Machine learning optimized in silico design of a de novo RAGE inhibitor: a small molecule approach to slowing the progression of inflammatory disease

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Inflammatory diseases affect billions of patients worldwide. Receptor for Advanced Glycation End products (RAGE) has been identified as a promising target for many inflammatory diseases, including cancer, diabetes, and neurodegenerative disease. I hypothesized that computational methods could effectively design oral small molecules with a strong affinity for RAGE and favorable pharmacokinetic properties. Proteomics analysis showed that RAGE is not involved in major protein pathways and inhibition will have few downstream effects. The ZINC20 database was filtered from 883 million compounds to 405 million using standard drug-likeness properties. A deep neural network created a pharmacophore model by identifying interaction sites on the structure of RAGE using instance segmentation. I then screened the filtered database for fit to binding sites on RAGE using this pharmacophore model, ranking compounds by the distance from pharmacophore features. This resulted in 208 molecules, which were optimized for docking affinity to RAGE through evolutionary fragment-based optimization. Binding affinities were validated through SwissDock. An ensemble of ADMET tests predicted the final compounds to be safe. Cardiac drug-drug interactions with common chemotherapeutics were evaluated as RAGE is known to increase resistance to chemotherapies. Two compounds were isolated, one intentionally blood-brain barrier (BBB) permeable, and both with affinities below -10 kcal/mol and favorable ADMET properties, confirming the hypothesis. The first drug (PUV6060) will be applicable in treating inflammatory disease. The second drug (PUV4259), which is BBB permeable, will be used to treat neuroinflammatory disease. Future directions include validation in animal models and reaching patients.

Awards Won: