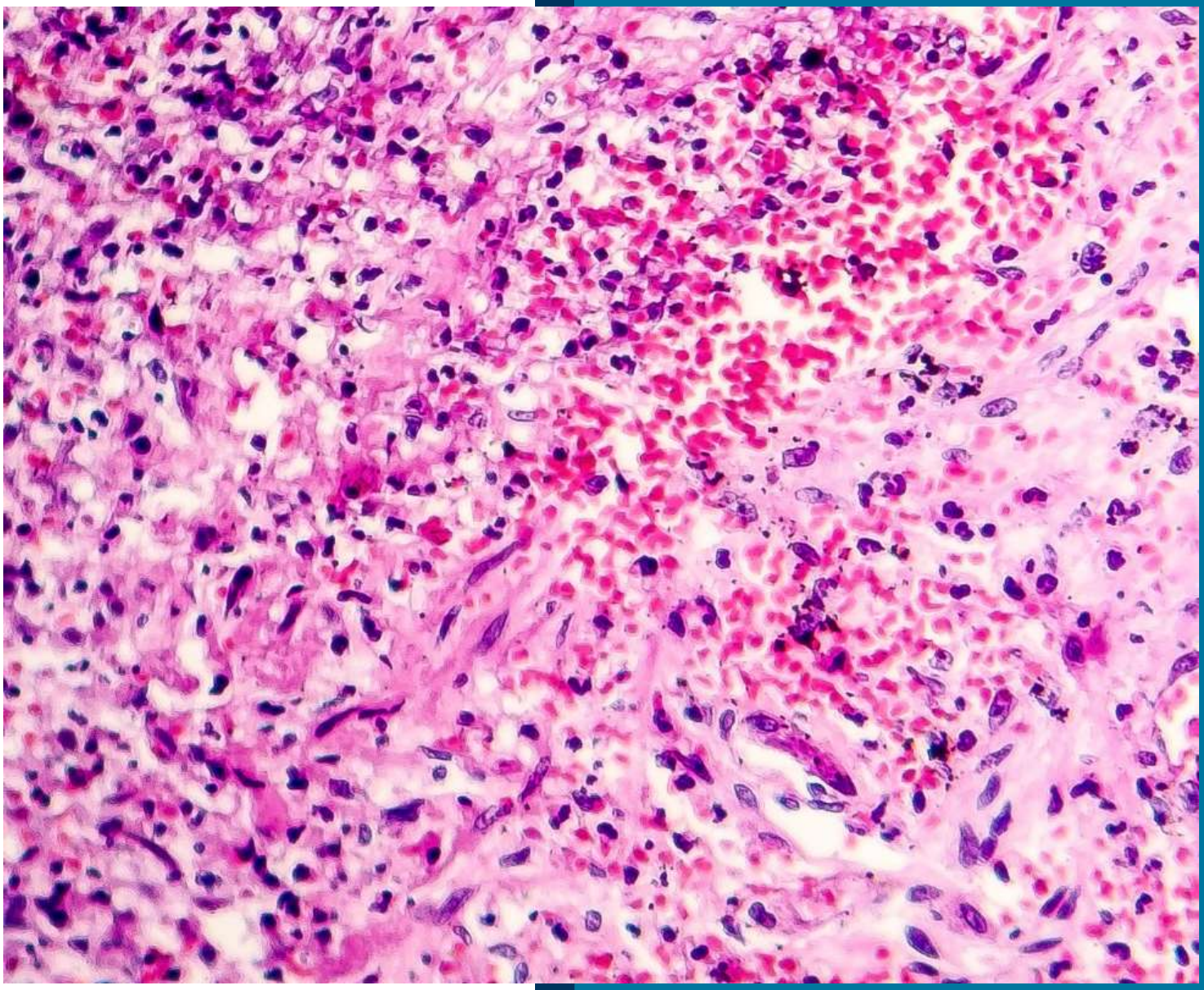
2024



SCTR Scientific Retreat

Inflammation and Fibrosis

Friday, February 2, 2024

8:30 AM Check-In | 9:00 AM Program Start

Bioengineering Auditorium (Room 110) & Lobbies

Medical University of South Carolina

MUSC Medical University of South Carolina

South Carolina Clinical & Translational Research Institute

TABLE OF CONTENTS

SCTR Retreat Contact Information

Sydney Bollinger, MS
Special Projects Coordinator
bollinger@musc.edu

RETREAT AGENDA

8:30 **Check In & Registration**

9:00 **Welcoming Remarks**
Kathleen T. Brady, MD, PhD, SCTR Co-Principal Investigator; Distinguished University Professor, Department of Psychiatry and Behavioral Sciences, Associate Dean for Clinical Research, College of Medicine, MUSC

Opening Remarks
Lori L. McMahon, PhD, MUSC Vice President for Research; Professor of Neuroscience, College of Medicine, MUSC

Keynote Speaker Introduction
Gary S. Gilkeson, MD, Professor, Department of Medicine, and Associate Dean for Faculty Affairs and Faculty Development, College of Medicine, MUSC

9:10 **Keynote Address: "Standing on Shoulders: A History of Interferon Research"**
Peggy Crow, MD, Professor of Medicine, Weill Cornell Medical College

10:10 **Coffee Break and Networking** (*Drug Discovery & Bioengineering Building Lobbies*)

10:20 **Oral Presentations Session 1** *(6 7-minute talks followed by 3-minute Q&A sessions)*
Speaker Introductions & Moderator: Carol Feghali-Bostwick, PhD, Professor, College of Medicine, MUSC
Session Co-Chair: Paula Ramos, PhD, Associate Professor, College of Medicine, MUSC

10:25 CD8 T-cell transfer effects on biomechanics of post-myocardial infarction scar formation
Shaoni Dasgupta, Graduate Student, College of Graduate Studies, Medical University of South Carolina

10:35 IL32 overexpression contributes to an extracellular matrix (ECM) remodeling in EpCAM-/CD49f-enriched breast cancer cells.
Charlotte McGuinness, Student, Presbyterian College

10:45 Persistence of fetal gene signatures along the mesenchymal lineage trajectory defines heterogeneity and function of pancreatic cancer associated fibroblasts
Lu Han, Post-doctoral Fellow, College of Medicine, Medical University of South Carolina

10:55 Control of Fibrotic Gene Expression in Cardiac Fibroblasts via the Rap1 GTPase.
Adi Dubash, PhD, Associate Professor of Biology, Furman University

11:05 Differential expression of Interferon lambda receptor-1 isoforms influence gene expression and hepatitis B virus replication in stem cell-derived hepatocytes
Laura Novotny, PhD, College of Medicine, Medical University of South Carolina

11:15 **Coffee Break and Networking** (*Drug Discovery & Bioengineering Building Lobbies*)

11:25 **Oral Presentation Session 2** *(6 7-minute talks followed by 3-minute Q&A sessions)*
Speaker Introductions & Moderator: Kevin M. Gray, MD, Professor, College of Medicine, MUSC
Session Co-Chair: Diane Kamen, MD, MSCR, Professor, College of Medicine, MUSC

11:30 Linking Ayurvedic Medicine, Computational Biology, and Experiential Learning to Discover Molecular Mechanisms of Ayurvedic Super Spices

Shivani Gupta, Founder & CEO, Fusionary Formulas
Alex Feltus, PhD, Professor, College of Science, Clemson University

11:40 The Clinical Burden of Systemic Lupus Erythematosus (SLE), Lupus Nephritis (LN), and Associated X-linked Genes in a Diverse Cohort of Women
Angela Malek, Associate Professor, Department of Public Health Sciences, College of Medicine, Medical University of South Carolina

11:50 Pregnancy Outcome Disparities Among Women with Systemic Lupus Erythematosus
Jessica English, MD, Rheumatology Fellow, Department of Medicine, Medical University of South Carolina

12:00 Effects of Neurogenic Hypertension and Anxiety on Aortopathy
Heather Holman, College of Graduate Studies, Medical University of South Carolina

12:10 PTSD-like mice display negative cardiac characteristics post-inescapable foot shock
Alexa Corker, Student, College of Graduate Studies, Medical University of South Carolina

12:20 Defining mechanisms of fungal-bacterial interactions during cystic fibrosis infection
Stephen Dolan, Assistant Professor, College of Science, Clemson University

12:30 **Working Lunch & Poster Presentations**
The full list of poster titles and presenters is included in the pages that follow.

12:50 **Poster Presenters at Posters**

1:30 **Interactive Panel Session: State of the Art Techniques and Tools to Leverage in Inflammation and Fibrosis Research**
Panelists: Alex Alekseyenko PhD, Alex Feltus, PhD, Leslie Lenert, MD, Lori McMahon, PhD, Peggi Angel, PhD, Ozlem Yilmaz, DDS, PhD
Facilitator: Alex Feltus, PhD

2:30 **SCTR Institute Pilot Project Program Funding Opportunities**
Sydney Bollinger, MS, Special Projects & Pilot Studies Program Coordinator, SCTR, MUSC

2:35 **Closing Remarks**
Kevin M. Gray, MD, Director, SCTR Pilot Studies; Professor and Director of Addiction Sciences, Department of Psychiatry and Behavioral Sciences, Assistant Vice President for Advancing Research Partnerships, MUSC

POSTER PRESENTATIONS

Location: Bioengineering Building & Drug Discovery Build Lobbies

Poster ID **Title & Presenter**

1 **Novel Therapeutics for Fibrotic and Other Diseases: Modified Versions of the Caveolin-1 Scaffolding Domain Peptide with Improved Characteristics for Drug Development**
Stanley Hoffman, PhD, Professor, Department of Medicine, College of Medicine, MUSC
Charles Reese, PhD, Postdoctoral Scholar, Department of Medicine, College of Medicine, MUSC

2 **The Role of Bhlhe40 In Systemic Sclerosis-Associated Pulmonary Fibrosis**
Adegboyega "Tim" Adewale, Student, College of Graduate Studies, MUSC

3 **The Clinical Burden of Systemic Lupus Erythematosus (SLE), Lupus Nephritis (LN), and Associated X-linked Genes in a Diverse Cohort of Women**
Angela Malek, PhD, Associate Professor, College of Medicine, MUSC

4 **Association of Biologic Sex, Glycosphingolipids, and the N-glycome in Renal Mesangial Cell Function**
Sandy Mungaray, Research Specialist, College of Medicine, MUSC

5 **Targeting of Endothelial Dysfunction in Lupus Nephritis: Effect on Human Renal Endothelial Cell Gene Expression and Outcomes in Murine Lupus Nephritis**
Dayvia Russell, Research Specialist, College of Medicine, MUSC

6 **PTSD-like mice display negative cardiac characteristics post-inescapable foot shock**
Alexa Corker, Student, College of Graduate Studies, MUSC

7 **Influence of Social Support on Lupus Outcomes in a Health Disparity Population**
Sarah Smith, MD, College of Medicine, MUSC

8 **Effects of Neurogenic Hypertension and Anxiety on Aortopathy**
Heather Holman, Student, College of Graduate Studies, MUSC

9 **IL32 overexpression contributes to an extracellular matrix (ECM) remodeling in EpCAM-/CD49f-enriched breast cancer cells.**
Charlotte McGuinness, Student, Presbyterian College

10 **CD8 T-cell transfer effects on biomechanics of post-myocardial infarction scar formation**
Shaoni Dasgupta, Graduate Student, College of Graduate Studies, MUSC

11 **Characterizing Human Cardiac Fibroblast Responsiveness to Hemodynamic Unloading in Heart Failure with Reduced Ejection Fraction**
Rachel Biggs, PhD Candidate, College of Graduate Studies, MUSC

12 **Defining mechanisms of fungal-bacterial interactions during cystic fibrosis infection**
Stephen Dolan, PhD, Assistant Professor, College of Science, Clemson University

13 **Predicting mechanisms of IGF2-mediated fibrosis in primary human lung fibroblasts.**
Kristy Waldrep, Research Specialist, College of Medicine, MUSC

14 **From lungs to blood - An "omics" approach to Pulmonary Sarcoidosis biomarker identification**

Jessalyn Rodgers, Research Specialist, College of Medicine, MUSC

15 **Comparison of the transcriptomic signature of pulmonary fibrosis according to gender in patients with systemic sclerosis.**
Ludivine Renaud, PhD, Instructor, College of Medicine, MUSC

16 **Persistence of fetal gene signatures along the mesenchymal lineage trajectory defines heterogeneity and function of pancreatic cancer associated fibroblasts**
Lu Han, PhD, Post-doctoral Fellow, College of Medicine, MUSC

17 **Development of a Novel Drug Candidate for Scleroderma**
Galina Bogatkevich, MD, PhD, Associate Professor, College of Medicine, MUSC

18 **YAP1- A key mediator in Enolase-1 driven pulmonary fibrosis**
Shailza Sharma, PhD, Post-doctoral Fellow, College of Medicine, MUSC

19 **Linking Ayurvedic Medicine, Computational Biology, and Experiential Learning to Discover AMolecular Mechanisms of Ayurvedic Super Spices**
Shivani Gupta, Founder & CEO, Fusionary Formulas
Alex Feltus, Professor, College of Science, Clemson University

20 **Lupus-Associated Vascular Dysfunction in Females Correlates with Elevated Endothelin-1: Symptomatic or Causative?**
Marice McCrorey, Student, College of Graduate Studies, MUSC

21 **Control of Fibrotic Gene Expression in Cardiac Fibroblasts via the Rap1 GTPase.**
Adi Dubash, PhD, Associate Professor of Biology, Furman University

22 **Pregnancy Outcome Disparities Among Women with Systemic Lupus Erythematosus**
Jessica English, MD, Rheumatology Fellow, Department of Medicine, Medical University of South Carolina

23 **Effect of altered glycosphingolipid levels on the inflammatory response of human renal glomerular cells**
Anna Tingler, Student, College of Graduate Studies, MUSC

24 **Elucidating the Role of Estrogen Receptor Alpha in Systemic Lupus Erythematosus**
Lauren Bracken, Research Specialist, College of Medicine, MUSC

25 **Differential expression of Interferon lambda receptor-1 isoforms influence gene expression and hepatitis B virus replication in stem cell-derived hepatocytes**
Laura Novotny, PhD, Staff Scientist, College of Medicine, MUSC

PLANNING COMMITTEE

Ordered alphabetically by last name.

Sydney Bollinger, MS

Amy Bradshaw, PhD

Shanora G. Brown, PhD

Carol Feghali-Bostwick, PhD*

Alex Feltus, PhD

Kevin Gray, MD

Gayenell Magwood, PhD, RN, FAHA, FAAN

Anand Mehta, PhD

Jim Oates, MD*

Don C. Rockey, MD

Tracey Schock, PhD

Kit Simpson, DrPH

Hongjun Wang, PhD

Ozlem Yilmaz, DDS, PhD

*Committee Co-Chair

KEYNOTE SPEAKER

Keynote Presentation: Standing on Shoulders: A History of Interferon Research

Keynote Speaker: Peggy Crow, MD

Mary K. “Peggy” Crow, MD, is Physician-in-Chief Emeritus at Hospital for Special Surgery, Professor of Medicine, Weill Cornell Medical College, and Senior Scientist, Hospital for Special Surgery Research Institute.

Dr. Crow’s research focuses on the type I interferon pathway in systemic autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and Sjogren’s Syndrome. She is the Physician-in-Chief Emeritus at Hospital for Special Surgery (HSS), Professor of Medicine at Weill Cornell Medical College, and Professor of Immunology in the Graduate School of Medical Sciences. She is Director of the Autoimmunity and Inflammation Program at the HSS Research Institute.

Full Profile

PRESENTATION ABSTRACTS

ORAL PRESENTATION SESSION 1

*Denotes presenting author

Abstracts listed in presentation order.

CD8 T-cell transfer effects on biomechanics of post-myocardial infarction scar formation

Authors Names:
Shaoni Dasgupta*, Maya Learmonth, Alexa Corker, Miguel Troncoso, Philip Broughton, Catalin F. Baicu, Amy D. Bradshaw, Michael R. Zile, Kristine Y. DeLeon-Pennell

Introduction/Objectives:
Our lab has demonstrated that CD8+ T-cells are adverse regulators of post-myocardial infarction (MI) remodeling. Based on previous studies, we hypothesize that CD8+ T-cells impair cardiac function by altering scar composition

Methods:
MI was induced by ligating the left anterior descending coronary artery on C57BL6/J wildtype (WT; 3-7 months of age, n≥2/sex) and CD8atm1mak (CD8-/-; 3-7 months of age, n≥2/sex/ group) mice. CD8-/- mice were given either vehicle or naïve splenic CD8+ T-cells via tail vein injection, 4-hours post-coronary artery ligation to assess effects on the scar. On Day 7 post-MI, infarct tissue was collected for passive stretch biomechanical analysis or histological assays for collagen composition. The effects of granzyme (Gzm) B and K on collagen cleavage were tested through a fluorogenic collagen cleavage assay, assessing possible mechanisms of scar alteration.

Results:
Mice lacking CD8+ T-cells had improved ejection fraction and decreased dilation compared to WT mice at post-MI Day 7. CD8-/- mice that received splenic CD8+ T-cells lost this protective effect. Biomechanical analysis demonstrated CD8-/- mice had 2-fold increase in regional stiffness compared to WT mice and re-supplementation with splenic CD8+ T-cells decreased scar tissue stiffness mimicking biomechanics of WT mice. Picrosirius red staining showed no significant differences in total collagen levels ($p=0.51$). Collagen 1 immunoblotting of the infarct trended an increase in the 250 kDa band in CD8-/- mice that decreased after supplementation, indicating loss of pro-collagen formation ($p=0.051$). Ex-vivo cleavage assay demonstrated GzmK cleaved collagen in concentration (0-50 AU) and temporal-dependent manner (0-24 hrs). Moreover, GzmK demonstrated 10-fold greater capacity in collagen cleavage compared to GzmB at 25 AU, suggesting the role GzmK plays during post-MI remodeling may be distinctly separate from that of GzmB.

Discussion/Conclusions:
In conclusion, our data demonstrates that CD8+ T-cells regulate cardiac fibrosis potentially through the release of granzymes, leading to alterations in the left ventricle biomechanical capability.

Acknowledgements:
Funding: This work was supported by the National Institutes of Health T32GM123055, R25GM113278; the Biomedical Laboratory Research and Development Service of the Veterans Affairs Office of Research and Development Award IK2BX003922 and BX005848; and South Carolina Translational Research Center UL1TR001450.

IL32 overexpression contributes to an extracellular matrix (ECM) remodeling in EpCAM-/CD49f- enriched breast cancer cells.

Authors Names:
Margaret V. Leonard, Charlotte B. McGuinness*, Elayne M. Benson, Megan A. Wilson, Emma V. Gray, Paris L Rizzo, Maria Ouzounova, Hasan Korkaya, Austin Y. Shull

Introduction/Objectives:
Basal-like breast cancers typically correspond with increased enrichment of EpCAM-/CD49f- cancer stem cells (CSC) and a propensity toward metastasis. However, the molecular mechanisms underlying these general characteristics are not well understood.

Methods:
To provide further insight concerning CSCs and their intrinsic metastatic mechanisms, we compared the 450K DNA methylation profile of EpCAM-/CD49f- poor breast cancer cell lines to that of EpCAM-/CD49f- enriched breast cancer cell lines.

Results:
From our results, we were able to determine and highlight IL32 as a gene whose promoter is hypomethylated in EpCAM-/CD49f- enriched cell lines. The hypomethylated IL32 promoter corresponded with increased IL32 expression in both cell lines and inflammatory expression in basal-like breast cancer patients from The Cancer Genome Atlas (TCGA) database. Interestingly, increased IL32 expression preferentially occurred for the IL32 beta transcript and corresponds with previous reports demonstrating that IL32-beta is not secreted from the cell like other canonical interleukins and is intracellularly localized in breast cancer cells. Additionally, expression of the beta-transcript could be suppressed when CSC-enriched cells were treated with the BET-bromodomain inhibitor JQ1. Because of this phenomenon, we sought to determine the effects of suppressing IL32 in the EpCAM-/CD49f- enriched cell line SUM159PT via siRNA-mediated knockdown and subsequent RNAseq differential expression analysis. From our results, we determined that transcripts involved in extracellular matrix (ECM) organization and fibrosis were preferentially affected by IL32 silencing. Additionally, IL32 suppression decreased the invasiveness of SUM159PT based on an ECM-matrix cell invasion assay as well as increased tumor-centric fibronectin production. Furthermore, IL32 suppression decreased CXCL2/CXCL3 secretion, which is a chemokine canonically involved in inflammation and cell migration.

Discussion/Conclusions:
Collectively, our results reflect the notion that differential IL32 expression by promoter hypomethylation in breast CSCs plays a role in ECM/fibrosis remodeling for purposes of breast cancer cell invasion and metastasis.

Acknowledgements:
This work was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number P20GM103499 (SC INBRE).

Persistence of fetal gene signatures along the mesenchymal lineage trajectory defines heterogeneity and function of pancreatic cancer associated fibroblasts

Authors Names:
Lu Han*, Tom Walter, Joseph Beaudet, Caroline Everett, Kun Fang, Michael Zimmermann, Angela Mathison, Raul Urrutia, Victor Jin, Gustavo Leone, Michael Ostrowski

Introduction/Objectives:
Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer and is the most lethal type among all major cancer types. In PDAC, cancer associated fibroblasts (CAFs) play critical and complex roles in the tumor microenvironment. CAFs are also a major cell type in the stroma and may account for more than half of the entire tumor tissue volume. Here we aimed to investigate the origin, diversification, and function of CAFs.

Methods:
We constructed a dual-DNA-recombinase mouse genetic model, which allowed for genetic alternations in pancreatic epithelial cells and fibroblasts independently and simultaneously. Single cell RNA sequencing and immunostaining on tissues were performed to investigate gene expression dynamics of the pancreatic mesenchymal lineage. We further constructed mouse genetic models to delete one of the splanchnic factors GATA6 specifically in CAFs.

Results:
Our study identified the splanchnic mesenchyme, which is a tissue layer generated during early gestation, as the origin of pancreatic fibroblasts during adult homeostasis and tumorigenesis. Notably, the other two postulated origins, bone marrow and epithelial cells, have minimal contributions to fibroblasts. Additionally, single cell transcriptomic analysis indicated persistent and dynamic gene expressions along this mesenchymal trajectory during development, homeostasis, precancer lesion and cancer. Intriguingly, certain splanchnic factors are expressed in adult pancreatic fibroblasts in temporally and spatially distinct patterns. Moreover, Gata6 deletion in fibroblasts resulted in increased tumor burden in the pancreas.

Discussion/Conclusions:
In summary, this study delineated a continuous cell trajectory of the mesenchymal lineage in the pancreas across different life stages. Furthermore, persistent gene expressions along the mesenchymal trajectory contributes to pancreatic CAF heterogeneity. Importantly, such persistence may constitute an inherent mechanism to suppress pancreatic cancer through cancer stroma crosstalk. The enhancement of this mechanism could be explored further for therapeutic benefits.

Acknowledgements:
T32 CA193201 Howe (PI) NIH/NCI F32 CA254238 Han (PI) NIH/NCI PF-20-114-01-DDC Han (PI) American Cancer Society 1K99CA263005-01A1 Han (PI) NIH/NCI P01 CA203653-01A Guttridge, Ostrowski and Zimmers (PI) NIH/NCI

Control of Fibrotic Gene Expression in Cardiac Fibroblasts via the Rap1 GTPase.

Authors Names:
Kobby Frempong, Jonathan G. Heywood, Michael R McLeod, S Madison Thomas, William J Richardson and Adi D. Dubash*

Introduction/Objectives:
Fibrosis describes the excessive deposition of extracellular matrix components by cardiac myofibroblasts (CFs), a process which frequently promotes the adverse effects of pathological conditions damaging cardiac muscle, such as myocardial infarction and arrhythmogenic cardiomyopathy. Roughly 1 million Americans suffer a myocardial infarction each year, after which necrotic cardiac myocytes (CMs) are replaced by CF-derived extracellular matrix (ECM), in response to (a) biochemical signaling cues from necrotic CMs and (b) mechanical cues from the contracting myocardium and ventricle cavity pressure. Accumulation of ECM proteins (such as collagen) within the infarct scar is initially critical to prevent further tissue damage, but chronic and excessive collagen deposition is detrimental to regeneration of CMs and healing of the myocardium. While the physiological outcomes of cardiac fibrosis are well studied, the biochemical and mechano-responsive signaling mechanisms which regulate fibrotic gene expression remain poorly investigated. The GTPase Rap1 is very well-known to mediate both inside-out and outside-in signaling via attachment of integrins to ECM proteins, but less is known about its role in fibrotic gene expression. Based on prior data, we hypothesized that expression of constitutively active Rap1A(63E) would inhibit fibrotic gene expression in cardiac fibroblasts.

Methods:
In our study, we investigated the mRNA and protein expression of fibrotic markers (via quantitative PCR and western blot) in Neonatal rat ventricular cardiac fibroblasts expressing either GFP alone (control) or GFP-Rap1A(63E).

Results:
We show that expression of constitutively active (63E) Rap1A in cardiac fibroblasts results in a dramatic decrease in myofibroblast activation, measured via smooth muscle alpha-actin (ACTA2). Further, Rap1A(63E) also inhibits expression of many different ECM proteins (COL1A1, COL3A1, COL4A1 and FN1), as well as other markers of fibrotic gene expression. In contrast, Rap1A(63E) increases the expression of matrix remodeling enzymes (such as MMP3 and MMP9) which have been shown to play a role in increasing collagen turnover, reducing ECM rigidity/stiffness and repair of damaged myocardial tissue. Lastly, we provide evidence that Rap1A(63E) mediates its effects on these fibrotic and inflammatory markers via Src and NFkB signaling.

Discussion/Conclusions:
Altogether, these data point to a significant role for Rap1A GTPase in reducing fibrotic gene expression and myofibroblast activation and suggest possible new therapeutic strategies to combat the damaging effects of cardiac fibrosis.

Acknowledgements:
This project was funded by an SC INBRE administrative supplement award for collaborative INBRE/COBRE research (Co-PIs: Adi Dubash at Furman University & William Richardson at Clemson University).

Differential expression of Interferon lambda receptor-1 isoforms influence gene expression and hepatitis B virus replication in stem cell-derived hepatocytes

Authors Names:

Laura A. Novotny*, J. Grayson Evans, Christiana S. Kappler, and Eric G. Meissner

Introduction/Objectives:
Hepatitis B virus (HBV) causes chronic liver infection and individuals are at risk to develop liver fibrosis, cirrhosis and hepatocellular carcinoma. HBV disease persists due to continuous viral gene transcription from the covalently closed circular DNA (cccDNA) genome deposited in the nucleus of infected hepatocytes. Lambda interferons (IFNLs) are cytokines that bind the interferon lambda receptor-1 (IFNLR1)-IL10RB complex to initiate antiviral responses. Three IFNLR1 transcriptional variants are predicted whose role in regulation of IFNL signaling is unclear: a full-length and signaling-capable form (isoform 1), a form that lacks a portion of the intracellular JAK1 binding domain (isoform 2), and a secreted form (isoform 3), the latter two predicted to be signaling-defective. We hypothesized that altering expression of IFNLR1 isoforms would differentially impact the hepatocellular response to IFNL treatment and HBV replication.

Methods:
iPSCs that stably expressed doxycycline (dox)-inducible, FLAG-tagged IFNLR1 isoform 1, 2, or 3 constructs, or vector-control, were differentiated to hepatocyte-like cells (iHeps). After establishing HBV infection, each line was treated +/- dox concomitant with +/- IFNL3 for 8 days. Antiviral and pro-inflammatory gene expression were quantitated, and HBV replication evaluated by measure of HBV-DNA, cccDNA and HBeAg levels.

Results:
Minimal overexpression of IFNLR1 isoform 1 markedly augmented antiviral expression, induced de novo proinflammatory gene expression, and enhanced inhibition of HBV replication after IFNL treatment. In contrast, overexpression of IFNLR1 isoforms 2 or 3 partially augmented antiviral gene expression after IFNL treatment but did not support proinflammatory gene expression and HBV replication was minimally impacted.

Discussion/Conclusions:
Relative expression of each IFNLR1 isoform uniquely and differentially influenced antiviral and pro-inflammatory gene expression and HBV replication in IFNL3-treated iHeps. These data suggest regulated expression of IFNLR1 could limit the capacity of IFNL treatment to counteract HBV replication.

Acknowledgements:
EGM- NIGMS (P20GM120457), NIDDK (P30DK123704). JGE- NCATS (TL1TR001451). Additional support- MUSC CDLD (GM130457) and DDRCC (DK123704).

ORAL PRESENTATION SESSION 2

*Denotes presenting author

Abstracts listed in presentation order.

Linking Ayurvedic Medicine, Computational Biology, and Experiential Learning to Discover AMolecular Mechanisms of Ayurvedic Super Spices

Authors Names:
Shivani Gupta*, Edward Mabry, David J. Clarke IV, F. Alex Feltus*

Introduction/Objectives:
Nutrigenomics is an area of research that explores how foods and their ingredients interact with our 62,696 genes. Through nutrigenomics biohackathons, teams learn how any ingredient upregulates and downregulates human gene expression in response to an ingested compound. In application of our approach, Praxis AI collaborated with Dr. Shivani Gupta (www.shivanigupta.com), a passionate practitioner of Ayurvedic medicine, to explore the medicinal properties of turmeric and its primary active molecule, curcumin. Curcumin research that has grown exponentially over the last decade, with over 6,000 scientific studies published on the topic, and clinical trials growing. Together, we recruited 30+ scientists across three research teams to explore the effects of curcumin on cancer, cardiovascular disease, and Alzheimer's. Our goal was to understand how and why different Ayurvedic SuperSpices and various spice derivatives interact with our genes. New product development from this deep research could be profound for the exploration of better solutions to support health and prevention for mankind.

Methods:
One BioHacker citizen scientist continued research after the event and has written valuable open-source Python code, cartoflow (github.com/ZealousGeneticist/cartoflow), that scours databases for nutritional compound-gene interactions. The python code is able to search an input list of chemical identifiers through APIs at The Comparative Toxicogenomics Database and Intact Database to discover chemical-gene and protein-protein interactions, respectively.

Results:
We will present both the generalizable cartoflow code and the curcumin-inflammation pathway genes we discovered as well as our perspective on using experiential hackathon approaches for scientific discovery. We will also discuss downstream applications for turmeric and ginger for addressing diseases associated with inflammation.

Discussion/Conclusions:
While further exploration and validation is required to understand the genetic mechanism of curcumin impact on phenotype, we aim to bridge this proven Ayurvedic therapeutic with genome analysis to understand the genetic mechanisms that can potentially ameliorate specific disease pathology.

Acknowledgements:
All biohackathon participants to be named in the presentation.

The Clinical Burden of Systemic Lupus Erythematosus (SLE), Lupus Nephritis (LN), and Associated X-linked Genes in a Diverse Cohort of Women

Authors Names:
Angela M. Malek*, Mara Lennard Richard, Bethany Wolf, Tamara Nowling, Stefano Berto, Bryan Granger, Martin Romeo, Silvia Vaena, Jonathan Flume, Lori Ann Ueberroth, James Oates

Introduction/Objectives:
Systemic lupus erythematosus (SLE) is a heterogeneous, chronic, autoimmune disease largely affecting women. Disparities exist as African Americans (AA) experience earlier onset and increased

prevalence and disease severity, with incidence high among Gullah AAs. The mechanisms for racial/ethnic differences in SLE and lupus nephritis (LN) are unclear. Some SLE X-linked genes escape inactivation (4/6) and 1/3 affect the type I interferon pathway. We aimed to describe the clinical burden of SLE including LN and SLE X-linked gene expression in a diverse group of women in South Carolina.

Methods:
The CCCR and SLEIGH cohorts have followed SLE patients since 2004. Differences in SLE clinical burden (disease activity, damage, comorbidities) and progression to LN were assessed in women of three racial/ethnic groups. Cox regression evaluated associations between time from SLE to LN diagnosis adjusted for sociodemographic, behavioral, and clinic characteristics.

Results:
The 663 women with SLE (non-Gullah AA [36.2%], Gullah AA [40.6%], European American [EA; 23.2%]) had a mean±SD diagnosis age of 32.3±15.0. Approximately 45.4% were classified as having LN based on diagnosis, labs, or biopsy confirmation, and 18.1% had hyperlipidemia. Increasing SLE diagnosis age (HR=0.92, 95% CI: 0.87-0.97), EA vs. AA (HR=0.41, 95% CI: 0.29-0.58), and hyperlipidemia (HR=0.47, 95% CI: 0.26-0.85) were associated with decreased risk of progression from SLE to LN diagnosis after adjustment and multiple imputation. Of the nine women with SLE who provided samples, five had LN. No significant differences were observed in expression of X-linked genes of interest (TLR7, TMEM187, IRAK1, CXorf21, GPR173, LINC01420) by ethnicity, LN, or end-stage renal disease status; however, other X-linked genes were differentially expressed (e.g., MTRNR2L12 [humanin isoform], chrXp21, LMNA).

Discussion/Conclusions:
Women with older age at SLE diagnosis, EA race/ethnicity, and hyperlipidemia, experienced slower progression to LN after covariate adjustment. Gene set analysis-indicated differences in X-linked gene expression warrant further examination.

Acknowledgements:
This work was supported by the South Carolina Clinical & Translational Research Institute (SCTR) Discovery grant award (SCTR 2010) and by SCTR (UL1 TR001450). We thank Brianna Sanders (MUSC) for assistance with the project.

Pregnancy Outcome Disparities Among Women with Systemic Lupus Erythematosus

Authors Names:
Jessica English, MD*, Katie Kirchoff, Bethany Wolf, PhD, and Diane Kamen, MD MSCR

Introduction/Objectives:
Women with systemic lupus erythematosus (SLE) have increased rates of pre-term birth, small for gestational age babies, and pre-eclampsia compared to women without a diagnosis of SLE. Ongoing research has shown a dysregulated immune system, adversely affects patients even if SLE is not yet diagnosed suggesting a "pre-SLE disease state" exists. We hypothesize that a pre-SLE disease state impacts pregnancy outcomes among women with circulating SLE-associated autoantibodies prior to a diagnosis of SLE.

Methods:
Case control study including women with at least one prior recorded pregnancy from an ongoing longitudinal SLE registry at a single center. Controls (related or unrelated) were included if unaffected by SLE. Associations between different pregnancy outcomes with patient-pregnancy type and demographic variables were evaluated with univariate and multivariable modeling.

Results:
630 women (SLE and controls) were included in our analysis with 1715 pregnancies, Table 1. Of those, 303 women (736 pregnancies) were prior to a diagnosis of SLE. A higher proportion of related controls were ANA positive (47.7%) as compared to unrelated controls (30.5%). Multivariable analysis, Table 2, revealed no differences in ANA positive versus negative controls in odds of live birth, preeclampsia, low-birth-weight, or premature delivery. Those with pregnancies prior to a diagnosis of SLE had lower odds of live birth, OR 0.64 (0.45-0.92) and increased odds of preeclampsia, OR 2.12 (1.04-4.35) as compared to ANA positive controls.

Discussion/Conclusions:
In a large SLE cohort, we note differences in pregnancy outcomes among women with SLE compared to two groups of controls. Women prior to their diagnosis of SLE had fewer live births (76.6 vs 81.3%) & higher preeclampsia risk (9.3% vs 4.9%) compared to ANA positive controls, which remained statistically significant after controlling for potential confounders. A pre-disease state, beyond ANA positivity, may exist increasing pregnancy risk before the diagnosis of SLE in some patients.

Acknowledgements:
We would like to thank the patients and controls whose participation made this research possible, as well as the research coordinators and investigators who have given their time, effort and expertise. Funding for this project was made possible by the National Institutes of Health under award numbers: NIAMS P30 AR072582 (Gilkeson, Oates), NIAMS R21 AR067459 (Kamen), NIAMS K24 AR068406 (Kamen), and NCRR UL1 RR029882 to MUSC. There are no other relevant financial disclosures.

Effects of Neurogenic Hypertension and Anxiety on Aortopathy

Authors Names:
Heather Holman*, Ying Xiong, Jean Marie Ruddy, Rupak Mukherjee, Jeffrey A. Jones

Introduction/Objectives:
Neurogenic hypertension is defined as uncontrolled blood pressure while on more than 5 different anti-hypertensives resulting from an unknown cause. It's estimated that 50% of patients with essential hypertension have neurogenic hypertension. Although the mechanism behind neurogenic hypertension is under investigation, its direct effects on aortopathy has yet to be elucidated.

Methods:
Adult male and female BPH/2J and BPN/3J mice underwent noninvasive blood pressure measurement to confirm hypertension (BPH/2J) and normotension (BPN/3J). Mice underwent a series of behavioral tests assessing for anxiety. Composite t-scores were generated for each of the mice from the average z-scores on the individual behavior tests. Thoracic aortae were harvested and assessed for changes in compliance by parallel-wire myography and alterations in aortic wall structure via histology. Thoracic aortic

aneurysms were induced in BPH/2J and BPN/3J mice through periadventitial application of a 0.5M CaCl2 solution to the descending thoracic aorta. Thoracic aortic diameter was measured 4-weeks post-surgery by digital microscopy.

Results:
BPH/2J mice had significantly elevated systolic blood pressures as compared to BPN/3J mice (BPH/2J (n=5), 172 ± 5mmHg; BPN/3J (n=6), 129 ± 10mmHg, p<0.05). Behavioral testing revealed that 83% (5 of 6) of the BPH/2J mice had high anxiety. Furthermore, BPH/2J mice developed significantly larger thoracic aortic aneurysms (BPH/2J (n=6), 68.8 ± 16% increase from baseline diameter; BPN/3J (n=5), 21.8 ± 3.6%, p <0.05).

Discussion/Conclusions:
Chronic neurogenic hypertension can trigger extracellular matrix remodeling resulting in compensatory stiffening of the thoracic aorta. In the presence of aortic pathology, elevated mechanical tension (increased blood pressure) can accelerate disease progression. BPH/2J mice display increased anxiety, which could result from alterations in neural circuits propagating the neurogenic hypertension. Future studies investigating the aorta's response to mechanical tension and the mechanism behind neurogenic hypertension may further our understanding of how hypertension accelerates aortopathy, particularly in the setting of PTSD.

Acknowledgements:
Funding: NIH-NCATS TL1 TR00145-08 & UL1TR001450-08 and VA Merit Award I01-BX000904-08A1

PTSD-like mice display negative cardiac characteristics post-inescapable foot shock

Authors Names:
Alexa Corker*, Miguel Troncoso, Maya Learmonth, Philip Broughton, Sara Sidles, Ryan Kelly, Amanda LaRue, Kristine Y. DeLeon-Pennell

Introduction/Objectives:
Post-traumatic stress disorder (PTSD) is a risk factor for cardiovascular disease, however the mechanism behind this correlation is unknown. We hypothesized that PTSD alters cardiac homeostasis by increasing macrophage numbers and initiating cardiac fibrosis.

Methods:
To induce experimental PTSD, male and female C57BL/6 mice (4-weeks: n=16-17/sex, males=4.7±0.4 months old; females=4.8±0.3 months old; 8-weeks: n=13-16/sex, males=6.0±0.3 months old; females=6.3±0.5 months old) were exposed to 5 separate foot-shock incidences (IFS; 1.0 mA, 1 sec duration) in 6 min. Control mice (n=8-9/sex) were placed in the same chambers but experienced no foot shocks. Behavioral tests (16 parameters based on the DSM-5 clinical standards) were performed to characterize mice that do not demonstrate PTSD-like behavioral characteristics (NR) and PTSD-like mice.

Results:
Doppler echocardiography measurements were collected serially up to 8-weeks post-IFS. Histological and gene assessments were collected 4- and 8-weeks post-IFS to measure markers of adverse cardiac remodeling that resulted in later functional changes. Over time PTSD-like mice demonstrated a decline in cardiac function becoming significantly impaired by 8-weeks as shown by an increase in E/e' ratio along with left atrial diameter compared to controls, indicative of impaired LV filling pressure and diastolic dysfunction (p<0.05 for all). Beginning at 4-weeks post-IFS, PTSD-like mice had increased picrosirius red staining (PSR) compared to control mice (p<0.05) that remained elevated at 8-weeks. PTSD-like mice had increased macrophage numbers (Mac3) at 4-weeks post-IFS compared to control mice (p<0.05) and showed an increased trend when compared to controls 8-weeks post-IFS (p=0.09). To determine potential signaling mechanisms, Ccl2, Ccl5, and discoidin domain receptor tyrosine kinase 2 (DDR2) mRNA levels were assessed. Gene expression of Ccl2 demonstrated a decreased trend in PTSD-like mice (p=0.13), while Ccl5 (p=0.08) and DDR2 (p=0.06) mRNA demonstrated an increased trend in PTSD-like mice when compared to controls.

Discussion/Conclusions:
Our data indicates that in a mouse model of PTSD, animals that demonstrate PTSD-like behaviors show signs of increased cardiac inflammation stimulating cardiac remodeling and cardiac dysfunction.

Acknowledgements:
This work was supported by the National Institutes of Health T32GM123055; the American Heart Association Innovator Project IPA35260039, GM113278; the Biomedical Laboratory Research and Development Service of the Veterans Affairs Office of Research and Development Award IK2BX003922, I01BX00584; and South Carolina Translational Research Center UL1TR001450

Defining mechanisms of fungal-bacterial interactions during cystic fibrosis infection

Authors Names:
Stephen Dolan*

Introduction/Objectives:
Bacteria and fungi frequently exist as complex, polymicrobial communities during infection. Reconstructing ecological structure in the laboratory is challenging and, consequently, the precise molecular mechanisms which underpin microbial interactions remain elusive. Pseudomonas aeruginosa (Pa) is the most prevalent and persistent bacterium isolated from cystic fibrosis (CF) sputum and is a leading cause of mortality in CF patients. Approximately 15% of people with CF are infected with Aspergillus fumigatus (Af), a devastating human fungal pathogen. Af can accelerate lung function decline in people with CF.

Methods:
Using multi-omics approaches combined with reverse genetics, this investigated how the physiology of both Pa and Af change in co-culture when compared to monoculture, and to dissect the specific cues which drive these physiological changes.

Results:
Using a pre-clinical model that mimics the CF lung, we discovered that the bacterium Pa detects and defends against a disulfide-containing toxin produced by the fungus Af. In a remarkable example of both convergent evolution of toxin defense and environmental cue sensing across kingdoms, we discovered that

these organisms use the same cue to produce/sense this toxin, and the same enzymatic mechanism to protect against toxicity.

Discussion/Conclusions:
This discovery of convergent evolution provides strong evidence for Pa exposure to microbially-produced disulfide-containing toxins in natural environments. These data will begin to answer the fundamental question of how coinfecting microbes interact during polymicrobial infection, and impact pulmonary disease.

Acknowledgements:
S.K.D. was supported by a Herchel Smith Postdoctoral Fellowship and a Cystic Fibrosis Postdoctoral Fellowship (DOLAN20F0).

POSTER PRESENTATIONS

*Denotes presenting author

Novel Therapeutics for Fibrotic and Other Diseases: Modified Versions of the Caveolin-1 Scaffolding Domain Peptide with Improved Characteristics for Drug Development

Authors Names:
Stanley Hoffman*, Charles Reese*, Dhandapani Kuppuswamy, Panneerselvam Chinnakkannu, Saraswathi Panneerselvam

Introduction/Objectives:
Caveolin-1 levels are decreased in multiple cell types in diseases involving fibrosis and vascular leakage. Beneficial effects are obtained in animal models for these diseases using peptides derived from the active site of caveolin-1 (CSD) that can mimic and thereby replace the "missing" caveolin-1. We have developed modified versions of CSD more suitable for drug development than is native CSD. In a separate thrust, we have determined that the myofibroblasts that overexpress collagen in the fibrotic lung are primarily derived from the immune system and are a major target of our therapeutic peptides.

Methods:
Bleomycin treatment provided mouse models for lung, skin, and kidney fibrosis. Angiotensin II treatment provided mouse models for heart and kidney fibrosis. Single cell RNA Seq demonstrated that the myofibroblasts present in fibrotic lung tissue are primarily derived from the immune system.

Results:
CSD has been broken down into three subregions. Each of these four peptides has been similarly modified to make it water soluble, better taken up by cells, and protected from proteolysis. When tested in mouse model systems, all four peptides are beneficial but one of them is routinely the best. Depending on the model and tissue, beneficial effects are observed on dermal thickening; overexpression of collagen and myofibroblast markers; heart function; vascular leakage; fibrocyte (CD45+/ColI+ cells) accumulation; and tumor growth. Inhibition of fibrocyte accumulation as a mechanism of action fits well with our Single Cell RNA Seq data indicating that the cells in the fibrotic lung that overexpress collagen are primarily of immune origin.

Discussion/Conclusions:
Data suggest that our Lead Compound will be beneficial in treating any disease in involving fibrosis and vascular leakage. This includes not only lung and skin fibrosis, but also heart failure, kidney failure, cancer, Alzheimer's disease, wound healing, radiation-induced disease, aging, Covid-19, sepsis, and diabetic retinopathy.

Acknowledgements:
This work was funded in large part by three STTR grants (1R41HL164283-01A1, 1R41AR081740-01, 1R41HL167327-01) from NIH.

THE ROLE OF BHLHE40 IN SYSTEMIC SCLEROSIS-ASSOCIATED PULMONARY FIBROSIS

Authors Names:
Adegboyega "Tim" Adewale*, Carol Feghali-Bostwick, PhD

Introduction/Objectives:
The dominant complication of Systemic Sclerosis (SSc) is clinically severe and commonly fatal pulmonary fibrosis (PF). We sought to determine the downstream regulatory role of the basic Helix-Loop-Helix protein 40 (bHLHe40), in response to Insulin-like Growth Factor II (IGF-II) on Pro-Lysyl Oxidase cleavage products.

Methods:
We examined the response of primary pulmonary fibroblasts cultured from the lungs of control donors and SSc lung explants to IGF-II as well as human recombinant Lysyl Oxidase Propeptide (LOX-PP). In addition, we utilized an experimentally-induced model of lung fibrosis with intratracheal bleomycin administration. We used qPCR and immunoblotting to quantify mRNA and protein levels, respectively. We used sequence-specific small-interfering RNA to silence targeted genes. Immunoblots were quantified in ImageJ (NIH)and statistical analyses were performed in GraphPad Prism.

Results:
IGF-II regulates levels of Pro-LOX, active LOX, and LOX-PP, as well as isoforms of proteases Bone Morphogenetic Protein 1 (BMP1) and Tolloid-like 1 (TLL1). The transcription factor bHLHe40 localizes to the nucleus in response to IGF-II. bHLHe40 silencing downregulated TLL1, abrogating the enzymatic cleavage of Pro-LOX. SSc lungs have higher baseline levels of the total (N-glycosylated/unglycosylated) LOX-PP than normal lung tissues, and baseline levels of LOX-PP correlated with TLL1 Isoform 2 in SSc lungs. LOX-PP contributes to the development and progression of SSc-PF by mediating changes consistent with the extracellular matrix deregulation implicated in SSc-PF: elevated levels of Collagen 3A1 (COL3A1), Fibronectin-1 (FN1), and Plasminogen Activator Inhibitor-1 (PAI1).

Discussion/Conclusions:
Our findings indicate that bHLHe40, TLL1, and LOX-PP may serve as targets of therapeutic intervention to stop the progression of SSc-PF. Since activation of common fibrotic pathways are involved in different diseases characterized by lung fibrosis such as IPF, our findings may have wider implications for lung fibrosis associated with other diseases.

Acknowledgements:
Feghali-Bostwick lab MUSC Medical Scientist Training Program SCTR TL1 NIH Ruth Kirschstein NRSA (F31 - PI: AT Adewale)

Association of Biologic Sex, Glycosphingolipids, and the N-glycome in Renal Mesangial Cell Function

Authors Names:
Sandy Mungaray*, Bethany Wolf, Mariia Stefanenko, Mykhailo Fedoriuk, Oleg Palygin, Hongxia Bai, Rick Drake, Tamara Nowling

Introduction/Objectives:
SLE primarily afflicts women and many SLE patients develop nephritis, a serious complication of lupus. Identification of the pathogenic mechanisms underlying LN is crucial to better understand sex bias and disease progression. Therefore, we interrogated glycosphingolipid (GSL) metabolism and the N-glycome with respect to biologic sex in the response of human primary renal mesangial cells (hRMCs) to inflammatory stimuli.

Methods:
Serum was collected from 20 healthy control (HC) subjects and 20 LN patients who met the ACR criteria for active disease. Ten males and 10 females were included in each group. The sera was used to stimulate male- and female-derived hRMCs. Cell responses were assessed by measuring intracellular calcium (Ca2+) using fluor8 indicator, cytokine secretion by ELISA, GSLs levels by SFC-MS/MS, and N-glycans by MALDI-QTOF. Associations were evaluated using linear mixed models. P-values were adjusted using a False Discovery Rate with <0.05 considered meaningful.

Results:
No differences were observed in the responses of hRMCs to female- vs male-derived LN or HC sera. However, the female-derived hRMCs exhibited significantly higher Ca2+ flux and higher CXCL5 and CCL5 secretion compared to male-derived hRMCs in response to LN sera. The female-derived hRMCs expressed higher levels of GSLs than the male-derived hRMCs.

Discussion/Conclusions:
The significantly higher levels of LacCers observed in the female-derived hRMCs may partly explain the heightened pathologic response of the cells to LN sera. Thus, elevated GSL metabolism in females may poise renal cells to be more sensitive to or respond more robustly to inflammatory stimuli.

Acknowledgements:
The authors acknowledge the Lipidomics Shared Resource, Hollings Cancer Center, Medical University of South Carolina (P30 CA138313 and P30 GM103339); the Core Center for Clinical Research (CCCR) at the Medical University of South Carolina and its Director Dr. Jim Oates for assistance in identifying subjects and providing samples for this study; and Sophia LeClerc for assisting laboratory personnel in culturing and collecting hRMCs, and the performance of ELISAs.

Targeting of Endothelial Dysfunction in Lupus Nephritis: Effect on Human Renal Endothelial Cell Gene Expression and Outcomes in Murine Lupus Nephritis

Authors Names:
Dayvia L Russell*, Sandra Mungaray, Evelyn Bruner, Jim C. Oates

Introduction/Objectives:
Lupus nephritis (LN) constitutes one of the most severe manifestations of Systemic Lupus Erythematosus (SLE). Evidence points to endothelial nitric oxide synthase (eNOS) uncoupling, which produces harmful reactive oxygen species, as a mechanism leading to chronic endothelial cell dysfunction (ECD) and damage in LN. Treatment with sepiapterin (L-Sep), which results in coupling of eNOS, has been shown to restore endothelial function in lupus serum-treated endothelial cells. The aim of this study was to determine whether treatment with L-Sep could improve outcomes in a murine model of LN, and to better understand the protective mechanism of L-Sep by identifying genes involved in inflammatory redox pathways in human LN that are regulated by L-Sep.

Methods:
Female NZM2410/J mice, a model of lupus nephritis, were examined for proteinuria using metabolic cages. Once mice began to exhibit proteinuria above trace levels, mice were randomized into treatments groups of vehicle, 20 mg/kg/day L-Sep, or 60 mg/kg/day L-Sep. Urine proteinuria was assessed weekly, and histopathological grading of kidneys using NIH activity and chronicity indices, along with C3 and IgG renal expression were examined. Kaplan-Meier curves and log-rank test were applied to assess survival. One-way ANOVA with Tukey's multiple comparisons test was used to determine differences in proteinuria. Human renal glomerular endothelial cells (HRGECs) were grown to confluence then cultured in media containing 10% human healthy control (HC) serum (n=5, negative for connective tissue disease), or lupus nephritis serum (n=5, class IV LN) +/- 5 uM L-Sep. RNA was extracted and RNA sequencing, using NovaSeq PE 150, was performed to find genes that were differentially expressed between LN and HC, and LN after treatment with L-Sep.

Results:
NZM2410 lupus nephritis-prone mice receiving L-Sep showed improved renal function as measured by urine albumin/creatinine compared to those receiving vehicle (p=0.001 for vehicle vs. 20 mg/kg L-Sep; p=0.017 for vehicle vs. 60 mg/kg L-Sep), along with enhanced survival as demonstrated by Kaplan-Meier curves and log rank test. Mice receiving L-Sep had lower renal activity and chronicity scores and decreased renal C3 and IgG compared to vehicle. RNA sequencing revealed that genes involved in oxidative-stress and hypertension were differentially upregulated in HRGECs cultured with LN serum compared to Healthy Control (HC) serum (STK24, padj= 0.001; STK39, padj= 0.005). PIM3, which increases eNOS expression, was the most significantly downregulated gene in LN compared to HC (padj=0.0006). HRGECs treated with L-Sep had increased expression of SDC4 (padj=2.49E-11), a component of the glycocalyx that functions to protect ECs.

Discussion/Conclusions:
This study suggests L-Sep, a drug that activates eNOS, may be beneficial in the treatment of LN, in part by ameliorating renal endothelial cell damage. RNA sequencing further implicates the eNOS pathway is impaired in ECs in LN and may be a useful therapeutic target.

Acknowledgements:
Department of Veterans Affairs, Lupus Research Alliance

Influence of Social Support on Lupus Outcomes in a Health Disparity Population

Authors Names:
Sarah Smith*, Chloe Mattila, L. Quinnette King, Lori Ann Ueberroth, Edith M. Williams, Diane L. Kamen, Bethany J. Wolf, Paula S. Ramos

Introduction/Objectives:
Systemic lupus erythematosus (SLE) disproportionately impacts African American women, yet they are underrepresented in research. The relationship between social support and SLE disease outcomes has not been investigated in African American female patients with SLE. The goal of this study was to investigate the relationship between social support and disease outcomes in this health disparity population using data from validated participant questionnaires.

Methods:
This study had 89 cases with SLE, and 78 population controls unaffected by SLE who were recruited in our ongoing Social Factors, Epigenomics, and Lupus in African American women (SELA) study. Social support was measured using the Medical Outcomes Study-Social Support (MOS-SS) survey. SLE disease activity and damage were measured using the physician assessed SLE Disease Activity Index (SLEDAI), and the patient reported Brief Index of Lupus Damage (BILD), respectively. Association between SLE, average MOS-SS score and MOS-SS support domains were analyzed using a series of Wilcoxon Rank-Sum tests. Among patients with SLE, analysis of the associations between MOS-SS, SLEDAI and BILD data was evaluated using Spearman's rank correlation.

Results:
Patients with SLE didn't have significantly different overall MOS-SS scores compared to controls ($p = 0.101$) (Figure 1). The positive social interaction domain scores were significantly lower for patients with SLE (Figure 2). A significant association was found between overall MOS-SS score and physician reported disease activity (SLEDAI score), such that patients with higher SLEDAI scores tend to have lower MOS-SS scores ($\rho = -0.28$, $p = 0.039$). No significant association was found between patient reported organ damage (BILD score) and overall MOS-SS score ($p = 0.36$).

Discussion/Conclusions:
This study found a significant difference within domains of social support between patients with SLE and controls. The potential clinical relevance of these findings suggests that targeted interventions to improve social support could potentially improve SLE outcomes, though further research is needed.

Acknowledgements:
The Social Factors, Epigenomics and Lupus in African American Women (SELA) Study Group: GA Hawkins, TD Howard, DL Kamen, CD Langefeld, SS Lim, LH Moultrie, Queen Quet, PS Ramos, EM Williams, BJ Wolf. This project was supported by NIH grants R01 MD015395, P30 AR072582, and a Rheumatology Research Foundation (RRF) Resident Research Preceptorship (SS).

Characterizing Human Cardiac Fibroblast Responsiveness to Hemodynamic Unloading in Heart Failure with Reduced Ejection Fraction

Authors Names:
Rachel M. Biggs, BS*, Daniel N. Silverman, MD, Yuhua Zhang, MD, Catalin F. Baicu, PhD, Lauren Wakefield, MHA, Stephanie Masline, BS, Devki Bhatt, Michael R. Zile, MD, Amy D. Bradshaw, PhD

Introduction/Objectives:
Introduction: Myocardial interstitial fibrosis is a common pathology in cardiomyopathies leading to ventricular dilation and increased hemodynamic load resulting in heart failure with reduced ejection fraction (HFrEF). Previous research has shown that HFrEF patients treated with a left ventricular assist device (LVAD) undergo hemodynamic unloading resulting in partial cardiomyocyte recovery. However, evidence supports that these patients do not experience a regression of fibrosis. We hypothesize that human cardiac fibroblasts (HCFs) are constitutively activated in HFrEF myocardium but remain unresponsive to hemodynamic unloading with LVAD placement.

Methods:
Methods: Forty human subjects with HFrEF undergoing LVAD implantation were enrolled to provide a portion of myocardium removed during surgery. Also, 7 biopsies previously collected from transplanted hearts with extended LVAD treatment were evaluated (LVEX).

Results:
Results: Quantification of PSR stained sections revealed a significant increase in collagen volume fraction (CVF) in the HFrEF tissue (CVF = 2.8□0.2) in comparison to control tissues (0.9□0.2) that remained elevated in LVEX hearts (3.1□0.3). HCFs from biopsies received at LVAD placement were isolated and grown to confluence. HCFs from HFrEF patients and control HCFs were then plated on substrates with mechanical stiffnesses reflective of either normal myocardium (2kPa) or failing myocardium (8kPa). Cells were collected at 4- and 7-day timepoints and levels of collagen I (Col I) and alpha-smooth muscle actin (□-SMA) were quantified through western blot analysis with □-actin as a loading control. Whereas control HCFs were responsive to changes in substrate stiffness producing more Col I and □-SMA on 8kPa versus 2kPa, HCFs from HFrEF patients were unresponsive to changes in stiffness exhibiting no significant difference in production of Col I and □-SMA on 2kPa versus 8kPa.

Discussion/Conclusions:
Conclusion: These data suggest that HCFs isolated from the failing myocardium do not respond to changes in mechanical load and might contribute to persistent increases in fibrosis in failing and unloaded hearts.

Acknowledgements:
This project was supported, in part, by the National Center for Advancing Translational Sciences of the National Institutes of Health under Grant Numbers TL1 TR001451 & UL1 TR001450. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Predicting mechanisms of IGF2-mediated fibrosis in primary human lung fibroblasts.

Authors Names:
Kristy M. Waldrep*, Ludivine Renaud, Carol A. Feghali-Bostwick

Introduction/Objectives:
Pulmonary fibrosis (PF) is defined by excessive extracellular matrix (ECM) production. It causes significant morbidity and mortality in patients with systemic sclerosis (SSc) and idiopathic pulmonary fibrosis (IPF). We previously reported that lung tissues and fibroblasts from SSc-PF patients overexpressed insulin-like growth factor 2 (IGF2), and IGF2 upregulated the transcription factor SOX9 in primary human lung fibroblasts. Our goal was to identify SOX9-dependent and -independent pathways downstream of IGF2 using an unbiased approach.

Methods:
We transfected normal lung (NL) fibroblasts from different donors with non-targeting control (siCtrl) or SOX9-targeting siRNA (siSOX9) and stimulated with vehicle (PBS) or recombinant human IGF2 for 24h. We identified differentially expressed genes (DEG) using RNA sequencing and bioinformatic analysis. We compared "IGF2+siCtrl vs. PBS+siCtrl" to "IGF2+siSOX9 vs. PBS+siSOX9" to find common and unique genes and pathways regulated by IGF2 and SOX9.

Results:
RNA sequencing identified 752 DEGs in "IGF2+siCtrl vs. PBS+siCtrl" fibroblasts and 918 DEGs in "IGF2+siSOX9 vs. PBS+siSOX9" fibroblasts with 302 DEGs (20%) commonly dysregulated. Thirty-five pathways were enriched in both comparisons, while 32 pathways were unique to "IGF2+siCtrl vs. PBS+siCtrl" and 24 were unique to "IGF2+siSOX9 vs. PBS+siSOX9."

Discussion/Conclusions:
We identified SOX9-dependent and -independent genes and pathways involved in the IGF2 fibrotic response in NL fibroblasts. Our data identify novel targets downstream of IGF2 that may mediate fibrosis.

Acknowledgements:
This work was supported by R01 HL153195 from NIH/NHLBI and K24 AR060297 from NIAMS.

From lungs to blood - An "omics" approach to Pulmonary Sarcoidosis biomarker identification

Authors Names:
YunYun Su, Ludivine Renaud, Joe E. Mouawad, Willian A. da Silveira, Joseph M. Pilewski, Jessalyn I. Rodgers*, W. Ennis James, Carol A. Feghali-Bostwick

Introduction/Objectives:
Sarcoidosis, a multi-organ disease, is distinctly characterized by the formation of fibrotic granulomas. Lung involvement is present in >90% of sarcoidosis patients which can lead to severe end stage pulmonary fibrosis. Biomarkers of pulmonary sarcoidosis are urgently needed for treatment assessment, patient stratification, disease severity prognosis and therapy development.

Methods:
RNA from lung tissue of patients with sarcoidosis who underwent lung transplantation, normal donors whose lungs were not used for transplantation, and primary fibroblasts derived from these tissues were analyzed via microarray. Gene/protein expression signatures were validated via qRT-PCR, Western blot, and Immunostaining. Levels of two were also measured in bronchoalveolar lavage fluid (BALF) and plasma of sarcoidosis patients from the Genomic Research in Alpha-1 Anti-trypsin Deficiency and Sarcoidosis (GRADS) study using ELISA.

Results:
1032 differentially expressed genes (DEGs) were identified in sarcoidosis lungs and 346 DEGs in sarcoidosis fibroblasts compared to their normal lung (NL) counterparts. Moreover, 44 DEGs were commonly deregulated in sarcoidosis lung and fibroblasts. Of those CTSK, MXRA5, PTGDS, THBS2 upregulation and HOPX downregulation were validated by qPCR. 861 and 279 DEGs are unique to lung and fibroblasts, respectively. Preliminary data indicate elevated BALF and plasma levels of CTSK and S100A8 associated with disease severity in sarcoidosis patients.

Discussion/Conclusions:
Utilizing lung tissue of patients with pulmonary sarcoidosis compared to normal donors and primary fibroblasts derived from them, our "omics" approach has identified novel potential biomarkers of pulmonary sarcoidosis. Furthermore, the overlap of commonly deregulated DEG genes in sarcoidosis lungs and fibroblasts suggests the deregulation of these genes is driven by the fibroblast population while the other DEG genes may be representative of other cell types. Using this approach, we have identified potential biomarkers that associate with sarcoidosis disease severity.

Acknowledgements:
This project is funded by a College of Medicine Translational Team Science grant.

Comparison of the transcriptomic signature of pulmonary fibrosis according to gender in patients with systemic sclerosis.

Authors Names:
Ludivine Renaud*, Carol Feghali-Bostwick.

Introduction/Objectives:
Systemic sclerosis (SSc) is a chronic connective tissue disease of unknown etiology characterized by immune cell dysregulation, vasculopathy, cutaneous and visceral fibrosis. SSc-associated pulmonary fibrosis (SSc-PF) is currently the leading cause of death in SSc patients, and males experience a greater decline in lung function and a higher mortality rate than females. No effective therapies are yet available that stop the progression of SSc-PF. Thus, identifying novel targets for the development of effective therapies remains a critical and unmet need. The goal of our study is to compare the transcriptomic signatures of SSc-PF in men and women to identify genes and pathways that are uniquely and commonly deregulated.

Methods:
RNA sequencing was performed on lung tissues from patients with SSc-PF and compared to sex- and age-matched normal lungs (NL). The differential expression analysis "SSc-PF vs. NL" was performed on male and female samples to define disease mechanisms. Pathway and functional enrichment analyses were performed on iPathwayGuide and ToppFun, and downstream validation

experiments (qPCR and immunoblotting) were conducted for selected genes.

Results:
We identified 2679 and 838 differentially expressed genes (DEGs) in men and women, respectively, out of which only 272 were commonly deregulated (8.4% overlap). Common perturbed pathways included PI3K-AKT, ECM-receptor interaction, Hippo, Focal adhesion and Hedgehog signaling. The 2,407 DEGs unique to men impacted pathways related to Calcium, Steroid biosynthesis, Wnt, Metabolic and IL17 signaling. The 566 DEGs unique to women enriched the Biosynthesis of amino acids, C-type lectin receptor, Relaxin, NF-kappa B, Cholesterol metabolism and TNF signaling pathways.

Discussion/Conclusions:
Our data show that disease mechanisms between men and women have little overlap, providing insights into the gender disparity observed in SSc-PF patients. Information extracted from the unique transcriptomic signature of SSc-PF in men and women will contribute in the development of customized therapeutic approaches.

Acknowledgements:
Carol Feghali-Bostwick K24 grant

Development of a Novel Drug Candidate for Scleroderma
Authors Names:
Bogatkevich GS*, Atanelishvili I, Ismail AA, Perry CB, and Silver RM

Introduction/Objectives:
Scleroderma (systemic sclerosis, SSc) is a rare autoimmune connective tissue disease characterized by diverse clinical manifestations, high mortality rates, and the absence of effective treatments. The mortality rate for SSc exceeds that for any other rheumatic disease, with the leading cause of mortality being interstitial lung disease (ILD) resulting from chronic inflammation and fibrosis. Although immunosuppressive agents and several other drugs such as recently approved nintedanib and tocilizumab may stabilize lung function in some patients, long-term treatment is required, significant toxicity often occurs, and many patients will fail to respond. Therefore, there is an urgent and unmet need for new therapeutic approaches that would be more effective and less toxic than current treatments. We recently identified a unique 10 amino acid peptide (M10) characterized by potent anti-fibrotic and anti-inflammatory properties. In this study, we investigate efficacy, immunogenicity, and toxicity of M10 in rodents and in human cells.

Methods:
Efficacy of M10 was studied in two different murine models of lung fibrosis: the bleomycin-induced therapeutic mouse model of SSc-ILD and the fibroblast-specific protein (FSP)-driven constitutively active ALK5 receptor TβR1CA mouse model of scleroderma. Immunogenicity was investigated in primary CD4+ T cells (ATCC® PCS-800-016) and cellular toxicity was studied in primary lung fibroblasts. Single dose toxicity and maximum tolerated dose (MTD) of M10 was studied in C57BL/6 mice. Statistical analysis was performed using GraphPad Prism 7 software.

Results:
In both mouse models of SSc-ILD, M10 administered in a dose of 1mg/kg subcutaneously every 24 h noticeably reduced fibrosis of lung. A semi-quantitative evaluation of histopathology by Ashcroft scale demonstrated a significant ($p < 0.01$) decrease in bleomycin- and TβR1-induced lung fibrosis of M10-treated mice as compared to control mice treated with scrambled peptide. We observed that M10 in doses of 1 μg/ml, 10 μg/ml, and 100 μg/ml for 24 h does not affect secretion of IFN-γ by CD4+ T cells, suggesting that M10 does not induce immunogenicity under the conditions tested. In contrast, phytohaemagglutinin-activated CD4+ T cells (used as a positive control) increased the secretion of IFN-γ from 45.2±9.7 pg/ml to 529±82.4 pg/ml, $p < 0.001$. M10 had no effects on cellular viability in all studied doses in normal and SSc-ILD lung fibroblasts. The experimentally determined MTD of subcutaneously delivered M10 in rodents was equal to 1000 mg/kg. We have not observed any mortality or critical weight loss of mice including those receiving the highest tested dose of 1000mg/kg within all 14 days of observation. The H&E staining of tissue sections from animals treated with any dose of M10 showed no morphologic changes compared to the placebo-treated controls. VetScan Comprehensive Diagnostic Profile of serum samples from mice that received 1000 mg/kg M10 showed no abnormalities and displayed no significant difference in any parameters when compared with placebo-treated control animals.

Discussion/Conclusions:
Lack of immunogenicity and low toxicity in combination with high efficacy of M10 peptide in an animal model of lung fibrosis suggest that M10 may be a safe and effective treatment for SSc that warrants further development.

Acknowledgements:
This work is funded by the NIH R41AR079303 and R41 HL167504 (to GSB and RMS).

YAP1- A key mediator in Enolase-1 driven pulmonary fibrosis
Authors Names:
Shailza Sharma*, Carol Feghali-Bostwick

Introduction/Objectives:
Fibrosis is characterized by excessive extracellular matrix (ECM) component production and deposition. Systemic sclerosis (SSc) is a connective tissue disease of unknown etiology. Two drugs, tocilizumab and nintedanib, approved by the FDA for the treatment of SSc, slow disease progression but do not stop or reverse the fibrosis. We recently demonstrated that the glycolytic enzyme Enolase-1 (ENO) promotes a fibrotic phenotype, independently the pro-fibrotic factor TGF-β1. Yes-associated protein (YAP-1), a downstream nuclear effector of Hippo signaling whose function is primarily regulated by its subcellular localization, translocates to the nucleus, and increases the expression of ECM proteins in TGF-β1-treated fibroblasts via the transcription factor TWIST-1. Here, we aim to elucidate the role of YAP-1/TWIST-1 signaling as a potential mechanism mediating the profibrotic activity of ENO.

Methods:
Silencing ENO and YAP-1 in human lung fibroblasts followed by TGF-β1 stimulation, Cloning and overexpression of ENO, Subcellular fractionation, Immunoblotting.

Results:

Plasmid-encoded ENO upregulated the expression of YAP-1 and TWIST-1 in primary human lung fibroblasts. Comparable results were obtained with rENO protein. Silencing ENO not only reduced the TGF-β1 mediated translocation of YAP-1 into the nucleus of primary lung fibroblasts but also downregulated the expression of TWIST-1 in the nucleus. Additionally, a significant downregulation of the ECM proteins Fibronectin (FN), Collagen Type I, alpha chain 1 (COL1α1), and α-smooth muscle actin (α-SMA), Plasminogen Activator Inhibitor-1 (PAI-1) and Connective tissue growth factor (CTGF) was observed in TGF-β1 treated fibroblasts in which YAP-1 was silenced. Similarly, the profibrotic activity of ENO was significantly reduced upon YAP-1 silencing in fibroblasts.

Discussion/Conclusions:
Our study demonstrates that ENO mediates its profibrotic activity via YAP-1. Silencing ENO ameliorates fibrosis by inhibiting YAP-1 nuclear localization and blocking its downstream signaling mediated by transcription factor TWIST-1 in fibroblasts derived from normal lungs. Our findings identify novel pathways that can be targeted therapeutically in SSc-associated lung fibrosis.

Acknowledgements:
Funding: NIH R01 HL121262, R01 HL133751, T32 HL144470, K24 AR060297.

Lupus-Associated Vascular Dysfunction in Females Correlates with Elevated Endothelin-1: Symptomatic or Causative?

Authors Names:
Marice K. McCrorey, B.S.*, Kennedy P. Hawkins, B.S., C. Alex Colvert, B.S., Thomas B. Dempster, B.S., Samantha Kindsvater, B.A., Jim C. Oates, M.D., Yasir Abdul, Ph.D., Adviye Ergul, M.D., Ph.D., Melissa A. Cunningham, M.D., Ph.D., and Justin P. Van Beus

Introduction/Objectives:
Systemic Lupus Erythematosus (SLE) is an autoimmune disease classified by IgG complex deposition in target organs including the kidney, heart, and vasculature. SLE disproportionally affects women to men (9:1), with a high prevalence in African Americans. Clinically, patients present with heterozygous symptoms including heart and renal failure, and more commonly chronic hypertension (HTN). Chronic HTN is the leading risk factor for heart disease, yet its interplay with lupus-associated cardiovascular dysfunction remains poorly understood. Importantly, numerous studies have reported that patients with SLE or HTN have elevated plasma endothelin-1 (ET-1) levels. However, few studies have investigated the synergistic effects of SLE and HTN on ET-1. Therefore, we hypothesized that women with SLE and HTN would have elevated plasma ET-1 levels compared to SLE or HTN alone.

Methods:
To investigate this, we recruited non-SLE non-HTN controls (n=8), non-SLE HTN (n=9), SLE non-HTN (n=7), and SLE-HTN (n=6) female human subjects and analyzed clinical and demographic characteristics, plasma ET-1, c-reactive protein (CRP), and soluble vascular adhesion molecule-1 (sVCAM-1).

Results:
We found that plasma ET-1 levels are significantly higher in African Americans compared to European-American patients independent of SLE or blood pressure (p=0.0182). Plasma ET-1 levels correlated positively with age (r=0.4861;p=0.0118), but had no correlation with BMI (r=0.2137;p=0.2945). Females with a SLE diagnosis had elevated plasma ET-1 levels compared to non-SLE controls (p=0.0141). When stratified by blood pressure, only SLE-HTN subjects had significantly elevated plasma ET-1 levels compared to non-SLE non-HTN controls (p=0.0005) and trended towards elevated ET-1 over SLE non-HTN (p=0.0799). Lastly, plasma ET-1 correlated positively with systolic blood pressure (r=0.5621;p=0.0035) and pulse pressure (r=0.5810;p=0.0023) but not diastolic pressure (r=0.3177;p=0.1217).

Discussion/Conclusions:
These data demonstrate that plasma ET-1 levels are associated with SLE diagnosis and blood pressure status in our cohort of female SLE human subjects. ET signaling should be investigated further in SLE and SLE-HTN human subjects.

Acknowledgements:
Funding: Veterans Affairs Biomedical Laboratory Research & Development Career Development Award (CDA-2) 1IK2BX005605-01 to J.P.V.B, Medical University of South Carolina College of Medicine Program Project Grant to J.C.O and J.P.V.B., and Medical University of South Carolina Core Centers for Clinical Research Project Award P30AR072582 to M.A.C and J.P.V.B.

Effect of altered glycosphingolipid levels on the inflammatory response of human renal glomerular cells

Authors Names:
Anna Tingler*, Danielle Beaufort, Sandy Mungaray, Tammy Nowling

Introduction/Objectives:
Systemic lupus erythematosus (lupus) is a chronic autoimmune disease. Lupus attacks the immune system giving it the ability to affect many areas of the body. Lupus increases inflammation in the body and could cause permanent tissue damage in body parts such as the heart, lungs, and kidneys. One of the most common serious organ system complications is the development of glomerulonephritis (lupus nephritis). The increased inflammatory renal response in lupus nephritis patients may be attributed in part to an altered GSL metabolism pathway. Previous studies in mouse primary renal mesangial cells suggested that altered GSL metabolism increased the production of IL-6 by mesangial cells from lupus prone mice in vitro.

Methods:
Our current studies are based on the hypothesis that reducing levels of GSLs will decrease the inflammatory response by primary human renal mesangial cells (hRMCs) or by co-cultured hRMCs and primary human renal endothelial cells 9hRGECs). Two independent hRMC lines, each derived from an individual, with high or low levels of hexosylceramides (HexCers) and lactosylceramides (LacCers) were compared.

Results:
The hRMCs with high levels of these GSLs responded more robustly to serum from LN patients exhibiting higher intracellular Ca2+ flux and higher levels of released cytokines. Treating the hRMCs expressing high levels of GSLs with the GSL synthesis inhibitor eliglustat effectively decreased GSL HexCers and LacCers levels by more than 50%. However, the cells released more IL-6 in response to LN sera or other inflammatory stimuli when treated with eliglustat. Similar effects are being observed in the hRMCs-hRGEC co-cultures.

Discussion/Conclusions:
Additional conditions are being tested to confirm the effect of eliglustat on these in vitro cultures.

Elucidating the Role of Estrogen Receptor Alpha in Systemic Lupus Erythematosus

Authors Names:
Lauren Bracken1*, Cameron Leyers2, Jena Wirth1, and Melissa Cunningham1 1Department of Medicine, Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston SC 29407 2Darby Children's Research Institute, Medical University

Introduction/Objectives:
Research has shown an increased incidence of Lupus in women of reproductive age as compared to men, leading to an investigation into the role of estrogen and estrogen receptors (ERs) and how they modulate the function of immune cells. We investigated two ERα variants, the classic ERα66 and a short variant, ERα46,whose function is proposed to modulate inflammatory pathways. Our data reveal differences in gene expression in dendritic cells and B cells that overexpress ERα46,ERα66,or the combination of ERα46/ERα66.Based on our accumulating data, we hypothesize that ERα46 protects against the development of Lupus by down regulating TLR7-induced effects thus modulating specific innate immune cell functions.

Methods:
In vitro transfection studies were conducted using a murine dendritic cell line (DC2.4) and human SLE EBV-transformed B cells, using Neon Electroporation. Cells were transfected with a plasmid containing ERα46, ERα66, or ERα46/66 +/- a TLR7 agonist (loxoribine) for 1.5 hours. RNA was then isolated from the transfected cells after 48h for NanoString analysis utilizing an inflammation panel (248 genes). NanoString N solver mapped differential gene expression using an error model with a 95% confidence interval.

Results:
In vitro transfection studies in DCs showed changes in expression between cells transfected with ERα46 vs. both ERα46/66- and ERα66-transfected cells with or without TLR7 stimulation. Unstimulated DCs expressing ERα46 versus ERα66 downregulated il1α,il1β,il6,ccl7, and ccl2 while genes oas2 and ifi44 were upregulated. Stimulated ERα46 DCs downregulated nfkb1,myd88,il1α and il1β compared to ERα66. In transfected B cells, co-expression of ERα46/66 vs. ERα66 alone resulted in a >200 fold change in hifa1,a major regular of survival and proliferation among other functions. These results will be confirmed and further investigated.

Discussion/Conclusions:
NanoString analysis of transfected DCs and B-cells demonstrated that ERα46 and ERα66 have different effects on immune cells based on preliminary gene expression data. This exploratory NanoString data supports our earlier findings on BMDCs from mice expressing ERα short (structurally similar to ERα46) in that expression of multiple genes/pathways were similarly regulated, suggesting a correlation between ERα short and endogenous ERα46, which may be a future therapeutic target.

Acknowledgements:
Thank you to Gary Gilkeson, Ivan Molano, Mara Lennard, Jen Scott, Jackie Eudaly, Paula Ramos, Betty Tsao, Diane Kamen, Jim Oates, Bob Watson, Geoffrey Greene (University of Chicago) Supported by a NIH-NIAMS T32 Training in Inflammatory and Fibrosing Diseases, VA Merit Award, KL2 CTSA CDA, ACR RRF K Bridge, NIH/NIAMS K08, Doris Duke Foundation

UPCOMING SCTR FUNDING OPPORTUNITIES

Discovery Grants

Purpose:
Discovery grants support translational science projects that involve basic research, clinical research and/or community/population health research approaches for the purposes of collecting critical preliminary data for submission of extramural grant applications and to publish, disseminate or implement research findings. We place a premium on applications proposing interdisciplinary team science and new collaborations.

Applications emanating from SCTR Scientific Retreat/s, patient-centered and community-engaged research, and those focused on dissemination and implementation science are strongly encouraged.

2024 Key Dates:

	Spring Cycle	Fall Cycle
RFA Release	February 1, 2024	August 12, 2024
Applications Due (by 5:00 pm)	April 6, 2024	October 11, 2024
Recommendation for Funding Notification	June 3, 2024	December 1, 2024
Earliest Possible Start	July 1, 2024	January 1, 2025

Read more about this grant.
Apply for a Discovery Grant.

Translational Science Challenge Grants

Purpose:
Aims to support projects focused on understanding a scientific or operation principle underlying a step of the translational process.

Learn more about the Translational Science Challenge Grant.

Applications are open on a rolling deadline.

High Innovation High Reward

Purpose:
The purpose of the HIHR grant opportunity is to support new and innovative, cross-disciplinary pilot projects that propose **substantial development of intellectual property and/or commercialization opportunities**.

Applications are open on a rolling deadline.

Learn more and apply.