# Section of Neonatology, Perinatal and Pulmonary Biology

## RESEARCH AND TRAINING DETAILS

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## CLINICAL ACTIVITIES AND TRAINING

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Research Highlights

LungMAP
A new National Heart, Lung, and Blood Institute (NHLBI)-funded research consortium was initiated to provide a detailed molecular atlas of the developing human and mouse lung. Single cell transcriptomics, high-resolution confocal microscopy, epigenetics, proteomics, lipidomics, and metabolomics data will be integrated using new bioinformatics approaches. Yan Xu, PhD, and Bruce Aronow, PhD, lead the bioinformatics studies. Jeffrey Whitsett, MD, and Steve Potter, PhD, lead the Cincinnati Children’s program, and Whitsett serves as the chair of the multi-institutional program. The consortium seeks to provide deep knowledge related to perinatal and postnatal lung formation and function.

Rare Lung Consortium
A new multicenter consortium was funded by the National Institutes of Health (NIH) to create a clinical network for translational studies seeking to understand and treat rare lung diseases. The work is led by Bruce Trapnell, MD, and Frank McCormack, MD, with UC College of Medicine. Rare life-threatening lung diseases affecting children and adults are being carefully phenotyped and evaluated for diagnosis and entry into clinical-translational studies. Lung diseases including lymphangioleiomyomatosis, alveolar proteinosis, disorders of surfactant metabolism, pulmonary fibrosis and emphysema are being studied. New diagnostic treatments are being developed with investigators throughout the world.

Asthma
Research in the Division of Pulmonary Biology spans all ages, from early development to maturity. Lung pathology associated with chronic lung diseases causes tissue remodeling, inflammation and loss of function. Many common lung diseases like cystic fibrosis, asthma and bronchopulmonary dysplasia are complicated by ongoing inflammation and mucus hyperproduction. Recent studies led by Jeffrey Whitsett, MD, identified genes causing mucus hyperproduction in the airways. Their recent paper published in the Journal of Clinical Investigation demonstrated that in the mouse, genes causing mucus production cause allergic asthma-like lung disease after birth. The genes controlling mucus production are required for allergic sensitization of the lung during development and at maturity. These studies identify new pathways mediating asthma that are being used to develop new therapies for chronic lung diseases like cystic fibrosis and asthma.

Significant Publications

Bone marrow transplantation is an effective cell therapy but requires myeloablation, which increases infection risk and mortality. Recent lineage-tracing studies documenting that resident macrophage populations self-maintain independently of haematological progenitors prompted us to consider organ-targeted, cell-specific therapy. Here, using granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor-β-deficient (Csfr2rb(-/-)) mice that develop a myeloid cell disorder identical to hereditary pulmonary alveolar proteinosis (hPAP) in children with CSF2RA or CSF2RB mutations, we show that pulmonary macrophage transplantation (PMT) of either wild-type or Csfr2rb-gene-corrected macrophages without myeloablation was safe and well-tolerated and that one administration corrected the lung disease, secondary systemic manifestations and normalized disease-related biomarkers, and prevented disease-specific mortality. PMT-derived alveolar macrophages persisted for at least one year as did therapeutic effects. Our findings identify mechanisms regulating alveolar macrophage population size in health and disease, indicate that GM-CSF is required for phenotypic determination of alveolar macrophages, and support translation of PMT as the first specific therapy for children with hPAP.


SAM-pointed domain-containing ETS transcription factor (SPDEF) is expressed in normal prostate epithelium. While its expression changes during prostate carcinogenesis (PCa), the role of SPDEF in prostate cancer remains controversial due to the lack of genetic mouse models. In present study, we generated transgenic mice with the loss- or gain-of-function of SPDEF in prostate epithelium to demonstrate that SPDEF functions as tumor suppressor in prostate cancer. Loss of SPDEF increased cancer progression and tumor cell proliferation, whereas over-expression of SPDEF in prostate epithelium inhibited carcinogenesis and reduced tumor cell proliferation in vivo and in vitro. Transgenic overexpression of SPDEF inhibited mRNA and protein levels of Foxm1, a transcription factor critical for tumor cell proliferation, and reduced expression of Foxm1 target genes, including Cdc25b, Cyclin B1, Cyclin A2, Plk-1, AuroraB, CKS1 and Topo2alpha. Deletion of SPDEF in transgenic mice and cultures prostate tumor cells increased expression of Foxm1 and its target genes. Furthermore, an inverse correlation between SPDEF and Foxm1 levels was found in human prostate cancers. The two-gene signature of low SPDEF and high FoxM1 predicted poor survival in prostate cancer patients. Mechanistically, SPDEF bound to, and inhibited transcriptional activity of Foxm1 promoter by interfering with the ability of Foxm1 to activate its own promoter through auto-regulatory site located in the -745/-660 bp Foxm1 promoter region. Re-expression of Foxm1 restored cellular proliferation in the SPDEF-positive cancer cells and rescued progression of SPDEF-positive tumors in mouse prostates. Altogether, SPDEF inhibits prostate carcinogenesis by preventing Foxm1-regulated proliferation of prostate tumor cells. The present study identified novel crosstalk between SPDEF tumor suppressor and Foxm1 oncogene and demonstrated that this crosstalk is required for tumor cell proliferation during progression of prostate cancer in vivo.


Epithelial cells that line the conducting airways provide the initial barrier and innate immune responses to the abundant particles, microbes, and allergens that are inhaled throughout life. The transcription factors SPDEF and FOXA3 are both selectively expressed in epithelial cells lining the conducting airways, where they regulate goblet cell differentiation and mucus production. Moreover, these transcription factors are upregulated in chronic lung disorders, including asthma. Here, we show that expression of SPDEF or FOXA3 in airway epithelial cells in neonatal mice caused goblet cell differentiation, spontaneous eosinophilic inflammation, and airway hyperresponsiveness to methacholine. SPDEF expression promoted DC recruitment and activation in association with induction of Il33, Csf2, thymic stromal lymphopoietin (Tslp), and Ccl20 transcripts. Increased Il4, Il13, Ccl17, and Il25 expression was accompanied by recruitment of Th2 lymphocytes, group 2 innate lymphoid cells, and eosinophils to the lung. SPDEF was required for goblet cell differentiation and pulmonary Th2 inflammation in response to house dust mite (HDM) extract, as both were decreased in neonatal and adult Spdef(-/-) mice compared with control animals. Together, our results indicate that SPDEF causes goblet cell differentiation and Th2 inflammation during postnatal development and is required for goblet cell metaplasia and normal Th2 inflammatory responses to HDM aeroallergen.

**Division Publications**


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**Faculty, Staff, and Trainees**

**Faculty Members**

**Jeffrey A. Whitsett, MD, Professor**

- **Leadership** Co-Director, Perinatal Institute; Chief, Section of Neonatology, Perinatal and Pulmonary Biology
- **Research Interests** Lung development; surfactant.

**Shawn K. Ahfeld, MD, Assistant Professor**

- **Research Interests** Lung development and repair following injury; bronchopulmonary dysplasia; pulmonary inflammation.

**Henry T. Akinbi, MD, Professor**

- **Research Interests** Neonatal infections and blood transfusions.

**Paritha Arumugam, PhD, Instructor**

- **Research Interests** Gene correction; pulmonary macrophage transplantation therapy for children with hPAP.

**Sandip Bhattacharyya, MSc, PhD, Assistant Professor**

- **Research Interests** Inflammation immunology; signal transduction.

**James P. Bridges, PhD, Assistant Professor**

- **Research Interests** Hypoxia inducible factors and downstream target genes in chronic lung disease.

**Tanya E. Cahill, MD, Assistant Professor**

- **Leadership** Director, High Risk Infant Follow-Up Program
- **Research Interests** Neonatal abstinence syndrome and high risk infant follow-up.

**Michael W. Crossman, MD, PhD, Assistant Professor**

- **Research Interests** Bioethics.
Hitesh Deshmukh, MD, PhD, Assistant Professor  
**Research Interests** The role of intestinal microbes in development of several innate immune cell lineages, with a particular focus on recently discovered group of lineage negative lymphocytes, known as innate lymphoid cells.

Jay H. Dritz, MD, Assistant Professor  
**Research Interests** Neonatal resuscitation; quality improvement.

Stephan W. Glasser, PhD, Associate Professor  
**Research Interests** Gene regulation in the lung.

Neera K. Goyal, MD, MSHP, Assistant Professor

James M. Greenberg, MD, Professor  
**Leadership** Co-Director, Perinatal Institute; Director, Division of Neonatology  
**Research Interests** Preterm birth; community health; pulmonary vascular development.

Beth E. Haberman, MD, Associate Professor  
**Leadership** Medical Director, Cincinnati Children’s NICU & Co-Medical Director, Mercy Anderson Hospital Nurseries  
**Research Interests** Infant follow-up.

Eric S. Hall, PhD, Assistant Professor  
**Research Interests** Biomedical informatics.

Crystal D. Hill, MD, Assistant Professor  
**Research Interests** Simulation and motility.

Steven B. Hoath, MD, Professor Emeritus  
**Research Interests** Skin development and environmental interactions.

Alan H. Jobe, MD, PhD, Professor  
**Leadership** Director, Division of Perinatal Biology  
**Research Interests** Injury and repair of the preterm lung.

Beth Ann Johnson, MD, Assistant Professor

Tanya V. Kalin, MD, PhD, Associate Professor  
**Research Interests** Transcriptional regulation of carcinogenesis and radiation-induced lung fibrosis.

Vladimir V. Kalinichenko, MD, PhD, Professor  
**Research Interests** Fox proteins in lung development.

Suhas G. Kallapur, MD, Professor  
**Leadership** Director, Neonatology CME  
**Research Interests** Fetal inflammation/physiology; lung development/inflammation; BPD; developmental immunology.

Beena D. Kamath-Rayne, MD, MPH, Assistant Professor  
**Research Interests** Neonatal outcomes and public health; fetal lung maturity; global health.

Heather C. Kaplan, MD, MSCE, Assistant Professor  
**Research Interests** Health services research; improvement science.

Alan P. Kenny, MD, PhD, Instructor  
**Research Interests** Molecular development of the foregut organs.

Paul S. Kingma, MD, PhD, Associate Professor  
**Research Interests** Innate immune systems; cystic fibrosis; neonatal infection.
Thomas R. Korfhagen, MD, PhD, Professor
Research Interests Lung defense.

Timothy D. Le Cras, PhD, Associate Professor
Leadership Director of Admissions, Molecular & Developmental Biology Graduate Program
Research Interests Chronic lung diseases; lung development; pulmonary hypertension.

Yutaka Maeda, DVM, PhD, Assistant Professor
Research Interests Lung cancer; asthma.

Kristin R. Melton, MD, Associate Professor
Leadership Associate Director, Neonatal-Perinatal Medicine Fellowship Training Program
Research Interests Developmental biology; neural crest biology.

Stephanie L. Merhar, MD, MS, Assistant Professor
Research Interests Neonatal neuroimaging; infant follow up.

Nagendra K. Monangi, MD, Assistant Professor
Research Interests Maternal/infant nutrition and vitamin D in preterm infants.

Ardythe L. Morrow, PhD, Professor
Leadership Director, Center for Interdisciplinary Research in Human Milk and Lactation
Research Interests Molecular epidemiology of human milk; epidemiologic methods; prevention of infectious disease; predictive biomarkers of neonatal outcomes.

Laurel B. Moyer, MD, Assistant Professor
Research Interests Implementation science; international health.

Louis J. Muglia, MD, PhD, Professor
Leadership Co-Director, Perinatal Institute; Division of Neonatology; Director, Center for Prevention of Preterm Birth
Research Interests Genetics of birth timing; neurobiology of the stress response.

Vivek Narendran, MD, MBA, Professor
Leadership Medical Director, Univ. Hosp. NICU and Newborn Nursery; Medical Director, The Christ Hospital Nursery; Chair, Department of Pediatrics, the University Hospital
Research Interests C-PAP; business case for quality improvements; preterm infant skin.

Amy T. Nathan, MD, Assistant Professor
Leadership Medical Director, TriHealth Nurseries
Research Interests Immunobiology.

Laurie A. Nommsen-Rivers, PhD, RD, IBCLC, Assistant Professor
Leadership Co-Chair, Seminar Series in Human Milk and Lactation
Research Interests Human lactation and breastfeeding.

Mihaela Pavlicev, PhD, Assistant Professor
Research Interests The genetic basis of complex traits, in particular the regulatory component and its evolutionary past.

Anne-Karina T. Perl, PhD, Assistant Professor
Research Interests Alveolar regeneration and bronchiolar injury/repair.

Brenda B. Poindexter, MD, Professor

John H. Reuter, MD, PhD, Associate Professor
Leadership Chair, Department of Pediatrics at Bethesda North Hospital Nurseries
Ward R. Rice, MD, PhD, Professor
  Leadership Director, Neonatal Fellowship Training Program; Director, Newborn Services, St. Elizabeth Medical Center
  Research Interests Lung development; surfactant biology.

Jerod M. Rone, MD, Associate Professor
  Leadership Medical Director, Kettering Medical Center NICU

Kurt R. Schibler, MD, Professor
  Leadership Director, Neonatology Clinical Research Program
  Research Interests Neonatal immunology; necrotizing enterocolitis.

John M. Shannon, PhD, Professor
  Leadership Director of Graduate Studies, Program in Molecular and Developmental Biology
  Research Interests Lung development; foregut embryology.

Debora I. Sinner, PhD, Assistant Professor
  Research Interests Wnt signaling and sox transcription factors in lung development and disease.

Kristen R. Suhrie, MD, Assistant Professor
  Research Interests Neonatology; genetic disorders presenting in the neonatal period.

Andrew P. South, MD, MPH, Assistant Professor
  Research Interests Outcomes and etiology of gastroschisis; epidemiology of late-preterm birth.

Jean J. Steichen, MD, Professor Emeritus
  Research Interests Infant follow-up.

Takuji Suzuki, MD, PhD., Assistant Professor
  Research Interests The molecular mechanisms of alveolar macrophages in pulmonary surfactant homeostasis and lung host defense; focusing on the studies of the pathogenesis and the new therapy for pulmonary alveolar proteinosis (PAP) by using disease model mice and human

Bruce C. Trapnell, MD, MS, Professor
  Leadership Director, Rare Lung Diseases Network; Scientific Director, PAP Foundation; Co-Director, Cystic Fibrosis TDN Center
  Research Interests Rare lung diseases; GM-CSF; gene therapy.

Christina J. Valentine, MD, Assistant Professor
  Research Interests Maternal and infant nutrition to improve perinatal health.

Laura Ward, MD, Assistant Professor
  Leadership Co-Medical Director, Mercy Anderson Hospital Nurseries
  Research Interests Use of human milk in the NICU.

Timothy E. Weaver, MS, PhD, Professor
  Leadership Associate Director, Division of Pulmonary Biology; Co-Director, Molecular and Developmental Biology Program
  Research Interests Pathogenesis of interstitial lung diseases.

Kathryn E. Wedig, MD, Associate Professor
  Leadership Director, High Risk Clinic at GSH; Medical Director, Mercy Hospital Fairfield
  Research Interests Infant follow-up; neonatal abstinence syndrome.

Susan E. Wert, PhD, Associate Professor
  Leadership Director, Molecular Morphology Core, Division of Pulmonary Biology
  Research Interests Lung development; molecular morphology of the lung; ultrastructural analysis of the lung; genetic surfactant disorders.
Scott L. Wexelblatt, MD, Assistant Professor
Leadership Medical Director, Regional Newborn Services; Co-Medical Director Bethesda North Hospital Nurseries
Research Interests Late preterm infant; quality improvement.

Jonathan R. Wispé, MD, Professor
Research Interests Perinatal ethics; theological studies.

Yan Xu, PhD, Professor
Leadership Director, Bioinformatics Microarray Core, Division of Pulmonary Biology
Research Interests Bioinformatics; systems biology; transcriptional network.

Joint Appointment Faculty Members

Kathryn A. Wikenheiser-Brokamp, MD, PhD, Associate Professor (Pathology)
Research Interests Pulmonary pathology; pediatric and adult lung diseases.

Clinical Staff Members

- Beth A. Baisden, MD
- Brooke Barnes, MD
- Stephen Bird, MD
- Daniel Bruzzini, MD
- Mary Burwinkel, MD
- Thomas Catalanotto, MD
- Diane Donley, MD
- Horacio Falciglia, MD
- Angelique Gloster, MD
- Steven Hoath, MD
- Jill Klein, MD
- Melissa Landis, MD
- Katie Loudermilk, MD
- Paige Marks, MD
- Jennifer McAllister, MD
- Alisa McGill, MD
- Steve Milligan, MD
- John Morrison, MD
- Vasudha Narayanaswamy, MD
- Patricia O'Brien, MD
- Miriam Peri, MD
• Kathryn Peterson, MD
• Ajay Ponkshe, MD
• Danna Premer, MD
• Janice Roeder, MD
• Deborah Rufner, MD
• Balzer Sandrock, MD
• Kelley Shultz, MD
• Blair Simpson, MD
• Crystal Singewald, MD
• Heather Smith, MD
• Ellen Springer, MD
• Jean Steichen, MD
• Audrey Veach, MD
• Wambui Waruingi, MD
• Kira Zimmerly, MD

Trainees
• Thomas Acciani, BS, University of Illinois, Urbana, IL
• Amil Allen, MD, Cincinnati Children's Hospital Medical Center
• Melinda Arnett, PhD, University of Kansas Medical Center, Kansas City, KS
• Jonas Bacelis, PhD, University of Gothenburg, Sweden
• Maria Barnes, MD, Mount Sinai Medical Center, New York, NY
• Katie Bezold, BS, Xavier University, Cincinnati, OH
• Yuqi Cai, PhD, Zhejiang University School of Medicine, Hangzhou, China
• Kimberly Carpenter, MD, North Shore-Long Island Jewish Health System, New Hyde Park, NY
• Xin-Hua Cheng, PhD, Miami University, Oxford, OH
• Juan Manuel Coya, PhD, Universidad Complutense, Madrid, Spain
• Rebecca Currier, BS, Louisiana Tech University, Ruston, LA
• Yina Du, MS, University of Cincinnati, Cincinnati, OH
• Joshua Euteneuer, MD, St. Louis Children's Hospital, St. Louis, MO
• Ene Fairchild, MD, Nationwide Children's Hospital, Columbus, OH
• Jill Fritz, BS, Miami University, Oxford, OH
• Ting Ting Fu, MD, Maine Medical Center, Portland, ME
• Logan Fulford, BS, Indiana State University, Terre Haute, IN
• David Hahn, BS, Northern Kentucky University, Highland Heights, KY
• Jamie Havrilak, BS, Susquehanna University, Selinsgrove, PA
• Melissa House, MD, Children's National Medical Center, Washington, DC
• Suyog Kamatkar, MD, Indiana School of Medicine, Indianapolis, IN
• Melissa Landis, MD, Morgan Stanley Children's Hospital of NY Presbyterian, New York, NY
• Gloria Laryea, BS, University of Maryland, Eastern Shore, Princess Anne, MD
• Candice Lengyel, MD, University of Michigan, Ann Arbor, MI
• Gunlawadee Maneenil, MD, Prince of Songkla University, Songkhla, Thailand
• Kera McNelis, MD, Rainbow babies and Children's Hospital, Cleveland, OH
• Masahiko Murase, MD, PhD, IBCLC, Showa University, Tokyo, Japan
• Chan-Wook Park, MD, PhD, Seoul National University College of Medicine, Seoul, Korea
• Priya Rajavelu, PhD, University of Madras, Chennai, Tamil Nadu, India
• Benjamin Reed, MD, The Cleveland Clinic
• Stefanie Riddle, MD, Cincinnati Children's, Cincinnati, OH
• Melissa Rice, MD, Indiana University School of Medicine, Indianapolis, IN
• Amy Rouse, MD, Rainbow Babies and Children's Hospital, Cleveland, OH
• Tony Sallese, BS, University of St. Francis, Joliet, IL
• Augusto Schmidt, MD, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
• Jessica Seeberger, MBA, University of Cincinnati, Cincinnati, OH
• Laura Seske, MD, Washington University, Saint Louis, MO
• Teresa Seto, MD, Nationwide Children's Hospital, Columbus, OH
• Sneha Sitaraman, MS, BS, VIT University, Vallore, India, University of Pune, Pune India
• Heather Smith, MD, Miller School of Medicine, Miami, FL
• Diana Taft, PhD, University of Cincinnati, Cincinnati, OH
• Xiaofang Tang, PhD, Tsinghua University, Beijing, China
• Tayaramma Thatava, PhD, University of Braunschweig - Institute of Technology, Germany
• Emily Wayman, BS, University of Alabama, Tuscaloosa, AL
• Emily Wiland, MD, Rainbow Babies and Children's Hospital, Cleveland, OH
- **Jason Wiles, MD**, University of Louisville School of Medicine, Louisville, KY
- **Sadie Williams, MD**, University of Florida at Arnold Palmer Hospital, Orlando, FL
- **Koryse Woodroffe, MD**, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
- **Giridhar Vummidi Giridhar, PhD**, University of Madras, Tamil Nadu, India
- **Hongping Xia, PhD**, Fudan University, Shanghai, China
- **Yvonne Yui, MD**, University of Cincinnati College of Medicine, Cincinnati, OH

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## Grants, Contracts, and Industry Agreements

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**Jobe, A**
Initiation and Progression of Preterm Lung Injury with Ventilation
National Institutes of Health
R01 HD072842 8/1/2012-5/31/2017 $207,815

Data Coordinating Center for the Prematurity and Respiratory Outcomes Program
National Institutes of Health (University of Pennsylvania)
U01 HL101794 5/1/2012-4/30/2016 $11,373

Kalin, T
Transcriptional Regulation of Cancer Progression and Metastasis by Foxm1
American Cancer Society National
RSG1332501 7/1/2013-6/30/2017 $150,000

Role of Foxm1 in Lung Cancer Microenvironment
National Institutes of Health
R01 CA142724 7/1/2010-6/30/2015 $195,237

Kalinichenko, V
Foxf1 Transcription Factor in Development of Pulmonary Capillaries
National Institutes of Health
R01 HL084151 5/8/2015-4/30/2019 $250,000

Transcriptional Regulation of Goblet Cell Metaplasia
National Institutes of Health
R01 HL123490 8/5/2014-6/30/2018 $250,000

Kingma, P
Intestinal Motility and Gastrochisis
The Gerber Foundation
1557-3464 7/1/2013-6/30/2016 $53,251

LeCras, T
Identification of Biomarkers for Patients with Generalized Lymphatic Anomaly (GLA), Kaposiform Lymphangiomatosis (KLA), Gorham-Stout disease (GSD)
The Lymphatic Malformation Institute
5/1/2015-4/30/2016 $131,828
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<td>Serial Neuroimaging in Infants with Necrotizing Enterocolitis</td>
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<td>DNA Attenuates Inflammatory Responses through Altering RAGE Signaling</td>
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<td>Taking the Guesswork Out of Pediatric Weight Estimation: Ensuring Accurate Weight Assessment in Newborns and Young Infants (Baby TAPE)</td>
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<td>Pharmacokinetics of Antistaphylococcal Antibiotics in Infants</td>
<td>National Institutes of Health</td>
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<td>The Role of Autophagy in the Pathogenesis of Interstitial Lung Disease</td>
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**Current Year Direct** $10,575,664
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**Current Year Direct Receipts**  
$167,672

**Total**  
$10,743,336