

Molecular Basis of Pulmonary Disease

RESPIRATORY MEDICINE

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and Bruce C. Trapnell, 2010

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Molecular Basis of Pulmonary Disease

Insights from Rare Lung Disorders

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Preface

Dr. Sharon Rounds, the editor for this series who invited us to write a book on rare lung diseases, developed the idea after attending the 2004 Lymphangioleiomyomatosis (LAM) Foundation annual research meeting. She was a keynote speaker at that event (during her tenure as the president of the American Thoracic Society) and was witness to the power of patient advocacy and the mission-based scientific effort that had brought this rare disease of women from obscurity to clinical trials with targeted molecular therapies in under a decade. The progress in pulmonary alveolar proteinosis (PAP), pulmonary alveolar microlithiasis (PAM), inherited disorders of surfactant metabolism, and pulmonary arterial hypertension, to name a few, has been no less astounding. Advances have come from the most surprising directions; fruit flies for LAM, genetically engineered mice made for other purposes for PAP, and groundbreaking high-density SNP (single-nucleotide polymorphism) analyses done on a handful of families for PAM. In many cases, insights into biology gained from rare diseases have informed research approaches and treatment strategies for more common diseases; for example, knowledge gained from the study of PAP about the role of GM-CSF in the lung has sparked interest in the use of anti GM-CSF approaches to control both pulmonary and extrapulmonary inflammation in a variety of diseases. The finding that interstitial lung disease develops in families with cytotoxic mutations in surfactant protein C (SP-C), a gene which is expressed only in alveolar type cells, has underscored the importance of the integrity of the alveolar epithelium in the pathogenesis of parenchymal fibrosis. Opportunities to approach lung disease pathogenesis from the vantage point of a primary molecular defect are gifts from nature that are uniquely abundant among the rare lung disorders.

We salute the NIH and the National Center for Research Resources for their vision in facilitating the translation of basic research advances in rare lung diseases into clinical reality through the Rare Lung Disease Consortium, a network of 13 US and international sites that is currently conducting clinical trials and studies in LAM, alpha one antitrypsin deficiency, pediatric interstitial lung disease, and PAP. It has been a rare privilege to work on such fascinating diseases with such capable investigators from all over the world over the past 6 years.

The format for this volume is unique. Most chapters have been authored by a clinician and a basic scientist who are expert in the disease topic and underlying molecular defect, respectively. Their charge was to focus on the genetic basis and molecular pathogenesis of disease, animal models, clinical features, diagnostic approach, conventional management and treatment, and future therapeutic targets and directions. The intent was not to provide a broad overview, but rather to shed light on the molecular mechanisms that evoke the clinical presentation and engender treatment strategies for each disease. We hope that this approach will prove useful for pulmonary clinicians and scientists alike.

We thank our wives, Holly, Jean, and Vicky, for their support and indulgence with late night emails and work-filled weekends, Dr. Rounds for the invitation to write the book, and all of the authors who contributed.

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