Allergy and Immunology

Division Details

RESEARCH AND TRAINING DETAILS	
Faculty	**15**
Joint Appointment Faculty	**2**
Research Fellows and Post Docs	**9**
Research Graduate Students	**8**
Total Annual Grant Award Dollars	**$5,962,281**
Total Annual Industry Award Dollars	**$1,439,381**

CLINICAL ACTIVITIES AND TRAINING	
Clinical Fellows	**6**
Inpatient Encounters	**328**
Outpatient Encounters	**7,702**

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

Row 2: P Fulkerson, S Logsdon, T Wen, T Fischer, S Hogan, Y Wang

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Division Highlights

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 received recognition for their achievements throughout the year:

- Rachel Ernst and Tarah Wagner, summer students in the Rothenberg Lab, and mentored by Mark Rochman, PhD, won the Poster of Distinction at the Nutrition Research Day Poster Session at Cincinnati Children's for their work on peanut protein levels. Ernst and Wagner went on to take first place in the Agriculture / Food Science category at their high school's capstone competition on April 28.
- Justin Wheeler, MD, a clinical fellow in the Hogan Lab, was the recipient for the award for the 2017 AAAAI / APFED Best Oral Abstract on eosinophilic gastrointestinal diseases by a fellow-in-training at the 2017 American Academy of Asthma, Allergy & Immunology (AAAAI) Annual Meeting.
- Assistant professor, Ting Wen, MD, PhD, received a Trustee Grant Award by Cincinnati Children's to support the Wen Lab in investigating the roles of FFAR3 in Th2 cytokine production by esophageal lymphocytes.
- Assistant professor, Andrew W. Lindsley, MD, PhD, received a K08 from the National Institute of Allergy and Infectious Diseases (NIAID). This National Institutes of Health clinical scientist career development award will support the Lindsley Lab in investigating how the sphingolipid ORMDL3 regulates dendritic cells in asthma.
- Assistant professor, Patricia C. Fulkerson, MD, PhD, received an R01 from National Institute of Allergy and Infectious Diseases (NIAID). This R01 will support the Fulkerson Lab in investigating the role of the transcription factor Aiolos in eosinophilic asthma.

p65: A Step Back from Sepsis

Sepsis is a life-threatening condition caused by the body's response to infection injuring a person's own organs and tissues and causing endotoxic shock. Sepsis is primarily caused by Gram-negative bacteria, which trigger immune cells and cytokines. A study, published in *Innate Immunity,* and led by Simone Vanoni, PhD, and our division's director of research, Simon P. Hogan, PhD, demonstrates that lack of the protein p65, a part of the NF-κB transcription complex, in macrophages caused increased mortality in mice with endotoxic shock and that there is an association with the excessive production of proinflammatory cytokines. These findings identify a new role for NF-κB in the negative regulation of myeloid cell proinflammatory activity and function in sepsis.

Cadherin 26: Adhesion and Immunomodulation During Allergic Inflammation

Cadherins mediate diverse processes critical in inflammation, including cell adhesion, migration and differentiation. A recent study, published in *Mucosal Immunology* and led by Julie Caldwell, PhD, and Marc E. Rothenberg, MD, PhD, reported that an uncharacterized cadherin, cadherin 26 (CDH26), is highly expressed by epithelial cells in human allergic gastrointestinal tissue, such as the stomach tissue of patients with eosinophilic gastritis (EG) and esophageal tissue of patients with eosinophilic esophagitis (EoE). In vitro characterization revealed that CDH26 not only enhanced cellular adhesion through binding catenin and integrin, but also had an interesting inhibitory role when expressed as an Fc-fusion protein, with CDH26-Fc inhibiting activation of human CD4+ T cells in vitro, including secretion of IL-2. As CDH26 regulated leukocyte adhesion and activation, it may represent a novel checkpoint for immune regulation and therapy of eosinophilic gastrointestinal disorders (e.g., EG and EoE) via CDH26-Fc. A patent concerning this work was recently granted by the USA patent office.

Memory T Cell Epigenome Encodes Rapid Recall Ability

Even though T-cell receptor (TCR) stimulation with a co-stimulation is sufficient for the activation of both naïve and memory T cells, the memory cells are capable of producing lineage-specific cytokines much more rapidly than the naïve cells. The mechanisms behind this rapid recall response of the memory cells are still not completely understood. In a study published in *Scientific Reports*, Artem Barski, PhD, together with colleagues from the National Institutes of Health (NIH) and New York University, epigenetically profiled human resting naïve, central and effector memory T cells using ChIP-Seq and found that unlike the naïve cells, the regulatory elements of the cytokine genes in the memory T cells marked by activating histone modifications even in the resting state. Therefore, the ability to induce expression of rapid recall genes upon activation associates with the deposition of positive histone modifications during memory T cell differentiation. The researchers propose a model of T cell memory, in which immunologic memory state encoded epigenetically, through poising and transcriptional memory.

Siglec-8: Engaging Eosinophil Cell Death

Activation of Siglec-8 receptor on human eosinophils leads to eosinophil reactive oxygen species production and cell death. A study published in Immunobiology and led by Dr. Nives Zimmermann, MD, evaluated the suspected role of Src family kinases (SFKs) in this pathway. They discovered the requirement of SFKs for the production of intracellular reactive oxygen species via this pathway and that both the reactive oxygen species and the requirement of SFKs for Siglec-8–induced cell death in activated eosinophils. Deciphering the molecular basis of eosinophil cell death may inform translational and clinical research, as accumulation of activated eosinophils can contribute to inflammation and damage in conditions such as asthma and eosinophilic gastrointestinal disorders.

Tissue Identity in Organ-specific Responses of Allergy

Despite systemic sensitization to the triggering allergens, allergic inflammation manifests in different organs—lungs, skin and esophagus for patients with asthma, atopic dermatitis and eosinophilic esophagitis (EoE), respectively. The disparity between the systemic trigger yet organ-specific response is not well understood. In a study published in *The Journal of Allergy and Clinical Immunology*, Mark Rochman, PhD; Jared Travers, PhD; and Marc E. Rothenberg, MD, PhD, assessed the potential role of organ-specific genes in the differential manifestation of allergy. They characterized the expression of esophagus-specific genes identified by The Human Protein Atlas Project, which maps the molecular signature of tissues, in esophageal biopsy specimens of patients with EoE, a chronic, inflammatory, food allergen–driven disorder of the esophagus. Strikingly, about 39% of esophagus-specific genes had altered expression in EoE biopsies, with the downregulation of approximately 90% of these genes. These findings reveal a profound loss of differentiation within the esophageal epithelium. The whole-exome sequencing revealed mutations in several esophagus-specific genes in EoE tissue. Notably, prior research showed that the gene most strongly associated with EoE disease risk, *CAPN14*, encodes an esophagus-specific protease. These collective findings suggest that the pathogenesis of EoE involves a loss of esophageal differentiation and expand our understanding of the

propagation of allergic inflammation on the level of tissue molecular identity, suggesting that genetic profiling of tissue-specific genes may have diagnostic and prognostic value for EoE and potentially other allergic conditions.

2017 NIAID Addendum Guidelines for Preventing Peanut Allergy

In 2015, findings from a landmark National Institute of Allergy and Infectious Diseases (NIAID)-funded clinical trial, called the Learning Early About Peanut (LEAP) study, showed that introducing peanut-containing foods to infants at high risk for developing peanut allergy was safe, and led to an 81% relative reduction in the subsequent development of peanut allergy. Due to the strength of these results, NIAID established a coordinating committee that convened an expert panel to update the 2010 Guidelines to specifically address the prevention of peanut allergy. The division's director of clinical services, Amal H. Assa'ad, MD, contributed through service on the coordinating committee and expert panel to these Addendum Guidelines for the Prevention of Peanut Allergy in the United States published in the January 2017 issue of *Annals of Allergy and Immunology* along with an editorial by Amal H. Assa'ad, MD. These addendum guidelines are a major paradigm reversal by recommending early peanut introduction to infants, the importance evidenced by these guidelines published in seven prestigious journals in the fields of allergy, dermatology, nutrition and general pediatrics. Read the National Public Radio segment (by Patti Neighmond), the Reuter's article (by Rob Goodier), and a related *Journal of Allergy and Clinical Immunology* editorial about the LEAP study findings about early allergen consumption.

Food Allergy Desensitization and Tolerance Induction and Disparities

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 manufactured as Viaskin®), oral immunotherapy for peanut allergy and oral immunotherapy for multiple food allergens, with the last employing an anti-immunoglobulin E under the marketed name of Xolair® (omalizumab) to reduce the incidence of side effects that accompany oral immunotherapy. The peanut (LAMP-based) vaccine study was also initiated, with participants progressing from randomized, placebo-controlled trials to a higher dose phase. Furthermore, Amal H. Assa'ad, is collaborating in National Institutes of Health (NIH)-funded research to examine racial and ethnic disparities in food allergy, the FORWARD study, showed that children who were parent-identified as African American, or Hispanic, had different food allergen profiles, higher rates of associated atopic conditions, and increased rates of food allergen–associated anaphylaxis and emergency department visits than children who were parent-identified as Caucasian.

Physician Receives 2017 Clinical Care Award

The Faculty Awards Committee at Cincinnati Children's selected Michelle B. Lierle, MD, for the Clinical Care Award. This is a well-deserved honor for Dr. Lierl, who is now in her 30th anniversary year at Cincinnati Children's. In addition to her great clinical service, Dr. Lierl researches fungal allergens and has created a fungal spore photo website.

Fellowship Director Receives 2017 AAAAI Distinguished Service Award

The American Academy of Asthma, Allergy & Immunology (AAAAI) selected the director of our Allergy / Immunology Fellowship Program, Kimberly A. Risma, MD, PhD for their 2017 Distinguished Service Award based on her leadership with the Chrysalis Project. The Chrysalis Project is a program for medical students and internal medicine and/or pediatric residents that provides them the opportunity to explore a career in allergy / immunology. Housed within the AAAAI Annual Meeting, it includes pairing the Chrysalis mentee with a fellow-in-training mentor, didactic lectures with allergy/immunology faculty, career option presentations, and free conference registration and access to the leading knowledge in the hundreds of AAAAI meeting sessions, workshops, symposia, seminars and oral abstracts. Dr. Risma has helped to propel this program to become a jewel of our society; thus greatly impacting our field and its future. Through her efforts, she has established a 'pipeline' of strong physicians in our field. In 2010, Dr. Risma received a nomination from the Board of AAAAI to assume the co-Chair position of the Chrysalis Program Project after a pause in the program's funding. Under her leadership, the program has expanded from 20 to 50 attendees per year. The Chrysalis Project has been extraordinarily well received as evident from the growing number of highly qualified applicants and attendees, the positive reviews, and the growing number of fellowship applicants who credit the Chrysalis Project.

Division Publications

1. Lyons JJ; Yu X; Hughes JD; Le QT; Jamil A; Bai Y; Ho N; Zhao M; Liu Y; O'Connell MP. **Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number.** *Nature Genetics*. 2016; 48:1564-1569.

2. Rosen MJ; Karns R; Vallance JE; Bezold R; Waddell A; Collins MH; Haberman Y; Minar P; Baldassano RN; Hyams JS. **Mucosal Expression of Type 2 and Type 17 Immune Response Genes Distinguishes Ulcerative Colitis From Colon-Only Crohn's Disease in Treatment-Naive Pediatric Patients.** *Gastroenterology*. 2017; 152:1345-1357.e7.

3. Loyer X; Paradis V; Hénique C; Vion AC; Colnot N; Guerin CL; Devue C; On S; Scetbun J; Romain M. **Liver microRNA-21 is overexpressed in non-alcoholic steatohepatitis and contributes to the disease in experimental models by inhibiting PPAR alpha expression.** *Gut*. 2016; 65:1882-1894.

4. Rothenberg ME. **A hidden residential cell in the lung.** *Journal of Clinical Investigation*. 2016; 126:3185-3187.

5. Litosh VA; Rochman M; Rymer JK; Porollo A; Kottyan LC; Rothenberg ME. **Calpain-14 and its association with eosinophilic esophagitis.** *Journal of Allergy and Clinical Immunology*. 2017; 139:1762-1771.e7.

6. Goldberg MR; Elizur A; Nachshon L; Appel MY; Levy MB; Golobov K; Goldberg R; Stein M; Rothenberg ME; Katz Y. **Oral immunotherapy-induced gastrointestinal symptoms and peripheral blood eosinophil responses.** *Journal of Allergy and Clinical Immunology*. 2017; 139:1388-1390.e4.

7. Nowak-Wegrzyn A; Chehade M; Groetch ME; Spergel JM; Wood RA; Allen K; Atkins D; Bahna S; Barad AV; Berin C. **International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology.** *Journal of Allergy and Clinical Immunology*. 2017; 139:1111-1126.e4.

8. Togias A; Cooper SF; Acebal ML; Assa'ad A; Jr BJR; Beck LA; Block J; Byrd-Bredbenner C; Chan ES; Eichenfield LF. **Addendum guidelines for the prevention of peanut allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel.** *Journal of Allergy and Clinical Immunology*. 2017; 139:29-44.

9. Travers J; Rochman M; Miracle CE; Cohen JP; Rothenberg ME. **Linking impaired skin barrier function to esophageal allergic inflammation via IL-33.** *Journal of Allergy and Clinical Immunology*. 2016; 138:1381-1383.

10. Venter C; Groetch M. **LEAPing ahead with early allergen consumption.** *Journal of Allergy and Clinical Immunology*. 2016; 138:1119-1121.

11. 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.** *Journal of Allergy and Clinical Immunology*. 2016; 138:915-918.e5.

12. 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.** *Journal of Allergy and Clinical Immunology*. 2016; 138:676-699.

13. Lages CS; Simmons J; Maddox A; Jones K; Karns R; Sheridan R; Shanmukhappa SK; Mohanty S; Kofron M; Russo P. **The Dendritic Cell-T Helper 17-Macrophage Axis Controls Cholangiocyte Injury and Disease Progression in Murine and Human Biliary Atresia.** *Hepatology*. 2017; 65:174-188.

14. Lyons JJ; Liu Y; Ma CA; Yu X; O'Connell MP; Lawrence MG; Zhang Y; Karpe K; Zhao M; Siegel AM. **ERBIN deficiency links STAT3 and TGF-beta pathway defects with atopy in humans.** *The Journal of Experimental Medicine*. 2017; 214:jem.20161435.

15. McNally JP; Millen SH; Chaturvedi V; Lakes N; Terrell CE; Elfers EE; Carroll KR; Hogan SP; Andreassen PR; Kanter J. **Manipulating DNA damage-response signaling for the treatment of immune-mediated diseases.** *Proceedings of the National Academy of*

Sciences of the United States of America. 2017; 114:E4782-E4791.

16. Dellon ES; Collins MH; Bonis PA; Leung J; Capocelli KE; Dohil R; Falk GW; Furuta GT; Menard-Katcher C; Gupta SK. **Substantial Variability in Biopsy Practice Patterns Among Gastroenterologists for Suspected Eosinophilic Gastrointestinal Disorders.** *Clinical Gastroenterology and Hepatology*. 2016; 14:1842-1844.
17. Shik D; Tomar S; Lee JB; Chen CY; Smith A; Wang YH. **IL-9-producing cells in the development of IgE-mediated food allergy.** *Springer Seminars in Immunopathology*. 2017; 39:69-77.
18. Kottyan LC; Rothenberg ME. **Genetics of eosinophilic esophagitis.** *Mucosal immunology*. 2017; 10:580-588.
19. Verma AH; Bueter CL; Rothenberg ME; Deepe GS. **Eosinophils subvert host resistance to an intracellular pathogen by instigating non-protective IL-4 in CCR2 (-/-) mice.** *Mucosal immunology*. 2017; 10:194-204.
20. Stevens ML; Chaturvedi P; Rankin SA; Macdonald M; Jagannathan S; Yukawa M; Barski A; Zorn AM. **Genomic integration of Wnt/beta-catenin and BMP/Smad1 signaling coordinates foregut and hindgut transcriptional programs.** *Development (Cambridge)*. 2017; 144:1283-1295.
21. Roberts G; Boyle R; Bryce PJ; Crane J; Hogan SP; Saglani S; Wickman M; Woodfolk JA. **Developments in the field of clinical allergy in 2015 through the eyes of Clinical and Experimental Allergy.** *Clinical and Experimental Allergy*. 2016; 46:1389-1397.
22. Roberts G; Boyle R; Bryce PJ; Crane J; Hogan SP; Saglani S; Wickman M; Woodfolk JA. **Developments in the field of allergy mechanisms in 2015 through the eyes of Clinical & Experimental Allergy.** *Clinical and Experimental Allergy*. 2016; 46:1248-1257.
23. Peter JG; Lehloenya R; Dlamini S; Risma K; White KD; Konvinse KC; Phillips EJ. **Severe Delayed Cutaneous and Systemic Reactions to Drugs: A Global Perspective on the Science and Art of Current Practice.** *The journal of allergy and clinical immunology. In practice*. 2017; 5:547-563.
24. Mahdavinia M; Fox SR; Smith BM; James C; Palmisano EL; Mohammed A; Zahid Z; Assa'ad AH; Tobin MC; Gupta RS. **Racial Differences in Food Allergy Phenotype and Health Care Utilization among US Children.** *The journal of allergy and clinical immunology. In practice*. 2017; 5:352-357.e1.
25. Daly MC; Atkinson SJ; Varisco BM; Klingbeil L; Hake P; Lahni P; Piraino G; Wu D; Hogan SP; Zingarelli B. **Role of matrix metalloproteinase-8 as a mediator of injury in intestinal ischemia and reperfusion.** *The FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. 2016; 30:3453-3460.

Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Marc E Rothenberg, MD, PhD	Regulation of Gastrointestinal Eosinophils	National Institutes of Health	R37 AI045898	12/01/2014 - 11/30/2019	$390,000
Marc E Rothenberg, MD, PhD	Consortium of Eosinophilic Gastrointestinal Disease Researchers	National Institutes of Health	U54 AI117804	08/15/2014 - 07/31/2019	$1,596,844
Simon Patrick Hogan, PhD	Leukocyte Immunoglobulin-like Receptor B3 in Innate Colonic Inflammation in Pediatric UC	Crohn's & Colitis Foundation of America	272118	07/01/2014 - 06/30/2017	$115,830

Marc E Rothenberg, MD, PhD	Comparative Efficacy of Therapies for Eosinophilic Esophagitis	Patient-Centered Outcome Research Inst.	CER-1403-11593	01/01/2015 - 12/31/2017	$877,202
Yui Hsi Wang, PhD	IL-9-Producing Mast Cell Precursors and Food Allergy	Department of Defense	W81XWH-15-1-0517	09/30/2015 - 09/29/2018	$546,000
Simon Patrick Hogan, PhD Yui His Wang, PhD	Food Allergy and Goblet Cell Antigen Passages	National Institutes of Health	R01 AI112626	05/04/2015 - 04/30/2020	$480,858
Ting Wen, PhD	Defining Esophageal Lymphocyte Phenotype and Function in Eosinophilic Esophagitis	Am Partnership for Eosinophilic Disorder	Wen_Apfed	07/01/2015 - 06/30/2017	$50,000
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	07/01/2015 - 06/30/2020	$150,000
David Morris, MD	Immunology/Allergy Fellowship Training Grant	National Institutes of Health (University of Cincinnati)	T32 AI060515	09/01/2014 - 09/01/2016	$7,850
Marc E Rothenberg, MD, PhD	Genetic and Immunological Dissection of Eosinophilic Esophagitis	National Institutes of Health	R01 AI124355	09/01/2015 - 02/29/2020	$555,000
Jared Travers	Role of Nuclear IL-33 in Mucosal Inflammation	National Institutes of Health	F30 DK109573	04/01/2016 - 03/31/2018	$36,257
Amal H Assa'ad, MD	FARE Clinical Center of Excellence (CCE)	Food Allergy Research & Education, Inc	FARE_Assa'ad	07/01/2015 - 06/30/2020	$118,447.80
Marc E Rothenberg, MD, PhD	The Expression and Function of CD300f in Adipose Tissue Eosinophils	US-Israel Binational Science Foundation	2015163	10/01/2016 - 09/30/2020	$10,692
Andrew W Lindsley, MD, PhD	ORMDL3 Enhances Macrophage Function in Asthma Pathogenesis	Amer Acad of Allergy, Asthma & Immunol	AAAAI_Lindsley	07/01/2016 - 06/30/2019	$80,000
Huyen-Tran Nguyen, MD	Immunology/Allergy Fellowship Training Grant	National Institutes of Health (University of Cincinnati)	T32 AI060515	07/01/2015 - 06/30/2017	$62,066
Patricia C Fulkerson, MD, PhD	Role of Aiolos in Eosinophilic Asthma	National Institutes of Health	R01 AI130033	03/16/2017 - 02/28/2022	$390,000

Andrew W Lindsley, MD, PhD	ORMDL3 Regulation of Dendritic Cells in Asthma	National Institutes of Health	K08 AI125675	03/15/2017 - 02/28/2020	$189,000
Artem Barski, PhD	Dendritic cell KLF2/Notch Axis and Th2 Responses to Eukaryotic Pathogens	National Institutes of Health (University of Cincinnati)	R01 AI126818	06/10/2016 - 05/31/2021	$25,958
Marc E Rothenberg, MD, PhD	Development of Non-Invasive Biomarkers for Eosinophilic Esophagitis by Genetic Testing and Molecular Profiling of the Buccal Mucosa	Ending Allergies Together (EAT)	EAT_Rothenberg	01/01/2017 - 12/31/2018	$76,416
Eric M Schauberger DO, PhD	Immunology/Allergy Fellowship Training Grant	National Institutes of Health (University of Cincinnati)	T32 AI060515	09/01/2016 - 06/30/2019	$43,430
Andrew T Dang, MD	Immunology/Allergy Fellowship Training Grant	National Institutes of Health (University of Cincinnati)	T32 AI060515	09/01/2016 - 06/30/2019	$43,430
Daniel Prows, PhD Nives Zimmermann	A Novel Mouse Model of Eosinophilic Vasculitis with Cardiac Complications	National Institutes of Health	R21 HL135507	01/12/2017 - 12/31/2019	$117,000
Total Annual Grant Award Dollars					**$5,962,280.80**

Annual Industry Award Dollars

Investigator	Industry Sponsor	Amount
Amal H Assa'ad, MD	Aimmune Therapeutic Inc.	$672,376.40
Amal H Assa'ad, MD	Astellas Pharma US, Inc.	$252,000
Amal H Assa'ad, MD	Teva Pharmaceuticals	$16,900
Ting Wen, PhD	Aimmune Therapeutic Inc.	$498,105
Total Annual Industry Award Dollars		**$1,439,381.40**