XXXe Congrès

Marseille 24-26 Novembre 2021

Anti-Type I IFN Auto-Antibodies and Severe COVID-19

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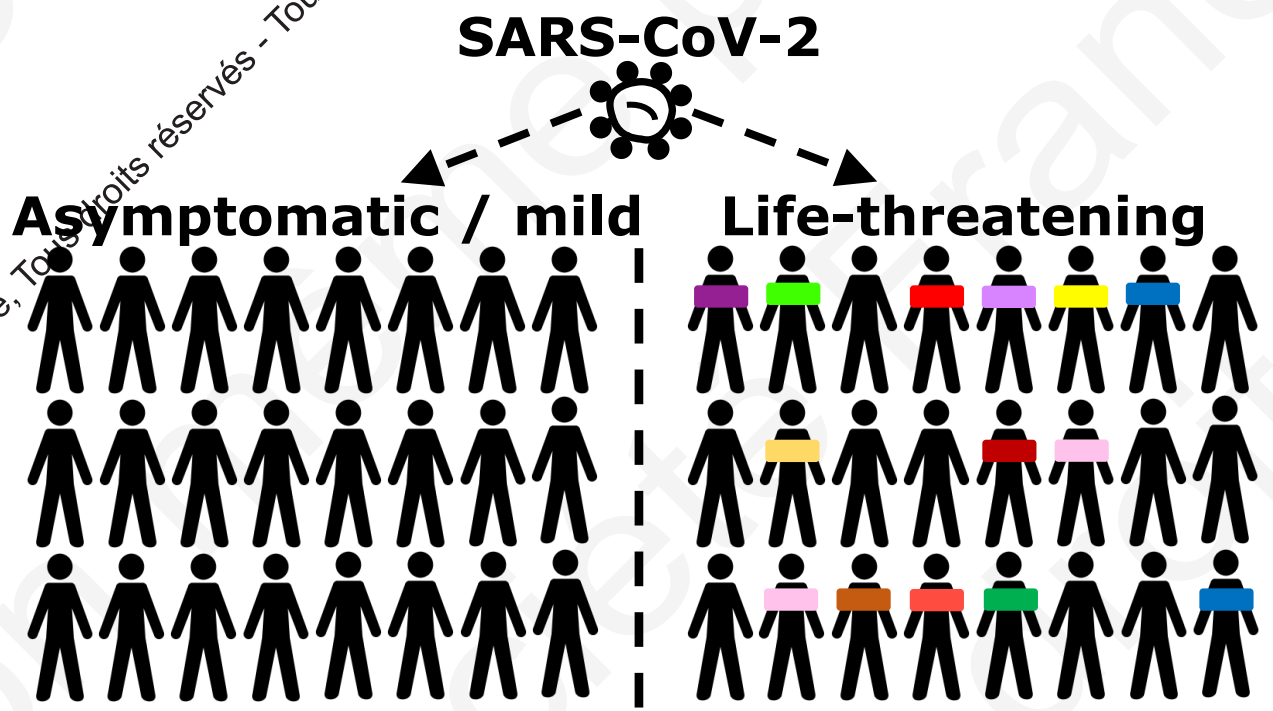
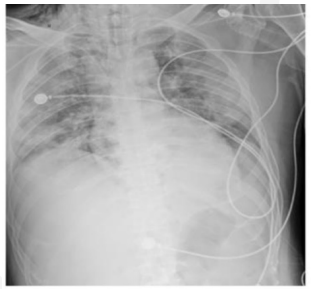
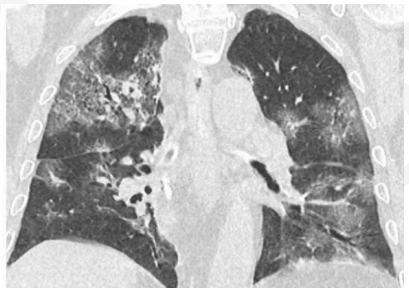
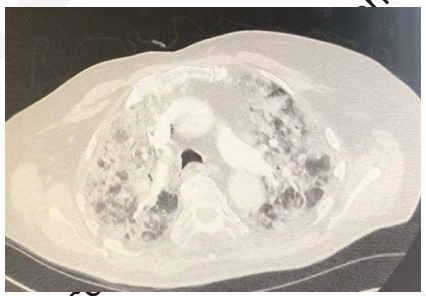
Inter-individual Variability in the Course of Infectious Diseases



Life-threatening COVID-19 pneumonia


ARDS (Chest X-ray)

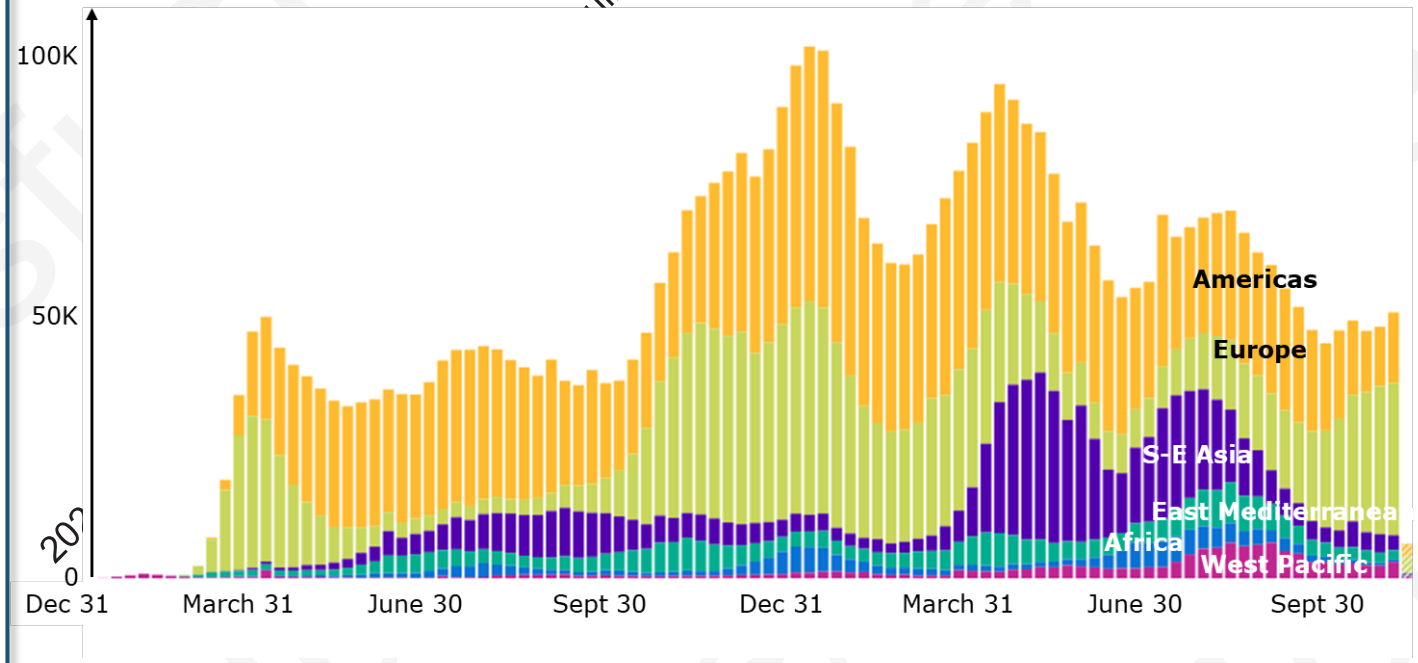

Severe Covid pneumonia (Chest CT)


Critical pneumonia, ARDS (Chest CT)

Casanova JL, Su HC, *Cell* 2020

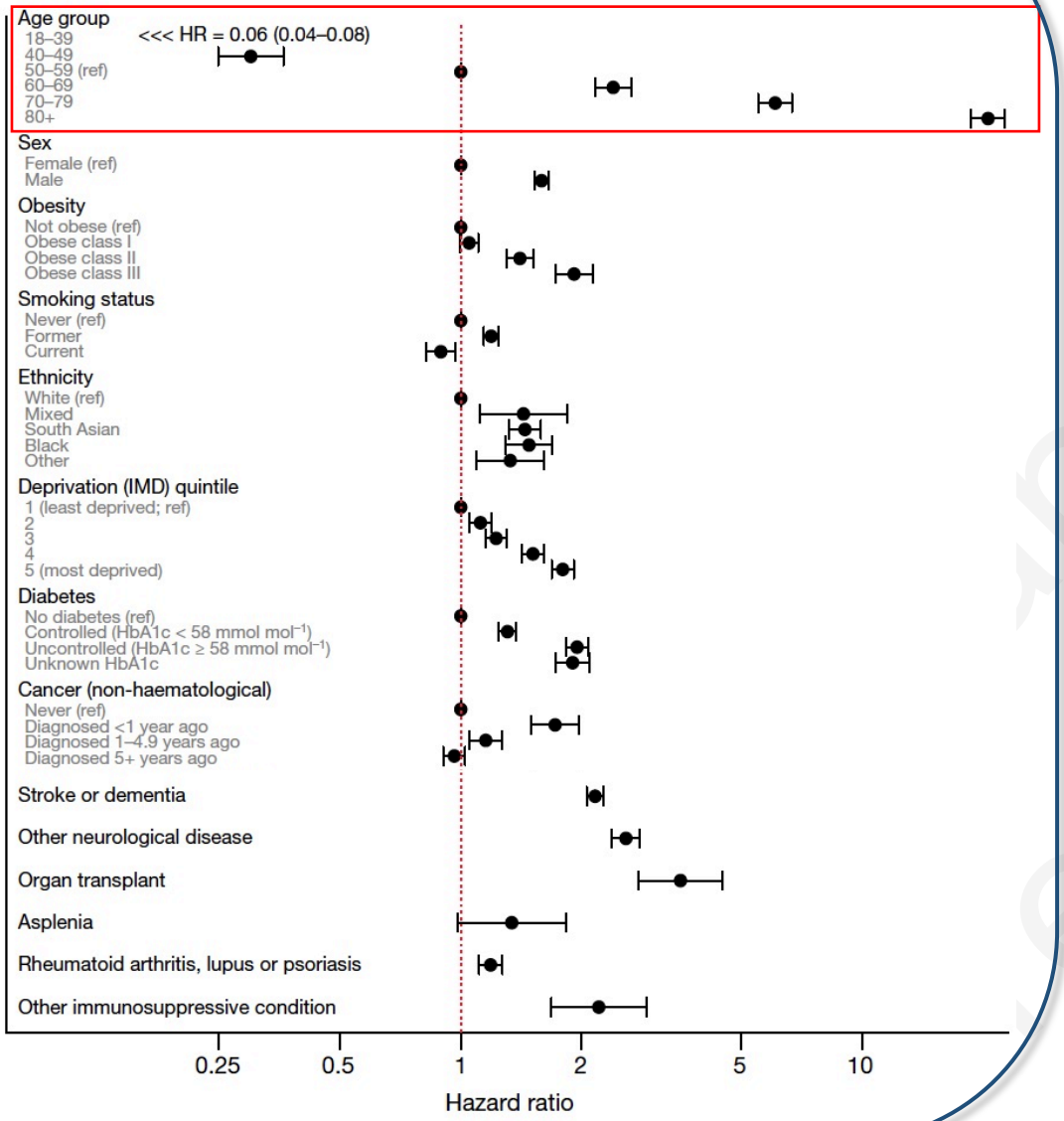
WHY DO PEOPLE DIE OF COVID-19?

Number of weekly deaths for COVID-19 (source: WHO)



Total deaths > 5.1 million

COVID-19 death hazard ratios (study on 17 million individuals)

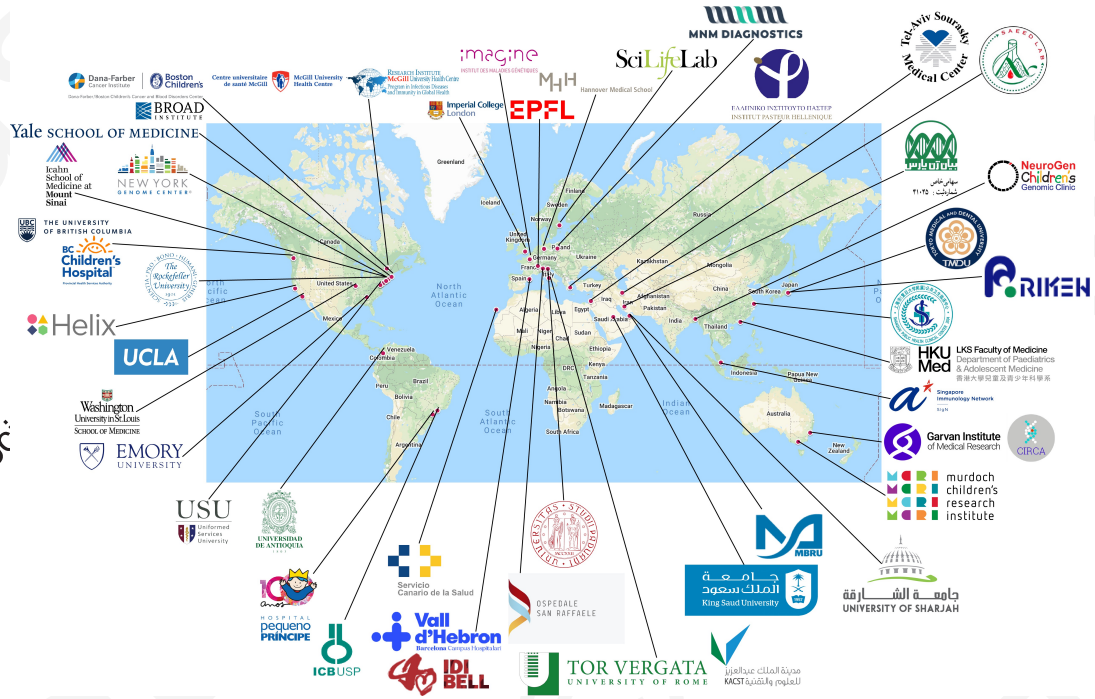


Williamson *et al.*, *Nature*, 2020

COVID HUMAN GENETIC EFFORT

Jean-Laurent Casanova and Helen Su

>40 sequencing hubs worldwide



>400 participating centers worldwide

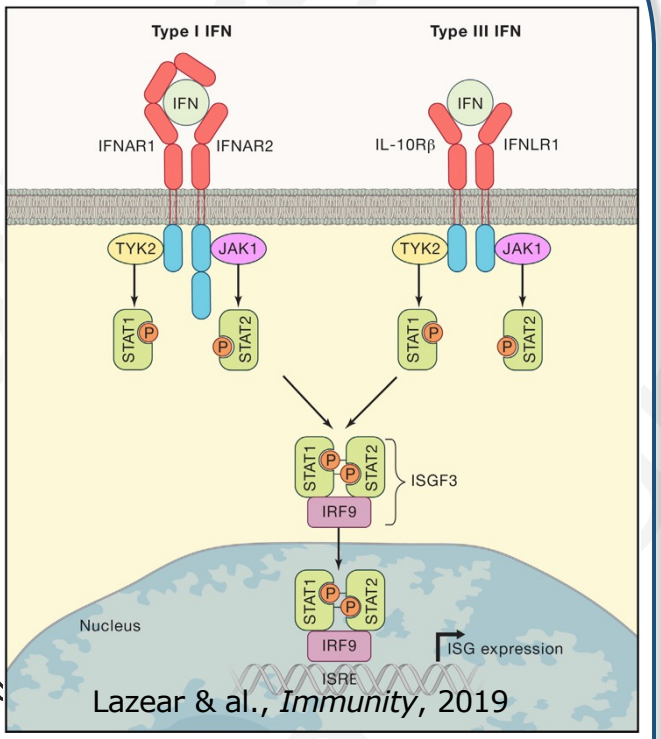
November 1st, 2021:
>13,000 subjects recruited

COULD INBORN ERRORS OF IMMUNITY OR THEIR AUTOIMMUNE PHENOCOPY UNDERLIE LIFE-THREATENING COVID-19?

Inborn Errors of Type I IFNs

17 type I IFNs (13 IFN-α, IFN-β, IFN-ε, IFN-κ, IFN-ω), all binding to the IFNAR1/IFNAR2

Inborn Errors of Type I IFN response pathway: **severe viral illnesses, including Live Attenuated Viral Vaccine Diseases** (e.g. MMR, YFV)



Lazear & al., *Immunity*, 2019

AR IFNAR1 deficiency: severe reaction to MMR, YFV vaccines, HSE, life-threatening COVID-19

AR IFNAR2 deficiency: Severe reaction to MMR, and YFV vaccines

AR TYK2 deficiency: various "mild" viral diseases, HSV

AR partial JAK1 deficiency: mild viral infections

AR STAT1 deficiency: various viral life-threatening diseases, HSV1/CMV/EBV/IAV/VZV

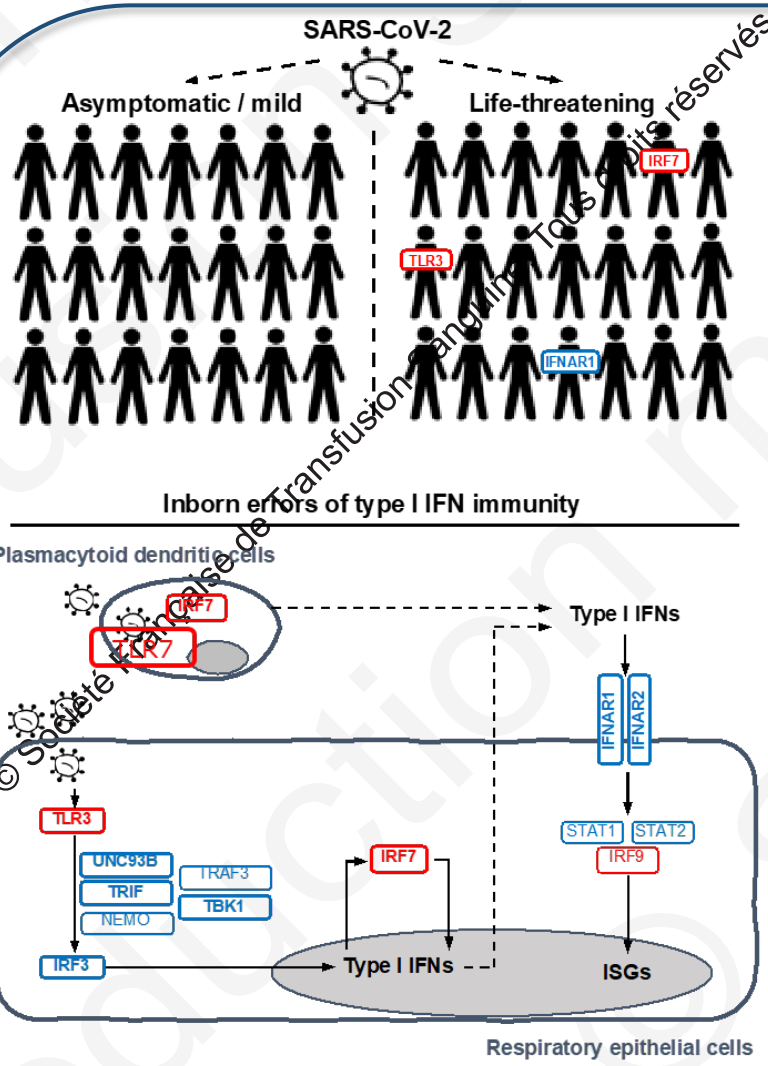
AR STAT2 deficiency: Severe reactions to MMR, severe viral disease, recurrent HSV/VZV/CMV/IAV infections

AR IRF9 deficiency: severe IAV pneumonia, biliary perforation after MMR

Could Inborn of Type I IFN Immunity underlie Life-Threatening COVID-19?

Meyts I *et al. Eur J Immunol* 2021

Inborn Errors of Type I IFN Immunity Underlie Life-Threatening COVID-19 Pneumonia



659 patients with critical COVID-19 pneumonia versus 534 subjects with asymptomatic benign infection:

3.5% carried rare variants of the TLR3- and IRF7-dependent IFN-I pathway

1202 male patients (0.5 to 99yrs, [52.9yrs]) with unexplained critical COVID-19 pneumonia

~ 1% of male patients had XR-TLR7 deficiency and impaired TLR7-dependent IFN-I induction

Could phenocopies of type I IFN IEI also underlie Life-Threatening COVID-19?

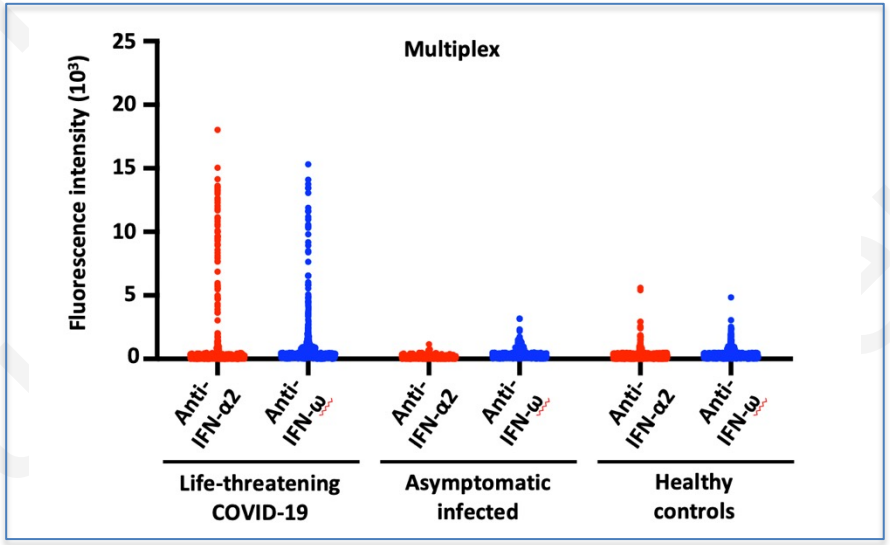
Zhang et al., *Science*, 2020; Asano et al., *Sci Immunol*, 2021

Auto-Abs against Type I IFNs

In some patients treated with IFN-α2b or IFN-β	(1981-)	
In a small minority of women with SLE	(1982-)	
In nearly all patients with thymoma	(2003-)	**Clinically silent**
In nearly all patients with APS-1 (*AIRE*)	(2006-)	
In several patients with IPEX (*FOXP3*)	(2018-)	
In one patient with severe varicella (Ion Gresser)	(1984)	**Severe VZV infection**
In a few patients with Combined ID (*RAG1*, *RAG2*)	(2015)	**Unusual viral illnesses**

Could auto-Abs to type I IFNs underlie life-threatening COVID-19?

High Titers of Anti-Type I IFN Neutralizing Auto-Abs in >10% of Patients with Severe COVID-19

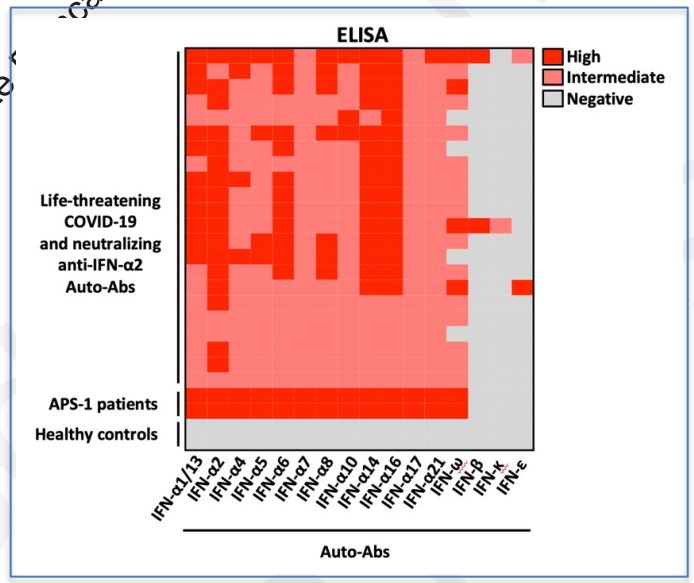


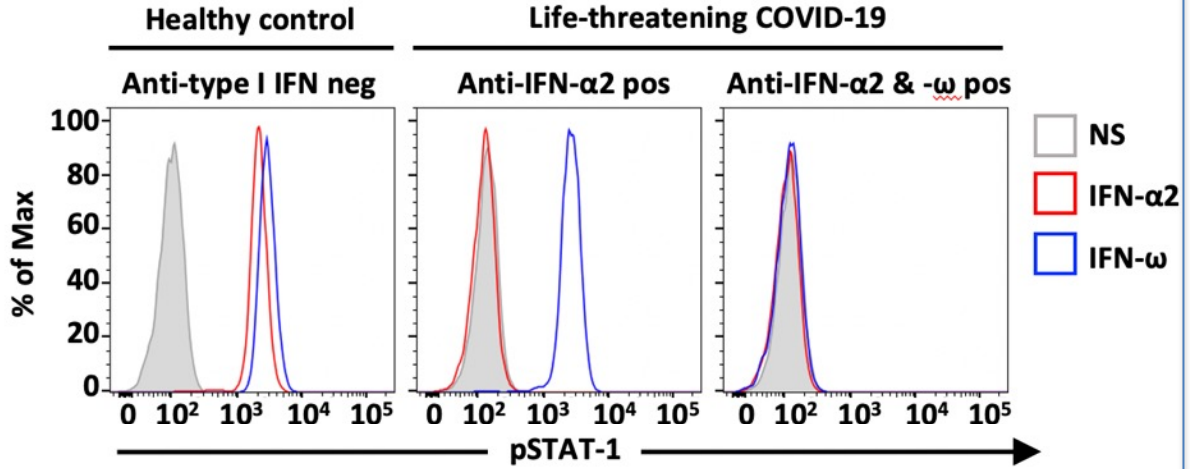
	N total	Anti-type I IFN auto-Abs positive		p-value
		N	%	
Life-threatening COVID-19	987	101	10.2	
Asymptomatic or mild infected	663	0	0	$p < 10^{-16}$
Healthy controls	1224	4	0.3	$p < 10^{-16}$

95 of 101 patients with Auto-antibodies (94%) were men

51 of 101 (50%) were > 65 years of age

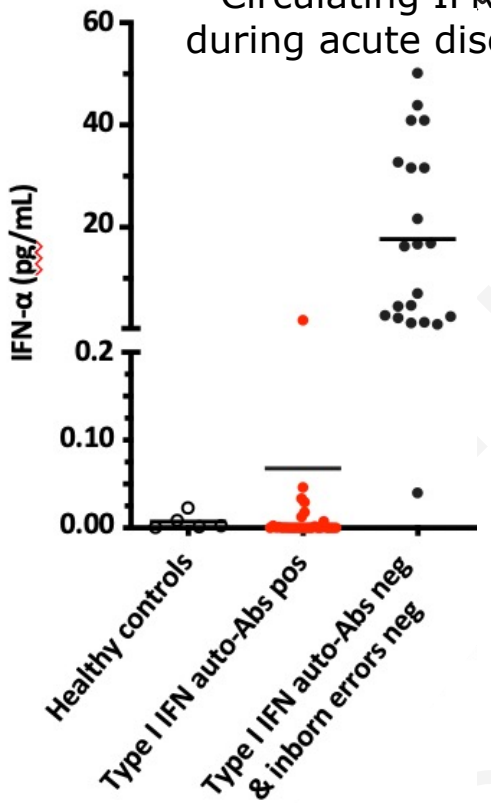
In informative cases: preceded infection



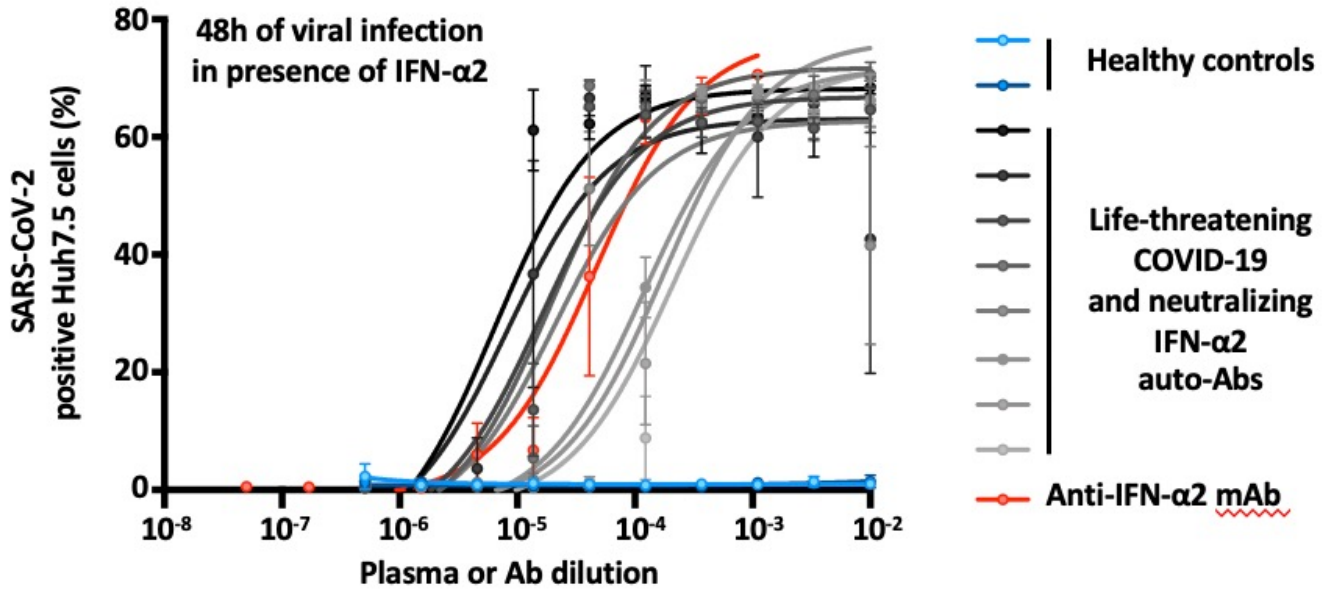


The Anti-IFN-I auto-Abs Block the protective Effect of IFN-α Against SARS-CoV2

Circulating IFN-α during acute disease



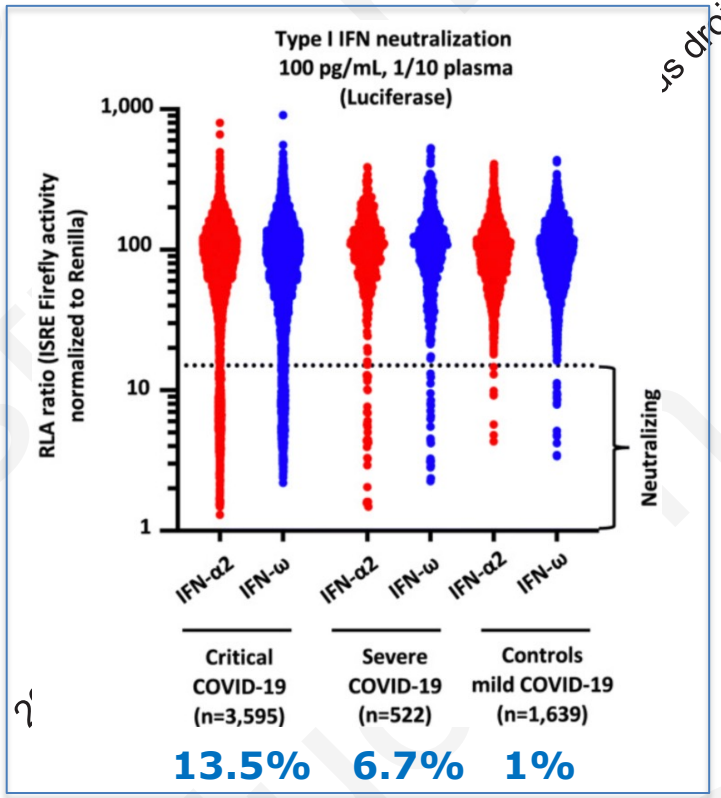
SARS-CoV-2 replication in presence of IFN-α

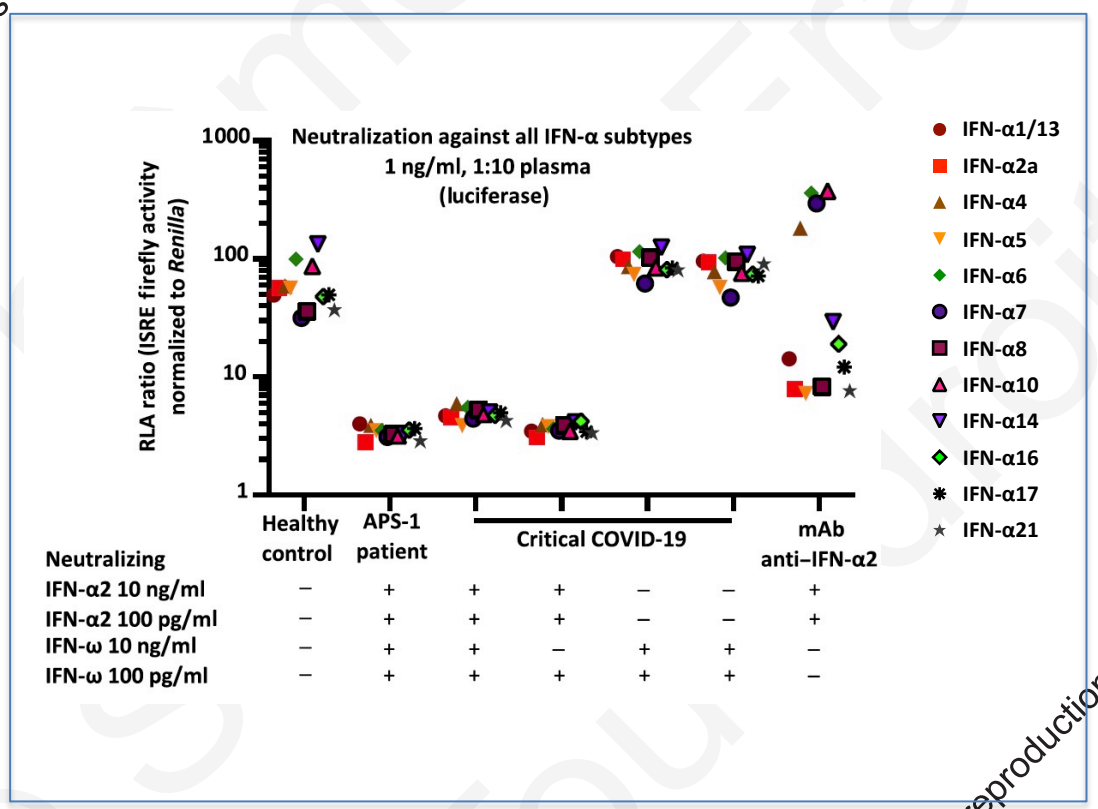


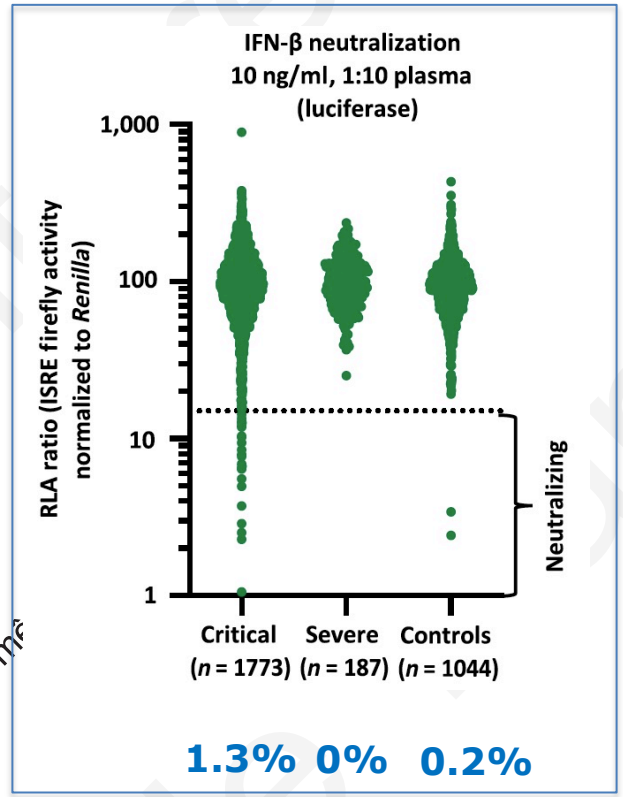
Anti-IFN-I auto-Abs can block type I IFN Function, *in vivo* and *in vitro* including in the upper respiratory tract

Bastard P *et al.* Science 2020 (Lopez J et al. J Exp Med 2021)

Anti-Type I IFN Auto-Abs Neutralizing 100 pg/mL of IFN-α and/or IFN-ω in Almost 20% of Severe/Critical COVID-19 Patients

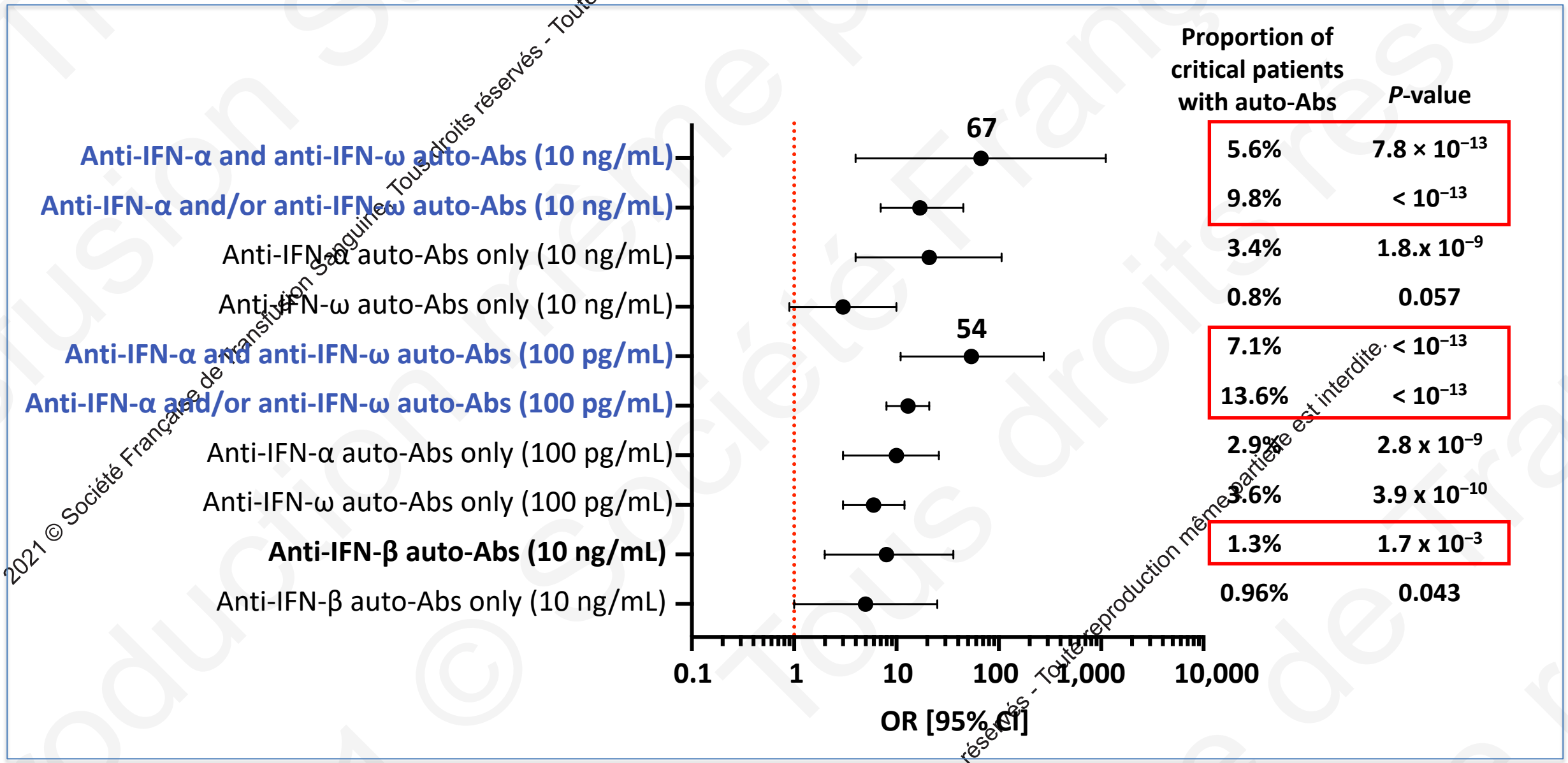






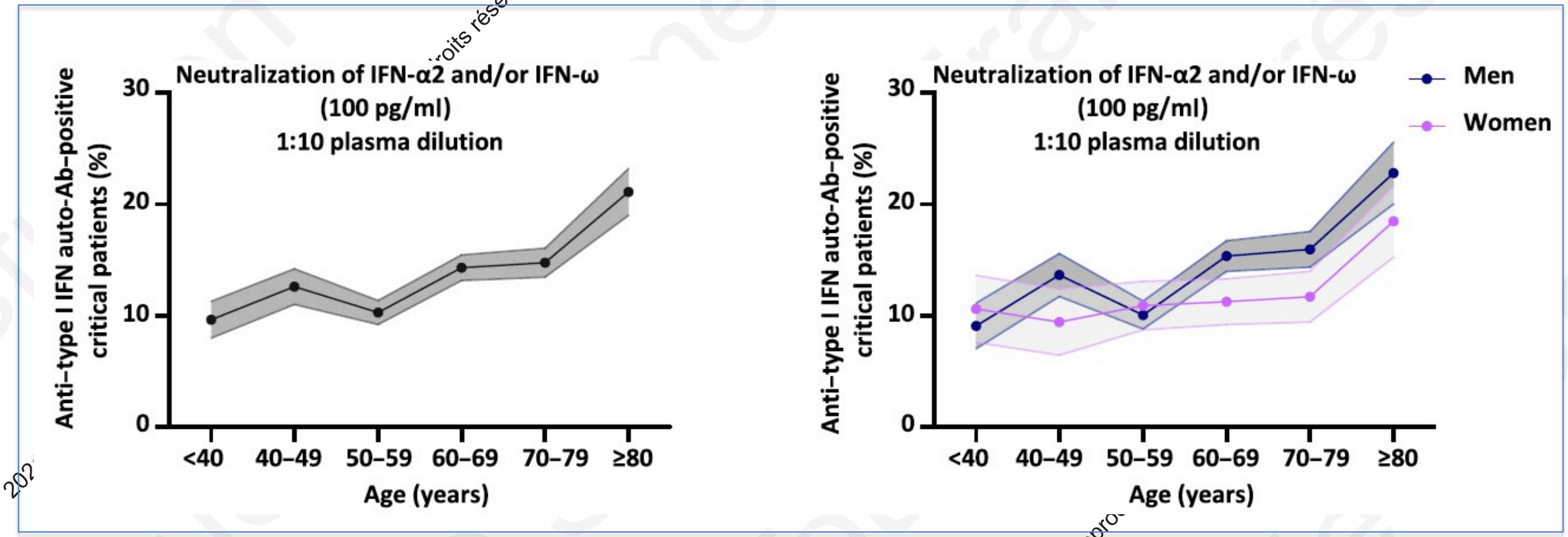
Bastard P *et al.* Sci Immunol 2021

Anti-Type I IFN Auto-Abs: Major Risk Factors of Critical COVID-19



Adapted from Bastard P *et al.* Sci Immunol 2021

Anti-Type I IFN Auto-Abs Account for 20% of Critical Covid-19 after 80yo and of The Total Fatal Cases



Auto-Abs neutralizing IFN-α2 and/or IFN-ω Increase with Age in Critical COVID-19 Patients

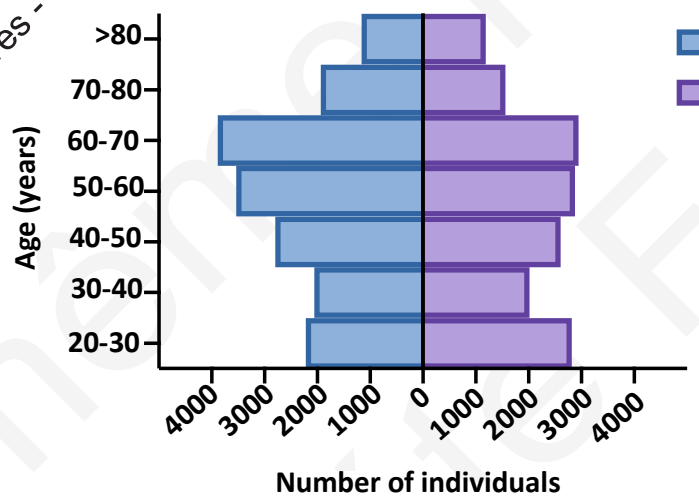
High Prevalence of Neutralizing Auto-Abs against TYPE I IFNs in the Elderly with Critical COVID-19

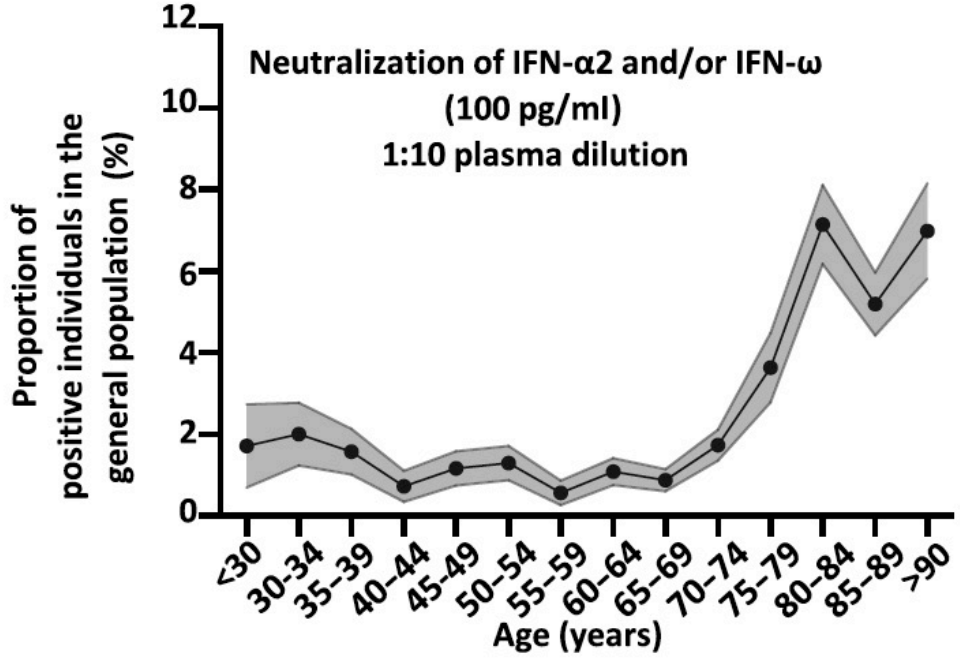
Neutralizing Auto-Abs Against TYPE I IFNs in ~ 20% of All Deceased Individuals

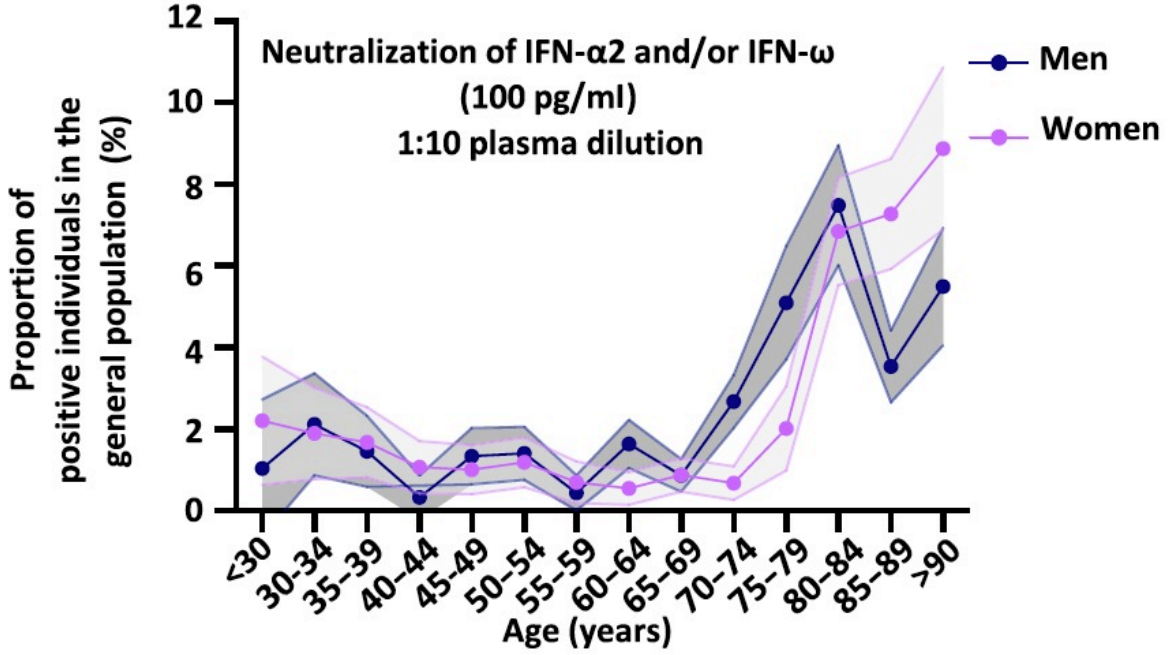
Bastard P *et al.* Sci Immunol 2021

Anti-Type I IFN Auto-Abs Sharply Increase in the General Population >70yo

> 34,000 individuals







Bastard P *et al.* Sci Immunol 2021

Anti-Type I IFN Auto-Abs

Autoantibodies against type I IFNs in patients with life-threatening COVID-19

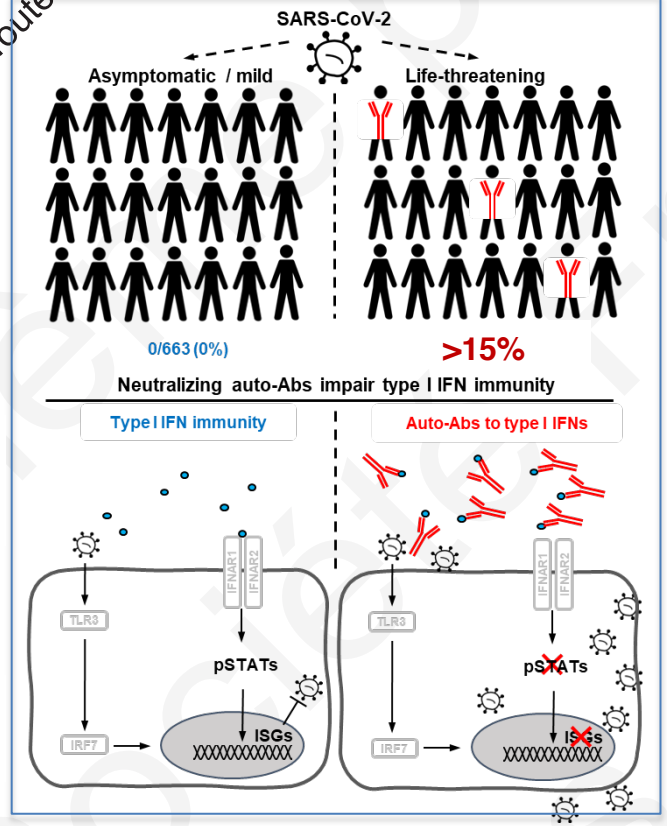
Paul Bastard[1,2,3]*†, Lindsey B. Rosen[4]†, Qian Zhang[3]‡, Eleftherios Michailidis[5]‡, Hans-Heinrich Hoffmann[5]‡, Yu Zhang[4]‡, Karim Dorgham[6]‡, Quentin Philippot[1,2]‡, Jérémie Rosain[1,2]‡, Vivien Béziat[1,2,3]‡, Jérémy Manry[1,2], Elana Shaw[4], Liis Haljasmägi[7], Pärt Peterson[7], Lazaro Lorenzo[1,2], Lucy Bizien[1,2], Sophie Trouillet-Assant[8,9], Kerry Dobbs[4], Adriana Almeida de Jesus[4], Alexandre Belot[10,11,12], Anne Kallaste[13], ... John S. Tsang[70,71], Raphaela Goldbach-Mansky[4], Kai Kisand[7], Michail S. Lionakis[4], Anne Puel[1,2,3], Shen-Ying Zhang[1,2,3], Steven M. Holland[4]¶, Guy Gorochov[6,72]¶, Emmanuelle Jouanguy[1,2,3]¶, Charles M. Rice[5]¶, Aurélie Cobat[1,2,3]¶, Luigi D. Notarangelo[4]¶, Laurent Abel[1,2,3]¶, Helen C. Su[4]#, Jean-Laurent Casanova[1,2,3,42,73]*#

Science 2020

Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths

Paul Bastard[1,2,3]*, Adrian Gervais[1,2†], Tom Le Voyer[1,2†], Jérémie Rosain[1,2†], Quentin Philippot[1,2†], Jérémy Manry[1,2‡], Eleftherios Michailidis[4‡], Hans-Heinrich Hoffmann[4‡], Shohei Eto[5§], Marina Garcia-Prat[6§], Lucy Bizien[1,2§], Alba Parra-Martínez[6§], Rui Yang[3§], Liis Haljasmägi[7§], Mélanie Migaud[1,2§], Karita Särekannu[7§], Julia Maslovskaja[7§], Nicolas de Prost[8,9], ... Peter K. Gregersen[72¶], Lorenzo Piemonti[74¶], Carlos Rodríguez-Gallego[158,159¶], Luigi D. Notarangelo[34#], Helen C. Su[34,160#], Kai Kisand[7#], Satoshi Okada[5#], Anne Puel[1,2,3#], Emmanuelle Jouanguy[1,2,3#], Charles M. Rice[4#], Pierre Tiberghien[19,20#], Qian Zhang[1,2,3#], Aurélie Cobat[1,2,3#], Laurent Abel[1,2,3]**, Jean-Laurent Casanova[1,2,3,105]*,**

Sci Immunol 2021



- ~15% of patients with life-threatening COVID-19 have auto-Abs to type I IFNs, 20% elderly, 20% of deaths
- Prevalence increases with age in the general population, >4% after 70 yo
- Neutralize type I IFNs *in vivo*, *in vitro*, and block type I IFN protective effect against SARS-CoV-2
- ! Clinical Implications (screening; IFN-β/plasma exchange, vaccination, or mAb therapy)
- Exclusion from donating convalescent plasma or for ongoing clinical trials, or at least they should be tested before plasma donations are accepted

Preexisting autoantibodies to type I IFNs underlie critical COVID-19 pneumonia in patients with APS-1

Paul Bastard[1,2,3], Elizaveta Orlova[4], Leila Sozaeva[4], Romain Lévy[1,2,5], Alyssa James[6], Monica M. Schmitt[6], Sebastian Ochoa[6], Maria Kareva[4], Yulia Rodina[7], Adrian Gervais[1,2], Tom Le Voyer[1,2], Jérémie Rosain[1,2], Quentin Philippot[1,2], Anna-Lena Neehus[1,2], Elana Shaw[6], Mélanie Migaud[1], Lucy Bizien[1], Olov Ekwall[8,9], Stefan Berg[8], Guglielmo Beccuti[10], Lucia Ghizzoni[10], Gérard Thiriez[11], Arthur Pavot[12], Cécile Goujard[13], Marie-Louise Frémond[5,14], Edwin Carter[15], Anya Rothenbuhler[16], Agnès Linglart[16], Brigite Mignot[17], Aurélie Comte[17], Nathalie Cheikh[18], Olivier Hermine[2,19], Lars Breivik[20], Eystein S. Husebye[20,21,22], Sébastien Humbert[23], Pierre Rohrlich[24], Alain Coaquette[25], Fanny Vuoto[26], Karine Faure[26], Nizar Mahlaoui[5,27], Primož Kotnik[28,29], Tadej Battelino[28,29], Katarina Trebušak Podkrajšek[28,29], Kai Kisand[30], Elise M.N. Ferré[6], Thomas DiMaggio[6], Lindsey B. Rosen[6], Peter D. Burbelo[31], Martin McIntyre[32], Nelli Y. Kann[7], Anna Shcherbina[7], Maria Pavlova[33], Anna Kolodkina[4], Steven M. Holland[6], Shen-Ying Zhang[1,2,3], Yanick J. Crow[14,15], Luigi D. Notarangelo[6], Helen C. Su[6], Laurent Abel[1,2,3], Mark S. Anderson[34], Emmanuelle Jouanguy[1,2,3], Bénédicte Neven[2,5], Anne Puel[1,2,3], Jean-Laurent Casanova[1,2,3,35], and Michail S. Lionakis[6]

J Exp Med 2021

Auto-antibodies to type I IFNs can underlie adverse reactions to yellow fever live attenuated vaccine

Paul Bastard[1,2,3], Eleftherios Michailidis[4*], Hans-Heinrich Hoffmann[4*], Marwa Chbihi[1,2*], Tom Le Voyer[1,2], Jérémie Rosain[1,2], Quentin Philippot[1,2], Yoann Seeleuthner[1], Adrian Gervais[1,2], Marie Materna[1,2], Patricia Mouta Nunes de Oliveira[5], Maria de Lourdes S. Maia[5], Ana Paula Dinis Ano Bom[6], Tamiris Azamor[6], Deborah Araújo da Conceição[5], Ekaterini Goudouris[7], Akira Homma[5], Günther Slesak[8], Johannes Schäfer[8], Bali Pulendran[9,10], Joseph D. Miller[9,11], Ralph Huits[12], Rui Yang[3], Lindsey B. Rosen[13], Lucy Bizien[1,2], Lazaro Lorenzo[1,2], Maya Chrabieh[1,2], Lucia V. Erazo[1], Flore Rozenberg[14], Mohamed Maxime Jeljeli[15], Vivien Béziat[1,2,3], Steven M. Holland[13], Aurélie Cobat[1,3], Luigi D. Notarangelo[13], Helen C. Su[13], Rafi Ahmed[9], Anne Puel[1,2,3], Shen-Ying Zhang[1,2,3], Laurent Abel[1,2,3], Stephen J. Seligman[3,16**], Qian Zhang[3**], Margaret R. MacDonald[4***], Emmanuelle Jouanguy[1,2,3***], Charles M. Rice[4***], and Jean-Laurent Casanova[1,2,3,17***]

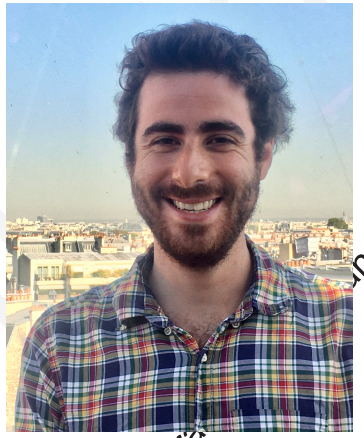
J Exp Med 2021

Crucial Role of TYPE I IFNs in Protective Immunity Against SARS-CoV-2

Université de Paris · imagine INSTITUT DES MALADIES GÉNÉTIQUES · Inserm Institut national de la santé et de la recherche médicale · Necker Enfants Malades Hôpital Universitaire · The Rockefeller University 1901 · ST. GILES FOUNDATION New York, NY · ANR Agence Nationale de la Recherche · Investissements d'Avenir · NIH National Institutes of Health · hhmi Howard Hughes Medical Institute

THE PATIENTS AND THEIR FAMILIES

LABORATORY OF HUMAN GENETICS OF INFECTIOUS DISEASES



PAUL BASTARD

JEAN-LAURENT CASANOVA AND HELEN SU

COVID HUMAN GENETIC EFFORT

1000's COLLABORATORS WORLDWIDE

ESPECIALLY ETABLISSEMENT FRANÇAIS DU SANG

>400 PARTICIPATING CENTERS

ANTI-CYTOKINE AUTO-ABS: AUTOIMMUNE PHENOCOPIES OF INBORN ERRORS OF IMMUNITY

ANTI-CYTOKINE AUTO-ABS BLOCK THE TARGET CYTOKINE BIOLOGICAL FUNCTION

- A UNIQUE INFECTIOUS PHENOTYPE, **MIMICKING** THAT OF PATIENTS WITH GERMLINE MUTATIONS OF THE GENES ENCODING THE CORRESPONDING CYTOKINES/RECEPTORS/SIGNALING MOLECULES

MYCOBACTERIAL DISEASE

AUTO-ANTIBODIES (ABS) TO **IFN-γ**	(2003-)
INBORN ERRORS OF IFN-γ (*IFNG*, *IFNGR1*, *IFNGR2*)	(1996-)

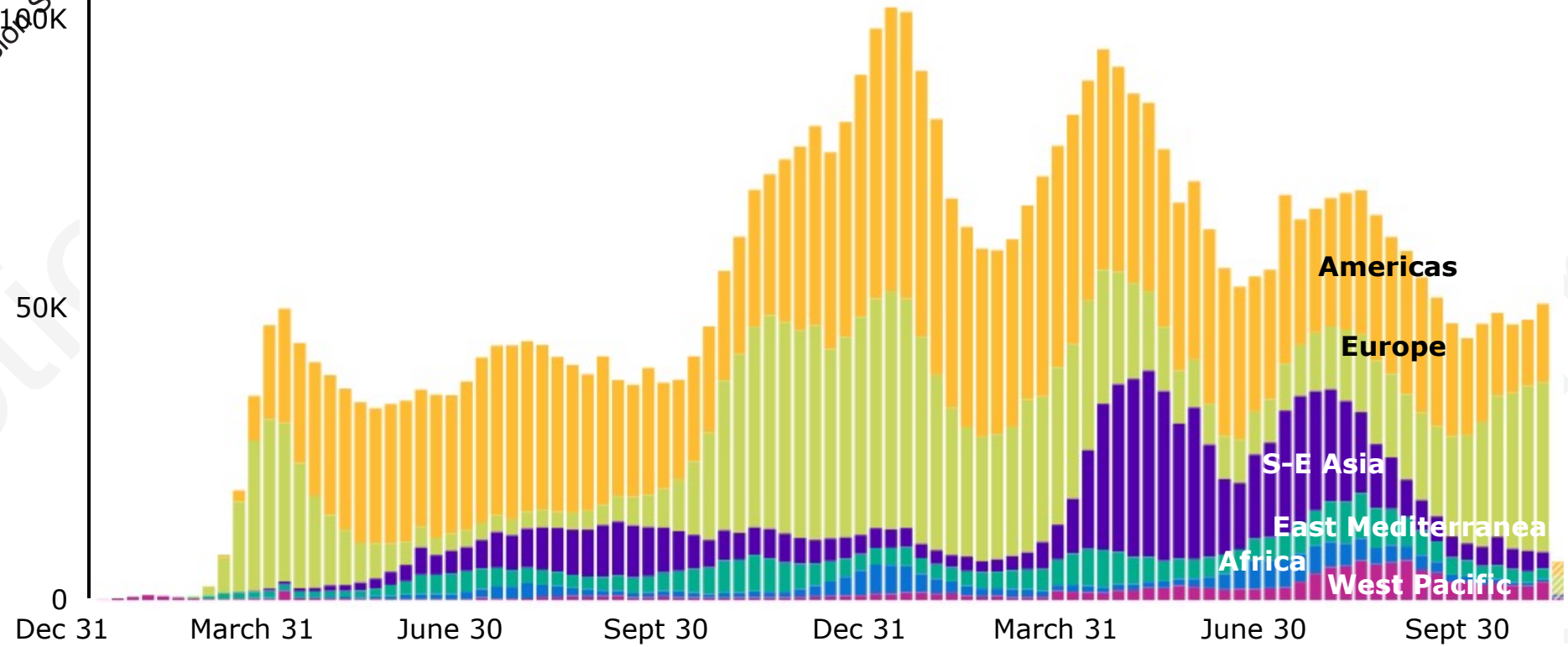
MUCOCUTANEOUS CANDIDIASIS

AUTO-ABS TO **IL-17A** AND **IL-17F**	(2010-)
INBORN ERRORS OF IL-17 (*IL17F*, *IL17RA*, *IL17RC*)	(2011-)

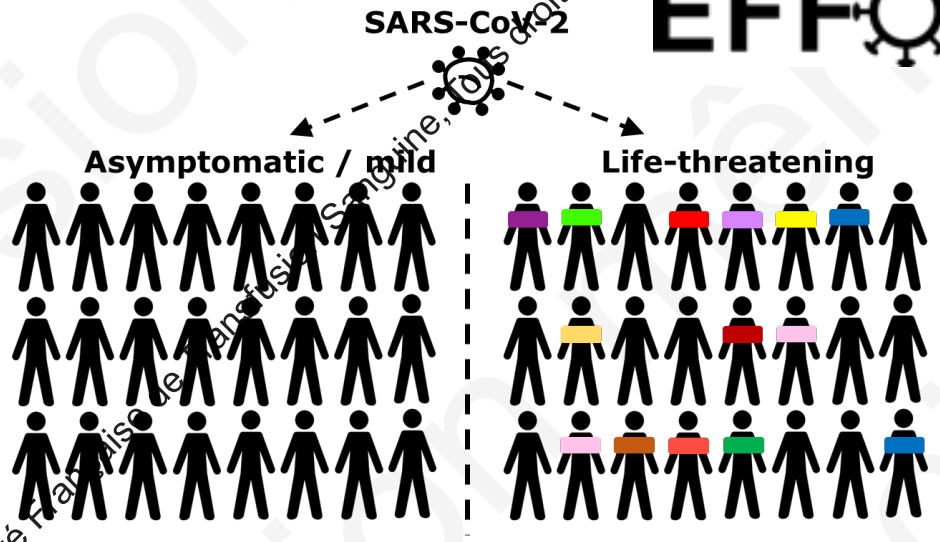
STAPHYLOCOCCAL DISEASE

AUTO-ABS TO **IL-6**	(2008-)
INBORN ERRORS OF IL-6 (*IL6R*)	(2019-)

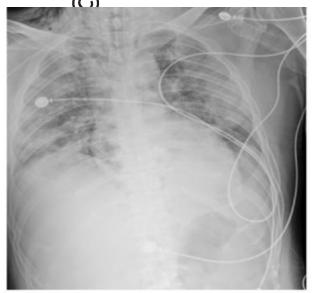
Ku CL et al. *Hum Genet* 2020



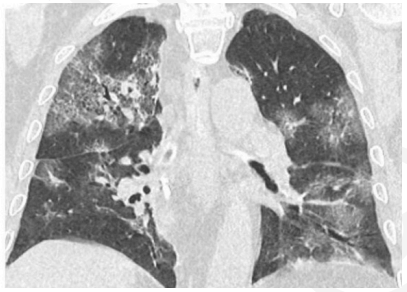
COVID HUMAN GENETIC EFFORT



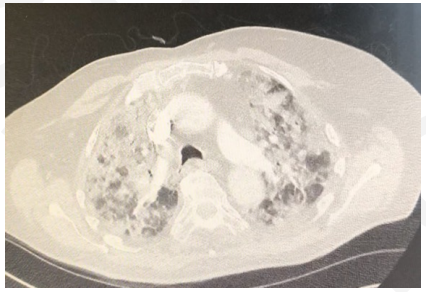
Life-threatening COVID-19 pneumonia



ARDS (Chest X-ray)



Severe Covid neumonia (Chest CT)



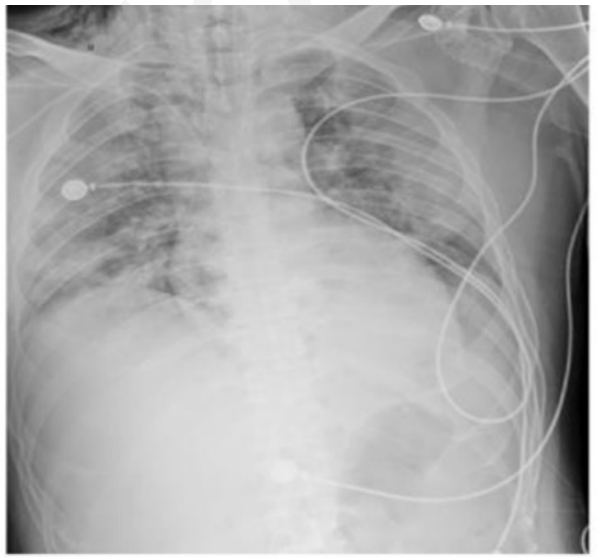
Critical neumonia, ARDS (Chest CT)

>400 participating centers worldwide

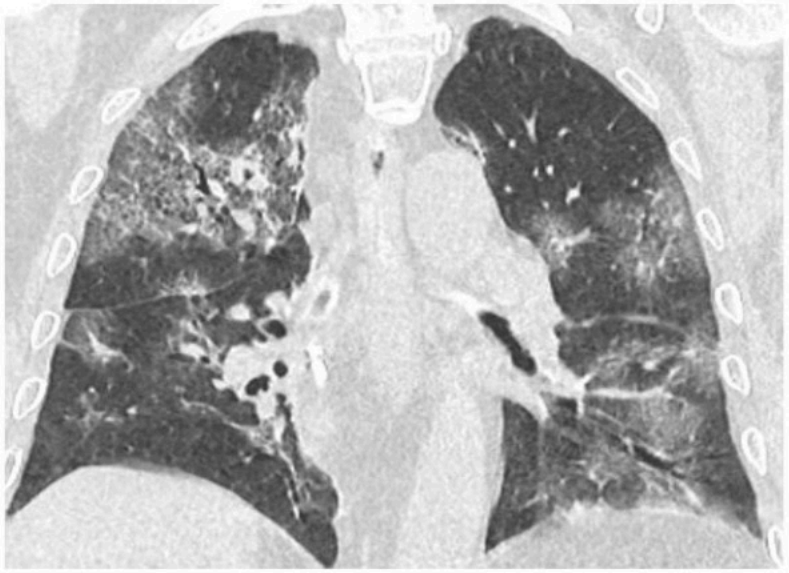
CASANOVA JL, SU HC, CELL 2020

Life-threatening COVID-19 pneumonia

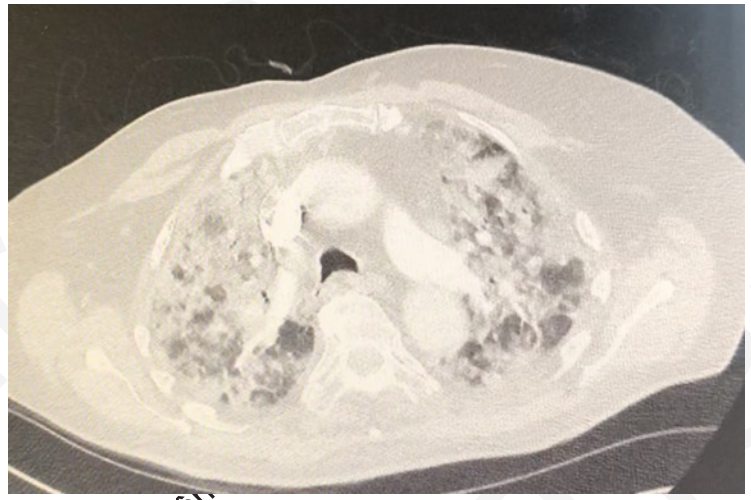
ARDS (Chest X-ray)



Severe Covid neumonia (Chest CT)



Critical neumonia – ARDS (Chest CT)



Prevalence is low, and most infected individuals are asymptomatic or mildly symptomatic

How do we explain such interindividual variability ?