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Editorial

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In its unique function of bringing the oxygen-containing atmosphere into intimate contact with the first pass of the entire venous blood return, the lung finds itself at risk of disease from a number of fronts. External pathogens have direct access to the intimacies of the lung *via* inhalation and systemic processes frequently access the lung *via* the lung's vascular filtration function. Thus, evolution has brought with it a number of ingenious mechanisms that protect the lung from external challenges, while leaving the lung's critical functions unimpaired. These mechanisms, however, are still not fully understood and disease likely results when these protective mechanisms go astray. This series for *Drug Discovery Today: Disease Mechanisms* has chosen to highlight several areas of lung biology in which we have made significant strides in understanding mechanisms of disease and for which novel therapeutic targets are likely to arise.

We have selected a sample of lung disorders in order to focus on diverse perspectives, ranging from systemic challenges, such as septic shock and HIV infection, to specific lung cell defects affecting the lung airway (cystic fibrosis), the lung innate host defense and, finally, the role of the external lining (pleural surface) in lung biology.

As a case in point, the changes in our understanding of the lung's innate mechanisms have been greatly stimulated by the discovery of the gene responsible for cystic fibrosis. The discovery of the CFTR gene almost 20 years ago brought with it great promise and excitement (1). However, this initial excitement is tempered by our limited knowledge of lung defense mechanisms that determine the clinical outcome of patients with cystic fibrosis. This experience taught us that therapeutic applications require more than knowing a central genetic deficit but also a detailed and complex understanding of the interactions and networks regulated by this gene in the intricacies of airway biology. Clunes and Boucher bring us up to date with this story and tell of the novel ways that the lung (a relatively new organ from an evolutionary perspective) deals with the challenge of maintaining immune homeostasis despite its intimate linkage to the blood and the external environment.

This theme of our evolving understanding of lung defense systems is further expanded by the chapter from Valdivia-Arenas *et al.* who focus on the innate host responses of the lung. Within the past 10 years our knowledge of pathogen sensors has undergone a revolution with the discovery of Toll-like receptors, NOD proteins and novel macrophage receptors. This innate host defense review highlights the key discoveries in surfactant biology and pathogen recognition, which emphasize the importance of the innate responses to host defense particularly with regards to common lung pathogens.

Systemic infectious challenges are also critically linked to lung biology. Two particularly important scourges that find the lung as an ultimate target for injury and infection are sepsis and HIV. Seam and Suffredini take the focus to systemic infection, *i.e.*, sepsis. They highlight

how we have applied new knowledge about the host response to infectious challenges to the design of future therapies. Sepsis has probably received more press than most disorders in this regard. As Seam and Suffredini highlight, the complexity of the sepsis response has challenged our ability to design rational treatments. Both whole body and individual intracellular signaling approaches are discussed, which have application to a broad array of human disease.

HIV-associated disease is intimately linked to the lung. In the case of this series, HIV pathophysiology turns from innate host defense to focus on the importance of the adaptive immune response in lung pathophysiology. As Twigg and Knox emphasize, the role of lung diseases in HIV has changed dramatically in the era of highly active antiretroviral therapy (HAART). Whereas HIV infections demonstrated the important role of adaptive host responses in preventing the growth of unusual lung pathogens such as *Pneumocystis*, the HAART era has brought new understanding of how adaptive immunity causes disease when its activity returns in full force. The immune reconstitution syndrome is diagrammed, as it is currently understood, with the focus on lung adaptive immunity.

External challenges to the lung may also cause disease that affect not the airways or the blood vessels, but extend to the space surrounding the lung parenchyma, the pleural space. In the final section in this series, Sriram and Antony review recent advances in our comprehension of two major global disorders that affect the pleura, tuberculosis and malignant mesothelioma. They review the known pathogenetic pathways, describe new diagnostic tools that relate to the pathophysiology, and discuss treatment options that have immediate impact for those practitioners challenged with management of these major disorders of the lung lining.

Although we have much to know about the lung and its ability to serve at this delicate interface between the environment and the circulation, there have been major advances in the past two decades that have closed the gap. These new understandings have produced an abundance of opportunities for drug discovery and effective new therapies. These 5 reviews provide excellent examples of this progress.

Reference List

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Biography

Clay Marsh, M.D. is currently Professor of Medicine in the College of Medicine and Director of the Center for Critical Care; Director of the Division of Pulmonary, Allergy, Critical Care and Sleep Medicine; and Vice Chair, Research, Department of Internal Medicine. He is a physician-scientist where his laboratory focuses on intracellular signaling in mononuclear phagocytes and their role in angiogenesis, organ injury, remodeling and repair and systems biology applications to human health and disease. He has a specific interest in the biology of prediction and prevention of human disease, focusing on lung repair and remodeling. Dr. Marsh trained in internal medicine and pulmonary and critical care medicine at The Ohio State University, where he remained as faculty. He serves as a member of the national advisory board

for Battelle Industries in the area of lung disease research and is currently the Chair of the Board of the Sarnoff Foundation for Cardiovascular Research. He reviews grants for the NIH, ALA, and the Wellcome Foundation and past member of the NIH Lung Injury, Repair and Remodeling study section. Currently, his research focuses upon how innate inflammation is regulated in advanced lung disease and in applications of systems biology to preventive, predictive, and personalized health care.

Mark Wewers, M.D. is currently the John Prior Professor of Medicine in the College of Medicine and Associate Director of the Davis Heart and Lung Research Institute where his laboratory focuses on intracellular pathogen sensors and innate immune responses of macrophages. He has a specific interest in the biology of sepsis and lung inflammation. Dr. Wewers trained in clinical medicine at the University of Arkansas and did his research training in the Pulmonary Branch of the National Institutes of Health (1981-1986). At the NIH he spearheaded the clinical trial for alpha 1-antitrypsin augmentation therapy (Prolastin) which is currently accepted treatment for alpha 1 deficient patients. There he also developed an interest in the biology of lung macrophages with an emphasis upon interleukin-1 biology. He was Division Director of the Pulmonary and Critical Care Division at Ohio State University (1996-2002) and Interim Director of the Davis Heart and Lung Institute (2000-2002). He is a frequent reviewer for NIH, ALA and the Alpha 1 Foundation and past member of the NIH Lung Biology study section. Currently, his research focuses upon how caspase-1 is regulated by intracellular signaling molecules that recognize pathogen associated molecular patterns.