Immunobiology

Division Photo

First Row: M. Jordan, M Wills-Karp, F. Finkelman
Second Row: D. Hildeman, H. L. Grimes
Missing: J. Mattner

Division Data Summary

Research and Training Details	
Number of Faculty	6
Number of Joint Appointment Faculty	3
Number of Research Fellows	8
Number of Research Students	9
Number of Support Personnel	20
Direct Annual Grant Support	$3,617.395
Direct Annual Industry Support	$31,421
Peer Reviewed Publications	30
Clinical Activities and Training	
Number of Clinical Staff	1
Number of Clinical Fellows	2

Significant Publications

Khodoun M, R Strait, T Orekov, et al., Peanuts can contribute to anaphylactic shock by activating complement. J Allergy Clin Immunol 2009, 123:342-51.

Dr. Finkelman and his group have discovered a potential mechanism for the development of anaphylactic shock in children allergic to peanuts. Specifically, they show that peanuts, not other common allergens, can cause shock by activating complement factor 3, which in turn stimulates inflammatory cells leading to the production of platelet-activating factor and histamine. Identification of this putative pathway might provide a strategy for the development of therapies aiming at inhibiting complement activation pathways in children susceptible to peanut-induced anaphylaxis or to the development of strategies for engineering peanuts that have reduced ability to activate these pathways.

Nathan AT, EA Peterson, J Chakir, et al., Innate immune responses of airway epithelium to house dust mite are mediated through beta-glucan-dependent pathways. J Allergy Clin Immunol 2009, 123:612-8

Drs. Nathan and Wills-Karp made the novel discovery that the aberrant immune responses to the most common allergen, house dust mite, are initiated at the airway surface via a specific pattern recognition receptor in the beta-glycan receptor family. This is the first description of an allergen initiating innate immune responses through a specific protein receptor. These results should fuel further studies to develop new therapeutic strategies to prevent the development of allergic sensitization and the lifetime consequences of such sensitization in genetically susceptible individuals.

Lewis CC, B Aronow, J Hutton, et al., Unique and overlapping gene expression patterns driven by IL-4 and IL-13 in the mouse lung. J Allergy Clin Immunol 2009, 123:795-804 e8..

Dr. Wills-Karp and her group have previously reported that the cytokine, IL-13, is the main mediator of allergic asthma in children (Science, 1998). In this publication, her group identifies the downstream pathways by which IL-13 induces the symptoms of asthma through a series of transcriptome profiling experiments. Identification of the downstream pathways activated by IL-13 in the lung may provide novel targets for therapeutic development for this ever-increasing, debilitating disease of children.

Division Highlights

David Hildeman, PhD

Dr. Hildeman in collaboration with Claire Chougnet's lab in Molecular Immunology has found that a "suppressive" population of T cells accumulates in aging mice and humans. These suppressive T cells impair the ability to combat chronic infection and can lead to infectious disease reactivation. Moreover, they have found that these suppressive cells accumulate due to their decreased expression of the pro-apoptotic molecule Bim. These studies have broad implications for the development of therapies which could enhance the efficacy of vaccines, enhance immunosurveillance of cancer cells, and/or control aberrant immune responses in autoimmunity.

Division Collaboration

Collaboration with Allergy/Immunology

Collaborating Faculty: Kimberly Risma, MD

Drs. Jordan and Risma collaborated on studies characterizing how perforin, a critical molecule for immune 'killer cell' function, performs it's duty. They used naturally occurring mutants of this protein and a unique liposome based assay to describe how perforin latches on to cell membranes. They report for the first time that perforin disruption of target cell membranes requires binding of a calcium-dependent, lipid-inserting, C2 domain. Moreover, they report that in a family affected by hemophagocytic lymphohistiocytosis, a severe inflammatory disorder caused by perforin deficiency, 2 amino acid substitutions in the perforin C2 domain are associated with impaired perforin function (Blood, 2009).

Collaboration with Bone Marrow Transplantation and Immune Deficiency

Collaborating Faculty: RA Marsh, MD

Dr. Jordan collaborated with Dr. Marsh and colleagues to help develop a new assay for diagnosing XLP-2, a rare but devastating disorder of immune regulation affecting children (Cytometry B. CLin. Cytom., 2009).

Collaboration with Experimental Hematology

Collaborating Faculty: Yi Zhang, PhD

Dr. Hildeman, in collaboration with Dr. Zhang in the Division of Experimental Hematology, reported that Rac1 and Rac2 have unique roles in common lymphoid progenitor production and share a redundant but essential role in later stages of T-cell development by regulating survival and proliferation signals (Blood, 2008).

Collaboration with Loyola University Medical Center

Collaborating Faculty: R. Popovic, PhD

Dr. Grimes in collaboration with investigators at Loyola University Medical Center, reported that a specific microRNA (mir-196B) is required for the chromosomal transolocations involving the mixed lineage leukemia gene (MLL) that produce chimeric proteins that cause leukemia. Furthermore, overexpression of mir-196b was found specifically in patients with MLL associated leukemias. Their results suggest a mechanism whereby increased expression of mir-196b by MLL fusion proteins significantly contributes to leukemia development (Blood, 2009).

Collaboration with Molecular Immunology

Collaborating Faculty: Christopher Karp, MD

Dr. Wills-Karp in collaboration with Dr. Karp has reported that a component of the common allergen, house dust mite, contributes to the initiation of immune responses through reconstituting the TLR4 receptor signaling pathways in the lungs, through its structural homology with the TLR4 adapter protein, MD-2. This discovery may explain why this allergen and others are allergenic and provide novel avenues for the development of therapies for these ever increasing allergic disorders (Nature, 2009).

Collaboration with Johns Hopkins University

Collaborating Faculty: Estelle Gauda, MD

Dr. Wills-Karp in collaboration with investigators at Johns Hopkins University have shown that caffeine which is commonly used to treat apnea in premature infants, increases cAMP production and inhibits the production of the proinflammatory cytokine, TNF-alpha, by cord blood monocytes through blocking the adenosine 1 receptor. These studies suggest that caffeine treatment of neonates may reduce inflammatory processes (Ped. Res., 2009).

Collaboration with Mediator & Cytokine Measurement Core

Collaborating Faculty: Marsha Wills-Karp, PhD

The Mediator and Cytokine Measurement Core run by the Division of Immunobiology has provided measurements of various biological mediators for numerous investigators at CCHMC (Gastroenterology, Experimental Hematology, Asthma Research, Infectious Disease, Developmental Biology, Molecular Cardiology, Molecular Immunology, Allergy/Immunology, Psychiatry, Neonatology & Pulmonary Biology,Rheumatology,Digestive Diseases,Pathology & Lab Medicine, Environmental Health, Psychiatry) and other institutions (Johns Hopkins University, UCCOM (ID, Neurology, EHS, Physiology, Surgery, Rheumatology, Cancer Cell Biology, Molecular Genetics), Wright State University).

Faculty Members

Marsha Wills-Karp, PhD, Professor ; *Division Director; Director of Immunobiology Graduate Program; Associate Dean for Basic Science and Special Projects - UCCOM*

Fred Finkelman, MD, Professor ; *McDonald Professor, UC Department of Internal Medicine, Division of Rheumatology and Immunology*

H. Leighton Grimes, PhD, Associate Professor ; *Scholar, Leukemia and Lymphoma Society; Director Cancer Pathology Program*

David A. Hildeman, PhD, Associate Professor ; *Associate Director, Immunobiology Graduate Program*

Michael B. Jordan, MD, Assistant Professor

Jochen Mattner, MD, Assistant Professor

Joint Appointment Faculty Members

Eman Al-Khadra, MD, Assistant Professor
Critical Care Medicine

Amy Nathan, MD, Assistant Professor
Neonatology and Pulmonary Biology

Kristen Page, PhD, Associate Professor
Critical Care Medicine

Trainees

- **Pulak Tripathi, PhD,** PGY-6,
- **Adora Lin, BS,** GS-5,
- **Vanessa Saunders, BS,** GS-6,
- **Marat Khodoun, PhD,** PGY5,
- **Ian Lewkowich, PhD,** PGY-5,
- **Erin Zoller, BS,** GS-5,
- **Chinavenmeni Velu, PhD,** PGY-4,
- **James Phelan, BS,** GS-4,
- **Meghan Rojas, BS,** GS-4,

- **Stephane Lajoie, PhD,** PGY-3,
- **Sema Kurtulus, BS,** GS-3,
- **Aditya Chaubey, PhD,** PGY-2,
- **Yuzaburo Inoue, MD/PhD,** PGY-2,
- **Theodore Johnson, MD,** PGY-2,
- **Yusuke Suzuki, PhD,** PGY-2,
- **Robert Thacker, MD,** PGY-2,
- **Mark Webb, BS,** GS-2,
- **Catherine Hair, BS,** GS-1,
- **Stacey Burgess, BS,** GS-1,
- **Jana Raynor, BS,** GS-1,

Significant Accomplishments

Identification of a novel receptor for the common allergen, house dust mite.

The Division of Immunobiology has had a successful year in exploring the immunologic and genetic basis of immune-driven diseases. The Division is continuing to mature and grow in stature as evidenced by the productivity of the faculty (34 articles in top ranked journals this year), their continued success in securing funding for their respective programs (3 new RO1s, several foundation grants), their numerous invitations to speak at national and international meetings and their invitations to serve on NIH study sections (4 members are currently participating on study sections). One of the exciting discoveries made in the division this year by Dr. Wills-Karp and her group is that aberrant immune responses to the most common allergen, house dust mite, are initiated at the airway surface via a specific pattern recognition receptor in the b-glycan receptor family. This is the first evidence that allergens elicit innate immune responses via activation of specific receptor pathways at the surface of the airways. This work was published in JACI, 2009. In collaboration, with Dr. Karp's group, they reported that other components of the house dust mite (Der p 2) also contribute to the initiation of immune responses through reconstituting the TLR4 receptor signaling pathway in the lungs, through its structural homology with the TLR4 adapter protein, MD-2 (Nature, 2009). Determination of the extent that each of these pathways contributes to the aberrant immune responses associated with asthma is currently underway. These discoveries will hopefully lead to a better understanding of disease pathogenesis as well as the development of novel disease modifying therapies for this ever-increasing debilitating disease.

Disruption of ancient transcriptional circuitry may contribute to myeloid leukemia.

Dr. Grimes, a Leukemia and Lymphoma Society Scholar, has had an exceptional year with several important discoveries. He originally identified Growth factor independent-1 (Gfi1), a transcriptional repressor that is mutated in patients with severe congenital neutropenia (SCN) and non-immune chronic idiopathic neutropenia of adults (NI-CINA). This year, the lab has described the deregulation of microRNA in mice and humans with Gfi1 loss of function. Interestingly, the forced expression of two of these microRNA recapitulates the phenotype seen in SCN patients; a complete block to granulopoiesis. Moreover, Dr. Grimes' group has described a novel transcriptional circuit underlying the accumulation of arrested myeloid progenitors in Gfi1-mutant SCN patients. The genetic interaction of Gfi1 with the HoxA9-Meis1-Pbx1 complex was shown to control myeloid progenitor accumulation and monopoiesis, but was separable from Gfi1 control of granulopoiesis. Dr. Grimes collaborated with Brian Gebelein to show that this transcriptional interaction is conserved in *Drosophila* anterior posterior patterning. Importantly, the conditional deletion of Gfi1 in the context of mutant K-Ras activation leads to a potent leukemia in just 17 days. Thus, work this year by the Grimes lab has illustrated an ancient transcriptional circuit underlying myeloid progenitor transformation. As patients with SCN are at a greater risk for developing myeloid leukemia, this pathway may underlie the development of leukemia in these patients. He was invited to give the Plenary Session on this important work at the American Society of Hematology. His work is funded by the National Cancer Institute, the National Heart Lung and Blood Institute and several independent international organizations. He is also currently serving as a permanent member of an NIH study section.

Infectious Origins of Autoimmunity

Dr. Jochen Mattner, who joined the Division in January 2008, has discovered a novel association between bacterial infections and the development of autoimmune diseases [i.e. primary biliary cirrhosis (PBC]. Specifically, he has provided evidence in a mouse model that infection with a specific bacterial species, *Novosphingobium spp*., is sufficient to induce a liver disease which mimics that seen in human PBC patients. As patients with PBC demonstrate evidence of chronic infection of the liver with *Novoshingobium*, these results suggest that an infectious trigger may drive the development of autoimmunity. Dr. Mattner has also identified a susceptibility gene, CD101, which may alter the ability to clear the bacterial infection and thus enhance the development of autoimmunity in susceptible individuals. These studies may

revolutionize our thinking of the etiology of autoimmunity and lead to development of novel therapies for the treatment of these debilitating diseases. Evidence of the novelty and importance of his work is the fact that he was awarded his first NIH RO1 on the 1st submission. In addition, he has successfully submitted several local grants including the: Microbial Pathogenesis Pilot Grant, the Digestive Health Center Pilot Project Grant, and the Trustee Award over his first year here at CCHMC and given invited talks at several national and international conferences this year.

Division Publications

1. Lewkowich I, Wills-Karp M. "Animal models of allergic diseases." *Middleton's allergy : principles & practice.* Philadelphia, PA: Mosby/Elsevier; 2009: 437-454.
2. Niese KA, Collier AR, Hajek AR, Cederbaum SD, O'Brien WE, Wills-Karp M, Rothenberg ME, Zimmermann N. Bone marrow cell derived arginase I is the major source of allergen-induced lung arginase but is not required for airway hyperresponsiveness, remodeling and lung inflammatory responses in mice. *BMC Immunol.* 2009; 10: 33.
3. Lewis CC, Aronow B, Hutton J, Santeliz J, Dienger K, Herman N, Finkelman FD, Wills-Karp M. Unique and overlapping gene expression patterns driven by IL-4 and IL-13 in the mouse lung. *J Allergy Clin Immunol.* 2009; 123: 795-804 e8.
4. Popovic R, Riesbeck LE, Velu CS, Chaubey A, Zhang J, Achille NJ, Erfurth FE, Eaton K, Lu J, Grimes HL, Chen J, Rowley JD, Zeleznik-Le NJ. Regulation of mir-196b by MLL and its overexpression by MLL fusions contributes to immortalization. *Blood.* 2009; 113: 3314-22.
5. Zhang X, Lewkowich IP, Kohl G, Clark JR, Wills-Karp M, Kohl J. A protective role for C5a in the development of allergic asthma associated with altered levels of B7-H1 and B7-DC on plasmacytoid dendritic cells. *J Immunol.* 2009; 182: 5123-30.
6. Gu Y, Harley IT, Henderson LB, Aronow BJ, Vietor I, Huber LA, Harley JB, Kilpatrick JR, Langefeld CD, Williams AH, Jegga AG, Chen J, Wills-Karp M, Arshad SH, Ewart SL, Thio CL, Flick LM, Filippi MD, Grimes HL, Drumm ML, Cutting GR, Knowles MR, Karp CL. Identification of IFRD1 as a modifier gene for cystic fibrosis lung disease. *Nature.* 2009; 458: 1039-42.
7. Chavez-Valdez R, Wills-Karp M, Ahlawat R, Cristofalo EA, Nathan A, Gauda EB. Caffeine modulates TNF-alpha production by cord blood monocytes: the role of adenosine receptors. *Pediatr Res.* 2009; 65: 203-8.
8. Khodoun M, Strait R, Orekov T, Hogan S, Karasuyama H, Herbert DR, Kohl J, Finkelman FD. Peanuts can contribute to anaphylactic shock by activating complement. *J Allergy Clin Immunol.* 2009; 123: 342-51.
9. Morris SC, Heidorn SM, Herbert DR, Perkins C, Hildeman DA, Khodoun MV, Finkelman FD. Endogenously produced IL-4 nonredundantly stimulates CD8+ T cell proliferation. *J Immunol.* 2009; 182: 1429-38.
10. 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.
11. Urrea Moreno R, Gil J, Rodriguez-Sainz C, Cela E, LaFay V, Oloizia B, Herr AB, Sumegi J, Jordan MB, Risma KA. Functional assessment of perforin C2 domain mutations illustrates the critical role for calcium-dependent lipid binding in perforin cytotoxic function. *Blood.* 2009; 113: 338-46.
12. Trompette A, Divanovic S, Visintin A, Blanchard C, Hegde RS, Madan R, Thorne PS, Wills-Karp M, Gioannini TL, Weiss JP, Karp CL. Allergenicity resulting from functional mimicry of a Toll-like receptor complex protein. *Nature.* 2009; 457: 585-8.
13. Nathan AT, Peterson EA, Chakir J, Wills-Karp M. Innate immune responses of airway epithelium to house dust mite are mediated through beta-glucan-dependent pathways. *J Allergy Clin Immunol.* 2009; 123: 612-8.
14. Yin N, Long X, Goff RD, Zhou D, Cantu C, 3rd, Mattner J, Mezard PS, Teyton L, Bendelac A, Savage PB. Alpha anomers of iGb3 and Gb3 stimulate cytokine production by natural killer T cells. *ACS Chem Biol.* 2009; 4: 199-208.
15. Velu CS, Baktula AM, Grimes HL. Gfi1 regulates miR-21 and miR-196b to control myelopoiesis. *Blood.* 2009; 113: 4720-8.
16. Horman SR, Velu CS, Chaubey A, Bourdeau T, Zhu J, Paul WE, Gebelein B, Grimes HL. Gfi1 integrates progenitor versus granulocytic transcriptional programming. *Blood.* 2009; 113: 5466-75.
17. Lewkowich IP, Lajoie S, Clark JR, Herman NS, Sproles AA, Wills-Karp M. Allergen uptake, activation, and IL-23 production by pulmonary myeloid DCs drives airway hyperresponsiveness in asthma-susceptible mice. *PLoS One.* 2008; 3: e3879.
18. Wills-Karp M. **"Immunological mechanisms of allergic disease."** *Fundamental immunology.* Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2008: 1375-1425.
19. Wills-Karp M, Finkelman FD. Untangling the complex web of IL-4- and IL-13-mediated signaling pathways. *Sci*

Signal. 2008; 1: pe55.

20. Li-Kroeger D, Witt LM, Grimes HL, Cook TA, Gebelein B. Hox and senseless antagonism functions as a molecular switch to regulate EGF secretion in the Drosophila PNS. *Dev Cell.* 2008; 15: 298-308.
21. Lages CS, Suffia I, Velilla PA, Huang B, Warshaw G, Hildeman DA, Belkaid Y, Chougnet C. Functional regulatory T cells accumulate in aged hosts and promote chronic infectious disease reactivation. *J Immunol.* 2008; 181: 1835-48.
22. Hildeman D, Janssen E. IFN-gamma and self-absorbed CD4+ T cells: a regulatory double negative. *Nat Immunol.* 2008; 9: 1210-2.
23. Montoya-Durango DE, Velu CS, Kazanjian A, Rojas ME, Jay CM, Longmore GD, Grimes HL. Ajuba functions as a histone deacetylase-dependent co-repressor for autoregulation of the growth factor-independent-1 transcription factor. *J Biol Chem.* 2008; 283: 32056-65.
24. Herbert DR, Orekov T, Perkins C, Finkelman FD. IL-10 and TGF-beta redundantly protect against severe liver injury and mortality during acute schistosomiasis. *J Immunol.* 2008; 181: 7214-20.
25. Vas J, Mattner J, Richardson S, Ndonye R, Gaughan JP, Howell A, Monestier M. Regulatory roles for NKT cell ligands in environmentally induced autoimmunity. *J Immunol.* 2008; 181: 6779-88.
26. Jordan MB, Filipovich AH. Hematopoietic cell transplantation for hemophagocytic lymphohistiocytosis: a journey of a thousand miles begins with a single (big) step. *Bone Marrow Transplant.* 2008; 42: 433-7.
27. Chen W, Tabata Y, Gibson AM, Daines MO, Warrier 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.
28. Guo F, Cancelas JA, Hildeman D, Williams DA, Zheng Y. Rac GTPase isoforms Rac1 and Rac2 play a redundant and crucial role in T-cell development. *Blood.* 2008; 112: 1767-75.
29. Le Gros G, Ben-Sasson SZ, Seder R, Finkelman FD, Paul WE. Generation of interleukin 4 (IL-4)-producing cells in vivo and in vitro: IL-2 and IL-4 are required for in vitro generation of IL-4-producing cells. *J Immunol.* 2008; 181: 2943-51.
30. Yamada Y, Sanchez-Aguilera A, Brandt EB, McBride M, Al-Moamen NJ, Finkelman FD, Williams DA, Cancelas JA, Rothenberg ME. FIP1L1/PDGFRalpha synergizes with SCF to induce systemic mastocytosis in a murine model of chronic eosinophilic leukemia/hypereosinophilic syndrome. *Blood.* 2008; 112: 2500-7.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct / Project Period Direct
GRIMES, L		
Molecular Mechanism of Severe Congenital Neutropenia National Institutes of Health R01 HL 079574	10/01/05 - 07/31/09	$237,045 / $976,500
A Molecular Basis for Neuroendocrine Carcinogenesis National Institutes of Health R01 CA 112405	02/01/06 - 12/31/09	$155,502 / $640,584
The Molecular Basis of Acute Myeloid Leukemia The Leukemia and Lymphoma Society	10/01/05 - 06/30/10	$105,000 / $525,000
Molecular Control Lung Adenocarcinoma Initiating Cell University of Cincinnati Cancer Center	07/01/08 - 06/30/09	$40,000 / $40,000
9q23 Leukemia Children's Leukemia Research Association	01/01/09 - 12/31/09	$20,000 / $20,000
A Potential Cure for Myeloid Leukemia Cancer Free Kids	05/06/09 - 05/05/10	$36,000 / $36,000
HILDEMAN, D		
Regulation of Apoptosis in Activated Primary T Cells National Institutes of Health R56 AI 057753	09/01/08 - 08/31/09	$250,000 / $250,000

Transforming Growth Factor Beta in T-Cell Homeostasis and Tolerance
National Institutes of Health (Arizona Board of Regents)
R01 AI 067903 03/01/07 - 02/28/11 $20,485 / $81,940

Regulation of Apoptosis in Activated Primary T Cells
National Institutes of Health
R01 AI 057753 12/01/08 - 11/30/13 $70,997 / $1,107,613

JORDAN, M

An Animal Model of Hemaophagocytic Lymphohistiocytosis
National Institutes of Health
R01 AI 091769 08/10/07 - 06/30/12 $250,000 / $1,250,000

Mechanisms of Interferon Gamma Induced Hemophagocytosis
Histiocytosis Association of America
11/01/08 - 10/31/09 $50,000 / $50,000

MATTNER, J

Sphinogomonas Breaks Peripheral Tolerance Due to NKT Cell
Lupus Research Institute
01/01/08 - 10/31/09 $100,000 / $186,400

Primary Biliary Cirrhosis: Molecular Genetics and Microbial Pathogenesis
National Institutes of Health
R01 DK 084054 06/01/09 - 05/31/14 $250,000 / $1,250,000

Autoimmune Liver Disease Triggered by Bacterial Commensals
University of Cincinnati
08/01/08 - 07/31/09 $20,000 / $20,000

WILLS-KARP, M

Interleukin-13 in Experimental Asthma
National Institutes of Health
P01 HL 076383 07/01/04 - 06/30/09 $1,360,858 / $7,008,574

Wills-Karp, M	Component I	281,378
Finkelman, F	Component 2	281,378
Rothenberg, M	Component 3	281,378
Hershey, G	Component 4	281,378
Witte, D	Scientific Core #1	82,891
Rothenberg, M	Scientific Care #2	94,971
Wills-Karp, M	Administrative Core	57,484

Asthma Positional Candidate Genes in Mice And Humans
National Institutes of Health
R01 HL 067736 12/01/05 - 11/30/10 $242,750 / $1,250,000

Mechanism of PM Induced Dendritic Cell Activation
National Institutes of Health (Johns Hopkins University)
P50 ES 015903 09/29/07 - 06/30/12 $218,731 / $1,122,049

Epithelial Genes in Allergic Inflammation
National Institutes of Health
U19 AI 070235 09/15/06 - 08/31/11 $190,027 / $978,425

Current Year Direct **$3,617,395**

Industry Contracts

Wills-Karp

Allertein Therapeutics $ 31,421

Current Year Direct Receipts	**$ 31,421**
Total	**$3,648,816**

Immunobiology Graduate Program

The Immunobiology Graduate Program is an inter-departmental program within the University of Cincinnati that offers PhD and MS degrees in Immunology. The Division of Immunobiology serves as the administrative home of the Graduate Program. The program is governed by the director Dr. Wills-Karp and Associate Director Dr. Christopher Karp and a Steering Committee composed of members of several departments/divisions at CCHMC and UC. Dr. Jonathan Katz is the coordinator of the Foundations in Immunology Courses.

The Immunobiology Program provides broadly based instruction in immunology, along with rigorous research training that emphasizes modern approaches to understanding the function of the immune system in health and disease. To this end, the program currently has 45 faculty members from 4 departments and 12 divisions within the College of Medicine and CCHMC. Since its inception in 2003, we have enrolled 25 outstanding students from around the country and abroad. Milestones achieved this year include the graduation of our first student and the successful completion of the written qualifier by all of the first year students. Our students have distinguished themselves already by receiving several travel and research awards (AAAI, Keystone Symposium, XXI International Complement Workshop).

The Program is supported financially by a variety of sources. This year, tuition support was provided through University Graduate Scholarships awarded by the University of Cincinnati. Student stipends were supported through a variety of sources including funds from the University of Cincinnati (UGA), NIH training grants, external grants to their advisors, and funds from Cincinnati Children's Research Foundation. The program anticipates sustained growth over the next few years with a target class size of 10 new students per year.

Immunobiology Graduate Program Students, 2007-2008

Student	Faculty Mentor	Admission Year
Jessica Allen	Christopher Karp	2004
Adora Lin	David Hildeman	2004
Vanessa Saunders	Marsha Wills-Karp	2004
Leah Kottyan	Nives Zimmermann	2005
Xun Zhang	Joerg Koehl	2005
Erin Zoller	Michael Jordan	2005
Katherine Groschwitz	Simon Hogan	2005
Erin Klenk	Robert Colbert	2006
James Phelan	H. Leighton Grimes	2006
Manuel Alvarez	Sherry Thornton	2006
Jill Fritz	Timothy Weaver	2006
Joni Ullman	Jay Degen	2006
Amanda Beichler	Simon Hogan	2007
Cortez McBerry	Julio Aliberti	2007
Rachael Mintz	Suzanne Wells	2007
Sema Kurtulus	David Hildeman	2007
Ibrahim Aksoylar	Kasper Hoebe	2007

Student Honors

- **Jessica Allen** Supported by NIH Bioterrorism Training Grant
- **Jill Fritz** Supported by Cardiovascular and Pulmonary Training Grant
- **Katherine Groschwitz** Received ST*AR Travel Award from AAAAI, and Keystone Symposia Scholarship; "Mast Cell-Mediated Intestinal Permeability," National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

- **Leah Kottyan** Received ST*AR Travel Award from AAAAI, Outstanding Trainee Award from International Eosinophil Society meeting and P.E.O Scholar Award (PEO is a philanthropic organization that provides competitive, merit-based awards for women of the United States and Canada who are either pursuing a doctoral level degree or engaged in postgraduate study or research at an accredited college or university).
- **Cortez McBerry** Received Yates Scholarship Award
- **Vanessa Saunders** Received ST*AR Travel Award from AAAAI, Travel Award from American Thoracic Society, UC Conference Travel Award for Autumn Immunology Conference, Preparing Future Faculty Program
- **Xun Zhang** Received Trainee Award from the XXI International Complement Workshop

Publications (2007-08)

1. Tuner MJ, ML DeLay, S Bai, E Klenk, and RA Colbert. **HLA-B27 up-regulation causes accumulation of misfolded heavy chains and correlates with the magnitude of the unfolded protein response in transgenic rats: Implications for the pathogenesis of spondylarthritis-like disease.** *Arthritis Rheum.* 56(1):215-223. 2007.
2. Zhang X, J Clark, G Köhl, M Wills-Karp and J Köhl. **Opposing roles for C5aR- and C3aR signaling in the development of maladaptive immunity in allergic asthma.** *Mol Immunol.* 44(16):3912. 2007.
3. Phelan JD, T Orekov, and F Finkelman. **Cutting edge: Mechanism of enhancement of in vivo cytokine effects by anti-cytokine monoclonal antibodies.** *J Immunol.* 180(1):44-8. 2008.
4. Smith JA, MJ Turner, ML DeLay, EI Klenk, DP Sowders, and RA Colbert. **Endoplasmic reticulum stress and the unfolded protein response are linked to synergistic IFN-beta induction via X-box binding protein 1.** *Eur J Immunol,* 38(5):1194-1203. 2008.

Abstracts

1. Saunders V, I Lewkowich., N Herman, K Dienger, J Clark, P Breysse and M Wills-Karp. **"Ambient Particulate Matter Exposure Results in Recruitment and Activation Myeloid Dendritic Cells in the Murine Lung."** *American Thoracic Society,* May, 2008
2. Zoller E, J Lykens, L Filipovich and M Jordan. **Systemic activation of macrophages by interferon gamma causes consumptive cytopenias and hemophagocytosis.** *Experimental Biology* 2008, April 2008. San Diego CA.
3. Saunders VC, B Sakthivel, CC Lewis, K Dienger, P Breysse, B Aronow and M Wills-Karp. **"Ambient Particulate Matter Induced Epithelial Cell Gene Changes in Susceptible versus Resistant Mouse Strains".** *American Academy of Allergy Asthma and Immunology* March, 2008
4. Klenk EI and RA Colbert. **The role of the unfolded protein response (UPR) in IL-23 regulation.** *36th Annual Autumn Immunology Conference,* November, 2007. Chicago IL
5. Allen JL, R Madan, DJ Rawlings, FD Finkelman and CL Karp. **Regulation of TLR4 signaling by RP105 in B cells.** *36th Annual Autumn Immunology Conference,* November, 2007. Chicago IL
6. Saunders VC, B Sakthivel, CC Lewis, K Dienger, P Breysse, B Aronow, M Wills-Karp. **"Ambient Particulate Matter Induced Epithelial Cell Gene Changes in Susceptible and Resistant Mouse Strains".** *36th Annual Autumn Immunology Conference,* November 2007, Chicago IL
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