Gut-stable peptide therapeutics

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Peptides have emerged as a therapeutically and commercially important drug class with the advantage of great specificity and potency as well as low toxicity. Peptides are furthermore invaluable research tools to investigate the physiological functions of receptors and the underlying mechanisms of diseases. Peptide research has innovated the treatment of numerous diseases including diabetes, cancer, multiple sclerosis, gastrointestinal disorders, obesity and pain, with >75 peptide therapeutics approved and >150 peptides in clinical trials [1].

A main limitation of peptides is their intrinsic susceptibility to proteolytic degradation and lack of oral bioavailability. However, multiple endogenous peptide families exist that are expressed in the gastrointestinal tract, arguably the most hostile environment for peptides. We are particularly interested in the structural makeup of these peptides to understand how they can function in such an environment and how we can take advantage of this knowledge to develop gut-stable peptide therapeutics. We recently investigated the trefoil factor family (TFF), which comprises three peptides (TFF1-3) with a rigid disulfide bond-stabilised multiloop structure, reminiscent of a trefoil [2,3]. They are important gut peptides mediating gastrointestinal protection and repair, with promising therapeutic potential for the treatment of gastrointestinal disorders. We further systematically studied several naturally occurring peptide scaffolds and medicinal chemistry approaches to identify motifs and strategies for the development of next-generation orally administrated peptide therapeutics for gut-specific treatment of gastrointestinal disorders [4].

References:

[1]. Muttenthaler M...Alewood PF. Trends in peptide drug discovery. Nature Reviews Drug Discovery 2021,20,(4),309.

[2]. Braga Emidio N…Muttenthaler, M. Trefoil factor family: unresolved questions and clinical perspectives. Trends in Biochemical Sciences. 2019,44,(5),387.

[3]. Braga Emidio N…Muttenthaler M. Chemical synthesis of TFF3 reveals novel mechanistic insights and a gut-stable metabolite. Journal of Medicinal Chemistry. 2021,64,(13),9484.

[4]. Braga Emidio N…Muttenthaler M. Improving the gastrointestinal stability of linaclotide. Journal of Medicinal Chemistry. 2021,64,(12),8384.