Abstract

The vast array of molecular functions carried out by naturally occurring proteins is made possible by their precisely folded structures, which are encoded in their amino acid sequences. Protein folds have undergone evolutionary changes to display diverse and distinct functional properties essential for biological processes. Moreover, interaction between proteins, protein-protein interactions (PPI), play a pivotal role in most of the biological processes. Misfolding of proteins or aberrant PPIs is associated with many diseases such as cancer, infections, or neurodegenerative diseases. Hence, understanding the fold of proteins and its relationship to functionality is crucial for the efficient design of protein or PPIs modulators.

In recent decades, miniproteins have emerged as an excellent model system for studying protein fold. Miniproteins, which are polypeptides that weight less than 10 KDa, can fold into well-defined structures capable of retaining structural and functional elements of full-length proteins. Because of their relatively small size, miniproteins are synthetically available, allowing for investigation of the effects of single mutations on the fold, solvent conditions, and/or activity. In addition to enriching our knowledge of native protein folds, miniproteins have emerged as valuable tools in the design of *de novo* proteins and peptide-based therapeutics. By manipulating the amino acid sequence, miniproteins can be engineered with customised folds, opening new avenues for rational drug design.

Since the introduction of foldamers in the 1990s by Seebach and Gellman, α/β peptides have been extensively studied. The use of α-amino acids enables the introduction of specific functionalities by available side-chains, while β-amino acids are commonly used to control the overall shape of the molecule. The combination of peptide foldamers with miniprotein design, can derive in a wide range of new folds and functionalities not found in nature. Yet, there is no established methodology for the *de novo* design of β-amino acid containing miniproteins. In the present dissertation, our aim is to develop a methodology that will efficiently allow the design of a complex tertiary structure that incorporates cyclic β-amino acids. The miniproteins designed will be used as scaffolds for the design of inhibitors of complex targets involved in PPIs.