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

Elucidating The Precise Mechanism Of α-conotoxin Antagonism At The Muscle-type Nicotinic Acetylcholine Receptor

Michael Capper University of Glasgow **Nicola Wade** University of Glagow **Jesko Köhnke** Leibniz Universität Hannover
Andrew Jamieson University of Glasgow

α-Conotoxins (α-CTX) are disulfide rich peptide neurotoxins found in cone snail venom. They are muscle-type nicotinic acetylcholine receptor (nAChR) antagonists and form part of a cocktail of toxins produced by cone snails to incapacitate prey. The prevention of nAChR ion channel activation by acetylcholine prevents the subsequent cascade of events that normally culminates in muscle contraction. The result is flaccid paralysis, which in severe cases can lead to asphyxiation. Recent interest in α-CTX has focussed on their possible use as tool compounds and drugs but there is also potential for illicit use as chemical agents. These peptides are highly diverse in sequence, which has thus far precluded the development of medical countermeasures.

Our efforts have been focussed on determining of the mechanism of binding and identification of the α-CTX pharmacophore. This approach combines structural biology and biochemical assays with complementary AI and machine learning computational approaches.

The work described herein leverages the power of cryo-EM to reveal the first high-resolution structures of several α-CTXs bound in their active form to muscle-type nAChR. This has revealed key residues and structural features responsible for α-CTX potency and specificity. Our data have also allowed us to delineate a generalisable structural pharmacophore that explains both potency and selectivity across the diverse α-CTX family. This work provides unprecedented insights into the molecular basis of α-CTX pharmacology and serves as a blueprint for the rational design of peptide-based therapeutics and medical counter measures.