The influence of non-trivial topology on protein degradation by ClpXP in the context of degron design

Protein degradation is a process that helps maintain cellular homeostasis and regulates several biological activities. When protein degradation is dysregulated, it may trigger diseases such as breast, colon, lung, and prostate cancers. In cancers, certain proteins that are involved in cell growth, survival, and proliferation are often overexpressed or mutated. As a consequence, an uncontrolled cell growth and tumor formation occurs. Therefore, targeting protein degradation pathways present a promising approach for cancer therapy.

Understanding the mechanisms of protein degradation and their regulation is crucial in many fields, such as in biomedicine, biotechnology, and molecular biology. In this project, I aim to explore protein degradation pathways using ClpXP, a member of the Clp/Hsp100 family of ATP-dependent proteases, in degrading knotted proteins by designing novel degrons. ClpXP recognize and degrade proteins that are misfolded, damaged, or no longer needed by the cell. This process is facilitated by the presence of specific degradation signals, known as degrons. Therefore, degradation mechanisms will be investigate using experimental and computational approach and machine learning techniques to design new degrons based on a survey of existing data.

Knotted proteins pose a natural challenge for the degradation systems like ClpXP. Especially, proteins with complex knots like double-knots, 8_3 knotted protein, helical knotted protein, selonoid protein with knot. These non-trivial topologies were considered unrealistic for many years because such a configuration would be too complicated. However, our laboratory has recently determined protein structure with these topologies and the degradation mechanism for TrmD-Tm1570, a double-knotted protein. Understanding the degradation mechanism for such complex structures, combined with novel degrons, may help identify short amino acid sequences or specific structural features, which can be recognized by the ClpXP protease to maintain cellular proteostasis and prevent the accumulation of non-functional proteins. These discoveries may also lead to new developments in several other disciplines - in particular, in medicine and protein engineering.

The project will be carried out at the Center for New Technologies, which brings together various experimental and theoretical experts, specialists in the topology of non-trivial proteins. This will allow me to independently develop my own ideas under the guidance of experts. The Principal Investigator can successfully tackle the problem, protein degradation by ClpXP and design a novel degron, due to his broad experience in protein folding, topological properties, protein degradation, and machine learning.