Center for Biomolecular Structure and Dynamics - Research

Pilot Project Leader:  J. Stephen Lodmell

Project Title:  Mechanism of novel inhibitors of Rift Valley fever virus nucleocapsid-RNA interactions

Project Abstract:
Rift Valley fever virus (RVFV) is an emerging infectious disease affecting humans and livestock that has potential for global spread. An essential step in the RVFV replication cycle involves the binding of nucleocapsid protein, N, to viral RNA. We constructed a robust molecular target high throughput screening assay that reports on N-RNA binding using fluorescence polarization. During a recent screen of 26,424 compounds at a national screening laboratory at Harvard Medical School, we identified potent inhibitors of the N-RNA interaction coming from libraries of FDA approved drugs and other drug-like molecules. In general, viral nucleocapsid proteins can bind to their RNA targets singly, in a specific binding mode, or cooperatively, exhibiting generic RNA binding along the length of the viral genome. Thus, we hypothesize that our inhibitors specifically interfere with binding of the RNA to the binding cleft in N, or they could affect multimerization and protein-protein contacts, which would affect non-specific RNA binding. To test this hypothesis, we will construct site-directed mutants of N that are compromised in their ability to multimerize or to bind RNA, or both. We will test the ability of wild-type or mutant RVFV N to bind RNA in the presence and absence of inhibitors using fluorescence polarization, electrophoretic, and biochemical methods. Results obtained from this study will provide vital molecular mechanism of action data required for a major grant proposal to develop antiviral agents against RVFV.