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Translational modeling in Irritable Bowel Syndrome (IBS)

Angelean Hendrix
Associate Director, Quantitative Clinical Development
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Irritable bowel syndrome is a relatively common gastrointestinal illness characterized by a constellation of clinical symptoms including abdominal pain and discomfort, abnormal bowel habits, and bloating (Camilleri, 2012; Halland and Talley, 2013; Longstreth et al., 2006). Most authors in the field agree that the sensory inputs/outputs in the peripheral and central nervous system are altered in such a way that a patient with IBS has a heightened and disproportionate sensory experience for a given stimulus, i.e. visceral hypersensitivity which drives a patient to seek medical care. Therefore, an agent that significantly ameliorates visceral hypersensitivity, a major contributor to the reduced quality of life of IBS patients, is greatly needed.

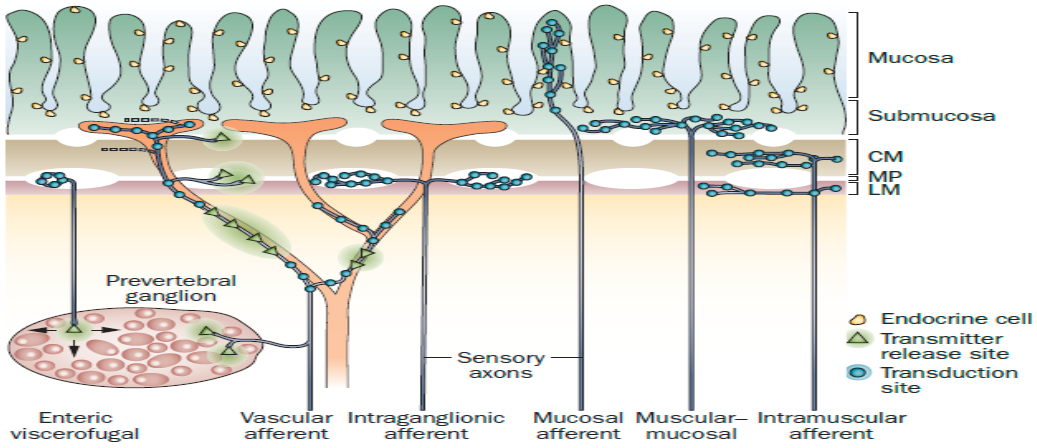

Figure 1. Five Different Types of Enteric Neurons
Enteric neurons can be characterized by the tissue layers they innervate, their structure and the stimuli to which they respond.

Typically, preclinical support for compounds includes pharmacokinetic investigations which typically identify correlative evidence between plasma concentrations biomarkers of engagement and/or efficacy. These are then used to determine dose regimens for FTIH (first time in human) studies. For this particular development program, no such relationship was identified, yet animal studies were very promising. As the target tissue was intestinal, the team decided that tissue concentrations were of utmost importance for dose selection. A simple systems model of gut transit and tissue absorption was developed as an extension of Bergstrand et al. The model's application to multiple compounds has been invaluable to the program, but revealed the need for additional work on the specific tissue gradient and metabolism.

Abstract Information (continued)

This project will attempt to address these limitations to the model with the goal of becoming identifiable, interfacing with traditional PK modeling, focused on clinically relevant endpoints, and translating animal data to human. The project will use dynamical systems modeling, parameter identification and estimation using sparse data, and some light statistical theory, with a focus on understanding the biological mechanisms and how to translate them into a working model.

Suggested Reading and Biological Background:

Camilleri, M. (2012). Peripheral mechanisms in irritable bowel syndrome. The New England journal of medicine *367*, 1626-1635. https://www.ncbi.nlm.nih.gov/pubmed/23094724

DeSesso, J.M., and Jacobson, C.F. (2001). Anatomical and physiological parameters affecting gastrointestinal absorption in humans and rats. Food Chem Toxicol *39*, 209-228. https://www.ncbi.nlm.nih.gov/pubmed/11278053

Identifiability: http://www4.ncsu.edu/~smsulli2/Slides/Identifiability.html
Finding CI in Matlab: https://www.mathworks.com/help/stats/nlparci.html