THE HARTWELL FOUNDATION

2014 Individual Biomedical Research Award

Rachel Fearns, Ph.D.

Associate Professor
Department of Microbiology

Boston University

Treating Respiratory Syncytial Virus Infection by Targeting the Viral Polymerase

Respiratory Syncytial Virus (RSV) is the major cause of severe lower respiratory tract disease and viral deaths in infants and children in the United States. It is a single-stranded RNA virus, similar to common respiratory viruses and those causing measles and mumps. Children are most at risk of severe RSV infection early in life when their lungs are poorly developed and their immune system is naïve. It poses a significant risk for those who are immunocompromised, such as with children treated with chemotherapy. RSV is unusual because it does not stimulate an effective memory immune response and so re-infection may occur multiple times throughout life. Every child at one time or another endures RSV infection and 25-40% will suffer symptoms of bronchiolitis and pneumonia. Such RSV infections result in over 150,000 pediatric hospitalizations annually. Despite decades of research there is no vaccine or effective treatment for RSV and consequently there is a pressing need to develop safe and effective drugs against the virus. RSV has an RNA genome and replicates within the cytoplasm of an infected cell. It encodes its own machinery to produce new copies of its viral genome, rather than relying on host cellular proteins. It can very rapidly adapt to selective pressure, meaning that it will certainly be necessary to develop multiple drugs with different RSV targets to reduce the appearance of resistant viruses. The key to developing an effective treatment for RSV is identifying protein activities in the virus that are unique and essential to viral infectivity, and that small medicinal drugs can target. To address this unmet need, the focus of Rachel's proposal is the large, multifunctional RSV protein complex, called RSV polymerase. The polymerase has activities that are essential for the virus to multiply, but the means to pharmacologically interrupt the process is unknown. Recently, however, she discovered what appears to be a previously undescribed and consistent property of the RSV polymerase that is absent in any related virus. If integral to RSV polymerase, the finding would be transformative because it would suggest a new means to interrupt the RSV process. Hence, the goal of her proposal is to determine if this new property is necessary for virus growth in human cell cultures, RSV genome replication or mRNA transcription; and whether it represents a bona fide characteristic of the RSV polymerase or is simply a contaminant. If she is successful in demonstrating that the previously undescribed property is critical for RSV replication, it will open up a very promising approach for drug discovery in the fight against this viral infection. Clinical translation of this finding into a widely available treatment for RSV in infants and children would have profound clinical implications in the US for controlling this severe respiratory disease.