Pediatric Center for Pulmonary & Vascular Biology – 2020 Annual Report

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.

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

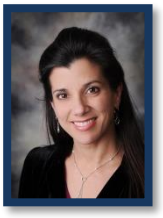
The Center provides a valuable resource for investigative endeavors in pulmonary biology and vascular biology across the UT Southwestern campus. This is represented by active collaborations between PVB faculty and other UT Southwestern faculty in the Departments of Internal Medicine, Cell Biology, Physiology,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

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 2020.

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.
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.
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.
Instructor, Center for Pulmonary and Vascular Biology

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Honors / Awards

Best Pediatric Specialists in Dallas, *D Magazine*

- Jessica Moreland

Chieko Mineo

- Promoted to Professor

Michelle Gill

- Promoted to Professor

Texas Super Doctor, *Texas Monthly*

- Rashmin Savani

Council Member, International Perinatal Collegium

- Rashmin Savani

Invited Lectures

Chieko Mineo

American Heart Association Vascular Discovery Meeting, Chicago, IL, 2020, Virtual Meeting

- *"Endothelial Cell Lipoprotein Transport and Atherosclerosis"*

- UT Southwestern Division of Cardiology Research Seminar Series, Dallas, TX, 2020, Virtual Meeting

"Molecular Basis of Maternal Hypertension in the Antiphospholipid Syndrome"

Rashmin Savani

- TCHMB Annual Summit, Austin, TX, February 2020
  - *"Making Quality Improvement Local"*

Philip Shaul

- European Atherosclerosis Society Congress, Geneva, Switzerland, 2020, Virtual Meeting

  - *"Endothelial Cell Lipoprotein Transport in Atherosclerosis."*

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

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 allergic airway diseases and 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. She also collaborates with Dr. David Farrar in the Department of Immunology in studying the role of Type I interferon and T lymphocyte immune responses in allergic disease pathogenesis. Dr. Gill's lab also investigates the impact of allergen-specific and targeted biologic immunotherapies on dendritic cell and T follicular helper cell phenotype and function, with the goal of identifying novel mechanisms that contribute to the clinical efficacy of these therapies.

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).

With an overarching focus on endothelial cell biology, Dr. Sacharidou has made major discoveries regarding a common cause of thrombosis. She has also discovered and continues to characterize a new kinase for Akt kinase which is critical to the cardiovascular protection afforded by HDL cholesterol. Dr. Sacharidou is currently additionally pursuing a number of projects determining how mechanisms in endothelial cells govern the role of the skeletal muscle in normal glucose homeostasis and in type 2 diabetes.

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. This year studies have also focused on the role of hyaluronan and its receptors in the cytokine storm generated by activation of TLR7 responses as a model of SARS-CoV-2 infection, and the use of therapeutic agents to block the activation of this pathway in innate immunity.

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. Their ultimate goal is to identify new targets for therapies to combat cardiovascular and metabolic disorders.

Current Grant Support

Michelle Gill

Grantor: NIAID; Inner City Asthma Consortium (ICAC); University of Wisconsin, Madison
Title of Project: Immunologic Approaches to Reduce Asthma
Role: Co-Investigator (PI: R Gruchalla)
Dates: 08/2014 – 07/2021

Grantor: NIAID; Inner City Asthma Consortium3 (ICAC3); University of Wisconsin, Madison
Title of Project: Mechanistic Study Development for ICAC3 Protocols, Year 7
Role: Principal Investigator
Dates: 08/2015 – 07/2021

Grantor: NIAID; Immune Tolerance Network (ITN); Benaroya Research Institute at Virginia Mason
Title of Project: Dendritic cell and T follicular helper cell pilot studies for the ITN CATNIP study ("Anti-TSLP plus antigen-specific immunotherapy for induction of tolerance in individuals with cat allergy")
Role: Principal Investigator
Dates: 02/2019 – 01/2020

Grantor: NIAID; Immune Tolerance Network (ITN); Benaroya Research Institute at Virginia Mason
Title of Project: Impact of Anti-TSLP and antigen-specific immunotherapy on Dendritic Cell and T follicular helper cells in individuals with cat allergy
Role: Principal Investigator
Dates: 02/2020 – 01/2021

Grantor: NIAID; Immune Tolerance Network (ITN); Benaroya Research Institute at Virginia Mason
Title of Project: Thymic Stromal Lymphopoietin (TSLP) Bioactivity Pilot Study
Role: Principal Investigator
Dates: 02/2020 – 01/2021

Chieko Mineo

Grantor: NIH-National Institutes of Health
Title of Project: Endothelial SR-BI and Metabolic Health
Role: Principal Investigator
Dates: 08/2015 – 06/2021

Grantor: NIH-National Institute of DDK Diseases
Title of Project: Endothelial Basis of Obesity-induced Insulin Resistance
Role: Principal Investigator
Dates: 07/2016 – 06/2021

Grantor: NIH-National Institute of DDK Diseases
Title of Project: Endothelial Basis of Obesity-induced Insulin Resistance (Supplement)
Role: Principal Investigator
Dates: 07/2019 – 06/2021

Grantor: University of Kentucky College of Medicine
Title of Project: Mechanism of Adrenal Insufficiency as a Risk Factor for Sepsis
Role: Co-Investigator
Dates: 09/2016 – 08/2021

Grantor: American Heart Associate (Postdoctoral Fellowship Award for Haiyan Chu)
Title of Project: Molecular Basis of Maternal Hypertension in the Antiphospholipid Syndrome
Role: Principal Investigator
Dates: 07/2018 – 06/2020

Grantor: NIH-National Heart, Lung and Blood Institute
Title of Project: Molecular Basis of Pregnancy Complications in the Antiphospholipid Syndrome
Role: Principal Investigator
Dates: 08/2018-05/2023

Rashmin Savani

Grantor: Mallinckrodt Pharmaceuticals, Inc.
Title of Project: RHAMM-Based Peptides to Block NFkB and NLRP3 Inflammasome Activation
Role: Principal Investigator
Dates: 7**/**2020 – 6/2022

Philip Shaul

Grantor: NIH-National Institute of Child Health and Human Development
Title of Project: Antecedents and Sequelae of Childhood Onset Disease (K12)
Role: Training Director (PI: J. Perez-Fontan)
Dates: 12**/**2015 – 11/2020

Grantor: NIH-National Heart, Lung and Blood Institute
Title of Project: Dichotomous Role of Endothelial SR-B1 in Atherosclerosis
Role: Principal Investigator
Dates: 12**/**2016 – 11/2021

Grantor: American Heart Association (Postdoctoral Fellowship Award for Jun Peng)
Title of Project: Endothelial Regulation of Insulin Sensitivity
Role: Principal Investigator
Dates: 01**/**2019 – 12/2020

Grantor: NIH-National Heart, Lung and Blood Institute
Title of Project: Endothelial Estrogen Receptor Alpha and Cardiometabolic Disease
Role: Principal Investigator
Dates: 06**/**2019 – 04/2023

Grantor: NIH-National Heart, Lung and Blood Institute
Title of Project: Unraveling ApoE4 Promotion of Cardiometabolic Disease
Role: Principal Investigator
Dates: 07**/**2020 – 04/2024

Grantor: NIH-National Heart, Lung and Blood Institute
Title of Project: Training Program in Lung Biology and Disease (T32)
Role: Co-Director (with Co-Director L. Terada)
Dates: 04**/**2020 – 03/2025

Peer-Reviewed Publications

1. Calvier L, Demuth G, Manouchehri N, Wong C, Sacharidou A, **Mineo C**, **Shaul PW**, Monson NL, Kounnas MZ, Stüve O, Herz J. Reelin depletion protects against autoimmune encephalomyelitis by decreasing vascular adhesion of leukocytes. *Sci Transl Med.* 2020 Aug 12;12(556):. PMID:32801146

2. Cardoso AC, Lam NT, Savla JJ, Nakada Y, Pereira AHM, Elnwasany A, Menendez-Montes I, Ensley EL, Petric UB, Sharma G, Sherry AD, Malloy CR, Khemtong C, Kinter MT, Tan WLW, Anene-Nzelu CG, Foo RS, Nguyen NUN, Li S, Ahmed MS, Elhelaly WM, Abdisalaam S, Asaithamby A, Xing C, Kanchwala M, Vale G, Eckert KM, Mitsche MA, McDonald JG, Hill JA, Huang L, **Shaul PW**, Szweda LI, Sadek HA. Mitochondrial Substrate Utilization Regulates Cardiomyocyte Cell Cycle Progression. *Nat Metab.* 2020 Feb;2(2):167-178. PMID:32617517

3. Chen F, Rowe RK, **Gill MA**, Farrar JD. Type I interferon suppresses memory Th2 cell cytokine secretion from allergic subjects. *Allergy.* 2020 Mar;75(3):695-698. PMID:31541610

4. Chow TG, **Gill MA**. Regulation of allergic inflammation by dendritic cells. *Curr Opin Allergy Clin Immunol.* 2020 Feb;20(1):56-63. PMID:31789871

5. Hook JS, Cao M, Weng K, Kinnare N, **Moreland JG**. Mycobacterium tuberculosis Lipoarabinomannan Activates Human Neutrophils via a TLR2/1 Mechanism Distinct from Pam 3 CSK 4. *J Immunol.* 2020 Feb 1;204(3):671-681. PMID:31871022

6. Jackson DJ, Bacharier LB, Calatroni A, **Gill MA**, Hu J, Liu AH, Wheatley LM, Gern JE, Gruchalla RS, Khurana Hershey GK, Kattan M, Kercsmar CM, Kim H, O'Connor GT, Patel S, Pongracic JA, Wood RA, Busse WW. Serum IL-6: A biomarker in childhood asthma? *J Allergy Clin Immunol.* 2020 Jun;145(6):1701-1704.e3. PMID:32004524

7. Khan HS, Nair VR, Ruhl CR, Alvarez-Arguedas S, Galvan Rendiz JL, Franco LH, Huang L, **Shaul PW**, Kim J, Xie Y, Mitchell RB, Shiloh MU. Identification of scavenger receptor B1 as the airway microfold cell receptor for Mycobacterium tuberculosis. *Elife.* 2020 Mar 5;9():. PMID:32134383

8. Lingappan K, **Savani RC**. The Wnt Signaling Pathway and the Development of Bronchopulmonary Dysplasia. *Am J Respir Crit Care Med.* 2020 May 15;201(10):1174-1176. PMID:32101467

9. **Mineo C**. Lipoprotein receptor signalling in atherosclerosis. *Cardiovasc Res.* 2020 Jun 1;116(7):1254-1274. PMID:31834409

10. Niu X, Daniel S, Kumar D, Ding EY, **Savani RC**, Koh AY, Mirpuri J. Transient neonatal antibiotic exposure increases susceptibility to late-onset sepsis driven by microbiota-dependent suppression of type 3 innate lymphoid cells. *Sci Rep.* 2020 Jul 31;10(1):12974. PMID:32737397

11. Oezdemir I, Peng J, Ghosh D, Sirsi S, **Mineo C**, **Shaul PW**, Hoyt K. Multiscale and morphological analysis of microvascular patterns depicted in contrast-enhanced ultrasound images. *J Med Imaging (Bellingham).* 2020 May;7(3):34001. PMID:32509915

12. Rowe RK, Pyle DM, Farrar JD, **Gill MA**. IgE-mediated regulation of IL-10 and type I IFN enhances rhinovirus-induced Th2 differentiation by primary human monocytes. *Eur J Immunol.* 2020 Oct;50(10):1550-1559. PMID:32383224

13. Sheehan WJ, Krouse RZ, Calatroni A, Gergen PJ, Gern JE, **Gill MA**, Gruchalla RS, Khurana Hershey GK, Kattan M, Kercsmar CM, Lamm CI, Little FF, Makhija MM, Searing DA, Zoratti E, Busse WW, Teach SJ, NIAID-sponsored Inner-City Asthma Consortium. Aeroallergen Sensitization, Serum IgE, and Eosinophilia as Predictors of Response to Omalizumab Therapy During the Fall Season Among Children with Persistent Asthma. *J Allergy Clin Immunol Pract.* 2020 Oct;8(9):3021-3028.e2. PMID:32376491

14. Sisman J, Jaleel MA, Moreno W, Rajaram V, Collins RRJ, **Savani RC**, Rakheja D, Evans AS. Intrauterine Transmission of SARS-COV-2 Infection in a Preterm Infant. *Pediatr Infect Dis J.* 2020 Sep;39(9):e265-e267. PMID:32658097

15. Vyas-Read S, Wymore EM, Zaniletti I, Murthy K, Padula MA, Truog WE, Engle WA, **Savani RC**, Yallapragada S, Logan JW, Zhang H, Hysinger EB, Grover TR, Natarajan G, Nelin LD, Porta NFM, Potoka KP, DiGeronimo R, Lagatta JM, Children's Hospitals Neonatal Consortium Severe BPD Focus Group. Utility of echocardiography in predicting mortality in infants with severe bronchopulmonary dysplasia. *J Perinatol.* 2020 Jan;40(1):149-156. PMID:31570799

Book Chapters

1. **Savani RC**, Garantziotis S, Ibrahim J. (2020) The Inflammation Superhighway: Tolls, Signals and Pathways to BPD. In: Kallapur S, Pryhuber G. (Eds.) *Updates on Neonatal Chronic Lung Disease.* (pp 131-150) Elsevier.