Foldamers as Protein Mimics

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The discovery that synthetic sequence-specific oligomers can adopt well-defined folded structures – foldamers[1] – has profoundly changed our view of biopolymer mimicry, raising prospects for exploring new chemical spaces and creating novel synthetic architectures with defined functions.[2] In this presentation, we will discuss some of our efforts towards this goal, showing how de novo design, careful structural investigation and subsequent sequence engineering of non-peptide helical foldamers may be used to generate effective peptide and protein mimics.

Besides aliphatic and aromatic oligoamide foldamers (β-peptides, peptoids, sulfono-γ-AApeptides, quinoline-based oligoamides,…) which have received much of the attention in the field, a few other backbones that do not contain an amide linkage but similarly show a high folding propensity (*e.g.* aliphatic urea-based oligomers studied in our group) have emerged. Oligourea foldamers which form well-defined and stable helical secondary structures reminiscent of the α-helix combine a number of characteristics – synthetic accessibility, sequence modularity, folding fidelity, and stability to proteolysis – that bode well for their use in various applications. Moreover, it was recently recognized that this synthetic helical backbone can be interfaced with regular α-peptides to generate helically folded peptide-oligourea hybrids that display additional features in terms of helix mimicry and protein-surface recognition properties.[3]

Applications developed in our group with a focus on molecular recognition include the design of (*i*) bioactive peptide mimics with a reduced peptide character and improved pharmacological properties (*i.e.* modulators of protein-protein interactions and receptor ligands); (*ii*) composite proteins; (*iii*) protein-like quaternary structures and (*iv*) foldamer-based organocatalysts.

References:
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