mercredi, août 31, 2022

INTERNATIONAL PhD PROPOSAL

PhD Supervisor full name **Pr. Jean-Laurent Casanova, MD PhD**

PhD PROPOSAL IDENTIFICATION

PhD Project title	Human genetic and immunological determinants of life-threatening viral pneumonia
Project Acronym	HGIDLVP
Project Keyword	Human genetic, viral pneumonia

LABORATORY PRESENTATION

Laboratory Team Name	Human Genetics of Infectious Diseases
Department IP	Imagine Institute
Doctoral school	BioSPC
University	Paris Cité
Laboratory website	https://www.institutimagine.org/fr/jean-laurent-casanova-177

PhD PROPOSAL

PhD Supervisor full name	Pr. Jean-Laurent Casanova, MD PhD
PhD Supervisor position	PU-PH
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PhD Proposal abstract (1000 characters maximum)

Since 2015, the Casanova lab has discovered that both inborn errors of type I interferon (IFN) immunity and autoantibodies neutralizing type I IFN, can lead to life-threatening influenza or COVID-19 pneumonia in otherwise healthy children and adults. These discoveries illustrate that there are shared human genetic and immunological determinants of life-threatening viral pneumonia. Therefore, we propose to search for novel inborn errors, and their immunological phenocopies, in patients who suffered from severe viral pneumonia, including influenza, COVID-19, and other respiratory viral infections.

PhD Proposal (4000 characters maximum)

There is vast inter-individual variability clinically observed in any infectious diseases, ranging from asymptomatic infections to life-threatening diseases. Inborn errors of immunity (IEIs) are extreme examples of this inter-individual variability, which are caused by monogenic defects and presented with unique clinical phenotypes. Studies of IEIs led to fundamental understanding of infectious diseases and immunological mechanisms. In the past 25 years, the Casanova lab focuses our research on IEIs in patients with severe infections and the underlying immunological mechanisms. Since 2015, we discovered three monogenic causes of critical influenza pneumonia, showing that the type I IFN response is crucial to control influenza infection. Since 2020, we discovered inborn errors of type I IFN immunity, and autoantibodies to type I IFN, can lead to both critical COVID-19 and influenza pneumonia, indicating that influenza and COVID-19 pneumonia share the same genetic and immunological determinants.

Based on these discoveries, we hypothesize that novel inborn errors, and their immunological phenocopies, can cause life-threatening viral pneumonia, including influenza and COVID-19. We plan to recruit patients with mild (control cohort) and severe (case cohort) and search for novel IEIs using next generation sequencing (either whole-genome or whole-exome sequencing) and the bioinformatic pipeline developed in the lab. Novel mutations that are enriched in case but not control cohort will be further studied on molecular, biochemical, and cellular levels to validate their causality and mechanisms. Furthermore, we will search for phenocopies of the IEIs based on the immunological functions of these genes in the same cohort of patients. We will continue to focus on patients with critical influenza or COVID-19 pneumonia, but also expand our cohort to other respiratory viral infections including common coronavirus, respiratory syncytial virus, rhinovirus, and adenovirus. Our project is well-established with strong preliminary data, and well-funded by French, European, and international grants.

1.Ciancanelli MJ et al. Infectious disease. Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency.*Science* 2015

2.Hernandez N et al. Life-threatening influenza pneumonitis in a child with inherited IRF9 deficiency.*J Exp Med* 2018

3.Lim HK et al. Severe influenza pneumonitis in children with inherited TLR3 deficiency.*J Exp Med* 2019

4.Casanova JL, Su HC,Effort CHG. A Global Effort to Define the Human Genetics of Protective Immunity to SARS-CoV-2 Infection.*Cell 2020*

5.Zhang Q et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19.*Science* 2020

6.Bastard P et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19.*Science* 2020

7.Asano T et al. X-linked recessive TLR7 deficiency in ~1% of men under 60 years old with life-threatening COVID-19.*Sci Immunol* 2021

8.Bastard P et al. Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths.*Sci Immunol* 2021

9.Campbell TM et al. Respiratory viral infections in otherwise healthy humans with inherited IRF7 deficiency.*J Exp Med* 2022

10.Zhang Q et al. Recessive inborn errors of type I IFN immunity in children with COVID-19 pneumonia. *J Exp Med* 2022

11.Zhang Q et al. Human genetic and immunological determinants of critical COVID-19 pneumonia. *Nature* 2022

12.Zhang Q et al. Autoantibodies against type I IFNs in patients with critical influenza pneumonia.*J Exp Med* 2022

13.Casanova JL, Abel L. From rare disorders of immunity to common determinants of infection: following the mechanistic thread.*Cell* 2022

Expected profile of the candidate

We invite talented and motivated young scientists to join our lab and contribute to this cutting-edge project. A strong scientific background skills in genetics, molecular, and cellular biology is appreciated.