**Significant Publications**

Evidence is provided that the esophagus produces local antibodies in eosinophilic esophagitis.

This study demonstrates the pathogenicity of the T435M mutation and illustrates, for the first time, the critical role of
the human perforin C2 domain for calcium-dependent, cytotoxic function.


This study revealed that activation of Siglec-F, an eosinophil receptor that leads to apoptosis, results in reduction of blood and tissue eosinophils in vivo. As such, this may be one approach to target eosinophils in eosinophil-mediated diseases.


This work demonstrates the role of the secreted protein periostin in eosinophilic diseases by increasing the adhesion of eosinophils to the extracellular matrix and may thus facilitate eosinophil migration into the tissue.


The data demonstrates that intestinal macrophage and epithelial cell-derived eotaxin-1 play a critical role in the regulation of eosinophil recruitment in colonic eosinophilic disease such as pediatric ulcerative colitis (UC) and provides a basis for targeting the eosinophil/eotaxin-1 axis in UC.

**Division Highlights**

**Marc E. Rothenberg, MD, PhD**

The Rothenberg laboratory is focused on elucidating the mechanisms of allergic responses especially in mucosal tissues such as the lung and the gastrointestinal tract. The goal of the research is to identify novel pharmaceutical targets for the treatment of patients with eosinophilic diseases including eosinophilic gastrointestinal disorders, hypereosinophilic syndromes, asthma and food allergies. The laboratory has identified and biologically characterized several critical pathways that regulate allergic responses.

**J. Pablo Abonia, MD**

Dr. Abonia is responsible for multicenter clinical trials for eosinophilic esophagitis which are entering patients into an ongoing open label study. This work in particular provides the exciting potential for a new therapeutic option for patients with eosinophilic esophagitis.

**Amal Assa’ad, MD**

In 2008-9, Dr. Assa’ad led a group of experts in food allergy in compiling and publishing a document that is to be used a reference for allergists performing oral food challenges. The document was published by the Journal of Allergy and Clinical Immunology as a stand alone supplement in order to be kept as a desk reference by the users. The authors wrote the manuscript on behalf of the Adverse Food Reactions Committee of the American Academy of Allergy Asthma and Immunology.

Dr. Assa’ad received the 2009 Firmie Award, which is a Resident teaching award for the attending with highest impact on Firm Rounds given by residents of Cincinnati Children’s Hospital Medical Center

**Carine Blanchard, PhD**

Dr. Blanchard’s primary research is focused on the molecular pathogenesis involved in food allergy related disorders. To better understand the molecular mechanisms underlying these diseases, her laboratory has studied eosinophilic esophagitis (EE) and murine models. Dr. Blanchard and her colleagues recently discovered that these Th2 diseases and models were characterized by an increased expression of the secreted protein TSG6 mRNA, tumor necrosis factor induced gene 6. As a result of this observation, Dr. Blanchard has focused on discovering the regulation of expression and role of TSG6 in food allergy related responses. Starting in July 2008, this work was supported by a 2 year NIH R21 grant and a one year award from Digestive Health Center. Dr Blanchard was also awarded a 2009 Hope grant from the American Partnership for Eosinophilic Disorders (APFED) for junior faculty to study the expression of human uroplakin 1B upregulation in the human food allergy related disease, eosinophilic esophagitis.

**Michelle Lierl, MD**
Dr. Lierl is researching the role of basidiospores (spores from mushrooms and related fungi) and myxomycete spores as potential environmental allergens.

Anil Mishra, PhD
Dr. Mishra researched the key role of IL-15 in the pathogenesis of eosinophilic esophagitis (EE). Global quantitative microarray analysis revealed that IL-15 gene expression was significantly induced in EE patients compared to the normal. Quantitative real time PCR analysis (LightCycler) indicated that IL-15 mRNA has increased in the EE patients compared with normal individuals and correlated with the increase of tissue eosinophilia in EE patients. Additionally, experimental IL-15 overexpression induced esophageal eosinophilia in mice. Interestingly, allergen challenged IL-15 gene-deficient mice were protected against the induction of esophageal eosinophilia compared to allergen challenged wild type mice. Notably, comparable airway eosinophilia was observed in allergen challenged wild type and IL-15 gene-deficient mice. These data indicate that IL-15 is critical for inducing esophageal eosinophilia compared to pulmonary eosinophilia and suggests an important role of IL-15 in promoting EE. On the basis of these preliminary findings, the NIAID funded an RO1 grant on this topic for two years.

Kimberly A. Risma, MD, PhD
Dr. Risma attained national recognition by being awarded the 2009 AAAAI/ART Junior Faculty Development Award from the American Academy of Allergy, Asthma, and Immunology (AAAAI). This three year award is given annually to a single junior investigator in the field of Allergy and Immunology who shows the greatest potential to advance translational research in Allergy and Immunology. This award will allow her to continue her laboratory research that is focused on understanding how mutations in the human cytotoxic protein, perforin, lead to the devastating inflammatory disorder of childhood, familial hemophagocytic lymphohistiocytosis.

Yui-Hsi Wang, PhD
Dr. Wang’s studies have demonstrated that IL-25 functions to evoke TH2-mediated inflammatory responses, possibly via a cross talk between IL-25R+CD4+TH2 memory cells and structural or innate cells through the interaction between IL-25 and IL-25R. Notably, he recently found that IL-25 expression is rapidly elevated in the inflamed duodenum at the early phase in an experimental OVA antigen-induced food allergy model, suggesting that the elevated intestinal IL-25 production is associated with the onset of food allergy. One other ongoing research project is focusing on accessing the role of IL-25 in triggering the dysregulated TH2-driven immune response in the GI tract, leading to the exacerbation of IgE-mediated food allergy.

Nives Zimmermann, PhD
Dr. Zimmermann received funding from the NIH/NIAID to study the pathophysiological role and mechanism of airway acidification in asthma. Her studies found that acidity enhances viability of eosinophils; hallmark cells of allergic inflammation. Furthermore, the mechanism of these effects was found to involve a receptor that senses acidity on eosinophils called GPR65, a G-protein coupled receptor, and cAMP, a second messenger. This work was recently published in the journal Blood.

Division Collaboration

Collaboration with Asthma Research
Collaborating Faculty: Marc E. Rothenberg, MD, PhD
The major goal of this project is to understand the role of eotaxin-3 in human eosinophilic esophagitis. Studies involve cellular distribution of eotaxin-3 and its receptor, the role and mechanism of an eotaxin-3 SNP in disease pathogenesis, and the effect of glucocorticoid therapy on eotaxin-3 expression and esophageal transcript profiles.

Collaboration with Department of Pediatrics
Collaborating Faculty: Marc E. Rothenberg, MD, PhD
NICHD Pediatric center for gene expression and developmental sciences. The major goal of this grant is to support the early career development of pediatric physician scientists.

Collaboration with Molecular Immunology
Collaborating Faculty: Carine Blanchard, PhD
Aeroallergy results from maladaptive immune responses to ubiquitous, otherwise innocuous environmental proteins. Although the proteins targeted by aeroallergic responses represent a tiny fraction of the airborne proteins humans are exposed to, allergenicity is a quite public phenomenon-the same proteins typically behave as aeroallergens across the human population.

Collaboration with Gastroenterology, Hepatology, and Nutrition
Eosinophilic esophagitis has become a prominent chronic esophageal disorder in clinical pediatric and adult gastroenterology. Its manifestations are protean in childhood, but dysphagia predominates the clinical presentation in adults. Intense investigations to explain the underpinnings of the disorder and to discover effective therapy are ongoing.

Collaboration with Pathology and Laboratory Medicine; Gastroenterology, Hepatology, and Nutrition

Collaborating Faculty: Marc E. Rothenberg, MD

The Cincinnati Center for Eosinophilic Disorders at Cincinnati Children's is a center that brings together experts in allergy/immunology, gastroenterology and pathology to evaluate, treat and study chronic medical problems in children to help patients and families affected by eosinophilic disorders.

Collaboration with Immunology

Collaborating Faculty: Simon P. Hogan, PhD

Peanut allergy is the most common food-related cause of lethal anaphylaxis and, unlike other food allergies, typically persists into adulthood. This collaboration is to evaluate whether peanut molecules might also promote anaphylaxis through an innate immune mechanism. Resistance to digestion and dendritic cell activation by the major peanut allergen Ara h 1 are reported to contribute to its allergenicity.

Collaboration with Gastroenterology, Hepatology, and Nutrition

Collaborating Faculty: Simon P. Hogan

This is a clinical study that demonstrates a link between the eosinophil-selective chemokines, eotaxins (eotaxin-1/CCL11 and eotaxin-2/CCL24), eosinophils, and the inflammatory bowel diseases, Crohn's disease and ulcerative colitis (UC). This study demonstrates by gene array and quantitative PCR, elevated levels of eotaxin-1 mRNA in the rectosigmoid colon of pediatric UC patients.

Collaboration with Pathology and Laboratory Medicine; Gastroenterology, Hepatology, and Nutrition

Collaborating Faculty: J. Pablo Abonia, MD

This is a collaboration to develop a clinical registry for eosinophilic gastrointestinal disorders that is currently focused upon eosinophilic esophagitis. This registry has several outcome measures that should benefit patient care and is near completion at this time. In concert with Allergy, Gastroenterology, and Pathology, the registry will be modified to provide measurement of clinical outcomes for the varied standard therapies that are currently employed for patients with eosinophilic esophagitis.

Collaboration with Emergency Medicine

Collaborating Faculty: Michelle Lierl, MD

A randomized controlled clinical trial researching nebulized magnesium sulfate compared to saline in addition to albuterol and ipratoipium treatments in moderate to severe pediatric asthmatic patients.

Faculty Members

Marc E. Rothenberg, MD, PhD, Professor; Division Director
Research Interests: Elucidating the mechanisms of allergic responses especially in mucosal tissues such as the lung and the gastrointestinal tract

J. Pablo Abonia, MD, Research Assistant Professor
Research Interests: The role of mast cells in eosinophilic esophagitis

Amal H. Assa’ad, MD, Professor Clinical; Clinical Director
Research Interests: The occult effect of allergic sensitization to foods on the bronchial hyper-responsiveness seen in asthmatic and the genetic basis of food allergy

Carine Blanchard, PhD, Research Instructor
Research Interests: To study food allergy; eosinophilic esophagitis; asthma

Thomas J. Fischer, MD, Adjunct Professor Clinical
Research Interests: The pharmacologic management of asthma, immune deficiency diseases

Simon P. Hogan, PhD, Assistant Professor
Research Interests: To study allergies, food allergies, eosinophil biology & gastrointestinal inflammation

Michelle B. Lierl, MD, Adjunct Associate Professor
Research Interests: To reduce environmental tobacco smoke exposure in children with asthma

Anil Mishra, PhD, Research Assistant Professor
Research Interests: Understanding the mechanism of aeroallergen-induced allergic responses in the lung and lower gastrointestinal tract

Kimberly A. Risma, MD, PhD, Research Assistant Professor

Research Interests: The molecular and cellular bases of primary disorders of immune deficiency and dysregulation, especially as it relates to lymphocyte cytotoxicity

Yui-Hsi Wang, PhD, Research Assistant Professor

Nives Zimmermann, MD, Research Associate Professor

Research Interests: The molecular understanding of eosinophil survival in allergic inflammation and asthma

Li Zuo, MD, Instructor Clinical

Research Interests: To understand the molecular pathogenesis involved in food allergy related disorders.

Joint Appointment Faculty Members

Gurjit Khurana Hershey, MD, Professor
Asthma Research

Alexandra Filipovich, MD, Professor
Hematology/Oncology Diagnostic Laboratory
Primary immunodeficiencies; BMT for primary immunodeficiencies; Hemophagocytic lymphocytosis; Post-BMT immune reconstruction

Clinical Staff Members

- Kalra Harpinder, MD

Trainees

- Gerald Lee, MD, PL-7, Saint Vincent’s Catholic Medical Centers, New York
- Kelly Metz, MD, PL-6, University of Cincinnati, Ohio
- Charles DeBrosse, MD, PL-5, Ohio State University, Ohio
- Muthuvel Arumugam, PhD, University of Madras, Chennai, India
- Julie Caldwell, PhD, University of Cincinnati, Ohio
- Chen Chun-Yu, PhD, University of Rochester, New York
- Carlos Fernandez Gimenez, MD, Clinical Hospital of Salamanca, Spain
- Eun Jin Lim, PhD, University of Kentucky, Kentucky
- Ariel Munitz, PhD, Hebrew University of Jerusalem, Israel
- Joseph Sherrill, PhD, University of Cincinnati, Ohio
- Zeenath Unnisa, PhD, Osmania University, Hyderabad, India
- Ramon Urrea-Moreno, PhD, Hospital Gregorio Maranon, Madrid, Spain
- Ting Wen, PhD, Rutgers University/UMDNJ, New Jersey
- Katherine Groschwitz, Xavier University, Ohio
- Hongyan Zhu, Hubei College of Traditional Medicine, China
- Amanda Beichler, Ohio Northern University, Ohio
- Tom Lu, University of Cincinnati, Ohio
- Leah Kottyan, Huntingdon College, Alabama

Significant Accomplishments

Rothenberg and Hogan Awarded 2 Grants for Food Allergy Research

The Division of Allergy and Immunology's Marc Rothenberg, MD, PhD, Director, and Simon P. Hogan, PhD, Assistant Professor, are two of six leading scientists across the country to share in a $1.1 million grant for food allergy research. The funding is provided by the Food Allergy & Anaphylaxis Network (FAAN) and represents the largest commitment since FAAN’s research grant program began in 2004.
Dr. Rothenberg’s project focuses on developing new diagnostic and treatment approaches to Eosinophilic Esophagitis, an emerging type of food allergy and disorder characterized by the infiltration of a large number of eosinophils (a type of white blood cell) in the esophagus. He hopes to uncover the molecular basis for EE.

Dr. Hogan is studying anaphylaxis by comparing the levels of IL-9, a factor in the body thought to be associated with anaphylaxis, in children who are at risk for this life-threatening reaction against children who are not at risk. This information could help in the diagnosis of food-triggered, life-threatening anaphylaxis.

The fact the Cincinnati Children's was selected for 2 of the 6 national awards of FAAN is a testament to our excellence.

**New Pathway for Cell Survival Identified**

Nives Zimmermann, MD, Associate Professor and Leah Kottyan, Graduate Student, along with UCLA collaborators identified a new cellular pathway in eosinophils triggered by pH.

Their findings, currently published in the journal Blood, show that eosinophil viability is increased in acidic environments, such as those found in asthma. They identified the mechanistic pathway, including a novel receptor that senses acidity and transmits the survival signal in eosinophils. Importantly, in models of asthma, they identified that this receptor (GPC65) was important for accumulation of eosinophils in the lungs.

These studies were funded in part by the CCHMC Trustee grant, the American Academy of Asthma, Allergy and Immunology and the NIH.

**Risma, Physician-Scientist Earns Schmidlapp Scholar Award For Research**

Kimberly Risma, MD, PhD, Assistant Professor, has been selected to receive a Schmidlapp Scholar Award from the Fifth Third Bank / Charlotte R. Schmidlapp Women Scholars Program. The $100,000 honor is given annually to a female faculty member at Cincinnati Children's. Dr. Risma focuses her research on understanding how lymphocytes kill target cells by secretion of toxic proteins.

"Our research is motivated by clinical observations—children who are born with impaired cellular immunity may present with severe inflammatory diseases or recurrent infections," she says. "By delineating the molecular mechanisms that have gone awry in children with defects in lymphocyte killing, we hope to design novel treatments for the future."

In addition to her research, Dr. Risma sees patients from around the nation in consultation for primary immune deficiency, immune dysregulation, and allergic disorders.

The Charlotte R. Schmidlapp Fund was created in 1907 by a gift from former Fifth Third president Jacob G. Schmidlapp in memory of his daughter, Charlotte, who died at the age of 19. Mr. Schmidlapp directed that grants be restricted to helping women establish themselves in life. The tradition and history of the fund has been to assist women by helping them gain an education and access to services.

**Division Publications**


30. Prausa SE, Fukuda T, Masek D, Curtsinger KL, Liu C, Zhang K, Nick TG, Sherbotie JR, Ellis EN, Goebel J, Vinks AA. UGT genotype may contribute to adverse events following medication with mycophenolate mofetil in pediatric


53. Langberg JM, Epstein JN, Altaye M, Molina BS, Arnold LE, Vitiello B. The Transition to Middle School is


Grants, Contracts, and Industry Agreements

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<tr>
<td>Urplakin 1b: A Genetic Risk Marker for Eosinophilic Esophagitis</td>
<td>02/10/09 - 01/31/10 $25,000 / $25,000</td>
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<td>American Partnership for Eosinophilic Disorders</td>
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<td>IgE, MCH and TSG6 in Eosinophilic Esophagitis Pathogenes</td>
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| DEBROSSE, C               |                                     |
| Immunology/Allergy Fellowship Training Grant | 07/01/08 - 06/30/09 $45,048 / $45,048 |
| National Institutes of Health | 07/01/08 - 06/30/09 $45,048 / $45,048 |
| T32 AI 060515             |                                     |

| GROSCHWITZ, K             |                                     |
| Mast Cell-Mediated Intestinal Permeability | 07/01/08 - 06/30/11 $32,384 / $95,421 |
| National Institutes of Health | 07/01/08 - 06/30/11 $32,384 / $95,421 |
| F30 DK 082113             |                                     |


HOGAN, S

**Intestinal IL-9 and Mast Cells in Food-Induced Anaphylaxis**
Food Allergy and Anaphylaxis Network
02/02/09 - 01/31/11 $124,773 / $249,546

**Eosinophils and Pediatric Inflammatory Bowel Disease**
Crohn's and Colitis Foundation of America
01/01/07 - 12/31/09 $90,000 / $360,000

**Mast Cell PAF-Dependent Intravascular Leakage in Food-Induced Anaphylaxis**
American Heart Association - Ohio
0765196B 07/01/07 - 06/30/09 $55,000 / $110,000

**Interleukin-9 in Experimental Intestinal Anaphylaxis**
National Institutes of Health
R01 AI 073553 04/01/08 - 03/31/13 $250,000 / $1,000,000

METZ, K

**The Impact of Second Hand Smoke on the Clinical and Molecular Phenotypes of Children**
National Institutes of Health (University of Cincinnati)
P30 ES 006096 04/01/09 - 03/31/10 $24,600 / $24,600

MISHRA, A

**Mechanistic Analysis of Eosinophilic Esophagitis**
National Institutes of Health
R01 DK 067255 04/01/05 - 03/31/10 $152,392 / $820,000

MUNITZ, A

**Regulation of Eosinophils by PIR-B**
American Heart Association - Ohio
PF0825621D 07/01/08 - 06/30/10 $43,000 / $88,000

**The Expression and Function of ILT-3 LIR-5 in Pediatric Eosinophilic Esophagitis**
Thrasher Research Fund
06/01/09 - 05/31/11 $11,000 / $25,000

RISMA, K

**Center for Career Development for Women in Academic Pediatrics**
Charlotte R. Schmidlapp Fund, Trustee
01/01/09 - 12/31/10 $50,000 / $100,000

**Biophysical Consequences of Missense Mutations in Perforin**
University of Cincinnati Research Council
07/01/08 - 06/30/09 $25,000 / $25,000

**Proteolytic Maturation of Perforin: Determining the Requirements for Cytotoxic Function in Patients with Hemophagocytic Lymphohistiocytosis**
Histiocytosis Association of America
01/01/09 - 12/31/09 $50,000 / $50,000

**Mechanisms of Altered Lymphocyte Cytotoxicity**
Doris Duke Charitable Foundation
08/01/06 - 07/31/09 $125,000 / $375,000

**The Pathophysiologic Basis of Perforin Misfolding in Cytotoxic Granules**
American Academy of Allergy, Asthma and Immunology
07/01/07 - 06/30/09 $50,000 / $100,000

ROTHENBERG, M

**The Role of CREB Binding Protein in Eosinophilic Esophagitis**
Food Allergy and Anaphylaxis Network
02/02/09 - 01/31/11 $61,932 / $123,864

**IL-13 and Eosinophilic Esophagitis**
National Institutes of Health
R01 DK 076893 09/01/07 - 06/30/12 $100,000 / $100,000
### Novel Genetic and Therapeutic Approaches Focusing on Siglec-8 for the Diagnosis and Treatment of Human Idiopathic Eosinophilic Disorders

The Dana Foundation

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### Epithelial Genes in Allergic Inflammation

National Institutes of Health

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### Interleukin-13 in Experimental Asthma

National Institutes of Health

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### STRAUSS/ROTHENBERG

Pediatric Center for Gene Expression and Development

National Institutes of Health

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### ZIMMERMAN, N

Role of Acidic Environment in Eosinophil Inflammation

National Institutes of Health

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### ZUO, L

Mechanistic Dissection of IL-13 Transgene Induced Eosinophilic Esophagitis in Mice

American Academy of Allergy, Asthma and Immunology

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**Current Year Direct Receipts**

$355,127

**Total**

$3,051,568