THE USE OF AI AND ADVANCED COMPUTER SYSTEMS TO DEVELOP DRUGS AGAINST NEW EMERGING THREATS

Deep Learning-guided Discovery And Structural Validation Of Marine Toxin Inhibitors

James J. Collins MIT **Aarti Krishnan** MIT **Andreas Luttens** MIT **Kaixiong Zhou** MIT **Parijat Bandyopadhyay** Broad Institute **Melis N. Anahtar** MGH **Jacqueline A. Valeri** MIT **Satotaka Omori** Broad Institute **Felix Wong** MIT

The marine environment is laden with organisms capable of producing biotoxins that pose significant health and biosecurity threats to humans. The mechanism of action of these biotoxins and potential counter-measures remain underexplored, in part, due to the lack of suitable chemical probes that modulate host receptors that directly or indirectly interact with these toxins. We focused on identifying potent antidotes of brevetoxin, which are polyether neurotoxin compounds produced by the dinoflagellate Karenia brevis that bind to voltage-gated sodium channels, resulting in an influx of sodium into cells and a blockage of neuronal excitability. Upon exposure to brevetoxin-contaminated shellfishes or water, humans experience significant neurological, gastrointestinal, and respiratory distress and marine animals are killed en masse. We optimized a high-throughput assay to screen for compounds with potent anti-brevetoxin activity using mouse neuroblasts with neuronal and amoeboid stem cell morphology (Neuro2a). We used the assay to screen 2,560 small molecules, comprising clinically-approved drugs and natural products, and identified 194 (7.6%) compounds as potent anti-brevetoxins. Seven of the compounds were highly-selective and appear to modulate membrane-bound receptors, including calcium ion-channels. All 2,560 screening data points were then used to train graph neural networks (GNNs), large-language models (LLMs) and hybrid models to predict anti-toxin properties, with hybrid models that use few-shot learning techniques, achieving a mean AUROC of 0.20 and AUPR of 0.70 on a held-out test set. Prospective testing within the Broad Institute's internal compound library comprising ~800,000 molecules demonstrated model validation rates reaching 24% (40/169). Eleven of the forty hits were orthogonally validated as potent and selective anti-brevetoxin molecules in human neuroblastoma cells (Sk-N-SH), with one molecule containing a nicotine substructure, known to target neuronal transmembrane receptors. Ongoing work includes the elucidation of these hits' mechanisms of action using structural biology-based approaches, such as molecular docking calculations, testing of in vivo efficacy in mouse models of neurotoxicity, and iteratively augmenting machine learning-guided exploration of vast chemical spaces. Taken together, we have determined novel chemical antidotes of marine toxins and established a pipeline to enable the development of rapid-response antitoxin medical countermeasures.

This work was supported by the DTRA grant HDTRA1-22-1-0010: Deep Learning-Guided Discovery of Marine Toxin Inhibitors