Development of tools for the rational design of peptide therapeutics

Discovery and design of peptide drugs is currently a very active research area that has wide applications in addressing unmet medical needs. Peptides attract much attention as versatile therapeutic agents because of their good binding affinity, low toxicity, and the capability of targeting traditionally “undruggable” proteins. The discovery of new peptide-based drugs is presently carried out using the vast array of new technologies. Among them, metabolomic, proteomic, and genomic screenings can identify bioactive peptides that require further structural characterization. Determining the structural details of protein–peptide complexes is fundamental for the understanding of the molecular mechanisms underlying protein–peptide recognition and the design of peptide therapeutics. However, the experimental characterization can be very challenging because of the complex and dynamic nature of protein-peptide interactions. Hence, in the last year’s we observed rapid development of computational tools for protein-peptide docking, that is predicting the binding structures of protein–peptide complexes, as the alternative or supporting guidance tools for experimental techniques.

The main goal of this project is to develop new computational tools for rational, structure-based, discovery, and the design of peptide therapeutics based on protein-peptide docking. The project will stem from the well-established protein-peptide docking method developed in our laboratory, the CABS-dock. The new tools will include machine-learning scoring functions for the selection of the best models from the myriads of generated models and protocols for template-driven docking and cyclic peptide docking. The developed tools will be integrated with each other to form larger workflows for the prediction of protein-peptide complexes and high-throughput screening. Our goal is to outperform existing docking protocols, especially for complexes in which receptors undergo large conformational changes upon binding. Within the project, the tools will be applied and tested in peptide design for cancer immunotherapy and other therapeutic applications.

The developed tools will be made available to the scientific community as freely-available web services. In addition, they will be implemented as standalone applications, which will run on a regular computer or on a supercomputer in a parallel manner for massive computations. Our project aims also to facilitate the integration of the developed solutions with other computational tools that may enhance the overall accuracy or enrich our knowledge by additional analyses. In time, we expect that such the integrative structure-based analyses will become essential to peptide target prediction and design of peptide therapeutics.