

Division of Immunobiology

| DIVISION PROFILE | |
|---|-------------|
| Number of Faculty | 8 |
| Number of Joint Appointment Faculty | 3 |
| Number of Fellows | |
| Clinical Fellows | 1 |
| Research Fellows | 11 |
| Number of Graduate Students | 8 |
| Number of Other Students (full and part-time) | 4 |
| Number of Support Personnel | 22 |
| Annual Total Grant Support (direct) | \$3,142,092 |
| Annual Total Industry Contracts (direct) | \$119,350 |
| Number of Peer Reviewed Publications | 19 |

FACULTY LISTING

Marsha Wills-Karp, PhD, Professor of Pediatrics, Director, Division of Immunobiology; Director Immunobiology Graduate Program

Monica Chiaramonte, PhD, Assistant Professor

Fred Finkelman, MD, Professor of Pediatrics; McDonald Professor and Director, UC Division of Internal Medicine-Immunology

H. Leighton Grimes, PhD, Associate Professor

David Hildeman, PhD, Assistant Professor

Michael Jordan, MD, Assistant Professor

Amy Nathan, MD, Research Instructor

Richard Strait, MD, Assistant Professor

FACULTY JOINT APPOINTMENT LISTING

Fred Finkelman, MD, Professor of Pediatrics; McDonald Professor and Director, UC Division of Internal Medicine-Immunology

Amy Nathan, MD, Research Instructor, Section of Neonatology, Perinatal and Pulmonary Biology

Richard Strait, MD, Assistant Professor, Division of Emergency Medicine

OVERVIEW

The Division of Immunobiology has both research and educational goals within the Cincinnati Children's Research Foundation with some faculty also having clinical responsibilities. The mission of the division is threefold: 1) to build an internationally recognized research program in immunology within the Cincinnati Children's Research Foundation; 2) to foster and strengthen collaborations within the immunology community and to provide expertise in utilization of immunological research approaches for both research and clinical investigators at Cincinnati Children's Research Foundation and the University of Cincinnati as a whole; and 3) to build a premiere graduate training program in immunobiology within the School of Medicine. To this end, the broad research aims of the division are directed towards understanding the cellular, molecular and genetic mechanisms that drive immunologically-mediated disorders in children. The long-term goals will be to apply molecular technologies to the elucidation of disease mechanisms, and to the development of novel therapies for immunologically-mediated diseases which afflict children.



*Left to Right: H. L. Grimes, M. Jordan, M. Wills-Karp,
F. Finkelman, M. Chiaramonte, D. Hildeman*

The Division of Immunobiology currently consists of five primary faculty, Marsha Wills-Karp, the division director, Leighton Grimes, David Hildeman, Michael Jordan, Monica Chiaramonte, and three associate members, Drs. Fred Finkelman, Richard Strait, and Amy Nathan. Faculty members within our division study various aspects of the immune response as it relates to human disease. In addition to running their own productive research programs, the members of our division are committed to providing expertise in immunological research and techniques to the wider community at CCRF. To this end, we provide a research home for several faculty and trainees from clinical divisions. Secondly, we provide technical expertise to numerous groups through joint research collaborations, as well as through providing the Cytokine/Mediator Assessment Core. Thirdly, we provide educational opportunities in immunological research on several levels including: 1) being the administrative home of the Immunobiology Graduate Program; 2) coordinating multiple immunologically-based research conferences; 3) participating in other graduate educational programs around the campus such as in the MD/PhD program and the Molecular and Developmental Biology Graduate Program (separate entry); and 4) providing research training opportunities for post-doctoral fellows, clinical fellows and junior faculty in our own division as well as from many others within CCHMC.

Several members of our faculty also have clinical responsibilities including: Drs. Jordan, Strait, Nathan, and Finkelman.

HIGHLIGHTS

This year the Division of Immunobiology underwent its first 5-year scientific advisory council (SAC) review. The external reviewers commended the division on its “remarkable achievements in the short time period since its inception”. Despite our current achievements, the reviewers strongly recommended that the division continue to grow and expand in order to maintain a critical mass and to continue to achieve. Our expansion will be based on scientific needs identified in the recent strategic planning process. These areas include: transplant immunology and neonatal immunology. These areas of research are underrepresented at CCHMC and at other institutions around the country. Thus, expansion in these areas is a unique opportunity for CCHMC to excel in areas that are critical to children’s health. This year has also seen the crystallization of the Immunology Matrix that includes several divisions within CCHMC (Rheumatology, Allergy and Immunology, Molecular Immunology, Immunobiology) with the goal of coordinating talents and resources to further immunological research here at CCHMC and UC. We look forward to exciting opportunities in the future.

Research

On the research front, we have had a highly successful year both in terms of publications (31) and obtaining research funding (over \$3.3 million in direct costs). This year marked the arrival of Dr. Grimes to spearhead a program on transcriptional control of hematopoiesis and cancer. He brings with him a well-funded program (3RO1s and a career development award). One particular achievement since his arrival, is that he has utilized mutations that he and his colleagues identified in the transcription factor (GFI1) in Severe Congenital Neutropenia patients to generate the only mouse model of this devastating disease. This model should greatly improve the ability to study the pathogenesis of this disease and to develop therapies for the treatment of this immunodeficiency disorder. Also of note, Dr. Wills-Karp and her colleagues have reported this year that genetic susceptibility to asthma may be associated with impaired expansion of a newly described subset of T cells referred to as T regulatory cells. This paper was accompanied by a commentary in the Journal of Experimental Medicine. In addition, a paper resulting from the collaboration between Drs. Wills-Karp and Kohl, reporting a novel role for complement factor 5 in asthma pathogenesis, was also accompanied by a commentary in the Journal of Clinical Investigation. Dr. Hildeman's lab has developed novel "MHC tetramers", soluble proteins that allow tracking of antigen-specific T cells. He has used these reagents to further understand how protective memory T cells develop and, conversely, how destructive autoreactive T cells develop. These tools should enable the development of novel therapies to enhance T cell responses in some cases (i.e. vaccines) and to decrease T cell responses in other (i.e. autoimmune disease). His novel findings were received well at NIH as evidenced by the award of a NIH RO1 and an R21. Drs. Finkelman and Strait reported in the Journal of Clinical Investigation this year a novel mechanism by which allergen immunotherapy effectively inhibits allergic responses. Dr. Jordan has received funding for his work on the role of T cells in the pathogenesis of the hemophagocytic lymphohistiocytosis, a lethal childhood condition from the USIDNET, the American Cancer Society, and the Histiocytosis Foundation. Several of our post-doctoral fellows have also obtained external grant funding from the American Lung Association and Cancer Free Kids.

Integration

One of the primary missions of the Division of Immunobiology is to foster and strengthen collaborations within the immunology community and to provide expertise in utilization of immunological research approaches. Great strides have been made in this area this year. First, the Cytokine/Mediator Assessment Core is continuing to provide service to numerous divisions within CCHMC and universities around the state. Secondly, our collaborative efforts have led to funding of 7 joint grant proposals with a variety of CCHMC and UC faculty members. Of particular note, a collaborative effort between Drs. Molloy in the Division of Epidemiology and Biostatistics and Dr. Wills-Karp has led to the funding of a Dana Foundation Award to examine the role of aberrant immune function in the development of autism.

TRAINING

| | | |
|------------------------|--------------------|---|
| Marat Khodoun, PhD | Research Associate | National Research Institute of Biotechnology, Moscow, Russia |
| Kathy Schleifer, PhD | Research Associate | University of Wisconsin, Madison, Wisconsin |
| Pulak Tripathi, PhD | Research Associate | Jadavpur University, Calcutta, India |
| David Wu, MD | Research Associate | University of Bern, Switzerland |
| Shane Horman, PhD | Research Fellow | University of London, England |
| Rakhika Iyer, PhD | Research Fellow | Ohio State University, Columbus, Ohio |
| Ian Lewkowich, PhD | Research Fellow | University of Manitoba, Winnipeg, Canada |
| Samuel Pope, PhD | Research Fellow | University of Cincinnati, Ohio |
| Xioameng Ren, PhD | Research Fellow | Chinese Academy of Medical Science, Beijing, China |
| Chinamenmeni Velu, PhD | Research Fellow | University of Madras, India |
| Adrian Zarebsky, PhD | Research Fellow | Krakow University, Poland |
| Philip Roehrs, MD | Clinical Fellow | University of South Carolina, Columbia, South Carolina |
| Jessica Allen | Graduate Student | Ohio State University, Columbus, Ohio |
| Matthew Dance | Graduate Student | Brigham Young University, Provo, Utah |
| Katherine Groschwitz | Graduate Student | Xavier University, Cincinnati, Ohio |

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| Wills-Karp, M | | |
| Interleukin-13 in Experimental Asthma | | |
| National Institutes of Health | | |
| P01 HL 076383 | 07/01/04 – 06/30/09 | \$1,354,604/\$7,008,574 |
| Wills-Karp | \$257,500 | Component 1 |
| Finkelman | \$257,500 | Component 2 |
| Rothenberg, M | \$257,507 | Component 3 |
| Hershey, G | \$257,500 | Component 4 |
| Witte, D | \$126,940 | Scientific Core 1 |
| Rothenberg, M | \$145,714 | Scientific Core 2 |
| Wills-Karp | \$51,949 | Administrative Core |
| Center for Childhood Asthma in Urban Environment | | |
| National Institutes of Health (Johns Hopkins University subcontract) | | |
| P01 ES 009606 | 05/07/04 – 10/31/08 | \$60,344/\$679,340 |
| Center for Childhood Asthma in Urban Environment | | |
| Environmental Protection Agency (Johns Hopkins University subcontract) | | |
| RD 83213901 | 11/01/04 – 10/31/08 | \$61,796/\$247,184 |
| Asthma Positional Candidate Genes in Mice and Humans | | |
| National Institutes of Health | | |
| R01 HL 067736 | 12/01/05 – 11/30/10 | \$250,000/\$1,250,000 |
| Mechanisms: IL-13 Induced Mucus Hypersecretion in Asthma | | |
| National Institutes of Health | | |
| R01 HL 072987 | 08/06/03 – 07/31/07 | \$250,000/\$1,000,000 |
| Role of Inflammatory Cytokines in Allergic Response | | |
| National Institutes of Health (University of Cincinnati subcontract) | | |
| R01 AI 055848 | 07/01/03 – 12/31/07 | \$27,977/\$142,181 |

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| Current Year Direct | \$3,142,092 |
|---------------------|-------------|

Industry Contracts

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| Wills-Karp, M | |
| Centacor | \$23,100 |
| Abgenix, Inc. | \$96,250 |

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| Current Year Direct Receipts | \$119,350 |
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| TOTAL | \$3,261,442 |
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Funded Collaborative Efforts

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| Hildeman, D | | |
| TGF Beta in T-Cell Homeostasis and Tolerance | | |
| National Institutes of Health | | |
| PI: Doetschman, T | 01/01/05 – 12/31/09 | 10% |
| CD 40 Ligand Dysregulation and HIV Pathogenesis | | |
| National Institutes of Health | | |
| PI: Chougnnet, C | 01/01/05 – 12/31/09 | 7% |
| Wills-Karp, M | | |
| Biology of IL-13 Receptor Alpha 2 | | |
| National Institutes of Health | | |
| PI: Hershey, G | 01/01/04 – 12/31/08 | 1% |
| Complement in Allergic Asthma: The role of C3a and C5a | | |
| National Institutes of Health | | |
| PI: Koehl, J | 07/01/04 – 06/30/09 | 5% |

PUBLICATIONS

1. Addis-Lieser E, Kohl J, Chiaramonte MG. Opposing regulatory roles of complement factor 5 in the development of bleomycin-induced pulmonary fibrosis. *J Immunol* 2005;175(3):1894-902.
2. Morimoto M, Zhao A, Madden KB, Dawson H, Finkelman FD, Mentink-Kane M, Urban JF, Jr., Wynn TA, Shea-Donohue T. Functional importance of regional differences in localized gene expression of receptors for IL-13 in murine gut. *J Immunol* 2006;176(1):491-5.
3. Morris SC, Orekhova T, Meadows MJ, Heidorn SM, Yang J, Finkelman FD. IL-4 induces in vivo production of IFN-gamma by NK and NKT cells. *J Immunol* 2006;176(9):5299-305.
4. Strait RT, Morris SC, Finkelman FD. IgG-blocking antibodies inhibit IgE-mediated anaphylaxis in vivo through both antigen interception and Fc gamma RIIb cross-linking. *J Clin Invest* 2006;116(3):833-41.
5. West EE, Lavoie TL, Orens JB, Chen ES, Ye SQ, Finkelman FD, Garcia JG, McDyer JF. Pluripotent allospecific CD8+ effector T cells traffic to lung in murine obliterative airway disease. *Am J Respir Cell Mol Biol* 2006;34(1):108-18.
6. Zhao A, Morimoto M, Dawson H, Elfrey JE, Madden KB, Gause WC, Min B, Finkelman FD, Urban JF, Jr., Shea-Donohue T. Immune regulation of protease-activated receptor-1 expression in murine small intestine during *Nippostrongylus brasiliensis* infection. *J Immunol* 2005;175(4):2563-9.
7. Duan Z, Zarebski A, Montoya-Durango D, Grimes HL, Horwitz M. Gfi1 coordinates epigenetic repression of p21Cip/WAF1 by recruitment of histone lysine methyltransferase G9a and histone deacetylase 1. *Mol Cell Biol* 2005;25(23):10338-51.
8. Tripathi P, Madan R, Chougnet C, Divanovic S, Ma X, Wahl LM, Gajewski T, Karp CL, Hildeman D. An adenoviral vector for probing promoter activity in primary immune cells. *J Immunol Methods* 2006;311(1-2):19-30.
9. Zhu Y, Liu X, Hildeman D, Peyerl FW, White J, Kushnir E, Kappler J, Marrack P. Bax does not have to adopt its final form to drive T cell death. *J Exp Med* 2006;203(5):1147-52.
10. Barnes KC, Grant AV, Baltadzhieva D, Zhang S, Berg T, Shao L, Zambelli-Weiner A, Anderson W, Nelsen A, Pillai S, Yarnall DP, Dienger K, Ingersoll RG, Scott AF, Fallin MD, Mathias RA, Beaty TH, Garcia JG, Wills-Karp M. Variants in the gene encoding C3 are associated with asthma and related phenotypes among African Caribbean families. *Genes Immun* 2006;7(1):27-35.
11. Follettie MT, Ellis DK, Donaldson DD, Hill AA, Diesl V, DeClercq C, Sypek JP, Dorner AJ, Wills-Karp M. Gene expression analysis in a murine model of allergic asthma reveals overlapping disease and therapy dependent pathways in the lung. *Pharmacogenomics J* 2006;6(2):141-52.
12. Goebel J, Forrest K, Wills-Karp M, Roszman TL. Tubulin polymerization modulates interleukin-2 receptor signal transduction in human T cells. *J Recept Signal Transduct Res* 2006;26(1-2):87-106.
13. Goebel J, Logan B, Forrest K, Mieczkowski A, Roszman TL, Wills-Karp M. Atorvastatin affects interleukin-2 signaling by altering the lipid raft enrichment of the interleukin-2 receptor beta chain. *J Invest Med* 2005;53(6):322-8.
14. Hessel EM, Chu M, Lizcano JO, Chang B, Herman N, Kell SA, Wills-Karp M, Coffman RL. Immunostimulatory oligonucleotides block allergic airway inflammation by inhibiting Th2 cell activation and IgE-mediated cytokine induction. *J Exp Med* 2005;202(11):1563-73.
15. Keen JC, Cianferoni A, Florio G, Guo J, Chen R, Roman J, Wills-Karp M, Casolaro V, Georas SN. Characterization of a novel PMA-inducible pathway of interleukin-13 gene expression in T cells. *Immunology* 2006;117(1):29-37.
16. Kohl J, Baelder R, Lewkowich IP, Pandey MK, Hawlisch H, Wang L, Best J, Herman NS, Sproles AA, Zwirner J, Whitsett JA, Gerard C, Sfyroera G, Lambris JD, Wills-Karp M. A regulatory role for the C5a anaphylatoxin in type 2 immunity in asthma. *J Clin Invest* 2006;116(3):783-96.

17. Lewkowich IP, Herman NS, Schleifer KW, Dance MP, Chen BL, Dienger KM, Sproles AA, Shah JS, Kohl J, Belkaid Y, Wills-Karp M. CD4+CD25+ T cells protect against experimentally induced asthma and alter pulmonary dendritic cell phenotype and function. *J Exp Med* 2005;202(11):1549-61.
18. Molloy CA, Morrow AL, Meinzen-Derr J, Schleifer K, Dienger K, Manning-Courtney P, Altaye M, Wills-Karp M. Elevated cytokine levels in children with autism spectrum disorder. *J Neuroimmunol* 2006;172(1-2):198-205.
19. Wills-Karp M, Koehl J. New insights into the role of the complement pathway in allergy and asthma. *Curr Allergy Asthma Rep* 2005;5(5):362-9.

IMMUNOBIOLOGY GRADUATE PROGRAM

The Immunobiology Graduate Program is an inter-departmental program within the University of Cincinnati that offers the 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 43 faculty members from 4 departments and 12 divisions within the College of Medicine and CCRF. Since its inception in 2003, we have enrolled 14 outstanding students from around the country and abroad. Milestones achieved this year include the advancement to candidacy of our first class of students and the successful completion of the written qualifier by all of the second year students. Our students have distinguished themselves already by receiving travel awards to national meetings, a University of Cincinnati Distinguished Graduate Fellowship, and several Pre-doctoral Fellowship Training Awards in Biological Threat Agents.

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, 2005-2006

| Student | Faculty Mentor | Admission Year |
|----------------------|-------------------|----------------|
| Jessica Allen | Christopher Karp | 2004 |
| Matthew Dance | Marsha Wills-Karp | 2004 |
| Katherine Groschwitz | Simon Hogan | 2005 |
| Adora Lin | David Hildeman | 2004 |
| Leah Nesbitt | Nives Zimmermann | 2005 |
| Vanessa Saunders | Marsha Wills-Karp | 2004 |
| Xun Zhang | Joerg Koehl | 2005 |
| Erin Zoller | Michael Jordan | 2005 |

Student Honors

Jessica Allen Supported by NIH Bioterrorism Training Grant

Katherine Groschwitz Received travel award from AAAI

Adora Lin Supported by NIH Bioterrorism Training Grant, and a Distinguished Graduate Fellowship