### Introduction

The Center for Pulmonary and Vascular Biology (PVB) provides a programmatic research home for pediatric faculty and trainees pursuing basic research in pulmonary biology and vascular biology. The Center's mission is to expand the basic understanding of lung and vascular diseases, striving to gain new knowledge that will ultimately lead to new diagnostic, prophylactic, and therapeutic strategies. The science being pursued is focused on lung and vascular development and responses to inflammation, metabolic stress and injury.

The Center provides a valuable resource for investigative endeavors in pulmonary biology and vascular biology across the UT Southwestern campus. This is represented by active collaborations between PVB faculty and other UT Southwestern faculty in the Departments of Internal Medicine, Cell Biology, Physiology, Pharmacology and Molecular Genetics, and by participation of PVB faculty in numerous training grants across the campus.

Notably, since 2009 Dr. Shaul in PVB and Dr. Lance Terada in the Division of Pulmonary and Critical Care Medicine in the Department of Internal Medicine have codirected an NIH T32 program to support postdoctoral research training in lung biology and disease at UT Southwestern. The T-32 award was successfully renewed in 2014.



Philip Shaul, M.D. Professor, Vice Chair of Research

### **Faculty**

The Pediatric PVB faculty are basic scientists and physician-scientists from four pediatric divisions working in partnership.



Philip W. Shaul, M.D.
Professor, Vice Chair of Research
Director, Center for Pulmonary and Vascular
Biology. Director, Physician-scientist
Training Program in Pediatrics
Associates First Capital Corporation
Distinguished Chair in Pediatrics



Michelle Gill, M.D., Ph.D.
Associate Professor of Pediatric,
Immunology and Internal Medicine
Division of Pediatric Infectious Disease



Rashmin C. Savani, M.B.Ch.B.
Professor and Division Director, Neonatal and Perinatal Medicine
Associate Director, Center for Pulmonary and Vascular Biology
The William Buchanan Chair in Pediatrics



**Chieko Mineo, Ph.D.**Associate Professor, Center for Pulmonary and Vascular Biology



Jessica Moreland, M.D.
Professor of Pediatrics and Microbiology
Division Chief, Pediatric Critical Care
Medicine
Thomas Fariss Marsh, Jr. Chair in Pediatrics



Anastasia Sacharidou, Ph.D.
Assistant Instructor, Center for Pulmonary and Vascular Biology



### **Honors / Awards**

#### Best Pediatric Specialists in Dallas, D Magazine

### Texas Super Doctor, Texas Monthly

- Michelle Gill
- Jessica Moreland

#### Rashmin Savani

#### **Invited Lectures**

### Michelle Gill

- Japan Pediatric Society 121<sup>st</sup> Annual Meeting, Fukuoka, Japan, April 2018
  - "Evaluating Disease Mechanisms in Pediatric Asthma: Evidence for IgE-Mediated Regulation of Plasmacytoid Dendritic Cell Antiviral Responses"
- Invited Speaker for Infectious Disease, American Academy of Pediatrics, PREP Board Review Course, Las Vegas, NV, March 2018
- Boston City Wide Allergy & Immunology Grand Rounds, Boston, MA, April 2018
  - "Evaluating Disease Mechanisms in Pediatric Asthma: Evidence that IgE Regulates Dendritic Cell Antiviral Responses"
- Pediatric Academic Societies Annual Meeting, Toronto, Canada, May 2018
  - "Enhanced Plasmacytoid Dendritic Cell Antiviral Responses after Omalizumab"

#### Rashmin Savani

- 2018 Telemedicine Summit for Hospitals, Las Vegas, NV, September 2018
  - "New Approaches to Tele Medicine Within Neonatal Care"
- 1<sup>st</sup> Federation of European Biochemistry Societies (FEBS), Patras, Greece, September-October 2018
  - Advanced Lecture Course on Extracellular Matrix: "Cell Regulation, Epigenetics and Modeling"
- 2018 American Society for Matrix Biology, Las Vegas, NV, October 2018
  - "Extracellular Superoxide Dismutase (EC-SOD) Knockout Mice Have Worse Alveolarization, Inflammation and Cytokine Elaboration After Neonatal Hyperoxia Exposure"
- 2018 10<sup>th</sup> Annual Children's Hospital Neonatal Consortium, Columbus, OH, October 2018
  - "Tele NICU: Extending the Reach of Level IV Care and Optimizing the Triage of Patient Transfers"

#### **Philip Shaul**

- The Endocrine Society's 100<sup>th</sup> Annual Meeting, Chicago, IL, March 2018
  - o "Estrogen Receptors and Cardiometabolic Health and Disease"
- Gulf Coast Vascular Research Consortium Annual Meeting, College Station, TX, March 2018
  - "Endothelial Cell Transcytosis and Cardiometabolic Disease"
- Duke-National University of Singapore Medical School, Annual Graduate Student Research Symposium, Singapore, May 2018
  - o "Endothelial Cell Transcytosis and Cardiometabolic Disease"
- Institute of Molecular and Cell Biology, Singapore, May 2018
  - "Endothelial Cell Transcytosis and Cardiometabolic Disease"
- 20<sup>th</sup> Anniversary Rapid Responses to Steroid Hormones Meeting, Dublin, Ireland, September 2018
  - "Manipulating Extranuclear Estrogen Receptor Biology to Combat Cardiometabolic Disease"



### **Conference Presentations**

### Pediatric Academic Societies Meeting, Toronto, Canada, May 2018

Gill M, Presenting Author

Invited Science Presentation, "Enhanced Plasmacytoid Dendritic Cell Antiviral Responses After Omalizumab"

Ibrahim J, Liao J, Cheong N, Longoria C, Grayck E, Savani R

• Poster, "Extracellular Superoxide Dismutase (EC-SOD) Knockout Mice have Worse Alveolarization, Inflammation and Cytokine Elaboration After Neonatal Hyperoxia Exposure"

Mirpuri J, MD, Thomas S, Kumar D, Hooper L, Savani R

 Poster, "Empiric Antibiotics Increase Susceptibility to K. pneumoniae Induced Sepsis Through an Expansion of Proteobacteria and Suppression of ILC type 3 Cells in Neonatal Mice"

#### Savani R

- Invited Science Presentation, "IL-1RA in the Therapy of BPD: An Update"
- Invited Science Presentation, "Inflammsome Blockade for the Prevention of BPD"

Yallapragada S, Murthy K, Lagatta J, Porta N, Savani R, et al

 Poster, "Exploring Potential Indications for Tracheostomy and Chronic Mechanical Ventilation in Patients with Severe Bronchopulmonary Dysplasia"

### **Education and Training**

The primary teaching activities of the PVB faculty occur at the laboratory bench where residents, clinical pediatric subspecialty fellows, graduate students, and Ph.D. postdoctoral fellows are trained in pulmonary biology research and vascular biology research.

### **Research Activities**

The overall goal of the Shaul-Mineo laboratory is to identify mechanisms in endothelial cells that govern cardiovascular and metabolic health and disease. The disorders that they study include thrombosis (blood clotting), atherosclerosis, obstructive vascular disease (stenosis), hypertension and type 2 diabetes. Dr. Sacharidou has made major discoveries regarding a common cause of thrombosis and processes that underlie type 2 diabetes. Their ultimate goal is to identify new targets for therapies to combat cardiovascular and metabolic disorders.

Dr. Michelle Gill, whose research centers on evaluating the role of dendric cells in pediatric respiratory viral infections, partners with Dr. Rebecca Gruchalla and the Division of Pediatric Allergy and Immunology to study asthma pathogenesis. By defining how dendritic cell function is affected in patients with asthma, they hope to better understand how to interrupt, and eventually design strategies to prevent the deleterious immune responses associated with the clinical symptoms of asthma.

Dr. Jessica Moreland focuses her research on better understanding the cell biology of inflammation with a specific interest in neutrophil biology. Her laboratory studies neutrophil priming by infectious and inflammatory stimuli, with a specific interest in Toll-like receptor signaling, and the role of NADPH oxidase in pro- and anti-inflammatory signaling. The Moreland laboratory studies both primary human neutrophils from healthy donors and from patients, and also utilizes a murine model of the systemic inflammatory response syndrome (SIRS) and multi-organ dysfunction syndrome (MODS).



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Dr. Rashmin Savani's laboratory studies the pathogenesis of bronchopulmonary dysplasia and development of novel therapies for this devastating disorder of preterm infants. With over 20 years' experience in the biology of the glycosaminoglycan hyaluronan and its receptors, they have developed the expertise and tools, including antibodies, peptides, cDNAs, knockout and transgenic mice, that allow examination of this system in angiogenesis, inflammation and lung development, as well as in responses to injury. Specific mechanistic studies of the role of hyaluronan in the activation of nitric oxide production and of the NLRP3 inflammasome are being pursued.

### **Current Grant Support**

### Michelle Gill

**Grantor:** NIH / University of Wisconsin

Title of Project: Mechanistic Study Development for ICAC3 MUPPITS and CoNAC Protocols

**Role:** Co-Investigator **Dates:** 2015 – 2019

Grantor: NIH NIAID Inner City Asthma Consortium 3 (ICAC3, UM1AI 114271)

Role: Co-investigator (PI: R Gruchalla)

Title of Project: Immunologic Approaches to Reduce Asthma

**Dates:** 2014 – 2021

#### Chieko Mineo

Grantor: NIH 1R01HL126795

Title of Project: Endothelial SR-BI and Metabolic Health

**Role:** Principle Investigator **Dates:** 08/2015 – 06/2019

Grantor: NIH 1R01DK110127

Title of Project: Endothelial Basis of Obesity-induced Insulin Resistance

**Role:** Principle Investigator **Dates:** 07/2016 – 06/2020

Grantor: NIH 1R01HD094395

Title of Project: Molecular Basis of Pregnancy Complications in the Antiphospholipid Syndrome

**Role:** Principle Investigator **Dates:** 08/2018-05/2023

### Jessica Moreland

Grantor: UT Southwestern Center for Translational Medicine

**Title of Project:** Improving Bone Health in Cystic Fibrosis by Targeting the Neutrophil-bone Axis.

Role: Co-Investigator
Dates: 06/2017 – 04/2018

### Rashmin Savani

Grantor: Novare Pharmaceutical, Inc.

Title of Project: Hyaluronan Binding Peptides to Block Inflammation after Lung Injury

**Role:** Principle Investigator **Dates:** 03/2016 – 07/2019



**Grantor:** Ikaria Therapeutics

Title of Project: Inhaled NO in Neonatal Asphyxia

**Role:** Joint Principle Investigator **Dates:** 11/2010 – 12/2019

### **Philip Shaul**

Grantor: NIH 5K12HD68363

**Title of Project:** Antecedents and Sequelae of Childhood Onset Disease

Role: Training Director (PI: Pérez Fontán)

Dates: 12/2010 - 11/2020

Grantor: NIH 5R01-HL115122

Title of Project: FcgammaRIIB and Inflammation-Related Vascular Disease

**Role:** Principle Investigator **Dates:** 08/2013 – 06/2018

Grantor: NIH 2R01-HL118001

Title of Project: Role of Endothelial and Macrophage ApoER2 in Atherosclerosis Modulation

**Role:** Principle Investigator **Dates:** 02/2014 – 01/2018

Grantor: NIH 2T32HL098040

Title of Project: Training Program in Lung Biology and Disease

Role: Project Director/Principle Investigator (Co-PD/PI with Lance Terada)

Dates: 07/2014 - 06/2019

**Grantor:** The Hartwell Foundation

Title of Project: Preventing Obesity-induced Diabetes

**Role:** Principle Investigator **Dates:** 09/2016 – 08/2019

**Grantor: NIH 1R01-HL131597** 

Title of Project: Dichotomous Role of Endothelial SR-B1 in Atherosclerosis

Role: Principle Investigator Dates: 12/2016 – 11/2020

### **Peer-Reviewed Publications**

1. Ağaç D, **Gill MA**, Farrar JD. <u>Adrenergic Signaling at the Interface of Allergic Asthma and Viral Infections.</u> *Front Immunol*. 2018 Apr 11;9:736. PMID: 29696025

- 2. Anton-Martin P, Braga B, Megison S, Journeycake J, **Moreland J**. <u>Craniectomy and Traumatic Brain Injury in Children on Extracorporeal Membrane Oxygenation Support</u>. *Pediatr Emerg Care*. 2018 Nov;34(11):e204-e210. PMID: 27749813
- 3. Babu ST, Niu X, Raetz M, **Savani RC**, Hooper LV, Mirpuri J. <u>Maternal high-fat diet results in microbiota-dependent expansion of ILC3s in mice offspring.</u> *JCI Insight*. 2018 Oct 4;3(19). PMID: 30282818
- 4. Chu H, Jiang S, Liu Q, Ma Y, Zhu X, Liang M, Shi X, Ding W, Zhou X, Zou H, Qian F, **Shaul PW**, Jin L, Wang J. <u>Sirtuin1 Protects against Systemic Sclerosis-related Pulmonary Fibrosis by Decreasing Proinflammatory and Profibrotic Processes</u>. *Am J Respir Cell Mol Biol*. 2018 Jan;58(1):28-39. PMID: 28800254



- 5. **Gill MA**, Liu AH, Calatroni A, et al. Enhanced plasmacytoid dendritic cell antiviral responses after omalizumab. *J Allergy Clin Immunol*. 2018 May;141(5):1735-1743.e9. PMID: 28870461
- 6. **Gill MA**, Schlaudecker EP. <u>Perspectives from the Society for Pediatric Research: Decreased Effectiveness of the Live Attenuated Influenza Vaccine. *Pediatr Res.* 2018 Jan;83(1-1):31-40. PMID: 28945700</u>
- 7. Goleva E, Babineau DC, **Gill MA**, et al. <u>Expression of corticosteroid-regulated genes by PBMCs in children with asthma.</u> *J Allergy Clin Immunol*. 2018 Jul 27. pii: S0091-6749(18)31064-9. PMID: 30059697
- 8. Lagatta JM, Hysinger EB, Zaniletti I, Wymore EM, Vyas-Read S, Yallapragada S, Nelin LD, Truog WE, Padula MA, Porta NFM, **Savani RC**, et al. <u>The Impact of Pulmonary Hypertension in Preterm Infants with Severe Bronchopulmonary Dysplasia through 1 Year.</u> *J Pediatr*. 2018 Dec;203:218-224.e3 PMID: 30172426
- Markasz L, Savani RC, Sedin G, Sindelar R. <u>The receptor for hyaluronan-mediated motility (RHAMM) expression in neonatal bronchiolar epithelium correlates negatively with lung air content.</u> *Early Hum Dev.* 2018 Dec;127:58-68. PMID: 30312861
- 10. Mir IN, Chalak LF, Liao J, Johnson-Welch S, Brown LS, Longoria C, **Savani RC**, Rosenfeld CR. <u>Fetal-placental crosstalk</u> occurs through fetal cytokine synthesis and placental clearance. Placenta. 2018 Sep;69:1-8. PMID: 30213477
- 11. Morel E, Ghezzal S, Lucchi G, Truntzer C, Pais de Barros JP, Simon-Plas F, Demignot S, **Mineo C**, **Shaul PW**, Leturque A, Rousset M, Carrière V. Cholesterol trafficking and raft-like membrane domain composition mediate scavenger receptor class B type 1-dependent lipid sensing in intestinal epithelial cells. Biochim Biophys Acta Mol Cell Biol Lipids. 2018 Feb;1863(2):199-211. PMID: 29196159
- 12. Peng J, Yu J, Xu H, Kang C, **Shaul PW**, Guan Y, Zhang X, Su W. <u>Enhanced Liver Regeneration After Partial Hepatectomy in Sterol Regulatory Element-Binding Protein (SREBP)-1c-Null Mice is Associated with Increased Hepatocellular Cholesterol Availability. *Cell Physiol Biochem.* 2018;47(2):784-799. PMID: 29807364</u>
- 13. Rowe RK, **Gill MA**. <u>Targeting Antiviral Pathways for Treatment of Allergic Diseases.</u> J Pediatric Infect Dis Soc. 2018 Dec 26;7(suppl 2):S54-S56. PMID: **30590620**
- 14. **Sacharidou A**, Chambliss KL, Ulrich V, Salmon JE, Shen YM, Herz J, Hui DY, Terada LS, **Shaul PW**, **Mineo C**. Antiphospholipid antibodies induce thrombosis by PP2A activation via apoER2-Dab2-SHC1 complex formation in endothelium. *Blood*. 2018 May 10;131(19):2097-2110. PMID: 29500169 *Plenary Paper*
- 15. **Sacharidou A, Shaul PW, Mineo C**. <u>New Insights in the Pathophysiology of Antiphospholipid Syndrome</u>. *Semin Thromb Hemost*. 2018 Jul;44(5):475-482. PMID: 28129662
- 16. Savani RC. Modulators of inflammation in Bronchopulmonary Dysplasia. Semin Perinatol. 2018 Nov;42(7):459-470. PMID: 30446300
- Selvaraj UM, Zuurbier KR, Whoolery CW, Plautz EJ, Chambliss KL, Kong X, Zhang S, Kim SH, Katzenellenbogen BS, Katzenellenbogen JA, Mineo C, Shaul PW, Stowe AM. <u>Selective Nonnuclear Estrogen Receptor Activation Decreases</u> <u>Stroke Severity and Promotes Functional Recovery in Female Mice.</u> *Endocrinology*. 2018 Nov 1;159(11):3848-3859. PMID: 30256928
- 18. Tanigaki K, **Sacharidou A**, Peng J, Chambliss KL, Yuhanna IS, Ghosh D, Ahmed M, Szalai AJ, Vongpatanasin W, Mattrey RF, Chen Q, Azadi P, Lingvay I, Botto M, Holland WL, Kohler JJ, Sirsi SR, Hoyt K, **Shaul PW**, **Mineo C**. <u>Hyposialylated IgG activates endothelial IgG receptor FcyRIIB to promote obesity-induced insulin resistance</u>. *J Clin Invest*. 2018 Jan 2;128(1):309-322. PMID: 29202472
- 19. Walls T, Cavuoti D, Channabasappa N, Yang M, Southern P, **Gill MA**, Park JY. <u>Abdominal Angiostrongyliasis: A Presentation of Eosinophilic Granulomatous Colitis.</u> Int J Surg Pathol. 2018 Aug;26(5):475-478. PMID: 29278974



# Center for Pulmonary & Vascular Biology

# 2018 Annual Report

### **Book Sections**

- 1. **Savani RC**. <u>Modulators of inflammation in Bronchopulmonary Dysplasia</u>. In: *Seminars in Perinatology*, "BPD Emerging Concepts" 2018 Nov;42(7):459-470. Elsevier, Inc. (PMID: 30446300)
- 2. Wu S, **Savani RC**. Molecular Bases for Lung Development, Injury, and Repair. In: Bancalari E, Keszler M, Davis P, eds. *The Newborn Lung*. 3<sup>rd</sup> ed. Philadelphia, PA. Elsevier; 3-30, 2018.