‘All disease begins in the gut’. So said Hippocrates, many years ago. We now realize the wisdom of those words, with our appreciation of the microbiome, the influence it has on our general health and well-being, and its association with diseases as diverse as diabetes and autism. In this lecture, I will talk of our studies related to a receptor guanylyl cyclase (GC-C) expressed in the gut which serves as the target for bacterial toxins that cause diarrhoea. I will discuss our attempts to understand the allosteric regulation of this multi-domain receptor, and its role in regulating intestinal cell proliferation. Finally, I will talk of our work on discovering and characterizing human mutations that are correlated with congenital secretory diarrhoea, and our attempts to generate novel transgenic mice to understand the molecular bases of this severely debilitating disorder.