

Division Photo



U. Sivaprasad, C. Chen, G. Khurana Hershey, M. Butsch Kovacic, T. Mersha

Division Data Summary

Research and Training Details

Number of Faculty	5
Number of Joint Appointment Faculty	1
Number of Research Fellows	1
Number of Research Students	2
Number of Support Personnel	6
Direct Annual Grant Support	\$1,393,901
Peer Reviewed Publications	10

Clinical Activities and Training

Number of Clinical Staff	1
Number of Clinical Fellows	1
Number of Clinical Students	1
Number of Other Students	6
Outpatient Encounters	600

Significant Publications

Salma M.A. MUSAAD, Tia Patterson, Mark Ericksen, Mark Lindsey, Kim Dietrich, Paul Succop, and Gurjit K. Khurana Hershey. Comparison of Anthropometric Measures of Obesity in Childhood Asthma. *J Allergy Clin Immunol.* 2009 Jun;123(6):1321-7.e12.

The analysis revealed that measures of central obesity are more associated with the presence of asthma and asthma severity in children with allergic rhinitis when compared with standard BMI measures.

Kathy T.Schroer, Jocelyn M. Biagini, Patrick H. Ryan, Grace K. LeMasters, David I. Bernstein, Manuel Villareal, James E. Lockey, Tiina Reponen, Sergey Grinshpun, and Gurjit K. Khurana Hershey. Interactions Between Oxidative Stress and Glutathione S-1 transferase P1 on Persistent Wheezing in a Birth Cohort. J Pediatr. Mar;154(3)401-8, 2009.

This study concluded that there is evidence for an environmental effect of DEP among carriers of the GST-P1 Val(105) allele in the development of persistent wheezing in children. The protective effect of the GST-P1 Ile(105) genotype may be overwhelmed by multiple environmental exposures that converge on oxidative stress pathways.

Weiguo Chen, Yasuhiro Tabata, Aaron M. Gibson, Michael O. Daines, Manoj R. Warriar, Marsha Wills-Karp, and Gurjit K. Khurana Hershey. Matrix metalloproteinase-8 contributes to solubilization of interleukin-13 receptor alpha-2 in vivo. J Allergy Clin Immunol. 2008 Sep;122(3):625-32. Epub 2008 Aug 9.

Among several MMPs tested, only MMP-8 cleaved IL-13R alpha 2. Treatment of transfected human or murine cells expressing high levels of surface IL-13R alpha 2 with MMP-8 resulted in release of soluble IL-13R alpha 2 into the supernatants, with a concomitant decrease in surface IL-13R alpha 2 levels. The IL-13R alpha 2 solubilized by MMP-8 retained IL-13 binding activity. In an asthma model MMP-8-deficient mice displayed increased airway hyperresponsiveness and decreased soluble IL-13R alpha 2 protein levels in bronchoalveolar lavage fluid compared with those seen in wild-type mice after house dust mite challenge. This revealed that MMP-8 cleaves IL-13R alpha 2 in vitro and contributes to the solubilization of IL-13R alpha 2 in vivo.

Division Highlights

Gurjit Khurana Hershey, MD, PhD

Dr. Khurana Hershey is the PI of the NIH funded Asthma and Allergic Diseases Cooperative Research Center. In addition, she has several ongoing NIH funded projects focused on elucidating the genetic and environmental factors that contribute to the development of asthma and dissecting the mechanisms by which they confer their contributions. The Division of Asthma Research was selected by the Kindervelt organization for a 4 year commitment of support and Dr. Khurana Hershey was named the Kindervelt Endowed Chair in Asthma Research. Dr. Khurana Hershey was also appointed as the new Associate Director of Physician Scientist Training Program at the University of Cincinnati. She serves on a regular NIH Study section panel. This year, Dr. Khurana Hershey has worked on several research projects leading to several new collaborations, including Pulmonary Biology, Immunobiology, Emergency Medicine, and General and Community Pediatrics. In addition, Dr. Khurana Hershey graduated from the Executive Leadership in Academic Medicine Program in April of this year.

Melinda Butsch Kovacic, PhD

As part of her recently funded NIH R21, Dr. Butsch Kovacic is evaluating the association between exposure to diesel exhaust particles and products of systemic oxidative stress among children with asthma with Dr. Tianying Wu at UC. Identifying fluorescent plasma oxidation products as biomarkers that can predict asthma severity is highly innovative, as these findings could suggest preventive interventions to reduce asthma morbidity and mortality. Dr. Butsch Kovacic is also a collaborator with Drs. Susanne Wells and Stella Davies on a grant from the Fanconi Anemia Research Foundation. The goal of this study is better understand the role of human papillomavirus infection in Fanconi anemia patients. She serves on the national AAAAI Genetics, Molecular Biology & Epidemiology Committee.

Weiguo Chen, MD, PhD

Dr. Chen's current research involves: 1) the biological role of interleukin-13 receptor alpha2 in the development of allergic asthma 2) Asymmetric dimethylarginine (ADMA)/dimethylarginine dimethylaminohydrolase (DDAH) pathway and allergic asthma. Dr. Chen is also participating in collaborative research with Immunobiology and Pulmonary Biology. ->

Tesfaye Mersha, PhD

Tesfaye is a newly recruited Asthma Research Faculty member focusing on research in the area of Human Genetics. His current research projects include: 1) the study of Admixture mapping in African American asthmatic population with Dr. Ranajit Chakraborty at UC. The overall purpose of this project is to develop and evaluate an efficient approach to localize asthma liability genes in an admixed African American population; 2) a comprehensive expression profiling study to identify the genes and regulatory networks that impact the atopic dermatitis (AD) phenotype.

Umasundari Sivaprasad, PhD

Dr. Sivaprasad's current research projects include: 1) Elucidating the role of serpins in asthma 2) Elucidating the role

of IL-13R alpha2 in atopic dermatitis. She has ongoing collaborations including with investigators at the University of Pittsburgh, as well as investigators at CCHMC in Pulmonary Biology, Immunobiology, and Pathology. Her work has been submitted for publication and for additional funding. Uma gave several presentations to various Kindervelt local chapters on her current research on asthma this year and has participated in judging several scientific poster sessions at CCHMC,UC, and various high schools.

Division Collaboration

Collaboration with Allergy/Immunology; Epidemiology and Biostatistics; Immunobiology

Collaborating Faculty: Marc Rothenberg, MD, PhD; Lisa Martin, PhD; Marsha Wills-Karp, PhD

Asthma and Allergic Diseases Cooperative Research Centers

Collaboration with Immunobiology; Allergy/Immunology

Collaborating Faculty: Marsha Wills-Karp, PhD; Fred Finkelman, PhD; Marc Rothenberg, MD, PhD

Program Project Grant

Collaboration with Immunobiology

Collaborating Faculty: Fred Finkelman, PhD

Biology of IL-13 Receptor Alpha 2

Collaboration with Emergency Medicine; Pulmonary Medicine; General & Community Pediatrics; Adherence Psychology ; Biomedical Informatics; Allergy/Immunology

Collaborating Faculty: Richard Ruddy, MD; Rick Strait, MD; Laurie Johnson, MD; Carolyn Kercksmar, MD; Jeffrey Simmons, MD; Rob Kahn, MD; Dennis Drotar, PhD; Bruce Aronow, PhD; Kelly Metz, MD

Gene Expression Profiles of Acute Asthma Study

Collaboration with Pulmonary Medicine

Collaborating Faculty: Carolyn Kercksmar, MD

The Asthma Center; Clinical Centers for the NHLBI Networks; Development of an Asthma Research Core Center

Collaboration with Neonatology/Pulmonary Biology

Collaborating Faculty: Tim LeCras

Impact of Early Life Diesel Exposure on Immune Patterning and Lung Structure/Function

Collaboration with Hematology/Oncology

Collaborating Faculty: Susanne Wells; Stella Davies; Parinda Mehta

HPV prevalence studies in Fanconi Anemia Population

Collaboration with

Collaborating Faculty:

Faculty Members

Gurjit Khurana Hershey, MD, PhD, Professor ; *Division Director*

Melinda Butsch Kovacic, MPH, PhD, Research Assistant Professor

Weiguo Chen, MD, PhD, Research Assistant Professor

Tesfaye Mersha, PhD, Research Assistant Professor

Umasundari Sivaprasad, PhD, Research Assistant Professor

Trainees

- **Kathy Schroer, PhD**, PL-5, University of Cincinnati
- **Kelly Metz, MD**, PGY4, University of Cincinnati
- **Tolly Epstein, MD**, PGY4, University of Cincinnati
- **Rachael Mintz-Cole, BS**, PL-2, University of Cincinnati
- **Jayanta Gupta, MD/PhD**, PGY2, University of Cincinnati
- **Gerald Lee, MD**, PGY2, University of Cincinnati
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Significant Accomplishments

U19 Asthma and Allergic Diseases Cooperative Research Center

The Division of Asthma Research and Dr. Khurana Hershey received one of only 14 NIH-funded Asthma and Allergic Diseases Cooperative Research Center grants. As part of this grant, we are working to identify epithelial genes important in allergic inflammation. Asthma, a chronic inflammatory disorder of the airways, is estimated by the World Health Organization to affect 150 million people worldwide and its global pharmacotherapeutic costs exceed \$5 billion per year. Although asthma patients share similar symptoms, the disease is heterogenous in terms of phenotypes and natural history, stemming largely from genetic variation. This heterogeneity contributes to the difficulty in studying and treating asthma. In children, asthma remains the leading cause of emergency care and hospitalization. Nearly two-thirds of asthmatic children reported at least one attack in the previous year highlighting suboptimal disease management in this age group. Epithelial cells have recently been implicated as critical initiators of allergic inflammation and asthma. However, relevant epithelial candidate genes for asthma have not been identified. To address this, we developed a novel unbiased method that collectively took advantage of available nasal epithelial RNA expression arrays from asthmatics and controls, the HapMap database and published literature. Using this approach, we identified six candidate genes and customized an Illumina Golden Gate assay that included their non-synonymous and tagging SNPs. We then genotyped 1,152 children enrolled in the Greater Cincinnati Pediatric Clinic Repository. We evaluated the association of each genetic variant with asthma and allergic disease and using recursive partitioning, identified the combination of SNPs within all six genes that best predicts asthma risk. The results collectively substantiate the validity of our gene selection approach and identified *KIF3A* as a new childhood asthma and allergic disease susceptibility gene.

Identification of Biomarkers of Oxidative Stress in Childhood Asthma

The Division of Asthma Research and Dr. Butsch Kovacic were granted an R21 grant from the NIH to identify biomarkers of diesel exhaust particle (DEP) induced oxidative stress in asthma. Our group recently reported a dose response relationship with DEP exposure and wheeze in a birth cohort. Similarly, other investigators have found associations between asthma and traffic-related particulate matter. However, the mechanisms by which DEP contribute to asthma development and exacerbation are not well understood. DEP contain compounds which induce oxidative stress by causing inflammatory cells to generate reactive oxygen species (ROS). Inhaled DEP produce ROS in the lungs of mice contributing to protein and lipid oxidation, DNA damage in epithelial cells and macrophages, and activate the nuclear factor-kappa B signaling pathway. Although oxidative stress is generally accepted as a determinant of asthma, **reliable and consistent methods to quantify biologically relevant products of oxidative stress are lacking**. Assessments typically involve measurement of a single oxidation product (i.e. protein, lipid or DNA) in bronchoalveolar lavage fluid, exhaled air, sputum, or blood. As organic compounds in DEP generate ROS through multiple pathways, concurrent measurement of systemic oxidative stress products from multiple sources would likely better reflect DEP exposure. Importantly, individuals exposed to equal levels of ambient DEP may experience very different biologic consequences. To date, there are no established biomarkers distinguishing between actual DEP exposure in one child and biologically relevant exposure in another. Our preliminary data suggest that fluorescent plasma oxidation products (FPOP), a global systemic measure of oxidative stress from multiple pathways may be most relevant. We will determine whether high levels of DEP exposure are associated with a significant increase in FPOP and whether this measurement will better predict risk of childhood asthma.

Identification of SerpinB4 as a key regulator of mucus production in asthma

Asthma is a major public health burden worldwide. Excessive mucus production and mucus plugging is a key pathologic feature of asthma, yet the mechanisms responsible for mucus production remain largely unknown and therapies to effectively target mucus hypersecretion are lacking. We recently found that the serine protease inhibitor, SERPINB4, is strongly induced in respiratory epithelial cells of children with asthma. In a mouse asthma model, house dust mite-induced airway hyperresponsiveness (AHR) was attenuated in Serpinb3a (mouse homolog of SERPINB4) deficient mice. Mucus production and goblet cell hyperplasia were significantly decreased, as were induction of SPDEF and FOXA3, transcription factors associated with goblet cell differentiation. IL-13 induced AHR and mucus production was attenuated in Serpinb3a null mice. Microarray analysis revealed that the Serpinb3a modulates the expression of multiple genes that regulate mucus production. Our study has demonstrated a key role for Serpinb3a in regulating mucus production. Excessive mucus production is a key pathologic feature of asthma and contributes to plugging of small airways. Current asthma therapies primarily target inflammation and bronchoconstriction. SERPINB4 may be an important new target for therapeutic intervention to specifically target mucus production, and may have some anti-inflammatory effects as well. There are several other conditions, such as viral infection, chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF), in which mucus accumulation significantly contributes to the disease phenotype. Given our observations in asthma, Serpinb3a may regulate mucus production in these other conditions as well.

Division Publications

1. Baye TM, Tiwari HK, Allison DB, Go RC. [Database mining for selection of SNP markers useful in admixture mapping](#). *BioData Min.* 2009; 2: 1.
2. Iossifova YY, Reponen T, Ryan PH, Levin L, Bernstein DI, Lockey JE, Hershey GK, Villareal M, LeMasters G. [Mold exposure during infancy as a predictor of potential asthma development](#). *Ann Allergy Asthma Immunol.* 2009; 102: 131-7.
3. Metz KA, Johnson T, Hershey GK, Lierl MB, Seidu L, Burns K, Assa'ad A. [Successful administration of cytarabine in a 16-month-old girl with acute myelogenous leukemia and cytarabine syndrome](#). *Ann Allergy Asthma Immunol.* 2009; 102: 173-4.
4. Brandt EB, Munitz A, Orekov T, Mingler MK, McBride M, Finkelman FD, Rothenberg ME. [Targeting IL-4/IL-13 signaling to alleviate oral allergen-induced diarrhea](#). *J Allergy Clin Immunol.* 2009; 123: 53-8.
5. Musaad SM, Patterson T, Ericksen M, Lindsey M, Dietrich K, Succop P, Khurana Hershey GK. [Comparison of anthropometric measures of obesity in childhood allergic asthma: central obesity is most relevant](#). *J Allergy Clin Immunol.* 2009; 123: 1321-7 e12.
6. Jie HB, Yim D, Kim YB. [Porcine Fc gammaRIII isoforms are generated by alternative splicing](#). *Mol Immunol.* 2009; 46: 1189-94.
7. Newcomb DC, Zhou W, Moore ML, Goleniewska K, Hershey GK, Kolls JK, Peebles RS, Jr.. [A functional IL-13 receptor is expressed on polarized murine CD4+ Th17 cells and IL-13 signaling attenuates Th17 cytokine production](#). *J Immunol.* 2009; 182: 5317-21.
8. Kovacic MB, Katki HA, Kreimer AR, Sherman ME. [Epidemiologic analysis of histologic cervical inflammation: relationship to human papillomavirus infections](#). *Hum Pathol.* 2008; 39: 1088-95.
9. Baye TM, Zhang Y, Smith E, Hillard CJ, Gunnell J, Myklebust J, James R, Kisebah AH, Olivier M, Wilke RA. [Genetic variation in cannabinoid receptor 1 \(CNR1\) is associated with derangements in lipid homeostasis, independent of body mass index](#). *Pharmacogenomics.* 2008; 9: 1647-56.
10. Chen W, Tabata Y, Gibson AM, Daines MO, Warriar MR, Wills-Karp M, Hershey GK. [Matrix metalloproteinase 8 contributes to solubilization of IL-13 receptor alpha2 in vivo](#). *J Allergy Clin Immunol.* 2008; 122: 625-32.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards

Annual Direct / Project Period Direct

BUTSCH-KOVACIC, M

Exposure-Induced Systemic Oxidative Stress in Children with Asthma

National Institutes of Health

R21 ES 016830

06/01/09 - 05/31/11

\$150,000 / \$275,000

HERSHEY, G

Genetic Susceptibility for Occupational Asthma

National Institutes of Health (University of Cincinnati)

R01 OH 008795

09/01/06 - 08/31/10

\$49,642 / \$179,424

Epithelial Genes in Allergic Inflammation

National Institutes of Health

U19 AI 070235

09/15/06 - 08/31/11

\$688,288 / \$3,567,767

Hershey, G

Administrative Core

37,418

Nick, T

Scientific Core

79,250

Hershey, G

Project 1

191,630

Rothenberg, M

Project 2

189,963

Wills-Karp

Project 3

190,027

Role of IL-13 Receptors in Atopic Dermatitis

National Institutes of Health

R01 AR 054490

09/01/07 - 07/31/12

\$210,700 / \$1,075,000

Diesel, Allergens and Gene Interaction in Child Atopy

National Institutes of Health (University of Cincinnati)

R01 ES 011170

07/01/07 - 06/30/09

\$13,893 / \$27,574

Interleukin-13 in Experimental Asthma

National Institutes of Health

P01 HL076383

06/30/04 - 07/01/11

\$281,378 / \$1,360,000

Current Year Direct

\$1,393,901

Total \$1,393,901
