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

Exploring The Utility Of A Human-relevant Mouse Model For Detecting And Quantifying Medical Countermeasures In The Brain.

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Serum carboxylesterase (CaE) confers resistance to nerve agent intoxication. Additionally, amino acid differences across species cause acetylcholinesterase (AChE) to interact differentially with both organophosphorus nerve agents (OPNAs) and reactivator countermeasures. A genetically modified mouse strain was developed to address both of these limitations by incorporating a loss of expression mutation of CaE (C57BL/6-Ces1ctm1.1Loc/J; Es1 KO) as well as the alteration of the protein coding sequence of the AChE loci to express the human enzyme homolog (C57BL/6-AChEtm1.1Loc/J; AChE KI). The strain combining both the knock in and knock out (KIKO) modifications presents an opportunity to evaluate compounds that interact with AChE in a humanized model. In this study, matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) will be utilized to spatially detect unmodified compounds in the tissue of KIKO mice. With MALDI-MSI, a variety of endogenous molecules can be imaged, including neurotransmitters using sprayed gold nanoparticles, brain and heart lipids using established methods for organic matrices, and proteins including AChE using tryptic digestion and MALDI IHC methods. Many drug candidates proposed to interact with target enzymes in the brain can also be detected with these methodologies. We propose to directly measure unaltered reactivators of OPNA-inhibited AChE with spatial quantification of these compounds within distinct regions of the brain. If successful, the combination of the human-relevant KIKO mouse and MALDI-MSI would create a robust system for the characterization of OPNA medical countermeasures in the central nervous system. Information would be obtained about a compound's ability to cross the blood-brain barrier in physiologically relevant concentrations to interact with the OPNA-inhibited AChE target. Elucidation of the distribution of candidate OPNA countermeasure drugs in a human-relevant animal model would assist in obtaining regulatory approval for the use of these new drugs by warfighters and civilians alike.

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