort was composed of 49 SLT patients (24 LR and 25 RFA) and 49 PLT patients. The 5-year risk of recurrence after LT was 21% in the PLT vs. 33% in the SLT group, (p=0.28). The 5-year actuarial survival after PLT was 69% vs. 68% in the SLT group (p=0.68).

**Conclusion:**
SLT is an acceptable treatment for recurrent HCC following curative-intent therapies with comparable long-term recurrence rates and patient survival.
PREDICTIVE FACTORS FOR SURVIVAL IN SURGICAL SERIES OF SYMPTOMATIC METASTATIC EPIDURAL SPINAL CORD COMPRESSION: A PROSPECTIVE NORTH AMERICAN MULTI-CENTRE STUDY IN 142 PATIENTS

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Purpose: Symptomatic Metastatic Epidural Spinal Cord Compression (MESCC) is associated with shortened survival and worsened quality of life. This study aims to identify the key survival predictive factors in patients surgically treated for a single, symptomatic MESCC lesion.

Methods: 142 MESCC patients were enrolled in a prospective North American multi-center study and followed for 12 months postoperatively. The predictive value of various clinical predictors was assessed using Kaplan-Meier method and log-rank test. Non-collinear predictors with p < 0.05 in univariate analyses were included in the final Cox proportional hazards model.

Results: The overall median survival was 7.7 months. Ten patients (7.0) died within 30-days postoperatively and 88 died at 12 months (62.0%). Univariate analyses yielded eight significant predictors: Tomita grade, BMI, sex, preoperative SF-36 physical component, EQ-5D, and ODI scores, the presence of visceral or extraspinal bony metastasis. The multiple regression analysis revealed that the Tomita grade (Grade 1 vs Grade 2 and 3; HR: 2.81, p=0.0007), the absence of visceral metastasis (HR: 2.01; p=0.0044), and higher score on SF-36 physical component (HR: 0.945, p<0.0001) were independent predictors for longer survival.

Conclusion: Slow growing tumor (Tomita Grade 1), absence of visceral metastasis, and lower degree of preoperative physical disability, i.e. a higher score on the SF-36 physical component, are independent predictive factors for survival in surgical MESCC patients.
Background
Glioma patients continue to carry a very poor prognosis despite maximal therapy. Several genetic alterations are linked with better survival outcome in glioma patients, including mutations in isocitrate dehydrogenase 1 and 2 (IDH1/2). Mutant IDH leads to preferential accumulation of the R relative to the S enantiomer of 2HG.

Purpose
A much-needed area of progress is the application of innovative methods to enable detection of IDH mutation intraoperatively to guide extent of resection while avoiding the need for a second high-risk cranial surgery.

Methods
High performance liquid chromatography tandem mass spectrometry (HPLC-MS) was utilized to quantify the R-2-HG and S-2-HG enantiomers (rRS) and total 2-HG levels in 70 frozen brain tumor samples (IDH WT n=18, IDH mutated n=52). 30 patients had paired serum that was included in our analysis.

Results
Using glioma tissues, rRS clearly distinguished MUT vs WT (median 574 vs 1.3, p<1x10^{-9}) with only three outliers. In contrast, rRS was not elevated in serum samples (median 1.5 vs 1.2, p=0.13). Overall survival (OS) was significantly longer for MUT vs WT (median 178 vs 33 months, p<1x10^{-7}). Progression-free survival results corresponded to OS.

Conclusions
Unlike current methods, tissue rRS enables real-time determination of IDH status, and thus may guide clinical practice by determining extent of resection and adjuvant therapy.
A MARKOV MODEL OF CARPAL TUNNEL SYNDROME MANAGEMENT IN BREAST CANCER SURVIVORS AT RISK FOR LYMPHEDEMA

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HYPOTHESIS/PURPOSE: Breast cancer (BC) survivors that have had an axillary lymph node dissection (ALND) have an increased risk of developing upper extremity lymphedema. The problem faced by patients and clinicians is the decision to proceed with a carpal tunnel release (CTR) if the patient fails conservative management. We hypothesize that BC survivors benefit from early CTR as the benefits outweigh the risk of lymphedema when evaluating quality adjusted life years (QALY)s. The purpose of this study was to determine the treatment decision that yields the highest QALYs for BC survivors presenting with carpal tunnel syndrome (CTS).

METHOD: A Markov model was developed to evaluate the treatment options for BC survivors presenting with CTS, as this allowed weighing the advantages and disadvantages of performing carpal tunnel release (CTR) or continuing with non-surgical management. The model reflected three treatment strategies: 1) early surgical intervention, 2) delayed surgical intervention, 3) non-surgical management. QALYs for each strategy were calculated over a lifetime time horizon.

RESULTS: Over a lifetime (30-year) horizon, the preferred strategy was delayed surgery, which resulted in 21.41 QALYs. Early surgery and non-surgical management yielded 20.42 and 21.06 QALYs, respectively. The model was not sensitive to variation in any of the parameters within the clinically plausible ranges.

CONCLUSION: Based on this robust decision analytic model, BC survivors with mild CTS who are at risk for lymphedema would gain the most QALY by delaying CTR until severe CTS develops. This strategy balances the increased risk of lymphedema following CTR to the decreased long-term risk of severe CTS. The model comprehensively assesses a controversial area in the BC and hand surgery literature in order to guide decision making for patients and clinicians.
CANNABINOIDS ALTER PROLIFERATION, INVASION AND MIGRATION IN AN IN VITRO MODEL OF PROSTATE CANCER

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Hypothesis:
WIN 55,212-2 will act as an anti-cancer agent in preclinical models of prostate cancer.

Methods:
LNCaP, DU145, and PC3 human prostate cancer cells were treated with 10, 15, 20 and 25 μM WIN and analyzed for proliferation (MTS assay), cell migration (scratch assay), and cell invasion (matrigel invasion assay).

Results:
There was a significant reduction in the proliferation of DU145 and PC3 cells following 24hrs treatment with 10 μM WIN (p=0.01), and a significant reduction in the proliferation of LNCaP cells following 24hrs treatment with 15 μM WIN (p=0.001). Cell migration and invasion studies on DU145 and PC3 cells revealed a significant reduction in cell motility at 10 μM WIN (p<0.001) as well as a significant reduction in cell invasion at 1 μM and 5 μM (p<0.005).

Conclusion:
Interim results have demonstrated that WIN significantly influences cell proliferation, migration and invasion. Further analysis on the role of WIN in these pathways is underway exploring alterations in expression levels of key proteins implicated in cell migration and apoptosis. Elucidating the role of cannabinoids in PCa cells will allow for approaches that reduce the psychoactive effects while maintaining its therapeutic benefits, necessary for a successful introduction into conventional PCa treatment.
PERIOPERATIVE PLASTIC SURGERY PATIENTS ARE MALNOURISHED
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Purpose: It has been determined that a quarter of Plastic Surgery patients are at malnutrition risk prior to surgery. Malnutrition leads to longer length of stays, increased post-operative complications and increased mortality rates. Optimization of patients prior to surgery and recognition of risk is important as it improves patient outcomes. The purpose of this study was to identify which kind of patients may be malnourished prior to or following a plastic procedure and to classify the degree of malnutrition with the SGA (Subjective Global Assessment). Methods: This REB approved cross-sectional study was performed at a Toronto tertiary care center from October to December 2016. All patients presenting to the Plastic Surgery outpatient clinic were screened with the Canadian Nutritional Screening Tool (CNST), a two-question validated tool used to determine malnutrition risk. Participants identified as being at nutritional risk were then assessed with the SGA to determine macronutrient malnutrition classification (well nourished, moderately malnourished or severely malnourished). Results: A total of 111 patients were recruited with a mean of 49 years (SD 17.1) with almost equal numbers of men and women (55:56). According to the CNST, 15.3% (n = 17) were found to be at nutritional risk and had a wide range of diagnoses. Of those, 12 (70.6%) had a diagnosis involving a surgical procedure, only 6 (35.3%) had had a previous nutritional assessment, BMI was on average 24.2 kg/m² (SD 4.7). Of the 17 patients, 13 were confirmed to be malnourished by the SGA: 10 were moderately malnourished (SGA class B) and 3 were severely malnourished (SGA class C). Conclusions: These results suggest that the CNST over-predicts nutritional risk in 18.8% of cases, but is generally an accurate predictor of macronutrient deficiency in a diverse plastic surgery patient population. In this study, a total of 10 patients were moderately malnourished and 3 were severely malnourished. These patients with numerous plastic surgery diagnoses would have benefited from pre-operative screening and nutritional optimization. Based on the findings of our study, our hospital is actively transitioning to universal nutritional screening, implementing the CNST to all divisions both for inpatients and outpatients.
THE EFFECT OF RENIN-ANGIOTENSIN SYSTEM BLOCKADE ON ABDOMINAL AORTIC ANEURYSM PROGRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: In animal models, angiotensin-II has been found to induce abdominal aortic aneurysms (AAA) while angiotensin-1 receptor blockade attenuates AAA growth and rupture.

Purpose: To review the literature regarding angiotensin converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARBs) effects on human AAA growth, rupture, and mortality.

Methods: We conducted a systematic review in accordance with PRISMA guidelines. We searched MEDLINE, EMBASE, and The Cochrane CENTRAL databases from inception to 2017 for studies examining the effects of ACEi or ARB treatment on AAA growth, rupture or mortality. Review and abstraction steps were conducted in duplicate. A third author resolved discrepancies. We assessed study quality using the Cochrane, and Newcastle-Ottawa scales.

We used random effects models to calculate pooled mean differences and odds ratios (OR) with 95% confidence intervals. Heterogeneity was quantified using the I² statistic.

Results: Our search yielded 525 articles. One randomized and 8 observational studies involving 35,565 patients were included. Inter-rater agreement was excellent (κ=0.78), and risk of bias was low to moderate. All studies investigated ACEi; three studies investigated ARBs; and two studies included a composite ACEi or ARB group. Four studies assessed rupture and 30-day mortality, and 5 studies assessed AAA growth. There was no difference in AAA growth rate between ACEi vs control (mean difference 0.17 mm/yr, 95% CI -0.18-0.52, p=0.35, I²=46%) or ARB vs control (mean difference -0.57, 95% CI -1.33-0.18, p=0.14, I²=0%). No protective effect of ACEi was demonstrated for AAA rupture (OR 0.90, 95% CI 0.73-1.12, p=0.36, I²=85%).

Conclusion: Angiotensin converting enzyme inhibitors do not affect AAA growth or rupture rates. Further prospective, long-term research is needed to determine the effect of renin-angiotensin system blockade on AAA growth, rupture and peri-operative mortality.

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PREDICTING STENT GRAFT ROTATION IN PATIENT SPECIFIC ABDOMINAL AORTIC ANEURYSM REPAIR USING COMPUTATIONAL MODELS

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Purpose: The purpose of this study was to use computational methods to simulate fenestrated endovascular aneurysm repair (FEVAR) within a patient specific abdominal aortic aneurysm (AAA) in order to predict whether or not stent graft rotation was likely to occur.

Hypothesis: Computational methods can be used to determine whether or not stent graft rotation is likely to occur in a patient undergoing FEVAR.

Methods: Pre-operative CT scans of a FEVAR patient were obtained, and the iliac artery and AAA geometries were segmented. Models of the guidewire, stent graft, and sheath were developed using SolidWorks (Dassault Systèmes, Waltham, MA, USA). Representative material properties were used for all components based on literature values. The computational study was completed using the explicit finite element solver LS-DYNA (LSTC, Livermore, California, USA). Blood pressure was applied as a boundary condition and frictional effects were considered. The rotation of the graft was measured via a tracking of the initial and final position of two points on opposite sides of the graft.

Results: Stent graft rotation is defined as being clinically significant when it exceeds 10°. Clinically, the present case was classified as having no rotation (i.e. rotation was less than 10°). Simulation results show a rotation of 11°, which is comparable to what was observed clinically.

Conclusions: The simulation results show good agreement with the clinical data. With further validation, this computational model has the potential to be used for stent graft rotation prediction within the clinical workflow.
NECROTIZING ENTEROCOLITIS IS ASSOCIATED WITH ENTERIC NERVOUS SYSTEM IMMATURITY

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Hypothesis and purpose: The enteric nervous system (ENS) plays a role in maintaining gastrointestinal motility and barrier function. ENS immaturity may contribute to necrotizing enterocolitis (NEC) development, although this hypothesis has not been fully explored. The aim of this study was to investigate ENS maturation in experimental NEC.

Methods: On postnatal day 9, the ileum was harvested to histologically score the severity of NEC and to assess ENS by western blot for Polysialylated Neural Cell Adhesion Molecule (PSA-NCAM: immature neuron marker), Tyrosine Hydroxylase (TH: mature neuron marker), and Protein Gene Product 9.5 (PGP9.5: total neuron marker).

Results: 11 pups developed NEC (histological score ≥2) (figure A). In the NEC group, protein expression of ENS immaturity marker PSA-NCAM was significantly increased compared to control (p<0.05; figure B), whereas there were no differences in maturity marker TH (figure C), and total neuron marker PGP9.5 (figure D).

Conclusion: NEC is associated with intestinal neuron immaturity. This may explain the gastrointestinal dysmotility and barrier dysfunction in neonates with NEC.
REFILX: A SOFT TISSUE FILLER FOR THE RECONSTRUCTION OF SOFT TISSUE DEFECTS

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Introduction: Lumpectomy is an essential component of most breast cancer treatments, but it can often result in poor cosmetic outcomes due to large soft tissue defects. There is a demand for better cosmetic outcomes as these patients are now expected to survive long-term, and poor cosmesis can be a source of psychological distress. Objective: Evaluate novel biodegradable polymer foams, referred to as ReFilx, as soft tissue fillers for lumpectomy defects. Hypothesis: Implantation of ReFilx into lumpectomy defect sites immediately post-lumpectomy will maintain breast shape and size and promote tissue regeneration around the material, in contrast to sham controls. Methods: Three female Yucatan Minipigs (retired breeders, age=4 years, weight=100-120 kg) received lumpectomy carried out using electrocautery to remove normal breast tissue of approximately 2 cm diameter, after which defect sites were filled with ReFilx Formulation A, ReFilx Formulation B, or no filler (sham control). At 6, 12, 24, and 36 weeks post-implantation (n=3 per group), ultrasound breast examination was performed and select sites were excised by mastectomy. Samples were fixed in 10% buffered formalin and histological (H&E, Masson’s Trichrome) and immunohistochemical (CD31) staining were performed on specimens. Results: ReFilx formulations maintained breast size and shape, with similar stiffness to native breast tissue, while sham controls collapsed over 36 weeks. The ReFilx fillers supported cell and tissue infiltration and neovascularization, as indicated by Masson’s Trichrome and CD31 staining, respectively, without eliciting foreign body giant cell formation, fibrosis, or chronic inflammation, commonly associated with implanted medical devices. Conclusions: ReFilx are promising soft tissue fillers for breast volume restoration, representing a simple, versatile, permanent, and aesthetically superior solution for soft tissue defect correction. Acknowledgements: MaRS PoP fund, grant # MI 2011-170, NSERC # SYN 430828.
ELECTROSPUN POLYURETHANE-GELATIN SCAFFOLDS FOR MANUFACTURING SKIN SUBSTITUTE

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There is an immediate need for skin substitute despite significant developments in the management of severe skin loss. Gelatin is a low cost, natural biomaterial which is frequently used for tissue engineering applications. However it suffers from a lack of sufficient mechanical strength and associated difficulties with handling. Polycarbonate urethanes (PU) are biodegradable elastomeric biomaterials that can be spun into fibrous scaffolds, with excellent cell compatibility and non-toxic degradation products. We hypothesized that the addition of a small amount of PU to gelatin would improve the mechanical strength of electrospun gelatin.

Methods: A new gelatin-based electrospun scaffold was fabricated for skin tissue engineering via the addition of PU. Gelatin-PU scaffolds with a ratio of 80:20 (Gel80-PU20) exhibited no significant difference in average fiber size and fiber morphology, however the yield strength, and elongation of these scaffolds increased relative to 100% gelatin scaffolds (Gel100). These properties are essential for the optimal performance of the scaffold in vivo. Human dermal fibroblasts (HDF) were employed as one of the main cell sources in the dermis.

Results: By incorporating cells, more than 90% of the cells were viable at 7 days post seeding, comparable to the Gel100 in an in vitro assay. Unlike the HDF cultured on Gel100 scaffolds which showed an aligned orientation, HDF cultured on Gel80-PU20 had a random orientation, reminiscence of human skin. The depth of cell infiltration into the scaffold was similar for Gel100 and Gel80-PU20, as well as for commercial skin substitute Integra™. The results show that Gel80-PU20 scaffold is an ideal 3D environment for essential cell component of skin and might serve as an ideal scaffold for manufacturing skin substitute using various skin progenitor cells.
ADIPOSE TISSUE SECRETIONS INDUCE POST-BURN HEPATIC HYPERMETABOLISM

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Hypothesis and Purpose: The hypermetabolic response to severe burn injury is strongly correlated to patient mortality. Despite its impact, the underlying cause of this response remains uncertain. The presence of hyperlipidemia and hepatic steatosis post-burn injury suggests that crosstalk between adipose tissue and the liver is involved. This study investigated the effects of factors released from the adipose tissue of burn patients on the bioenergetics and metabolism of hepatocytes, specifically HepG2 cells, in an ex vivo explant model.

Methods: HepG2 cells were incubated in adipose tissue-conditioned media for 24 hours. High throughput respirometry, western blotting, and Oil Red O staining of mitochondria isolated from the HepG2 cells was conducted to determine the effects of explants on mitochondrial respiration and fatty acid metabolism. Milliplex was used to obtain a cytokine profile of the adipose tissue-conditioned media.

Results: HepG2 cells displayed higher basal levels of mitochondrial respiration, increased lipid accumulation, and increased fatty acid synthesis when treated with conditioned media obtained from the adipose tissue of burn patients versus healthy controls. Adipose tissue received from burned patients released greater levels of IL-6, IL-8, IL-10, TNF-α than adipose tissue received from control subjects.

Conclusion: The data described above indicates that burn injury induces adipose tissue to release mediators that influence hepatocyte metabolism. These changes are synonymous with hyperactive liver mitochondria and hepatic steatosis reported after burn injury, thus supporting the role of adipose tissue-secreted factors in promoting liver dysfunction and hypermetabolism.
DEVELOPMENT OF A DECISION AID FOR YOUNG CANADIANS DIAGNOSED WITH BREAST CANCER AT RISK OF INFERTILITY FOLLOWING CANCER TREATMENT

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Purpose: Young breast cancer patients are at risk of temporary or permanent treatment-related infertility. The study aimed to determine the fertility-related information health care providers and breast cancer survivors consider valuable for inclusion in a Canadian fertility decision aid for young breast cancer patients by reviewing existing decision support resources.

Methods: A qualitative descriptive approach was used to evaluate 6 decision support resources. Using purposeful sampling, 8 multi-disciplinary health care providers and 8 breast cancer survivors from across Canada evaluated 1 to 2 decision support resources in structured interviews. Interviews were conducted in-person and by telephone from March to June 2016 and ranged in length from 30 to 90 minutes. Interviews were transcribed verbatim, organized in NVivo, and analyzed deductively against the components of the interview guide.

Results: Each decision support resource had useful components to adapt for the Canadian fertility decision aid. Participants felt it would be useful to include Canadian-specific and accurate information on resources for additional support, and the success rates and cost ranges of fertility preservation procedures. Discrepancies were seen on the value of personal stories and including an exercise to help patients clarify the value they place on the different fertility options. There was overall consensus on the inclusion of only pertinent fertility-related information that does not replicate information in supplementary patient education material to avoid overwhelming patients.

Conclusions: The evaluation revealed sections of existing decision support resources that can be adapted for the Canadian fertility decision aid. Findings were used in combination with the International Patient Decision Aid Standards criteria to ensure the decision aid met best practices and the information needs of young women with breast cancer.
GENOMIC LANDSCAPE OF RADIATION-INDUCED MENINGIOMAS

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**Purpose:** Majority of pediatric cancers require the irradiation of the central nervous system (CNS), and as more patients survive into adulthood from improved oncological therapy the sequelae of brain radiation are increasing in prevalence. Radiation-induced meningiomas (RIMs), one such secondary effect, demonstrate a clinically more aggressive behaviour than sporadic meningiomas (SMs). We aimed to describe the genomic mutational landscape of RIMs. **Methods:** We performed integrated multiplatform genomic interrogation of radiation-induced meningiomas. A primary cohort of 18 RIMs had whole exome and RNA sequencing. Our findings were validated in a validation cohort with targeted sequencing for specific genetic mutations and gene fusions. Finally, methylation profiles were analyzed with supervised and unsupervised clustering. **Results:** Compared to sporadic meningiomas, RIMS had a five-fold increase in copy number alterations and significantly more frequent loss of chromosome 1p (94%) and 22q (94%). Notably, RIMs did not harbor any mutations in genes that have been observed to be recurrently mutated in sporadic meningiomas, such as TRAF7, AKT1, KLF4 and SMO. We also observed significantly lower frequency of NF2 mutations; however, RNA sequencing identified a NF2 gene fusion even in 35.3% percent of RIMs. Furthermore, all tumours with the NF2 fusion also had monosomy of chromosome 22, rendering the cell with homozygous NF2 inactivation. **Conclusion:** These findings have serious implications for the development of therapies focused towards the treatment of radiation-induced meningiomas. Our study demonstrates that RIMs have distinct genomic drivers of oncogenesis compared to SMs, specifically through inactivation of NF2 by fusion events. In summary, this is the largest cohort of profiled meningiomas to date, providing a robust characterization of distinct radiation induced meningioma features that can be exploited for the development of future therapies.
Purpose: Administration of FK506, an FDA approved immunosuppressant, has shown to enhance nerve regeneration following peripheral nerve injuries. However, the severe side effects of the systemically delivered FK506 has prevented clinicians from using this drug routinely. Therefore, we have developed a novel fibrin gel based local delivery system for FK506. In this study, for the first time, we analyzed the effectiveness of the FK506 local delivery system to promote axon regeneration following peripheral nerve injury. In addition, we analyzed FK506 transport to the surrounding tissues, in vivo, from the delivery system at the nerve injury site. Methods: FK506 was incorporated into fibrin gel in solubilized, particulated or poly(lactic-co-glycolic) acid microspheres-encapsulated forms. A rat nerve transection model was used, where the proximal tibial nerve stump was cross-sutured to the distal stump of a cut common peroneal nerve. Rats in the negative control groups either did not receive any delivery system treatment or received fibrin gel with empty microspheres. The experimental groups included rats treated with fibrin gel loaded with the three forms of FK506 formulation. Three weeks after repair, nerve regeneration was assessed by retrograde labeling and histomorphometric analysis. Using mass spectrometry, FK506 tissue concentrations were analyzed at the site of the nerve injury, in sciatic nerve, dorsal root ganglia (DRGs), spinal cord, brain, heart, liver, kidney, and plasma at 7, 14, and 28 days post repair. Results: Rats in experimental groups receiving FK506-loaded microspheres and the particulated FK506 had significantly highest number of motor and sensory neurons that regenerated their axons and allowing all tibial motoneurons regeneration. Histomorphometric analysis indicated increased number of myelinated axons following particulated FK506 and FK506 microspheres treatment compared to the negative control groups. FK506, in vivo, was found mainly at the nerve injury site, sciatic nerve, spinal cord, DRGs, and the surrounding gluteal muscles, decreasing in concentration over time, with little to no drug detection in other vital organs. Conclusion: The local application of FK506 via our proposed delivery systems resulted in excellent axon regeneration while minimizing the toxicity of systemic FK506 that has prevented clinicians from using FK506 routinely for treating severe cases of peripheral nerve injuries.
TRANSIENT RECEPTOR POTENTIAL MELASTATIN 2 CHANNELS (TRPM2) MEDIATE NEONATAL HYPOXIC-ISCHEMIC BRAIN INJURY IN MICE

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BACKGROUND: Transient receptor potential melastatin 2 (TRPM2), a calcium-permeable non-selective cation channel, is reported to mediate brain damage following ischemic insult in adult rodents. However, the role of TRPM2 channels in neonatal hypoxic-ischemic brain injury remains unknown. HYPOTHESIS: We hypothesized that TRPM2\textsuperscript{+/+} and TRPM2\textsuperscript{−/−} neonatal mice will have reduced hypoxic-ischemic brain injury. METHODS: To study the effect of TRPM2 on neonatal brain damage, we used 2,3,5-triphenyltetrazolium chloride (TTC) staining to assess the infarct volume and whole brain imaging to assess morphological changes in the brain. In addition, we also evaluated neurobehavioral outcomes for sensorimotor function and activation of immune cells in the ischemic penumbra using immunohistochemistry 7 days following hypoxic-ischemic brain injury. We also assessed the activation of TRPM2-mediated signaling pathway by western blot. RESULTS: We report that the infarct volumes were significantly smaller and behavioral outcomes were improved in both TRPM2\textsuperscript{+/+} and TRPM2\textsuperscript{−/−} mice compared to that of wildtype mice. Next, we found that TRPM2-null mice showed reduced dephosphorylation of GSK-3β following hypoxic ischemic injury unlike sham mice. TRPM2\textsuperscript{+/+} and TRPM2\textsuperscript{−/−} mice also had reduced activation of astrocytes and microglia in ipsilateral hemispheres, compared to wildtype mice. These findings suggest that TRPM2 channels play an essential role in mediating hypoxic-ischemic brain injury in neonatal mice. CONCLUSION: Genetically eliminating TRPM2 channels can provide neuroprotection against hypoxic-ischemic brain injury and this effect is elicited in part through regulation of GSK-3β.
Hypothesis & Purpose: We hypothesized that the alloimmune response is augmented by ischemia-reperfusion injury (IRI) in a mouse model of lung transplantation. The purpose of this study is to determine whether IRI augments alloimmune response in a mouse minor alloantigen mismatched orthotopic lung transplant (OLT) model (C57BL/10 [B10] \( \rightarrow \) C57BL/6 [B6]).

Method: OLT was performed using B10 or B6 donors and B6 recipients with or without extended cold and warm preservation. Cold ischemic time (CIT) was set at minimal (mCIT, 45 min) or 6 hours (6hCIT). Warm ischemic time (WIT) was the period from the end of CIT to reperfusion, including a fixed 15-minute period during anastomosis (15WIT), without or with an additional 45 minutes of antecedent storage at 37°C (60WIT). mCIT-15WIT B10-B6 OLT, 6hCIT-60WIT B10-B6 OLT, and 6hCIT-60WIT B10-B6 OLT were performed. Grafts were assessed with histology and immunofluorescence 28 days after OLT. CT scans were performed at 2-3 days and 27 days after OLT.

Result: CT showed increased graft density in the 6CIT+60WIT group at 2-3 days after OLT: these changes resolved in isografts but not allografts. Acute rejection was seen in all allografts but not isografts, and its severity was increased in the 6CIT+60WIT group. Obliterative airway and parenchymal fibrosis, similar to pathology seen in patients with chronic lung allograft dysfunction (CLAD), was found only in the 6hCIT+60WIT allografts. Immunofluorescent staining demonstrated an increased number of PNAd⁺ tertiary lymphoid organs in 6CIT+60WIT allografts compared with control allografts.

Conclusion: In a minor alloantigen-mismatched model, IRI enhances acute rejection histology, CLAD-like pathology, and lymphoid neogenesis.
IDENTIFYING CELL TYPE-SPECIFIC OR COMMON BIOMARKERS FOR ISCHEMIA-REPERFUSION-INDUCED INJURY IN LUNG TRANSPLANTATION

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Purpose: Ischemia-reperfusion induced acute lung injury is a major cause of mortality following lung transplantation. An accumulation of damage to the epithelium and endothelium during cold ischemic time/reperfusion (CIT/R), contribute to the severity of injury. The objective of this study is to identify cell type-specific and common biomarkers to determine the severity and type of injury.

Methods: Human lung epithelial and pulmonary microvascular endothelial cells were subjected to our cell culture model that simulates CIT/R. Cells were cultured in growth media at 37°C. To simulate preservation (CIT), cells had their media replaced with preservation solution at 4°C under a 50% oxygen atmosphere. To simulate reperfusion (R), cells were returned to growth media at 37°C. Cells were collected before CIT and after 18hCIT/2hR for RNA microarray analysis.

Results: Epithelium-specific expression differences were selected using cutoffs of $FDR_{\text{epi}} \leq 0.05$ and $p_{\text{endo}} > 0.05$. This resulted in 1454 epithelial specific genes. Similarly, cutoffs of $FDR_{\text{endo}} \leq 0.05$, $p_{\text{epi}} > 0.05$ resulted in 969 endothelium specific genes, respectively. In epithelial cells, SPRY4 (sprouty homolog 4) was the top-ranked marker. The top-ranked marker in endothelial cells was HSPA7 (heat shock 70kDa protein 7).

Conclusion: This analysis has identified cell-type specific and common candidate biomarkers for ischemia-reperfusion induced injury. These will be further studied in human transplant transcriptome data for validation.
ROLE OF TRPM7 IN GLIOBLASTOMA CELLULAR FUNCTIONS

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Glioblastoma (GBM) remains the most common and aggressive malignant brain tumor originating in the central nervous system. Diagnosis is lethal with a median survival of <15 months. Aberrant TRPM7 expression has been linked to GBM cellular functions (i.e. proliferation, migration and invasion).

**Hypothesis:** Inhibition of TRPM7 suppresses GBM cellular functions.

**Purpose:** To establish TRPM7 as a potential drug target by evaluating the TRPM7 potentiator, naltriben, on GBM viability, migration, and invasiveness.

**Methods and results:** Using the human GBM cell line U87, with the whole-cell patch-clamp technique, we first demonstrated that naltriben enhanced the endogenous TRPM7-like current. With Fura-2 Ca^{2+} imaging, we showed robust Ca^{2+} influx following naltriben application. U87 cell migration and invasion (assessed with scratch wound assays, Matrigel invasion experiments, and MMP-2 protein expression) were significantly enhanced with naltriben, but not viability and proliferation (evaluated with MTT assays). With Western immunoblots, we also assessed the protein levels of p-Akt/t-Akt, and p-ERK1|2/t-ERK1|2. We found that, in U87, naltriben enhanced the MAPK/ERK signaling pathway, but not the PI3k/Akt pathway.

**Conclusion:** Because potentiated TRPM7 activity contributes to the devastating migratory and invasive characteristics of GBM, our study confirm the involvement of TRPM7 in GBM cellular functions.
Background: Enhanced Recovery after Surgery (ERAS) guidelines have been widely promoted and supported largely due to several studies showing decreased postoperative complications and length of stay. The objective of this study was to review the ER visits and readmission rates and reasons for both in patients following an ERAS guideline.

Methods: All patients having elective colorectal surgery at 15 academic hospitals were enrolled in a government-supported ERAS implementation program. All patients were followed until 30-days post-discharge. Data was analyzed using descriptive statistics and multivariate analysis.

Results: A total of 2,876 patients (48% female; mean 60 years old) were enrolled. Cancer was the most frequent indication (68.2%) for surgery. Overall, the mean LOS was 6.9 days. In total, 359 (11.6%) of patients were seen in the ER post discharge. The most common reasons for visiting the ER were SSI (34.5%), other wound complications (10.0%) and UTI (8.6%). In total, 260 (8.2%) patients were readmitted to hospital. The most common reasons for readmission were nausea and vomiting (26.2%), intra-abdominal infection (23.9%), and SSI (11.5%). On multivariate analysis, shorter LOS (1.03, 95%CI 1.02-1.05) and rectal procedure (1.52, 95%CI 1.28-1.79) were associated with ER visits while shorter LOS (1.06, 95%CI 1.04-1.09), rectal procedure (2.04, 95% CI 1.45-2.86), reoperation (5.52, 95% CI 4.09-7.44) and presence of a stoma (1.39, 95% CI 1.07-1.82) were associated with readmission.

Conclusion: Approximately 10% of patients visit the ER or are readmitted following discharge after colorectal surgery. The most common reasons are wound complications and nausea and vomiting. Furthermore, individuals having a rectal procedure, who have a stoma or a reoperation appear to be the highest at risk groups.
RAPID DETERMINATION OF MEDULLOBLASTOMA SUBGROUP AFFILIATION USING A NOVEL HAND-HELD LASER ABLATION MASS SPECTROMETRY TOOL

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Medulloblastoma (MB) is a heterogeneous pediatric brain tumor comprised of at least 4 distinct molecular subgroups. Subgroup information is becoming relevant for patient care and will be part of risk stratification in the future. As such, MB patients could benefit from molecularly tailored therapy. Currently, no intraoperative means of determining subgroup affiliation exists to allow for reduced resection in low risk MB patients, minimizing post-operative neurological morbidity. Picosecond InfraRed Laser (PIRL) has also been shown to rapidly extract tissue lipids and small molecule metabolites to the gas phase for capture and analysis, in real time, by means of Mass Spectrometry (MS). Typical sampling and analysis times of 5-10 seconds are generally sufficient to produce tissue identifying MS spectra. We hypothesized that MB subgroups could be differentiated based on their MS lipid profile using a hand held PIRL ablation system coupled to a 2 m long tube for real time collection and analysis of the laser extracted lipids. In essence, we have a hand-held tumor grading tool that does not thermally damage the surrounding tissue, an important step towards in vivo MS analysis.

Subcutaneous xenograft models of Group 3 MB cell lines (D341, D458, Med8A) and SHH MB cell lines (ONS-76 and DAOY) were prepared in SCID mice and subjected to 5-10 second PIRL-MS analysis. Using multivariate statistical methods on 157 MS datasets from 15 independent tumors, a successful prediction rate of 97% has been achieved, with robustness confirmed through a 5% leave out and remodel test. Currently approvals are being sought to evaluate the performance of the PIRL-MS technology on patient MB samples from local tissue banks.

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METFORMIN TREATMENT RESCUES MUSCLE WASTING AND INCREASES THE NUMBER OF SATELLITE CELLS FOLLOWING THERMAL INJURY IN MICE

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Hypothesis and Purpose: Severe burn results in a prolonged hypermetabolic response that causes significant muscle atrophy. Metformin has several metabolic effects and can modulate stem cells which makes it an ideal candidate drug for this injury. The objective of this project was to examine the effect on metformin in rescuing muscle atrophy in two different age groups of animals. We hypothesize that metformin treatment will mitigate muscle atrophy by increasing the proliferation of muscle stem cells. Methods: Young (8 weeks) and aged (52 weeks) mice were subjected to a 30% TBSA dorsum thermal injury via a 98°C water bath. The groups were: sham, burn, and burn + metformin treatment. The animals were sacrificed at 2 and 7 days and gastrocnemius muscle was collected for histological and protein analysis. Results: Consistent with previous studies, there was a decrease in the muscle cross-sectional area (CSA) at 2 days post-burn in young mice which is indicative of muscle atrophy. In aged animals, muscle atrophy was observed at 7 days, indicating a delay in muscle atrophy that may be attributed to a delayed inflammatory response. Metformin treatment rescued muscle wasting at 7 days in young mice. To understand the mechanism of this rescue effect, we performed immunohistochemistry and western blotting for Pax7, a transcription factor which is characteristic of muscle stem cells. In both young and aged mice, there was a significant increase in Pax7+ cells and protein level at 7 days in the metformin group compared with sham and burn. Conclusions: Metformin treatment after thermal injury can rescue muscle atrophy partially through its beneficial effect on the number of muscle stem cells in mice. Treating burn patients with metformin may mitigate muscle wasting in addition to managing hyperglycemia without the risk of hypoglycemia like insulin.
COMPOSITE PATHOLOGIC OUTCOMES IN PATIENTS WITH RECTAL CANCER TREATED WITH A TRANS-ANAL TOTAL MESORECTAL EXCISION

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Purpose/Hypothesis: Transanal total mesorectal excision (TATME) facilitates dissection for low to mid rectal cancers but composite pathologic outcomes have not been reported. The objective of this study is to compare the pathologic outcomes post TATME with a similar cohort from the ACOSOG Z6051 trial. Our secondary objectives are to examine the operative and perioperative complications.

Methods: A retrospective review was conducted including all mid or low T3 or less rectal cancer patients, which were all treated with TATME by a single surgeon between 2015-2017. A successful surgical resection was defined as: 1) complete or near complete TME, 2) >1mm radial and 3) >1mm distal margin. Outcomes were compared to the laparoscopic and open cohorts from the ACOSOG trial.

Results: 45 patients met inclusion criteria. 33 (73%) were male and the mean age and BMI was 58.4 years and 27.7, respectively. Clinical stage I, II, III, and IV were encountered in 9 (20%), 15 (33%), 18 (40%) and 3 (7%) patients, respectively. Neo-adjuvant treatment was administered to 33 (73%) patients. Operations involved a low anterior resection in 41 (91%) and a low Hartmann in 4 (9%) patients. Complete pathologic response was encountered in 6 (18%). Successful pathologic resection was obtained in 96% of patients compared to 81.7% in the laparoscopic (p=0.02) and 86.9% in the open (p=0.1) ACOSOG cohorts. A grade 3 complication occurred in 1 patient. The median length of stay was 3 days with 5 patients (11%) re-admitted within 30 days. Conclusion: TATME is safe and yields pathologic outcomes that are comparable to the open and superior to the laparoscopic approach. Randomized studies are warranted.
The Goal of this study was to determine whether surgical gloves and instruments harbour malignant cells after the extirpative phase of a cancer resection, potentially contributing to wound recurrence. **Aim:** To measure the presence of tumour cells on gloves and instruments used intra-operatively in a spectrum of surgical procedures. **Methods & Results:** We prospectively collected washings from gloves and instruments used intra-operatively on patients undergoing a range of procedures: 1) incisional biopsy of extremity sarcoma, 2) cytoreductive surgery of peritoneal malignancy and 3) wide local excision of extremity sarcoma. Effluent from glove and instrument washings was collected and slides were examined by an expert cytopathologist (AP) who was blinded to diagnosis and procedure. **Incisional biopsies of extremity soft tissue sarcoma.** In 14 cases of incisional biopsy for what proved to be soft tissue sarcoma, 29% of the glove samples and 86% of instrument washings were positive for atypical/malignant cells. **Cytoreductive surgery for appendiceal adenocarcinoma, colorectal carcinoma or mesothelioma.** In 50 patients undergoing cytoreductive surgery for peritoneal malignancy, 26% of samples retrieved from gloves and 34% from instruments were positive for atypical or malignant cells. **Wide local excision extremity sarcoma.** In the 64 pairs of washings collected, atypical/malignant cells were identified in only one case, and only in instrument washings. On final pathologic evaluation of the resected sarcoma specimen, this proved to be an R1 (microscopic margin positive) resection of a chondrosarcoma of the thigh in a patient who had not received neo-adjuvant radiation. **Conclusions & Discussion:** We show here that malignant cells can be directly transferred to gloves and instruments used at operations during which malignant tissue is directly handled. Importantly, in margin negative resections of extremity soft tissue sarcoma, malignant cells were not detected on gloves and instruments.
ILIAC ARTERY TORSION AND CALCIFICATION PREDICTS ENDOVASCULAR DEVICE ROTATION AND POOR PATIENT OUTCOMES IN ADVANCED EVAR.

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Purpose and Hypothesis: The purpose of the current study is A) to quantify the short-term clinical outcomes in patients with stent graft rotation and B) to identify anatomical markers that can predict stent graft rotation. We hypothesize that patients with stent graft rotation will have higher rates of perioperative complications and higher iliac artery torsion and calcification.

Methods: A prospective study evaluating all patients undergoing advanced EVAR was conducted at two university affiliated hospitals between Nov 2015 and Dec 2016. Stent graft rotation (defined as ≥ 10°) was measured on an intraoperative fluoroscopic video of the deployment sequence. Standard pre-operative CTA imaging was used to calculate the geometric properties of the arterial tree. Any in-hospital and/or 30-day complications were prospectively documented and a composite outcome of any end-organ ischemia and/or death was used as the primary endpoint.

Results: Thirty-seven patients undergoing advanced EVAR were enrolled in the study with a mean age of 75 [64-89] and a mean aneurysm diameter of 63 mm [42-90mm]. The incidence of stent graft rotation was 39% (n=14) with a mean rotation of 25.4° [10.2-51°]. The total net torsion and the total volume of calcific plaque was higher in patients with stent graft rotation, 8.9±0.84 mm⁻¹ vs 4.1±0.53 mm⁻¹ (P<0.0001) and 1054±143 mm³ vs 537±89 mm³ (P<0.01) respectively. The composite outcome of any end-organ ischemia and/or death was also substantially higher in patients with stent graft rotation, 43% vs 4.5% (P<0.01). Additionally, patients with stent graft rotation had significantly higher rates of type 1 and type 3 endoleaks 36% vs 9% (p<0.05).

Conclusions: Patients with intraoperative stent graft rotation have a significantly higher rate of severe postoperative complications and this is strongly associated with higher levels of iliac artery torsion and calcification. These findings suggest that pre-operative quantitative analysis of iliac artery torsion and calcification is essential for patient risk stratification prior to advanced EVAR.
**Background:** Burn injury is one of the most horrific and lethal traumas affecting millions of people worldwide. Rapid excision of the burned skin and wound closure is lifesaving. Unfortunately, large wounds exceed intrinsic wound-healing capacities and available coverage materials are insufficient, due to immunologic rejection and lack of cells. Mesenchymal stem cells (MSCs) have been shown promote wound healing, but their use is limited by lack of availability and invasive extraction methods. To this date, we are still lacking an ideal cellular source to replace the burned skin, to improve wound coverage and save the lives of burn patients. **Hypothesis and purpose:** We hypothesize that the excised burned skin contains viable MSCs (burn derived MSCs; BD-MSCs) that can promote wound healing and serve as a cell source for skin regeneration. The aim of this study is to extract, culture, and characterize BD-MSCs, as well as to show their regenerative potential in vivo. **Methods:** First, BD-MSCs were compared to umbilical cord (UC)-MSCs (n=3) in terms of key biological characteristics. Second, BD-MSCs were incorporated into FDA-approved acellular skin-scaffolds (Integra®). **Results:** After confirming the mesenchymal stem cell nature of the BD-SCs (CD105,90,73+, CD34-; positive adipose, cartilage, and bone tissue formation), we found no difference in key biological characteristics between BD- and UC-MSCs: mitochondrial function, anaerobic glycolysis, proliferation, colony formation, cell cycle stage distribution, expression reactive oxygen species, absence of tumor formation, and MHC I/II expression. Human BD-MSCs could be successfully incorporated into acellular skin scaffolds without cell loss in vitro. **Conclusion:** Severely burned skin contains healthy mesenchymal stem cells. Key biological functions are not altered by burn trauma. BD-MSCs can be incorporated into skin scaffolds. Future studies need to determine the optimal dosage and application on a porcine wound model.
EFFECT OF OPERATOR SPECIALTY ON THE OUTCOMES OF CAROTID ARTERY REVASCULARIZATION

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Hypothesis and Purpose: To examine the effect of operator specialty on 30-day outcomes among patients undergoing carotid endarterectomy (CEA) and carotid-artery stenting (CAS).

Methods: We conducted an observational cohort study of all individuals who underwent CEA or CAS in Ontario (2002-2015) using administrative claims databases. We stratified CEA and CAS patients according to operator specialty, and followed them for 30 days after the procedure. We built multilevel multivariable logistic regression models adjusted for patient demographics, comorbidities, and annual institutional/operator volume to examine rates of stroke or death.

Results: A total of 16,544 patients were studied. Vascular surgeons performed the majority (55.7%) of CEA procedures, followed by neurosurgeons (21.0%), general surgeons (15.3%), and cardiac surgeons (7.9%). Radiologists (82.5%) and neurosurgeons (17.5%) performed CAS. In the CEA group, the risk of stroke or death was higher among patients treated by non-vascular surgeons (4.0%) compared with vascular surgeons (2.9%) (adjusted OR, 1.32; 95% CI, 1.08-1.62; P=.008). With respect to specific non-vascular surgery specialties, the rate of 30-day stroke or death was higher in CEA patients treated by neurosurgeons (adjusted OR, 1.27; 95% CI, 1.00-1.61) and cardiac surgeons (adjusted OR, 1.54; 95% CI, 1.04-2.30) compared with vascular surgeons. Patients who underwent CAS by radiologists versus neurosurgeons experienced 30-day stroke or death at similar rates (adjusted OR, 1.07; 95% CI, 0.66-1.74).

Conclusions: The risk for periprocedural stroke or death was significantly higher among CEA patients treated by non-vascular surgeons compared with vascular surgeons. Operator specialty did not appear to have a significant effect on outcomes among patients who underwent CAS. These results can have implications for physician referral practices and local policies.
POST-STEMOTIC DILATATION IN A MURINE MODEL OF AORTIC STENOSIS AND ITS APPLICABILITY TO BICUSPID AORTOPATHY

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Background: Bicuspid aortic valve (BAV) is the most common congenital cardiac defect. Aortic dilation occurs in 50% of BAVs and may progress to dissection or rupture. Aberrant shear stress is one of the principle etiologies of BAV aortopathy.

Hypothesis: Greater mechanical wall stress initiates aortic dilation through increased activity of matrix metalloproteinases (MMPs).

Purpose: To establish a murine model of aortic stenosis with aortic dilation to investigate the molecular mechanisms of post-stenotic dilatation and their applicability to BAV aortopathy.

Methods: C57BL/6 mice underwent constriction of the ascending aorta. The animals’ ascending aortas and left ventricular function were monitored with weekly transthoracic echocardiography. Ascending aortas were collected at 3 days, 2 weeks, and 4 weeks for reverse transcription quantitative polymerase chain reaction and histology.

Results: Constriction was applied at 2.69 ± 0.06 mm above the aortic valve (n=27). Maximum flow velocities and pressure gradients increased after constriction (n=27; p≤0.0001). Ascending aortas showed 28.5 ± 2.1% dilation by 4 weeks (n=27; p≤0.0001). Elastin disruption was localized to the region of higher shear stress on color flow Doppler. Tissue inhibitors of metalloproteinases (TIMPs) 1 and 2 showed a trend towards reduced transcription at 3 days (n=4; p>0.05). MMP2 and 9 showed increased transcription at 2 weeks (n=4; p≤0.05).

Conclusions: Our preliminary results in a novel murine model of aortic stenosis and post-stenotic dilation suggest that higher mechanical stress initiates aortic dilation through increased transcription of MMP2 and 9 with localized elastin disruption. MMP inhibition may be a potential therapeutic target in the early phase of post-stenotic dilatation that may include BAV disease.
PPAR-γ ACTIVATION ATTENUATES HEPATIC ISCHEMIA-REPERFUSION INJURY IN A MOUSE MODEL BY REGULATING KUPFFER CELL POLARIZATION

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Background: PPAR-γ agonists have shown protective effect on ischemia-reperfusion injury (IRI) in cerebral and renal tissue. The effects of PPAR-γ on hepatic IRI is unclear. Purpose: We investigated the effects and mechanisms of protection of PPAR-γ agonists on hepatic ischemia and reperfusion injury. Methods: Ischemia of 70% of the liver was induced for 60min. PPAR-γ agonist Rosiglitazone (RGZ-3mg/kg) or vehicle (control) were administrated 24 and 1hr before reperfusion. Aspartate aminotransferase (AST) was measured 1, 6, 12 and 24hrs after reperfusion as a marker of hepatocyte injury. H&E and TUNEL staining was performed to evaluate hepatic necrosis and apoptosis, respectively. Flow-cytometry was used to assess Kupffer cells polarization (M2-CD206+, M1-Nitric Oxide +). Results: AST in the RGZ group presented significant reduction after 1hr (RGZ: 3092±279 vs Control: 4469±1559, p=0.042), 6hr (RGZ: 7041±3281 vs Control: 12193±4329, p=0.015), and 12hr (RGZ: 5746±868 vs Control: 8608±3560, p=0.049) of reperfusion. TUNEL staining was significantly reduced in the RGZ vs control group at 1hr (RGZ: 2.46±1.47 vs Control: 6.90±2.42, p=0.001) and 6hrs (RGZ: 28±22 vs Control: 54±20, p=0.027) after reperfusion. H&E staining demonstrated a decreased percentage of necrotic tissue in the treated group 24hr (RGZ: 59±15 vs Control 76±12) after reperfusion. Flow-cytometry revealed that previous to the ischemic insult the percentage of M2-CD206+ Kupffer cells was increased in the RGZ vs control group (RGZ: 9.6±0.7 vs Control: 4.8±0.8, p=0.04). Percentage of M1-Nitric Oxide + polarization was diminished in the treated group when compared with the control group since 1hr after reperfusion (RGZ: 23±10 vs Control: 45±22, p=0.083), this difference became significant 6hs (RGZ: 3.9±3 vs Control: 31±21, p=0.025) and 24hs (RGZ: 4.15±3 vs Control: 17.10±9, p=0.043) following reperfusion.

Conclusion: PPAR-γ reduces hepatic IRI injury and decreases M1 polarization of Kupffer cells. Kupffer cell polarization is a novel target to reduce hepatic reperfusion injury.
REGULATION OF LONG NON-CODING RNA BY CYCLIC MECHANICAL STRETCH IN VASCULAR SMOOTH MUSCLE CELLS: IMPLICATIONS FOR AORTIC ANEURYSMS

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Background: Emerging evidence suggests that long noncoding RNAs (lncRNAs) may represent a cellular hub for coordination of cellular processes involved in vascular health and disease. We hypothesized that lncRNAs are involved in the pathogenesis of mechanical stretch-induced changes in human aortic smooth muscle cells (HASMCs). Methods: HASMCs were subjected to 20% elongation (1 Hz) for 24 h (Flexcell® FX4000™). LncRNAs were profiled using the Arraystar Human LncRNA Microarray V3.0. Human aneurysmal and non-aneurysmal aortic samples were collected from patients undergoing aortic arch repair and coronary artery bypass grafting, respectively. Aneurysmal samples were also collected from the aorta of ApoE\textsuperscript{-/-} mice after 4-week infusion of angiotensin II. Gene expression was quantified via qRT-PCR. Results: Of the 30,586 human lncRNAs screened, 580 were differentially expressed (\(P < 0.05\)) in the stretched vs. static group. Human long intergenic non-coding RNA-p21 (lincRNA-p21) was significantly upregulated in stretched HASMCs (\(N = 3, P < 0.05\)) and human aneurysmal samples (\(N = 10, P < 0.05\)). The murine ortholog of lincRNA-p21 was upregulated in aortic tissues from angiotensin-II-infused ApoE\textsuperscript{-/-} mice (\(N = 3, P < 0.05\)). Upon silencing of lincRNA-p21 in stretched HASMCs, there was a decrease in total apoptosis (\(N = 3, P < 0.05\)) and expression of the p53-downstream genes Bax, Puma, Noxa, and Mdm2 (\(N = 3, P < 0.05\)). Conclusions: Our data provides the first transcriptome profile of stretched HASMCs and implicates lincRNA-p21 as a mechanoresponsive regulator of aneurysm formation in mice and humans. This data provides novel insights into the regulatory switches governing aberrant VSMC remodeling, which may have importance in the pathogenesis of aneurysms and hypertension.
INCREASED RISK OF LONG-TERM MORTALITY AMONG BURN SURVIVORS: A POPULATION-BASED MATCHED COHORT STUDY

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Introduction: The effect of sustaining a major burn injury on long-term life expectancy is unknown. Emerging data from the critical care literature suggests that survivors of critical illness have shorter life expectancy than matched controls. We aimed to estimate long-term mortality and causes of death following major burn injury, compared to matched controls.

Methods: Using administrative data, all adults who survived to discharge after major burn injury between 2003-2013 were matched to 1-5 uninjured controls on age, sex, marginalization index, presence of a major physical comorbidity, and presence of a major psychological comorbidity. The marginalization index is derived from census data and accounts for residential instability, material deprivation, ethnic concentration, and dependency. The primary outcome was post-discharge all-cause mortality. Patients were followed until death or 2014, and censored at five years. Cumulative mortality estimates for all-cause mortality were estimated using the Kaplan Meier method. Cox proportional hazards modeling was used to estimate the association of burn injury with mortality while accounting for the correlated failure times within matched groups. The proportional hazards assumption was verified graphically and using interaction terms.

Results: 1965 burn survivors of mean age 44 (SD 17) with median total body surface area burn of 15% (IQR 5-15) were matched to 8671 controls and followed for a median 1958 (IQR 934-2937) days. Five-year mortality was significantly higher among burn survivors (11 vs 4%, hazard ratio 4.71 (95% CI 3.38-6.03)). Burn survivors had increased mortality related to trauma (MRR 7.83, 95% CI 3.95-15.52) and mental illness (MRR 4.69, 95% CI 2.26-9.71).

Conclusions: Burn survivors have increased risk of late mortality. As future work characterizes the psychological and physiological sequelae of burn injury, burn follow-up should be focused on the prevention of injury, and detection and treatment of new disease.
A SYSTEMATIC REVIEW AND META-ANALYSIS OF CHORDAL REPLACEMENT VERSUS LEAFLET RESECTION TECHNIQUES FOR ISOLATED POSTERIOR MITRAL LEAFLET PROLAPSE

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Purpose: To compare outcomes of chordal replacement versus leaflet resection techniques for repair of isolated posterior mitral leaflet prolapse. Methods: We searched MEDLINE and EMBASE databases for studies that compared chordal replacement (“Respect” group) versus leaflet resection (“Resect” group) techniques for the treatment of posterior mitral leaflet prolapse. Data were extracted by two independent investigators and meta-analyzed using random effects.

Results: One randomized controlled trial (RCT), one propensity-matched, and six unadjusted observational studies met inclusion criteria (n=1926 patients). Two studies only reported perioperative outcomes; mean follow-up ranged from 1.0 to 5.9 years in the remaining studies. Pooling data from unadjusted observational studies, annuloplasty ring diameter was higher in the Respect group (+1.5 mm; p=0.003), but with high heterogeneity (I²=91%). Based on limited data, post-procedural left ventricular ejection fraction may be greater in the Respect group, but this difference only reached statistical significance in the RCT (+3.4%; p=0.03), and not in two observational studies that reported this outcome (+2.7%; p=0.10). There was no difference in recurrent mitral regurgitation at follow-up between the Resect and Respect groups. However, patients in the Respect group had a lower rate of mitral valve reoperation at follow-up in the unadjusted observational studies (incidence rate ratio 0.22; p=0.0008 [I²=0%; 4 studies, 1331 patients]). Conclusions: Data from primarily observational studies suggest that chordal replacement may be associated with greater freedom from reoperation compared to leaflet resection. In addition, chordal replacement may lead to improved post-operative left ventricular function. High-quality RCTs of chordal replacement versus leaflet resection are needed.
SMOOTH MUSCLE PROTEIN-22-MEDIATED DELETION OF ATG7 RESULTS IN ADVERSE AORTIC REMODELING AND CONGESTIVE HEART FAILURE

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Objective: The pathophysiologies of abdominal aortic aneurysms (AAAs) and atherosclerosis often intersect. Given that anomalies in vascular smooth muscle cell (SMC) autophagy have been noted in models of atherosclerosis, we sought to evaluate the potential role(s) SMC autophagy may play in the initiation and progression of AAAs.

Methods: Studies were conducted in ATG7<sup>flx/flx</sup>, SM22α-Cre<sup>tg/+</sup> (SMC-ATG7-KO) and ATG7<sup>WT/WT</sup>, SM22α-Cre<sup>tg/+</sup> (SMC-ATG7-WT) littermates that were infused with angiotensin II (Ang II; 1.5 mg/kg/day) for up to 12 weeks. Mortality, morbidity and aortic remodeling were documented.

Results: Over the 12-week observation window, all of the Ang II-treated SMC-ATG7-WT mice (n=6) survived while 10 of the 19 Ang II-treated SMC-ATG7-KO mice had died by week 7 (Log-rank test P < .001). Cardiac rupture, myocardial infarct, end organ damage, pleural effusion and venous distension were noted in Ang II-SMC-ATG7-KO but not Ang II-SMC-ATG7-WT mice. Although the suprarenal aortic diameters of Ang II-SMC-ATG7-KO group demonstrated a trending increase (at week 4, 1.26 ± 0.06 mm (n=14) for Ang II-SMC-ATG-KO vs. 1.09 ± 0.02 mm (n=5) for Ang II-SMC-ATG-WT mice; P < .05), only 2 of the 19 developed AAAs.

Conclusions: Mice with SMC ATG7 deficiency that are chronically infused with Ang II do not demonstrate significant AAA development but do exhibit adverse aortic remodeling and appreciable cardiac failure-associated mortality.
Background: Hypoxia/Reoxygenation (H/R) induced endothelial dysfunction during heart transplantation is a key event that incites development of primary graft failure and allograft vasculopathy. STEEN Solution is a primary perfusate component for ex-vivo organ perfusion. Somah was developed to meet the energy requirements of cardiomyocytes and coronary endothelium. We investigated the effects these solutions exert over human coronary artery endothelial cells (HCAECs) activation in response to H/R. Methods and Results: HCAECs were exposed to hypoxia (0.1% O2) in Endothelial Culture Media (ECM) followed by reoxygenation (21% O2) treated with ECM, STEEN or Somah to simulate the ex-vivo reperfusion setting. STEEN significantly increased gene expression of IL-1, IL-6, E-selectin, MCP-1 and ICAM-1 (p<0.05). Somah presented similar results to controls and ECM. STEEN significantly increased VCAM-1 and ICAM-1 total and cell surface protein expression; Somah demonstrated similar levels to ECM and controls (H/R ECM: 107%, H/R STEEN: 938%, H/R Somah: 260% of normalized controls; p<0.05). Finally, leukocyte adhesion to the endothelium was significantly increased in the STEEN group (H/R Medium: 0.27, H/R STEEN: 14.5, H/R Somah: 0.47 cells/field; p<0.001). Conclusions: STEEN increased H/R induced endothelial activation, while Somah demonstrated similar effects as ECM. This provides evidence of the protective effects Somah exerts against endothelial reoxygenation injury when compared to STEEN. This novel cardioprotective solution may have utility in enhancing cardiac organ preservation during Ex-Vivo Perfusion.
LIVER TRANSPLANTATION FOR NASH RELATED HEPATOCELLULAR CARCINOMA OFFERS COMPARABLE OUTCOMES VERSUS NON-NASH ETIOLOGIES OF HEPATOCELLULAR CARCINOMA

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Hypothesis & Purpose: Non-Alcoholic Steatohepatitis (NASH) related Hepatocellular Carcinoma (HCC) is the fastest growing indication for liver transplantation (LT) for HCC in North America. We aimed to examine differences in characteristics and outcomes of patients who had LT for NASH-HCC (NASH) vs. HCC from other liver diseases (non-NASH). Methods: Patients with HCC who received a LT over a 10-year period were analyzed using a two-centre retrospective design. Subgroup analysis stratified patients according to explant pathology (within and beyond Milan). Results: 929 patients were transplanted for HCC. 60/929 (6.5%) had HCC with NASH as the underlying disease and 869/929 (93.5%) had other etiologies. The proportion of LT for NASH-HCC significantly increased over time (p=0.001). There were no significant differences between groups for pre-transplant or explant tumor characteristics. In each group, 31% of the tumors were beyond Milan criteria. The actuarial 1-, 3- and 5-year overall survival was 98%, 96% and 80% in NASH vs. 95%, 84% and 78% in non-NASH (p=0.1). Tumor recurrence was 13.3% in NASH vs. 14% in non-NASH (p=0.9). No differences in tumor recurrence were observed in patients within and beyond Milan in the NASH group. However, the recurrence rate in the non-NASH group was 8.8% in those within Milan and 29.2% in beyond Milan, p<0.001. Multivariate Cox Regression demonstrated NASH status to be a protective factor for recurrence among patients with tumors beyond Milan, HR 0.21 (0.05-0.86), p=0.029. Conclusions: This is the largest cohort to date that examined LT in patients with NASH related HCC. Overall outcomes are similar between NASH and non-NASH etiologies. We have generated a hypothesis that NASH patients with beyond Milan HCC tumors may have more favourable outcomes after LT, but this hypothesis needs to be further studied.
A CANADIAN COST-UTILITY ANALYSIS OF TRANSCATHETER VERSUS SURGICAL AORTIC VALVE REPLACEMENT FOR THE TREATMENT OF AORTIC STENOSIS IN THE INTERMEDIATE SURGICAL RISK POPULATION

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Purpose: A recently published randomized controlled trial showed that transcatheter aortic valve implantation (TAVI) was non-inferior to surgical aortic valve replacement (SAVR) in the treatment of severe aortic stenosis (AS) who are at intermediate surgical risk. A formal cost-utility analysis evaluating lifetime costs and benefits is warranted to examine the cost-effectiveness of TAVI compared to SAVR in the intermediate risk population. Methods: A fully probabilistic Markov model with 30 day cycles was constructed from the Canadian third party payer’s perspective to estimate the difference in cost and effectiveness (measured as Quality-Adjusted Life Years, QALYs) of TAVI versus SAVR for the intermediate risk population over a lifetime time horizon. Trial data from the Placement of Aortic Transcatheter Valve (PARTNER) 2 trial was used to inform the efficacy inputs. Data from the Canadian Institute of Health Information and the Ontario Schedule of Benefits were obtained for costs (2016 Canadian dollar). Incremental Cost-Effectiveness Ratios (ICERs) were calculated. Results: In the base case analysis, the total lifetime costs in present values for the TAVI and SAVR arms were $46,690±4,208 and $36,646±7,324 respectively while the QALYs gained were 4.61±1.18 and 4.42±1.19 for TAVI and SAVR respectively. This resulted in an ICER of $52,197/QALY. The results of the Monte Carlo probabilistic sensitivity analysis indicated that approximately 52.5% and 55.7% of the 10,000 iterations fell below the $50,000 and $100,000 per QALY willingness-to-pay threshold when TAVI was compared to SAVR respectively. Conclusions: Compared to SAVR, TAVI was found to be a cost-effective option for the treatment of severe AS in the intermediate surgical risk population with an ICER of $52,197/QALY. There was substantial uncertainty in our estimates; thus more rigorous clinical evidence is needed prior to widespread expansion of TAVI indications to lower risk patients.
NORMOTHERMIC EX-VIVO KIDNEY PERFUSION IMPROVES THE FUNCTION OF EXTREME MARGINAL RENAL GRAFTS SUBJECTED TO PROLONGED ISCHEMIA

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Background: Normothermic ex-vivo kidney perfusion (NEVKP) is an emerging technique for renal graft preservation. We investigated whether NEVKP could promote improved marginal graft function compared to cold storage in a model of donation after cardiac death. Methods: Kidneys from 30kg Yorkshire pigs were removed following 30, 60, 90, or 120 minutes of warm ischemia (WI). These grafts were then preserved in either cold solution or subjected to pressure-controlled NEVKP for 8 hours prior to heterotopic autotransplantation. Results: Prolonging WI time prior to kidney retrieval and subsequent storage in cold solution resulted in grafts that demonstrated incremental post-transplant increases in serum creatinine. While on NEVKP circuits, 120min WI grafts cleared lactate from perfusion solution (0hr: 10.48+/-0.93mmol/L vs 7hr: 1.48+/-0.85mmol/L, p<0.01), had decreasing intra-renal resistance (0hr: 2.26+/-0.9 mmHg/mL/min vs 7hr: 0.37+/-0.6mmHg/mL/min, p<0.01), and consistent urine production. Post-transplantation, 120min WI grafts with NEVKP, compared to cold storage, demonstrated significantly decreased serum creatinine peak values (POD4: 12.62+/-2.34mg/dl vs POD5: 18.95+/-1.11mg/dL, p=0.001) and higher creatinine clearance (POD4: 6.61+/-4.03mL/min vs 0.35+/-0.30mL/min, p=0.02 and POD7: 26.31+/-11.54mL/min vs 9.78+/-4.6mL/min, p=0.03). On POD7, serum creatinine also returned to baseline values in the NEVKP group (POD7: 4.88+/-5.57mg/dL vs baseline: 1.02+/-0.16mg/dL, p=0.16). Conclusion: Kidney grafts subjected to 120min of warm ischemia before retrieval showed significant improvement in function following 8hrs of continuous pressure controlled NEVKP compared to cold storage. This suggests NEVKP could be utilized to expand the donor pool through the consideration of marginal grafts for transplantation.
ADJUVANT VERSUS SALVAGE RADIOTHERAPY FOR PATIENTS WITH ADVERSE PATHOLOGICAL FINDINGS RADICAL PROSTATECTOMY: A DECISION ANALYSIS

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Purpose: Patients undergoing surgery for prostate cancer who have adverse pathological findings experience high rates of recurrence. While there are data supporting adjuvant radiotherapy compared to a wait-and-watch strategy to reduce recurrence rates, there are no randomized controlled trials comparing adjuvant radiotherapy with the other standard of care, salvage radiotherapy (radiotherapy administered at the time of recurrence).

Methods: We constructed a health state transition (Markov) model employing two-dimensional Monte Carlo simulation using a lifetime horizon to compare the quality adjusted survival associated with adjuvant and salvage radiotherapy strategies. Prior to analysis, we calibrated and validated our model using the results of previous randomized controlled trials. We considered clinically important oncological health states from immediately post-operative to prostate cancer-specific death, commonly described complications from prostate cancer treatment, and other causes of mortality. Transition probabilities and utilities for disease states were derived from a literature search of MEDLINE and expert consensus.

Results: Salvage radiotherapy was associated with an increased quality-adjusted life expectancy (58.3 months) as compared to adjuvant radiotherapy (53.7 months), a difference of 4.6 months (standard deviation 8.8). Salvage radiotherapy was preferred in 53% of hypothetical cohorts. There was minimal difference in overall life expectancy (-0.1 months). Our model showed validity when compared with available randomized controlled data.

Conclusions: A salvage radiotherapy strategy appears to provide improved quality-adjusted life expectancy for patients with adverse pathological findings following radical prostatectomy, compared with adjuvant radiotherapy. Specific patient and tumor factors, and patient preferences, remain central for individualized management.