

# Division of Molecular Immunology

## DIVISION PROFILE

Number of Faculty	4
Number of Joint Appointment Faculty	1
Number of Fellows	
Clinical Fellows	3
Research Fellows	9
Number of Graduate Students	5
Number of Other Students (full and part-time)	9
Number of Support Personnel	13
Annual Total Grant Support (direct)	\$1,862,624
Number of Peer Reviewed Publications	17

## FACULTY LISTING

Christopher L. Karp, MD, Gunnar Esiason/Cincinnati Bell Chair of Life Sciences; Professor of Pediatrics, Director, Division of Molecular Immunology; Associate Director, Graduate Program in Immunobiology; Associate Director for CF Research, Division of Pulmonary Medicine  
Julio C. S. Aliberti, PhD, Assistant Professor of Pediatrics  
Claire Chougnnet, PhD, Associate Professor of Pediatrics  
Jörg Köhl, MD, Professor of Pediatrics

## FACULTY JOINT APPOINTMENT LISTING

Jonathan D. Katz, PhD, Associate Professor of Pediatrics, Endocrinology

## OVERVIEW

The Division of Molecular Immunology has both research and teaching goals within CCHMC/UCCOM. The charges of the division are to: (a) establish an internationally recognized research program in molecular immunology, with a particular focus on diseases of children; (b) develop effective interfaces across divisional, departmental, organ system, disease process and methodological divides, throughout CCHMC and UCCOM, in order to strengthen institutional research and training efforts, and to mentor faculty with immunology-related research efforts; (c) provide leadership for, and facilitate the integration of, research efforts in Immunology throughout the institution; and (d) work closely with the Division of Immunobiology to anchor the Graduate Program in Immunobiology. The overall research focus of the division is on the molecular mechanisms underlying innate immunity and the interface between innate and adaptive immunity.

## HIGHLIGHTS

The division was externally reviewed this year by an expert Scientific Advisory Committee (SAC). The SAC was very positive about the division and its programs, noting that an outstanding division had been developed in a remarkably short time. Strengths that were underlined, included: leadership and mentoring; the faculty; the research programs, productivity and funding; the fact that the division, along with the Division of Immunobiology, represents the core of basic immunology, serving the entire campus; the establishment of key, funded strategic collaborations with physicians and scientists throughout CCHMC/UCCOM; and the divisional role in graduate education. The SAC did determine, however, that the division should be expanded to achieve and maintain a critical mass. This will provide an important focus for the next years.

A major highlight of this last year was the recruitment of Dr. Julio Aliberti to the division from Duke University. Dr. Aliberti's research focus is on the molecular mechanisms underlying both the induction of innate immunity to infection, and counter-regulation of the immune responses so induced. To date, this work has largely been carried out in mouse models of infection with *Toxoplasma gondii* and *Mycobacterium tuberculosis*. With his

move to CCHMC (and his co-appointment in the Division of Pulmonary Medicine), Dr. Aliberti is pursuing a related area of investigation as well: the host-pathogen interface in the cystic fibrosis (CF) airway. As such, Dr. Aliberti's recruitment represents an important programmatic addition to the ongoing basic research effort in CF.

Dr. Chougnet's research program focuses principally on delineating the molecular pathogenesis of immunosuppression in HIV infection. Specific projects include: a) definition of the molecular mechanisms underlying dysregulated expression of CD40 ligand (a molecule critical to antigen presenting cell/T cell interactions) in HIV infection; (b) delineation of the role of regulatory T cells in the lack of immune control of HIV replication; and (c) characterization of the function of dendritic cells in neonates and infants born to HIV-infected mothers. In a closely related research program, Dr. Chougnet aims at mechanistic analysis of the ontogeny of immune responses in early life, and defects therein in the aged, with a special emphasis on antigen-presenting cell function.



*Left to Right: C. Karp,  
C. Chougnet, J. Köhl, J. Aliberti*

The research program of Dr. Karp focuses on understanding the molecular mechanisms underlying regulation and dysregulation of inflammatory responses in human infectious and autoimmune diseases. Ongoing areas of study include: (a) the role of anti-inflammatory lipid mediators in the pathogenesis of CF lung disease; (b) the therapeutic role of anti-inflammatory lipid mediators in CF; (c) validation of anti-inflammatory lipid mediators as endogenous ligands for the aryl hydrocarbon receptor; (d) the identification of modifier genes for CF lung disease; (e) the molecular mechanisms of control of Toll-like receptor (TLR)-driven signaling pathways, focusing on a novel endogenous inhibitor of TLR4 signaling, RP105; (f) the role of aeroallergen mimics of TLR4 complex proteins in the pathogenesis of allergic asthma; (g) regulatory T cell biology and therapy, focusing on models of Leishmania infection; and (i) characterization of the molecular mechanisms underlying IL-12 and IL-10 regulation. After many years under the leadership of Dr. Jeffrey Whitsett, the Cystic Fibrosis RDP Center is now under the direction of Dr. Karp (Dr. Whitsett, co-PI). This center directs basic and translational research into CF. Pilot projects, training and cores are supported.

The overall emphasis of the research program of Dr. Köhl is directed towards molecular dissection of the regulatory networks between complement and other arms of innate immunity, and the impact of this cross-talk on innate and adaptive immune responses. More specifically, the focus is on the anaphylatoxic peptides, C3a and C5a, and their corresponding G-protein coupled receptors. Primarily considered as pro-inflammatory mediators that activate myeloid lineage-derived cells, it has become increasingly clear that the signaling pathways downstream of these receptors are part of a regulatory network including TLRs and IgG Fc receptors that sense and/or transmit danger signals to the host. Several lines of evidence suggest that the complex signaling network formed by these arms of innate immunity shape, not only innate immune responses, but also the quality and the magnitude of adaptive immune responses. The focus of Dr. Köhl's research program is on the regulatory role of the anaphylatoxins in: (a) allergic asthma; (b) immune complex disease; (c) TLR-mediated immune responses; and (d) ischemia/reperfusion injury. Of translational note, ongoing studies are aimed at defining the role of the C5a receptor as a drug target in kidney transplantation using a C5a receptor antagonist that was developed in Dr. Köhl's laboratory.

## TRAINING

Brad Pasternak, MD	PGY-IV	SUNY Downstate Medical Center
Patrick Sobande, MD	PGY-IV	Harlem Hospital Center, Columbia University
Lisa Petiniot, MD	PGY-V	CCHMC
Jessica Allen	PhD Student	Ohio State University
YuanYuan Gu, MD	PhD Student	Nanjing University, China
Rajat Madan, MD	PhD Student	Ajmer Medical School, India
Paula Andrea Velilla	PhD Student	University of Antioquia, Columbia
Xun Zhang	PhD Student	Beijing University, China
Ralf Baelder, PhD	Research Fellow	Fraunhofer Medical School, Germany
Gail Corbin, PhD	Research Fellow	University of Iowa
Senad Divanovic, PhD	Research Fellow	CCHMC/UCCOM
Fabiana Machado, PhD	Research Fellow	University of Sao Paulo, Brazil
Alice Nyakeriga, PhD	Research Fellow	University of Stockholm, Sweden
Manoj J. Pandey, PhD	Research Fellow	Kanpur University, India
Moon Sen, PhD	Research Fellow	Bose Institute, India
Celine Silva-Lages, PhD	Research Fellow	University of Paris, France
Naonori Uozumi, MD, PhD	Visiting Scientist	University of Tokyo, Japan

## GRANTS, CONTRACTS AND INDUSTRY AGREEMENTS

Grant and Contract Awards	Annual Direct/Project Period	Direct
<b>Chougnet, C</b>		
CD40 Ligand Dysregulation and HIV Pathogenesis		
National Institutes of Health		
R01 AI 056927	01/01/05 - 12/31/09	\$244,125/\$1,250,000
Immunosuppression and Regulatory T Cells in Aging		
National Institutes of Health		
R21 AG 025149	09/01/05 - 07/31/07	\$100,000/\$225,000
<b>Karp, C</b>		
Role of Regulatory T Cells in Leishmania Major Infections		
National Institutes of Health		
R01 AI 057992	03/01/04 – 02/28/09	\$195,300/\$1,000,000
Multicenter Investigation of Genetic Modifiers in CF Lung and Liver Disease		
Cystic Fibrosis Foundation (University of North Carolina subcontract)		
	12/15/05 – 12/31/06	\$2,625
Novel Lipid-Based Therapies for Cystic Fibrosis		
National Institutes of Health (Avrion Molecular, Inc subcontract)		
R41 HL 078526	08/01/04 – 07/31/05	\$54,545
Hepatitis C Pathogenesis and the Human Genome		
National Institutes of Health (Johns Hopkins University subcontract)		
R01 DA 013324	09/01/04 – 08/31/09	\$9,478/\$48,855
Lipid Mediators and Dysregulated Inflammation in CF		
National Institutes of Health		
R01 HL 079312	04/01/05 – 03/31/10	\$311,896/\$1,635,205
Regulation of Toll-Like Receptor Signaling by RP105		
National Institutes of Health		
R21 AI 063183	03/15/05 – 02/28/07	\$146,475/\$300,000

Cystic Fibrosis Foundation Research Development Program

Cystic Fibrosis Foundation

R457-CR02	09/01/05 – 08/31/07	\$309,930/\$619,860
Whitsett, J	\$39,930	Admin. & Enhancement
Wert, S	\$50,000	Molecular Morphology Core
Whitsett, J	\$50,000	Transgenic Animal Core
Yan, X	\$50,000	Microarray-Informatics Core
Gardner, P	\$40,000	Pilot Study #1
Ikegami, P	\$40,000	Pilot Study #2
Karp, C	\$40,000	Pilot Study #3

Köhl, J

Molecular Regulation of Immune Complex Disease

National Institutes of Health

R01 AI 059305 12/15/04 – 11/30/09 \$244,125/\$1,187,500

Complement in Allergic Asthma: The Role of C3a and C5a

National Institutes of Health

R01 AI 057839 05/01/04 – 04/30/09 \$244,125/\$1,250,000

Current Year Direct \$1,862,624

Industry Contracts

Current Year Direct Receipts \$0

**TOTAL \$1,862,624**

Funded Collaborative Efforts

Chougnet, C

Immunologic Dysfunction in Billiard Artesia

National Institutes of Health

PI: Bezerra, J 07/01/03 – 06/30/07 15%

**PUBLICATIONS**

1. Machado FS, Johndrow JE, Esper L, Dias A, Bafica A, Serhan CN, Aliberti J. Anti-inflammatory actions of lipoxin A4 and aspirin-triggered lipoxin are SOCS-2 dependent. *Nat Med* 2006;12(3):330-4.
2. Herbeuval JP, Grivel JC, Boasso A, Hardy AW, Chougnet C, Dolan MJ, Yagita H, Lifson JD, Shearer GM. CD4+ T-cell death induced by infectious and noninfectious HIV-1: role of type 1 interferon-dependent, TRAIL/DR5-mediated apoptosis. *Blood* 2005;106(10):3524-31.
3. Szigligeti P, Neumeier L, Duke E, Chougnet C, Takimoto K, Lee SM, Filipovich AH, Conforti L. Signalling during hypoxia in human T lymphocytes--critical role of the src protein tyrosine kinase p56Lck in the O2 sensitivity of Kv1.3 channels. *J Physiol* 2006;573(Pt 2):357-70.
4. Tripathi P, Madan R, Chougnet C, Divanovic S, Ma X, Wahl LM, Gajewski T, Karp CL, Hildeman DA. An adenoviral vector for probing promoter activity in primary immune cells. *J Immunol Methods* 2006;311(1-2):19-30.
5. Zhang R, Lifson JD, Chougnet C. Failure of HIV-exposed CD4+ T cells to activate dendritic cells is reversed by restoration of CD40/CD154 interactions. *Blood* 2006;107(5):1989-95.
6. Atabani SF, Thio CL, Divanovic S, Trompette A, Belkaid Y, Thomas DL, Karp CL. Association of CTLA4 polymorphism with regulatory T cell frequency. *Eur J Immunol* 2005;35(7):2157-62.
7. Divanovic S, Trompette A, Atabani SF, Madan R, Golenbock DT, Visintin A, Finberg RW, Tarakhovskiy A, Vogel SN, Belkaid Y, Kurt-Jones EA, Karp CL. Inhibition of TLR-4/MD-2 signaling by RP105/MD-1. *J Endotoxin Res* 2005;11(6):363-8.

8. Karp CL, Colebunders R. Approach to the patient with HIV and coinfecting tropical infectious diseases. In: Guerrant RL, Walker DH, Weller PF, editors. *Tropical infectious diseases: principles, pathogens, and practice*; 2nd ed. Philadelphia: Elsevier Churchill Livingstone; 2006. p. 1642-1684.
  9. Karp CL, Flick LM, Yang R, Uddin J, Petasis NA. Cystic fibrosis and lipoxins. *Prostaglandins Leukot Essent Fatty Acids* 2005;73(3-4):263-70.
  10. Wills-Karp M, Köehl J. New insights into the role of the complement pathway in allergy and asthma. *Curr Allergy Asthma Rep* 2005;5(5):362-9.
  11. Addis-Lieser E, Köhl 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.
  12. Hawlisch H, Köhl J. Complement and Toll-like receptors: key regulators of adaptive immune responses. *Mol Immunol* 2006;43(1-2):13-21.
  13. Hillebrandt S, Wasmuth HE, Weiskirchen R, Hellerbrand C, Keppeler H, Werth A, Schirin-Sokhan R, Wilkens G, Geier A, Lorenzen J, Köhl J, Gressner AM, Matern S, Lammert F. Complement factor 5 is a quantitative trait gene that modifies liver fibrogenesis in mice and humans. *Nat Genet* 2005;37(8):835-43.
  14. Köhl J. Self, non-self, and danger: a complementary view. *Adv Exp Med Biol* 2006;586:71-94.
  15. Köhl J. The role of complement in danger sensing and transmission. *Immunol Res* 2006;34(2):157-76.
  16. Köhl 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, Köhl 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.
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