

# Asthma Research

## Division Details

### RESEARCH AND TRAINING DETAILS

Faculty	5
Research Fellows and Post Docs	6
Research Graduate Students	1
Total Annual Grant Award Dollars	\$4,006,732
Total Publications	23



Row 1: V Yadagiri, H Ji, G Khurana Hershey

Row 2: T Mersha, S Kirk, C Malott, A Baatyrbek Kyzy, K Titus, B Grashel, Z Zhang, K Grise, A Witt

Row 3: J Burleson, S Sauter, H Johansson, V Kholi, P Bolcas, G Hill, S Austin, E Brandt, C Perkins, J Biagini Myers, M Butsch Kovacic, T Baker, S Ghandikota

## Research Highlights

### Biomarker of Poor Steroid Treatment Responders: Gurjit Khurana Hershey, MD, PhD

In 2016, the Adare Drug Repurposing and Optimization Innovation Fund selected [Dr. Khurana Hershey, MD, PhD](#), and colleagues as recipients. Her laboratory previously identified a genetic basis for understanding why some children with asthma respond effectively to medicines that control underlying inflammation—and why other children do not. Based on these findings, they will evaluate an already approved FDA drug for use in pediatric asthma. They will develop a point-of-care, rapid and reliable clinical assay, optimize desired treatment goal concentrations by establishing normative ranges and prepare to repurpose the drug for indication in asthmatics.

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

[Gurjit Khurana Hershey, MD, PhD](#), is the primary investigator of an ongoing [NIH-funded Asthma and Allergic Diseases Cooperative Research Center \(AACRC\)](#) U19, currently in its 11th year. The Cincinnati center is one of only 11 centers in the United States, and in 2016, the grant received a five year renewal. This multi-project grant focuses on delineating the role of epithelial genes in allergic inflammation. The grant includes three integrated and synergistic projects focused on epithelial cell biology to study multiple end-organs involved in allergic responses (e.g. skin, lung, gut, and esophagus). These projects will provide novel insights into a key unanswered question in the allergy field: Why is allergic inflammation restricted to one tissue in some cases, while it progresses to involve additional tissues in other individuals? As a part of this project, we will recruit 500 toddlers with atopic dermatitis and follow them over five years in the Mechanisms of Progression of Atopic Dermatitis to Asthma (M-PAACH) cohort. This new cohort will be the first of its kind in the US, and only the second atopic dermatitis cohort worldwide. M-PAACH will enable us to better understand the pathogenesis of atopic

dermatitis and asthma phenotypes including their natural history, and specifically the mechanisms of progression and persistence/remission.

## Children's Studies Inner City Asthma: Gurjit Khurana Hershey, MD, PhD

Cincinnati Children's is one of nine contracted clinical research sites funded to study the treatment and prevention of asthma in inner-city asthma populations by conducting several clinical trials and mechanistic studies in order to understand the immunopathogenesis of the disease and to evaluate and develop effective interventions tailored to inner-city populations. [Dr. Gurjit Khurana Hershey, PhD](#), is the PI of the Inner City Asthma Consortium (ICAC) at the Cincinnati site. The goals of this study are: 1) improving asthma control; 2) improving asthma phenotyping using biomarkers; 3) developing allergen immunotherapy approaches for cockroach allergy; 4) designing and conducting mechanistic studies involving human subjects with the goal of elucidating the immunopathogenesis of asthma in the inner-city; 5) developing, validating and implementing basic science methodology to support the studies conducted under the above objectives. ICAC is the nation's largest effort to study asthma in the inner city. To date, Cincinnati Children's has participated in seven ICAC clinical trial studies, including three that are currently enrolling, and we look forward to participating in many more in the years to come.

## Unraveling Ancestry and Environmental Exposure Interactions in Childhood Asthma

[Dr. Tesfaye Mersha, PhD](#), awarded a 3.4 million dollar grant from the [National Institutes of Health](#), will use this to study the relationship between ancestry and environmental exposure and how they play a role in childhood asthma. Specifically, this study, designed to uncover fundamental information about whether individual genetic ancestry and selected environmental exposure factors, as well as their interactions, can affect asthma risk and prediction in an African-American population. Despite advances in asthma care, the burden of asthma is disproportionately high amount minority children, in particular children of African descent (four times more likely to be hospitalized and seven times more likely to die from asthma than non-African Americans).

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## Significant Publications

**Brandt EB, Biagini Myers JM, Acciani TH, Ryan PH, Sivaprasad U, Ruff B, LeMasters GK, Bernstein DI, Lockey JE, LeCras TD, Khurana Hershey GK. Exposure to allergen and diesel exhaust particles potentiates secondary allergen-specific memory responses promoting asthma susceptibility. *J Allergy Clin Immunol*. 2015 Aug;136(2):295-303.e7.**

These findings suggest that DEP exposure results in accumulation of allergen-specific TH2/TH17 cells in the lungs, potentiating secondary allergen recall responses and promoting the development of allergic asthma.

**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, Kercksmar CM, Khurana Hershey GK. Vanin-1 Expression and Methylation Discriminate Pediatric Asthma Corticosteroid Treatment Response. *J Allergy Clin Immunol*. 2015 Oct;136(4):923-31.e3.**

This study identifies a biological basis for poor corticosteroid treatment response used to distinguish a subgroup of asthmatic children who respond poorly to systemic corticosteroid treatment. It concludes 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.

**Butsch Kovacic M, Martin LJ, Biagini Myers JM, He H, Lindsey M, Mersha TB, Ji H, Khurana Hershey GK. Genetic Approach Identifies Distinct Asthma Pathways in Overweight vs. Normal Weight Children. *Allergy*. 2015 Aug;70(8):1028-32.**

This study demonstrates that the underlying heterogeneity of asthma is likely due, in part, to distinct pathogenetic pathways that depend on preceding or comorbid overweight and/or allergy. It is therefore important to consider both obesity and asthma when conducting studies of asthma.

**Somineni HK, Zhang X, Biagini Myers JM, Kovacic MB, Ulm A, Jurcak N, Ryan PH, Khurana Hershey GK, Ji H. TET1 methylation is associated with childhood asthma and traffic-related air pollution. *J Allergy Clin Immunol*. 2016 Mar;137(3):797-805.e5.**

In this study, we sought to examine the association of TET1 methylation with asthma and traffic-related air pollution (TRAP). Our findings suggest a possible role of TET1 methylation in asthmatic patients and response to TRAP.

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## Division Publications

1. Abdel-Hameed EA, Ji H, Shata MT. **Hiv-Induced Epigenetic Alterations in Host Cells.** *Adv Exp Med Biol.* 2016; 879:27-38.
2. Abdel-Hameed EA, Rouster SD, Ji H, Ulm A, Hetta HF, Anwar N, Sherman KE, Shata MT. **Evaluating the Role of Cellular Immune Responses in the Emergence of Hcv Ns3 Resistance Mutations During Protease Inhibitor Therapy.** *Viral Immunol.* 2016; 29:252-8.
3. Brandt E, Khurana Hershey G. **A Combination of Dexamethasone and Anti-IL-17a Treatment Can Alleviate Diesel Exhaust Particle-Induced Steroid Insensitive Asthma.** *J Allergy Clin Immunol.* 2016; 138:924-28.
4. Brandt EB, Biagini Myers JM, Acciani TH, Ryan PH, Sivaprasad U, Ruff B, LeMasters GK, Bernstein DI, Lockey JE, LeCras TD, Khurana Hershey GK. **Exposure to Allergen and Diesel Exhaust Particles Potentiates Secondary Allergen-Specific Memory Responses, Promoting Asthma Susceptibility.** *J Allergy Clin Immunol.* 2015; 136:295-303 e7.
5. Brandt EB, Myers JM, Ryan PH, Hershey GK. **Air Pollution and Allergic Diseases.** *Curr Opin Pediatr.* 2015; 27:724-35.
6. Brunst KJ, Ryan PH, Brokamp C, Bernstein D, Reponen T, Lockey J, Khurana Hershey GK, Levin L, Grinshpun SA, LeMasters G. **Timing and Duration of Traffic-Related Air Pollution Exposure and the Risk for Childhood Wheeze and Asthma.** *Am J Respir Crit Care Med.* 2015; 192:421-7.
7. Butsch Kovacic M, Martin LJ, Biagini Myers JM, He H, Lindsey M, Mersha TB, Khurana Hershey GK. **Genetic Approach Identifies Distinct Asthma Pathways in Overweight Vs Normal Weight Children.** *Allergy.* 2015; 70:1028-32.
8. Ghosh D, Ding L, Sivaprasad U, Geh E, Biagini Myers J, Bernstein JA, Khurana Hershey GK, Mersha TB. **Multiple Transcriptome Data Analysis Reveals Biologically Relevant Atopic Dermatitis Signature Genes and Pathways.** *PLoS One.* 2015; 10:e0144316.
9. Gupta J, Johansson E, Bernstein JA, Chakraborty R, Khurana Hershey GK, Rothenberg ME, Mersha TB. **Resolving the Etiology of Atopic Disorders by Using Genetic Analysis of Racial Ancestry.** *J Allergy Clin Immunol.* 2016; 138:676-99.
10. Hall SL, Baker T, Lajoie S, Richgels PK, Yang Y, McAlees JW, van Lier A, Wills-Karp M, Sivaprasad U, Acciani TH, LeCras TD, Myers JB, Kovacic MB, Lewkowich IP. **IL-17a Enhances IL-13 Activity by Enhancing IL-13-Induced Signal Transducer and Activator of Transcription 6 Activation.** *J Allergy Clin Immunol.* 2016.
11. Klein M, Hershey GK, Devarajan P, Muglia LJ, Wikenheiser-Brokamp KA, Loch J, Hostetter MK, Strauss AW, DeWitt TG. **Enhancing Pediatric Fellows' Research Training: Development of an Office of Pediatric Clinical Fellowships.** *J Pediatr.* 2015; 167:506-7 e1.
12. Maglo KN, Mersha TB, Martin LJ. **Population Genomics and the Statistical Values of Race: An Interdisciplinary Perspective on the Biological Classification of Human Populations and Implications for Clinical Genetic Epidemiological Research.** *Front Genet.* 2016; 7:22.
13. Mersha TB. **Mapping Asthma-Associated Variants in Admixed Populations.** *Front Genet.* 2015; 6:292.
14. Mersha TB, Martin LJ, Biagini Myers JM, Kovacic MB, He H, Lindsey M, Sivaprasad U, Chen W, Khurana Hershey GK. **Genomic Architecture of Asthma Differs by Sex.** *Genomics.* 2015; 106:15-22.
15. Mpollo MSEM, Brandt EB, Shanmukhappa SK, Arumugam PI, Tiwari S, Loberg A, Pillis D, Rizvi T, Lindsey M, Jonck B, Carmeliet P, Kalra VK, Le Cras TD, Ratner N, Wills-Karp M, Hershey GKK, Malik P. **Placenta Growth Factor Augments Airway**

**Hyperresponsiveness Via Leukotrienes and Il-13.** *J Clin Invest.* 2016; 126:571-84.

16. Nanda MK, LeMasters GK, Levin L, Rothenberg ME, Assa'ad AH, Newman N, Bernstein D, Khurana-Hershey G, Lockey JE, Ryan PH. **Allergic Diseases and Internalizing Behaviors in Early Childhood.** *Pediatrics.* 2016; 137.
17. Oh S, Ji H, Barzman D, Lin PI, Hutton J. **Pediatric Asthma and Autism-Genomic Perspectives.** *Clin Transl Med.* 2015; 4:37.
18. Sadhasivam S, Zhang X, Chidambaran V, Mavi J, Pilipenko V, Mersha TB, Meller J, Kaufman KM, Martin LJ, McAuliffe J. **Novel Associations between Faah Genetic Variants and Postoperative Central Opioid-Related Adverse Effects.** *Pharmacogenomics J.* 2015; 15:436-42.
19. Somineni HK, Zhang X, Biagini Myers JM, Kovacic MB, Ulm A, Jurcak N, Ryan PH, Khurana Hershey GK, Ji H. **Ten-Eleven Translocation 1 (Tet1) Methylation Is Associated with Childhood Asthma and Traffic-Related Air Pollution.** *J Allergy Clin Immunol.* 2016; 137:797-805 e5.
20. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ, Jr., Calatroni A, Wildfire JJ, Gergen PJ, Cohen RT, Pongracic JA, Kerckmar CM, Khurana Hershey GK, Gruchalla RS, Liu AH, Zoratti EM, Kattan M, Grindle KA, Gern JE, Busse WW, Szefer SJ. **Preseasonal Treatment with Either Omalizumab or an Inhaled Corticosteroid Boost to Prevent Fall Asthma Exacerbations.** *J Allergy Clin Immunol.* 2015; 136:1476-85.
21. Ulm A, Mayhew CN, Debley J, Khurana Hershey GK, Ji H. **Cultivate Primary Nasal Epithelial Cells from Children and Reprogram into Induced Pluripotent Stem Cells.** *J Vis Exp.* 2016.
22. 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, Kerckmar CM, Khurana Hershey GK. **Vanin-1 Expression and Methylation Discriminate Pediatric Asthma Corticosteroid Treatment Response.** *J Allergy Clin Immunol.* 2015; 136:923-31 e3.
23. Zhang Z, Biagini Myers JM, Brandt EB, Ryan PH, Lindsey M, Mintz-Cole RA, Reponen T, Vesper SJ, Forde F, Ruff B, Bass SA, LeMasters GK, Bernstein DI, Lockey J, Budelsky AL, Khurana Hershey GK. **B-Glucan Exacerbates Allergic Asthma Independent of Fungal Sensitization and Promotes Steroid-Resistant Th2/Th17 Responses.** *J Allergy Clin Immunol.* 2016.

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## Grants, Contracts, and Industry Agreements

### Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Melinda Butsch Kovacic, PHD	Fanconi Anemia as a Model for Susceptibility to Human Papillomavirus Infection	National Institutes of Health	R01 HL108102	7/1/2011 - 6/30/2017	\$376,453
Gurjit Khurana Hershey, MD- PHD	Ohio Children's Hospital Asthma Task Force	Ohio Department of Medicaid (ODM) (Ohio Children's Hospital Association Fdn)	OCHAF- ODM	7/1/2015 - 6/30/2017	\$500,000
Gurjit Khurana Hershey, MD- PHD	Epithelial Genes in Allergic Inflammation	National Institutes of Health	U19 AI070235	9/1/2011 - 8/31/2016	\$1,389,901
Gurjit Khurana Hershey, MD- PHD	Inner City Asthma Consortium 3	National Institutes of Health (University of Wisconsin- Madison)	UM1 AI114271	8/5/2014 - 7/31/2021	\$766,586
Hong Ji, PHD	Epigenetic Programming of Innate Immunity in Pediatric Airway Epithelium	National Institutes of Health (U.C. Davis Medical Center)	R21 AI116129	7/15/2015 - 6/30/2017	\$26,575

Hong Ji, PHD	The Role of Tet1 in Childhood Asthma	National Institutes of Health	R21 AI119236	5/1/2015 - 4/30/2017	\$195,000
Tesfaye B Mersha, PHD	Unraveling Ancestry and Environmental Exposure Interactions in Childhood Asthma	National Institutes of Health	R01 HL132344	4/1/2016 - 3/31/2021	\$701,121
Zhonghua Zhang	Molecular Epidemiology in Children's Environmental Health Training Program	National Institutes of Health (University of Cincinnati)	T32 ES010957	9/1/2012 - 8/31/2015	\$51,096

**Total Annual Grant Award Dollars**

**\$4,006,732**