Department of Surgery
The Ohio State University

20th Annual Surgery Research Conference

Biomedical Research Tower, Room 115
Thursday, May 21, 2015
DEPARTMENT OF SURGERY
THE OHIO STATE UNIVERSITY

20TH ANNUAL SURGERY RESEARCH CONFERENCE

BIOMEDICAL RESEARCH TOWER, ROOM 115
THURSDAY, MAY 21, 2015
Welcome

Welcome to the 20th Annual Department of Surgery Research Conference! This conference is designed to bring students, residents, fellows, faculty and guests together to share and discuss results of research relevant to a variety of surgical disciplines. It is also an opportunity for Department of Surgery (DOS) residents, graduate students and postdoctoral research trainees to develop their scientific communication skills. Each year the Department of Surgery invites a leader in surgery to visit The Ohio State University and get to know the students and faculty in the department through a variety of activities including participation as a faculty judge at the Annual DOS Research Conference. This year we are delighted to have Dr. Selwyn M. Vickers, Senior Vice President for Medicine and Dean of the School of Medicine at the University of Alabama Birmingham, as our guest.

Over the years the format for the conference has developed into two oral sessions and a poster session. The oral and poster presentations are competitively selected based on the quality of the science, impact of the work, and novelty and diversity of the topic. DOS faculty serve as “Faculty Discussants” and comment on the presentation to put the work into context for the audience and stimulate additional discussion. This year the poster presenters created three minute videos to highlight their research findings. Many of the residents who participate in this conference are trainees in the Department of Surgery Master of Medical Science Program which includes structured didactics in Research Design, Biostatistics, Research Ethics, Scientific Communication (including grant writing) and Electives relevant to the area of research.

Ginny L. Bumgardner, MD, PhD
Associate Dean for Research Education
Agenda

Thursday, May 21, 2015

Zollinger Visiting Professor Grand Rounds, 7:00 am
Selwyn M. Vickers, MD
Senior Vice President for Medicine and Dean of the School of Medicine
University of Alabama Birmingham

Welcome and Introduction of Visiting Professor, 8:30 am
Robert S. D. Higgins, MD, MSHA
Professor and Chairman, Department of Surgery
John H. and Mildred C. Lumley Medical Research Chair
Surgeon-in-Chief, Wexner Medical Center
Director, Comprehensive Transplant Center

Introduction to the Conference
Ginny L. Bumgardner, MD, PhD
Professor of Surgery, Division of Transplantation
Associate Dean for Research Education, OSU College of Medicine
Director, Master of Medical Science Program

Judges: Selwyn M. Vickers MD, Robert S. D. Higgins, MD, MSHA, and E. Christopher Ellison, MD

Moderator: Session 1 and 2 moderated by Ginny Bumgardner, MD, PhD

Session 1: Oral Presentations, 8:40 to 10:10 am
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Methylene blue attenuates neuroinflammation, cortical lesion volume, and acute depressive-like behavior following traumatic brain injury in mice. John Skendelas, BS • Faculty Advisor: Daniel Eiferman, MD • Discussant: Kyle Perry, MD ........................................................................................................ 19

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Dr. Vickers and Residents

Conclusion, 1:15 pm
Visiting Professor

Selwyn M. Vickers, MD

Selwyn M. Vickers, MD is senior vice president for Medicine and dean of the School of Medicine at University of Alabama Birmingham. Dr. Vickers, a member of the Institute of Medicine, is a world-renowned surgeon, pancreatic cancer researcher, pioneer in health disparities research and a native of Alabama.

As dean, Dr. Vickers leads the medical school's main campus in Birmingham and the regional campuses in Montgomery, Huntsville and Tuscaloosa. He also is part of UAB Medicine’s joint operational leadership (JOL) team. The JOL steers operations and finances for all UAB Hospital and ambulatory medical services, including The Kirklin Clinic and the UAB Callahan Eye Hospital.

Dr. Vickers earned baccalaureate and medical degrees from the Johns Hopkins University and completed surgical training there, including a chief residency. He completed two summer post-graduate research fellowships with the National Institutes of Health and training at John Radcliffe Hospital of Oxford University, England and was an instructor of surgery at Hopkins for one year. In 1994 he joined the UAB faculty as an assistant professor in the Department of Surgery. From 2000 to 2006 he directed the section of gastrointestinal surgery. During his first tenure at UAB Dr. Vickers received numerous honors, including the Argus Society for Excellence in Teaching Award numerous times, the Best Clinical Professor award and the President's Award for Excellence in Teaching. From 1995 to 1999 he was a Robert Wood Johnson Research Fellow. In 2000 he became the first member of the faculty chosen by students as commencement speaker. In 2006 Dr. Vickers became the Jay Phillips Professor and Chair of the Department of Surgery at the University of Minnesota Medical School, where he served until his return to UAB in 2013.

Dr. Vickers continues to see patients and conduct research. His major research interests include gene therapy as an application in the treatment of pancreatobiliary tumors, the role of growth factors and receptors in the oncogenesis of pancreatic cancer, the implications of FAS expressions and Tamoxifen in the growth and treatment of cholangiocarcinoma, assessment of clinical outcomes in the surgical treatment of pancreatobiliary tumors and the role of death receptors in the treatment of pancreatic cancer.

Dr. Vickers is co-principal investigator for the UAB Comprehensive Cancer Center’s Specialized Program of Research Excellence (SPORE) in Pancreatic Cancer and he is co-principal investigator of a $13.5 million grant to create the National Transdisciplinary Collaborative Center for African-American Men's Health.
Presenters

Eliza Beal, MD
General Surgery Resident
Hometown: Ann Arbor, MI
BS: Anthropology-Zoology, University of Michigan, Ann Arbor, MI
MD: The Ohio State University, Columbus, OH
Research interests: Solid organ abdominal transplant, hepatocellular carcinoma
Mentors: Sylvester Black, MD, PhD & Carl Schmidt, MD

Shayna Brathwaite, MD
General Surgery Resident, Master of Medical Science Program Candidate
Hometown: Solon, OH
BA: Psychology, Case Western Reserve University, Cleveland, OH
MD: Case Western Reserve University School of Medicine, Cleveland, OH
Research interests: Chemopreventative agents in colorectal cancer
Mentors: Ching-Shih Chen, PhD & Christina Wu, MD

Amitava Das, M.Pharm
Graduate Research Associate
Hometown: Kolkata, India
B. Pharmacy: PES College of Pharmacy, Bangalore, India
M. Pharmacy: PES College of Pharmacy, Bangalore, India
Research interests: Wound healing, inflammation, microRNA
Mentor: Sashwati Roy, PhD

Ryan Dickerson, BS
Graduate Research Associate
Hometown: Sylvania, OH
BS: Biology, Ohio State University, Columbus, OH
Research interests: Type 2 diabetes mellitus, chronic wounds, innate immune function
Mentor: Chandan Sen, PhD

Joseph Drosdeck, MD, MS
General Surgery Resident
Hometown: Milwaukee, WI
BA: Psychology, University of Wisconsin - Milwaukee, WI
MS: Medical Science, The Ohio State University, Columbus, OH
MD: University of Wisconsin, Madison, WI
Research Interests: Minimally invasive surgery, surgical education
Mentor: Kyle Perry, MD
Presenters

Subhadip Ghatak, PhD
Post-Doctoral Researcher
Hometown: Kolkata, India
BS: Physiology, University of Calcutta, Calcutta, India
MS: Physiology, University of Calcutta, Calcutta, India
PhD: West Bengal University of Health Science, Kolkata, India
Research interests: MicroRNA in tissue injury and repair
Mentor: Chandan Sen, PhD

Justin Huntington, MD, MS
General Surgery Resident
Hometown: Dayton, Ohio
BA: Zoology, Miami University, Oxford, OH
MS: Medical science, The Ohio State University, Columbus, OH
MD: The Ohio State University, Columbus, OH
Research interests: Hepatocellular carcinoma, foregut malignancies
Mentor: Gustavo Leone, PhD

Folasade Imeokparia, MD
General Surgery Resident
Hometown: Springfield, Illinois
BA: Sociology, Cornell University, Ithaca, NY
MD: The Ohio State University College of Medicine, Columbus, OH
Research interests: Wound healing, disparity outcomes, breast cancer
Mentor: J. Kevin Bailey, MD

Nicholas Latchana, MD, MS
General Surgery Resident, Master of Medical Science Program Candidate
Hometown: Toronto, Canada
BMSc: Biochemistry, University of Western Ontario, Canada
MD: Albany Medical College, Albany NY
Research Interest: Cancer biology
Mentor: William Carson, III, MD

Daniel Lodwick, MD, MS
General Surgery Resident
Hometown: Royal Palm Beach, Florida
BS: Nuclear Engineering, University of Florida, Gainesville, Florida
MS: Nuclear Engineering Sciences, University of Florida, Gainesville, Florida
MD: University of Florida College of Medicine, Gainesville, Florida
Research interests: Radiation exposure estimation, ultrasound elastography, pediatric surgical outcomes
Mentors: Peter Minneci, MD, MHS & Katherine Deans, MD, MHS
Presenters

Sara Mansfield, MD, MS
General Surgery Resident, Master of Medical Science Program Candidate
**Hometown:** Pomeroy, OH  
**BS:** Biological Sciences and German, Ohio University, Athens, OH  
**MD:** University of Cincinnati, Cincinnati, OH  
**Research interest:** Virology, immunology, global surgery  
**Mentor:** Robert Baiocchi, MD, PhD

Sara Martin del Campo, MD, MS
General Surgery Resident  
**Hometown:** Peoria, IL  
**BS:** Biology, Indiana University, Bloomington, IN  
**MS:** Medical science, The Ohio State University, Columbus, OH  
**MD:** The University of Iowa Carver College of Medicine, Iowa City, IA  
**Research interest:** Minimally invasive surgery, foregut surgery  
**Mentor:** Kyle Perry, MD

Shomita Mathew-Steiner, PhD
Postdoctoral researcher  
**Hometown:** Chennai, India  
**BSc:** Womens Christian College, Chennai, India  
**MSc:** Christian Medical College and Hospital, Vellore, India  
**PhD:** Miami University, Oxford, OH  
**Research interest:** Biofilm infection/wound healing  
**Mentor:** Chandan Sen, PhD

Elizabeth McMichael, BS
Graduate Research Associate, PhD Candidate  
**Hometown:** Rochester, PA  
**BS:** Allegheny College, Meadville, PA  
**Research interest:** Cancer biology  
**Mentor:** William Carson, III, MD

Ekene Onwuka, MD
General Surgery Resident, Master of Medical Science Program Candidate  
**Hometown:** Gary, IN  
**BS:** Biology, Tufts University, Medford, MA  
**MD:** Howard University College of Medicine, Washington, DC  
**Research interest:** Tissue engineering  
**Mentor:** Christopher Breuer, MD
Presenters

Durba Pal, PhD, MS
Post Doctoral Researcher
**Hometown:** Kolkata, India  
**BS:** Zoology, University of Calcutta, India  
**MS:** Zoology, University of Calcutta, India  
**PhD:** Visva Bharati, Kolkata, India  
**Research Interest:** Cell Reprogramming in regenerative medicine  
**Mentor:** Chandan Sen, PhD

John Skendelas, BS
Med II Student Researcher
**Hometown:** Upper Arlington, OH  
**BS:** Microbiology, The Ohio State University, Columbus, OH  
**Research interest:** Trauma, neuroimmunology  
**Mentor:** Daniel Eiferman, MD

David Strosberg, MD
General Surgery Resident
**Hometown:** Albany, NY  
**BS:** Biological Science, University at Albany, State University of New York, Albany, NY  
**MD:** Upstate Medical University, State University of New York, Syracuse, NY  
**Research interest:** Coagulation and hemostasis  
**Mentors:** Jeffrey Hazey, MD; Kyle Perry, MD & Bradley Needleman, MD
Routine staging with endoscopic ultrasound in patients with esophageal cancer and dysphagia rarely impacts treatment decisions

Sara A. Mansfield, Samer El-Dika, Somashekar G. Krishna, Jon P. Walker, Kyle A. Perry

Introduction: Endoscopic ultrasound (EUS) has been routinely employed for the locoregional staging of esophageal cancer. One important aspect of clinical staging has been to stratify patients to treatment with neoadjuvant chemoradiation or primary surgical therapy, with patients with T3 tumor stage or lymph node involvement receiving neoadjuvant therapy. We hypothesized that EUS may have a limited impact on clinical decision making in patients with dysphagia and obstructing esophageal masses.

Methods: We tested this hypothesis in a retrospective cohort study of patients undergoing EUS for staging of esophageal cancer between 2009 and 2014 (n=220). Patients without dysphagia (n=82) were excluded. Patient demographics, endoscopic tumor characteristics, presence of dysphagia, sonographic staging, and post-EUS therapy were recorded. Pathologic staging for patients who underwent primary surgical therapy was also recorded. Locally advanced disease was defined as at least T3 or N1, as these patients are typically treated with neoadjuvant therapy.

Results: EUS was performed on 138 patients with dysphagia for staging of esophageal cancer during the study period. Patients had an average age of 63.0 ± 10.8 years with an average BMI of 27.8 ± 6.6 kg/m², and 86.2% of patients were male. At endoscopy, 128 (94%) patients had esophageal adenocarcinoma, 96 (70%) had partially obstructing lesions, 25 (18%) had completely obstructing lesions, and 17 (12%) had non-obstructing tumors. Overall, 128 (93%) patients had clinical staging indicative of locally advanced disease. Of the 10 patients with early stage via EUS, 6 underwent primary surgical resection for which pathologic staging demonstrated locally advanced disease with lymph node involvement in 4 of these patients. In 121 patients with obstructing lesions, 96% had EUS staging indicative of locally advanced disease, compared to 71% of the 17 patients with non-obstructing tumors (p<0.01). Three patients with obstructing lesions and early stage via EUS underwent primary surgical resection, and 2 were found to have locally advanced disease. Overall, 132 (96%) patients with dysphagia were found to have locally advanced disease by sonographic or pathologic staging. For patients with dysphagia and obstructing tumors, locally advanced or metastatic disease was identified in 98% of patients in this series.

Conclusions: An overwhelming majority of patients presenting with dysphagia at the time of esophageal cancer diagnosis had an EUS that demonstrated at least locally advanced disease. In the cases where patients with dysphagia and esophageal mass underwent primary surgical therapy, surgical pathology actually revealed a more advanced stage than diagnosed on EUS. These patients may have actually benefited from neoadjuvant therapy rather than surgery. The present study supports the hypothesis that endoscopic ultrasound may be of limited benefit for staging esophageal cancer in patients with dysphagia, particularly in the setting of an obstructing mass lesion.
Colonoscope mediated vaginoscopy for diagnostic evaluation of colovaginal fistulas

Nicholas Latchana, Iyare Esemuede, Alan Harzman, Mark Arnold, Daniel Geissler, Syed Husain

Introduction: Objective confirmation of a clinically suspected colovaginal fistula is often challenging. Conventional diagnostic modalities include colposcopy, barium enema and computed tomography. However, these studies are suboptimal with high false negative rates. Vaginography has been suggested as a useful alternative. We describe a novel modified endoscopic technique involving the utilization of a standard colonoscope for vaginoscopy representing a cost effective and easily performed approach for diagnostic confirmation of colovaginal fistulas. We hypothesize that colonoscope mediated vaginoscopy will improve the diagnostic accuracy over conventional methods used in the identification of colovaginal fistulas.

Methods: A retrospective chart review was conducted to identify patients with colovaginal fistulas confirmed at surgery. A standard colonoscope was used to perform a vaginoscopy at the time of colonoscopic examination.

Results: A total of 26 patients matched inclusion criterion. Eleven vaginoscopy examinations were performed and evidence of a fistula was identified in 9/11 (82%) exams. No adverse events related to the vaginoscopy occurred. One patient with a false negative vaginoscopy also had a negative barium enema, vaginogram, and three CT scans. In our experience, fistula identification by the proposed method compares favorably to the conventional modalities: lower endoscopy 5/26 (19%), CT scan 15/32 (47%), barium enema 3/8 (38%), and vaginogram 10/11 (91%).

Conclusions: Our results support the need for further investigation into this approach as a primary diagnostic modality for colovaginal fistulas. Potential strengths of this approach include technical simplicity and cost savings that may result through the judicious use of diagnostic studies.
Minimally invasive ileal pouch anal anastomosis with rectal eversion allows for equivalent outcomes in continence

Laura A. Boomer, Victoria K. Pepper, Justin T. Huntington, Karen A. Diefenbach, Jennifer L. Dotson, Benedict C. Nwomeh (presented by Laura Boomer for Justin Huntington)

Introduction: Different techniques for ileal pouch anal anastomosis (IPAA) have been described in children with ulcerative colitis (UC), including rectal eversion. This method allows for precise identification of the dentate line, and a more complete proctectomy, but has also raised concerns for sphincter injury from traction. The purpose of this study was to evaluate the outcomes and continence rates for patients undergoing IPAA for UC at our institution.

Methods: After obtaining approval from the Institutional Review Board, all patients that underwent IPAA were reviewed. Data collected included demographics (age, sex, weight, and BMI among others), procedure details, proctocolectomy technique, operative time, total hospital and post-operative length of stay, and continence outcomes at 1 month, 6 months and 12 months post-ileostomy closure. All minimally invasive procedures (standard laparoscopic and robotic-assisted) were considered together for statistical analysis (MIS group).

Results: Thirty-three patients were identified that underwent proctocolectomy and IPAA between July 2006 and October 2014. Twenty (60.6%) patients had a standard laparoscopic procedure, 8 (24.2%) had an open procedure, and 5 (15.2%) had a robotic-assisted laparoscopic procedure. Three patients in the standard laparoscopic group had a two-stage procedure, while the rest had three-stage procedures. There were no statistically significant differences in regards to demographics, mean operative time, or length of stay (LOS) when comparing the MIS group (standard laparoscopic and robotic-assisted) to the open group. All patients in the MIS group underwent the eversion technique, while none of the patients in the open group underwent rectal eversion. Two patients within the MIS cohort were excluded from the continence data as they had yet to undergo ileostomy reversal. Average number of stools per day for the entire cohort was 7 at 1 month, 6 at 6 months, and 5 at 12 months. There were no differences in the two groups in terms of number of daily stools (p=0.96 for 1 month, p=0.09 for 6 months and p=0.87 for 12 months), night-time stooling (p=0.29 for 1 month, p=0.10 for 6 months and p=0.25 for 12 months), soiling (p=0.43 for 1 month, p=0.36 for 6 months and p=0.52 for 12 months), or stool-altering medication usage (p=0.37 for 1 month, p=0.12 for 6 months and p=0.24 for 12 months).

Conclusions: The rectal eversion technique can be used safely and effectively during MIS for proctocolectomy and IPAA in children and adolescents without resulting in a decrease in continence rates.
IL-21 enhances natural killer cell response to cetuximab-coated pancreatic tumor cells


Introduction: Pancreatic cancer has a dismal 6 month survival rate of 5% for patients diagnosed with Stage IV pancreatic cancer. 95% of patients diagnosed with pancreatic cancer have KRAS mutations, rendering the use of monoclonal antibodies (mAb) against the epidermal growth factor receptor (EGFR) ineffective. Alternative strategies to EGFR blockage by mAbs is necessary in order to improve the efficacy of therapy and to enhance the survival of patients with locally advanced or metastatic pancreatic cancer. One such strategy would be to make use of the immune system to clear cetuximab-coated tumor cells, as the need for novel therapeutic approaches to enhance the efficacy of cetuximab is evident. Given the interactions between the innate immune system and antibody therapy, our group has suggested that the efficacy of Ab therapy could be enhanced via the administration of immune stimulatory cytokines with the capacity to activate NK cells. We hypothesized that IL-21 would enhance NK cell mediated effector functions against cetuximab-coated pancreatic tumor cells irrespective of KRAS mutation status.

Methods: NK cells from normal human donors or donors with pancreatic cancer were plated overnight with or without IL-21 (10 ng/ml) and their percent lysis of cetuximab-coated wild-type and mutant KRAS pancreatic tumor cells was determined in a standard four-hour chromium release assay. NK cell activation was determined by measuring the release of IFN-γ, IL-8, MIP-1α, MIP-1β, and RANTES via the use of enzyme-linked immunosorbent assays following a co-culture system of IL-21-activated or unactivated NK cells with cetuximab-coated pancreatic tumor cells. The ability of co-culture supernatants to recruit T cells was measured using a transwell assay system. NK cell signal transduction was measured via flow cytometry following previously listed stimuli. Both a subcutaneous and intraperitoneal murine model was implemented to determine the efficacy of combination therapy in vivo using tumor volume measurements and in vivo bioluminescence imaging respectively. The importance of NK cells and monocytes of the efficacy of combination therapy in vivo was determined by depletion studies of both cell types. Finally, the combination of gemcitabine to IL-21 and cetuximab was determined in vivo.

Results: NK cell lysis of cetuximab-coated tumor wild-type and mutant KRAS pancreatic cancer cell lines was significantly higher following NK cell IL-21 treatment, as compared to controls. In response to cetuximab-coated pancreatic tumor cells, IL-21 treated NK cells secreted significantly higher levels of IFN-γ, which peaked at 72 hours post stimulation. Co-stimulation of NK cells led to higher secretion of chemokines, increased chemotaxis of T cells, and enhanced NK cell signal transduction via activation of ERK and STAT1. Treatment of mice bearing subcutaneous EGFR-positive pancreatic tumor xenographs with mIL-21 and cetuximab led to significant inhibition of tumor growth as compared to control conditions. Combination therapy was found to be dependent on the presence of NK cells, but not monocytes. This result was confirmed in a second intraperitoneal model of pancreatic cancer. Treatment of tumor bearing mice with gemcitabine and cetuximab in combination led to reduced tumor burden in vivo, and this effect was markedly enhanced by the addition of IL-21.

Conclusions: Overall, this data suggests that cetuximab treatment in combination with IL-21 adjuvant therapy in patients with EGFR-positive pancreatic cancers results in significant NK cell activation, irrespective of KRAS mutation status, and may be a potential therapeutic strategy.
Targeting glucose transporters to prevent colon carcinogenesis

Shayna Brathwaite, Christina Wu, Tanios Bekaii-Saab, Ching-Shih Chen

**Introduction:** Colorectal cancer is the fourth most common cancer in the United States. There were over 130,000 new cases diagnosed and over 50,000 deaths in 2014. Colon cancer carcinogenesis is a stepwise progression from normal epithelium to adenoma to carcinoma. Mutations in adenomatous polyposis coli (APC) have been implicated in this process. Inactivating mutations in APC lead to constitutive activation of the Wnt/β-catenin signaling pathway, which leads to tumor proliferation and malignant progression. Recently mutations in the Wnt signaling pathway have been linked to a well known cancer phenomenon called the Warburg effect. The Warburg effect notes that cancer cells preferentially undergo aerobic glycolysis, rather than oxidative phosphorylation, independent of the amount of oxygen that is in the environment. Increased glycolysis and glucose uptake provides a tumor cell survival advantage. This process may be mediated by up regulation of glucose transporter 1 (GLUT 1) which is the most prevalent GLUT in colon cancer and has been linked clinically to worse prognosis. We hypothesize that inhibition of glucose metabolism and the glycolytic pathway represents a therapeutically relevant strategy to inhibit tumor proliferation through down regulation of the Wnt signaling pathway.

**Methods:** Our lab has developed a novel class of glucose transporter inhibitors, of which CG-5 represents a proof of concept compound. We will use multiple colon cancer cell lines including HCT-116, SW-48 and DLD-1 to assess the in vitro efficacy of CG-5 to inhibit GLUT 1, Wnt signaling mediators and thus tumor proliferation.

**Results:** CG-5 leads to 50% cell death in HCT-116, SW-48 and DLD-1 cell lines at 3-4µM after 48hours of treatment. CG-5 also leads to dose dependent decrease in GLUT 1 protein but not mRNA. CG-5 also leads to dose dependent inhibition of Wnt signaling mediators, β-catenin and TCF-4, in addition to downstream targets cyclin D1 and c-myc at the protein and RNA level.

**Conclusions:** CG-5 inhibits colon cancer cell proliferation by decreases in Wnt signaling mediators and inhibition of GLUT 1 protein. CG-5 represents a potential therapeutic agent to halt the adenoma to carcinoma sequence.
Nanoparticle-based therapeutic silencing of hypoxamiR miR-210 accelerates ischemic wound closure

Subhadip Ghatak; Mithun Sinha; Bryant Yung; Savita Khanna; Sashwati Roy; Robert Lee; Chandan K. Sen.

Introduction: Peripheral vasculopathies, commonly associated with chronic wounds, are primarily responsible for wound ischemia. Limitations in the ability of the peripheral vasculature to deliver O2-rich blood to the wound tissue leads to, among other consequences, hypoxia. Tissue hypoxia induces hypoxamiRs which, in the wounded skin, are aimed at turning down metabolism/growth and bringing the ischemic tissue to a silent survival mode. This mode is in conflict with active metabolism and growth required for healing. It is thus essential that this genetic “ischemic memory” be erased in order to jump-start the healing process. Master hypoxamiR miR-210 represses mitochondrial respiration and associated downstream functions which in turn causes keratinocyte growth arrest and compromises wound closure.

Methods: In this study, using ischemic flap wound model on K-14 Cre-miR-210 +/- mice developed in our laboratory (targeted knock out of miR-210 in epithelium of skin), we observed that such knock-out mice displayed improved wound healing compared to wild-type controls. We sought to improve healing of ischemic wounds of wild-type mice using strategies to minimize wound tissue hypoxamiR content. Lipid nanoparticles (LNP) represent a promising delivery system in RNA interference therapy because of their biocompatibility and the feasibility of large-scale production. We designed and developed a novel cationic based LNP to deliver small RNA/DNA called small peptide lipid nanoparticle containing gramicidin (SPLN-G). The linear peptide gramicidin forms prototypical ion channels specific for monovalent cations and facilitates their entry through the cell membrane.

Results: Intradermal delivery of anti-miR-210 in SPLN-G caused significant suppression of miR-210 in keratinocytes. Anti miR-210 SPLN-G treatment improved the closure of ischemic wounds placed on bipedicle flap of wild-type mice. Such treatment accelerated wound re-epithelization. This was accompanied by increased abundance of proliferating Ki67+ cells in the wounded skin epithelium.

Conclusions: Collectively, these observations introduce the opportunity for LNP-based therapeutic manipulation of miRs in the wound tissue.
Macrophage MFG-E8 resolves wound inflammation and drives wound angiogenesis


Introduction: Impaired cutaneous wound healing is a debilitating complication in diabetes mellitus. This work rests on our observation that dead cell clearance activity (efferocytosis) is compromised in wound macrophages (mΦ) of diabetic mice. Milk fat globule EGF factor 8 (MFG-E8), secreted by activated mΦ, supports efferocytosis by binding to phosphatidyl serine (PS) on apoptotic cell surface and tethering them to mΦ via αvβ3 or αvβ5 integrin receptors. Glycation of MFG-E8 protein, compromised PS binding, impairing efferocytosis. We hypothesized that diminished MFG-E8 activity in mΦ of diabetics impairs resolution of inflammation and contributes to wound chronicity.

Methods: To test the significance MFG-E8 in wound healing, MFG-E8-/- mice were utilized. Full thickness splinted excisional wounds were developed on the back of mice. To study the role of macrophage MFG-E8 on wound healing outcomes, adoptive transfer of bone marrow cells (BMT) from MFG-E8 +/- mice to MFG-E8 -/- mice was performed.

Results: Wound closure was significantly impaired (p<0.05; n=5) in MFG-E8-/- mice as compared to wild-type (MFG-E8+/-). Wound macrophages isolated from MFG-E8-/- mice exhibited impaired (p<0.05; n=4) efferocytosis activity. Such impairment was associated with increased production of the pro-inflammatory cytokine, TNF-α. Transcriptome (Affymetrix Genechip™) profiling demonstrated down regulation of key angiogenesis related genes in MFG-E8-/- mice suggesting that lack of MFG-E8 may derail wound angiogenesis. Injecting mice with fluorescent beads as well as staining of wound tissues with CD31 demonstrated marked decrease (p<0.05; n=3) in wound angiogenesis response in MFG-E8-/- mice. Repletion of MFG-E8 via BMT resulted in improved blood flow and wound closure pointing towards a key role of wound macrophage MFG-E8 in wound angiogenesis. Finally, MFG-E8 treatment facilitated diabetic wound closure by improved efferocytosis.

Conclusions: This work provides first evidence establishing a critical role of wound-site macrophage MFG-E8 in resolving wound inflammation through facilitated efferocytosis, which switches the macrophage phenotype favoring wound angiogenesis and improved healing outcomes.
The role of losartan in the prevention of tissue engineered vascular graft stenosis

Ekene A. Onwuka, Yong U. Lee, Cameron A. Best, Tai Yi, Avione Y. Lee, Shuhei Tara, Tadahisa Sugiura, Nathan Mahler, Toshiharu Shinoka, Christoher K. Breuer

Introduction: Taken together cardiac anomalies represent the most common birth defect, affecting nearly 1% of all live births. One source of morbidity and mortality among these patients arises from use of synthetic biomaterials in the form of vascular grafts or patches for the various reconstructive cardiac operations. Complications include thromboembolic events, infection, poor durability due to neointimal hyperplasia, and lack of growth capacity. In response to this challenge, we have developed a tissue engineered vascular graft (TEVG) with growth capacity, which has been safely used as an extra-cardiac conduit in 25 children undergoing modified Fontan operations for treatment of single ventricle cardiac anomalies. The most significant complication is graft stenosis, which has occurred in 16% of treated patients. Our attention has turned towards the mechanism of stenosis, which we believe to be secondary to a macrophage driven, TGF-β mediated process termed endovascular to mesenchymal transformation. Losartan has been demonstrated to down regulate the expression of TGF-β types I and II receptors. We hypothesize that Losartan can inhibit the formation of TEVG stenosis by down-regulating Tgfbr1 and Tgfbr2, thereby disrupting TGF-β signaling and blocking Endo-MT.

Methods: We will investigate our hypothesis by comparing the incidence of stenosis between animals treated with Losartan and control animals. We will perform implantation of TEVGs as infra-renal inferior vena cava (IVC) interposition grafts into a mouse model over a two-week time course. We will perform quantitative histomorphometry to determine the incidence and degree of TEVG stenosis and compare these data between animals treated with Losartan and controls. We will then compare long-term administration of Losartan to short-term administration using an IVC interposition TEVG murine model over a six-month time course. We will investigate and compare the safety and efficacy of both dosing regimens.

Results: Untreated, negative controls demonstrated graft patency of 48%, while positive controls, mice receiving grafts seeded with bone marrow derived mononuclear cells (BM-MNC), demonstrated patency of 92%. Mice that received unseeded grafts and a two-week course of Losartan demonstrated graft patency of 81%, whereas those that received a six-month course showed graft patency of 67%. Finally, mice that received a graft seeded with BM-MNC, as well as a two-week treatment course of Losartan, were monitored for one-year and demonstrated 100% graft patency.

Conclusions: Successful development of a second generation of TEVG free from stenosis formation will have significant clinical implications for the treatment of congenital cardiac defects. Losartan treatment has a significant effect on graft patency, the most benefit seen when combining implantation of a graft seeded with BM-MNC with a short course of drug therapy.
Combinational effects of early laser treatment and pirfenidone on hypertrophic burn scar reduction

J. Kevin Bailey, Jae You Kim, Folasade Imeokparia, Danielle M. Dunham, Britani N. Blackstone, John A. Clark, Stephen P. Smith, Rebecca A. Coffey, Larry M. Jones, Marty O. Visscher, Juan Armendariz-Borunda, Heather M. Powell

Introduction: Successful treatment of burn injury may still result in functional and cosmetic defects due to hypertrophic scar formation. Pulsed Dye Laser (PDL) and fractional CO2 (FxCO$_2$) laser have enjoyed increasing clinical support in hypertrophic scar management after burn injuries. Nevertheless, evidence to support and guide the application of laser treatment is lacking. There is also growing interest in the ability to use FxCO$_2$ lasers to increase the permeability of the skin to allow for more efficient topical delivery of drugs such as pirfenidone (Esbriet) – a novel anti-fibrotic, anti-inflammatory agent. Pilot study goals: Examine the effectiveness of early laser treatment of burn scar and skin graft alone or in combination with pirfenidone.

Methods: Eight Red Duroc pigs had standardized burn sites created. These were immediately excised and grafted with an autologous split-thickness skin graft. These grafted wounds were allowed to heal for 4 weeks. Each site was then treated with PDL, FxCO$_2$, or pirfenidone alone or in combination. Treatment assignments were randomized to account for potential scarring difference from the relative position of grafted wounds on the animals. Therapy was repeated every 4 weeks for a total of 3 treatment sessions. Immediately prior to each treatment, non-invasive measures of color, scar dimensions and elasticity were completed. A tissue biopsy of each site was also taken for biochemical characterization. Four weeks after the last treatment, the animals were euthanized and the wound sites excised. Sections of scar were then tested with destructive measures of ultimate tensile strength and stiffness.

Results: Combination laser therapy (PDL + FxCO$_2$) appears to be superior with decrease in scar contracture and decrease in erythema. PDL (alone) may be most promising for decreasing stiffness of scars.

Conclusions: Results suggest that treatment effect is observable within study period. Treatment appears to improve function, and pirfenidone appears to have an effect as well.
Methylene blue attenuates neuroinflammation, cortical lesion volume, and acute depressive-like behavior following traumatic brain injury in mice

John P. Skendelas, Ashley M. Fenn, Daniel N. Moussa, Megan M. Muccigrosso, Phillip G. Popovich, Jonathan Lifshitz, Surya Gnyawali, Cameron Rink, Jonathan P. Godbout, Daniel S. Eiferman

Introduction: Traumatic brain injury (TBI) is a leading cause of neurologic disability in the United States and is at the forefront of public health concerns worldwide. TBI is characterized by edema, neuroinflammation, and blood-brain barrier breakdown that contribute to injury severity and impair long-term functional recovery. Unfortunately, there are no effective therapies for limiting either the immediate or chronic neurologic sequelae associated with TBI. Therefore, the objective of these studies was to determine the efficacy of methylene blue (MB), an antioxidant agent, in reducing neuroinflammation, behavioral complications, and structural lesions identified by magnetic resonance (MRI) and diffusion-weighted (DWI) imaging in a murine model of moderate, diffuse TBI.

Methods: Adult BALB/c mice (2-3 mo) received a sham or midline fluid percussion injury, and were administered either vehicle (ddH₂O) or MB (1%; 2 mg/kg) by tail vein injection within 15-30 min of injury. Mice were sacrificed 24 h following injury for tissue collection or examined one week later for motor coordination and depressive-like behavior by Rotarod and tail-suspension test respectively. In a series of follow-up studies, MRI and DWI modalities (Small Animal Imaging Core Lab) were utilized to correlate imaging findings 24 post-injury with acute neuroinflammatory activity and behavioral sequelae in the injury model.

Results: MB infusion (i.v. 15-30 min after injury) attenuated cerebral edema, and reduced inflammatory gene expression (TNF-α, IL-1β) in enriched microglia/macrophage populations and the hippocampus 1 day post-injury (dpi). Moreover, MB inhibited the development of depressive-like behavior 7 dpi. In a series of follow-up studies, repeat injection of MB (15-30 min, 12 h, and 1 dpi) reduced volumetric lesion size, as determined by DWI, in cortical regions inferior to the injury site 1 dpi. Interestingly, no significant lesions were identified in TBI or MB-treated groups in this timeframe using conventional T2-weighted MRI.

Conclusions: Moderate TBI induces a robust acute neuroinflammatory response in the brain following injury that is associated with self-limited and chronic behavioral complications. Immediate and repeat administration of MB was effective in attenuating neuroinflammation and improving behavioral recovery, and reducing cortical lesion size respectively after diffuse brain injury. Furthermore, radiologic evaluation of TBI may require more sensitive imaging modalities, e.g. DWI, for full appreciation of neuroinflammatory pathology and assessment of treatment efficacy. Overall, MB intervention may serve as a prospective therapeutic agent in the management of acute and chronic TBI complications.
Oral supplementation of a standardized naturally fermented papaya preparation (FPP) may correct type 2 diabetes mellitus-induced reactive oxygen species (ROS) dysregulation

Ryan Dickerson, Douglas R. Pfeiffer, Gayle M. Gordillo, Savita Khanna, Kwame Osei, Sashwati Roy, Chandan K. Sen

Introduction: Carica papaya Linn is widely known as a medicinal fruit. Fermented papaya preparation (FPP) is a nutritional antioxidant supplement rich in carbohydrates and amino acids produced by yeast fermented of unripe, organic, non-genetically modified papaya. During innate immune response, leukocytes are stimulated to produce their characteristic "respiratory burst", which produces superoxide anion (\(O_2^-\)) and derivative reactive oxygen species (ROS), utilized for bactericidal purposes. It is previously reported that peripheral blood mononuclear cells (PBMC) from T2DM individuals cannot mount a proper respiratory burst when stimulated. In 2010, it was estimated that chronic wounds affected ~6.5 million patients in the United States, resulting in over US$25 billion dollars spent in treatment costs. More than 23 million Americans (7.8% of the population) are currently diagnosed with T2DM, with ever increasing prevalence of the disease resultant from poor diet and sedentary lifestyle. Identification of a product capable of bolstering T2DM patients' ability to stave off wound infection would prove widely beneficial in their wound healing outcomes.

Methods: In this work, we established both mouse and human models to investigate whether FPP taken orally may act as a functional food able to benefit diabetes mellitus (T2DM) patients' innate immune response. Animal Model: anesthetized diabetic db/db, and control non-diabetic db/+, mice were given two 6mm full-thickness excisional wounds via skin punch biopsy equidistant from the midline on the dorsum. Wound closer was measured over 7 days. Human Model: T2DM patients consumed FPP (9g/day) after providing a blood sample at a baseline visit (0wk), then returned at 2wk and 6wk blood draws before discontinuing supplementation and returning for washout analysis (7wk and 8wk). At each visit, blood chemistry was analyzed and PBMC inducible respiratory burst function was measured. NADPH oxidase subunits were quantified via Western blot.

Results: Unsupplemented diabetic mice wound area showed impaired wound closure. When diabetic mice were supplemented with FPP, wound area 7 days post-wounding was significantly smaller than in the placebo group. In our human studies, we observed PBMC from T2DM patients suffer from compromised inducible respiratory burst potential. T2DM ROS production after FPP supplementation was rescued to near non-T2DM levels. NADPH oxidase, the enzyme responsible for catalyzing the production of \(O_2^-\), is an assembly of several protein subunits which require localization and assemblage on the cell membrane to function properly. We discovered two of the protein subunits differed significantly after FPP supplementation. Firstly, p47phox, whose activity is modulated post-translationally and is active in the phosphorylated state, showed significantly more phosphorylation after FPP supplementation. Secondly, Rac2- a Rho family GTPase required for activation of the complex, expression was significantly upregulated in FPP supplemented PBMC.

Conclusions: Our work demonstrates the novel concept that the use of a naturally produced nutritional supplement may possess the ability to enhance the ability of T2DM patients to mount a more efficient defense against wound infection, allowing for increased wound healing outcomes for T2DM patients.
Variation in utilization of computed tomography imaging at large pediatric hospitals

Daniel L. Lodwick, Jennifer N. Cooper, Kelly J. Kelleher, Richard Brilli MD; Peter C. Minneci, Katherine J. Deans

Introduction: Computed tomography (CT) is the largest medical source of ionizing radiation to the population. Recent efforts have focused on reducing the use of CT imaging, particularly in children. However, the consistency with which this has been implemented is unknown. While published reports demonstrate variability in the rate of pediatric CT scanning for particular indications across both adult and pediatric hospitals, variability in the overall rate of CT scanning across tertiary pediatric hospitals is not well described. We evaluated variation and trends in the use of CT scanning among patients treated at tertiary pediatric hospitals in the United States during 2009 - 2013.

Methods: Data were extracted from the Pediatric Health Information System (PHIS) from 2009 - 2013 utilizing the computed tomography imaging code 51 and separated according to inpatient/observation and emergency department (ED) encounters. The rate of CT imaging for each encounter type in each hospital was calculated. The trend in rate of CT scanning over time and the variability in the rate of CT scanning across hospitals were evaluated using negative binomial regression models with random hospital intercepts. The relative contribution of ED, inpatient and observation patients, and the relationship between hospital size and CT use were also evaluated.

Results: Thirty tertiary care pediatric hospitals were included. There were 12,531,184 patient encounters and 701,644 CT scans resulting in a mean of 56 scans per 1000 encounters. There was statistically significant variability in the rate of CT scanning across hospitals with a range of 26 to 108 scans per 1000 encounters (p < 0.001). The most common scan types were head (60.3%), abdomen/pelvis (19.8%), neck (8.4%), and chest (7.7%). The rate of CT imaging decreased from 69.2 scans to 49.6 scans per 1000 encounters across the study period (p < 0.001), with a significantly larger decrease in the mean absolute rate of scanning from the hospitals that were the highest utilizers of CT imaging in 2009 (t test, p = 0.009). There was a significant inverse relationship between the rate of CT use and annual hospital volume with higher volume hospitals having lower CT scan rates (p=0.002). In addition, there was a significant positive correlation between the rate of CT scanning for inpatient/observation patients and the rate of CT scanning for patients treated-and-released from the ED; hospitals with high inpatient scanning rates also had high ED scanning rates (r = 0.63, p < 0.001).

Conclusion: The use of CT imaging across tertiary pediatric institutions is widely variable with nearly a fourfold difference in the rate of CT scanning across hospitals. A hospital's rate of CT scanning was consistent regardless of encounter type, suggesting that the decision to image is institutionally influenced. Hospitals with larger annual volume had lower rates of CT imaging which may be due to the availability of other diagnostic methods.
Complete pathologic tumor kill is not common after bridging therapy for HCC

Eliza W. Beal, Rachel Roth, Joshua Ebel, Adam J. Hanje, Anthony J. Michaels, Sylvester M. Black, Mark Bloomston, Carl R. Schmidt

Introduction: In patients with hepatocellular carcinoma (HCC), bridging therapy is common prior to liver transplant (LT) using therapies such as ablation or trans-arterial chemoembolization (TACE). It is unknown whether complete pathologic tumor kill is needed for superior outcome.

Methods: The medical records of all patients who underwent LT between 2008 and 2013 at a single hospital were reviewed. The incidence of viable HCC within the hepatic explant was determined for patients who underwent LT after bridging therapy. Outcomes were compared between those with complete and incomplete tumor kill.

Results: There were 125 patients who underwent LT during the study period, and 42 (34%) had HCC. Twenty-eight (65%) were treated with bridging therapy, specifically 13 (46%) underwent ablation and 15 (54%) underwent TACE. Viable tumor within the hepatic explant was found in 11 (69%) patients after ablation and 10 (67%) after TACE. Median follow-up after LT in the HCC group was 29.8 months. Estimated 5-year survival was 79% in the TACE group and 56% in the ablation group (P=0.45). There was one perioperative death (3%). There was one patient with recurrent cancer in the cohort who was initially treated with ablation and died 13.3 months after LT with multifocal disease.

Conclusions: After bridging therapy with either ablation or TACE, rates of viable tumor are high. Despite this, recurrence is uncommon and overall survival is comparable to patients transplanted without HCC. Depending on regional waitlist mortality, it may not always be necessary to achieve complete pathologic tumor kill with bridging therapy.
Efficacy and durability of robotic Heller myotomy for achalasia: patient symptoms and satisfaction at long-term follow-up

Kyle A. Perry • Aliyah Kanji • Joseph M. Drosdeck • John G. Linn • Anthony Chan • Peter Muscarella • W. Scott Melvin

Introduction: Laparoscopic Heller myotomy (LHM) has become the standard treatment for achalasia in the USA. Robot-assisted Heller myotomy (RHM) has emerged as an alternative approach due to improved visualization and fine motor control, but long-term follow-up studies have not been reported. We sought to report the long-term outcomes of RHM and compare them to those of LHM.

Methods: A retrospective cohort study was performed for patients who underwent laparoscopic or RHM between 1995 and 2006. Long-term follow-up was performed via mail or telephone questionnaire. The primary outcome measure was durable relief of dysphagia without need for further intervention. Secondary outcomes included gastroesophageal reflux symptoms, disease-specific quality of life, and patient satisfaction with their operation.

Results: Seventy-five patients underwent laparoscopic (n = 19) or robotic (n = 56) myotomy during the study period. Long-term follow-up was obtained in 53 (71%) patients with a median interval of 9 years. RHM was associated with a decreased mucosal injury rate (0 vs 0.16%, p = 0.01) and median hospital stay (1 vs. 2 days, p < 0.01) compared to conventional laparoscopy. All patients reported initial dysphagia relief, and 80% required no further intervention. This did not differ between groups. Sixty-two percent required medications to control reflux symptoms at long-term follow-up, including 56% following robotic myotomy and 80% after laparoscopic myotomy (p = 0.27). Overall, 95% of patients were satisfied with their operation, and 91% would choose surgery again given the benefit of hindsight.

Conclusions: There is a dearth of long-term follow-up data to support the effectiveness of RHM. This study demonstrates durable dysphagia relief in the vast majority of patients with a high degree of patient satisfaction and a low rate of esophageal mucosal injury. While a significant proportion of patients report reflux symptoms, these symptoms are well controlled with medical acid suppression.
Direct Reprogramming of fibroblast to endothelial by nano-electroporation technology

Durba Pal, Daniel Gallego-Perez, Surya Gynawali, Subhadip Ghatak, Cameron Rink, Savita Khanna, Sashwati Roy, L. James Lee and Chandan K. Sen

Introduction: Recent advances in cell reprogramming have opened up the possibility for the development of patient specific therapies and are thus a great leap forward in regenerative medicine. Moreover, although lineage commitment has been assumed to be an irreversible process under physiological conditions, new evidence suggests that adult cells/tissues are also amenable to reprogramming in vivo, which could facilitate the transition from the lab bench to the clinic. Nevertheless, although in vivo cell reprogramming has been successfully demonstrated recently, heavy reliance on viral methods could significantly hamper clinical applications.

Methods: We used our newly developed nanochanne- based electroporation (NEP) technology allows for non-viral gene delivery in a targeted, controlled and benign manner, which is not attainable by any of the existing transfection technologies.

Results: Here we found efficient reprogramming of human fibroblasts to endothelial cells (both in vitro and in vivo) via NEP. Moreover, rapid transdifferentiation into functional endothelial cells was successfully achieved by shortening or bypassing induced pluripotency. We further demonstrated for the first time that NEP-based endothelial induction promoted significant re-vascularization of ischemic tissues in a mouse model.

Conclusions: We used nanochannel electroporation to transfec a set of reprogramming transcriptions factors capable of mediating the transdifferentiation of adult skin cells into endothelial cells in a safe and efficient manner. Ongoing studies involve the identification of key pathway components responsible for the modulation of this reprogramming process.
Laparoscopic redo fundoplication improves disease-specific and global quality of life following failed laparoscopic or open fundoplication

Sara E. Martin del Campo, Sara A. Mansfield, Andrew J. Suzo, Jeffrey W. Hazey, Kyle A. Perry

Introduction: Redo fundoplication following failed anti-reflux surgery has been shown to improve patient symptoms; however, its impact on patient quality of life remains unclear. We hypothesized that laparoscopic redo fundoplication improves disease-specific and global quality of life in patients with recurrent symptoms following failed laparoscopic or open fundoplication.

Methods: A retrospective review of a prospective database was conducted for patients undergoing redo fundoplication between August 2009 and June 2014. Outcomes of interest included symptom and quality of life scores, operative time, blood loss, complications, and subsequent procedures. Reflux symptoms and quality of life were assessed using the validated Gastro-Esophageal Reflux Symptom Score (GERSS), Gastroesophageal Reflux Disease Health-Related Quality of Life (GERD-HRQL) questionnaire, and the global quality of life Short Form - 36 (SF-36). Dysphagia was measured on a 5 point Likert scale. Initial post-operative data were collected in the clinic setting, and follow-up was obtained by telephone questionnaire, with a median follow-up interval of 16.5 (2 - 61) months. Data are presented as incidence (%), mean ± SD, or median (range) as appropriate, and a p-value of < 0.05 was considered statistically significant.

Results: Forty-six patients underwent laparoscopic redo fundoplication during the study period, 8 (17%) following open fundoplication. Mean age was 53.8 ± 13.6 years, with a mean BMI of 29.5 ± 5.7 kg/m², and 36 (78%) patients were female. Patients underwent surgery for symptomatic recurrent paraesophageal hernia (n = 11, 24%), recurrent GERD (n = 18, 39%), or postoperative dysphagia (n = 17, 37%), and the median time to reoperation was 3.5 (0 - 14) years. Median operative time following laparoscopic repair was 136 (73 - 286) minutes compared to 147 (108 - 248) minutes following open fundoplication (p = 0.16). The median length of stay was 2 (1 - 15) days, and did not differ between patients with previous laparoscopic or open fundoplication. There were no perioperative mortalities, and one patient required conversion to an open procedure following previous laparoscopic fundoplication. Overall, 8 (17.3%) patients experienced complications, including 1 patient following previous open fundoplication. Two patients with previous laparoscopic fundoplication required reoperation. Seventy-five percent of patients reported significant dysphagia at baseline compared to 25% post-operatively (p=0.004). Median dysphagia scores decreased from 4.5 (0-5) to 1 (0-5, p = 0.035), and 11 (23.9%) patients underwent an endoscopic dilation following redo fundoplication. GERSS improved from 41 (2 - 68) at baseline to 9 (0 - 55) at follow-up (p < 0.001), and GERD-HRQL scores improved from 30 (3 - 47) at baseline to 7 (0 - 45) at follow-up (p < 0.001). SF-36 scores demonstrated a significant improvement in general health (p = 0.016) and emotional well being (p = 0.036) and a trend toward improved physical function (p = 0.068) in the post-operative period, but these improvements were not statistically significant at longer-term follow-up. Overall, 82% of patients reported satisfaction with their operation, and 96% reported that they would have the operation performed again given the benefit of hindsight.

Conclusions: While associated with long operative times and significant complications, laparoscopic redo fundoplication produces durable improvement in reflux symptoms and disease-specific quality of life, as well as high patient satisfaction in patients following failed laparoscopic or open fundoplication.
Wound healing in the Ossabaw porcine model of obesity and pre-metabolic syndrome

Shomita S. Mathew-Steiner, Kasturi Ganesh Barki, Sriteja Dixith, Daniel Vanzant, Matthew Joseph, Elizabeth Schwab, Sashwati Roy, Chandan K. Sen

Introduction: Obesity is a significant problem affecting 1 in 3 adults and 1 in 6 children in the United States. This silent epidemic is a leading non-communicable threat to public health and a risk factor for chronic wound development. Limitations in mouse diabetic models of wound healing due to the acute onset of metabolic dysfunction necessitates appropriate clinically translatable chronic models like the Ossabaw porcine model recommended by the NIDDK. The Ossabaw pigs become morbidly obese and develop symptoms of pre-metabolic syndrome, including dyslipidemia and high blood pressure upon prolonged exposure to a sedentary mode of life and a diet rich in sugars and fats (m-Ath diet).

Methods: Pigs were maintained on m-Ath diet or control diet throughout the period of the study (8-10 months) and a comprehensive assessment of metabolic, hepatic and renal parameters were performed on a regular basis from plasma and serum samples taken at months 2, 4, 6, 8 and 10.

Wounding: Further, 2”x2” full thickness excisional wounds were created on the dorsum of the pigs (at 6-8 months on m-Ath diet) and followed up to 31 days post wounding with and without infection with the clinically relevant mixed bacterial species consisting of *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Acinetobacter baumannii*. Analyses of wound microperfusion (laser speckle imaging), wound depth, volume and elasticity (harmonics ultrasound imaging and elastography) and skin barrier function (transepidermal water loss, TEWL) were performed throughout the length of the study.

Methods: Weight gain and metabolic analyses: Compared with pigs maintained on standard chow (control), we found that m-Ath diet fed pigs have a sustained increase in weight (m-Ath diet >300 lbs; control diet <150 lbs) concurrent with an acute spike in serum cholesterol and triglycerides that remain elevated above normal levels despite a gradual decrease of the diet (100% to 25%). Other tested parameters also showed differences based on the diet fed to the pigs. Wound healing: Compared to uninfected wounds, those infected with the biofilm forming bacteria consistently remained open, indicating that a significant driver of wound chronicity under the influence of metabolic dysregulation is persistent infection. This is further corroborated by observations made from studies in obese patients where wound chronicity is strongly linked to the presence of infection.

Conclusions: This work reports the first studies on a chronic (>30d open) pre-clinical model of wound healing in Ossabaw pigs. The notion that biofilm infection of wounds interferes with timely wound healing sets the stage for strategies that can clear infections in wounds and aid in proper wound healing.
Perioperative antiplatelet therapy and surgical outcomes in emergent and major elective general surgical, thoracic, and vascular procedures

David S. Strosberg, Jon C. Henry, Todd Corbey, Loren Masterson, Jean E. Starr

Introduction: Antiplatelet drugs including clopidogrel (Plavix) in conjunction with acetylsalicylic acid are considered the gold standard in the treatment of patients with coronary stent implantation in preventing stent thrombosis, as well as in the management of patients with acute coronary syndromes with or without percutaneous coronary intervention. Antiplatelet drug use in patients with pre-existing coronary artery diseases remains an important consideration when these patients require an emergent or major elective procedure. Surgeons often face the dilemma between stopping antiplatelet therapy and risking adverse cardiac outcomes, specifically coronary stent thrombosis, or continuing treatment risking increased surgical bleeding and its associated consequences. Our aim was to evaluate whether perioperative antiplatelet drug use, specifically clopidogrel, increased the rate of adverse surgical outcomes in emergent or major elective general surgical, thoracic, and vascular procedures.

Methods: We chose 35 different CPT codes to represent major emergent and elective general, thoracic, and vascular surgeries from 2009 to 2012. Patient charts were reviewed, and those on clopidogrel prior to surgery were included for study. Patients were excluded if there was no way to decipher whether clopidogrel was held pre-operatively. Demographics, comorbidities, transfusion requirements, and perioperative events were collected. Statistical significance was determined using Fisher’s exact test and student t-test.

Results: 1137 patients underwent one of the defined major surgical procedures during the study period. 66 patients (5.8%) were taking clopidogrel preoperatively. 27 patients were excluded as it was unclear if clopidogrel was held preoperatively; therefore 39 patients comprised the study population. Clopidogrel was held in 20 patients (51.8%, Group A), and 19 patients (48.2%, Group B) received clopidogrel within 5 days of surgery. Two patients (10.5%) in Group B received preoperative platelets due to the emergent nature of the surgery and choice of the surgical team. One patient in Group A suffered perioperative MI due to acute cardiac stent thrombosis. Seven (36%) of Group B patients required immediate or delayed packed red blood cell (PRBC) transfusion, compared to three (15%) of patients in Group A. There was also no statistical significance between the two groups regarding intra-operative estimated blood loss, number of PRBC transfusions, myocardial infarction, stroke, acute visceral or peripheral ischemia, or death within 30 days.

Conclusions: Antiplatelet use including clopidogrel (Plavix) remains an important consideration in patients undergoing major general, thoracic, and vascular surgery. We did not identify a difference in perioperative complications in those patients who received or held clopidogrel preoperatively. We recommend continuing clopidogrel preoperatively in elective and emergent surgical situations.