Final Report
National Heart, Lung, and Blood Institute
Level 1 Strategic Planning Working Group
April 10-11, 2006

Lung Program – Theme # 3: Inflammation/Injury; Remodeling, Repair and Replacement

Introduction: This theme includes all the basic elements and various stages or phases of lung diseases in general. It includes the initial agent or injury which provokes a response, all the events which occur as the lung tries to heal itself, and the final stage at which the lung is either healed, or must be replaced.

Vision: The goal in the next ten years is:
1) To explain how disturbances in cellular responses (both extrinsic and intrinsic) trigger lung disease, instead of enabling self-limited tissue repair and restoration of normal function; and
2) To therapeutically direct aberrant lung responses to injury to halt disease progression and/or return lungs to a normal state.

Recommendations:

1. Develop molecular markers that identify "phenotypic diversity" of the normal and diseased lung. Such molecular phenotyping will enable an understanding of normal lung biology and how it is altered in the diseased state, ultimately allowing patients to be classified according to the molecular pathogenesis of their lung diseases.

- Develop biological markers of normal and diseased lungs using new technological approaches, such as proteomics, cluster analysis, SNP analyses. Such markers might be used alone or in combination to better classify patients according to risk for disease, and severity and outcome once it develops. In some cases, they also might be used to assess heritability.
- Develop large longitudinal patient populations in which biological and genetic markers of molecular phenotype can be identified and validated.
- The NIH should develop and maintain tissue banks of samples (e.g. tissue, serum, sputum, bronchoalveolar lavage) from animal models, from patients enrolled in ongoing clinical trials, or from large groups of volunteers. These samples will be used to search for molecular phenotypes, elucidate mechanisms, identify genes involved in a specific lung disease, or genes common to lung diseases (asthma, COPD, pulmonary fibrosis, pulmonary hypertension etc.).

2. Develop new methodologies to specifically identify and track each of the putative cell types in the lungs in humans and animal models.

- Identify new cellular markers and techniques that can distinguish between cell types (e.g. new monoclonal antibodies, promoters, expression profiling).
- Use multiple techniques (i.e., nanotechnology, genetics, biochemistry) to develop new labels for specific cell types *in vivo*.

3. Develop ways to identify and measure the activity of key biological systems in vivo. Create the ability to image key biological pathways *in vivo* when they are being activated in people. Examples include activation of: receptor-mediated signaling pathways, NFκB, oncogenes, pro-fibrotic pathways and others.

- Develop new and more sensitive methods for molecular imaging *in vivo* in humans and experimental animals.

- Develop methods to track 'real time' cell biological events, such as division of specific cell types, damage to the epithelial and endothelial barriers in the lungs, the beginning of fibroblast replication, and destruction of lung matrix.
- Develop new animal and human models that more accurately reflect pathophysiological processes involved in lung disease

4. Develop ways to understand and measure environmental and host interactions that cause or contribute to lung disease.

- Elucidate environmental influences on different compartments of the respiratory system i.e. nasopharynx, conducting airways, alveolar units, interstitium/matrix and vascular compartments
- Identify host factors that mediate susceptibility, e.g. genetic determinants and specific molecular pathways

5. Develop new approaches to bring together scientists with very diverse backgrounds in order to encourage novel multidisciplinary approaches to problems in lung biology and disease. We would like to see 'scientific teams of the future' put into place that:

- Encourage the multiple PI concept
- Emphasize the intersections between new technologies and the biological sciences e.g. nanotechnology, proteomics, genomics, bioengineering, plant sciences, mathematics, including complexity theory
- Encourage inter-institutional, interstate and international collaborations
- Encourage the involvement of new investigators

6. Emphasize new initiatives in Regenerative Medicine. We would like to be able to regenerate the normal human lung and its various components.

- Develop a more detailed understanding of the cellular and molecular mechanisms that regulate lung development, homeostasis in the adult and functional decline during aging.
- Develop a better understanding of endogenous, and exogenous lung stem cells, and the potential to manipulate these stem cells for use in lung regenerative medicine.
- Explore the uses of nanotechnology for creating 3-D lung matrix scaffolds for creation of new alveoli. Scaffolds would provide surface for the growth of new airway epithelial and other cells and mimic the intricate alveolar structure and function found in vivo.

7. Develop methods for cell specific delivery of drugs and agents to all lung cell types. We would like to be able to deliver specific therapeutic agents to precise cellular locations in order to turn specific genes off and on at specific locations in the lungs.

- Nanotechnology for the delivery of specific agents.
- Improved cellular targeting
- Improved control of cellular entry

Other comments: in the general discussion, strong support was expressed for enhancing individual investigator-initiated grants, and for promoting the career development of new investigators.

09/29/06