Title: A New Synergy for Flavivirus Therapy: RNAi Enhancement and Viral Mutagens

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Summary:
The genus Flavivirus, comprising 80 species of single-stranded, positive-sense RNA viruses, includes a large number of globally significant emerging pathogens. In the last 50 years many flaviviruses, such as dengue, West Nile, and tick-borne encephalitis viruses, have exhibited dramatic increases in incidence, disease severity and/or geographic range. For example the annual number of cases of dengue hemorrhagic fever cases worldwide has risen from nearly 0 in the 1950's to 500,000 today. These trends are exacerbated by failure of vector control to limit virus spread as well as the absence of vaccines for viruses such as dengue and West Nile. Thus effective antiviral therapies are urgently needed to ameliorate the disease burden imposed by flaviviruses. At present, however, no licensed therapies are available for any flavivirus, largely because existing broad-spectrum drugs have failed to show efficacy against flaviviruses or have generated unacceptably high levels of toxicity. To overcome these limitations, it will be necessary to develop not only new antiviral drugs but also innovative strategies to lower their effective dose and thereby mitigate toxicity. The recent discovery that certain FDA-approved fluoroquinolone antibiotics enhance the activity of the RNA interference pathway suggests one promising new strategy. RNA interference is a ubiquitious antiviral defense of eukaryotes that acts by targeting small interfering RNA's (siRNA's) to complementary regions in the viral genome; genomes bound to siRNA's are marked for cleavage and degradation. Because binding of siRNA's to a target sequence requires nearly perfect complementarity, RNAi imposes selection pressure for viral mutation that disrupts such complementarity. The proposed research will test the hypothesis that enhancing RNAi will amplify the effect of mutagenic nucleoside analogs on dengue virus mutation rate and replication, and that the synergistic effect of RNAi enhancement will accelerate lethal mutagenesis driven by nucleoside analogs. If this hypothesis is correct, the finding of this study will represent a significant advance in the development of new therapies for flaviviral disease.