OVERCOMING LIMITATIONS OF ORGAN-ON-CHIP (OOC) TECHNOLOGIES TO ADVANCE THE CHARACTERIZATION AND MEDICAL MANAGEMENT OF CHEMICAL AND BIOLOGICAL (CB) THREATS

Inception: Integrated Omics Of Emergent Pathways For Therapeutic Intervention Of New And Emerging Threats

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Organophosphates (OPs) are highly toxic compounds with 1000's of unique structures that see commercial use as insecticides and are potent chemical warfare agents. OPs are nerve toxins owing to a mechanism of action via phosphorylation of cholinesterase enzymes. Recent events namely, the poisoning of the Russian politician Alexei Navalny, have highlighted the importance of new therapeutic interventions for this class of compounds. While acute toxicity of OP exposure is understood to be caused by cholinesterase inhibition, neither low dose repeat exposure, the long-term effects of sub-lethal exposure, nor all symptoms of toxicity can be explained by this mechanism. In short, cholinesterase inhibition is not the whole story. Recent findings suggests that the acute symptoms observed in individuals poisoned with OP CWAs are likely due to "secondary" metabolic targets (e.g. isocitrate dehydrogenase II) rather than the conventional neurotoxicity mediated by acetylcholinesterase inhibition. However, the biochemical details and pathway interactions of these "secondary" targets remains elusive largely owing to 1) few institutions can handle these compounds and 2) the experimental designs require a critical mass of field-bridging experts. To address this urgent need we have established an integrated threat multiomics pipeline as part of LANL's Emerging Threat Laboratory. Utilizing these resources and our state-of-the-art framework, we will fully characterize the biomolecular response to multiple classes of OPs using a human organ-on-a-chip model with the goal of identifying new entry points for medical countermeasures. This work allows us to challenge an overly simplistic mechanism of action that has been the 'catch all' explanation for a complex and highly relevant class of toxicologically potent chemical compounds.