Generating and screening large libraries of cyclic peptides for drug development

Christian Heinis

Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
christian.heinis@epfl.ch

Our 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 target-specific peptides that are membrane permeable. Guided by membrane permeable cyclic peptides identified in nature, we focus on generating cyclic peptides that have a rather small size (< 1000 Da) and a limited polar surface so that they have a high chance of passively crossing membranes.

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 by reacting with a myriad of chemical building blocks. 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, present nanomolar ligands that we have developed against different proteins, including a protein-protein interaction target, and show data about the membrane permeabiltiy of the peptides.

[1] S. Kale, et al., Science Advances. 2019, 5 (8).
[2] S. Habeshian, et al., Nature Communications. 2022, 13(1).
[3] M. Merz, et al., Nature Chemical Biology. 2023.