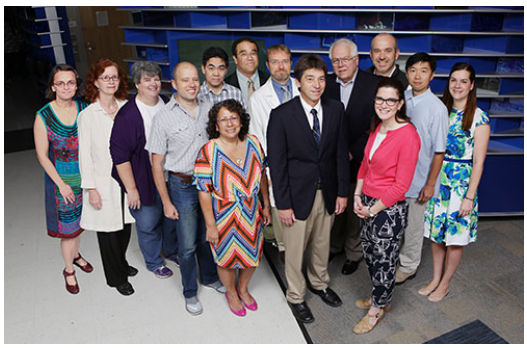
Allergy and Immunology

Division Details

RESEARCH AND TRAINING DETAILS	
Faculty	**16**
Joint Appointment Faculty	**2**
Research Fellows and Post Docs	**8**
Research Graduate Students	**6**
Total Annual Grant Award Dollars	**$7,651,283**
Total Annual Industry Award Dollars	**$1,387,925**
Total Publications	**50**

CLINICAL ACTIVITIES AND TRAINING	
Staff Physicians	**1**
Clinical Fellows	**8**
Inpatient Encounters	**396**
Outpatient Encounters	**7,574**



Row 1: A Assa'ad, M Rothenberg, K Risma

Row 2: A Barski, A Lindsley, T Fischer, T Wen

Row 3: N Zimmerman, M Lierl, P Fulkerson, Y Wang, P Abonia, S Hogan, S Logsdon

Research Highlights

Division Director Receives 2016 Faculty Award: Research Achievement Award

The Fifth Annual Faculty Awards by Cincinnati Children's recognized our division director, Marc E. Rothenberg, MD, PhD, for his dedicated efforts with a Research Achievement Award. Rothenberg is one of the most productive researchers in the field of Allergy and Immunology. The scope of his work includes basic biology, translational research, genetics and epigenetics, and clinical trials of novel agents. Rothenberg primarily focuses on molecular analysis of allergic inflammation, particularly the pathogenesis of eosinophilic gastrointestinal diseases (EGIDs). He is a pioneer in identifying, studying and treating EGIDs and has built a comprehensive program, making Cincinnati Children's the leading site for study and treatment of these disorders. He also founded and directs the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR), a group of national leaders funded by the National Institutes of Health (NIH). Rothenberg's research has resulted in over 300 peer-reviewed, and in some cases landmark, articles published in the highest-impact journals. His work has been cited over 17,000 times. He has received a number of prestigious national awards, and has served as a research mentor to students and colleagues around the world. Rothenberg's research also sheds light on other atopic diseases, including asthma. His efforts in basic research, and clinical trials, contributed to the FDA approval in 2015 of the first new class of drugs in over a decade to treat severe asthma.

Recognized Excellence of Division Trainees and Faculty

The Division of Allergy and Immunology is proud of the excellence of its undergraduate, graduate, postdoctoral and clinical trainees and junior investigators. Several were recognized for their achievements throughout the year:

- Jeffrey Rymer, predoctoral fellow in the Rothenberg Lab, won the first prize for his poster at the 2016 Annual Scientific Symposium from the Digestive Health Center.
- Jared Travers, MD, and PhD predoctoral fellow in the Rothenberg Lab, will study the role of nuclear IL-33 in mucosal inflammation through an NIH F30 fellowship grant awarded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).
- Allergy/immunology clinical fellow, Michael Goodman, MD, received K12 support through the NIH Pediatric Scientist Development Program.
- Artem Barski, PhD, assistant professor, received a Trustee Award from Cincinnati Children's for his research project "Epigenetic Suppression of IL4 Expression in T Cells" in the Barski Lab and a T1 Core grant by the CCTST to establish the Epigenomics Data Analysis Core.
- Patricia C. Fulkerson, MD, PhD, assistant professor, selected as a 2015 Schmidlapp Woman Scholar by the Fifth Third Bank / Charlotte R. Schmidlapp Women Scholars Program to support her career development and research in the Fulkerson Lab.
- Our division's Director of Research, Simon P. Hogan, PhD, received funding from the Cincinnati Children's Research Innovation/Pilot Funding Program in 2016. This program will support the Hogan Lab in investigating the involvement of antibiotics in antigen sensitization in food allergy.

Fostering the Future through Clinical and Research Fellowship Education

David W. Morris, MD, matriculated from our division's Allergy/Immunology Fellowship Program in the Summer of 2015. After working further as a clinician and clinical researcher at Cincinnati Children's, Dayton Children's Hospital recruited him to expand the clinical allergy program. During his fellowship, he conducted research mentored by Patricia C. Fulkerson, MD, PhD. He initiated two research projects in the Fulkerson Lab: 1) evaluation of human samples for eosinophil progenitor populations in the peripheral blood of patients with eosinophilic esophagitis (EoE) and 2) the development of a murine cell model to evaluate the effect of toll-like receptor 2 stimulation on eosinophil development. The former's results published in the *Journal of Allergy and Clinical Immunology*. As an indication of his excellence, his clinical and research fellowship training is supported with our division's Allergy/Immunology T32 training award. In addition, he received a peer-reviewed grant in 2014 from the American Academy of Allergy, Asthma and Immunology (AAAAI).

Tipping the Scales: the Interplay of IL-25, CD4+ TH2 Cells and Type 2 Innate Lymphoid Cells in Promoting Food Allergy

After food sensitization occurs, a strong allergic reaction to ingested food is essential for the development of food allergy. However, the immunologic mechanisms that drive the propagation of food allergic reactions in the intestine remain elusive. A recent study, led by Yui-Hsi Wang, PhD, associate professor, shows that interleukin 25 (IL-25) enhances anaphylactic responses in a mouse model of food allergy by stimulating type 2 innate lymphoid cells (ILC2s) in the intestines. ILC2s produce IL-5 and IL-13, which promote immunoglobulin E (IgE)–mediated food allergy and drive uncontrolled type-2 immune responses. Repeated exposure to the food antigen increased the number of CD4(+) T helper type 2 (TH2) cells, which fueled further IL-13 production by IL-25–stimulated ILC2s. These findings, published in the Journal of Allergy and Clinical Immunology, suggest that the IL-25–mediated, collaborative interactions between ILCs and adaptive CD4+ TH2 cells are a pivotal step in amplifying the cascade of allergic reactions to ingested antigens and underscore the importance of understanding the mechanisms that underlie intestinal allergic responses to ingested food. Future, in-depth studies of the molecular and cellular factors composing these stepwise pathways may facilitate the discovery of biomarkers and therapeutic targets for diagnosing, preventing and treating food allergy.

Research Suggests Less Invasive Monitoring of Eosinophilic Disorder

Patricia C. Fulkerson, MD, PhD, assistant professor, led recent, preliminary research suggesting that eosinophil progenitors (EoPs) in the blood may be a potential marker for disease activity of eosinophilic esophagitis (EoE) in children. This potential method of monitoring is less invasive, sparing children with EoE the discomfort and risk of endoscopic procedures to assess whether their disease is active. The disease activity of EoE is currently monitored using peak esophageal eosinophil count, which requires invasive endoscopy to collect esophageal tissue biopsies for assessment. People with EoE, a lifelong disease, must continue monitoring disease activity, even after effective treatment with restricted diets or steroids. Treatment changes, such as reintroducing a single food, requires additional

endoscopic exams to assess for disease flare-ups. Research led by the Fulkerson lab and published in the *Journal of Allergy and Clinical Immunology* found elevated EoP levels in the blood of pediatric patients with active EoE disease, suggesting a promising, blood-based marker. Measuring EoP blood levels to monitor disease activity has the potential to reduce discomfort, costs and side effects for patients. However, additional research is needed to validate the EoP-based marker before its routine use in clinic.

How to Stop Eosinophilic Esophagitis Tissue Damage? Target Calpain 14

Drugs that target the protein calpain 14 may someday help treat the inflammation and scarring that can occur in people with eosinophilic esophagitis (EoE), according to new research from the Cincinnati Center for Eosinophilic Disorders. Previous research, led by division director Marc E. Rothenberg, MD, PhD, has established a powerful link between EoE and the *CAPN14* gene, which codes for calpain 14. In the latest findings, published in *JCI Insight*, Rothenberg and colleagues detail the biochemical and functional properties of calpain 14 and the disruptions in esophageal cells that occur when the expression of *CAPN14* is experimentally regulated. The new information suggests that controlling the activity of calpain 14 may prevent the development of EoE, thus making the protein an important target for further drug research.

Putting the Brakes on Anaphylactic Reactions

A study, published in *Immunity, Inflammation and Disease*, and led by our division's director of research, Simon P. Hogan, PhD, demonstrates that loss of the phosphatidylinositol 3-kinase (PI3K) activating signal triggered by interleukin 4 receptor alpha (IL-4Rα) does not alter susceptibility to food-induced experimental anaphylaxis. Symptoms of experimental anaphylaxis, namely diarrhea, antigen-specific IgE and intestinal mastocytosis, are comparable between mice with, and without, functional IL-4Rα and PI3K signaling. However, mice without functional IL-4Rα-mediated PI3K signaling have accelerated disease progression. This quickened anaphylactic response associates with a more rapid decrease in blood volume caused by histamine. Notably, endothelial IL-4Rα PI3K signaling negatively regulates the histamine-induced endothelial leak response. These results define an unanticipated role for IL-4Rα–mediated PI3K signaling in putting the brakes on IgE-mediated anaphylactic reactions.

EoGenius Diagnostic Test for Eosinophilic Esophagitis

Research, led by division director Marc E. Rothenberg, MD, PhD, and instructor Ting Wen, PhD, yielded an RNA expression test to help diagnose eosinophilic esophagitis (EoE). Through collaboration with Miraca Life Sciences, they brought this innovation from the bench to bedside, and it is now commercially available as the EoGenius test. This achievement represents a meaningful stride forward for this often misdiagnosed condition.

Kabuki Syndrome

Kabuki syndrome is a rare developmental disorder that affects many systems of the body that associates with mutations in genes encoding histone-modifying proteins. This study, led by Andrew W. Lindsley, MD, PhD, and published in the *Journal of Allergy and Clinical Immunology*, characterizes the humoral immune defects of this understudied condition in patients with mutations in lysine methyltransferase 2D (KMT2D). The research showed that mutations in KMT2D associate with dysregulation of terminal B-cell differentiation. This dysregulation is what leads to the humoral immune deficiency observed in Kabuki syndrome, and the autoimmunity that sometimes develops. These findings support the importance of a change in clinical practice in that patients with Kabuki syndrome would benefit from undergoing serial clinical immune evaluations.

Food Allergy Desensitization and Tolerance Induction

Clinical trials for the desensitization and induction of tolerance in children and adults with food allergy continued with the contributions of our division's director of Clinical Services, Amal H. Assa'ad, MD; physicians, such as Michelle B. Lierl, MD, and Stephanie L. Logsdon, MD; fellows; research nurses and coordinators; and the Shubert Clinic. Completed studies include epicutaneous immunotherapy (known as the peanut patch and marketed as Viaskin®), oral immunotherapy for peanut allergy and oral immunotherapy for multiple food allergens under the marketed name of Xolair® (omalizumab) to reduce the incidence of side effects.

Allergic Diseases and Internalizing Behaviors in Early Childhood

Research recent conducted during the fellowship of Maya Nanda, MD with the Allergy/Immunology Fellowship Program examined whether having multiple allergic diseases in early childhood associated with having internalizing disorders in the school-age years. The

study was published in *Pediatrics*. Children who were enrolled in the Cincinnati Childhood Allergy and Air Pollution Study underwent skin testing and examinations at ages 1, 2, 3, 4, and 7 years. When the children were age 7, their parents completed the Behavior Assessment System for Children, Second Edition (BASC-2), a validated measure of childhood behavior and emotion. The study, led by Patrick H. Ryan, PhD, concluded that children with allergic rhinitis and allergic persistent wheezing at age 4 are at increased risk of internalizing behaviors at age 7. Furthermore, there was a dose-dependent association between the number of allergic diseases that a child had and the degree of elevation of the internalizing scores.

Division Director Receives First Bunning Chair

Our division director, Marc E. Rothenberg, MD, PhD, was named the first recipient of the Denise and Dave Bunning Chair for the Division of Allergy and Immunology. Cincinnati Children's established the chair in honor of the Bunnings, who have been generous supporters of Rothenberg's work and the advancement of the Division of Allergy and Immunology for nearly 10 years. In particular, they have helped Cincinnati Children's make great strides in diagnosing, understanding and treating eosinophilic gastrointestinal disease, known as eosinophilic gastrointestinal disorders (EGIDs). EGIDs cause the body to treat food like a foreign invader, causing inflammation, pain and tissue damage. Rothenberg has focused on alleviating the suffering of patients with these severe, life-altering allergies throughout his medical career. He is a pioneer in his field, leading Cincinnati Children's as the first to form an EGID center, which stands as an example for dozens of EGID centers that have since been set up across the country. Rothenberg established and is the principal investigator of the Consortium of Eosinophil Gastrointestinal Disease Researchers, which is one of only 22 rare disease consortia supported by the NIH, through three NIH institutes (NIAID, NIDDK and NCATS). Other recent EGID achievements include Rothenberg receiving an R01 by the NIAID for his project "Genetic and Immunological Dissection of Eosinophilic Esophagitis", and the "Most Outstanding Translational Research Achievement between 2010-2015" at Cincinnati Children's for his work towards the *Nature Genetics* publication, "Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease". The Bunning endowed chair provides an enduring way of ensuring that Cincinnati Children's will have the best faculty and outstanding research of EGIDs in perpetuity.

BioWardrobe: an Integrated "-omics" Analysis Platform

High-throughput sequencing has revolutionized biology by enhancing our ability to perform genome-wide studies. However, due to lack of bioinformatics expertise, modern technologies are still beyond the capabilities of many laboratories. Andrey Kartashov, MSc, and Artem Barski, PhD, developed the BioWardrobe platform, which allows users to store, visualize and analyze epigenomics and transcriptomics data using a biologist-friendly web interface, without the need for programming expertise. Predefined pipelines allow users to download data, visualize results on a genome browser, calculate RPKMs (reads per kilobase per million) and identify peaks. Advanced capabilities include differential gene expression and binding analysis and creation of average tag-density profiles and heatmaps. BioWardrobe was published in *Genome Biology*.

Division Leading the Way to Measure Eosinophilic Esophagitis Pathology

Our division director, Marc E. Rothenberg, MD, PhD, established and is the principal investigator (PI) of the Consortium of Eosinophil Gastrointestinal Disease Researchers (CEGIR), which is one of only 22 rare disease consortia supported by the NIH, through three NIH Institutes (NIAID, NIDDK and NCATS). CEGIR is pushing boundaries with much-needed research of eosinophil gastrointestinal diseases (EGIDs), and the management of that research as well. For instance, EGID researchers have developed and validated a histologic scoring system to objectively analyze pathologic features of eosinophilic esophagitis (EoE), a severe, often painful food allergy that renders children unable to eat a wide variety of foods. This study, led by Margaret Collins, MD, and other professors of pathology in the Cincinnati Center for Eosinophilic Disorders at Cincinnati Children's was in collaboration with our national CEGIR colleagues, and published in *Diseases of the Esophagus*. This scoring system encourages pathologists to evaluate more than eosinophilic inflammation and reduces our dependence on a single feature for diagnosis. By having validated tools to measure other pathologic features of EoE, the reported findings provide a new opportunity for evaluating disease activity and treatments going forward. CEGIR is also implementing cloud technology involving a virtual microscope across consortium sites to improve collaboration between its network of researchers, providers, patients and organizations. From improving the interactions between researchers at nine different centers located across the country, to connecting patients with clinical studies and patient advocacy groups, CEGIR is leading the charge on bringing digital health to the clinical research field.

The Untold Story of a New Asthma Drug

The FDA approved the drug mepolizumab in November 2015 and then reslizumab in March 2016 to help treat severe asthma, which was an achievement grounded in many years of research and testing by innumerable physicians and scientists, including those at Cincinnati Children's, such as Division Director Marc E. Rothenberg, MD, PhD; our division's Director of Clinical Services, Amal H. Assa'ad, MD, and Director of Research, Simon P. Hogan, PhD. These medications target a subset of patients (ages 12 and up) with asthma whose current drug regimens are insufficient to control their condition. This is the first class of new asthma drugs approved in over a decade based on targeting the allergy-associated, inflammatory cells called eosinophils. Rothenberg and his research team are considered pioneers in the field, and Cincinnati Children's has become a global leader in researching and treating eosinophilic conditions. The institution's researchers characterized a critical genetic/molecular pathway (involving the protein interleukin 5) that helps fuel severe asthma, which is caused by eosinophils. Mepolizumab and reslizumab inhibit interleukin 5 and block the production of eosinophils, which drives certain types of severe asthma. In addition to basic laboratory studies that established the molecular target for this therapy, Cincinnati Children's also helped conduct clinical trials testing the safety and efficacy of mepolizumab in patients, not only those with asthma but also those with other eosinophilic disorders such as eosinophilic esophagitis.

Research of a New Cell Type May Explain Why Some Individuals Develop Severe Allergic Reactions to Food

Yui-Hsi Wang, PhD, and his colleagues, report their discovery of a new cell type that appears to drive life-threatening food allergies, and may help explain why some people get severe allergic reactions, and others do not. Food allergy is a harmful immune reaction that occurs shortly after a person eats certain foods. For some people, the reaction to a particular food may merely be uncomfortable. For others, food allergy can trigger a severe, or life-threatening anaphylaxis, reaction. It has been perplexing why only some individuals among those with food allergy are more prone to develop life-threatening anaphylactic response to ingested food. A key study led by Dr. Wang, published in *Immunity*, reports the findings of a new type of mucosal mast cells, termed IL-9–producing mucosal mast cells (MMC9s), which may provide some clues to this enigma. MMC9s produce large amounts of an inflammatory immune protein called interleukin 9 (IL-9) and mast cell mediators, which amplifies anaphylactic shock in response to ingested food. Data from murine experiments support that triggering MMC9s is a key step for mice to gain susceptibility to developing food allergy. Analyzing small intestine biopsy samples from patients with food allergy, Wang's team found significantly increased expression of the IL9 genetic transcript, and other related transcripts, suggesting a possible connection. The results obtained from these studies, published in *Immunity*, will likely greatly influence and improve our conceptual understandings of why some individuals may be more susceptibility to developing food allergy–induced, life-threatening anaphylaxis and thus make possible new designs for medicines to treat and/or prevent food allergy. This research will be further pursued by Dr. Wang, who received a FY 14 Peer Reviewed Medical Research Program (PRMRP) Investigator-Initiated Research Award from the United States Department of Defense (DoD) for his project "IL-9-Producing Mast Cell Precursors and Food Allergy".

Biosensors: Measuring Early Events in Cell Death

Natural killer (NK) cells are cytotoxic lymphocytes and first responders of the human immune system in identifying and eliminating tumor cells and virally infected cells. As natural killer (NK) cell–based therapy is being considered for treating human cancer, developing new tools to measure early events in cell death is critical. After recently demonstrating that protease-cleavable luciferase biosensors detect granzyme B and pro-apoptotic caspase activation within minutes of target cell recognition by murine cytotoxic lymphocytes, researchers led by Kimberly A. Risma, MD, PhD, successfully adapted the biosensor technology to assess perforin-dependent and -independent induction of death pathways in tumor cells recognized by human NK cell lines and primary cells and also developed biosensors for granzyme A and K, for which no other functional reporters are available. These studies, published in *Blood*, establish the sensitivity of protease-cleaved luciferase biosensors to measure previously undetectable events in live cells in real time. Further development of caspase and granzyme biosensors will allow interrogation of additional features of granzyme activity in live cells including localization, timing and specificity, which will inform NK cell–based therapy development.

Eosinophils Outside of Inflammation: Homeostatic Regulation of IgA Production

Eosinophils are a multifunctional type of white blood cell that resides in the gastrointestinal lamina propria. They are widely known for their roles in inflammatory response; however, their non-inflammatory functions remain largely unexplored. Researchers, led by division director Marc E. Rothenberg, MD, PhD, used mice with a selective deficiency of systemic eosinophils (by lineage ablation) or

gastrointestinal eosinophils (eotaxin-1/2 double deficient or CC chemokine receptor 3 deficient). They found that eosinophils support immunoglobulin A (IgA) class switching, maintain intestinal mucus secretions, affect intestinal microbial composition and promote the development of Peyer's patches. Eosinophil-deficient mice showed reduced expression of mediators of secretory IgA production, including intestinal interleukin 1β (IL-1β). Gastrointestinal eosinophils expressed a relatively high level of IL-1β, and IL-1β–deficient mice manifested the altered gene expression profiles observed in eosinophil-deficient mice and decreased levels of IgA(+) cells. The study's collective data, published in *Mucosal Immunology*, suggest the requirement of eosinophils for homeostatic intestinal immune responses including IgA production, and that their affect is mediated via IL-1β in the small intestine.

Neurotrophins: Another Piece in the IL-13 Inflammation Puzzle

Researchers, led by division director Marc E. Rothenberg, MD, PhD, explored the interaction of the interleukin (IL) 13 and neurotrophin pathways, which are functionally important for the pathogenesis of immune responses, particularly those involving pain such as in eosinophilic esophagitis (EoE). By interrogating IL-13–induced responses in human epithelial cells, they found an early transcriptional target of IL-13, neurotrophic tyrosine kinase receptor, type 1 (NTRK1). NTRK1 is a cognate, high-affinity receptor for nerve growth factor (NGF). NTRK1's induction accompanied by accumulation of activating epigenetic marks in the promoter. In human EoE, an allergic inflammation disease, NTRK1 was increased in inflamed tissue and dynamically expressed as a function of disease activity, and a downstream mediator of NTRK1 signaling was elevated in allergic inflammatory tissue compared with control tissue. Unlike NTRK1, its ligand NGF was constitutively expressed in control and disease states, indicating that IL-13–stimulated NTRK1 induction is a limiting factor in pathway activation. In epithelial cells, NGF and IL-13 synergistically induced several target genes, including chemokine (C-C motif) ligand 26 (eotaxin-3). In summary, these results, published in the *Journal of Clinical Investigation Insight*, demonstrate that IL-13 confers epithelial cell responsiveness to NGF by regulating NTRK1 levels by a transcriptional and epigenetic mechanism and that this process likely contributes to allergic inflammation.

Significant Publications

Lindsley AW, Saal HM, Burrow TA, Hopkin RJ, Shchelochkov O, Khandelwal P, Xie C, Bleesing J, Filipovich L, **Risma K**, **Assa'ad AH**, Roehrs PA, Bernstein JA. **Defects of B-cell terminal differentiation in patients with type-1 Kabuki syndrome**. *J Allergy Clin Immunol*. 2016 Jan;137(1):179-87.e10.

Kabuki syndrome is a rare developmental disorder that affects many systems of the body. It's associated with mutations in genes encoding histone-modifying proteins. This study, led by Andrew W. Lindsley, MD, PhD, characterizes the humoral immune defects of this understudied condition in patients with mutations in lysine methyltransferase 2D (KMT2D). The research showed that mutations in KMT2D associate with dysregulation of terminal B-cell differentiation. This dysregulation is what leads to the humoral immune deficiency observed in Kabuki syndrome and the autoimmunity that sometimes develops. These findings support the importance of a change in clinical practice in that patients with Kabuki syndrome would benefit from undergoing serial clinical immune evaluations.

Morris DW, **Stucke EM**, Martin LJ, **Abonia JP**, Mukkada VA, Putnam PE, **Rothenberg ME**, **Fulkerson PC**. **Eosinophil progenitor levels are increased in patients with active pediatric eosinophilic esophagitis**. *J Allergy Clin Immunol*. 2016 Sep;138(3):915-918.e5.

Eosinophilic esophagitis (EoE) is a lifelong, severe and often painful food allergic disease whose activity is monitored, even after an effective treatment with restricted diets and steroids is in place. The disease activity of EoE is currently monitored using peak esophageal eosinophil count, which requires invasive endoscopy to collect esophageal tissue biopsies for assessment. Treatment changes, such as reintroducing a single food, requires additional endoscopic exams to assess for disease flare-ups. In searching for a less invasive marker of disease activity, researchers led by Patricia C. Fulkerson, MD, PhD, investigated a precursor cell to eosinophils, a lineage-committed eosinophil progenitor (EoP), as a potential marker. They found elevated EoP levels in the blood of pediatric patients with active EoE disease, suggesting a promising, blood-based marker. Measuring EoP blood levels to monitor disease activity has the potential to reduce discomfort, costs and side effects for patients; however, additional research will work to validate the EoP-based marker before its routine use in clinical settings.

Vrazo AC, Hontz AE, Figueira SK, Butler BL, **Ferrell JM**, Binkowski BF, Li J, **Risma KA**. **Live cell evaluation of granzyme delivery and death receptor signaling in tumor cells targeted by human natural killer cells**. *Blood*. 2015 Aug 20;126(8):e1-e10.

Natural killer (NK) cells are cytotoxic lymphocytes and first responders of the human immune system in identifying and eliminating tumor cells and virally infected cells. As we consider using natural killer (NK) cell–based therapy for treating human cancer, developing new tools to measure early events in cell death is critical. After recently demonstrating that protease-cleavable luciferase biosensors detect granzyme B and pro-apoptotic caspase activation within minutes of target cell recognition by murine cytotoxic lymphocytes, researchers led by Kimberly A. Risma, MD, PhD, successfully adapted the biosensor technology to assess perforin-dependent and -independent induction of death pathways in tumor cells recognized by human NK cell lines and primary cells and also developed biosensors for granzyme A and K, for which no other functional reporters are available. These studies establish the sensitivity of protease-cleaved luciferase biosensors to measure previously undetectable events in live cells in real time. Further development of caspase and granzyme biosensors will allow interrogation of additional features of granzyme activity in live cells including localization, timing, and specificity, which will inform NK cell–based therapy development.

Kartashov AV, Barski A. **BioWardrobe: an integrated platform for analysis of epigenomics and transcriptomics data**. *Genome Biol*. 2015 Aug 7;16:158.

High-throughput sequencing has revolutionized biology by enhancing our ability to perform genome-wide studies. However, due to lack of bioinformatics expertise, modern technologies are still beyond the capabilities of many laboratories. Andrey Kartashov, MSc and Artem Barski, PhD developed the BioWardrobe platform, which allows users to store, visualize and analyze epigenomics and transcriptomics data using a biologist-friendly web interface, without the need for programming expertise. Predefined pipelines allow users to download data, visualize results on a genome browser, calculate RPKMs (reads per kilobase per million) and identify peaks. Advanced capabilities include differential gene expression and binding analysis and creation of average tag-density profiles and heatmaps. Find more about BioWardrobe at http://biowardrobe.com.

Sledd J, Wu D, Ahrens R, Lee J, Waggoner L, Tsai YT, Wang YH, Hogan SP. **Loss of IL-4Rα-mediated PI3K signaling accelerates the progression of IgE/mast cell-mediated reactions**. *Immun Inflamm Dis*. 2015 Sep 17;3(4):420-30.

This study, led by Simon P. Hogan, MD, PhD, demonstrates that loss of the phosphatidylinositol 3-kinase (PI3K) activating signal triggered by interleukin 4 receptor alpha (IL-4Rα) does not alter susceptibility to food-induced experimental anaphylaxis. Symptoms of experimental anaphylaxis, namely diarrhea, antigen-specific IgE and intestinal mastocytosis, are comparable between mice with and without functional IL-4Rα and PI3K signaling. However, mice without functional IL-4Rα-mediated PI3K signaling have accelerated disease progression. Histamine causes this quickened anaphylactic response associated with a more rapid decrease in blood volume. Notably, endothelial IL-4Rα PI3K signaling negatively regulates the histamine-induced endothelial leak response. These results define an unanticipated role for IL-4Rα-mediated PI3K signaling in putting the brakes on IgE-mediated anaphylactic reactions.

Division Publications

1. Alsubait S, Deeb A, Zimmermann N, Bhaskaran J, Salkeni M. **Resolution of Telangiectasia Macularis Eruptiva Perstans with Successful Treatment of Synchronous Large Granular Lymphocytic Leukemia.** *Ann Hematol Oncol*. 2015; 2:1052.

2. Asosingh K, Vasanji A, Tipton A, Queisser K, Wanner N, Janocha A, Grandon D, Anand-Apte B, Rothenberg ME, Dweik R, Erzurum SC. **Eotaxin-Rich Proangiogenic Hematopoietic Progenitor Cells and Ccr3+ Endothelium in the Atopic Asthmatic Response.** *J Immunol*. 2016; 196:2377-87.

3. Beigelman A, Durrani S, Guilbert T. **Should a Preschool Child with Acute Episodic Wheeze Be Treated with Oral Corticosteroids? A Pro/Con Debate.** *J Allergy Clin Immunol Pract*. 2016; 4:27.

4. Bian F, Gao F, Kartashov AV, Jegga AG, Barski A, Das SK. **Polycomb Repressive Complex 1 Controls Uterine Decidualization.** *Sci Rep*. 2016; 6:26061.

5. Bouffi C, Kartashov AV, Schollaert KL, Chen X, Bacon WC, Weirauch MT, Barski A, Fulkerson PC. **Transcription Factor Repertoire of Homeostatic Eosinophilopoiesis.** *J Immunol*. 2015; 195:2683-95.

6. Chen CY, Lee JB, Liu B, Ohta S, Wang PY, Kartashov AV, Mugge L, Abonia JP, Barski A, Izuhara K, Rothenberg ME, Finkelman FD, Hogan SP, Wang YH. **Induction of Interleukin-9-Producing Mucosal Mast Cells Promotes Susceptibility to Ige-Mediated Experimental Food Allergy.** *Immunity*. 2015; 43:788-802.

7. Collins M, Martin L, Alexander E, Boyd J, Sheridan R, He H, Pentiuk S, Putnam P, Abonia J, Mukkada V. **Newly Developed and Validated Eosinophilic Esophagitis Histology Scoring System and Evidence That It Outperforms Peak Eosinophil Count for Disease Diagnosis and Monitoring.** *Dis Esophagus*. 2016.

8. Collison AM, Sokulsky LA, Sherrill JD, Nightingale S, Hatchwell L, Talley NJ, Walker MM, Rothenberg ME, Mattes J. **Tnf-Related Apoptosis-Inducing Ligand (Trail) Regulates Midline-1, Thymic Stromal Lymphopoietin, Inflammation, and Remodeling in Experimental Eosinophilic Esophagitis.** *J Allergy Clin Immunol*. 2015; 136:971-82.

9. Davis B, Stucke E, Khorki M, Litosh V, Rymer J, Rochman M, Travers J, Kottyan L, Rothenberg M. **Eosinophilic Esophagitis-Linked Calpain 14 Is an Il-13-Induced Protease That Mediates Esophageal Epithelial Barrier Impairment.** *JCI insight*. 2016; 1:e86355.

10. Davis BP, Epstein T, Kottyan L, Amin P, Martin LJ, Maddox A, Collins MH, Sherrill JD, Abonia JP, Rothenberg ME. **Association of Eosinophilic Esophagitis and Hypertrophic Cardiomyopathy.** *J Allergy Clin Immunol*. 2016; 137:934-6 e5.

11. Davis BP, Rothenberg ME. **Mechanisms of Disease of Eosinophilic Esophagitis.** *Annu Rev Pathol*. 2016; 11:365-93.

12. Dellon E, Collins M, Bonis P, Capocelli K, Dohil R, Falk G, Furuta G, Gupta S, Hirano I, Hiremath G. **Substantial Variability in Biopsy Practice Patterns among Gastroenterologists for Suspected Eosinophilic Gastrointestinal Disorders.** *Clin Gastroenterol Hepatol*. 2016.

13. D'Mello RJ, Caldwell JM, Azouz NP, Wen T, Sherrill JD, Hogan SP, Rothenberg ME. **Lrrc31 Is Induced by Il-13 and Regulates Kallikrein Expression and Barrier Function in the Esophageal Epithelium.** *Mucosal Immunol*. 2016; 9:744-56.

14. Durrani S, Guilbert T. **Short- and Long-Term Efficacy of Prednisolone for First Acute Rhinovirus-Induced Wheezing Episode**. In: M Cabana, ed. *Yearbook of Pediatrics 2016*. San Francisco CA: Elsevier; 2015:403-07.

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Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Amal H Assa'ad, MD	FARE Clinical Center of Excellence (CCE)	Food Allergy Research & Education, Inc	FARE_Assa'ad	7/1/2015 - 6/30/2020	$120,000
Nurit Pereg Azouz, PHD	The Novel Role of Periostin in Modulating Mast Cell Function	American Heart Association	14POST20140000	7/1/2014 - 6/30/2016	$47,000

Artem Barski, PHD	The American Association of Immunologists Careers in Immunology Fellowship	American Association of Immunologists	AAI_Barski	9/1/2015 - 8/31/2016	$46,344
Artem Barski, PHD	Direct Epigenetic Reprogramming of T Cells	National Institutes of Health	DP2GM119134	9/30/2015 - 5/31/2020	$2,340,000
Patricia C Fulkerson, MD-PHD	Regulation of Eosinophil Progenitors by Toll-Like Receptors	ARTrust	Artrust_Fulkerson	7/1/2013 - 6/30/2016	$100,000
Simon Patrick Hogan, PHD	Leukocyte Immunoglobulin like Receptor B3 in Innate Colonic Inflammation in Pediatric UC	Crohn's & Colitis Foundation of America	272118	7/1/2014 - 6/30/2017	$115,830
Simon Patrick Hogan, PHD	Vascular Endothelium-C-Abl Kinase Axis Underpins the Onset of a Severe Food-induced Anaphylactic Reaction	Food Allergy Research & Education, Inc	FARE_Hogan	7/1/2015 - 6/30/2020	$150,000
Simon Patrick Hogan, PHD Yui His Wang, PHD	Food Allergy and Goblet Cell Antigen Passages	National Institutes of Health	R01 AI112626	5/4/2015 - 4/30/2020	$494,532
Chuan-Hui Kuo, PHD	Mast Cells and Inflammatory Mediators in Burns, Wound Healing and Post-Burn Infection	Shriners Hospital for Children	85230	1/1/2014 - 12/31/2016	$197,984
Michelle B Lierl, MD	A Double Blind, Randomized, Sham Controlled Trial to Investigate the Effect of the CREON2000A on Asthma Control in Children with Mild to Moderate Persistent Allergic Asthma	National Institutes of Health (General Innovations and Goods, Inc.)	U44 AI095051	3/10/2016 - 3/9/2019	$27,763
David Morris, MD	Immunology/Allergy Fellowship Training Grant	National Institutes of Health (University of Cincinnati)	T32 AI060515	9/1/2014 - 8/31/2016	$54,216
Huyen-Tran Nguyen, MD	Immunology/Allergy Fellowship Training Grant	National Institutes of Health (University of Cincinnati)	T32 AI060515	7/1/2015 - 6/30/2017	$51,096
Marc E Rothenberg, MD-PHD	Expression and Function of Paired Immunoglobulin-like Receptor B in Eosinophils	US-Israel Binational Science Foundation	2011244	10/1/2012 - 9/30/2016	$2,550
Marc E Rothenberg, MD-PHD	Comparative Efficacy of Therapies for Eosinophilic Esophagitis	Patient-Centered Outcome Research Inst.	CER-1403-11593	1/1/2015 - 12/31/2017	$803,459

Marc E Rothenberg, MD-PHD	Genetic and Immunological Dissection of Eosinophilic Esophagitis	National Institutes of Health	R01 AI124355	9/1/2015 - 2/29/2020	$832,501
Marc E Rothenberg, MD-PHD	Regulation of Gastrointestinal Eosinophils	National Institutes of Health	R37 AI045898	12/1/2014 - 11/30/2019	$390,000
Marc E Rothenberg, MD-PHD	Consortium of Eosinophilic Gastrointestinal Disease Research	National Institutes of Health	U54 AI117804	8/15/2014 - 7/31/2019	$1,245,751
Jared Travers	Role of Nuclear IL-33 in Mucosal Inflammation	National Institutes of Health	F30 DK109573	4/1/2016 - 3/31/2020	$36,257
Yui Hsi Wang, PHD	IL-9-Producing Mast Cell Precursors and Food Allergy	Department of Defense	W81XWH-15-1-0517	9/30/2015 - 9/29/2018	$546,000
Ting Wen, PHD	Defining Esophageal Lymphocyte Phenotype and Function in Eosinophilic Esophagitis	Am Partnership for Eosinophilic Disorder	Wen_Apfed	7/1/2015 - 6/30/2017	$50,000
Total Annual Grant Award Dollars					**$7,651,283**

Annual Industry Award Dollars

Investigator	Industry Sponsor	Amount
Amal H Assa'ad, MD	Aimmune Therapeutic Inc.	$258,224
Amal H Assa'ad, MD	DBV Technologies	$251,142
Marc E Rothenberg, MD-PHD	Regeneron Pharmaceuticals, Inc.	$121,754
Yui Hsi Wang, PHD	MedImmune, Inc.	$756,805
Total Annual Industry Award Dollars		**$1,387,925**