Surgery Research Day 2019

18TH ANNUAL WILLIAM C. WOOD RESEARCH SYMPOSIUM

APRIL 25, 2019 | EMORY UNIVERSITY HOSPITAL AUDITORIUM

Keynote Speaker: Michael B. Yaffe, MD, PhD

David H. Koch Professor of Science and Professor of Biology and Biological Engineering, MIT
Scientific Director, MIT Center for Precision Cancer Medicine
Attending Trauma Surgeon, Beth Israel Deaconess Medical Center
Colonel, U.S. Army Reserve Medical Corps

EMORY UNIVERSITY SCHOOL OF MEDICINE | Department of Surgery

SCHEDULE OF EVENTS

7:00-8:00 AM	**Introduction of keynote speaker by Craig Coopersmith, MD**
	A Critical Protein Kinase controls inflammation, wound healing, and cancer at sites of tissue injury. *Michael B. Yaffe M.D., Ph.D. FACS*
8:05 AM	**Welcome remarks by Nicole Turgeon, MD**
	Oral Presentation - Session I *Moderators: Muralidhar Padala, MD and Rachel Patzer, PhD*
8:15 AM	Targeted hyaluronic acid nanoparticles improve treatment response in pancreatic cancer *Mohammad Jajja*
8:25 AM	Safety of del Nido Cardioplegia in Complex Adult Cardiac Surgery: A Propensity Matching Analysis *Jason Schwarz*
8:35 AM	Anti-CD154/CD40 Costimulation Blockade is Superior to Tacrolimus in Prolonging Survival in Pig-to-Nonhuman Primate Renal Xenotransplantation *Brendan Lovasik*
8:45 AM	Anti-CD28 Antibody Improves Survival in Septic Memory Mice through IL-10 Release *Sun Yini*
8:55 AM	Avoiding Pitfalls in Insulinomas by Preoperative Localization with A Dual Imaging Approach *Kimberly Ramonell*
9:05-9:55 AM	**Poster Session and Coffee Break** (poster presenters and judges transition to classrooms)
10:00 AM	**Oral Presentations - Session 2** *Moderators: Preeti Subhedar, MD and Lily Yang, MD*

10:05 AM	Dialysis Facility Provider Transplant Knowledge after a Randomized Multilevel Intervention to Increase Kidney Transplant Referral and Evaluation in the Southeast *Kieran Maroney*
10:15 AM	A Trans-ventricular Reshaping Device to Reduce Left Ventricular Wall Stress Ameliorates Systolic Function in a Rodent Model of Chronic Ischemic Cardiomyopathy *Daisuke Onohara*
10:25 AM	Lung Surveillance Strategy for High-Grade Soft Tissue Sarcomas: CT Scan or Chest X-ray? *Adriana Gamboa*
10:35 AM	IFNAR Signaling Augments Plasmacytoid Dendritic Cell Activation During Costimulation Independent Rejection *Jakob Habib*
10:45 AM	Frailty in the Polytraumatized Patient: A Powerful Predictor of Mortality and Complications *Andrew Isaacson*
10:55 AM	**Closing remarks & awards presentation by Nicole Turgeon, MD**
11:00 AM	**Announcement of the symposium winners and adjourn** *(Winners are asked to remain in the auditorium for group photo)*
11:10 AM – 12:00 PM	**Presenters Luncheon** All presenters are invited to join Dr. Michael B. Yaffe and the Surgery Research Advisory Committee in the Whitehead Room, EUH, 2nd Floor, Administration Wing

KEY NOTE SPEAKER

Michael B Yaffe M.D., Ph.D. FACS

Michael B Yaffe M.D., Ph.D. FACS is the David H. Koch Professor of Science and Professor of Biology and Biological Engineering at MIT, where he has been a faculty member since 2000; he is also an attending trauma surgeon at the Beth Israel Deaconess Medical Center. Yaffe earned his doctoral degree in biophysical chemistry and his medical degree from Case Western Reserve University. He completed residencies in both general surgery and surgical oncology, at University Hospitals of Cleveland and New England Deaconess Hospital, respectively, and a fellowship in surgical critical care at Harvard Medical School's Harvard-Longwood Critical Care Program. He was a postdoctoral fellow with Lewis Cantley in the Department of Cell Biology at Harvard Medical School. In recognition of his accomplishments, he received the Howard Hughes Physician Scientist Award, the Burroughs Wellcome Career Development Award, and the MIT Science Teaching Prize. A founder of Consensus Pharmaceuticals, the DNA Repair Company, and Merrimack Pharmaceuticals, Professor Yaffe is also the Chief Scientific Editor of Science Signaling. He serves as a Colonel in the U.S. Army Reserve Medical Corps and in 2015 received the Bronze Star Medal from the U.S. Army for his service as a trauma surgeon on active duty in Afghanistan. In 2017, Yaffe became the inaugural scientific director of the MIT Center for Precision Cancer Medicine

ORAL PRESENTATIONS

8:15 AM

Category: Basic Science

#4 - Targeted hyaluronic acid nanoparticles improve treatment response in pancreatic cancer
MR Jajja, L Zhu, D Wang, CA Staley, B El-Rayes, DA Kooby, L Yang

Introduction: Pancreatic cancer has poor response to chemotherapy with desmoplastic stroma identified as a delivery barrier. To overcome this, we developed a nanoparticle (NP) drug system using an engineered ligand of urokinase plasminogen activator (ATF) and catalytic-domain of metalloprotease (MMP14). Hyaluronic acid (HA), a naturally occurring protein, was used to form a biocompatible nanoparticle. HA can bind to CD44, highly expressed in epithelial cancers. Dual uPAR, CD44 targeting allows for targeted delivery and receptor mediated endocytosis of NP-drug complex. MMP14 activity degrades extracellular-matrix.

Methods: SN38 (CPT-11 analog) was encapsulated and recombinant ATFmmp14 conjugated to surface of self-assembled HA spheres (200nm) to form complete particle (HANP). In-vitro cytotoxicity assays were conducted. Patient derived xenograft (PDX) model of a drug resistant pancreatic cancer was used for efficacy studies. Orthotopic tumors were treated with HANP (10mg/kg SN38) for 6 weeks and overall survival compared to conventional chemotherapy.
Results: HANP in-vitro cytotoxicity was greater than irinotecan (>80x) and liposomal irinotecan (>900x) in a PDX derived cell line. In-vivo efficacy study demonstrated significant improvement in survival of PDX bearing mice with HANP (n=9) (median survival 50 days), compared to FOLFIRINOX (n=9), Gemcitabine-nab-Paclitaxel (n=9) (37 days each) and no treatment (n=13) (22 days). Combination of HANP with a modified-FOLFIRINOX regimen (n=9) led to median survival >72 days ($p<0.001$).

Conclusion: HANP alone or in combination with modified FOLFIRINOX led to significantly improved survival in a pancreatic cancer PDX model. Further studies are underway to evaluate preclinical PD/PK for eventual translation as targeted therapy for pancreatic cancer.

8:25 AM

Category: Clinical Science

#45 - Safety of del Nido Cardioplegia in Complex Adult Cardiac Surgery: A Propensity Matching Analysis
Jason Schwarz BA, Jose Binongo PhD, Omar Lattouf MD PhD, Chao Zhang BS, Jane Wei, William B Keeling MD

Purpose: Del Nido cardioplegia (dNC) is increasingly used in adult cardiac surgery, and recent studies show equipoise with blood-based cardioplegia (BBC) for short operative times. This study compared

outcomes of complex cardiac surgeries with aortic crossclamp times exceeding 120 minutes using dNC or BBC for cardiac protection.

Methods: A retrospective review of the Society of Thoracic Surgery (STS) Adult Cardiac Surgery Database for patients who underwent surgery with aortic crossclamp times exceeding 120 minutes at a single U.S academic institution from 9/2013 through 4/2018 was performed. A propensity score was estimated for each patient based on preoperative characteristics. Patients were matched by propensity scores in a 1:1 ratio within calipers to compare outcomes between dNC and BBC patients.

Results: 1,609 patients met inclusion criteria. 163 (10.1%) had dNC for cardioplegic arrest and 1,446 (89.9%) had BBC. Propensity matching yielded 152 pairs for a total of 304 patients included in the analysis. Mean crossclamp times were similar (163 min for dNC, 162 for BBC; p=0.75) while mean cardiopulmonary bypass times were significantly longer in the dNC group (222 min vs. 202 min, p=0.02). Matched analysis of postoperative outcomes, including cardiac arrest and 30-day mortality, demonstrated no statistical differences with exception of higher rates of prolonged ventilation (OR 1.6, p=0.04) and longer median ventilation time overall (19.3 hours for dNC, 13 hours for BBC, p=0.005) for dNC patients.

Conclusions: Del Nido cardioplegia can be used safely in complex adult cardiac cases with longer aortic crossclamp times. Postoperative outcomes were similar for patients with dNC and BBC, providing impetus for further trials comparing these cardiac protection strategies.

Table 1: Propensity Score Matched Postoperative Outcomes

Outcome	# events or median (dNC group)	# events or median (BBC group)	OR/HLE	95% CI	p-value
Cerebrovascular Accident	4	6	0.66	0.18, 2.38	0.52
Death (30 days)	17	15	1.15	0.55, 2.40	0.71
Postoperative Cardiac Arrest	7	7	1.00	0.34, 2.92	1.0
Postoperative IABP Insertion	4	3	1.34	0.30, 6.10	1.0
Heart Block Requiring Pacemaker	10	7	1.46	0.54, 3.94	0.45
Postoperative Atrial Fibrillation	60	68	0.81	0.51, 1.27	0.35
New Renal Failure	18	15	1.23	0.59, 2.53	0.58
New Dialysis	15	14	1.08	0.50, 2.32	0.85
Postoperative Ventilator (hours)	19.3	13.0	-6.00	-10.00, -1.00	0.005
Prolonged Ventilation	61	44	1.65	1.02, 2.65	0.04
Total ICU Time (hours)	94.9	89.7	4.20	-5.70, 22.80	0.41
Postoperative LOS (days)	9.0	8.0	-1.00	-2.00, 0.00	0.17

*# events and OR: Number of events and Odds Ratio for dichotomous variables
*Median and HLE: Median value and Hodges-Lehmann Estimator for continuous variables

8:35 AM

Category: Basic Science

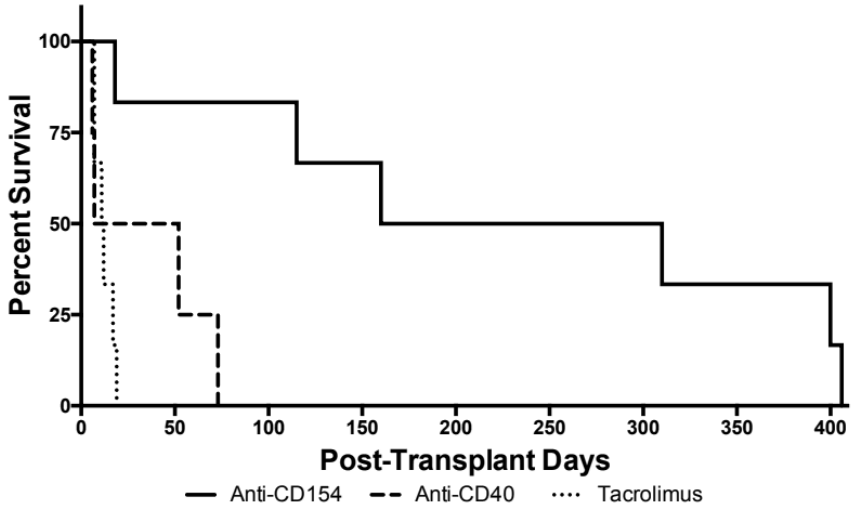
#32 - Anti-CD154/CD40 Costimulation Blockade is Superior to Tacrolimus in Prolonging Survival in Pig-to-Nonhuman Primate Renal Xen

BP Lovasik, AJ Matar, C Breeden, J Jenkins, SC Kim, AB Adams

Introduction: Costimulation blockade strategies targeting the CD40/CD154 pathway are highly effective in preventing xenograft rejection in pig-to-nonhuman primate (NHP) transplantation models. The aim of this study was to assess the relative therapeutic efficacy of tacrolimus, a clinically applicable immunosuppressive agent, compared to either anti-CD40 or anti-CD154 therapies.

Methods: Rhesus macaques (n=17) with low pre-transplant xenoreactive antibody titers were selected following recipient screening. Selected recipients underwent bilateral nephrectomy and life-sustaining porcine renal xenotransplantation using GGTA1 KO/CD55 transgenic donor pigs (NSRRC, St. Louis MO). Animals underwent T cell depletion and were randomized to one of three maintenance treatment regimens: tacrolimus (target trough 8-12ng/mL), anti-CD40 (clone 2C10R4), or anti-CD154 (clone 5C8), plus mycophenolic acid and steroids.

Results: Recipients treated with anti-CD154 therapy (n=6) experienced the longest survival (MST=235 days, p=0.015), including three rhesus macaques with survival over 300 days (406, 400, 310 days). Recipients treated with anti-CD40 therapy (n=4) exhibited a moderate prolongation in survival (MST=29.5 days) whereas tacrolimus-treated recipients (n=6) experienced the shortest survival (MST = 11.5 days). Graft failure was associated with an increase in serum creatinine (Panel B). Conclusion: Here we demonstrate that immunosuppression with anti-CD154 or anti-CD40 therapy is associated with prolonged survival of kidney xenografts relative to tacrolimus in a porcine-to-NHP xenotransplantation model. These data provide further rationale for clinical translation of these costimulation blockade reagents which demonstrate the strongest survival benefit for xenotransplant recipients.



8:45 AM

Category: Basic Science

#37 - Anti-CD28 Antibody Improves Survival in Septic Memory Mice through IL-10 Release

Yini Sun, Ching-wen Chen, Zhe Liang, Wenxiao Zhang, Kristen N. Morrow, Craig M. Coopersmith and Mandy L. Ford

Introduction: Immune dysregulation during sepsis is mediated by an imbalance of T cell costimulatory and coinhibitory signaling. CD28, a critical T cell costimulatory receptor, is downregulated in sepsis, and CD28 expression is significantly altered on memory T cells. Laboratory animals possess fewer memory T cells than adult humans. Therefore, we established a novel model to investigate the role of CD28 in sepsis.

Methods: C57BL/6J mice were infected with Listeria monocytogenes and 30 days later were infected with LCMV. 30 days later, memory mice and age-matched naïve controls were subjected to cecal ligation and puncture (CLP) to induce polymicrobial intra-abdominal sepsis. Mice were randomized to receive αCD28 antibody (Ab) or vehicle and were sacrificed after 24 hours or followed 7 days for survival.

Results: Sequential infection resulted in 52% memory T cells compared with only 18% in the naïve controls. CD28 expression decreased after CLP in memory and naïve mice. While αCD28 Ab failed to impact survival in septic naïve mice, it significantly improved survival in septic memory mice. Apoptosis of CD4+ CD44+ T cells in the treated memory mice was significantly reduced compared to untreated memory mice. Mechanistically, increased frequencies of IL-10-producing FoxP3+ regulatory T cells were detected in treated memory mice relative to controls. Blockade of IL-10 eliminated the survival benefit in the treated memory mice following CLP.

Conclusion: αCD28 Ab improves sepsis survival in memory (but not naïve) mice by increasing IL-10 secretion by regulatory T cells. It highlights the importance of immunotherapy in a novel sepsis model.the next AJCC staging system for distal cholangiocarcinoma should be considered

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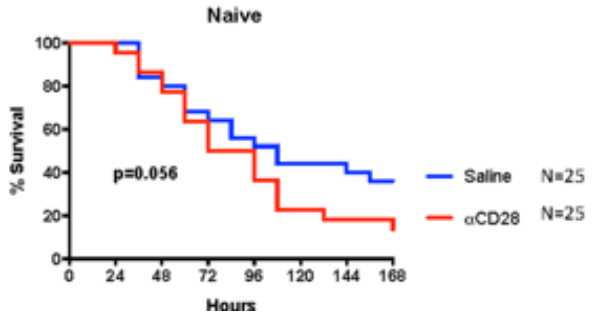

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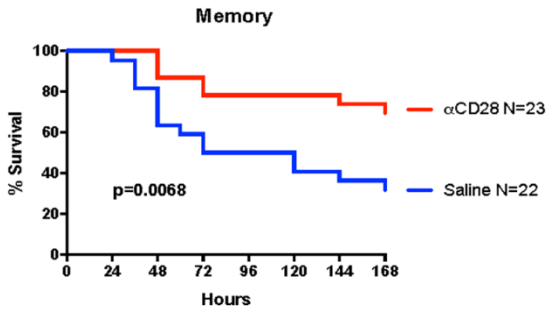


8:55 AM

Category: Clinical Science

#1- Avoiding Pitfalls in Insulinomas by Preoperative Localization with A Dual Imaging Approach

Ramonell KM, Chen CW, Fay KT, Klingensmith NJ, Lyons JD, Liang Z, Coopersmith CM, and Ford ML

Introduction: Insulinomas are rare endocrine malignancies of the pancreas that require surgical resection but can be difficult to localize preoperatively. We sought to compare and improve the accuracy of preoperative localization techniques for insulinomas.

Method: A single center retrospective review of all surgically resected insulinomas between 1998-2016 was performed. Patients underwent preoperative localization studies with Selective Arterial Calcium Stimulation (CaStim) testing, Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI). CaStim was performed by selective arteriography with calcium gluconate injection and hepatic venous measurement of insulin. Preoperative localization was compared to surgical localization for accuracy.

Results: 38 patients had pathologically proven insulinomas. CaStim was performed on 35 patients with a localization accuracy of 89% (31/35). Localization accuracies of CT and MRI were 62% (15/30) and 40% (8/20), respectively. When compared with CT alone and CaStim alone, the combination of these two modalities resulted in 100% localization (30/30), whereas the use of CaStim alone was 80% (4/5) localizing and the use of CT alone was 66% (2/3) localizing. Four patients had both negative CT and MRI. Among these patients, CaStim was 100% localizing and the only positive modality. Additionally, CaStim was the only study to identify multiple synchronous tumors in 10.5% patients.

Conclusion: This data confirms that CaStim is accurate in preoperatively identifying single and multiple insulinomas; and when combined with CT this accuracy is increased to 100%. Based on this data, we propose that a dual imaging approach, with CT plus CaStim is a superior means of preoperative localization of insulinomas.

10:05 AM

Category: Clinical Science

#13 - Dialysis Facility Provider Transplant Knowledge after a Randomized Multilevel Intervention to Increase Kidney Transplant Referral and Evaluation in the Southeast

Kieran Maroney, Reem Hamoda, Laura McPherson, Alexandra Cruz, Stephen Pastan, Laura Plantinga, Sudeshna Paul, Matthew Ellis, Derek DuBay, Amber Reeves-Daniel, Randal Detwiler, Erica Hartmann, Heather Jones, Carlos Zayas, Laura Mulloy, Shannon Wright, Rachel Patzer

Purpose: Dialysis facility provider kidney transplantation (KTx) knowledge influences patient transplant access. The Reducing Disparities in Access to kidNey Transplantation (RaDIANT) Regional Study is a multicomponent intervention aimed to educate dialysis patients and staff on KTx to improve access to

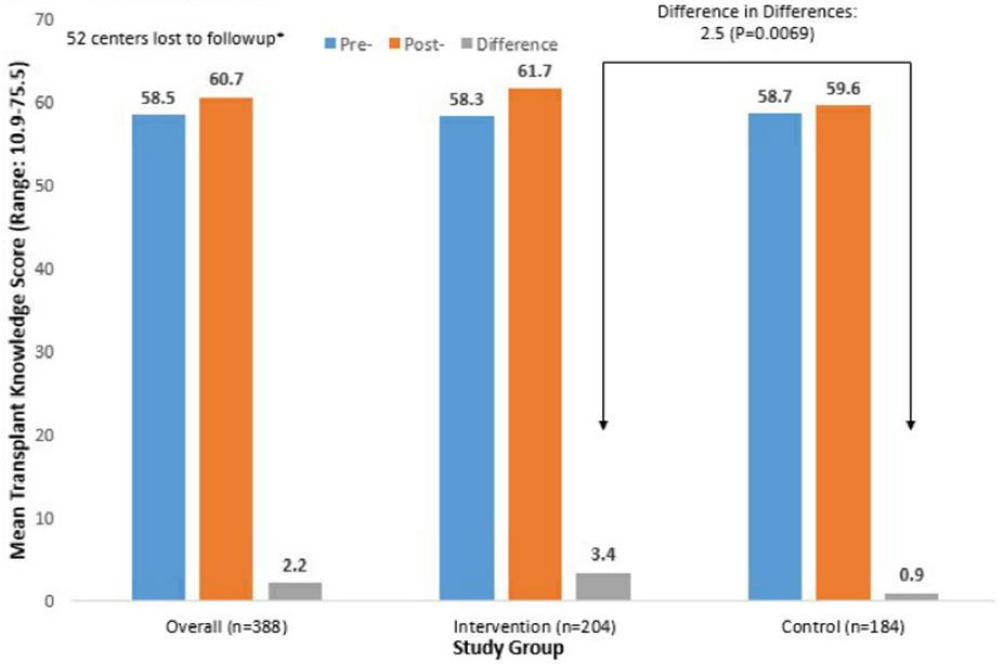
KTx referral and evaluation in the Southeast (Georgia, North Carolina, South Carolina). We describe the effect of the RaDIANT Regional intervention on KTx knowledge among dialysis facility providers.

Methods: From January - September 2018, we 1:1 randomized 440 dialysis facilities to receive the RaDIANT multicomponent intervention or standard improvement materials. Dialysis providers completed baseline and follow-up surveys containing a validated 15-item Knowledge Assessment of Renal Transplantation (KART) scale measuring KTx knowledge. KART items were weighted (correct=2, incorrect=1, unsure=0) and converted to a T score (range 10.9-75.5). Generalized linear models and difference-in-difference analysis examine the effect of the RaDIANT intervention on KART scores pre- and post-intervention.

Results: The 440 participating facilities were 90.2% for-profit, with a mean of 13.5 Â± 7.1 staff and 68.1 Â± 40.1 patients per facility; facility characteristics did not meaningfully differ by group. Overall, KART scores increased by an average of 2.2 points (Â±9.2) post-intervention (Figure 1). Intervention providers had significantly higher KART score increases post-intervention compared to control providers (3.4 vs. 0.9, p=0.0069). The effect size was moderately small (Cohenâ€™s d=0.29).

Conclusions: The RaDIANT Regional multicomponent intervention is effective in improving dialysis facility provider KTx knowledge in the Southeast. Future work will examine if this increase in provider knowledge is associated with improved access to KTx.

Figure 1 Mean dialysis facility staff Knowledge Assessment of Renal Transplantation (KART) scores (*T*-score scaled range: 10.9 - 75.5) pre-intervention (January 2018), post-intervention (September 2018), and differences (pre- to post-intervention) according to the assigned study group in the 2018 RaDIANT Regional randomized pragmatic trial, 2018



10:15 AM

Category: Basic Science

#30 - A Trans-ventricular Reshaping Device to Reduce Left Ventricular Wall Stress Ameliorates Systolic Function in a Rodent Model of Chronic Ischemic Cardiomyopathy

Daisuke Onohara MD PhD, Daniella Corporan BS, Takanori Kono MD PhD, Roberto Hernandez-Merlo DVM, Robert A. Guyton MD, Muralidhar Padala PhD

Introduction: Elevated wall stress (WS) from ventricular dilatation and wall thinning is a hallmark of left ventricular (LV) remodeling towards heart failure after a myocardial infarction. Reducing WS by reshapingthe LV could halts adverse remodeling. In this study, we sought to investigate if a trans-ventricular reshaping device (TRD-Fig A1, A2) can preserve cardiac function in anMI rodent model.

Hypothesis: Reducing WScan preserve cardiac function and inhibit LV remodeling in ischemic cardiomyopathy. Methods:Thirty-eight rats were induced with an MI by left coronary ligation. At 3 weeks after an MI, theTRDwas implantedon a beating heart in 19 rats (MI+TRD) (Fig A3-5) and no surgery in others (n=19, MI only).All the rats were followedwith biweekly echo, and invasive hemodynamicswere acquired at 6 and 12 weeks. Results: TRD implantation was successful in all the rats in MI+TRD group, with a 26.6% immediate reduction in LVIDand a30.5% reduction in sphericity index(Fig B1, B2).At12weeks post-MI, EDV and ESV were significantly reduced in MI+TRD compared to MI only(EDV: 624.2±22.2µlvs 534.6±25.0µl; p=0.0155; 355.2±20.9µlvs 247.1±23.0µl; p=0.0027), indicative of halted adverse remodeling with the TRD. LVwall thickness was preserved in MI+TRD, but significantly thinned in MI, indicating containment of infarct expansion.Pre-load adjusted LV dP/dt maxand ESPVRweresignificantly higher in MI+TRD group (Figure B3-8).

Conclusion: Left ventricular reshaping with a trans-ventricular device can improve cardiac contractile function in this rodent model of ischemic cardiomyopathy.

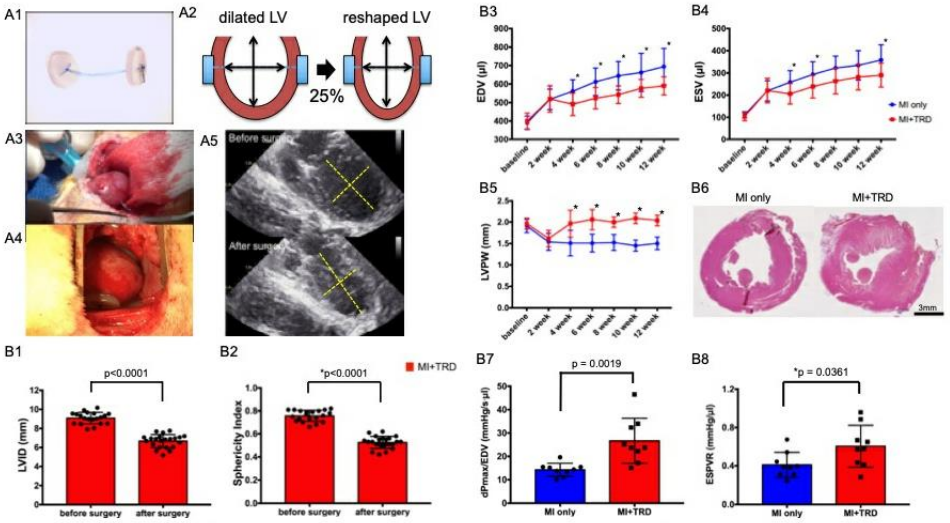


Figure: (A1) Photograph of the TRD device including two silicone pads; (A2) TRD device shorten LV dimension; (A3, A4) Pictures showed how to implant the TRD device on beating heart; (A5) Sphericity index was measured by TEE during surgery; (B1, B2) LVID and sphericity index before and after TRD implantation at 3 weeks; (B3, B4) Temporal changes of EDV and ESV; (B5) Temporal changes of LV wall thickness; (B6) Representative H&E stain depicting higher thickness of the remote region in the MI+TRD group; (B7,B8) Pre-load adjusted LV dp/dt (max) and end-systolic pressure-volume relationship at 12 weeks, indicators of systolic function

10:25 AM

Category: Clinical Science

#10 - Lung Surveillance Strategy for High-Grade Soft Tissue Sarcomas: CT Scan or Chest X-ray?

Joyce Kim, Mohua Basu, Laura Plantinga, Stephen Pastan, Cam Escoffery, Rachel E. Patzer

Background: Given the propensity for lung metastases (LM), NCCN guidelines recommend lung surveillance with either computed tomography (CT) or chest x-ray (CXR) in pts with high-grade soft tissue sarcoma (STS). Considering survival, diagnostic sensitivity and cost, the optimal modality is unknown.

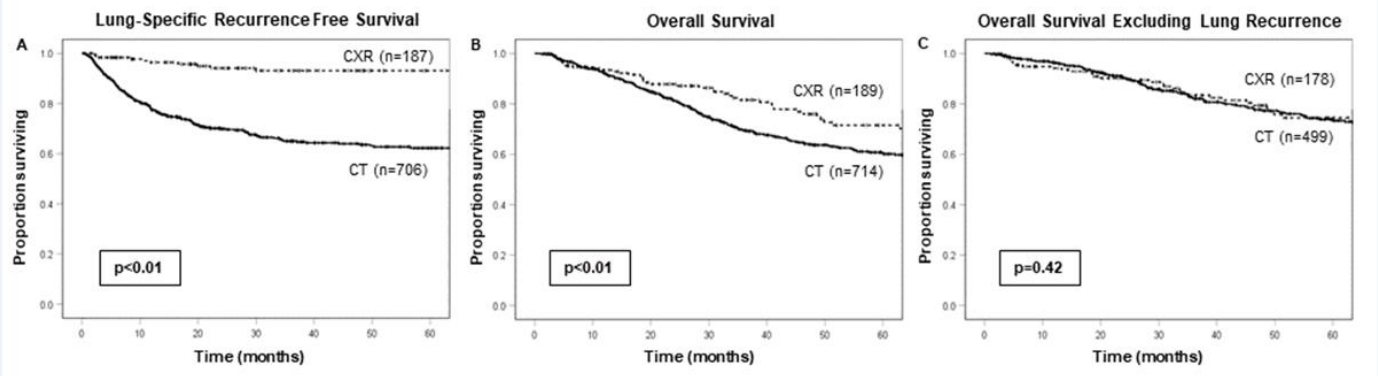
Methods: The US Sarcoma Collaborative database (2000-2016) was reviewed for pts who underwent resection of a primary high-grade STS. Primary outcomes were lung recurrence-free survival (L-RFS) and overall survival (OS). Cost analysis for each modality based on 2017 Medicare Physician Fee Schedule was performed.

Results: Of 968pts identified, 83% had truncal/extremity and 17% had retroperitoneal (RPS) tumors. Recurrence at any site occurred in 48% of which 52% were in the lung. Lung surveillance was performed with CT in 80% and CXR in 20%. Both groups were similar for baseline demographics although CT pts had more RPS and recurrences. Regardless of imaging modality, 85-90% of LM were detected within the first 2yrs of surveillance and both groups had a similar reintervention rate (p=0.77). LM was associated with decreased OS (HR:3.91; 95%CI 3.11-4.92; p<0.01).

CT patients had a decreased 5yr L-RFS (62 vs 93%, p<0.01; Fig1A) and 5yr OS (60 vs 71%, p<0.01; Fig1B). However, when considering age, tumor size, location, margin status, receipt of radiation, and presence of LM, CXR was not associated with worse OS (HR:1.01; 95%CI 0.71-1.4; p=0.97). Furthermore, when analyzing pts in whom no LM was detected, both imaging cohorts had a similar OS (73 vs 74%, p=0.42; Fig1C), suggesting equivalent diagnostic sensitivity.

When adhering to a guideline-specified surveillance protocol for a projected 4,406 cases in 2018, lung surveillance for initial 5yrs would cost $314/pt in a CXR vs $2,579/pt in a CT protocol, with a potential savings of $6M/yr to the US healthcare system.

Conclusion: In this large multicenter study, when considering adverse clinicopathologic factors, utilizing CXR for lung surveillance of high-grade STS was not associated with decreased OS. Considering a potential cost savings of 88%/pt, a CXR-based protocol may optimize resource utilization for lung surveillance in pts with high-grade STS.



10:35 AM

Category: Basic Science

#40 - IFNAR Signaling Augments Plasmacytoid Dendritic Cell Activation During Costimulation Independent Rejection

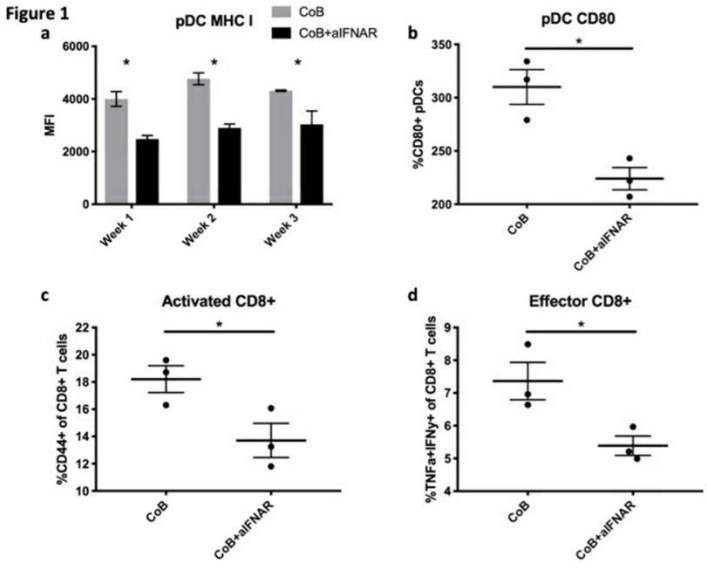
Jakob Habib, Dave Mathews, Ying Dong, Allison Stephenson, Abheek Ghosh, Cindy Breeden, Andrew Adams

Purpose: Costimulation blockade (CoB) is a promising new transplant immunosuppression strategy offering improved long-term patient and allograft survival without the nephrotoxicity of calcineurin inhibitors. However, increased risks of acute rejection have impeded widespread adoption of CoB. Type I interferons (IFN), produced mainly by plasmacytoid dendritic cells (pDCs), induce systemic inflammation that may prime the adaptive immune system for acute rejection. In this study, we examine the contribution of signaling through the type I IFN receptor (IFNAR) to CoB-resistant allograft rejection.

Methods: We performed fully MHC-mismatched skin grafts from BALB/cJ donors to C57BL/6 recipients. Mice were treated with CoB alone (250ug CTLA4-Ig+250ug anti-CD154 IP at day 0, 2, 4, 6) or in conjunction with anti-IFNAR (250ug). Mice were euthanized 1, 2 and 3 weeks post-transplant and the lymphocytes were analyzed by flow cytometry.

Results: Transplanted untreated mice rejected rapidly (MST=11 days), CoB treatment improved survival but resulted in CoB-independent rejection (MST=23d), and CoB+aIFNAR significantly improved survival (MST>60d). IFNAR was highly expressed on murine pDCs (PDCA1+SiglecH+B220+CD11b-) relative to conventional DCs and T cells. Combination treatment with CoB+anti-IFNAR significantly reduced MHC I expression on pDCs compared to CoB alone (Fig1a), and reduced CD80 expression on pDCs at the peak of rejection (Fig1b). CoB+anti-IFNAR also led to a reduction in activation (CD44+, Fig1c) and effector functions (IFNy+TNFa+, Fig1d) of CD8+ T cells compared to CoB alone.

Conclusions: These data suggest that signaling through IFNAR augments pDC activation and is associated with CD8+ T cell activation and effector functions in order to promote CoB-resistant rejection.



10:45 AM

Category: Clinical Science

#31 - Frailty in the Polytraumatized Patient: A Powerful Predictor of Mortality and Complications

Isaacson A, Staley C, Schenker M, Gelbard R

Introduction: The modified frailty index (mFI) can stratify the risk of mortality and morbidity in many surgical specialties, particularly in geriatric patients. There is limited data demonstrating the predictive utility of mFI in younger patients, including severely injured trauma patients. The purpose of this study is to evaluate the role of mFI in predicting 30-day morbidity and mortality in the polytraumatized patient.

Methods: The 2014 NTDB database identified patients aged 18-89 who presented with an injury severity score (ISS) >15. For each patient, a previously validated mFI score was calculated using 11 NTDB variables. The relationship between mFI and 30-day morbidity and mortality was examined.

Results: 110,459 patients were included. Of these, 69.9% were men and the mean age was 51.2 years (SD 20.9). mFI ranged from 0/11 (0) to 7/11 (0.64). Mortality (10.3% to 20.6%), unplanned intubation (1.8% to 11.2%), and both planned (67.5% to 84.0%) and unplanned (1.5% to 3.4%) ICU admission increased with increasing mFI score ($p<0.001$). The rate of any complications increased from 36.4% to 38.8%, and the rate of Clavien-Dindo grade IV (life threatening) complications increased from 7.5% to 17.8% ($p<0.001$). mFI remained a statistically significant predictor of mortality in the multivariate model (aOR for mFI 0.36+: 2.9, 95% CI: 1.6-5.0) compared to age (aOR 1.03, 95% CI: 1.03-1.04) and ISS (aOR 1.05, 05% CI: 1.05-1.06) ($p<0.001$).

Conclusions: mFI is a significant predictor of morbidity and mortality in the polytraumatized population. These findings can communicate risk, and help direct structured, interdisciplinary care pathways following trauma.

Table 1. Outcomes associated with mild (0/11, 0.0) mFI vs. Severe (3+/11, 0.27+) mFI

	Overall (n= 67,117)			Head (n= 39,493)			Face (n= 27,151)			Thorax (n= 34,886)			Abdomen & Pelvis (n= 20,489)			Spine (n= 22,235)		
Outcome	%	OR 95% CI	P value	%	OR 95% CI	P value	%	OR 95% CI	P value	%	OR 95% CI	P value	%	OR 95% CI	P value	%	OR 95% CI	P value
Mortality																		
Mild	10.4	-	-	13.4	-	-	10.2	-	-	9.0	-	-	9.9	-	-	8.1	-	-
Severe	18.1	1.9 (1.6-2.2)	<0.001	18.3	1.7 (1.5-2.1)	<0.001	17.7	2.1 (1.7-2.8)	<0.001	17.2	2.6 (2.0-3.4)	<0.001	18.6	2.3 (1.5-3.3)	<0.001	17.2	2.3 (1.7-3.1)	<0.001
Any comp.																		
Mild	36.4	-	-	36.2	-	-	36.6	-	-	62.5	-	-	40.6	-	-	40.3	-	-
Severe	38.6	1.2 (1.1-1.3)	0.001	36.2	1.2 (1.1-1.3)	0.003	39.4	1.2 (1.1-1.4)	0.005	52.3	1.4 (1.2-1.7)	<0.001	49.8	1.3 (1.0-1.7)	0.026	48.1	1.3 (1.1-1.6)	0.003
Clavien IV																		
Mild	7.2	-	-	6.6	-	-	6.7	-	-	8.3	-	-	9.9	-	-	9.2	-	-
Severe	12.2	1.9 (1.7-2.2)	<0.001	9.9	1.9 (1.6-2.2)	<0.001	11.9	2.0 (1.6-2.5)	<0.001	19.6	2.3 (1.9-2.8)	<0.001	19.3	1.8 (1.3-2.4)	<0.001	17.4	2.0 (1.5-2.5)	<0.001
U/p intubation																		
Mild	1.9	-	-	1.8	-	-	1.8	-	-	2.2	-	-	2.1	-	-	2.6	-	-
Severe	4.7	2.1 (1.7-2.6)	<0.001	3.7	1.8 (1.4-2.4)	<0.001	4.5	2.0 (1.4-2.9)	<0.001	7.8	2.6 (1.9-3.5)	<0.001	8.4	2.7 (1.7-4.1)	<0.001	7.0	2.1 (1.5-3.0)	<0.001
U/p reoperation																		
Mild	1.3	-	-	1.1	-	-	1.1	-	-	1.4	-	-	2.3	-	-	1.4	-	-
Severe	0.7	0.9 (0.6-1.5)	0.899	0.7	0.8 (0.5-1.5)	0.518	0.5	0.9 (0.4-1.9)	0.704	0.9	0.9 (0.4-2.1)	0.875	1.7	0.9 (0.4-2.2)	0.882	1.3	1.3 (0.6-2.7)	0.557
U/p ICU																		
Mild	1.6	-	-	1.4	-	-	1.5	-	-	1.7	-	-	2.0	-	-	2.1	-	-
Severe	3.2	1.4 (1.1-1.9)	0.008	2.7	1.4 (1.0-2.0)	0.034	3.2	1.5 (1.0-2.3)	0.077	4.3	1.6 (1.1-2.4)	0.024	3.2	1.2 (0.6-2.4)	0.511	4.2	1.4 (0.9-2.2)	0.152
ICU admission																		
Mild	70.8	-	-	74.8	-	-	73.2	-	-	69.9	-	-	75.4	-	-	73.2	-	-
Severe	74.2	1.1 (1.0-1.3)	0.037	74.7	1.1 (0.9-1.2)	0.415	75.6	1.2 (1.0-1.4)	0.124	78.0	1.5 (1.3-1.9)	<0.001	80.9	1.2 (0.9-1.7)	0.231	78.1	1.4 (1.1-1.7)	0.005
Vent Supp																		
Mild	40.1	-	-	44.4	-	-	43.6	-	-	41.0	-	-	44.1	-	-	41.7	-	-
Severe	33.0	1.3 (1.1-1.4)	<0.001	30.9	1.2 (1.0-1.4)	0.023	32.9	1.3 (1.0-1.6)	0.016	41.7	1.7 (1.4-2.0)	<0.001	47.9	1.7 (1.2-2.2)	0.001	39.8	1.3 (1.1-1.6)	0.015
DVT																		
Mild	2.6	-	-	2.4	-	-	2.7	-	-	2.9	-	-	3.4	-	-	3.6	-	-
Severe	2.3	0.9 (0.7-1.3)	0.694	2.1	1.1 (0.8-1.5)	0.715	2.2	1.1 (0.7-1.7)	0.704	3.1	1.0 (0.6-1.5)	0.901	4.5	1.2 (0.7-2.1)	0.456	3.3	0.8 (0.5-1.2)	0.757
Infection																		
Mild	4.7	-	-	4.1	-	-	4.3	-	-	5.0	-	-	6.4	-	-	6.4	-	-
Severe	5.8	1.5 (1.2-1.8)	<0.001	5.1	1.5 (1.2-1.9)	0.001	6.2	1.5 (1.1-2.0)	0.020	6.6	1.0 (0.6-1.5)	0.901	7.8	1.4 (0.9-2.2)	0.142	8.7	1.4 (1.0-1.9)	0.045
Cardiac																		
Mild	2.1	-	-	1.9	-	-	1.8	-	-	2.5	-	-	3.0	-	-	2.4	-	-
Severe	4.1	2.6 (2.1-3.3)	<0.001	3.2	2.8 (2.0-3.8)	<0.001	4.5	2.7 (1.9-4.0)	<0.001	6.9	2.9 (2.1-4.0)	<0.001	7.4	2.3 (1.5-3.7)	<0.001	6.3	3.0 (2.1-4.2)	<0.001
Pulmonary																		
Mild	9.4	-	-	9.9	-	-	10.2	-	-	10.5	-	-	10.7	-	-	12.4	-	-
Severe	9.6	1.4 (1.2-1.6)	<0.001	8.0	1.5 (1.2-1.8)	<0.001	9.8	1.7 (1.3-2.2)	<0.001	16.0	1.8 (1.4-2.2)	<0.001	15.2	1.5 (1.1-2.1)	0.020	15.6	1.4 (1.1-1.9)	0.006
Renal																		
Mild	1.2	-	-	1.0	-	-	1.0	-	-	1.5	-	-	2.2	-	-	1.5	-	-
Severe	2.2	1.7 (1.2-2.4)	0.001	1.5	1.6 (1.0-2.5)	0.035	1.2	1.2 (0.6-2.3)	0.633	4.1	2.2 (1.5-3.4)	<0.001	4.3	1.3 (0.7-2.3)	0.483	3.2	1.7 (1.0-2.9)	0.050
Adverse D/c																		
Mild	53.6	-	-	56.6	-	-	54.0	-	-	51.8	-	-	50.9	-	-	62.0	-	-
Severe	80.1	2.3 (2.0-2.5)	<0.001	79.2	2.2 (2.0-2.5)	<0.001	79.3	2.2 (1.8-2.6)	<0.001	80.4	2.7 (2.2-3.3)	<0.001	81.4	2.5 (1.8-3.3)	<0.001	85.6	2.3 (1.8-2.8)	<0.001

	Upper Extremity (n= 24,513)			Lower Extremity (n= 25,620)			External Burns and other trauma (n= 8,598)			<50 (n= 41,303)			50-64 (n= 14,210)			≥65 (11,604)		
Outcome	%	OR 95% CI	P value	%	OR 95% CI	P value	%	OR 95% CI	P value	%	OR 95% CI	P value	%	OR 95% CI	P value	%	OR 95% CI	P value
Mortality																		
Mild	7.7	-	-	8.1	-	-	10.6	-	-	8.7	-	-	11.3	-	-	17.6	-	-
Severe	18.3	3.5 (2.6-4.7)	<0.001	17.7	3.2 (2.4-4.2)	<0.001	25.1	2.0 (1.2-3.2)	0.004	10.1	1.9 (0.8-4.7)	0.164	16.8	2.3 (1.6-3.1)	<0.001	18.8	1.7 (1.4-2.0)	<0.001
Any comp.																		
Mild	36.9	-	-	38.6	-	-	38.0	-	-	35.8	-	-	38.7	-	-	35.9	-	-
Severe	42.5	1.6 (1.3-1.9)	<0.001	45.8	1.4 (1.2-1.6)	<0.001	48.2	1.5 (1.1-2.0)	0.016	46.4	1.7 (1.2-2.5)	0.007	41.1	1.3 (1.1-1.5)	0.012	37.5	1.2 (1.0-1.3)	0.009
Clavien IV																		
Mild	7.4	-	-	8.2	-	-	8.3	-	-	6.6	-	-	8.5	-	-	8.1	-	-
Severe	14.8	2.5 (1.9-3.2)	<0.001	17.7	2.4 (1.9-3.0)	<0.001	18.3	2.0 (1.4-2.9)	<0.001	16.1	2.6 (1.5-4.4)	<0.001	15.5	2.5 (1.9-3.2)	<0.001	11.2	1.7 (1.4-2.1)	<0.001
U/p intubation																		
Mild	1.9	-	-	1.9	-	-	1.9	-	-	1.5	-	-	2.6	-	-	2.6	-	-
Severe	6.2	2.9 (2.0-4.2)	<0.001	7.1	2.9 (2.0-4.1)	<0.001	7.0	2.1 (1.1-3.7)	0.017	8.3	4.5 (2.2-9.1)	<0.001	5.2	2.8 (1.9-4.1)	<0.001	4.3	1.8 (1.4-2.5)	<0.001
U/p reoperation																		
Mild	1.3	-	-	1.5	-	-	1.2	-	-	1.5	-	-	1.2	-	-	0.7	-	-
Severe	0.7	1.1 (0.4-2.7)	0.899	1.2	1.4 (0.7-2.8)	0.310	0.6	1.1 (0.2-4.7)	0.948	3.0	2.5 (0.9-7.3)	0.087	1.3	1.3 (0.6-2.7)	0.485	0.4	0.4 (0.2-1.0)	0.058
U/p ICU																		
Mild	1.6	-	-	1.7	-	-	1.5	-	-	1.3	-	-	2.1	-	-	1.9	-	-
Severe	2.8	1.6 (0.9-2.7)	0.080	4.2	1.9 (1.2-2.9)	0.009	3.4	1.9 (0.9-4.2)	0.101	2.4	1.5 (0.4-4.9)	0.552	2.7	1.4 (0.8-2.3)	0.246	3.3	1.3 (0.9-1.9)	0.111
ICU admission																		
Mild	69.9	-	-	69.8	-	-	70.5	-	-	70.9	-	-	70.2	-	-	70.9	-	-
Severe	75.4	1.4 (1.1-1.7)	0.002	73.5	1.2 (0.9-1.4)	0.152	78.5	1.4 (0.9-2.1)	0.099	73.2	1.0 (0.6-1.5)	0.921	77.4	1.2 (0.9-1.5)	0.197	73.4	1.0 (0.9-1.2)	0.712
Vent Supp																		
Mild	39.6	-	-	40.8	-	-	42.4	-	-	42.3	-	-	37.7	-	-	32.9	-	-
Severe	35.0	1.6 (1.3-2.1)	<0.001	37.1	1.5 (1.2-1.9)	<0.001	46.3	1.3 (0.9-1.9)	0.173	39.9	1.4 (0.8-2.2)	0.235	42.7	1.7 (1.4-2.2)	<0.001	30.1	1.2 (1.0-1.4)	0.082
DVT																		
Mild	2.9	-	-	3.4	-	-	2.7	-	-	2.6	-	-	2.8	-	-	2.1	-	-
Severe	2.6	0.9 (0.5-1.5)	0.613	3.0	0.8 (0.5-1.3)	0.367	1.4	0.7 (0.3-2.1)	0.563	4.8	1.2 (0.5-3.2)	0.725	3.1	1.0 (0.6-1.8)	0.870	1.9	0.9 (0.6-1.4)	0.752
Infection																		
Mild	5.0	-	-	5.8	-	-	5.0	-	-	4.7	-	-	4.8	-	-	4.4	-	-
Severe	5.7	1.3 (0.9-1.8)	0.253	7.2	1.4 (1.0-1.9)	0.063	6.5	1.0 (0.5-2.0)	0.966	6.5	1.3 (0.6-2.9)	0.572	5.5	1.2 (0.8-1.7)	0.443	5.8	1.4 (1.1-1.8)	0.006
Cardiac																		
Mild	2.1	-	-	2.2	-	-	2.3	-	-	1.9	-	-	2.3	-	-	2.7	-	-
Severe	5.7	3.6 (2.4-5.4)	<0.001	6.2	3.1 (2.1-4.6)	<0.001	5.9	2.4 (1.3-4.6)	0.008	5.4	4.5 (2.1-9.8)	<0.001	4.9	2.9 (1.9-4.5)	<0.001	3.8	2.4 (1.8-3.3)	<0.001
Pulmonary																		
Mild	9.9	-	-	10.0	-	-	11.2	-	-	9.6	-	-	10.4	-	-	7.1	-	-
Severe	11.4	1.8 (1.3-2.3)	<0.001	12.5	1.7 (1.3-2.2)	<0.001	15.5	1.6 (1.0-2.5)	0.041	10.7	0.9 (0.4-1.7)	0.851	13.5	1.6 (1.2-2.1)	0.001	8.5	1.5 (1.2-1.8)	0.001
Renal																		
Mild	1.4	-	-	1.6	-	-	1.7	-	-	1.1	-	-	1.4	-	-	1.4	-	-
Severe	2.0	1.6 (0.9-2.8)	0.137	2.8	1.2 (0.7-2.1)	0.419	5.9	3.0 (1.5-5.8)	0.001	4.8	4.6 (1.9-11.2)	0.001	3.2	2.0 (1.1-3.4)	0.018	1.8	1.5 (1.0-2.4)	0.078
Adverse D/c																		
Mild	52.6	-	-	59.9	-	-	56.8	-	-	48.1	-	-	57.9	-	-	73.8	-	-
Severe	82.6	2.8 (2.3-3.5)	<0.001	86.0	2.3 (1.8-2.9)	<0.001	83.9	2.4 (1.6-3.5)	<0.001	58.9	1.6 (1.1-2.4)	0.019	73.3	2.1 (1.7-2.6)	<0.001	83.0	2.0 (1.7-2.3)	<0.001

U/p, unplanned; Any Comp, any complication; Vent supp, ventilator support; DVT, deep vein thrombosis; Adverse D/c, adverse discharge (not home)

POSTER PRESENTATIONS

In order by category and poster number

Basic Science

#9- NADPH oxidases 4 inhibition using a hyaluronic acid nanoparticle drug delivery system sensitized therapeutic response to chemo- and radiotherapy in drug resistant breast cancer

Lei Zhu, Yi Zhao, Wei Ping Qian, Dazhi Wang, Binghua Jiang, and Lily Yang

Objectives: Resistance to therapy is the unmet challenge in management of breast cancer. To improve the therapeutic efficacy, we have developed a hyaluronic acid nanoparticle (HANP) carrying a NOX4 inhibitor and examined the anti-tumor effect in combination with radiotherapy (RT) or chemotherapy.

Methods: Biodegradable HANP was synthesized and encapsulated with GKT831 (HANP/GKT831), a NOX4 inhibitor. Targeted delivery of GKT831 with HANP was studied by optical imaging in a human breast cancer patient tissue derived xenograft (PDX) model. The ability of HANP/GKT831 in inhibition of tumor cells and sensitization of tumor cells to chemotherapy and RT was evaluated in breast PDX models following intravenous administration of HANP/GKT831 (5 mg/kg equivalent dose of GKT831) in combination with Doxorubicin (DOX, 5 mg/kg) and RT (2 Gy) for 5 times, once per week. Mechanism of NOX4 inhibition on improving therapeutic response in breast cancer was investigated.

Results: The accumulation of HANP/GKT831 in breast PDX tumors was demonstrated by optical imaging. Nude mice bearing breast PDX tumors that received HANP/GKT831 in combination with DOX or RT had significant stronger tumor growth inhibition compared with either DOX or RT alone (73.71Â±13.87% and 79.33Â±19%, respectively). Examination of tumor tissues revealed that the level of poly (ADP-ribose) polymerase (PARP) expression was reduced in tumors treated with HANP/GKT831 in combination of RT or DOX.

Conclusions: HANP/GKT831 is a promising therapy agent for targeted therapy of breast cancer. One of the possible mechanisms is the downregulation of DNA-damage repairing functions, such as downregulation of PARP.).

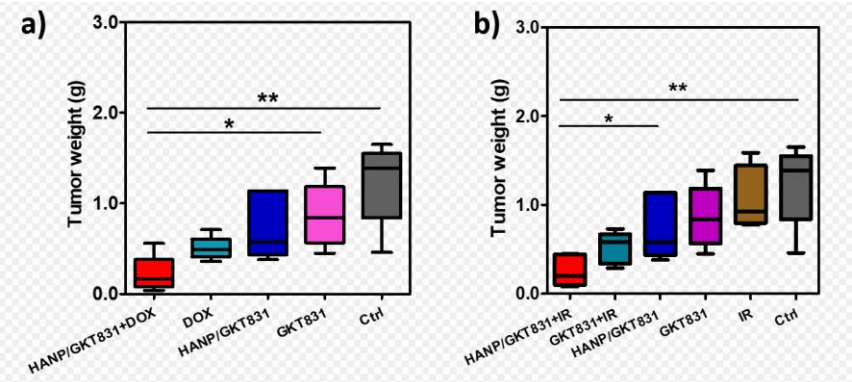


Figure 1. Inhibition of NOX4 with HANP/GKT831 improves the radiotherapy (a) and chemotherapy (b) efficacy of breast cancer in PDX model.

Basic Science

#16- In vitro and In vivo Assessment of an Electrospun Nanofiber Coated Decellularized Bovine Pericardium as a Regenerative Valve Substitute vs. Glutaraldehyde Fixed Pericardium

Jahnavi Mudigonda, Dongyang Xu, Vivian Wang, Muralidhar Padala

OBJECTIVE: Decellularized bovine pericardium(DBP) fixed with glutaraldehyde(GA) is the current standard of choice, for valve tissue reconstructions in children. DBP-GA cannot regenerate with the child, and often precipitates calcium leading to structural degeneration. Replacing GA with a biodegradable polymeric nanofiber mesh(NM) was attempted in this study, and the mechanical strength and regenerative potential of such a DBPNM was investigated.

METHODS: N=10 DBPs were prepared using 1% deoxycholic acid, and acellularity was confirmed. Part of the DBP was stored unprocessed, and the rest layered with 10:1 polycaprolactone chitosan nanofiber mesh (NF). DBP-NF interactions were assessed with scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), & x-ray photon spectroscopy (XPS). Uniaxial and biaxial mechanical testing were performed. Cells were cultured on both fresh BP and NF layered DBP and tested in blood flow loops, followed by rodent implants. RESULTS: Fig A shows a prototype with NF layer and DBP, with the corresponding SEM showing the two layers. Fig B depicts XPS and FTIR data, demonstrating formation of new functional groups between the NF and DBP. Fig C & D summarize uniaxial and biaxial mechanical testing data demonstrating significant increase in ultimate tensile extensibility of the DBP-NF, with strength equivalent to human valve tissue. Fig E demonstrates cellular viability after 48 hours of culture on the DBP-NF, and Fig F depicts very low platelet adhesion to the DBP-NF.

CONCLUSIONS: Replacing glutaraldehyde fixation with a nanofiber mesh can yield good mechanical strength and enable regeneration, providing a potential cardiovascular tissue substitute for children.

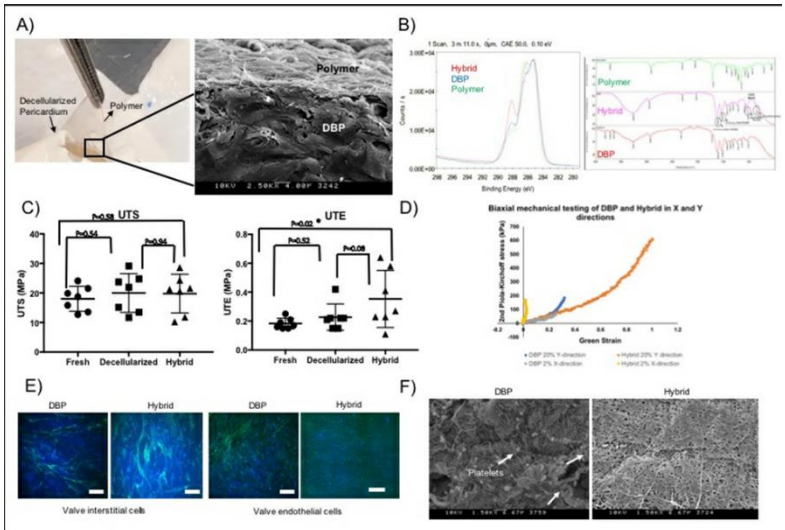


Figure: Functional, mechanical and biological properties of DBP and hybrid scaffolds. **A)** Photograph and scanning electron microscopic image of hybrid scaffold showing layer of polymer adhered to the decellularized bovine pericardium (DBP), **B)** Functional characterization of polymer, DBP and hybrid with X-ray photon spectroscopy (XPS) and Fourier transform infrared spectroscopy (FT-IR) showing carbon scanning and presence of new functional groups confirming the polymer adhesion to DBP, **C)** Uniaxial mechanical testing showing Ultimate tensile strength (UTS) and Ultimate tensile extensibility (UTE) for DBP and hybrid (n=10), **D)** Representative biaxial stress- strain curve of DBP and hybrid with 2% and 20% stretch in X and Y directions (only loading data is shown in the figure), **E)** Biocompatibility testing of DBP and hybrid using valve interstitial endothelial cells for 48 hrs on DBP and hybrid scaffolds and **F)** Hemocompatibility testing of DBP and hybrid showing platelet adhesion on the samples.

Basic Science

#21 - Undersized Mitral Annuloplasty Impairs Mechanics of the Left Ventricle in a Swine Model of Chronic Ischemic Mitral Regurgitation

Dongyang Xu MS, Eric L. Sarin MD, Weiwei Shi MD PhD, Kanika Kalra MD,

Objective: Undersized mitral annuloplasty (UMA), a mainstay in mitral valve repair, could alter left ventricular (LV) geometry and mechanics. In this study, we sought to quantify LV mechanics in pigs with ischemic mitral regurgitation (IMR) that underwent repair with UMA, compared against pigs repaired with papillary muscle approximation (PMA).

Methods: IMR was surgically introduced to 15 adult pigs, which underwent either UMA (n=9) or PMA (n=6) using standard cardiopulmonary bypass techniques. At 12-14 weeks post-surgery, cardiac MRI was performed to quantify LV mechanics, and images were post-processed with a custom software to compute LV wall thickening, radial velocity and myocardial strain (Figure 1A).

Results: Representative MRI images from UMA and PMA are shown in Figure 1B, with their corresponding 3D reconstructions with curvature data mapped onto them. Significant inward deformation of the posterior wall is observed in UMA, but not PMA. Myocardial radial velocity in diastole and systole is lower consistently in all regions of the basal and equatorial regions of the LV in the UMA group than the PMA group (Figure 1C). The average diastolic and systolic radial velocities in the UMA group were significantly lower than the PMA group (i.e. diastolic: basal lateral: -1.70Â±0.18 vs -2.64Â±0.40 cm/s, p=0.03*; equatorial anterior: -1.49Â±0.21 vs -2.30Â±0.27 cm/s, p=0.03*; systolic: basal posterior 2.06Â±0.21 vs 3.25Â±0.26 cm/s, p=0.0031**; equatorial posterior: 1.83Â±0.20 vs 2.63Â±0.11 cm/s, p=0.0098**)

Conclusion: In swine model of IMR, UMA reduces both diastolic relaxation and systolic contraction velocities at basal and equatorial levels in LV, compared with PMA.

Basic Science

#22 - FcÎ³RIIB is a novel CD8+ effector T cell intrinsic regulatory pathway that underlies freedom from rejection in renal transplant patients

Anna B. Morris, David F. Pinelli, Danya Liu, Jeremy M. Boss, Christopher D. Scharer, Miguel Fribourg, Paolo Cravedi, Peter S. Heeger, Mandy L. Ford*

Introduction: FcγRIIB is a cell-surface receptor that binds to the Fc portion of IgG and signals negatively, providing a mechanism by which endogenous antibody can modulate immune responses. FcγRIIB is the sole inhibitory Fcγ receptor and has been known to be expressed on B cells and myeloid cells. We recently discovered that FcγRIIB is upregulated on CD44hiCD62Llo effector CD8+ T cells. Here we aimed to elucidate the impact of T cell-expressed FcγRIIB on alloimmunity in mice and humans.

Methods and Results: To determine if FcγRIIB plays a cell-intrinsic role in inhibiting CD8+ T cells, we generated a CD8+ T cell conditional KO system and observed enhanced accumulation of FcγRIIB-/- CD8+ T cells post-transplant ($p<0.05$) relative to WT controls. RNAseq of donor-reactive CD8+ T cells revealed an enrichment of apoptosis-related genes in FcγRIIB+ vs. FcγRIIB- cells. Further, FcγRIIB-/- CD8+ cells

exhibited lower expression of active caspase 3/7 following transplant compared to WT cells (p=0.0315). We then interrogated gene expression profiles in renal transplant recipients enrolled in the CTOT09 study in which patients were weaned from tacrolimus immunosuppression. Results indicated that FcγRIIB was one of only 7 genes that were significantly upregulated in PBMC from patients that experienced freedom from rejection following tacrolimus withdrawal. CellCODE analysis revealed tighter associations of FcγRIIB with CD8+ T cell transcripts than with other immune cells.

Conclusions: Based on these experiments, we conclude that FcγRIIB is a novel, cell-intrinsic CD8+ T cell regulatory pathway that promotes apoptosis and that FcγRIIB on T cells may predict transplantation tolerance.

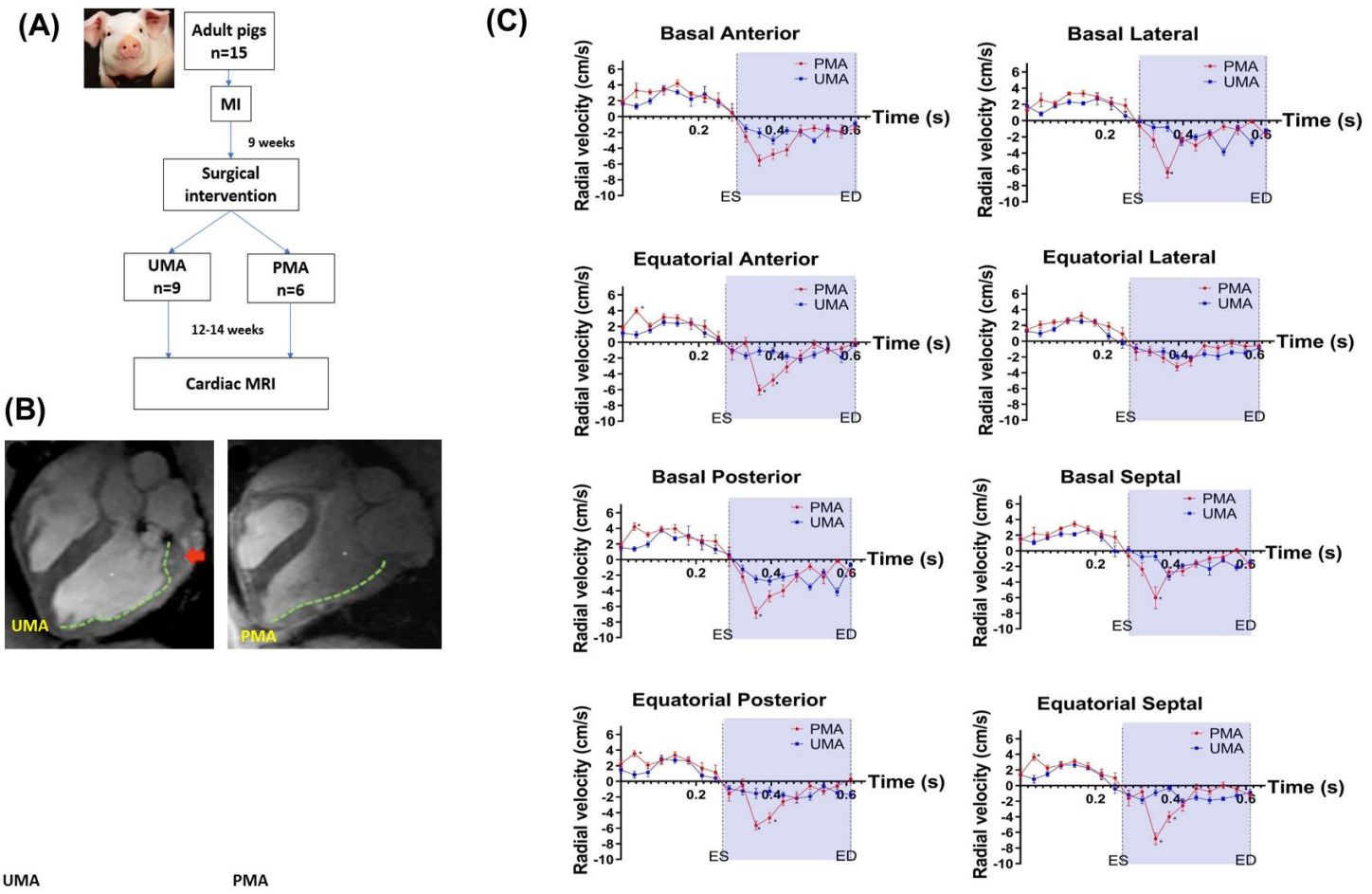


Figure 1 **(A)** Experimental design of the study; **(B)** Representative cardiac MRI images from the UMA and PMA groups, with a sample reconstructed LV depicting anterior, lateral, posterior and septal regions and curvature map on the surface; **(C)** Temporal radial velocity traces with the shaded part depicting diastole. The traces in each graph compare PMA and URA, and the different graphs compare these traces at different regions of the basal and equatorial LV regions. Generally, it is clearly evident that the radial velocity in the UMA group remains low consistently in all the regions, whereas the PMA group shows an early rapid relaxation and then gradual plateauing.

Basic Science

#23 - Transforming Growth Factor Î² (TGFÎ²) Induced Mitral Valve Interstitial Cell Activation and Phenotypic Shift Is Differentially Inhibited by a TGFÎ² Upstream Blocker (losartan) and a TGFÎ² Receptor Blocker (SB505124)

Alicja Sielicka, Alan Amedi, Muralidhar Padala

Introduction: Our recent work in a chronic swine model demonstrated that abnormal mechanical stresses imposed on the mitral valve after surgical repair, activates mitral valve interstitial cells (VICs) and leads to extensive valve fibrosis via the Transforming Growth Factor-beta (TGFβ) pathway. In this study, we sought to investigate if such pro-fibrotic remodelling in mitral valve leaflets via TGFβ mediated cellular activation, can be inhibited with a TGFβ receptor 1 blocker (SB505124), and compared to an AT1 receptor antagonist (Losartan) that acts upstream of TGFβ signalling.

Methods: Porcine mitral valves (N=3) were excised, washed and incubated in a collagenase solution to extract VICs. Cells were plated on collagen for 1, 7 or 12 days with or without TGFβ1, and with or without inhibition with Losartan/SB505124 (Fig A). Quiescent phenotype was evaluated as CD90+/αSMA-, whereas activated phenotype regarding a synthetic/fibrotic phenotype was assessed as CD90-/αSMA+, confirmed by western blotting and immunohistochemistry.

Results: Immunoblotting (Fig B) demonstrated increase in αSMA after treatment with TGFβ1 for 1,7 or 12 days with inhibition in presence of Losartan or SB505124. Immunofluorescence (Fig C) confirmed the immunoblotting results, and further demonstrated that TGFβ1 inhibitors not only reduced αSMA expression, but also restored a more spindle shaped cell structure that is representative of a quiescent phenotype.

Conclusion: TGFβ1 mediated VIC phenotypic shifts in the mitral valve that are implicated in post-surgical valve fibrosis, can be inhibited with Losartan or SB505124. Efficacy of these drugs in reducing mitral valve fibrosis needs to be further investigated.

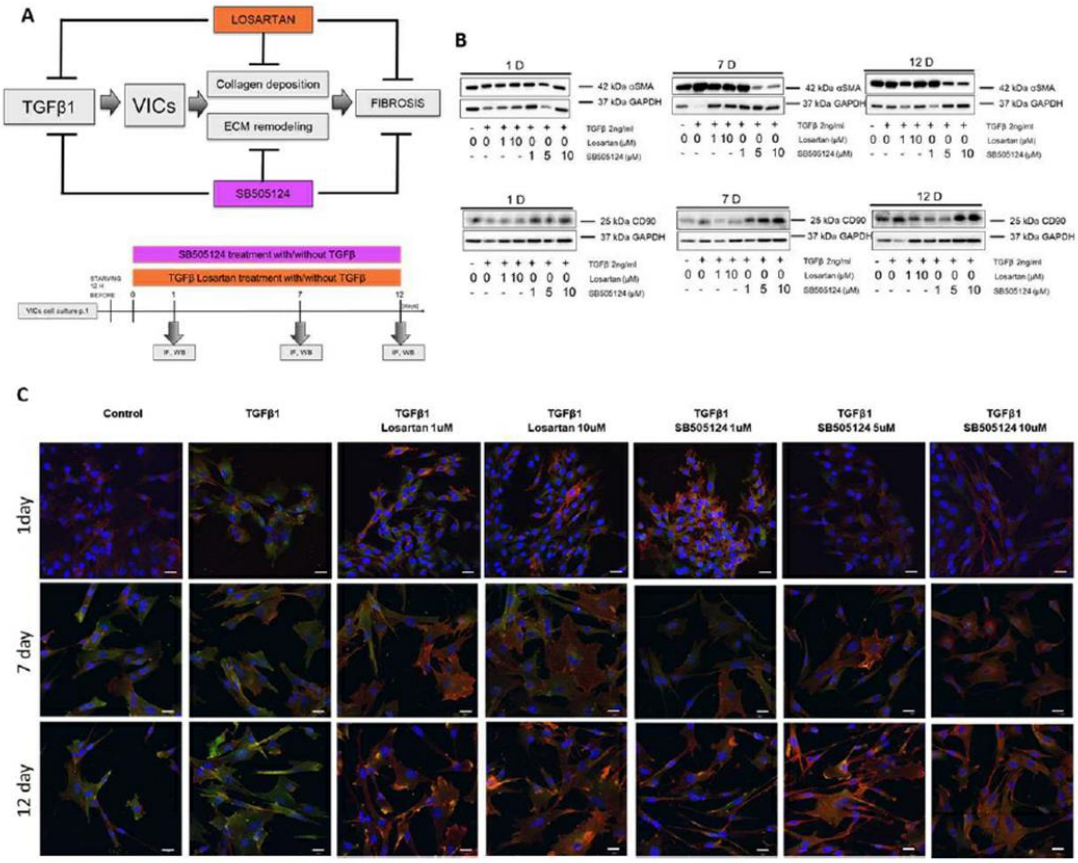


Figure A. Experimental design. **B.** Western blot data from 1, 7 and 12 day treatments present reduced αSMA expression in both Losartan and SB505124 groups but with robust reduction depend on timepoints in all groups. **C.** Immunofluorescence for CD90 (quiescent phenotype, red) and αSMA (activated phenotype, green) in VICs from different treatment groups, presenting high levels after TGFβ treatment, with partiall inhibition after Losartan and robust inhibition after SB505124 treatment.

Basic Science

#27 - Chronic Mitral Valve Regurgitation Alters Passive Mechanical Properties of the Left Ventricular Myocardium in a Rodent Model

Daniella Corporan, Vindhyasree Rapolu, Muralidhar Padala

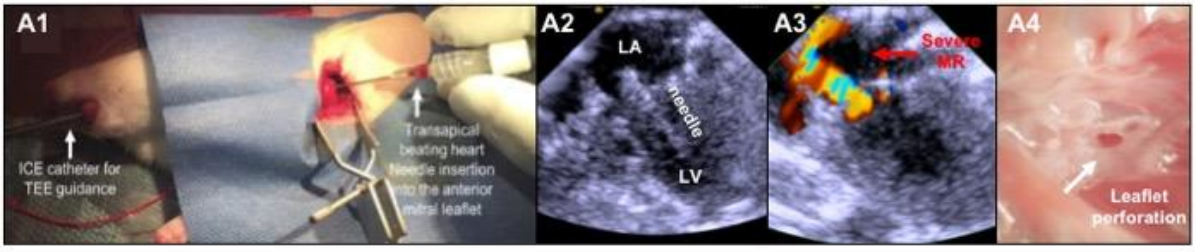
OBJECTIVE: Mitral regurgitation(MR) is a common valvular lesion, which imposes volume overload on the left ventricle(LV) and drives its remodeling. It is hypothesized that MR induces increase in LV compliance, followed by fibrosis and stiffening. In this study, we sought to develop a rodent model of MR and investigate changes in LV mechanical properties.

METHODS: 22 adult rats were assigned to two groups, severe MR(n=8) and sham surgery(n=14). MR was induced by piercing the anterior mitral leaflet with a 23G needle, on a beating heart with echo guidance(Fig.A1-4). In sham the needle was introduced and withdrawn, without any valve damage.

Some rats were survived to 2wks and others to 10wks, invasive pressure-volume loops were measured, and equibiaxial-mechanical testing was performed on the LV(Fig.C1).

RESULTS: Severe MR was induced in all MR rats. End diastolic volume(EDV) and end systolic volume(ESV) were significantly higher in the MR group at 10wks compared to sham($p<0.0001$,Fig.B). LV posterior wall was thinner compared to sham($p<0.01$,Fig.B). At 10wks, load-independent parameters of contractility showed decreased ESPVR slope($p<0.05$,Fig.B) and dP/dtmax-EDV($p<0.01$,Fig.B) compared to sham. Taug, indicating diastolic function, was increased compared to sham($p<0.01$,Fig.B). At 2wks, myocardial stiffness in the circumferential direction remained unchanged compared to sham(Fig.C2), but was increased in the longitudinal direction(Fig.C3). At 10wks, stiffness was increased in both directions compared to sham(Fig.C2-3).

CONCLUSIONS: In this rodent model of severe MR, LV was dilated and thinned by 10wks. Despite preserved LVEF, myocardial stiffness increased. These results highlight structural and mechanical alterations in the LV in response to MR.



B	End diastolic volume (uL)	End systolic volume (uL)	Ejection fraction (%)	LVPWT (mm)	ESPVR (mmHg/uL)	dP/dt_{max}-EDV (mmHg/s*uL)	EDPVR (mmHg/uL)	Tau_g (ms)
Sham 10wk	439.9 ± 30.9	147.6 ± 26.2	66.6 ± 4.4	1.8 ± 0.1	1.19 ± 0.15	29.7 ± 9.9	0.009 ± 0.001	9.03 ± 1.3
MR 10wk	711.2 ± 105.6****	252..7 ± 41.1****	64.4 ± 5.6	1.3 ± 0.3**	0.75 ± 0.19*	11.9 ± 4.1**	0.004 ± 0.002	14.5 ± 1.2**

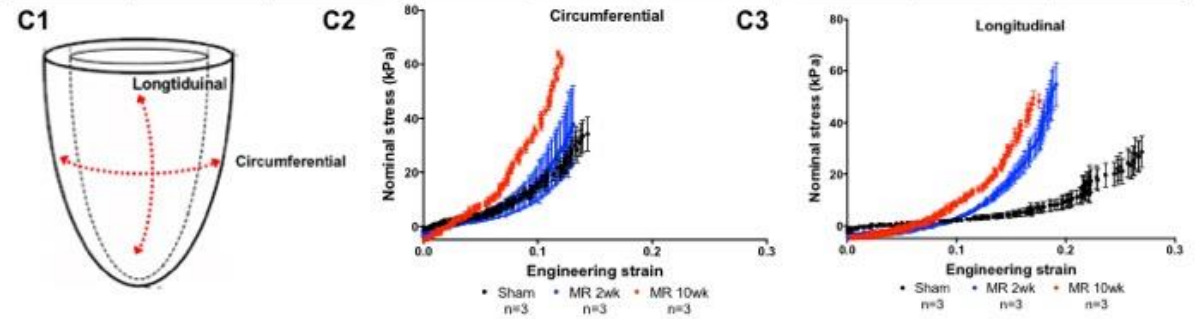


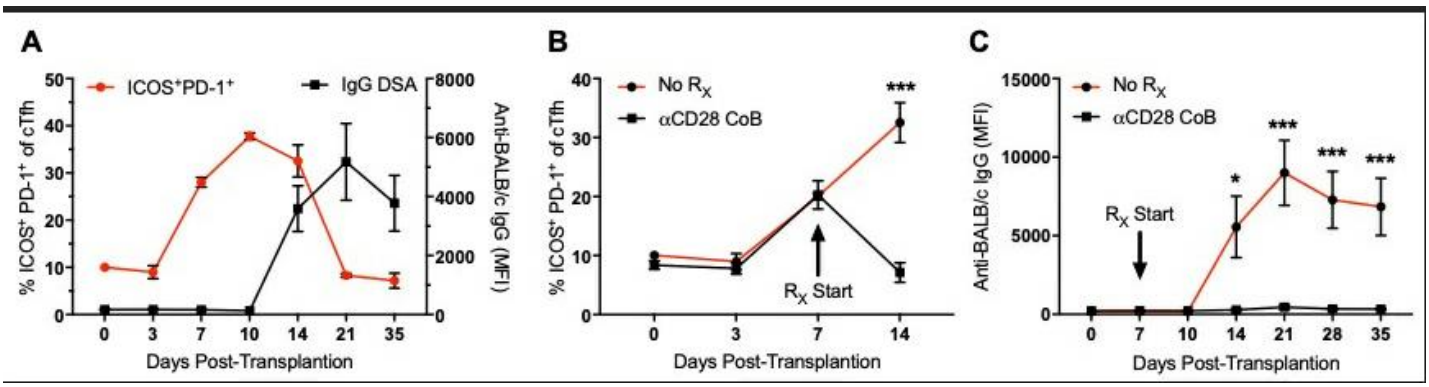
Figure: (A1) Needle insertion into the beating rat heart to create MR with echocardiography guidance; **(A2)** Needle piercing the mitral leaflet on echo; **(A3)** Severe MR on Doppler; (A4) Confirmation of leaflet perforation; **(B)** Changes in end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), left ventricular posterior wall thickness (LVPWT), end-systolic pressure volume relationship (ESPVR) slope, dP/dt_{max}-EDV, end-diastolic pressure volume relationship (EDPVR) slope, and Tau_g. Data is shown as mean ± SD. *p<0.05, **p<0.01, ****p<0.0001. **(C1)** Schematic of equibiaxial mechanical testing on LV free wall myocardium stretched in the circumferential and longitudinal directions. **(C2-C3)** Stress strain curves in the circumferential and longitudinal directions for sham (black), MR 2wk (blue) and MR 10wk (red) tissue. Error bars represent SEM.

Basic Science

#33 - ICOS+PD-1+ Circulating T Follicular Helper Cells Are a Biomarker of Humoral Alloreactivity and Predict Donor-Specific Antibody Generation Following Transplantation

G. Michael La, Muraglia II, Maylene E Wagener, Mandy L Ford, I. Raul Badell

Mounting evidence in kidney transplantation suggests that donor-specific antibodies (DSA) contribute to allograft loss. However, biomarkers to guide clinical management of DSA post-transplant through the detection of humoral alloimmune responses before pathologic alloantibodies develop are not available. Circulating T follicular helper (Tfh) cells are CD4+CXCR5+ Tfh-like cells in the blood that correlate with humoral immune responses, but little is known about them in transplantation. Here, we utilized full MHC mismatch and minor antigen (OVA) mismatch murine skin transplant models to determine the relationship between both polyclonal-endogenous and antigen-specific circulating Tfh (cTfh) cells, graft-draining lymph node germinal center (GC) reactivity and DSA formation. Donor-reactive CD4+CXCR5+ T cells phenotypically and functionally similar to Tfh cells expanded in the blood of skin-grafted mice post-transplantation. cTfh cell kinetics and phenotypic differentiation temporally correlated with GC alloreactivity, and the emergence of an effector-like ICOS+PD-1+ cTfh cell population preceded DSA generation (Fig.1A). Antecedent cTfh cell expansion and differentiation was not observed with selective CD28 CoB-mediated inhibition of GC reactivity and DSA formation. Conversely, cTfh cell activity was detected with less potent CoB (CTLA-4Ig) and preceded breakthrough GC reactivity and DSA. Interestingly, delayed selective CD28 CoB initiated after the detection of ICOS+PD-1+ cTfh cells in the blood post-transplant reversed the ongoing humoral alloresponse (Fig.1B) and prevented the development of DSA (Fig.1C). These findings provide experimental evidence that cTfh cells could serve as a clinical biomarker for nascent or ongoing humoral alloimmune responses prior to the detection of anti-donor antibodies and inform interventional therapeutic approaches to prevent DSA.



Basic Science

#38 - Claudin-2 Deletion Improves Gut Permeability and Decreases Mortality in Murine Sepsis

Takehiko Oami, Zhe Liang, Craig M. Coopersmith

Objective: Claudin-2 is a pore-forming tight junction (TJ) protein, predominantly expressed in the gut and upregulated during intestinal inflammation. Although intestinal hyperpermeability has been hypothesized to play a role in sepsis pathogenesis, the functional significance and specific mechanisms underlying gut barrier failure remain to be determined.

Methods: Wild-type (WT) and claudin-2 knockout (KO) mice underwent cecal ligation and puncture, a model of intraabdominal sepsis. Gut permeability was assayed with orally administered dyes of different size to assay the pore, leak and unrestricted pathways of permeability. Jejunal TJ, cytokines and histology were assayed. A separate group of mice was followed for survival.
Measurements and main results: Survival was markedly improved in KO mice (90% vs. 50%). Concentrations of Creatinine (6â„«), Fluorescein isothiocyanateâ€“dextran (28â„«), and Rhodamine B isothiocyanateâ€“dextran (120â„«) were all significantly decreased in KO mice at 24 and 48 hours. Protein expression of phospho-myosin light chain (leak pathway) was decreased. Claudin-4 was increased and claudin 12 was decreased (pore pathway) whereas no changes were detected in claudins 1, 3, 5, 7, 8, 13, or 15 in KO mice. Bacterial counts were lower in the peritoneal cavity of KO mice although there was no difference in systemic bacteremia. Crypt epithelial apoptosis was decreased in KO mice. Gene expression of IL6 and IL1B in jejunum were both decreased in KO mice.

Conclusions: Deletion of claudin-2 improved gut permeability and decreased mortality in sepsis, suggesting claudin-2 plays a protective role potentially through interaction with other TJ proteins and modulation of proinflammatory cytokines.providing critical proliferative signals for alloreactive T cells.

Clinical Science

#2 - Thirty-year experience in pediatric heart transplantation for the failing Fontan

Joshua M Rosenblum, Brendan Lovasik, Scott Gillespie, B Alsoufi, WT Mahle, KR Kanter

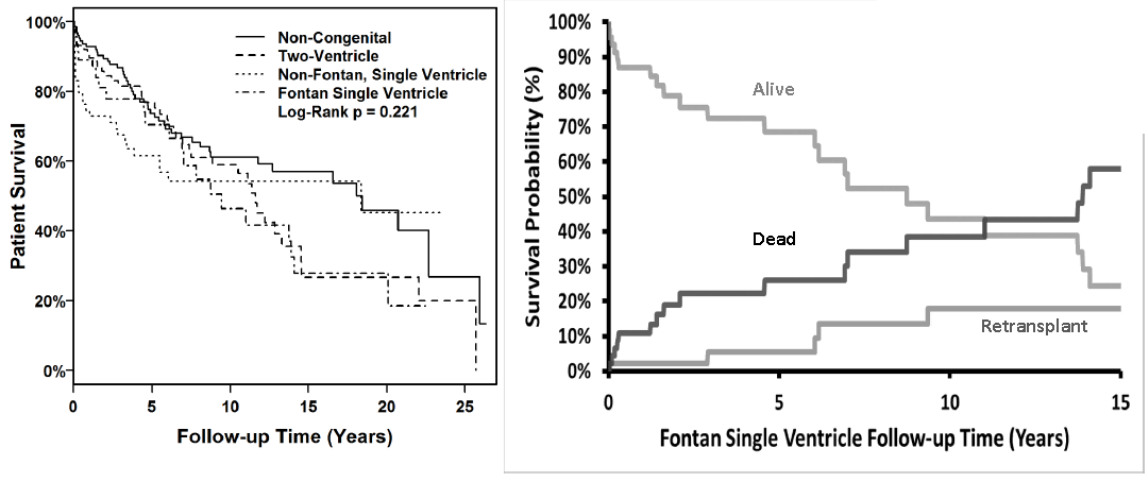
Objective: Total cavopulmonary connection (Fontan) is the final palliation for single-ventricle patients. Patients with failing Fontan may require heart transplantation, often with inferior outcomes compared with either non-Fontan or non-congenital recipients.

Methods: We reviewed 319 consecutive primary heart transplants (mean age 3.23y; IQR 2.69-3.88y) from 1/1988 to 5/2017. Underlying diagnosis was idiopathic cardiomyopathy (CM) in 126 (39.5%), two-ventricle physiology (2V) in 88 (27.6%), non-Fontan single ventricle (1V) in 59 (18.5%) , and Fontan in 46 (14.4%). Preoperative characteristics were similar between groups.

Results: Pretransplant mechanical ventilation was required in 16% of patients, and mechanical circulatory support in 11.3%. In the Fontan group, protein-losing enteropathy and plastic bronchitis were present in 11 patients (24%) and resolved in 9 (82%) of those patients after transplant. Bypass time and donor ischemia time were significantly longer in the Fontan group (mean 201min and 209min, respectively, $p<0.001$) compared to all other recipient groups. Thirty-day survival was excellent in the Fontan (97.8%) and CM groups (98.4%), but lower in the 2V (93.2%) and 1V (89.8%) groups. Median follow-up was 18.4y in the CM group, 11.6y in the 2V group, 18.4y in the 1V group, and 9.5y in the Fontan group. Survival

was similar among groups. In the Fontan group, competing risk analysis showed retransplant-free survival at 5, 10, and 15 years was 70%, 45%, and 25%.

Conclusion: Transplantation is a reasonable option for patients with a failing Fontan. We show similar long-term outcomes to congenital and non-congenital cardiomyopathy patients. the presence of LVI was found to be associated with multiple positive LNs (OR=8.374, p = 0.010).



Clinical Science

#6- A Novel Validated Recurrence Risk Score to Guide a Pragmatic Surveillance Strategy after Resection of Pancreatic Neuroendocrine Tumors: An International Study of 1006 Patients

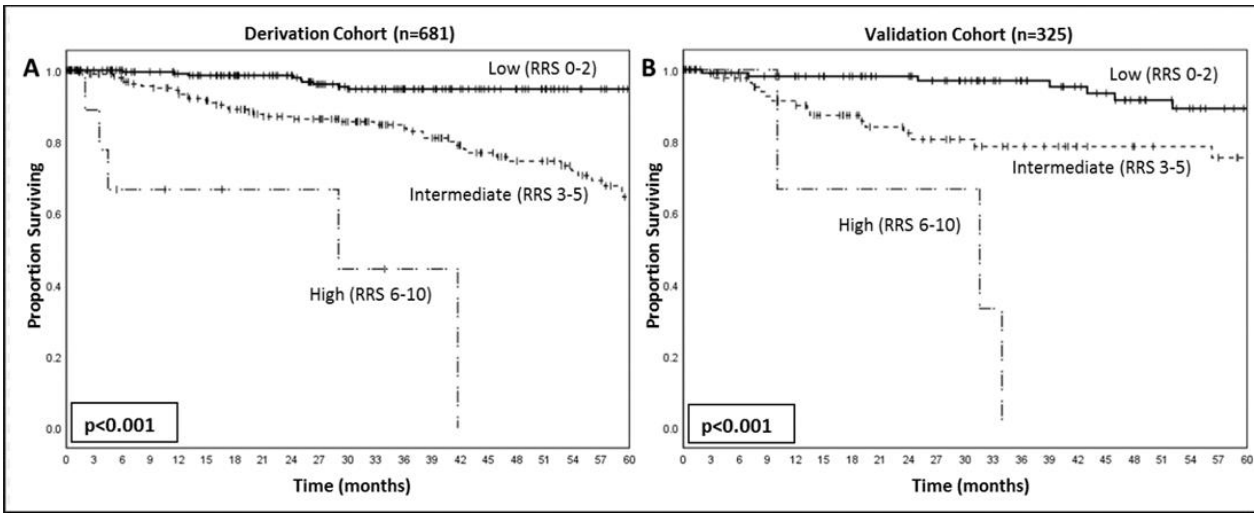
Mohammad Y. Zaidi, MD, MS; Alexandra G. Lopez-Aguiar, MD, MS; Valentina Andreasi, MD; Stefano Partelli, MD, PhD; George A. Poultsides, MD3; Mary Dillhoff, MD; Flavio G. Rocha, MD; Kamran Idrees, MD; Clifford S. Cho, MD; Sharon M. Weber, MD; Ryan C. Fields, MD; Charles A. Staley III, MD, Massimo Falconi, MD and Shishir K. Maithel, MD

Objective: Despite heterogeneous biology, similar surveillance schemas are utilized after resection of all pancreatic neuroendocrine tumors (PanNETs). Given concerns regarding excess radiation exposure and financial burden, our aim was to develop a prognostic score for disease-recurrence to guide individually-tailored surveillance strategies.

Methods: All patients with primary nonfunctioning, non-metastatic well/moderately-differentiated PanNETs who underwent curative-intent resection at 9-institutions from 2000-2016 were included (n=1006). A Recurrence Risk Score (RRS) was developed from a randomly-selected derivation-cohort comprised of 67% of patients and verified on the validation-cohort comprised of the remaining 33%.

Results: On multivariable analysis, patients within the derivation-cohort (n=681) with symptomatic tumors (jaundice, pain, bleeding), tumors>2cm, Ki67>3%, and LN(+) disease had increased recurrence. Each factor was assigned a score based on their weighted odds-ratio that formed a RRS of 0-10: symptomatic=1, tumor>2cm=2, Ki67 3-20%=1, Ki67>20%=6, LN(+)=1. Patients were grouped into Low (RRS=0-2; n=247), Intermediate (RRS=3-5; n=204), or High (RRS=6-10; n=9) risk groups. At 24mos, 33% of High RRS recurred, while only 2% of Low and 14% of Intermediate RRS recurred (Figure1A). This persisted in the validation-cohort (n=325;Figure1B).

Conclusion: This international, novel, internally-validated recurrence risk score accurately stratifies recurrence-free survival for patients with resected pancreatic neuroendocrine tumors. Given their unique recurrence patterns, surveillance intervals of 12-, 6-, and 3-months are proposed for Low, Intermediate, and High RRS patients, respectively, in order to minimize radiation exposure and optimize cost/resource utilization.



Clinical Science

#7 - Studying a Rare Disease Using Multi-Institutional Research Collaborations vs Big Data: Where Lies the Truth?

Koerner, C. Gillespie, T. Liu, Y. Sheng, X. Shaffer, V. Balch, G. Staley, C. Sullivan, P.

Background: Multi-institutional collaborations provide granularity lacking in epidemiologic datasets to enable in-depth study of rare diseases. For pts with superficial, high-grade soft tissue sarcomas (STS) of the trunk/extremity, the value of radiation therapy (RT) is not clear. We aimed to utilize the 7-institution US-Sarcoma-Collaborative (USSC) and the National Cancer Database (NCDB) to investigate this issue.

Study Design: All adult pts with superficial truncal/extremity high-grade STS who underwent primary curative-intent resection from 2000-2016 at USSC institutions or were included in the NCDB from 2004-2013 were analyzed. Propensity-score matching was performed. Endpoints were locoregional recurrence-free survival(LRFS), overall-survival(OS), and disease-specific survival(DSS).

Results: Of 4,153pts in the USSC, 169pts with superficial high-grade tumors underwent primary curative-intent resection, of whom 38% received RT. On multivariable Cox-regression analysis, RT was not associated with improved LRFS(p=0.56), OS(p=0.31), or DSS(p=0.20). On analysis of 51 propensity-score matched-pairs, RT was still not associated with increased LRFS, OS, or DSS. Analysis of 631 propensity-score matched-pairs in the NCDB demonstrated improved 5-yr OS associated with RT (80%vs70%;p=0.02). LRFS and DSS were not evaluable.

Conclusion: Granular data afforded by collaborative research enables in-depth analysis of patient outcomes. The NCDB, although powered with large numbers, cannot assess many relevant outcomes

(recurrence, DSS, or complications). In this study, the approaches yielded conflicting results. USSC data suggested no value of radiation while the NCDB demonstrated improved overall survival, contradicting all randomized-controlled trials in sarcoma. The pros/cons of either approach must be considered when applying results to clinical practice, and underscore the importance of randomized-controlled trials.

Clinical Science

#14- Creating geographic catchment areas for solid organ transplant centers

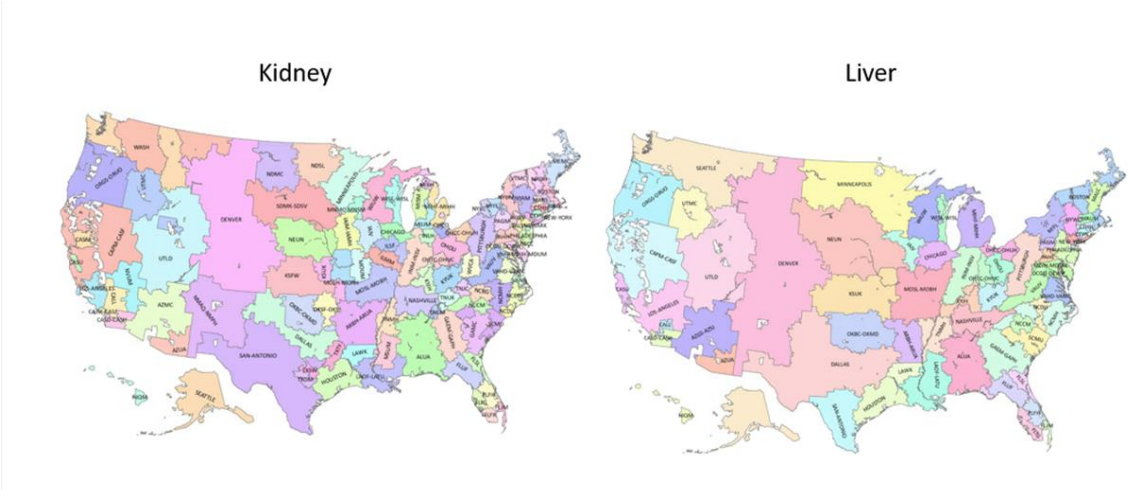
Katherine Ross, David Axelrod, Rachel Patzer

Purpose: There is a significant population of patients with end-stage organ disease who may benefit from transplant but lack access. Understanding how well transplant centers serve this population requires a system to attribute candidates to the transplant program, such as geographic catchment areas. We created transplant referral regions (TRRs) for kidney, liver, pancreas, heart and lung transplants based on prevailing care delivery patterns.

Methods: Data sources included the Scientific Registry of Transplant Recipients (SRTR) and the Dartmouth Atlas. To define TRRs, we used patient permanent zip codes to identify their hospital referral region (HRR). We assigned HRRs to the center at which the plurality of resident candidates from 2006 -16 were waitlisted. Centers located within 10 miles were clustered. TRRs were described using data from the 2010 U.S. Census.

Results: We defined 110 unique TRRs for kidney, 65 for liver (Figure 1), 86 for pancreas, 67 for heart, and 42 for lung. Approximately three out of four patients for each solid organ type were listed in the TRR of their permanent zip code (kidney: 71.4%, liver: 73.5%, pancreas: 71.5%, heart: 73.1%, lung: 70.8%). The mean area, population size, and demographics of the TRRs varied markedly.

Conclusions: TRRs represent geographic catchment areas for solid organ transplant centers, can be accurately identified and vary substantially in terms of size, population, and composition. Future research in this area will examine variation in disease burden, access to the waiting list, and outcomes by TRR to inform center-level quality metrics.



Clinical Science

#15- Skin Closure Techniques Following Trauma Laparotomy: Is Secondary Closure as Beneficial as We Think?

Caitlin A. Fitzgerald, MD, Bryan Morse, MD, Randi Smith, MD, MPH, Jonathan Nguyen, MD, Omar Danner, MD, Peter M. Rhee, MD, Rondi B. Gelbard, MD

Introduction: Trauma laparotomy incisions are often left open in the setting of enteric injuries to reduce the risk of wound infection, but there are limited data to support this practice. The purpose of this study was to determine if primary or delayed skin closure after trauma laparotomy is associated with an increased incidence of surgical site infections (SSI) and other wound complications.

Methods: Retrospective review of all patients who underwent a trauma laparotomy at a Level I trauma center from 2015-2017. Patients were separated into three groups: Group 1: fascia and skin both closed, Group 2: fascia closed, skin open for secondary closure, Group 3: delayed primary skin closure.

Results: A total of 819 patients were included. Most patients were male (81.8%) and had penetrating injuries (66.4%). There were 556 (67.9%) patients in Group 1, 244 (29.8%) in Group 2 and 19 (2.3%) in Group 3. The incidence of hollow viscus injury (HVI) was 256 (46%), 222 (90.9%) and 18 (94.7%) in Groups 1, 2 and 3, respectively. There were 25 (4.5%) damage control laparotomies in Group 1, 57 (23.4%) in Group 2, and 1 (5.2%) in Group 3. Group 2 had longer ICU and hospital lengths of stay (10.4ï,±14.8 vs. 5.8ï,±9.3 vs. 6.2ï,±12.0, p<0.001, and 25.1ï,± 24.1 vs. 15.2ï,±14.5 vs. 17.8ï,±12.2, p<0.001). Group 2 had a higher rate of organ space infections compared to Groups 1 and 3 (40/244, 16.4% vs. 35/556, 6.3%, vs. 1/19, 5.2%, p=0.0003) while Group 3 was associated with a significantly higher rate of fascial dehiscence and enterocutaneous fistula (ECF) among patients with HVI. There was no difference in the incidence of superficial or deep SSI or overall mortality between groups (Table 1).

Conclusions: Leaving skin incisions open following trauma laparotomy appears to be associated with higher morbidity without reducing the rate of surgical site infections. Closing skin at the time of initial laparotomy should be considered to reduce hospital stays and lower the risk of fascial dehiscence and ECF.

	Group 1	Group 2	Group 3	p-value
Age	34.6 ± 14.2	35.5 ± 14.4	34.3 ± 9.0	0.6
ED SBP	118.3 ± 28.9	117.3 ± 30.1	116.6 ± 28.7	0.9
ED GCS	13.2 ± 3.9	13.6 ± 3.4	14.1 ± 2.9	0.3
ISS	19.6 ± 12.3	20.9 ± 11.6	17.7 ± 13.0	0.1
ICU Days	5.8 ± 9.3	10.4 ± 14.8	6.2 ± 12.0	**<0.001***
Vent Days	3.1 ± 7.0	5.6 ± 10.4	2.6 ± 8.4	**<0.001***
Hospital LOS	15.2 ± 14.5	25.1 ± 24.1	17.8 ± 12.2	**<0.001***
Operative Time	149.1 ± 107. 3	205.3 ± 109.4	248.0 ± 93.3	**<0.001***
Open Abdomen Days	0.1 ± 0.9	0.8 ± 1.8	0.3 ± 1.4	**<0.001***
Total Number of Laps	1.1 ± 0.3	1.5 ± 0.9	1.3 ± 0.7	**<0.001***
Hollow Viscus Injury	256 (46.0%)	222 (90.9%)	18 (94.7%)	**<0.001***
Colostomy	48 (8.6%)	65 (2.7%)	5 (26.3%)	**<0.001***
DCL	25 (4.5%)	57 (23.4%)	1 (5.2%)	**<0.001***
SSI	21 (3.8%)	11 (4.5%)	0	0.9
OSI	35 (6.3%)	40 (16.4%)	1 (5.2%)	**0.0003***
Failed Fascial Closure	2 (0.4%)	15 (6.1%)	3 (15.8%)	**<0.001***
ECF	2 (0.4%)	9 (3.7%)	2 (10.5%)	**0.0002***
Death	22 (4.0%)	9 (3.7%)	0	0.9

ED: emergency department; SBP: systolic blood pressure; GCS: Glasgow Coma Scale; ISS: injury severity score; ICU: intensive-care unit; LOS: length of stay; DCL: damage control laparotomy; SSI: surgical site infection; OSI: organ space infection; ECF: enterocutaneous fistula.

Table 1. Comparison of outcomes based on method of wound closure.

Clinical Science

#19 - Real World Outcomes of Talimogene Laherparepvec Therapy: A Multi-Institutional Experience

Matthew C. Perez, Mohammad Raheel Jajja, Raphael J. Louie, James Sun, Frances Collichio, Keith A. Delman, Amod A. Sarnaik, Jonathan S. Zager, David W. Ollila, Michael Lowe

Background: Talimogene laherparepvec (TVEC) is a unique FDA-approved oncolytic herpes virus used to treat unresectable stage IIIB-IV metastatic melanoma via intralesional injection. This study aims to characterize the efficacy of this agent.

Methods: We performed a multi-institutional, IRB-approved review of patients who received TVEC at three centers from 10/2015â€“10/2018. Clinicopathologic characteristics, TVEC treatment data and outcomes were assessed.

Results: One hundred twenty one patients received TVEC, of which 80 patients had available treatment response data with at least three-month follow up. Anatomic sites treated: 19 (24%) head and neck, 9 (11%) upper extremity, 12 (15%) torso and 40 (50%) lower extremity. Thirty-four (42.5%) patients did not receive therapy prior to TVEC. Side effects were mild and self-limited, most commonly flu-like symptoms seen in 22 (28%) patients. Mean follow-up was 11.1 (3-28) months, with complete response (CR) in 31 (39%) and partial response (PR) in 14 (18%) patients. Of complete responders, 29 (37%) had no evidence of disease (NED) at last follow up and received on average 6.5 cycles of therapy.

Conclusions: Our data demonstrates TVEC has a promising complete response rate particularly when given as first-line therapy. TVEC is well tolerated and can be considered as first line therapy in patients with unresectable, injectable stage IIIB/C and IV M1a disease.

Clinical Science

#36 - Perioperative Anxiety in Patients Undergoing Abdominal Surgery

Hannah Williams, Mohammad Raheel Jajja, Wendy Baer, Glen C Balch, Shishir K Maithel, Ankit D Patel, Dipan Patel, Snehal G Patel, Jamil L Stetler, Joshua H Winer, Theresa W Gillespie and David A Kooby

Introduction: Etiologies, levels and associated factors for anxiety in patients facing abdominal surgery are not well defined. We conducted a prospective observational comparative study of perioperative anxiety in patients undergoing abdominal surgery for either malignant or benign disease.

Methods: With IRB approval, cancer and non-cancer patients consented for abdominal surgery were prospectively enrolled. At both the preoperative and first postoperative appointment, participants were assessed for demographics, substance use, psychiatric history (PSYHx) and anxiety. All patients completed the GAD-7 questionnaire and listed their top three sources of anxiety.

Results: Between July-September 2018, 79 patients completed the preoperative assessment and 44 (55.6%) the postoperative survey. The mean age was 58.8 years, 41 (51.9%) were male, 47 (59.5%) had cancer and 32 (40.5%) had benign disease. Overall, 7 (8.9%) patients had preoperative anxiety. Although not statistically significant, cancer patients had a four-fold higher incidence of preoperative anxiety

compared with noncancer patients (12.8% vs. 3.1%, p=0.23). There was no difference in postoperative anxiety between the two groups (p=1.0). The main preoperative concern was “undergoing surgery” (23%), while “finances” (27.9%) became the main postoperative worry. PSYHx was a risk factor for perioperative anxiety (p<0.01), while prolonged opioid use (p=0.01) was associated with postoperative anxiety.

Conclusion: Cancer patients had a four-fold higher incidence of preoperative anxiety compared to benign disease patients. Socioeconomic worries are prevalent throughout the perioperative period, and efforts to alleviate distress should focus on providing financial counseling. Postoperative anxiety and prolonged opioid use appear to have an association, and anxiety after surgery may serve as a target for opioid abuse reduction.

Table 1: Baseline Characteristics Malignant versus Benign Disease

	ALL	MALIGNANT	BENIGN	p-value
Total number of patients	79	47 (55.6)	32 (40.5)	
Mean age (SD)	58.8	63.4 (12.5)	52 (15.9)	***0.001***
Male gender (%)	41 (51.9)	28 (59.6)	13 (40.6)	0.154
Race (%)				
Caucasian	46 (58.2)	33 (70.2)	13 (40.6)	***0.017***
Not Caucasian	33 (41.8)	14 (29.8)	19 (59.4)	
In a relationship (%)	52 (65.8)	33 (70.2)	19 (59.4)	0.45
Higher education (%)	43 (54.5)	27 (57.5)	16 (50)	0.073
Comorbidities (%)				
Hypertension	38 (48.1)	25 (53.2)	13 (40.6)	0.385
Hyperlipidemia	21 (26.6)	11 (23.4)	10 (31.3)	0.606
COPD	6 (7.6)	3 (6.4)	3 (9.4)	0.682
Stroke	3 (3.8)	3 (6.4)	-	0.268
Cirrhosis	1 (1.3)	1 (2.1)	-	1
Coagulation disorder	6 (7.6)	3 (6.4)	3 (9.4)	0.682
Autoimmune disease	1 (1.3)	1 (2.1)	-	1
Cancer history	52 (65.8)	47 (100)	7 (21.9)	***<0.001***
Renal disease	3 (3.8)	-	3 (9.4)	1
Substance use (%)				
Current smoker	4 (5.1)	3 (6.4)	1 (3.1)	0.643
Opioid use	13 (16.5)	7 (14.9)	6 (18.8)	0.885
Other drug use	3 (3.8)	2 (4.3)	1 (3.1)	0.515
Positive alcohol screening	10 (12.7)	5 (10.6)	5 (15.6)	0.243
Positive psychiatric history (%)	12 (15.2)	6 (12.8)	6 (18.8)	0.532
Prior surgery (%)	59 (74.7)	42 (89.4)	17 (53.1)	***<0.001***
Frail (%)	7 (8.9)	6 (12.8)	1 (3.1)	0.231
Median days to surgery (range)	18 (1-103)	17 (1-85)	24 (1-103)	0.139
Median length of stay (range)	3 (0-69)	4 (0-69)	1 (0-13)	***0.003***
Median days to postoperative survey (range)	17 (7-37)	18.5 (7-37)	16 (8-31)	0.405
Clavien Dindo Grade IIII/IV complications (%)	5 (6.8)	4 (8.9)	1 (3.4)	0.662
Clinically significant preoperative depression	13 (16.5)	9 (19.1)	4 (12.5)	0.636
Clinically significant preoperative anxiety	7 (8.9)	6 (12.8)	1 (3.1)	0.231

Clinical Science

#43 - Machine Learning Based Stability Assessment for Individualizing Antibiotic Duration in Hospitalized Community Acquired Pneumonia Patients

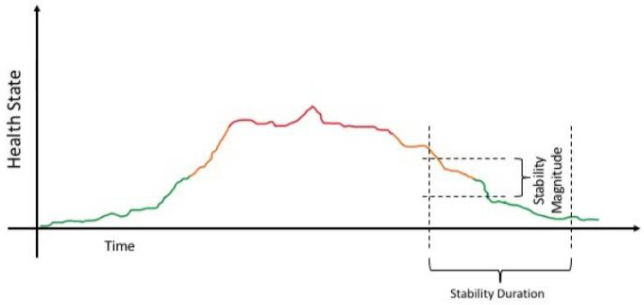
Christopher Josef MD, Russell Jeter PhD, Max Adelman MD, Timothy Buchman MD PhD, Shamim Nemati PhD, Scott Fridkin MD

Intro: The optimal treatment duration for community acquired pneumonia (CAP) has not been well established, prompting numerous investigations into tailored durations based on patient stability. The most widely used stability criteria for CAP was validated by Halm et al. and relies on a combination of seven patient features. Nemati et al. have developed AISE (Artificial Intelligence Sepsis Expert) a peer reviewed, high dimensional machine learning algorithm capable of predicting the onset of sepsis through the continuous assessment of 65 unique patient features. The AISE algorithm is now considered as a high dimensional tool for assessing clinical stability.

Methods: In this retrospective analysis an hourly AISE score was calculated for a cohort 775 unventilated patients with CAP. An AISE score threshold and duration for stability were selected using Bayesian optimization to match Halm criteria. The outcomes for patients whose antibiotics were discontinued within 6 hours of AISE determined stability were then compared to those using Halm criteria determined stability.

Results: Patients that maintain an AISE score below 0.37 for 24 hours can be reliably classified as meeting Halm criteria with an AUC of 0.71 (Sen:0.72, Spec:0.70). Table 1 demonstrates outcomes for antibiotics discontinued in conjunction with AISE and Halm determined stability to be nearly identical; however, AISE identified stability an average of 24 hours earlier.

Conclusion: AISE is a high dimensional model that can match Halm criteriaâ€™s ability to identify stability, supporting the notion that a tailored stability endpoint can be used to guide and potentially shorten antibiotic duration for CAP.



A graph of the AISE stability score. Bayseian optimization was used to select the optimal stability magnitude and duration.

Table 1: Comparison of Early and Late Antibiotic Treatment End Points

	AISE			Halm		
	Early	Late	Unstable	Early	Late	Unstable
Number of pts	50 (6.5%)	459 (60.2%)	266 (34.3%)	75 (9.7%)	412 (53.2%)	288 (37.2%)
SOFA Score after stability*	1.03 [2.37]	0.47 [1.51]	2.36 [2.84]	1.00 [2.00]	0.48 [2.00]	1.78 [2.81]
LOS (hrs)*	171 [200]	157 [325]	NA	167 [199]	166 [123]	NA
LOS after stability (hrs)*	165 [117]	141 [325]	NA	32 [102]	86 [99]	NA
LOS after stability (hrs)**	97	137		74	108	
In Hospital Mortality ***	1 (2%)	33 (7.2%)	65 (24.4%)	1 (1.3%)	19 (4.6%)	79 (24.4%)
Restarted antibiotics ***	13 (26%)	NA	NA	12 (16%)	NA	NA

* Median [Interquartile Range]
** Mean
*** Number (%)

HONORABLE MENTION

Clinical Science

#3- Race, Ethnicity, and Socioeconomic Factors in Cholangiocarcinoma: What is Driving Disparities in Receipt of Treatment?

Rachel M. Lee, Yuan Liu, Mohammad Y. Zaidi, Adriana C. Gamboa, David A. Kooby, Kenneth Cardona, Maria C. Russell, Shishir K. Maithel

Background: Racial/ethnic and socioeconomic-factors (SEFs) are associated with worse cancer outcomes. Our aim was to determine the association of these factors with receipt of surgery and multimodality-therapy for cholangiocarcinoma (CCA).

Methods: Pts with CCA in the National-Cancer-Data-Base were identified. Racial/ethnic groups were defined as non-Hispanic White (NH-W), non-Hispanic Black (NH-B), Asian, and Hispanic. SEFs considered were insurance-status, income, and educational-attainment.

Results: Of 12,095pts with non-metastatic CCA, 42% received surgery as initial therapy. Accounting for clinicopathologic variables, NH-B race was associated with decreased odds of receiving surgery (OR:0.66l,p<0.001) compared to NH-W patients. SEFs accounted for 21% of this racial disparity. Even when accounting for both socioeconomic and clinicopathologic variables, NH-B race remained associated with decreased receipt of surgery (OR:0.73,p<.001), along with uninsured status (OR:0.43,p<0.001) and Medicaid insurance (OR:0.63,p<0.001).

Of 4,808pts who received surgery, 22% received multimodality-therapy with chemotherapy, and 23% with both chemotherapy/radiation. There were no differences in receipt of multimodality-therapy among racial/ethnic or socioeconomic groups once patients had accessed surgical care.

Conclusions: Racial/ethnic disparities only partially account for difference in treatment for CCA. Medicaid insurance and uninsured status were independently associated with decreased odds of receiving surgery. This indicates a significant barrier to accessing healthcare for non-White and non-privately insured patients. In patients who received surgery, the receipt of multimodality-therapy was not driven by race/ethnicity or socioeconomic status. This emphasizes the need to improve and extend insurance coverage to our patients with socioeconomic challenges to increase initial access to healthcare. Persistent disparities associated with race/ethnicity require prompt attention.

Clinical Science

#5- Increasing the Number of Pre-Reversal Imaging Studies for Trauma Colostomies Delays Reversal without Improving Outcomes

Brett Tracy MD; Caitlin Fitzgerald MD; Jonathan Nguyen DO; Randi Smith, MD MPH; Bryan C. Morse MD; Rondi Gelbard MD

Background: Obtaining multiple imaging studies prior to colostomy reversal may delay surgery without affecting outcomes. We sought to determine the impact of pre-reversal imaging on time to colostomy reversal (TTCR) and postoperative complications.

Methods: This study was a retrospective chart review of trauma patients who underwent colostomy reversal at our trauma center between 2009 and 2016. Demographic data, number and type of pre-reversal imaging studies were collected. Outcomes included TTCR and postoperative complications such as fistulae, leak, obstruction, and surgical site infection.

Results: The cohort included 135 patients; 85% (115/135) were men and mean age was 32.2 years. Of these patients, 64.4% (87/135) had an end colostomy. Most patients (56.3%, 76/135) had one pre-reversal study, 37% (50/135) had two, and 3.7% (5/135) had three or more. The most common initial imaging modality was a barium enema (BE) (88.5%, 116/131) followed by CT (11.5%, 15/131). Mean TTCR was 12.5 Â± 18.3 months. Number of pre-reversal studies was associated with increased TTCR (OR=1.5, 95% CI= 1.41, 1.59). There was no difference in TTCR between no imaging versus an initial BE or CT. Increasing the number of pre-reversal studies did not lead to a lower incidence of postoperative complications (p>0.14). End colostomies were associated with superficial (OR=10.6, 95% CI=1.4, 82.6) and organ space infections (OR=6.4, 95% CI=1.4, 28.9).

Conclusion: Increasing the number of pre-operative imaging studies increases TTCR with no effect on postoperative complications. Further studies are needed to determine if preoperative imaging should be limited to trauma patients with certain risk factors.

Clinical Science

#8- Merkel cell carcinoma outcomes- does AJCC8 underestimate survival?

Farley CR, Perez MC, Soelling S, Lowe MC, Harit A, Sondak VK, Zager JS, Delman KA

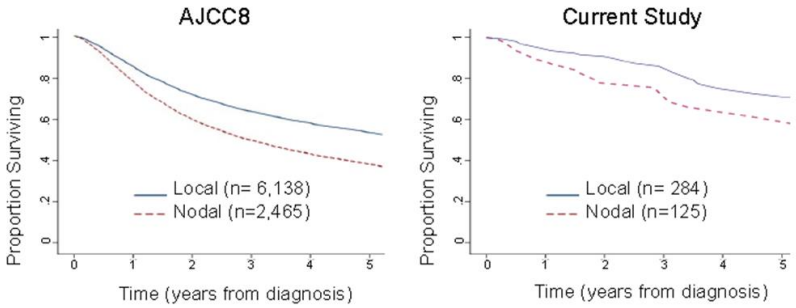
Introduction: The eighth edition of the American Joint Committee on Cancer (AJCC8) Staging Manual provides important information for staging and prognostication. However, given the rare nature of Merkel cell carcinoma (MCC), survival estimates for patients with Stage I-III disease may be as practical using data from large volume centers as that collated for the AJCC analysis.

Methods: Patients with Stage I-III MCC who presented from 2005 to 2017 to two high-volume centers were included. Demographics, clinicopathologic characteristics, survival and recurrence data were compiled, and outcomes were compared to AJCC8.

Results: 409 patients were included. Median age was 75 (range 29-98) years, 68% male. Median follow up was 16 months (0-157). 5-year overall survival (OS) was 70%; 5-year disease-specific survival (DSS) was 86%. When stratified by extent of disease, 5-year OS was higher for patients with local (stage I and II) disease compared to those with nodal (stage III) disease (72.6% vs 62.7%; p=0.009). Similarly, patients with local disease had a higher 5-year DSS than those with nodal disease (90.1% vs 76.8%, p=0.002).

Conclusions: In this series, MCC patients with local or nodal disease have substantially higher OS rates than predicted in AJCC8 (5-year: 72.6% vs 50.6%; 62.7.6% vs 35.4%, respectively). Importantly, 5-year DSS was significantly higher than either the OS rates reported in the present study or AJCC8 manual. As clinicians and patients alike rely on AJCC to accurately predict outcomes and guide treatment decisions, these estimates should be reassessed and updated to more accurately predict survival outcomes.

Figure 1: Five-year overall survival for all patients



	5-yr Overall Survival	
	AJCC8	Current Study
Local	50.6%	72.6%
Nodal	35.4%	62.7%

Clinical Science

#11- Interaction of Race and Pathology for Neuroendocrine Tumors: Epidemiology, Natural History, or Racial Disparity?

Danielle K. DePalo BS; Rachel M. Lee MD MPH; Alexandra G. Lopez-Aguiar MD MS; Mohammad Y. Zaidi MD MS; Flavio Rocha MD; Zaheer Kanji MD; George Poultsides MD; Eleftherios Makris MD; Mary Dillhoff MD; Eliza Beal MD; Ryan C. Fields MD; Roheena Panni MD; Kamran Idrees MD; Paula Marincola Smith MD; Hari Nathan MD; Megan Beems MD; Daniel Abbott MD; Victoria Rendell MD; Shishir K. Maithel MD; and Maria C. Russell MD

Background: We previously demonstrated a limited prognostic role of lymph node(LN) positivity in small bowel NETs(SBNET) compared to pancreatic NETs(panNET). Although minority race is often associated with worse cancer outcomes, the interaction of race with outcomes of patients with gastroenteropancreatic neuroendocrine tumors(GEP-NETs) is unknown.

Methods: Patients with GEP-NETs who underwent curative-intent resection at 8 institutions of the US NET Study Group from 2000-16 were included. Only Black and White race patients were analyzed.

Results: Of 2182 patients, 1143 met inclusion criteria. Median age was 58yrs, median follow-up was 3yrs, 48% were male, 14%(n=157) were Black, and 86%(n=986) were White. Black patients were more likely uninsured(7vs2%,p=0.005), had symptomatic bleeding(13vs7%,p=0.006), required emergency surgery(7vs3%,p=0.003), and had LN-positive disease(47vs36%,p=0.016). Despite this, Black patients had improved 5yr recurrence-free survival(RFS) compared to White patients(90vs80%,p=0.008). Black patients were more likely to have SBNET(22vs13%) and less likely to have panNET(43vs68%) compared to White patients(p<0.001). Consistent with prior data, patients with LN-positive panNET had decreased 5yr RFS(67vs83%,p=0.001); however, for SBNET, LN involvement was not prognostic(77vs96%,p=0.08). The prognostic value of LN positive disease was similar between Black and White patients in SBNET(p=0.34) and panNET(p=0.95).

Conclusions: Black patients with GEP-NET present with more advanced disease, including higher LN positivity, but have improved RFS compared to White patients. Black patients received similar quality of care compared to White patients, despite possible delays in accessing care. The improved RFS seen in Black patients may be attributed to epidemiological differences in the site of GEP-NETs and variable prognostic value of LN-positive disease.

Clinical Science

#12- Disparities in Pediatric Liver Transplant Waitlist Access

Steven C Kim, Katherine Ross, Evelyn Hsu, Rachel Patzer, Raymond Lynch

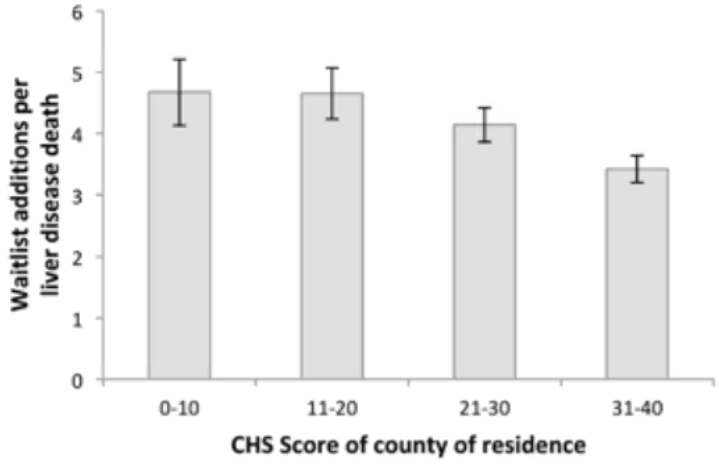
Background: While disparities in access to liver transplant are well documented among adults, differences in access to the waitlist for children in remote or underserved communities remains incompletely understood.

Methods: Centers for Disease Control county-level records of pediatric liver disease deaths from 2002-2016 were compared with SRTR records of waitlist additions. Sociodemographic vulnerability was assessed by county Community Health Score (CHS), and proximity to care approximated by the presence of a high volume (>100/study period) liver transplant center in-state.

Results: From 2002-2016, 9112 patients were listed and 2138 children died of liver disease. Children in underserved (CHS 30-40) counties had observed death rates 30% higher than those in more fortunate (CHS 0-10) areas (2.23 vs. 1.75 deaths per million person-years, $p < 0.001$), and were 27% less likely to be waitlisted than CHS 0-10 counterparts ($p < 0.001$, Figure 1). The presence of at least one high-volume transplant center in-state corresponded with greater waitlist access. Outcomes on the waitlist and at 1 and 3 years post-transplant did not differ by county CHS or presence of a high-volume in-state center.

Conclusions: Children with liver disease in underprivileged areas have lesser access to the liver transplant waitlist and a higher death rate from liver disease. Greater distance to a transplant center is associated with lesser waitlist access. Further research is necessary to identify means by which to reduce disparities in waitlisting and facilitate receipt of care for patients in remote and underserved communities.

Figure 1: Pediatric patients living in high (adverse) Community Health Score (CHS) counties have less access to the liver transplant waitlist.



Clinical Science

#17- Identifying Practice Patterns in the Utilization of FDG PET/CT for Staging Breast Cancer Patients at a Safety Net Hospital

T. Ho DO, J. Short PA, Y. Liu PhD, P. Subhedar MD, J. Okoli MD, K. Gogineni MD, E. Paplomata MD, J. Lin MD, D. Yu MD, C. Arciero MD, S. Gabram MD

Background/Objective: FDG PET/CT is preferentially used at our institution to evaluate for metastatic disease in breast cancer patients. PET/CT has been listed as â€œoptionalâ€ depending on certain criteria in the National Comprehensive Cancer Network (NCCN) Guidelines resulting in varying practice patterns of ordering this exam. Our goal is to determine if our Center is overutilizing PET/CT based on these guidelines with the aim of modifying practice patterns and reducing unnecessary exams.

Methods: We reviewed all breast cancer patients with FDG PET/CT ordered for initial treatment strategy between January to December 2017. The 2017 NCCN Guidelines were reviewed for indications for ordering PET/CT. Analysis was performed on characteristics of those who did and did not meet indications.

Results: 66.2% (n=43) of patients met NCCN indications while 33.8% (n=22) did not. Scans that met criteria were more likely ordered for recurrent cancers and patients receiving preoperative chemotherapy. Within the group that did not meet indications, 50% had clinically node positive disease while 36.6% were clinically node negative (Table 1).

Conclusion: 1/3 of all FDG PET/CT scans ordered for initial staging and treatment guidance were ordered unnecessarily based on NCCN criteria. Practice patterns indicate that physicians were more apt to order a PET/CT if the patient had a positive clinical nodal status, despite not in itself an indication to order the study. In an effort to apply a more uniform approach utilizing FDG PET/CT, our Center has created a checklist of criteria to be reviewed during multidisciplinary conference to minimize ordering unnecessary exams.

Table 1

	Met NCCN Indications for PET		
	Yes (%)	**No (%)**	**P-value**
Recurrent Cancer	11 (25.6)	0 (0)	0.011
Not Recurrent Cancer	32 (74.4)	22 (100)	
Preoperative Systemic Therapy	36 (83.7)	8 (36.4)	<.001
No Preoperative Systemic Therapy	7 (16.3)	14 (63.6)	
Clinically Node Positive	24 (55.8)	11 (50)	0.510
Clinically Node Negative	17 (39.53)	8 (36.6)	
Unknown	2 (4.65)	3 (13.64)	

Clinical Science

#18- Lower Socioeconomic Status Is Associated With Groin Wound Complications Following Revascularization for Peripheral Artery Disease

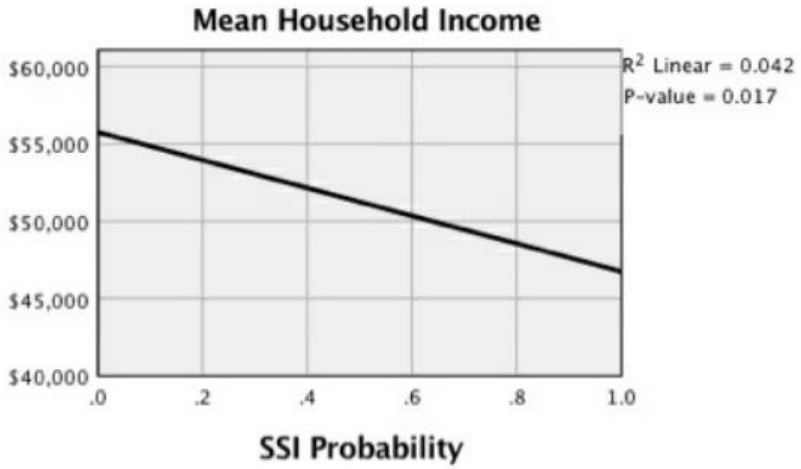
Saagar C Bakshi, Amanda Fobare, Jaime Benarroch-Gampel, Victoria Teodorescu, Ravi R Rajani

Introduction: Surgical site infections (SSIs) following lower extremity revascularization are a common cause of morbidity in patients with peripheral artery disease. Understanding the multifaceted risk factors for SSIs may suggest closer monitoring for certain patients. The objective of this study is to evaluate risk factors associated with incidence of SSIs.

Methods: A retrospective review of a prospectively maintained database was queried for patients who underwent femoral exposure to treat peripheral artery disease from 2014-2017 at an academic, public hospital. Demographics and procedural data were collected from chart review, while zip code geo-coding was used to obtain surrogates for various socioeconomic factors. The primary outcome measure was SSI within 90 days of operation.

Results: 136 total patients were identified, of which 19 (14%) developed an SSI. The only demographic variable associated with risk of infection was BMI ($p<0.05$). Major preoperative comorbid conditions, smoking status, and insurance status were not associated with complications. Additionally, the type of procedure performed was not associated with SSI risk. Estimated blood loss ($p<0.05$), post-operative glucose ($p<0.05$), and post-operative WBC count ($p<0.05$) were the only peri-procedural variables associated with SSI. Lower mean household income, mean family income, and per capita income were associated with increased risk of post-operative infection (all $p<0.05$).

Conclusion: Socioeconomic factors are strongly associated with risk of SSI following lower extremity revascularization. Modifiable variables, such as preoperative optimization and procedural conduct, had a smaller effect on SSI development. Models describing complications and readmissions following vascular surgery must account for differing access to healthcare.

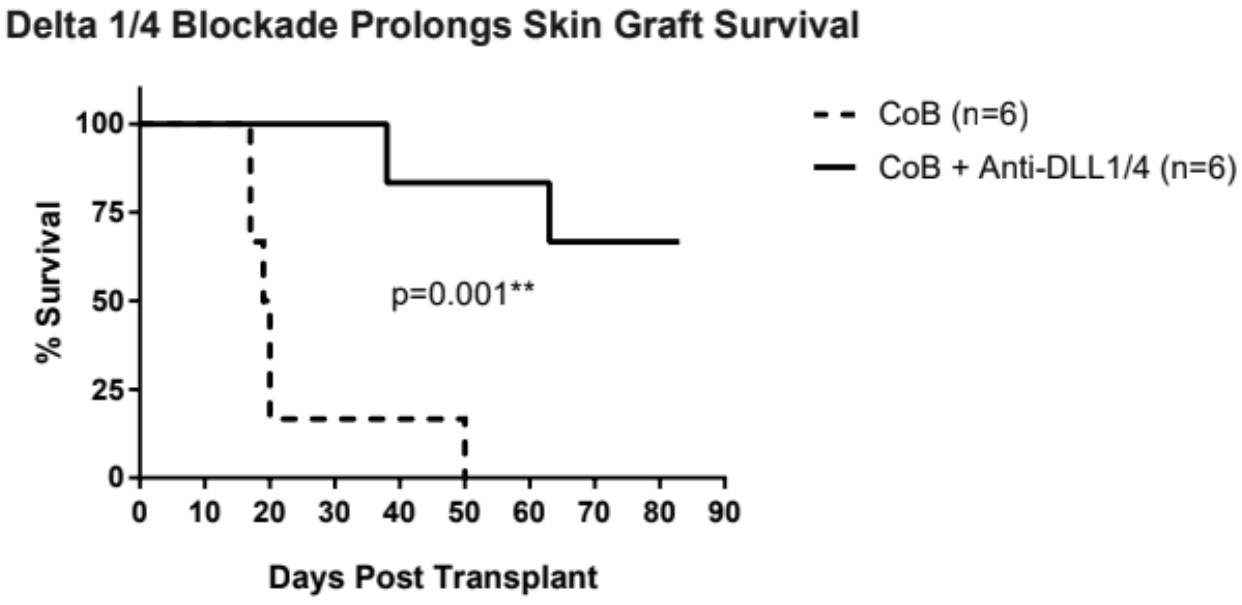


Basic Science

#20 -Interruption of Notch Signaling via Blockade of Delta-like Ligands 1 and 4 Prevents Co-stimulation Blockade Resistant Allograft Rejection

Abraham J. Matar, Ying Dong, Brendan P. Lovasik, David V. Mathews, Cynthia A Breeden, Abheek Ghosh, Allison Stephenson, William H. Kitchens, Andrew B. Adams

Co-stimulation blockade (CoB) has emerged as a promising immunosuppression strategy with the advent of belatacept, a novel CTLA4-Ig fusion protein that blocks CD28-mediated T cell co-stimulation. Belatacept confers long-term advantages in graft survival and function in renal transplant recipients compared to traditional calcineurin inhibitor-based immunosuppression but is associated with increased rates of early acute rejection. Using a mouse model of MHC-mismatched skin transplantation, we investigated the role of Notch pathway inhibition via blockade of Delta-like ligands 1 and 4 (Delta 1/4) on CoB-resistant allograft rejection. In our model of Balb/C to C57BL/6 skin transplantation, combined CoB (CTLA-4Ig + anti-CD154) and Delta 1/4 blockade significantly prolonged skin graft survival compared to CoB alone (MST 20 days vs. >83 days, p = 0.001**). Delta 1/4 blockade did not inhibit T cell proliferation in vivo, but instead induced T cell apoptosis. Anti-donor IgG antibody was also significantly reduced in the combined treatment group. We next examined donor-specific T cell responses using mOVA skin grafts in recipients which received an adoptive transfer of Thy1.1+ ovalbumin-specific OT-I T cells. Combined CTLA-4Ig and Delta1/4 blockade suppressed donor-specific CD8+ T cell accumulation in draining lymph nodes compared to CTLA-4-Ig alone. Further, the combined blockade regimen suppressed both IFN-gamma and TNF production by donor-specific CD8+ T cells. These data demonstrate that Delta 1/4 blockade suppresses donor-specific T cell responses in the setting of CoB and prevents CoB-resistant rejection. We have identified the Notch signaling pathway as a promising target for future large animal and clinical studies of CoB-resistant rejection.



Clinical Science

#24- Failure to Adhere to Process Measures on the Weekends: Hospital Level Predictors of Reduced Quality of Care

Jessica Y Liu, MD, MS ; Ryan P Merkow, MD, MS; Ryan J Ellis, MD, MS Mark Cohen, PhD; Clifford Y Ko, MD, MS, MSHS; Karl Y Bilimoria, MD, MS ; John F Sweeney, MD ; Jyotirmay Sharma, MD

Background: Successful postoperative recovery is contingent on early mobilization and avoidance of infectious complications. The success of Enhanced Recovery Protocols is particularly dependent on high adherence to process measures (PM). Whether PM adherence is impacted by "weekend effect" remains unknown. Our objectives were to determine if there is an association between day of the week and PM adherence, and identify hospital level factors associated with weekend adherence.

Methods: Using the ACS Enhanced Recovery in NSQIP program, we identified patients undergoing elective colorectal surgery between 2014-2017. Adherence to nine postoperative PM was compared between patients undergoing surgery on Monday through Wednesday compared to Friday while risk adjusting for surgical complexity. American Hospital Association data was utilized to obtain hospital level factors that were modeled to determine association with adherence to PM on the weekend.

Results: Among 27,617 patients analyzed from 362 hospitals, those that underwent surgery on Friday compared to Monday-Wednesday had decreased adherence to mobilization on postoperative day (POD) 1 (73.48% vs. 77.45%), mobilization on POD 2 (83.33% vs 85.57%), and Foley removal by POD 1 (68.79% vs 74.50%; all p<0.05). Hospital level factors associated with lower weekend adherence rates included having more hospital beds, more admissions, fewer nurses per bed, and fewer part time unit staff per bed (all p<0.05).

Conclusions: Reduced adherence to mobilization and Foley removal was noted during the weekend and it was associated with certain organizational and unit based factors including nurse staffing. These are potential targets to improve surgical quality and resource utilization to achieve desirable patient care.

Table 1: Differences in process measure adherence between cases performed on Mon-Wed vs Fri

Process Measure Adherence	Monday – Wed % Adherence	Friday % Adherence	P value	OR	95% CI
Mobilization by POD 1	77.45	73.48	0.02	1.26	1.04 – 1.53
Mobilization by POD 2	85.57	83.33	0.04	1.20	1.01 – 1.42
Foley Removed by POD 1	74.50	68.79	<0.01	1.35	1.10 – 1.66
Discontinue IV Fluids by POD 1	24.92	24.36	0.81	1.03	0.80 – 1.34
Multimodal Pain Management	88.04	87.84	0.88	1.02	0.83 – 1.24
Antiemetic Prophylaxis	85.66	86.15	0.66	0.96	0.78 – 1.17
Mobilization by POD 0	57.86	53.65	0.18	1.19	0.96 – 1.49
Clear Liquid Diet by POD 0	67.65	64.88	0.37	1.13	0.86 – 1.49
Solid Diet by POD 1	41.28	39.19	0.49	1.09	0.85 – 1.40

Clinical Science

#25- Reducing Early Readmissions after Ventral Hernia Repair with the Americas Hernia Society Quality Collaborative

DeAngelo A Harris, MD, MS, Benjamin K Poulose, MD, MPH, Sharon Phillips, MSPH, Randy J Janczyk, MD, Jonathan Yunis, MD, Guy R Voeller, MD

Background: Early readmission after ventral hernia repair (VHR) can hinder patient recovery and increase resource use. The objective of this study was to evaluate the effectiveness of the Americas Hernia Society Quality Collaborative Early Readmission Reduction Initiative in reducing early readmissions after VHR.

Study Design: Risk factors for early readmission and best practices of surgeons with the lowest readmission rates after VHR were determined through collaborative learning. Two interventions for reducing early readmissions were developed: a structured questionnaire administered to patients within 1 week after discharge from the hospital or an early clinic visit after discharge and before a regularly scheduled postoperative visit. Multivariable logistic regression was used to evaluate the impact of these interventions on early readmission.

Results: Use of the questionnaire and early clinic visit was tracked in 3,007 patients. Of these, 343 received the questionnaire (2.6% readmission rate), 761 had an early clinic visit after discharge (3.0% readmission rate), 138 had both (4.3% readmission rate), and 1,765 patients received neither (5.9% readmission rate). After controlling for factors associated with early readmissions, administration of the questionnaire (odds ratio 0.42; 95% CI 0.21 to 0.84; $p < 0.05$) or having an early clinic visit (odds ratio 0.48; 95% CI 0.30 to 0.76; $p < 0.05$) were both associated with reduced odds for readmission.

Conclusions: The Americas Hernia Society Quality Collaborative Early Readmission Reduction Initiative successfully reduced readmissions after VHR using a structured questionnaire or early clinic visit implemented after discharge and before routine 30-day postoperative follow-up.

Emergency Department Visits and Readmissions Within 30 Days after Operation

Variable	Early readmission reduction questionnaire (n = 343)	Early clinic visit (n = 761)	Questionnaire plus early clinic visit (n = 138)	No intervention (n = 1,765)	p Value
Emergency department visit, %	5.0	0	0	9.3	<0.001*
Readmission, %†	2.6	3.0	4.3	5.9	0.003*
Readmission reason, n					0.299
Gastrointestinal complication	0	1	0	17	
Wound complication	5	14	4	28	
Pain	1	1	0	18	
Thrombotic complication	1	0	0	5	

*Significant.
†Includes patients placed in observation status.

Clinical Science

#26 -The Prevalence of Nonadherence in Pediatric Kidney Transplant Recipients and Associated Post-Operative Consequences

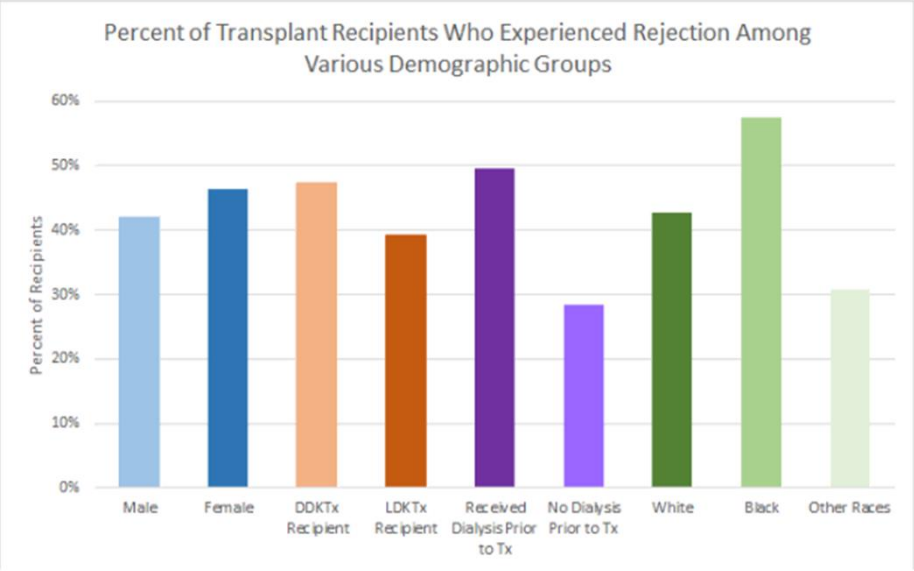
Taylor Melanson, Julien Hogan, Kieran Maroney, Rachel Patzer, Roshan George

Kidney Transplantation is the optimal treatment for ESRD but outcomes of this surgical procedure depend on patient behavior. Transplant recipients must follow an immunosuppression regimen to maximize graft survival. Nonadherence is associated with increased rejection and graft loss. We examine the reporting of Nonadherence in national claims data and its association with transplant outcomes.

Using 2005-2015 USRDS data, we examine nonadherence in pediatric kidney transplant recipients. We select all recipients who received their first transplant within our study period, before age 22 (N=11,419). We describe rates of nonadherence and rejection as reported via ICD9 codes. We examine the distribution of nonadherence and rejection across demographic groups. We examine the association of nonadherence and rejection and the timing of the associated claims.

8.58% of patients had nonadherence claims and 44% of patients had rejection at some point in the study period. Older age and being black were both associated with higher reporting of nonadherence. 97% of rejection occurred prior to any claim of nonadherence. Preemptive transplant recipients experienced roughly half the rate of rejection seen in other patients: 28% vs 50% (P<.01).

The rate of nonadherence in USRDS claims data is lower than reported in monocentric studies assessing nonadherence by self-report, drug-levels, or missed appointments. This suggests that there may be barriers to reporting nonadherence in claims data and that providers seem reluctant to report nonadherence prior to a complication arising. Improving reporting may allow the development of interventions aiming at improving adherence and graft survival in pediatric transplant recipients.



Basic Science

#28- Role of FcγRIIB as a Novel T Cell Checkpoint Inhibitor in Melanoma

Marvi Tariq, Clara R. Farley, Michael C. Lowe, Mandy L. Ford

Introduction: The immune system plays a critical role in protection against tumorigenesis. Inhibitory receptors including CTLA-4 and PD-1 dampen the immune response to malignancy and are important targets for immunotherapy in melanoma. We recently discovered that FcγRIIB, the only inhibitory IgG-Fc receptor, is expressed on highly differentiated effector CD8+ T cells in mice. Preclinical data using FcγRIIB-/- transgenic mice with B16 melanoma demonstrated significant reduction in tumor burden, while adoptive transfer of FcγRIIB-/- OT-I cells into WT B6 mice resulted in enhanced CD8+ T cell response. These clinically relevant findings illuminate a mechanism by which humoral immunity and Fc-containing immunotherapies can regulate CD8+ T cell tumor immunity. Here, we discovered that FcγRIIB is expressed on human CD8+ T cells, and sought to determine its distribution within this subset.

Methods and Results: Using freshly isolated PBMCs from healthy human controls, we demonstrated the expression of FcγRIIB on CD8+ T cells (29%) using FcγRIIB-specific monoclonal antibody. Amongst T cell subsets, we detected a high frequency of CD8+ FcγRIIB+ cells within the effector memory T cell population (41%), compared to central memory and naïve T cell populations (31% and 24%). Using FACS-sorted T cells and qPCR, we identified the presence of mRNA transcripts for FcγRIIB in all CD8+ T cell subsets, showing that FcγRIIB is transcribed and not trogocytosed from other myeloid lineages expressing FcγRIIB.

Conclusion: We conclude that FcγRIIB is a novel co-inhibitory molecule expressed intrinsically on human CD8+ T effector cells and has potential as target for checkpoint inhibition in melanoma.

Basic Science

#29- 2B4 but not PD-1 blockade improves mortality and T cell co-signaling in a pre- existing cancer sepsis model

Ching-wen Chen, Wenxiao Zhang, Craig M. Coopersmith, Mandy L. Ford

In addition to its well known beneficial effects for the treatment of several types of cancer, PD-1 blockade has shown encouraging results in pre-clinical models of sepsis and in a recent sepsis clinical trial. Because cancer is the most common co-morbidity in septic patients, here we aimed to determine the efficacy of PD-1 checkpoint blockade in the setting of sepsis complicated with pre-existing malignancy. Despite the fact that PD-1 blockade shows clinical efficacy in both cancer and sepsis separately, in a model of established lung cancer followed by cecal ligation and puncture (CLP)-induced sepsis, PD-1 blockade exhibited no therapeutic effect on sepsis survival. Mechanistically, this diminished efficacy of PD-1 blockade in cancer septic animals was characterized by a reduction in both the quality and quantity of PD-1+ responder cells. Specifically, CD8+ T cells isolated from cancer septic animals exhibited decreased

CD28 expression and a reduction in the frequency of CXCR5+PD-1int cells. Next, we utilized SPADE analysis to determine the expression of other coinhibitory molecules on T cell in cancer septic animals and identified 2B4 as another possible checkpoint blockade target. In contrast to anti-PD-1, anti-2B4 administration significantly improved sepsis survival in cancer septic animals. These results identify unique functions of distinct coinhibitory receptors in the setting of sepsis complicated with cancer, further highlighting the importance of personalized immunotherapy for the treatment of septic patients.

Basic Science

#34- Impact of IL-27 Signaling in Memory T Cells on Sepsis Pathophysiology

Kristen N. Morrow, Jianfeng Xie, Ching-wen Chen, Yini Sun, Craig M. Coopersmith, Mandy L. Ford

Sepsis is associated with a dysfunctional immune response characterized by increased lymphocyte expression of co-inhibitory receptors and alterations in systemic cytokines. Recent seminal studies have found that blocking IL-27 signaling improves survival in septic mice. However, the cell type(s) on which IL-27 is acting during sepsis pathophysiology to mediate the immune dysregulation and mortality are not known. In this study we used the cecal ligation and puncture (CLP) model of sepsis and measured systemic IL-27 and the frequency of lymphocytes expressing the IL-27 receptor (IL-27Ra). We observed that septic mice have significantly increased systemic levels of IL-27 starting at 24 hours post-CLP (sham: 19.65% ± 19.10, n=5; CLP: 788.5% ± 197.9, n=6; p=0.004). Of note, we also observed a significant increase in the expression of IL-27Ra on CD44 hi memory CD4+ T cells in CLP mice during sepsis relative to CD44 lo (naïve) CD4 T cells (CD44hi: 18.6% ± 4.12, CD44lo: 5.4% ± 1.74, p=0.038, n=7). In contrast, there was no difference in IL-27Ra expression between CD44hi and CD44lo CD4+ T cells in sham animals (CD44hi: 25.33% ± 7.39, CD44lo: 8.207% ± 4.68, n=3). Moreover, no difference was observed in the frequency of IL-27Ra+ CD44hi vs. CD44lo cells in the CD8+ T cell compartment either in CLP animals (CD44hi: 45.87% ± 10.39, CD44lo: 29.66% ± 7.32, p=0.097, n=7) or in sham controls. These results suggest that IL-27 may contribute to sepsis pathophysiology via IL-27Ra signaling on CD4+ CD44hi memory T cells.

Basic Science

#35- Myosin Light Chain Kinase (MLCK) Knockout Mice Demonstrate Increased Mortality in Pseudomonas Pneumonia-Induced Sepsis

Deena B. Chihade, Prestina Smith, Shunsuke Otani, Wenxiao Zhang, Ching-Wen Chen, Lauren Jeffers, Zhe Liang, Eileen M Burd, Brad Farris, Michael Koval, Craig M Coopersmith

Tissue barrier integrity involves a complex interplay of tight junctions, whose dysregulation leads to subsequent hyperpermeability in sepsis. Myosin light chain kinase (MLCK) is a central regulatory protein involved in phosphorylation of myosin light chain causing increased permeability in the lung. Previously, we demonstrated that MLCK-/- mice had improved survival compared to wild-type (WT) mice in a model of abdominal sepsis. Our aim was

to determine if this survival advantage was replicated in a pulmonary septic model. MLCK-/- and WT mice received an intratracheal injection of Pseudomonas, triggering pneumonia-induced sepsis and were followed for survival or sacrificed at 24 hours. Survival was unexpectedly significantly decreased in septic MLCK-/- mice (7% vs 40%, n=34, p=0.02). Cultures revealed a significantly increased bacterial load in MLCK-/- bronchoalveolar lavage (BAL) versus WT (p<0.0001). A non-significant trend towards increased permeability by Evans Blue was detected in BAL and lung tissue from septic MLCK-/- mice. Claudin-4 expression was increased in MLCK-/- compared to WT mice (p<0.009) although Claudins-3,-5,-15 were similar between groups. Proinflammatory cytokines IL-1beta and IL-6 were increased in the sera of septic MLCK-/- mice (p=0.04, p=0.01) whereas TNF was elevated in BAL of MLCK-/- mice (p=0.02). Quantitative histology demonstrated intra-alveolar hemorrhage was higher in MLCK-/- mice (p<0.04) in addition to endothelialitis (p=0.01) and an elevation in lymphocytic infiltrate in MLCK-/- mice. Taken together, MLCK plays a model-specific role in mediating mortality in sepsis, potentially due to its role in mediating infection clearance and inflammation.

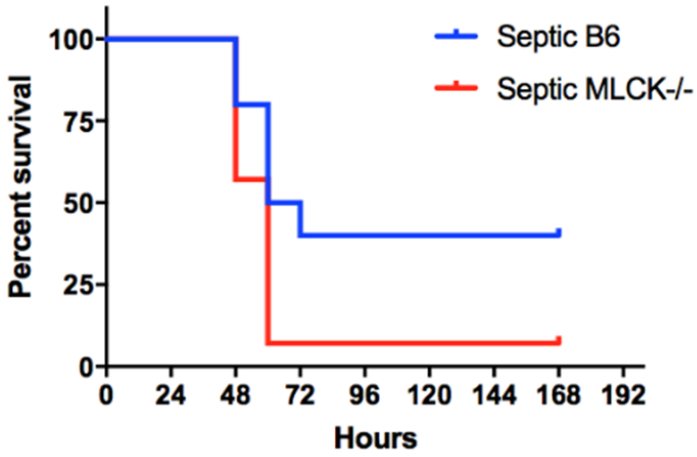


Figure 1: 7-day survival curve (7% vs 40%, n=14-20/ group, p=0.02).

Clinical Science

#39- The Novel use of Combining Autografts, Dermal Regeneration Templates, Cultured Epidermal Autografts and Regenerative Skin Cell Solution on a Large Burn for Optimal Outcome and Cosmesis

Neha Amin, DO, Thao Nguyen, PA, Juvonda Hodge, MD

The skin is the largest organ in the body and in addition to its protective function has immunologic, neurosensory, thermoregulatory, fluid, protein and electrolyte homeostatic functions. Thermal burn injuries disrupt these functions in healing as a complex interaction between cells and extracellular matrix. Satisfactory wound coverage is required to prevent excessive fluid and protein loss, exclude bacterial colonization, and encourage prompt wound healing. Skin grafts have been used for many years to achieve this, but commonly pose problems of availability, adequacy, and immunological rejection. For patients with large total body surface area (TBSA) burns, issues with availability and

adequacy of donor sites increase exponentially. Donor sites often must be re-harvested multiple times to achieve wound closure, and with each subsequent re-harvesting, the viability of the graft is decreased.

Patient PS presented to Grady Burn Center with >80% TBSA. The mortality rate for this major burn is 60-65%, with the leading cause to be septicemia, often caused by major open wounds followed by multi organ failure. His extensive burn injuries left little suitable unburned skin available for autografting using traditional means and so, Integra, Epicel and Recell were used to help achieve wound coverage along with traditional autografting. Currently, the use of Epicel and Recell are under FDA review and only proposed for compassionate use.

In this case, the use of Integra, Recell and CEA helped to quickly and effectively prevent excessive fluid and protein loss, exclude bacterial colonization, and encourage prompt wound healing. His extensive burn injuries left little suitable unburned skin available for autografting using traditional means and so, Integra, Epicel and Recell were used to help achieve wound coverage along with traditional autografting. Currently, the use of Epicel and Recell are under FDA review and only proposed for compassionate use. Patient PS was discharged home safely at HD 81. He has followed up outpatient with no major impairments and has almost reached back to his baseline activities of daily living, including work.

Basic Science

#41- Elucidation of the effects of Aavasimibe on signal pathways in tumor and T lymphocytes that lead to its potential application in cancer immunotherapy.

Dahzi Wang, Lily Yang, Tongrui Liu, Lei Zhu

Recent clinical success in immune checkpoint therapy has shown promising potential of immunotherapy to treat metastatic human cancers. However, small percentage of patients showed good therapeutic responses. Therefore, there is a need to develop novel approaches for enhancing the response to immunotherapy. Results from recent studies revealed that acyl-coenzyme A-cholesterol acyltransferase inhibitor Avasimibe had the effect of anti-tumor growth, activation of cytotoxic T cells and synergistic enhancement of the therapeutic response to PD-1 inhibitor in mouse melanoma model. Our preliminary results showed that Avasimibe inhibited cell growth in human and mouse tumor cell lines. Avasimibe treatment markedly decreased immune check point protein PDL-1 expression in human pancreatic cancer cells. Furthermore, the combination of hyaluronic acid nanoparticles carrying both PDL-1 inhibiting peptides and Avasimibe treatment significantly suppressed tumor growth in a mouse colon cancer model. In this study, we aim to investigate the mechanism behind Avasimibe on both tumor cells and CD8 T cells. One of the research focuses is on the potential effect of Avasimibe on Myc signal pathway that is involved in transcriptional control of PD-1 in T lymphocytes and PD-L1 in tumor cells. We hypothesized that Avasimibe inhibits Myc/Mkk3 interaction, leading to cell proliferation, tumor invasion and downregulation of immune checkpoint proteins. We will also examine key signaling molecules in tumors harvested from mice receiving Avasimibe and the combination of Avasimibe and PDL-1 blockage treatment. Changes in signal molecules will be correlated with tumor responses and cytotoxic T cell response to demonstrate a novel drug synergy.

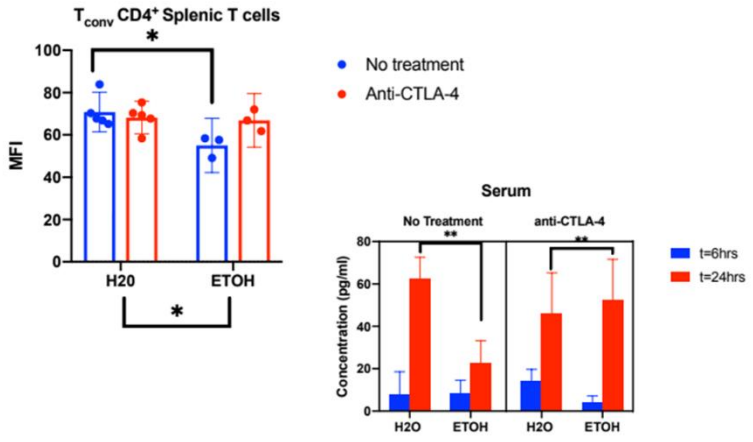
Basic Science

#42- Mechanisms Underlying Decreased Mortality with CTLA-4 Checkpoint Inhibition in a Model of Murine Sepsis with Premorbid Chronic Alcohol Exposure

Cameron Paterson, Mandy Ford, Craig Coopersmith

Mortality from sepsis frequently occurs from secondary infections following a shift to host immunosenesce. This is exacerbated in the setting of alcohol use disorder, and mortality is higher in septic patients with chronic alcohol use. In mice, 12 weeks of alcohol exposure prior to sepsis (ETOH/Sepsis) increases CD4+ T cell expression of the coinhibitory receptor CTLA-4 as well as the frequency of immunosuppressive, CTLA-4 abundant regulatory T cells (Treg). We previously showed that blockade of CTLA-4 improved survival in ETOH/Sepsis. To understand underlying mechanisms, we measured cytokine expression in splenic T cells and serum in mice with chronic alcohol or water ingestion followed by cecal ligation and puncture and then CTLA-4 blockade or vehicle. In ETOH/sepsis, serum values of the pro-inflammatory cytokines IL-2(p=0.004), TNF (p=0.0003) and IL-1B (p=0.04) 24 hours post-sepsis were decreased relative to H2O/sepsis but were rescued with CTLA-4 blockade to levels resembling untreated H2O/sepsis (p=0.94, 0.10, 0.87 respectively). A similar pattern of IL-2 production among ETOH/sepsis was seen in flow cytometry data for conventional CD4+ splenic T cells (Tconv) stimulated ex vivo 24 hours following sepsis (untreated p=0.02, treated p=0.84), as well as in IL-17 for both Tconv (p=0.12 vs 0.99) and Treg (p=0.13 vs 0.99). Together, these data suggest a state of increased immunosuppression in ETOH/sepsis characterized by disparities in pro-inflammatory cytokine signaling related to differential CTLA-4 expression among septic mice with chronic alcohol use, that in turn responds favorably to CTLA-4 blockade. This work provides future targets for investigating the role of CTLA-4 in ETOH/sepsis.

IL-2 Expression In Serum and Splenic T cells Following Sepsis



Mean fluoresence intensity (MFI) of IL-2 in conventional CD4+ splenic T cells 24 hours following cecal ligation and puncture compared with serum concentration (pg/ml) of IL-2 at both 6 and 24 hours. Anti-CTLA-4 was administered 6hrs after sepsis induction. Data were aquired using flow cytometry and bioplex assay, respectively, and were compared with 2-way ANOVA or Mixed-effects analysis, respectively, followed by Tukey's multiple comparisons test.

In T_{conv}, IL-2 expression is significantly different between water and alcohol drinking animals (p=0.02), with significantly different impacts of anti-CTLA-4 treatment on each group respectively (p=0.04). Untreated alcohol drinking animals express significantly less IL-2 than do untreated water drinking animals (p=0.02), but alcohol drinking animals treated with anti-CTLA-4 are not significantly different than untreated water drinking animals (p=0.84)

In serum, IL-2 expression is similar between all groups at t=6 hours, but by t=24 hours untreated alcohol drinking mice fail to increase IL-2 expression compared to H2O drinking mice (p=0.004). However, in anti-CTLA-4 treated mice IL-2 expression is rescued and not significantly different than in untreated water drinking mice (p=.94)

Clinical Science

#44- Dysglycemia with Pancreatic Ductal Adenocarcinoma: A Harbinger Of Survival and Recurrence?

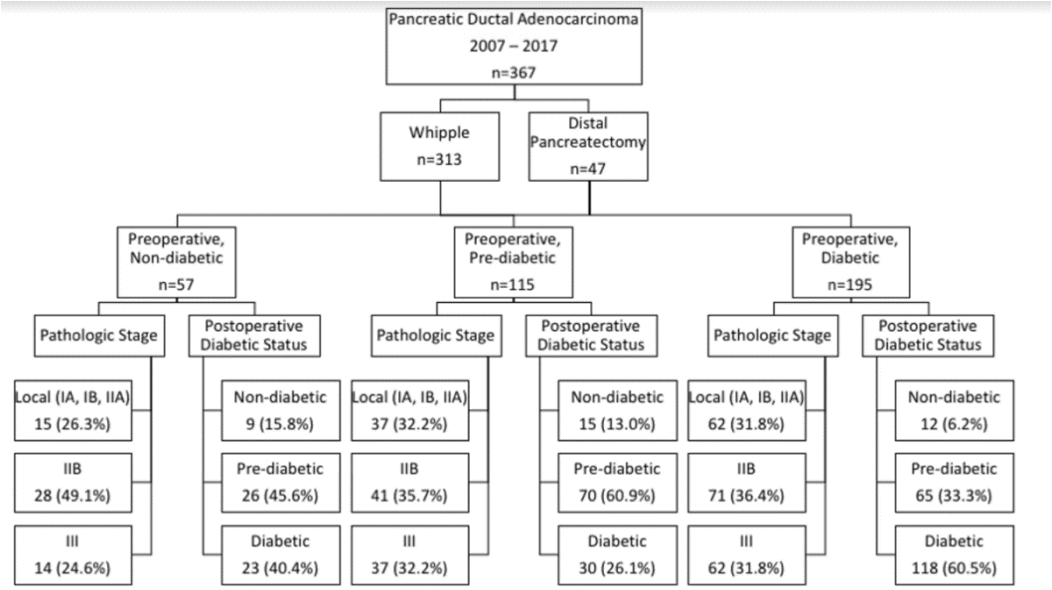
Daniel W. Maxwell, Mohammad Raheel Jajja, Rodolfo J. Galindo, Juan M. Sarmiento

Background: Literature is varied regarding the effect of diabetic status on post-surgical outcomes for patients with pancreatic ductal adenocarcinoma (PDAC). The primary aim was to determine the effect of dysglycemia on outcomes, recurrence, and mortality following resection of PDAC.

Methods: In this prospective study, pre- and postoperative fasting and postprandial (OGTT) plasma glucose, A1c, insulin, and c-peptide were measured in select consecutive patients undergoing intent-to-cure pancreatectomy by the senior author from 2007-2017. American Diabetes Association glycemic definitions and AJCC cancer staging criteria for PDAC were utilized. Dysglycemia was defined as a pre-diabetic or diabetic status. Outcomes, risk, and survival analysis were performed.

Results: Of 1023 patients, 367 patients were included with PDAC and classified as non-diabetic (n=57), pre-diabetic (n=115), and diabetic (n=195) with the following characteristics: 50.9% male, mean age and BMI of 66.5-years and 26.6 kg/m2. The overall incidence of postoperative pre-diabetes and diabetes at 5-years was 43.9% (161/367) and 42.8% (157/367). Recurrence was demonstrated in 154 patients (42.0%) at a median of 14.8 months (range 0-133.4). As preoperative dysglycemia worsened, the median time to recurrence decreased for patients with regional disease (stages IIB and III: HR 1.689, p=0.038). There was no association with new-onset or worsening postoperative dysglycemia and development of recurrence. The median overall 5-year survival was 19.4Â±18.0-years. Non-diabetics demonstrated a clear trend of decreased 5-year survival compared to dyglycemic patients.

Conclusion: Preoperative dysglycemia is directly associated to recurrence and inversely to survival. New-onset and worsening postoperative dysglycemia are not harbingers of recurrence.



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