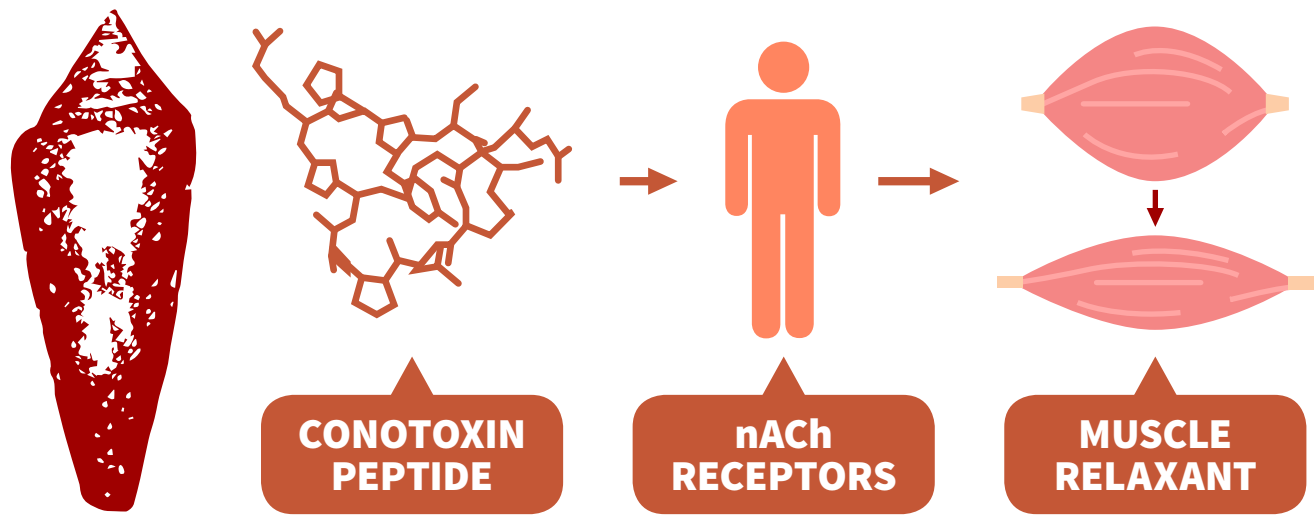
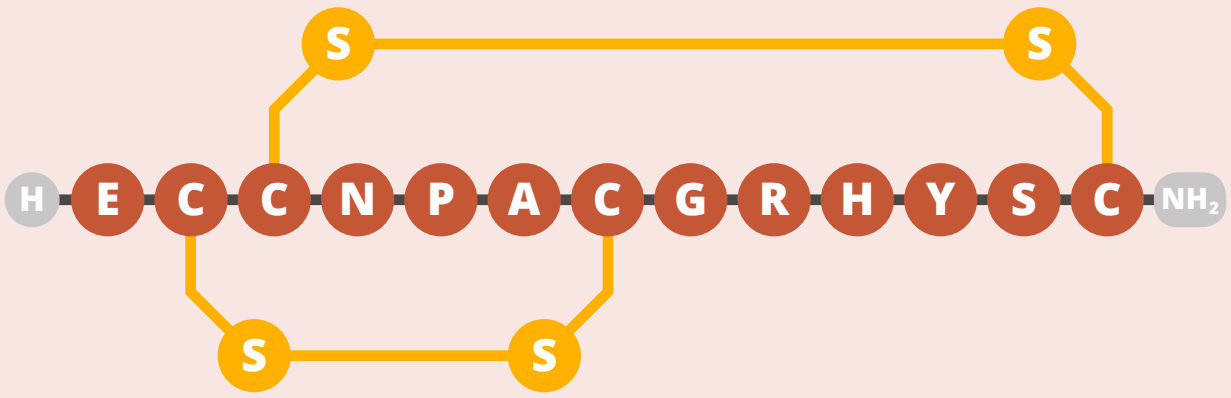
IMPROVING STABILITY OF CONE SNAIL TOXINS FOR THERAPEUTIC USE

WHAT ARE CONE SNAIL TOXINS?

Conotoxin peptides are the toxic components of the venom of fish-hunting cone snails. Some make muscles relax by binding to nACh receptors, giving them possible uses in anaesthesia. Many others are of interest as drugs to control pain and treat other medical conditions.

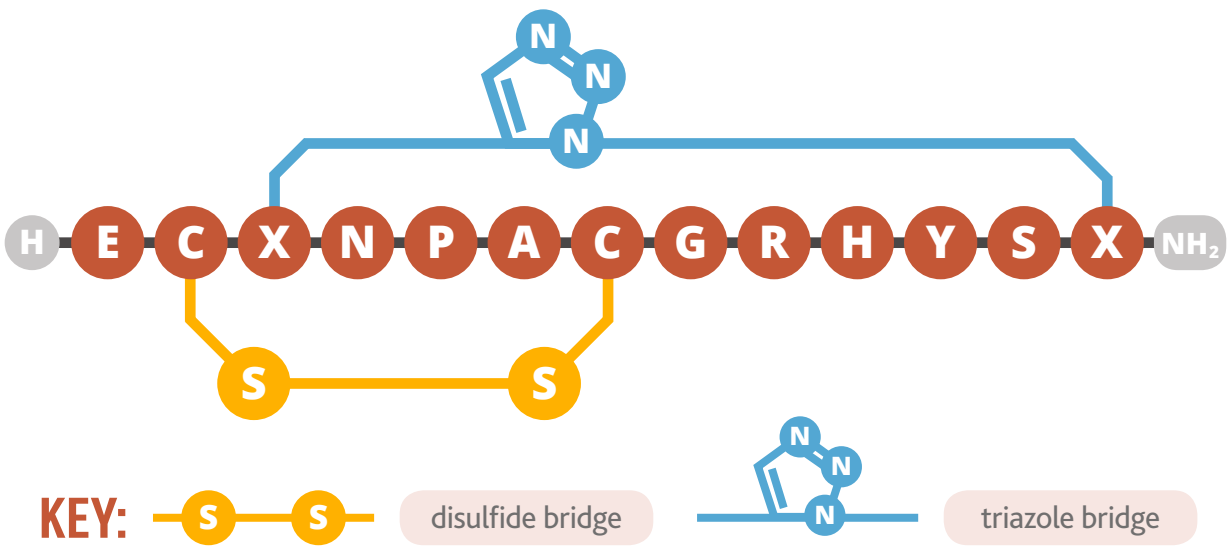




KEY: E C C amino acid chain — S S disulfide bridge

STABILITY PROBLEMS

Conotoxins have poor stability in blood and this can limit their potential to be used as drugs. Reaction of the disulfide bridges can cause the shape of conotoxins to change. This means the peptides can no longer bind to their targets to produce medical effects.



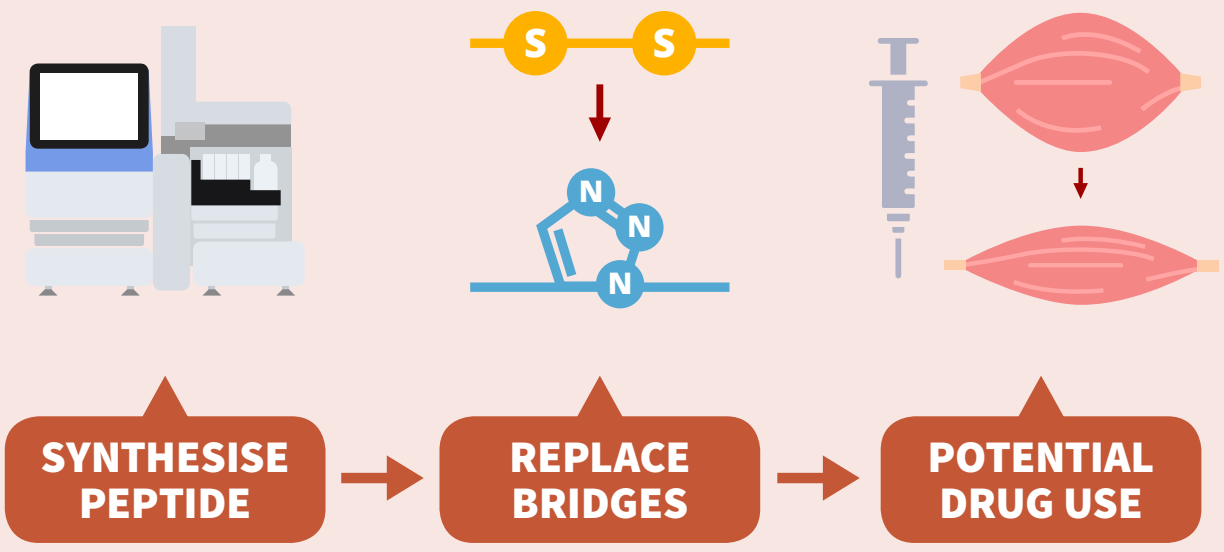
KEY: S S disulfide bridge — N N N triazole bridge

IMPROVING STABILITY

One of the disulfide bridges in alpha-conotoxin GI can be replaced with a 1,2,3-triazole bridge. This mimics the shape and arrangement of the disulfide bridge. It is also more stable and tests in human cells showed that, with the 1,2,3-triazole bridge shown in place, GI is held in the correct shape to retain its full biological activity.

WHY THIS RESEARCH MATTERS

The modification of GI was easily achieved with commercially available reagents and could be used with other peptides, including other conotoxins, containing disulfide bridges to make more stable compounds for medical use. In addition, the NMR method used to determine GI's structure could inform future drug discovery efforts.



α-Conotoxin GI Triazole-Peptidomimetics: Potent and Stable Blockers of a Human Acetylcholine Receptor – DOI: 10.1039/C8SC04198A
A Knuhtsen, C Whitmore, F S McWhinnie, L McDougall, R Whiting, B O Smith, C M Timperley, A C Green, K I Kinnear, A G Jamieson

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