Welcome

Welcome to the 23rd Annual Ohio State University 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 surgery. It is also an opportunity for a variety of students training with faculty in the Department of Surgery (DOS) (including medical students, 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 welcome Kelly M. McMasters, MD, PhD, FACS; the Ben A. Reid, Sr., MD Professor; and chairman of the Hiram C. Polk, Jr., MD Department of Surgery at the University of Louisville School of Medicine as our guest.

We received a number of exceptional abstract submissions this year, reflecting a broad collection of basic/translational, clinical, health services, and surgical education research topics. The abstracts were reviewed and scored by members of the Department of Surgery Research Council and selected for oral and poster presentation based on the quality of the science, novelty and diversity of the topic. DOS faculty were invited to serve as faculty discussants, who will provide comments to frame the context and importance of the research and to stimulate discussion. To enhance our residents’ experience with public comment and discussion, each oral presentation also has an invited resident discussant. Several of the conference presenters are either currently enrolled in or graduates of the College of Medicine (COM) Master of Medical Science Program or other Ohio State advanced degree programs. Some of the presenters are current or prior NIH T32-supported research trainees. Again welcome, and we hope that these conference interactions will stimulate new ideas, projects and collaborations.

Ginny L. Bumgardner, MD, PhD
Associate Dean for Research Education
Professor of Surgery
Director, DOS Research Training Program
Director, Master of Medical Science Program
Program Director/PI, NIH T32 “Advanced Research Training in Immunology for Surgical Trainees”
Comprehensive Transplant Center
The Ohio State University

43rd Annual Zollinger Visiting Professor

Kelly M. McMasters, MD, PhD, FACS

Kelly M. McMasters, MD, PhD, FACS is the Ben A. Reid, Sr., MD Professor; chairman in the Hiram C. Polk, Jr., MD Department of Surgery at the University of Louisville School of Medicine, and director of the Multidisciplinary Melanoma Clinic, James Graham Brown Cancer Center, Louisville, Kentucky.

Dr. McMasters earned his medical degree at the University of Medicine and Dentistry of New Jersey Robert Wood Johnson Medical School and his PhD in Cell and Developmental Biology from Rutgers University. He completed a fellowship in Surgical Oncology at the University of Texas MD Anderson Cancer Center in Houston. He is the author and principal investigator of the Sunbelt Melanoma Trial, a multi-institutional study involving 3,500 patients from 79 institutions across North America. His research has been funded by the American Cancer Society, the National Institutes of Health, and the Melanoma Research Foundation, among other agencies. He has two patents for his research inventions.

Dr. McMasters is currently president of the Society of Surgical Oncology, president of the Society of Surgical Chairs and the secretary of the Southern Surgical Association (2014 – 2018). He was a member of the Melanoma Staging Committee of the American Joint Committee on Cancer and is former president of the Western Surgical Association (2017) and Southeastern Surgical Congress (2009 – 2010). He has authored more than 400 publications and is editor of the book “Hepatocellular Carcinoma: Targeted Therapy and Multidisciplinary Care.” Dr. McMasters is the current editor-in-chief of the Annals of Surgical Oncology.
Agenda

Wednesday, May 30, 2018
Welcome and Introduction of Visiting Professor
11:30 a.m.
Timothy M. Pawlik, MD, MPH, PhD
Professor and Chair, Department of Surgery
The Urban Meyer III and Shelley Meyer Chair for Cancer Research Surgeon in Chief

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

Judges
Kelly M. McMasters, MD, PhD, Professor and Chair of the Department of Surgery, University of Louisville
Gail E. Besner, MD, Professor and Division Director, Pediatric Surgery, Nationwide Children’s Hospital
Heena P. Santry, MD, MS, Associate Professor and DOS Vice Chair for Health Services Research
Chandan K. Sen, PhD, Professor and Associate Dean of Translational Research, COM
Bryan A. Whitson, MD, PhD, Associate Professor and Director, COPPER Lab

Moderator: Session I and 2 moderated by Ginny L. Bumgardner, MD, PhD

Biographies of the conference presenters begin on page 46.

Session I: Oral Presentations
11:45 a.m. – 1 p.m.

A Novel Probiotic Platform Therapy for the Treatment of Clostridium Difficile Colitis. Rita D. Shelby, MD – Faculty Advisor: Gail E. Besner, MD – Faculty Discussant: Syed G. Husain, MD, MS

Robot-Assisted Mechanical Therapy Uncovers Acute Mediators of Post-Stroke Skeletal Muscle Recovery. Maria H. H. Balch, MS – Faculty Advisor: Mary E. Dillhoff, MD, MS, and John E. Phay, MD – Faculty Discussant: William E. Carson III, MD

Preoperative Cytokine Expression is Associated with Perioperative Outcomes after Pancreatectomy. Malcolm H. Squires III, MD, MS – Faculty Advisor: Mary E. Dillhoff, MD, MS, and John E. Phay, MD – Faculty Discussant: Sylvester M. Black, MD, MPH – Resident Discussant: Nakesha D. King, MD, MS

From Bench to Bedside: Vitamin A Deficiency after Bariatric Surgery and its Impact on Adipocyte Vitamin A Metabolism. Anahita D. Jalilvand, MD – Faculty Advisor: Carl R. Schmidt, MD, and Lawrence A. Shirley, MD

Higher frequency of IFN-γ+CD8+ T cells correlate with reduced risk of humoral allograft immunity posttransplant. Matthew Basinger, BS – Faculty Advisor: Ginny L. Bumgardner, MD, PhD – Faculty Discussant: Wael N. Jarjour, MD – Resident Discussant: Anahita D. Jalilvand, MD

Targeted Activation of Innate Immune Cells with Antibody Conjugated Fluorescent Nanodiamonds. Lorena P. Suarez-Kelly, MD – Faculty Advisor: William E. Carson III, MD – Faculty Discussant: Andrei V. Manilchuk, MD – Resident Discussant: Clifford Akateh, MD

Break
1 p.m. – 1:15 p.m.

Poster Session
1:15 p.m. – 2:15 p.m.

Judged Posters
Epithelial hypoxamir MIR-210 directly contributes to ischemic skin injury. Ayan Biswas, PhD – Faculty Advisor: Chandan K. Sen, PhD

Reversible stenosis in a juvenile lamb model of tissue-engineered vascular grafts. Joseph D. Drews, MD, MS – Faculty Advisor: Christopher K. Breuer, MD

Design and test of targeted lipid-nanoparticles in burn wound care. Subhabdi Ghatak, PhD – Faculty Advisor: Chandan K. Sen, PhD

Stop flying the patients! Helicopter transport of trauma patients is over utilized and increases costs unnecessarily. Chelsea R. Horwood, MD – Faculty Advisor: Daniel Eiferman, MD, MBA

Use of Quality Improvement (QI) Methodology to Decrease Length of Stay (LOS) for Newborns with Uncomplicated Gastroschisis. Sara A. Mansfield, MD, MS – Faculty Advisor: Jennifer H. Adrlik, MD

The role of a multidisciplinary tumor board in management of patients with pancreatic cystic lesions. Kasey W. Rawlins, BS – Faculty Advisor: Carl R. Schmidt, MD, and Lawrence A. Shirley, MD

General Posters
Nonotechnology-driven platforms to study and target myeloid-derived suppressor cells in cancer. Silvia M. Duarte Sanmiguel, BS – Faculty Advisor: Daniel Gallego-Perez, PhD

Stabilized collagen matrix dressing improves wound macrophage function and epithelialization. Mohamad S. El Masry, MD – Faculty Advisor: Chandan K. Sen, PhD

Ossabow pigs as a natural preclinical model of metabolic syndrome and impaired wound healing. Nandini Ghosh, MS – Faculty Advisor: Chandan K. Sen, PhD

Antibody-suppressing CD8+ T cells require IFN-γ/IFN-γR interactions for effector function development. Kalyn Hoffman, BS – Faculty Advisor: Ginny L. Bumgardner, MD, PhD

How well are we really doing since the NETT? Results of high-volume single academic Lung Volume Reduction (LVR) Program. Chelsea R. Horwood, MD – Faculty Advisor: Susan Moffatt-Bruce, MD, PhD, MBA

From Bench to Bedside: Vitamin A Deficiency after Bariatric Surgery and its Impact on Adipocyte Vitamin A Metabolism. Anahita D. Jalilvand, MD – Faculty Advisor: Willia A. Hsueh, MD – Faculty Discussant: Subhadip Ghatak, PhD
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The Bromo and Extraterminal Domain Protein (BET) Family Drives Endothelial-to-Mesenchymal Transition and Contributes to Vein Graft Stenosis. Mengxue Zhang, MD, MS – Faculty Advisor: Lian-Wang Guo, PhD 33

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Indocyanine Green Lymphangiography for Thoracic Duct Identification and Injury Recognition During Neck Dissection. Jeffery M. Chakedis, MD – Faculty Advisor: John E. Phay, MD – Faculty Discusant: Steven H. Sun, MD 35

Differences in Letters of Recommendation for Applicants to Complex General Surgical Oncology Fellowship Based on Gender. Tasha M. Hughes, MD, MPH – Faculty Advisor: Lawrence A. Shirley, MD, MS – Faculty Discusant: Kara K. Rossfeld, MD, MS 36


Porethenolide Inhibits Inflammatory Dysfunction of Human Aortic Endothelial Cells and Proliferation of Smooth Muscle Cells in vitro and Restenosis in a Rat Model. Bowen Wang, PhD – Faculty Advisor: K. Craig Kent, MD – Faculty Discusant: Michael R. Go, MD, MS – Resident Discusant: Taehwan Yoo, MD, MS 38

Improving Glucose tolerance in diabetes: Inducing islets in the skin. Natalia Higuita-Castro, PhD – Faculty Advisors: Daniel Gallego-Perez, PhD, and Chandan K. Sen, PhD – Faculty Discusant: Amer Rajab, MD, PhD – Resident Discusant: Shayna A. Brathwaite, MD, MS 39

Research Conference Conclusion 3:45 p.m.

Reception for Kelly M. McMasters, MD, PhD, FACS 4:15 – 4:45 p.m.

43rd Annual Zollinger Visiting Professor Ben A. Reid, Sr., MD Professor and Chairman

Hiram C. Polk Jr., MD Department of Surgery

University of Louisville School of Medicine

Louisville, Kentucky

115 BRT

Rocking Chair Conference 4:45 p.m. – 5:30 p.m.

Dr. McMasters and the General Surgery Residents 115 BRT

Thursday, May 31, 2018

43rd Annual Zollinger Visiting Professor Grand Rounds

7:30 a.m.

Kelly M. McMasters, MD, PhD, FACS

Ben A. Reid, Sr., MD Professor and Chairman

Hiram C. Polk Jr., MD Department of Surgery

University of Louisville School of Medicine

Louisville, Kentucky

115 BRT
Abstracts
Oral Session I

A Novel Probiotic Platform Therapy for the Treatment of Clostridium Difficile Colitis

Rita Shelby MD*, Natalie Tengberg BS, Jacob Olson MD, Miriam Conces MD, Jason Navarro BS, Jacob Allen PhD, Yijie Wang MS, Michael Bailey PhD, Steven D. Goodman PhD, Gail E. Besner, MD.

Correspondence: Rita Shelby, MD, Nationwide Children’s Hospital, 700 Children’s Drive, Columbus OH 43205 Phone: (214) 695-7200; Email: Rita.Shelby@nationwidechildrens.org

Introduction: Clostridium difficile infection is the most common cause of antimicrobial-associated diarrhea, affecting all patient populations across all healthcare centers worldwide. It affects over 450,000 patients with 29,000 deaths a year, with an associated annual excess medical cost of $4.8 billion worldwide. We sought to evaluate the effect of a novel probiotic delivery system on reducing the severity and incidence of this infection.

Methods: A murine model of C. difficile infection was created using an oral antibiotic cocktail for 4 days, followed by an intraperitoneal clindamycin injection a day later, and an oral dose of 1x10^8 colony forming units of C. difficile. Mice received: 1) no treatment (N=15), 2) planktonic (free-living) Lactobacillus reuteri (Lr; N=7), or 3) Lr pre-adhered to maltose-loaded dextranomer microspheres to promote biofilm formation (Lr+DM-malt; N=8) prior to C. difficile inoculation. Evaluation utilized a novel 12-point clinical sickness scoring (CSS) system (score ≥6 consistent with CDI), a 9-point histologic injury scoring (HIS) system (score ≥4 consistent with CDI), and a survival analysis. Mice were sacrificed once they exhibited severe illness or at 6 days post C. difficile inoculation.

Results: CSS ≥6 occurred in 66.7% of untreated mice exposed to C. difficile, 85.7% of mice treated with Lr alone, and 0% of mice treated with Lr+DM-malt (p=0.0002). HIS ≥4 occurred in 80% of untreated mice, 66.7% of mice treated with Lr, and 0% of mice who received Lr+DM-malt (p<0.0002). Mice treated with Lr+DM-malt demonstrated increased survival compared to untreated mice (p=0.0159).

Conclusion: We have developed a novel probiotic delivery system in which Lr is adhered to microspheres leading to increased biofilm formation. When delivered in its biofilm state, Lr significantly reduces the incidence of experimental C. difficile infection and improves survival. This novel probiotic delivery system may be beneficial in preventing clinical C. difficile infections in the future.

*Acknowledgment: This author is supported by Federal Award Number R01GM123482-01S1 from the National Institutes of Health. The project content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
Robot-Assisted Mechanical Therapy Uncovers Acute Mediators of Post-Stroke Skeletal Muscle Recovery

M Batch MS1-2, CK Sen PhD3, S Khanna PhD4, H Harris BS1, S Gnyawali PhD4, C Rink PhD MBA1
1Department of Surgery, Davis Heart and Lung Research Institute, The Ohio State University Wexner Medical Center, Columbus, Ohio 43210; 2Division of Anatomy, Department of Biomedical Education and Anatomy, The Ohio State University College of Medicine, Columbus, Ohio 43210

Introduction: Stroke survivors require rehabilitative therapy to facilitate functional recovery. We developed a software-controlled Robot-Assisted Mechanical Therapy (RAMT) device to objectively quantify effects of mechanical therapy on recovery in a rat model of ischemic stroke. As recently published, RAMT treatment improved paretic limb perfusion and preserved motor function. Furthermore, we identified myostatin as a RAMT-sensitive target of post-stroke functional recovery. These observations within just two weeks of the stroke event uncovered acute stroke-induced changes in skeletal muscle signal transduction. With much of stroke research focusing on the CNS injury, little is known about peripheral skeletal muscle response. Typical physiological response to muscle injury presents with neutrophil recruitment, followed by pro-inflammatory M1 macrophages that later shift to an anti-inflammatory M2 phenotype. Non-canonical recruitment patterns have been observed with chronic neuromuscular disease, traumatic injury, and aging, but this immune cell response has not been fully defined after stroke. This work examines acute skeletal muscle injury after stroke and uses RAMT as a tool to investigate molecular mechanisms of recovery.

Methods: Ischemic stroke was induced in male Wistar rats via transient middle cerebral artery occlusion (tMCAO). Using our established model, rats received RAMT treatment (targeting stroke-affected medial hindlimb) or none (controls, anesthesia only) beginning post-stroke day (PSD)1 and continuing daily through PSD3 or PSD7. Stroke was confirmed with brain MRI, and only animals with consistent MCA-territory infarcts remained in the study. Medial hindlimb muscles were collected for analysis, as well as pair-matched muscles from the non-paretic hindlimb.

Results: RAMT induced expression of anti-inflammatory IL-1Ra while suppressing expression of stroke-induced pro-inflammatory IP10/CXCL10. In our analysis of post-stroke inflammatory cell recruitment, RAMT-treated rats presented with significantly higher numbers of neutrophils infiltrating gastrocnemius tissue at PSD3 compared to untreated controls. Immunohistochemistry also demonstrated an absence of pro-inflammatory M1 macrophages at PSD3 while RAMT prompted a robust reparative M2 macrophage presence by PSD7. Notably, IL-1ra is included in the M2 cytokine release profile. Of further interest, RAMT increased miRNA (miR-22) expression. miR-22 has been shown to target and silence IRF5, a transcription factor of the interferon regulatory factor (IRF) family that induces M1 polarization. Ongoing efforts will further test miR-22 as a potential RAMT-sensitive mediator of functional recovery and its contribution to post-stroke inflammatory cell presentation.

Conclusions: We previously developed RAMT for reproducible, objective, pre-clinical study of post-stroke mechanical therapy. We have shown that stroke induces acute inflammatory changes in skeletal muscle and that RAMT rescues against such pathophysiology. We have also begun to characterize post-stroke inflammatory cell recruitment patterns and identify potential molecular mediators of recovery through RAMT. This work seeks to further our understanding of peripheral stroke disability and ultimately translate to stroke rehabilitation paradigms that expand therapeutic targets and advance patient care.

Preoperative Cytokine Expression is Associated with Perioperative Outcomes after Pancreatectomy

Malcolm H. Squires MD MS, Jeffrey Chakedis MD, Eliza W. Beal MD, Erin Talbert PhD, Denis Guttridge PhD, Timothy M. Pawlik MD PhD MPH, Carl R. Schmidt MD, Mary E. Dilhoff MD

Introduction: Serum levels of various cytokines are related to increased risk of sepsis and inflammation. The association of preoperative cytokine expression with perioperative outcomes after pancreatectomy is unknown.

Methods: Preoperative serum specimens were prospectively collected on patients undergoing pancreatectomy at a single institution from 2013-2015. Enzyme-linked immunosorbent assays (ELISA) quantified serum levels of 27 cytokines. Clinical data were retrospectively analyzed from an institutional database. Primary outcomes included any complication within 30 days and Clavien Grade III-IV major complications. Perioperative risk factors for complications were analyzed by univariate (UV) and multivariate (MV) logistic regression.

Results: 71 patients who underwent pancreatectomy for malignancy had available serum cytokine levels; operative procedures included Whipple (n=43), distal (n=21), and total pancreatectomy (n=7). Diagnoses included pancreatic (n=68) and duodenal adenocarcinoma (n=2) and cholangiocarcinoma (n=1). The incidence of any complication and major complications were 35% and 28%, respectively. On UV analysis, increasing hepatocyte growth factor (HGF) levels were associated with increased risk of complications (Table). On MV analysis accounting for other known clinical risk factors, HGF remained independently associated with increased risk of any complication (OR 2.32, 95% CI:1.03-5.23;p=0.048). IL-4 expression was associated with increased risk of major complications and on MV analysis remained an independent negative prognostic factor (OR 5.69, 95% CI:1.05-12.05;p=0.044).

Conclusions: In patients undergoing pancreatectomy for malignancy, increased preoperative serum HGF and IL-4 levels were independently associated with increased risk of any complication and major complications, respectively. These data may aid in preoperative risk stratification for patients undergoing pancreatectomy.
From Bench to Bedside: Vitamin A Deficiency after Bariatric Surgery and its Impact on Adipocyte Vitamin A Metabolism

Anahita Jalilvand MD, Alecia Blaszczak BS, Bradley Needleman MD, Sabrena Naria MD PhD, Wile Hsuhe MD

Introduction: Adipose tissue (AT) physiology plays an important role in obesity-mediated insulin resistance and diabetes development. Previous studies have shown that AT from obese patients have significantly elevated expression of pro-inflammatory mediators and decreased anti-inflammatory regulatory T cells (Tregs) in comparison to lean counterparts. Following bariatric surgery (BS), many of these changes are reversed, although disruptions in Treg abundance and vitamin A metabolism have been noted. Although vitamin A is known to be an important mediator in regulating inflammation and Treg differentiation, the clinical relevance vitamin A deficiency (VAD) after BS and its impact on adipocyte physiology has not been elucidated. Therefore, the objective of this study was to determine 1) the prevalence of VAD in patients pre and post BS, 2) factors associated with changes in Vitamin A levels, and 3) how BS bariatric surgery may impact adipocyte mediated vitamin A physiology.

Methods: A retrospective review of all patients undergoing BS from 2014-2016 (n=589) was conducted at a single academic center. Demographic and operative data were collected on all patients through review of the electronic medical record. Vitamin A levels (VALs), hemoglobin A1C (hbA1C), albumin levels, and excess body weight (EBW) and percent EBW loss (%EBWL) were obtained preoperatively. This suggests that malnutrition may play a role in the development of VAD. Importantly, prior VAD was associated with VAD at later time points, highlighting the importance of more aggressive vitamin A supplementation. Finally, adipocytes after BS demonstrate changes in vitamin A associated gene expression (CRBP1, 2, 5, Aldh1a, RDH10&12, LRAT, ISX, BCM01) were compared in subcutaneous adipocytes (SAd) obtained from patients at the time of BS and one year post BS (n=21).

Results: The prevalence of VAD was 17.5% preoperatively, 35% 6 months after BS, and 24.9% one year post-operatively. Preoperative VAD was significantly associated with younger age (p=0.04), and trended towards an association with increasing preoperative EBW (p=0.06) and female gender (p=0.08). At 6 months after surgery, increasing %EBW was a negative predictor of vitamin A levels (p=0.03), while albumin level was a positive predictor (p<0.005), when adjusting for age, baseline EBW, and surgery type. One year after BS, albumin levels was the only predictor of vitamin A levels, when adjusting for %EBWL, baseline BMI, and male gender. Prior VAD status was significantly associated with 6 and 12 month VAD status. Vitamin A-associated gene expression in SAd, expression of LRAT, BCM01, RDH10 trended towards a decrease after BS, while total CRBP expression was significantly reduced post-operatively. Alha1a expression, however, trended towards an increase after surgery.

Conclusions: VAD is prevalent in obese patients and increases significantly after bariatric surgery, with a peak prevalence 6 months post-operatively. Albumin was a strong predictor of Vitamin A levels 6 and 12 months after BS, while %EBWL was a significant negative predictor of VALs six months post-operatively. This suggests that malnutrition may play a role in the development of VAD. Importantly, prior VAD was associated with VAD at later time points, highlighting the importance of more aggressive vitamin A supplementation. Finally, adipocytes after BS demonstrate changes in vitamin A associated gene expression that are consistent with a disruption in vitamin A physiology and metabolism.

Higher frequency of IFN-γ-CD8+ T cells correlate with reduced risk of humoral alloimmunity posttransplant

Matthew W. Bosinger BS, Jason M. Zimmerman PhD, Bryce A. Ringwald BS, Robert T. Warren, Ronald P. Pelletier MD, Amer Rajab MD PhD, Ashraf El-Hinnawi MBBS, Mahmoud Abdel-Rasoul MS MPH, Hemant Perekh, Ginny L. Bumgardner MD PhD

Introduction: Kidney transplant is the optimal treatment for patients with end stage renal disease to increase patient survival and quality of life. While advances in immunosuppression have reduced the incidence of acute cellular rejection and short-term graft survival has improved over the last 20 years, long-term survival of kidney allografts remains unchanged. Clinical data supports a pathogenic role of MHC-directed alloantibody in acute and chronic rejection posttransplant and higher levels of donor-specific antibody (DSA) correlate with poor graft outcome. Our group has discovered a novel subset of DSB T cells in mice, which express IFN-γ and negatively regulate alloantibody production by killing B cells and downregulating Th1 (IFN-γ+) and Th2 (IL-4+) CD4+ T cells. Based on the foundation of our experimental data, we hypothesized that antibody-suppressing CDB- T cells exist in human kidney transplant patients and that their frequency inversely correlates with the risk for development of posttransplant DSA. This is the first prospective study correlating T cell subsets with posttransplant de novo DSA production.

Methods: Participants were first time kidney transplant patients at OSU who were DSA-negative prior to transplant and treated on standard immunosuppression therapy per OSU Comprehensive Transplant Center Protocol. Blood specimens were analyzed by OSU Tissue Typing Laboratory to determine DSA status. Peripheral blood from each patient was analyzed at months 0, 1, 3, 6, 9, and 12. PBMCs were isolated, washed, and stained for extracellular and intracellular markers. This study was reviewed and approved by the OSU Wexner Medical Center IRB (IRB 211H0256). All study participants consented to participation through written informed consent.

Results: Of 42 recipients, ten (23.8%) developed DSA (average 6.5±2.2 months posttransplant). Distinct immune profiles were observed prior to DSA development in patients who later developed DSA, including significantly fewer peripheral IFN-γ-CD8+ T cells (~2-fold lower at month=1,3,9, p<0.04) and increased frequency of IL-4+CD4+ T cells (~2-fold higher at months=3,6, p<0.04) and IFN-γ-CD4+ T cells (~2-fold higher at months=0,1,3,9, p<0.02) were significantly lower in recipients that became DSA-positive compared to those who remained DSA-negative. At one-year posttransplant, DSA-positive recipients have significantly higher serum creatinine (2.1±0.3mg/dl, p=0.01) compared to DSA-negative patients (1.5±0.7mg/dl). There was no difference in infection rates, immunosuppression regimen, or total CD4- and CD8- T cells between DSA-positive and DSA-negative groups.

Conclusions: Our data supports the hypothesis that antibody-suppressing IFN-γ-CD8+ T cells exist in humans and serial monitoring of the ratio of IFN-γ-CD8+ T cells to IL-4-CD4+ T cells and IFN-γ-CD4- T cells may be predictive of de novo DSA production.
Targeted Activation of Innate Immune Cells with Antibody Conjugated Fluorescent Nanodiamonds

Lorena P. Suarez-Kelly MD, Isaac V. Rampersaud, David Albertson, Eric Morris, Tiffany C. Noel, Niathaniel J. Buteyn BS, Jonathan P. Butchar PhD, Lianbo Yu PhD, Vedat O. Yildiz MS, Nicholas Courtney, Casey Ren BS, Susheela Tridandapani PhD, Arfaan A. Rampersaud PhD, and William E. Carson III MD

Introduction: Fluorescent nanodiamonds (FNDs) are nontoxic, infinitely photostable, emit near infrared fluorescence and have a modifiable surface chemistry that allows for generation of protein FND conjugates. Natural killer (NK) cells and monocytes detect and destroy cancerous cells through the process of neoplastic immunosurveillance. FND mediated immune cell activation may serve as a strategy to enhance anti-tumor activity and promote immune cell visualization.

Methods: Uncoated FNDs (u-FND) were fabricated and then conjugated with glycidol (a chemical linker, g-FND) or immunoglobulin G (IgG-FND). In vitro cellular FND uptake, viability, surface markers of activation and cytokine production in a breast cancer/NK/monocyte co-culture system were evaluated. Intratumoral FND delivery and fluorescence emission was evaluated in a breast cancer mouse model.

Results: On flow cytometry, u-FND uptake was seen in both tumor cells (SKBR3 and EMT6) and immune cells, with monocytes having the highest uptake overall. There was increased uptake of IgG-FND compared to g-FND by monocytes (p=0.004) and NK cells (p<0.001). In co-culture, FNDs were preferentially taken up by monocytes compared to NK cells or SKBR3 cells (p<0.001). Confocal microscopy localized FND uptake to the cytoplasm. FND treatment did not affect immune cell viability. There was increased surface expression of CD69 and NKG2D activation markers in FND-treated NK cells compared to untreated (p<0.001 and p=0.013, respectively) or IgG-treated (p<0.001 and p<0.016, respectively) NK cells. In co-culture, IgG-FND treatment significantly enhanced monocyte TNF-α production and NK cell IFN-γ production compared to untreated (p<0.015 and p<0.036, respectively) or IgG-treated (p=0.028 and p=0.011, respectively) immune cells. In vivo, IgG-FNDs were visualized intratumorally for a longer duration compared to u-FNDs. On necropsy, mice treated with u-FNDs demonstrated increased liver fluorescence compared to mice treated with IgG-FNDs.

Conclusions: FND conjugation with IgG enhanced FND uptake and immune cell activation with no effect on cell viability. FNDs were well-visualized following intratumoral injection and remained within the tumor. Fluorescent nanodiamonds can be conjugated to antibodies, or other immunomodulatory agents, and thereby targeted to innate immune cells to promote directed anti-tumor activity. Additionally, fluorescent nanodiamonds have the potential to serve as a targeted immune drug delivery vehicle with “track and trace” capabilities.
Epithelial hypoxamir MIR-210 directly contributes to ischemic skin injury

Ayan Biswas PhD, Subhadip Ghatok PhD, Mohamed El Masry MD, Savita Khanna PhD, Sashwati Roy PhD and Chandan K. Sen PhD

Introduction: Chronic wounds are commonly associated with peripheral vasculopathies. Limitations in the ability of the vasculature to deliver O2-rich blood to the wound tissue leads to, among other consequences, hypoxia. Thus, hypoxia is a subset of ischemia. Hypoxia inducible microRNAs, or hypoxymiRs play a significant role in determining outcomes following ischemic insult. miR-210 is widely regarded as a master hypoxymiR.

Methods: To determine the significance of keratinocyte specific miR-210 during ischemic injury, an animal model with keratinocyte specific knockout of miR-210 (K14cremiR-210Δ/Δ) was developed by crossbreeding mice carrying floxed miR-210 allele (miR-210fl/fl) with tamoxifen inducible K14-Cre mice. A mono-pedicle flap was developed on the back of the mice by making 30-mm-long full-thickness parallel incisions 10 mm apart. Flap edges were cauterized and then sutured to the adjacent skin. Epithelial keratinocytes were collected using Laser Capture Microdissection (LCM) from the skin flap.

Results: Significant knockdown (~50%) of miR-210 was noted in the skin epithelium of the K14cremiR-210Δ/Δ mice compared to their wildtype littermates. Using mono-pedicle model of graded ischemia, induction of miR-210 was dependent on the extent of lack of blood flow at d3 post-surgery. The extent of ischemia was categorized by dividing the flap into three parts (proximal, intermediate and distal). The level of ischemia gradually increased from the proximal to the distal part. Similar finding was observed for miR-210 abundance in LCM-captured epithelium pointing towards the involvement of keratinocytes. Interestingly, miR-210 was elevated, potentially contributed by inflammatory cells, in the distal region of the flap in the K14cremiR-210Δ/Δ. Furthermore, K14cremiR-210Δ/Δ mice showed increased perfusion 3 days after mono-pedicle ischemic flap surgery compared to that of the wildtype. Such advantage in blood flow caused flap survival in K14cremiR-210Δ/Δ mice.

Conclusions: Inhibition of keratinocyte specific miR-210 in the ischemia-affected limb is an effective therapy strategy to improve ischemic chronic wound outcomes.

Reversible stenosis in a juvenile lamb model of tissue-engineered vascular grafts

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Introduction: Tissue-engineered vascular grafts (TEVGs) provide a promising option for repair of congenital heart defects, but are hampered by stenosis. In an American clinical trial of TEVGs as extracardiac Fontan conduits, 3 of 4 patients developed critical stenosis within the first year and underwent successful balloon angioplasty. A comparison to Japanese TEVG outcomes suggests that the threshold for angioplasty in the United States may have been too low. Our objective was to determine the natural history of neotissue formation in a previously-validated large animal model of TEVG stenosis.

Methods: Bone marrow (5 ml/kg) was aspirated from the iliac crest of juvenile lambs, and the mononuclear cell (BM-MNC) fraction was isolated by Ficoll separation. Size-matched polyglycolic acid/polydioxanone and polyactic acid (PGA/PCLA) scaffolds were vacuum-seeded with BM-MNC and implanted as 2 cm intrathoracic inferior vena cava interposition grafts. Laminar velocimetry was assessed with angiography, intravascular ultrasound (IVUS), and hemodynamic pressure monitoring at a baseline of 1 week postoperatively, followed by serial imaging at 6 weeks, 6 months, and 1 year. No endovascular interventions were performed. Histology and immunohistochemistry were performed following graft explantation.

Results: TEVGs (14-18 mm nominal diameter) were implanted in 24 juvenile lambs, two of whom died in the perioperative period (8% mortality). Invasive imaging was performed at 1 week (n = 22), 6 weeks (n = 22), 6 months (n = 20), and 1 year (n = 10). At 1 week, the midgraft measured significantly less than the nominal graft size (mean decrease of 3.8 mm by angiography, p < 0.001; 5.6 mm² by IVUS, p < 0.0001). The narrowest point of the graft decreased significantly from 1 to 6 weeks (-4.7 mm compared to nominal diameter at 1 week vs. -10.4 mm at 6 weeks by angiography, p < 0.001; -62.9 mm² vs. -163.5 mm² by IVUS, p < 0.001), with a corresponding increase in mean pressure gradient (0.5 mmHg at 1 week vs. 11.8 mmHg at 6 weeks, p < 0.001). Stenosis resolved spontaneously over time. By 1 year, there was no significant difference from the baseline measurements (-5.1 mm at 1 year vs. -4.7 mm at 1 week by angiography, p = 0.99; -84.4 mm² vs. -62.9 mm² by IVUS, p = 0.97; mean pressure gradient 0.8 mmHg vs. 0.5 mmHg, p = 1). Only 9% of animals developed critical graft stenosis (symptomatic with narrowest point < 4 mm by angiography and mean pressure gradient > 19 mmHg) and would have been candidates for intervention.

Conclusions: Short-term tissue-engineered vascular graft stenosis is spontaneously reversible. Critical stenosis is rare, and only seems to occur with more substantial narrowing than was previously appreciated. Together, these findings suggest that TEVGs should be treated differently than synthetic conduits, and that traditional angioplasty criteria should be modified for TEVGs.

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Design and test of targeted lipid-nanoparticles in burn wound care

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Introduction: Active-targeted lipid nanocarriers minimize off-target effects. Transferrin-conjugation strategy serves that purpose but may not be well suited for non-cancer applications such as wound. In wounds, although skin barrier function is breached, abundance of inflammatory cells at the site of injury poses a major challenge for delivery. Phagocytic clearance of nanoparticles is a threat.

Methods: Novel lyophilized keratinocyte-targeted nanocarriers (TLNκ) were designed and loaded with anti-miR to test efficacy in treating cutaneous burn injury. TLNκ employed DOTAP/DODAP combination pH-responsive lipid components to improve endosomal escape. Keratinocyte-targeting was achieved using the peptide sequence ASKAIQVFLLAG. To minimize interference of clearance by non-targeted cells, especially immune cells in the acute wound microenvironment, surface charge was neutralized. Lyophilization extended shelf life of these nanoparticles.

Results: Encapsulation efficiency of anti-miR in lyophilized TLNκ was 96.54%. Cargo stability of lyophilized TLNκ was tested. After 9 days of loading with anti-miR-210, TLNκ was effective in lowering abundance of the hypoxamiR miR-210 in keratinocytes challenged with hypoxia. Keratinocyte uptake of DiD-labelled TLNκ/anti-miR-107 was selective and exceeded 90% within 4h. Topical application of hydrogel-dispersed lyophilized TLNκ/anti-miR-107 encapsulating LNA anti-miR-107 twice a week effectively sequestered keratinocyte miR-107. On day 24, the wound area in TLNκ/anti-miR-107 treated group was reduced to 4% of the initial wound area. Barrier function of the skin, a functional measure of wound closure, as measured by trans-epidermal water loss was restored. Application of TLNκ/anti-miR-107 depleted miR-107 and upregulated dicer expression causing differentiation of keratinocytes. Expression of junctional proteins such as claudin, loricrin, filaggrin, ZO-1 and ZO-2 were significantly upregulated following TLNκ/anti-miR-107 treatment.

Conclusions: The nanoparticles reported herein are promising as topical therapeutic agents in the management of burn injury. A translational advantage of TLNκ is that all material used for its formulation has prior history of FDA approval for human use.

Stop flying the patients! Helicopter transport of trauma patients is over utilized and increases cost unnecessarily

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Introduction: Helicopter transport of trauma patients is significantly more expensive than ground transportation. Air transport has the theoretical advantage of allowing patients to receive injury treatment more quickly. However, there are no defined criteria for which patients require time-sensitive interventions and patients are frequently transported by helicopter based on imprecise field or referring hospital triage. This study examines the appropriateness of all trauma patients transported by helicopter to an urban level 1 trauma center.

Methods: All trauma patients transported by helicopter from January 2015-December 2017 to an urban level 1 trauma center from referring hospitals or the scene were analyzed for need for any procedure or operation to treat injuries. For patients requiring a procedure during their hospitalization, time from arrival to the trauma center to first procedure was recorded. Patients were also reviewed for their level of trauma activation as well as destination (floor, OR, ICU, home, 23-hour observation) from the trauma bay. Descriptive statistics were performed to determine the need for emergent helicopter transport.

Results: 1584 trauma patients were transported by helicopter during the three-year study period. Only 36% of patients (n=563) required a procedure/operation to treat their injuries. 31% of patients (n=505) were Level 1 activations, 61% patients (n=960) were Level 2 activations, and 8% (n=119) were not trauma activated. 28% of patients were admitted directly to the ICU, 19% went directly to the OR from the trauma bay, 33% were admitted to the floor, 7% were admitted to the observation unit, 7% were discharged home, and 6% other (nursing home, AMA, rehab, etc.). For patients requiring a procedure, the mean time to first procedure was 18.5 hours. Only 11% of patients (n=18) underwent an intervention within the first hour of their arrival to the trauma bay.

Conclusion: This analysis demonstrates that helicopter transport was not necessary for the majority of trauma patients as they did not meet Level 1 trauma activation and did not require emergent interventions to treat injuries. The cost of transport cannot be justified, and stricter selection is necessary to determine which patients should be transported by helicopter.
Use of Quality Improvement (QI) Methodology to Decrease Length of Stay (LOS) for Newborns with Uncomplicated Gastrochisis

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Introduction: Gastrochisis is a congenital defect of the abdominal wall leading to considerable morbidity and long hospitalizations. The purpose of this study was to use quality improvement methodology to standardize care in the management of gastrochisis that may contribute to length of stay (LOS).

Methods: A gastrochisis quality improvement team established a best-practice protocol in order to decrease LOS in infants with uncomplicated gastrochisis. Uncomplicated gastrochisis was defined as gestational age at the time of delivery >34 weeks from date of last menstrual period, without evidence of intestinal atresia, stenosis, perforation, volvulus, or short bowel syndrome, and without other major congenital anomalies. Members of pediatric surgery, neonatology, nursing, and quality improvement formulated the guidelines based on current evidence-based practices. These guidelines included delivery recommendations, initial resuscitation targets, antibiotic algorithms, analgesia recommendations, feeding pathways, and discharge planning. The type of surgical closure was left to the discretion of the surgeon and included: bedside silo placement, silo placement in the operating room, and primary surgical closure. The specific aim was to decrease median LOS from a baseline of 34 days. We used statistical process control charts including rational subgroup analysis to monitor LOS.

Results: From December 2008 to December 2016, 114 patients with uncomplicated gastrochisis were evaluated. Retrospective data was obtained on 25 patients prior to protocol implementation. Ninety-three patients with uncomplicated gastrochisis comprised the prospective process stage. The median LOS for this retrospective cohort was 34 days (IQR: 30.5-50.5), while the median LOS for the prospective cohort following implementation of the protocol decreased to 29 days (IQR: 23-43). Due to a temporal shift in surgical practice during the study period, bedside silos were not placed in any patients during the period of the retrospective review, but is the current preferred method of initial treatment for infants with uncomplicated gastrochisis. There were several subgroup differences noted in the prospective cohort. Median LOS was significantly shorter for patients undergoing bedside silo placement (28.0 days, IQR: 22.0-35.5) compared to patients undergoing operative silo placement (43.0 days, IQR: 29.3-60.8) (p=0.001). Similarly, median LOS for patients undergoing primary closure (270 days, IQR: 210-378) was significantly shorter than for patients undergoing operative silo placement (p=0.003).

Conclusions: With the use of quality improvement methodology, including standardization of care and a change in surgical approach, the median LOS for newborns with uncomplicated gastrochisis at our institution decreased from 34 days to 29 days. Future steps to continue to decrease LOS and improve quality care for these infants include protocol modification for preferential bedside silo placement as the default initial surgical management, and tracking protocol compliance real time with electronic order sets to determine potential areas of improvement.

The role of a multidisciplinary tumor board in management of patients with pancreatic cystic lesions

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Introduction: The incidental discovery of pancreatic cystic lesions is becoming more frequent in recent years due to the increased use of axial imaging. Some of these lesions carry a risk of progression to malignancy, which makes proper diagnosis and management of these patients very important. We sought to examine whether case presentation to a multidisciplinary tumor board was associated with changes in working diagnosis and care plan of patients with pancreatic cystic lesions.

Methods: Retrospective chart review was performed for all patients presented to our institution’s multidisciplinary tumor board with a pancreatic cystic lesion from 2012-2015. Patients were divided into six categories based upon presenting lesion type. Pre-discussion diagnosis and care plan were compared to post-discussion diagnosis and plan. Corresponding change in diagnosis and plan were examined according to lesion type. We graded each change in plan as 1, 2 or 3 based on severity of change. Grade 1 was a change in follow-up length or imaging schedules, grade 2 for a change in diagnostic studies or treatment regimen, and a grade 3 was for a change in surgical recommendations. Changes in care plan were also determined to be either more or less aggressive when compared to pre-discussion plan. Standard descriptive statistical methods were employed.

Results: A total of 208 cases were presented to the tumor board representing 169 unique individuals who met study criteria. Types of lesion included branch-duct intraductal papillary mucinous neoplasm (BD-IPMN) (32.7%), serous cystadenoma (44.4%), main-duct IPMN (MD-IPMN) (13.9%), pseudocyst (5.8%), mucinous cystic neoplasm (MCN) (3.8%), and unknown cystic lesions (29.3%). Overall, post-tumor board diagnosis differed from preliminary 96% of the time, varying from unknown cystic lesion (23.0%), MCN (12.5%), BD-IPMN (5.9%), and serous cystadenoma (3.3%) (P=0.002). Tumor board recommendations differed from the initial care plan for 44.2% of cases, with 66.3% of these recommendations actually being implemented. Care plan change occurred most frequently with patients who presented with a preliminary diagnosis of serous cystadenoma (60%) followed by unknown cysts (55.7%), MD-IPMN (41.4%), MCN (37.5%), pseudocyst (33.3%) and BD-IPMN (30.9%) (P=0.034). Grade of change frequency differed from preliminary 9.6% of the time, varying from unknown cystic lesion (23.0%), MCN (12.5%), BD-IPMN (5.9%), and serous cystadenoma (3.3%) (P=0.002). Grade of change frequency was roughly equal, with a grade 3 change occurring 37% of the time, and grade 1 and 2 at 31.5% each. Of the tumor board care plan changes, 64.8% were to a more aggressive option.

Conclusions: Presentation to the tumor board is associated with a change in both diagnosis and treatment plan in a number of cases, suggesting that tumor board discussion has a substantial effect on patient care for individuals with pancreatic cystic lesions.
Nanotechnology-driven platforms to study and target myeloid-derived suppressor cells in cancer

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Introduction: The tumor microenvironment is characterized by its heterogeneity. Besides malignant cells, it also contains stromal and specialized immune cells, such as myeloid derived suppressor cells (MDSC). Such complex cellular interplay has been known to play a key role in modulating tumor progression. MDSCs in particular, provide immunosuppressive activity that protects the tumor from the host immune system (and other therapies), thus favoring tumor progression. As MDSCs continue to draw significant interest from the scientific and medical communities, new tools capable of probing behavioral singularities at the single-cell level are needed in order to better understand and counteract the mechanisms by which these cells escape from the circulation to reach the primary tumor and exert immunosuppression. Here we introduce a new nanotechnology-enabled strategy for in situ probing of MDSCs based on the implementation of single-clone biomimetic motility assays. Moreover, we will discuss the development of novel strategies for therapeutic targeting of MDSCs based on designer extracellular vesicles (EVs).

Methods: Biomimetic polydimethylsiloxane (PDMS) micro/nanotextured surfaces were fabricated from photolithographically patterned silicon masters via replica molding. MDSCs (cell line and patient-derived) were seeded on the PDMS surfaces, and single-clone migration was monitored for 24h. Designer EVs were obtained via nanochannel-based non-viral transfection of donor cells. Such cells were transfected with plasmids encoding for MDSC-targeting ligands (ICAM-1), and MDSC-suppressive miR146a. Such an approach allowed us to derive EVs decorated with ICAM-1, and loaded with miR146a.

Results: We were able to use nanotextured surfaces to study MDSC migration with single-clone resolution. MDSCs exhibited significant intra- and inter-population differences in motility capabilities (e.g., velocity, persistence and total traveled distance), indicating the presence of multiple sub-populations with presumably different myelosuppressor activity. Velocities ranged from <5 µm/h to >40 µm/h. Flow cytometry analyses further confirmed the presence of multiple sub-populations, and subsequent migration studies on nanotextured PDMS indicate that indeed each subpopulation exhibits a characteristic migratory signature. Single cell analyses uncovered a clonal subset with superior motility compared to the bulk MDSC population, which exhibited a diverse phenotype with granulocytic and monocytic subtypes. Unclassified subtypes exhibiting either low or high Ly6-C/G were also present. Preliminary studies with designer EVs indicate that our method allowed us to derive ~10^{13} designer EVs/ml from primary cultures of dendritic cells. qRT-PCR analysis of the EV content suggest a ~400-fold loading of miR146a compared to control EVs (i.e., EVs derived from cells transfected with sham/mock plasmids). In addition, experiments using ICAM-1 decorate the EVs show preferential internalization by MDSCs compared to cancerous cells (i.e., A549). Therefore, these data indicate cells could conceivably be used as “biofactories” to synthesize designer EVs that can selectively target MDSCs and deliver therapeutic payloads against these cells.

Conclusions: Our study demonstrated that nanotextured PDMS surfaces successfully allowed the identification of different MDSC subpopulations of potential therapeutic interest. Moreover, we showed the possibility of using designer EVs to targetedly deliver therapeutics to MDSCs within the tumor niche. Ongoing studies are focused on evaluating targeted designer EV delivery to MDSCs in murine models of breast cancer (i.e., PyMT mice).
Stabilized collagen matrix dressing improves wound macrophage function and epithelialization

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Introduction: Naturally derived biomaterials such as decellularized matrix of biological tissue have performed very well as wound care dressings. Such dressings present the advantage of native extracellular matrix. However, the challenge faced by any ECM-based wound care dressing product is their rapid degradation by the excessive MMPs and other proteases present in the wound environment. Stabilized, acellular, equine pericardial collagen matrix (sPCM) wound care dressing is flexible cross-linked proteolytic enzyme degradation resistant.

Methods: The dressing was structurally characterized utilizing scanning electron and atomic force microscopy. Two rectangular (8×16 mm) full-thickness excisional wounds were made on dorsal skin of each mouse of 8 weeks old C57BL/6 mice, sPCM applied on one side and the other side of dorsal wound was covered with semi occlusive dressing (Tegaderm™) as a control for 14 days. Then immunohistochemical and Herovichi staining of the collected tissues were done. The concentration of IL-1β, TNF-α, VEGF, and IL-10 cytokines in wound tissues were quantified using ELISA. PVA (polyvinyl alcohol) sponges were implanted subcutaneously in the back of another 2 groups of C57BL/6 mice. Polycarbonate membrane served as a control to the sPCM, and cells were harvested on day 3 and day 7 post implantation. Macrophages were selected via CD11b magnetic bead isolation. Apoptotic cell clearance assay was conducted using wound macrophages co-cultured with thymocytes ex vivo. Expression of inflammatory markers was measured using qPCR from d3 macrophages, and the data is presented as mean ± SD .n=5,*p<0.05.

Results: In murine excisional wounds, sPCM was effective in mounting the acute inflammatory response. sPCM stimulated an early, robust recruitment of activated macrophages to wound site. Post-wound inflammation resolved rapidly as indicated by elevated levels of IL-10, arginase-1 and VEGF, and lowering of IL-1β and TNFα. sPCM induced antimicrobial proteins S100A9 and β-defensin-1 in keratinocytes (n=5, *p<0.05). Such upregulation of AMPs in keratinocytes adhered to sPCM provide effective defenses against bacterial colonization and wound infection. Adherence of Pseudomonas aeruginosa (PA01) on sPCM pre-exposed to host immune cells in vivo was inhibited. Excisional wounds dressed with sPCM showed complete closure at day 14 while control wounds remained open. sPCM accelerated wound re-epithelialization. sPCM not only expedited wound closure but improved the quality of healing by increased collagen deposition and maturation.

Conclusions: Taken together, the naturally derived biomaterial sPCM is a single application collagen-based wound dressing that is capable of presenting scaffold functionality during wound healing, potently induces endogenous antimicrobial defense systems and supports the healing process through accelerated epithelialization, improved collagen deposition and enhanced immune responses. It mounts robust inflammation, a process that rapidly resolves making way for wound healing to advance. Randomized clinical trial testing this promising dressing material in a clinical setting is warranted.

Ossabaw pigs as a natural preclinical model of metabolic syndrome and impaired wound healing

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Background: Infected chronic wounds in the metabolic syndrome (MetSyn) patients represent a major public health burden. The current study recognizes Ossabaw swine as a powerful pre-clinical experimental model to study mechanisms of impaired wound healing under conditions of metabolic syndrome.

Hypothesis: High fat diet induced MetSyn in Ossabaw pigs impairs wound healing.

Methods: Ossabaw pigs (n=20) were fed either high fat diet (HFD, n=15) or standard chow for 8 months. Blood parameters of the Ossabaw pigs were measured monthly. Following 8 months of diet, full thickness (2”×2”) excisional wounds were created on the dorsum of the pigs that were infected with 10^8 cfu/ml of mixed species of Pseudomonas aeruginosa (PA01), Staphylococcus aureus (USA300) and Acinetobacter baumannii (19606) strains. The infected wounds were followed up to day 31 post-wounding.

Results: The HFD Ossabaw pigs developed pre-MetSyn symptoms including dyslipidemia, abdominal obesity and high blood pressure. Insulin and glucose levels were slightly elevated. Excisional wounds of the Ossabaw pigs on HFD showed increased expression of adipocyte marker perilipin in the granulation tissue indicating that the wounds were closed primarily by subcutaneous fat. Pigs on HFD showed exaggerated and persistent inflammation in their wounds. Furthermore, HFD pigs showed lower abundance of endothelial cells in the granulation tissue pointing towards impaired vascularization (n=4, p<0.05). Masson's trichrome staining of the wound bed showed reduced collagen vascularization (n=4, p<0.05). Masson's trichrome staining of the wound bed indicated that the wounds were closed primarily by subcutaneous fat. Pigs on HFD showed exaggerated and persistent inflammation in their wounds. Furthermore, HFD pigs showed lower abundance of endothelial cells in the granulation tissue pointing towards impaired vascularization (n=4, p<0.05). Masson's trichrome staining of the wound bed showed reduced collagen vascularization (n=4, p<0.05). Masson's trichrome staining of the wound bed showed reduced collagen vascularization (n=4, p<0.05). Masson's trichrome staining of the wound bed showed reduced collagen vascularization (n=4, p<0.05). Masson's trichrome staining of the wound bed showed reduced collagen vascularization (n=4, p<0.05). Masson's trichrome staining of the wound bed showed reduced collagen vascularization (n=4, p<0.05). Masson's trichrome staining of the wound bed showed reduced collagen vascularization (n=4, p<0.05). Masson's trichrome staining of the wound bed showed reduced collagen vascularization (n=4, p<0.05). Masson's trichrome staining of the wound bed showed reduced collagen vascularization (n=4, p<0.05).

Conclusion: HFD induced MetSyn in Ossabaw pigs with characteristics comparable to clinical outcomes. Specific mechanisms of cutaneous wound healing were compromised offering an outstanding opportunity to study the cellular and molecular bases of such impairment.

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Antibody-suppressing CD8+ T cells require IFN-γ/IFN-γR interactions for effector function development

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Introduction: Antibody-mediated rejection continues to threaten allograft survival despite reduction in rates of cell-mediated rejection. We have discovered novel antibody-suppressing CD8+ T cells, CD8+ TAbsupp cells, that kill alloprimed B cells (FasL- and perforin-dependent mechanism) and inhibit IL-4+CD4+ T cells (IFN-γ-dependent mechanism). Further studies to understand the developmental requirements of CD8+ TAbsupp cells will be critical to investigate novel cell-based therapies. Interestingly, CD8+ T cells from IFN-γ KO recipient mice do not exhibit CD8+ TAbsupp cell characteristics including cytotoxic killing of alloprimed B cells. We hypothesize that CD8+ TAbsupp Cell maturation or cytotoxic functions directly depends on IFN-γ/IFN-γR interactions.

Methods: In vivo studies in which CD8+ T cells from wild-type, IFN-γ KO, or IFN-γR KO mice adoptively transferred into wild-type, IFN-γ KO, or IFN-γR KO hepatocyte transplant recipients were assessed for CD8+ TAbsupp cell development and cytotoxic molecules.

Results: While there were no significant changes in the total number of CD8+ TAbsupp cells, initial studies show an abrogation of FasL+CD8+ TAbsupp cells when CD8+ T cells are deficient in IFN-γ, a 4-fold reduction of FasL-CD8+ TAbsupp cells and a 2-fold reduction of IFN-γ+CD8+ TAbsupp cells when host mice are deficient in IFN-γ, and a 2-fold reduction of IFN-γ+CD8+ TAbsupp cells when host mice are deficient in IFN-γR.

Conclusions: To date our data strongly suggests that antibody suppressing CD8+ T cells require IFN-γ/IFN-γR interactions for development of effector function posttransplant. Further analysis and repeat studies are needed to confirm these results and to explore specific cellular interactions critical for CD8+ TAbsupp cell development.

How well are we really doing since the NETT? Results of a high-volume single academic Lung Volume Reduction (LVRS) Program

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Objectives: Lung Volume Reduction Surgery (LVRS) was first used over 60 years ago as a treatment for patients with moderate to severe emphysema. The National Emphysema Treatment Trial (NETT) showed a clear survival and quality of life benefit for carefully selected patients that undergo LVRS. However, individualized program approaches and outcomes to this patient population still require ongoing evaluation as the number of centers performing the surgery decline. The aim of this study is to evaluate overall mortality and functional improvement in the largest single institutional cohort of patients undergoing LVRS.

Methods: A single institution registry was queried to identify all patients who had undergone LVRS from January 2006 through August of 2017. Records were retrospectively reviewed, and data was collected to include pulmonary functions test values, shortness of breath questionnaire (SOBQ, specifically, the University of California, San Diego SOBQ), complications, post-operative complications (POC) and mortality.

Results: LVRS was performed in 135 patients with a 2.2% 90-day mortality rate (n=3). There was a 36.3% total POC rate (n=49). Over 91% (n=123) of patients were discharged to home with a median length of stay 8 days (IQR 6.0 to 11.5). There was an estimated 1-year survival of 0.94 (95% CI 0.88 to 0.97), 2-year survival of 0.91 (95% CI 0.83 to 0.95), and 5-year survival of 0.71 (95% CI 0.57 to 0.81). There was a mean improvement from baseline at time of LVRS in FEV1% predicted from baseline at the time of LVRS surgery of 5.27 (95% CI 3.15 to 7.39, p<0.001) at 1-year and 4.28 (95% CI 1.94 to 6.62, p<0.001) at 2-years post-LVRS. There was no significant improvement seen in FEV1% predicted at 5-years. There was a mean increase of 5.07 watts (95% CI 0.77 to 9.38, p=0.02) in maximum workload was seen after one year, with no significant increase from baseline seen after 2- or 5-years post LVRS. There was also a significant improvement in SOBQ scores with mean decrease of 22.4 points (95% CI 18.69 to 26.20, p<0.001), 19.5 points (95% CI 15.59 to 23.36, p<0.001), 8.0 points (95% CI 2.86 to 13.20, p<0.003) at 6-months, 1-, and 2-years respectively with no significant improvement at 5-years post-LVRS.

Conclusions: There was an overall improvement in functional status and quality of life outcomes after LVRS. These findings, in conjunction with an overall low mortality, a reasonable complication rate and home disposition allow us to conclude that LVRS can still be safely recommended to patients who fit selection criteria for operative intervention.
Practices and perceptions among surgical oncologists in the perioperative care of obese cancer patients

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Introduction: Obesity and cancer are two common diseases in the United States. Although a great deal is known about the interaction of obesity and cancer, little is known about surgeons’ perceptions and practices in the care of obese cancer patients. We surveyed surgical oncologists to understand perceptions and practices in the care of obese cancer patients.

Methods: A cross-sectional survey methodology was used. This investigator-designed survey was generated. A commercially available e-mail list of surgical oncologists was used to identify participants and an online survey platform used for survey distribution. Statistical analyses were completed using SPSS.

Results: Of the 1,731 electronic invitations, 172 recipients initiated the survey and 157 submitted responses (response rate 91.2% among surgeons who opened email invitation). Many surgeons (65.7%) believed obese patients are more likely to present with more advanced cancers and were more likely than systemic factors to explain this delayed treatment (t(87)=4.84, p<0.001). Nearly 2/3 of providers (64.5%) reported that obese had no impact on the timing of surgery, however 1/3 of respondents (34.2%) were more likely to recommend preoperative non-surgical therapy rather than upfront surgery among obese patients. For both operations of the chest/abdomen and those involving the breast/soft tissue, surgeons thought obesity was a stronger risk factor of post-operative than intra-operative complications (chest/abdomen mean 4.13 vs. 3.26, p<0.001; breast/soft tissue 4.11 vs. 2.60, p<0.001).

Conclusions: This is the first study to evaluate surgeons’ perceptions and practices related to obese cancer patients. Further research is necessary to completely explore implicit and explicit anti-obesity biases among surgeons understand their effect on medical decision-making and surgical outcomes.

Laparoscopic gastric devascularization reduces anastomotic complications following minimally invasive esophagectomy

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Introduction: Laparoscopic gastric devascularization (LGD) is an innovative method to improve gastric perfusion and optimize anastomotic healing following esophagectomy. This study evaluates the impact of LGD on outcomes following minimally invasive esophagectomy (MIE).

Methods: We performed a retrospective cohort study from 2011-2017 of patients who underwent MIE with (n=118) and without (n=27) LGD. LGD was performed two weeks prior to MIE. The primary outcome metrics were anastomotic leak and stricture rates. Secondary outcomes included length of stay (LOS), and discharge disposition according to an established enhanced recovery pathway.

Results: The groups did not differ in terms of patient characteristics or use of neoadjuvant radiation therapy. MIE was completed successfully in 94% of patients with an R0 resection rate of 96% and median lymph node yield of 18.5 (15-23), and these did not differ between groups. Operative mortality was 3.7% (n=1) and 1.7% (n=2) for MIE and MIE with LGD respectively (p=0.51). The rate of anastomotic leak was significantly decreased in MIE with LGD compared to MIE (3.4% vs. 22.2%, p<0.01) as were rates of anastomotic stricture (2.5% vs. 11.1%, p=0.04), and overall complications (30.5% vs. 70.4, p<0.05). Patients undergoing MIE with LGD also demonstrated significantly decreased LOS (8 vs. 11.5, p<0.01), and increased discharge to home versus an extended care facility (94.9% vs. 81.5, p<0.01).

Conclusions: MIE with LGD performed 2 weeks prior is associated with decreased anastomotic complications, including anastomotic stricture and leak rate, as well as decreased complications overall compared to MIE alone. Furthermore, patients undergoing MIE with LGD had significantly decreased hospital LOS and were more likely to be discharged home after surgery. These findings suggest that LGD not only improves surgical outcomes after MIE, but it also facilitates a faster and safer post-operative recovery.
Truncated Anoctamin 5 expression in a CRISPR-engineered mutant rabbit model results in the development of muscular dystrophy

Yeh Siang Lau PhD, Tingting Sui PhD, Li Xu PhD, Di Liu PhD, Tingjun Liu PhD, Yandi Gao MS, Liangxue Lai PhD, Zhanjun Li PhD, Renzhi Han PhD

Introduction: Limb girdle muscular dystrophy type-2L (LGMD2L) and Miyoshi myopathy type 3 (MMD3) are autosomal recessive diseases caused by mutations in the gene encoding anoctamin-5 (Ano5), which belongs to the anoctamin protein family. Studies from our group and others have previously shown that complete ablation of Ano5 expression in mice did not recapitulate human muscular dystrophy. Many of the Ano5-related patients carry nonsense mutations or small insertions/deletions (indels) in the ANOS5 gene. To more closely mimic the human ANOS5 mutations, we engineered mutant Ano5 rabbits carrying small indels via co-injection of Cas9 mRNA and sgRNA into rabbit zygotes. The histopathological features of the Ano5-KO rabbits were assessed by H&E, Masson’s trichrome and Van gieson staining of the gastrocnemius muscle sections as well as the serum creatine kinase (CK) was measured using the CK Test Kit.

Methods: An Ano5 mutant rabbit model was generated using a pair of sgRNAs targeting exon 12 and exon 13 to disrupt the translation of Ano5 in rabbit through micro-injection of clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (Cas9)/sgRNA mRNA into rabbit zygotes. The histopathological features of the Ano5-KO rabbits were assessed by H&E, Masson’s trichrome and Van gieson staining of the gastrocnemius muscle sections as well as the serum creatine kinase (CK) was measured using the CK Test Kit.

Results: In comparison with wild-type (WT) littermates, Ano5-/- rabbits exhibited biochemical and pathological phenotypes characteristic of human LGMD at the age of 15 months, including elevated serum CK levels, muscle degeneration/regeneration and muscle damage. The pathological phenotypes were also found in various skeletal muscle groups including gastrocnemius, tibialis anterior, tongue and diaphragm of the Ano5-/- rabbits.

Conclusions: CRISPR-engineered mutant rabbits carrying small indels in the exon 12 and/or 13 develop typical signs of muscular dystrophy with close resemblance to its human counterpart. This novel Ano5 mutant rabbit model would be useful in studying the disease pathogenesis and therapeutic treatments for Ano5-deficient muscular dystrophy.

A Comparison of the Acute Care versus non-Acute Care Surgery Cholecystectomy Experience

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Introduction: The acute care surgery (ACS) model is a relatively new concept implemented in surgical departments to provide care to patients with urgent surgical needs. The purpose of this study was to investigate the outcomes of those undergoing cholecystectomy by acute care surgeons compared to those performed by non-ACS general surgeons.

Methods: An IRB-approved, retrospective review was conducted of all non-cancer patients who underwent cholecystectomy between July 2012 and June 2015 in an academic health system. Data collected included service, demographics and history, operative details, post-operative complications, and costs. Data are presented as incidence (%) or mean ± SD, and a p-value of <0.05 was considered statistically significant.

Results: There were 1,995 patients who underwent cholecystectomy during the three-year time period. ACS performed 516 cholecystectomies and 1,479 were performed by non-ACS general surgeons. ACS patients were slightly older (48.7 ± 18.15 vs non-ACS 45.7 ± 15.8; p < 0.01), were more likely to have a history of cirrhosis (3.7% vs non-ACS 1.3%; p = 0.01), and were more likely to have had prior percutaneous cholecystostomy tubes (2.9% vs 0.9%; p < 0.01). There was no difference in history of prior laparotomy (ACS 24.0% vs non-ACS 21.4%; p = 0.51). The pre-operative diagnoses included more acute cholecystitis (50% vs. 13.3%; p < 0.01), gallstone pancreatitis (13.8% vs. 5.1%; p < 0.01) and choledocholithiasis (12.6% vs 4.3%; p < 0.01) in the ACS group compared to the non-ACS group, respectively. The rate of post-operative complications was 13.2% in the ACS group versus 4.9% in the non-ACS group. Acknowledging there are differences due to underlying pathology, we further compared only patients with acute cholecystitis between ACS and non-ACS. Among those with acute cholecystitis, there was no difference in bile leaks (3.9% vs 1.0%; p = 0.07), CBD injuries (0.8% vs 1.1%; p = 0.99), or bleeding (3.5% vs 2.0%; p = 0.41) between ACS and non-ACS patients, respectively. The overall complication rate, which includes cardiopulmonary complications, was 16% in ACS patients compared to 9.6% non-ACS patients with acute cholecystitis (p = 0.51). There was a greater proportion of cases performed open or converted to open (28.4% vs 9.8%; p < 0.01) for the ACS group, and longer operative times (1.8 hours vs. 1.5 hours; p < 0.01). Post-operative length of stay was 3.8 ± 4.1 days for the ACS group compared to 2.5 ± 4.2 days for the non-ACS group. Total charges for the index hospitalization was $74,319 ± 4,139 for the ACS group compared to $55,015 ± 3,894 for the non-ACS group (p < 0.01).

Conclusions: The acute care surgery model was adopted to meet a need for in-house emergency general surgery procedures. This study demonstrates that in the setting of cholecystectomy, compared to other general surgeons in a large academic health system, ACS performs a greater percentage of non-elective cases for acute gallbladder diseases with longer operative times, longer length of stay, and at a greater cost, perhaps due to the higher acuity of patients and the gallbladder diseases encountered.
Neutrophil to Lymphocyte Ratio Predicts Outcomes After Chemoembolization for Neuroendocrine Tumors

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Introduction: The neutrophil to lymphocyte ratio (NLR) has been shown to be predictive of outcomes in various cancers, including neuroendocrine tumors (NETs), as well as response to cancer related treatments, including transarterial chemoembolization (TACE). However, the role of NLR in patients with NET treated with TACE is incompletely understood. We hypothesized that, in patients with liver metastases from NETs, a lower NLR value pre-TACE, as well as post-procedure, would correlate with improved long-term outcomes.

Methods: After IRB approval, we reviewed 262 patients who underwent TACE for metastatic NET at a single institution. NLR was calculated from the pre-TACE complete blood count (CBC) drawn the day of the procedure and the post-TACE CBC drawn approximately one day, one week, and six months after initial treatment. NLR levels were then correlated with overall survival from the time of TACE.

Results: The median post-TACE overall survival (OS) of the entire cohort was 30.1 months. Mean NLR for patients who survived less than 3 years was 4.4 while the mean NLR for patients who survived more than 3 years was 3.3. Median OS of patients with a pre-TACE NLR < 4 was 33.3 months vs 21.1 months for patients with a pre-TACE NLR > 4 (p = 0.005). The median OS for patients with post-TACE NLR higher than pre-TACE NLR was 21.4 months vs 25.8 months for patients with a post-TACE NLR less than or equal to pre-TACE NLR (p = 0.007). On multivariate analysis, both pre-TACE NLR and 6 month post-TACE NLR were independent predictors of survival. NLR values from one day and one week post-TACE did not correlate with outcome.

Conclusions: An elevated NLR pre-TACE, as well as an NLR value that has not returned to its pre-TACE value several months after the TACE, are associated with worse survival in patients with NET and liver metastases. This value can be easily calculated from the CBC with differential routinely obtained from patients as part of their pre-procedural and post-procedural care. Calculating and trending NLR values for these patients may impact treatment strategies.

Cancer patient attitudes and preferences regarding surveillance: preliminary results from a single-institution survey

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Introduction: Cancer surveillance is the ongoing, timely and systematic collection of patient information on current cancer status. Currently, there is no standard of care regarding how information on cancer surveillance is shared with patients leading to practice variations. Clinical visits associated with cancer surveillance contribute to health care costs and may represent an inconvenience to patients. The objective of the current study was to assess patient preferences about cancer surveillance. Specifically, we sought to elucidate patient preferences around the means of communication, frequency and timing of appointments, as well as personal barriers and psycho-social barriers to follow-up.

Methods: A cross-sectional descriptive survey was administered in oncology clinics at The Ohio State Wexner Medical Center or Arthur G. James Cancer Hospital clinics. Surveys were administered according to the patient’s preference either as a paper handout or via the web-based Qualtrics® program. The survey was designed based on topical fields derived from previously published and validated surveys, as well as content expert input. Patients ≥18 years old who had undergone a previous curative intent operation for a solid tumor were eligible for survey inclusion. Preferences were assessed using Likert scale.

Results: At the time of the interim analysis, 75 patients had completed the survey. Median patient age was 60.8 years (SD=13.7) and most respondents were female (male n=21 vs. female n=56). Most patients were seen for follow-up at the Stephanie Spielman Cancer Center (50.7%), while other patients had clinical care at Martha Morehouse Medical Plaza (33.8%), The James Cancer Hospital (12.7%), or University Hospital (2.8%). Most patients reported the length of the relationship with their cancer surgeon was > 1 year (73.6%) and the median number of follow-up visits in the last 12 months was 2 (range 1-7). Respondents reported a strong preference to receive normal laboratory results via MyChart (30.3%), over the phone (26.3%), or over secure email (28.9%), rather than during an in-person office visit (14.5%). While cancer patients noted an equal preference that normal imaging test results be communicated via MyChart (23.8%), over the phone (25%), or through secure email (23.8%), almost one-third (27.5%) did indicate a desire to review even normal imaging results during an in-person visit. Of note, when laboratory and imaging surveillance results were normal, patients either preferred a nurse practitioner (40.9% and 37.7%, respectively) or had no preference (34.8% and 31.9%, respectively) about who discussed the results with them; only a small subset expressed a desire to have normal laboratory or imaging surveillance results communicated by the cancer surgeon (13.6% and 20.3%, respectively). In contrast, when the surveillance laboratory or imaging tests were abnormal, most patients expressed a preference that their surgeon (54.2% and 49.3%, respectively) communicate these results. In addition, rather than MyChart or phone, most patients wanted abnormal surveillance results discussed via an in-person face-to-face clinic appointment (58.3% and 56.2%, respectively).

Conclusions: Patient preferences on how surveillance results were communicated varied. Most patients preferred to have abnormal surveillance results discussed by their surgeon during an in-person clinic appointment. In contrast, many patients preferred that other members of the health care team share normal surveillance laboratory and imaging results via MyChart or phone without the need for a clinic appointment. Shifting routine communication of normal surveillance results to cancer patients may improve patient satisfaction, mitigate patient travel, avoid wait times, and decrease health care system costs.
Epigenetic mapping of wound edge from chronic wound patients using next generation sequencing

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Introduction: The loud biochemical microenvironment of the chronic wound sharply departs from that of the skin under homeostatic conditions and is likely to induce epigenetic changes thus influencing wound healing outcomes.

Methods: Unbiased whole-genome DNA methylation (methylome) was studied in normal skin (NS) and in wound edge tissue of chronic wound (CW) patients. DNA (1 µg) isolated from CW or NS was sonicated to generate 100-300 bp size fragments followed by methylated DNA fragment enrichment and Illumina-compatible sequencing library generation. Single-end 50 bp sequencing was done using Illumina HiSeq 2500. Separate methylation status of proximal promoters (1 Kb), distal promoters (10 kb), non-CpG promoters and within exons of genes were calculated using MethylCap-Seq data analysis and PrEMer-CG analysis. Differential methylation analysis was performed using mean vector test.

Results: In proximal promoter, genes of ERK, mTOR and Notch signaling were hypomethylated. In contrast, genes involved in epithelial to mesenchymal transition were hypermethylated in CW compared to NS (p<0.0001). Hypomethylation of mTOR and ERK genes was also observed in non-CpG promoters and within exons (p<0.0001). Bisulfite sequencing was used to validate hypermethylation of candidate genes (TP53, BRCA1, and ESR1). microRNA promoters were differentially methylated in CW compared to NS (71 hyper methylated, 20 hypomethylated in CW, p<0.05). The significance of these epigenetic changes on the transcriptome was studied. A sum total of 1281 genes were found to be differentially methylated compared to NS (71 hyper methylated; 20 hypomethylated in CW, p<0.05). The significance of these candidate genes (TP53, BRCA1, and ESR1). microRNA promoters were differentially methylated in CW compared to NS (p<0.0001). Hypomethylation of mTOR and ERK genes was also observed in non-CpG promoters and within exons of genes were calculated using MethylCap-Seq data analysis and PrEMer-CG analysis. Differential methylation analysis was performed using mean vector test.

Conclusions: Epigenetic activity is high at the chronic wound site. Such activity has significant impact on gene expression at the wound-edge and is therefore likely to influence healing outcomes.

Intraoperative parathyroid localization by autofluorescence detection in patients with primary hyperparathyroidism

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Introduction: Intrinsic autofluorescence of the parathyroid gland may allow improved identification and localization of glands intraoperatively, without the need for contrast injection. We sought to analyze the results of real-time autofluorescence imaging in patients with primary hyperparathyroidism

Methods: Data were prospectively gathered on patients undergoing surgery for primary hyperparathyroidism by two experienced endocrine surgeons. Intraoperative imaging was performed with a handheld near-infrared autofluorescence device (Hamamatsu Photonics Co.) and images were captured for analysis.

Representative areas of greatest autofluorescence from the parathyroid gland, thyroid gland, and adjacent soft tissue were quantified by Image J software (NIH, Bethesda, MD) and reported as mean values with standard deviation (mean +/- SD). Association of autofluorescence values with parathyroid adenoma size and weight were analyzed by Pearson’s correlation coefficient.

The attending surgeon completed a form immediately after surgery to document intraoperative confidence, on a scale of 1-5, in parathyroid gland identification by direct visualization versus the addition of autofluorescence.

Results: Fifty-three consecutive patients from June 2017 to February 2018 with a diagnosis of primary hyperparathyroidism underwent resection of a total of 60 parathyroid glands. The mean autofluorescence for parathyroid in situ (78.4 +/- 21.4) was significantly greater than that of thyroid gland (63.3 +/- 17.6) or soft tissue (57.7 +/- 19.8; p<0.001 for both). The mean absolute difference in parathyroid versus background thyroid autofluorescence was +15.4 (range, 2.5-53.1). The value of this difference between parathyroid and thyroid autofluorescence was significantly associated with parathyroid gland weight (Pearson coefficient 0.45; p=0.043) and gland volume (Pearson coefficient 0.534; p<0.009).

The average surgeon confidence score with parathyroid identification was 4.0 by direct visualization vs. 4.5 by autofluorescence. The addition of autofluorescence helped find the parathyroid gland in 12 patients (39%), and helped rule out other soft tissue as not parathyroid in an additional 8 patients (15%). In 13 patients (25%), intense autofluorescent identification of the parathyroid adenoma obviated the need for frozen section, saving operative time and expense.

Conclusion: Intraoperative identification and localization of parathyroid glands by real-time near-infrared imaging of their intrinsic autofluorescence appears feasible and effective. Further investigation of this promising technology is warranted.
Inhibitors of histone deacetylases 3 and 6 impair the phenotype change of vascular smooth muscle cells and formation of neointima lesion

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*Equal contributors

Introduction: Under pathogenic stimulation vascular smooth muscle cells (SMCs) change to a proliferative, migratory, and de-differentiated phenotype. This phenotypic transformation leads to the development of neointima lesion on the vessel wall that narrows the lumen (restenosis). Histone deacetylases (HDACs) are chromatin remodeling factors that regulate gene transcription. Pan HDAC inhibitors have been shown to influence SMC behaviors and neointima, yet specific roles of different HDACs remain little understood. We used Apicidin and Tubastatin-A, selective inhibitors of HDAC3 and HDAC6, respectively, to explore the roles of these representative Class-I and Class-II HDACs in SMC phenotypic transformation and neointima formation.

Methods: Primary rat aortic SMC phenotypic transformation was determined in vitro by assays of CellTiterGlo (proliferation), scratch (migration), and Western blotting of SMC markers (de-differentiation). Neointima was induced in the rat common carotid artery via balloon angioplasty, and HDAC inhibitors were applied in Pluronic gel around the injured artery. Morphometric analysis was performed on H&E-stained cross sections collected at 14 days post angioplasty.

Results: Compared to vehicle control, both Apicidin and Tubastatin-A inhibited serum-stimulated SMC proliferation in a concentration-dependent manner. Apicidin at 0.5 μM inhibited serum-stimulated SMC proliferation by ~80% (P<0.05, n=3). SMC de-differentiation was stimulated with recombinant TGFbeta and overexpression of its signaling protein Smad3, as evidenced by reduced protein levels of SMC markers myosin heavy chain (SM-MHC) and alpha smooth muscle actin (SMA). Pretreatment with Apicidin partially restored MHC and SMA levels. In vivo treatment with Apicidin (0.5mg, n=2 rats) and Tubastatin-A (3mg, n=3 rats) inhibited neointima formation by 50% and 41%, respectively.

Conclusions: HDAC3 and HDAC6 inhibitors mitigate vascular SMC's phenotypic change in vitro and neointima formation in vivo. Therefore, these two HDACs could be targeted for treating post-angioplasty restenosis. Future experiments are designed to explore differential molecular mechanisms underlying the effects of HDAC3 and HDAC6 inhibitors on SMC behaviors.

Cardiovascular tissue engineering in the fetus

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Introduction: Hypoplastic heart syndromes (HHSs) are a fatal set of syndromes in which one of the ventricles is underdeveloped, and blood therefore cannot be effectively pumped throughout the body. HHSs arise due to in-utero aortic stenosis which leads to poor intracardiac blood flow during development. This leads to ventricular dilation, dysfunction, and ultimately ventricular growth arrest. In this population, in-utero fetal valvuloplasty has emerged as a technique which restores flow and enables postnatal biventricular circulation in patients who otherwise have a high likelihood of developing HHSs. After birth, however, these patients are at high risk for aortic valve regurgitation and may require early valve replacement. Currently available replacement valves are incapable of growth, which means the child must undergo serial reoperations as he or she grows. Tissue engineering offers a potential solution to this problem. Tissue engineered heart valves (TEHVs) consist of biodegradable scaffolds which are replaced over time with native tissue (neotissue), forming a valve that can grow and remodel with the patient. It is not known if the in-utero implantation of a valve with growth potential could prevent the development of HHSs and simultaneously reduce the need for postnatal interventions. There is a critical need to correct this gap in knowledge because, until it is filled, the best available options will remain palliative surgery or the relatively novel valvuloplasty followed by postnatal valve replacement.

Methods: A twin fetal lamb model will be used for implantation. The TEHV will be implanted in the right ventricular outflow tract of one fetus. No intervention will be taken in the twin, who will act as control (n = 12 pairs of twins). This will be performed between 100-110 days gestation. We will manufacture TEHVs constructed from poly(glycerol sebacate) (PGS) and polycaprolactone (PCL) using a tube-within-a-tube technique, placed in a zinc bioresorbable stent for implantation into a twin fetal lamb model. No intervention will be taken in the twin who will act as a control. Post TEHV implantation, valve function and potential could prevent the development of HHSs and simultaneously reduce the need for postnatal interventions. There is a critical need to correct this gap in knowledge because, until it is filled, the best available options will remain palliative surgery or the relatively novel valvuloplasty followed by postnatal valve replacement.

Results: To date, we have performed procedures on 5 mothers for a total of 8 fetuses. We have successfully placed stents percutaneously in 2 fetuses. The biggest deterrent to percutaneous heart access is poor fetal positioning due to sheep uterine anatomy. The most common complication has been fetal bradycardia, followed by pericardial effusion. Of the procedures completed, mean right ventricular outflow tract diameter is 6.68 mm (SD 0.52 mm).

Conclusions: The endovascular implantation of a TEHV has never been reported in the literature and is expected to be technically challenging. While this feasibility study is ongoing, at this time point we have demonstrated the viability of a large animal sheep model for studying fetal cardiac interventions. The remainder of this study will focus on perfecting our technique and protocol prior to future proposals, with the goal of applying this translational work to fetal interventions in patients at risk for HHSs.
The Bromo and Extraternal Domain Protein (BET) Family Drives Endothelial-To-Mesenchymal Transition and Contributes to Vein Graft Stenosis

Mengxue Zhang MS MD, Bowen Wang PhD, Go Urabe MD PhD, K. Craig Kent MD, Lian-Wang Guo PhD

Introduction: Vein graft bypass remains the most commonly used open procedure for flow-limiting cardiovascular diseases. However, vein grafts are prone to stenosis, which ultimately leads to graft failure (4-year failure rate at ~43%). Previous studies have provided strong evidence supporting that dysfunctional endothelial cells (ECs) of the vein grafts contribute significantly to neointima formation (and hence stenosis) by undergoing EndoMT. Our group has recently shown that BRD4, a member of the BET epigenetic reader protein family, is up-regulated in the neointima lesion of stenotic failed vein grafts. Here we have determined whether BRD4, and possibly other BET proteins, would be involved in EndoMT in vein grafts, and ultimately vein graft stenosis/failure.

Methods: For in vitro experiments, we treated rat primary vascular ECs with 100ng/ml TGFβ-1 (to induce EndoMT), and/or BET inhibitors (Pan inhibitor: JQ1; Domain-selective inhibitors: Olinone and RVX208), and/or siRNAs for BRD2, 3, and 4. For in vivo experiments, we used a cuff-based technique to establish jugular vein to carotid artery interposition graft in rats, and lentiviral shRNA delivery to achieve specific knockdown of BRD4 in the graft.

Results: BET pan-inhibition significantly reduced EndoMT of rat primary vascular ECs in vitro. Similar effects were observed via selective inhibition of bromodomain 2, but not bromodomain 1. Knockdown of BRD4 protein expression in vitro fully recapitulated the inhibitory effect of BET pan-inhibition on EndoMT, whereas knockdown of BRD2 and BRD3 could only lead to partial and marginal abrogation of EndoMT, respectively. In the rat vein graft model, local lentiviral delivery of BRD4 shRNA led to decrease of neointima formation.

Conclusions: BET proteins, especially BRD4, play an important role in EndoMT of vascular ECs and also neointima formation in vein grafts. Blockage of BRD4 protein could potentially serve as a novel strategy to achieve prolonged patency of vein graft conduits.
Wound fluid as a biomarker: A metabolomics approach

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Introduction: The wound fluid bathing the wound tissue reflects the wound microenvironment and shapes the functional response of wound-related cells. Building on the scientific premise that metabolites in the wound microenvironment will shape the fate of the wound, we sought to identify biochemical markers in wound fluid that can delineate between wounds that will and will not heal.

Methods: Subjects (N=50) participating in the study were chronic wound patients seen at OSU Comprehensive Wound Center (CWC) clinics and have been undergoing NPWT (negative pressure wound therapy) as part of standard clinical care. Wound fluid and cells were derived from the NPWT dressing by lavaging the wound dressing with saline solution. Using different mass-spectrometry platforms, global biochemical profiles were compared in wound fluid samples from healing (>65% closure after 4 weeks) and non-healing (<20% closure after 4 weeks) wounds. Samples from each experimental group were measured and analyzed in an equivalent manner across the analytical platforms and analyzed after normalization based on measured protein values (Bradford assay).

Results: Out of 622 metabolites screened, more than a third were found to be significantly lower in the non-healing group (p<0.05; n=25) indicative of blunted tissue metabolism in wounds not engaged in active tissue repair. Consistently, the non-healing cohort exhibited decreases in metabolites linked to amino acid and polyamine homeostasis, energy utilization and lipid homeostasis (p<0.05; n=25). Interestingly, in the wound fluid of non-healing group a 3-fold increase (p<0.05; n=25) in fibrinogen-derived peptide DSGEGDFXAEGGGVR levels was noted compared to the healing cohort. This metabolite is a proteolytic fragment of fibrinogen. How this metabolite contributes to the overall proteolytic activity of the chronic wound, which is known to be high, warrants further study.

Conclusions: This patient based study recognizes the value of wound fluid metabolite profile as a biomarker of wound outcome.

Indocyanine Green Lymphangiography for Thoracic Duct Identification and Injury Recognition During Neck Dissection

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Introduction: Injury to the thoracic duct causing a chyle leak is the most common complication following a left neck dissection, carrying a high degree of morbidity when it occurs. There are no diagnostics routinely used to assist with thoracic duct identification intra-operatively. Lymphangiography using Indocyanine Green (ICG) has previously been described; however there have been no reports of its use in mapping the thoracic duct during neck dissection.

Methods: In patients undergoing left modified radical neck dissection for either thyroid cancer or melanoma, ICG (2.5 mg/mL) 2 mL was injected subcutaneously on the dorsum of the left foot 5-15 minutes before imaging. Intraoperative imaging of the neck was performed with a hand-held Near InfraRed (NIR) camera (Hamamatsu, PDE-Neo).

Results: In 8 patients imaging of the base of the neck was performed after lymph node dissection was completed. The thoracic duct was visualized in 7 using the NIR camera, and time from injection to identification of the thoracic duct was variable at 15 to 90 minutes, Imaging was optimized by positioning the camera at the angle of the mandible and pointing in a caudal direction into the space below the clavicle. ICG was re-dosed in 4 patients to assist with visualization by increasing the intensity of the fluorescence. In one patient the inability to locate the thoracic duct was likely due to obliteration due to chylous fluid in the wound. The thoracic duct was located using NIR imaging and found to be transected. It was then successfully ligated such that the patient had no chylous fistula post-operatively.

Conclusions: This is the first description of using ICG lymphangiography for identification of the thoracic duct in the neck. Identification with ICG is technically feasible, simple to perform with NIR imaging, and safe. This technique may become an important adjunct for the surgeon to facilitate identification of the thoracic duct and recognize intra-operative injury.

Figure 1 Positive thoracic duct identification using NIR imaging
Differences in Letters of Recommendation for Applicants to Complex General Surgical Oncology Fellowship Based on Gender

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Introduction: Women comprise 38% of applicants to complex general surgical oncology fellowships but only 23% of surgical faculty nationally. We evaluated letters of recommendation (LOR) for an ACGME-accredited surgical oncology fellowship to understand gender differences in communication about applicants by letter writers.

Methods: Data on applicants, authors and word count and phrasing within the LOR were extracted. Differences between applicant and author gender were analyzed.

Results: We analyzed 227 letters (66.8%) for male candidates and 113 (32.2%) letters for female candidates. Males authored 83.5% of letters. Word count, academic rank of the letter writer or use of applicant's first name did not differ between applicant genders. Female letter writers more frequently used 'grindstone' adjectives (GA) (mean 3.61 v 2.90, p=0.03). Interestingly, the increased use of GA by female writers was only significantly for male applicants (mean 3.82 v 2.73, p=0.03). Female authors also more frequently used compassion adjectives (CA) (mean 1.63 v 1.18, p=0.03). Among thirteen other variables analyzed, only comments on physical appearance differed between male and female applicants, with 4.4% of letters written for female applicants containing at least one reference to physical appearance, compared to just 0.9% in letters for male applicants (p<0.03).

Table 1: Letter Features with No Significant Difference by Applicant or Author Gender

<table>
<thead>
<tr>
<th>Feature of Letter</th>
<th>Definition of Variable</th>
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<tbody>
<tr>
<td>Gets Along Well with Others</td>
<td>&quot;Gets along with others&quot; or mention of working well with 2 or more distinct groups of people</td>
</tr>
<tr>
<td>Team Player</td>
<td>Good team player or team member</td>
</tr>
<tr>
<td>Technically Capable/Excellent</td>
<td>Mention of technical excellence or ability to complete operations independently</td>
</tr>
<tr>
<td>Intelligent/Smart</td>
<td>Use of words intelligence or intelligent or smart</td>
</tr>
<tr>
<td>Bright</td>
<td>Use of word bright</td>
</tr>
<tr>
<td>Personal Life</td>
<td>Any mention of personal life, history, extracurricular activities or family</td>
</tr>
<tr>
<td>Sense of Humor</td>
<td>Reference to having a sense of humor</td>
</tr>
<tr>
<td>Leadership Potential</td>
<td>&quot;Future leadership potential&quot; or &quot;future leader&quot;</td>
</tr>
<tr>
<td>High Match Rank</td>
<td>Mention of writer’s intent to rank applicant highly or recruit back to institution</td>
</tr>
<tr>
<td>Stringing</td>
<td>Any four favorable adjectives in single sentence</td>
</tr>
<tr>
<td>Standout adjectives</td>
<td>Aggregate count of 15 “standout terms” (e.g. star, stellar, superb)</td>
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</table>

Conclusions: Female LOR authors have substantively different letters than males, with increased use of both GA and CA. The implication of these differences should be explored further. Physical appearance remains a topic more likely to present in LOR for females, representing an area of improvement in the promotion of women in academic surgery.

Influence of English Proficiency on Patient-Provider Communication and Shared Decision-Making

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Introduction: The number of patients in the United States who speak a language other than English is expected to increase. The effect of English proficiency on health care outcomes has been poorly studied. We sought to define the impact of English proficiency on self-reported patient-provider communication (PPC) and shared decision-making (SDM).

Methods: The 2013-2014 Medical Expenditure Panel Survey database was utilized to identify respondents who spoke a language other than English. PPC and SDM scores ranging from 4 to 12 were categorized as "poor" (4-7), "average" (8-11), and optimal (12). The relationship between PPC, SDM and English proficiency was analyzed using regression analysis.

Results: Among 13,880 respondents, most were white (n=10,281, 75%), age 18-39 years (n=6,677, 48%), male (n=7,275, 52%), middle income (n=4,125, 30%), and born outside of the United States (n=9,125, 65%). English proficiency was rated as "very well" (n=7,221, 52%), "well" (n=2,378, 17%), "not well" (n=2,820, 20%) or "not at all" (n=1,463, 10%). On multivariable analysis, compared with patients who self-reported English proficiency as "very well," patients who rated their English as "well" (OR 1.73, CI 1.37–2.18) or "not well" (OR 2.82, 20%) or "not at all" (OR 1.463, 10%) were more likely to report "poor" PPC (both p<0.01). Similarly, SDM was more commonly self-reported as "poor" among patients who reported English proficiency as "not well" (OR 1.31, CI 1.04–1.65, p=0.02).

Conclusions: Decreased English proficiency was associated with worse self-reported PPC and SDM. Attention to patient’s language needs is critical to patient satisfaction and to improved perception of care delivered.
Parthenolide Inhibits Inflammatory Dysfunction of Human Aortic Endothelial Cells and Proliferation of Smooth Muscle Cells in vitro and Restenosis in a Rat Model
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Introduction: Cardiovascular diseases remain the leading cause of death in developed countries. Endovascular surgical interventions trigger uncontrolled proliferation of smooth muscle cells (SMCs) in the intima (intimal hyperplasia) leading to lumen re-narrowing (restenosis). Despite extensive efforts devoted to therapeutic methods with a focus on inhibiting SMC proliferation, restenosis persists at a significant rate. In recent years, a growing body of knowledge has underscored a crucial role for endothelium damage in the pathophysiology of restenosis, suggesting that preservation of the endothelium would provide an effective approach for effectively curbing restenosis.

Methods and Results: We utilized high-throughput screening methods to search for small molecules that could inhibit the proliferation of human aortic SMCs without damaging human aortic endothelial cells (ECs). We identified such a lead compound in Prestwick Library; i.e. Parthenolide, a sesquiterpene lactone extracted from feverfew. When cells were cultured under normal conditions, treatment with a low dose (1 µM) of Parthenolide for 96h inhibited SMC but not EC proliferation. When the cells were stimulated with inflammatory cytokines (TNF-α or IL-1β), Parthenolide mitigated cytokine-induced proliferation and MCP-1 production of SMCs, but rescued cytokine-induced endothelial dysfunction, including apoptosis, senescence, impaired migration and proliferation, decrease of eNOS, and increase of ICAM-1/VCAM-1/Tissue Factor. Mechanistic studies showed that while Parthenolide treatment in both SMCs and ECs induced NRF-2 activation (nuclear translocation), NRF-2 knockdown with siRNA diminished the aforementioned beneficial effects of Parthenolide in both cell types. In contrast, NFkB activation was not significantly affected by Parthenolide. In a rat balloon angioplasty model, perivascular delivery of Parthenolide in Pluronic gel effectively inhibited intimal hyperplasia and restenosis 14 days after surgery.

Conclusions: These results indicate that the natural compound Parthenolide differentially attenuates pathological behaviors of both human vascular SMCs and ECs, whereas known agents as such are scarce. Thus Parthenolide may serve as a promising lead compound for future development of next-generation anti-restenotic therapeutics.

Improving Glucose tolerance in diabetes: Inducing islets in the skin
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Introduction: type 1 diabetes (T1D) is characterized by impaired insulin production and marked glycemic fluctuations that lead to serious complications (e.g., neuropathies and vasculopathies). Current management strategies are focused on administering insulin. Nevertheless, the use of exogenous insulin still has limitations, including stability issues, the need for daily injections, and continued glycemic fluctuations. Cell therapies have emerged as a promising strategy towards insulin independence. The Edmonton protocol for example, which involves allogenic islet transplantation combined with immunosuppressive regimens, has shown to lead to partial insulin independence. Widespread implementation, however, is hampered by the lack of donors. Differentiating naturally or artificially derived progenitor cells to β-cells, on the other hand, faces additional hurdles, including scarce/functionally impaired sources, and the need for cumbersome and/or highly immunogenic ex vivo pre-processing. Advances in cell reprogramming in vivo could potentially overcome these limitations by utilizing more readily available sources (e.g., skin fibroblasts) and bypassing the need for ex vivo cell handling. Current methodologies, however, have several limitations including heavy reliance on viral vectors. This work describes the implementation of a groundbreaking nanotechnology for islet biogenesis via ectopic skin reprogramming. This disruptive technology could potentially establish a safer and simpler to implement approach to islet replacement/replenishing therapies under T1D, based on the innovative concept of skin reprogramming.

Methods: for this novel in vivo transfection technique, the molecular cargo is loaded inside the chip’s reservoir and then the chip is placed in contact with the skin. Subsequently an electric field is applied for 100 milliseconds which causes rearrangement of the phospholipids on the cell membrane and opens up transient nanopores (nanoporation) to drive the molecular cargo into the cells via electrophoresis. This nanotransfection method has higher efficiency (close to 100%) and cell viability compared to commercially available systems. A cocktail of transcription factors associated with pancreatic development (Pdx1, Ngn3, and Mafa - PMI) was transferred using this novel technique to induce skin reprogramming towards insulin-producing islet-like foci in diabetic mouse skin. Reprogramming of the skin was characterized by fluorescence microscopy, immunofluorescence (IF), qRT-PCR, and glucose challenge tests at multiple time points.

Results: IF showed insulin immunoreactivity around the epidermis at first and later on invading into the dermis. Studies on diabetic mice indicate that tissue nanotransfection of insulinogenic factors foment ectopic derivation of insulin-expressing β-like tissue from skin. Insulin-expressing β-like tissue homed for the most part within follicular structures, with some remnant expression in epidermis. Clear insulin and Glut2 immunoreactivity was detected with improved glucose tolerance compared to control animals. Control mice showed increasing glycemia with no recovery within 1h. Moreover, skin-derived islets fomented normoglycemia in T1D mice for approximately 11 weeks. Control mice (i.e., mice treated with mock plasmids), on the other hand, showed continued and worsening levels of hyperglycemia over the same time interval.

Conclusions: Our findings highlight the potential of our non-viral in vivo transfection technology to reprogram the skin into insulin-expressing β-like tissue, to improve glucose tolerance and achieve normoglycemia under T1D. Ectopic insulin-expressing β-like tissue in the skin offers numerous advantages compared to previous attempts to convert hepatocytes or acini into β-cells, such as easy monitoring and accessibility enabling focal treatment (e.g., immunomodulators, trophic factors) or retrieval if needed.

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