THE HARTWELL FOUNDATION

2019 Individual Biomedical Research Award

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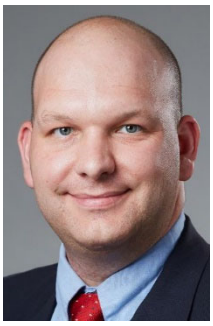

Unbiased Cellular Response Profiling of Viral-Induced Lung Injury: Catalyzing Therapeutics and Diagnostic Assays

Viral-induced lung injury is a respiratory condition caused by a viral infection (e.g., flu, respiratory syncytial virus, enterovirus, rhinovirus, coronavirus, etc.) that produces inflammation mucous and congestion in the small airways (bronchioles) of the lung. Children with viral-induced lung injury have trouble breathing, ranging in severity from mild to life threatening. In the United States, viral-induced lung injury is the most common reason for pediatric hospitalizations with over 150,000 admissions annually. Many will require breathing tube placement and mechanical ventilation, which may lead to a life-long increased risk for asthma. Currently, no laboratory testing exists to predict disease severity or duration, and there are no vaccines to prevent or therapies to treat viral lung injury. Management of hospitalized children is limited to supportive care. Therefore, rational, effective interventions are needed to mitigate the acute and long-term health risks caused by viral lung infections in young children. Based upon animal models of the viral infection, it is known that acute lung injury due to viral infection is a complex host response that involves recruitment, activation, and dysfunction of multiple cell types; and that virus-mediated infection and immune-mediated inflammation depends on gene expression (transcription) and cell signaling metabolites. Yet, the contribution of each cell type to lung injury remains largely unknown, particularly from the standpoint of the human condition. The lack of progress in this regard has hindered development of effective therapeutics. To address this unmet need, Ric proposes an unbiased multifaceted approach that has not previously been described. Using state-of-the-art technologies and timely patient samples, he proposes to examine the type, activity and metabolism of the individual cells involved in the cellular response to viral-induced lung injury and link them to clinical outcome. He will then leverage single-cell RNA sequencing (scRNA-seq) to acquire the expression profiles of individual cells, which will generate a comprehensive description of the cellular response to infection. To identify changes in metabolic pathways, he will combine single cell transcriptome analysis (gene expression level of individual cells) to identify active cell types and metabolomics analysis to evaluate the end products of cellular function and communication (cell signaling through metabolites and cytokines). Finally, he will integrate transcriptional and metabolic activity at single-cell resolution and correlate activity with improved clinical outcomes. If Ric is successful, a comprehensive profile of the cellular and molecular dynamics underlying disease progression of all types of viral-induced lung injury will provide a platform for developing much-needed diagnostic assays and the first targeted drugs for the infection. Understanding the pathogenesis of viral lung injury will benefit children by finally moving beyond supportive care to testing of rational, targeted therapies.