PASTEUR PARIS UNIVERSITE (PPU) INTERNATIONAL DOCTORAL PROGRAM 2020

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PROJECT

- **FILE #01**
- **ACRONYM:** GENCOVID
- **TITLE:** Identifying inborn errors of immunity predisposing to severe forms of COVID-19

LABORATORY

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  Human Genetics of Infectious Diseases laboratory
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LABORATORY PRESENTATION AND RESEARCH TOPICS

- **SUPERVISOR HDR:** Aurélie COBAT, aurelie.cobat@inserm.fr
- **SPECIFY THE TEAM NAME:** Human genetics of infectious diseases: Complex predisposition
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DESCRIPTION OF THE PROPOSED PROJECT

- **KEYWORDS:** Severe viral infections, human genetics, inborn errors of immunity, next generation sequencing, COVID-19, influenza, computational genetics

- **ABSTRACT**

There is a huge inter-individual variability in the response to viral infections ranging from asymptomatic infection to lethal disease. We have already identified a number of monogenic inborn errors of immunity (IEIs) underlying life-threatening viral diseases. We hypothesize that severe SARS-CoV-2 infection can be the consequence of a diverse collection of IEI to the virus. Since the beginning of the SARS-CoV2 we have performed > 800 exomes or genomes of severe COVID-19 patients and >500 exomes/genomes of asymptomatic infected subjects, and the collection is still ongoing. We already identified mutations in 8 loci related to TLR3- and IRF7-dependent type I IFN immunity involved in the development of severe COVID. However, these mutations explained about 3% of the patients, and the main goal of this PhD project is to search for novel rare mutations in severe COVID-19 through the use and development of specific approaches to perform an in-depth analysis of the exome/genome data of these patients. Rigorous statistical analysis of this cohort of severe COVID-19 patients will integrate dimensions of incomplete penetrance and oligogenic predisposition, as well as the ethnic diversity of the sample. Identifying the genetic determinism of severe COVID-19 will have major immunological and clinical implications, in particular to guide future treatment.

- **DESCRIPTION OF THE PROJECT**

Viral infections remain a major threat for humankind with a number of alarming signs including 1) the limited effect or the absence of vaccines and/or efficient anti-viral drugs against a large number of viral infections, and 2) the recurrent emergence of new viral infections as attested by the recent pandemics of influenza viruses, Ebola virus, and coronaviruses with the current dramatic example of SARS-CoV-2 infection. In all these viral infections, there is a huge inter-individual variability in the response ranging from asymptomatic infection to lethal disease. In most cases, only a small proportion of otherwise healthy, young people develop the most severe forms of the disease, strongly suggesting the role of human genetic factors. We have already identified a number of monogenic inborn errors of immunity (IEIs) underlying life-threatening acute viral diseases, such as herpes

simplex virus encephalitis (HSE) (1-6), severe cytomegalovirus primary infection (7), and severe influenza pneumonitis (8-10). However, most patients with severe viral infections have no identified genetic defects yet, and we hypothesize that life-threatening pneumonitis due to SARS-CoV-2 infection can be the consequence of a diverse collection of IEI to the virus, at least in a substantial proportion of patients (11).

With the development of next generation sequencing (NGS) it is now possible to interrogate the entire human genome at single-base resolution, especially in the coding regions of the genome (called exome). This major technological advance has revolutionized the study of the genetic determinism of human rare and common diseases (12, 13) . This was the case in the context of rare and severe infectious diseases where exome analyses of one or a few patients, in particular by our laboratory, allowed the identification of many mutations in novel genes leading to monogenic predisposition to the severe viral infections mentioned above as well as many other severe infections (14). Over the last few years, our laboratory has collected more than 7000 exomes of patients of various ethnic origin suffering from rare and severe infectious diseases. In addition, the recent SARS-CoV-2 infection epidemics led us to start a huge national and international collection of patients with severe COVID-19 as well as asymptomatic infected subjects (15). The recruitment is still ongoing, and we have already performed whole exome sequencing (WES) or whole genome sequencing (WGS) in > 800 severe patients and > 500 infected controls to search for IEI involved in the development of severe COVID-19.

We started this search by testing the hypothesis that inborn errors in 13 loci involved in TLR3- and IRF7-dependent type I IFN immunity, which underlie life-threatening influenza pneumonia, may also underlie severe COVID-19. We found mutations in 8 of these loci, involved in the development of severe COVID-19 (16). However, these mutations explained about 3% of the patients, and the main goal of this PhD project will be to search for novel mutations in severe COVID-19 through the use and development of specific approaches to perform an in-depth analysis of the WES/WGS data of these patients. On the basis of our previous discoveries, we hypothesize that severe COVID-19 could be due in a subset of patients to a monogenic defect probably with low penetrance, which limits their identification. In addition, we hypothesize that severe COVID-19 could be due to a more complex mode of inheritance involving two (digenic inheritance) or a few (oligogenic inheritance) genes that may explain the incomplete penetrance.

The search for the genes (and variants) involved in the determinism of severe COVID-19 should therefore greatly benefit from a systematic and rigorous statistical analysis of the cohort of severe COVID-19 patients that would integrate these dimensions of incomplete penetrance and oligogenic predisposition, as well as the ethnic diversity of the sample. We have already developed several methods to optimize the analysis of NGS data (17-22), including a specific approach to analyze digenic inheritance from NGS data (23). The development of additional methods together with their application to the severe COVID-19 cohort will be the major aims of the PhD project. The analysis could also take advantage of our cohort of >80 severe influenza patients to test whether some novel genes could be common to both diseases characterized by life-threatening pneumonia, as it was already found for TLR3 and IRF7-related genes (8, 10). Genes and variants identified by the monogenic and oligogenic models will be followed-up by the genetic immunology team of the laboratory to validate their

functional role. Identifying the genetic determinism of severe COVID-19 will have major immunological and clinical implications, in particular to guide future treatment.

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EXPECTED PROFILE OF THE CANDIDATE

- **EXPERIENCE REQUIRED**
  M.Sc. in bioinformatics, statistical genetics, biostatistics, or related field with strong computational genetics background. Solid programming skills and some experience in the analysis of next-generation sequence data will be a plus.