MICROBIOME

We study the impact of the microbiome on health and disease. Through the founding of the Center for Microbiome Innovation in 2015 (https://cmi.ucsd.edu/), 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 in 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), (Gonzalez et al., Microbiome 2022), (Russell et al., Cell 2022)**. More recently, to understand how host–microbiota interactions become disrupted in Ulcerative Colitis (UC), an inflammatory bowel disease (IBD), we collected and analyzed six fecal- or serum based omic datasets (metaproteomic, metabolomic, metagenomic, metapeptidomic and amplicon sequencing profiles of fecal samples and proteomic profiles of serum samples) from 40 UC patients at a single inflammatory bowel disease centre. Various clinical, endoscopic and histologic measures of disease activity were also collected. A validation cohort of 210 samples (73 UC, 117 Crohn's disease, 20 healthy controls) was collected and analyzed separately and independently. Data integration across both cohorts showed that a subset of the clinically active UC patients had an overabundance of proteases that originated from the bacterium *Bacteroides vulgatus*. To test whether *B. vulgatus* proteases contribute to UC disease activity, we first profiled *B. vulgatus* proteases found in patients and bacterial cultures. Use of a broad-spectrum protease inhibitor improved *B. vulgatus*-induced barrier dysfunction *in vitro*, and prevented colitis in *B. vulgatus* mono-colonized, IL10-deficient mice. Furthermore, transplantation of feces from UC patients with a high abundance of *B. vulgatus* proteases into germ-free mice induced colitis dependent on protease activity. These results, stemming from a multi-omics approach, improve understanding of functional microbiota alterations that drive UC and identify other pathways that could be inhibited as a strategy to treat this disease **(*Mills & Dulai et al., Nature Microbiology 2022*)**. *Mills & Dulai et al.* has been highlighted in several independent commentaries and a patent was filed by UCSD on this important work, which was licensed by Precidig Inc. This project has **received funding through an NIH R01 NIDDK (2022-2025 funding period)**.

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