Group 13

VirCAD: bioCAD for Viral Engineering

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Abstract

ReNU syndrome is a rare neurodevelopmental disorder lacking targeted therapies. While adeno-associated virus (AAV) vectors show promise for central nervous system gene delivery, systemic administration is constrained by inefficient blood-brain barrier penetration and high manufacturing costs. To address these limitations, we developed VirCAD, a comprehensive computational drug discovery platform that allows researchers to rationally design and screen viral vectors. Using ReNU syndrome as a proof of concept, we established an in silico workflow targeting the surface-exposed Variable Region V on AAV9 and AAV-rh10 capsids. We generated 4-mer peptide variants and utilized structural prediction tools, including AlphaFold and Boltz, to evaluate sequence integrity, predicted binding affinity (IC50), and binding probability against a curated panel of neuronal receptors. Our computational screening successfully identified two mutated AAV-rh10 variants, DYPF and DMPF, which exhibited statistically significantly lower IC50 values and higher binding probabilities compared to wild-type motifs. Subsequent structural validation confirmed that these insertions maintained essential capsid loop geometry and effectively targeted the desired receptor binding pockets. These findings demonstrate that the VirCAD pipeline can effectively identify and optimize viral vector interactions prior to physical prototyping, offering a cost-effective way to accelerate early-stage drug discovery. Future work will focus on expanding the platform to model multi-point mutations and transitioning these top computationally prioritized candidates into wet-lab experimental validation.