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

Effectors That Reduce Aging Of Organophosphate Adducts Of Acetylcholinesterase

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Organophosphate (OP)-based nerve agents and pesticides covalently inhibit the enzyme acetylcholinesterase (AChE), resulting in a buildup of neurotransmitter which causes cholinergic crisis. The initial adduct of organophosphate can be reversed by oximes and some non-oxime reactivators if it is treated before it undergoes additional rearrangement (aging); after this, however, there is no effective strategy for overcoming OP-inhibition of AChE. We have established an assay to screen for effectors (activators, reactivators, and resurrectors) at each stage in the reaction pathway between OP and AChE that can be targeted for allosteric control to overcome inhibition and we have established both positive and negative controls for this assay. Using this platform, we have identified several molecules with the potential to alleviate inhibition of AChE by OP. These molecules will serve as starting points for further characterization and development as therapeutics.

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