PASTEUR PARIS UNIVERSITE (PPU) INTERNATIONAL DOCTORAL PROGRAM 2020

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PROJECT

- **FILE #04**
- **ACRONYM:** GEN-VIR
- **TITLE:** Genetic Dissection of severe viral infections

LABORATORY

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LABORATORY PRESENTATION AND RESEARCH TOPICS

- **SUPERVISOR HDR:** Emmanuelle Jouanguy emmanuelle.jouanguy@inserm.fr

- **SPECIFY THE TEAM NAME:** Human genetic of infectious diseases – Monogenic predisposition

- **CO-SUPERVISOR:** Jean-Laurent Casanova, jean-laurent.casanova@inserm.fr

- **WEBSITE OF THE TEAM:** https://www.institutimagine.org/en/jean-laurent-casanova-177

DESCRIPTION OF THE PROPOSED PROJECT

- **KEYWORDS:** viral infections, genetic predisposition, interferons

- **ABSTRACT**

Some viral diseases (VDs) occur in patients with known acquired or primary immunodeficiencies (ID) and, less frequently, in otherwise healthy patients without any overt ID. We hypothesize that these specific VDs may be caused by single-gene inborn errors of immunity. We intend to investigate patients with proven specific VDs. We will identify and characterize the underlying genetic defects by a strategy combining powerful genome-wide explorations and in-depth functional experiments.

- **DESCRIPTION OF THE PROJECT**

Viral diseases (VDs) can be life-threatening infections that usually occur in patients with immunodeficiencies (ID), acquired or primary (PIDs). In rare cases, however, VDs occur in otherwise healthy patients without any known risk factors. These “idiopathic” VDs represent a unique opportunity to gain insight into VD pathogenesis. We hypothesized that these VDs may be due to as yet undiscovered “pathogen-specific” inborn errors of immunity (IEI), which we aim to discover and decipher. Our hypothesis is based on the observations that (i) idiopathic VDs affect a very small minority of individuals while these viruses are ubiquitous in the environment, (ii) some well-characterized PIDs are associated with VDs and (iii) an increasing number of infectious diseases are being shown to result from single-gene IEI, including some VDs, as we have recently reported. We will focus our project on three virus families, namely papillomaviruses, herpes viruses and hepatitis viruses. Interestingly, some viruses have a specific tissue-tropism: skin or mucosa for papillomaviruses, liver for hepatitis viruses. In contrast, herpes viruses might be associated with severe diseases affecting either the brain, the skin or the liver, all these clinical phenotypes being exclusive. This observation

suggests that the immune response is specific against one virus in a given tissue. This project capitalizes on a unique collection of patients with proven idiopathic VDs enrolled thanks to a worldwide network. We have enrolled more than 200 patients and we intend to recruit, within the next three years, a total of 350 patients. We will search for and characterize the underlying genetic defects using 1) cutting-edge genome-wide strategies, including next-generation sequencing (NGS) technologies, and 2) in-depth functional studies to validate the genetic variants identified. Using whole exome sequencing, we have identified promising rare variants, which impact on anti-viral immune response by ad hoc *in vitro* studies has to be deciphered. The implications of this project will be at fundamental and clinical levels. The genetic dissection of these VDs will shed new light on the molecular and cellular mechanisms conferring protective immunity against these viruses in a specific tissue/organ, and provide insight into the underlying pathogenesis. Moreover, this project will benefit the patients and their families in terms of diagnosis, treatment and outcome. Finally, these advances might pave the way for novel prophylactic or curative therapeutic interventions, based on a rational understanding of the pathogenesis.

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EXPECTED PROFILE OF THE CANDIDATE

- **EXPERIENCE REQUIRED**
  M.Sc. in molecular biology, genetics, immunology or microbiology.
  Strong computational skills.