The motilin receptor (MLNR) has been identified as a target for gastroparesis (GP) disorders including gastroparesis, postoperative ileus and functional dyspepsia along with the Ghrelin receptor. The incidence of GP is not well described; however, the number of individuals affected by symptoms of GP in the United States is estimated to be over 4 million. The etiology of GP is diverse. Approximately 25% of cases are associated with diabetes, whereas nearly 50% are classified as idiopathic. The motilin receptor is a Gq/11-protein-coupled receptor that mediates prokinetic effects. It is found at its highest concentrations in the nerves of the antral wall of the stomach and is also found at significant levels throughout the smooth muscle of the upper GI tract.

Presently there are no compounds useful in the clinic which have overcome the tachyphylaxis issue associated with β-arrestin pathway. Domperidone (D2 antagonist), Metoclopramide (black box warning for neurological issues) and Erythromycin, an antibiotic with loss of efficacy after 4 weeks due to tachyphylaxis.

1. Motilin is the natural peptide ligand for the motilin receptor which was aptly named due to its ability to stimulate gastric activity.
2. Agonism of motilin results in activation of PLC resulting in IP₃ induction and DAG as motilin is a Gq linked GPCR.

No knock out data
There are no useful KO rodent models of motilin as the gene is not native to rodents and exists as a pseudo gene.

In vivo assays
There is a rodent model using a house musk shrew (Suncus murinus), however these are not readily available and will require assay development. In lieu of a model for primary in vivo screens, an organ bath model analyzing contractile responses using rabbit tissue can be utilized to evaluate compounds for efficacy. Compounds of interest can be verified in a human tissue organ bath model.

Desired compound profile
Identify a small molecule which is G-protein biased to avoid internalization associated with β-arrestin recruitment/activation.
1. G-protein: Ca²⁺ EC₅₀ < 100nM, Eₘₐₓ=100%
2. β-arrestin: EC₅₀ >1000nM, Eₘₐₓ <20%

Tool compounds are available.

References

