Molecular Immunology

Division Data Summary

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<th>Research and Training Details</th>
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Significant Publications


Why specific proteins tend to act as allergens in susceptible hosts is a basic mechanistic question that has remained largely unclear. This important paper reports that the major allergen derived from dust mites, Der p 2, tends to be targeted by adaptive immune responses because it behaves as a functional mimic of the ligand-binding component (MD-2) of the innate immune receptor for bacterial lipopolysaccharide, TLR4. The fact that other members of the MD-2-like lipid binding family are allergens, and that more than 50% of defined major allergens are lipid-binding proteins, suggests that intrinsic adjuvant activity by such proteins and their accompanying lipids is likely to have some generality as a mechanism underlying the phenomenon of allergenicity.


Aging is associated with impaired immune function, something that is thought to contribute significantly to disease
burden in the elderly. This seminal paper reports that: (a) there is expansion of regulatory T cells in the blood of elderly humans as well as in lymphoid tissues of aged mice; (b) in vitro depletion of peripheral regulatory T cells from elderly humans leads to increased effector T cell responses; (c) regulatory T cells from old mice exhibit greater suppressive capacity than those from young mice; and (d) the increasing proportion of regulatory T cells correlates directly with spontaneous reactivation of chronic Leishmania major infection in old mice. These data strongly suggest that accumulation of regulatory T cells plays an important role in the frequent reactivation of chronic infections that occurs in the elderly.


This important paper provides novel mechanistic insight into the development and differentiation of regulatory T cells. Following ENU mutagenesis, mice were identified that had peripheral regulatory T cells in the absence of thymic regulatory T cells. Positional cloning revealed the causative mutation to be in Carma1. Data in this paper provide genetic evidence for two distinct mechanisms controlling regulatory T cell lineage commitment, and demonstrate that peripheral regulatory T cells are a dynamic population that can expand to either limit immunopathology or promote chronic infection.


This seminal publication demonstrates that natural killer (NK) cells can drive robust adaptive immune responses—including CD8+ T cell, CD4+ T cell and B cell responses—through killing of antigen-expressing target cells. This newly-recognized pathway is now being translationally exploited by Dr. Hoebe in order to develop novel vaccines for chronic infectious diseases such as HIV/AIDS, as well as for cancer vaccine development.


This important paper reports the results of the first genome-wide single nucleotide polymorphism scan to identify genes that modify the severity of cystic fibrosis lung disease. Polymorphisms in IFRD1, which encodes a histone deacetylase-dependent transcriptional co-regulator, were found (and validated in a second cohort) to contribute to lung disease severity in cystic fibrosis, independent of CFTR genotype. Immunobiological investigation strongly suggests that IFRD1 modulates the pathogenesis of CF lung disease by regulating neutrophil effector function. These data suggest therapeutic utility for targeting neutrophils in cystic fibrosis, and suggest that IFRD1 may provide a useful therapeutic target in this and other diseases in which neutrophilic inflammation plays an important pathogenetic role.

### Division Collaboration

#### Collaborating with Immunobiology

**Collaborating Faculty: Michael Jordan, M.D.**

- The role of the macrophage IFN-gamma receptor in mediating resistance to Toxoplasma gondii infection (manuscript submitted for publication).
- Dissection of cytolytic effector mechanisms.
- IFN-g signaling by macrophages in leishmanial infection.

**Collaborating with Immunobiology**

**Collaborating Faculty: Jochen Mattner, M.D.**

- The role of AhR in mediating resistance to Salmonella oral infection in mice (experiments ongoing).

**Collaboration with Immunobiology**

**Collaborating Faculty: David Hildeman, Ph.D.**

- Homeostasis of regulatory T cells in aging (R01 funded in 2009; manuscript in revision at PNAS).
- Collaboration seeks to obtain a better understanding of the role of NK and NKT cells in CD4 T cell activation upon LCMV infection. In addition, a second project involves the study of Gimap5 in lymphocyte survival (currently submitted for publication).
CD4 and CD8 T cell responses; priming, effector function and memory development. (published in Nature Immunology).
In vivo immunobiology of IL-10 (published in Journal of Immunology).

**Collaboration with Immunobiology**

**Collaborating Faculty: Marsha Wills-Karp, Ph.D.**
- Role of PD-1 and its ligands in immune suppression associated with aging (manuscript submitted).
- Molecular underpinnings of allergy (published in Nature; R01 submitted) Genetic modifiers of cystic fibrosis lung disease (published in Nature; R01 obtained).
- The role of complement in allergic asthma (published in Journal of Immunology).

**Collaboration with Immunobiology**

**Collaborating Faculty: Suzanne Morris, Ph.D.; Fred Finkelman, M.D.**
- Collaboration involves genetic linkage analysis of existing differences in memory CD8 T cell populations observed in mice on a C57BL/6 and BALB/c background.

**Collaboration with Immunobiology**

**Collaborating Faculty: Lee Grimes, M.D.**
- Collaboration involves studying the role of Gimap5 function in hematopoietic stem cells.
- Regulation of neutrophil effector function by the genetic modifier of CF lung disease, IFRD1 (published in Nature; R01 obtained).

**Collaboration with Immunobiology**

**Collaborating Faculty: Fred Finkelman, M.D.**
- Molecular mechanisms underlying the development of peanut allergy (published in Journal of Allergy & Clinical Immunology).
- RP105 regulation of B cell function (ongoing R01).
- B cell IL-10 production (published in Journal of Immunology).

**Collaboration with Experimental Hematology**

**Collaborating Faculty: James Mulloy, Ph.D.**
- Development of a humanized mouse model for HIV infection.

**Collaboration with Experimental Hematology**

**Collaborating Faculty: Marie-Dominique Philippi, Ph.D.**
- Regulation of neutrophil effector function by the genetic modifier of CF lung disease, IFRD1 (published in Nature; R01 obtained).

**Collaboration with Gastroenterology, Hepatology and Nutrition**

**Collaborating Faculty: Jorge Bezerra, M.D.**
- Dysfunction in biliary atresia (ongoing R01; published paper in J. Clin. Invest.; second manuscript submitted).
- Collaboration involves the characterization of a novel ENU germline mutant designated Lampe1 that develops spontaneous hepatic steatosis.

**Collaboration with Gastroenterology, Hepatology and Nutrition**

**Collaborating Faculty: Kris Steinbrecher, Ph.D.**
- Collaboration involves studying colitis development in Gimap5-deficient mice.

**Collaboration with Gastroenterology, Hepatology and Nutrition**

**Collaborating Faculty: Lee Denson, M.D.**
- Collaboration involves studying colitis development in Gimap5-deficient mice.
- Regulation of inflammatory bowel disease by TLR signaling (paper submitted).

**Collaboration with Pulmonary Biology/Neonatology**

**Collaborating Faculty: Alan Jobe, M.D., Ph.D.; Suhas Kallapur, M.D.**
- Late Preterm Birth, Ureaplasma Species and Childhood Lung Disease (R01 funded in 2009).
- Biomarkers of immunologic function and preterm respiratory outcomes (U01 submitted, CTSA pilot project submitted).
Collaboration with Developmental Biology
Collaborating Faculty: Jay Degen, Ph.D.
Collaborative efforts involve the ENU mutagenesis program in mice where Dr. Degen seeks to identify non-redundant genes involved in the effective clearance of Listeria monocytogenes from the peritoneum.

Collaboration with Developmental Biology
Collaborating Faculty: Rashmi Hegde, Ph.D.
Molecular underpinnings of allergy (published in Nature; Sandler Foundation Grant; R01 submitted).

Collaboration with Endocrinology
Collaborating Faculty: Jonathan Katz, Ph.D.
Dissection of the role of a novel Dendritic Cell subset in the breaking of T cell tolerance (JDRF Innovative Grant 5-2009-69).

Collaboration with Allergy and Immunology
Collaborating Faculty: Kimberly Risma, M.D., Ph.D.
Dissection of cytolytic effector mechanisms.

Collaboration with Allergy and Immunology
Collaborating Faculty: Carine Blanchard, Ph.D.
IL-10 production by eosinophils.

Collaboration with Hematology/Oncology
Collaborating Faculty: Joe Palumbo, M.D.
Generation of CD8 T cell responses to live tumor cells.

Collaboration with Biomedical Informatics
Collaborating Faculty: Bruce Aronow, Ph.D.
Genetic identification of DC subsets.
Genetic modifiers of CF lung disease allergy (published in Nature; R01 submitted), RP105 regulation of B cell function (ongoing R01).

Collaboration with Pulmonary Biology
Collaborating Faculty: Jeffrey Whitsett, M.D.
Pro-resolution lipid mediators in CF lung disease and airway remodeling (ongoing R01).

Collaboration with Pulmonary Biology
Collaborating Faculty: Timothy Weaver, M.S., Ph.D.
Analysis of B cell function in ERdj4-deficient mice.

Collaboration with Pulmonary Biology; Pulmonary Medicine
Collaborating Faculty: Jeffrey Whitsett, M.D.; Henry Akinbi, M.D.; Paul Kingma, Ph.D.; Jamie Wooldridge, M.D.; Carolyn Kercsmar, M.D.
Cystic Fibrosis Foundation Research Development Program Grant.

Collaboration with Infectious Diseases
Collaborating Faculty: Nancy Sawtell, Ph.D.
Role of indolamine 2,3 dioxygenase in HSV infection.

Collaboration with Infectious Diseases
Collaborating Faculty: Rhonda Cardin, Ph.D.
Role of B cell IL-10 production in MCMV infection (published in Journal of Immunology).

Collaboration with Pathology
Collaborating Faculty: Kenneth Setchell, Ph.D.
Molecular underpinnings of allergy; regulation of obesity by the RP105/TLR axis.

Collaboration with Nephrology & Hypertension
Collaborating Faculty: Prasad Devarajan, M.D.
Establishment of a murine congenic kidney transplantation model (published in Clinical & Experimental Immunology).
Faculty Members

Christopher Karp, MD, Professor; Associate Director, Immunobiology Graduate Program; Director, CF Research Program; Director, Trustee and Procter Scholar Programs

Julio Aliberti, PhD, Assistant Professor
Claire A. Chougnet, PhD, Associate Professor
Kasper Hoebe, PhD, Assistant Professor
Edith M. Janssen, PhD, Assistant Professor
Joerg Koehl, MD, Adjunct Professor

Joint Appointment Faculty Members

Jonathan Katz, PhD, Associate Professor
Endocrinology

Trainees

- Rajat Madan, MD, GSY-8,
- Celine Silva-Lages, PhD, PGY-5,
- Manoj Pandey, PhD, PGY-5,
- Yuan Yuan Gu, MD, GSY-5,
- Jessica Allen, BS, GSY-5,
- Naonori Uozumi, MD, PhD, PGY-10, Visiting Scientist, University of Tokyo
- Senad Divanovic, PhD, PGY-3,
- Pietro Pressice, PhD, PGY-3,
- Isaac Harley, BS, GSY-2,
- Xun Zhang, BS, GSY-4,
- Cortez McBerry, BS, GSY-2,
- Ibrahim Aksoylar, BS, GSY-2,
- Stephanie Walters, BS, GSY-1,
- Rebecca Currier, BS, GSY-1,

Significant Accomplishments

Defining the molecular basis for allergenicity

With the prevalence, morbidity and mortality of allergic asthma continuing its dramatic rise in the Westernized world, it is clear that new therapies are needed. The rational development of novel therapeutic approaches will likely depend upon a better molecular understanding of pathogenesis. Allergic asthma is thought to arise from maladaptive, immune responses to ubiquitous, otherwise innocuous environmental proteins. While the proteins so targeted represent a tiny fraction of the airborne proteins humans are exposed to, the same proteins typically behave as aeroallergens across the human population. Why particular proteins tend to act as allergens in susceptible hosts is a fundamental mechanistic question that has remained largely unclear. The major house dust mite allergen, Der p 2, has structural homology with MD-2, the lipopolysaccharide (LPS)-binding component of the TLR4 signaling complex. Data from the Karp lab have shown that: (a) Der p 2 has functional homology with MD-2 as well, facilitating signaling through direct interactions with the TLR4 complex, and reconstituting LPS-driven TLR4 signaling in the absence of MD-2; (b) Der p 2 facilitates LPS signaling in primary antigen presenting cells, with or without MD-2 being present; and (c) the in vivo allergenic activity of Der p 2 mirrors its in vitro functional and biochemical activity: Der p 2 efficiently drives airway Th2 inflammation in vivo in a TLR4-dependent manner, retaining this ability in the absence of MD-2. These data suggest that Der p 2 tends to be targeted by adaptive immune responses because of its auto-adjuvant properties. The fact that other members of the MD-2 lipid-binding domain family are major allergens and, more broadly, that more than 50% of defined major allergens are lipid-binding proteins, suggests that intrinsic adjuvant activity by such proteins and their accompanying lipid cargo is likely to have some generality as a mechanism underlying the phenomenon of allergenicity.

Exploiting novel pathways of immune activation for vaccine development
Identifying genetic modifiers of cystic fibrosis lung disease, and the biological pathways that they regulate

Cystic fibrosis (CF) is the most common, lethal autosomal recessive disorder in the U.S. Novel therapeutic approaches to CF lung disease, the major cause of morbidity and mortality, are clearly needed. Published studies indicate significant heritability of lung disease severity in CF, independent of CFTR genotype. To search for genes modifying CF lung disease, the Karp lab performed a genome-wide association scan in one cohort of CF patients, with replication of top candidates in an independent cohort. Using this approach, genetic variation in IFRD1 was identified and replicated as a modifier of lung disease severity in CF. IFRD1 is a transcriptional co-regulator. In vivo and in vitro analysis has indicated that IFRD1 modulates the pathogenesis of airway disease in CF through regulation of neutrophil effector function. These data suggest therapeutic utility for targeting neutrophils in cystic fibrosis, and suggest that IFRD1 may provide a useful therapeutic target in this and other diseases in which neutrophilic inflammation plays an important pathogenetic role. In addition to continuing to define the molecular mechanisms underlying IFRD1-mediated modulation of neutrophil function, with the goal of developing novel therapeutic approaches to CF lung disease, the Karp lab continues to work on novel CF modifier genes with collaborators from Johns Hopkins (Garry Cutting), the University of North Carolina (Michael Knowles) and Case Western Reserve University (Mitch Drumm).

Division Publications


### Grants, Contracts, and Industry Agreements

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<td>A Novel NK Cell Mediated Adjuvant Approach to Generate Robust CD8+T Cell Responses</td>
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<td>Sphinx: A New Cause of Hepatic Neoplasia</td>
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KARP, C

Lipid Mediators And Dysregulated Inflammation In CF
National Institutes of Health
R01 HL 079312 04/01/05 - 02/28/10 $325,278 / $1,635,205

Regulation of TLR Signaling and Innate Immunity by RP105
National Institutes of Health
R01 AI 075159 07/01/07 - 06/30/12 $242,250 / $1,250,000

Cystic Fibrosis Foundation Research Development Program
Cystic Fibrosis Foundation
09/01/07 - 06/30/12 $370,000 / $1,850,000

Karp, C Project 4/Core2 150,000
Whitsett, J Transgenic Core 50,000
Kercsmar, C Core 3a 30,000
Kingma, P Project 1 50,000
Woolridge, J Project 2 50,000
Akinbi, H Project 3 40,000

Role of Aeroallergen Mimics of TLR Complex Proteins in Asthma Pathogenesis
American Asthma Foundation
06-0284 07/01/06 - 06/30/10 $250,000 / $1,000,000

Hepatitis C Pathogenesis and the Human Genome
National Institutes of Health (Johns Hopkins University)
R01 DA013324 09/01/04 - 08/31/09 $10,357 / $51,785

Cincinnati Rheumatic Diseases Center
National Institutes of Health
P30 AR 047363 07/01/08 - 06/30/09 $50,000 / $50,000

KOEHL, J

Molecular Regulation of Immune Complex Disease
National Institutes of Health
R01 AI 059305 12/15/04 - 11/30/09 $232,541 / $1,162,705

Current Year Direct 2,956,851

Total  $2,956,851