Peptide Discovery using CLIPS™ Phage Display (PDL)

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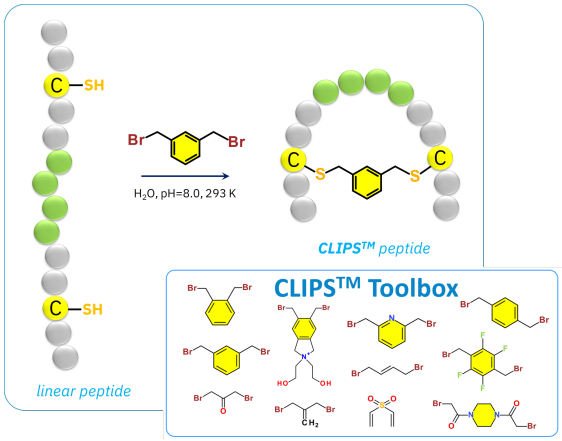
Cyclic peptides are an attractive molecular format for the development of therapeutics [1]. Currently, only a handful of these are used in the clinic, including the somatostatin-derived anti-cancer drugs *Lantreotide* and ^{177}Lu-DOTATOC [2], which is used in **P**eptide **R**eceptor **R**adionucleotide **T**herapy (**PRRT**), as well as the natural immune-suppressant *cyclosporin*. In this lecture, e present here a high-throughput phage display platform for the identification of *de novo* CLIPS™ peptides against a target protein of choice. A similar mRNA-based platform was used for the discovery of Merck's oral *anti*-PCSK9 inhibitor *enlicitide chloride* (previously known as MK-0616) that is currently in Phase-III clinical trials.



In this lecture, we present a few case examples where this platform was used. The first example involves the identification of a series of CLIPS™ peptide binders to the monoclonal antibody Infliximab (Remicade™), a clinically approved mAb to treat autoimmune diseases, like Rheumatoid Arthritis (RA) and Crohn's Disease (CD). Another example involves a mirror-image PDL-project in collaboration with the University of Maastricht, where we identified a series of sub-nM all-D CLIPS™ binders against the C-X-C motif *L*-CXCL8. All CLIPS™ binders exclusively recognize the *L*-form of CXCL8 and not the *D*-form. Yet another example involves our first selection campaign with our novel tricyclic CLIPS™/CLICK-technology platform that we published in 2018 [2]. Selection against a benchmark membrane protein target delivered a ~50 nM tricycle-peptide that shows strong binding to live cells that overexpress the same target on their cell membranes. The final case example also describes a new technological development in our lab, *i.e.* biopanning on live cells in Phage Display. Using the same benchmark protein receptor we identified a set of 7 strong binders that showed binding in FACS of cells overexpressing the membrane receptor. This new technology is of growing interest to identify CLIPS™ binders against target proteins that do not fold properly when expressed recombinantly.

[1] V. Baeriswyl, C. Heinis, *ChemMedChem* **2013**, *8*, 377-84.
[2] U. Heinrich, K. Kopla, *Pharmaceuticals* **2019**, *12(3)*, 114, 1-8.
[3] G. J. J. Richelle, S. Ori, H. Hiemstra, J. H. van Maarseveen, P. Timmerman, *Angew. Chem. Int. Ed.* **2018**, *57(2)*, 501-5.