Development of orally available peptide macrocycles by phage display

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A major challenge in the pharmaceutical industry is the development of orally available peptide-based therapeutics.[1] The oral delivery of protein and peptide drugs is mainly limited by their proteolytic degradation and the poor absorption across the intestinal epithelia.[2] In this work, we have developed a method for the screening of proteolytic-resistant peptide macrocycles by phage display. In brief, peptides displayed on phage are cyclized in a chemical reaction, exposed to pancreatic proteases, and subjected to affinity selections. Affinity selections against the therapeutic target Factor XIa yielded potent inhibitors with K_is below 10 nM. Due to the protease pressure during phage display, the peptide macrocycles showed half-lifes of > 2 hours in presence of intestinal proteases at physiological concentration (10 mg/mL). Work is ongoing to test the oral availability of the cyclic peptide Factor XIa inhibitor in mice.

[1] K. Fosgerau and T. Hoffmann, *Drug Discovery Today*, **2015**. 20, 122-128.
[2] J. Wang, V. Yadav, A. L. Smart, S. Tajiri, A. W. Basit, *Molecular Pharmaceutics,* **2015**, 12, 966-973.