

Division of Molecular Immunology

DIVISION PROFILE

Number of Faculty	4
Number of Fellows	
Clinical Fellows	1
Research Fellows	4
Number of Graduate Students	4
Number of Other Students (full and part-time)	6
Number of Support Personnel	11
Annual Total Grant Support (direct)	\$1,210,942
Number of Peer Reviewed Publications	12

FACULTY LISTING

Christopher L. Karp, MD, Professor of Pediatrics, Director, Division of Molecular Immunology; Associate Director, Graduate Program in Immunobiology

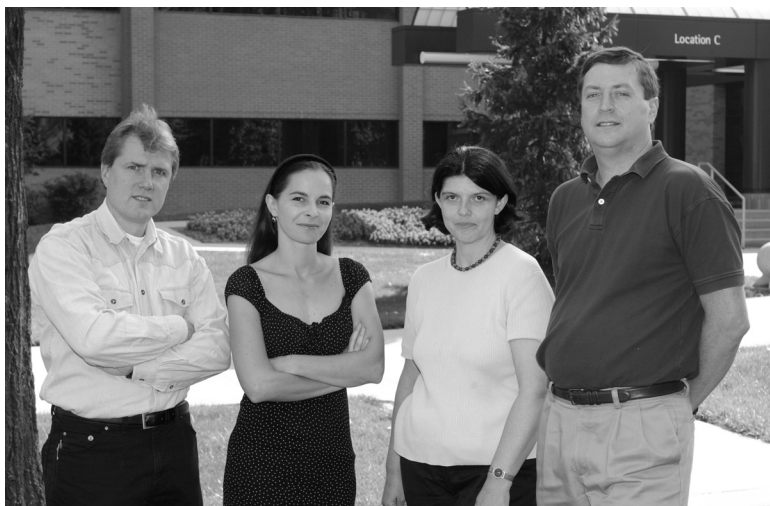
Yasmine Belkaid, MD, Assistant Professor of Pediatrics

Claire Chougnet, MD, Research Associate Professor

Joerg Koehl, MD, Professor of Pediatrics

OVERVIEW

The division's goals are to develop a world class research center in Molecular Immunology, with broad horizontal links across divisional, organ system, disease process, and methodological divides, and with the clear intent of pursuing translational research. As such, Molecular Immunology is integral to ongoing planning for an Immunology Matrix at CCHMC. The division is also integrally involved in the recently launched Graduate Program in Immunobiology. Dr. Karp is currently the Associate Director of this nascent Graduate Program. The initial research focus of the division is, and will be, on the molecular mechanisms underlying innate immunity and the interface between innate and adaptive immunity.



Left to Right: J. Koehl, Y. Belkaid, C. Chougnet, C. Karp

HIGHLIGHTS

The division's goals are to develop a world class research center in Molecular Immunology, with broad horizontal links across divisional, organ system, disease process, and methodological divides, and with the clear intent of pursuing translational research. As such, Molecular Immunology is integral to ongoing planning for an Immunology Matrix at CCHMC. The division is also integrally involved in the recently launched Graduate Program in Immunobiology. Dr. Karp is currently the Associate Director of this nascent Graduate Program. The initial research focus of the division is, and will be, on the molecular mechanisms underlying innate immunity and the interface between innate and adaptive immunity.

A major highlight of the current year has been the garnering of almost full NIH extra-mural support by all of the members of this newly constituted research division.

The research program of Dr. Belkaid is aimed at understanding the molecular mechanisms (and consequences) of latent infection-- the asymptomatic persistence of pathogens within host tissues. Recent work has shown that CD4+CD25+ regulatory T-cells (Treg), are essential for the development and maintenance of latent infection with Leishmania. The mechanisms by which Treg favor parasite persistence, promote reactivation and suppress immunity are currently under investigation. This work has garnered Dr. Belkaid an international reputation as a leader in the highly competitive field of Treg biology.

Dr. Chougnet's research program is focused on two basic problems: (1) Understanding the molecular pathogenesis of immunosuppression in HIV infection, with a focus on characterizing the molecular mechanisms underlying dysregulated expression of CD40 ligand (a molecule critical to antigen presenting cell/T cell interactions) in HIV infection; and (2) Understanding the ontogeny of antigen presenting cell functions in early life, and defects therein in the aged.

The research program of Dr. Karp focuses on understanding the molecular mechanisms underlying cytokine-mediated dysregulation of cell mediated immune responses in human infectious and autoimmune diseases. Ongoing areas of study include: (a) the molecular mechanisms underlying IL-12 regulation and dysregulation; (b) the mechanisms underlying dysregulation of pulmonary inflammatory responses in cystic fibrosis; (c) Ebola virus pathogenesis and therapy; (d) the molecular mechanisms underlying endotoxin tolerance; (e) the molecular mechanisms of control of Toll-like receptor-driven signaling pathways; and (f) regulatory T cell immunogenetics. A recent highlight of this work was the delineation of a defect in lipoxin-mediated anti-inflammatory activity in the airway in cystic fibrosis, findings that have clear translational potential in this lethal, common autosomal disease.

The research program of Dr. Koehl focuses on the cross-talk between different arms of the innate immune system, and its impact on adaptive immunity. In particular, the lab is interested in understanding the mechanisms underlying the cross-talk between receptors for complement cleavage products C3a and C5a, IgG Fc receptors, and Toll-like receptors. Recent data obtained from this work demonstrate that the cross-talk between such pathways is of critical importance in the pathogenesis of immune complex disease, allergic asthma and delayed type hypersensitivity.

TRAINING

Sowsan Atabani, MD MD	University of London
Ralph Baelder, MD	Fraunhofer Institute
Heiko Hawlisch, MD	Hanover Medical school
Isabelle Suffia, MD	University of Nice
Lisa Petiniot, MD	University of Wisconsin; CCHMC Pediatrics
Senad Divanovic	Molecular and Developmental Biology, CCHMC
Rajat Madan, MD	Molecular and Developmental Biology, CCHMC
Veronica Schmitz	Federal University of Rio de Janeiro
Gerson Salay, Visiting Scientist	Federal University of Sao Paulo

GRANTS, CONTRACTS AND INDUSTRY AGREEMENTS

Grant and Contract Awards	Annual Direct/Project Period Direct
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Belkaid, Y	
Latency Reactivation and Immunity in Chronic Parasitic Disease	
The Ellison Foundation	
08/01/03 - 07/31/07	\$46,296/\$197,184

Role of Regulatory T Cells in Leishmania Major Infections

National Institutes of Health

R01 AI 057992

03/01/04 – 02/28/09

\$200,000/\$1,000,000

Karp, C

IFN-Beta and Immunoregulation in Multiple Sclerosis

National Institutes of Health

R01 NS 39435

09/01/00 – 06/30/04

\$175,000/\$695,947

Ebola Virus Immunopathogenesis and Therapy

National Institutes of Health

R21 AI 53539

09/01/02 – 08/31/04

\$150,000/\$300,000

Hepatitis C: IFN-Alpha, IL-12 and Immunoregulation

National Institutes of Health

R01

09/01/00 – 08/31/04

\$139,646/\$534,652

Koehl, J

Molecular Regulation of Immune Complex Disease

National Institutes of Health

R21 AI 059305

03/15/04 – 02/28/05

\$250,000/\$250,000

Complement in Allergic Asthma: The Role of C3a and C5a

National Institutes of Health

R01 AI 057839

05/01/04 – 04/30/09

\$250,000/\$1,250,000

Current Year Direct**\$1,210,942****Industry Contracts****Current Year Direct Receipts****\$0****TOTAL****\$1,210,942****PUBLICATIONS**

1. **Belkaid Y.** The role of CD4(+)CD25(+) regulatory T cells in Leishmania infection. *Expert Opin Biol Ther* 2003;3(6):875-85.
2. Feng CG, Collazo-Custodio CM, Eckhaus M, Hieny S, **Belkaid Y**, Elkins K, Jankovic D, Taylor GA, Sher A. Mice deficient in LRG-47 display increased susceptibility to mycobacterial infection associated with the induction of lymphopenia. *J Immunol* 2004;172(2):1163-8.
3. Hesse M, Piccirillo CA, **Belkaid Y**, Prufer J, Mentink-Kane M, Leusink M, Cheever AW, Shevach EM, Wynn TA. The pathogenesis of schistosomiasis is controlled by cooperating IL-10-producing innate effector and regulatory T cells. *J Immunol* 2004;172(5):3157-66.
4. Mendez S, Tabbara K, **Belkaid Y**, Bertholet S, Verthelyi D, Klinman D, Seder RA, Sacks DL. Coinjection with CpG-containing immunostimulatory oligodeoxynucleotides reduces the pathogenicity of a live vaccine against cutaneous Leishmaniasis but maintains its potency and durability. *Infect Immun* 2003;71(9):5121-9.
5. Wills-Karp M, **Belkaid Y**, **Karp CL.** I-Tim-izing the pathways of counter-regulation. *Nat Immunol* 2003;4(11):1050-2.
6. **Chougnnet C.** Role of CD40 ligand dysregulation in HIV-associated dysfunction of antigen-presenting cells. *J Leukoc Biol* 2003;74(5):702-9.
7. Zhang R, Fichtenbaum CJ, Hildeman DA, Lifson JD, **Chougnnet C.** CD40 ligand dysregulation in HIV infection: HIV glycoprotein 120 inhibits signaling cascades upstream of CD40 ligand transcription. *J Immunol* 2004;172(4):2678-86.

8. Hawlisch H, Wills-Karp M, **Karp CL**, Kohl J. The anaphylatoxins bridge innate and adaptive immune responses in allergic asthma. *Mol Immunol* 2004;41(2-3):123-31.
9. Hawlisch H, Wills-Karp M, **Karp CL**, Kohl J. The complex role of anaphylatoxins in asthma and autoimmune disease. In: Szebeni J, editor. *The Complement System: Novel Roles in Health and Disease*. Boston: Kluwer Academic; 2004. p. 315-344.
10. Hensley LE, Fritz LE, Jahrling PB, **Karp CL**, Huggins JW, Geisbert TW. Interferon-beta 1a and SARS coronavirus replication. *Emerg Infect Dis* 2004;10(2):317-9.
11. **Karp CL**, Flick LM, Park KW, Softic S, Greer TM, Keledjian R, Yang R, Uddin J, Guggino WB, Atabani SF, **Belkaid Y**, Xu Y, Whitsett JA, Accurso FJ, Wills-Karp M, Petasis NA. Defective lipoxin-mediated anti-inflammatory activity in the cystic fibrosis airway. *Nat Immunol* 2004;5(4):388-92.
12. Otto M, Hawlisch H, Monk PN, Muller M, Klos A, **Karp CL**, Kohl J. C5a mutants are potent antagonists of the C5a receptor (CD88) and of C5L2: position 69 is the locus that determines agonism or antagonism. *J Biol Chem* 2004;279(1):142-51.