REPURPOSING TO SPEED CHEMICAL AND BIOLOGICAL MEDICAL COUNTERMEASURE DISCOVERY AND DEVELOPMENT

Bridging The Gap: Providing Selectivity And Specificity For Potential Therapeutics Against Organophosphorus Intoxication By Connecting Quinone Methide Precursors To Peripheral Binding Site Linkers

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Many countermeasures toward organophosphorus (OP) intoxication involve protecting the enzyme acetylcholinesterase (AChE) through the reversal of OP binding and/or inhibition in or around the catalytic active site. Administered to military personnel during the Gulf War, pyridostigmine bromide reversibly blocks the path leading towards the catalytic active site, preventing AChE from performing its catalytic function, and limiting phosphylation by OP nerve agents. Unfortunately, due to the rapid phosphylation by OP nerve agents, post-exposure treatments with pyridostigmine bromide are typically not effective, and instead, its use is often as a prophylactic measure, especially with rapidly aging OP agents, such as soman (GD). Methods are needed to mitigate the effects of the OP toxicant, by scavenging the OP compound or by reversing the inhibition or aging steps. Current FDA-approved medical countermeasures only treat the OP-inhibited forms of AChE. To counter these major concerns, our team is developing a new series of quinone methide precursors (QMPs) which can treat both stages of OP intoxication – both OP-inhibited and OP-aged forms of AChE – and possibly block other molecules from entering the catalytic active site of AChE. Drawing inspiration from the Alzheimer's treatment Aricept® and other compounds, these QMPs can "link" the entrance of the peripheral binding site to the catalytic active site of AChE, where the QMP can perform its treatment on the phosphylated serine residue, while also obstructing the entrance to the gorge by other molecules. Moreover, linked QMPs have shown a high binding affinity toward native AChE, and they have demonstrated efficiency in reversing OP-inhibited and OP-aged AChE after exposure to OP pesticides in vitro, and with an interesting selectivity for the OP, such as ethyl paraoxon (EP) and diisopropyl fluorophosphate (DFP). Specifically, some of our linked QMPs with an indanone peripheral binding site ligand work most effectively against EP-inhibited or DFP-aged human AChE and show little ability in treating methylphosphonate-aged AChE. In our presentation, we will discuss the in vitro data for a variety of linked QMP compounds, and also illustrate the protective efficacy from in vivo studies in a KIKO mouse model wherein the human AChE has replaced the mouse AChE (knock-in, KI) and the carboxylesterase has been knocked-out (KO), demonstrating the potential to treat OP-intoxicated AChE in the central nervous system.

We would like to thank DTRA for their funding and support of the program. MCDC Base Agreement No. 2107-380; MCDC 1905-006