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Project Number: 5R21ES023384-03

Title: FUNGAL EXPOSURE AND THE RESPIRATORY TRACT MICROBIOME

Contact PI / Project Leader: EVANS, CHRISTOPHER M

Awardee Organization: UNIVERSITY OF COLORADO DENVER

## Abstract Text:

DESCRIPTION (provided by applicant): The respiratory system is a central host-environment interface that is exposed to billions of particles and pathogens daily. Airway mucus is critical to eliminating deposited environmental agents and limiting pathogen accumulation through a process called mucociliary clearance (MCC). Mucus production and composition are dramatically altered in numerous lung diseases. Recent studies have identified changes in the lung microbiome in asthma and COPD, but direct links between altered MCC function and changes in the respiratory microbiome have not been tested. In this exploratory grant proposal, mechanisms by which fungal toxicant exposure elicits changes will be identified in the upper and lower respiratory tract microbiomes along with the functional consequences of these changes. This work focuses on the major macromolecular components of airway mucus - mucin glycoproteins encoded by the MUC5AC and MUC5B genes. Recent studies in patients with asthma and COPD show that alterations in mucus production are related to differential regulation of MUC5AC (which goes up) and MUC5B (which remains stably expressed or goes down). To address whether mucins determine respiratory microbial diversity, Muc5ac and Muc5b knockout mice were recently generated. In the absence of an inflammatory challenge, Muc5b (but not Muc5ac) deficiency causes spontaneous lethal infections marked by acquisition of pulmonary *Staphylococcus aureus* infection. Thus, Muc5b is essential for controlling homeostatic and pathological microbial populations in the lungs. Here, the intent is to accomplish the primary purpose of this RFA - to test "how environmental exposures impact the composition and/or function of the microbiome" - in mouse models of respiratory inflammation. *Aspergillus* fungal exposure is a major cause of asthma exacerbations and several types of hypersensitivity pneumonitis, a related occupational lung disease. In preliminary studies, wild type mice exposed to an aerosol *Aspergillus oryzae* extract (AOE) show inflammation, increased Muc5ac, and reduced Muc5b expression similar to that seen in humans with asthma. Thus, it is hypothesized that AOE-induced changes in respiratory microbiome composition are dependent upon Muc5b expression levels and that these changes affect disease pathology and susceptibility to opportunistic pathogen infection. To test this, wild type mice will be exposed to aerosolized AOE. Changes will be measured in the upper and lower airway microbiota, and we will assess changes in inflammation, histopathology, and susceptibility to *S. aureus*. These data will be compared to that seen in Muc5b deficient and Muc5b overexpressing mice. Collectively, these studies will be used to develop a framework for designing and analyzing subsequent investigations in mice and in humans. MUC5B expression varies significantly in humans, and common genetic polymorphisms significantly regulate its expression. In addition treatments such as inhaled hypertonic saline enhance MCC effectively. Thus, successful completion of the proposed studies may significantly impact human health in the near-term.

## Public Health Relevance Statement:

PUBLIC HEALTH RELEVANCE: Respiratory infections and chronic airway diseases are common and have major impacts on human health, health care costs, and economic well-being. The sinuses and lungs are primary sites of environmental exposures to natural and man-made particulates. Millions of particulates are inhaled during normal breathing and many of these particles are (or contain) *Aspergillus* type mold species. This research proposal focuses on defining how *Aspergillus* affects the composition of the nasal and lung flora (the "respiratory microbiota") and on how changes in their changes affect susceptibility to respiratory infections and the development of chronic lung diseases.

## Project Terms:

Address; aerosolized; Aerosols; Affect; airway hyperresponsiveness; allergic airway disease; Alveolar; Animal Model; Antifungal Agents; antimicrobial; Applications Grants; Area; *Aspergillus*; *Aspergillus oryzae*; Asthma; Automobile Driving; Bacteria; base; Biology; body system; Breathing; Child; Chronic; Chronic lung disease; Chronic Obstructive Airway Disease; Complex; Data; Deposition; design; Development; Disease; Distal; Economics; Environment; environmental agent; Environmental Exposure; Environmental Health; Exposure to; Extrinsic allergic alveolitis; Extrinsic asthma; Fostering; Funding Mechanisms; Future; Genetic Polymorphism; Genus *staphylococcus*; Glycoproteins; Growth; Health; Health Care Costs; Histopathology; Host Defense; Human; Immune; Immunity; Impairment; In Vitro; in vivo; Infection; Inflammation; Inflammatory; Inflammatory Response; Inhalation Exposure; interest; Investigation; Knockout Mice; Link; Lower respiratory tract structure; Lung; Lung diseases; man; Measures; microbial; microbiome; microbiota; Modeling; Molds; mouse model; MUC5AC gene; MUC5B gene; Mucins; Mucociliary Clearance; Mucositis; Mucous body substance; Mucous Membrane; Mus; Nature; Nose; novel; Occupational; Organism; Oropharyngeal; overexpression; particle; Particulate; pathogen; Pathogenesis; Pathology; Patients; Personal Satisfaction; Play; Population; Predisposition; Process; Production; Regulation; Research; Research Proposals; respiratory; Respiratory System; Respiratory Tract Infections; Respiratory tract structure; response; Rest; Role; Saline; Sinus; Site; *Staphylococcus aureus*; Surface; Taxon; Testing; Tissues; toxicant; Toxicant exposure; Tracheobronchial; Viral; Wild Type Mouse; Work

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