

Lung Program – Theme # 2: Integrative Approaches to Pathogenetic Research

Introduction:

Vision: Prevention and effective treatment of respiratory diseases and sleep disorders through a comprehensive understanding of their pathogenesis.

While other leading causes of death have been steadily decreasing, illness and death attributed to chronic pulmonary disease have continued to increase. Though symptomatic treatments are available and the major inciting or aggravating factors are known for many respiratory conditions (allergens/viruses for asthma, cigarette smoking for COPD, sepsis for ARDS, etc.), we are far from understanding the fundamental disease processes. There is poor understanding of the complex genetic basis of lung diseases; why asthma is difficult to cure or reliably control; why lung repair malfunctions in fibrosis, COPD and ARDS; and how disordered sleep contributes to vascular, metabolic, and immunological abnormalities.

Deficits in knowledge regarding pulmonary diseases and sleep disorders are most serious at the molecular and cellular levels where the vast majority of events contributing to disease remain to be elucidated. This is due in part to the uniqueness and complexity of the lung. The lung differs from other organs in its significant mechanical strain, microstructural complexity, cellular diversity, and extreme exposure to the external environment. Hence, the lung sustains different types of injury and uses different mechanisms for repair and regeneration. There is an urgent need for enhanced pathogenetic research that is targeted to the lung and that encompasses the changes occurring during growth, in response to injury, and during the development and progression of chronic disease.

Fortunately, the scientific approaches and emerging technologies of the post-genomic era are well suited for elucidating the pathogenesis of complex conditions such as pulmonary diseases and sleep disorders. Available and anticipated tools for genetics, functional genomics, proteomics, molecular imaging, and systems and computational biology offer unprecedented opportunities for understanding lung function and dysfunction and for translating this knowledge into improved medical care for patients. Pathogenetic research in pulmonary and sleep medicine is a particularly promising avenue for transforming medicine and health through discovery in the next 10 years. To advance these fields more rapidly, **research must become more integrative, and that integration must occur**

... **Across different respiratory conditions.** Research across disease boundaries can evaluate the ubiquitous involvement of common biological processes – molecular signaling, pulmonary innate and adaptive immune responses, microbial colonization and infection, genetic information flow, clock-like cycling of gene expression and cellular function, oxidative stress, apoptosis, and progenitor cell-based regeneration. Research must also target early disease to define mechanistic sequences of events.

... **Across different organ systems.** Systemic manifestations and co-morbidities are the rule, rather than the exception, in pulmonary and sleep diseases – especially for COPD and the fibrotic lung disorders. Interactions of the lung with other organs may be important during the development of disease. Environmental exposure is a key factor to be considered.

- ... **Across different levels of study.** Collaborative research is needed to elucidate mechanistic linkages from genetic and environmental inputs, through molecules and cells, through intermediate phenotypes, to clinical characteristics and outcomes.
- ... **Across different research perspectives and experimental approaches.** Advances in bioinformatics and computational biology and better use of these methods are needed to enable data sharing, systems analysis, and predictive modeling in lung/sleep research.

Recommendations:

- 1. Link genotype to biological function in lung and sleep-related diseases**
 - a. Build well phenotyped human cohorts, with and without a spectrum of diseases and exposures, for genetics studies. Include biomarkers and exposure assessments.
 - b. Develop and use animal models and high-throughput phenotyping to elucidate functions of genes that are likely relevant to lung disease pathogenesis.
 - c. Develop predictive computational models and employ methods of systems biology to characterize disease states and responses to biological events and environmental challenges, including temporal characteristics.
- 2. Characterize the relationships between respiratory diseases and the environment**
 - a. Determine the microbiomes of each anatomic compartment of the respiratory tract in health and lung diseases.
 - b. Define molecular and cell-specific responses to environmental challenges.
 - c. Delineate gene-environment interactions in the origin and progression of lung diseases.
- 3. Understand development, maintenance, and disordering of lung microstructure**
 - a. Determine the ‘omics’ of, and develop markers for, every cell type in the lung. Expand capabilities for making cell-specific alterations of genes (“knock-ins”, “knock-outs”).
 - b. Understand the mechanisms of cell death and tissue regeneration and the biology and function of stem cells in health and respiratory diseases.
 - c. Define the roles of host defenses and immune function/tolerance in lung maintenance.
- 4. Develop novel approaches for risk assessment, early diagnosis, and therapy**
 - a. Identify and validate biomarkers for early diagnosis and for therapeutic stratification.
 - b. Identify and validate intermediate outcome measures to enable therapeutic trials.
 - c. Build infrastructure for translational research, including the development of probes for molecular imaging and the production of biologicals.
 - d. Develop, assess, and validate cell specific targets for treatment of lung diseases.
- 5. Identify shared pathogenetic mechanisms among different respiratory and sleep-related diseases and across organ systems within diseases.**
 - a. Include assessments of co-morbidities in all clinical studies.
 - b. Delineate mechanisms of interactions between the lung and other organ systems.
 - c. Elucidate mechanisms linking sleep apnea and deprivation to co-morbid cardiopulmonary disease risk factors such as obesity.
 - d. Identify the roles of clock genes in the control of cell function throughout the body.

6. Create an environment to enable interdisciplinary respiratory research

- a. Develop a controlled vocabulary, ontologies, and data elements to facilitate the exchange and utilization of data related to lung and sleep research.
- b. Employ novel funding mechanisms for interdisciplinary and translational studies that will bring together researchers working at different levels from molecules to systems.
- c. Design systems, including hardware and software, to facilitate data sharing.
- d. Create strategies for communication to effectively utilize expertise at multiple levels (clinical to molecular) in the design, performance, and analysis of studies. For example, include basic scientists in the planning of clinical research.
- e. Implement new paradigms for training that broaden the perspective of investigators and nurture the skills needed for interdisciplinary research.

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