

2013 Research Annual Report

Section of Neonatology, Perinatal and Pulmonary Biology



Division Details

Division Data Summary

RESEARCH AND TRAINING DETAILS

Number of Faculty	54
Number of Joint Appointment Faculty	1
Number of Research Fellows	6
Number of Research Students	12
Direct Annual Grant Support	\$8,157,006
Direct Annual Industry Support	\$285,409
Peer Reviewed Publications	126

CLINICAL ACTIVITIES AND TRAINING

Number of Clinical Staff	25
Number of Clinical Fellows	12
Number of Other Students	2

Division Photo



Row 1: S Bhattacharyya, L Muglia, J Greenberg, S Wert, A Perl, A Nathan K Wedig
 Row 2: H Kaplan, B Kamath-Rayne, T Le Cras, S Glasser, M Pavlicev, S Kallapur, T Kalin, J Whitsett, K Wikenheiser-Brokamp, K Melton
 Row 3: L Nommsen-Rivers, T Weaver, E Hall, T Korfhagen, T Suzuki, Y Maeda, J Shannon, W Rice, D Sinner, A Jobe, A Morrow, V Kalinichenko, J Bridges
 Row 4: L Ward, B Trapnell

Significant Accomplishments

March of Dimes Prematurity Research Center Ohio Collaboration

The March of Dimes Prematurity Research Center Ohio Collaborative comprises a new transdisciplinary group of investigators aimed at discovering the fundamental causes of preterm birth. It brings together investigators from 20 different disciplines to work together for healthier newborns. We believe this collaborative will become a world leader in research to discover the unknown causes of preterm birth and develop precise ways to prevent it. The March of Dimes has pledged \$10 million over five years to fund this initiative. The project brings together Ohio's leading health research institutions – Cincinnati Children's Hospital Medical Center (the coordinating site; Dr. Louis Muglia, MD, PhD; Drs. James Greenberg, Jeffrey Whitsett, and SK Dey, Co-Directors) and the University of Cincinnati; the Ohio State University and Nationwide Children's Hospital; and Case Western Reserve University and University Hospitals / MetroHealth.

National Institutes of Health

New awards were obtained from the NHLBI, including the T32 training grant entitled "Pulmonary and Cardiac Development and Disease" Drs. Jeffrey Whitsett, Bruce Trapnell and Frank McCormack (Co-PIs), a new K12 "Omics of Lung Diseases" Dr. Jeffrey Whitsett (PI), a collaborative project with the Divisions of Biomedical Informatics and the College of Engineering at the University of Cincinnati College of Medicine; and the NHLBI

R01 “Transcriptional Programming of Asthma Related Pathology in Respiratory Epithelia” Dr. Jeffrey Whitsett (PI).

Collaborative for Infant Mortality Reduction

The Perinatal Institute facilitated the creation of a regional public/private/governmental collaborative to reduce the infant mortality rate. The collaborative brings together leaders from Hamilton County, the City of Cincinnati, the University of Cincinnati Colleges of Medicine and Nursing, Cincinnati Children’s, all regional hospital maternity providers, and local nonprofit agencies as a collective impact collaborative. The collaborative has a five year, \$1.25 million funding commitment based upon an agreement between the Board of Hamilton County Commissioners, UC Health and Drake Center, LLC. Collaborative operations are based at CCHMC. Drs. James M. Greenberg and Elizabeth Kelly provide operational leadership of the Collaborative, along with a newly appointed Director, Mr. Ryan Adcock. County Commissioner Todd Portune and City of Cincinnati Councilmember Wendell Young Co-Chair the Advisory Board created through a memorandum of understanding signed by all parties on June 13, 2013.

Research Highlights

Suhas Kallapur and Alan Jobe

Suhas Kallapur and Alan Jobe in the Perinatal Institute, together with Claire Chougnet in the Division of Cellular and Molecular Immunology, have developed a novel non-human primate model for investigating the effects of intra-uterine inflammation on the developing fetus. Administration of the cytokine interleukin-1 beta to pregnant rhesus macaques resulted in chorioamnionitis and induction of robust lung inflammation in the fetus and preterm newborn. Their findings suggest that boosting regulatory T cells and/or controlling IL-17 may provide a means to prevent or limit the complications for preterm infants exposed to infection or inflammation prior to birth.

Louis Muglia

Louis Muglia and colleagues have identified genes in families with recurrent preterm birth as contributors to the risk of preterm birth in the general population. Whole-exome sequencing was performed on two mother-daughter pairs, and genes harboring rare variants were tested for association with preterm birth in the general population. The complement and coagulation cascade was one of the most enriched pathways in our two mother-daughter pairs, and was confirmed by analysis in six other mothers’ exomes and association analysis in over 500 nuclear families. These results demonstrated the importance of the complement and coagulation cascades in the pathophysiology of preterm birth, and suggest potential screening and intervention approaches to prevent prematurity that target this pathway.

Scott Wexelblatt, Laura Ward, Eric Hall, and James Greenberg

Scott Wexelblatt, Laura Ward, Eric Hall and James Greenberg in the Perinatal Institute, evaluated the value of a universal testing strategy in a community hospital setting to improve diagnostic accuracy and treatment for neonatal abstinence syndrome. They found that universal testing is feasible, cost effective, and does not generate an excessive burden upon social service providers or local government agencies. This strategy identifies newborns, exposed to in-utero narcotics, not identified through standard risk-based screening approaches, who would otherwise be at high risk to develop untreated neonatal abstinence syndrome.

Significant Publications

Balli, D., Ustiyani, V., Zhang, Y., Wang, I.-C., Masino, A.J., Ren, X., **Whitsett, J.A.**, **Kalinichenko, V.V.**, **Kalin, T.V.**, **Foxm1 transcription factor is required for lung fibrosis and epithelial-to-mesenchymal transition.** *EMBO* 2013. J 32, 231-244.

This work was part of Dr. Balli's Ph.D. graduate thesis in the Molecular and Developmental Biology program. The work demonstrates a critical role of the Foxm1 transcription factor in the pathogenesis of pulmonary fibrosis. Epithelial-to-mesenchymal transition (EMT) was demonstrated during radiation-induced pulmonary fibrosis and the molecular targets of Foxm1 were identified. Inhibition of this pathway provides a novel, potential, therapeutic target for pulmonary fibrosis, a enigmatic disease that remains without effective therapy.

Kamath-Rayne, B.D., DeFranco, E.A., Chung, E., Chen, A., **Subtypes of preterm birth and the risk of postneonatal death.** *J Pediatr* 2013. 162, 28-34.

This work demonstrates increased morbidity and mortality in preterm birth, showing risks even at older gestational ages when many clinicians consider that the infants are mature enough to adapt normally after birth. The work emphasizes the risk of "late preterm" birth, and the need to minimize the "iatrogenic" prematurity. This paper examined the differences in post-neonatal death risk among the three most common clinical subtypes of preterm birth: preterm premature rupture of membranes (PROM), indicated preterm birth, and spontaneous preterm labor. The authors found that preterm PROM was associated with significantly higher risk of post-neonatal death compared with spontaneous preterm labor in infants born at 27 weeks gestation or later. Similarly, indicated preterm birth was associated with a significantly higher risk of post-neonatal death than spontaneous preterm labor in infants born at 25 weeks gestation or later. Thus, different etiologies for preterm birth carry different risks of post-neonatal mortality and suggest preventative measures may be different amongst these groups.

Kenny, A.P., A., R.S., Allbee, A.W., Prewitt, A.R., Zhang, Z., Tabangin, M.E., Shifley, E.T., Louza, M.P., Zorn, A.M., **Sizzled-tolloid interactions maintain foregut progenitors by regulating fibronectin-dependent BMP signaling.** *Dev Cell* 2012. 23, 292-304.

This work utilizes *Xenopus* (the frog) to identify the genes and processes involved in the induction of foregut from which critical organs, including thyroid, liver, lung, stomach, and pancreas are formed. The work identifies a new role for Sizzled and Tolloid in the formation of foregut organs relevant to common birth defects affecting newborn infants.

Korfhagen, T.R., Kitzmiller, J., Chen, G., Sridharan, A., Haitchi, H.M., Hegde, R.S., Divanovic, S., Karp, C.L., **Whitsett, J.A.**, **SAM-pointed domain ETS factor mediates epithelial cell-intrinsic innate immune signaling during airway mucous metaplasia.** *Proc Natl Acad Sci.* 2012 109, 16630-16635.

This work identifies a critical role of the transcription factor SPDEF in mucous metaplasia and host defense in the airway. SPDEF is induced in asthma, cystic fibrosis, and chronic obstructive lung diseases where it is required for mucus hyperproduction. SPDEF was shown to inhibit cellular responses to infection, providing a molecular mechanism by which patients with these disorders are susceptible to viral and bacterial infections. The work provides a potential therapeutic target for treatment of these diseases.

Ren, X., Shah, T.A., Ustiyani, V., Zhang, Y., Shinn, J., Chen, G., **Whitsett, J.A.**, **Kalin, T.V.**, **Kalinichenko, V.V.**, **FOXM1 Promotes Allergen-Induced Goblet Cell Metaplasia and Pulmonary Inflammation.** *Mol Cell Biol* 2013 33, 371-386.

This work demonstrates a novel role for Foxm1 in the pathogenesis of inflammation and mucus hyperproduction related to asthma. Foxm1 was shown to be induced during allergy and to enhance goblet cell differentiation by regulating a number of genes controlling mucus production. Inhibition of the Foxm1 pathway provides a potential therapeutic strategy for asthma and other common lung diseases complicated by mucus hyperproduction and

infection.

Division Publications

1. Albert RK, Jobe A. **Gas exchange in the respiratory distress syndromes.** *Compr Physiol.* 2012; 2:1585-617.
2. Althabe F, Belizán JM, Mazzoni A, Berrueta M, Hemingway-Foday J, Koso-Thomas M, McClure E, Chomba E, Garces A, Goudar S, Kodkany B, Saleem S, Pasha O, Patel A, Esamai F, Carlo WA, Krebs NF, Derman RJ, Goldenberg RL, Hibberd P, Liechty EA, Wright LL, Bergel EF, Jobe AH, Buekens P. **Antenatal corticosteroids trial in preterm births to increase neonatal survival in developing countries: study protocol.** *Reprod Health.* 2012; 9:22.
3. Ambalavanan N, Carlo WA, McDonald SA, Das A, Schendel DE, Thorsen P, Hougaard DM, Skogstrand K, Higgins RD, Cytokine, Generic Database Subcommittees of the Eunice Kennedy Shriver National Institute of Child Health Human Development Neonatal Research N. **Cytokines and posthemorrhagic ventricular dilation in premature infants.** *Am J Perinatol.* 2012; 29:731-40.
4. Ballard O, Morrow AL. **Human milk composition: nutrients and bioactive factors.** *Pediatr Clin North Am.* 2013; 60:49-74.
5. Balli D, Ren X, Chou FS, Cross E, Zhang Y, Kalinichenko VV, Kalin TV. **Foxm1 transcription factor is required for macrophage migration during lung inflammation and tumor formation.** *Oncogene.* 2012; 31:3875-88.
6. Balli D, Ustiyani V, Zhang Y, Wang IC, Masino AJ, Ren X, Whitsett JA, Kalinichenko VV, Kalin TV. **Foxm1 transcription factor is required for lung fibrosis and epithelial-to-mesenchymal transition.** *EMBO J.* 2013; 32:231-44.
7. Bancalari EH, Jobe AH. **Reply to Been et al.** *J Pediatr.* 2013; 162:657-8.
8. Bancalari EH, Jobe AH. **Reply to Hjalmarson and Sandberg.** *J Pediatr.* 2013; 162:656-7.
9. Bancalari EH, Jobe AH. **The respiratory course of extremely preterm infants: a dilemma for diagnosis and terminology.** *J Pediatr.* 2012; 161:585-8.
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11. Belizán JM, McClure EM, Goudar SS, Pasha O, Esamai F, Patel A, Chomba E, Garces A, Wright LL, Koso-Thomas M, Moore J, Althabe F, Kodkany BS, Sami N, Manasyan A, Derman RJ, Liechty EA, Hibberd P, Carlo WA, Hambidge KM, Buekens P, Jobe AH, Goldenberg RL. **Neonatal death in low- to middle-income countries: a global network study.** *Am J Perinatol.* 2012; 29:649-56.
12. Bell SM, Zhang L, Xu Y, Besnard V, Wert SE, Shroyer N, Whitsett JA. **Kruppel-like factor 5 controls villus formation and initiation of cytodifferentiation in the embryonic intestinal epithelium.** *Dev Biol.* 2013; 375:128-39.
13. Bhattacharya S, Go D, Krenitsky DL, Huyck HL, Solleti SK, Lunger VA, Metlay L, Srisuma S, Wert SE, Mariani TJ, Pryhuber GS. **Genome-wide transcriptional profiling reveals connective tissue mast cell accumulation in bronchopulmonary dysplasia.** *Am J Respir Crit Care Med.* 2012; 186:349-58.
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Faculty, Staff, and Trainees

Faculty Members

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Leadership Co-Director, Perinatal Institute; Chief, Section of Neonatology, Perinatal and Pulmonary Biology

Research Interests Lung Development; Surfactant

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Research Interests Neonatal Infections and Blood Transfusions

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Research Interests Inflammation Immunology, Signal Transduction

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Research Interests Implementation Science, International Health

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Research Interests Hypoxia Inducible Factors and Downstream Target Genes in Chronic Lung Disease

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Leadership Director, High Risk Infant Follow-Up Program

Research Interests Neonatal Abstinence Syndrome and High Risk Infant Follow-Up

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Research Interests Gene Regulation in the Lung

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Research Interests Pulmonary Pathology, Pediatric and Adult Lung Diseases

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Diane Donley, MD

Dena Elkeeb, MD

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Michelle French, MD

Angelique Gloster, MD

Girish Gowda, MD

Pamela Holmes, MD

Jill Klein, MD

Katie Loudermilk, MD

Alisa McGill, MD

John Morrison, MD

Miriam Peri, MD

Ajay Ponshe, MD

Danna Premer, MD

John Robinson, MD

Deborah Rufner, MD

Kelley Shultz, MD

Jean Steichen, MD

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Jennifer Goetz, MD, PL6, University of Louisville School of Medicine, Louisville, KY
David Hahn, BS, Northern Kentucky University, Highland Heights, KY
Jamie Havrilak, BS, Susquehanna University, Selinsgrove, PA
Melissa Landis, MD, PL5, Columbia University School of Medicine, New York, NY
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Candice Lengyel, MD, PL4, University of Michigan, Ann Arbor, MI
Masahiko Murase, MD, PhD, IBCLC, Showa University, Tokyo, Japan
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Priya Rajavelu, PhD, University of Madras, Chennai, Tamil Nadu, India
Malia Ray, MD, University of Louisville, Louisville, KY
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Emily Wayman, BS, University of Alabama, Tuscaloosa, AL
Emily Wiland, MD, PL4, Rainbow Babies & Children's Hospital, Cleveland, OH
Jason Wiles, MD, PL5, University of Louisville School of Medicine, Louisville, KY
Tim Wolfs, PhD, Royal Netherlands Academy of Arts and Sciences, The Netherlands
Koryse Woodrooffe, MD, PL4, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
Giridhar Vummidi Giridhar, PhD, University of Madras, Tamil Nadu, India
Hongping Xia, MS, PhD, Fudan University, Shanghai, China

Division Collaboration

Reproductive Sciences; Developmental Biology; Pulmonary Medicine; Biomedical Informatics; Safety - The James A. Anderson Center; Infectious Disease; Human Genetics; Biostatistics and Epidemiology; Cellular and Molecular Immunology; General Pediatrics; Gastroenterology; Radiology; Fetal Care Center; Rheumatology/CAGE; Cancer and Blood Disease Institute » SK Dey, Takiko Daikoku, Christopher Wylie, James Wells, Noah Schroyer, Aaron Zorn, Richard Lang, William Hardie, Imre Solti, Steven Muething, Margaret Hostetter, Ge Zhang, and Maurizio Macaluso

The causes of preterm birth, complications of prematurity and birth defects span the spectrum of divisional interests and approaches at Cincinnati Children's. To make substantial progress in reducing infant mortality from these causes requires collaborative efforts across many programs. The Perinatal Institute at Cincinnati Children's provides an organizing center, and driver, for efforts to improve outcomes for infants born prematurely, prevent prematurity, and reduce the incidence of birth defects to synergistically reduce infant mortality in our region. As such, our Institute's faculty have close collaborations with investigators in multiple divisions within Cincinnati Children's, the University of Cincinnati, the other leading research institutions in Ohio, and globally in Japan, Germany, Mexico, Argentina, Finland, China, and Australia. For the past three years, the Division has offered a day-long educational seminar series addressing new approaches to patient care and clinical research for visiting faculty neonatologists from China Taiwan, and Southeast Asia.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards

Annual Direct

BRIDGES, J

The Role of HIF2a in Airway Smooth Muscle Remodeling

American Lung Association

07/01/11-06/30/13

\$40,000

CHEN, G

The Role of Foxa3 in the Regulation of Mucus Metaplasia and Innate Immunity in the Lung

American Lung Association

07/01/12-02/28/13

\$21,323

GLASSER, S

Role of Surfactant Protein-C and Innate Lung Defense

National Institutes of Health

R01 HL 050046

08/01/09-07/31/13

\$247,500

HILLMAN, N

Lung Injury with Resuscitation in the Preterm

National Institutes of Health

K08 HL 097085

08/01/09-02/28/13

\$63,589

JOBE, A / CHOUGNET, C (MPI)

Biomarkers of Immunologic Function and Preterm Respiratory Outcomes

National Institutes of Health

U01 HL 101800

05/01/10-04/30/14

\$364,354

Jobe, A	Core	\$171,178
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Chougnet, C	Project	\$80,237
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Chougnet, C	Project	\$31,216
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Kingma, P	Project	\$20,228
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Hardie, W	Project	\$55,739
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Morrow, A	Project	\$14,011
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Data Coordinating Center for the Prematurity and Respiratory Outcomes Program

National Institutes of Health(University of Pennsylvania)

U01 HL 101794

09/20/10-04/30/15

\$28,079

Jobe, A

Capitation

\$80,542

Initiation and Progression of Preterm Lung Injury with Ventilation

National Institutes of Health

R01 DH 072842

08/01/12-05/31/17

\$202,274

JOBE, A / KALLAPUR, S**Late Preterm Birth, Ureaplasma Species and Childhood Lung Disease**

National Institutes of Health

R01 HL 097064

09/24/09-07/31/13

\$347,743

KALIN, T**Role of Foxm1 in Lung Cancer Microenvironment**

National Institutes of Health

R01 CA 142724

07/01/10-06/30/15

\$201,275

KALINICHENKO, V**Foxf1 Transcription Factor in Development of Pulmonary Capillaries**

National Institutes of Health

R01 HL 084151

05/01/11-04/30/15

\$238,000

KALLAPUR, S**Mechanisms of Fetal Inflammatory Response Syndrome Induced by Chorioamnionitis**

National Institutes of Health

R01 HD 057869

02/03/09-01/31/14

\$237,900

KAMATH, B**Novel Amniotic Fluid Biomarkers to Predict Fetal Lung Maturity**

National Institutes of Health(University of Cincinnati)

K12 HD 051953

07/01/11-06/30/13

\$100,000

KENNY, A**Secreted BMP Antagonists in Foregut Organ Development**

National Institutes of Health

K08 HL 105661

12/08/10-11/30/15

\$121,300

KINGMA, P**Surfactant Protein D in Pulmonary and Systemic Host Defense**

National Institutes of Health

K08 HL 089505

07/01/08-06/30/13

\$121,600

LECRAS, T / HERSHEY, G

Impact of Early Life Diesel Exposure on Immune Patterning and Lung Structure/Function

National Institutes of Health

R01 HL 097135	09/01/09-07/31/14	\$332,402
LeCras		\$131,186
Hershey		\$201,548

MERHAR, S**Functional MRI to Predict Visual, Auditory, and Motor Outcomes in Infants with Brain Injury**

Thrasher Research Fund

08/01/12-07/31/14 \$9,450

Protein Supplementation in Infants with Brain Injury

The Gerber Foundation

06/01/12-05/31/15 \$6,664

MORROW, A**Novel Genetic and Salivary Glycan Biomarkers for Risk of NEC in ELBW Infants**

National Institutes of Health

R01 HD 059140 01/15/09-12/31/13 \$537,158

The Role of Human Milk in Infant Nutrition and Health

National Institutes of Health

P01 HD 013021 08/01/09-07/31/14 \$957,390

Morrow Core A, C & Project 1, 3 \$504,629

Morrow Core B \$177,233

Jiang Project 2 \$115,600

Jiang Core D \$85,577

MUGLIA, L**Genetic Analysis of Human Preterm Birth**

March of Dimes National

21-FY11-583 01/01/12-02/28/14 \$177,044

Amygdala Glucocorticoid Receptor Function in Stress

National Institutes of Health

R01 MH 079010 01/01/12-12/31/13 \$236,027

PERL, A**FGF and PDGF Regulate Myofibroblast Differentiation in Alveolar Regeneration**

National Institutes of Health

R01 HL 104003	07/01/10-06/30/14	\$247,500
SCHIBLER, K		
NICHD Cooperative Multicenter Neonatal Research Network		
National Institutes of Health		
U10 HD 027853	04/01/11-03/31/16	\$186,953
Schibler, K	Capitation	\$84,882
SHANNON, J		
LPCAT1 is Essential for Perinatal Lung Function and Survival		
National Institutes of Health		
R01 HL 098319	07/01/10-06/30/14	\$313,566
SINNER, D		
Molecular Mechanisms Underlying Lung Growth and Hypoplasia: Role of Wntless		
March of Dimes		
	02/01/12-01/31/14	\$68,182
Molecular Mechanisms Underlying Upper Airway Patterning and Tracheomalacia		
National Institutes of Health		
K01 HL 115447	08/01/12-07/31/17	\$104,071
TRAPNELL, B		
Role of GM-CSF in Myeloid Cell Function and Innate Immunity		
National Institutes of Health		
R01 HL 085453	04/01/11-03/31/16	\$238,000
Cincinnati Center for Clinical and Translational Sciences and Training (Pilot/Collaborative Studies)		
National Institutes of Health(University of Cincinnati)		
UL1 TR 000077	04/03/09-03/31/14	\$23,181
VALENTINE, C		
DHA Attenuates Inflammatory Responses through Altering RAGE Signaling		
National Institutes of Health(The Research Institute at Nationwide Hospital)		
R01 AT 006880	09/30/11-06/30/15	\$17,787
WEAVER, T		
Role of SFTPC in Pathogenesis of Interstitial Lung Disease		
National Institutes of Health		
R01 HL 086492	12/01/08-11/30/13	\$292,260
The Role of Autophagy in the Pathogenesis of interstitial Lung Disease		
National Institutes of Health		
R01 HL 103923	08/01/11-06/30/15	\$333,612

WEXELBLATT, S**Neonatal Abstinence Syndrome (NAS) Project**

University Hospitals Case Medical Center(Nationwide Children's Hospital)

G1213070561 07/01/12-06/30/13 \$35,970

Wexelblatt, S

Capitation

\$1,402

WHITSETT, J**Airway Progenitor Cell Proliferation and Differentiation During Lung Repair**

National Institutes of Health

U01 HL 110964 01/01/12-12/31/16 \$520,096

Pulmonary and Cardiovascular Development Training Grant

National Institutes of Health

T32 HL 007752 07/01/09-06/30/14 \$258,283

Transcriptional Control of Submucosal Gland Formation and Function

National Institutes of Health

R01 HL 108907 07/01/11-04/30/15 \$246,546

Transcriptional Programming of Asthma Related Pathology in Respiratory Epithelia

National Institutes of Health

R01 HL 095580 4/15/13-03/31/18 \$328,882

Cystic Fibrosis Foundation Research Development Program (Core 1)

Cystic Fibrosis Foundation

03/01/12-06/30/15 \$50,000

XU, Y**Role of SREBP Network in Surfactant Lipid Homeostasis and Lung Maturation**

National Institutes of Health

R01 HL 105433 07/01/11-06/30/15 \$301,045

Current Year Direct \$8,157,006**Industry Contracts**

KALLAPUR, SMerck & Company, Inc \$19,250

KINGMA, PAirway Therapeutics \$13,000

MORROW, A

Glycosyn LLC \$8,983

Mead Johnson & Company	\$116,502
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VALENTINE, C

Mead Johnson & Company	\$81,045
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Nestle Infant Nutrition, USA	\$46,629
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Current Year Direct Receipts	\$285,409
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Total	\$8,442,415
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