COMBATTING EMERGING BIOLOGICAL THREATS – PREPARING FOR THE FUTURE TODAY

Gladtier: A High Throughput Analysis For Characterizing Toxin/receptor Interactions For Disruption Or Reversibility Of Toxin Activity

Brooke Ahern U.S. Army DEVCOM Chemical Biological Center **Vishaka Santosh** U.S. Army DEVCOM Chemical Biological Center, Excet **Gabrielle Rizzo** U.S. Army DEVCOM Chemical Biological Center **Conor Jenkins** U.S. Army DEVCOM Chemical Biological Center **Tyler Goralski** U.S. Army DEVCOM Chemical Biological Center **Chris Ellis** U.S. Army DEVCOM Chemical Biological Center **Andrew Walz** U.S. Army DEVCOM Chemical Biological Center

Conotoxins are short neurotoxic peptides that can be isolated from the venom cone snail to inhibit ion channel activity within the body to induce dysfunction, paralysis and death. The potential for conotoxins to be used as biological weapons requires further investigation into how these peptides bind to neurotransmitter receptors and ion channels so that effective disruption or reversibility of toxin activity can be found. Current through ion channels in response to conotoxin is significantly reduced; however, it remains unknown as how the structural of the channel changes in response to exposure. This is due, in part, to techniques that require a significant amount of time and highly trained individuals that make high-throughput analysis extremely difficult. Therefore, our objective is to test the hypothesis that there are critical residues within the ion channel structure that promote reduced current in response to conotoxin exposure in a manner that provides higher throughput. We test this by combining recent advancements in technology: cross-linking mass spectrometry and automated patch-clamp. These techniques are applied to CaV2.2 channels (N-type voltage gated calcium channels) and nicotinic acetylcholine receptors (nAChR). Both of these channels are well studied and serve as perfect models to establish a high-throughput analysis we have termed GLADTIER – Guided Linking Application to Decide Threat Interaction Effect Radius. By establishing this analysis process with two known targets of conotoxin, we are validating known interaction partners, as well as working to discover potential novel target sites. These new sites can then be exploited to design new peptides to counter the effects of conotoxin on the channel. This new form of investigation of toxin exposure to ion channel can then be applied to other types of toxin besides conotoxin, and their respective receptor targets.

Funding was provided by the U.S. Army via the In-house Laboratory Independent Research Program (PE 0601101A Project 91A) at the Combat Capabilities Development Command (DEVCOM) Chemical Biological Center.