

Microsymposium

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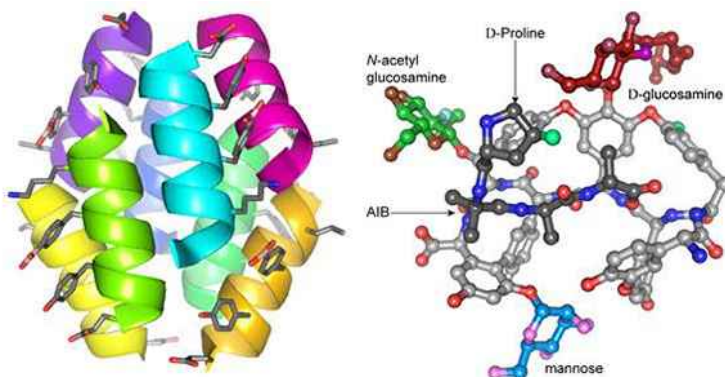
A Macromolecular approach to peptide-based molecular recognition and catalysis

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Synthetic peptides incorporating non-natural amino acids provide an opportunity to apply biomimetic principles in the design of both chemical scaffolds and novel pharmaceuticals. Crystallographic analysis can be of significant utility in this area just as elsewhere, but blur the line between small-molecule and macromolecular systems. I will present recent examples combining the tools of macromolecular crystallography techniques with chemical biology to elucidate structures of peptide-based binding and catalytic motifs. First, I will discuss recent structures of a beta-peptide known to spontaneously self-assemble into an octameric bundle with a defined tertiary-fold. By introducing a non-natural amino acid at the solvent-exposed surface, a binding epitope for poly-alcohols is introduced. [1] Conversely, by modifying the hydrophobic core, the tertiary fold can be re-organized. [2] Second, I will discuss a peptide-based catalyst for the site-specific modification of saccharide units in the scaffold of the antibiotic teicoplanin. [3] While glycosylated small-molecules can be challenging structural-targets, native chemical ligation of the peptide to a macromolecular scaffold allowed for structure determination of the peptide and its binding target. Further structure-based design of more complex non-natural amino acid structures is a promising route to novel peptide-based tools and therapeutics.

[1] Melicher MS, Chu J, Walker AS, et al., (2013) "A beta-boronopeptide bundle of known structure as a vehicle for polyol recognition." *Org Lett.* 15, 5048-51., [2] Wang PS, Craig CJ, Schepartz A. (2012) "Relationship between side-chain branching and stoichiometry in beta(3)-peptide bundles" *Tetrahedron* 68, 4342-4345., [3] Han S, Miller SJ. (2013) "Asymmetric catalysis at a distance: catalytic, site-selective phosphorylation of teicoplanin" *J Am Chem Soc.* 135, 12414-21.



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