REVOLUTIONIZING BIOMEDICAL RESEARCH: INTEGRATING CUTTING-EDGE AI/ML TO UNLEASH INNOVATION IN DRUG DISCOVERY AND THERAPEUTICS DEVELOPMENT

In Silico Discovery and Optimization Tool for Peptide Discovery for Traumatic Brain Injury Therapeutics

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Currently, there are no preventative therapeutics for traumatic brain injury, and state-of-the-art body armor does not protect against blast induced traumatic brain injury (BI-TBI). All attempts to design a therapeutic have failed in clinical trials primarily due to the use of universal anti-inflammatory molecules that block the toxic effects of edema and inflammation in the brain also block reparative mechanisms necessary for recovery. Furthermore, all failed countermeasures focused on treatment instead of prevention. An effective prophylactic must demonstrate efficacy to prevent pathological cascade initiation in the first 5 seconds, specificity to prevent side effects, safe persistence in the body in stealth mode until needed, and bioactivity at the right place and time upon blast. A limitation for developing prophylactic TBI systems is targeting a master regulator of the pathologic molecular cascade early enough to shut down the cascade. Here we describe our in silico discovery and optimization tool for peptide-based therapeutics to treat or prevent BI-TBI. The screening tool utilizes state-of-the-art deep learning architectures including contextualized language models, convolutional neural networks, graph attention networks to predict efficacy, toxicity, and feasibility of putative peptides. Peptides are prioritized using a multi objective optimization framework where individual objectives (efficacy, toxicity, and feasibility) are combined into a single objective using a weighted scalarization approach. The prioritization module will be combined with a de novo design module that employs genetic algorithms to generate novel candidates with improved performance profile (“fitness”). In evaluating the peptide library against a set of targets, the initial work started with available open-source data from curated databases of healthy brain and then analyzed multi-omic data derived from ferret and mouse BI-TBI studies. In vivo studies will be used to test and characterize peptide therapeutic candidates derived from the in silico screening and optimization tool.

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