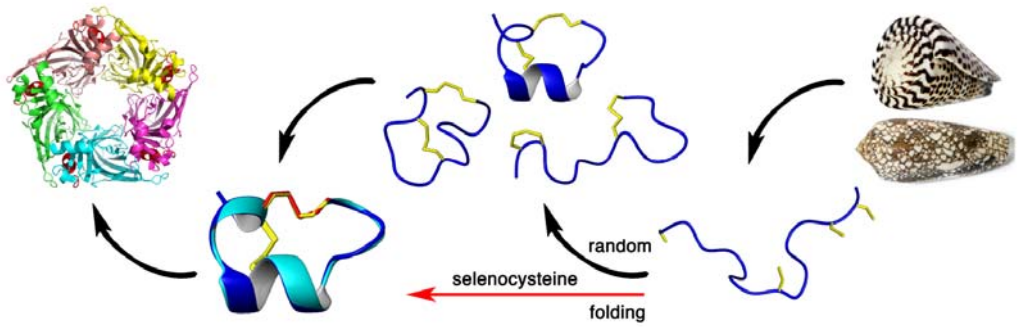
Selenocysteine and its role in peptide drug development

Peptides have emerged as a therapeutically and commercially important class of drugs offering the advantage of greater specificity, potency and lower toxicity over small molecule pharmaceuticals. More importantly, peptides have proven to be invaluable research tools helping to dissect physiological functions of many human receptors and elucidating the biological mechanism underlying diseases. Particularly cysteine-rich peptides that are able to stabilize protein-like secondary structures such as alpha helices, beta turns or sheets with their rigid disulfide bond network turned out to be a great source for highly potent and selective lead compounds targeting a diverse range of receptors.

With solid-phase peptide synthesis and next-generation sequencing becoming highly automated, the bottleneck in discovery and development of this intriguing class of peptides is their correct folding. Here we would like to present a recently developed solution and solid-support method to produce the desired isoforms of disulfide-rich peptides more efficiently: strategic replacement of pairs of cysteine with selenocysteine residues takes advantage of the preferred diselenide over disulfide bond formation during the folding process, hence avoiding the misfolding into non-native and inactive conformations. This makes it possible to synthesize and screen the compounds for biological activity more quickly and opens the door for in depth structure-activity relationship studies for drug lead optimization. Additionally, we would like to show through a series of elegant and interdisciplinary studies (crystallography, ^{77}Se NMR, CD, analytical HPLC, stability assays, electrophysiology and receptor docking models) the small, but important differences between selenocysteine and cysteine, and how these differences can be exploited in new reactions and in the development of more selective, potent and stable peptide drug molecules.



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