MIMICRY OF PROTEIN RECOGNITION SURFACES WITH PEPTIDIC FOLDAMERS

Samuel H. Gellman

Department of Chemistry, University of Wisconsin - Madison

ABSTRACT:
Interactions between specific proteins are essential for in biology, with key roles in normal physiological signal transduction and disease-related processes. Many such interactions have proven recalcitrant to modulation with small molecules because the protein surface areas involved are large. In these cases, clinical modulation is generally achieved with large peptides or proteins. We are exploring an alternative approach to this challenge, based on unnatural oligomers that fold to specific conformations and display protein-like surfaces ("foldamers"). We have found that informational alpha-helices can be mimicked effectively with oligomers containing both alpha- and beta-amino acid residues ("alpha/beta-peptides"). Placement of beta residues throughout a sequence can confer substantial resistance to proteolysis. Successful alpha-helix mimicry has been demonstrated in the context of BH3 recognition by Bcl-2-family proteins and formation of CHR+NHR helix-bundles from gp41-derived segments. Current efforts include expansion of protein-surface mimicry beyond isolated alpha-helices.

BIO:
Sam Gellman has been a member of the UW-Madison faculty for over 25 years. The interests of his research laboratory span the realms of organic chemistry and chemical biology. Gellman's research program focuses on the origins of folding preferences among conventional peptides and proteins and on the development of synthetic protein-mimetic oligomers, among other topics.