Résumé du projet de thèse *(1 page maximum, en anglais)*
Indiquer la participation de chaque co-directeur et structure dans la gestion du projet. Please indicate explicitely the specific contribution of each supervisor to the PhD project.

The intimate association between humans and their microbiota is recognised as a determining element of health while several diseases and disorders involving digestion, the immune response or the nervous system, correlate to alterations in the composition of the intestinal microbiota. The nature of the mechanisms involved remain obscure and studies are strongly needed to delineate the role of individual components, with the goal to re-establish health or prevent disease. An attempt at modulating the gut microbiota is represented by **faecal material transplant** (FMT), which shows excellent clinical results in resolving the recurrence of *Clostridioides difficile* infection. Yet, the mechanism of microbiota transfer and installation, as well as the active transplanted components, are so far unknown.

Viruses represent, after bacteria, the second most abundant microbial component of the intestinal microbiota. Those infecting bacteria, **bacteriophages** (phages), dominate but their role in this ecosystem has been little investigated. They appear to be unique to individuals[2] and stable over time. However, when the physiological conditions of the host deviate from health the viral stability is altered.

Non biological determinants also impact the microbiota, as shown by products from the bacterial metabolism. For example, secondary **bile acids** produced by intestinal bacteria regulates intestinal physiology, inflammation, and microbiota composition.

In this project, we will dissect the efficacy of FMT by assessing the impact of gut bacteria, gut phages and bile acids, alone and in combination, to modulate intestinal inflammation.

The impact of these components will be tested:

(1) *In vitro*: Using cellular models of epithelial and immune cells at **Sorbonne Université** to assess the host response to bile acids and phages.

(2) *In vivo*: Performing TMF on a murine model of gut inflammation from *Salmonella enterica,* which was developed by the two co-supervisors during the M2 internship of the Ph. D. candidate, and that is based on a gnotobiotic mouse model (OMM[12]) hosted at the **Institut Pasteur.**

The results of this doctoral project will include: ***(i)*** the identification of bile acids and phages displaying immunomodulatory properties in cellular models; ***(ii)*** FMT components able to modulate the microbiota composition and; ***(iii)*** FMT components able to modulate inflammation. Together, these results will shed light on the role of each of these factors during FMT and by which mechanism they exert their regulatory action. The possible mechanisms include the predatory action of phages infecting bacteria, bacterial competition, the immunomodulatory properties of phages and /or bile acids and the positive or negative impact of bile acids on bacterial growth. Ultimately, we will propose guidance to develop efficient FMT based on, still overlooked, defined components.

Participation and role of the 2 co-supervisors: The work proposed in this project will directly build on recent tools and knowledge developed by both partners in collaboration. Our preliminary results show that bile acids can modulate both inflammatory markers and the microbiota (bacteria and their phages) *in vitro* and *in vivo*. Luisa De Sordi studies phage and metabolite interactions with gut bacteria and eukaryotic cells and the laboratory at the Centre de Recherche Saint Antoine will assure anaerobic bacterial culture, cell culture and tools for studying microbe/metabolite-host interactions and the host inflammatory responses. Laurent Debarbieux is an expert in the field of phage biology and masters murine models to study phage-bacteria interactions in the gut. He has imported to Institut Pasteur the OMM[12] mouse line that provide the appropriate controlled intestinal environment required for this study and his laboratory will assure the tools for analysing microbial and host markers of intestinal inflammation *in vivo*.