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# Monogenic basis of resistance to SARS-CoV2 and predisposition to severe COVID-19

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## General context and objectives of the project

In December 2019, a pneumonia due to a novel coronavirus (SARS-CoV-2) emerged in the city of Wuhan, China, and quickly spread world-wide. In populations naive to this new pathogen, there has been stunning inter-individual clinical variability among infected individuals, ranging from asymptomatic infection to lethal coronavirus infectious disease-19 (COVID-19). The importance of monogenic lesions governing immunity to infection is now well established, in particular for viral infections. On the other hand, cases of monogenic resistance to infection have also been identified, in humans with confirmed and sustained viral exposure who have remained free of infection, as detected by PCR and serology. In this context, we hypothesized that monogenic inborn errors of immunity (IEI) may underlie life-threatening COVID-19 infections in previously healthy individuals, whereas monogenic inborn variants of resistance (IVR) may underlie individuals who remain free of infection despite repeated SARS-CoV-2 exposure. We will follow a three-step strategy:
**Objective 1:** To recruit an IEI cohort (previously healthy young patients with severe COVID-19) and IVR cohort (confirmed exposure to SARS-CoV-2 yet remain seronegative) at international level.
**Objective 2:** To search for candidate IEI and IVR variants by whole exome sequencing (WES), using a cutting-edge strategy developed in our laboratory to analyze such data.
**Objective 3:** To perform in-depth functional studies to characterize the products of the candidate variants biochemically, and to analyze the corresponding patients' cells immunologically.

## Achievements and results

### *Collection of subjects and next generation sequencing*

We have organized a French and international network to recruit patients and collect samples, in particular through an international consortium, Covidhge (www.covidhge.com) that we are coordinating in collaboration with the NIH. We have now recruited > 5500 patients with Covid-19 pneumonia, > 2500 subjects with pauci/asymptomatic SARS-CoV-2 infection, >900 Multisystem inflammatory syndrome in children (MIS-C), >200 with vaccine breakthrough infection, >100 with Neuro-Covid, > 80 with long COVID, and > 650 with resistance to SARS-CoV-2 infection.

### *Identification of inborn errors of type I IFN underlying critical COVID-19 pneumonia*

We first discovered that 3.5% of patients with critical COVID-19 pneumonia were carrying loss of function mutations in eight type I IFN related genes (TLR3, UNC93B1, TICAM1, TBK1, IRF3, IRF7, IFNAR1, and IFNAR2), including 4 patients with autosomal recessive IRF7 or IFNAR1 mutations. We subsequently found an additional genetic cause of severe pneumonia due to X-linked recessive TLR7 deficiency explaining about 1% of male patients. We also showed that recessive complete deficiencies of type I IFN immunity may underlie about 10% of hospitalizations for COVID-19 pneumonia in children. Finally in a larger sample, we confirmed that inborn errors of TLR3- and/or TLR7-dependent type I IFN immunity in respiratory epithelial cells and plasmacytoid dendritic cells underlie critical COVID-19 pneumonia in 1-5% of cases.

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Main articles


Zhang, Q. *et al.* Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. ***Science*** **370**, eabd4570 (2020). https://doi.org:10.1126/science.abd4570

Asano, T. *et al.* X-linked recessive TLR7 deficiency in ~1% of men under 60 years old with life-threatening COVID-19. ***Sci Immunol*** **6**, eabl4348 (2021). https://doi.org:10.1126/sciimmunol.abl4348

Zhang, Q. *et al.* Recessive inborn errors of type I IFN immunity in children with COVID-19 pneumonia. ***J Exp Med*** **219** (2022). https://doi.org:10.1084/jem.20220131

Matuozzo, D. *et al.* Rare predicted loss-of-function variants of type I IFN immunity genes are associated with life-threatening COVID-19. ***Genome Med*** **15**, 22 (2023). https://doi.org:10.1186/s13073-023-01173-8


***Identification of inborn errors of OAS-RNase L in MIS-C***

Multisystem inflammatory syndrome in children (MIS-C) emerged in April 2020 in communities with high COVID-19 rates. We reported autosomal recessive deficiencies of OAS1, OAS2, or RNase L in ~1% of an international cohort of MIS-C patients. Single-gene recessive inborn errors of the OAS–RNase L pathway unleash the production of SARS-CoV-2–triggered inflammatory cytokines by mononuclear phagocytes, thereby underlying MIS-C.

Main articles


Sancho-Shimizu, V. *et al.* SARS-CoV-2-related MIS-C: A key to the viral and genetic causes of Kawasaki disease? ***J Exp Med*** **218** (2021). https://doi.org:10.1084/jem.20210446

Lee, D. *et al.* Inborn errors of OAS-RNase L in SARS-CoV-2-related multisystem inflammatory syndrome in children. ***Science*** **379**, eabo3627 (2023). https://doi.org:10.1126/science.abo3627


***Identification of auto-antibodies against type I IFN underlying critical COVID-19 pneumonia***

We discovered that auto-antibodies against type I IFNs explains about 15% of critical COVID-19 pneumonia. These auto-antibodies preexist infection, and provide a major increase in the risk of developing critical COVID-19 (relative risk up to 100). In the general population, they are at a frequency of 0.5-1% before 65 years of age, and then strongly increase up to 5-6% around 80 years of age. We also found that they underly severe COVID-19 in patients who presented vaccine breakthrough hypoxemic pneumonia.

Main articles


Bastard, P. *et al.* Autoantibodies against type I IFNs in patients with life-threatening COVID-19. ***Science*** **370**, eabd4585 (2020). https://doi.org:10.1126/science.abd4585

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*** **6**, eabl4340 (2021). https://doi.org:10.1126/sciimmunol.abl4340

Bastard, P. *et al.* Vaccine breakthrough hypoxemic COVID-19 pneumonia in patients with auto-Abs neutralizing type I IFNs. ***Sci Immunol***, eabp8966 (2022). https://doi.org:10.1126/sciimmunol.abp8966

Manry, J. *et al.* The risk of COVID-19 death is much greater and age dependent with type I IFN autoantibodies. ***Proc Natl Acad Sci U S A*** **119**, e2200413119 (2022). https://doi.org:10.1073/pnas.2200413119

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***Identification of auto-antibodies against type I IFNs underlying other severe viral conditions***

Following our findings in severe COVID-19 pneumonia, we discovered the major role of autoantibodies to type I IFN in the development of severe viral infections due live yellow fever vaccine, influenza, and more recently, in ~40% of patients with West Nile virus encephalitis.

Main articles


Bastard, P. *et al.* Auto-antibodies to type I IFNs can underlie adverse reactions to yellow fever live attenuated vaccine. ***J Exp Med* 218** (2021). https://doi.org:10.1084/jem.20202486

Zhang, Q. *et al.* Autoantibodies against type I IFNs in patients with critical influenza pneumonia. ***J Exp Med* 219** (2022). https://doi.org:10.1084/jem.20220514

Gervais, A. *et al.* Autoantibodies neutralizing type I IFNs underlie West Nile virus encephalitis in approximately 40% of patients. ***J Exp Med* 220** (2023). https://doi.org:10.1084/jem.20230661


***Identification of inborn errors underlying the production of auto-antibodies against type I IFNs***

We showed that patients with autoimmune polyendocrinopathy syndrome type 1 (APS-1) caused by autosomal recessive AIRE deficiency produce autoantibodies (auto-Abs) neutralizing type I IFNs, and have therefore a strong predisposition to life-threatening COVID-19 pneumonia. We recently found that patients with autosomal recessive NIK or RelB deficiency, or a specific type of autosomal dominant (AD) NF-κB2 deficiency also have neutralizing auto-Abs against type I IFNs and are prone to life-threatening COVID-19 pneumonia. Overall, we found that human inborn errors of the alternative NF-κB pathway impair the development of AIRE-expressing medullary thymic epithelial cells (mTECs), thereby underlying the production of auto-Abs against type I IFNs and predisposition to viral diseases.

Main articles


Bastard, P. *et al.* Preexisting autoantibodies to type I IFNs underlie critical COVID-19 pneumonia in patients with APS-1. ***J Exp Med* 218** (2021). https://doi.org:10.1084/jem.20210554

Le Voyer, T. *et al.* Impaired thymic AIRE expression underlies autoantibodies against type I IFNs in humans with inborn errors of the alternative NF-κB pathway. ***Nature*** (in press).


***Conclusion***

Overall, our discoveries highlight the major role of the type I IFN pathway in the development of severe COVID-19. We identified the major role of auto-antibodies against type I IFNs in severe COVID-19, and extended this role to several other severe viral conditions. These findings led to the writing of several reviews and position papers in high profile journals (refs 5, 15, 17-20, 24, 39, 40, 42, 49, 51, 52)). We are pursuing our research in particular for 1) additional IEIs underlying several COVID-19 related phenotypes, in particular the resistance to SARS-CoV-2 infection, 2) additional severe diseases caused by auto-antibodies against type I IFNs, and 3) the root causes of the production auto-antibodies against type I IFNs. Our findings already open new avenues of prevention and treatment based on large scale screening of auto-antibodies against type I IFNs, and early treatment in infected subjects based on type I IFN not targeted by auto-antibodies such as IFN-β (ref 10).

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**Full list of articles related to the project acknowledging the SCOR foundation**


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