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INTERNATIONAL PhD PROPOSAL

PhD Supervisor full name **Michela Deleidi**

PhD PROPOSAL IDENTIFICATION

PhD Project title	Tackling genetic brain diseases by understanding intestinal neuroimmune interactions
Project Acronym	GEN-GUTBRAIN
Project Keyword	Parkinson's disease, organoids, iPSC, scRNAseq, LRRK2, gut, neuroimmune

LABORATORY PRESENTATION

Laboratory Team Name	Mechanisms and therapy of genetic brain diseases
Department IP	Imagine Institute
Doctoral school	BioSPC
University	Université de Paris
Laboratory website	https://micheladeleidi.wixsite.com/website

PhD PROPOSAL

PhD Supervisor full name	Michela Deleidi
PhD Supervisor position	Group Leader
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PhD Proposal abstract (1000 characters maximum)

Several genes have emerged for their pleiotropic role in the brain and defense against pathogens. Among these, LRRK2 is the most frequent genetic cause of Parkinson's disease (PD) and it has been linked to susceptibility to infections and inflammatory bowel diseases (IBDs). Interestingly, patients with IBDs have an increased risk of PD and they show gut proteinopathy, similar to that observed in PD. Data from the literature and our own observations support the role of LRRK2 in intestinal immune homeostasis and defense against enteric pathogens. By means of human cell lines, patient stem cell-derived organoids, and single-cell sequencing, we aim at identifying genetic determinants of cell type-specific host immune response to intestinal pathogens and their link to PD. This project will integrate competences in neuroscience, immunology, genetics, and microbiology to dissect shared mechanisms among these seemingly unrelated diseases: PD, infections, and IBDs.

PhD Proposal (4000 characters maximum)

Background & preliminary data. Genetic polymorphisms in *LRRK2* have been associated with susceptibility to infections as well as inflammatory bowel diseases (IBDs). Patients with IBDs have an increased risk of PD. Interestingly, Crohn's disease patients show increased a-synuclein levels and aggregation in the gut, similar to that observed in PD patients several years before the onset of motor symptoms. Recent data strongly support the role of LRRK2 in intestinal immune homeostasis and immune defense against *Salmonella Typhimurium*, the most common cause of foodborne gastroenteritis. This project aims at dissecting shared mechanisms among these seemingly unrelated diseases: PD, infections, and IBDs.

Workplan

WP1. *To dissect the role of genetic vulnerability in intestinal inflammation.* To define how IBD and PD risk variants affect responses to intestinal immune triggers, we will use human intestinal epithelial cells, macrophages (MΦs), and patient induced pluripotent stem cell (iPSC) lines carrying PD or IBD-associated SNPs in LRRK2. Furthermore, we will establish iPSC lines from patients with genetic early onset IBD. *Salmonella* will be used to model human intestinal inflammation. Our preliminary data suggest that LRRK2 modulates *Salmonella* entry and survival in human MΦs. Transcriptomic analyses of wild-type and *LRRK2* knockout MΦs will be conducted to identify signaling pathways involved in Salmonella infection. During year 2, data will be validated in patient cells and compared to transcriptomics of human epithelial cell cultures to identify LRRK2 immune signaling networks used by epithelial cells and MΦs to sense and control infection.

WP2. *To generate and characterize a tri-culture intestinal organoid system from LRRK2 PD and IBD patients.* To evaluate the role of gut neuro-immune interactions, we will employ human intestinal organoids (HIOs). To this end, iPSCs will be differentiated into MΦs, enteric neurons, and HIOs. We will trial different cell densities and cell media to best recapitulate the *in vivo* tissue and efficient cell maturation. HIOs will be histologically assessed for cell-type specific markers to ensure model validity.

WP3. *Unveiling the role of intestinal inflammation as a ftrigger of enteric PD pathology*. To dissect the role of intestinal inflammation in gut proteinopathy, we will combine an immune challenge (*Salmonella*) with proteotoxic stress (a-synuclein) in the complex HIOs. Isogenic LRRK2 PD (p.G2019S), CD protective/risk variants, and control iPSCs will be employed to capture specific inflammatory signatures associated with enteric pathology. Organoids will be longitudinally analyzed at the histochemical and biochemical level. To decode cell-specific responses (those of MΦs, epithelial cells, and enteric neurons) to the immune challenge and proteotoxic stress, scRNA-seq will be performed.

Feasibility

As the proposed research builds on the host lab expertise and resources, all the experiments are feasible. This patient-oriented research will benefit substantially from the collaborative environment and platforms at Imagine/SFR Necker (bioinformatics, scRNA-Seq, cell imaging). We plan to collaborate with Nadine Cerf-Bensussan to obtain primary tissues from patients with genetic early onset IBD. The goal is to explore monogenic diseases to identify key mechanisms that initiate and aggravate proteinopathy in the inflamed human gut.

References

Giachino et al, 2022. BioRxiv; Keraditi et al, 2022. PMID: 35853899, Provenzano F, Deleidi M., 2021. PMID: 34284880, Panagiotakopoulou et al, 2020. PMID: 33057020; Shutinoski et al, 2019. PMID: 31554740; Liu et al, 2011. PMID: 21983832; Barrett et al., 2008. PMID: 18587394.

Expected profile of the candidate

We are looking for a highly motivated student with a strong background in neuroscience and immunology. Prior experience with stem cell biology and modelling, basic molecular biology, and bioinformatics is highly recommended.