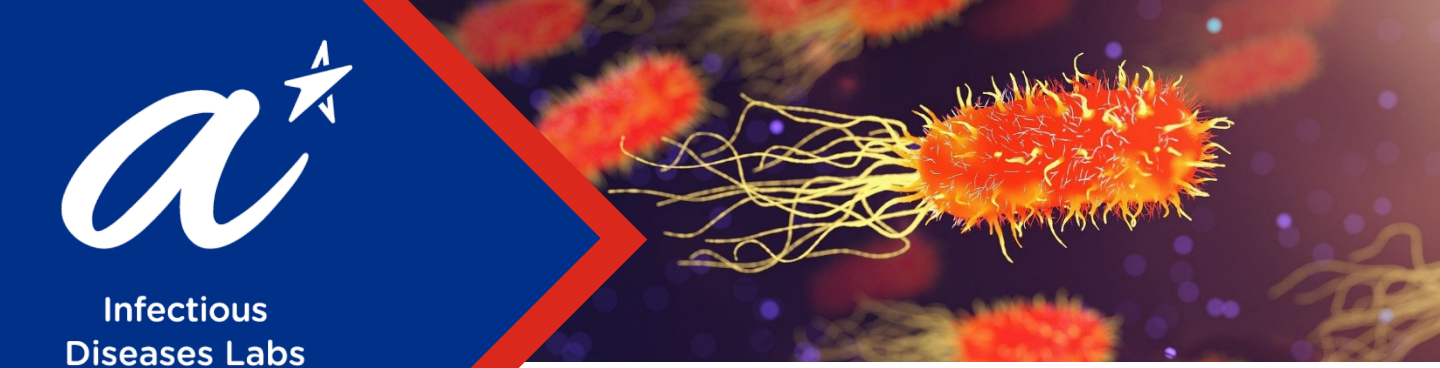
Infectious Diseases Labs

ID LABS



ID LABS SEMINAR SERIES

Dr Jean-Laurent Casanova

Levy Family Professor, The Rockefeller University
Investigator, Howard Hughes Medical Institute
Head, St. Giles Laboratory of Human Genetics of Infectious Diseases
Senior Attending Physician, The Rockefeller University Hospital

Friday 17th September 2021
4pm to 5pm (SGT)

Join zoom meeting **here**
Meeting ID: 965 5210 0855
Passcode: 983962

Webinar is open to all
No registration required

Genetic and immunological causes of life-threatening COVID-19

Clinical outcome upon infection with SARS-CoV-2 ranges from silent infection to lethal COVID- 19. We have found an enrichment in rare variants predicted to be loss-of-function (LOF) at the 13 human loci known to govern TLR3- and IRF7-dependent type I interferon (IFN) immunity to influenza virus, in 659 patients with life-threatening COVID-19 pneumonia, relative to 534 subjects with asymptomatic or benign infection. By testing these and other rare variants at these 13 loci, we experimentally define LOF variants in 23 patients (3.5%), aged 17 to 77 years, underlying autosomal recessive or dominant deficiencies. We show that human fibroblasts with mutations affecting this pathway are vulnerable to SARS-CoV-2. Inborn errors of TLR3- and IRF7-dependent type I IFN immunity can underlie life-threatening COVID-19 pneumonia in patients with no prior severe infection.

Also, interindividual clinical variability in the course of SARS-CoV-2 infection is immense. We report that at least 101 of 987 patients with life-threatening COVID-19 pneumonia had neutralizing IgG auto-Abs against IFN-ω (13 patients), the 13 types of IFN-a (36), or both (52), at the onset of critical disease; a few also had auto-Abs against the other three type I IFNs. The auto-Abs neutralize the ability of the corresponding type I IFNs to block SARS-CoV-2 infection in vitro. These auto-Abs were not found in 663 individuals with asymptomatic or mild SARS- CoV-2 infection and were present in only 4 of 1,227 healthy individuals. Patients with auto- Abs were aged 25 to 87 years and 95 were men. A B cell auto-immune phenocopy of inborn errors of type I IFN immunity underlies life-threatening COVID-19 pneumonia in at least 2.6% of women and 12.5% of men.

Dr Jean-Laurent Casanova received his M.D. in 1987 and his Ph.D. in 1992, after training at the Pasteur Institute in Paris and the Ludwig Institute for Cancer Research in Lausanne. He was appointed professor at Necker in 1999 and with Laurent Abel, cofounded the Laboratory of Human Genetics of Infectious Diseases. He was appointed professor at Rockefeller University in 2008 and named HHMI investigator in 2014. He continues to partner with Dr. Abel, maintaining their lab in Paris and NY. Over the last 25 years, they discovered the first monogenic inborn errors of immunity, rare and common, which predispose otherwise healthy individuals to a single infectious disease, including a variety of viral, bacterial, and fungal infections. In response to the SARS-CoV2 Global Pandemic, Dr Casanova cofounded the COVID Human Genetic Effort with Helen Su at the NIAID. He discovered monogenic inborn errors of type I interferon immunity underlying severe forms of COVID-19 in previously healthy individuals. This led to his discovery that pre-existing autoantibodies to type I interferons account for at least 10% of severe cases.

Dr. Casanova was recipient of multiple international awards, including the Dautrebande Prize (Belgium, 2004), Richard Lounsbery Award (USA/France, 2008), E. Mead Johnson Award (USA, 2010), InBev Baillet-Latour Health Prize (Belgium, 2011), Ilse and Helmut Wachter Foundation Award (Austria, 2012), Milstein Award (USA, 2012), Robert Koch Award (Germany, 2014), Sanofi-Institut Pasteur Award (France, 2014), Stanley J. Korsmeyer Award (USA, 2016), and Inserm Grand Prix (France, 2016). He was elected to EMBO (2005), USA National Academy of Sciences (2015), USA National Academy of Medicine (2015), and Royal Academy of Medicine of Belgium (2021).