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MEETING ABSTRACTS

DEMONSTRATION OF THE FIRST SMALL MOLECULE THERAPEUTICS FOR RESURRECTION OF THE AGED FORM OF ACETYLCHOLINESTERASE AFTER EXPOSURE TO ORGANOPHOSPHORUS CHEMICAL NERVE AGENTS AND PESTICIDES

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Organophosphorus (OP) compounds are potent acetylcholinesterase (AChE) inhibitors that have found use as both chemical warfare agents (CWAs) and as pesticides. Following inhibition of AChE by OP compounds, a competitive dealkylation reaction of the phosphylated serine residue occurs – a process referred to as aging. Current therapeutic reactivators of OP-inhibited AChE, mainly oximes, are not effective once aging has occurred. For the first time, we have demonstrated *in vitro* conversion of the aged AChE to the native form using small drug-like molecular therapeutics. As part of this effort, a diverse library of small molecule therapeutics have been developed to both recover the activity of aged-AChE, termed resurrection, as well as the activity of inhibited-AChE, referred to as reactivation. The structure of such therapeutics is derived from pyridyl-based quinone methide precursors (QMPs), sharing structural similarities to known therapeutic oximes. A structure-activity relationship study of synthesized QMP therapeutics was conducted to determine the effect electron-donating and electron-withdrawing groups have on the efficiency of both processes and to design optimized small molecule therapeutics for *in vivo* biological efficacy. Our successes will be presented.