AI/ML AND VIRTUAL HUMAN PLATFORMS FOR THREAT AGENT HAZARD ASSESSMENT AND MEDICAL COUNTERMEASURE DISCOVERY AND DRUG DEVELOPMENT

Improved Nerve Agent Treatment System Early Development Pipeline (inats Edp): Utilizing In Silico, In Vitro, Ex Vivo, And In Vivo Assays In Human-relevant Systems To Evaluate Proposed Reactivator Drug Candidates As Organophosphorus Nerve Agent Countermeasures

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Organophosphorus nerve agents (OPNAs) present a threat to both civilian and warfighter populations. Generally known as chemical warfare agents since their initial discovery during World War II, OPNAs act by covalently inhibiting acetylcholinesterase (AChE), an enzyme that catalyzes the hydrolysis of the neurotransmitter acetylcholine (ACh). Exposure to OPNAs results in an accumulation of ACh which then leads to a systemic cholinergic crisis characterized by mucosal secretions, convulsions, and eventually death. Current OPNA countermeasures fall into two main categories: 1) treatments such as atropine (an antimuscarinic) or diazepam (an anticonvulsant) aimed at managing the symptoms of a cholinergic crisis and 2) drugs commonly known as reactivators that are designed to treat the cause of OPNA intoxication by reversing the inhibition of AChE. Highly restricted access to OPNAs combined with the complex biochemical interactions required for effective reactivation of OPNA-inhibited AChE has hindered research efforts to identify and characterize prime novel reactivator drug candidates.

Recently, the United States Army Medical Research Institute of Chemical Defense has worked closely with the Defense Threat Reduction Agency to establish the Improved Nerve Agent Treatment System Early Development Pipeline (INATS EDP) as a robust tool for the evaluation of novel reactivator drug candidates. These efforts have led to the establishment of standardized assays that can simultaneously characterize and down-select reactivator drug candidates for pre-clinical evaluation and further development. These assays are grouped into four main categories:
1. In Silico Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) Modeling à An initial characterization of the pharmacokinetic profiles of a reactivator drug candidate.
2. In Vitro Multi-Agent Screening Assay à As a critical decision point, the reactivation potential of a reactivator drug candidate against a variety of OPNAs is evaluated in a simplified biochemical environment utilizing human recombinant AChE. Alternate expanded versions of this assay can also be utilized to characterize kinetic parameters of reactivator drug candidates, informing the structure-activity relationships of the biochemical interactions.
3. Ex Vivo Nerve Response Assay à Utilizing tissue from a genetically modified mouse model expressing only human AChE, the capacity of a reactivator drug candidate to restore functional activity in an OPNA-exposed tissue is measured.
4. In Vivo Reactivation Assay à Using the genetically modified mouse model previously mentioned, the reactivation of AChE by a reactivator drug candidate in a variety of central nervous system (CNS) and peripheral tissues after exposure of a live animal to an OPNA is evaluated.

With standardized scoring matrices developed for each of the INATS EDP assays, a prime reactivator drug candidate can be identified quickly and easily. For reactivator drug candidates identified for further development, initial efficacy studies in the mouse model mentioned previously and industry standard in vitro ADMET testing can also be conducted as part of the INATS EDP.
As a tool for the research community, the INATS EDP combines standardized assays using actual OPNA threats and human-relevant models with consistent evaluation metrics to provide a uniform, streamlined pathway for reactivator drug candidates to reach the hands of warfighters and civilians as quickly as possible.

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