Technology offer:
New serine protease inhibitors to treat visceral pain for preclinical drug testing

The University of Antwerp has developed an in vivo proof of concept with serine protease inhibitors in a validated gastrointestinal IBS model for visceral pain. Pharmaceutical companies looking to further test these preclinical candidates for further development in visceral pain-related pathologies can benefit from this established expertise.

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LEMP
Laboratory Experimental Medicine & Pediatrics
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Situation before

Visceral pain or hypersensitivity is a well-known problem in *e.g.* the irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). Currently no therapeutic strategies are available that work through normalizing the visceral pain sensation. The presence of huge unmet needs is a result of the lack of a significant number of drugs approved by the FDA: for the treatment of IBS there are only four approved medications on the market. The use of off-label drugs is also a common practice but causes several adverse side effects.

Serine proteases have been suggested to play a role in the pathogenesis of visceral hypersensitivity, a major factor contributing to visceral pain. Serine proteases function as signaling molecules through the activation of protease-activated receptors (PARs). PARs belong to the G protein-coupled receptors (GPCRs) family. A series of enzymes are reported to activate PAR2 and PAR4. Therefore a multi-target compound seems highly desirable in order to target several of the PAR activating enzymes simultaneously. Until recently, no small drug-like molecule serine protease inhibitor has shown a therapeutically relevant effect in an in vivo model related to visceral pain specifically, except for nafamostat, a broad spectrum serine protease inhibitor which also inhibits blood coagulation, hence more selective serine protease inhibitors are highly needed.

Technology

UAntwerp: A collaboration between the Laboratory of Medicinal Chemistry (UAMC) and the Laboratory of Gastroenterology and Hepatology (part of LEMP) resulted in an *in vivo* proof of concept with a well-defined multi-target **serine protease inhibitor**, identified from a diverse library of around 300 serine protease inhibitors, on a validated in house model for IBS.

About the researchers - research group

The Laboratory of Gastroenterology and Hepatology (LEMP, Prof. B. De Winter, www.uantwerpen.be/lemp) has elaborate expertise in the study of gastrointestinal motility and sensitivity and in the immunological mechanisms of intestinal inflammation. They have several experimental gastrointestinal models to measure GI inflammation in an acute, chronic and/or post-inflammatory setting: (i) rat and mouse TNBS and DSS colitis, (ii) mouse chronic colitis transfer model and (iii) the golden standard septic model of caecal ligation and puncture (CLP). They are well equipped to measure in vitro GI contractility, peristalsis, in vivo motility, next to permeability assays, and pain assays including the visceromotor response (VMR) and in vitro afferent nerve recordings.

The **University of Antwerp Medicinal Chemistry** (UAMC, Prof. K. Augustyns, https://www.uantwerpen.be/en/rg/medch) has all the necessary expertise to run chemical optimization programs and drive projects towards the 'quality lead' stage: the team has state-of-the-art facilities for *in silico* molecular design, synthesis and analysis (400 MHz NMR, 2 UPLC-MS), biophysics/enzymology (SPR, microtiterplate readers, protein analysis,) and ADME/PK experiments.

LEMP and UAMC belong to the research Consortium of Excellence Infla-Med at the University of Antwerp which performs preclinical research in the field of inflammatory diseases. UAMC also belongs to the Antwerp Drug Discovery Network (ADDN).

LEMP and UAMC are partners of the **FWO-SBO project 'TRP channel sensitization as target for treatment of hypersensitivity'** in collaboration with the University of Leuven (2017-2020).

More information

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