Development of cyclic peptides that are orally available

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My laboratory is engaged in the discovery and development of cyclic peptides for therapeutic application. In recent years, we have started to address the long-standing goal of developing orally available peptides. Towards this end, we focus on generating cyclic peptides that have a rather small size (< 700 Da) and a limited polar surface so that they have a high chance of passively crossing membranes and thus being orally available.

For generating sub-kilodalton cyclic peptides that bind to disease targets of interest, we have established an approach based on nanomole-scale cyclic peptide synthesis and high-throughput screening (1, 2, 3). In brief, we produce thousands of peptides by solid phase peptide synthesis and diversify them combinatorially with a myriad of chemical building blocks in 1,536-well plates. In this approach, the peptides and chemical building blocks are transferred in nanoliter volumes by acoustic dispensing and the reactions performed at a nanomole scale, allowing the synthesis and screening of ten-thousands of cyclic peptides in a short time.

In my talk, I will explain the cyclic peptide library synthesis and screening approach, show examples of libraries and their screening, and present nanomolar ligands that we have developed against different proteins, including a protein-protein interaction target.

[1] S. Kale, *et al.*, Science Advances. 2019, 5 (8).
[2] G. Sangouard, *et al.*, Angewandte Chemie Int. Ed. 2021, 60 (40).
[3] S. Habeshian, *et al.*, Nature Communications. 2022.

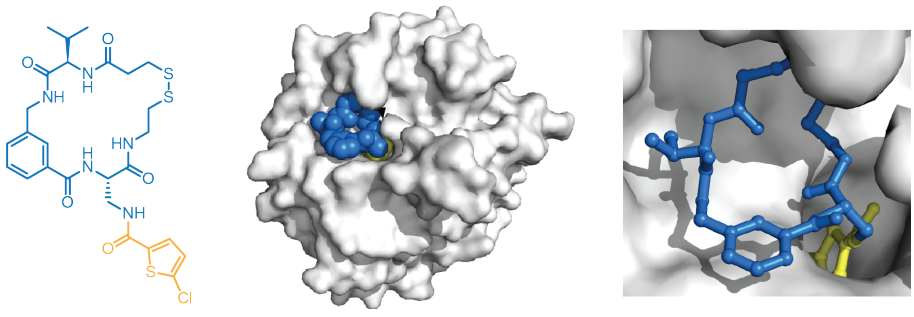

Figure: Target-selective cyclic peptides at the edge of the rule-of-five developed for oral application.