Designed, folded and functionalized polypeptides and proteins constitute an enormous pool of new shapes, new functions and new materials. By taking advantage in the chemical laboratory of the principles of protein folding used by nature, strategies have so far been developed for the engineering of new catalysts, metalloproteins, heme proteins, glycoproteins, receptors and mimics of the components of the immune system. Catalysts have been developed that catalyze reactions not performed by nature and uncommon folded polypeptide motifs have been engineered and structurally characterized. The search for and exploitation of the tremendous number of proteins yet to be discovered has thus begun. Understanding of the protein folding problem has now reached a level where the design of peptides that approach a hundred residues in size is feasible, although not trivial, and clearly sequence dependent. The most frequently designed motif is the four-helix bundle, but recently monomeric triple-stranded $\beta$-sheet structures have also been reported as well as a $\beta\beta\alpha$-motif, helical coiled coils and triple helices. Template-assembled polypeptides as well as linear sequences have been shown to fold into designed solution structures and these and other motifs are now key targets for functionalization. This review describes the principles and strategies used in the design of these motifs, as well as their structural characterization. Strategies for functionalization using both the naturally occurring amino acids and post-synthetic incorporation of non-natural functionality will be described, as well as the level of function that has been achieved by rational design.

**Keywords:** Design, Polypeptide, Catalysis, Metalloprotein, Heme, Structure, Protein folding, Glycopeptide.

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1 Introduction

The number of naturally occurring proteins is few in comparison with those that can be made from the twenty commonly occurring amino acids. There are $10^{200}$ possible 150-residue proteins and there are $10^{38}$ that have less than 20% sequence homology and that therefore represent unique folds. If the conservative assumption is made that one in a billion of the unique folds will form stable tertiary structures there are still $10^{29}$ new proteins to be discovered! The number of naturally occurring ones are less than $10^6$, probably because they have