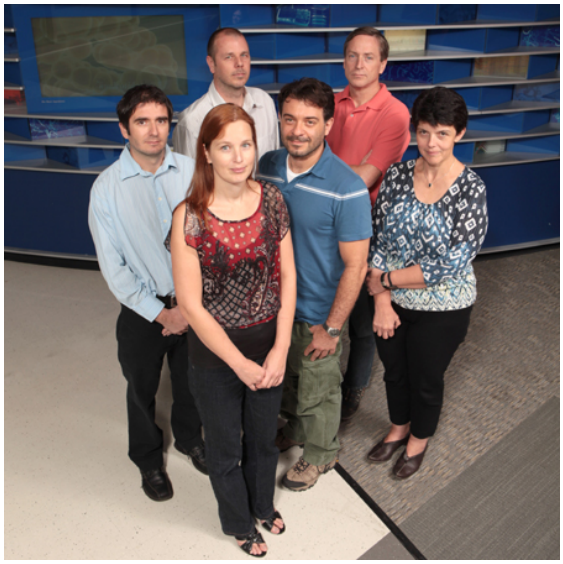
# Molecular Immunology

## Division Data Summary

| Research and Training Details | |
|---|---|
| Number of Faculty | 7 |
| Number of Joint Appointment Faculty | 1 |
| Number of Research Fellows | 6 |
| Number of Research Students | 7 |
| Number of Support Personnel | 13 |
| Direct Annual Grant Support | $3,379,319 |
| Peer Reviewed Publications | 19 |

## Division Photo



Row 1: E Janssen, J Aliberti, C Chougnet
Row 2: S Divanovic, K Hoebe, C Karp

## Significant Publications

Reboulet RA, Hennies CM, et al. **Prolonged antigen storage endows merocytic dendritic cells with enhanced capacity to prime anti-tumor responses in tumor-bearing mice**. *J Immunol*. 185(6): 3337-3347. 2010.

Hennies CM, Reboulet RA, et al. **Selective expansion of merocytic dendritic cells and CD8DCs confers anti-tumour effect of Fms-like tyrosine kinase 3-ligand treatment in vivo**. *Clin Exp Immunol*. 163(3): 381-391. 2011.

The research program of Edith Janssen aims at molecular analysis and translational exploitation of immune responses to self. Dr. Janssen has made major strides over the last year in defining the unique capabilities, and likely therapeutic utility, of a novel dendritic cell population that she discovered, merocytic dendritic cells. Merocytic dendritic cells orchestrate effector immune responses to self. Harnessing these dendritic cells significantly increases the efficacy of anti-tumor vaccines in mice (*J. Immunol* 185:3337; *Clin Exp Immunol* 163:381). On the other hand, merocytic dendritic cells can play an important pathogenic role in autoimmune disease—breaking T cell tolerance to beta cell antigens and driving type I diabetes in mice (*J Immunol* 185:1999; work done in collaboration with J. Katz).

Moreno-Fernandez ME, Rueda CM, et al. **Regulatory T cells control HIV replication in activated T cells through a cAMP-dependent mechanism**. *Blood*. 117(20): 5372-5380. 2011.

Chougnet CA, Tripathi P, et al. **A major role for Bim in regulatory T cell homeostasis**. *J Immunol*. 186(1): 156-163. 2011.

Homeostasis and avoidance of immune-mediated pathology demands tight regulation of the amplitude, duration and class immune responses—something provided by numerous, often overlapping mechanisms of

immune counter-regulation. Claire Chougnet's research program on regulatory T cells, a subset of immune cells with important counter-regulatory roles across the immune system, continues to bear important fruit. Work published in the last year has demonstrated that: (a) regulatory T cells act in a contact-dependent manner to restrain HIV replication in activated T cells—something that may be of particular relevance to the course of early HIV infection (*Blood* 117:5372); (b) the pro-apoptotic molecule, Bim, plays a major role in regulatory T cell homeostasis (*J Immunol* 186:156; work done in collaboration with D. Hildeman); and (c) chorioamnionitis, which leads to ileal inflammation that interferes with gut maturation, is associated with depletion of intestinal regulatory T cells in sheep models (*PLoS One* 6:e18355; work done in collaboration with S. Kallapur, A. Jobe, and investigators from Maastricht University Medical Center).

## Division Collaboration

**Molecular Immunology »** Senad Divanovic, Ph.D.;

Regulation of obesity by RP105, TLRS and Baff (Karp)

Regulation of leishmanial infection by IDO, and 5-LO (Karp)

Obesity and denddritic cell functions (Janssen)

**Molecular Immunology »** Julio Aliberti, Ph.D.

Role of indolamine 2,3 dioxygenase in TB (Karp)

Regulation of toxoplasma infection by ATF3 (Karp)

A new role for C5aR in HIV infection (Chougnet)

**Molecular Immunology »** Kasper Hoebe, Ph.D.

Modeling development and progression of NAFLD (Divanovic)

**Molecular Immunology »** Edith Janssen, Ph.D.

Obesity driven modulation of immune responses (Divanovic)

Effect of aging on merocytic dendritic cells (Chougnet)

**Molecular Immunology »** Claire Chougnet, Ph.D.

Effect of aging on DC function (Janssen)

Human DC subsets (Janssen)

**Molecular Immunology »** Christopher Karp, M.D.

Effect of temperature on DC function (Janssen)

Role of IDO during tuberculosis and leishmaniasis (Aliberti)

**Immunobiology »** David Hildeman, Ph.D.

Molecular control of LCMV infection (Karp)

Immunobiology of RP105 (Karp)

Immuneresponses to oncolytic viruses (Janssen)

Strain-specific NK cell control of CD4+ T cell responses during LCMV infection (Hoebe)

Homeostasis and function of regulatory T cells in aging (Chougnet)

**Immunobiology »** Marsha Wills-Karp, Ph.D.

Molecular underpinnings of allergy (Karp)

Thermoneutrality and experimental allergic asthma (Karp)

**Immunobiology »** Fred Finkelman, M.D.

RP105 regulation of B cell function (Karp)

Molecular regulation of the immunopathogenesis of helminth infection (Karp)

**Immunobiology »** DeBroski Herbert, Ph.D.

Macropage-derived IDO prevents hepatic inflammation and mortality in IL-4R? deficient mice during Schistosoma mansoni infection (Divanovic)

TFF2 and priming to tumor cell-associated antigens (Janssen)

TFF2 as a regulator of innate immunity to infection (Aliberti)

**Experimental Hematology & Cancer Biology »** Marie-Dominique Filippi, Ph.D.

Regulation of neutrophil effector function by IFRD1 (Karp)

**Experimental Hematology & Cancer Biology »** Matthew Flick, Ph.D.

The hemostatic protease thrombin in non-alcoholic fatty liver disease pathogenesis

**Neonatology & Pulmonary Biology »** Jeffrey Whitsett, M.D.

Pro-resolution lipid mediators in CF lung disease and airway remodeling (Karp)

Airway epithelial signaling and immunobiology of mucous metaplasia (Karp)

**Neonatology & Pulmonary Biology »** Timothy Weaver, M.S., Ph.D.

Analysis of B cell function of ERdj4-deficient mice (Karp)

**Neonatology & Pulmonary Biology »** Paul Kignma, M.D., Ph.D.

Analysis of neutrophil function in cystic fibrosis (Karp)

**Neonatology & Pulmonary Biology; ; ; Pulmonary Medicine; Developmental Biology; Gastroenterology, Hepatology & Nutrition »** Jeffrey Whitsett, M.D.; Paul Kingma, M.D., Ph.D.; Yan Xu, Ph.D.; Carolyn Kercsmar, M.D.; James Wells, Ph.D.; Noah Shroyer

Cystic Fibrosis Foundation Research Development Program Center (Karp)

**Allergy & Immunology »** Simon Hogan, Ph.D.

Intestinal myeloid cell function under high fat diet stress (Karp)

**Biomedical Informatics »** Bruce Aronow, Ph.D.

Genetic modifiers of CF lung disease (Karp)

Functional genomics of LCMV infection (Karp)

**Developmental Biology »** Rashmi Hegde, Ph.D.

Molecular underpinninggs of allergy (Karp)

**Infectious Diseases »** Nancy Sawtell, Ph.D.

Role of indolamine 2,3 dioxygenase in HSV infection (Karp)

**Reproductive Sciences »** S.K. Dey, Ph.D.

Regulation of TLR signaling by cannabinoid receptors; regulation of preterm birth by innate immune receptors (Karp)

**Gastroenterology; ; Molecular Immunology »** Rohit Kohli, M.D.; Stavra Xanthakos, M.D.; Christopher Karp, M.D.

Role of IL-17 in NAFLD development and progression (Divanovic)

**Preventive Cardiology; Human Genetics; Molecular Immunology »** John Morrison, Ph.D.; Lisa Martin, Ph.D.; Christopher Karp, M.D.

Regulation of energy metabolism and obesity development by BAFF (Divanovic)

**Reproductive Sciences; Molecular Immunology »** S.K. Dey, Ph.D.; Christopher Karp, M.D.

Endocannabinoid signaling via CB2 protects against preterm birth by modulating immune responses (Divanovic)

Defining the mechanisms underlying inflammation-driven preterm birth (Divanovic)

**Endocrinology »** Jonathan Katz, Ph.D.

Diabetes and dendritic cells (Janssen)

**Hematology/Oncology »** Timothy Cripe, M.D., Ph.D.

Immuneresponses to oncolytic viruses (Janssen)

**Hematology/Oncology »** Joseph Palumbo, M.D.

The effect of the hemostatic system on T cell responses (Janssen)

MCMV susceptibility in thrombin-deficient mice (Hoebe)

**Molecular Cardiovascular Biology »** Jeffrey Molkentin, Ph.D.

Genetic dissection of heart function using ENU mutagenesis (Hoebe)

**Gastroenterology, Hepatology & Nutrition; Human Genetics; Molecular Immunology »** Jorge Bezerra, M.D.; Mehdi Keddache, Ph.D.; Senad Divanovic, Ph.D.

An ENU-germline mutation causing spontaneous hepatosteatosis identified through targeted exon-enrichment and next-generation sequencing (Hoebe)

**Experimental Hematology & Cancer Biology »** James Mulloy, Ph.D.

Development of a new humanized mouse model (Chougnet)

NSGS Tg mice as a humanized model for in vivo infectious diseases (Aliberti)

**Neonatology »** Alan Jobe, M.D., Ph.D.; Paul Kingma, M.D., Ph.D.; Jim Greenberg, M.D.

Biomarkers of immunologic function and preterm respiratory outcomes (Chougnet)

**Neonatology »** Suhas Kallapur, M.D.; Alan Jobe, M.D., Ph.D.

Late preterm birth, Ureaplasma species and childhood lung disease (Chougnet)

**Gastroenterology, Hepatology & Nutrition »** Jorge Bezerra, M.D.

Dysfunction in biliary atresia (Chougnet)

**Pediatric & Thoracic Surgery »** Gregory Tiao, M.D.

The molecular determinants of virus induced biliary atresia (Chougnet)

**Gastroenterology, Hepatology & Nutrition »** Alexander Miethke, M.D.

Role of regulatory T cells in biliary atresia (Chougnet)

**Experimental Hematology & Cancer Biology »** Jose Cancelas, M.D., Ph.D.; Yi Zheng, Ph.D.

Cincinnati Center for Excellence in Molecular Hematology (Chougnet)

## Faculty Members

**Christopher Karp, MD**, Professor

*Director, Division of Molecular Immunology*
*Gunnar Esiason/Cincinnati Bell Chair*
*Director, CF Research Center*
*Director, Trustee and Procter Scholar Programs*

**Research Interests** Molecular mechanisms underlying regulation and dysregulation of inflammatory responses in infectious, allergic, and genetic metabolic diseases

**Julio Aliberti, PhD**, Associate Professor

**Research Interests** Induction and regulation of immune responses to intracellular pathogens

**Claire A. Chougnet, PhD**, Associate Professor

**Research Interests** Mechanisms of immune dysregulation in HIV and aging; ontgeny of immune responses in early life

**Senad Divanovic, Ph.D.**, Instructor

**Research Interests** Role of the innate immune system in obesity and its sequelae. Role of innage immune system in induction of preterm labor

**Kasper Hoebe, PhD**, Assistant Professor

**Research Interests** Forward genetic analysis of the host immune response using ENU mutagenesis

**Edith M. Janssen, PhD**, Assistant Professor

**Research Interests** Mechanistic analysis and translational exploitation of adaptive immune responses to antigens expressed by apoptotic cells

**Joerg Koehl, MD**, Adjunct

**Research Interests** Regulation of innate and adaptive immune responses by the complement system

## Joint Appointment Faculty Members

**Jonathan Katz, PhD**, Professor

Endocrinology

**Research Interests** The immunology of Type 1 Diabetes Mellitus

## Trainees

- Jessica Allen, Ph.D., PGY-2, The Ohio State University
- Jaclyn McAlees, Ph.D., PGY-2, The Ohio State University
- Isaac Harley, B.S., GSY-3, University of Oklahoma
- Nicholas Boespflug, B.S., GSY-2, Seattle University
- Halil Aksoylar, B.S., GSY-4, Middle East Technical University, Ankara, Turkey
- Hao Fang, Ph.D., PGY-3, University of Texas Medical Branch
- Maria Moreno Fernandez, B.S., GSY-2, Universidad de Antioquia
- Pietro Presicce, Ph.D., PGY-5, University of Pavia, Italy
- Jonathan McNally, B.S., GSY-2, St. Mary's College, Maryland

- Cortez McBerry, B.S., GSY-4, Southern Illinois University Carbondale
- Rosa Maria Salazar-Gonzalez, Ph.D., PGY-2, Emory University, Atlanta, Georgia
- Jordan Downey, B.S., GSY-2, Hendrix College
- Robert Thacker, Ph.D., PGY-4, The University of Cincinnati

# Significant Accomplishments

### Advances in Defining Merocytic Dendritic Cells

The research program of Edith Janssen, PhD, aims at molecular analysis and translational exploitation of immune responses to self. Janssen has made major strides in defining the unique capabilities, and likely therapeutic utility, of a novel dendritic cell population that she discovered, merocytic dendritic cells. Merocytic dendritic cells orchestrate effector immune responses to self. Harnessing these dendritic cells significantly increases the efficacy of anti-tumor vaccines in mice (*J. Immunol*, 185:3337; *Clin Exp Immunol*, 163:381). On the other hand, merocytic dendritic cells can play an important pathogenic role in autoimmune disease – breaking T-cell tolerance to beta cell antigens and driving type 1 diabetes in mice (*J Immunol,* 185:1999; work done in collaboration with Jonathan Katz, PhD).

### Understanding Regulatory T Cells

Homeostasis and avoidance of immune-mediated pathology demands tight regulation of the amplitude, duration and class immune responses – something provided by numerous, often overlapping mechanisms of immune counter-regulation. The research program of Claire Chougnet, PhD, DPharm, on regulatory T cells, a subset of immune cells with important counter-regulatory roles across the immune system, continues to bear important fruit. Work published in the last year has demonstrated that: (a) regulatory T cells act in a contact-dependent manner to restrain HIV replication in activated T cells – something that may be of particular relevance to the course of early HIV infection (*Blood*, 117:5372); (b) the pro-apoptotic molecule, Bim, plays a major role in regulatory T-cell homeostasis (*J Immunol*, 186:156; work done in collaboration with David Hildeman, PhD); and (c) chorioamnionitis, which leads to ileal inflammation that interferes with gut maturation, is associated with depletion of intestinal regulatory T cells in sheep models (*PLoS One,* 6:e18355; work done in collaboration with Suhas Kallapur, MD, Alan Jobe, MD, PhD, and investigators from Maastricht University Medical Center).

### Seeking a More Humanized Mouse Model

Mice have triumphed as the *in vivo* experimental model system of choice in biomedical research. However, there are clear limitations to mouse models. The literature is full of therapeutic approaches that worked in mice but failed in humans. Further, mice often provide poor mimics of the human diseases being modeled. Christopher Karp, MD, is addressing the novel hypothesis that the cold stress that laboratory mice are ubiquitously subjected to (a practical “paradigm” employed systematically for nonscientific reasons – the comfort of their clothed human handlers) profoundly affects mouse pathophysiology in ways that directly impair modeling of human immunology and immune-mediated disease. The goal of this research program is the rapid development of better, more humanized models of immunity and immune-mediated disease.

# Division Publications

1. Aliberti J. **Pathogens and Inflammation**. *Fundamentals of Inflammation.* New York: Cambridge University Press; 2010: 448-456. .

2. Bestebroer J, Aerts PC, Rooijakkers SH, Pandey MK, Kohl J, van Strijp JA, de Haas CJ. **Functional basis for complement evasion by staphylococcal superantigen-like 7**. *Cell Microbiol*. 2010; 12:1506-16.
3. Chougnet CA, Tripathi P, Lages CS, Raynor J, Sholl A, Fink P, Plas DR, Hildeman DA. **A major role for Bim in regulatory T cell homeostasis**. *J Immunol*. 2011; 186:156-63.
4. Fritsche LG, Lauer N, Hartmann A, Stippa S, Keilhauer CN, Oppermann M, Pandey MK, Kohl J, Zipfel PF, Weber BH, Skerka C. **An imbalance of human complement regulatory proteins CFHR1, CFHR3 and factor H influences risk for age-related macular degeneration (AMD)**. *Hum Mol Genet*. 2010; 19:4694-704.
5. Gutierrez FR, Mariano FS, Oliveira CJ, Pavanelli WR, Guedes PM, Silva GK, Campanelli AP, Milanezi CM, Azuma M, Honjo T, Teixeira MM, Aliberti JC, Silva JS. **Regulation of Trypanosoma cruzi-induced myocarditis by programmed death cell receptor 1**. *Infect Immun*. 2011; 79:1873-81.
6. Hennies CM, Reboulet RA, Garcia Z, Nierkens S, Wolkers MC, Janssen EM. **Selective expansion of merocytic dendritic cells and CD8DCs confers anti-tumour effect of Fms-like tyrosine kinase 3-ligand treatment in vivo**. *Clin Exp Immunol*. 2011; 163:381-91.
7. Janssen EM, Lemmens EE, Gour N, Reboulet RA, Green DR, Schoenberger SP, Pinkoski MJ. **Distinct roles of cytolytic effector molecules for antigen-restricted killing by CTL in vivo**. *Immunol Cell Biol*. 2010; 88:761-5.
8. Karp CL. **Links between innate and adaptive immunity**. *Fundamentals in Inflammation.* New York: Cambridge University Press; 2010: 28-38. .
9. Karp CL, Mahanty S. **Approach to the patient with HIV and coinfecting tropical infectious diseases**. *Tropical Infectious Diseases: Principles, Pathogens, and Practice.* Philadelphia: Elsevier Churchill Livingstone; 2011: 1046-1065. .
10. Karsten CM, Kohl J. **The complement receptor CD46 tips the scales in T(H)1 self-control**. *Nat Immunol*. 2010; 11:775-7.
11. Katz JD, Ondr JK, Opoka RJ, Garcia Z, Janssen EM. **Cutting edge: merocytic dendritic cells break T cell tolerance to beta cell antigens in nonobese diabetic mouse diabetes**. *J Immunol*. 2010; 185:1999-2003.
12. Lages CS, Lewkowich I, Sproles A, Wills-Karp M, Chougnet C. **Partial restoration of T-cell function in aged mice by in vitro blockade of the PD-1/ PD-L1 pathway**. *Aging Cell*. 2010; 9:785-98.
13. Laumonnier Y, Schmudde I, Kohl J. **The role of complement in the diagnosis and management of allergic rhinitis and allergic asthma**. *Curr Allergy Asthma Rep*. 2011; 11:122-30.
14. Moreno-Fernandez ME, Rueda CM, Rusie LK, Chougnet CA. **Regulatory T cells control HIV replication in activated T cells through a cAMP-dependent mechanism**. *Blood*. 2011; 117:5372-80.
15. Reboulet RA, Hennies CM, Garcia Z, Nierkens S, Janssen EM. **Prolonged antigen storage endows merocytic dendritic cells with enhanced capacity to prime anti-tumor responses in tumor-bearing mice**. *J Immunol*. 2010; 185:3337-47.
16. Tripathi P, Kurtulus S, Wojciechowski S, Sholl A, Hoebe K, Morris SC, Finkelman FD, Grimes HL, Hildeman DA. **STAT5 is critical to maintain effector CD8+ T cell responses**. *J Immunol*. 2010; 185:2116-24.
17. Tsuboi N, Ernandez T, Li X, Nishi H, Cullere X, Mekala D, Hazen M, Kohl J, Lee DM, Mayadas TN. **Regulation of human neutrophil Fcgamma receptor IIa by C5a receptor promotes inflammatory arthritis in mice**. *Arthritis Rheum*. 2011; 63:467-78.
18. Zhang X, Schmudde I, Laumonnier Y, Pandey MK, Clark JR, Konig P, Gerard NP, Gerard C, Wills-Karp M, Kohl J. **A critical role for C5L2 in the pathogenesis of experimental allergic asthma**. *J Immunol*. 2010; 185:6741-52.
19. Zoller EE, Lykens JE, Terrell CE, Aliberti J, Filipovich AH, Henson PM, Jordan MB. **Hemophagocytosis causes a consumptive anemia of inflammation**. *J Exp Med*. 2011; 208:1203-14.

# Grants, Contracts, and Industry Agreements

| Grant and Contract Awards | | | Annual Direct / Project Period Direct |
|---|---|---|---|
| **ALIBERTI, J** | | | |
| **Innate Immune Responses During Toxoplasmosis** | | | |
| National Institutes of Health | | | |
| R01 AI 078969 | | 09/01/09-08/31/12 | $250,000 |
| **Control of Immune Responses by Lipoxins During Tuberculosis** | | | |
| National Institutes of Health | | | |
| R01 AI 075038 | | 02/01/08-01/31/13 | $208,574 |
| **Long-Term Immunity Against Toxoplasmosis** | | | |
| National Institutes of Health(George Washington University) | | | |
| R01 AI 033325 | | 07/01/08-06/30/13 | $33,759 |
| **CHOUGNET, C** | | | |
| **Role of Regulatory T Cells in HIV Infection** | | | |
| National Institutes of Health | | | |
| R01 AI 068524 | | 08/01/06-07/31/12 | $239,575 |
| **Homeostasis and Function of Regulatory T Cells in Aging** | | | |
| National Institutes of Health | | | |
| R01 AG 033057 | | 09/15/09-08/31/11 | $323,293 |
| **Biomarkers of Immunologic Function and Preterm Respiratory Outcomes (MPI)** | | | |
| National Institutes of Health | | | |
| U01 HL 101800 | | 05/01/10-04/30/15 | $346,019 |
| Jobe, A (MPI) | Core | $152,329 | |
| Chougnet, C (MPI) | Project | $92592 | |
| Young, L | Project | $49,538 | |
| Kingma, P | Project | $20266 | |
| Morrow, A | Project | $30,933 | |
| **DIVANOVIC, S** | | | |
| **Regulation of Energy Metabolism and Obesity Development by BAFF** | | | |
| University of Cincinnati | | | |
| | | 01/15/11-06/30/11 | $50,000 |
| **Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Health (Pilot and Feasibility Study)** | | | |
| National Institutes of Health | | | |
| P30 DK 078392 | | 08/01/07-05/31/12 | $50,000 |
| **HOEBE, K** | | | |
| **Functional Analysis of NK Cells and Their Potential to Generate CTL Responses** | | | |
| National Institutes of Health | | | |
| R01 AI 074743 | | 07/10/09-06/30/13 | $247,500 |
| **A Novel NK Cell-Mediated Adjuvant Approach to Generate CD8+ T Cell Responses** | | | |
| Bill & Melinda Gates Foundation(International AIDS Vaccine Initiative) | | | |
| | | 05/01/2008-06/30/11 | $237,272 |
| **JANSSEN, E** | | | |
| **Activating Robust Immunity to Tumor-Associated Antigens: Mechanisms and Biology** | | | |
| National Institutes of Health | | | |
| R01 CA 138617 | | 04/01/09-02/28/14 | $186,750 |
| **KARP, C** | | | |
| **Regulation of TLR Signaling and Innate Immunity by RP105** | | | |

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|---|---|---|---|---|
| National Institutes of Health | | | | |
| R01 AI 075159 | | 07/01/07-06/30/12 | | $242,798 |
| **Immunobiology of IFRD1, a Gene Modifying CF Lung Disease** | | | | |
| National Institutes of Health | | | | |
| R01 HL 094576 | | 08/01/09-07/31/13 | | $258,673 |
| **Novel Immune-Based Therapy for Leishmaniasis and TB** | | | | |
| National Institutes of Health(NewLink Genetics Corporation) | | | | |
| R41 AI 082812 | | 07/20/09-06/30/12 | | $126,020 |
| **Cystic Fibrosis Foundation Research Development Program** | | | | |
| Cystic Fibrosis Foundation | | | | |
| | | 07/01/07-06/30/11 | | $333,000 |
| Karp, C | Core 2 | | $83,000 | |
| Whitsett, J | Core 1 | | $50,000 | |
| Shroyer, N / Wells, J | Project 2 | | $80,000 | |
| Xu, Y | Project 3 | | $80,000 | |
| Bridges, J | Project 4 | | $40,000 | |
| **Allergenicity Resulting from Functional Mimicry of the TLR Complex** | | | | |
| National Institutes of Health | | | | |
| R01 AI 088372 | | 03/01/10-02/28/15 | | $260,627 |
| | | | **Current Year Direct** | **$3,379,319** |
| | | | **Total** | **$3,379,319** |