Description for general public

De novo designed, structurally extended peptide foldamers and their use for construction of PD-1/PD-L1 interaction inhibitors

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Peptide foldamers constitute an emerging class of compounds, which is defined as oligomers with a high tendency to form compact conformations in solution. α/β-Peptides containing constrained β-amino acids are one of the most promising group of peptide foldamers due to the possibility of rational design of secondary structures and the possibility of incorporation of chosen functions. Although, numerous studies on peptide foldamers have been published, a general strategy of construction of structurally extended peptide foldamers incorporating tertiary structures is still missing. α/β-Peptide foldamers exhibit also several advantages for building biologically active compounds, including: high proteolytic stability, biocompatibility, and the possibility of incorporation of various non-canonical amino acids.

The main goals of this project include the development of computer-aided methodology for *de novo* construction of structurally extended peptide foldamers of chosen geometry, and the application of created structures as scaffolds for building effective inhibitors of chosen protein-protein interactions, namely PD-1/PD-L1, that could be applied for cancer immunotherapy.

On the basis of chosen topologies incorporating helices as well as strands, and known secondary structures of α/β-peptides containing constrained β-amino acids, three-dimensional templates, that describe the shape of peptide backbone, will be generated. Subsequently, using these templates, sequences of peptide foldamers will be designed by application of computer-aided approach. Peptides will be obtained using microwave-assisted automated solid phase peptide synthesis and their three-dimensional structures will be studied in solution and in solid state.

Protein-protein interaction inhibitors will be constructed with the use of scaffolds elaborated in the first part of the project. Structurally extended peptide foldamers will be designed by computer-aided approach to target either PD-1 or PD-L1. The synthesized peptides will be analyzed for their conformational preferences in solution and evaluated for inhibitory activity against PD-1/PD-L1 interaction. The mode of binding of most active inhibitors will be further analyzed in detail.

There are numerous innovative aspect of this project which will impact various branches of science. Better understanding of protein folding principles will be achieved by studies on structurally extended peptide foldamers containing tertiary structures. Structural insight in the three-dimensional arrangements formed by α/β-peptides will also be made. The developed methodology of building structurally complex molecules with feasible synthesis could find several applications in various fields of science and technology including: medicinal chemistry, catalysis, material science and nanotechnology. In particular, the use of structurally extended peptide foldamers for development of protein-protein interaction inhibitors will be evaluated. This approach will be particularly useful in the most problematic cases where no specific binding clefts in protein targets are present. Finally, the found PD-1/PD-L1 interaction inhibitors could find the application for cancer immunotherapy.