

# THE HARTWELL FOUNDATION

## 2010 Individual Biomedical Research Award

### Review of Proposed Research

**Investigator:** **Randi B. Silver, Ph.D.**  
**Professor**  
**Department of Physiology and Biophysics**

**Institution:** **Cornell University**

**Proposal:** **Mast Cells in Chronic Lung Disease in  
Premature Birth Infants**



About 1 of every 8 babies born in the United States are born preterm and each year over 5,000 will develop bronchopulmonary dysplasia or chronic lung disease. The survival of preterm infants has improved, but the long term respiratory morbidity has remained high. This occurs because in ventilated preterm infants the immature lung predisposes them to subsequent development of the two most common chronic respiratory diseases in the Western World, asthma (chronic inflammation of the lungs in which the airways are reversibly narrowed) and chronic obstructive pulmonary disease (characterized by the limitation of airflow in the airway that is not fully reversible). While the mechanisms responsible for these conditions are unknown, inflammation is central to the development of lung disease. Inflammatory mast cells (MC) appear prominent in the tissue between the pulmonary alveoli and the bloodstream, as well as in the air spaces of the lung. The accumulation and impact of MC in the premature lung for the development of pulmonary disease however, has not been examined. To address this unmet need, Randi proposes experiments founded on a novel hypothesis: the consequence of MC infiltration is the release chemicals that inflame and scar underdeveloped lungs of premature infants. The normal function of these immune cells is unknown, but they are well known to be activated in allergic reactions. MC appear to be "trigger" cells that elicit bronchoconstriction, edema, and mucus secretion as the result of their release of histamine and a variety of mediators and thus lead to both acute and chronic airway constriction and inflammation. She has demonstrated in pilot experiments that newborn mice breathing high oxygen concentrations, similar to oxygen received by premature infants on ventilators, had a 100-fold increase in lung mast cells, inflammation and scarring. Lung function tests performed on these mice returned to room air for 4.5 months, suggested evidence for bronchitis and emphysema, paralleling the human situation. The presence of reactive mast cell chemicals known to cause lung tissue destruction was also observed. Based on these observations, she proposes to analyze fluid samples from the lungs of premature infants for mast cell produced chemicals. Identifying a cell type that could cause chronic lung disease, and the therapeutic options emerging from this discovery, will transform medical practice and treatments for the premature infant. If she is successful in demonstrating the link between mast cells and the development of chronic lung disease linked to ventilation in premature infants, drugs that specifically target mast cells could be developed to reduce the adverse consequences of mast cell-derived substances.