MODELLING OF GASTROINTESTINAL FOOD AND DRUG ADSORPTION

Raffaele Mennella – Advisor: Prof. Paolo Antonio Netti

Curriculum: Ingegneria dei Materiali e delle Strutture

The gut is inhabited by a complex set of microorganisms, generally called gut microbiota, whose architecture depends upon many factors and has proven effects on host health (Thursby et Juge, 2017). Once absorbed by the intestinal epithelium, the products of degradation by gut microbes flow to the liver where they are rapidly metabolised and eventually converted into other compounds via pathways such as gluconeogenesis or adipogenesis (Oliphant et al., 2019). The intestinal mucosa is constantly exposed to these complex microbial communities that contain commensal microorganisms and microbes with pathogenic potential that, in general, contribute to normal intestinal homeostasis. This host-microbiota crosstalk allows the induction of protective responses to pathogens and the maintenance of tolerance to innocuous antigens. However, overuse of antibiotics, changes in diet composition, or psychological and physical stress may cause microbial dysbiosis that contributes to the development of multiple intestinal bowel diseases including the most common irritable bowel syndrome (IBS) that can alter the physiological environment and function, influencing the intestinal mucosal cell biology and microbial behavior.

Approaches to modulate the gut microbiome therapeutically or nutritionally to treat disease pathogenesis are receiving a lot of interest. Previous research on microbiome-host interactions and consequences were based on the analysis of human faecal samples or on animal-based experiments. Here, genome approaches such as metabolomics and metagenomics were used to extrapolate information on this complex environment (Shoaie et al., 2013). However, this methodology does not perfectly recapitulate the dynamics between microorganisms and gut barrier. For this reason, to further interrogate this complex crosstalk, new in vitro models, namely microphysiological systems or organs-on-chip, have been developed. These small representations of the human physiology better recreate the intricate 3D architecture by using expertise in microfluidics, cell culture techniques, microbiology, and analytical skills. Several approaches have been recently utilised to reproduce models of the intestine integrating with gut microbiome (Jalili-Firoozinezhad et al., 2019).

In this perspective, here we aim to apply innovative bioengineering principles to develop *in vitro* a gut-microbiome-on-chip model with human gut tissue including live microbiome (commensal and/or pathogens) to truly capture the human situation in health and illness -IBS- conditions. The realization of a strumentalized gut-microbiome-on-chip device will be able to control tissue context and microenvironment by recapitulating the cellular, molecular and physical cues that highly affect the biological response of the tissue *in vivo*. The gut-microbiome-on-chip provides a dynamic and controlled environment to quantitatively and qualitatively assess the interactions between the gut and live microbiota. Key analytical functions of gut-microbiome on-chip can be analyzed including the mucosa-associated microbiota evaluation, the intestinal barrier function as well as the microbiota diversity in pathophysiological conditions. Furthermore, the implementation of the gut-microbiome-on-chip device with micro-electrical or mechanical tools can allow us to monitor the resultant changes in microbiota metabolism after pathogenic infection with the final goal to investigate host/microbiota as well as commensal/pathogen microbes interactions in a physiologically relevant *in vitro* context.

Jalili-Firoozinezhad, S., Gazzaniga, F.S., Calamari, E.L. *et al.* A complex human gut microbiome cultured in an anaerobic intestine-on-a-chip. *Nat Biomed Eng* **3,** 520–531 (2019).

Oliphant, K., Allen-Vercoe, E. Macronutrient metabolism by the human gut microbiome: major fermentation by-products and their impact on host health. *Microbiome* **7,** 91 (2019).

Shoaie, S., Karlsson, F., Mardinoglu, A. *et al.* Understanding the interactions between bacteria in the human gut through metabolic modeling. *Sci Rep* **3,** 2532 (2013).

Thursby E, Juge N. Introduction to the human gut microbiota. *Biochem J.* 2017 May 16;474(11):1823-1836.

Raffaele Mennella, PhD student XXXVII cycle, July 2022