## BIOGRAPHICAL SKETCH

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NAME: Medoff, Benjamin David

eRA COMMONS USER NAME (credential, e.g., agency login): BDMEDOFF

POSITION TITLE: Associate Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Yale University | B.S. | 1990 | Mol Biophys + Biochem |
| Harvard Medical School | M.D. | 1994 | Medicine |
| Massachusetts General Hospital, Boston, MA | Intern | 1994-1995 | Internal Medicine |
| Massachusetts General Hospital, Boston, MA | Resident | 1995-1997 | Internal Medicine |
| Harvard Medical School, Boston, MA | Fellow | 1997-2000 | Pulmonary/Critical Care |

**A. Personal Statement**

I have been engaged in biomedical research for over 20 years. The focus of my research has been on the mechanisms of lung inflammation, epithelial injury and fibrosis and the role of these processes in the pathophysiology of asthma, idiopathic pulmonary fibrosis, viral pneumonitis, lung transplant rejection, and COPD. My laboratory utilizes basic cellular and molecular biology techniques, animal models of disease, and translational human studies to investigate properties of the pathologic responses in the lung. The laboratory is part of the Center for Immunology and Inflammatory Diseases, a scientifically diverse and collaborative environment for the study of immune mechanisms of disease, the MGH Fibrosis Center, a multi-disciplinary center focused on mechanisms and treatment of organ fibrosis, and the Division of Pulmonary and Critical Care Medicine. I have a demonstrated record of successful and productive research projects in lung inflammation/fibrosis and translational immunology. This includes extensive experience with research bronchoscopy (with over 200 procedures performed) and research in epithelial cell biology, fibrosis, and lung innate immunity and adaptive immunity. In addition, I have been a successful mentor for post-doctoral trainees and junior faculty having served as the mentor for multiple trainees on F32, T32, LRP, and K awards. Most of my trainees remain in research careers with academic appointments or research scientist positions in industry.

As the former Chief of the Division of Pulmonary and Critical Care Medicine at Massachusetts General Hospital and leader of the sponsoring program for the Harvard Combined Fellowship Program in Pulmonary and Critical Care, I am highly invested in the training of fellows and junior faculty for careers in academic medicine. I have formally mentored 19 trainees (6 current) including 5 with K awards. Seven of my mentees now have faculty appointments, and 6 run laboratories at pharmaceutical companies. In addition, I have served as the PI on a T32 on lung research and I am currently a co-PI on a T32 focused on lung disease and allergy. My role in this project will be to serve as Dr. Alladina's mentor. In this role I will monitor her progress on her project and provide mentorship in immunology and translational research techniques as well as career advice.

Ongoing and recently completed projects that I would like to highlight include:

**<u>Ongoing:</u>**

R01 HL133664 Suter 07/01/17-06/30/2022
NIH/NHLBI

Phenotyping Asthma for Bronchial Thermoplasty: Airway Smooth Muscle Structure and Function
This project aims to develop a novel optical imaging platform that will allow adequate quantification of airway smooth muscle cell and epithelial cell morphology in vivo.
Role: Co-Investigator

2R01 AI040618-21 Luster 12/01/17 – 11/30/2022
NIAID / NIH
Title: Lung-Resident Memory Th2 Cells In Asthma - New Therapeutic Targets
The major goals of this project are to determine the role of memory Th2 cells in asthma.
Role: Co P.I.

2T32HL116275-06 Luster/Christiani 07/01/18 – 06/30/2023
NIH /NHLBI
Title: Research Training in Pulmonary Immunology and Allergy at MGH
The Training Program is designed to prepare the next generation of physician-scientists who, through mentored research and rigorous training in new technologies, are prepared to be leaders in pulmonary immunology and allergy related biomedical research.
Role: Co-Director

1UH2AI144434-01 Cho 04/18/19 – 03/31/2022
NIH/NIAID
Title: Airway Dendritic Cells In The Allergic Asthma Phenotype
The major goals of this study are to profile airway dendritic cells in human subjects with allergic asthma.
Role: Co-P.I.

R01HL152075-01 Hariri 06/01/20 – 05/31/2025
NIH-National Institutes of Health
In vivo endobronchial OCT for IPF diagnosis and therapy response assessment
The major goals of this project are to validate low-risk, minimally-invasive OCT for microscopic IPF diagnosis and monitoring of therapy response in early disease in a multi-center study.
Role: Co-Investigator

**Completed (last 3 years):**
PR150903/W81XWH-16-1-0493 (Medoff) 8/15/2016 to 8/14/2020 (NCE)
U.S. Army Medical Research Acquisition Activity
Title: The GPCR-CARMA3 Signaling Axis Mediates Inflammation in Asthma
The goal of this project is to determine the role of CARMA3 in mediating allergic inflammation in asthma.
Role: P.I.

1 U01 HL121827-01 Medoff/Kwon 09/26/2013–11/30/2018 (NCE)
NIH/NHLBI
Title: HIV and COPD: Immune mediated mechanisms.
The major goal of this program project is to define the immune activation state in the lungs of HIV infected individuals and correlate this to the incidence of COPD.
Role: P.I.

**B. Positions, Scientific Appointments, and Honors**
Positions and Scientific Appointments
2018 Scientific Review Group Mentored Clinical and Basic Science Review Committee meeting, NIH-NHLBI
2018- Physician in Medicine, Massachusetts General Hospital
2017-2019 Program Chair - Allergy, Immunology & Inflammation Assembly, American Thoracic Society
2015 Nominating Committee - Allergy, Immunology & Inflammation Assembly, American Thoracic Society
2012- Associate Professor of Medicine, Harvard Medical School
2009-2021 Chief, Pulmonary & Critical Care Unit, Massachusetts General Hospital
2009-2018 Associate Physician in Medicine, Massachusetts General Hospital
2006-2012 Assistant Professor of Medicine, Harvard Medical School
2005-2009 Assistant Physician in Medicine, Massachusetts General Hospital

2003-2009 Associate Director, Medical Intensive Care Unit, Massachusetts General Hospital
1999-2006 Instructor in Medicine, Harvard Medical School
1999-2005 Assistant in Medicine, Massachusetts General Hospital

Other Experience and Professional Memberships
1999- Board Certification in Critical Care Medicine (recertified 2010, pending 2022)
1998- Board Certification in Pulmonary Medicine (recertified 2009, 2019)
1997-2007 Board Certification in Internal Medicine
1996- Massachusetts Medical License Registration

Honors and Awards
2006 American Thoracic Society Unrestricted Research Award
2001 National Research Service Award, National Institute of Allergy and Infectious Diseases
2000 GlaxoWellcome Pulmonary Fellowship Award
1995 Distinguished Asthma Scholarship
1994 cum laude, Harvard Medical School
1990 Honors in Molecular Biophysics and Biochemistry, Yale University
1990 cum laude, Yale University

**C. Contributions to Science**

I) Epithelial cell - immune interactions: The role of epithelial cell and innate immune cells in airway inflammation. It is now clear that the airway epithelium is a key modulator of the immune response in the lung through its interactions with innate immune cells. My research program has looked at the role of the airway epithelium and innate immune cells in the establishment of airway inflammation. Using animal models of disease and in vitro assays we have established a critical role of CARMA3 for the immune response to allergens in the lungs. Specifically, CARMA3 mediates the production of inflammatory cytokines by airway epithelial cells in response to allergens and other mediators, leading to dendritic cell activation. In other work we have established the key role for dendritic cells and macrophages for the recruitment of neutrophils and T cells into the lung.

1. Medoff BD, Landry AL, Wittbold KA, Sandall BP, Derby MC, Cao Z, Adams JC, Xavier RJ. CARMA3 Mediates Lysophosphatidic Acid Stimulated Cytokine Secretion by Bronchial Epithelial Cells. Am J Respir Cell Mol Biol. 2009 40(3):286-94.

2. Medoff BD, Seung E, Hong S, Thomas SY, Sandall BP, Duffield JS, Kuperman DA, Erle DJ, Luster AD. CD11b+ Myeloid Cells are the Key Mediators of Th2 Cell Homing into the Airway in Allergic Inflammation. J Immunol. 2009 Jan 1;182(1):623-35. PMID: 19109196

3. Causton B, Ramadas RA, Cho JL, Jones K, Pardo-Saganta A, Rajagopal J, Xavier R, Medoff BD. CARMA3 is Critical for the Initiation of Allergic Airway Inflammation. J Immunol 2015,195(2): 683-94. PMID: 26041536.

4. Causton B, Pardo-Saganta A, Gillis J, Discipio K, Kooistra T, Rajagopal J, Xavier RJ, Cho JL, Medoff BD. CARMA3 Mediates Allergic Lung Inflammation in Response to Alternaria alternata. Am J Respir Cell Mol Biol. 2018 Jun 29 - Epub ahead of print. PMID: 29958012

II) Mechanisms of fibrosis: Modulators of lung fibroblast, endothelial and epithelial cell functions in the development of fibrosis. Accumulating evidence demonstrates that the two Rho kinase isoforms ROCK1 and ROCK2 contribute to the development of pulmonary fibrosis via effects in multiple lung cell-types. Rho associated coiled coil protein kinase (ROCK) has been implicated in the pathogenesis of pulmonary fibrosis in studies using nonselective pharmacologic inhibition. We have taken a genetic approach to differentiating the relative contributions of the 2 isoforms and eliminating off target effects through use of isoform specific haploinsufficient mice. We have shown that both ROCK1 and ROCK2 haploinsufficient mice are protected from bleomycin-induced pulmonary fibrosis. In addition, we have shown that the mechanism for ROCK1 protection appears to be mediated through epithelial cell apoptosis, vascular leak and fibroblast to myofibroblast differentiation. ROCK2 protection appears to be mainly caused by vascular leak and fibroblast to myofibroblast differentiation. Other work has focused on the role of epithelial stem cells in lung homestasis, the role of lipid mediators in pulmonary fibrosis, including lysophosphatidic acid and sphingosine-1-phosphate, and the role of YAP-TAZ in mediating fibrosis.

1. Knipe RS, Probst CK, Lagares D, Franklin A, Spinney JJ, Brazee PL, Grasberger P, Zhang L, Black KE, Sakai N, Shea BS, Liao JK, Medoff BD, Tager AM. The Rho Kinase Isoforms ROCK1 and ROCK2 Each Contribute to the Development of Experimental Pulmonary Fibrosis. Am J Respir Cell Mol Biol. 2018 Apr;58(4):471-481. PMID: 29211497

2. Santos DM, Pantano L, Pronzati G, Grasberger P, Probst CK, Black KE, Spinney JJ, Hariri LP, Nichols R, Lin Y, Bieler M, Seither P, Nicklin P, Wyatt D, Tager AM, Medoff BD. Am J Respir Cell Mol Biol. 2020 Apr;62(4):479-492. PMID: 31944822.

3. Probst CK, Montesi SB, Medoff BD, Shea BS, Knipe RS. Vascular Permeability in the Fibrotic Lung. Eur Respir J. 2020 Apr 7. In press. PMID: 32265308.

4. Knipe RS, Spinney JJ, Abe EA, Probst CK, Franklin A, Logue A, Giacona F, Drummond M, Griffith J, Brazee PL, Hariri LP, Montesi SB, Black KE, Hla T, Kuo A, Cartier A, Engelbrecht E, Christoffersen C, Shea BS, Tager AM, Medoff BD. Endothelial-Specific Loss of Sphingosine-1-Phosphate Receptor 1 Increases Vascular Permeability and Exacerbates Bleomycin-Induced Pulmonary Fibrosis. Am J Respir Cell Mol Biol. 2021 Aug 3. Online ahead of print. PMID: 34343038

III) T cell activation/regulation: Regulators of T cell activation and function. My research program has focused on the mechanisms that control T cell activation and effector functions in asthma, pulmonary infections, and lung transplantation. Specifically, we have utilized murine models of disease, genetically modified mice, cellular immunology, and translational human studies to characterize the role of effector and regulatory T cells in health and disease. This includes demonstrating the importance of CARMA1 in the development of allergic airway inflammation and regulatory T cell development, the role of Tim3 in modulating the response to influenza infection and transplant rejection, and the role of Mst1 in T cell development and activation.

1. Medoff BD, Seed B, Jackobek R, Zora J, Yany Y, Luster AD, Xavier R. CARMA1 is critical for the development of allergic airway inflammation in a murine model of asthma. J Immunol. 2006; 176(12): 7272-7277.

2. Medoff BD, Sandall BJ, Landry A, Nagahama K, Mizoguchi A, Luster AD, Xavier RJ. Differential Requirement for CARMA1 in Agonist-Selected T Cell Development. Eur J Immunol. 2009, 39: 78-84. PMID: 19130560.

3. Ramadas RA, Roche MI, Moon JJ, Ludwig T, Xavier RJ, Medoff BD. CARMA1 is Necessary for Optimal T Cell Responses in a Murine Model of Allergic Asthma. J Immunol. 2011, 187(12):6197-207. PMID: 22075698.

4. Cho JL, Roche MI, Sandall B, Brass AL, Seed B, Xavier RJ, Medoff BD. Enhanced Tim3 Activity Improves Survival After Influenza Infection. J Immunol. 2012 189(6):2879-89. PMID:22875804.

IV) Chemokines: Role of chemokines in inflammatory lung disease. My early publications focused on the role of chemokines in the development of airway inflammation in asthma and lung transplant rejection. For this work, we utilized animal models of disease, genetically modified mice, cellular immunology, as well as human samples to characterize many of the critical mediators of cellular recruitment in these disorders. As part of this work we also established a novel murine model of lung transplant rejection.

1. Tager AM, Bromley SK, Medoff BD*, Islam SA, Bercury SD, Friedrich EB, Carafone AD, Gerszten RE, Luster AD. Leukotriene B4 receptor BLT1 mediates early effector T cell recruitment. Nat Immunol. 2003; 4(10):982-90. *second author publication.

2. Medoff BD, Seung E, Wain JC, Means TK, Campanella GS, Islam SA, Thomas SY, Ginns LC, Grabie N, Lichtman AH, Tager AM, Luster AD. BLT1-mediated T cell trafficking is critical for rejection and obliterative bronchiolitis after lung transplantation. J Exp Med. 2005; 202(1):97-110.

3. Medoff BD, Wain JC, Seung E, Jackobek R, Means TK, Ginns LC, Farber JM, Luster AD. CXCR3 and its Ligands in a Murine Model of Obliterative Bronchiolitis: Regulation and Function. J Immunol. 2006; 176(11): 7087-7095.

4. Medoff BD, Thomas SY, Luster AD. T cell trafficking in allergic asthma: The ins and outs. Annual Rev. Immunol. 2008, 26: 205-32.

V) Human studies: Translational human studies. For over 10 years we have had a translational research program that seeks to use human samples from the lung to determine the pathogenesis of various inflammatory lung disease. The program was initially focused on defining the mechanisms of T cell recruitment

and activation in the lungs of human subjects with allergic asthma, HIV and COPD, and after lung transplantation. More recently we have started studies focused on defining the innate immune cell profile and changes in epithelial cell functions in the human lung in health and disease. Samples are obtained from human subjects using bronchoalveolar lavage and airway brushings, and the samples are studied using advanced flow cytometry, CyTOF, RNA sequencing, and in vitro cellular assays. The subjects are further classified using advanced imaging techniques such as HRCT-PET and optical coherence tomography to better define their pulmonary anatomy and physiology.

1. Harris RS, Venegas JG, Wongviriyawong C, Winkler T, Kone M, Musch G, Vidal Melo MF, de Prost N, Hamilos DL, Afshar R, Cho JL, Luster AD, Medoff BD. 18FDG uptake rate is a biomarker of eosinophilic inflammation and airway response in asthma. J Nucl Med 2011, (11):1713-20. PMID: 21990575.

2. Adams DC, Hariri, LP, Miller AJ, Wang Y, Cho JL, Villiger M, Holz JA, Szabari1 MV, Hamilos DL, Harris RS, Griffith JW, Bouma BE, Luster AD, Medoff BD, and Suter MJ. Birefringence Microscopy Platform for Assessing Airway Smooth Muscle Structure and Function in vivo. Sci Transl Med. 2016, 8(359):359ra131. PMID: 27708064.

3. Cho JL, Ling MF, Adams DC, Faustino L, Islam SA, Afshar R, Griffith JW, Harris RS, Ng A, Radicioni G, Ford AA, Han AK, Xavier R, Kwok WW, Boucher R, Moon JJ, Hamilos DL, Kesimer M, Suter MJ, Medoff BD*, Luster AD. Allergic Asthma is Distinguished by Sensitivity of Allergen-Specific CD4+ T Cells and Airway Structural Cells to Type 2 Inflammation. Sci Transl Med. 2016, 8(359): 359ra321. PMID: 27708065. *co-last author publication.

4. Corleis B, Cho JL, Gates SJ, Linder AH, Dickey A, Lisanti-Park AC, Schiff AE, Ghebremichael M, Kohli P, Winkler T, Harris RS, Medoff BD*, Kwon DS. Smoking and Human Immunodeficiency Virus 1 Infection Promote Retention of CD8+ T Cells in the Airway Mucosa. Am J Respir Cell Mol Biol. 2021 Nov;65(5):513-520. PMID: 34166603. *co-last author publication.

A full list of my published work can be found on My Bibliography (86 total publications): https://www.ncbi.nlm.nih.gov/myncbi/benjamin.medoff.1/bibliography/public/