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

Discovery Of Non-canonical Protein Targets Of Chemicals Of Concern Using Activity-based Protein Profiling (abpp)

Vivian Lin PNNL **Agne Sveistyte** Pacific Northwest National Laboratory **Lydia Griggs** Pacific Northwest National Laboratory **Gerard Lomas** Pacific Northwest National Laboratory **Sankar Krishnamoorthy** Pacific Northwest National Laboratory **Katherine Schultz** Pacific Northwest National Laboratory **William Nelson** Pacific Northwest National Laboratory **Jordan Smith** Pacific Northwest National Laboratory **Stephen Callister** Pacific Northwest National Laboratory **Aaron Wright** Pacific Northwest National Laboratory

Acute exposures to known toxic chemicals, such as nerve agents and pharmaceutical-based agents, lead to well-documented adverse health effects, yet significant efforts are still needed to achieve a comprehensive molecular level understanding of how these chemicals impact human biology. Elucidating the molecular mechanisms by which chemicals of concern perturb protein functions is necessary for developing effective medical countermeasures and gaining a predictive understanding of the potential for an unknown chemical to cause harm. Activity-based protein profiling (ABPP) is a chemical biology technique that uses selective chemical probes to identify protein-small molecule interactions and/or protein activities or functions within complex biological systems. We designed and synthesized 13 probes that mimic the structures and/or reactivity of organophosphates, benzodiazepines, GABA-A receptor antagonists, fentanyl, ketamine, dexmedetomidine, and sevoflurane for ABPP of mammalian tissue lysates. Molecular docking simulations were used to evaluate and select probe designs which yielded similar physicochemical properties and predicted interactions with known receptors for each compound. Application of these probes to tissues (brain, heart, lung, liver, and kidney) from various animal models and humans is now generating comprehensive profiles of the proteins that these different chemical compounds interact with. These results are also being applied to determine homology of identified protein targets from animals to humans using sequence-based homology modeling and to develop preliminary physiologically based pharmacokinetic (PBPK) models for in vitro to in vivo extrapolation and animal model to human translation. Further analysis of these data will help to characterize the potential molecular mechanisms by which these chemicals of concern impact human health and may provide insight into the biological pathways and markers that can be targeted for future broad-spectrum medical countermeasure development.