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 gastrointestinal tract integrity is fundamental for maintaining overall body homeostasis, with its disruption leading to diverse health issues. Although the gut can regenerate its epithelium under steady conditions, its capacity to recover from severe damage affecting all cell layers is significantly limited. Utilizing the zebrafish (*Danio rerio*) model, known for its remarkable regenerative capabilities and genetic similarities to mammals, our laboratory has established a method to induce severe gut injury. Our model revealed that the zebrafish larval gut undergoes complete regeneration following total organ transection with functional recovery, including restored peristalsis and nutrient absorption.

Recent studies have underscored the key roles of cytokines in immune modulation and tissue regeneration. Interleukin-26 (IL-26), implicated in human inflammatory bowel disease, remains understudied largely due to its absence in rodent models. To study IL-26 functions in gut homeostasis and regeneration, our laboratory developed the first *il26* knockout zebrafish model. Our data reveal that *il26*$^{-/-}$ show increased gut epithelial proliferation and, enhanced regeneration post-injury but increased mortality. We also discovered that in zebrafish gut, *il26* is primarily produced by innate lymphoid cells and, similar to humans, exhibits intrinsic antibacterial properties. This could potentially affect the composition of the microbiota, indirectly influencing regeneration.

Hypothesis: We hypothesize that IL-26, produced by innate lymphoid cells, modulates the gut regeneration post-severe injury by interacting with the microbiota, affecting both epithelial proliferation and organismal survival.

Objectives: This project aims to dissect the relationship between innate lymphoid cell-derived IL-26 and the gut microbiota, to understand their combined effect on gut regeneration and survival in zebrafish larvae following severe injury. We also aim to explore whether the key findings in zebrafish also take place in mice.

Our specific aims are to:

Aim 1: Reveal the mechanisms by which IL-26 regulates gut regeneration and organismal survival in our new regeneration model after severe gut injury by examining regeneration dynamics using live imaging and gene expression analysis via RNA sequencing.

Aim 2: Determine the role of the microbiota and its interplay with IL-26 in our new gut regeneration model by profiling gut microbiota changes using 16S rRNA sequencing, and performing microbiota transfer experiments to evaluate effects on regeneration efficiency and survival.

Aim 3: Evaluate the role of IL-26 in gut regeneration and microbiota composition in mammals.

Although IL-26 is absent in the mouse, it expresses the IL-26 receptor which can be activated by the human IL-26 protein. In collaboration with Dr. Fabian Guendel (senior postdoc at Gerard Eberl's group, Institut Pasteur), we will evaluate IL-26 role in gut regeneration after inflammation using mice (DSS), and in shaping gut microbiota composition.

In addition, microbiota sequencing (zebrafish and mouse) will be performed in the Pasteur Institute's Biomics Core Facility platform (directed by Marc Monot).

This proposal aims to deepen our understanding of the cytokine-microbiota interplay in gut regeneration, providing a basis for designing novel therapeutic strategies in treating gastrointestinal disorders.