From Fire to Silence: AI-Assisted Discovery of C381 to Cure NeuroHIV

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Human Immunodeficiency Virus (HIV) infection is associated with neurocognitive dysfunction (NeuroHIV), which can occur in 30–50% of people with HIV, despite successful combination antiretroviral therapy (cART). The transactivator of transcription (Tat) protein contributes to NeuroHIV by impairing lysosomal acidification and promoting microglial inflammation. C381, a small molecule previously discovered to restore lysosomal acidification, led us to hypothesize that it could also reduce HIV Tat-induced neuroinflammation. Molecular docking utilizing P2Rank was performed to identify C381 binding sites on the Lysosome (PDB: 6VQ7) using AutoDock Vina. Molecular Dynamics was performed through Gromacs on Samson and ADME-Tox analysis was conducted through SwissADME. Mouse primary microglial cells and BV2 (microglial cells) were pre-treated with C381 (30 uM) and post-treated with Tat (50 ng/mL). Lysosomal pH was assessed using the pFUGW FIRE pHLy plasmid and membrane integrity was evaluated. Microglial activation and inflammasomal markers were assessed by Western blotting, and pro-inflammatory cytokine expression was quantified by qPCR. AI-Assisted Molecular Docking identified the V-ATPase as the primary binding site of C381. The strongest sites on the V-ATPase were the pro-renin-receptor and the V-ATPase C-rings 4/5 region which both play a role in acidifying the lysosome. Further Molecular Dynamics and Machine-Learning based ADME-Tox analysis confirmed safety and non-toxicity of C381. In vitro, a C381 pre-treatment was able to significantly restore lysosomal function and reduce Tat induced neuroinflammation markers. These findings suggest that C381 represents a promising therapeutic compound for attenuating HIV Tat-induced microglial activation and neuroinflammation.

Awards Won:
Fourth Award of $600