

# Perinatal Institute

## Division Details

### RESEARCH AND TRAINING DETAILS

Faculty	87
Joint Appointment Faculty	1
Research Fellows and Post Docs	13
Research Graduate Students	18
Total Annual Grant Award Dollars	\$18,465,903
Total Annual Industry Award Dollars	\$78,145

### CLINICAL ACTIVITIES AND TRAINING

Staff Physicians	23
Clinical Fellows	15



L Muglia, J Whitsett, J Greenberg

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## Division Highlights

### Omics of Lung Development and Disease

Dr. Yan Xu, PhD, leads a team of bioinformatician, computer scientists and biologists with a mission to use transcriptomics, proteomics and lipidomics to understand lung development and disease. Dr. Minzhe Guo developed new computer programs to handle and display large datasets from single cell RNA sequence data. With Dr. Yan Xu, he developed the code for “Sincera” and “SLICE” to enable the field to use big data from single cell RNA studies of developing lung to understand the cellular and molecular mechanisms that instruct the formation of the organ. “SLICE”, based on a calculation of entropy, predicts cell lineages and fate decisions regulating organ formation: Guo M, Bao E, Wagner M, Whitsett JA, Xu Y. **SLICE: determining cell differentiation and lineage based on single cell entropy**. *Nucleic Acids Res*. 2016 Apr 20;45(7):e54.

Ms. Yina Du developed Lung Gene Expression Atlas (LGEA), a web tool that displays big data enabling rapid search of cells, genes, RNAs, and proteins: Du Y, Kitzmiller JA, Sridharan A, Perl AK, Bridges JP, Misra RS, Pryhuber GS, Mariani TJ, Bhattacharya S, Guo M, Potter SS, Dexheimer P, Aronow B, Jobe AH, Whitsett JA, Xu Y. **Lung Gene Expression Analysis (LGEA): an integrative web portal for comprehensive gene expression data analysis in lung development**. *Thorax*. 2017 May;72(5):481-84. Dr. Yan Xu, and her team, use these tools to explore the pathogenesis of Idiopathic Pulmonary Fibrosis (IPF) an enigmatic, lethal chronic lung disease. Her work provides new insights into the cellular and molecular processes causing the loss of tissue and respiratory failure in this disorder: Xu Y, Mizuno T, Sridharan A, Du Y, Guo M, Tang J, Wikenheiser-Brokamp KA, Perl A-KT, Funari VA, Gokey JJ, Stripp BR, Whitsett JA. **Single-cell RNA sequencing identifies diverse roles of epithelial cells in idiopathic pulmonary fibrosis**. *JCI Insight*. 2016 Dec 8;1(20):e90558. The application of systems biology to the ever expanding “omic” data provides new opportunities to uncover the mysteries of organ formation during normal development from which to explore the cellular and molecular causes of diseases that are presently considered “idiopathic”.

## Understanding Rare Lung Disease in Newborns – Alveolar Capillary Dysplasia

Dr. Vladimir Kalinichenko, MD, PhD, leads a team of scientist seeking to understand the causes and mechanisms underlying the pathogenesis of ACD, a rare but devastating lung disease affecting newborn infants. Infants with ACD suffer respiratory failure and hypoxemia, and usually die soon after birth despite of intensive care. Mutations cause most ACD in the gene FOXF1. Dr. Kalinichenko developed transgenic mouse models by inserting mutations in the FOXF1 gene. His work shows the critical role of FOXF1 in directing lung vascular development before birth, and its role in maintaining the pulmonary microvasculature critical for lung function after birth. His team is uncovering the genetic networks directed by FOXF1 developing new approaches to enhance FOXF1 activity for therapy of ACD and other lung diseases: Dharmadhikari AV, Szafranski P, Kalinichenko VV, Stankiewicz P. **Genomic and epigenetic complexity of the FOXF1 locus in 16q24.1: Implications for development and disease.** *Curr Genomics*. 2015 Apr;16(2):107-16.

\*Cai Y, Bolte C, Le T, Goda C, Xu Y, Kalin TV, Kalinichenko VV. **FOXF1 maintains endothelial barrier function and prevents edema after lung injury.** *Science Signaling*. 2016 Apr 19; 9(424):ra40. \*This paper is on the cover page of Science Signaling, April 19, 2016 issue.

## Elucidation of the Gut-Lung Axis in Innate Defense of the Neonatal Lung

Newborn preterm infants are highly susceptible to bacterial pneumonia, a major cause of infant mortality worldwide. Dr. Hitesh Deshmukh, MD, PhD, and his team, have uncovered a novel pathway by which the colonization of the GI tract with normal bacterial flora after birth is required for the development of innate defenses of the lung to fight bacterial infection. His work in *Science Translational Medicine* (Gray J, Oehrle K, Worthen G, Alenghat T, Whitsett J, Deshmukh H. **Intestinal commensal bacteria mediate lung mucosal immunity and promote resistance of newborn mice to infection.** *Sci Transl Med*. 2017 Feb 8;9(376)) demonstrates lack of gut bacteria, caused by administration of antibiotics before birth blocks signals required for recruitment and expansion of specialized innate lymphocytes (ILC3 cells) to the lung, where they activate defenses against bacterial pneumonia. He found that the ILC3 precursors traffic to the lung and secrete IL-22 that enhances resistance to pneumonia, and that this “trafficking” requires normal gut bacterial flora. Mothers, and babies, are often exposed to broad spectrum antibiotics that alter the gut microbiome. His work shows the requirement of normal gut flora for the education and migration of innate lymphocytes needed to protect the lung from infection. These findings explain the relationship between the widespread use of antibiotics and increased susceptibility of the newborn lung to bacterial infections.

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## Publications

1. Kugathasan S; Denson LA; Walters TD; Kim MO; Marigorta UM; Schirmer M; Mondal K; Liu C; Griffiths A; Noe JD. **Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study.** *The Lancet*. 2017; 389:1710-1718.
2. McCracken KW; Aihara E; Martin B; Rawford CMC; Broda T; Treguier J; Zhang X; Shannon JM; Montrose MH; Wells JM. **Wnt/beta-catenin promotes gastric fundus specification in mice and humans.** *Nature*. 2017; 541:182-187.
3. Weiler SME; Pinna F; Wolf T; Lutz T; Geldiyev A; Sticht C; Knaub M; Thomann S; Bissinger M; Wan S. **Induction of Chromosome Instability by Activation of Yes-Associated Protein and Forkhead Box M1 in Liver Cancer.** *Gastroenterology*. 2017; 152:2037-2051.e22.
4. Gray J; Oehrle K; Worthen G; Alenghat T; Whitsett J; Deshmukh H. **Intestinal commensal bacteria mediate lung mucosal immunity and promote resistance of newborn mice to infection.** *Science Translational Medicine*. 2017; 9:eaaf9412-eaaf9412.
5. Sweeney EL; Dando SJ; Kallapur SG; Knox CL. **The Human Ureaplasma Species as Causative Agents of Chorioamnionitis.** *Clinical microbiology reviews*. 2017; 30:349-379.
6. Abman SH; Bancalari E; Jobe A. **The Evolution of Bronchopulmonary Dysplasia after 50 Years.** *American journal of respiratory and critical care medicine*. 2017; 195:421-424.

7. Ahlfeld SK; Davis SD; Kelley KJ; Poindexter BB. **Early Elevation of Plasma Periostin Is Associated with Chronic Ventilator-Dependent Bronchopulmonary Dysplasia.** *American journal of respiratory and critical care medicine.* 2016; 194:1430-1433.
8. Hawkins F; Kramer P; Jacob A; Driver I; Thomas DC; McCauley KB; Skvir N; Crane AM; Kurmann AA; Hollenberg AN. **Prospective isolation of NKX2-1-expressing human lung progenitors derived from pluripotent stem cells.** *Journal of Clinical Investigation.* 2017; 127:2277-2294.
9. Hall SL; Baker T; Lajoie S; Richgels PK; Yang Y; McAlees JW; van Lier A; Wills-Karp M; Sivaprasad U; Acciani TH. **IL-17A enhances IL-13 activity by enhancing IL-13-induced signal transducer and activator of transcription 6 activation.** *Journal of Allergy and Clinical Immunology.* 2017; 139:462-471.e14.
10. Pavlicev M; Wagner GP; Chavan AR; Owens K; Maziarz J; Dunn-Fletcher C; Kallapur SG; Muglia L; Jones H. **Single-cell transcriptomics of the human placenta: inferring the cell communication network of the maternal-fetal interface.** *Genome research.* 2017; 27:349-361.
11. Guo M; Tomoshige K; Meister M; Muley T; Fukazawa T; Tsuchiya T; Karns R; Warth A; Fink-Baldauf IM; Nagayasu T. **Gene signature driving invasive mucinous adenocarcinoma of the lung.** *EMBO Molecular Medicine.* 2017; 9:462-481.
12. Guo M; Bao EL; Wagner M; Whitsett JA; Xu Y. **SLICE: determining cell differentiation and lineage based on single cell entropy.** *Nucleic Acids Research.* 2017; 45:gkw1278.
13. Pammi M; Cope J; Tarr PI; Warner BB; Morrow AL; Mai V; Gregory KE; Simon Kroll J; McMurtry V; Ferris MJ. **Intestinal dysbiosis in preterm infants preceding necrotizing enterocolitis: a systematic review and meta-analysis.** *Microbiome.* 2017; 5:31.
14. Du Y; Kitzmiller JA; Sridharan A; Perl AK; Bridges JP; Misra RS; Pryhuber GS; Mariani TJ; Bhattacharya S; Guo M. **Lung Gene Expression Analysis (LGEA): an integrative web portal for comprehensive gene expression data analysis in lung development.** *Thorax.* 2017; 72:481-484.
15. Milewski D; Pradhan A; Wang X; Cai Y; Le T; Turpin B; Kalinichenko VV; Kalin TV. **FoxF1 and FoxF2 transcription factors synergistically promote rhabdomyosarcoma carcinogenesis by repressing transcription of p21(Cip1) CDK inhibitor.** *Oncogene: Including Oncogene Reviews.* 2017; 36:850-862.
16. Sun L; Ren X; Wang IC; Pradhan A; Zhang Y; Flood HM; Han B; Whitsett JA; Kalin TV; Kalinichenko VV. **The FOXM1 inhibitor RCM-1 suppresses goblet cell metaplasia and prevents IL-13 and STAT6 signaling in allergen-exposed mice.** *Science Signaling.* 2017; 10:eaai8583.
17. Mucci A; Kunkiel J; Suzuki T; Brenning S; Glage S; Kühnel MP; Ackermann M; Happel C; Kuhn A; Schambach A. **Murine iPSC-Derived Macrophages as a Tool for Disease Modeling of Hereditary Pulmonary Alveolar Proteinosis due to Csf2rb Deficiency.** *Stem Cell Reports.* 2016; 7:292-305.
18. Mueller C; Gernoux G; Gruntman AM; Borel F; Reeves EP; Calcedo R; Rouhani FN; Yachnis A; Humphries M; Campbell-Thompson M. **5 Year Expression and Neutrophil Defect Repair after Gene Therapy in Alpha-1 Antitrypsin Deficiency.** *Molecular Therapy.* 2017; 25:1387-1394.
19. Dingess KA; Valentine CJ; Ollberding NJ; Davidson BS; Woo JG; Summer S; Peng YM; Guerrero ML; Ruiz-Palacios GM; Ranssler RR. **Branched-chain fatty acid composition of human milk and the impact of maternal diet: the Global Exploration of Human Milk (GEHM) Study.** *American Journal of Clinical Nutrition.* 2017; 105:177-184.
20. deSante-Bertkau JE; Haberman B. **Resuscitation Decisions of Extremely Premature Infants at the Limits of Viability: Defining Best Interests.** *The American Journal of Bioethics.* 2017; 17:86-88.
21. Kazi AM; Cortese MM; Yu Y; Lopman B; Morrow AL; Fleming JA; McNeal MM; Steele AD; Parashar UD; Zaidi AKM. **Secretor and Salivary ABO Blood Group Antigen Status Predict Rotavirus Vaccine Take in Infants.** *Journal of Infectious Diseases.* 2017; 215:786-789.

22. Senthamarai kanna n P; Presicce P; Rueda CM; Maneenil G; Schmidt AF; Miller LA; Waites KB; Jobe AH; Kallapur SG; Chougnet CA. **Intra-amniotic Ureaplasma parvum-Induced Maternal and Fetal Inflammation and Immune Responses in Rhesus Macaques.** *Journal of Infectious Diseases.* 2016; 214:1597-1604.
23. Campo I; Luisetti M; Griese M; Trapnell BC; Bonella F; Grutters JC; Nakata K; Van Moorsel CHM; Costabel U; Cottin V. **A Global Survey on Whole Lung Lavage in Pulmonary Alveolar Proteinosis.** *Chest.* 2016; 150:251-253.
24. Iams JD; Applegate MS; Marcotte MP; Rome M; Krew MA; Bailit JL; Kaplan HC; Poteet J; Nance M; McKenna DS. **A Statewide Progestogen Promotion Program in Ohio.** *Obstetrics and Gynecology.* 2017; 129:337-346.
25. Yang L; Na CL; Luo S; Wu D; Hogan S; Huang T; Weaver TE. **The Phosphatidylcholine Transfer Protein Stard7 is Required for Mitochondrial and Epithelial Cell Homeostasis.** *Scientific Reports.* 2017; 7:46416-46416.

## Grants, Contracts, and Industry Agreements

### Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Eric Kirkendall, MD Kristin R Melton	Improving Intensive Care Medication Safety through EHR-based Algorithms.	National Institutes of Health	R01 LM012230	09/15/2015 - 08/31/2019	\$170,959
Tatiana Viktorovna Kalin, MD, PhD	Transcriptional Regulation of Cancer Progression and Metastasis by FoxM1	American Cancer Society National	RSG1332501	07/01/2013 - 06/30/2017	\$180,000
Jeffrey A Whitsett, MD Bruce C Trapnell, MD	Lung and Cardiovascular Development and Disease Pathogenesis Training Program	National Institutes of Health	T32 HL007752	07/01/2014 - 06/30/2019	\$308,475
James Patrick Bridges, PhD	Role of GPR116 in the Regulation of Alveolar Surfactant Pool Size	American Heart Association - National	13SDG17090028	07/01/2013 - 06/30/2017	\$77,000
Timothy E Weaver, PhD	Stard7, a Novel Inhibitor of Allergic Lung Disease	National Institutes of Health	R01 HL122130	01/01/2014 - 12/31/2017	\$390,000
Jeffrey A Whitsett, MD	Molecular Atlas of Lung Development - Data Coordinating Center	National Institutes of Health (Duke University)	U01 HL122638	06/15/2014 - 04/30/2019	\$53,102
Jeffrey A Whitsett, MD S Steven Potter, PhD	Lung MAP Atlas Research Center	National Institutes of Health	U01 HL122642	06/15/2014 - 04/30/2019	\$390,732.50
Bruce C Trapnell, MD	Macrophage Based Gene Therapy for Hereditary Pulmonary Alveolar Proteinosis	National Institutes of Health	R01 HL118342	05/01/2014 - 04/30/2018	\$554,394
Vladimir V Kalinichenko, MD, PhD	Transcriptional Regulation of Goblet Cell Metaplasia	National Institutes of Health	R01 HL123490	08/05/2014 - 06/30/2018	\$390,000

Bruce C Trapnell, MD	RLDC: Molecular Pathway-Driven Diagnostics & Therapeutics for Rare Lung Diseases	National Institutes of Health	U54 HL127672	09/18/2014 - 07/31/2019	\$625,000
James M Greenberg, MD	Healthy Start Cincinnati	Health Resources & Services Admin	H49 MC27823	09/01/2014 - 03/31/2019	\$391,041
Vladimir V Kalinichenko, MD, PhD	Foxf1 Transcription Factor in Development of Pulmonary Capillaries	National Institutes of Health	R01 HL084151	05/08/2015 - 04/30/2019	\$390,000
Hitesh Deshmukh, MD, PhD	Role of Commensal Bacteria in Regulating Neutrophil-mediated Host Defense in Neonates	National Institutes of Health	K08 HD084686	08/01/2015 - 05/31/2019	\$163,037
Louis Muglia	Systems Biology Approaches to Birth Timing and Preterm Birth Risk	Bill & Melinda Gates Foundation	OPP1113966	11/17/2014 - 10/31/2017	\$15,925
Brenda Poindexter, MD, MS	NICHD Cooperative Multicenter Neonatal Research Network	National Institutes of Health	UG1 HD027853	04/01/2016 - 03/31/2021	\$326,595
James Patrick Bridges, PhD	Role of GPR116 in Alveolar Homeostasis	National Institutes of Health	R01 HL131634	03/18/2016 - 02/28/2021	\$392,012
Alan Hall Jobe, MD, PhD	Antenatal Steroid Treatment Strategies for Low Resource Countries	Bill & Melinda Gates Foundation	OPP1132910	10/26/2015 - 12/31/2017	\$523,055
Margaret K Hostetter, MD	Child Health Research Career Development Award (K12)	National Institutes of Health	K12 HD028827	12/01/2015 - 11/30/2017	\$178,537
Tatiana Viktorovna Kalin, MD, PhD	Targeting Foxm1 in Pulmonary Fibrosis	National Institutes of Health	R01 HL132849	09/01/2016 - 06/30/2020	\$312,000
Debora Ines Sinner, PhD	Molecular Basis of Dorsal-ventral Patterning of the Conducting Airways	National Institutes of Health	R03 HL133420	09/01/2016 - 08/31/2018	\$78,000
Timothy E Weaver, PhD	Deficiency of Phospholipid Transfer Protein, a Driver of Allergic Airway Disease	National Institutes of Health	R01 HL134186	08/04/2016 - 05/31/2020	\$990,746
Bruce C Trapnell, MD	The 2016 International Rare Lung Diseases Clinical Research Conference	National Institutes of Health	R13 HL134326	08/01/2016 - 07/31/2017	\$15,000
Bruce C Trapnell, MD	Pathogenesis-Based Diagnostics and Pharmacotherapeutics for PAP	National Institutes of Health	R01 HL085453	07/01/2016 - 04/30/2020	\$780,000

Jeffrey A Whitsett, MD	Editing Alveolar Progenitor Cells for Correction of Monogenic Disease	National Institutes of Health	U01 HL134745	09/23/2016 - 05/31/2023	\$2,002,148
Jeffrey A Whitsett, MD	Transcriptional Programming of Asthma Related Pathology in Respiratory Epithelia	National Institutes of Health	R01 HL095580	04/01/2016 - 03/31/2018	\$528,560
Bruce C Trapnell, MD	Multicenter Interventional Lymphangioliomyomatosis Early Disease Trial (MILED Trial)-CC	National Institutes of Health (University of Cincinnati)	U01 HL131755	09/20/2016 - 06/30/2021	\$46,461
Anne Karina Perl, PhD	Interstitial Resident Fibroblasts Direct Alveolar Epithelial Differentiation	National Institutes of Health	R01 HL131661	01/01/2017 - 11/30/2020	\$475,847
Suhas G Kallapur, MD David A Hildeman, PhD Andrew Herr, PhD	Novel Therapeutic Target for Intrauterine Inflammation	National Institutes of Health	R21 HD090856	12/10/2016 - 11/30/2018	\$78,000
Xiaofang Tang, PhD	Lung Repair and Regeneration Consortium	National Institutes of Health (Duke University)	U01 HL110967	01/01/2016 - 12/31/2016	\$20,000
Jeffrey A Whitsett, MD	Omics of Lung Diseases	National Institutes of Health	K12 HL119986	06/01/2016 - 05/31/2018	\$657,654
Takuji Suzuki, PhD	Genome Edited iPSC Cell-derived Macrophages as a Novel Lung Cell Therapy	National Institutes of Health	R01 HL136721	02/06/2017 - 01/31/2021	\$390,000
Jeffrey A Whitsett, MD Xinhua Lin, PhD	Role of EMC3/TMEM111 in Alveolar Epithelial Cell Function	National Institutes of Health	R01 HL136722	04/01/2017 - 03/31/2021	\$239,610.50
Debora Ines Sinner, PhD	Molecular Mechanisms Underlying Upper Airway Patterning and Tracheomalacia	National Institutes of Health	K01 HL115447	08/01/2016 - 07/31/2017	\$112,397
Yan Xu, PhD	Foundational Mapping of the Neural Circuits that Control Intrinsic Lung Function	Department of Health and Human Services (University of California San Diego)	OT2OD023857	02/01/2017 - 07/31/2018	\$101,235
Louis Muglia	Maternal Genetics and Micronutrient Status as Risk Factors for Preterm Birth in the AMANHI Study	Bill & Melinda Gates Foundation	OPP1152451	09/12/2016 - 07/31/2018	\$574,209
Louis Muglia Claire A Chougnnet, PhD	Maternal Temperament, Stress, and Inflammation in Preterm Birth	National Institutes of Health	R01 HD078127	09/01/2016 - 08/31/2017	\$188,569.50
Daniel Todd Swarr, MD	The Long Non-coding RNA Fanci	Francis Family	swarr, dan,	07/01/2016	\$45,125

	in Lung Development and Differentiation	Foundation	parker	-	06/30/2018	
Daniel Todd Swarr, MD	The Role of the Long Non-coding RNA Falcor in Early Endoderm and Lung Development	National Institutes of Health	K08 HL130666	09/01/2016	\$252,884.05	
				-	11/30/2020	
Nehal A Parikh, DO	A New Model to Identify Preterm Neonates at High-Risk for Cognitive Deficits	National Institutes of Health	R01 NS094200	09/01/2016	\$1,086,100	
				-	01/31/2021	
Nehal A Parikh, DO	Early Prediction of Cerebral Palsy in Premature Infants using Advanced MRI Biomarkers	National Institutes of Health	R01 NS096037	09/30/2016	\$1,078,924	
				-	05/31/2021	
Bruce C Trapnell, MD	Cincinnati Center for Clinical and Translational Sciences and Training	Natl. Ctr for Advancing Translational Sc (University of Cincinnati)	UI1 TR001425	07/07/2016	\$712,738	
				-	04/02/2017	
Louis Muglia	Recipient in the California Preterm Birth Initiative (PTBi-CA)	Bill & Melinda Gates Foundation (The Regents of the Univ of California)	mrandchmc00sc	07/01/2016	\$30,033	
				-	06/30/2017	
Louis Muglia	March of Dimes Prematurity Research Center Ohio Collaborative Year 5	March of Dimes - Ohio	#22-FY17-889	01/01/2017	\$2,000,000	
				-	12/31/2017	
Timothy D LeCras, PhD	Biomarkers And Pathogenesis Of Lymphatic Anomalies	The Lymphatic Malformation Institute	Lecras, T., LMI	05/01/2017	\$149,797	
				-	04/30/2018	
<b>Total Annual Grant Award Dollars</b>						<b>\$18,465,902.55</b>

## Annual Industry Award Dollars

Investigator	Industry Sponsor	Amount
Ardythe Morrow, PhD	Prolacta Bioscience Inc.	\$78,145
<b>Total Annual Industry Award Dollars</b>		<b>\$78,145</b>

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