A Toxidromic Approach for Chemical Medical Countermeasure Development

Efficacy Evaluation of a Novel Oxime Reactivator Against Nerve Agent Exposure

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Organophosphate (OP) compounds remain a major concern for both military and civilian populations. Current fielded therapies to mitigate toxicity from OPs include an acetylcholinesterase (AChE) oxime reactivator, pralidoxime chloride (2-PAM), to reactive inhibited AChE and a competitive muscarinic receptor antagonist, atropine, to mitigate excitotoxicity from excess acetylcholine. While 2-PAM has demonstrated efficacy for reactivating AChE, its action is primarily limited to the peripheral nervous system (PNS). Therefore, efforts to develop novel AChE oxime reactivators with enhanced antidotal efficacy for both the PNS and the central nervous system have been ongoing. Using an iterative approach that combines synthetic chemistry, computation, and in vitro and in vivo evaluation, we have recently developed a new candidate oxime (LLNL-02) that exhibits both blood-brain barrier penetration and reactivation capacity. Here, we will present efficacy outcomes for LLNL-02 in the guinea pig for both intravenous and intramuscular administrations. Upon challenge, we have observed enhanced survival and reactivation of brain AChE for LLNL-02 relative to 2-PAM. Our findings for survival, blood and brain AChE reactivation will be presented.