Tuesday, September 5, 2023

International PhD PPU-IMAGINE Proposal

Call 2023/2024

PhD PROPOSAL IDENTIFICATION

PhD Project title	Unlocking the Potential of Organoids: Diving into Intestinal Neuroimmune Interactions
Project Acronym	ORGANO-DIVE
Project Keywords	Parkinson's disease, organoids, iPSC, neuroimmune

LABORATORY PRESENTATION

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PhD PROPOSAL

PhD Supervisor full name	Michela Deleidi
PhD Supervisor position	DR2
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Number of ongoing PhD students supervised by the Supervisor	1

PhD Proposal abstract (1000 characters maximum)

Several genes have emerged for their pleiotropic roles in the brain and in defense against pathogens. Among these, LRRK2 is the most common genetic cause of Parkinson's disease (PD) and has been linked to susceptibility to infection and inflammatory bowel disease (IBD). Interestingly, patients with IBD have an increased risk of PD and show intestinal proteinopathy similar to that observed in PD. Data from the literature and our own observations support a role for LRRK2 in intestinal immune homeostasis and defense against enteric pathogens. Using human cell lines, patient stem cell-derived organoids, and single cell sequencing, we aim to identify genetic determinants of cell type-specific host immune responses to intestinal pathogens and their association with PD. This project will integrate expertise in neuroscience,

immunology, genetics, and microbiology to dissect common mechanisms among these seemingly unrelated diseases: PD, infections, and IBD.

PhD Proposal (10 000 characters maximum)

Background and preliminary data. Genetic polymorphisms in LRRK2 have been associated with susceptibility to leprosy, mycobacterial infections, and inflammatory bowel disease (IBD). Patients with IBD have an increased risk of developing PD. Interestingly, patients with Crohn's disease show elevated levels of a-synuclein and intestinal aggregation similar to that observed in PD patients several years before the onset of motor symptoms. Data from the literature and our own data strongly support the role of LRRK2 in intestinal immune homeostasis and immune defense against Salmonella Typhimurium, one of the most common causes of foodborne gastroenteritis. Based on these premises, this project aims to dissect common mechanisms among these seemingly unrelated diseases (PD, infections, and IBD).

Workplan

WP1. *To dissect the role of genetic vulnerability in intestinal inflammation.* To define how IBD and PD risk variants affect responses to intestinal inflammatory triggers, human intestinal epithelial cell lines, macrophages (MΦs), and patient induced pluripotent stem cell (iPSC) lines carrying PD or IBD-associated SNPs in LRRK2 will be used. In addition, iPSC lines will be generated from patients with genetic early-onset IBD. Salmonella will be used to model human food poisoning and 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 performed by RNAseq to identify signaling pathways involved in Salmonella infection. In year 2, transcriptomic 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 an organoid model to dissect intestinal neuroimmune interactions.* To evaluate the role of neuro-immune interactions in the gut, we will use human intestinal organoids (HIOs) coupled with microfluidics. The model will be evaluated histologically and functionally to ensure its validity. A gut-brain microfluidic system will also be generated.

WP3. *Unveiling the role of intestinal inflammation as a first insult of enteric PD pathology*. To dissect the role of intestinal inflammation in intestinal proteinopathy, we will combine an immune challenge (Salmonella) with proteotoxic stress in the complex HIOs. The goal is to explore monogenic diseases to identify key mechanisms that initiate proteinopathy in the inflamed human gut. Patient-specific (PD, IBD) iPSCs will be used to capture inflammatory signatures associated with intestinal pathology. Organoids will be longitudinally analyzed at the histochemical and biochemical level. To decipher cell-specific responses (those of MΦs, epithelial cells and enteric neurons) to immune challenge and proteotoxic stress, scRNA-seq will be performed.

Feasibility

As the proposed research builds on the expertise and resources the lab assembled over the past years, all the experiments are feasible. This patient-oriented research will benefit substantially from the collaborative environment and platforms at Imagine/SFR Necker (bioinformatics, single cell RNA-Seq, cell imaging).

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

Laboratory's best 5 publications

1. Baden P, Perez MJ, Kalb S, Raji H, Illescas M, Giuliano C, Bertoli F, Oldrati M, Calogero A, Cappelletti G, Brockmann K, Gasser G, Schapira AHV, Ugalde C, Deleidi M*. “Glucocerebrosidase, a Parkinson´s disease-associated protein, is imported into mitochondria and regulates complex I assembly and function”. Nature Communications, 2023 Apr 6;14(1):1930. doi: 10.1038/s41467-023-37454-4.

2. Perez MJ, Ivanyuk D, Panagiotakopoulou V, Di Napoli G, Kalb S, Brunetti D, Al-Shaana R, Kaeser S, Fraschka SA, Jucker M, Zeviani M, Viscomi C, Deleidi M*. "Loss of function of the mitochondrial peptidase PITRM1 induces proteotoxic stress and Alzheimer’s disease-like pathology in human cerebral organoids". Molecular Psychiatry. 2021 Oct;26(10):5733-5750. Citations:75

3. Panagiotakopoulou V, De Cicco S, Ivanyuk D, Haq W, Arsic A, Yu C, Messelodi D, Oldrati M, Schöndorf DC, Perez MJ, Cassatella RP, Jacobi M, Schneiderhan-Marra N, Nikic I, Gasser T, Deleidi M*. " Interferon-γ signaling synergizes with LRRK2 in human neurons and microglia". Nat Commun. 2020 Oct 14;11(1):5163. doi: 10.1038/s41467-020-18755-4. Citations:53

4. Hallett PJ, Deleidi M, Astradsson A, Smith GA, Cooper O, Osborn TM, Sundberg M, Moore MA, Perez-Torres E, Brownell AL, Schumacher JM, Spealman RD, Isacson O. "Successful Function of Autologous iPSC-Derived Dopamine Neurons following Transplantation in a Non-Human Primate Model of Parkinson's Disease". Cell Stem Cell. 2015 Mar 5;16(3):269-74. Citations: 342.

5. Schöndorf DC, Aureli M, McAllister FE, Hindley CJ, Mayer F, Schmid B, Sardi SP, Valsecchi M, Hoffmann S, Schwarz LK, Hedrich U, Berg D, Shihabuddin LS, Hu J, Pruszak J, Gygi SP, Sonnino S, Gasser T*, Deleidi M *. "iPSC-derived neurons from GBA1-associated Parkinson's disease patients show autophagic defects and impaired calcium homeostasis". Nat Commun. 2014 Jun 6;5:4028. Citations: 484.

Expected profile of the candidate

Expected profile of the candidate
We are looking for a highly motivated student with a strong background in neuroscience and immunology. Previous experience in (stem) cell biology and modeling (organoids) and molecular biology and/or bioinformatics is highly recommended.