

**NUS Graduate School for Integrative Sciences and Engineering
Research Project Write-up**

Title of Project : The role of host RNA binding proteins in dengue virus infection

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Short Description. The long-term problem addressed by this proposal is the lack of effective therapy for dengue fever (DF). DF is caused by one of four dengue viruses (DEN 1-4), which are members of the mosquito-borne cluster of flaviviruses. DF is a major and resurging health problem in tropical and sub-tropical countries. A conservative estimate calculates that a staggering 2.5 billion people are at risk. Furthermore, the frequency of dengue epidemics has increased in Southeast Asia probably due to urbanization. There is no licensed vaccine for DF. Experimental dengue vaccines are currently in clinical trials and there is hope that vaccination will provide a powerful tool in the armamentarium against this disease. Significant problems, however, must be solved before an effective vaccine is available for all four DEN serotypes. Although there are no proven therapies to inhibit or prevent these viral infections, several potential therapeutic strategies have been investigated. In an early trial of interferons (IFNs) for prophylaxis and treatment of YFV infection we showed that IFN γ treatment could ameliorate the course of YF in *Saimiri sciureus* (squirrel monkeys), but did not affect mortality in *Macaca mulatta* (rhesus monkeys) a model for severe YF in humans. More specific therapies have targeted viral gene products (e.g., RNA-dependent RNA polymerase (RdRp) and the recent discovery of VP32947, a compound that inhibits the RdRp of the related pestiviruses, suggests these efforts should continue. Nonetheless, the ability of RNA viruses to rapidly acquire resistance represents a commonly observed problem in anti-viral therapy. To overcome this problem one can target host factors required for viral propagation. The obvious problem with this strategy is the limited therapeutic index obtained by inhibiting an activity that is presumably important for the host. A more sophisticated approach involves the development of therapies that target host-viral interactions and in this proposal we will focus on functionally relevant interactions between host proteins and viral RNAs.

The overarching goal of this proposal is to develop novel therapeutics for YF and DF by discovery of reagents that block critical interactions mediated by the viral RNAs. In order to accomplish this goal we propose the following objectives:

1. To determine the structure of the terminal regions of the YF and DEN genomes.
2. To identify small molecules that would bind these RNA structures and inhibit viral propagation.
3. To identify host gene products that specifically interact with important viral RNA elements and are required for efficient viral propagation.
4. To identify inhibitors of the required interactions between host factors and viral RNAs.