Computational Approaches to Bridge Linear and Cyclic Peptides in Drug Discovery

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Cyclic peptides offer advantages over their linear counterparts in drug discovery, including enhanced stability, resistance to enzymatic degradation, and improved binding specificity. However, experimentally assessing ligandability is often more straightforward with linear peptides. The challenge arises in converting these findings into cyclic peptides, as structural constraints introduced by cyclization can significantly alter binding affinity, conformation, and overall drug-like properties.

To address this, we have developed an AI-driven tool integrated into our Mexa software, combining computational molecular modeling with intelligent design principles. This tool enables the transformation of experimentally validated linear peptides into cyclic analogs while preserving or improving their therapeutic potential.

Additionally, we incorporate AI-supported methods to integrate non-canonical amino acids (ncAAs) into peptide sequences, expanding the available chemical space. By predicting the impact of ncAAs on binding affinity, stability, and bioavailability, we can systematically explore their role in optimizing therapeutic properties.

In this talk, we will present applications of this approach to various drug discovery challenges, including competitive inhibition and protein-protein interactions, and discuss the broader implications for peptide-based therapeutics.