Combating Neurovirulence of Zika and Flavivirus Epidemics Using In Silico Phylogenetic Analysis and RNAi Gene Silencing

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Neurological manifestations of recent viral outbreaks such as congenital microcephaly and Guillain-Barré Syndrome associated with Zika (ZIKV) infection are a global concern. An urgent need exists to understand why viral infections are teratogenic and to inhibit replication and neurovirulence. Using open source software, this project identified reasons and solutions for neurovirulence of ZIKV and flaviviruses in 5 stages: (1) Phylogenetic analysis in MEGA and 3'UTR RNA secondary structure analysis in RNAfold revealed that neurovirulent ZIKV strains evolved from Asian (Malaysian), not African (Ugandan) clade, with mutations in prM, NS1 and NS5 regions. (2) Alignment Free Analysis in Python on neurovirulent genomes revealed increased count of AGGTCA Retinoic Acid Response Element (RARE), TGGAACA, GCTGGG and other sequence motifs. (3) Pearson's test indicated correlation between count of identified motifs and degree of neurovirulence. (4) Viral cross-dependency analysis indicated correlation in attack ratios of prior DENV infection to ZIKV infection and prior CHIKV infection to microcephaly. (5) Effective siRNA molecules for silencing NS5 and 3'UTR regions and inhibiting ZIKV replication were designed and authenticated using siDirect software. For the first time, this project has identified excess endogenous retinol as a potential reason for ZIKV-induced neurovirulence. Retinoic acid influences the neural tube and HOX genes crucial to brain development. Correlation of RARE sequence count to degree of neurovirulence indicates that mutations impacting RARE affect retinoic acid pathway, causing fetal malformations. By creating viral vectors with identified siRNA and introducing them into hosts, RARE mutations may be silenced, preventing microcephaly and neurovirulence.

Awards Won:
Second Award of $2,000