MICROBIOME

We study the impact of the human microbiome on health and disease. Through the founding of the Center for Microbiome Innovation in 2015, UCSD has made the commitment to be a world leader in microbiome research. Although considerable progress has already been made in linking the microbiome to patient stratification in human disease, understanding mechanisms of action and of interaction between microbe and host will require a proteomics view, and recent advances in mass spectrometry hardware, labeling techniques for multiplexing samples, and analysis software, including those pioneered by the Gonzalez laboratory, are now enabling such studies to performed for the first time: ***(Singh et al., Cell 2018), (Mills et al., mSystems 2019), (Quinn et al., Microbiome 2019), (Tran et al., Molecular & Cellular Proteomics 2019), (O'Neill et al., Journal of Investigative Dermatology 2019), (Mills et al., Genome Research 2020), (Golonka et al., Am J Physiol Gastrointest Liver Physiol 2020), (Chandrashekar et al., PLoS One 2020).***

More recently, to address the lack in understanding of how the microbiome contributes to Ulcerative colitis (UC), an inflammatory bowel disease (IBD), we recently performed an unprecedented bioanalytical experiment that integrated six -omic data sets from 40 patient-matched fecal and serum samples with a wide range of clinical severity. The six datasets provided powerful evidence towards a central hypothesis of proteolysis co-occurring with increased disease activity. Metaproteomics pinpointed *Bacteroides vulgatus* proteases as a distinguishing feature of severity. Shotgun metagenomics guided taxonomic inferences and revealed that the *B. vulgatus* association was driven primarily by protein regulation as opposed to microbial abundances. Serine protease inhibitors found in the patient serum suggested the importance of proteases. The metapeptidome showed that increased peptide fragments correlated with UC disease severity. A separate 210-person validation cohort confirmed the connection between *B. vulgatus* proteases and UC severity. Our strong *in vitro* and *in vivo* data suggest that *B. vulgatus* can indeed disrupt human colonic epithelia, induce colitis in monocolonized IL-10 deficient mice, and that transplantation of fecal material from UC high severity patients into an established IBD mouse model resulted in increased colitis phenotypes. Notably, administration of protease inhibitors attenuated disease severity in both *in vitro* and *in vivo* settings. Moving forward, our main hypothesis is that over-activated proteases from *B. vulgatus* are a major cause of elevated UC severity levels, and a better mechanistic understanding of how these proteases function in pathological situations associated with UC can open the door for protease inhibition as a therapeutic treatment (***Mills et al., in revision***).

DEPARTMENT OF PHARMACOLOGY
9500 GILMAN DRIVE, LA JOLLA, CALIFORNIA 92093-0636 Telephone (858) 822-1218 Fax (858) 822-0041