

PROMOTION RECOMMENDATION
UNIVERSITY OF MICHIGAN MEDICAL SCHOOL
DEPARTMENT OF INTERNAL MEDICINE
DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY

Gary B. Huffnagle, Ph.D., Associate Professor of Internal Medicine, with tenure, Department of Internal Medicine, and Associate Professor of Microbiology and Immunology, without tenure, Department of Microbiology and Immunology, Medical School, is recommended for promotion to Professor of Internal Medicine, with tenure, Department of Internal Medicine, and Professor of Microbiology and Immunology, without tenure, Department of Microbiology and Immunology, Medical School.

Academic Degrees:

Ph.D.	1990	University of Texas Southwestern Medical Center
B.S.	1984	Pennsylvania State University

Professional Record:

2002-Present	Associate Professor of Internal Medicine, with tenure, University of Michigan
2000-Present	Associate Professor of Microbiology & Immunology, University of Michigan
2000-2002	Associate Professor, without tenure, and Senior Associate Research Scientist, Department of Internal Medicine, University of Michigan
1999-2000	Assistant Research Scientist, Department of Microbiology & Immunology, University of Michigan
1997-2000	Assistant Research Scientist, Department of Internal Medicine, University of Michigan
1992-1997	Research Investigator, Department of Internal Medicine, University of Michigan

Summary of Evaluation:

Teaching: Dr. Huffnagle is importantly involved in the education of undergraduate students, graduate students in microbiology and immunology, and M.D. and Ph.D. postdoctoral students. Dr. Huffnagle spearheaded a President and Provost supported initiative to design and implement an undergraduate major in Microbiology that would be taught by faculty from five departments drawn from the Medical School, School of Public Health, and of the College of Literature, Science, and the Arts. This committee developed the concentration requirements to meet approval by the departments and the College of LS&A (the degree granting unit). Dr. Huffnagle completely designed a new course Internal Medicine 460/Microbiology 460 "Eukaryotic Microbiology" which is a 3-credit course. All lectures in this course were delivered by Dr. Huffnagle in 2005. Dr. Huffnagle is a sought after mentor in the University of Michigan Undergraduate Research Opportunity Program (UROP). He has served as an undergraduate research mentor for five students in the past three years. Dr. Huffnagle is actively involved in

graduate student education. He is the course director and sole lecturer for "Immunity to Infection," a 2-credit course for second-year students. He is the course director and sole lecturer for Immunol 850 "Regulation of Adaptive Immunity," a 2-credit course for first and second-year students. Dr. Huffnagle has served as the thesis advisor for four students (two graduated with Ph.D.'s; two currently in lab) in the Microbiology and Immunology graduate program since 2002. He served as the thesis advisor for two students (1 graduated with a Ph.D.; one currently in lab) from the Immunology graduate program since 2002. Dr. Huffnagle has served as the fellowship mentor for four Ph.D. post-doctoral fellows supported by a T32 Training Grant since 2002. Dr. Huffnagle has served on dissertation thesis committees (20) in Microbiology and Immunology, Immunology, Epidemiology, Chemistry, Biomedical Engineering, and Pathology.

Research: Dr. Huffnagle has performed pioneering work in host responses to fungal disease. Dr. Huffnagle has made three seminal observations. First, Dr. Huffnagle made the startling observation that disruption of the normal microflora of the gut in mice by antibiotics could alter the immune response in the lungs. These studies have defined a novel arena of immunoregulation that is crucial to the pathogenesis of allergic disease; Dr. Huffnagle has recently received RO1 funding to pursue this novel arena of experimentation. Second, Dr. Huffnagle has characterized the immunoregulatory events which occur in a chronic allergic bronchopulmonary mycosis murine model which is dependent on a genetic component in the immune response. These studies document that strong polarization of the cell mediated response to *C. neoformans* does not occur in the lymph nodes; rather, early polarization of the response occurs largely at the site of infection, the lungs. Dr. Huffnagle's studies document that while T-cell activation occurs within the lung associated lymph nodes, activated cells then immediately migrate to the lung where a strongly polarized immune response develops. Utilizing this same model, Dr. Huffnagle was the first to document that alternatively activated macrophages develop during allergic bronchopulmonary mycosis. These studies document that chronic fungal infections likely result from an inappropriate cytokine balance which is dependent, in part, on genetic factors. Third, Dr. Huffnagle has demonstrated that CD4 T cells are not required for the expansion and trafficking of CD8 T cells to the site of *C. neoformans* infections. CD4 T cells are also not required for the generation IFN- γ producing CD8 T cells effectors in the lung. Neutralization of IFN- γ in CD4-/CD8+ mice increased macrophage infection with *C. neoformans*. In aggregate, these data document that effector CD8 T cell function is independent of CD4 T cells. These studies document the presence of a potent antifungal effector mechanism which is likely present in patients with CD4 deficiencies (HIV infection).

Dr. Huffnagle is the author of 60 peer-reviewed manuscripts; he is the first or senior author of 35 of these manuscripts. Dr. Huffnagle's research has been published in highly respected journals, including the *Journal of Immunology*, the *American Journal of Pathology*, *Journal of Experimental Medicine*, *Nature Immunology*, and the *Journal of Clinical Investigation*. Dr. Huffnagle has funded his research throughout his career at the University of Michigan. He is presently a principal investigator on two RO1 grants and co-investigator on a third. Dr. Huffnagle is the mentor for a Parker B. Francis Pulmonary Fellowship for Mairi Noverr, Ph.D. fellow.

Recent and Significant Publications:

Lindell DM, Moore TA, McDonald RA, Toews GB, Huffnagle GB: Generation of anti-fungal effector CD8+ T cells in the absence of CD4+ T cells during *Cryptococcus neoformans* infection. *J Immunol* 174(12):7920-7928, 2005.

Arora S, Hernandez YS, Erb-Downward JR, Toews GB, Huffnagle GB: Role of IFN- γ in regulating T2 immunity and the development of alternatively activated macrophages during allergic bronchopulmonary mycosis. *J Immunol* 174(10):6346-6356, 2005.

Hernandez YS, Arora S, McDonald RA, Toews GB, Huffnagle GB: Distinct roles for IL-4 and IL-10 in regulating T2 immunity during allergic bronchopulmonary mycosis. *J Immunol* 174(2):1027-1036, 2005.

Noverr MC, Falkowski NR, McDonald RA, McKenzie AN, Huffnagle GB: The development of allergic airway disease in mice following antibiotic therapy and fungal microbiota increase: Role of genetics, antigen and IL-13. *Infect Immun* 73(1):30-38, 2005.

Noverr MC, Noggle RM, Toews GB, Huffnagle GB: Role of antibiotics and fungal microbiota in driving pulmonary allergic responses. *Infect Immun* 72(9):4996-5003, 2004.

Service: Dr. Huffnagle serves as a Section Editor for the *Journal of Immunology*. He was a member of the NIH Bacteriology/Myiology Study Section 2, and is presently a member of the NIH Pathogenic Eukaryotic Microbiology (PTHE) Study Section. Dr. Huffnagle has been an invited plenary lecturer at the American Society for Microbiology, the National Cancer Institute, the American Thoracic Society International Meeting, the Woods Hole Molecular Mycology Course, and the Keystone Symposium. He has been an invited lecturer at symposia in Brazil, the United Kingdom, Argentina, and Ireland. By all criteria, Dr. Huffnagle is a distinguished, cutting-edge, internationally recognized independent investigator.

External Review:

Reviewer A: “[Dr. Huffnagle] is generally regarded as one of the top 3 scientists in the field of immune responses to fungal pathogens....He is an extremely prominent scientist who brings great credit to your institution.”

Reviewer B: “...Dr. Huffnagle is a leader in the scientific community and his work is some of the best, if not the best, in the field.”

Reviewer C: “Gary presents outstanding, and lucid talks at scientific meetings and is a natural teacher. He is a gifted and committed reviewer for the NIH, giving of his valuable time and serving as an advocate for excellence in science.”

Reviewer D: “Dr. Huffnagle’s studies have bridged the gap between basic immunology and infectious diseases. His studies are characterized by unusual insight and exceptional rigor.... Gary is one of those individuals whose work is characterized by insight, infectious energy and rigor. He is a credit to your university.”

Reviewer E: “Dr. Huffnagle is clearly a nationally and internationally recognized leader in the field of the immunological response to fungal pathogens such as *Cryptococcus neoformans*. He has made outstanding contributions to our understanding of the immune

response in the context of bronchopulmonary mycoses and, more recently, his group has carried out groundbreaking work in the area of antibiotic treatment and allergic responses.”

Reviewer F: “He is recognized internationally as one of the leaders in fungal immunology and has been a sought after speaker at various national and international meetings.”

Reviewer G: “Dr. Huffnagle’s contributions to fungal immunology have been vast both in terms of quality and quantity. I would rank Gary among the top five in this competitive field which includes hundreds of scientists.”

Reviewer H: “He is simply a scientist who will continue to lead rather than follow others and provides the framework for making new paradigm shifts in our understanding of pathogenesis.”

Reviewer I: “His work has the potential of benefiting millions of Americans and people throughout the world.”

Reviewer J: “In my opinion Dr. Huffnagle has established the definite niche in the immunology of fungal infection which is internationally recognized and places him in the top 10% or so of his peers.”

Reviewer K: “Gary would definitely be promoted to the rank of Professor in my department. We would take one look at his grant support, publication record, and level of intramural and extramural service, then we’d thank our lucky stars that we have such a talented colleague!”

Summary of Recommendation:

Dr. Huffnagle is a distinguished independent investigator who has made novel, paradigm defining observations in host defenses against pulmonary microbes. He is a capable and original thinker, and a charismatic teacher of undergraduates, graduate students, and postdoctoral M.D. and Ph.D. fellows. I am delighted to recommend Dr. Gary Huffnagle for promotion to Professor of Internal Medicine, with tenure, and Professor of Microbiology and Immunology, without tenure, Medical School.



Allen S. Lichter, M.D., Dean
*Newman Family Professor
of Radiation Oncology*

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