Machine Learning Identification of Potential PARP-1 Inhibitors for Alzheimer's Disease Treatment

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Alzheimer’s disease (AD) is the most prevalent neurodegenerative disease worldwide, but disease-modifying treatments are still lacking. Poly (ADP-ribose) polymerases (PARPs) consume nicotinamide adenine dinucleotide (NAD) to repair DNA. PARP has been recently shown to be overactivated in AD. Excessive PARP activation can deplete NAD in neurons, contributing to mitochondrial dysfunction and cell death. Mutations in the PARP-1 gene leading to lower PARP-1 levels are protective in AD. This suggests that molecular inhibitors of PARP-1 could have therapeutic potential for AD. Here, I trained a machine learning model to predict potential inhibitors of PARP-1 from FDA-approved drugs. First, I generated multimodal molecular descriptors and trained a random forest regression model. I then performed in silico screening on over 1000 compounds and generated their IC50 on PARP-1. The predicted top 3 most potent inhibitors were Bryamycin, Topotecan, and Irinotecan. Bryamycin is a peptide while Topotecan and Irinotecan are small molecules. To further characterize the binding conformations of these small molecules, I performed molecular modeling to determine the binding poses and energy of Topotecan and Irinotecan. The in silico docking results showed that Topotecan is a more potent inhibitor of PARP-1 than Irinotecan. I then analyzed the differential gene expression in the brain upon Topotecan treatment and found putative neuroprotective pathways. I conclude that Topotecan could be a potential therapeutic method against neurodegeneration through PARP-1 inhibition. Future studies are required to reveal the biochemical effect of Topotecan on PARP-1 activity and the therapeutic potential of Topotecan in animal models of AD.

Awards Won:

NC State College of Engineering: Alternates (not read aloud)