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Disulfide bonds as structural scaffolds for neurotoxic peptides

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Animal venoms are mostly composed of cysteine and disulfide-rich peptides. These peptides are neurotoxins and are highly selective in attacking a wide range of neuroreceptors and ion channels.1-2 Among these peptide toxins, conopeptides (natural toxins expressed by the carnivorous marine cone snails of the genus *Conus*) are used extensively in neurophysiological studies to investigate isoforms of specific neuro-receptors. These neurotoxins are often characterized by structural motifs of cysteine (Cys) and disulfide bonds, which play a vital role in dictating the overall folds in the structure of these peptide-toxins. The structure in turn is significantly responsible for the determination of toxin function and selectivity. A major challenge, which makes experimental work with the disulfide-rich venom peptides difficult, is to obtain sufficient material for structural and functional characterization. The synthesis is very difficult for these venom peptides, as they often form isoforms due to the presence of non-native disulfide-linkages. Hence, computer simulation has become an indispensable tool to study the shape, size, conformational stability, hydrodynamic behavior, folding patterns and denaturation of these peptide-toxins.3 In the present work, using microsecond order all-atom Molecular Dynamics simulation with classical force field, we are proposing to develop a general understanding of the folding pattern of such venom peptides in water in realistic time scales. How far the disulfide bond scrambling induces deviation in the structure of these neurotoxins from the native form is the fundamental answer that we are looking for. Further, we estimate quantitatively, the ratio of the different disulfide bond isoforms that would appear in equilibrium under a given reaction condition using classical MD data.

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De novo design of disulfiderich miniproteins: Scaffolds for engineering proteinbased therapeutics

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Naturally occurring disulfiderich miniproteins are often touted as "natures drugs," and are employed by organisms as signaling molecules, antiviral and antimicrobial defense proteins, and toxins. These scaffolds have great potential to succeed under circumstances where antibody based therapies are unsuitable. They are poorly or nonimmunogenic, thermostable, protease resistant, and they can be chemically synthesized. The presence of multiple covalent disulfide crosslinkages confers extreme stability to these proteins, and could be the key to unlocking inhaled, topological, or oral protein drug delivery. However, engineering these proteins into drugs with novel function has been hindered by the limited diversity of naturally existing scaffolds. To circumvent this issue, we have developed a de novo protein design method to custom tailor small, hyperstable affinity reagents against a given target interface by rational design. By utilizing massively parallel, chipbased gene synthesis and yeast cellsurface display, we have created a highthroughput experimental assay. To validate our method, we have successfully produced affinity reagents against a neutralizing epitope of influenza hemagglutinin. Our technology is the first to allow rapid, cost effective generation of highly targeted protein therapeutics with the potential to treat a wide variety of diseases.

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