

THE HARTWELL FOUNDATION

2023 Nominee Individual Biomedical Research Award

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Targeted Immunotherapies for Bronchiolitis Caused by RSV



Respiratory syncytial virus (RSV) is responsible for causing bronchiolitis, a common lung infection in young children. Although most children are exposed to RSV before the age of two manifest only mild symptoms, it is responsible for over two million outpatient visits and 80,000 US hospitalizations annually in children under five years old. The virus primarily affects small airways in the lung causing inflammation, swelling and irritation in the lining of the bronchioles. Persistent symptoms include difficulty breathing, wheezing, severe cough, fever and often, middle ear infections. Severe infections may lead to pneumonia. The main modality of treatment is limited to supportive care through positive pressure ventilation strategies, as ongoing effort with antivirals, vaccines, including monoclonal antibodies, have either met with limited success or remain at an early stage. Sadly, the virus predisposes children who recover from their acute illness to a greater risk of developing childhood asthma. Recent findings implicate the unique biology of early childhood immune cells in severe viral bronchiolitis, in which immune responses act as a double-edged sword by protecting from viruses while also causing damage by inflammation. Despite our understanding of the developing immune system in children, little work has been done to trial immune-modulating therapies in children with RSV. A key barrier is the lack of knowledge about the unique biology of early childhood immune cells, particularly cytotoxic CD8 T cells that normally serve to kill virus-infected cells and represent a crucial component of anti-viral immunity. Infants have lower counts of CD8 T cells and thus, any weakness in CD8 T cell regulation can predispose to severe lung disease, either through uncontrolled viral infection or through dysregulated pathogenic inflammation. Based upon my preliminary data, I hypothesize that neonatal CD8 T cells possess unique biochemical characteristics that contribute to worse outcomes. Specifically, I propose that these CD8 T cells have a decreased threshold for PI3K/mTOR regulation of an intracellular signaling pathway responsible for cell growth and survival that augments short-lived effector cytotoxic T cell fates and contributes to immunopathology. Patients at the higher end of the spectrum of PI3K/mTOR signaling and TNF α secretion by CD8 T cells (high systemic TNF α) are therefore at risk for more severe RSV bronchiolitis. Using immune cells from RSV bronchiolitis patients, I will determine how bronchiolitis severity depends on the underlying cellular regulatory mechanisms, test how patients' cells respond to FDA-approved medications that modulate immune regulation and identify biomarkers that enable selection of an optimal therapy for individual patients. If successful, my approach will reveal new therapeutic targets for RSV and lay the groundwork for clinical trials of novel diagnostics and personalized treatments, particularly in those children at risk for severe disease.