9TH ANNUAL

research *summit*

UNIVERSITY OF WISCONSIN • DEPARTMENT OF SURGERY

The New Frontier

Abstracts

Welcome

Welcome to the 9th Annual University of Wisconsin Department of Surgery Research Summit.

Our theme this year is *The New Frontier*, and we anticipate that the Summit will be an opportunity to showcase the bold thinking and innovation that characterize our departmental research efforts. We are honored by the presence of two guest keynote speakers this year: **Paul Cerderna, MD, FACS**, Robert Oneal Collegiate Professor of Plastic Surgery, Professor in the Department of Biomedical Engineering, and Chief of the Section of Plastic Surgery at the University of Michigan Health System; and **Jo Handelsman, PhD**, Director of the Wisconsin Institute for Discovery, Vilas Research Professor at UW-Madison, Howard Hughes Medical Institute Professor, and for the past 3 years Associate Director for Science in the Obama Administration's White House Office of Science and Technology Policy.

Five awards will be given in honor of five individuals whose iconic contributions have made possible our research enterprise. The *Layton F. Rikkers, MD, Best Oral Presentation Award* is named in honor of our previous Chairman, who established the academic rigor and strength of our Department. The *K. Craig Kent, MD, Best Basic Science Poster Award* honors another previous Chairman, who led our department to its current national standing as a top-ranked, NIH funded Department of Surgery. The *Charles N. Ford, MD, Best Translational-Clinical Poster Award* is named after our previous Otolaryngology Division Chairman, who built a world-class voice and laryngology enterprise within our Department. The *Debra A. Hullett, PhD, Best Basic Science Poster Award – Student* honors a beloved colleague who made important contributions as a leader and mentor to many in our Department. The *Louis C. Bernhardt, MD, Best Translational-Clinical Poster Award – Student* honors a man whose long-standing mentorship to our medical students and residents is legendary. A separate award will be given to the top research-related image in our "Cool Science Image" contest.

Thank you for taking time out of your busy schedules to attend the 2018 Research Summit. We hope that today's activities will increase your awareness of the innovative research activities that take place every day in the Department of Surgery.

Welcome to the Summit.

Samuel O. Poore, MD, PhD and **Robert R. Redfield III, MD**
Program Co-Chairs

Acknowledgements

Program

University of Wisconsin Department of Surgery
9th Annual Research Summit: *The New Frontier*
Wednesday, January 17, 2018

AM

7:30   **Continental Breakfast and Registration**

8:00   **Welcome and Opening Remarks, The Marquee**

Samuel Poore, MD, PhD, Program Co-Chair
Robert Redfield III, MD, Program Co-Chair

8:15   **UW Department of Surgery Research Talks**
Four 10-minute talks each followed by 5-minute Q&A

Carla Pugh, MD, PhD
"Pivoting: An Exciting and Cautionary Tale of Surgeon Scientists"

David Francis, MD
"Perspectives on Vocal Fold Paralysis from Patient to Policy"

Samuel Poore, MD, PhD
"Beyond Neuroma Surgery: The Osseointegrated Neural Interface for Prosthetic Control"

Dai Yamanouchi, MD, PhD
"Recent Advances in Vascular Surgery"

9:15   **Coffee Break, Poster Viewing, and Judging, Varsity Hall**
If you are presenting a poster, we encourage you to stand by your poster
during this time to answer any questions that may arise.

10:15   **Invited Speaker, The Marquee**

Paul Cederna, MD
Chief, Plastic Surgery, University of Michigan
Robert Oneal Collegiate Professor of Plastic Surgery
Professor, Department of Biomedical Engineering

"The Bionic Man: Not Too Far Away!!"

11:00   **Top Six Abstract Presentations**
7 minutes + 3 minutes Q&A

Jennifer Philip
"Contributions of myocardial mechanics to right ventricular failure: model simulations and predictions"

Joseph Imbus
"Characterizing Surgeon Prescribing Practices and Opioid Use after Outpatient General Surgery"

Daniel Tremmel
"A human pancreatic ECM scaffold for beta cell co-culture and co-transplantation"

Weifeng Zeng
"Anatomical and electrophysiological analysis of the mouse infraorbital nerve as a neural interface"

Sara Misurelli
"The impact of hearing loss on executive function"

Nick Zaborek
*"The Optimal Levothyroxine Dosing Scheme After Thyroidectomy:
A Comprehensive Comparison and Evaluation"*

PM

12:00 **Lunch, Poster Viewing and Judging, Varsity Hall**
If you are presenting a poster, we encourage you to stand by your poster
during this time to answer any questions that may arise.

1:30 **Invited Speaker, The Marquee**

Jo Handelsman, PhD
Director, Wisconsin Institute for Discovery (WID),
University of Wisconsin-Madison
Professor, Plant Pathology, Systems Biology

Appointed by President Barack Obama as the Associate Director for Science at the White House Office
of Science and Technology Policy, where she served for three years until January 2017.

"Fallacy of Fairness."

2:30 **Coffee and Ice Cream Break**
If you are presenting a poster, we encourage you to stand by your poster
during this time to answer any questions that may arise.

3:00 **UW Department of Surgery Research Talks**
Four 10-minute talks each followed by 5-minute Q&A

Dixon Kaufman, MD, PhD
"Transplant tolerance in Rhesus Monkeys"

Susan Pitt, MD, MPHS
"Low-risk thyroid cancer: To Treat or Not to Treat?"

Angela Gibson, MD, PhD
"In the Eye of the Beholder"

Corrine Voils, PhD
"Incentivizing behavior change skills to promote weight loss: The Log2Lose trial"

4:00 **Research Update, The Marquee**

Rebecca M. Minter, MD
A.R. Curreri Professor and Chair, Department of Surgery

4:45 **Closing and Announcement of Research Prize and ''Cool Science Image'' Contest Winners**

YOU MUST BE PRESENT TO WIN AN AWARD.
There will be no excpetions. If you win an award but are not present,
the award will be given to the runner-up.

5:00 **Reception, lounge area outside Varsity Hall at Union South**
Join us to honor the award winners and meet our new chair, Dr. Minter!

List of Abstracts

Alphabetized by PI/Lab within each group. Number represents poster number.

GROUP ONE: Basic Science

CARCHMAN
PIK3CA E545K Mouse Model of Anal Cancer*; Louise Meske, Taylor Steeno, Andrew Auyeung, Emily LaCount, Evie Carchman*
Poster Number: **B20**

CHESLER
Analysis of Pulmonary Vascular Impedance and Remodeling in Ischemic Heart Failure; *Thomas Murphy, Jennifer Philip, David Schreier, Diana Tabima, Timothy Hacker, Naomi Chesler*
Poster Number: **B22**

Contributions of Myocardial Mechanics to Right Ventricular Failure: Model Simulations and Predictions; *Jennifer L. Philip, Ryan J. Pewowaruk, Claire S. Chen, Mark Nyame, Diana M. Tabima, Anthony J. Baker, and Naomi C. Chesler*
Poster Number: **B25**

Direct Association between Mitochondria Alterations and Impaired Contractile Function in Right Ventricular Failure due to Pressure Overload in Rats; *Tik-Chee Cheng, Jennifer L. Philip, Diana M. Tabima, Timothy A. Hacker, Naomi C. Chesler*
Poster Number: **B37**

CIUCCI
Social-Enrichment Changes Ultrasonic Vocalization Frequency and Ventral Tegmental Dopamine in the Pink1 -/- Rat Model of Parkinson Disease; *Cynthia A. Kelm-Nelson, Angel D. Chavez-Rivera, and Michelle*
R. Ciucci
Poster Number: **B15**

CONNOR
Reduced Tongue Force and Altered Muscle Fiber Type Composition in a Rat Model of Post Stroke Dysphagia; *Miranda Cullins, Kellie Bowen, Nadine Connor*
Poster Number: **B6**

Sensorimotor Behavioral Assays of Alexander Disease in a Rat Model; *Cullen, Jared; Cullins, Miranda; Szot, John; Hagemann, Tracy L.; Messing, Albee; Connor, Nadine*
Poster Number: **B5**

GIBSON
Molecular Signatures of Cellular Injury and Regeneration in Burn Tissue; *Amin Afrazi, Ziyue Wang, Ying Li, Christina Kendziorski and Angela Gibson*
Poster Number: **B1**

HRM LAB
Coordination of Oropharyngeal Pressures during Swallowing; *Kazuhiro Hori, Corinne Jones, Sarah Rosen, Suzan Abdelhalim, Timothy McCulloch*
Poster Number: **B13**

JIANG
Comparing Success Rates of Mechanical and Labial Airflow Interruption for Pediatric Aerodynamic Assessment; *JJ Lamb, Calvin Hedberg, Austin Scholp, Mattew Hoffman, Adriana Chou, Jack Jiang*
Poster Number: **B18**

Quantitative Second Harmonic Generation Imaging of Vocal Fold Collagen Composition in Leporine and Porcine Models; *Erine Devine, Yuming Liu, Adib Keikhosravi, Robert Leggon, Kevin Eliceiri, Jack Jiang*
Poster Number: **B7**

Reliability of Mechanical and Labial Interruption for Aerodynamic Measurements in the Pediatric Population; *Calvin Hedberg, JJ Lamb, Austin Scholp, Adriana Chou, Jack Jiang*
Poster Number: **B12**

LIU
PkcÎ´ Mediated Serine Phosphorylation of Stat3 Worsens AAA by Enhancing Ripk3 Expression & Necrosis; *Kartik Gupta, Bo Liu*
Poster Number: **B11**

Smooth Muscle Cells Accelerate Endothelial Regeneration through a Protein Kinase C-delta-Dependent Secretion of CXCR2 Ligands; *Ting Zhou, PhD ,Jun Ren, PhD , Matthew B. Parlato, PhD, Bernard Y. Binder, PhD , Noel Phan, PhD , Qiwei Wang, PhD, Danielle Stewart, PhD , Kartik Gupta, MS, Conner Feldman, BS, Yi Si, MD, PhD , Zhenjie Liu, MD, PhD, Nader Sheibani, PhD , William L. Murphy, PhD , and Bo Liu, PhD*
Poster Number: **B32**

Targeting FoxM1 in Vascular Smooth Muscle Cells Induces Apoptotic Cell Death; *Sarah Franco, Amelia Stranz, Fiona Ljumani, Danielle Stewart, Kartik Gupta, Mirnal Chaudhary, K. Craig Kent, and Bo Liu*
Poster Number: **B10**

MEZRICH
Autoimmunity and Pollution: Identifying Tools for Assessing Pollution Samples for Autoimmune Promoting Activity; *O'Driscoll, C.A., Hoffmann, E., Afrazi, A., Tran, H., Fechner, J.H., Mezrich, J.D.*
Poster Number: **B33**

Differential Effects of Atmospheric Particulate Matter on a Model of Autoimmune Disease; *O'Driscoll, C.A., Owens, L.A., Gallo, M.E., Hoffmann, E.J., Afrazi, A., Han, M., Tran, H., Fechner, J.H., Schauer, J.J., Mezrich, J.D*
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Prolongation of Transplant Skin Allograft Survival with Dietary Supplementation of Aryl Hydrocarbon Receptor Ligands; Amin Afrazi, Leah Owens, John H. Fechner, Chelsea O'Driscoll, Walker Julliard and Joshua D. Mezrich
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Use of TCR Transgenic Splenocytes to Characterize the Impact of Pollutants on Immune Responses; *Lexi Worthy, Helen Tran, Chelsea O'Driscoll, John Fechner, and Josh Mezrich*
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MURPHY
Bioengineering Pre-vascularized Scaffolds Using Decellularized and Biofunctionalized Plant Tissues; *G.Fontana, T. Spearman-White , J. Gershlak, M. Adamski, J. Wirth, G. Gaudette, H. D. Le, W. L. Murphy*
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Increased Apoptosis Does Not Co-localize to the Distal Colon in the Fibroblast Growth Factor Receptor 2IIIb (Fgfr2IIIb-/-) Mouse Model of Intestinal Atresia; *Anna Kowalkowski MS, Andrew Rogers MD, Krys*

Zaremba BS, Olivia Hoffman, Peter F. Nichol MD PhD
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ODORICO

Novel Platform for Transplantation of Pluripotent Stem Cell-Derived Beta Cells; *Aida Rodriguez, Sara Dutton Sackett, Daniel M Tremmel, Laura Jo Zitur, Luis A Fernandez and Jon Odorico*
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2D and 3D Models for Endothelial and Stem Cell-Derived Beta Cell Co-Culture and Transplantation; *Rachel Maguire, Austin Feeney, Dan Tremmel, Vansh Jain, Aida Rodriguez, Sam Mitchell, Marina Ignatowski, Andrew Curran, Sara Dutton Sackett, Jon Odorico*
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Functional Recovery and Regrowth after Nerve Transection: Comparison of Five Repair Techniques in a Rat Sciatic Nerve Model; *Jacqueline S. Israel MD, Aaron M. Dingle PhD, Jane A. Pisaniello BS, Madison A. Hesse, Joseph Novello MS, Jared P. Ness MS, Yuming Liu PhD, Adib Keikhosravi MS, Kevin W. Eliceiri PhD, Justin C. Williams PhD, Samuel O. Poore MD, PhD*
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The Osseointegrated Neural Interface (ONI): A Rabbit Model for Chronic Peripheral Nerve Interfacing in Bone with Percutaneous Osseointegrated Connectors; *Aaron M. Dingle1 PhD, Jared P. Ness2 MS, Joseph Novello2 MS, Weifeng Zeng1 MD, Jacqueline S. Isreal1 MD, Conner Feldman1 BS, Brett Nemke3 BS, Yan Lu3 MD, Aaron J. Suminski4 PhD, Mark D. Markel3 DVM, Justin C. Williams2 PhD, Samuel O. Poore1* MD, PhD.*
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Laryngotracheal Microbiota in Subglottic Stenosis; *Sharon Tang, Camila Carlos, Joseph Skarlupka,*

Madhu Gowda, Linda Yin, Kevin Motz, Cameron Currie, Garret Suen, Susan Thibeault, Alexander Hillel
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Laryngeal Microbial Colonization in a Gnotobiotic Murine Model; *Sharon Tang, Samuel Schmitz, Kimberly Dill-McFarland, Federico Rey, Susan Thibeault*
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Migration and Contraction of Fibroblasts from Normal and Scar Vocal Folds with Applications to Wound Healing; *Anete Branco, Aashrith Saraswathibhatla, Jacob Notbohm, Susan L. Thibeault*
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Can Functional Rhinoplasty Treat Chronic Headaches? A Systematic Review; *Rebecca L. Farmer, MD PhD; Ravi K. Garg, MD; Ahmed M. Afifi, MD*
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Facebook Facts: Breast Reconstruction Patient-Reported Outcomes Using Social Media; *Sherry Y.Q. Tang BS, Jacqueline S. Israel MD, Samuel O. Poore MD, PhD, Ahmed M. Afifi MD*
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AUDIOLOGY
The Impact of Hearing Loss on Executive Function; *Sara M. Misurelli & Ruth Y. Litovsky*
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CONNOR
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GARLAND
Postoperative Management of Lower Extremity Free Tissue Transfer: A Systematic Review; *Carol E. Soteropulos, Jenny Chen, Catharine B. Garland*
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GIBSON
A Phase III Open-label, Controlled, Randomized, Multicenter Study Evaluating the Efficacy and Safety of StrataGraft Skin Tissue in Promoting Autologous Skin Tissue Regeneration of Complex Skin Defects Due to Thermal Burns that Contain Intact Dermal Elements and for which Excision and Autografts Are

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The Optimal Levothyroxine Dosing Scheme After Thyroidectomy: A Comprehensive Comparison and Evaluation; *Nick Zaborek, Andy Cheng, Joseph Imbus, Kristin L. Long, Susan C. Pitt, Rebecca S. Sippel, David F. Schneider*
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Patient-Perceived Impact of Paradoxical Vocal Fold Motion Disorder on Function and Quality of Life; *Katherine McConville*
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Outcomes Measurement following Cricopharyngeal Myotomy: A Systematic Review; *Molly A Knigge MS, Susan Thibeault PhD*
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GROUP THREE: Education

CIUCCI

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Competence-based Mastery Learning Module for Graduating Medical Students: A Study of Anxiety, Confidence, and Performance; *Andrew J. Velic, BS, Allison A. Blumenfeld, BS, Elizabeth K. Bingman, MS, Ann P. ORourke, MD FACS, Sarah A. Sullivan, PhD, Amy E. Liepert, MD, FACS*
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Improving Diagnosis in Healthcare: Local versus National Adoption of Recommended Guidelines for the Clinical Breast Examination; *Jay N. Nathwani MD, Lauren J. Taylor MD, Anna Garren, Shlomi Laufer PhD, Calvin Kwan BS, Carla M. Pugh MD, PhD*
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Poster Number: **T11**

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Poster Number: **T2**

CONNOR

Computational Analysis of Rodent Swallowing Biomechanics; *Heidi Kletzien & Nadine P Connor*
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KAUFMAN

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Induction of Tolerance To Kidney Transplants in Rhesus Macaque; *Jennifer Post, Lynn D. Haynes, W. John Haynes, Steve Kempton, Ewa Jankowska-Gan, Debra Bloom, Luis Fernandez, Tony D'Alessandro, Lisa Forrest, Peiman Hematti, William J. Burlingham and Dixon B Kaufman.*
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<u>Poster Number:</u> **T14**

SHANMUGANAYAGM

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<u>Poster Number</u>: **T1**

Abstracts

GROUP ONE

Basic Science

PIK3CA H1047R Mouse Model to Study Anal Cancer

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Keywords	Anal, Cancer, PIK3CA, Mutant, Mouse Model

Abstract begins on following page

Introduction: It is estimated by the American Cancer Society that in 2017 alone there were 8,200 new cases of anal cancer and 1,100 reported deaths. The number one risk factor in anal cancer development is human papillomavirus (HPV) infection. This does not explain the few cases of HPV negative cancer. The PIK3CA gene is mutated in about 15% of human cancers, and 30% anal cancer cases. The H1047R mutation, is found in the kinase domain, resulting in an activating mutation of the gene, and is one of the two most common of the PIK3CA mutations found in anal cancer. Therefore, we examined the effect of this mutation in our established mouse model of anal carcinogenesis.

Methods: We have an established murine model of anal cancer. Controls in this study were mice with wildtype PIK3CA gene and inducible CreER$_{TM}$ (12 mice). For the mutant mice, mice contained both the mutant PIK3CA gene and inducible CreER$_{TM}$ and were treated with tamoxifen, resulting in the expression of the mutant gene (6 mice). At 5 weeks of age, 0.1mg tamoxifen was applied topically to the anus daily for 5 days. All mice were treated with DMBA once a week with topical application of the carcinogen DMBA (0.12μM) at 5 weeks of age or the week following application of tamoxifen until time of sacrifice. The mice were monitored weekly to determine tumor onset.

Results: 4 of the 12 mice (33%) with the wildtype PI3KCA gene developed anal cancer over the 16 weeks of DMBA treatment while 5 of 6 mice (83%) expressing the mutant PI3KCA gene developed anal cancer over 16 weeks.

Mutant H1047R/Cre
Mice without E6E7 oncogenes

	No Tamoxifen	Tamoxifen
DMBA	4/12	5/6

Conclusions: These preliminary results demonstrate that the expression of the H1047R gene can produce anal cancer even without human papillomavirus expression, indicating the strength of this genetic mutation in the model.

B22

Analysis of Pulmonary Vascular Impedance and Remodeling in Ischemic Heart Failure

Thomas Murphy, Jennifer Philip, David Schreier, Diana Tabima, Timothy Hacker, Naomi Chesler

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Keywords	Heart Transplant, Vascular Remodeling, Pulmonary Hypertension, Myocardial Infarction, Animal Model

Abstract begins on following page

Background: Pulmonary hypertension secondary to left heart disease (PH-LHD) is the most common form of pulmonary hypertension and a leading cause of morbidity and mortality in patients with heart failure (HF). The mechanisms underlying the pathologic pulmonary vascular remodeling in PH-LHD remain poorly understood. This study aims to characterize the development of PH-LHD in a mouse model of ischemic HF.

Methods: Male C57/BL6 mice ages 6-8 weeks underwent left anterior descending artery ligation to induce myocardial infarction (MI). Sham animal underwent thoracotomy alone. Mice were studied at 12-weeks post-surgery. Cardiac function was assessed noninvasively via echocardiography and invasively via catheterization. Isolated lung perfusion was also performed. Pulmonary vascular fibrosis was assessed with picrosirus red histology staining.

Results: MI mice demonstrated evidence of HF at 12-weeks post-surgery evidenced by reduced left ventricle (LV) ejection fraction (35.2±3.5% vs 52.5±1.7%, p<0.01) and increased LV volumes (167±20 vs 87±3 µL p<0.01) compared to Sham mice. Diastolic dysfunction was present, evidenced by increased isovolumic relaxation time (22.1±1.0 vs 17.8±0.6 ms, MI vs Sham, p<0.01). MI mice also developed significant biventricular hypertrophy (increased LV and RV weights) compared to Sham mice. Development of PH-LHD was demonstrated by increased RV systolic pressure (29.0±1.2 vs. 19.6±1.0 mmHg p<0.01) in MI mice compared to Sham mice. In addition to increased LV end diastolic pressure (8.6±1.5 vs 2.0±0.1 mmHg p<0.05), MI mice had significant elevation in pulmonary vascular resistance (PVR), measured ex vivo (5.8±0.4 vs 4.1±0.6 mmHg- min/mL, MI vs Sham, p<0.05). Consistent with increased PVR, which suggests small pulmonary arteriolar narrowing, there was a 70.6% increase in perivascular collagen in the pulmonary arterioles post-MI compared to sham (p<0.001).

Conclusions: This study used a model of ischemic HF to study and characterize the development of PH-LHD. We demonstrate the development of pulmonary perivascular fibrosis and increased PVR, key pathologic features of human PH-LHD. Future studies with this novel animal model will improve understanding of the pathophysiology of this deadly disease as well as help to identify novel therapeutic targets.

Contributions of Myocardial Mechanics to Right Ventricular Failure: Model Simulations and Predictions

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Abstract begins on following page

Introduction: Pulmonary arterial hypertension (PAH) causes pressure overload of the right ventricle (RV) ultimately leading to right ventricular failure (RVF). Recent studies give evidence of important associations between myocardial structure, myocyte mechanics and RV function. However, no direct functional connections have been established. A computational model of the cardiovascular system which integrates cellular function into whole organ function has recently been developed. This model is an important tool to aid in investigating if and how the changes in myocyte mechanics associated with RVF contribute to impaired organ level RV function. We use the model to determine how observed changes in myocyte and myocardial mechanics from a mouse model of RVF impact organ level cardiac function. We compare results to published organ level RV functional outcomes.

Methods: RVF in the setting of PH due to bleomycin exposure has been previously shown to be characterized pressure overload, myocardial fibrosis and impaired myocyte maximum force generation (Fmax). We adapted a multiscale computational model that is tuned to the rodent cardiovascular system and which integrates a model of myocyte mechanoenergetics into a lumped parameter model of the cardiovascular system. Pressure overload was modeled by increasing pulmonary vascular resistance (PVR) and decreasing pulmonary artery compliance (PAC) to match experimental results. Simulations were carried out to explore the impact of pressure overload alone (↑PVR+↓PAC), plus myocardial fibrosis (↑PVR+↓PAC+fibrosis), and plus decreased Fmax (↑PVR+↓PAC+fibrosis+↓Fmax).

Results: Increase in afterload measured by RV systolic pressure and arterial elastance in simulations matched experimental results for bleomycin exposure. Simulation further demonstrated that pressure overload alone (↑PVR+↓PAC) results in decrease RV ejection fraction (EF) which is similar to experimental findings but relative preservation of cardiac output (CO) which does not recapitulate the reduction of CO observed *in vivo* (Figure 1). Simulations of myocardial fibrosis in the setting of pressure overload (↑PVR+↓PAC+fibrosis) show no impact on EF or CO compared to pressure overload alone (Figure 1). Simulation of impaired myocyte function (↑PVR+↓PAC+fibrosis+↓Fmax) resulted in further reduction of CO which approached the experimental results and as well as impaired contractility compared to pressure overload alone (Figure 1).

Conclusions: This work uses a multiscale computational model to explore contributions of cellular level changes to organ function. Furthermore, this study gives strong evidence that impaired myocyte maximum force generation is a key feature which directly contributes to hemodynamic hallmarks of RVF (reduced EF and CO) whereas myocardial fibrosis had limited impact on ventricular function.

Direct Association between Mitochondria Alterations and Impaired Contractile Function in Right Ventricular Failure Due to Pressure Overload in Rats

Tik-Chee Cheng, Jennifer L. Philip, Diana M. Tabima, Timothy A. Hacker, Naomi C. Chesler

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Keywords	Right Ventricular Failure, Pressure Overload, Hemodynamics, Pressure-Volume Analysis, Mitochondrial Structure

Abstract begins on following page

Introduction: Right ventricular failure (RVF) secondary to pressure overload is the main cause of death in pulmonary arterial hypertension (PAH). Reduced cardiac output and ejection fraction are the clinical hallmarks. Recent animal studies have shown RVF is associated with downregulation of energy metabolism. Mitochondria, via oxidative pathways, produce ATP necessary to sustain cardiac contraction and relaxation. The phenotype of dysfunctional mitochondria includes altered structure and diminished capacity for ATP production. Changes in mitochondrial structure are associated with mitochondrial biogenesis, a process regulated by peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α). Downregulation of PGC-1α has been demonstrated in RVF. However, the link between mitochondrial structure and right ventricular (RV) function has not been fully investigated. We hypothesize that hemodynamic changes of the RV are linked to abnormalities in mitochondrial structure in RVF.

Methods and results: Pulmonary artery banding (PAB) was used to induce RVF in rats. Rats with sham surgery were used for comparison. At 8 weeks post-PAB, pressure-volume analysis demonstrated RVF (35% decrease in ejection fraction and 42% reduction in cardiac index, $p<0.05$). RVF in PAB was associated with RV hypertrophy (1.5-fold increase in RV mass, $p<0.05$), ventricular-vascular uncoupling, diastolic dysfunction (75% decrease in ventricular compliance, $p<0.05$), and fibrosis. There was a significant, 2-fold increase in energy consumption by the RV as measured by pressure-volume area which was not matched by the increase in external work, which resulted in mechanical inefficiency in the PAB group.

Transmission electron microscopy demonstrated decreased RV mitochondrial cross-sectional area in the PAB group (0.585 vs. 0.444 μm2, PAB vs. Sham, $p<0.05$), which modestly correlated with RV ejection fraction. Associated with these changes in mitochondrial structure, PAB rats exhibited a 37% decrease in PGC-1α gene expression ($p<0.05$). PGC-1α levels were modestly correlated with RV contractility.

Conclusions: We demonstrate that RVF in pressure overload is characterized by mechanical inefficiency and diastolic dysfunction in addition to impaired contractile function and reduced cardiac output. These hemodynamic changes are associated with smaller mitochondria and impaired biogenesis. Correlations suggest a moderate but interesting relationship between mitochondrial changes and systolic function. Future investigation will evaluate the impact of these changes in mitochondrial structure and biogenesis on mitochondrial function and their impact on RV organ-level function to determine the therapeutic potential of targeting mitochondria to treat RVF.

Social-Enrichment Changes Ultrasonic Vocalization Frequency and Ventral Tegmental Dopamine in the *Pink1 -/-* Rat Model of Parkinson Disease

Cynthia A. Kelm-Nelson, Angel D. Chavez-Rivera, and Michelle R. Ciucci

Abstract begins on following page

Background: Approximately 90% of individuals with Parkinson disease (PD) have vocal communication deficits that negatively affect quality of life. Currently, only behavioral therapies have limited success in treating vocal communication deficits. The neural mechanisms underlying behavioral improvement of vocal communication is unknown. Our overarching hypothesis is that the frequent social contact aspect of therapy may be modulating brainstem regions affected by PD. For example, the dopamine-rich ventral tegmental area (VTA) (i) mediates motor behaviors including vocalization frequency, (ii) is susceptible to PD-related pathology, (iii) may significantly contribute to vocal dysfunction, and (iv) is an excellent neural candidate for examining the modulation of vocalizations by a behavioral treatment.

Objective and Methods: We use a validated *Pink1* -/- rat model of PD to test the hypothesis that daily socialization (defined as interactions with a conspecific female) of male *Pink1* -/- rats would increase VTA dopamine and decrease VTA GABA (GABA is the primary neuromodulator of dopamine in the VTA) compared to rats in a socially-isolated (no conspecific interactions) condition. Further, we hypothesized that VTA dopamine concentrations would positively correlate to increases in ultrasonic vocalization frequency in the *Pink1* -/- rat. To address these hypotheses, we analyzed average bandwidth (kilohertz-kHz) and peak frequency (kHz) of ultrasonic vocalizations, and quantified VTA dopamine and GABA protein concentrations in: (A) male socially-enriched *Pink1* -/- rats (n=12), (B) socially-isolated *Pink1* -/- rats (n=8), and compared these findings to (C) unaffected, age-matched wild type (WT) controls (n=6). A one-way analysis of variance was used to determine significant acoustic differences between treatment groups and controls. Independent student t-tests were used to determine differences in VTA protein concentrations between WT and social *Pink1* -/- animals; in cases where assumptions failed, non-parametric statistics (Mann Whitney U) test were used. Additionally, Pearson correlations were used to identify significant relationships among independent variables. The critical level for significance was set *a priori* to 0.05.

Results: We show that the average bandwidth of ultrasonic vocalizations in socially-enriched *Pink1* -/- rats are equivalent to WT control values (p=0.94) and are significantly increased compared to socially-isolated *Pink1* -/- rats (p=0.028). However, the average peak frequency is significantly reduced in socialized *Pink1* -/- rats compared to isolated (p=0.007) and WT (p<0.001). Compared to WT, socialized *Pink1* -/- rats had significantly increased dopamine concentrations in the VTA (Mann Whitney U Statistic=8.0, T=29, p=0.010). There was no significant difference in VTA GABA concentrations between WT and social *Pink1* -/- rats (p=0.14). Additionally, the average bandwidth positively correlated to increases in VTA dopamine concentrations within the *Pink1* -/- genotype (r=0.637, p=0.026).

Conclusions: These data demonstrate the importance of social experiences, and are critical in testing our overarching hypothesis that socialization-related therapies have positive effects on the mesolimbic dopaminergic system and vocalization behavior in PD. A better understanding of the pathology, how it pertains to voice and speech deficits, and how it is modulated by behavioral interventions will ultimately lead to improved treatments for individuals with PD.

Reduced Tongue Force and Altered Muscle Fiber Type Composition in a Rat Model of Post Stroke Dysphagia

Miranda Cullins, Kellie Bowen, Nadine Connor

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Keywords	Stroke, Dysphagia, Tongue, Muscle, Lingual

Abstract begins on following page

Purpose: Therapeutic interventions for post stroke dysphagia target the lingual muscles. While stroke has been shown to alter limb muscle fiber type, size, and number, the impact of stroke on lingual muscles is not known. Understanding what changes occur in lingual muscles after stroke may help guide clinical research on therapeutic interventions.

Method: Middle cerebral artery occlusion (MCAO) in the rat is a widely used model of unilateral ischemic stroke. Maximum voluntary tongue pressing forces were determined in 6-week old male Sprague-Dawley rats prior to receiving either a left MCAO (N = 6) or sham (N = 5) surgery. Tongue pressing forces were reassessed at one and two weeks post-surgery. Fluorescent immunohistochemistry was used to assess myosin heavy chain (MyHC) muscle fiber types.

Results: Post-MCAO tongue forces were significantly reduced from baseline at 1 and 2 weeks post-surgery (p = 0.001, p = 0.021). The contralateral genioglossus muscles (right) of the MCAO rats had significantly higher percentages of MyHC IIb than both the left genioglossus (p = 0.025) and the sham animal group (p = 0.003). The reduction in tongue force was correlated with both the infarct volume (Pearson's r = 0.91) and the percent of right genioglossus muscle fibers positive for MyHC IIb (r = 0.45).

Conclusion: The MCAO rat model of post stroke dysphagia develops tongue weakness and altered muscle biochemistry of contralateral lingual muscles. Future studies will determine the neural, muscular, and functional swallowing changes that occur due to the interactions of age, stroke, and therapeutic interventions.

Sensorimotor Behavioral Assays of Alexander Disease in a Rat Model

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Abstract begins on following page

Introduction: Alexander disease (AxD) is a fatal neurodegenerative condition caused by an autosomal dominant mutation in the glial fibrillary acidic protein (GFAP) gene. Individuals with AxD often have difficulty swallowing and speaking, poor coordination, and loss of motor control. Our purpose was to examine clinically relevant oral-motor function in a translational rat model of AxD (Gfap+/R237H) versus age-matched controls (wildtype; WT).

Method(s): Male Sprague Dawley rats (AxD, n=10; WT, n=9) were assessed for: mastication [biting; chewing], tongue force and press rates, functional swallowing via videofluoroscopy [bolus area, jaw motion rate, bolus velocity, head compensation, gag, aberrant bolus flow], and ultrasonic vocalization (USV) characteristics [number of calls, duration, max amplitude, mean frequency, type]. Dependent variables were analyzed with one-tailed t-tests ($\alpha < 0.05$).

Result(s): We found significantly reduced tongue force ($p < 0.001$) in AxD rats compared to WT. AxD rats showed significantly fewer bites/sec ($p < 0.007$) and higher number of chewing events during mastication ($p < 0.001$). The AxD rats had a significantly greater number of USVs ($p < 0.05$). No significant differences were found with videofluoroscopy.

Conclusions (including clinical relevance): AxD rats showed oral motor deficits (tongue function and mastication) in the absence of USV or functional swallowing deficits. These data parallel clinical findings in children with AxD. Since the rat R237H is equivalent to the common R239H mutation in humans, this model may be useful for research examining underlying mechanisms and treatment for AxD.

Molecular Signatures of Cellular Injury and Regeneration in Burn Tissue

Amin Afrazi, Ziyue Wang, Ying Li, Christina Kendziorski and Angela Gibson

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Abstract begins on following page

Introduction: The depth and healing potential of burn wounds are determined primarily by visual assessment in the clinical setting, which may result in an incomplete assessment of regenerative capacity. There is a scarcity of data for understanding the biological processes associated with regenerative capacity following burn injury in humans. Using RNA-Seq, we sought to identify candidate genes linked to cellular damage/injury signaling and wound healing that are differentially expressed in human burn tissue compared to uninjured skin. Our goal was to identify genes that may be targeted for development of novel therapeutics or modifications in surgical therapy to enhance autologous wound regeneration.

Methods: Fifteen patients undergoing excision and grafting for their burns were consented for tissue collection. Biopsies of the wounds were obtained after depth identification using visual assessment by the operating burn surgeon. Depth determination was validated by 34 burn surgeons using digital images obtained at the time of intraoperative visual assessment to determine inter-rater reliability. RNA Sequencing was performed on biologic replicates of deep partial thickness (DPT) burns, full thickness (FT) burns and normal (NRL) skin. Differentially expressed (DE) gene analyses and enrichment analyses were performed comparing DPT, FT, and NRL tissue.

Results: There was a 90% agreement in depth categorization among all burn surgeons surveyed suggesting reliable wound stratification for further analyses. Altogether, 7501 DE genes were identified amongst the samples. Analysis demonstrated that Endoplasmic Reticular (ER) stress, antigen processing, pro-inflammatory cytokines, metabolic, and mitotic pathways were most affected in burn tissue compared to normal tissue. Specifically, the transcription factor CHOP and Apoptosis-inducing factor (AIFM3), known drivers of apoptosis from ER stress, were upregulated, 3.2 and 6.3-fold respectively in FT versus NRL tissue. Additionally, the innate immune receptor Toll-like Receptor 4, a sentinel receptor of Damage-Associated Molecular Pattern (DAMPs) molecules released following cellular injury and known activator of ER stress, was upregulated in FT 3.5-fold. IL1b (DPT v NRL) increased 30-fold. A decrease in stem cell markers, CD34 and LGR5, was also noted by 3.3 and 10-fold in FT versus NRL respectively. Genes that were differentially expressed in DPT burns compared to FT tissue were associated with keratinocyte/epidermal differentiation (Loricrin 1102-fold, LCE1A 1167-fold increases) and filament cytoskeleton organization (KRT13 3217.49-fold increase). Signaling proteins associated with cellular regeneration, WNT5a and WNT7a, were found to be upregulated 6 and 48-fold respectively while a marker of undifferentiated stem cells, ERAS, was downregulated 33-fold.

Conclusions: DE pattern comparisons of DPT or FT versus NRL tissue suggest that burn injury induces inflammation and apoptosis in parenchymal and/or stem cells. DE of genes in DPT versus FT highlight key regenerative and differentiation pathways that are dysregulated in FT. These data lay the foundation to identify and characterize targets for therapeutics or modifications in surgical therapy aimed at enhancing autologous wound regeneration and preventing burn injury propagation. Future studies will focus on the development of an *ex vivo* injury model system using human skin to further elucidate the fundamental molecular players in healing and injury that are present within varying depths of burn injured tissue.

Coordination of Oropharyngeal Pressures during Swallowing

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Abstract begins on following page

Introduction: Oro-pharyngeal swallowing is a complicated movement which involves the coordination of multiple structures. Additionally, appropriate propagation of pressure is required to propel a bolus from the oral cavity to the esophagus. Recently, the technique for oral and pharyngeal pressure measurement has evolved using new pressure sensing methods. However, little is known about synchronous tongue and pharyngeal pressures and oropharyngeal pressure propagation. This study aimed to measure tongue pressure and pharyngeal pressure, and to clarify the detail of pressure generation of oropharyngeal pressure during swallow. In this presentation, the preliminarily results were reported.

Material and Methods: Four healthy volunteers (1 male, 3 females, 51.6 +/- 17.8 years old) participated. Tongue and pharyngeal pressure was measured using two, synchronized, pressure recording systems, a sensor sheet system (Swallow Scan, Nitta) and high-resolution manometry (Mano Scan, Given Imaging) respectively. For synchronization measurement, the signal from the sensor sheet system and high-resolution manometry system was entered to AD converter (Powerlab ML880, AD Instrument). Before measurement, the time difference of events measured by all devices was calculated to confirm synchronization. The time lag between the two pressure recording systems was 0.10 +/- 0.01 seconds, this was thus accounted for in the subsequent analysis. The sensor sheet for tongue pressure is 0.1 mm thick and has five pressure sensing points. The sheet was attached to the palatal mucosa directly using sheet-type denture adhesive. The high- resolution manometry catheter, has sensors located one cm apart for a 36 cm distance and is inserted transnasally into the pharynx and esophagus. After an accommodation period, each participant performed, multiple queued swallow and non-swallow tasked. Pressure measurements were recorded at a frequency of 100 Hz. The maximum magnitude and duration of pressure was calculated, and the onset, peak, offset time of pressure generation was compared among each tongue sensor sheet and pharyngeal manometry sensor. Here we reviewed only the queued, 10 ml water swallows.

Results: Either tongue pressure or pressure at the velopharynx appeared first, and the onset of tongue pressure was earlier than onset of UES opening. The tongue pressure and pharyngeal pressure at tongue base and hypopharynx return to baseline at approximately the same time and the pressures were maintained until UES closure. The time of peak pressure at each sensor gradually appeared at a later time point moving for rostral to caudal sensors. The tongue pressure (7.0 +/- 4.6 kPa) was lower than pharyngeal pressures, and the pharyngeal pressure at post-UES location and time point (24.4 +/- 6.9 kPa) was the greatest. The duration of tongue pressure (0.71 +/- 0.15 sec) was longer than the duration of UES opening (0.59 +/- 0.08 sec). This is consistent with the necessity maintain a pressure gradient to transport the bolus from the oral cavity to the esophagus and to prevent backflow.

Conclusion: This preliminarily study suggested that tongue and pharyngeal pressure are generated in a measureable and coordinated pattern. We are planning to collect further data on additional bolus conditions and to apply this assessment of swallowing coordination in dysphagic patients.

Comparing Success Rates of Mechanical and Labial Airflow Interruption for Pediatric Aerodynamic Assessment

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Keywords	Aerodynamics, Pediatrics, Subglottal Pressure, Labial Interruption, Mechanical Interruption

Abstract begins on following page

Objectives: Subglottal pressure (Ps) is the driving force behind voice production. Phonation threshold pressure (PTP) is the minimum pressure needed to produce voice. Both are measures of vocal health and can be measured noninvasively, though reliability can be inconsistent. Complete airflow interruption has been validated for measuring the subglottal pressure and phonation threshold pressure in adults, but has not yet been tested in children. Our objective was to identify successful methods of measuring these parameters in a pediatric population.

Methods: 40 subjects (22 females) performed 10 trials using each of these setups: labial interruption (L), mechanical interruption with a mask (MA), and mechanical interruption with a mouthpiece (MO). A successful trial was defined as at least one airflow interruption achieving a phonation cutoff with a corresponding spike in the pressure trace. Success rates were compared by age group and testing method using ANOVA, Tukey's HSD analysis, and correlation coefficient analysis.

Results: For children aged 4-7 years, success rates were 30.8%, 48.1%, and 78.9% for MA. MO, and L respectively. For children aged 8-12, success rates were 47.8%, 55.7%, and 92.6%. For children aged 13-17, success rates were 72.8%, 83.0%, and 88.5%. Using ANOVA, there was a significant difference in success rate based on method for ages 4-7 ($p=0.004$) and 8-12 ($p<0.001$), but not for 13-17 ($p=0.312$). Using ANOVA, there was a significant difference in success rate based on age for MA ($p=0.008$) and MO ($p=0.032$), but not L ($p=0.057$). Correlation coefficients comparing success rate with age were calculated: for MA $r=0.470$ ($p=0.002$); MO $r=0.375$ ($p=0.017$); and L $r=0.275$ ($p=0.081$).

Conclusions: This study found that the success rate of pediatric SGP and PTP measurement was higher when using labial interruption than mechanical interruption. The mechanical methods showed an increasing success rate with increasing subject age. More research into increasing success rates in younger children is warranted.

Quantitative Second Harmonic Generation Imaging of Vocal Fold Collagen Composition in Leporine and Porcine Models

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Keywords	Second Harmonics Generation, Vocal Fold Viscoelasticity, Animal Models, Collagen Alignment, Collagen Gradient

Abstract begins on following page

Objective: Vocal fold viscoelasticity is determined in part by collagen composition; a vertical stiffness gradient is suggested to facilitate mucosal wave propagation. Collagen alignment and straightness is quantitatively characterized by nonlinear second harmonic generation (SHG) imaging. We examine leporine and porcine vocal folds, showing collagen composition variation that is species, location, and strain-specific, as well as a vertical collagen gradient that may correspond with stiffness and vocalization.

Methods: Leporine (n=4) and porcine (n=4) larynges were harvested and fixed in situ. Samples were transversely sectioned and collagen was imaged via SHG for two inferior-superior sections at five anterior-posterior locations. Porcine samples were also fixed and imaged under tensile strain (0%, 5%, 15%, 20%, n=4 per group). Two-way RM-ANOVA tested for section and location differences in each species. Multi-way RM-ANOVA tested for section, location, and strain differences in porcine samples.

Results: Porcine collagen alignment and straightness were higher inferiorly (p=0.0053, p=0.002), while leporine (p=0.438, p=0.933) results showed no difference. Significant interactions between strain and inferior-superior location for alignment (p=0.006) and straightness (0.0487) were found in the porcine model.

Conclusion: Porcine results correspond to porcine and human vocal fold stiffness gradient findings in the literature; therefore, the porcine model may be best when collagen architecture is relevant. Absence of a leporine collagen gradient is notable because rabbits are less vocal, indicating collagen composition may be related to voice use. Finally, porcine collagen composition changes with strain support collagen involvement in strain-stiffening that may impact the stiffness gradient.

Reliability of Mechanical and Labial Interruption for Aerodynamic Measurements in the Pediatric Population

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Abstract begins on following page

Introduction: Complete mechanical airflow interruption and labial interruption are noninvasive methods of estimating subglottal pressure (PS) and phonation threshold pressure (PTP). PS is the driving pressure for voice production and PTP is the minimum pressure required to produce voice; both are reflective of laryngeal health and function, which can be affected by pathology. A reliable means of measuring these vocal parameters allows for easier diagnosis and treatment monitoring of vocal pathologies. Labial interruption is currently utilized clinically as it is fast, noninvasive and can produce valid estimations of PS and PTP with proper subject training. Mechanical interruption was developed as an alternative to labial interruption, requiring less subject training to obtain the same reliable results with less subjectivity. Both methods introduce a complete interruption to the subject's phonation; immediately after the interruption, the intra-oral and subglottal pressure equilibrate, and the intra-oral pressure reading represents Ps. The same measurement performed at a minimal volume represents PTP. While both methods have been tested to produce valid and reliable results in adults, the reliability of these techniques has yet to be determined in the pediatric population. The purpose of this study was to compare the reliability of mechanical interruption methods with that of labial interruption in the pediatric population.

Methods: A repeated measures study was performed with 40 healthy, non-dysphonic subjects. Each subject completed 40 trials: 10 trials with a mask and 10 with a mouthpiece using the complete mechanical interrupter device; 10 trials at a normal volume and 10 at a quiet volume using labial interruption. During a mechanical trial, subjects phonated an /a/ vowel sound at a constant volume while they were interrupted 5 times by a mechanical balloon valve. During a labial trial, subjects phonated the labial plosive /pa/ 5 times to create interruptions. Pressure, audio, sound pressure level and flow were recorded. The pressure traces produced by each interruption were averaged from each trial and analyzed to obtain PS and PTP for each subject. A paired t-test was used to compare the standard deviations of each mechanical method against labial interruption.

Results: The mean standard deviations across all subjects for PTP were 0.6647 for labial and 0.4426 and 0.4392 for the mechanical mask and mouthpiece, respectively. Mean standard deviations for PS were 1.0119 for labial and 0.7991 and 0.7457 for mechanical mask and mouthpiece. In paired t-tests, differences between mechanical and labial methods were significant for PTP measurements ($p < 0.05$) with mechanical having a lower standard deviation for both mask and mouthpiece. There were no significant differences between PS measurements. (67 words)

Conclusion: Mechanical interruption has demonstrated more reliable PTP measurements than labial methods in the pediatric population. Reliability of PS measurements were similar between the two methods. This method of aerodynamic assessment is reliable even in children and is a valuable adjunct to pediatric voice assessment.

PkcÎ´ Mediated Serine Phosphorylation of Stat3 Worsens AAA by Enhancing Ripk3 Expression & Necrosis

Kartik Gupta, Bo Liu

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Abstract begins on following page

Introduction: Excessive necrosis is undesirable in many cardiovascular conditions including plaque ruptures and aneurysm progression. Receptor interacting kinase 3 (RIP3/ RIPK3) plays a decisive role in necroptosis which is highly immunogenic. The upregulated levels of RIP3 found in atherosclerosis, stroke and aneurysm is likely to skew the cellular injury response from apoptosis toward necroptosis. Vascular smooth muscle cells (VSMCs) are targeted to undergo necroptosis in AAA. Although RIP3 ablation protects against these diseases conditions, our knowledge regarding Rip3 gene regulation is nearly blank.

Objective: to define the signaling and transcriptional mechanisms underlying Rip3 regulation in vascular smooth muscle cells

Results: We treated mouse VSMCs with various cytokines and observed TNFa, LPS and Poly (I:C) increased RIP3 expression. To study the mechanism by which inflammation might upregulate RIP3, we analyzed the proximal and distal regions of Rip3 gene and identified a highly conserved GAS-motif in a distal region. Further, we demonstrate using chromatin immunoprecipitation assay that this element is bound to STAT3 S727in a PKCÎ´-dependent manner and when stimulated by the PKCÎ´ agonist PMA. Further, RIP3 upregulation in mouse VSMCs was lost when PKCÎ´ was ablated; conversely, activation of PKCÎ´ signaling could not induce RIP3 when STAT3 was knocked down. Therefore, PKCÎ´ dependent phosphorylation of STAT3-Ser 727 in aortic SMCs causes its binding to the distal enhancer and may regulate RIP3 expression in a cytokine-inducible manner.

Smooth Muscle Cells Accelerate Endothelial Regeneration through a Protein Kinase C-delta-Dependent Secretion of CXCR2 Ligands

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Abstract begins on following page

Background: Efficient regeneration of denuded endothelial cells (ECs) is an important process that counteracts the pro-stenotic activities. Unfortunately, this natural healing process is frequently compromised by disease conditions such as diabetes. Protein kinase C-delta (PKCδ) plays a complex role in the arterial injury response by regulating apoptosis of vascular smooth muscle cells (SMCs) as well as production of chemokines capable of attracting resident and circulating cells. In this study, we explored whether SMCs participate in endothelial repair through a PKCδ-dependent paracrine mechanism.

Methods and Results: Following balloon injury to the rat carotid, SMC-specific gene transfer of *Prkcd* accelerated reendothelialization compared to the empty vector, reflected by a larger area excluded from Evans blue measured 14 days post injury (59.60±5.01% vs 25.38±7.52%). In contrast, SMC-specific knockdown of endogenous *Prkcd* delayed reendothelialization compared to the non-targeting shRNA control (41.31±6.54% vs 70.31±5.97%). *In vitro*, media conditioned by AdPKCδ-infected SMCs increased endothelial wound healing without affecting their proliferation and viability. In addition, SMCs in a PKCδ-dependent fashion attracted circulating angiogenic cells (CACs), a cell population that promotes neovascularization via production of angiogenic factors. A PCR- based array analysis identified *Cxcl1* and *Cxcl7* among others as PKCδ-mediated chemokines produced by SMCs. Blocking CXCL7 or CXCR2 significantly inhibited endothelial wound healing and CAC migration in response to AdPKCδ-infected SMC conditioned media. *In vivo*, PKCδ overexpression in SMCs following balloon injury increased CXCL7 production and stimulated CACs recruitment to injured arteries. Furthermore, insertion of a *Cxcl7* cDNA in the lentiviral vector that carries a *Prkcd* shRNA overcame the negative effects of *Prkcd* knockdown on reendothelialization.

Conclusions: Regeneration of denuded endothelium involves multiple cell types from the vascular wall as well as circulation. SMCs stimulate reendothelialization in a PKCδ- dependent paracrine mechanism, likely through CXCL7-mediated recruitment of ECs from uninjured endothelium and CACs from circulation.

Targeting FoxM1 in Vascular Smooth Muscle Cells Induces Apoptotic Cell Death

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Keywords	Smooth Muscle Cells, Apoptosis, Mitotic Failure, Balloon Angioplasty. Vascular Injury

Abstract begins on following page

Purpose: To delineate the molecular mechanisms underlying smooth muscle cell phenotypic transformation during vascular pathogenesis.

Background: Smooth muscle cells (SMCs), one of the major cell types lining vessel walls, undergo multiple signaling and functional changes during the pathogenesis of vascular diseases including atherosclerosis, restenosis (the re-narrowing of the vessel lumen post-vascular reconstructive procedures such as balloon angioplasty and bypass), and aortic aneurysm. It is well appreciated that the phenotypic plasticity of SMCs allows them to initiate survival programs and acquire a proliferative and migratory phenotype in response to environmental insults such as injury. However, how these responses become dysregulated is not fully understood. FoxM1 is a proliferation-associated transcription factor shown to play a role in a variety of biological processes including cell cycle progression, cell survival, DNA damage repair, and apoptosis. Furthermore, FoxM1 has been shown to be required for SMCs during embryonic development, and has also been implicated in functioning in hypoxia-induced pulmonary SMC proliferation. Here, we hypothesize that FoxM1 re-activation in injured arteries functions as a critical mechanism triggering the phenotypic transformation of smooth muscle cells.

Methods & Results: The carotid artery balloon injury of male Sprague-Dawley rats was used to model vascular injury. Immunofluorescence staining was carried out using an anti-FoxM1 antibody on sections from injured carotid arteries or uninjured controls collected at 3, 7, or 14 days post injury. We observed that FoxM1 expression was up-regulated in injured arteries primarily at day 7 and 14 post-balloon angioplasty. Expression of FoxM1 in injured arteries co-localized with PCNA, a marker of proliferation. The up-regulation of FoxM1 protein could be replicated in cultured rat SMCs by serum stimulation. Using thymidine synchronization, we observed that FoxM1 expression followed a cell cycle specific pattern *in vitro*. In order to begin testing if FoxM1 might play a role in SMC viability, we used thiostrepton, a chemical inhibitor of FoxM1, to inhibit FoxM1 expression and measured cell viability via CCK-8 assay. Thiostrepton resulted in a decrease in cell viability compared to control. Additionally, both siRNA and thiostrepton inhibition of FoxM1 led to induction of apoptosis measured by flow cytometry and cleaved caspase 3 induction. To corroborate our findings, we tested an additional chemical inhibitor, FDI-6, and observed that it also led to cleaved caspase 3 induction and cell death. Because FoxM1 has been shown to regulate microtubule dynamics and be necessary for mitosis, we utilized immunocytochemistry to visualize potential changes in microtubules upon FDI-6 treatment. We observed that FDI-6 treated SMCs exhibit disorganized microtubule networks. Furthermore, FDI-6 treatment decreased expression of Eg5, a motor protein essential for proper microtubule orientation and critical for mitosis execution.

Conclusions: In conclusion, our data suggest that vascular injury stimulates FoxM1 expression in SMCs. The expression pattern of FoxM1 both *in vivo* and *in vitro* corresponds with the proliferative status of SMCs. The loss of FoxM1 induces apoptosis and our data suggest this could be due to FoxM1 modulation of Eg5. Downregulation of Eg5 could result in the microtubule disorganization and subsequent aberrant mitosis we observed in FoxM1-inhibited SMCs. We anticipate our findings to be a starting point for more in depth analysis to define the cellular and molecular mechanisms underlying vascular disease, which can pave the way for development of novel pharmacological strategies.

Autoimmunity and Pollution: Identifying Tools for Assessing Pollution Samples for Autoimmune Promoting Activity

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Abstract begins on following page

Introduction: Autoimmune diseases have been dramatically increasing in incidence worldwide with over 80 recognized diseases. Particulate matter (PM) from airborne pollution has been strongly associated with aggravating autoimmunity in humans, but it has been difficult to characterize mechanisms for aggravation of disease and identify which exposures are most pathological. Our group studies the role the aryl hydrocarbon receptor (AHR) on T-cell differentiation and effector function. Our previous studies suggest that inhalation of polycyclic aromatic hydrocarbons (PAHs) found in PMs may impact autoimmune disease through the AHR. We hypothesized that different pollution samples will induce varying, yet predictable effects on autoimmune disease depending on the balance of the fractions of chemicals in the sample. To characterize this, mice were exposed to inhaled pollution samples (urban dust particle (UDP) and two diesel emission particles (DEP1 and DEP2)) and control two weeks prior to induction of experimental autoimmune encephalomyelitis (EAE). Inhalation of both diesel samples significantly aggravated EAE, while exposure to UDP trended towards ameliorating disease. In this study we explored in vitro assays that could characterize the pathologic effects of different exposures.

Methods: Splenocytes of 2D2 mice, transgenic for a T-cell receptor specific to MOG (the antigen that mice respond to in EAE), were stimulated with MOG peptide and LPS (to mature DCs). Dilutions of the three samples were added to the cells. The cells were cultured for 4-5 days and the supernatants of the cultures were harvested. ELISA was used to measure IFNg and IL-17 levels, as measures of immune activation. Cytokine bead arrays were also used to measure additional cytokines. We cultured bone-marrow derived dendritic cells (BMDC) in another assay, exposed them in culture for 24 hours with pollutants or control, and assayed them for cytokine production.

Results: In the MOG assay, all three PMs led to decreased levels of IL-6. Diesel exposure increased IFNg, but decreased IL-10 expression, a cytokine known to suppress immune responses. In contrast, UDP had no effect on IFNg expression, but increased IL-17 and IL-10 expression. In the BMDC assay, exposure to UDP increased levels of IL-10 production while the diesel samples did not. UDP also increased IDO expression in DCs, an enzyme involved in the production of regulatory T cells.

Conclusion: The current data suggests that the in vitro assays may have potential for screening the autoimmune promoting activity in samples of pollution. UDP, which is made up of multiple different sources of pollution, is known to include a complex mixture of chemicals, which may affect many different cell-types, whereas diesel samples, derived from single sources of pollution, may have more predictable and specific consequences on T-cell differentiation and disease. Further characterization of this will allow improved strategies for avoidance and remediation of polluted environments.

Differential Effects of Atmospheric Particulate Matter on a Model of Autoimmune Disease

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Keywords	Atmospheric particulate matter (PM), Th17 Cells, EAE, Autoimmunity, polycyclic aromatic hydrocarbons (PAHs)

Abstract begins on following page

Exposure to atmospheric particulate matter (PM) is associated with increased incidence and severity of autoimmune disease. Despite a clear correlation between pollution exposure and autoimmunity in humans, a definitive mechanism has not been defined, and identifying specific exposures or chemicals that are most pathologic remains elusive. In this manuscript we test the hypothesis that exposure to inhaled PM containing specific mixtures of polycyclic aromatic hydrocarbons (PAHs) enhances Th17 differentiation through the aryl hydrocarbon receptor (AHR), leading to aggravation of autoimmunity. Various atmospheric PM samples were fractionated and the organic fraction (OF), synthetic PAH mixtures, and PM were tested. First, we tested whether atmospheric PM samples aggravate autoimmunity *in vivo* using experimental autoimmune encephalomyelitis (EAE), a murine model of MS. Our results show that atmospheric PM differentially affects EAE, with aggravation of disease by two different diesel PM samples, but amelioration of disease by a complex mixture of urban dust PM. However, when the organic fraction was tested, the diesel samples revealed differential results. To address these differences, we investigated the ability of the PM, OF, and PAH mixtures to enhance Th17 differentiation *in vitro*. Organic fraction samples enhance Th17 differentiation in an AHR-dependent manner to varying degrees. Additionally, only two of the PAH mixtures enhance Th17 differentiation in an AHR-dependent manner. The findings of this study have important ramifications for understanding the components of atmospheric PM that lead to pathology and the mechanisms in which the target components act.

Prolongation of Transplant Skin Allograft Survival with Dietary Supplementation of Aryl Hydrocarbon Receptor Ligands

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Abstract begins on following page

Introduction: The Aryl Hydrocarbon Receptor (AhR) is a cytosolic transcription factor with numerous endogenous and xenobiotic ligands playing a key role in various cellular processes especially immune cell function and development. Differential effects of AhR ligands upon CD4 naïve T-cell differentiation have been described with toxin 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) promoting regulatory T-cells while FICZ, a tryptophan metabolite, promotes Th17 responses. Previously we have demonstrated prolongation of graft survival in fully mismatched skin allograft transplant models (Balb/c to C57BL/6) with intraperitoneal administration of TCDD and early rejection with FICZ treatment. Additionally, prior work demonstrated dietary AhR ligands modulate local mucosal immune responses conferring protection in a murine *C. Difficile* colitis model. In the present work we assess the regulatory effect of dietary AhR ligands on peripheral immunity via a minor mismatch skin transplant model. Our goal is to further characterize the immune-modulatory effects of dietary AhR ligands elucidating a previously unrecognized influence of the host diet upon augmenting allograft rejection.

Methods: 7 week old C57BL/6, AhR+/- or AhR null female mice were maintained on semi-purified base (SPB) diet deficient of AhR-ligands or SPB diet with Indole-3-Carbinol supplementation at 3ppm (I3C diet) for 3wks prior to and throughout the model. Skin grafts were obtained from male donors and monitored daily for evidence of rejection post-transplant. Other animals were sacrificed at Post-op day 10 at which time grafts were analyzed for infiltrates via flow cytometry. Spleens or draining LNs were tested for reactivity to HY peptide *in vitro*. Cytokines were assessed via ELISA after female splenocytes were exposed to male-derived HY peptide. Intestinal immunophenotyping via Flow cytometry was completed on animals maintained on both diets.

Results: Animals on SPB demonstrated decreased graft survival time (GST) while those given I3C diet demonstrated significantly increased GST (Median GST of 46 vs 15.5 days $p<0.05$). AhR null animals demonstrated accelerated graft lost vs AhR+/- counterparts which was not prolonged on I3C diet (Median GST, AHR null on SPB vs I3C diet were 17 vs 15.5 days respectively). Animals maintained on SPB diet demonstrated a loss of intestinal Treg, Innate Lymphoid Cells type 3, and γδ T-cells. However, I3C supplementation led to maintenance of these mucosal immune cell populations. AhR-mediated graft survival was correlated to decreased IFNγ-producing CD4-positive Graft-Infiltrating Leukocytes (GILs). Interestingly, splenocytes and LN-derived leukocytes obtained from animals on I3C diet demonstrated blunted IFNγ, TNFa and IL10 production following HY peptide exposure, with no effects on IL6 production.

Conclusions: These data demonstrate a novel regulatory pathway for AhR-mediated prolongation of graft survival via dietary supplementation of AhR ligands. While the mechanism remains unclear, these data suggest modulation of peripheral immune responses through possible effects on GIL trafficking and/or IFNγ production by GILs. Ongoing studies focus upon AhR downstream signaling responsible for protection through assessment of transgenic CD4-specific knockouts in our transplant model and *in vitro* T-cell differentiation studies. These data demonstrate the importance of the diet upon peripheral immune responses which may play an important role in augmentation of future immunosuppressive therapy regimens post-transplantation.

B30
Use of TCR Transgenic Splenocytes to Characterize the Impact of Pollutants on Immune Responses

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Abstract begins on following page

Introduction: Particulate matter (PM) from airborne pollution has been strongly associated with aggravating autoimmunity and transplant rejection in humans, but it has been difficult to characterize mechanisms for aggravation of disease and identify which exposures are most pathological. Our group studies the role the aryl hydrocarbon receptor (AHR) on T-cell differentiation and effector function. Our previous studies suggest that inhalation of polycyclic aromatic hydrocarbons (PAHs) found in PMs may impact autoimmune disease through the AHR. We hypothesized that different pollution samples will induce varying, yet predictable effects on autoimmune disease depending on the balance of the fractions of chemicals in the sample. To characterize this in vitro, splenocytes from TCR transgenic mice that recognize a single antigen were stimulated in vitro with the antigen in the presence or absence of pollutants +/- LPS to activate dendritic cells.

Methods: Splenocytes of 2D2 mice (transgenic for a T-cell receptor specific to MOG that induces EAE in mice) or OT-II mice (transgenic for a T-cell receptor specific to ovalbumin) were stimulated with their appropriate antigenic peptide +/- LPS (to mature DCs). Dilutions of the three PM samples were added to the cells. The cells were cultured for 4-5 days and the supernatants and cells were harvested. ELISA was used to measure IFNg and IL-17 levels in the culture supernatant. Cytokine bead arrays were also used to measure additional cytokines. Cells were used to isolate RNA for RT-PCR analysis of markers of AHR activation and other immune markers.

Results: In the MOG assay, all three PMs led to decreased levels of IL-6. Diesel emission particles (DEP) increased IFNg, but decreased IL-10 expression, a cytokine known to suppress immune responses. In contrast, Urban Dust Particles (UDP) had no effect on IFNg expression, but increased IL-17 and IL-10 expression. RT-PCR analysis is ongoing as is the OT-II experiments.

Conclusion: The current data suggests that the in vitro assays may have potential for screening the autoimmune promoting activity in samples of pollution. UDP, which is made up of multiple different sources of pollution, is known to include a complex mixture of chemicals, which may affect many different cell-types, whereas diesel samples, derived from single sources of pollution, may have more predictable and specific consequences on T-cell differentiation and disease. Further characterization of this will allow improved strategies for avoidance and remediation of polluted environments.

Bioengineering Pre-vascularized Scaffolds Using Decellularized and Biofunctionalized Plant Tissues

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Abstract begins on following page

Background: Despite the recent advances in regenerative medicine, it is still challenging to engineer tissues for replacement such as muscle fascia. The main challenge is to manufacture scaffolds with an internal vascular network able to transport fluids, nutrients and oxygen to fulfill the energy needs of the hosted cells. Although decellularized animal tissues can be used as pre-vascularized scaffolds, cost and limited supply are major limiting factors. Our group has pioneered the use of decellularized plant tissues to manufacture perfusable and pre-vascularized scaffolds with goals to turn them into muscle and fascia.

Methods: Plant tissues were decellularized by immersion in baths of bleach and detergents. Different approaches for surface functionalization were explored to enable human cells adhesion. These methods comprised: surface coating with a RGD-dopamine conjugate (RGDOPA) and biomineralization. In vitro and in vivo experiments were performed to demonstrate the ability of these scaffolds to support stem cell culture.

Results: Scanning electron microscopy characterization revealed that the plant-derived scaffolds maintain their porosity and vascular network after decellularization. The surface of these scaffolds was amenable to functionalization. In fact, RGDOPA-coating and biomineralization of the scaffolds both enabled human cells adhesion. Moreover, it was possible to harness the high surface area of decellularized plant stems to significantly expand human cells for up to 50 days of in vitro culture. On the other hand, decellularized leaves were successfully used to culture functional cardiomyocytes in vitro. Interestingly, we also observed the typical contact guidance behavior: human cells conformed to the structural patterns inherent of the plants surface. In vivo characterization also confirmed elevate biocompatibility of plant-scaffolds. Decellularized leaves implanted subcutaneously were well tolerated and seem to facilitate angiogenesis and deposition of organized matrix.

Conclusion: Plant-scaffolds maintain desirable traits even after decellularization. They can be functionalized to enhance their interaction with human cells. High surface area and excellent fluid transport abilities enable cell expansion for prolonged periods of time. Decellularized plant-scaffolds bear the structural sophistication required to engineer functional and vascularized tissues.

Extracellular Matrix Breaks in the Embryonic Intestine of the *Fgfr2IIIb* Mutant Mouse Model of Intestinal Atresias

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Abstract begins on following page

Introduction: Cellular identity changes, either mesenchymal to epithelial transition (MET) or epithelial to mesenchymal transition (EMT) are important processes during organogenesis that are also found in pathologies such as cancer. Our lab has previously shown invasion of the epithelium by mesenchymal cells in a *Fibroblast growth factor receptor 2IIIb (Fgfr2IIIb-/-)* intestinal atresia mouse model. We also hypothesize that cells undergo EMT at the atretic regions where cells lose their epithelial identity and move out into the mesenchymal space. In either of these cases, we expect changes to be present in the extracellular matrix surrounding the epithelial compartment of the *Fgfr2IIIb-/-* intestines as compared with wild type controls with heavy breaks at regions where cellular movement occurs.

Methods: C57BL/6J wild type or *Fgfr2IIIb-/-* embryos were harvested at embryonic age (E) 10.5 and E11.5. Embryos were fixed in 4% paraformaldehyde, dehydrated, embedded in paraffin, and sectioned at 5µm for immunostaining. E-cadherin was used as an epithelial cell marker, DAPI was used as a nuclear stain, and laminin was used as an extracellular matrix marker. Images were taking on a confocal microscope and measurements were done using Fiji software. The percentage of extracellular matrix circumference containing laminin breaks was calculated along with average number of breaks seen per image Z-stack.

Results: The extracellular matrix (ECM) in control intestines showed a high level of continuity with few laminin breaks (as a percentage of total circumference). Within the *Fgfr2IIIb-/-* intestines, we saw an increase in both the number of extracellular matrix breaks and the percentage of the circumference made up of such breaks. These occurred in both the proximal colon and in the very distal colon at the area of the atresia formation within this model.

Conclusion: An increase in extracellular matrix breaks in the intestine of *Fgfr2IIIb-/-* embryos corresponds to the regions of the intestine in which we have previously observed potential cellular migration. Future experiments need to be conducted to see if these breaks correspond to the exact locations where we observe cellular migration and if these breaks are seen when examining other extracellular matrix components (such as collagen IV).

Increased Apoptosis Does Not Co-localize to the Istal Colon in the *Fibroblast Growth Factor Receptor 2IIIb (Fgfr2IIIb-/-)* Mouse Model of Intestinal Atresia

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Abstract begins on following page

Introduction: The etiology of intestinal atresias is not fully understood though increased epithelial apoptosis and decreased epithelial proliferation during intestinal organogenesis has been hypothesized to cause colonic atresia in the *Fibroblast growth factor receptor 2IIIb (Fgfr2IIIb-/-)* mouse model. We hypothesize these events co-localize to distal colon (where an atresia will form) while being excluded from the proximal colon.

Methods: TUNEL staining of 5µm sections of intestine allowed for quantification of epithelial apoptosis from embryonic (E) day 9.5-12.5. PHH3 staining of 5µm sections allowed for quantification of cellular proliferation from E10.5-E11.5. E-cadherin staining marked epithelial cells and laminin staining allowed for visualization of the extracellular matrix surrounding the epithelial cells.

Results: Epithelial apoptosis increased in the *Fgfr2IIIb-/-* embryos as compared to the wild type controls from E10.5-E12.5 across the colon. However, this increase in apoptosis is not restricted to the region that will develop an atresia. Only at E10.5 is the apoptotic rate of the distal colon in *Fgfr2IIIb-/-* statistically significantly greater than that of the distal colon in controls. In the *Fgfr2IIIb-/-*, at E10.5 the apoptotic rate in the distal colon is indistinguishable to that of the proximal colon. At both E11.5 and E12.5, the apoptotic rate is greater in the proximal colon of the nulls than in the distal colon.

Proliferation as measured through PHH3 staining shows no difference in the epithelial cells of the colon between wild type and *Fgfr2IIIb-/-* at either E10.5 or E11.5.

E-cadherin staining shows normal epithelial structure in the colon of wild type intestines at E11.5. In the *Fgfr2IIIb-/-*, E-cadherin is present in the cytoplasm and is no longer restricted to the plasma membrane. Individual E-cadherin stained cells are also seen in the mesenchyme.

Laminin staining of the extracellular matrix demonstrates breaks at the atretic region of the *Fgfr2IIIb-/-* with intact extracellular matrix proximally.

Conclusions: Increased apoptosis and decreased proliferation do not co-localize to the distal colon in *Fgfr2IIIb-/-* throughout a critical window of intestinal organogenesis as hypothesized. The pattern of epithelial apoptosis is complex across E10-12.5, often with regions that will develop normally displaying greater rates of cellular death than the regions that will develop atresias. Breaks in the extracellular matrix at the region of the atresia along with changes in E-cadherin expression suggest that cells at the atretic regions may be losing their epithelial identity and migrating away in an epithelial to mesenchymal transition.

Novel Platform for Transplantation of Pluripotent Stem Cell-Derived Beta Cells

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Abstract begins on following page

Background: Human pluripotent stem cell (hPSC) therapy has been envisioned for use in regenerative medicine as a surrogate source of beta cells for diabetic patients. An ideal beta cell replacement therapy strives towards both generating an abundant supply of functional beta cells and identifying a minimally invasive, well-vascularized, retrievable site for transplantation that is clinically applicable. Islet transplantation, a current treatment for type I diabetes, requires multiple donors per patient as a large percentage of islets are lost due to ischemia, hypoxia and inflammatory reactions, which are amplified by anoikis and the loss of vascular networks from islets during the isolation process. Our **hypothesis** is that a human pancreatic matrix hydrogel (hP-HG) will provide a microenvironment that promotes better engraftment and function of islets and hPSC-derived islet-like clusters (hPSC-ILCs) after transplantation into a prevascularized subcutaneous (PV-SQ) site.

Methods: To create the PV-SQ site a 6-Fr nylon catheter was implanted subcutaneously in immunodeficient mice for 4-6 weeks and the site tissue analyzed for vascularization (CD31+) through immunohistochemistry (IHC). To determine if the PV-SQ site was beneficial to the survival of the grafts, the catheter was removed and cells immediately transplanted into either the PV-SQ or unmanipulated SQ space for 2, 4, 8 and 12 weeks. Transplantations included ILCs or islets ±hP-HG, ±hPSC-derived endothelial cells (hPSC-ECs) and ±mesenchymal stem cells (MSCs) to determine if different combinations will accelerate and enhance engraftment by promoting the survival. Blood glucose, weight and human c-peptide levels were measured throughout the time course and IHC was performed after graft retrieval to evaluate differences in vascularization and cell survival.

Results: 3-4 weeks of catheter placement was sufficient to produce a vascularized bed (PV-SQ) for the transplantation of cells as indicated by increased CD31+ IHC. Mice transplanted with human islets (2,000IEQ) ±hP-HG after 4 weeks showed increased CD31+ cells in the PV-SQ space vs. the unmanipulated SQ space, which continued to increase throughout the time course. Islets were viable as indicated by IHC for islet markers (insulin, Pdx1) and CD31+ cells were found within the hP-HG embedded grafts in the PV-SQ space. Transplantation of hP-HG with ECs (500,000) showed increased CD31+ cells in PV-SQ space vs. the SQ space, suggesting that the construct has the ability to improve the site. Quantification of CD31+ cells from the grafts is in progress to corroborate IHC. ILCs (2,500IEQ) +hP-HG +ECs (500,000) +MSCs (500,000) transplanted in the PV-SQ and SQ spaces for 12 weeks, will be analyzed for graft vascularization, survival and function.

Conclusions: Preliminary results showed ILCs and islets embedded in hP-HG within the PV-SQ site were viable and vascularization increased over time. The hP-HG was nontoxic to the cells as indicated by cell viability and phenotype stability. The addition of ECs appeared to increase vascularization in the PV-SQ site however, further experiments and CD31 quantification need to be performed. If successful this novel transplantation approach may overcome many of the limitations which exist in clinical beta cell replacement therapies.

2D and 3D Models for Endothelial and Stem Cell-Derived Beta Cell Co-Culture and Transplantation

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Abstract begins on following page

Stem cell-based therapies, such as the differentiation of beta cells from human pluripotent stem cells, hold great potential for the treatment of diabetes. One limitation to stem cell-derived beta cell (SC-BC) transplantation is cell death due to poor vascularization. We aim to create a co-culture system for the combined transplantation of endothelial cells (ECs) with SC-BCs, to improve vascularization and enhance engraftment.

The extracellular matrix (ECM) is a complex of proteins, unique to each tissue and capable of guiding cell morphology, signaling, and differentiation. We have developed a decellularized human pancreas ECM (hP-ECM) platform from discarded donor organs by removing cellular material and extracting the ECM. The decellularized matrix is characterized by the preservation of ECM proteins, low immunogenicity, removal of DNA, and can be lyophilized and digested to form a hydrogel.

We developed a protocol to coat tissue-culture plates with hP-ECM hydrogel, comparable to Matrigel coatings, thus enabling 2D cell culture. By plating cells onto this coating, we determined that the hP-ECM hydrogel is suitable for and compatible with both ECs and endocrine progenitors.

To make the hydrogel model more translatable for transplantation, we moved to 3D cell culture via hanging drops or cylindrical gels. Preliminary results from these experiments show that the 3D hydrogel environment is amenable to human pancreatic islets and supports differentiating stem cells. HUVECS embedded in hP-ECM hydrogel are capable of tube-formation which could provide key support for early SC-BC graft vascularization and survival.

Anatomical and Electrophysiological Analysis of the Mouse Infraorbital Nerve as a Neural Interface

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Abstract begins on following page

Introduction: The trigeminal nerve is the fifth cranial nerve, which divides into three branches: opthalmic (V1), maxillary (V2) and mandibular (V3), and carries most of the tactile, proprioceptive and nociceptive information from the face to the central nervous system (CNS).The latest preclinical and clinical data indicates that electrical stimulation of the V1 branch treats a variety of neurologic and psychiatric disorders of the CNS (i.e. epilepsy, depression, attention deficit hyperactivity disorder and traumatic brain injury). Despite positive preliminary results in humans, the mechanisms and potential side effects remain largely unknown. This study applies microsurgical technique to investigate trigeminal nerve interfacing in mice. We describe the development and evaluation of a mouse model of trigeminal nerve stimulation for future mechanistic studies.

Materials and Methods: The trigeminal nerve and its branches was mapped via microsurgical anatomical dissection in mice cadavers. Acute experiments utilized a whisker puffer generate the physiological response in the barrel cortex. Electrical stimulation of the infraorbital nerve was performed distal to the infraorbital foramen with a custom bipolar cuff electrode to replicate the physiological response. Electrical stimulation of the infraorbital nerve was performed using single, monophasic or biphasic (cathode leading) pulses (50-800uA, 100-300us per phase) initiated at pseudorandom intervals (varying between 3-4 seconds). Changes in cortical activity in the barrel cortex were recorded (somatosensory evoked potentials [SSEPs]) custom 16 channel uECoG array.

Results: Investigation of the trigeminal nerve and its branches identified the infraorbital branch as the best candidate for electrical stimulation in mice, measuring 1.6mm mm in diameter, 3.2mm in available length, and 2.8mm away from the skin surface. By comparison, the supraorbital branch measured 0.15mm diameter and 3mm available length. Dorsal and medial access to the infraorbital branch avoids interference with the facial nerve and provides substantial soft tissue to protect the electrode. The magnitude of SSEPs increased monotonically until saturation with increases in stimulation current and activation thresholds decreased with increases in phase duration.

Conclusions: These preliminary results suggest that an infraorbital nerve interface is the best candidate for examining the neural mechanisms of trigeminal nerve stimulation in the mouse. Furthermore, we found every whisker was supplied by individual nerve fiber of the infraorbital nerve, capable of generating a signal in precise areas of cortex dependent on the fiber activated. We are now investigating this model of sensory feedback in the human extremity, a critical component for ideal prosthetic control.

Functional Recovery and Regrowth after Nerve Transection: Comparison of Five Repair Techniques in a Rat Sciatic Nerve Model

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Abstract begins on following page

Introduction: Peripheral nerve injury may result in impaired function, poor sensation, and chronic pain, even after repair. No single technique for primary nerve repair has been consistently shown to be superior. One limitation is a lack in consistency in outcome assessments that are selected for studying functional recovery. In addition, functional and behavioral results and other tests of regeneration, such as axon counts, do not often correlate with one another. We hypothesize that there is a key difference between nerve "regrowth" and "functional recovery." The purpose of this study was to compare five techniques for primary nerve repair in a rat sciatic nerve model, and identify potential correlations between histomorphometric and functional assessments.

Methods: Sciatic nerve transection and repair was performed in male Lewis rats. Under isoflurane anesthesia, the nerve was exposed, transected proximal to its trifurcation, and repaired using one of five techniques: interrupted epineural, running epineural, grouped fascicular, epineural with absorbable type I collagen wrap, and tension (epineural repair after resection of a 9mm segment of nerve). A sixth sham surgery group was included. The contralateral limbs served as intra-animal controls. After a period of postoperative recovery, a combination of behavioral (Rotarod and horizontal ladder), electrophysiologic (compound muscle action potential (CMAP) amplitudes and nerve conduction velocity (NCV)), imaging (second harmonic generation with collagen quantification), and histomorphometric (quantitative stereology) assessments were performed. Statistical analysis was performed using one-way analysis of variance and Spearman's rank correlation coefficient.

Results: Nerve repair was performed in forty-eight male Lewis rats. In all animals, functional testing was performed at week 13, followed by electrophysiology, imaging, and histomorphometry at week 14. The sham group (n=7) performed the best on behavioral assays (p<0.001) and demonstrated the highest mean CMAP amplitude (p<0.001) and fastest NCV (p<0.001). Of the repair types, the collagen wrap group (n=8) performed better on the Rotarod and ladder rung assays (n=8, p=0.04). Behavioral and electrophysiologic results were poorest in the tension group (n=9, p=0.01). Qualitative inspection revealed that aberrant axon sprouting was greatest in the tension group (n=9). When all test results were compared between groups, several significant correlations emerged. Percent correct steps on the ladder correlated positively with Rotarod duration (0.466, p=0.001) and degree of myelination (0.360, p=0.02). NCV positively correlated with both degree of myelination (0.410, p=0.01) and mean axon fiber area (0.381, p=0.02). Axon fiber area positively correlated with degree of myelination 0.945 (p<0.001), and total axon count positively correlated with nerve specimen size 0.641 (p<0.001).

Conclusions: Among the tension-free repair techniques, no single method was associated with superior outcomes on all assessments of regeneration. We found the Rotarod and ladder rung assays to be useful, allowing for differentiation between satisfactory and suboptimal techniques. Surgeons should consider the use of acellular collagen wrap surrounding the repair site, as it minimizes adherence of the surrounding soft tissue to the nerve and may minimize dysfunctional fibrosis over time.

The Osseointegrated Neural Interface (ONI): A Rabbit Model for Chronic Peripheral Nerve Interfacing in Bone with Percutaneous Osseointegrated Connectors

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Abstract begins on following page

Introduction: Peripheral nerve interfaces represent a paradigm shift in the treatment and prevention of amputation neuromas. Rather than simply bury a transected nerve in muscle or bone in an effort to prevent/treat painful neuromas, attention has moved to exploiting the regenerative capacity of these nerves to actuate advanced robotic prostheses. Caveat to current interfacing technology are the motion artifact and long term stability of these devices in dynamic soft tissue environments.

The Osseointegrated Neural Interface (ONI) represents a novel approach to peripheral nerve interfacing- utilizing the medullary cavity of the amputated long bone to house and protect the amputated nerve and delicate electrode interfaces from motion artifact and damage. The ONI is based on the transposition of nerve in bone to treat amputation neuromas, first described by Edwin Boldrey in 1943. The premise of transposing amputation neuromas into bone is that the bone provides stability and protection from external stimuli that may cause neuropathic pain. These same principals of stability and protection are also key components to achieving robust, chronic interfaces with the peripheral nervous system.

Objective: To evaluate the stability and longevity of chronically implanted ONI devices.

Materials and Methods: We have developed a novel dual cuff electrode system with a percutaneous osseointegrated connecter for chronic implantation electrophysiology. The implant device consists of two cuff electrodes connected percutaneous connectors secured to a stainless steel intramedullary rod. Transfemoral amputation was performed in New Zealand white rabbits. The terminal end of the amputated sciatic was passed through a proximal corticotomy and threaded into the medullary cavity. The terminal end of the nerve was secured in a cuff electrode and inserted back into the medullary cavity, followed by the intramedullary rod, which was then secured with bone cement. The second electrode was attached to the nerve external to the bone, proximal to the corticotomy. All animals are undergo electrophysiology, recording afferent and efferent compound nerve action potentials (CNAPs) at weeks 3 and 5 with terminal somatosensory evoked potentials (SSEPs) recorded at 5 weeks. Peak amplitudes of CNAPs are analyzed with one-way ANOVA.

Results and Discussion: Efferent (motor) CNAPs are present at 3 weeks and improve by 5 weeks, as indicated by generating a significantly greater response from less stimulus (n=6, $p<0.05$). Afferent (sensory) CNAPs could not be achieved using the same method; however afferent SSEPs could be recorded. The ability to record afferent SSEPs demonstrates that there is still a connection between the distal end of the amputated nerve and the cortex, indicating that the ability to transmit sensory information through the ONI is not lost. Longer time points are currently being investigated to determine if the ability to record afferent signals improves with time.

APRIL and BLyS Deficient Rats

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Abstract begins on following page

Introduction: Many of the current immunosuppressant regimens to treat transplant rejection are aimed at T lymphocytes; however, antibody mediated rejection via alloantibody is often the culprit behind long-term kidney graft failure. APRIL (A proliferation inducing ligand) and BLyS (B Lymphocyte Stimulator) are two cytokines within the tumor necrosis factor family that have been established as playing a role in the maturation and long-term survival of B cells and plasma cells. Our ongoing study is examining the role that APRIL and/or BLyS deficient rats may have in antibody mediated rejection in kidney transplants. This deficiency in mature B lymphocytes through BLyS and APRIL knock outs may present a potential therapeutic target when treating antibody mediated rejection.

Methods: We examined Lewis rats that were genetically engineered to be deficient in APRIL and BLyS via CRISPR technology. The presence of APRIL and BLyS were determined using enzyme- linked immunosorbent assay (ELISA) and reverse transcription-polymerase chain reaction (RT- PCR). Spleen, bone marrow, blood, and lymph nodes were also analyzed using flow cytometry, enzyme-linked immunospot (ELISPOT), and immunohistochemistry. In vitro activation assays using CPG, IL-15, IL-2, and CD40L were used to stimulate APRIL knock out, BLyS knock out, and wild type rat splenocytes. Flow cytometry was used to analyze the cultures after 72 and 96 hours.

Results: BLyS knock out rats produced fewer marginal zone B lymphocytes at 0.68% compared to APRIL knock out or wild type (1.8% and 1.64%, respectively). BLyS deficient rats had an increase in transitional zone B cells at 54.1% versus 7.71% in APRIL deficient and 16.4% in wild type. Activation after 72 and 96 hours demonstrated a smaller production of marginal zone B cells in BLyS knock out when compared to APRIL and wild type.

Conclusions: Preliminary data indicates that BLyS deficient rats produce more transitional zone B cells when compared to wild type, which may indicate an arrest of B cell development in the transitional phase. This result may indicate that BLyS deficient rats may produce fewer antibodies thereby potentially decreasing the risk of antibody mediated rejection in kidney transplant recipients. Future investigations will look at the effect of kidney transplantation on antibody mediated rejection in APRIL/BLyS deficient rats.

Characterization of Porcine Xenoantibody Response In Vitro

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Abstract begins on following page

Introduction: One possible solution to the current shortage of donor organs is the use of xenografts. A potential model for viable xenotransplantation has been porcine organs but the associated immune barriers has delayed its transition to clinical practice. A key component to this barrier is the difference in carbohydrate structures expressed on porcine cells, which serve as antigens to humans. Using carbohydrate knock-out pigs in combination with immunosuppression, progress has been made such that the initial hyperacute reaction can be overcome in non-human primates. Yet, even with these advancements, there are still issues with long term graft survival and function in non-human primates. The goal of our experiment is to characterize the initial immune response of porcine xenotransplantation in vitro.

Methods: Using six samples of nave rhesus macaque serum, we performed a flow crossmatch assay with porcine peripheral blood mononuclear cells (PBMC). Porcine PBMCs were incubated with three different groups: R10 (used as a negative control), porcine plasma (self), and rhesus macaque plasma (the experimental group). We analyzed IgG and IgM binding between lymphocytes and macrophages using flow cytometry. Results were reported as median fluorescence intensity (MFI) and unpaired two- tailed T test was used for statistical analysis.

Results: It was found that naturally occurring anti-pig IgG binding was significantly increased in the six rhesus macaque plasma samples when incubated with porcine PBMC (P value < 0.01). Anti-pig IgG binding was also found to be most prevalent in cells outside the lymphocyte gate. In terms of IgG binding, MFI did not change for lymphocytes when compared to negative control (self and no plasma). IgG binding to macrophages resulted in an average delta MFI of 100 when compared to negative controls. Interestingly, there appeared to be a heterogeneous response when comparing individual amounts of anti-pig IgG and IgM. Ranges for IgG included MFI values of 737 to 1046. As for IgM, MFI ranged from 291 to 430.

Conclusion: With this experiment, we confirm previous reports that naturally occurring antibodies do bind to xenoantigens. There appears to be an increased presence of IgG binding, particularly among cells that may be macrophages. This is consistent with previous results that implicated cells which appeared to be macrophages and xenoantibody of the IgG isotype. However, we need to analyze the data to determine whether the cells in this gate, in which most binding occurred, bind CD68 to show they are indeed macrophages. Future considerations will involve a more in-depth investigation of the role of macrophages in this flow crossmatch assay and also if PBMCs represent a valid model for xenograft failure.

Changes in Cutaneous Gene Expression after Microvascular Free Tissue Transfer in Parry Romberg Disease

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Abstract begins on following page

Purpose: Parry Romberg Disease (PRD) is an enigmatic craniofacial disorder characterized by progressive facial atrophy. The pathogenesis and molecular mechanisms governing PRD have never before been described. The purpose of our current study was twofold - to begin to elucidate the pathophysiology of this disease using next generation RNA sequencing and to evaluate the effect of surgical treatment on gene expression.

Methods: Patients with PRD underwent microvascular free tissue transfer (MVFF) to the face to address contour deformity in both active and burned out disease. Tissue samples were collected for analysis at the time of initial MVFF, and 6 months later at a scheduled revision surgery. Patients presenting for rhytidectomy had tissue samples taken as control tissue. Patients with disease were compared to control samples.

Results: Twenty-two subjects were evaluated (six control and sixteen Parry Romberg patients). All patients with PRD underwent MVFF to the face. Thirteen patients underwent scheduled six month revision surgery. Disease samples were distinct from healthy controls, and postoperative patient samples were more similar to healthy control samples. Parry Romberg patients had a unique proinflammatory gene expression profile including upregulation of IL24, ADAMTS4, and GFCSF3. Postoperatively, more than 3,400 genes were changed (p < 0.005), and of the 460 genes dysregulated in disease, 118 were changed in a corrective fashion by MVFF.

Conclusions: We describe for the first time molecular signatures in Parry Romberg Disease. Molecular signatures in skin became more similar to healthy controls and were associated with clinical improvement after MVFF in PRD.

Laryngotracheal Microbiota in Subglottic Stenosis

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Keywords	Subglottic stenosis, Upper airway microbiota, microbiome, tracheal scar, fibrosis

Abstract begins on following page

Background: Laryngotracheal stenosis is an obstructive respiratory disease that leads to voicing difficulties and dyspnea with potential life-threatening consequences. Treatment remains difficult due to development and recurrence of scar tissue in the airway. The majority of incidences are associated with an iatrogenic etiology due to endotracheal tube intubation, however, airway scarring also has idiopathic causes. While recent evidence suggests a microbial contribution to mucosal inflammation, a characteristic hallmark in the pathogenesis of this disease, little work has thoroughly characterized the microbiota associated with different types of stenosis.

Results: High-throughput sequencing of the V4 region of the16S rRNA gene was performed to characterize the microbial communities of 61 swab samples from 17 iatrogenic and 10 idiopathic stenosis patients. Swabs were collected along scar and non-scar regions. Non-scar swabs from patients with stenosis were used for internal controls and 8 swabs from 4 patients without laryngotracheal stenosis served as external controls. Significant differences in diversity were observed between scar and non-scar samples, and among sample sites, with decreased diversity detected in scar samples and the glottis region. PERMANOVA results revealed significant differences in community composition for scar vs. non-scar samples, etiology type, sample site, groups (iatrogenic, idiopathic, internal and external controls) and individual patients. Pairwise Spearman's correlation revealed a strong inverse correlation between *Prevotella* and *Streptococcus* among all samples. Finally, bacteria in the family Moraxellaceae were found to be distinctly associated with idiopathic stenosis samples when compared with external controls.

Conclusions: Our findings suggest that specific microbiota and community shifts are present with laryngotracheal stenosis of various etiologies, with the family Moraxellaceae which includes known pathogens *Moraxella* and *Acinetobacter* identified in idiopathic scar. As the mechanisms that induce microbial shifts and disease states remain elusive and undefined, further work is warranted to elucidate the contributing role of bacteria on the pathogenesis of laryngotracheal stenosis.

B28
Laryngeal Microbial Colonization in a Gnotobiotic Murine Model

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Keywords	gnotobiotic animal, germ-free, larynx, microbiota, colonization

Abstract begins on following page

Background: The larynx is a mucosal organ situated between the respiratory and gastrointestinal tracts. While inflammatory pathologies occurring in this region can contribute to debilitating voice and swallowing dysfunction in humans, little is known regarding microbial influences on laryngeal mucosal health and disease. Previous clinical studies have focused on microbial community characterization for healthy and pathologic laryngeal samples; however, a lack of work investigates the direct contributions of microbiota to laryngeal biology. In this study, we conventionalized germ-free mice to explore the feasibility of establishing a gnotobiotic laryngeal murine model allowing for potential future investigations in this region.

Methods: Five germ-free adult c57bl6 mice housed in a gnotobiotic animal facility were inoculated with conventional c57bl6 mouse microbiota through oral gavage with cecal contents. Following a four-week incubation, the larynx and surrounding regions (esophagus, trachea, base of tongue) were harvested under microscopy. These regions were also collected from five conventional and five germ-free c57bl6 mice to serve as control groups. The germ-free control group was excluded from subsequent analysis following confirmation of germ-free status via 16S rRNA amplicon PCR. All remaining samples were analyzed using 16S rRNA sequencing with Illumina miseq. Differences in communities were evaluated using PERMANOVA and principle components analysis.

Results: While statistical differences were found in community profiles among germ groups (normal vs. conventionalized mice) and individual mice, the conventionalized mouse group displayed a sequenced microbial community, indicating successful inoculation. This conventionalized mouse group demonstrated similarities to the normal mouse group at the phyla level, with both groups exhibiting top 5 phyla encompassing: *Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria,* and *Cyanobacteria*. However, differences were noted at the family level, with Streptococcaceae, Lactobacillaceae, S24-7, Enterobacteriaceae, and Moraxellaceae identified in normal mice while Staphylococcaceae, Lachnospiraceae, Pasteurellaceae, S24-7, and Lactobacillaceae represented in conventionalized mice.

Conclusion: Despite shifts in community representation, we have demonstrated the feasibility for successful gnotobiotic murine colonization in the larynx using oral gavage methods. Establishing a protocol for developing a gnotobiotic laryngeal model can introduce new avenues for targeting our understanding of microbes in upper airway tissue biology, allowing for enhanced understanding of laryngeal health and disease processes.

Migration and Contraction of Fibroblasts from Normal and Scar Vocal Folds with Applications to Wound Healing

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Keywords	Migration, Wound Healing, Mechanical Forces, Vocal Folds, Scar

Abstract begins on following page

Vocal fold scarring has various causes, including inflammation, trauma, radiotherapy and laryngeal surgeries. The treatment for vocal fold scarring is a challenge in Laryngology practice. Scars disrupt the layered structure and induce disorder in the lamina propria extracellular matrix, which causes significant change in vocal fold biomechanics, resulting in voice disorders that often compromise patient quality of life. Vocal fold fibroblasts are responsible for synthesis of the extracellular matrix, playing a key role in support of the lamina propria in normal and diseased conditions. During tissue injury, vocal fold fibroblasts become activated and differentiate into myofibroblasts, initiating contractile forces that facilitate wound healing. The correct balance between contraction and extracellular matrix deposition is required for optimal healing. Using a scratch assay with live-cell time lapse microscopy and traction force microscopy, we analyze the migration and contraction of fibroblasts from normal and scar human vocal folds during wound healing. As expected, most of the normal and scar vocal fold fibroblasts migrated toward the free area within 24 hours, which is a critical time-point after laryngeal surgeries. Scar vocal fold fibroblasts moved less persistently but in a collective manner whereas normal cells had more persistent and individual patterns of migration. Additionally, scar cells contracted approximately two times more than normal vocal fold fibroblasts. We expect these results to clarify mechanisms of migration and contraction of normal and scar vocal fold fibroblasts. This data may be useful to design experiments that increase or decrease contraction and migration to cause faster healing or reduced scar formation.

Chylomicron-Mediated Trafficking of Dietary Vitamin A to the Rat Vocal Fold

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Keywords	Stellate Cell, Vitamin A Storage, Retinal Binding Protein, Multi-Organs, Liquid Chromatography Analysis

Abstract begins on following page

Objectives: The essential nutrient vitamin A (VA) is a potent regulator of multiple biologic processes. Most systemic VA is stored in hepatic stellate cells (SCs) and trafficked to extrahepatic target organs (including the larynx) in via retinol-binding protein (RBP). Alternatively, VA can bypass the liver and be trafficked directly to extrahepatic organs by chylomicra. Chylomicron-mediated VA transport can be evaluated via detection of alpha-retinol (aR), a VA isomer that cannot bind to RBP and therefore cannot be released from hepatic storage. The purpose of this study was to determine whether VA can be transported to the vocal fold mucosa via RBP-independent chylomicra, via aR dosing in a rat model.

Methods: VA-sufficient rats (n=120) were dosed with 2 mg aR acetate; control rats (n=5) received vehicle only. Vocal folds, liver, and various extrahepatic organs were harvested at 7 h and 72 h; sera were collected at 9 time points from 0-72 h. Samples were analyzed using ultra- performance liquid chromatography to obtain VA isomer profiles and concentrations.

Results: Serum aR concentration peaked at 3 h and was metabolized by 11 h. Vocal fold, kidney, and spleen αR concentrations peaked at 7 h and decreased substantially by 72 h; lung aR concentration peaked at 7 h and decreased slightly by 72 h; liver αR concentration increased at 7 h and was maintained through 72 h.

Conclusion: Orally dosed VA can be transported to the vocal fold via chylomicra, where it is almost completely metabolized by 72 h post dose.

Clinical Science

A Comparison of Outpatient and Inpatient Pediatric Rhinoplasty: Results from NSQIP-Pediatric, 2012-2014

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Abstract begins on following page

Introduction: Outpatient management of patients undergoing elective surgical procedures has been associated with significantly decreased health care costs compared to inpatient management. Given the increasing emphasis on reducing costs of care while improving quality, this study was designed to investigate current practices in outpatient versus inpatient management of pediatric rhinoplasty patients.

Methods: A query was performed of the 2012-2014 National Surgical Quality Improvement Program Pediatric data sets. Patients age 17 or younger undergoing rhinoplasty as the primary surgical procedure were included. Clinical characteristics and complications were compared among patients managed as inpatients versus outpatients using both univariate and multivariate logistic regression analyses.

Results: Among 938 pediatric rhinoplasty patients, 199 (21.2 percent) were managed as inpatients. Multivariate analysis revealed multiple variables significantly associated with an increased odds of inpatient management: age younger than 2 (OR 7.83, p<0.0001), age 2-8 (OR 1.92, p=0.02), unknown race (OR 2.12, p=0.03), presence of a congenital malformation (OR 1.90, p=0.01), neurologic history (OR 1.93, p=0.03), nutritional history (OR 4.31, p=0.04), procedure lasting 2-4 hours (OR 4.15, p=0.0002) or greater than 4 hours (OR 7.75, p<0.0001), management by a plastic surgeon compared to an otolaryngologist (OR 2.92, p=0.001), septorhinoplasty for nasal deformity secondary to cleft lip and/or palate (OR 2.27, p=0.02), secondary rhinoplasty with intermediate or major revision (OR 2.79, p=0.04), and patients receiving a rib cartilage graft (OR 4.34, p<0.0001). Complications among both inpatients and outpatients were rare, with the most common complication being readmission in 7 (3.5%) inpatients and 8 (1.1%) outpatients (p=0.02). Significant associations were noted between readmission and patients with a wound history (p=0.02) and patients undergoing secondary rhinoplasty or cleft rhinoplasty procedures (p=0.002).

Conclusions: This study indicates that multiple subgroups of pediatric patients undergoing rhinoplasty procedures have significantly increased odds of being managed as inpatients without any significantly increased likelihood of a complication or need for readmission. Efforts to manage these patients as outpatients warrants further investigation due to potential improvements in cost and quality of care.

Can Functional Rhinoplasty Treat Chronic Headaches? A Systematic Review

Rebecca L. Farmer, MD PhD; Ravi K. Garg, MD; Ahmed M. Afifi, MD

Abstract begins on following page

Background: Rhinoplasty is one of the most common operations performed by plastic surgeons. The link between functional rhinoplasty and improvement in nasal breathing is well established, but there are other metrics that have been shown to improve as a result of anatomic correction of the nose. Current literature suggests that surgery to remove nasal mucosal contact points can reduce headache symptoms in chronic headache patients. We conducted a systematic literature review to determine the validity of this hypothesis.

Methods: A systematic search of the literature was performed using the terms "headache", "rhinogenic headache", "contact point", "migraine" and "surgery/endoscopy", used alone or in combination.

Results: We identified 39 articles encompassing a total of 1577 patients who underwent functional rhinoplasty to treat mucosal contact point headaches. The most common contact points in headache patients resulted from turbinate hypertrophy or septal deviation. Septoplasty and turbinate reduction were the most commonly performed procedures, often in combination with functional endoscopic sinus surgery (ESS). Analysis of the combined data demonstrated improvement in the reported severity of patient symptoms, with 1289 patients (85 percent) reporting partial or complete resolution of headaches postoperatively. Average Visual Analog Scale scores and number of headache days in patients undergoing rhinoplasty were also significantly reduced from 7.4 ± 0.9 to 2.6 ± 1.2 ($p < 0.001$) and 22 ± 4.3 to 6.4 ± 4.2 ($p = 0.016$), respectively.

Conclusions: Available evidence suggests that functional rhinoplasty is a viable option to improve headache symptoms in appropriately selected patients.

Facebook Facts: Breast Reconstruction Patient-Reported Outcomes Using Social Media

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Keywords	Breast reconstruction, social media, patient satisfaction, DIEP flap reconstruction, Implant reconstruction

Abstract begins on following page

Background: Social media is used for information sharing among patients with similar health conditions, and analysis of social media activity could inform clinical decision-making. The aim of this study was to use Facebook© to evaluate a cohort of individuals' perceptions of and satisfaction with breast reconstruction.

Methods: In this observational study, we collected and analyzed posts pertaining to autologous and implant-based breast reconstruction from active Facebook© groups. Patient satisfaction data were categorized, and a thematic analysis of posts was conducted. Qualitative posts were grouped based on common themes and quantitatively compared using frequency and Chi-squared analysis.

Results: We evaluated 500 posts from two Facebook© groups. Two hundred and sixty-four posts referenced deep inferior epigastric perforator (DIEP) flap reconstruction and 117 were related to implant-based reconstruction. Among individuals referencing DIEP reconstruction, 52% were satisfied, compared to 20% of individuals who referenced satisfaction with implant-based reconstruction ($p<0.0001$). Individuals posting about DIEP flaps reported a higher rate of unexpected side effects ($p<0.001$) and numbness ($p=0.004$). When referencing implant-based reconstruction, individuals reported significantly higher rates of infection, contracture and implant failure ($p<0.001$).

Conclusions: Based on our review of social media activity, individuals undergoing DIEP flap breast reconstruction expressed relatively high individual satisfaction despite difficult postoperative recovery. Individuals who referenced implant-based reconstruction mentioned infection and implant failure, leading to high rates of dissatisfaction. Social media appears to provide informational and emotional support to patients. Plastic surgeons can utilize social media to gather unbiased information of patients' experience to inform clinical conversation and guide clinical practice.

C21
The Impact of Hearing Loss on Executive Function

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Keywords	Cochlear implants, executive function, hearing loss, working memory, aural rehibilitation

Abstract begins on following page

Executive function constitutes a multitude of cognitive components that are thought to be involved in the regulation and control of purposeful and goal-directed behaviors. Executive function is vital for communication, learning, and social-emotional behaviors. Deficits in executive function can lead to the inability to perform everyday tasks in an effective and efficient manner, such that completion of tasks requires more effort. Further, these deficits are exacerbated in complex auditory environments. Previous work suggests that individuals with cochlear implants (CIs) perform worse on measures of executive function, specifically tasks that assess working memory, than individuals with normal-hearing (NH). The present study is aimed at understanding factors that are likely to contribute to the gap in performance between CI users and NH listeners.

The study design includes individuals with NH and CI users. Participants completed two tests: (1) NIH Toolbox, List Sort Working Memory Test, and (2) Kaufman Brief Intelligence Test. The intelligence test was administered to rule out any possible effects of IQ on executive function. The List Sort Working Memory Test requires the participant to recall and sequence a series of stimuli. All individuals with CIs and half of the NH group were presented the auditory+visual stimuli, and the other half of the NH group were presented visual-only stimuli.

Preliminary results suggest that all individuals tested have approximately equivalent IQs, and therefore differences in working memory are not attributed to general intelligence. The CI auditory+visual and the NH visual-only groups had similar mean standardized scores of working memory (93 and 91, respectively), suggesting that the CI group, when presented stimuli in two modes (i.e. auditory and visual), performed similarly to the NH group, when presented stimuli in only one mode (i.e. visual). The NH auditory+visual group had the highest mean scores (105), indicating that auditory input provided important augmentative information for working memory in NH listeners. There were two outliers in the CI auditory+visual group who had working memory scores similar to the top performers in the NH auditory+visual group; however, it should be noted that these two CI users had a progressive hearing loss. The other CI participants had congenital deafness. This finding will be explored further to understand whether early auditory experience is related to the development of executive function.

Together, these results reveal that individuals with CIs, especially those with congenital deafness, may have to allocate more cognitive resources for comprehension of the auditory signal than their NH counterparts, even with a visual cue, and therefore leaving fewer resources available for other tasks. These findings have implications regarding aural rehabilitation after cochlear implantation. For example, there may be a benefit from including training of specific components of executive function (e.g. working memory) in therapy in order to enhance both auditory and neurocognitive mechanisms.

C14

Patient Adherence to Dysphagia Therapy and Recommendations: A Systematic Review

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Abstract begins on following page

Adherence to treatment recommendations may be critical to improvement in swallow function. This systematic review examined all relevant literature regarding adherence of patients to dysphagia management recommendations.

Five databases were used to search for articles relating to dysphagia that included a measured component of adherence. Abstracts were examined and selected by two masked reviewers, if discrepancies per inclusion arose they were settled by a third reviewer. Included in the review were papers relating to adherence to exercise recommendations, diet modifications or posturing for patients with dysphagia with varying etiologies. Excluded were papers focusing on caregiver compliance for patients with moderate to severe cognitive impairments or late stage disease.

Our initial search yielded 1379 abstracts, with only eleven full-text articles included in the review. Of these papers, six studies specifically examined adherence as a primary outcome and identified potential barriers to adherence. Only three studies considered adherence as a factor when interpreting results of desired outcomes from exercise-based therapies. The majority of research focused on patients with head and neck cancer.

There is a dearth of literature related to patient adherence to dysphagia treatment recommendations. Adherence must be more closely examined as a potential confounding factor in findings concerning exercise-based studies. In order to improve adherence, more work must be performed to identify and remedy barriers to adherence in all populations with dysphagia.

Kidney after Liver Transplant Matched Pair Analysis: Are Kidneys Allocated to Appropriate Patients?

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Keywords	Matched Pair, Kidney after Liver Transplant, KDPI, Kidney Transplant, Kidney Allocation

Abstract begins on following page

Background: End stage renal disease (ESRD), either pre-existing or new onset after orthotopic liver transplant (OLT), is associated with increased mortality rates. While it is known that kidney after liver transplantation (KAL) is the best therapy for ESRD after OLT when compared to hemodialysis, it is not clear whether these kidneys perform as well in previous liver recipients compared to kidneys transplanted in uremic patients. The goal of this study was to compare mortality, death censored graft survival and rejection from the utilitarian perspective among the two groups, stratified by kidney donor profile index (KDPI).

Methods: The UNOS/OPTN database was queried for adult patients over 18 years old who received kidney transplantation after prior OLT with matched KTA during 1988-2015. From a total of 415,332 primary kidney transplants, 1826 were kidneys transplanted into patients that previously received an OLT. These patients were compared to their paired primary KTA recipients. Patients were excluded if; a)they had any transplants prior to OLT, b)transplants other than KAL, and c)KDPI could not be calculated (n=1233). Kaplan-Meier survival analysis was performed and compared. Log-rank test was used to compare various cohorts (p<0.05 was considered to be statistically significant).

Results: The average time between OLT and kidney transplant was 7.8 years. Overall 1, 3 and 5-year patient survival was lower in the KAL group (93.5, 88.1 and 82.7%) compared to KTA (97.2, 93.3 and 89.5%) respectively (p<0.001). Similarly, death censored graft survival was also lower in the KAL group (83.9, 75.8 and 67.2%) compared to KTA (92.3, 83.5 and 75.5%) (p<0.001). Kidney rejection at 1-year was similar between KAL (10%) and KTA (13%) (p=0.10). Interestingly, when stratified by KDPI we observed that in those with KDPI <85%, patient survival was significantly lower in the KAL group at 1, 3 and 5-years (93.6, 87.9 and 82.9%) when compared to KTA (97.7%, 93.6% and 90%) (p<0.001). Death censored graft survival was equally lower in the KAL group (84.3, 76.5 and 67.9%) when compared to KTA (93.3, 84.2 and 76.3%) respectively (p<0.001). A total of 9% of donors had a KDPI ≥ 85. For those with KDPI ≥85, patient survival was similar in the KAL group (93.1, 89.7, 81.0%) when compared to KTA (93.1, 89.7, 85.3%) respectively (p=0.41). Death censored graft survival was also similar in the KAL group (80.2, 68.1, 61.2%) when compared to KTA (82.8, 76.7, 68.1%) (p=0.22).

Conclusions: In patients who received a kidney with KDPI <85%, KAL recipients had significantly worse patient and death censored graft survival when compared to KTA. Recipients of KDPI ≥85% kidneys had similar patient and death censored graft survival when KAL was compared to KTA. Rejection as a cause for graft failure was equal among both groups. From a utilitarian perspective, best results are obtained from patients that received a kidney transplant alone and a KDPI <85% and we recommend priority over KAL transplantation.

C33

Postoperative Management of Lower Extremity Free Tissue Transfer: A Systematic Review

Carol E. Soteropulos, Jenny Chen, Catharine B. Garland

Abstract begins on following page

Purpose: Free tissue transfer for lower extremity reconstruction is a safe and reliable option for a wide range of challenging wounds, however no real consensus exists regarding postoperative management.

Methods: A systematic review of postoperative management of lower extremity free tissue transfer was conducted using Medline, the Cochrane Database, and Web of Science. Multi-center surveys, case series, randomized controlled trials, and cohort studies were included for review.

Results: 14 articles investigating current protocols, flap physiology, and aggressive dependency protocols were reviewed. The following evidence based conclusions were made.

1) Free tissue transfer to the lower extremity is unique due to altered hemodynamics and dependency during orthostasis. Free flap circulation is dependent on locally mediated responses, and is deprived of the compensatory muscular and neurovascular mechanisms that exist in the normal lower extremity to prevent venous congestion.

2) Compressive wrapping reduces venous congestion and edema, and induces ischemic conditioning which increases blood flow.

3) Dangle protocols vary widely in timing of initiation, frequency and monitoring.

4) Weight bearing may begin after the completion of dangle protocol, if no orthopedic injury is present.

Conclusions: Lower extremity free flap physiology is unique. Aggressive mobilization protocols that initiate early dependency have led to earlier ambulation and hospital discharge, with no change in the rate of flap survival as compared to conservative protocols. Based on this systematic review, dangle can be started as early as postoperative day three without negatively impacting flap survival. Compressive wrapping is a useful adjunct. Clinical monitoring is sufficient. Weight bearing may begin after completion of dangle protocol, if not prevented by restrictions due to orthopedic injury. By providing additional outflow vasculature to reduce venous congestion, flow-through anastomoses may eliminate the need for a dangle protocol. Further research is needed for evidence-based conclusions in this area.

C9

A Phase III Open-label, Controlled, Randomized, Multicenter Study Evaluating the Efficacy and Safety of StrataGraft Skin Tissue in Promoting Autologous Skin Tissue Regeneration of Complex Skin Defects due to Thermal Burns that Contain Intact Dermal Elements and for which Excision and Autografts are Clinically Indicated

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Abstract begins on following page

Introduction: Annually in the United States, approximately 45,000 people experience burns that require hospitalization, and ~10 to 20% require surgical intervention. Autografting, the standard of care for serious burns, is the surgical harvest of healthy skin from an uninjured area followed by transplant to the wound after burn excision. It results in an iatrogenic donor site wound that requires medical management of pain, potential for infection, scarring, etc. StrataGraft skin tissue is a living, full-thickness human skin substitute under development to reduce or eliminate the need for autograft in the treatment of complex skin defects due to thermal burns. In the STRATA2011 clinical study, 27 of 28 per-protocol subjects experienced complete wound closure of treatment sites at 3 months, and no subjects required autografting by day 28. No evidence of DNA from cells of StrataGraft tissue was seen after 3 months in all tested patients. No safety concern signal associated with StrataGraft skin tissue has been seen.

Methods: A phase III open-label, controlled, randomized, study is being conducted at 12 to 15 ABA-verified burn centers across the United States. Enrollment of up to 70 adult subjects with thermal burns containing intact dermal elements and for which surgical excision and autograft placement are clinically indicated is targeted. Each subject will have one burn area treated with StrataGraft skin tissue and a second wound area of comparable depth treated with harvested autograft.

The two co-primary endpoints for the study are:

- The difference in the percent area of the StrataGraft treatment site and autograft (control) treatment site that is autografted by 3 months
- The proportion of subjects achieving durable wound closure of the StrataGraft treatment site at 3 months without autograft placement

Ranked secondary endpoints include:

- Difference between the StrataGraft and autograft donor sites in average pain intensity through day 14 based on the Faces Pain Rating Scale
- Difference between the StrataGraft and autograft donor site cosmesis at 3 months based on observer Patient and Observer Scar Assessment (POSAS) total score
- Difference between the StrataGraft and autograft treatment site cosmesis at 12 months based on observer POSAS total score

Results: Patient enrollment and assessment for this study is ongoing. Additional clinical sites are being identified and qualified to facilitate completion of the study. Data from the ongoing phase III study will be available after completion of patent enrollment and follow-up.

C10
Scan, Plan, Print, Practice, Perform: Combining 3D Printing and Surgical Simulation in Cardiac Surgery

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Keywords	3D Printing, Simulation, Myectomy, Hypertrophic Cardiomyopathy, Education

Abstract begins on following page

Objective: Three-dimensional printing (3Dp) is an emerging medical technology. Static 3Dp models have been used in cardiothoracic surgery for planning and intra-operative reference, particularly for challenging congenital anatomy. We sought to develop a functional 3Dp model for improved anatomic understanding and surgical practice in hypertrophic cardiomyopathy (HCM) patients undergoing myectomy.

Methods: 3Dp models were constructed pre-operatively for 7 patients. Stereolithography (.stl) files were generated by segmentation (ITK-SNAP open source software) of an electrocardiogram-gated, contrasted-enhanced chest computed tomography scan. 3D prints were made using a proprietary hydrogel material yielding a tissue-like model that can be surgically manipulated. Septal myectomy of the model was performed in standard trans- aortic fashion the day before operation in the simulation lab. Volumes of model and patient specimens were measured by liquid displacement for comparison.

Results: The 3Dp models were judged subjectively useful by two surgeons for pre-operative visualization and planning. Model resection volumes were closely correlated to patient resection volumes ($r2$=0.95). All patients had relief of left ventricular outflow tract obstruction.

Conclusions: 3Dp of functional HCM heart models allows for patient-specific pre-operative simulation. Model resection volume correlated to operative resection volume and may be useful in providing a target volume to guide resection intra-operatively. This model also holds educational promise for high fidelity simulation of a low-volume, high-risk operation that is traditionally difficult to teach.

C15

Cardiac Surgery Outcomes in Abdominal Solid Organ Transplant Recipients

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Abstract begins on following page

Purpose: Cardiovascular disease is a cause of morbidity and mortality in organ transplant recipients. Cardiac surgery (CS) following organ transplantation is not uncommon in this population. We evaluated 30-day outcomes and long-term survival of abdominal transplant (ATx) recipients undergoing CS at our institution.

Methods: 138 patients with previous kidney, kidney-pancreas and liver transplants underwent CS from 2000-2016. Propensity score (ratio 1:3) matched 115 ATx with 345 patients undergoing CS without a history of ATx. They were matched for type and year of CS, age, gender, BMI, history of diabetes and pre-CS creatinine.

Results: Median time from ATx to CS was 7 years (IQR: 3-12). Perioperative variables, including surgery and cardiopulmonary bypass time, aortic cross clamp and intubation time and ICU stay did not differ between the groups. Hospital length of stay and rate of 30-day hospital readmissions did not differ between the groups. Patients with ATx had more strokes (4% vs. 0.6%; p=0.005) within 30-days post-surgery. There were no differences in renal failure, bleeding, site infections, atrial fibrillation and pneumonia between the groups. Five patients (4%) died within 30-days post-surgery in the ATx group (4 kidneys, 1 liver, 0 kidney-pancreas) and 7 patients (2%) in the non-transplanted group (p=0.24).

Conclusions: Previous history of ATx is associated with an increased 30-day incidence of stroke after CS. ATx does not affect 30-day mortality after CS, while long-term survival is significantly reduced. Regular patient follow-up, prevention and early treatment of post-operative complications are key to patient survival.

C16

Zero 30-Day and In-Hospital Mortalities in Consecutive Isolated Cardiac Valve Surgery: Continuing Lifetime Quest of a Single Cardiac Surgeon

Takushi Kohmoto, Entela B. Lushaj

Abstract begins on following page

Introduction: Full sternotomy (FS) is the conventional approach for the surgical treatment of valve disease. Although this approach has shown excellent postoperative outcomes, minimally invasive valve surgery (MIVS) has been supported among surgeons as it has provided good quality, safety and patient satisfaction. The goal of our study was to compare peri-operative outcomes and 30-day survival in patient undergoing MIVS or full sternotomy for valve replacement therapy.

Methods: 244 isolated aortic and mitral valve replacement/repair (AVR; MVR) surgeries were performed at our institution by a single surgeon between February 2005 - March 2015. Of those, 17 interventions, in selected patients, were MIVS (partial lower hemi-sternotomy; 11 AVR and 6 MVR). Post-operative complications and patient survival were retrospectively retrieved and compared with full median sternotomy group (n=227).

Results: Mean age of patients undergoing MIVS was 62±14 years and 59% of them were males. Comorbidities included hypertension (53%), PVD (18%) and CHF (59%). CPB and OR time were significantly shorter than the conventional approach. Aortic cross clamp and surgery time were also lower than the conventional approach (p=0.076). Patients undergoing MIVS were discharged earlier (6±3 vs. 9±6 days; p<0.001). 30-day readmission rate was 6% (p=0.679). There were no differences between patients treated minimally invasive or through median sternotomy in regards to post-operative complications such as bleeding, infections, prolonged ventilation, renal failure, stroke, TIA and bleeding. 30-day mortality and in-hospital mortality were zero for both groups.

Conclusions: There were no 30-day and in-hospital mortalities in this series of isolated aortic and mitral valve surgeries with conventional full sternotomy or MIVS. This demonstrates that low volume surgeons can achieve excellent outcomes. In carefully selected patients, MIVS improves surgical quality and outcomes. Extremely low complication rate and mortality are needed when expanding TAVR indication to low surgical risk population.

Evaluating Sarcopenia as a Biomarker of Clinical Outcomes in Patients Undergoing Thoracic Endovascular Repair with a Conformable Graft

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Abstract begins on following page

Objective: To evaluate the effects of sarcopenia on clinical outcomes, including incidence of adverse events in patients who underwent endovascular repair for thoracic aortic aneurysm and dissection using a conformable graft device.

Methods: 16 aneurysm patients and 22 dissection patients (n=38) were evaluated using TeraRecon software at preoperative and 48-month postoperative intervals for sarcopenia by two readers previously validated for interobserver and intraobserver error. Total skeletal muscle area was measured at the T12 vertebra and the total psoas muscle area was measured at the L3 vertebra. Patients were considered sarcopenic if they had muscle areas lower than 42.6 cm^2/m^2 for males and 30.6 cm^2/m^2 for females at the T12 and values lower than 52.4 cm^2/m^2 for males and 38.5 cm^2/m^2 for females at the L3, as defined by previous literature. Patient data was collected for length of stay, incidence of adverse events, including death, myocardial infarction, pneumonia, reintubation, tracheostomy, dehiscence, superficial wound infection, deep wound infection, stroke, renal failure, deep vein thrombosis, arrhythmia, cardiac arrest, paraplegia, sepsis, urinary tract infection, access site complications, and endoleaks. Chi squared and Fisher test were used to analyze incidence of adverse events in patients with and without sarcopenia. Mortality was compared between sarcopenic and non-sarcopenic patients using a Kaplan-Meier survival curve and a log-rank test. ANCOVA was used to model outcomes based on varying demographics, including age, BMI, ethnicity, and sex.

Results: At the time of abstract submission, preliminary data suggests that sarcopenic patients undergoing thoracic endovascular repair will demonstrate greater frailty and therefore increased morbidity, mortality, postoperative length of stay, postoperative complications, and perioperative complications. Based on current measurements and data from the clinical database, we expect to see that preoperative sarcopenia will affect varying combinations of demographics differently, resulting in a multifaceted prediction model.

Discussion: It has been previously demonstrated that sarcopenia is a significant predictor of increased morbidity, mortality, and length of stay in patients undergoing abdominal aortic aneurysm repair and aortic valve replacement, in addition to other operative procedures. Understanding which patients are most vulnerable to perioperative and postoperative complications may help identify patients who are less likely to benefit from prophylactic endovascular repair of thoracic aneurysm or dissection. While endovascular repair has proven to reduce morbidity, mortality, and length of stay, it is important to consider patients who may deviate from the reduction of the aforementioned factors as a result of frailty. Quantifying frailty via CT analysis of skeletal muscle is an important step forward in determining which patients are at highest risk for complications in undergoing thoracic endovascular repair of aortic pathologies and can be useful in creating models that predict which patients are highest risk as a result of both low muscle area and demographic susceptibility.

Swallowing Pressure Variability in Effortful Swallowing Tasks in Patients with Early-Stage Parkinson's Disease and Healthy Controls

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Keywords	Swallowing, Parkinson's Disease, High-Resolution Manometry, Motor Control, Effort

Abstract begins on following page

Introduction: In healthy people, within-individual motor variability increases with age as individuals start to have a lesser control of fine motor movements and coordination. In addition to effects of age, one of the main symptoms of Parkinson's disease (PD) is a decline in motor function. Patients with PD have increased motor variability when completing limb motor tasks, such as finger-tapping or gait. It has been shown that motor variability in the limb decreases with increased effort, which may give physicians and therapists information that can help plan treatment. Although there is evidence for decreased variability in effortful limb movement, the effects on effortful swallowing on variability are unknown. We hypothesized that, similar to the limb motor tasks, motor variability would decrease with increased swallowing effort.

Methods: Twenty-two subjects participated in this study. Twelve patients with PD (8M/4F, mean age = 67.6) were compared to ten healthy controls (4M/6F, mean age = 66.8). We used high-resolution manometry (HRM) to measure pressures generated in 4 regions of the throat during swallowing: velopharynx, tongue base, hypopharynx, and upper esophageal sphincter. Each subject performed 10 swallows of 10cc of water, followed by 10 effortful swallows of 10cc of water, with a break in between each task. The effortful swallows were described to the patients as swallowing with gust in an effort to squeeze all of the muscles in the mouth and throat during the swallow. A 3-way repeated measures ANOVA was used to examine the effects of health, swallowing task, and pharyngeal region on swallowing pressure variability.

Results: There was a significant interaction effect of task and pharyngeal region on swallowing pressure variability (F(1.6,32.4)=9.2, p = 0.001). Pressure variability in the hypopharynx and upper esophageal sphincter was greater than in the velopharynx and tongue base (p < 0.001), regardless of task. During effortful swallowing, pressure variability in the upper esophageal sphincter was significantly greater than during 10cc swallows (p = 0.001).

Conclusions: Effortful swallowing increases swallowing pressure variability, but only in the upper esophageal sphincter region, thus violating our hypothesis. However, these findings support other evidence of distinct motor control of cranial and limb musculature. Knowing where in the throat increased pressure variability occurs can provide physicians and therapists valuable information to improve recognition and treatment of patients with dysphasia.

Characterizing Surgeon Prescribing Practices and Opioid Use after Outpatient General Surgery

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Keywords	Opioid Epidemic, Outpatient General surgery, Opioid Prescribing Practices, Patient Opioid Use, Opioid Over-Prescribing

Abstract begins on following page

Introduction: Surgeons typically prescribe opioids for patients undergoing outpatient general surgery operations, yet opioid prescribing practices are not standardized. Excess opioid supply in the community leads to abuse and diversion. Commonly prescribed opioids are responsible for approximately half of all opioid overdoses, and most heroin users report first abusing prescription opioid pills. Identifying patient and operative characteristics associated with postoperative opioid use could reduce overprescribing, and optimize prescribed quantity to patient need. Our aim was to characterize prescribing practices and opioid use after common outpatient general surgery operations, and to investigate predictors of opioid amount used.

Methods: We previously developed a postoperative pain questionnaire for adult patients undergoing outpatient inguinal hernia repair (IHR), laparoscopic cholecystectomy (LC), breast lumpectomy +/- sentinel lymph node biopsy, and umbilical hernia repair (UHR) at our institution. This facilitated a retrospective review of patients undergoing operations from January to May 2017, excluding those with postoperative complications. We collected opioid prescription data, operative details, and patient characteristics including age, sex, body mass index, chronic pain history, pre-operative opioid use, and pre-operative benzodiazepine use. All opioids were standardized to morphine milligram equivalents (MME) and reported as a corresponding number of 5mg hydrocodone pills for interpretability. Multivariable linear regression was used to investigate patient, procedure, and prescribing factors associated with amount of post-operative opioid use.

Results: The 374 eligible cases included 114 (30.6%) unilateral and 59 (15.8%) bilateral IHRs, 90 (24%) LCs, 17 (4.6%) lumpectomies, 33 (8.9%) lumpectomies with sentinel node biopsy, and 60 (16.1%) UHRs. Forty-eight providers prescribed six different opioids. There was variation in prescribed quantity for all procedures, ranging from zero to 80 pills. Median numbers of pills prescribed vs taken were 20 vs 5.5 for unilateral IHR, 20 vs 4 for bilateral IHR, 20 vs 10 for LC, 10 vs 1 for lumpectomy, 20 vs 2 for lumpectomy with sentinel node biopsy, and 20 vs 5 for UHR. Most patients (86%) were overprescribed. Nearly all (95%) patients took 30 or fewer pills. Twenty-four percent of patients took zero pills. Univariate analysis showed operation type (p<0.001), age (p<0.001), body mass index (p<0.01), chronic pain history (p<0.01), and pre-operative opioid use (p<0.01) to be associated with MME amount taken. On multivariable analysis, there was a significant relationship between opioid use and age (p<0.001), with 16-34% less MME taken for every ten year age increase. Patients who underwent LC took over twice as much opioids compared to patients undergoing UHR (p<0.05). Opioid amount taken was also associated with opioid amount prescribed (p<0.001), with patients taking 24% more MME for every additional ten pills prescribed.

Conclusion: Marked variation exists in opioid type and amount prescribed, and most patients receive more opioids than they consume. Higher prescription amounts contribute to more opioid use, and certain patient subsets may be more (LC) or less (elderly) likely to use opioids postoperatively. Overall, there is an opportunity to reduce post-operative opioid prescription amounts and thus, decrease excess opioids available in the community.

Impact of Prescription Drug Monitoring System on Prescribing Practices after Out Patient Procedures

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Abstract begins on following page

Introduction: The opioid epidemic continues. Overprescribing of opioids contributes to excess opioid supply for diversion and abuse. Recent data demonstrates wide variation in prescribing and significant over-prescribing following outpatient general surgery procedures. Many states have implemented prescription drug monitoring programs (PDMP) as a tool to help prevent and monitor prescription drug misuse and abuse. Beginning on April 1, 2017 Wisconsin law requires prescribers to review the WI electronic PDMP (ePDMP) prior to issuing most controlled substance prescriptions to their patients. Our aim was to investigate trends in opioid prescription amounts and to evaluate the impact of the ePDMP requirement on surgeon prescribing practices.

Methods: We collected prescription data retrospectively for three months before and after implementation of the law, as well as for two months one year prior. Eligible procedures included outpatient inguinal hernia repair, umbilical hernia repair, laparoscopic cholecystectomy, and breast lumpectomy +/- sentinel lymph node biopsy. All opioid prescriptions were converted to standard morphine milligram equivalents (MME). We compared mean MMEs prescribed for different time periods. To estimate the effect of mandatory ePDMP review in Wisconsin on weekly mean MMEs prescribed, we performed an interrupted time-series analysis using an autoregressive integrated moving average (ARIMA) model with weekly intervals.

Results: In January-March of 2017, the mean MME prescribed following outpatient operations was 135 ± 4.0 (~27 5mg hydrocodone pills). The amount in January 2016 was significantly higher (216 ± 10.2, ~43 5mg hydrocodone pills, p<0.001). There was a significant decrease in the mean MME prescribed in the three months following the implementation of the ePDMP requirement (114 ± 3.6 MME, ~23 5mg hydrocodone pills, p<0.001 vs. January-March 2017 & vs. January 2016). There was no difference in the procedure make-up across time periods. Figure 1 demonstrates a downward trend of opioids prescribed over time. Time-series analysis did not reveal a significant intervention effect (intervention parameter - 1.84, t-value = -0.99, p = 0.335) for the implementation of the mandatory ePDMP review.

Conclusion: We demonstrate a decrease in the amount of opioids prescribed by general surgeons for outpatient operations from January to June 2017 and a significant decrease compared to 2016. The implementation of mandatory ePDMP requirements for opioid prescribers does not appear to have had an effect on the amount of opioid prescribed in the early post-intervention period suggesting that additional factors have contributed to decreased prescription amounts.

Figure 1: Decrease in opioid prescribing for outpatient general surgery operations from January to June 2017
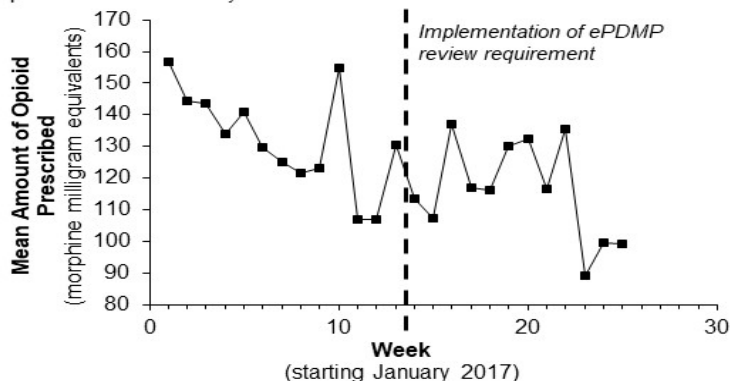
C30
Opioid Prescribing Trends in Plastic Surgery

Katherine Rose, MD; Lisa Block, MD; Brian Christie, MD; Venkat Rao, MD, MBA; Brett Michelotti, MD

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Abstract begins on following page

Introduction: Opioid over-prescription is a nationwide problem contributing to the current opioid epidemic. Methods to reduce the frequency with which opioids are prescribed are being investigated across multiple disciplines. Currently, there are no data detailing the prescribing habits and need for post-operative narcotics for patients undergoing Plastic Surgery procedures. The goal of this study was to evaluate opioid consumption, physician prescribing practices, and patient satisfaction with post-operative pain control following Plastic Surgery procedures.

Methods: Patients who underwent all types of Plastic Surgery procedures were given a post-operative questionnaire inquiring about pain control and medication use. We queried about procedure type, quantity of opioids prescribed and used, day of opioid cessation, opioid refill status, subjective pain scores, concurrent use of non-opioid analgesics, and overall satisfaction with their pain control.

Results: One hundred and sixty-five patients completed the survey. The most commonly prescribed opioids were hydrocodone-acetaminophen 5mg/325mg (42%) and oxycodone (39%). On average, patients took oral opioids for 4 days post-operatively. The average number of tablets prescribed was 27 (SD=12) and the average number of tablets consumed was 14 (SD=12). Breast reduction patients were taking opioids for approximately 6 days and, on average, were prescribed 25 pills but required 17 pills. This compares to non-breast soft tissue procedure patients who required opioids for 4 days and who were prescribed, on average 27 pills and used 12 pills. Approximately fifty percent of all patients used non-steroidal anti- inflammatories and acetaminophen in conjunction with opioids to control post-operative pain. The majority of patients (93.3%) reported satisfaction with their pain control post-operatively with 79.4% being very satisfied, 0.6% being satisfied, 14.5% being somewhat satisfied, and 3.6% being not satisfied. On a numeric rating scale of 1-10, the average worst post-operative pain score was 6.1.

Conclusion: We found that, on average, providers are prescribing almost double the amount of opioids that are consumed by patients after Plastic Surgery procedures. The results of this study will help guide prescribing practices for common Plastic Surgery procedures at the University of Wisconsin, and may ultimately lead to a reduction in over-prescribing of opioids after surgery.

Medication Usage and Quality of Life of Gastroparesis Patients with Gastric Neuro-stimulator Implant

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Keywords	Valve Surgery, Outcomes, Isolated, Full Sternotomy, Minimally Invasive

Abstract begins on following page

Gastroparesis (GP) is a disease of delayed stomach emptying. Severe cases cause nausea, vomiting, and abdominal pain leading to frequent emergency room visits and hospitalization. Gastric neurostimulation (GNS) is a surgical treatment intended to reduce symptoms, and may decrease the need for anti-nausea, pain, and psychiatric medications. Currently there are no studies looking at the long-term quality of life or medication usage (QOL) after GNS placement. This study compares pre- and postoperative QOL metrics collected through chart review and phone surveys of patients receiving GNS between 2005 and 2016.Twenty patients were evaluated. There was a significant decrease in the number stomach motility and anti-nausea medication taken after surgery. The QOL data is yet to be analyzed, however, our preliminary data suggests that GNS may be an effective treatment for gastroparesis long term.

Comparison of Endoscopic Versus Open Surgical Correction of Sagittal Craniosynostosis Using a Novel Technique

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Abstract begins on following page

Background: Surgical correction of sagittal craniosynostosis has been described using both open and endoscopic techniques. Open techniques can vary considerably, from a strip craniectomy to total calvarial vault remodeling, whereas endoscopic techniques primarily involve strip craniectomy with or without barrel stave osteotomies. Endoscopic techniques have been found to offer shorter operating times, lower estimated blood loss, lower rates of blood transfusion, and shorter length of hospital stay, but require post-operative helmet therapy to achieve similar outcomes as open techniques. Here we present a comparison of three techniques: open modified Jane, endoscopic strip craniectomy, and a novel technique: endoscopic modified Jane. Our purpose is to evaluate the safety and efficacy of this novel technique in comparison to previously established techniques.

Methods: This retrospective review of 81 consecutive patients undergoing surgical correction of isolated sagittal craniosynostosis at a single institution between 2002 and 2017 compares the safety and efficacy of three different surgical techniques: open modified Jane (n=43), endoscopic strip craniectomy (n=12), and endoscopic modified Jane (n=20). Variables included: age at surgery, operative time, estimated blood loss (EBL), blood transfusion events and volume, major and minor complications, length of hospital stay, length of ICU stay, elevated ICP events, and helmet therapy use. Outcomes assessment also included comparison of preoperative and postoperative photographs, as assessed by 4 blinded evaluators.

Results: Patients treated with the endoscopic modified Jane technique were younger (3.6 vs 7.9 mo) and had a lower EBL (91.3 vs 104.1 mL), shorter hospital stay (2.5 vs 2.9 days), and shorter operative time (130.6 vs 147.2 min) than patients treated with open modified Jane technique. Compared to patients treated with endoscopic strip craniectomy, there were no differences in age, EBL, or length of stay. Patients treated with endoscopic modified Jane were less likely to require postoperative helmet therapy (5.2 vs 66.7%) than patients treated with endoscopic strip craniectomy. Postoperative head shape was comparable between all techniques. Adverse ICP events and major and minor complications were rare events in all groups.

Conclusions: The endoscopic modified Jane is a novel, safe, and effective technique for treating isolated sagittal craniosynostosis that offers the advantages of endoscopic surgery while obviating the need for postoperative helmet therapy.

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A Randomized Controlled Trial Evaluating the Impact of Pre-Consult Information on Patient Participation in Decision-Making

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Keywords	Decision Aid, Patient Satisfaction, Breast Surgery, Breast Cancer, Decision Making

Abstract begins on following page

Introduction: We hypothesized that providing high quality treatment information to breast cancer patients prior to surgical consult would facilitate active participation in decision-making. The objective was to examine the impact of pre-consult information on patients' role in decision- making and the relationship between role and satisfaction with the decision process.

Methods: Stage 0-3 breast cancer patients were randomized to be emailed prior to the surgical consult a link to standard websites (e.g. National Cancer Institute) versus a decision aid (n=227). 68% completed surveys after surgical consult and treatment completion (n=154) that assessed patients' perceptions on being asked preference for surgery type, role in decision- making, and satisfaction with the decision process. Chi square tests compared role in decision- making by randomization arm. Multivariable logistic regression assessed the relationship between satisfaction with the decision process and patient factors (demographics, surgery, role in decision-making), randomization arm, and surgeon.

Results: Median age was 59 (27-80) years, 99% were white, and 88% had at least some college education. The majority perceived a shared role in decision-making (83%), though fewer reported being asked their surgical preference (63%). 62% were satisfied with the decision process (Table). Randomization arm was not associated with these outcomes (p>0.05). Whether patients reported being asked their surgical preference varied by surgeon (p=0.001) and education (p=0.05), with more educated patients less likely to report being asked. Patients not asked their preference reported less active roles in decision-making (p<0.005). There was no association between patient factors, randomization arm, or surgeon with satisfaction with the decision process.

Conclusion: Although the majority of women reported a shared role in decision-making, only 62% were satisfied with the decision process. Further research must identify factors contributing to the low satisfaction with the decision process observed in order to identify opportunities to intervene.

Table. Satisfaction with Decision Process		
	Agree %(n)	**Disagree %(n)**
I wish I had given more consideration to other surgical treatment options	39% (n=60)	61% (n=94)
I would like to have had more information when the decision about surgery was made	45% (n=70)	55% (n=84)
I would like to have been more active in making the decision about what kind of surgery to have	38% (n=59)	62% (n=95)
I did not have as much to say about what kind of surgery to have as I wanted	29% (n=44)	71% (n=110)
Overall satisfaction with decision process*	**Low: 38% (n=58)**	**High: 62% (n=96)**
*Satisfaction with Decision Process scale is scored on a Likert scale from 1-5 with the overall satisfaction score representing an average of the 4 individual questions; low satisfaction is defined as a score of <3		

Quantifying Pancreatic Lipid Content: Correlation with Clinical Markers Used in Assessing Pancreatic Graft Transplantability

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Keywords	Pancreas, Transplant, Steatosis, Organ Donation, Folch Method

Abstract begins on following page

Background: The overall pancreatic graft quality is considered a critical factor that is associated with outcomes of pancreatic transplants. One of the key visual criteria for suitability for transplant is the amount of fatty infiltration or steatosis, which is felt to correlate with poor outcomes. In an effort to characterize the transplantability of donor pancreata accurately, several clinical factors of the donor are assessed. Although parameters such as older age and higher BMI have been correlated with poor outcomes, these may not have a direct correlation to the pancreata quality and fat content. Consequently, there is a high discard rate of potentially transplantable pancreata, and many grafts from older and overweight donors could be successfully transplanted. The present study sought to determine how well BMI and other donor parameters correlate with actual lipid content in pancreata.

Methods: 24 donor pancreata were ethically obtained from the Organ Procurement Organization (OPO) at the University of Wisconsin, separated into male (n=13; ages:7-60) and female (n=11; ages:39-69) subgroups and analyzed for lipid content using a modified version of the Folch method. The pancreata were immediately prepared by dissecting the parenchyma from non-parenchymal tissues, such as the duodenum and vessels, and cut into 1cm cubes before freezing at -80°C. 30mg of lyophilized cubes were treated with a 1:3 chloroform/methanol solution for 30 minutes for lipid extraction. Following centrifugation, the liquid is transferred to a new tube and brought to a 2:1 chloroform/methanol ratio to separate the lipid phase. The lipids were then placed in a new tube to air-dry for 4-7 days to quantify the dry weight of lipids relative to the dry weight of tissue. Technical replicates (n=1-3) were collected for each donor. Donor clinical parameters were collected from the OPO records and cross-referenced to the extracted lipid content for each donor.

Results: We observed a wide range of lipid content in this cohort of pancreata (Average=35.8%; Range=17.2-82.8%). When we analyzed all pancreata for %Fat versus BMI or age using Pearson's correlation, we found no correlation. Additionally, we found that age and BMI are not correlated. After stratifying by sex, %Fat and BMI are somewhat correlated for the female subgroup (R_2 = 0.2423; p = 0.118), but not correlated in males. Interestingly, %Fat and age are significantly correlated for the male subgroup (R_2 = 0.4326; p = 0.0125), but not correlated in females. Additional relationships examined between %Fat and amylase, HbA1c, and lipase resulted in no significant correlations.

Conclusions: Differences in pancreatic graft quality related to fat content do exist. Currently, BMI is used as a surrogate marker in transplant practice for intraparenchymal fat content and pancreas quality; however, it does not correlate well with %Fat quantified via the Folch method for the male subgroup. There were notable sex differences in the correlation between %Fat and BMI or age. Further studies need to be conducted to include a larger dataset and more technical replicates for each donor to strengthen these results and to tease out other potential relationships.

Initial Outcomes of Trans-Catheter Aortic Valve Implantation with Self-Expandable Type Device (CoreValve) and Recapturable Device (CoreValve-Evolute R): University of Wisconsin Experience

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Abstract begins on following page

Introduction: Trans-catheter aortic valve implantation (TAVI) is an established treatment for severe symptomatic aortic valve stenosis (AS) patients. In our institution, TAVI program was initiated in 1/2012 and self-expandable type device (CoreValve) became available in 3/2015. Recently, recapturable device (CoreValve-Evolute R) is available for TAVI. The purpose of study is to evaluate our institutional results for TAVIs with these two self-expandable devices.

Method: We retrospectively reviewed 55 severe symptomatic AS patients who underwent TAVI with self-expandable devices from 3/2015 to 9/2016. Demographics, procedural characteristics, and outcomes were evaluated.

Results: Mean age of the patients was 79 y/o. Mean STS score was 7.9%. 49% of the patients underwent the procedure under conscious sedation. Access approaches were trans-femoral artery (89%), trans-aortic (4%) and left-subclavian artery (7%). Median length of hospital stay was 3 days. There was no hospital mortality.

Conclusions: Our initial institutional experience of TAVI with self-expandable devices was acceptable. Further study is needed for long-term results including durability of valve.

C12

Surgical Treatment of Adult Buried Penis Syndrome: A New Classification System

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Keywords	Buried Penis Syndrome, Penile Exhumation, Penile Reconstruction, Obesity, Trunk Reconstruction

Abstract begins on following page

Background: Adult Buried Penis syndrome may be associated with an inability to void, sexual dysfunction, recurrent infection, limited mobility, and psychological distress. Previously published classification systems rely on intraoperative findings, such as penile skin quality [1]. Variations in severity, etiology, and options for surgical management necessitate a reproducible and easily applied classification system to both study outcomes and guide preoperative counseling. The purpose of this study was to evaluate surgical outcomes after repair of adult buried penis and study technical refinements and variables that impact success.

Methods: The authors reviewed data from patients who underwent buried penis reconstruction at a single institution. Based on the history and physical examination, a classification system for surgical planning was proposed. Statistical analysis was performed using analysis of variance (ANOVA) and Pearson correlation coefficient. A p-value of < 0.05 was deemed statistically significant.

Results: Twenty-three patients underwent reconstruction between 2012 and 2017. The mean age at time of surgery was 55 +/- 16 years and mean BMI was 49 +/- 14 kg/m^2. Patients were classified into four groups: (I) Iatrogenic buried penis with scarring treated with excision of skin and grafting (n=3); (II) Excess abdominal skin and fat treated with panniculectomy and mons suspension (n=6); (III) Excess skin and fat with complete retraction of the penis treated with panniculectomy plus exhumation with skin excision and grafting (n=12); (IV) Type III plus severe scrotal edema treated with skin excision, grafting, scrotectomy, and translocation of testes (n=2). There was no significant association between age, BMI, repair type and complications. The mean operative time was 190 +/- 74 minutes and the mean hospital length of stay was 8 +/- 5 days. The mean drain duration was 19 +/- 15 days and was significantly different between groups (p=0.03). Of patients undergoing skin grafting, 14/16 (88%) had 100% graft take. The mean Foley catheter duration was 7 days. Complications included cellulitis (n=2), superficial wound dehiscence (n=3), hematoma (n=1), and AKI (n=1). Nearly all patients (22/23, 96%) reported early satisfaction and improvement in their symptoms postoperatively. Important technical modifications included the use of number 5 braided, polyester suture for four-point resuspension of the suprapubic fat pad to bone, as well as a Reston foam bolster for 5 days after skin grafting.

Conclusions: Individualized surgical treatment for buried penis is effective with a relatively low risk of major complications. Classifying patients with buried penis according to preoperative examination findings may guide surgical decision-making and preoperative counseling, and allow for improved evaluation of perioperative outcomes.

C26
Dysphagia Prevalence and Severity in Inpatients with Dementia Referred for Swallowing Evaluation

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Keywords	Dysphagia, swallowing, dementia, videofluoroscopy, prevalence

Abstract begins on following page

Purpose: The purpose of this study was to determine the prevalence and severity of dysphagia in inpatients with dementia referred for swallowing evaluation.

Methods: Billing data were used to identify inpatients with a clinical bedside evaluation (CPT code= 92610) at a large, university hospital in calendar year 2014. In-depth abstractions of 2035 electronic health records were performed using a standardized data instrument. Dementia diagnoses were characterized based on a previously validated classification method. Dysphagia severity ratings were derived from bedside swallow evaluation (BSE) and videofluoroscopic swallow study (VFSS) clinical reports.

Results: 343 patients (16%) were diagnosed with dementia. Those with dementia were significantly more likely to have dysphagia (89.4%; p<.0001) than normal swallowing. The majority were diagnosed with mild or mild-moderate dysphagia (65%) as compared to moderate (14%), moderate-severe (6%), or severe dysphagia (3%). 51% of patients received a BSE only; 46% a BSE and VFSS; and 2% a BSE and flexible endoscopic evaluation of swallowing. Median BSE dysphagia severity ratings were significantly higher than VFSS ratings (z=-6.889, p<.0001).

Conclusion: Clinicians can expect inpatients with dementia to have some level of dysphagia. BSE clinical judgments of dysphagia severity may be more severe than judgments based on VFSS results, emphasizing the importance of instrumental evaluation. Less frequent occurrences of moderate-severe dysphagia may be due to patients with advanced dementia and worse swallow function receiving palliative/hospice care without hospital admission.

C3
The Intersection of Surgery and the Opioid Epidemic

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Keywords	Opioid, Epidemic, Prescription Practices, Overdose, Public Health

Abstract begins on following page

Introduction: The opioid crisis is reaching epidemic proportions in the United States. Drugs now kill more people than both guns and motor vehicle accidents; drug overdose is the leading cause of accidental death in the United States, with 37% of those deaths related to prescription pain medications, compared to 24% that are related to heroin. The opioid epidemic is unquestionably related to prescription opioids, with 4 in 5 new heroin users starting out misusing prescription opioids, and 92% of unintentional opioid overdose deaths occurring in people who had been receiving legitimate opioid prescriptions from healthcare providers. In this review, we examine how the opioid epidemic intersects to post-operative prescription of opioid pain medications.

Methods: We performed a review of the literature to investigate the effect of post-operative prescribing practices on population health trends of the opioid abuse epidemic, as well as to investigate what, if any, affect there is on surgical patient development of opioid abuse.

Results: Twenty eight percent of patients were found to still be using opioid medications two months after surgery for musculoskeletal trauma, and 6% of patients were found to still be using opioid medications six months after a variety of surgeries. Risk of death increased about six-fold with opioid prescription after an acute pain episode such as surgery. Moreover, surgical contributors to the opioid epidemic take the form of (1) overprescribing leading to diversion of medication to other individuals, (2) prescribing patterns that risk harm to post-operative patients, and (3) failure of recognition of opioid dependence or abuse.

Conclusions: Surgical patients are at risk of opioid dependence and abuse, and subsequent risk of drug related injury or death. Post-operative prescribing practices are contributing to the opioid epidemic. Specific steps that can be taken to address the surgical contribution to the opioid epidemic are: (1) reduce opioid use in post-operative pain management protocols, (2) reduce overprescribing and misprescribing of opioid medications in order to reduce diversion, (3) reduce co-prescription of opioid and benzodiazepine medications in order to reduce risk of drug related death, (4) identify patients who may have developed opioid dependence or abuse in order to help facilitate treatment. The opioid crisis is a significant threat to the general population and especially the postoperative patient population. Surgical contributors are modifiable and can help reduce risk to both post-operative patients as well as the general public.

Rotation-Advancement Repair of a Canine Unilateral Complete Cleft Lip: Literature Review and Case Report

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Keywords	Dog, Cleft Lip, Cleft Palate, Primary Palate, Cleft Surgery

Abstract begins on following page

Objectives: There is a paucity of veterinary literature devoted to cleft lip repair techniques in the dog. This article reviews pertinent embryology, classification, etiology, epidemiology, comparative anatomy and management of the canine cleft lip. It then presents a novel adaptation of the Millard rotation-advancement closure, a popular technique used for human cleft lip repair, to that of a female pit bull terrier cross with a wide left unilateral complete cleft lip.

Methods: In adaptation to the canine, technical refinements to the Millard rotation-advancement closure were made based on differences in anatomical structure and physiologic endpoint. These are clearly illustrated in step-by-step figures and intraoperative photographs.

Results: The patient underwent simultaneous repair of a non-syndromic left unilateral complete cleft lip and cleft of the primary hard palate at 17 weeks of age. The complete cleft lip repair healed well without complication. Post-operative photographs display improvement in upper lip symmetry, establishment of the nostril floor, columella, and alar fold, and production of a favorable scar pattern.

Conclusion: This article provides a thorough review of the canine literature focused on cleft lip. It is the first described adaptation of the Millard rotation-advancement closure to the canine cleft lip. We are pleased to offer an additional technique dedicated to canine cleft lip closure, with multiple potential benefits over straight-line repair.

Identifying Predictors of Prolonged Levothyroxine Dose Adjustment after Thyroidectomy

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Abstract begins on following page

Introduction: Synthroid (LT4) is one of the most prescribed drugs in the US. Despite its widespread use and multiple dosing schemes, many patients struggle to achieve euthyroidism after thyroidectomy and suffer symptoms of hyper- or hypothyroidism. The objectives of this study are to describe time required for dose adjustment prior to achieving a euthyroid state and to identify predictors of prolonged dose adjustment (PDA+) after thyroidectomy.

Methods: This is a retrospective cohort study of patients from a single institution who achieved euthyroidism with LT4 therapy between 2008 and 2017 after undergoing total thyroidectomy or completion thyroidectomy for benign disease. PDA+ was defined as needing at least 3 dose adjustments (top quartile) prior to achieving euthyroidism. We compared patient characteristics of PDA+ patients to the remaining patients (PDA-) using Wilcoxon Rank Sum test or Chi-squared test where appropriate. Multivariate logistic regression was used to identify predictors of PDA+.

Results: The 605 patients in this study achieved euthyroidism in a median of 116 days (range 14 - 863) and 1 dose adjustment (range 0 - 7). The 508 (83.97%) patients who were PDA- achieved euthyroidism in a median of 101 days (range 14 - 627) and 1 dose adjustment (range 0 - 2). The 97 (16.03 %) patients who were PDA+ achieved euthyroidism in a median of 271 days (range 52 - 863) and 3 dose adjustments (range 3 - 7). PDA+ patients required more than twice the median number of days to achieve   euthyroidism (271 vs. 101 days, p<0.001).

PDA+ patients were more likely to have chronic renal insufficiency (5.2% vs. 1.6%, p=0.026). More than three times as many patients in the PDA+ group were taking iron (6.2% vs. 1.8%, p = 0.010). Similarly, nearly twice as many patients in the PDA+ group were taking multivitamin with minerals (22.7% vs. 11.6%, p = 0.003). When controlling for all other factors, iron supplementation (OR = 4.4, 95% C.I. = 1.43 - 13.55, p = 0.010) and multivitamin with mineral supplementation (OR = 2.4, 95% C.I. = 1.3 - 4.3, p = 0.004) were independently associated with PDA+. However, plain multivitamins were not associated with PDA+. Age, gender, preoperative thyroid disease, and co-morbidities did not independently predict PDA+.

Conclusion: After thyroidectomy at a high-volume center, achieving euthyroidism can take nearly four months. Iron and mineral supplementation are associated with PDA+. This information can be useful when counseling patients preoperatively and suggests that education about proper LT4 administration   and interfering supplements may expedite achieving euthyroidism.

The Optimal Levothyroxine Dosing Scheme after Thyroidectomy: A Comprehensive Comparison and Evaluation

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Keywords	Thyroidectomy, Machine Learning, Scoping Review, Euthyroidism, levothyroxine

Abstract begins on following page

Background: Patients often struggle to attain euthyroidism after thyroidectomy, and multiple dosing schemes have been proposed to supplant the standard weight-based approach for initial levothyroxine (LT4) dosing. The objectives of this study were to review the literature for existing LT4 dosing schemes and compare estimation accuracies with novel schemes developed with machine learning techniques.

Methods: This study retrospectively analyzed 598 patients from a single institution who attained euthyroidism with LT4 therapy between 2007 and 2017 after undergoing total or completion thyroidectomy for benign disease. We evaluated several machine learning algorithms for estimating euthyroid dose. Three reviewers independently reviewed articles from PubMed, Cochrane, Scopus, and Web of Science in a scoping review to identify existing LT4 replacement dosing schemes. Using repeated 10-fold cross-validation, we evaluated the accuracy of each dosing scheme by calculating the proportion of patients whose predicted dose was within 12.5 mcg/day of their actual euthyroid dose.

Results: Of the 264 articles reviewed, 9 articles proposed LT4 dosing schemes. Ultimately 7 articles proposed schemes that could be implemented retrospectively. After testing various machine learning algorithms to predict LT4 dose, a novel Poisson regression model proved most accurate, correctly predicting 64.8% of doses. Incorporating 7 clinical variables (BMI, weight, age, sex, preoperative TSH, iron supplement use, and multivitamin/mineral use), Poisson regression was significantly more accurate than the best existing dosing scheme in the literature (a BMI adjusted weight-based scheme) that correctly predicted 60.9% of doses (p=0.031). Weight-based LT4 dosing (1.6 mcg/kg/day) correctly predicted 51.3% of doses, and the least effective dosing scheme proposed in the literature (an age adjusted weight-based scheme) correctly predicted 40.1% of doses. Compared to existing schemes, Poisson regression had the lowest rate of dosing errors greater than 25 mcg/day at 19.1%. Examining extremes of patient weight, Poisson regression yielded the highest predictive accuracy within each BMI tertile (lower: 73.3%, middle: 63.6%, upper: 59.7%).

Conclusions: Using readily available variables, a novel Poisson regression dosing scheme outperforms other machine learning algorithms and all existing dosing schemes in calculating LT4 dose. Implementing Poisson regression into electronic medical systems to automatically calculate LT4 dose could potentially reduce morbidity associated with LT4 replacement after thyroidectomy.

Timely Evaluation and Management of Primary Hyperparathyroidism in Patients with Kidney Stones

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Keywords	Primary Hyperparathyroidism, Kidney Stones, Parathyroidectomy, Hyperparathyroidism, Calcium

Abstract begins on following page

Introduction: Kidney stones are a common manifestation of primary hyperparathyroidism (PHPT), and a strong indicator for surgical treatment of PHPT. Effective detection and treatment of PHPT is critical for managing the risk of recurrent stone disease and other complications of unmanaged PHPT. In this study, we examined predictors of kidney stones in PHPT patients and determined how effectively the diagnosis of PHPT is made in patients who first present with stones.

Methods: We performed a retrospective analysis of surgically treated PHPT patients, comparing 247 patients who were kidney stone-formers (SF) and 1,047 patients with no stones (NS). We identified 51 SF patients who presented with a stone before their PHPT diagnosis, and whose stone evaluation and treatment was completed entirely within our health system for further analysis. Extracted data included clinical assessment and treatment of stones as well as timing of PHPT evaluation.

Results: Compared to NS patients, SF patients were more likely to be male (28.6% vs 19.7%, p=0.002) and to be normocalcemic (26.6% vs. 16.9%, p=0.001) than the NS patients. SF patients also had higher alkaline phosphatase (92 IU/L vs. 85 IU/L, p=0.012) and higher 24-hour urinary calcium levels (342 mg/day vs 304 mg/day, p=0.005). On multivariate analysis, being male and having a higher 24-hour urine calcium and alkaline phosphatase were independently associated with a greater incidence of kidney stone formation. Despite these differences, 52.7% of SF had 24-hour urinary calcium levels within the normal range at the time of surgery. Of the 51 SF patients with full chart available for review, 72.5% (n=37) had a serum calcium drawn within 6 months of the first stone episode. Hypercalcemia was present in 43.2% of these patients (n=16), but only 10 (62.5%) of these patients had a serum PTH ordered within 3 months of their elevated calcium. Patients that had both a calcium and PTH drawn within 9 months of their first episode of kidney stones had a significantly shorter time from their first stone to surgical treatment than the other patients (median 8.5 months vs. 49.1 months, p=0.001).

Conclusions: SF patients were found to be stronger excreters of calcium, but elevated urinary calcium and serum alkaline phosphatase levels did not identify the majority of PHPT patients at risk of forming kidney stones. Many patients with kidney stones had normal serum calcium levels and normal urinary calcium levels highlighting the need to carefully evaluate all SF for the possible treatable cause of hyperparathyroidism. Timely consideration of PHPT as well as prompt serum calcium and PTH evaluation significantly reduces time to treatment and minimize the risks of complications of longstanding PHPT.

C19

Examining Transglottic Airflow and Perceptual Ratings of Breathiness in Dysphonic Patients

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Keywords	Voice Disorders, Perceptual ratings of voice, Aerodynamic assessment of voice, Transglottic airflow, Breathiness

Abstract begins on following page

Objective: The aim of the study was to determine if transglottic airflow measures differ significantly across perceptual ratings of breathiness severity in men and women with voice concerns.

Study Design: A prospective disease-specific outcomes database study

Methods: Transglottic airflow measures and perceptual ratings of voice quality were analyzed from 1140 adult patients (458 men, 682 women, ages 18-93) with voice-related complaints. Mean transglottic airflow was examined across the 4 severity ratings of breathiness (0,1,2,3) within the GRBAS scale. One-way analyses of variance with pairwise post hoc analyses were performed to determine if differences in transglottic airflow were significantly different across clinical perceptual ratings of breathiness. Two-way analyses of variance were performed to determine whether airflow measures at each severity rating differed across gender and chi-square contingency tables were used to examine the frequency distribution of the different breathiness ratings by gender.

Results: When males and females were examined together, mean transglottic airflow increased with each change in breathiness severity rating (B0: 0.17 L/s, B1: 0.23 L/s, B2: 0.28 L/s, B3: 0.42 L/s) and these differences were statistically significant. When males and females were examined separately, mean transglottic airflow continued to increase with each severity rating but means were not significantly different across all of the severity ratings. For female subjects, mean transglottic airflow increased by 0.06-0.07 L/s at each severity rating. This was significantly different from breathiness ratings of 0-1(0.06 L/s) and 1-2 (0.06 L/s) but not from 2-3 (0.07 L/s). Chi square analysis revealed a higher percentage of women (14% more) rated as having no breathiness B0). For male subjects, mean transglottic airflow increased across each severity rating, but changes were smaller from 0-1 (0.05 L/s) and 1-2 (0.03L/s) and were only significantly different from 2-3 (0.19 L/s) or when compared across two ordinal categories (0-2, 1-3). A higher percentage of men (8% more) were rated breathiness level 2 versus women. No interaction effect was observed between gender and transglottic airflow at each breathiness severity rating.

Conclusions: Although multiple factors contribute to clinical perceptual ratings of breathiness, some perceptual ratings of breathiness demarcate significant and successive changes in transglottic airflow in dysphonic subjects. Based on the data presented, differences in rating of breathiness between men and women do not seem related to differences in transglottic airflow in clinical populations.

C20
Patient-Perceived Impact of Paradoxical Vocal Fold Motion Disorder on Function and Quality of Life

Katherine McConville

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Keywords	Patient Perspectives, Paradoxical Vocal Fold Motion Disorder, Interviews, Quality of Life, Vocal Cord Dysfunction

Abstract begins on following page

Objective: The purpose of the present investigation was to document patient perspectives of paradoxical vocal fold motion disorder and the way in which it affects quality of life, in order to determine if there are consistent complaints that would ultimately lead to improved understanding of the disorder and treatment.

Study design: Qualitative content analysis of prospective patient interviews.

Methods: Twenty-six adult subjects (ages 18 to 72 years; 2 men and 25 women) diagnosed with PVFM were interviewed in-person. Interview questions were worded a neutral fashion to minimize bias and all interviews were transcribed. Transcripts were analyzed according to qualitative research methods based on grounded theory. Burnard's 14-step method for transcript analysis was employed with minimal alterations to organize content analysis. Categories were identified and the frequency with which these emerged in interviews was summarized.

Results: Common themes shared among patients with PVFM included fear associated with symptoms, change in abilities, concern for judgement from others, and changes to voice function.

Conclusions: Dyspnea can result in patient morbidity and distress irrespective of etiology. Although the dyspnea associated with PVFM may vary based on individual experience, the general impact of PVFM on quality of life as reported by patients appears to include several common themes that suggest perception of physical, emotional, and functional impairments. Treatment targeting improvement in symptoms may be most effective if common themes regarding specific impact on quality of life are taken into account.

C18

Pharyngeal versus Esophageal Stasis: Accuracy of Localization

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Keywords	Dysphagia, Swallow, Pharynx, Esophagus Radiology

Abstract begins on following page

Purpose: Patients with complaints of bolus stasis after swallowing are often referred to a speech pathologist for swallowing evaluation. Previous research has shown that patients with esophageal obstruction are more likely to localize stasis proximal to an obstruction on EGD, however, this has not been studied in patients with oropharyngeal stasis complaints. The purpose of this study was to determine if the location of patients' complaints of bolus stasis were accurate to physiologic location.

Methods: Prospective analysis was completed using the University of Wisconsin Voice & Swallow Outcomes Database of patients that complained of bolus stasis on their intake form and completed a standard of care combined videoflouroscopic swallow study (VFSS) and esophagram (n=387). Fisher's exact test was used to compare location of stasis complaint with patient's accuracy of localization.

Results: Only 34% of patients accurately localized bolus stasis. Accuracy was increased in patients that complained of stasis in esophagus (79%) versus pharynx (17-33%) ($p<0.0001$). Forty-one percent of patients with complaints of stasis in pharynx had stasis in the esophagus. No patients with complaints of esophageal stasis had pharyngeal stasis.

Conclusions: Patients that complain of bolus stasis in the pharynx are less likely to accurately localize their stasis than those that complain of bolus stasis in the esophagus. This highlights the importance of comprehensive evaluation of the esophagus in patients that complain of pharyngeal stasis that are referred for VFSS.

C13

Outcomes Measurement following Cricopharyngeal Myotomy: A Systematic Review

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Keywords	Pharyngeal Disease, Deglutition Disorders, Pharyngeal Muscles, Upper Esophageal Sphincter, Cricopharyngeus Muscle

Abstract begins on following page

Background: No practice guidelines have been established for swallowing outcomes following cricopharyngeal myotomy (CPM). The objective of this systematic review was to summarize evidence for swallowing outcomes in patients undergoing CPM to treat symptomatic cricopharyngeal dysfunction, in accordance with the Preferred Reporting Items for Systematic reviews and MetaAnalyses (PRISMA) protocol.

Methods: The population of interest was identified as adults age 19+ years with cricopharyngeal dysfunction identified on a videofluoroscopic swallowing study. Studies eligible for review investigated CPM as an intervention for cricopharyngeal dysfunction. Zenker's diverticulum, Botox injection and dilation of the CP were excluded from review. Eligible studies were required to include pre- and post-operative statistical comparison of at least one of the following swallowing outcomes: manometric measures of pharynx/UES; patient-rated dysphagia scale scores; clinician-rated dysphagia scale scores; penetration/aspiration ratings on VFSS; weight; and diet level. Statistical analysis results are summarized. Risk of bias for individual swallowing outcomes was categorized as low risk, uncertain risk, or high risk based upon the Cochrane Handbook summary assessments of the risk of bias.

Results: Three databases were queried for studies published between January 1995 and July 2015, resulting in a total of 122 full-text eligible records. Studies were screened and reviewed, culminating in 10 studies meeting inclusion criteria. Critical appraisal of study design, swallowing outcomes measures and statistical analysis are summarized. All swallowing outcomes reported were analyzed as a high

Conclusions: This systematic review revealed insufficient evidence for guiding clinical practice standards for patient selection, surgical approaches and functional outcome measurements. Future investigations should employ validated patient-rated and clinician-rated instruments as well as detailed high-resolution manometry measures to optimally capture post-operative swallowing outcomes.

C27

Is Primary Sclerosing Cholangitis-Related Gallbladder Cancer Associated with Worse Survival? Results from the U.S. Extrahepatic Biliary Malignancy Consortium

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Keywords	Gallbladder Cancer, Primary Sclerosing Cholangitis, Survival Outcomes, Multi-Institution Consortium Outcomes, Surgical Oncology

Abstract begins on following page

Introduction: Patients with Primary Sclerosing Cholangitis (PSC) have higher incidence of biliary cancer, including gallbladder cancer. The impact of PSC on survival for gallbladder cancer patients is unknown.

Methods: Our analysis included 375 patients with gallbladder cancer from a cohort of patients undergoing definitive resection from January 1, 2000 to December 31, 2014 at 10 US academic institutions. Overall survival (OS) was calculated from the date of initial cholecystectomy to the date of death or last follow up, and survival compared in patients with and without PSC. Univariable and multivariable Cox regression analyses were performed to assess OS.

Results: Of the patients with gallbladder cancer, ten had a diagnosis of PSC (2.7%). PSC patients were younger (age 57.8Â±17.9 years vs 65.7Â±11.1 years, P =0.03) with lower overall functional status (P=0.03), and more were male (70% vs 35%, P=0.02) compared to gallbladder cancer patients without PSC. No significant differences were observed between ASA class or presence of jaundice pre-operatively. Gallbladder cancer AJCC stage was significantly lower in patients with PSC with 40% having Stage 0 or Stage I disease compared with only 7% of the patients without PSC (P=0.002). Median follow-up interval for the cohort was 12.3 months. On multivariate analysis including age, functional status, PSC diagnosis and stage, PSC status was not associated with a difference in overall survival. For the entire group, stage remained independently associated with OS (HR 2.11, 95% CI 1.76-2.52, P =<0.001).

Conclusion: No differences in survival were seen between gallbladder cancer patients with PSC vs without PSC in our cohort. Further studies with greater representation of patients with PSC are needed to determine survival differences, which can help guide treatment decision making.

GROUP THREE

Education

Muscle Histopathology in the Thyroarytenoid Muscle in the Pink1 -/- Rat Model of Parkinsons Disease

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Keywords	Thyroarytenoid, Muscle, Parkinson's Disease, Myosin Heavy Chain Isoforms, Pink1

Abstract begins on following page

Introduction: The Pink1 -/- rat model of Parkinsons Disease (PD) recapitulates early behavioral vocalization phenotypes of translational relevance to the patient population. However, the peripheral muscle hallmarks of early-onset vocalization deficits in this model are unknown. We report phenotypes of the thyroarytenoid muscles (TA) at ages previously reported to coincide with early ultrasonic vocalization deficits in Pink1 -/-.

Methods: TA muscles were isolated from Pink1 -/- and unaffected wild type (WT) controls at 4 and 6 months of age (n=8-12/group). Muscles were sectioned, and the medial and lateral TA muscles were analyzed for myofiber characteristics. After sectioning, the remainder of each muscle was homogenized and processed to quantify myosin heavy chain isoforms (MyHC). In tissue sections, myofibers were analyzed for incidence of central nuclei, cross-sectional area (CSA), minimum Feret diameter, and Neural Cell Adhesion Molecule (NCAM). Two-way analysis of variance with a Fisher's Least Significant Differences post-hoc was used to compare genotypes (WT and Pink1 -/-) and age (4 mo and 6 mo).

Results: Incidence of centrally-nucleated myofibers was significantly greater in the lateral TA of Pink1-/- at both ages (p<0.001). Smaller myofibers in the medial TA were observed in 6 mo old Pink1-/- compared to WT (p=0.002). Compared to WT, Pink1-/- TA MyHC profiles showed significantly greater proportions of the MyHC 2L isoform (p=0.003), and significant reductions in the 2X isoform (p=.005).

Discussion: These findings suggest that myofiber differences, including differences of fiber type, occur in Pink1-/- TA and may coincide with altered vocalization reported previously at early stages of disease in this model. Muscle hallmarks of vocalization impairments in PD models are helpful for future use as early-stage biomarkers of PD and for therapy development efforts.

The Quality and Content of Internet Resources for Thyroid Cancer Patients

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Keywords	Thyroid Cancer, Treatment, Quality, Content, Internet Resources

Abstract begins on following page

Introduction: The internet is a key source of health information in the United States (US). Currently, little is known about websites for thyroid cancer. We aimed to examine the quality and content of information about thyroid cancer treatment on the internet.

Methods: We analyzed the top 20 websites identified by searching Google for thyroid cancer. To assess content, a 16-member board of patients/families, endocrinologists, and surgeons identified 29 factors important for treatment decision-making. We evaluated website quality with three valid measures: (1) DISCERN: assesses written information quality, scored 1-2 poor, 3 fair, and 4-5 good; (2) the Journal of the American Medical Association (JAMA) benchmark criteria: examines authorship, ownership, currency of content, and conflicts of interest; and (3) Health-on-Net Foundation Certification (HONcode): indicates ethical medical and health information.

Results: Fifteen of the 20 websites were unique after eliminating duplicates, Wikipedia, and non-US websites. Website sponsors were commercial (33.3%), non-profit (26.7%), hospital-affiliated (26.7%), and governmental (13.3%). The average DISCERN score was 3.4 (fair), and 26.7% of sites were good quality. The websites met 33.3% of JAMA criteria, 29.0% of content criteria, and 46.7% were HONcode certified. All sites discussed lobectomy, total thyroidectomy, and radioactive iodine. Only 33.3% included active surveillance. For treatment by cancer size, 26.7% mentioned lobectomy as standard treatment for ≤1cm cancers, and 6.7% included lobectomy as an option for 1-4cm cancers. For complications, 46.7% of websites noted permanent voice problems as possible after total thyroidectomy and 33.3% after lobectomy. Websites inconsistently described permanent hypocalcemia (40.0%) and symptoms of hypocalcemia (26.7%). For follow-up, 60.0% websites discussed the need for post-operative lab and ultrasound after total thyroidectomy and 53.3% after lobectomy. Websites did not always indicate the need for lifelong thyroid hormone after total thyroidectomy (80.0%) or possible need after lobectomy (53.3%). Additionally, only 20.0% of websites described how to take thyroid hormone. Websites infrequently referenced treatment guidelines (20.0%).

Conclusion: The overall quality and content of websites about thyroid cancer treatment is fair and needs improvement. Most sites lack critical information about treatment options, complications, and post-operative management that is necessary for patients to make informed treatment decisions.

Environment and Teaching Approaches for Effective Surgical Education

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Keywords	Surgical Culture, Surgical Education, Burnout, emotional contagion, confidence

Abstract begins on following page

Background: Despite a growing body of research in surgical education, there is little research about the types of environments and teaching approaches that best foster surgical skill acquisition and promote resident outlooks congruent with effective training.1

A culture of incivility has long been recognized in the business world to decrease work ethic, work quality, creativity, and efficiency.2 Positive leadership, conversely, has been shown to increase team engagement, performance, and the bottom line.3,4 Self-esteem and motivation play a crucial role in learning.5,6 While the business world has utilized these findings to boost profits and build productive teams, the surgical community has not yet integrated these concepts, despite evidence that malignant culture has negative effects on patient safety and personnel, including increasing burnout.8–11

The effects of surgical culture on resident education, in and out of the OR, have not yet been examined. We are interested in examining the environment (i.e. surgical culture) and teaching approaches to optimize effective training.

Methods: A survey was distributed to all surgical residents (general, plastic, vascular, orthopedic, otolaryngology, urology, and neurosurgery). Along with several multiple-choice questions, the survey consisted largely of open-ended questions that asked residents to describe what environments and teaching methods were conducive vs. obstructive to their learning. A theme analysis was done to extract recurring themes of responses.

Results: Forty of 134 residents (30%) responded. Largest numbers of responses were from general surgery (n=24) and plastic surgery (n=11). Juniors (PGY 1-3) constituted 75% of responses, and seniors (PGY 4-7), 25%.

Theme analysis revealed the following recurrent themes in resident responses. *Percentage of responders that mentioned a given theme is in parenthesis.*

Attendings who were effective educators were identified to possess: a focus on teaching (40%), an investment/interest in the resident (38%), patience (28%), and allowance of resident autonomy (25%). Pitfalls to effective surgical education were identified as time constraints (47%) and poor communication (16%). Mental outlooks that help residents excel in the O.R. and residency included: positivity/optimism (50%), confidence (41%), clarity/focus (27%), and feeling prepared (15%). When asked whether attendings/senior-residents influence these mental outlooks, 97% responded 'yes.' Factors contributing to poor OR performance included: attending short-temperedness (43%), feeling unprepared (43%), exhaustion (17%), and poor communication (17%). All responders (100%) identified confidence as important in becoming a surgeon, and 97% affirmed that attendings/senior-residents have an impact on their confidence. When asked about the positive and negative ways in which people change in surgical residency, positive themes included increased confidence (44%) and improved technical skills (23%); negative themes included: cynicism/bitterness (27%), impatience (24%), burnout (21%), and anger (18%).

Conclusion: To complete residency successfully and thrive, both as a surgeon and person, one must not only have 'good hands' but a healthy mental outlook, one of confidence, motivation, resilience, and collegiality. Attendings and senior residents have influence over resident mental outlooks, and thus an ability to promote or stifle them.

Surgeons are not taught to be teachers, yet our profession depends on it. Our success in teaching translates to both the culture we create and the mastery we pass on. Let us choose wisely in how we shape the next generation.

Assessment of Trauma Team Communication Using Automated Discourse Coding and Epistemic Network Analysis

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Abstract begins on following page

Background: Epistemic Network Analysis (ENA) is a technique that can model and compare the structure of connections between the elements of team communication and their impact on team performance. We hypothesized that team communication elements could be coded with an automatic discourse coder and that their connections, as modeled by ENA, would predict the quality of team performance in trauma simulation.

Methods: 28 teams of five trainees - a trauma chief resident, surgery resident, emergency medicine resident, and two nurses - participated in simulated trauma team resuscitations. The Team Emergency Assessment Measure (TEAM) was used to rate teamwork during each resuscitation.

An interdisciplinary group performed an in-depth qualitative analysis of two transcripts. Eight communication codes were identified. Algorithms matching codes to key phrases and patterns of words were developed. These were validated by measuring agreement of automated coding algorithms with coding by a trained human rater on a subset of total transcribed discourse (ƙ ≥ 0.86).

ENA was used to model the connections between communication codes. ENA sums the co-occurrences of codes in nearby lines of discourse and uses these sums to produce a network of connections between codes. ENA models of teams in the highest tertile of TEAM scores (n = 9, mean = 48.56±1.50) and lowest tertile (n = 10, mean = 40.90±2.34) were compared. Further qualitative analysis was used to identify the codes that accounted for significant and meaningful differences between groups: *Asking about Actions, Asking for Information, Intentions, Reasoning, Pathological Descriptions,* and *Status Quo Information.*

Results: ENA models of higher- and lower-performing teams were significantly different (p = 0.002). Higher scoring groups had stronger connections between S*tatus Quo Information* (describing completed actions or current status) and *Reasoning* (providing justification or weighing options based on known information). Reviewing the original data that produced these connections in the model suggests that this reflects when members provide their thoughts linked to information delivered about the current situation.

Conclusions: Connections between describing the current status and providing reasoning were associated with higher performing team performance. Trauma team communication performance can be assessed using automated discourse coding and ENA.

Examining the Impact of Using the SIMPL Application on Feedback in Surgical Education

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Abstract begins on following page

Purpose: The System for Improving and Measuring Procedural Learning (SIMPL) smartphone application allows attending physicians to provide dictated feedback to surgical residents. The impact of this novel feedback medium on the quality of feedback given is unknown. The purpose of this study was to compare the quality of operative performance feedback given via SIMPL to feedback given in-person.

Methods: We collected operative performance feedback given both in-person and via SIMPL on a variety of surgical procedures from four surgical attending physicians to nine general surgery residents over the course of six weeks. We coded each feedback encounter using a speech acts taxonomy, Verbal Response Modes (VRM), in order to compare how feedback is delivered in-person versus via dictation. We also evaluated the quality of each feedback encounter using a validated resident survey and a third-party scoring system adapted from validated rubrics.

Results: Nineteen SIMPL and 18 in-person feedback encounters were evaluated. Chi-square tests for equality of proportions showed feedback provided via SIMPL was more directive—containing thoughts, perceptions, evaluations of resident behavior, or advice—than in-person feedback (p=0.01). SIMPL feedback also contained more presumptuous utterances—in which the physician reflected on and assessed resident performance or offered suggestions for improvement—than in-person feedback (p=0.01).

Resident survey of feedback quality had a possible range of scores from 10 to 50, with a higher score representing better quality feedback. A t-test showed no significant difference between the quality of the feedback given via SIMPL and in-person (p=0.073). The average score was 47.74 (SD=2.997) for SIMPL feedback and 45.33 (SD=4.765) for in-person feedback.

Third party assessment was performed by two evaluators with an intraclass correlation of 0.957. A t-test showed no significant difference between the quality of the feedback given via SIMPL and in-person (p=0.486). The average score was 23.40 (SD=3.75) for SIMPL feedback and 22.25 (SD=5.94) for in-person feedback, with a possible score range of six to 30 and a higher score representing better quality feedback.

Conclusions: Although feedback given via SIMPL was significantly more direct and based on the attendings' perspective, the quality of the feedback did not differ significantly. Use of the dictation feature of the SIMPL smartphone application to deliver resident operative performance feedback is a reasonable alternative to in-person delivery of feedback.

Competence-Based Mastery Learning for Chest Tube Placement: A Study of Anxiety, Confidence, and Performance

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Abstract begins on following page

Introduction: Mastery Learning has been demonstrated to be an effective educational tool for procedural skills. The relationship between anxiety, confidence, and performance in graduating medical students utilizing a Mastery Learning module has not been described. This study evaluates anxiety and confidence as the Mastery Standard is achieved for chest tube insertion basic skills in graduating medical students during an intern preparatory course.

Methods: Fourteen graduating medical students completed a two-week surgery intern preparatory course, which including a Mastery Learning Chest Tube Module. Learners used a moderate fidelity model to demonstrate basic chest tube insertion skills on course day 1 (Pretest). Learners watched a chest tube placement video, participated in a didactic session, and participated in supervised deliberate practice. On course day 4 learners completed a Posttest. Any learner who did not achieve the Mastery Standard received remediation. On course day 10, learners completed a Retention Test on a live animal model.

Prior to each skill test, learners reported State anxiety with the STAI; immediately following each skills test, learners again completed the STAI and the Cato Confidence Scale. The Mastery Learning Standard checklist was validated by faculty trauma surgeons to reflect a level expected of an incoming surgical intern. Student scores were analyzed via a repeated measures ANOVA.

Results: Mastery was not attained by any learner during the pretest. During the Posttest and retention test, 92.2% of learners achieved mastery. With remediation, 100% achieved mastery. Applying a 95% confidence interval, assessment scores increased ($p < .001$), post-skill anxiety decreased ($p < .001$), learner confidence increased ($p < .001$) and State anxiety decreased significantly compared to Trait anxiety ($p = .012$).

Conclusion: Implementation of a Mastery Learning Chest Tube Module in graduating medical students pursuing a surgical residency demonstrated success in achieving the Mastery Standard with improved confidence and decreased anxiety.

Competency-Based Skills Assessment in Graduating Medical Students: A Mastery Learning Module for Sterile Technique

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Abstract begins on following page

Introduction: The educational method of Mastery Learning holds promise for use in Internship Preparatory Course (IPC) Modules. Mastery Learning is defined by all learners achieving a predetermined Mastery Standard through deliberate practice and assessment. Achievement of this Mastery Standard may allow for competency certification prior to internship matriculation. We hypothesize that the use of a Mastery Learning Sterile Technique Module during an IPC would lead to 100% of learners achieving Mastery and furthermore, increase learner confidence and decrease learner anxiety during performance of simulated sterile technique.

Methods: 41 graduating medical students entering surgical or emergency medicine internships completed a two- week IPC that included a Mastery Learning Sterile Technique Module. The module included a low fidelity model that learners prepped and draped while demonstrating proper gowning and gloving technique. The learners demonstrated baseline skills with a Pre-test. Over the next 3-5 days, learners watched a didactic online video and participated in supervised deliberate practice sessions. Learners then completed a Post- test. If learners did not achieve mastery on the Post-test, they received remediation and were re-tested. Test performance was evaluated by faculty physicians using a Mastery Checklist validated by a panel of multidisciplinary experts.

Immediately before and after the Pre-test and Post-test, learner anxiety was measured with the Short Form State Anxiety Inventory. Learner confidence was measured with the Cato Confidence Scale after each Pre-test and Post-test. Paired t-tests were used to analyze difference in learner confidence and anxiety from Pre-test to Post-test.

Results: Zero of the 41 learners achieved Mastery on the Pre-test. 66% (27) of the learners achieved Mastery on their first attempt of the Post-test. All learners who received remediation (14) achieved Mastery on their second Post-test attempt. 100% of learners achieved Mastery by the completion of the Mastery Module. Comparing Pre-test to first Post-test, learner confidence increased (Mean+SD; 2.96+.71 vs 3.32+.78; p<.001) and anxiety decreased (9.63+4.33 vs 8.63+3.7; p=.084).

Conclusion: Implementation of a Mastery Learning Module during an Internship Preparatory Course in a large group of graduating medical students is possible. We showed 100% Mastery achievement as well as decreased anxiety and increased confidence performing simulated sterile technique in our learner population with this method.

Mitigation of Learner Anxiety after Simulation Death: Importance of Systematic Debriefing

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Abstract begins on following page

Introduction: Simulator death during simulation-based medical education remains controversial. Exposure increases learner anxiety and their risk for psychological distress during simulation, which may negatively impact learning. Debriefing after simulation can reduce anxiety, which may positively impact learning. Successful debriefing after simulation may reduce participant anxiety following simulator death while maximizing learning outcomes.

Methods: Nineteen fourth-year medical students individually participated in a clinical decision-making simulation. Some learners experienced simulator death at the conclusion of the simulation regardless of their actions while others did not. Facilitators then led an individual debriefing session using the Gather-Analyze-Synthesize model. Each learner completed the State portion of the State-Trait Anxiety Inventory to assess anxiety before simulation and after debriefing. The Cato Confidence Scale was completed by learners after debriefing. Learners' verbal responses to the experience immediately following the simulation but before debriefing were transcribed, analyzed for sentiment, and coded by experts as pertaining to (1) medical knowledge and decision making, (2) emotion, communication, and confidence, and/or (3) environment. The reduction in State anxiety (pre – post), Cato confidence, and sentiment and content of learners' responses were compared between those who did and did not experience simulator death.

Results: Six learners experienced simulator death (SimD) and thirteen did not experience simulator death (NoD). There was no difference between the average reduction in State anxiety (pre – post) between SimD (M=1.67, SD=2.58) and NoD (M=2.17, SD=3.07; p=0.723). Confidence was similar between SimD (M=2.82, SD=0.906) and NoD (M=3.10, SD=0.690; p=0.519). Verbal responses to the simulation before debriefing produced 13 responses in SimD and 44 in NoD for sentiment analysis. For SimD, 7/13 (53.8%) of their responses contained negative sentiment whereas 14/44 (31.8%) of NoD responses contained negative sentiment (Table 1). Verbal responses to the simulation before debriefing produced 5 responses in SimD (categorized a total of 51 times) and 12 in NoD (categorized 111 times) for content analysis. For SimD, 12/51 (23.5%), 35/51 (68.6%), and 4/51 (7.8%) of responses and for NoD, 41/111 (36.9%), 57/111 (51.4%), and 13/111 (11.7%) pertained to (1) medical knowledge and decision making, (2) emotion, communication, and confidence, and (3) environment, respectively (Figure 1).

Conclusion: Successful debriefing mitigated the increased anxiety as detected by increased negative sentiment among those who experienced simulator death. Exposure to simulator death shifted the content of learner responses from knowledge based to a more emotional basis. Structured debriefing may allow learners to benefit from experiencing death while reducing their risk of psychological harm.

Table 1: Learner Comments Before Debriefing	
Simulation Death	No Simulation Death
"I still don't know what the hell is going on"	"I started running fluids but the heart rate kept going up and up and up"
"Oh my God- I'm going to kill someone. They should not graduate me, I am literally having a panic attack"	"Overall I felt like I had a pretty good grasp on the patient and where she was going"

E18

Nursing Education in Postoperative Free Flap Monitoring

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Abstract begins on following page

Introduction: Free tissue transfer is a common procedure in reconstructive surgery in order to reconstruct soft tissue defects. One of the most devastating complications following free tissue transfer is partial or total flap loss. Close monitoring postoperatively is imperative in avoiding flap failure as early detection of tissue compromise can lead to quick intervention and salvage of the flap. Nurses have a crucial role in monitoring free flaps and can be the first to notice a change that indicates flap deterioration. However, no formal education on flaps is provided to nursing staff prior to caring for these patients. Observations of nursing practices at our institution revealed deficiencies in knowledge of flap anatomy, monitoring practices, and postoperative complications. Our study aims to determine whether a structured multimodality educational program improves nursing knowledge of flaps and comfort in monitoring for postoperative complications.

Methods: Nurses on the Plastic Surgery unit were given a short survey with basic questions on free flap anatomy, monitoring, and postoperative issues. Nursing staff then participated in an educational program consisting of a lecture-based presentation and an online interactive module. After completion of the course, the survey was re-administered to assess whether scores improved and whether nurses felt subjectively more comfortable with assessing and caring for free flaps.

Results: Using our survey, we were able to identify common deficiencies in knowledge about free flaps among nurses caring for plastic surgery patients. Overall, nursing staff were open to ongoing education in these areas. By utilizing a multimodality educational curriculum, nursing knowledge about free flaps and comfort with free flap monitoring improved.

Conclusion: While the results are still preliminary, the information provided in this study could be used to supplement nurse training to improve monitoring of free flaps, thereby leading to early detection of complications and improving patient care and quality.

A Novel Resident Training Model for Micro- and Super-Microsurgery: The Blue-Blood Infused Chicken Thigh

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Abstract begins on following page

Background: Microsurgical training models are essential in helping trainees become familiar with the instruments and techniques of the craft. The current gold standard, the live laboratory rat, excels in technical simulation but is often prohibitively expensive with a high variability in return dependent on the trainee's skills. As such, the concept of training on the femoral structures of store-bought chicken thighs has been well entertained for decades. Nevertheless, a major deficiency in this model remains the inability to realistically simulate vessel perfusion. Current methods are mostly limited to repeated post-repair syringe injection. Our group aimed to develop a simple, inexpensive, and effective method for simulating vessel perfusion during ex vivo micro- and supermicro-surgical training.

Methods: We utilized a modification of the standard chicken thigh model incorporating bag infusion with gravity pump to perpetually or intermittently mimic real-time blood flow. Materials required included (a) two bags of IV fluids with tubing (e.g. 500 mL LR), (b) tubing of two to three angiocatheters (e.g. Saf-T E-Z Set®, 21G), (c) blue food-coloring, (d) needle (e.g. 24 gauge), (e) syringe (e.g. 3mL), (e) suture (e.g. 5-0), as well as a bone-in chicken thigh and standard microsurgical instruments and supplies. To prepare, we injected 1ml of blue food-coloring for every 500mL of fluid into one bag and elevated it above the field. We then placed the other collection bag below the field and connected angiocatheters to both bags. We prepared the thigh by isolating the neurovascular bundle located parallel to the femoral bone. Then, we inserted and sutured the cut angiocatheter tubing into the proximal and distal ends of the artery. For end-to-side and side-to-side capabilities, we ligated the proximal vein and connected angiocatheter tubing to the distal vein. Cautery of the tubing was helpful to create mace-like surface defects to improve intimal grip. To perfuse, we found running the drip at approximately ten drops per minute was efficacious. For venous capabilities, we clamped the distal artery angiocatheter and attached the collection bag to the vein angiocatheter. This model has since been used by almost all residents in our division for the past 6 months.

Results: Our method required few and readily-available materials, could be set-up in any microsurgical suite, took 5 minutes to set-up, and reliably perfused up to tertiary vessels for practicing supermicrosurgery. We were able to reuse the bags and tubing indefinitely with additional food-coloring and bag swapping. Continuous blue-blood qualitatively mimicked the viscerality of live surgery, gave immediate feedback to trainees when vessels were damaged, and allowed for the novel training of clamp placement on engorged vessels. Trainees were able to repeatedly practice multiple end-to-end, end-to-side, and side-to-side anastomoses on vessels 3mm to 0.3mm in diameter, and have free-flowing, high-contrast blue-blood readily available.

Conclusions: Our blue-blood chicken thigh model is simple, cost-effective, and offers a significantly more realistic training experience than the standard chicken thigh model. This theoretically translates to improved confidence and competence in trainee skills prior to progression to live animal and human surgery.

Immediate Visual Feedback and Its Effect on Technical Skills and Confidence during Complex Tourniquet Applications

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Keywords	Sensors, Junctional Tourniquet, Teaching, Technology, Femoral Hemorrhage

Abstract begins on following page

Introduction: Junctional hemorrhage is a leading cause of preventable military death. Tourniquets for these difficult anatomical regions exist and are approved by the FDA to stop bleeding until arrival at a medical facility. The purpose of this study is to compare preferences and changes in performance when using a newly designed visual bleeding feedback system (VBFS) when training novices. We hypothesize that users will indicate higher levels of confidence after training and greater improvements in training time with the bleeding feedback system compared to those who train without feedback (WF).

Methods: Medical students (N=15) and community emergency medics (N=4) with no junctional tourniquet experience were randomized in a single-blind, crossover, controlled study to start either in the VBFS group or the WF group. All subjects underwent training in the following order; instructional videos, hands on practice, three recorded skill trials in VBFS or WF, and crossover to WF or VBFS for another three trails. Participant agreement with statements asserting confidence in efficient and accurate tourniquet application and usefulness of the VBFS was assessed using a pre-and post-Likert scale with ratings from 1 to 7, with 1 being least agreement and 7 being most. Video and audio data were also collected and analyzed to assess total trail time and tourniquet application time. Group confidence scores and trial times were calculated via paired t-test.

Results: Participants indicated very high ratings for VBFS usefulness (6.37/7.0 +/-1.25) and recommendation to others (6.74/7.0 +/- 0.56). While there was no statistical difference in group confidence or time for the pre- and post-tests before the crossover, there was a significant reduction in application times between the 1st and 6th trial (80.5 s vs 44.4 s, p = 0.032) after crossover. It is also notable that participants in the in the VBFS spent more time than the WF groups (37.9 s vs 21.4 s, = 0.56) indicating active use of the visual feedback system. It is also noted that participants started with a fairly high confidence level in the pre- training phase compared to confidence after the 6th trial, (5.11/7.0 vs 5.37/7.0, p = 0.35).

Conclusion: Trial times were increased when using the VBFS and all users rated VBFS highly. Participants were equally confident in tourniquet application after just watching a video compared to finishing the entire training with its six applications on a bleeding and non-bleeding model. Given that most participants were novices to this type of tourniquet, it is possible that they were overly confident in their original self- assessed abilities. This over confidence necessitates the need for developing effective scenario based training curricula for this deceptively straightforward life-saving task.

Improving Diagnosis in Healthcare: Local versus National Adoption of Recommended Guidelines for the Clinical Breast Examination

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Keywords	Skills Retention, Physical Examination, Medical Students, Structured Curriculum, Pathology Detection

Abstract begins on following page

Introduction: Getting the right diagnosis in a timely fashion is critical in delivering high quality healthcare. In the recent Institute of Medicine report, Improving Diagnosis in Healthcare, a proper physical examination was a key component in this process. However, despite national recommendations for physical exam techniques and approaches, students, residents and physicians may not incorporate this into their practice. The purpose of this study was to investigate whether medical students adhere to national guidelines for the Clinical Breast Examination (CBE). We hypothesize that a random sample of medical students at a national meeting would perform the CBE differently compared to students exposed to a structured curriculum.

Methods: Students (N=40) were exposed, on a single occasion, to a structured, simulation-based, CBE curriculum. The same students returned one year later to perform the CBE. This group was compared to a convenience sample of medical students (N=15) attending national specialty meetings and not exposed to the skills curriculum. All students were given a clinical vignette and performed the CBE using a breast examination simulator. Physical exam techniques were video recorded for analysis. Chi-squared tests were used to assess differences in CBE technique between the student groups.

Results: Students exposed to a structured curriculum performed physical examination techniques more consistent with national guidelines than the random, national student sample. Structured curriculum students were more organized (structured=98% verses national = 60%), likely to use two hands (structured=75% verses national = 40%), use a linear search pattern (structured=93% verses national = 13%), and include the nipple-areolar complex (structured=88% verses national = 36%) in the physical exam compared to national sample ($p < .01$).

Conclusion: Students exposed to a structured skills curriculum more consistently performed the CBE according to national guidelines. The variability in technique compared with the national sample of students calls for major improvements in adoption and implementation of structured skills curricula. Moreover, given the wide variety in CBE techniques for practicing physicians, it is likely that we can also improve implementation of structured curricula for residency training.

E16

Learning through a Laparoscopic Trainer: Observations between PGY1-PGY4 OB/GYN Residents

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Abstract begins on following page

Introduction: With the increased use of laparoscopic hysterectomies, there is now a critical need to effectively teach residents how to properly suture the vaginal cuff. The vaginal cuff is the remaining tissue on top of the vagina after a total hysterectomy. The purpose of this study is to analyze how PGY1-PGY4 OB/GYN residents perceive and respond to a prototype laparoscopic vaginal cuff simulator. We also hope to investigate the educational value of the model. We hypothesize that the laparoscopic vaginal cuff simulator will provide educational value as indicated by participant surveys.

Methods: PGY1-PGY4 OB/GYN surgical residents (n=7) had ten minutes to complete a simulated vaginal cuff repair. The simulator is a newly developed box trainer performing a hysterectomy. Their task was to suture the vaginal cuff with 1 interrupted stitch and 3 intracoporeal knots. Before beginning the simulation, participants completed a demographic survey as well as Likert scaled questions regarding confidence and perceived performance. Participants then completed post procedure survey and overall performance. Analyses were conducted comparing pre and post survey answers.

Results: All participants thought that either the model's visual characteristics were "sufficient, but could be improved" or "highly realistic." 32.14% thought the model's tensile characteristics were "sufficient, but could be improved," 17.86% thought that that it was "highly realistic," and 50.00% were "unsure." The participants' confidence of suturing a vaginal cuff generally increased after the simulation (Figure 1).

All of the participants "Agreed" or "Strongly Agreed" that:

1. They would use this simulation in the future
2. They would recommend this simulation to other students at their institution
3. It would be valuable to use this simulator to teach students about laparoscopic hysterectomies
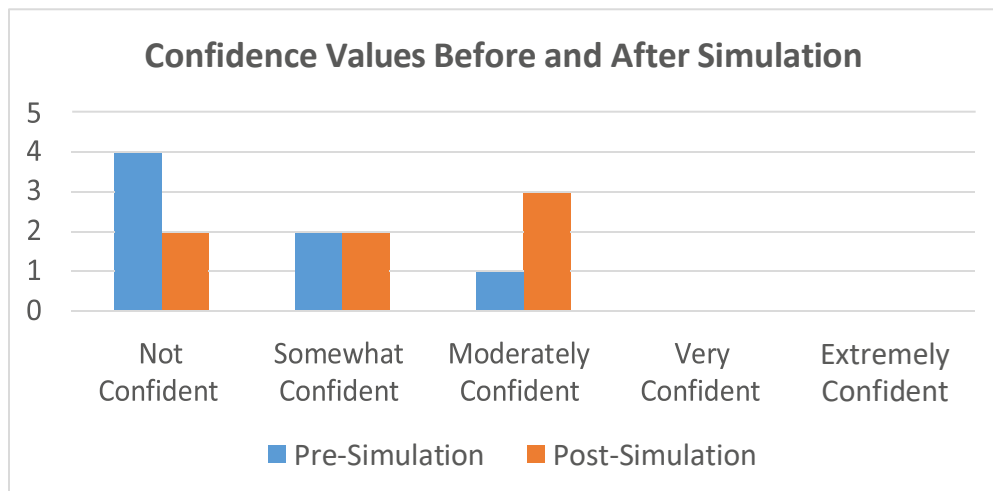
Figure 1

Conclusion: The results conclude that the laparoscopic vaginal cuff model has the potential to be a strong educational tool. Although the visual and tactile characteristics could be improved, participants thought it was realistic enough and useful for training and developing basic suturing skills. This model can provide a useful training tool to learn, develop, and refine essential surgical skills for a laparoscopic hysterectomy. The next steps of the research include collecting additional data from OB/GYN residents and further analyzing the survey responses.

E13

Pedagogical Strategies in Simulated CME Contexts: How Learners' Expertise Impacts Avoidant Instructional Approaches

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Abstract begins on following page

Background: Surgeons taking continuing medical education (CME) courses possess a wide variety of backgrounds. This study examines the relationship between surgeons' levels of operative experience and their instructors' teaching strategies during a simulation-based CME course. In particular, we studied the role of avoidant instruction, which emphasizes what *not* to do.

Methods: Audio-video data were collected from surgeons (n=58) who participated in a simulation-based laparoscopic hernia repair CME course. These learners were grouped by levels of self-reported laparoscopic and hernia repair experience and performed a total of two simulation sessions, each with a different instructor. Accordingly, each instructor taught two different groups of learners.

The learners' discourse was transcribed and coded for the presence of (a) four types of questions learners asked their instructors and (b) five types of instructor responses, including both avoidant and non-avoidant forms of instruction.

We used epistemic network analysis (ENA), which models co-occurrences of codes as networks, to compare how the connections between different pairs of questions and answers varied between students of relatively lesser and greater experience over the course of their simulated hernia repair sessions.

Results: As the didactic sessions progressed, instructors increasingly (and significantly) employed avoidant instructional styles when working with groups of novice learners. No such shift in instructional style was observed for intermediate or expert learners during their simulation sessions.

Conclusion: Our data suggest that instructors modify their teaching as a training session progresses when working with novice learners. This trend in our findings suggests a disposition amongst instructors to tailor their approach as they gradually learn more about what their learners know perhaps to provide language that better matches those learners' needs. While modifying teaching to match learners' needs is certainly a good teaching strategy, further inquiry is needed to determine whether a shift to avoidant instruction is beneficial to novice learners.

Residents' Surgical Performance during the Laboratory Years: An Analysis of Rule-based Errors

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Science Type	Education
Keywords	Education, Self-Assessment, Decay, Skills, Rule Based

Abstract begins on following page

Background: Nearly one-third of surgical residents will enter into academic development during their surgical residency by dedicating time to a research fellowship for 1-3 years. Major interest lies in understanding how laboratory residents' surgical skills are affected by minimal clinical exposure during academic development. A widely held concern is that the time away from clinical exposure results in surgical skills decay. This study examines the impact of academic development on residents' operative performance. We hypothesize that the use of repeated, annual assessments may result in learning, even without individual feedback on participants' simulated performance.

Methods: Surgical performance data were collected from laboratory residents (postgraduate years 2-5) during the summers of 2014, 2015, and 2016. Residents were allotted 15 minutes to complete a shortened, simulated laparoscopic ventral hernia repair procedure. Final hernia repair skins from all participants were scored using a previously validated checklist. An analysis of variance test compared the mean performance scores of repeat participants to those of first time participants.

Results: Twenty-seven (37% female) laboratory residents provided 2-year assessment data over the 3- year span of the study. Second time performance revealed improvement from a mean hernia repair score of 14 (standard error = 1.0) in the first year to 17.2 (SD = 0.9) in the second year, ($F[1, 52] = 5.6$, $P = 0.022$). Detailed analysis demonstrated improvement in performance for 3 grading criteria that were considered to be rule-based errors. There was no improvement in operative strategy errors.

Conclusions: Analysis of longitudinal performance of laboratory residents shows higher hernia repair scores for repeat participants in the category of rule-based errors. These findings suggest that laboratory residents can learn from rule-based mistakes when provided with annual performance-based assessments. This benefit was not seen with operative strategy errors and has important implications for using assessments not only for performance analysis, but also as a learning experience.

Skills Decay: Understanding How Time away from Surgery Affects Performance

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Keywords	Skill Decay, Objective Assessment, Rule-Based Errors, Education, Psychomotor Skills

Abstract begins on following page

Introduction: Time away from surgical practice inevitably leads to concerns for skills decay. This study seeks to understand how technical and decision-making skills change based on time away for two groups: surgical residents during their laboratory time and retired surgeons. We hypothesize that both groups will experience decay however; the type of decay will differ when comparing the two groups.

Methods: Longitudinal data, over a two-year period, was collected from surgical residents (N=29) in their laboratory years. Cross sectional data was collected from an additional group of laboratory residents (N=8), the Pure Decay group, who were at the end of their second year of research. In addition, data was collected from 12 retired surgeons. Participants were asked to perform four clinical stations and two virtual reality stations. Clinical stations included a subclavian central line insertion, open bowel repair, urinary catheterization, and laparoscopic ventral hernia repair. Virtual reality (VR) stations included seven modules with specific focus on reaction time, object tracking, force matching and other gross and fine motor skills. Clinical data of interest included errors, decisions, and final product analysis.

Results: Returning laboratory residents showed statistically significant improvement in their scores for rule-based errors and psychomotor skills. However, the pure decay group showed a statistically significant increase in number of errors committed when compared to returning laboratory residents. Retired surgeons showed statistically significant worsening in psychomotor skills when compared to returning laboratory residents.

Conclusion: The pure decay group's lack of equivalent performance with returning laboratory residents suggests that repeated use of simulators as assessment tools, even without performance feedback, could possibly lead to skills improvement. The retired surgeons' performance suggests that while cognitive knowledge of procedures may be well-protected, psychomotor skills are prone to significant decay with age and time.

What Do You Want to Know? How Surgical Experience Predicts the Types of Questions Asked in a Didactic CME Course

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Keywords	Continuing Medical education, simulation, linguistic analysis, learning science

Abstract begins on following page

Background: Surgeons taking continuing medical education (CME) courses possess a wide variety of backgrounds and surgical experience. As such, these surgeons may have very different learning needs which can be measured by the types of information requested by participants. This study examines the relationship between surgeons' levels of operative experience and what types of questions they asked in the context of a CME course.

Methods: Audio-video data were collected from surgeons (n=29) participating in a simulated laparoscopic hernia repair CME course. Participants were grouped in teams of three according to their self- reported laparoscopic and hernia repair experience and performed different forms of laparoscopic hernia repairs across two separate learning sessions. Their recorded conversations were then coded for the presence of four types of questions they asked their instructors. We computed the percentages associated with how often each type of question was asked for each participant. Finally, we performed linear regressions comparing how often these questions were asked based on the participants' self-reported levels of experience.

Results: Standard linear regressions of types of questions participants asked revealed significant differences between surgeons' of relatively lesser and greater experience with regards to three types of questions: *Requesting Guidance, Requesting Confirmation,* and *Asking about a Specific Case.* Both *Requesting Guidance* and *Requesting Confirmation* were inversely proportional to surgical experience, whereas *Asking about a Specific Case* was directly proportional to surgical experience. *Requesting Instructor Preference,* on the other hand, exhibited no significant correlation with participants' levels of experience, FIGURE 1.

Conclusion: Surgeons learning in a CME context exhibit statistically different needs as demonstrated by the types of information they request from their instructors; those with relatively less experience tend to focus on asking for confirmation and guidance, whereas those with relatively greater experience tend to focus on specific hypothetical scenarios related to their practice. This study not only gives insight into the learning needs of surgeons in CME courses, but also provides data that can be used to train the trainer by offering guidance on ways to tailor instruction to focus on content that learners of a particular level will benefit from most.

Health Services Research

Perioperative Outcomes after Extremity Sarcoma Resection: Results of a Contemporary Multi-Institutional Experience

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Keywords	Sarcoma, Extremity, Preoperative Outcomes, Multiinstitutional, Resection

Abstract begins on following page

Introduction: Soft tissue extremity sarcoma (STES) is rare with few multi-institutional experiences contributing to our understanding of perioperative outcomes after resection. Our aim was to identify pre- and intraoperative predictors of perioperative morbidity and mortality after STES resection.

Methods: Patients who underwent resection of STES from 2000-2016 were identified from a retrospective multi-institutional sarcoma database (United States Sarcoma Collaboration). 90-day morbidity and mortality were assessed, based on pre- and intraoperative risk factors, using Chi Squared and Fischer's Exact test. Statistically significant variables (p ≤ 0.05) were used in multinomial regression analysis to determine independent predictors of morbidity and mortality.

Results: 1334 patients underwent primary STES resection with a median age of 57.0 years. The most common histologic subtypes were undifferentiated pleomorphic sarcoma (28.9%), liposarcoma (16.1%), and leiomyosarcoma (8.1%). Overall 90-day morbidity was 22.5% and 90-day mortality was 1.3%. On multivariate analysis, independent predictors of increased 90-day morbidity were age > 65 years (OR=1.57, p=0.003), white v. other race (OR=1.74, p=0.01), obesity (OR=1.74, p=<0.001), lower versus upper extremity (OR=2.22, p<0.001), tumor size > 10 cm (OR=1.80, p<0.001), TNM/FNCLCC grade (OR=1.45, p=0.02), positive nodal status (OR=3.03, p=0.02), R1 v. R0 resection (OR 1.49, p=0.03), and vascular reconstruction (OR=4.52, p<0.001). Independent predictors of increased 90-day mortality on multivariate analysis were age > 65 years (OR=4.59, p=0.01), smoking (OR=5.65, p=0.003), emergency surgery (OR=27.03, p=0.04), tumor size > 10 cm (OR=4.10, p=0.03), and amputation (OR 6.45, p=0.001).

Conclusion: Based on the unique strengths of a multi-institutional collaborative with large numbers of STES patients, we identified factors associated with 90-day morbidity and mortality after resection. These data should guide patient counseling regarding perioperative outcomes in order to better align patient expectation and inform treatment sequencing.

Bariatric Surgeon and Registered Dietician Perspectives on Barriers and Facilitators to Severe Obesity Care within the VA: A Qualitative Analysis

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Keywords	Bariatric surgery, Severe Obesity, Veterans, Barriers, Interviews

Abstract begins on following page

Background: Bariatric surgery is the most effective treatment for severe obesity. Nearly 20% of U.S. Veterans are severely obese, yet less than 0.1% undergo bariatric surgery annually. The Veterans Health Administration (VA) recently convened a national, multi-disciplinary panel of physicians and researchers that identified patient, provider and system level barriers to bariatric surgery as a research and policy priority. The aim of our study was to assess perceived barriers to severe obesity care among bariatric surgeons and nutritionists who work with bariatric patients.

Methods: We conducted interviews with 16 providers, including 10 bariatric surgeons and 6 registered dieticians (RD) who provide severe obesity care to Veterans. At least two surgeons from each of the five regions in the VA system participated. RDs were recruited from VA weight management programs in the Great Lakes Health Care System region. Using a semi-structured interview guide, the interviewer asked providers to describe the preoperative and postoperative processes of care and challenges to providing surgery and follow-up care within the VA system. All interviews were audio-recorded and transcribed. A directed approach to content analysis was applied. Emergent themes were identified and finalized through a process of consensus among four coders. Atlas.ti software was used to organize themes into higher order domains. Participants also completed a demographic questionnaire upon the completion of each interview.

Results: The mean provider age was 42.1 (SD=9.8) years; 50% were male, 69% were white, and 6% considered themselves to be Hispanic/Latino. The average number of years in practice was 13.69 (SD=8.04), and 63% had a dual appointment at a University. We identified five general categories of barriers to bariatric surgery care in the VA: 1) primary care providers not supporting bariatric surgery; 2) difficulty accessing VA bariatric surgery programs; 3) difficulty meeting preoperative requirements (e.g. weight loss and smoking cessation); 4) patient apprehension about making postoperative lifestyle changes; and 5) difficulty coordinating postoperative care. Three facilitators of bariatric surgery care were identified: 1) patient motivation to improve their long-term quality of life 2) having social support; and 3) utilizing telehealth.

Conclusions: Numerous patient, provider and system-level barriers contribute to the low utilization of bariatric surgery. Educating referring providers about bariatric surgery options, expected health outcomes, and potential risks would increase utilization. Expanding availability of bariatric surgery centers and standardizing bariatric surgery criteria across VA centers may help increase access and improve coordination of care amongst VA providers. VA providers' push to utilize telehealth as a means to care for difficult to reach patients is likely improving patient care. Patient motivations for bariatric surgery emphasize their interest in improving their overall quality of life and stress the importance of social support in allowing patients to pursue bariatric surgery.

Asymptomatic Distant Recurrence Detection and Survival in Early Stage Breast Cancer: A Nationally Representative Study

Schumacher JR, Neuman HB, Zhang Y, Yu M, Vanness DJ, Si Y, Burnside ES, Ruddy KJ, Partridge AH, Schrag D, Edge SB, Jacobs EA, Havlena J, Francescatti AB, Winchester DP, McKellar DP, Spears PA, Chang GJ, Kozower BD, Greenberg CC

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Keywords	Breast Cancer, Recurrence, Mortality, Systemic Imaging, Cancer Survivorship

Abstract begins on following page

Background: Breast cancer follow-up guidelines recommend imaging for distant metastases only in the presence of signs/symptoms. However, data supporting this recommendation predates the current era of improved imaging and targeted therapies based on molecular subtype. The objective was to assess the relationship between mode of distant recurrence detection and survival.

Methods: A stage-stratified random sample of Stage II-III breast cancer patients diagnosed in 2006-7 was selected from NCDB records from 1,217 CoC-accredited facilities (10/hospital n=10,853). Women were categorized by subtype: 1) ER or PR+/HER2-; 2) ER and PR-/Her2- (triple negative); 3) HER2+. Medical records abstracted for 5-years post-surgery supplemented NCDB data and assessed distant recurrence and mode of detection (prompted by signs/symptoms or surveillance imaging), imaging (chest CT, abdomen/pelvis CT/MRI, head CT/MRI, bone scan, PET/CT), death date. The relationship between mode of recurrence detection and days from initial cancer diagnosis to death was assessed using propensity-weighted multivariable Cox proportional hazards regression stratified by subtype. Propensity weights, based on receipt of surveillance systemic imaging, accounted for sociodemographic and tumor/treatment factors.

Results: 5-year distant recurrence was 22.3% for triple negative, 14.8% HER2+, and 11.2% for ER or PR+/ HER2- patients. Asymptomatic imaging detected recurrence in 22.9% and signs/symptoms in 77.1%. Patients with asymptomatic as compared to sign/symptom detected recurrences had reduced risk of death in 5 years if triple negative (HR=0.68, 95% CI=0.50-0.93) or HER2+ (HR=0.40, 95% CI=0.24-0.65) with no significant association for ER or PR+/HER2- (HR=1.2, 95% CI=0.88-1.51). This translated to a between-group difference in weighted median survival of 5 months for triple negative and 13 months for HER2+ patients.

Conclusions: This is the first nationally representative study to show a survival advantage with asymptomatic detection of distant metastases for patients, with the benefit limited to triple negative and HER2+ disease. Further research to confirm observational findings is warranted.

H8

The Influence of Anatomic Stage and Receptor Status on First Recurrence for Breast Cancer within Five Years

Neuman HB, Schumacher JR, Hanlon B, Edge S, Ruddy K, Partridge A, Le-Rademacher J, Yu M, Vanness D, Yang DY, Havlena J, Greenberg CC

Abstract begins on following page

Introduction: Receptor status is increasingly recognized as an important prognostic factor for breast cancer, prompting its incorporation into AJCC staging. Our objective was to assess the relationship of both anatomic stage and receptor status with first recurrence within 5 years.

Methods: Data were included from 11 Alliance for Clinical Trials in Oncology legacy clinical trials that enrolled women diagnosed with stage I-III breast cancer. Women who had undergone surgery and modern era therapies, and had complete staging, receptor status, and recurrence information (n=10,357) were included. Smoothed estimates of hazards of recurrence were plotted at one-year intervals from the time of trial registration through the time of first recurrence. Patients were censored at the time of death, end of follow-up or at 5 years. Stratified Cox proportional hazards regression models were used to produce 3- and 5-year cumulative probabilities of recurrence. A log-rank test was used to assess the difference in distribution of recurrence time by receptor status.

Results: Annual hazards of first recurrence are presented (figure). Both anatomic stage (p<0.0001) and receptor status (p<0.0001) influenced likelihood of recurrence within 5 years. Timing of recurrence varied by receptor status (p<0.0001). 75% of recurrences occurred by 3.26 years for ER/PR+, Her2neu-; 1.94 years for ER/PR-, Her2neu-; 4.70 years for ER/PR+, Her2neu+; 2.87 years for ER/PR-, Her2neu+. Among stage 3 patients, ER/PR-, Her2neu- tumors recurred earlier and more often (3- and 5-year probability of recurrence was 34% and 39%) than ER/PR+, Her2neu+ tumors (3- and 5-year probability of recurrence was 11% and 15%), which were distributed over a longer time.

Conclusion: Our study supports the importance of considering not only anatomic stage but also receptor status in staging, as these factors influence the likelihood of recurrence within 5 years. Given the predictable variation in the likelihood and timing of recurrence, these data also support the need for a more personalized approach to follow-up than our current one-size fits all guidelines.

Drivers and Timing of Interhospital Transfers of Emergency General Surgery Patients

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Keywords	Emergency General Surgery, Interhospital Transfers, Allocation of resources, acute care surgery, Health Care needs

Abstract begins on following page

Introduction: Transferred acute general surgical patients have increased morbidity, mortality, and costs, yet little is known about the drivers of such transfers. Increased specialization and disparate workforce deployment have led to concerns about access to care for acute general surgery conditions. We sought to evaluate the drivers and efficiency of transfers to a tertiary academic medical center for common acute general surgical diagnoses.

Methods: We performed a retrospective review of patients transferred to our institution between 4/1/14–3/31/16 for bowel obstruction, appendicitis, cholecystitis/cholangitis/choledocholithiasis, diverticulitis, mesenteric ischemia, perforated viscus, or post-operative surgical complication. Referring hospital information was obtained from American Hospital Association Annual Survey Database. A heat map was made to show the density of transfers by location.

Results: 334 patients were transferred from 70 hospitals. Transfer reasons varied with the majority due to the need for a surgeon (26.6%) or specialized services (44.3%). 95.8% were imaged prior to transfer. 35.3% had documented surgeon contact. 7.5% (n=25) of patients underwent procedures at referring facilities while 60.6% (n=83) underwent a procedure at the accepting hospital. Median time between transfer request and arrival at our institution was lower for patients who subsequently underwent a procedure for patients originating in emergency departments (2.3 vs 2.8 hours, p<0.05) and inpatient units (4.6 vs 5.7 hours, p<0.05).

Conclusion: Access to care is a major contributor to interhospital transfers for acute general surgical conditions. Understanding the characteristics of transferred patients and the hospitals that refer them can inform decisions regarding the allocation of and provision of care by the limited number of general surgeons, particularly in rural areas.

Type of Fundoplication Is Not Associated with Persistent Dysphagia following Antireflux Surgery

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Keywords	Gastroesophageal Reflux, Dysphagia, Nissen Fundoplication, Partial Fundoplication, Postoperative Outcomes

Abstract begins on following page

Introduction: Laparoscopic fundoplication is the gold standard operation for control of gastroesophageal reflux disease. It has been suggested that persistent postoperative dysphagia is increased in Nissen fundoplication compared to partial fundoplication (Toupet, Dor). We aimed to determine risk factors for persistent postoperative dysphagia, specifically examining type of fundoplication, to inform operative planning.

Methods: Patients experiencing gastroesophageal reflux symptoms who underwent laparoscopic Nissen, Toupet, or Dor fundoplication between January 2009 and July 2016 were identified from our single academic institutional foregut surgery database. A dysphagia score was obtained by administering a standardized quality of life survey in clinic or by telephone. Persistent dysphagia was defined as a difficulty swallowing score ≥ 1 (noticeable) on a scale from 0 (no symptoms) to 5 (incapacitating) at least one year postoperatively. Adjusted odds ratios (OR) of persistent dysphagia among those who underwent Nissen compared to partial fundoplication with 95% confidence intervals (CI) were calculated in multivariate logistic regression models. The multivariate logistic regression model was adjusted for sex, age, body mass index (BMI), and redo operation.

Results: Of 441 patients in the database who met the inclusion criteria, 255 had at least one year of follow-up (response rate = 57.8%). The median follow-up interval was 3 years. 45.1% of patients underwent Nissen fundoplication and 54.9% underwent partial fundoplication. Persistent postoperative dysphagia was present in 25.9% (n=66) of patients. On adjusted analysis, there was no statistically significant association between the type of fundoplication (Nissen vs. partial) and the likelihood of dysphagia (Table 1).

Conclusions: The likelihood of persistent dysphagia was not associated with the type of fundoplication (Nissen vs. partial). While many surgeons believe partial fundoplication decreases the risk of persistent postoperative dysphagia compared to Nissen fundoplication, our study demonstrated equivalent rates of persistent postoperative dysphagia. This suggests that in patients who are equivalent candidates for either a Nissen or partial fundoplication, Nissen fundoplication is a sound choice for an antireflux operation.

Characteristic	OR (95% CI)	p-value
Age ≥ 65 (vs. < 65)	0.64 (0.34, 1.21)	0.170
BMI ≥ 30 (vs. < 30)	0.91 (0.51, 1.61)	0.739
Female (vs. male)	1.53 (0.77, 3.02)	0.221
Primary (vs. redo)	0.76 (0.37, 1.58)	0.465
Nissen (vs. partial) fundoplication	1.08 (0.60, 1.97)	0.792

Table 1. Multivariate regression analysis of risk factors for persistent dysphagia after antireflux surgery

Predictive Value of Pulmonary Function Measures for Short-Term Outcomes Following Lung Resection: Analysis of a Single High-Volume Institution

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Abstract begins on following page

Introduction: Consensus on precise measures to identify high-risk patients for pulmonary resection remains elusive. Multicenter trials established forced expiratory volume in 1 second or diffusion capacity for carbon monoxide of ≤50% predicted as major high-risk criteria. However, this definition reflects expert opinion rather than empirical data. We sought to investigate the relationship between pulmonary function and short-term postoperative outcomes using a cohort from a single high-volume institution.

Methods: Using our institutional Society of Thoracic Surgeons database, we identified 419 consecutive patients who underwent pulmonary resection for cancer between 2012 and 2016. We evaluated postoperative events based on predicted FEV1 or DLCO≤50% as compared to >50% and performed multivariable logistic regression to assess characteristics associated with postoperative complications and discharge disposition.

Results: On univariate analysis, DLCO≤50% was associated with any postoperative complication (p=0.03), but not predictive of cardiac events, pulmonary complications, or 30-day readmission. There was no significant difference in any of these short-term outcomes for patients with FEV1≤50% as compared to >50% (p>0.05 for all). On multivariable analysis, neither FEV1 nor DLCO≤50% were significantly associated with occurrence of postoperative complication (OR 1.67, 95% CI 0.60-4.63; OR 1.66, 95% CI 0.96-2.86, respectively).

Notably, DLCO≤50% – but not FEV1 – was associated with discharge to a skilled facility on univariate (p=0.01) and multivariable analysis (OR 2.54, 95% CI 1.08-5.99, p=0.03). Interestingly, when included in adjusted models as continuous variables, FEV1 (OR 0.99, p=0.008) but not DLCO (OR 1.01, p=0.4) was associated with postoperative complications, while the reverse held for discharge disposition (FEV1 OR 1.01, p=0.3; DLCO OR 0.96, p=0.001).

Discussion: For all-comers presenting to our institution for lung cancer resection, classification based on FEV1 or DLCO≤50% may not reliably identify those at highest risk for short-term postoperative complications. While more complex risk models exist to guide preoperative decision making, the ease of using discrete objective selection criteria is undeniably appealing. Nonetheless, reliance on these values for risk stratification may deny patients potentially curative resection.

Previous studies have challenged the prognostic value of pulmonary parameters, postulating that improved pain management and chest wall mechanics following thoracoscopic surgery blunt the sequelae of poor preoperative lung function. In our analysis, the significance of FEV1 and DLCO as continuous measures suggests that preoperative pulmonary function influences postoperative events, even when controlling for operative approach. However, a cutoff value of 50% may be too high to adequately capture this effect.

Notably, we observed a significant association between discharge to a skilled facility and DLCO as either a binary or continuous measure. A recent competing risks analysis describes an inverse relation between DLCO and 1-year mortality, noncancer specific mortality and overall survival, suggesting that DLCO may serve as a valuable proxy for comorbid disease with potential to forecast longer-term outcomes.

We operate at a high-volume center for lung volume reduction surgery, affording us extensive experience managing patients with poor pulmonary function that is not widely available. However, our findings advocate for caution when interpreting "high-risk" criteria in isolation and offer an opportunity to better characterize postoperative risk following pulmonary resection.

An Assessment of Surgical Disparities in Cleft Lip and Palate Treatment in Myanmar

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Abstract begins on following page

Background: Cleft lip and/or palate (CLP) prevalence is known to be highest in Asian countries, however few sources have surveyed the prevalence and disparate care of patients in Myanmar (Burma). The purposes of this study are to (a) increase current understanding of the demographics and socioeconomic status of the patient population to identify disparities of care; (b) evaluate how patients with CLP seek out surgical care; (c) estimate a prevalence of the CLP population; and (d) provide awareness of the needs Myanmar has in managing patients with CLP.

Methods: A single-center observational 3 month preliminary survey study on first-time patients with CLP was conducted from May – July 2017 in the New Look New Life Clinic (NLNL), a clinic under the umbrella organization SmileTrain in Yangon, Myanmar. All 30 patients were provided with a survey and responses were self-reported; either completed by guardians or themselves. Additionally, all surgeries conducted in NLNL were recorded to determine the variety of surgical interventions performed and volume of patients treated.

Results: During the enrollment period, 146 patients received surgical intervention and 30 patients enrolled and completed the study. The average age of the new patient was 5.8 years old, 63% were male, 67% had cleft lip and palate, 23% had isolated cleft lip, 10% had isolated cleft palate and 53% were first born. In the sample, 23% of patients had family members with history of CLP. The income of the majority of families was less than 120,000 kyats per month and the average travel costs to NLNL was 83,176 kyats excluding the cost of lodging, food, and loss of income. All patients used a car to travel to NLNL and 20% of patients and their families traveled from the northernmost regions: Kachin, Sagaing, and Chin states. During pregnancy with the patients, 60% of mothers took a multivitamin with folate. The majority of patients and their families learned about NLNL services either through the internet (40%) or word of mouth from their social community (40%).

Conclusion: The results of this study indicate significant delays to care occur because the average age of treatment is 5.8 years old, noting the ideal age for lip repair is at 3 months and palate repair is less than a year. Future studies must continue to identify barriers to care and prevalence of CLP patients in Myanmar to create resources that will better serve patients with CLP and the healthcare providers treating them.

Impact of the Receipt of Pre-Consultation Web-Based Material on Patients' Value-Concordant Decision-Making for Type of Breast Cancer Surgery

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Abstract begins on following page

Introduction: The decision for breast cancer surgery should consider patient preference, and a high-quality decision should be concordant with patients' values. We hypothesized that receipt of a web-based breast cancer surgery decision aid (DA) prior to a surgeon visit would enhance communication between the patient and surgeon by prompting patients to consider their values and preferences a priori. We used a novel implementation strategy to deliver two different types of web-based information to patients prior to the surgical consultation, and compared the impact on patients' baseline preferences for surgical type.

Methods: We prospectively randomized stage 0-3 breast cancer patients to be emailed a link to a web based decision aid versus standard web sites (National Cancer Institute, American Cancer Society, Breastcancer.org). Prior to meeting the surgeon, patients completed the Breast Cancer Surgery Decision Quality Instrument, which elicits patients' values relevant to surgical decision- making. Patients were asked their baseline preference for type of surgery. Concordance between patients' values and baseline preference for surgery was calculated by developing a multivariable logistic regression model of their baseline preference for surgery, including the elicited patient values as predictors. The model-predicted probability of a baseline preference for mastectomy versus breast conservation was then calculated for each patient. Patients were considered concordant if they had a stated preference for mastectomy with a predicted probability of ≥ 0.5, or breast conservation with predicted probability of < 0.5. The proportion concordant was compared between the two randomization arms using chi-square (and Fisher's exact test where appropriate).

Results: Two hundred forty-four patients were randomized and electronically received the web-based material; 222 answered the values and preference questions and are included in this analysis. Participants' median age was 58 (27-80), 99% were white, and 66% had at least a college degree; these demographics were consistent across study arms (p > 0.05). After receiving the web-based material but before meeting the surgeon, 44% of patients reported uncertainty regarding their preferred surgery; 38% stated a preference for breast conservation and 18% for mastectomy (distribution similar across study arms, p=0.4). Patients stated a preference for surgery type concordant with their reported values in 90% of cases. Likelihood of concordance was statistically different between study arms (p=0.04, DA 85% [n=9 discordant] vs standard websites 96% [n=3 discordant]). For those patients that reported uncertainty regarding their baseline preference for surgery, the vast majority (94%, n=89) had a model predicted probability based on their values that suggested a strong preference for either mastectomy (23%, n=22) or breast conservation (69%, n=67).

Conclusions: In our randomized study, there was a statistically but likely not clinically significant difference in the likelihood of patients having a values-concordant baseline preference for surgery based on the type of web-based information received. Importantly, most patients who state a preference for surgery are doing so in concordance with their values. Although a large proportion of patients stated they were uncertain which surgical procedure they preferred, most answered questions about key values relevant to breast cancer surgery in a way that suggested a baseline preference for type of surgery. Using this type of survey to elicit patients' baseline values and preferences for surgery prior to meeting the surgeon is feasible and may enhance patient-surgeon consultations by providing surgeons important insights into how their patients are approaching decision-making.

Incidental Breast Cancer Diagnosed after Reduction Mammaplasty despite Preoperative Mammography

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Abstract begins on following page

Background/Objective: Reduction mammaplasty is a common operation performed on healthy women. There are varying estimates of the incidence of breast cancer diagnosed at the time of reduction mammaplasty (0.3-2.3%), and there is limited information on these patients' preoperative care. The purpose of this study was to determine the incidence of incidental breast cancer identified during reduction mammaplasty. We also sought to characterize the preoperative imaging performed around reduction mammaplasty in order to optimize preoperative management of patients undergoing reduction mammaplasty and to provide accurate patient counseling.

Methods: Women > 18 years old who underwent reduction mammaplasty from 2013-2014 were identified from the Marketscan database. Patients with a prior diagnosis of breast cancer or those undergoing concurrent lumpectomy or mastectomy were excluded. Patients were categorized as having incidental breast cancer found at time of reduction mammaplasty if there was a breast cancer diagnosis 0-30 days after the operation. Descriptive statistics were calculated for preoperative mammography within 1 year prior to reduction mammaplasty.

Results: In our cohort, 18969 women underwent reduction mammaplasty and 186 (0.98%) were found to have incidental breast cancer. Of those with incidental breast cancer, 78.0% (N=134) had invasive breast cancer and 22.0% (N=134) had carcinoma in situ. The mean age of those who underwent reduction mammaplasty was 42.5 years old and the mean age of those found to have incidental breast cancer was 50.8 years old. Preoperative mammography varied by age with 58.2% overall undergoing mammography. In those ≥ 50 years old, 84.3% of all who underwent reduction mammaplasty had mammography and 79.3% of those diagnosed with incidental breast cancer had mammography.

Conclusion: Incidental breast cancer diagnosed at time of reduction mammaplasty is uncommon, and the majority of women older than 50 years old appropriately received preoperative mammography. However, the majority of women who were diagnosed with incidental breast cancer had preoperative mammography, which demonstrates that not all incidental breast cancers can be identified on mammography. These data should guide preoperative patient counseling to manage patient expectations on the potential for incidental breast cancer identified at reduction mammaplasty even with preoperative mammography.

Non-Clinical Factors Associated with Post-Mastectomy Reconstruction in a Contemporary Cohort of Breast Cancer Survivors

Jessica Schumacher, Lauren Taylor, Jennifer Tucholka, Jennifer Steiman, Lee Wilke, Caprice Greenberg, Heather Neuman

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Abstract begins on following page

Introduction: Rates of post-mastectomy reconstruction have increased over recent years. However, prior studies have suggested lower rates of reconstruction for subgroups of patients defined by factors such as race, income, and insurance status. Our objective was to determine contemporary rates of reconstruction in the United States and examine non-clinical factors associated with receipt of reconstruction.

Methods: The National Cancer Database was used to identify women with stage 0 or stage 1 breast cancer treated with mastectomy (n=297,121), as patients with early-stage disease are less likely to have a tumor or treatment-related contraindication for reconstruction. Women >75 years of age were excluded due to the low rate of reconstruction observed in this cohort (4.6%). Trends in reconstruction rates between 2004-2013 were examined using Join-point regression analysis. A contemporary cohort of patients diagnosed between 2010-2013 (n=145,577) was created. Multivariable logistic regression was used to identify non-clinical factors associated with reconstruction, controlling for patient age, comorbidities, tumor, and treatment characteristics.

Results: Rates of reconstruction increased from 27% in 2004 to 48% in 2013 at an annual percent change of 5.8%. Controlling for clinical factors within our contemporary cohort of patients, race, income, education, type of insurance, location of residence, and type of treating facility were all strongly associated with receipt of reconstruction (Table).

Conclusions: Although rates of reconstruction have increased dramatically over the past decade, lower rates persist for subgroups of vulnerable patients. This gap in care quality is likely mediated by a mix of fixed and modifiable factors at the patient, provider, and system levels. Determining modifiable factors that negatively impact receipt of reconstruction and identifying interventions to address them is a critical step towards improving the quality of breast cancer care for vulnerable populations.

Race
    White
    Black
    Other
	Ref
	0.87 (0.83-0.91)
	0.61 (0.57-0.74)
		<0.0001

Facility type
    Academic
    Comprehensive community cancer program
    Community
	Ref
	0.87 (0.84-0.89)
	
	0.52 (0.5-0.55)
		<0.0001

Insurance
    Private
    None
    Medicaid
    Medicare or other government
	Ref
	0.43 (0.39-0.47)
	0.54 (0.51-0.57)
	0.65 (0.63-0.68)
		<0.0001

Place of residence
    Metro
    Urban
    Rural
	Ref
	0.72 (0.69-0.76)
	0.63 (0.57-0.71)
		<0.0001

Income (by quartile)
    Highest-1
    2
    3
    Lowest-4
	Ref
	0.74 (0.71-0.77)
	0.63 (0.61-0.66)
	0.57 (054-0.60)
		<0.0001

Education level (by quartile)
    Highest-1
    2
    3
    Lowest-4
	Ref
	0.94 (0.91-0.97)
	0.91 (0.88-0.95)
	0.88 (0.83-0.93)
		<0.0001

Controlling for patient age, comorbidities, stage, ER/PR status, Her2neu status, grade, receipt of radiation, receipt of chemotherapy, bilateral mastectomy, geographic region, year of diagnosis, distance from reporting facility		

Multivariable logistic regression of non-clinical factors associated with post-mastectomy reconstruction

Barriers and Facilitators of Active Surveillance: Informational and Emotional

Megan C. Saucke, Jamia L. Jennings, Huda J. Khokhar, Corrine I. Voils, Susan C. Pitt

Abstract begins on following page

Introduction: The 2015 ATA guidelines include active surveillance (AS) as a management strategy for patients with papillary thyroid microcarcinomas (PTMC). Data are lacking on attitudes and beliefs about the acceptability of this nonsurgical option. The purpose of this study was to determine providers' views on AS.

Methods: This mixed-methods study used semi-structured interviews and a survey of 12 endocrinologists and 12 surgeons who treat patients with PTMC. We thematically analyzed interview transcripts using content analysis until we reached saturation (n=19).

Results: Survey respondents were 70.8% male and 87.5% white; 87.5% practiced at academic institutions. Almost all (91.7%) felt they knew enough about treatment alternatives for PTMC, but only 75% explain AS as an option. The majority (62.5%) agreed that treatment decisions about PTMC are hard to make, and 79.2% would use a decision support tool (DST).

Qualitative analysis revealed the following barriers to AS: worry about metastasis, fear of worse outcomes, the instinct to remove cancer, and reassurance provided by surgical removal. Providers believed these barriers were also significant to patients. Other barriers included the assumption that patients do not want AS, lack of resources to perform AS, ultrasound reliability, skepticism about data on AS, fear of patients not following up, expectation of surgery, and patients getting surgery elsewhere.

Facilitators of AS included physician recommendation, patients' fear of surgery, life circumstances, and avoidance of thyroid hormone replacement. When discussing AS, providers who recommend this approach framed the option by providing reassurance and decisional support. They emphasized the low-risk nature of PTMC, gave time to make a decision, educated patients, used analogies to low-risk events, and stressed that surgery remains an option. In contrast, providers who hesitated to offer AS described the approach as "reasonable."

Conclusions: The barriers to AS of patients with PTMC include practice limitations, but also emotional reactions to a cancer diagnosis and uncertainty about outcomes. Findings suggest that reassurance by providers and/or utilization of a DST may facilitate patients' consideration of AS.

Natural Language Processing of Thyroid Cytology Reports: Unlocking Valuable Data from Unstructured Text

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Keywords	Endocrine Surgery, Thyroid Cytology, Medical informatics, Natural Language Processing, Automated information extraction

Abstract begins on following page

Background: Thyroid cytology results are reported in unstructured text documents and contain valuable information that diagnosis codes fail to capture. Extracting data from text reports requires time- consuming and costly manual review. Alternatively, natural language processing (NLP) systems automatically convert unstructured text to structured, analyzable data. In this study, we describe our methodology and accuracy for capturing valuable data from thyroid cytology reports.

Methods: First, we iteratively developed a set of NLP tools on thyroid cytology reports using the clinical Text Analysis and Knowledge Extraction System (cTAKES) platform and thyroid cytology reports from our institution's electronic health record (1/1/07 – 12/31/2013). We incorporated the following elements in a schema for NLP extraction: date, specimen type, nodule laterality, nodule size, measurement units, and diagnosis. Next, we evaluated the accuracy of our NLP tools using a separate, held- out randomly selected test-set of cytology reports from the same period. Two physicians independently manually annotated each test-set report. Inter-annotator agreement (IAA) was assessed, and a third physician adjudicated annotation differences. Finally, the gold-standard, manually annotated reference was used to evaluate NLP performance on the test-set.

Results: A total of 527 cytology reports were evaluated. Twenty-eight non-thyroid reports were excluded, and the NLP system correctly identified 21 (75%) of these for exclusion. The remaining 499 cytology reports contained 2745 relevant data elements. IAA for all data elements was 98.9%. Compared to the gold-standard reference, the overall accuracy of the NLP system was 98.2%. The accuracy of each element was as follows: Date, 95.6%; specimen type, 99.6%; laterality, 99.4%; size, 93.4%; units, 98.8%; diagnosis, 99.4%. The precision/recall/F-measure of the NLP system was 0.956/1.00/0.98 for date, 1.00/0.996/1.00 for specimen type, 0.994/1.00/1.00 for laterality, 0.976/0.996/0.99 for size, 0.99/0.998/0.99 for units, and 0.994/1.00/1.00 for diagnosis. NLP retrieved Bethesda Category II, III, IV, and VI diagnoses with 100% accuracy. The two incorrect diagnosis retrievals resulted from reports for a non-diagnostic specimen and a specimen suspicious for papillary thyroid cancer.

Conclusions: NLP can extract critical information from thyroid cytology reports with a high level of accuracy. This methodology facilitates high volume, high throughput analysis of thyroid cytology results for clinical and research purposes.

Opportunities to Improve Patient Engagement in Dialysis Decisions for Older Adults with Life-Limiting Kidney Disease

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Abstract begins on following page

Objectives:

-Describe the current level of patient engagement in conversations between patients and nephrologists regarding the decision to undergo dialysis

-Consider how patient engagement in decision making about life-prolonging treatments can promote earlier access to palliative care

-Promote sound communication principles between specialists and patients

Original Research Background: Older adults who initiate dialysis often passively accept treatment without making an active choice to commit to life-supporting therapy. Interventional strategies that target the dialysis decision-making conversation between patients and their nephrologists may promote earlier access to palliative care, leading to better outcomes.

Research Objectives: To characterize communication about dialysis and evaluate the proof of concept of an intervention to change nephrologist communication.

Methods: Pre/post-intervention study design. We recorded 16 outpatient conversations between nephrologists and patients age 70 and older with an eGFR≤20 mL/min/1.73 m_2, not on dialysis. After recording the first 12 conversations, we trained seven nephrologists to use the Best Case/Worst Case (BC/WC) communication tool to describe treatment options and potential outcomes within the context of the patient's overall health. We used OPTION 5 and qualitative analysis to measure and characterize patient engagement in decision making before and after BC/WC training.

Results: Before training, OPTION 5 scores were low (median 20 out of 100 (IQR 15-35)), suggesting limited patient engagement in decision making. Nephrologists typically discussed lab values and considered when and how patients might receive dialysis. Few acknowledged the option of "no dialysis." After training, nephrologists used BC/WC with fidelity and OPTION 5 scores increased (median 65 (IQR 50-76)). Using the BC/WC tool, nephrologists presented a choice between dialysis and supportive care without dialysis, described how dialysis and other health events might be experienced, provided prognostic information, and used phrases to elicit patients' goals.

Conclusion: Currently nephrologists discuss the mode and timing of dialysis without disclosing prognosis or presenting dialysis as a choice. This leaves limited opportunity for patients to understand the role of supportive care or palliative care concurrent with dialysis. Interventions to support patient engagement in treatment decisions may improve access to palliative care.

Implications for Research, Policy, or Practice: Empirical studies should be designed to test the effect of communication interventions for specialists on the timing and access to palliative care.

Tumor Biology and Tumor Size Are Predictors of Complete Pathologic Response following Neoadjuvant Chemotherapy in the National Cancer Database

Devon Livingston-Rosanoff, MD, PhD; Jessica Schumacher, PhD; Heather Neumann, MD; Lee G Wilke, MD

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Keywords	Breast Cancer, Neoadjuvant Chemotherapy, Tumor size, Complete pathologic Response, National Cancer Database

Abstract begins on following page

Introduction/Objectives: Tumor size and lymph node status have historically been used to stage breast cancer and guide treatment recommendations. However no large studies have examined whether tumor size directly impacts response to neoadjuvant chemotherapy (NAC) for patients undergoing systemic therapy prior to surgical treatment. The recently released AJCC Edition 8 for cancer staging now incorporates receptor status as well as tumor size and lymph node status into the staging groups due to the impact tumor biology has on long term outcomes. We hypothesized that tumor size would not have an impact on whether a patient experienced a complete pathologic response (pCR) to NAC when receptor status was taken into account.

Methods: We utilized data from the National Cancer Database and included women >18 years old who underwent NAC and surgery for unilateral stage 1-3 invasive breast cancer. Women with T4 disease were excluded due to an inability to evaluate tumor size. Patients without complete information for clinical tumor stage, pathologic tumor stage and receptor status were excluded. Multivariable logistic regression models assessed sociodemographic, diagnosis, and treatment factors associated with pCR.

Results: The 40,670 women included in this study had a mean age of 52 with a majority presenting with stage 2 disease (62%) which was predominantly ER/PR+ Her2- or triple negative (45% and 28% respectively). 19% of patients had a pCR following NAC. In multivariate models, increasing tumor size was independently associated with lower pCR rates: T2 (OR 0.93 CI 0.87-1.0) and T3 (OR 0.61 CI 0.56-0.66) disease were both less likely to result in a pCR than T1 disease. However, receptor status had the largest effect of any variable tested with an OR of 2.90 for ER/PR+Her2+ (CI 2.72-3.18), 3.82 for triple negative (CI 3.57-4.10), and 6.24 for ER/PR-Her2+ (CI 5.74-6.79) in comparison to ER/PR+Her2- tumors. An additional finding was that patients with Medicaid or Medicare insurance were less likely to experience a pCR; however, this effect was no longer observed once time from diagnosis to NAC initiation was incorporated into the model. Delays in starting NAC for all groups were independently associated with a lower pCR rate.

Conclusions: In contrast to our initial hypothesis, tumor size is independently associated with pCR following NAC, however this effect is much smaller than that observed for tumors categorized with receptor status, a surrogate for tumor biology. These data support the 8th edition of AJCC staging guidelines that include receptor status as well as tumor size to better differentiate long term outcomes. An unexpected outcome from this analysis was the identification of potential disparities in outcomes for patients with a delay in the start of NAC, an area for further cancer care delivery research.

GROUP FIVE

Translational

T3

A Novel Humanized Mouse Model for Study of Pluripotent Stem Cell Immunogenicity

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Keywords	Transplant, Stem Cells, Humanized Mice, T Cells, Immunogenicity

Abstract begins on following page

BLT-type humanized mouse models, reconstituted with human hematopoietic stem cells and fetal thymus fragments, are particularly useful for pluripotent stem cell (PSC) immunogenicity studies. The human T cells in these models develop in the presence of human major histocompatibility complexes and self-antigens and are well-suited for studies of allogeneic and syngeneic T cell-mediated immune responses. However, the research use of human fetal tissue-based BLT-type models is complicated by ethical and logistical constraints, as well as the developmental immaturity of fetal tissues, which may negatively impact downstream applications. The NeoThy model incorporates human neonatal thymus and cord blood tissues, which are much more abundant than fetal sources, allowing for humanization of large numbers of animals per donor. This, in turn, allows for in-depth characterization of donor tissues and increased experimental consistency. The work presented here characterizes the NeoThy in comparison to fetal tissue models by using cell surface marker expression analysis, and *in vitro* and *in vivo* functional assays. Additionally, we reprogrammed and characterized multiple induced PSC (iPSC) lines from various neonatal donors and created matched NeoThy mice to demonstrate immune infiltration of allogeneic iPSC-derived cells. The NeoThy humanized mouse enables robust and reproducible experimental validation of allogeneic and syngeneic iPSC therapies, in a manner which was not previously possible using conventional models.

Topical Application of a Dual PI3K/mTOR Inhibitor for the Prevention of Anal Carcinogenesis *In Vivo*

BL Rademacher, LM Meske, KA Matkowskyj, ED LaCount, and EH Carchman

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Keywords	Anal Cancer, Carcinogenesis, Anal Dysplasia, Chemoprevention, Autophagy

Abstract begins on following page

Introduction: Patients with anogenital human papilloma virus (HPV) infection are at high risk of developing squamous cell dysplasia that can progress to squamous cell carcinoma of the anal canal (SCCA). We have previously shown that dual PI3K/mTOR inhibition results in decreased dysplasia and SCCA with systemic drug administration in our HPV mouse model of anal carcinogenesis. Here we sought to investigate the effect of local, topical application of a dual PI3K/mTOR inhibitor, BEZ235, on tumor free survival, histopathologic changes and autophagy.

Methods: *K14E6/E7* mice were given no treatment (Control), topical BEZ235 (BEZ), the carcinogen 7,12 dimethylbenz[a]anthracene (DMBA), or both DMBA and BEZ for a total of 20 weeks. Mice were assessed weekly for tumor development. At 20 weeks they were euthanized and their anal samples examined for histopathologic changes at the anal transition zone (ATZ). Slide sections of the ATZ were assessed for mTOR and PI3K activity by staining for pS6 and pAKT expression (immunohistochemistry), respectively, and evidence of autophagic function via LC3β and p62 expression (immunofluorescence). Tumor free survival analysis was conducted used Kaplan Meier statistics, and all comparisons of mean differences in histopathologic score or protein signal were conducted using a one-way ANOVA.

Results: Mice receiving DMBA alone survived, on average, 16.9 weeks prior to tumor onset, whereas mice receiving both DMBA and BEZ survived, on average, 19.3 weeks ($P<0.000001$). Histopathological analysis revealed a significant decrease in mean score comparing DMBA with DMBA plus BEZ ($P<0.000001$). Comparing DMBA versus DMBA plus BEZ, immunofluorescence revealed efficacy of topically applied dual PI3K/mTOR inhibitor, via significant decreases in both pS6 and pAKT ($P<0.001$ for both comparisons). Compared to Control mice, both BEZ and DMBA plus BEZ treated mice had significantly higher LC3β expression, signifying autophagic induction ($P<0.005$ for both comparisons), whereas DMBA, BEZ, and DMBA plus BEZ treated mice had significantly lower p62 expression, signifying increased autophagic function ($P<0.0005$ for all comparisons).

Conclusion: Consistent with systemic delivery of a dual PI3K/mTOR inhibitor, topical application of BEZ235 shows prolonged tumor free survival. Furthermore, this finding confirms that targeted inhibition of the PI3K/mTOR pathway results in the activation of autophagy and decreased anal carcinogenesis.

Effect of Socialization on Communication Deficits in Parkinson Disease Rat Model

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Keywords	Parkinson Disease, Pink1-/- Genetic Rat Model, Socialization, Social Isolation, Vocalizations

Abstract begins on following page

Introduction: Individuals with Parkinson disease (PD) have vocal communication deficits that can lead to social isolation and depression. We hypothesize that social enrichment may reverse/prevent vocal communication deficits and improve cognition, memory, and well-being. To test these hypotheses, we will provide social enrichment versus a control condition in a well-established genetic rat model of PD (*Pink1*-/-).

Methods: Animals: Thirty-six male *Pink1-/-* rats from Sage® (Oyertown, Pennsylvania) will arrive at 6 weeks of age and be randomly assigned into 3 groups: 1) socially isolated, 2) socially housed, and 3) socially housed with added social enrichment. The socially isolated group will be housed individually and handled twice/week to change cage bedding. The socially housed group will be housed in pairs and will also only be handled twice/week. The socially enriched group will be housed with a cage mate and will undergo social enrichment therapy, which involves grouping rats in a larger 'socialization' cage with another pair of cage mates 5x per week for 1 hour. All procedures were approved by the University of Wisconsin-Madison Animal Care and Use Committee (IACUC) and were conducted in accordance with the United States Public Health Service Guide for the Care and Use of Laboratory Animals. Behavioral measures: The following measures will be assayed at baseline, then at 4, 6, 8 months of age (representing pre-clinical to early-stage PD): Ultrasonic vocalizations (communication), novel object recognition (cognition/memory), sucrose preference test (anhedonia/depression), elevated-plus maze (anxiety).

Tissue analyses: Rats will be deeply anesthetized and trascardially perfused at 8 months of age. Fixed brains will be excised and mounted, and coronal slices will be harvested through the cortex and brainstem. This tissue will be analyzed with immunohistochemistry for key neurotransmitters and receptors (such as mu opioids) in regions vital to communication, cognition, and affect.

Statistical analyses: All statistical analyses will be conducted with SigmaPlot®12.5 (Systat Software, Inc., San Jose, CA). A mix-model repeated measures 3 x 4 ANOVA for the three categorical independent group variables across the 4 time points will be performed for the dependent variables. The critical level for significance will be set at .05 for all testing. *Post-hoc* analysis will be performed with a Fisher's Least Significant Differences (LSD) test.

Results/Discussion: This experiment is ongoing. Pilot data will be presented.

Computational Analysis of Rodent Swallowing Biomechanics

Heidi Kletzien & Nadine P Connor

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Keywords	Aging, Swallowing, Biomechanics, videofluoroscopy, morphometrics

Abstract begins on following page

Purpose: To assess swallow function in rodent models, validated, kinematic measures of deglutition are quantified from videofluoroscopic swallow studies (VSS). Although VSS is useful, it does not provide biomechanical information valuable in the determination of underlying musculoskeletal dysfunction. Our purpose was to develop a computation tool to assess swallow biomechanics in rodent models for investigation of underlying musculoskeletal degeneration in aging.

Methods: VSS, kinematic analyses (bolus area & velocity, mastication rate), and a rodent specific multivariate morphometric computational analysis of swallowing biomechanics were performed on 20 swallows from 5 young and 5 old F344/BN rats.

Results: Bolus area (p=.04) and mastication rate (p<.001) were significantly altered with age. Eight anatomical landmarks were identified to characterize morphology of rodent swallow mechanics to track the relative change in position of 3 skeletal levers (cranial base, vertebral column, mandible) and soft tissue landmarks (UES, base of tongue). Aging accounted for 77.1% (D=1.9, p<.001) of the variance in swallow biomechanics, and 18.7% was associated with swallow phase (oral vs pharyngeal; D=1.2, p<.001). Post hoc DFA analysis suggests that with aging tongue base retraction was reduced, masticatory movements were more variable, and increased head extension was observed.

Conclusion: Geometric morphometric analysis of rodent swallows suggests that swallow biomechanics are altered with age. When used in combination with biological assays of age-related adaptations in neuromuscular systems, this multivariate analysis may increase our understanding of underlying dysfunctions that contribute to swallowing disorders with aging.

Videofluoroscopic Analysis of Swallowing in Aged Ts65Dn and Dp(16)1Yey Mouse Models of Down Syndrome

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Keywords	Down Syndrome, Swallowing, Videofluoroscopy Ts65Dn, Dp(16)1Yey

Abstract begins on following page

Down Syndrome (DS), caused by a trisomy of the 21st chromosome, is associated with increased risks for atypical oromotor development, feeding difficulties, and dysphagia. While cognitive phenotypes of multiple mouse models of DS have been reported, relatively little is known about swallowing phenotypes of these models. Our prior work indicated normal swallowing performance in juvenile (5-6 week old) Ts65Dn mice. However, because impairments associated with DS can change during the aging process, we hypothesized that swallowing performance would be affected in adult mouse models of DS. We report the outcomes of videofluoroscopic swallow studies (VFSS) of two aged mouse models of DS; Ts65Dn, and Dp(16)1Yey. Methods: Male Ts65Dn and Dp(16)1Yey mouse models of DS in the same genetic background were analyzed for swallowing performance in comparison to age-matched euploid/WT controls at 20 weeks of age (n=9-13/group). Separately, both male and female Ts65Dn mice were evaluated in comparison to euploid/WT controls, in groups comprised of mice spanning the adult age range (9-36 weeks of age, n=7/group). VFSS footage was manually analyzed to quantify the measures of swallow rate, inter-swallow interval (ISI), and jaw excursion rate (JER). Rater reliability was evaluated by interclass correlation coefficient (ICC). One-way analysis of variance was used to evaluate the impact of genotype on swallowing measures for 20-week-old mice, and two-way analysis of variance was used to evaluate the impact of genotype and sex on swallowing measures for groups comprised of mice spanning the adult age range. Results: One-way ANOVAs indicated significant differences between genotypes for swallow rate (p=.0008), and ISI (p=.001), but not for JER. Ts65Dn mice showed slower swallow rates and higher ISIs relative to other groups at 20 weeks of age. In comparison of male and female Ts65Dn across an adult age range, analysis revealed significant main effects for genotype, but not for sex. Ts65Dn across the age range showed slower swallow rates than euploid controls (p = 0.03), and higher ISIs than euploid controls (p = .001). Conclusion: Current findings suggest significantly atypical swallowing performance in the adult Ts65Dn model of DS, which persists across the adult age range and affects both sexes. By comparison, the Dp(16)1Yey model appears relatively less affected.

Brain Death Conditions Impair Metabolic Gene Expression in Kidney and Liver

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Science Type	Translational
Keywords	Brain Death, Inflammation, Metabolism, Kidney, Liver

Abstract begins on following page

Introduction: Brain Death (BD) donors exhibit an inflammatory response associated with decreased graft survival in transplanted organs compared with living donors (LD). We utilized novel non-human primate models of 20-hour BD and 20-hour Sham to identify molecular signatures distinct from generalized inflammatory response. In addition, we investigated differences between BD and LD to guide future therapeutic strategies.

Methods: BD (n=7) induced by intracranial balloon Foley-catheter, and Sham (n=4) Rhesus macaques were ventilated and monitored for 20 hours under ICU-level standard of care. Blood/tissues collected from BD, Sham, and LD (n=6) were analyzed by ELISA, bead-array, and microarray. Significance was tested by Student T-test, ANOVA (post-test: Bonferoni/Benjamini-Hochberg). Significance threshold for gene-expression enrichment analysis was >2-fold, FDR<0.05.

Results: BD: Impaired Genetic Expression of Cellular Metabolism. Of known genes with significant expression differences in BD kidneys versus LD, 158 genes were up regulated in BD, with heavy enrichment for inflammatory responses ($p=9.2e^{-7}$) and 25 genes were down-regulated, enriching for oxygen transport ($p=5.8e^{-3}$). In BD kidneys versus Sham, 54 genes were up regulated in BD, with enrichment for angiogenesis ($p=1.5e^{-2}$) and genes related to stress response ($p=4.5e^{-2}$); 57 genes were down regulated, enriching in multiple metabolic processes, i.e. carbohydrate ($p=2.1e^{-5}$) and lipid ($p=1.3e^{-5}$) metabolism. Significant expression differences were also observed in BD livers versus LD. 117 genes were up- regulated in BD, enriching mainly in genes related to chemical response ($p=2.6e^{-2}$). 207 genes were down regulated, enriching in multiple metabolic processes, i.e. primary metabolism ($p=9.7e^{-5}$), and lipid, organic, and carbohydrate metabolism (respectively $p=2.e^{-16}$, $p=5.7e^{-9}$, $p=2.3e^{-3}$). Only 5 known genes were significantly down-regulated (0 were up regulated) in BD compared to Sham, 2 being P450-cytochrome genes.

BD: Coagulation/Fibrinolysis/Contact Dysregulation. BD revealed increased circulation of VWF (200%, p<0.05), thrombin (125%, p<0.05), and plasminogen (150%, p<0.05) over Sham. Both groups increased circulating Fibrinogen (300%) and tPA (200%) over baseline. No changes were observed in Prothrombin or activated partial Prothrombin times. BD yielded a 2-fold increase (p<0.05) over Sham in active Bradykinin, known for inflammatory and vasodilator properties.

BD and Sham: Inflammatory Response. BD and Sham elicited profound neutrophilia. Circulating IL-6 increased (BD:300-fold, Sham:30-fold [p<0.005]). Both groups increased circulating TNFa (3-fold), Il-8 (3-fold), CCL-2 (4-fold), and complement classical pathway activity (125%) compared to baseline. Lectin pathway activity increased in BD (120%) compared to Sham (50%)(p<0.05). In the kidney transcriptome, markers for cytokines (i.e Il-1b, Il-6), macrophages (i.e. Cd14, Cd68, Tlr molecules), inflammasome-related caspases (Casp1, Casp4, Casp5), complement molecules (i.e. C1q, C1r, C3), and acute kidney injury (Kim-1, Spp-1, Clu) were increased in BD and Sham compared to LD. Liver biopsy transcription exhibited minimal inflammatory response.

Conclusion: BD and Sham demonstrated general inflammatory responses, albeit with stronger intensity in BD. Transcription analysis of liver and kidney tissue unveiled dramatic BD-related down-regulation of genes involved in metabolic pathways for lipids, proteins, and carbohydrates. Understanding the nature of metabolic impairment observed in BD grafts coupled to an inflammatory environment is key to the development of therapeutic strategies that eradicate difference between BD and LD long-term graft survival to improve transplant outcomes

Targeted Donor Complement Blockade after Brain-Death Prevents Delayed Graft Function but Not Progression to Antibody-Mediated Rejection in a Non-Human Primate Model of Kidney Allo-Transplantation

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Keywords	Organ donation, Complement System, Delayed Graft Function, Antibody-mediated rejection, translational models

Abstract begins on following page

Introduction: Donor brain death (BD) triggers a complement-mediated inflammatory response that is linked to the pathogenesis of pre-transplant renal injury in deceased donors. Delayed graft function (DGF) is a common complication after renal transplantation and is strongly associated to reduced graft survival and increased rates of antibody-mediated rejection (ABMR). Here, we hypothesized that complement blockade in the brain-dead donor would potentially prevent the progression to DGF and ABMR in the transplant recipient.

Methods: We evaluated the role of targeted donor management using recombinant human C1 inhibitor (C1-INH) in the prevention of DGF and ABMR. BD was induced and maintained for 20 hours and recovered kidneys were cold-stored for a 44-hour period. They were then transplanted into ABO- compatible, MHC fully mismatched recipients. Donor animals were divided into three groups: G1) Vehicle (n=3 donors, 6 recipients), G2) C1INH 500 U/kg/dose + heparin (n=3 donors, 6 recipients) and G3) Heparin only (n=2 donors, 3 recipients). Animals were followed for a 90-day period and underwent interval biopsies. The main end-points of the study were: 1) Incidence of DGF defined as 10% reduction in creatinine level from the first post-operative day within 1 week of transplant and 2) development of ABMR within 90 days of transplant according to Banff 2013 criteria.

Results: Donor treatment with C1-INH showed a protective effect, with none (0/6) of the G2 recipients developing DGF post-operatively. In contrast, 4/6 (66.6%) animals receiving untreated kidneys from G1 donors and 3/3 (100%) from heparin-only treated G3 donors progressed to DGF (p= 0.008). In addition, recipients of G2 kidneys showed a statistically significant reduction in creatinine levels in the first post- operative week compared to G1 and G3 recipients, and renal function normalized to baseline levels by post-operative day 10 (p <0.01). Furthermore, recipients of G2 kidneys expressed markedly reduced urinary NGAL levels, a specific marker of DGF. We also observed a significant reduction in the activation of the donor classical pathway of complement as well as a decrease in markers of activation of the contact pathway in G2 donors. All transplanted animals from donors in G1 (4/4) and G2 (6/6) surviving over two weeks developed ABMR and showed sustained de-novo DSA development post transplantation. Histopathological findings were consistent with acute active ABMR in the kidney as evidenced by strong C4d staining and peritubular capillaritis and glomerulitis. FACS analysis revealed a higher proportion of class-switched memory B-cells (CD20+, CD27+, IgDlow) in mesenteric and inguinal lymph nodes. We did not observe differences in the incidence or severity of ABMR between animals receiving grafts from either vehicle or C1-INH treated donors.

Conclusion: We have generated a unique and reproducible model of DGF and de-novo accelerated ABMR in the rhesus macaque. Our data indicate that donor management targeting complement activation prevented the development of DGF but had no effect on the progression to ABMR in our model. These results suggest a pivotal role for complement activation in BD-induced renal injury and complement blockade as a promising strategy for the prevention of DGF after transplantation.

Defining a Phonomicrosurgical Learning Curve Using Motion Metrics in Novices

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Abstract begins on following page

Objective: Motion metrics are an objective measure of surgical dexterity, but have not been widely applied to phonosurgical training and evaluation. The Video-based Phonomicrosurgical Instrument Tracking System (V-PITS) has been shown to successfully measure changes in motion metrics in novice subjects who received training on a simulated phonomicrosurgical task. Our objective is to define the learning curve of novices, using number of repetitions on a simulator as an independent variable and each of the motion metrics captured by V-PITS as dependent variables.

Methods: In a prospective cohort study, 20 participants (11 females) without prior surgical experience completed 15 sessions with a validated vocal fold polypectomy simulation. At each session, participants operated on each hemifold in a randomized order. Microforceps, microknife, and microscissors movements were recorded and used to compute the following motion metrics: path length, depth perception, motion smoothness on three independent axes, net motion smoothness, and net orientation smoothness. The average metrics for each session were fit to a power function according to Wright's Cumulative Average Model: $Y = aX^b$.

Results: Data were analyzed by individual hemifold and cumulatively. For left-sided lesions, the depth perception data fit a power function for all 3 microinstruments ($p = 0.03$ for microforceps; $p < 0.01$ for microknife; $p = 0.01$ for microscissors), as did path length data for the microforceps ($p = 0.04$) and microknife ($p < 0.01$). For right-sided lesions, the path length and depth perception data fit a power function for microforceps ($p < 0.01$ for both). Cumulative path length ($p < 0.01$ for microforceps; $p = 0.01$ for microknife; $p < 0.01$ for microscissors) and depth perception ($p < 0.01$ for microforceps; $p = 0.02$ for microknife; $p = 0.03$ for microscissors) data fit a power model for all 3 instruments.

Conclusion: In a novice population performing a simulated phonomicrosurgical task, a learning curve can be defined in terms of path length and depth perception as measured by V-PITS.

Acquisition of Donor MHC (A01) Assists in Maintaining Graft Survival after Loss of Chimerism

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Keywords	Transplant, Chimerism, Tolerance, Antigen, Rhesus

Abstract begins on following page

Background: We are establishing a model in the Rhesus Macaque to induce tolerance, a condition where a transplant recipient's own immune system is modified to tolerate rather than reject the transplanted organ even without immunosuppression. In this model, the animals receive immunosuppression for a short time after transplant, and are then weaned off all immunosuppressant drugs. We believe that one way that induced tolerance of the transplanted organ after immunosuppression is occurring, is through acquisition of donor MHC's. We believe that donor extracellular vesicles are taken up by the recipient cell's, which in turn suppresses the immune response. We are specifically looking at recipients who are non-A01, but had A01 positive donors.

Hypothesis: Recipient acquisition of donor A01 induces temporary tolerance, and assists in maintaining graft survival.

Methods: We tested plasma of recipients that had A01 donors, at pre-transplant and post-transplant time points for acquisition of the A01 antibody with an enzyme-linked immunosorbent assay (ELISA).

Results: The majority of animals (2 of 3) that had A01 positive donors acquired A01 post transplant. Acquisition of the antigen was observed starting at week 6 and was maintained.

Conclusion: The acquisition of the A01 antigen by the recipient may mean that this aids in preventing rejection. The next step is to determine how this acquisition of the A01 antigen assists in preventing rejection. We believe that the recipients' cells take up extracellular vesicles (EVs) that are excreted by the donor cells, and these EVs contain the A01 antigen. We are planning to isolate EVs using a size exclusion column.

Induction of Tolerance to Kidney Transplants in Rhesus Macaque

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Keywords	Kidney Transplant, Chimerism, Tolerance, Rhesus, Engraftment

Abstract begins on following page

Background: Solid organ transplantation is the current treatment for many end stage diseases, but long-term use of immunosuppressive medications negatively impacts quality of life. Tolerance is the state where transplant recipients are able to maintain good graft function in the absence of immunosuppression. We have established a large animal model to induce tolerance using a post-renal transplant immuno-depletion therapy followed by an infusion of donor hematopoietic stem cells (HSC), allowing investigation of mechanisms underlying tolerant acceptance of both HSC and renal allografts. This protocol is based on experimental treatments developed at Stanford University.

Hypothesis: That this induction protocol creates conditions for establishing a state of chimerism which allow for kidney allograft acceptance without need for immunosuppression.

Methods: Rhesus Macaques were placed into 2 groups- those that received a living-related renal transplant only and those that received HSC 11 days post renal transplant. Animals also received post transplant induction regimen consisting of 5 days of anti-thymocyte globulin and 10 doses of total lymphocyte irradiation using tomotherapy. Maintenance immunosuppression consisted of mycophenolate mofitil, tapered 90 days post transplant with a 25% reduction every two weeks and tacrolimus, tapered after day 150 or 180 with a 25% reduction every month. Recipients are monitored for cell reconstitution, donor chimerism, and renal function before and after immunosuppression is withdrawn.

Results: Establishment of chimerism has been a challenge in this Rhesus model with only 2/5 animals transplanted with a kidney and HSC achieving transient mixed chimerism. However, once achieved, chimerism appears to be of benefit for successful weaning of immunosuppression. Recent analysis has shown a potential correlation between high levels of donor specific antibody (DSA), particularly on the B cells, in the recipients and a lack of achieving chimerism. Both of the animals that achieved transient mixed chimerism did not develop DSA and have stable renal function 30 and 36 months after discontinuation of all immunosuppression. In contrast, the 3 animals that did not become chimeric as well as 6/7 animals that did not receive HSC were not successfully weaned and all of these animals rapidly developed DSA. The one long-term survivor without HSC has now succumbed to antibody and cell mediated graft rejection.

Conclusions: Mixed chimerism, even temporarily, appears to benefit transplant survival and may potentiate renal transplant tolerance. We have piloted modifications of the protocol, including targeted B cell depletion in the recipient, to achieve more consistent mixed chimerism and to continue to perform immunological testing on the long-term survivors to understand the role of naturally acquired regulation on transplant tolerance.

Toward the Understanding of Mechanosensing and the Effects of Mechanical Forces on Lung Development

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Keywords	Mechanosensing, Pulmonary Development, Bronchopulmonary Dysplasia, Mechanical Ventilation, Bioreactor

Abstract begins on following page

Mechanical forces are constantly applied to our bodies from conception until death. They are heavily studied in understanding skeletal development. We observed that mechanical forces also play a major role in the development of softer and more compliant tissues such as the lungs, which are under constant dynamic forces generated by breathing. Disturbances in these forces can occur during embryonic development such as in congenital diaphragmatic hernia (CDH) where there is diminished negative ventilation, or during medical intervention such as with mechanical ventilation where negative ventilation is replaced with positive ventilation. We hypothesize that changes in mechanical stimuli to the lungs during development lead to abnormal alveologenesis, resulting in diseases such as pulmonary hypoplasia and bronchopulmonary dysplasia (BPD). Our laboratory seeks to understand these phenomena by studying how mechanical forces affect embryonic and post-natal lung development.

Fetal breathing physiology was assessed by measuring respiratory rate and intrathoracic pressure of fetal mouse day 17.5 in-utero using microscopy and pressure sensors. Bioreactors were built to study both embryonic and post-natal lung development in *ex vivo* culture of rodent lung explants. Mechanically sensitive genes (Cela1, Trpv4, Peizo-1 and Peizo-2) were analyzed to identify the mechanosensor(s) responsible for embryonic lung development using real time PCR and Western Blots during varying stages of embryonic development. Mice embryos exhibit regular breathing with maximal negative intrathoracic pressures of -2mmHg at embryonic day 17.5. Based on these data, two mechanical bioreactors were developed, mimicking the thoraces of a mouse embryo and post-natal mouse to study lung development under different mechanical environments.

Mechanically sensitive genes Peizo-1 and Peizo-2 showed significant decreases in expression, a reduction of ~50%, when the lungs are cultured at atmospheric pressure compared to the in utero environment. This suggests that these genes are possible mechanically dependent sensors that partake in regulating lung development. We have successfully created two innovative models to study the effects of mechanical forces on lung development. Preliminary molecular data point to Peizo-1 and Peizo-2 as possible mechanosensors that could play a role in regulating lung development. Future studies to investigate the effects of positive pressure ventilation versus negative pressure ventilation on lung development not only will give us an insight into how the expression of mechanosensing genes like Peizo-1 and Peizo-2 can effect lung growth and development, but will also allow us to develop possible therapies for tackling congenital and mechanically induced lung diseases.

A Human Pancreatic ECM Scaffold for Human Beta Cell Co-Culture and Co-Transplantation

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Keywords	ECM, Hydrogel, Pancreas, Human Islets, Stem Cells

Abstract begins on following page

Background: Extracellular matrix (ECM) plays an important role during human embryonic development by actively regulating cell behavior through structural support and biochemical stimulation. Tissue specific ECM has been proposed for use in a number of regenerative strategies for tissue and organ replacement. However, few studies have explored the potential of using pancreatic ECM to improve current islet transplantation procedures, or to specifically enhance the differentiation of human pluripotent stem cells (hPSCs) into functional beta cells.

Our objective is to apply decellularization techniques to human pancreas to produce acellular, 3D biological scaffolds that can be infused with isolated islets for transplantation or utilized with hPSCs differentiated toward pancreatic cell lineages.

Methods: We employed decellularization techniques to human pancreas (Fig.1a), using physical and chemical treatments to produce acellular human pancreatic ECM (hP-ECM) (Fig.1b). hP- ECM was digested in an acidic pepsin solution (Fig.1c), neutralized and warmed to $37_{o}C$ to form an hP-ECM derived hydrogel (hP-HG) (Fig.1d). The hP-ECM and hP-HG were examined for removal of lipids and DNA, for preservation of sulfated glycosaminoglycan (sGAG) content and ECM proteins, such as collagen I and IV, laminin, and fibronectin, and for ultrastructure integrity by scanning electron microscopy. hP-HG was combined with cells *in vitro* (Fig.1e) to test cytocompatibility and injected subcutaneously (Fig.1f) to assess *in vivo* immune response.

Results: We found that lipid content was significantly reduced following decellularization through the inclusion of a homogenization step; lipid removal significantly improved the hydrogel forming ability of the hP-ECM. Furthermore, DNA content is significantly reduced in the hP-ECM (4.2%) and hP-HG (0.44%) compared to the native pancreas (100%). sGAG content is moderately retained in the hP-ECM (20.8%) and hP-HG (4.0%) compared to native pancreas (100%). hP- ECM and hP-HG stain positively for ECM proteins such as Col1, Col4 and Laminin, but stain negatively for immunogenic proteins such as HLA Class I and II. hP-HG is cytocompatible with the rat beta cell line hINS-1, as well as other cell types like endothelial cells (HUVECs), both of which grow on hP-HG coated surfaces with equal proficiency as untreated or Col1-coated surfaces. Undifferentiated hPSCs embedded in hP-HG continue to proliferate and grow in a 3D spherical structure. We tested cytocompatibility with hPSC-derived pancreatic progenitor cells embedded in hP-HG; the cells retain their Pdx1+ fate, are proliferative (Ki67+) and non-apoptotic (Casp3-). Finally, when transplanted into humanized mice, hP-HG is hypoimmunogenic, being infiltrated to a very low extent by human T cells (CD3+) and B cells (CD20+), while allogeneic control tissue (human fetal pancreas) is acutely infiltrated and rejected.

Conclusions: We developed and optimized a novel decellularization protocol for developing hydrogel (hP-HG) from hP-ECM which removes lipids and DNA while retaining important ECM proteins and sGAG content. We demonstrated hP-HG cytocompatibility with a variety of cell culture platforms as an alternative to the standard 2D culture presently used in most beta cell differentiation conditions. hP-HG does not contain immunostimulatory proteins such as HLA class I and II, and is hyopimmunogenic when transplanted into humanized mice, making this biomaterial suitable for transplantation.

T14

TACI-Ig as a Desensitization Agent in a Rat Model of Antibody Mediated Rejection

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Abstract begins on following page

Highly sensitized candidates on the kidney transplant waitlist remain a significant challenge as current desensitization protocols have variable success rates. Improved desensitization therapies are therefore needed. APRIL and BLyS are critical survival factors for B lymphocytes and plasma cells, the main source of alloantibody production. We examined the effect of APRIL/BLyS blockade on donor specific antibody (DSA) in a preclinical rodent model as a possible novel desensitization strategy. Our rat model of antibody mediated rejection includes sensitizing Lewis rats with Brown Norway (BN) blood 21 days prior to transplant with a BN kidney. After sensitization, rats have been shown to have circulate alloantibodies, mainly IgG (Huang et al, AJT 2014). We examined the effect of TACI Ig on animals that were pre-sensitized to donor antigens as a possible desensitization strategy.

Lewis rats were sensitized by i.v. injections of 0.5 ml heparinized BN blood. 21 days after sensitization, rats were treated with 250 µg of TACI-Ig administered three times per week for 21 days. A minimum of 6 rats were analyzed per group. B cell subset analysis by flow cytometry and flow cross match (FXM) were performed to assess the effect of APRIL/BLyS inhibition. G1 are baseline animals, G2 are animals that were sensitized, but not treated, G3 are animals that were sensitized and treated with TACI-Ig. All statistical analyses were compared to G2.

In animals that were sensitized and treated with TACI-Ig, we observed a significant reduction in Marginal Zone B cells in the spleen ($p<0.01$, Fig 1A), as well as significant reductions in Transitional cells in bone marrow (BM, $p<0.002$), lymph nodes ($p<0.003$) and PBMC ($p<0.003$), Fig 1E-G. We also observed a significant reduction in Plasma Cells in both spleen ($p<0.005$) and bone marrow ($p<0.04$), Figure 1 B,C. Animals that were sensitized (G2) had significantly elevated DSA for all isotypes (Fig 2 A-E) tested by FXM, compared to baseline. Surprisingly, the only isotype that was reduced after TACI-Ig treatment was IgG2a (Fig 2B, $p<0.004$).

In Lewis rats, TACI Ig was able to reduce many B cell subsets, including plasma cells, but the reduction was not as profound as in our mouse model (Wilson et al, in preparation). Critically, only IgG2a isotype DSA were reduced by the TACI Ig treatment. The TACI used in the construct for the drug was optimized for mouse sequence, not rat sequence. Even though the mouse and rat proteins are related, evidently there are sufficient differences to result in reduced effect on DSA desensitization. It will be of interest to closely compare binding sites differences between the two species to elucidate whether affinity has changed or if binding specificity has shifted.

Development of an In-Vitro 3D Porcine Intestinal Stem Cell Culture Model

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Abstract begins on following page

Chronic diseases are the leading cause of death in developed and developing countries. Most of these diseases can be linked to dysregulations in the immune system, triggering dysfunctional inflammatory reactions. The function of our immune system is heavily dependent on our diets. Since the 1970s, the consumption of dietary fats has drastically changed and increased. These fats or lipids harmfully affect the immune system causing processes that stimulate dysfunctional immune reactions. To tackle this issue, we've examined stem cells of the gastrointestinal tract (GI) since the GI comes into direct contact with our diets. We aim to learn more about how the immune system works as well as how lipids affect the intestinal stem cells and epithelial cells housed in the intestine. In order to determine how lipids affect our immune system, our aim was to develop an in-vitro 3D porcine intestinal stem cell culture model. Through the development of this model, in the near future, we will be able to run experiments to distinguish and measure the lipids in our gastrointestinal tract. This will help us to determine to what extent lipids, specifically oxidized lipids, affect our gastrointestinal tract immune system. Successful creation of the model will allow us to characterize specialized GI cells and see the effects that oxidized lipids have on them.