Oral gut-specific peptide therapeutics

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Abstract

Irritable bowel syndrome (IBS) and inflammatory bowel diseases (IBD) are chronic gastrointestinal disorders affecting over 10% of the global population. Despite their growing prevalence, effective treatments remain limited, and disease mechanisms are poorly understood. Our research focuses on new therapeutic strategies to treat these disorders using orally active and gut-restricted peptides, a new frontier in peptide drug development.[1,2]

In recent work, we targeted oxytocin receptors upregulated in colonic nerves in IBS/IBD-associated abdominal pain. Using state-of-the-art medicinal chemistry, we developed gut-stable oxytocin-based drug leads that potently alleviated pain in preclinical mouse models when administered orally.[2]

We are also interested in the underlying causes of gut disorders. In a clinical study, we revealed a high prevalence of bacterial biofilms in IBS and IBD patients linked to gut microbiome dysbiosis and disease development.[3,4] We are now targeting these gut biofilms with nature-derived antibiofilm peptides and developing them for oral administration.

Another strategy is understanding how endogenous peptides can function in the hostile environment of the gut. The trefoil factor family (TFF) is particularly interesting as these disulfide-rich mini-proteins play key roles in gastrointestinal protection and repair.[5] Studying the TFF and other stable peptide scaffolds has led to new strategies for developing gut-specific peptide therapeutics,6 representing a major step forward in the field of oral peptide drug development and holding great promise for improving the lives of patients suffering from chronic gastrointestinal disorders.

[1] Nature Reviews Drug Discovery 2021 20 (4) 309-325
[2] Angewandte Chemie Int. Ed. 2024 63 (52) e202415333
[3] Clinical Microbiology Reviews 2024 37 (3) e00133-23
[4] Gastroenterology 2021 161 (4) 1245-1256
[5] Trends in Biochemical Sciences 2019 44 (5) 387-390
[6] Journal of Medicinal Chemistry 2022 65 (8), 6191-6206

Biography

Prof Markus Muttenthaler is an ARC Future Fellow heading the Neuropeptide Research Lab at the Institute for Molecular Bioscience at the University of Queensland, Australia, with a second affiliation at the Institute of Biological Chemistry at the University of Vienna, Austria. He is a medicinal chemist working at the interface of chemistry and biology with a strong passion for translational research. His research focuses on bioactive peptides and exploring nature's biodiversity to develop molecular tools, diagnostics and therapeutics. His background in peptide drug discovery and development, as well as his interdisciplinary training in the fields of chemistry, molecular biology, and pharmacology, assist him in the characterisation of these highly potent and selective compounds and allow him to study their interactions with human physiology for medical innovations in pain, cancer, and neurological and gastrointestinal disorders.