# Section of Neonatology, Perinatal and Pulmonary Biology

## RESEARCH AND TRAINING DETAILS

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<thead>
<tr>
<th>Category</th>
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<td>Faculty</td>
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<td>Joint Appointment Faculty</td>
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<tr>
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## CLINICAL ACTIVITIES AND TRAINING

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<td>Staff Physicians</td>
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[Click to view members](#)
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 (Csf2rb(-/-)) 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 Csf2rb-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 over-expression 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**


45. Hintz SR, Barnes PD, Bulas D, Slovis TL, Finer NN, Wrage LA, Das A, Tyson JE, Stevenson DK, Carlo WA, Walsh...


111. Taft DH, Ambalavanan N, Schibler KR, Yu Z, Newburg DS, Deshmukh H, Ward DV, Morrow AL. Center Variation in...


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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. Ahlfeld, 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 & 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, CCHMC
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• 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
Grants, Contracts, and Industry Agreements

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<th>Grant and Contract Awards</th>
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**Bridges, J**

*Role of GPR116 in the Regulation of Alveolar Surfactant Pool Size*

American Heart Association

13SDG17090028  7/1/2013-6/30/2017  $70,000

**Greenberg, J**

*Cradle Cincinnati: Pregnancy & Infant Health Promotion*

City of Cincinnati

6/17/2015-4/30/2016  $250,000

**Healthy Start Cincinnati**

Health Resources & Services Administration

H49 MC27823  9/1/2014-5/31/2019  $415,073

**Cradle Cincinnati: Pregnancy & Infant Health Promotion**

Interact for Health

8/1/2014-7/31/2015  $100,000

**Hostetter, M / Muglia, L**

*Child Health Research Career Development Award (K12)*

National Institutes of Health

K12 HD028827  12/1/2011-11/30/2016  $398,715

**Jobe, A**
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<td>Data Coordinating Center for the Prematurity and Respiratory Outcomes Program</td>
<td>National Institutes of Health (University of Pennsylvania)</td>
<td>U01 HL101794</td>
<td>5/1/2012</td>
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<td>Kalin, T, Transcriptional Regulation of Cancer Progression and Metastasis by Foxm1</td>
<td>American Cancer Society National</td>
<td>RSG1332501</td>
<td>7/1/2013</td>
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<td>Role of Foxm1 in Lung Cancer Microenvironment</td>
<td>National Institutes of Health</td>
<td>R01 CA142724</td>
<td>7/1/2010</td>
<td>6/30/2015</td>
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<td>Kalinichenko, V, Foxf1 Transcription Factor in Development of Pulmonary Capillaries</td>
<td>National Institutes of Health</td>
<td>R01 HL084151</td>
<td>5/8/2015</td>
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<td>Transcriptional Regulation of Goblet Cell Metaplasia</td>
<td>National Institutes of Health</td>
<td>R01 HL123490</td>
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<td>Kingma, P, Intestinal Motility and Gastrochisis</td>
<td>The Gerber Foundation</td>
<td>1557-3464</td>
<td>7/1/2013</td>
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<td>LeCras, T, Identification of Biomarkers for Patients with Generalized Lymphatic Anomaly (GLA), Kaposiform Lymphangiomatosis (KLA), Gorham-Stout disease (GSD)</td>
<td>The Lymphatic Malformation Institute</td>
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<td>Maeda, Y</td>
<td>Dissecting Tumor Heterogeneity in KRAS-Mutant Lung Cancer</td>
<td>American Lung Association</td>
<td>RG309608</td>
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<td>Merhar, S</td>
<td>Serial Neuroimaging in Infants with Necrotizing Enterocolitis</td>
<td>Cerebral Palsy International Research Foundation</td>
<td>EH-014-00</td>
<td>1/1/2015</td>
<td>12/31/2017</td>
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<td>Morrow, A</td>
<td>DNA Attenuates Inflammatory Responses through Altering RAGE Signaling</td>
<td>National Institutes of Health (The Research Institute at Nationwide Hospital)</td>
<td>R01 AT006880</td>
<td>7/1/2012</td>
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<td>Systems Biology Approaches to Birth Timing and Preterm Birth Risk - Supplement</td>
<td>Bill &amp; Melinda Gates Foundation</td>
<td>OPP1113966</td>
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<td>22-FY15-003</td>
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<td>Dey, S</td>
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<td>Muglia, L / Chougnet, C</td>
<td>Maternal Temperament, Stress, and Inflammation in Preterm Birth</td>
<td>National Institutes of Health</td>
<td>R01 HD078127</td>
<td>9/1/2013</td>
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<td>Researcher</td>
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<td>Nommsen-Rivers, L</td>
<td>Improving Lactation Success in Pre-Diabetic Mothers</td>
<td>National Institutes of Health (University of Cincinnati)</td>
<td>K12 HD051953</td>
<td>7/1/2014-6/30/2016</td>
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<td>Poindexter, B</td>
<td>Gastrin-Releasing Peptide and Bronchopulmonary Dysplasia</td>
<td>National Institutes of Health (Duke University)</td>
<td>R01 HL105702</td>
<td>10/1/2014-7/31/2016</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>
<td>National Institutes of Health (Duke University)</td>
<td>HHSN2752010000031</td>
<td>4/1/2015-3/22/2016</td>
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<td>Pharmacokinetics of Antistaphylococcal Antibiotics in Infants</td>
<td>National Institutes of Health (Duke University)</td>
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<td>Safety and Efficacy of High-Dose Acyclovir in Infants with HSV</td>
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<td>Molecular Mechanisms Underlying Upper Airway Patterning and Tracheomalacia</td>
<td>National Institutes of Health</td>
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Traphnell, B

Role of GM-CSF in Myeloid Cell Function and Innate Immunity

National Institutes of Health

R01 HL085453 4/1/2011-3/31/2016 $246,250

Macrophage Based Gene Therapy for Hereditary Pulmonary Alveolar Proteinosis

National Institutes of Health

R01 HL118342 5/1/2014-4/30/2018 $442,974

RLDC: Molecular Pathway-Driven Diagnostics & Therapeutic for Rare Lung Diseases

National Institutes of Health

U54 HL127672 9/18/2014-7/31/2019 $730,609

Weaver, T

The Role of Autophagy in the Pathogenesis of Interstitial Lung Disease

National Institutes of Health

R01 HL103923 8/1/2011-6/30/2015 $324,057

Stard7, a Novel Inhibitor of Allergic Lung Disease

National Institutes of Health

R01 HL122130 1/1/2014-12/31/2017 $225,000

Wexelblat, S

Neonatal Abstinence Syndrome (NAS) Project

Ohio Dept of Jobs and Family Services (University Hospitals, Case Medical Center)

7/1/2012-6/30/2015 $33,049

Whitsett, J

Transcriptional Programming of Asthma Related Pathology in Respiratory Epithelia

National Institutes of Health

R01 HL095580 4/15/2013-3/31/2018 $340,282

Omics of Lung Diseases

National Institutes of Health

K12 HL119986 09/01/2013-05/31/2018 $249,632
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<td>&quot;Lung MAP&quot; Atlas Research Center</td>
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<td>Xu, Y</td>
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<td>Role of SREBP Network in Surfactant Lipid Homeostasis and Lung Maturation</td>
<td>National Institutes of Health</td>
<td>R01 HL105433</td>
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**Current Year Direct**

$10,575,664
## Industry Contracts

**Morrow, A**

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<td>Prolacta Bioscience Inc.</td>
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<td>Mead Johnson &amp; Company</td>
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**Current Year Direct Receipts**  

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<td>Current Year Direct Receipts</td>
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SPDEF Transcription Factor Shown to Suppress Prostate Cancer

PUBLISHED SEPT. 25, 2014

PLOS Genetics

Prostate cancer continues to be the most common malignancy diagnosed in American men and the second leading cause of male cancer mortality.

Tanya Kalin, MD, PhD, leads a research team at Cincinnati Children’s that seeks to identify the direct role of several transcription factors (Foxm1, Foxf1, Foxf2, SPDEF) in prostate cancer. The team’s latest findings, published Sept. 25, 2014, in *PLOS Genetics*, explain how SPDEF transcription factor expression changes during prostate carcinogenesis, which suggests that new treatments could be developed that target Foxm1 via SPDEF dependent pathways.

“Our data demonstrate that SPDEF functions as a tumor suppressor in prostate cancers by inhibiting tumor cell proliferation via disruption of an auto-regulatory element in the Foxm1 promoter,” Kalin says. “It is possible that the loss of SPDEF causes increased expression of oncogenic Foxm1, accelerating tumor cell proliferation and leading to poor outcome in prostate cancer patients.”

Until now, researchers lacked useful transgenic mouse models to study the role of SPDEF in prostate cancer. Kalin and colleagues generated mice that either lacked or over-expressed SPDEF function. The mice revealed that loss of SPDEF increased cancer progression and tumor cell proliferation, whereas over-expression inhibited carcinogenesis and reduced tumor cell proliferation *in vivo* and *in vitro*.

Specifically, over-expression of SPDEF inhibited RNA 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. Furthermore, an inverse correlation between SPDEF and Foxm1 levels was found in human prostate cancers, with the two-gene signature of low SPDEF and high Foxm1 predicting poor survival.
Re-expression of Foxm1 restored cellular proliferation in SPDEF-overexpressing prostate tumor cells as demonstrated by increased numbers of Ki-67-positive (upper panels) and PH3-positive (bottom panels) cells. Percentages of Ki-67-positive and PH3-positive cells were counted in five random microscopic fields.
A new type of cell transplantation may one day become a treatment for hereditary pulmonary alveolar proteinosis (hPAP) and certain other rare lung diseases.

Bruce Trapnell, MD, and Takuji Suzuki, MD, PhD, discovered hPAP at Cincinnati Children's and first reported it in 2008. Children with hPAP have mutations in the genes of GM-CSF receptor alpha or beta (CSFR2RA or CSFR2RB). These mutations reduce the ability of alveolar macrophages to remove used surfactant from the lungs, which can lead to respiratory failure. The only current treatment is repeated, invasive whole-lung lavage.

In a recent study published in *Nature*, Suzuki and Trapnell report that macrophage transplantation (involving normal or gene-corrected cells) fully reversed the disease in mice bred to mimic hPAP. The treatment also prevented disease-specific mortality for at least one year.

“These are significant findings with potential implications beyond the treatment of a rare lung disease,” says Trapnell, senior author, and a researcher in the Translational Pulmonary Science Center at Cincinnati Children’s. “Our findings support the feasibility of pulmonary macrophage transplantation as the first specific therapy for children with hPAP.”

The research team utilized mice with the homologous CSFR2RB gene that mimics hPAP knocked out. The team then used a viral vector to deliver a correct version of CSFR2RB to abnormal alveolar macrophages taken from the animals. The gene-corrected cells were returned to the mice by direct instillation into the lungs.

Since publication, the researchers have begun the preclinical studies needed to prepare for human clinical trials.

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**THE PERINATAL INSTITUTE RESEARCH AND TRAINING DETAILS**

Faculty: 60
Joint Appointment Faculty: 1
Research Fellows: 14
Research Students: 14
Support Personnel: 95
Direct Annual Grant Support: $10.5M
Direct Annual Industry Support: $167,672
Peer Reviewed Publications: 134

Scientists at Cincinnati Children’s have demonstrated in mice bred to mimic hereditary pulmonary alveolar proteinosis (hPAP) that pulmonary macrophage transplantation of either wild-type or Csf2rb-gene-corrected macrophages without myeloablation was safe, well-tolerated, and that one administration corrected the lung disease. This illustration outlines the transplantation process planned for therapy of hPAP in children.

“Our findings support the feasibility of pulmonary macrophage transplantation as the first specific therapy for children with hPAP.”
Two Genes Expressed in Airway Epithelial Cells Play Important Roles in the Development of Asthma

Epithelial cells lining the airways are the first line of defense against infections and allergens, and doctors are increasingly understanding the role played by pulmonary immune responses — initiated early in development, in utero, and during infancy — in the development of asthma and other lung disorders.

Jeffrey Whitsett, MD, Co-Director of the Perinatal Institute, and a team of pulmonary biology researchers have shown that airway epithelial cells orchestrate immune responses after birth that influence subsequent allergic inflammation, leading to asthma.

Specifically, the researchers found that the genes SPDEF and FOXA3, which control mucus production and goblet cell differentiation, program pulmonary immune responses early in life and are sufficient and required to induce asthma. Goblet cells secrete the major components of mucus. The SDPEF and FOXA3 genes, expressed only in airway epithelial cells, control inflammatory responses to allergens and infections, programming subsequent asthma-like responses.

Whitsett’s study, which measured immune system responses in the lungs of neonatal mice, appeared May 4, 2015, in The Journal of Clinical Investigation. It concludes that exposure to commensal and pathogenic microbes and antigens influences goblet cells in the airways that determine the acquisition of immune responses after birth, responses that are likely to have long-term effects on the patterning of subsequent immune and inflammatory responses of the lung, leading to asthma.

“Inhibition of mucus cell hyperactivity induced by SPDEF following lung infections or exposure to allergies,” says Whitsett, “provides a novel, therapeutic approach for treatment and prevention of chronic airway diseases associated with excess mucus, including asthma and cystic fibrosis, common causes of severe lung disease in children.”

PUBLISHED MAY 4, 2015
The Journal of Clinical Investigation
This confocal microscope image shows airway goblet cells and mucus accumulation in the airways of mice caused by expression of FOXA3 and SPDEF. The mice develop “asthma” induced by expression of the genes controlling mucus production.