Cincinnati Children's

2015 Research Annual Report

Asthma Research

RESEARCH AND TRAINING DETAILS

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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 afflicts 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 immunotherapie (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

Xiao C, **Biagini Myers JM**, **Ji H**, Metz K, Martin LJ, Lindsey M, He H, Powers R, Ulm A, Ruff B, Ericksen MB, Somineni HK, Simmons J, Strait RT, Kercsmar CM, **Khurana Hershey GK**. Vanin-1 Expression and Methylation Discriminate Pediatric Asthma Corticosteroid Treatment Response. *J Allergy Clin Immunol*. 2015 Mar 28. Epub ahead of print.

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.

Ji H, Zhang X, Oh S, Mayhew CN, Ulm A, Somineni HK, Ericksen M, Wells JM, **Khurana Hershey GK**. Dynamic Transcriptional and Epigenomic Reprograming from Pediatric Nasal Epithelial Cells to Induced Pluripotent Stem Cells. *J Allergy Clin Immunol*. 2015 Jan;135(1):236-44.

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.

Biagini Myers JM, Simmons JM, Kercsmar CM, Martin LJ, Pilipenko VV, Austin SR, Lindsey MA, Amalfitano KM, Guilbert TW, McCoy KS, Forbis SG, McBride JT, Ross KR, Vauthy PA, **Khurana Hershey GK**. Heterogeneity in asthma care in a state-wide collaborative: the Ohio Pediatric Asthma Repository. *Pediatrics*. 2015 Feb;135(2)271-9.

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

1. Amin P, Levin L, Epstein T, Ryan P, LeMasters G, Khurana Hershey G, Reponen T, Villareal M, Lockey J, Bernstein DI. **Optimum predictors of childhood asthma: persistent wheeze or the Asthma Predictive Index?**. *J Allergy Clin Immunol Pract*. 2014; 2:709-15.

2. Biagini Myers JM, Martin LJ, Kovacic MB, Mersha TB, He H, Pilipenko V, Lindsey MA, Ericksen 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.

3. Biagini Myers JM, Simmons JM, Kercsmar CM, Martin LJ, Pilipenko VV, Austin SR, Lindsey MA, Amalfitano KM, Guilbert TW, McCoy KS, Forbis SG, McBride JT, Ross KR, Vauthy PA, Khurana Hershey GK. **Heterogeneity in asthma care in a statewide collaborative: the Ohio Pediatric Asthma Repository**. *Pediatrics*. 2015; 135:271-9.

4. Cheng G, Smith AM, Levin L, Epstein T, Ryan PH, LeMasters GK, Khurana Hershey GK, Reponen T, Villareal M, Lockey J, Bernstein DI. **Duration of day care attendance during infancy predicts asthma at the age of seven: the Cincinnati Childhood Allergy and Air Pollution Study**. *Clin Exp Allergy*. 2014; 44:1274-81.

5. Codispoti CD, Bernstein DI, Levin L, Reponen T, Ryan PH, Biagini Myers JM, Villareal M, Burkle J, Lummus Z, Lockey JE, Khurana Hershey GK, LeMasters GK. **Early-life mold and tree sensitivity is associated with allergic eosinophilic rhinitis at 4 years of age**. *Ann Allergy Asthma Immunol*. 2015; 114:193-198 e4.

6. Codispoti CD, LeMasters GK, Levin L, Reponen T, Ryan PH, Biagini Myers JM, Villareal M, Burkle J, Evans S, Lockey JE, Khurana Hershey GK, Bernstein DI. **Traffic pollution is associated with early childhood aeroallergen sensitization**. *Ann Allergy Asthma Immunol*. 2015; 114:126-33.

7. Ji H, Zhang X, Oh S, Mayhew CN, Ulm A, Somineni HK, Ericksen M, Wells JM, Khurana Hershey GK. **Dynamic transcriptional and epigenomic reprogramming from pediatric nasal epithelial cells to induced pluripotent stem cells**. *J Allergy Clin Immunol*. 2015; 135:236-44.

8. Katzenellenbogen RA, Carter JJ, Stern JE, Butsch Kovacic MS, Mehta PA, Sauter SL, Galloway DA, Winer RL. **Skin and mucosal human papillomavirus seroprevalence in persons with fanconi anemia**. *Clin Vaccine Immunol*. 2015; 22:413-20.

9. Kovacic MB, Stigler S, Smith A, Kidd A, Vaughn LM. **Beginning a partnership with PhotoVoice to explore environmental health and health inequities in minority communities**. *Int J Environ Res Public Health*. 2014; 11:11132-51.

10. LeMasters G, Levin L, Bernstein DI, Lockey SDt, Lockey JE, Burkle J, Khurana Hershey GK, Brunst K, Ryan PH. **Secondhand smoke and traffic exhaust confer opposing risks for asthma in normal and overweight children**. *Obesity (Silver Spring)*. 2015; 23:32-6.

11. LeMasters GK, Khurana Hershey GK, Sivaprasad U, Martin LJ, Pilipenko V, Ericksen MB, Burkle JW, Lindsey MA, Bernstein DI, Lockey JE, Gareri J, Lubetsky A, Koren G, Biagini Myers JM. **N-acetyltransferase 1 polymorphism increases cotinine levels in Caucasian children exposed to secondhand smoke: the CCAAPS birth cohort**. *Pharmacogenomics J*. 2015; 15:189-95.

12. Liu B, Lee JB, Chen CY, Hershey GK, Wang YH. **Collaborative interactions between type 2 innate lymphoid cells and antigen-specific CD4+ Th2 cells exacerbate murine allergic airway diseases with prominent eosinophilia**. *J Immunol*. 2015; 194:3583-93.

13. Mersha TB, Abebe T. **Self-reported race/ethnicity in the age of genomic research: its potential impact on understanding health disparities**. *Hum Genomics*. 2015; 9:1.

14. Mersha TB, Ding L, He H, Alexander ES, Zhang X, Kurowski BG, Pilipenko V, Kottyan L, Martin LJ, Fardo DW. **Impact of Population Stratification on Family-Based Association in an Admixed Population**. *Int J Genomics*. 2015; 2015:501617.

15. Sauter SL, Wells SI, Zhang X, Hoskins EE, Davies SM, Myers KC, Mueller R, Panicker G, Unger ER, Sivaprasad U, Brown DR, Mehta PA, Butsch Kovacic M. **Oral human papillomavirus is common in individuals with fanconi anemia**. *Cancer Epidemiol Biomarkers Prev*. 2015; 24:864-72.

16. Sivaprasad U, Kinker KG, Ericksen MB, Lindsey M, Gibson AM, Bass SA, Hershey NS, Deng J, Medvedovic M, Khurana Hershey GK. **SERPINB3/B4 contributes to early inflammation and barrier dysfunction in an experimental murine model of atopic dermatitis**. *J Invest Dermatol*. 2015; 135:160-9.

17. Winer RL, Huang CE, Cherne S, Stern JE, Butsch Kovacic MS, Mehta PA, Sauter SL, Galloway DA, Katzenellenbogen RA. **Detection of human papillomavirus in the oral cavities of persons with Fanconi anemia**. *Oral Dis*. 2015; 21:349-54.

18. Xiao C, Biagini Myers JM, Ji H, Metz K, Martin LJ, Lindsey M, He H, Powers R, Ulm A, Ruff B, Ericksen MB, Somineni HK, Simmons J, Strait RT, Kercsmar CM, Khurana Hershey GK. **Vanin-1 expression and methylation discriminate pediatric asthma corticosteroid treatment response**. *J Allergy Clin Immunol*. 2015; .

19. Zhang X, Ulm A, Somineni HK, Oh S, Weirauch MT, Zhang HX, Chen X, Lehn MA, Janssen EM, Ji H. **DNA methylation dynamics during ex vivo differentiation and maturation of human dendritic cells**. *Epigenetics Chromatin*. 2014; 7:21.

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

Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct

Butsch.Kovacic, M

Fanconi Anemia as a Model for Susceptibility to Human Papillomavirus Infection

National Institutes of Health

R01 HL108102	7/1/2011-6/30/2016	$260,744

Hershey, G

Epithelial Genes in Allergic Inflammation

National Institutes of Health

U19 AI070235	9/1/2011-8/31/2016	$1,050,055

Inner City Asthma Center

National Institutes of Health (University of Wisconsin-Madison)

UM1 AI114271	8/5/2014-7/31/2015	$392,713

Ji, H

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**

Genetic Biomarker Opens Doors to New Therapies for Hard-to-Treat Asthma

Gurjit Khurana Hershey, MD, PhD

PUBLISHED ONLINE APRIL 21, 2014
The Journal of Allergy and Clinical Immunology

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.

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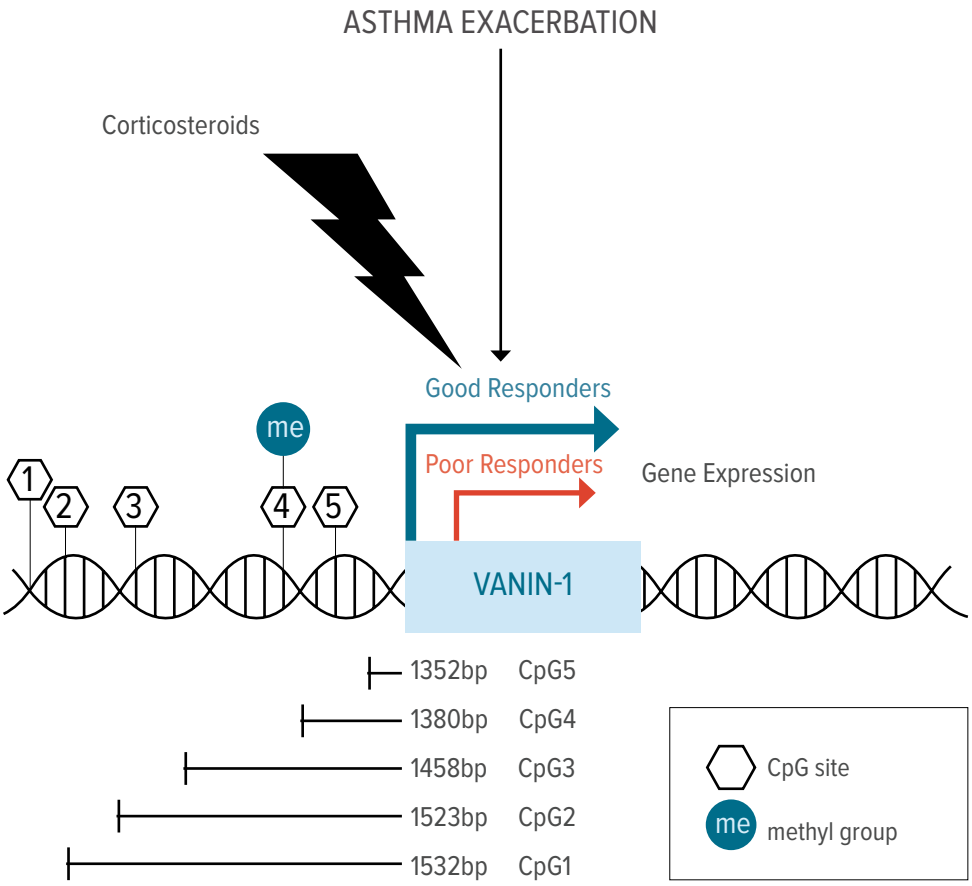
Xiao C, Biagini Myers JM, Ji H, Metz K, Martin LJ, Lindsey M, He H, Powers R, Ulm A, Ruff B, Ericksen MB, Somineni HK, Simmons J, Strait RT, Kercsmar CM, Khurana Hershey GK. Vanin-1 expression and methylation discriminate pediatric asthma corticosteroid treatment response. *J Allergy Clin Immunol.* 2015



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.

Asthma affects seven million children in the U.S.