

TOXIN MEDICAL COUNTERMEASURES - DEVELOPMENT OF NOVEL, BROAD-SPECTRUM COUNTERMEASURES FOR TOXIN EXPOSURE

Discovery Of Medical Countermeasures Against A-conotoxins Using A Mrna Cyclic Peptide Display Platform

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Conotoxin peptides, isolated from the venom of cone snails, are a collection of potent cyclic peptides which selectively target ion channels and receptors. Although rare, there have been reports of human fatalities from cone snail venom despite the primary function being for hunting fish. α -Conotoxin GI, isolated from the *Conus geographus* cone snail, is a highly potent competitive agonist for the muscle-type nicotinic acetyl choline receptor (nAChR). Inhibition of nAChR results in flaccid paralysis and, if left untreated, asphyxiation. α -GI is therefore a peptide of interest as a chemical probe, however there is also the potential for use as a chemical/biological agent.

As there are no anti-toxin clinically available, our objective was to identify and isolate a cyclic peptide with the ability to block α -GI binding to the receptor. To accomplish this, we designed and synthesized a biologically active, biotin-tagged α -GI analogue and established that it can be immobilized on magnetic streptavidin beads. We then used a mRNA cyclic peptide display platform to pan a library (1012 compounds) of different sized, disulfide bond constrained peptides against the immobilised α -GI conotoxin. Hit peptides were identified through next generation sequencing of the DNA barcode. Chemical synthesis and characterization of the hit peptides is ongoing, where binding affinity for α -GI is being established by surface plasmon resonance, and anti-toxin activity is being measured using an nAChR mediated fluorescent calcium uptake assay.