Cincinnati Children's

2015 Research Annual Report

Section of Neonatology, Perinatal and Pulmonary Biology

RESEARCH AND TRAINING DETAILS

Click to view members

Faculty	60
Joint Appointment Faculty	1
Research Fellows	14
Research Students	14
Support Personnel	95
Direct Annual Grant Support	$10,575,664
Direct Annual Industry Support	$167,672
Peer Reviewed Publications	134

CLINICAL ACTIVITIES AND TRAINING

Clinical Staff	17
Staff Physicians	19
Clinical Fellows	15
Clinical Students	28
Other Students	25

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Research Highlights

LungMAP

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

Rare Lung Consortium

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

Asthma

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

Significant Publications

Suzuki T, **Arumugam P**, Sakagami T, Lachmann N, Chalk C, Sallese A, Abe S, Trapnell C, Carey B, Moritz T, Malik P, Lutzko C, Wood RE, **Trapnell BC**. Pulmonary macrophage transplantation therapy. *Nature.* 2014 Oct 23;514(7523):450-4.

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.

Cheng XH, Black M, Ustiyan V, Le T, Fulford L, Sridharan A, Medvedovic M, **Kalinichenko VV**, **Whitsett JA**, **Kalin TV**.

SPDEF inhibits prostate carcinogenesis by disrupting a positive feedback loop in regulation of the Foxm1 oncogene. *PLoS Genet.* 2014 Sep 25;10(9):e1004656.

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.

Rajavelu P, Chen G, **Xu Y**, Kitzmiller JA, **Korfhagen TR**, **Whitsett JA**. Airway epithelial SPDEF integrates goblet cell differentiation and pulmonary Th2 inflammation. *J Clin Invest.* 2015 May 1;125(5):2021-31.

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

Division Publications

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3. Akeno N, Miller AL, Ma X, Wikenheiser-Brokamp KA. **p53 suppresses carcinoma progression by inhibiting mTOR pathway activation**. *Oncogene*. 2015; 34:589-99.

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- **Melissa Rice, MD**, Indiana University School of Medicine, Indianapolis, IN
- **Amy Rouse, MD**, Rainbow Babies and Children's Hospital, Cleveland, OH
- **Tony Sallese, BS**, University of St. Francis, Joliet, IL
- **Augusto Schmidt, MD**, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
- **Jessica Seeberger, MBA**, University of Cincinnati, Cincinnati, OH
- **Laura Seske, MD**, Washington University, Saint Louis, MO
- **Teresa Seto, MD**, Nationwide Children's Hospital, Columbus, OH
- **Sneha Sitaraman, MS, BS**, VIT University, Vallore, India, University of Pune, Pune India
- **Heather Smith, MD**, Miller School of Medicine, Miami, FL
- **Diana Taft, PhD**, University of Cincinnati, Cincinnati, OH
- **Xiaofang Tang, PhD**, Tsinghua University, Beijing, China
- **Tayaramma Thatava, PhD**, University of Braunschweig - Institute of Technology, Germany
- **Emily Wayman, BS**, University of Alabama, Tuscaloosa, AL
- **Emily Wiland, MD**, Rainbow Babies and Children's Hospital, Cleveland, OH

- **Jason Wiles, MD**, University of Louisville School of Medicine, Louisville, KY
- **Sadie Williams, MD**, University of Florida at Arnold Palmer Hospital, Orlando, FL
- **Koryse Woodrooffe, MD**, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
- **Giridhar Vummidi Giridhar, PhD**, University of Madras, Tamil Nadu, India
- **Hongping Xia, PhD**, Fudan University, Shanghai, China
- **Yvonne Yui, MD**, University of Cincinnati College of Medicine, Cincinnati, OH

Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct

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

Initiation and Progression of Preterm Lung Injury with Ventilation

National Institutes of Health

R01 HD072842	8/1/2012-5/31/2017	$207,815

Data Coordinating Center for the Prematurity and Respiratory Outcomes Program

National Institutes of Health (University of Pennsylvania)

U01 HL101794	5/1/2012-4/30/2016	$11,373

Kalin, T

Transcriptional Regulation of Cancer Progression and Metastasis by Foxm1

American Cancer Society National

RSG1332501	7/1/2013-6/30/2017	$150,000

Role of Foxm1 in Lung Cancer Microenvironment

National Institutes of Health

R01 CA142724	7/1/2010-6/30/2015	$195,237

Kalinichenko, V

Foxf1 Transcription Factor in Development of Pulmonary Capillaries

National Institutes of Health

R01 HL084151	5/8/2015-4/30/2019	$250,000

Transcriptional Regulation of Goblet Cell Metaplasia

National Institutes of Health

R01 HL123490	8/5/2014-6/30/2018	$250,000

Kingma, P

Intestinal Motility and Gastroschisis

The Gerber Foundation

1557-3464	7/1/2013-6/30/2016	$53,251

LeCras, T

Identification of Biomarkers for Patients with Generalized Lymphatic Anomaly (GLA), Kaposiform Lymphangiomatosis (KLA), Gorham-Stout disease (GSD)

The Lymphatic Malformation Institute

	5/1/2015-4/30/2016	$131,828

Maeda, Y

Dissecting Tumor Heterogeneity in KRAS-Mutant Lung Cancer

American Lung Association

RG309608	8/1/2014-7/31/2016	$40,000

Merhar, S

Serial Neuroimaging in Infants with Necrotizing Enterocolitis

Cerebral Palsy International Research Foundation

EH-014-00	1/1/2015-12/31/2017	$68,182

Morrow, A

DNA Attenuates Inflammatory Responses through Altering RAGE Signaling

National Institutes of Health (The Research Institute at Nationwide Hospital)

R01 AT006880	7/1/2012-6/30/2016	$11,375

Muglia, L

Systems Biology Approaches to Birth Timing and Preterm Birth Risk

Bill & Melinda Gates Foundation

OPP1113966	11/17/2014-10/31/2016	$394,922

Systems Biology Approaches to Birth Timing and Preterm Birth Risk - Supplement

Bill & Melinda Gates Foundation

OPP1113966	11/17/2014-10/31/2016	$120,000

March of Dimes Prematurity Research Center Ohio Collaborative

March of Dimes

22-FY15-003	1/1/2015-12/31/2015	$1,930,475
Dey, S	Theme 3	$250,000

Muglia, L / Chougnet, C

Maternal Temperament, Stress, and Inflammation in Preterm Birth

National Institutes of Health

R01 HD078127	9/1/2013-8/31/2017	$485,643
Muglia, L		$416,359

Chougnet, C		$69,283

Nommsen-Rivers, L

Improving Lactation Success in Pre-Diabetic Mothers

National Institutes of Health (University of Cincinnati)

K12 HD051953	7/1/2014-6/30/2016	$100,000

Poindexter, B

Gastrin-Releasing Peptide and Bronchopulmonary Dysplasia

National Institutes of Health (Duke University)

R01 HL105702	10/1/2014-7/31/2016	$40,386

Taking the Guesswork Out of Pediatric Weight Estimation: Ensuring Accurate Weight Assessment in Newborns and Young Infants (Baby TAPE)

National Institutes of Health (Duke University)

HHSN2752010000031	4/1/2015-3/22/2016	$4,945

Pharmacokinetics of Antistaphylococcal Antibiotics in Infants

National Institutes of Health (Duke University)

HHSN2752010000031	2/9/2015-8/26/2016	$4,000

Safety and Efficacy of High-Dose Acyclovir in Infants with HSV

National Institutes of Health (Duke University)

HHSN2752010000031	2/9/2015-8/26/2016	$7,000

Pharmacokinetics of Sildenafil in Premature Infants

National Institutes of Health (Duke University)

HHSN2752010000031	2/9/2015-8/26/2016	$13,000

Schibler, K

NICHD Cooperative Multicenter Neonatal Research Network

National Institutes of Health

U10 HD027853	4/1/2011-3/31/2016	$476,965

Sinner, D

Molecular Mechanisms Underlying Upper Airway Patterning and Tracheomalacia

National Institutes of Health

K01 HL115447	8/1/2012-7/31/2017	$104,071

Trapnell, 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 Abstinance 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

Airway Progenitor Cell Proliferation and Differentiation During Lung Repair		
National Institutes of Health		
U01 HL110964	1/1/2012-12/31/2016	$522,812
Single Cell NexGen RNA Sequencing of Human Lung		
National Institutes of Health (Duke University)		
U01 HL110967	1/1/2014-12/31/2015	$2,000
Molecular Atlas of Lung Development - Data Coordinating Center		
National Institutes of Health (Duke University)		
U01 HL122638	6/15/2014-4/30/2019	$33,256
Cleveland Clinic Center for Accelerated Innovations (CCCAI) - CCHMC		
National Institutes of Health (Cleveland Clinic Lerner College of Medicine)		
U54 HL119810	9/26/2013-7/31/2020	$14,000
CFF Research Development Program - Transgenic Core		
Cystic Fibrosis Foundation		
	7/1/2014-6/30/2015	$50,000

Whitsett, J/Potter, S

"Lung MAP" Atlas Research Center		
National Institutes of Health		
U01 HL122642	6/15/2014-4/30/2019	$512,240

Whitsett, J/Trapnell, B

Lung and Cardiovascular Development and Disease Pathogenesis Training Program		
National Institutes of Health		
T32 HL007752	7/1/2014-6/30/2019	$272,143

Xu, Y

Role of SREBP Network in Surfactant Lipid Homeostasis and Lung Maturation		
National Institutes of Health		
R01 HL105433	7/1/2011-6/30/2015	$293,104
	Current Year Direct	**$10,575,664**

Morrow, A

Prolacta Bioscience Inc,	$28,907
Mead Johnson & Company	$138,765
Current Year Direct Receipts	**$167,672**
Total	**$10,743,336**

SPDEF Transcription Factor Shown to Suppress Prostate Cancer

Tanya Kalin, MD, PhD

The Perinatal Institute includes the Divisions of Neonatology, Perinatal and Pulmonary Biology, Developmental Biology, Reproductive Sciences, the Center for Prevention of Preterm Birth, and the Cincinnati Fetal Center.

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

Cheng XH, Black M, Ustiyan V, Le T, Fulford L, Sridharan A, Medvedovic M, Kalinichenko VV, Whitsett JA, Kalin TV. SPDEF inhibits prostate carcinogenesis by disrupting a positive feedback loop in regulation of the Foxm1 oncogene. *PLoS Genet*. 2014;10(9):e1004656.

PUBLISHED SEPT. 25, 2014
PLOS Genetics

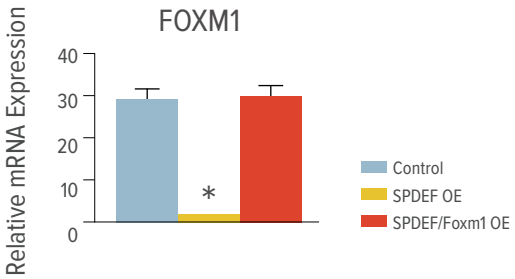
Prostate cancer continues to be the most common malignancy diagnosed in American men and the second leading cause of male cancer mortality.

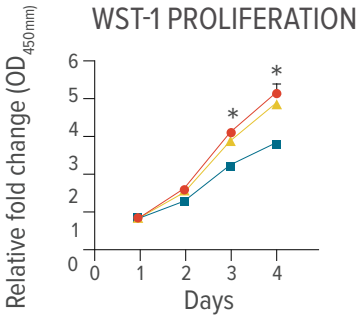
Tanya Kalin, MD, PhD, leads a research team at Cincinnati Children's that seeks to identify the direct role of several transcription factors (Foxm1, Foxf1, Foxf2, SPDEF) in prostate cancer. The team's latest findings, published Sept. 25, 2014, in *PLOS Genetics*, explain how SPDEF transcription factor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

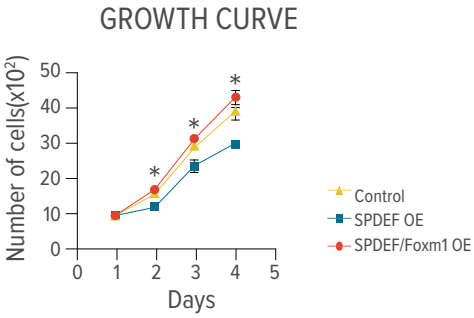
"Our data demonstrate that SPDEF functions as a tumor suppressor in prostate cancers by inhibiting tumor cell proliferation via disruption of an auto-regulatory element in the Foxm1 promoter," Kalin says. "It is possible that the loss of SPDEF causes increased expression of oncogenic Foxm1, accelerating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

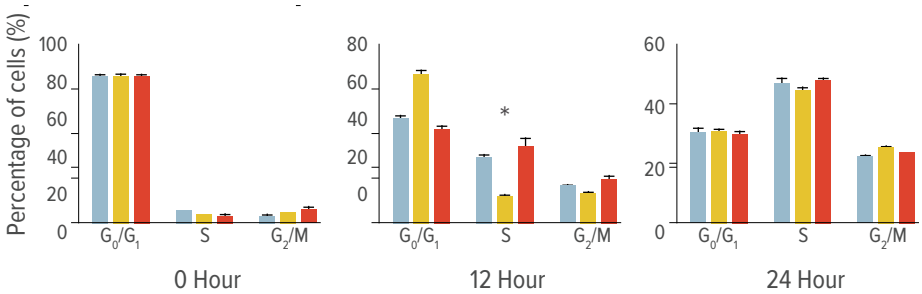
Until now, researchers lacked useful transgenic mouse models to study the role of SPDEF in prostate cancer. Kalin and colleagues generated mice that either lacked or over-expressed SPDEF function. The mice revealed that loss of SPDEF increased cancer progression and tumor cell proliferation, whereas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

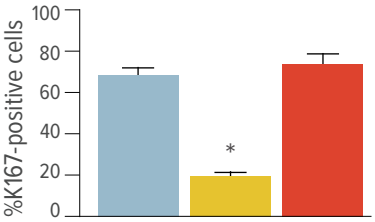
Specifically, over-expression of SPDEF inhibited RNA and protein levels of Foxm1, a transcription factor critical for tumor cell proliferation, and reduced expression of Foxm1 target genes, including Cdc25b, cyclin B1, cyclin A2, Plk-1, AuroraB, CKS1 and Topo2alpha. Furthermore, an inverse correlation 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.

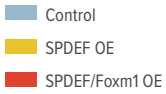


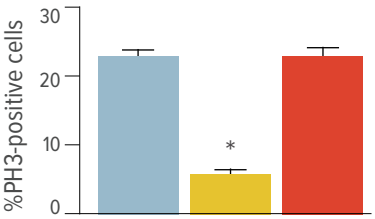












Re-expression of Foxm1 restored cellular proliferation in SPDEF-overexpressing prostate tumor cells as demonstrated by increased numbers of Ki-67-positive (upper panels) and PH3-positive (bottom panels) cells. Percentages of Ki-67-positive and PH3-positive cells were counted in five random microscopic fields.

Macrophage Transplantation Could Become Therapy for hPAP

Bruce Trapnell, MD

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

Suzuki T, Arumugam P, Sakagami T, Lachmann N, Chalk C, Sallese A, Abe S, Trapnell C, Carey B, Moritz T, Malik P, Lutzko C, Wood RE, Trapnell BC. Pulmonary macrophage transplantation therapy. *Nature.* 2014;514(7523):450-454.

PUBLISHED ONLINE OCT. 1, 2014
Nature

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.

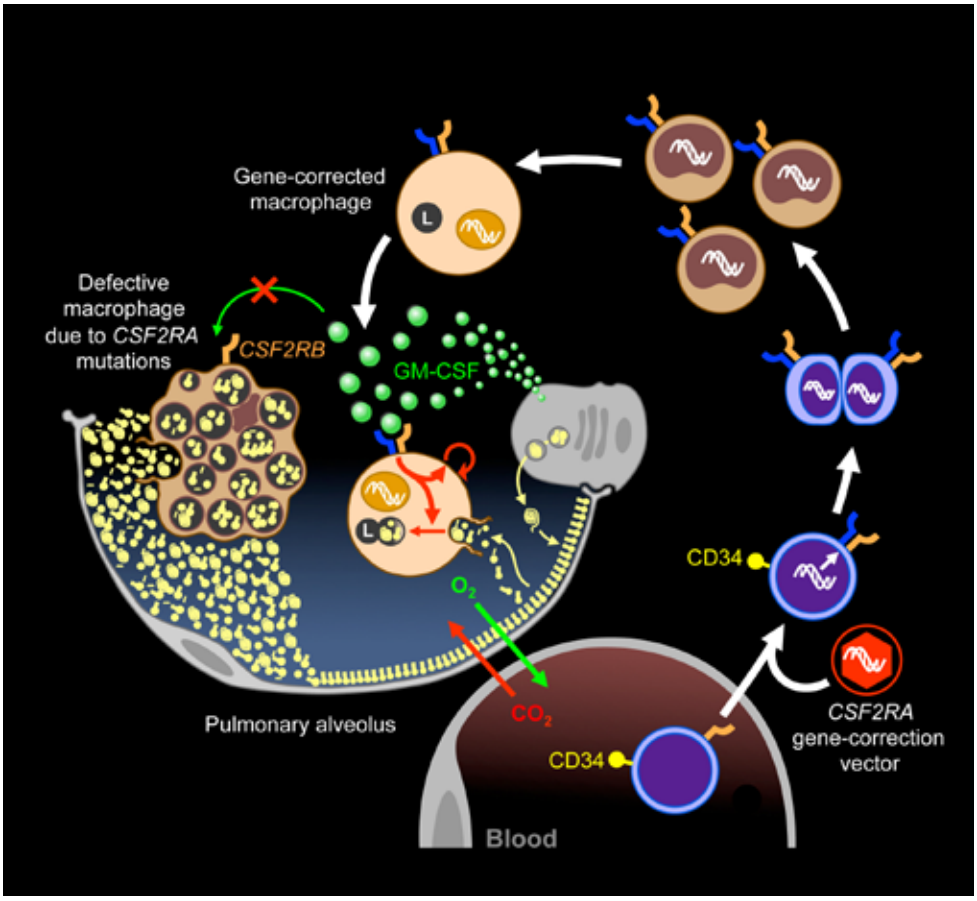
In a recent study published in *Nature*, Suzuki and Trapnell report that macrophage transplantation (involving normal or gene-corrected cells) fully reversed the disease in mice bred to mimic hPAP. The treatment also prevented disease-specific mortality for at least one year.

"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 pre-clinical studies needed to prepare for human clinical trials.

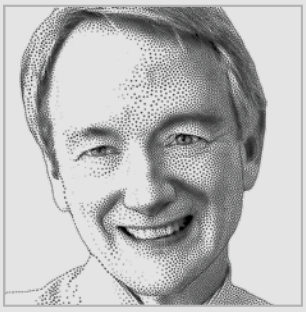
PULMONARY MACROPHAGE TRANSPLANTATION THERAPY



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



Jeffrey Whitsett, MD

THE PERINATAL INSTITUTE RESEARCH AND TRAINING DETAILS

Faculty	60
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Research Students	14
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Direct Annual Grant Support	$10.5M
Direct Annual Industry Support	$167,672
Peer Reviewed Publications	134

Rajavelu P, Chen G, Xu Y, Kitzmiller JA, Korfhagen TR, Whitsett JA. Airway epithelial SPDEF integrates goblet cell differentiation and pulmonary Th2 inflammation. *J Clin Invest*. 2015;125(5):2021-2031.

PUBLISHED MAY 4, 2015
The Journal of Clinical Investigation

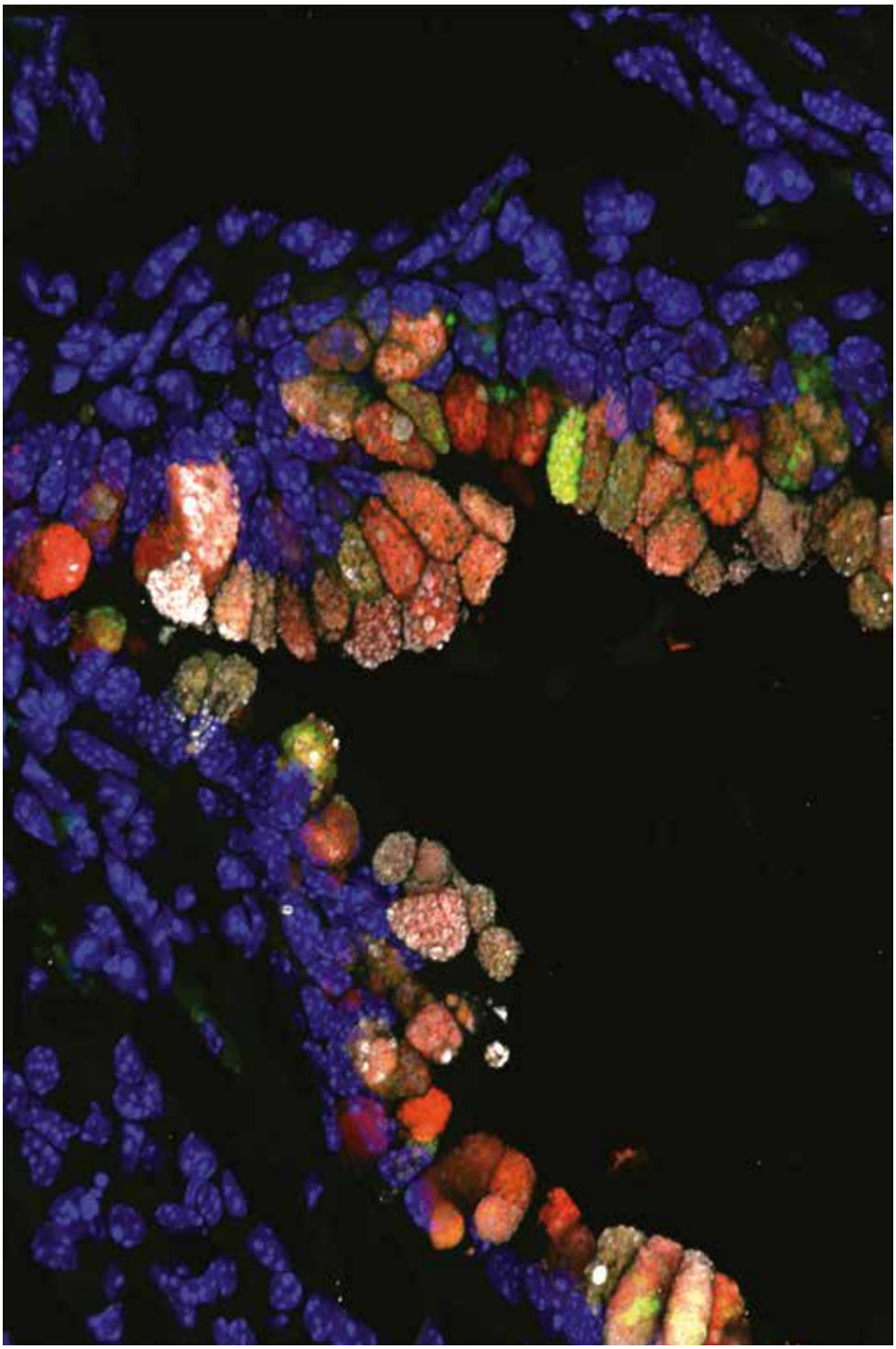
Epithelial cells lining the airways are the first line of defense against infections and allergens, and doctors are increasingly understanding the role played by pulmonary immune responses — initiated early in development, *in utero*, and during infancy — in the development of asthma and other lung disorders.

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."



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.