Final Report
National Heart, Lung, and Blood Institute
Level 1 Strategic Planning Working Group
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Lung Program – Theme # 1: Development of Early Origins of Disease

Introduction:

Vision: To discover early factors that predict the risk of lung disease to enable early interventions that prevent or cure lung diseases in children and adults, across all populations.

Lung diseases are the fourth leading cause of death and disability in the United States and are associated with a national economic burden of over 100 billion dollars per year. Moreover, the prevalence of many of these illnesses continues to increase. Current treatment of most lung diseases is unsatisfactory as it focuses on symptom control and cannot affect initiation or progression of disease. A critical gap in knowledge that contributes to the challenge of creating new therapeutic modalities that address the underlying disease defects is an incomplete understanding of normal pulmonary and immune system development and how alterations in, and interactions between, these systems cause or contribute to lung disease. It is also increasingly clear that many respiratory illnesses have their beginnings early in life and are influenced by developmental, genetic, and environmental factors. The exact stimuli and mechanisms by which these early events promote lung disease later in life are unknown. A thorough understanding is needed of lung and immune system development as well as how environmental and genetic factors affect these developmental processes.

Understanding the basic mechanisms that control development, regulation, integration, and interaction of the pulmonary and immune system and their combined processes is fundamental and essential to establish the pathogenesis of respiratory diseases. Lung and immune system development are complex, interactive processes that begin during gestation and continue into the first years of life. In the lung, emerging technologies in genetics, genomics, and cell biology will provide the opportunity to elucidate the complete genetic and cellular program of development in model organisms. A major challenge is to develop methods that will allow measurement and tracking of developmental changes in lung structure and function down to the cellular and molecular level in developing animals and patients. Immune system development and regulation are also influenced by a combination of developmental, genetic, and environmental factors and their interactions with resident lung cells, nerves, bronchial smooth muscle, and alveolar tissues. Balanced immune system development and function is critical for the respiratory system, because the lung is continually exposed to changing environmental factors including pollutants, infectious agents, and allergens. Early exposures can alter the developmental program of the pulmonary and immune systems, resulting in sustained changes in lung and immune function and lung disease susceptibility. While the research community must continue to work towards a more comprehensive understanding of development and regulation in each of these fields, the science of early origins of disease is at a critical juncture where the lung and the immune system must also be studied together in order to understand how specific events (e.g. preterm birth, oxygen stress, under-nutrition) and environmental exposures interrupt or alter developmental events and initiate pulmonary disease or affect susceptibility to such diseases later in life.

Studies of pulmonary and immune system development over the past few decades have begun to draw these two fields together, poised to combine their separate insights and technologies into a more comprehensive understanding of the early origins of lung disease. For major progress to occur, researchers need to determine how these developmental processes influence each other and result in a unique blueprint for each individual that initiates lung disease or determines their future risk of disease. Interdisciplinary programs are needed that bring researchers in these basic developmental fields together with clinicians studying later manifestations of lung disease, and with experts in cell imaging, computational biology, biomechanics, and other research perspectives that historically have not been integrated into studies of lung development and disease. Different levels of analysis must also be integrated to link genetic alterations and environmental exposures to cellular and molecular defects and clinical symptoms. Ultimately, this approach will lead to identification of disease risk markers and clinical outcomes based on underlying disease mechanism rather than symptoms, and enable the rational development of early interventions to prevent or cure lung disease.

Recommendations:

1. **Elucidate the complete program for building a healthy lung**
    - Characterize the normal process of lung development including the airways, vasculature, muscle, immune and nervous systems, and their interactions down to the cellular level at all stages of pre- and post-natal development.
    - Determine the complete genetic program of mammalian lung development including all the critical signaling molecules and transcription factors that control the process and their downstream effectors.
    - Establish animal and *ex vivo* models that represent each stage of human lung development, and integrate findings from rodent to other model systems and to human lung development.

2. **Determine how genetic alterations, immune stresses, and environmental exposures alter the lung development program to cause or predispose to lung disease**
    - Identify the key genetic and maternal factors and environmental influences including pollutants, infectious agents, and allergens that cause or predispose to lung disease and how these factors interact.
    - Define through cross sectional and longitudinal studies the age and gender dependency of these factors to identify vulnerable developmental "windows" of onset of lung disease.
    - Determine how the critical factors identified affect the developmental program and lead to lung disease.

3. **Determine how lung health can be promoted and maintained by altering development or environmental exposures and using developmental principles to restore damaged tissue**
    - Identify strategies to predict and prevent early onset of respiratory diseases, including personalized approaches that take into account individual genotype and differences in exposure to predict disease susceptibility
    - Identify immune modulators and other treatments that can be used during critical developmental windows to prevent or reverse lung disease.

- Establish operational and scientifically rigorous definitions of resident progenitor and differentiated cell populations in the lung.
- Explore the role(s) of endogenous and exogenous stem cells in lung regenerative programs.

4. Support translational research that will facilitate risk assessment, early diagnosis and therapeutic development

- Create funding mechanisms to support validation research for biomarkers and therapeutic targets.
- Support high risk/high gain research that will translate findings from animal models into humans.

5. Develop novel technologies that facilitate the above studies and extend them to clinical use, including:

- Methods for imaging lung cells and assessing lung function in developing animals and patients.
- Mechanisms for banking and sharing genomic data on lung development and disease.
- Methods for defining and standardizing environmental variables that influence lung disease and monitoring individual exposure to these variables.
- Methods for extracting clinically useful molecular markers of lung development and disease susceptibility from the developmental and disease data.

6. Develop and support programs and group projects that promote interdisciplinary training in development, genetics, genomics, computational biology, immunology, physiology, and environmental assessment as they pertain to lung development and disease.

- Develop novel programs and funding mechanisms to bring together researchers working in different fields and enable interdisciplinary and translational research.
- Establish new models for training that foster interactions among students, researchers, and clinicians in the above mentioned fields and attract researchers with non-traditional backgrounds including physics, chemistry, and engineering.
- Develop strategies and tools for communicating effectively across multiple levels and areas of expertise in design, performance and analysis phases (e.g. software, controlled vocabularies and ontologies).

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