

## Animal Models of Human Disease: Consider the Pig!

In the field of respiratory medicine, small animal models, particularly mice, have provided substantial information on normal and disease processes in the lungs. However, translation of this knowledge into progress in respiratory medicine has been frustratingly slow, and the gulf between mouse and patient remains significant. Dr. Eoin P. Judge and colleagues from Ireland are authors of a Translational Review in which the domesticated pig is considered as a better animal model for human disease. In recent years, a major limitation with porcine models was overcome with the successful generation of gene-targeted pigs and the publication of the pig genome. As a result, the porcine model is likely to become an important bridge between traditional small

laboratory animal models and human medicine. An increasing number of lung conditions are being studied and modeled in the pig. Porcine models of lung disease took a major step forward following the generation of the pig cystic fibrosis model. However, the scientific literature relating specifically to porcine lung anatomy and airway histology is limited, and methods for *in vivo* lung procedures in the pig are rarely described. This review aims to aid clinical researchers using the porcine model in the area of translational respiratory medicine by collating the disparate literature on porcine lung anatomy, histology, and microbiology, providing a comparison with the human lung and describing appropriate bronchoscopy procedures for the pig lungs.

*See Translational Review by Judge and colleagues on page 334*

## HIGHLIGHTED PAPERS BY JUNIOR INVESTIGATORS

### Gene Regulation Related to Allergic Airway Disease

The prevalence of allergic airway diseases (AADs), including asthma and allergic rhinitis, has increased dramatically over the last 50 years, heightening the need to identify underlying causes of these diseases. The etiology of AAD is enigmatic and complex and likely involves complex interactions between genes and environment. Genome-wide association studies in humans have identified several loci associated with AAD, but identifying the specific gene-environment interactions that lead to AAD remains a very difficult task. Samir Kelada, currently an assistant professor in the Department of Genetics and Marsico Lung Institute at the University of North Carolina in Chapel Hill, NC, began to address this issue while working as a postdoctoral fellow in the laboratory of Dr. Francis Collins at the National Institutes of Health in Bethesda, MD, and was co-advised by Dr. David Schwartz (University of Colorado School of Medicine, Denver, CO). Dr. Kelada is first author of a paper that describes an integrative approach to identify the genetic components of response to airway allergen challenge in a mouse model of AAD. The authors employed a new mouse genetics reference population known as the Collaborative Cross to first characterize response to allergen challenge among this genetically diverse population of mice, and then identified quantitative trait loci (QTL) for airway eosinophilia, serum IgE, and gene expression in the lung (expression QTL or “eQTL”). They found that many genes in the lung had gene eQTL and that genetically determined variation in expression of one gene (*Tlcd2*) may underlie eosinophil recruitment to the airways. Collectively, their data provide insight into gene regulation in the context of allergen challenge and also point to a novel candidate gene for allergic airway inflammation.

*See article by Kelada and colleagues on page 436*

### Alveolar Epithelial Autophagy and Influenza Virus

Autophagy is a complex process in which protein aggregates, damaged organelles and pathogens are identified, captured, and directed to the lysosome for degradation. Autophagy decreases with age and this decline likely contributes to the pathogenesis of many diseases, including chronic lung disease. David Hahn, who was a graduate student in Dr. Tim Weaver’s lab at Cincinnati, OH at the time of submission, is first author of a paper directly assessing the importance of autophagy for alveolar homeostasis by selectively deleting a key regulator of the pathway, Atg5, in respiratory epithelial cells. A 50% decrease in Atg5 expression in type II epithelial cells did not perturb alveolar structure or lung function at any age, including very old mice; however, ciliogenesis in the bronchiolar epithelium was disrupted. The lack of phenotype in the alveolar epithelium suggested that there was excess autophagic capacity (reserve autophagy) in these cells. Consistent with this hypothesis, genetic inhibition of autophagy was associated with significantly less morbidity and mortality following infection with influenza A virus, a pathogen that replicates in autophagosomes of the alveolar compartment. Collectively, these results suggest that pharmacologic inhibition of the alveolar autophagic reserve could provide an antigen-independent mechanism for limiting replication of influenza A virus. Although viruses can exploit the autophagic reserve, the authors speculate that the excess autophagic capacity of the alveolar epithelium confers an additional level of protection in this compartment by providing an important backup disposal pathway for protein aggregates associated with many diseases.

*See article by Hahn and colleagues on page 400*

## NIH CORNER

### News from the National Heart, Lung, and Blood Institute Managing Conflict of Interest in the Initial Review of NIH Applications

Have you ever requested your grant application be assigned to a particular Scientific Review Group (“study section”) only to have it assigned elsewhere? This is a scenario we occasionally hear about from applicants. There are various scientific reasons why this might occur, but one nonscientific reason is a real or apparent conflict of interest with a member of the review group. Examples include: (1) If any member of the study section is listed as “Senior/Key Personnel” on the

first page, or has a direct financial association with an application, the application cannot be reviewed in the study section; (2) in most cases, if a study section member writes a “Letter of Support”, the application cannot be reviewed in the study section; and (3) if you have suggested a particular reviewer by name, rather than an area of expertise. Some conflicts are managed by requiring a study section member to leave the room; for example, if the member has collaborated with the applicant within the last 3 years, or if they are employed at an institution listed on the application. The NIH Center for Scientific Review (CSR) (<http://public.csr.nih.gov>) has guidance and policies including NOT-OD-13-010, and rosters of review panels can be found at <http://public.csr.nih.gov/StudySections/>. Contact the CSR for more information.