Membrane-permeable cyclic peptides for intracellular targets and oral delivery

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Our laboratory is involved in the discovery and development of cyclic peptides for therapeutic applications. In recent years, we have begun to address the long-standing goal of developing target-specific peptides that are membrane-permeable and orally available. To this end, we are focusing on the generation of cyclic peptides that have a relatively small size (< 1 kDa) and a limited polar surface area, so that they have a high chance of passively crossing membranes.

To generate 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 of crude products (1, 2). In short, we generate thousands of peptides by solid-phase peptide synthesis and combinatorially diversify them by reacting them with a myriad of chemical building blocks. In this approach, all reagents are transferred in nanolitre volumes by acoustic dispensing and reactions are performed at the nanomole scale, allowing tens of thousands of cyclic peptides to be synthesized and screened in a short time. Recently, we have shown that cyclic peptides developed using this approach can achieve good oral availability (3).

In my talk, I will explain the approach to the synthesis and screening of cyclic peptide libraries, show examples of libraries and their screening, present nanomolar ligands we have developed against different proteins. In addition, I will present recent learnings about the structure-membrane permeability of cyclic peptides.

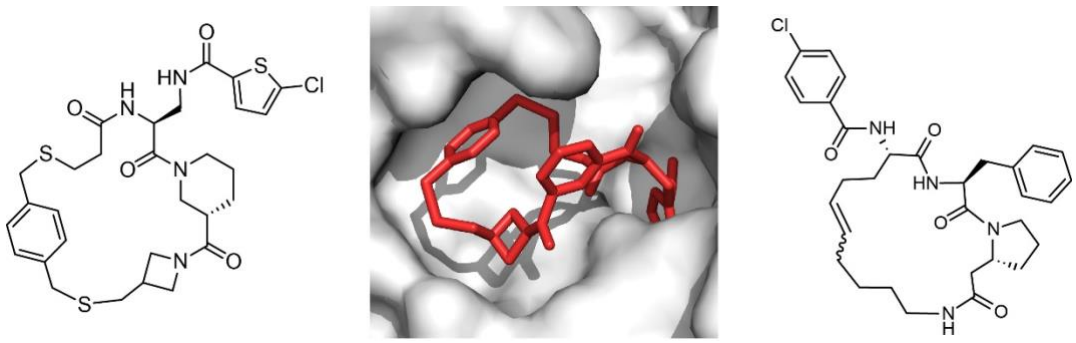

Figure: Structures of membrane permeable and orally available thrombin inhibitors identified by screening ten-thousands of random small synthetic peptides.

[1] S. Kale, et al., Science Advances. 2019, 5 (8).
[2] S. Habeshian, et al., Nature Communications. 2022, 13 (3823).
[3] M.L. Merz, et al., Nature Chemical Biology. 2024, 20 (5).