Design of a Workflow Generating Novel Broad-Spectrum siRNA Therapeutics Targeting Critical Conserved RNA Elements in the Viral Genome in silico: A Study in Dengue

Kumar, Akshay (School: American Heritage School)

Importance: The likelihood of another COVID-19-level pandemic occurring within 100 years is currently predicted to be 17% and is expected to increase to 44% after the next six decades. Emerging pathogens pose major threats to global health due to their ability to cause catastrophic pandemics. Traditional drug development, requiring an average of 12-15 years and $879.3 million per pathogen, is insufficient to combat pathogenic outbreaks, as shown by dengue: despite infecting ~100 million people yearly and being endemic to >100 countries, dengue still lacks universal treatments. Design: The bioinformatics workflow developed in this study uniquely produces siRNA therapeutics by targeting conserved cis-acting RNA elements (CREs) in the viral genome. The workflow was tested against dengue's four distinct serotypes to verify broad-spectrum capabilities. Generated siRNAs were filtered through stability, efficacy, conservancy, and specificity parameters. Molecular docking and dynamics analysis evaluated siRNA interactions with cellular machinery. Results: Three siRNA molecules were identified as promising candidates targeting all dengue serotypes, demonstrating ideal GC content (38.10-42.90%), strong binding free energies (-29.4 to -31.6 kcal/mol), and high predicted efficacy (84.95-92.98%). siRNAs exhibited excellent conservancy across dengue serotypes (90-100%) with minimal off-target interactions (E-values 0.66-2.6). High molecular docking scores (-308.79 to -381.49) and confidence scores (>0.95) confirmed robust interactions with cellular machinery vital for genomic silencing. Applications: This workflow could advance the rapid and flexible design of broad-spectrum antivirals for further wet-lab validation, potentially reducing development times by ~22% and costs by ~39%.

Awards Won: