Asthma Research

RESEARCH AND TRAINING DETAILS

<table>
<thead>
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<td>Peer Reviewed Publications</td>
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CLINICAL ACTIVITIES AND TRAINING

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Research Highlights

The study of Epithelial Genes and Allergic Inflammation: Gurjit Khurana Hershey, MD, PhD

Gurjit Khurana Hershey, MD, PhD, is the PI of an ongoing NIH-funded Asthma and Allergic Diseases Cooperative Research Center (AADCRC) U19. The Cincinnati center is one of only 11 centers in the United States. This multi project
grant is focused on delineating the role of epithelial genes in allergic inflammation. Significant progress has been made on this project and over 60 manuscripts have been published as a result.

Ohio Pediatric Asthma Repository: Gurjit Khurana Hershey, MD, PhD
Gurjit Khurana Hershey, MD, PhD, has been working with five other Children’s Hospitals in Ohio (the Ohio Children’s Hospitals Association) in an effort to develop the Ohio Pediatric Asthma Repository (OPAR) since 2012. This study is designed to compare the effectiveness of treatment strategies used at pediatric hospitals throughout Ohio – analyzing phenotypic, demographic, treatment and outcome data looking for differences between patients, treatments and site pathways to see what factors impact reutilization and length of hospital stay. To date, OPAR has enrolled 3,089 unique participants statewide. OPAR is a unique, valuable and innovated resource in which to conduct observational, comparative effectiveness, and ultimately intervention studies for pediatric asthma. The Ohio Children’s Hospital Association meet regularly to compare data and develop new strategies for the treatment of asthma. Governor John Kasich recently announced an additional $1 million in funding to continue these research efforts.

Inner City Asthma Consortium Subcontract (ICAC3): Gurjit Khurana Hershey, MD, PhD (PI)
The Inner City Asthma Consortium is a multi-center, multi-study initiative to the study the causes of urban asthma epidemic that affects millions of children and to develop treatments to improve control of asthma in this population and in general. Dr. Gurjit Khurana Hershey is the PI of the Cincinnati center. The goal of this study is to include further development of cockroach allergen immunotherapy and consideration of new allergen immunotherapies (for example, to mouse allergens), the development and execution of clinical and mechanistic studies targeted to inner-city asthma phenotypes, and interventions designed to prevent the incidence of asthma exacerbation or its progression.

Community Research Award: Melinda Butsch Kovacic, PhD
Dr. Melinda Butsch Kovacic and the 7 Hills Neighborhood Houses Findlay Street Center received a Community Health Grant from the Center for Clinical and Translational Science and Training (CCTST) for the "Community Youth Scientists" (CYS) Program. The CYS Program provided health education, drug prevention, and leadership training to West End teenagers. With the funding of this CCTST grant, the West End teen workers studied the "7 Habits of Highly Effective Teens" book, as well as participated in sessions on environmental health, community advocacy, research methodology, and urban planning and mapping using Geographic Information System software.

R21 to study TET1 in Childhood Asthma: Hong Ji, PhD
Dr. Hong Ji and colleagues were awarded an R21 grant from the National Institute of Allergy and Infectious Diseases (NIAID) to study the role of TET1, a DNA demethylase, in childhood asthma. This study will use samples collected from children, primary airway epithelial cells, and a high throughput epigenomic approach to identify locations in the human genome whose DNA methylation levels are associated with asthma and to explore possible mechanisms accounting for such associations.

Diversity and Health Disparities Award: Tesfaye Mersha, PhD
Dr. Tesfaye Mersha was the recipient of the inaugural Diversity and Health Disparities Award. This is a two-year award providing faculty members funds who are either underrepresented minorities or have a strong commitment to health disparities research. The long-term objective of this funding opportunity is to promote the career development of underrepresented faculty and to enhance the health disparities research effort at Cincinnati Children’s. Dr. Mersha’s proposal "Genetic ancestry and racial disparities in childhood asthma" was highly innovated and well aligned with the goals of the program.

PRIDE Program: Tesfaye Mersha, PhD
Dr. Tesfaye Mersha was selected to participate in the National Heart, Lung, and Blood Institute (NHLBI) sponsored
by Programs to Increase Diversity Among Individuals Engaged in Health-Related Research (PRIDE). This program addresses the difficulties experienced by junior investigators and postdoctoral scientists in establishing independent academic research programs and negotiating through the academic ranks. The primary outcome of this program is to increase the number of scientists and research-oriented faculty who are from ethnic groups currently under-represented in biomedical science and those with disabilities, to successfully compete for external funding for scientific research in the biomedical and behavioral sciences in heart, lung, blood, and sleep (HLBS) disorders.

### Significant Publications


This study sought to identify biomarkers of corticosteroid treatment response in children with asthma and evaluated the utility and mechanistic basis of these biomarkers. A biological basis for poor corticosteroid treatment response was identified and can be used to distinguish a subgroup of asthmatic children who respond poorly to systemic corticosteroid treatment. It was also found that VNN1 contributes to corticosteroid responsiveness, and changes in VNN1 nasal epithelial mRNA expression and VNN1 promoter methylation might be clinically useful biomarkers of treatment response in asthmatic children.


This publication concluded that nasal epithelial cells is an excellent tissue source to generate iPSCs in pediatric asthmatic patients, and detailed characterization of the resulting iPSC lines helps us to better understand the reprogramming process and retention of epigenetic memory.


Asthma heterogeneity causes difficulty in studying and treating the disease. In this study, a comprehensive statewide repository was built linking questionnaire and medical record data with health outcomes to characterize the variability of clinical practices at Ohio children's hospitals for the treatment of hospitalized asthma. The data reported highlighted the need for standardization of treatment practices for inpatient asthma care. There is considerable opportunity for personalized care plans that incorporate an individual's asthma impairment, risk, and treatment response history into hospital practices for asthma exacerbation treatment. The Ohio Pediatric Asthma Repository is a unique statewide resource to conduct observational, comparative effectiveness, and ultimately intervention studies for pediatric asthma.

### Division Publications


2. Biagini Myers JM, Martin LJ, Kovacic MB, Mersha TB, He H, Pilipenko V, Lindsey MA, Erickson MB, Bernstein DI,
LeMasters GK, Lockey JE, Khurana Hershey GK. Epistasis between serine protease inhibitor Kazal-type 5 (SPINK5) and thymic stromal lymphopoietin (TSLP) genes contributes to childhood asthma. J Allergy Clin Immunol. 2014; 134:891-899 e3.


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**Faculty, Staff, and Trainees**

**Faculty Members**

**Gurjit Khurana Hershey, MD, PhD**, Professor  
**Leadership** Division Director; Kindervelt Endowed Chair; Director, Medical Scientist Training Program; Co-Director, Office of Pediatric Clinical Fellowships  
**Research Interests** Integrating clinical, translational, & basic research to identify genetic and environmental factors that promote asthma, delineate the mechanisms underlying their contributions and develop new strategies for asthma prevention, management & treatment.

**Jocelyn Biagini Myers, PhD**, Assistant Professor  
**Leadership** Treasurer, Cincinnati Children’s Women’s Faculty Association  
**Research Interests** The role of genetics and environmental exposures in pediatric asthma.

**Melinda Butsch Kovacic, MPH, PhD**, Associate Professor  
**Leadership** President, Cincinnati Children’s Women’s Faculty Association  
**Research Interests** Using classical and molecular epidemiological and community-based approaches to evaluate environmental and socioeconomic causes of chronic disease with current focuses on asthma and Fanconi anemia.

**Weiguo Chen, MD, PhD**, Assistant Professor  
**Research Interests** Mechanisms underlying airway hyperresponsiveness, inflammation and remodeling of allergic asthma.

**Hong Ji, PhD**, Assistant Professor  
**Leadership** Director, Pyrosequencing Core  
**Research Interests** Epigenetic plasticity of development and disease; asthma epigenetics; environmental epigenetics; genome-wide and locus specific DNA methylation analysis; epigenetic regulation of gene expression.

**Tesfaye Mersha, PhD**, Assistant Professor  
**Research Interests** Integrating and using genomics, statistical genetics, biological profiling and pathway methods to elucidate the genetic architecture of complex diseases of public significance, including asthma.
Umasundari Sivaprasad, PhD, Assistant Professor

Research Interests Allergic inflammation; atopic dermatitis; asthma; development of anti-inflammatory therapies.

Joint Appointment Faculty Members

Melinda Mahabee-Gittens, MD, Professor (Emergency Medicine)
Research Interests Smoking cessation.

Trainees

- Jayeeta Roychoudhury, PhD, Washington University School of Medicine-St. Louis
- Eric Brandt, PhD, Institut Pasteur de Lille, France
- Lili Ding, PhD, University of Cincinnati
- Zonghua Zhang, MD, Vanderbilt University
- Chang Xiao, MD, PhD, University of Cincinnati
- Hanna Johansson, PhD, University of Cincinnati
- Siddhartha Yavvari, MS, University of Cincinnati
- Esmond Geh, PhD, University of Cincinnati

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Grants, Contracts, and Industry Agreements

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<td>Fanconi Anemia as a Model for Susceptibility to Human Papillomavirus Infection</td>
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The Role of Tet1 in Childhood Asthma
National Institutes of Health
R21 AI119236 5/1/2015-4/30/2017 $150,000

Xiao, C
Molecular Epidemiology in Children's Environmental Health Training Program
National Institutes of Health (University of Cincinnati)
T32 ES010957 7/1/2014-6/30/2016 $47,244

Zhang, Z
Molecular Epidemiology in Children's Environmental Health Training Program
National Institutes of Health (University of Cincinnati)
T32 ES010957 09/01/2014-08/31/2015 $42,580

Current Year Direct $1,943,336
Total $1,943,336
Asthma specialists may one day be able to use a biomarker to more easily identify and treat children whose asthma attacks do not respond well to commonly prescribed corticosteroids.

The discovery of the biomarker VNN-1, reported April 21, 2014, in *The Journal of Allergy and Clinical Immunology*, provides a genetic basis for understanding why some children with asthma respond effectively to medicines that control underlying inflammation — and why other children do not. It also holds out hope that difficult-to-treat patients can be identified quickly, and that researchers can find better therapies for asthma, which affects seven million children in the U.S.

Gurjit Khurana Hershey, MD, PhD, Director of Asthma Research, and her team collected and tested cells from the nasal passages of 57 children whose emergency room visits for acute asthma required hospitalization. From a list of 20,000 gene candidates, doctors singled out and tested one gene, vanin-1 or VNN1, as the primary target for their study.

According to Hershey, expression of the VNN-1 gene helps discriminate between good and poor responders to corticosteroids.

Laboratory tests showed that VNN-1 expression is required for inhaled corticosteroids to provide relief during an asthma attack. Children whose asthma did not respond well to corticosteroids exhibited a biochemical variation of VNN-1 that hindered its expression. Subsequent tests on laboratory mouse models of asthma suggested that targeting the VNN-1 pathway therapeutically might be valuable for improving outcomes for difficult-to-treat patients.
Asthma affects seven million children in the U.S.

In this proposed model, the VNN1 gene is modestly expressed at baseline and this level of expression is not altered in patients with stable or acute asthma. Corticosteroid treatment for an exacerbation induces DNA methylation at the CpG4 site of the VNN1 gene promoter, enhancing expression of the VNN1 gene. Enhanced VNN1 expression contributes to optimal response to corticosteroid treatment.