## CAMO (COMPARING ANIMAL MODELS TO ORGANOIDS) - TESTING MEDICAL COUNTERMEASURES WITH MICROPHYSIOLOGICAL SYSTEMS AND COMPARING TO TRADITIONAL ANIMAL MODELS AND CLINICAL TRAILS

# Evaluating Airway Responsiveness: Leveraging A Novel Assay For Assessing Functional Response In Precision-cut Lung Slices (pcls) From A Humanized Mouse Model

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Organophosphorus nerve agent (OPNA) poisoning leads to a cholinergic crisis resulting in difficulty breathing, seizures, and death due to the inhibition of acetylcholinesterase (AChE). This process can be reversed with the use of reactivators which interact with the inhibited enzyme, releasing the bound OPNA from the active site. A genetically modified mouse strain was developed to address both the inherent resistance to intoxication afforded by serum carboxylesterase (CaE) and the varied reactivation potential of species-specific AChE. These goals were achieved by incorporating a loss of expression mutation of CaE (KO) as well as the alteration of the protein coding sequence of the AChE loci (KI) to express the human enzyme homolog. 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. To confirm that the KIKO mouse accurately models the human response, direct comparison of tissue functionality as it relates to reactivation potential is required. In this study, precision-cut lung slices (PCLS) will be used as a comparative ex vivo model to visualize lung function and quantitate reactivation after exposure to OPNAs. These slices maintain the complexity of lung tissue, allowing for the study of airway function. Previous studies have utilized PCLS to demonstrate airway responsiveness, providing a system to test therapeutics for OPNA exposure. This study aims to develop an assay by measuring inhibition and reactivation as a function of airway response in KIKO lung tissues. PCLS samples will demonstrate airway contraction when exposed to OP and reversal of contraction when administered a reactivator, analyzed via brightfield microscopy. In the future, we anticipate that the functional reactivation of KIKO tissue will be compared to human tissue and presented as an adjunct for in vivo testing of OPNA reactivators.



The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense, and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals, the Public Health Service Policy on Humane Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended.

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