Section of Neonatology, Perinatal and Pulmonary Biology

Division Photo

First Row: Yan Xu, Tanya Kalin, James Greenberg, Jeffrey Whitsett, Alan Jobe, Amy Nathan, Kathryn Wedig; Second Row: Ann Akeson, Laurel Bookman, Beena Kamath, Kurt Schibler, Karen Sparling, Kathryn Wikenheiser-Brokamp, Dana Premer, Heather Kaplan, Kristin Melton; Third Row: Debra Sinner, Thomas Korfhagen, Madhavi Koneru, Anne-Karina Perl, Stephan Glasser, Noah Hillman, Eric Hall, Tanya Cahill, Steven Hoath, Bruce Trapnell, Vladimir Kalinichenko, Laura Ward, John Reuter, Alan Kenny, Jean Steichen, Timothy Weaver

Division Data Summary

Research and Training Details

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Clinical Activities and Training

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Significant Publications


This paper used conditional deletion of Forkhead box m1, a transcription factor previously known for its critical role in cell proliferation and tumorigenesis, in the maturation of the lung prior to birth. Deletion of Forkhead box m1 in the developing mouse lung did not alter cell proliferation, but was required for lung function. Foxm1 regulated the biosynthesis of surfactant associated genes critical for lung function at the time of birth. This work provides new insights into the functions of Forkhead box m1, as well as genes required for lung maturation and respiration.
insight both into the functions of Forkhead box m1, as well as genes required for lung maturation and respiration.


This paper demonstrates the critical role of IL-1ß in the modulation of lung inflammation and the fetal inflammatory syndrome associated with intrauterine infection. Approximately 60% of very low birth weight preterm infants have evidence of intrauterine infection that initiates both systemic and lung inflammation in the fetus. This paper demonstrates the important role of IL-1ß in this process. Fetal inflammation can affect both neurodevelopmental outcomes and pulmonary inflammation associated with bronchopulmonary dysplasia, a severe respiratory disorder that accompanies preterm birth and intrauterine infection. Understanding the pathogenesis of intrauterine infection will aid in the diagnosis and therapy of lung disease and other prematurity associated disorders in newborn infants.


This work shows a novel role for beta-glucan mediated lung inflammation in response to house dust mice, a common asthma inducing allergen. Components of the dust mice bind to and activate receptors for sugars on resident pulmonary cells, in turn stimulating lung inflammation that leads to lung remodeling associated with asthma. This new pathway has implications for prevention and therapy of pulmonary allergy and asthma.


In this multi-divisional collaborative work led by Dr. Bruce Trapnell, the underlying genetic cause of idiopathic pulmonary fibrosis was identified for the first time. Two siblings with severe and early Pulmonary Alveolar Proteinosis (PAP), a disease in which surfactant accumulates in the lungs, were studied. Mutations in the CSF2R, the receptor for GM-CSF (cytokine) required for surfactant removal from the airway caused PAP. The dysfunction of this receptor leads to the marked accumulation of surfactant material in the lung, impairing breathing and growth of these children. Since high doses of GM-CSF can stimulate the abnormal receptor, new therapies for this severe and life-threatening disease are likely to be developed for children who have this genetic defect. The paper provides a genetic basis for the diagnosis of familial pulmonary alveolar proteinosis, and a basis for future therapies.


In this work, Kruppel-like factor 5, a gene identified as an important mediator of “stem cells” was identified. Deletion of KLF-5 markedly inhibited perinatal lung function at birth, regulating the expression of surfactant proteins as well as the morphological maturation of the alveolar region of the lung required for gas exchange at birth. This work demonstrates a novel role for KLF-5 and its gene targets, furthering understanding the pathogenesis of respiratory disease in preterm infants, and repair of the lung after injury.

**Division Highlights**

**Drs. Ardythe Morrow and Kurt Schibler**

Clinical and translational research on novel predictive biomarkers for necrotizing enterocolitis and other outcomes of prematurity was launched this year with a 5-year R01 grant from the National Institute of Child Health and Human Development (NICHD). awarded to Drs. Ardythe Morrow and Kurt Schibler as co-PIs. These investigators have exciting preliminary data indicating that specific histo-blood group antigens measured in saliva provide powerful predictors of risk of necrotizing enterocolitis and death in premature infants. This grant supports the conduct of a cohort study of 600 premature infants through a collaboration in Cincinnati Children’s and the University of Alabama at Birmingham. The predictive value of salivary and genetic biomarkers will be tested, and the role of microbial colonization in risk of necrotizing enterocolitis and death will be examined using state of the art genomic and informatics methods.

**Division Collaboration**
Collaboration with Collaborating Faculty:
Divisional faculty have close collaborations with faculty in multiple divisions within CCHMC and with investigators throughout the world.

Faculty Members

Jeffrey A. Whitsett, MD, Professor; Chief, Section of Neonatology, Perinatal and Pulmonary Biology
Research Interests: Lung Development; Surfactant

Ann L. Akeson, PhD, Research Associate Professor
Research Interests: Pulmonary Vascular and Lymphatic Development

Henry T. Akinbi, MD, Associate Professor Clinical
Research Interests: Neonatal Infections and Blood Transfusions

Cindy J. Bachurski, PhD, Research Associate Professor; Director, Research in Pulmonary Biology and Neonatology Elective, University of Cincinnati College of Medicine; Director, Summer Internship Program for High School Students, CCHMC
Research Interests: Gene Regulation in the Lung

Thomas Bartman, MD, PhD, Assistant Professor
Research Interests: Cardiovascular Development

Tanya E. Cahill, MD, Assistant Professor Clinical
Research Interests: Neonatal Abstinence Syndrome and High Risk Infant Follow-Up

Michael W. Crossman, MD, PhD, Assistant Professor Clinical
Research Interests: Intestinal Function and Host-Microbial Interactions; Bioethics

Vrushank G. Dave’, PhD, Research Assistant Professor
Research Interests: Transcription, Lung Development and Cancer

Edward F. Donovan, MD, Professor Emeritus
Research Interests: Prematurity Prevention; Infant Mortality; Evidence-based Decision Making; and Clinical Research

Horacio Falciglia, MD, Professor Clinical; Director, Mother/Baby Unit Good Samaritan Hospital
Research Interests: Selenium Status and Neonatal Sepsis; Timing of Cord Clamping and Outcome; Vermont Oxford Data Base

Stephan W. Glasser, PhD, Associate Professor
Research Interests: Gene Regulation in the Lung

Lloyd Graf, Jr., PhD, Research Assistant Professor
Research Interests: Dysregulated Gene Expression in Inflammatory Lung Diseases

James M. Greenberg, MD, Associate Professor; Director, Division of Neonatology; Medical Director, Regional Newborn Services
Research Interests: Pulmonary Vascular Development

Beth E. Haberman, MD, Assistant Professor Clinical; Medical Director, RCNIC & Mercy Anderson Hospital Nurseries; Director, High Risk Infant Follow-Up Clinic
Research Interests: Infant Follow-up

Eric Hall, PhD, Research Instructor
Research Interests: Biomedical Informatics

Noah H. Hillman, MD, Assistant Professor

Steven B. Hoath, MD, Professor; Director, Skin Sciences Institute
Research Interests: Skin Development

Machiko Ikegami, MD, PhD, Professor; Director, Surfactant and Metabolic Function Core
Research Interests: Surfactant Metabolism

Alan H. Jobe, MD, PhD, Professor; Director, Division of Perinatal Biology
Research Interests: Surfactant Physiology

Tanya V. Kalin, MD, PhD, Research Assistant Professor
Research Interests: Fox Transcription Factors in Lung Cancer and Radiation-Induced Lung Fibrosis

Vladimir V. Kalinichenko, MD, PhD, Associate Professor
Research Interests: Fox Proteins in Lung Development
Suhas G. Kallapur, MD,  Associate Professor Clinical  
Research Interests: Lung Development/Inflammation, BPD, Developmental Immunology

Heather Kaplan, MD, MSCE,  Research Assistant Professor  
Research Interests: Health Services Research; Implementation Science

Alan P. Kenny, MD, PhD,  Research Instructor  
Research Interests: Molecular Development of the Foregut Organs

Paul S. Kingma, MD, PhD,  Assistant Professor Clinical  
Research Interests: Innate Immune Systems; Surfactant Protein D; Neutrophil function in Cystic Fibrosis

Madhavi Koneru, MD,  Assistant Professor Clinical  
Research Interests: Urine biomarkers in prenatal renal anomalies

Thomas R. Korfhagen, MD, PhD,  Professor  
Research Interests: Lung Defense

Timothy Le Cras, PhD,  Associate Professor  
Research Interests: Chronic Lung Disease; Lung Development

Kristin R. Melton, MD,  Associate Professor Clinical  
Research Interests: Developmental Biology

Vivek Narendran, MD,  Assistant Professor Clinical  
Research Interests: C-PAP; Business Case for Quality Improvements

Amy T. Nathan, MD,  Research Assistant Professor  
Research Interests: Immunobiology

Laurie A. Nommsen-Rivers, PhD, RD, IBCLC,  Research Assistant Professor  
Research Interests: Human Milk and Lactation; Perinatal Epidemiology

Anne-Karina Perl, PhD,  Research Assistant Professor  
Research Interests: FGF/PDGF Signaling in Alveolar Regeneration and EGFR Signaling in Bronchiolar Injury and Repair

Danna M. Premer, MD,  Assistant Professor Clinical  

John H. Reuter, MD, PhD,  Associate Professor Clinical  
Research Interests: Lung Development

Ward R. Rice, MD, PhD,  Professor  
Research Interests: Outcomes and Etiology of Gastroschisis, Epidemiology of Late-Preterm Birth

Jean J. Steichen, MD,  Professor  
Research Interests: Infant Follow-up

Bruce C. Trapnell, MD, MS,  Professor  
Research Interests: Pulmonary Gene Delivery

Laura Ward, MD,  Adjunct Assistant Professor  
Research Interests: Use of Human Milk in the NICU

Timothy E. Weaver, PhD,  Professor  
Research Interests: Protein Processing in the Lung

Kathryn E. Wedig, MD,  Associate Professor Clinical  
Research Interests: Infant Follow-up

Susan E. Wert, PhD,  Research Associate Professor  
Research Interests: Protein Processing in the Lung
Research Interests: Lung Development, Molecular Morphology of the Lung, Ultrastructural Analysis of the Lung, Genetic Surfactant Disorders

Scott Wexelblatt, MD, Assistant Professor Clinical; Associate Medical Director Regional Newborn Services; Co-medical Director Bethesda North Hospital

Kathryn Wikenheiser-Brokamp, MD, PhD, Assistant Professor
Research Interests: Pulmonary Pathology; Pediatric and Adult Lung Diseases

Yan Xu, PhD, Research Associate Professor; Director, Microarray-Bioinformatics Core, Division of Pulmonary Biology
Research Interests: Bioinformatics, Systems Biology, Transcriptional Network

Clinical Staff Members
- Samina Ahmed, MD
- Shana Alexander, MD
- Stephen Bird, MD
- Mary Burwinkel, MD
- Thomas Catalanotto, MD
- Diane Donley, MD
- Michelle French, MD
- Lisa Green, MD
- Jennifer Hardie, MD
- Evelyn Jones, MD
- Jillian Klein, MD
- Carrie Kluger, MD
- Katie Loudermilk, MD
- Alisa McGill, MD
- Kenton Pate, MD
- Miriam Peri, MD
- Ajay Ponkshe, MD
- John Robinson, MD
- Deborah Rufner, MD
- Kathy Sorge, MD
- Kara Tencza, MD
- Kira Zimmerly, MD

Trainees
- Valerie Besnard, PhD, Universite Rene Descartes - Paris V
- Stephanie Binder, MD, PL6, John H. Stronger Hospital Cook County, Chicago, IL
- Jim Bridges, PhD, University of Cincinnati
- Brenna Carey, PhD, University of Cincinnati
- Gang Chen, MS, Yangzhou University, China
- Fusheng Chou, MD, National Taiwan University
- Nikki Glenn, BS, Miami University
- David Hahn, BS, Northern Kentucky University
- Prakruti Jambula, MD, PL4, Univ. of Oklahoma HSC, Oklahoma City, OK
- Amer Jameel, BS, Ohio State University
- Brooke King, MD, PL5, Cincinnati Children's Hospital Medical Center - UCMC, Cincinnati, OH
- Elizabeth Kramer, BA, BS, Miami University
- Rishikesh Kulkarni, BPharmSc, University of Mumbai, India
- Venkata Kuppala, MD, PL5, The Cleveland Clinic, Cleveland, OH
- Tara Lang, MD, PL5, Mayo School GME, Rochester, MN
- Alexander Lange, PhD, University of Cincinnati
Yutaka Maeda, PhD, University of California
Karunyakanth Mandapaka, MS, University of Cincinnati
Rafael Mena, MD, PL4, Cincinnati Children's Hospital Medical Center - UCMC, Cincinnati, OH
Stephanie Merhar, MD, PL4, Cincinnati Children's Hospital Medical Center - UCMC, Cincinnati, OH
Bhuvana Murali, BTech, Vellore Institute of Technology, India
Elizabeth Mushaben, BS, College of Mount St. Joseph
Ross Ridsdale, PhD, University of Toronto
Chika Saegusa, PhD, RIKEN, Japan
Takuro Sakagami, MD, PhD, Niigata University, Japan
Christine Sarlone, MD, PL4, Univ. of Tennessee HSC, Memphis, TN
Tushar Shah, MD, MPH, PL5, Case Western Reserve Univ., Cleveland, OH
Jonathan Slaughter, MD, MSc., PL5, Medical Univ. of South Carolina, Charleston, SC
Gareth Stewart, MB BCH BAO, MRCP, PhD, Royal Infirmary of Edinburgh
Holly Strike, MD, PL6, Indiana Univ SOM, Indianapolis, IN
Takuji Suzuki, MD, PhD, Tohoku University, Japan
David Tompkins, MS, University of Texas
Huajing Wan, PhD, University of Cincinnati
Elizabeth Wetzel, MD, MSc, PL4, Indiana Univ. SOM, Indianapolis, IN

**Significant Accomplishments**

### A Master Gene Controlling Mucus Production

Scientists in the laboratory of Dr. Jeffrey Whitsett, Executive Director of the Perinatal Institute, and collaborators have identified a single gene required for mucus production in the airways of both mice and men called SPDEF (Sam-pointed domainEts-like factor). SPDEF regulates a group of genes synthesizing, packaging, and secreting mucus. SPDEF is induced in cystic fibrosis, asthma, and chronic obstructive pulmonary disease (COPD) in the lungs of children and adults, where it contributes to lung infections and other respiratory problems. Understanding the genes and processes influencing mucus secretion will lead to improved diagnosis and treatment of common, severe childhood lung diseases.

### Novel Genetic Mutations Cause Severe Lung Disease, Pulmonary Alveolar Proteinosis (PAP) in Children

Dr. Bruce Trapnell and collaborators identified a novel cause of severe lung disease, PAP, in children. Children with mutations in receptor for Granulocyte Macrophage Colony Stimulating Factor (GM-CSFReceptor) develop severe lung disease in which pulmonary surfactant accumulated, causing growth failure and respiratory distress. The receptor fails to signal macrophages in the lung to clear surfactant from the airways. The studies identified a new cause of this pulmonary disease, and provides the knowledge that will lead to improved diagnosis and therapy for this life-threatening pulmonary disorder, PAP.

### A New Gene, Foxm1, is Required for Lung Function and Survival at Birth, and Plays a Role in Lung Tumorigenesis

Drs. Vladimir Kalinichenko and Tanya Kalin have discovered that Foxm1, a gene critical for cell proliferation in many organs, plays a critical role in the maturation of the lung prior to birth. Deletion of Foxm1 in the lung caused lung failure at birth but, surprisingly, did not influence cell proliferation. Lung failure was related in part to the lack of pulmonary surfactant. When Foxm1 was deleted after birth, mice failed to develop lung tumors in response to carcinogens and genes associated with lung cancer. The studies identified a new pathway critical for perinatal lung maturation, a factor important for the survival of preterm infants after birth. The study also provides new therapeutic targets for future therapies of lung tumors.

### Division Publications


Grants, Contracts, and Industry Agreements

**Grant and Contract Awards**

**Annual Direct / Project Period Direct**

| AKESON, A | Pulmonary Lymphatic Development and Neonatal Lung Disease | March of Dimes - National | 6-FY07-317 | 06/01/07 - 05/31/10 | $76,779 / $221,209 |

| AKINBI, H | Role of Lysozyme in Airway Host Defense | | | | |


National Institutes of Health
R56 AI 050797 08/01/08 - 07/31/09 $250,000 / $250,000
Role of Goblet Cell Hyperplasia in Innate Defense of the Lung
Cystic Fibrosis Foundation
R457 CR02 07/01/08 - 06/30/10 $40,000 / $80,000

BACHURSKI, C
Novel Model of Adult Epithelial Stem Cell Expansion
National Institutes of Health
R21 HL 093706 04/01/09 - 03/31/11 $125,000 / $275,000

BARTMAN, T
Analysis of NFATc1 as the Mechanism by which Early Heart Function Regulates Endocardial Cushion and Valve Morphogenesis
American Heart Association - Ohio
SDG 01/01/06 - 12/31/09 $59,091 / $236,364

BRIDGES, J
Characterization of LPCAT, a Lung Lysopacyltransferase
Parker B Francis Fellowship Program
07/01/07 - 06/30/10 $48,000 / $144,000

DAVE, V
PTEN/PI3K/AKT Pathway in Lung Cancer
Ohio Cancer Research Association
07/01/08 - 06/30/09 $45,454 / $45,454
Calcineurin Effectors in Pulmonary Homeostasis
American Heart Association - National
SDG083010N 01/01/08 - 12/31/11 $70,000 / $280,000

HILL, K
ODH Division of Family Services Regional Outreach Education Program
Ohio Department of Health
31-3-001-1-BM-08 10/01/08 - 09/30/09 $110,000 / $110,000

IKEGAMI, M
Role of C/EBPalpha in Cytoprotection and Recovery from Lung Injury
National Institutes of Health
R01 HL 095464 04/01/09 - 03/31/13 $250,000 / $1,000,000
Efficacy of Sp-D Containing Surfactant for Treatment of Premature Newborns
March of Dimes - National
6-FY09-235 06/01/09 - 05/31/12 $86,628 / $271,996

JOBE, A
Antecedents to Lung Injury in the Preterm
National Institutes of Health
R01 HD 012714 05/01/06 - 03/31/11 $181,638 / $954,405

KALINICHENKO, V
Fox Transcription Factors in Development of Pulmonary Capillaries
National Institutes of Health
R01 HL 084151 05/01/08 - 04/30/11 $242,750 / $728,250
Foxm1 Transcription Factor in Development of Non-Small Lung Cancer
American Cancer Society - National
RSG-06-187-01-MGO 07/01/07 - 06/30/10 $167,256 / $496,650

KALLAPUR, S
Mechanisms of Fetal Inflammatory Response Syndrome Induced by Chorioamnionitis
National Institutes of Health
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<td>Impact of Context on QI Success: A Novel Framework</td>
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<td><strong>Role of SFTPC in Pathogenesis of Interstitial Lung Disease</strong></td>
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**WHITSETT, J**

**Pulmonary and Cardiovascular Development Training Grant**
National Institutes of Health
T32 HL 007752 07/01/04 - 06/30/09 $231,415 / $1,142,435

**ABCA3 and Alveolar Homeostasis**
National Institutes of Health
R01 HL 085610 07/10/06 - 06/30/11 $298,226 / $1,567,158

**Transcriptional Control of Respiratory Epithelial Progenitor Cells**
National Institutes of Health
R01 HL 090156 09/28/06 - 06/30/11 $332,146 / $1,372,968

**Transcriptional Control of Respiratory Epithelial Progenitor Cells**
National Institutes of Health
R01 HL 090156 (supplement) 08/15/08 - 06/30/09 $12,000 / $12,000

**Transcriptional Programming of Asthma Related Pathology in Respiratory Epithelial Cells**
National Institutes of Health
R01 HL 095580 04/01/09 - 03/31/13 $340,895 / $1,417,776

**Research Development Program- Transgenic Animal Core**
Cystic Fibrosis Foundation
R457 CR02 7/1/08 - 6/30/10 $50,000 / $50,000

**Kalin, Tatiana**

**Role of Foxm1 Protein in Macrophages during Lung Tumor Formation**
Concern Foundation
84974 07/01/08 - 06/30/10 $50,000 / $50,000

**Role of Foxm1 Protein in Initiation and Progression of Lung Cancer**
American Cancer Society - Ohio
09/01/08 - 08/31/09 $27,273 / $27,273

| Current Year Direct | $6,663,150 |

**Industry Contracts**

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