Phage selection of potent and selective ligands based on bicyclic peptides

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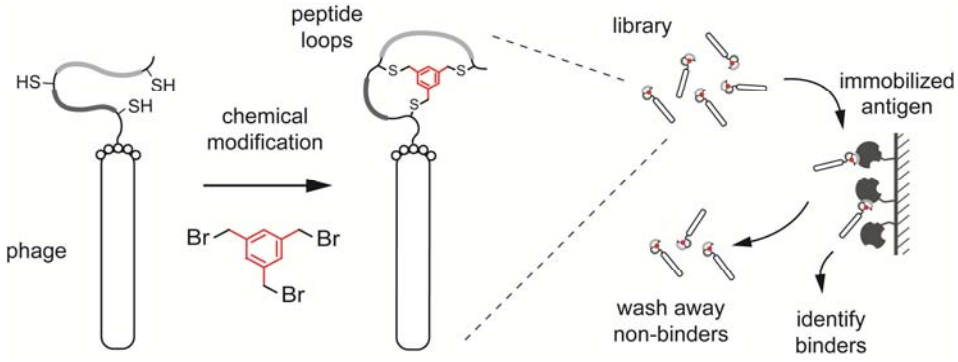
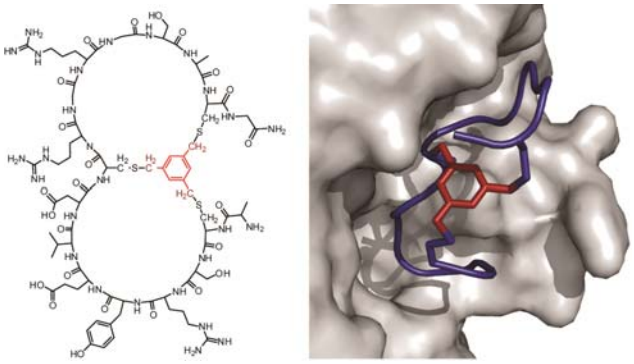
My laboratory at the Ecole Polytechnique Fédérale de Lausanne (EPFL) is developing bicyclic peptide ligands with high affinity and specificity for disease targets using an approach that I had developed with Sir Greg Winter at the Laboratory of Molecular Biology (LMB) in Cambridge, UK (1). Briefly, linear peptides on phage are chemically modified to obtain phage-encoded combinatorial libraries of bicyclic peptides and binders are isolated in affinity selections. With this approach, inhibitors with nanomolar affinites to human disease targets could be generated. The bicyclic peptides combine key qualities of antibody therapeutics (high affinity and specificity) and advantages of small molecule drugs.



Recently, we have developed a bicyclic peptide inhibitor of the cancer-associated protease urokinase-type plasminogen activator (uPA). X-ray crystallography of the complex revealed a large contact interface between the bicyclic peptide and the target.



(1) Heinis, C., Rutherford, T., Freund, S., Winter, G., Phage-encoded combinatorial chemical libraries based on bicyclic peptides. *Nat. Chem. Biol.* (2009).

(2) Angelini, A., Cendron, L., Chen, S., Touati, J., Winter, G., Zanotti, G. and Heinis, C. Bicyclic peptide inhibitor reveals large conact interface with protease target. *ACS Chemical Biology*. (2012)