TOXIN MEDICAL COUNTERMEASURES - DEVELOPMENT OF NOVEL, BROAD-SPECTRUM COUNTERMEASURES FOR TOXIN EXPOSURE

Development And Implementation Of Biomimetic Shuttles That Transport Charged Oximes Across The Blood Brain Barrier While Maintaining Their Therapeutic Potential

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Current therapeutics to treat exposure to organophosphorous-derived chemical warfare agents cannot effectively treat exposure in the central nervous system due to lack of blood brain barrier (BBB) permeability of the therapeutics. Current treatment regimes require large and repetitive dose administration which can only treat the peripheral nervous system. Many efforts have been tried to circumnavigate the problem with BBB permeability of nerve agent therapeutics through either modification of the therapeutics themselves or through the incorporation of an external shuttle or macromolecular cage. A suitable system to effectively transport nerve agent therapeutics across the BBB, remains elusive. The goal of our project is to develop a small molecule shuttle that can effectively transport charged oxime therapeutics across the BBB and the development of a new microphysiological model that combines BBB screening with a measurement of therapeutic potential, acetylcholinesterase (AChE) reactivation. We have chosen a class of small biomimetic molecules as effective shuttles for BBB transport of charged nerve agent therapeutics.

Materials were designed through an initial screening of compounds in silico and then screened for both BBB permeability and AChE docking using state-of-the-art computational models. Shuttles and oximes were synthesized and combined to form conjugates. These conjugates demonstrated both AChE reactivation and BBB permeability in separate experiments. Through a clever use of bioengineering, a combined experiment that demonstrated both BBB permeability and AChE reactivation in a single experiment was developed and implemented. This new microphysiological model can be used for in vitro efficacy studies and can be used in the screening of medical countermeasures against organophosphorus poisoning.

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