Wednesday, September 6, 2023

International PhD PPU-IMAGINE Proposal

Call 2023/2024

PhD PROPOSAL IDENTIFICATION

PhD Project title	Deciphering genetic ethology of predisposition to Whipple's disease
Project Acronym	WHIPIRF
Project Keywords	Rare inborn errors of immunity, interferon, IRF, Whipple's disease, Trophyrema

LABORATORY PRESENTATION

Laboratory Team Name	Human Genetics of Infectious Diseases
Laboratory Director full name	Jean-Laurent Casanova
Department IP	Institut Imagine
Doctoral school	BioSPC
University	Paris Cité
Laboratory Telephone	(014) 275-4329
Laboratory website	https://www.institutimagine.org/fr/jean-laurent-casanova

PhD PROPOSAL

PhD Supervisor full name	Jacinta Bustamante
PhD Supervisor position	MCU-PH-HDR
PhD Supervisor email	jacinta.bustamante@inserm.fr
Number of ongoing PhD students supervised by the Supervisor	0

PhD Proposal abstract (1000 characters maximum)

Whipple disease (WD) is a rare chronic systemic infection due to Tropheryma whipplei. Only a very small fraction of individuals infected with T. whipplei develop WD. In this context, we hypothesize that WD results from single-gene, rare, inborn errors of immunity. We already identified by whole exome sequencing (WES) the first genetic form of WD in a family with a heterozygous loss-of-function(LOF) mutation in IRF4. This project capitalizes an unique cohort of 120 WD patients. The main objective of the project is to identify novel variants and genes underlying WD using a cutting-edge strategy combining comprehensive WES analysis with in-depth functional studies. We have interesting preliminary results with promising candidate rare variants in genes related to IRF4. By experimental approaches, we will validate their disease-causality.

The clinical implications will help the patients and their families in terms of molecular diagnosis, genetic counseling, treatment and clinical outcome.

PhD Proposal (10 000 characters maximum)

Infectious diseases constitute a devastating public health burden worldwide. In this context, the human genetic dissection of infectious diseases should help to decipher the immunological mechanisms that play an important role in resistance against microbes in natural conditions of infection. Whipple's disease (WD) is a rare, chronic, curable, systemic infection due to Tropheryma whipplei (T.whipplei), which is fatal in the absence of appropriate antibiotic treatment. Although the disease was first described in 1907, it was no until 2000 that it was possible to cultivate T. whipplei and obtain the first clinical isolate. The classic form or systemic WD begins with recurrent arthritis in three-quarters of patients followed several years later by digestive problems associated with severe systemic manifestations. Polyarthritis, cardiac and neurological manifestations in absence of gastrointestinal tract disease have been also described in WD. While a large part of the population has been exposed to T. whipplei, only a small number of people develops WD or remains healthy carriers. Thus, the same bacterial may cause asymptomatic portage or genuine WD in subjects sharing the same environmental factors.
WD is now considered to result from selective immune disorder related to probable individual genetic susceptibility to T. whipplei. Rare familial cases of WD have been reported. Following linkage analysis and whole exome-sequencing (WES), we identified the first genetic etiology in WD. Four patients with WD in the same kindred carried a rare heterozygous variant (p.R98W) in IRF4. The mutant allele is loss-of-function (LOF). Haploinsufficiency at the IRF4 locus underlies WD in this kindred. To further investigate genetic susceptibility factors, we have extended the study to a larger number of WD patients and established a unique cohort of 120 WD patients. The main objective of the project is to identify novel mutations and genes underlying WD using a cutting-edge strategy combining comprehensive WES analysis with in-depth functional studies. We have interesting preliminary results of the WES analysis in some patients with promising candidate rare variants in genes linked to the IRF4 and IFN-g immunity. All the promising variants will be validated by in-depth functional
studies. We will tackle the following specific aims: i) to characterize experimentally the biological impact to the newly identified mutations in IRF4 and IRF8 in terms of the allele, ii) to characterize experimentally the biological impact of IRF4/IRF8 variants in primary cells (hematopoietic and non-hematopoietic cells) and iPSC-derived macrophages from the patients.
This study will therefore be highly mechanistic and innovative, both genetically in silico and immunologically in vitro and ex vivo. It is feasible and supported by strong preliminary evidence. All tools and facilities to success in this project are available in laboratory. This project has major clinical implications. The identification of new genetic etiologies of WD will offer molecular diagnoses to patients and genetic counseling to their families. This will also guide rational treatment through improvements in our understanding of the pathogenesis of WD. Importantly, molecular diagnoses for siblings and for offspring potentially carrying the WDassociated genotype may also lead to the selective prevention of T. whipplei infection with antibiotics. This project also has major immunological implications. The unique added value of human genetic studies of severe infectious diseases lies in the definition of host defense gene functions in natura, i.e. in a natural ecosystem
governed by natural selection. This proposal is thus important, as we aim to discover mutations in genes essential for protective immunity to T. whipplei, including in particular genes governing IRF4 immunity.

Laboratory's best 5 publications

Kerner G, Rosain J, Guérin A, et al. Inherited human IFN-γ deficiency underlies mycobacterial disease. J Clin Invest. 2020;130(6):3158-3171. doi:10.1172/JCI135460

Yang R, Mele F, Worley L, et al. Human T-bet Governs Innate and Innate-like Adaptive IFN-γ Immunity against Mycobacteria. Cell. 2020;183(7):1826-1847.e31. doi:10.1016/j.cell.2020.10.046

Neehus AL, Moriya K, Nieto-Patlán A, et al. Impaired respiratory burst contributes to infections in PKCδ-deficient patients. J Exp Med. 2021;218(9):e20210501. doi:10.1084/jem.20210501

Le Voyer T, Neehus AL, Yang R, et al. Inherited deficiency of stress granule ZNFX1 in patients with monocytosis and mycobacterial disease. Proc Natl Acad Sci U S A. 2021;118(15):e2102804118. doi:10.1073/pnas.2102804118

Rosain J, Neehus AL, Manry J, et al. Human IRF1 governs macrophagic IFN-γ immunity to mycobacteria.

Cell. 2023;186(3):621-645.e33. doi:10.1016/j.cell.2022.12.038

Philippot Q, Ogishi M, Bohlen J, et al. Human IL-23 is essential for IFN-γ-dependent immunity to mycobacteria. Sci Immunol. 2023;8(80):eabq5204. doi:10.1126/sciimmunol.abq5204

Expected profile of the candidate

Differentiation (macrophages) of human iPSCs will be performed by the student. Using the iPSCs and CRISPR/Cas9 technologies, the PhD student will also study the cellular basis of the IRF immunity in different derived macrophages. Human iPSCs from patients, healthy controls and an appropriate negative control will be generated. Scientific communication will be achieved through publications in peer reviewed journals of the highest possible rank. We will also share our results with the scientific community through poster or oral communications at various international congresses covering the different fields of research dealt with in this project.