

MICROBIOTIX, INC. RECEIVES SBIR PHASE I GRANT TO DISCOVER NOVEL THERAPEUTICS TARGETING INFLUENZA VIRAL ENTRY

15 August 2008. Microbiotix, Inc, a privately held biotechnology company, announced today that it was awarded a Phase I Small Business Innovation Research (SBIR) grant from the National Institutes of Health/NIAID. The SBIR Phase I grant entitled, "Identification of Novel Broad Spectrum Influenza Virus Inhibitors" provides two years of support to discover and characterize new agents inhibiting the entry of influenza virus into host cells.

Influenza is a highly infectious acute respiratory disease, characterized by recurrent annual epidemics and periodic major worldwide pandemics. Vaccines, currently the primary strategy for protection against influenza virus infection, are only effective if they match the circulating virus type(s) and cannot be developed in advance against new emerging pandemic strain(s). The goal of this research program is to develop an anti-influenza therapeutic that will prevent virus entry by targeting the conserved fusion and receptor binding domains of envelope protein hemagglutinin (HA) and will be active against all subtypes, including a newly emerging pandemic strain.

Broad-spectrum therapeutics against influenza virus infections are critically needed to address the problem of influenza pandemics, a major threat to public health globally. Interfering with virus entry is a novel and attractive therapeutic strategy to control virus infection. Proof of principle of this approach is provided by the HIV inhibitor enfuvirtide (T-20). The goal of this research program is to discover nonpeptidic small molecules that will inhibit entry of avian influenza J5N1 and other potentially pandemic influenza viruses. The strategy is to target envelope glycoprotein hemagglutinin (HA), which mediates influenza virus entry through receptor binding and fusion with host cells. Like the HIV Gp120 and F protein of paramyxoviruses, HA is a class I fusion protein that undergoes a series of conformational rearrangements during fusion resulting in a fusion hairpin structure. This structure promotes the juxtaposition of the viral and cellular envelopes during fusion and is sustained by protein-protein interactions. Small molecule entry inhibitors that interfere with the formation of this fusion hairpin structure in paramyxovirus infection have been identified previously. New inhibitors targeting this conserved site in influenza virus infection will be active against multiple subtypes, including a newly emerged pandemic strain. A pseudotype virus expressing HA (H5 subtype), which has been developed as a surrogate model, will be utilized to mimic HA mediated entry in a screen for entry inhibitors under BSL2 conditions. Preliminary studies at Microbiotix, Inc. have resulted in the development and characterization of a sensitive pseudotype virus assay for screening HA inhibitors.

The aims of the research program are as follows: Optimize the assay for rapid screening of a library of structurally diverse small molecules. Confirm hits in blinded experiments and evaluate hits for anti-influenza activity against live H5 avian influenza viruses in experiments. Confirmed hits will be evaluated for their spectrum against other subtypes and prioritized based on their mechanism of action. These novel influenza therapeutics will block virus entry and suppress cellular cytotoxicity resulting from virus-cell contact. They are also expected to exhibit a low frequency of resistance development since minor deviations in the conserved domains would likely prevent fusion of virus with endosomal membrane. Future development will optimize the most promising scaffolds through a rational drug design program with testing for efficacy and toxicity in animal models.

Arnab Basu, Ph.D., Senior Scientist will serve as the Principal Investigator of the grant.

About Microbiotix

Founded in 1998, Microbiotix, Inc. is a product-focused biopharmaceutical company engaged in the research and development of novel, small-molecule, anti-infective drugs that address commercially significant medical markets. The company currently has several active research programs in the fields of anti-bacterial and anti-viral discovery, with three compound series in pre-clinical development. More information can be found on the company's web site, www.microbiotix.com.