A Deep Learning Approach to de novo Drug Design: Generating Multi-Target Drugs to Inhibit Amyloid-Beta with Applications in Neurodegenerative Disorders

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Amyloid-beta is an intrinsically disordered protein involved in neurodegenerative disorders. Previously, amyloid-beta was considered “undruggable” due to its shape-shifting properties. However, recently, scientists found targeting amyloid-beta in its disordered state can reduce the toxic aggregates in neurodegeneration. New developments in deep learning have made it possible to generate novel target-specific structures to inhibit toxic proteins. Thus, designing a series of drugs to inhibit disordered regions in amyloid-beta could lead to new therapies. In this research, generative and predictive deep neural networks were trained to develop drugs that bind to disordered regions in amyloid-beta. For the generative model, a generative adversarial network was trained to produce SELFIES molecular graphs of compounds that cross the blood-brain barrier. For the predictive model, a deep neural network was trained to evaluate the affinity of compounds and targets using the Vinardo score. Both models were trained jointly via reinforcement learning to generate compounds with strong binding affinities. For proof-of-concept, four disordered regions of amyloid-beta were identified as drug targets. Compounds with strong docking scores were designed and filtered based on Lipinski’s rule, Pan-assay interference, and synthetic accessibility. Results indicated this approach generated various ligands that could inhibit amyloid-beta. Lastly, a program designed and analyzed a combination therapy of generated ligands to produce a multi-target drug. This research culminates the first deep learning strategy for multi-target drug design in intrinsically disordered proteins. Future research can further understanding of desired properties and produce a rich pipeline of drugs for in-vitro testing.

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