Genética Humana e (Auto)Imunidade na COVID-19

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COVID HUMAN GENETIC EFFORT

https://www.covidhge.com/

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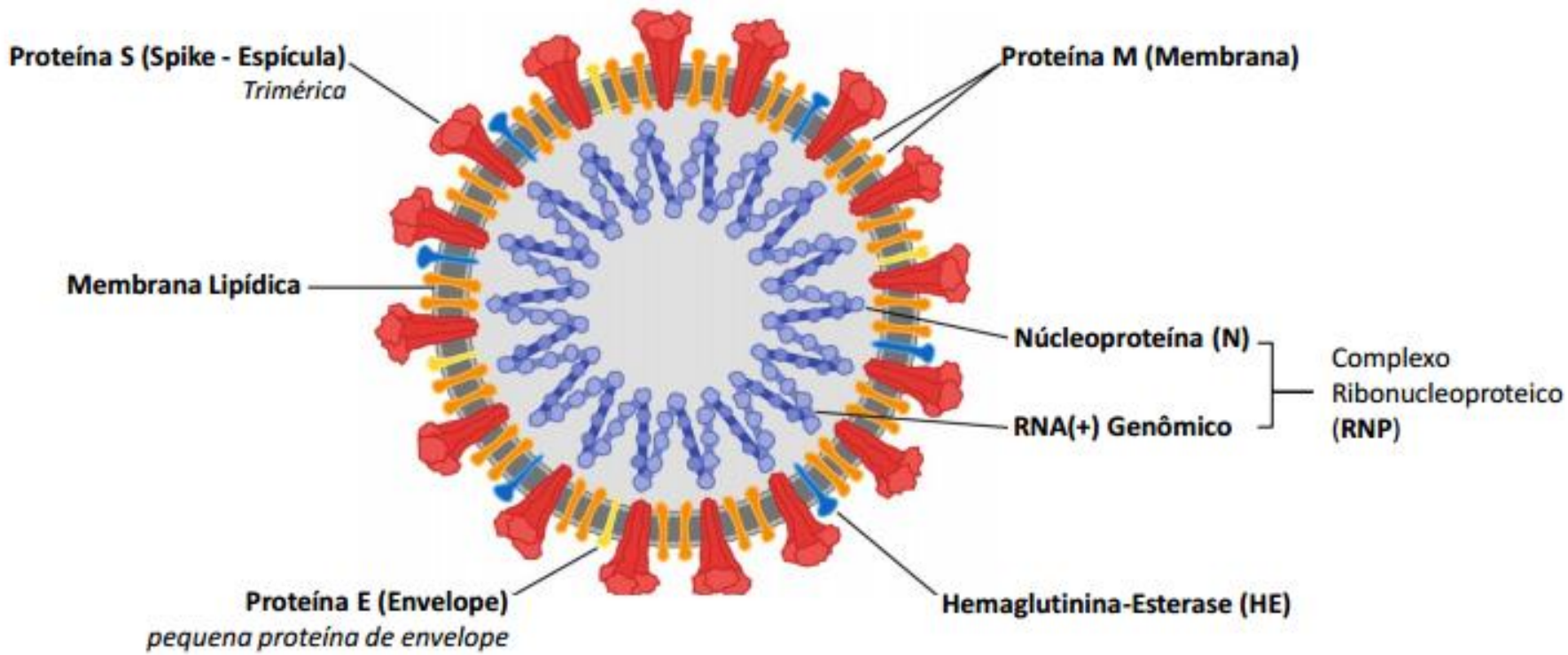
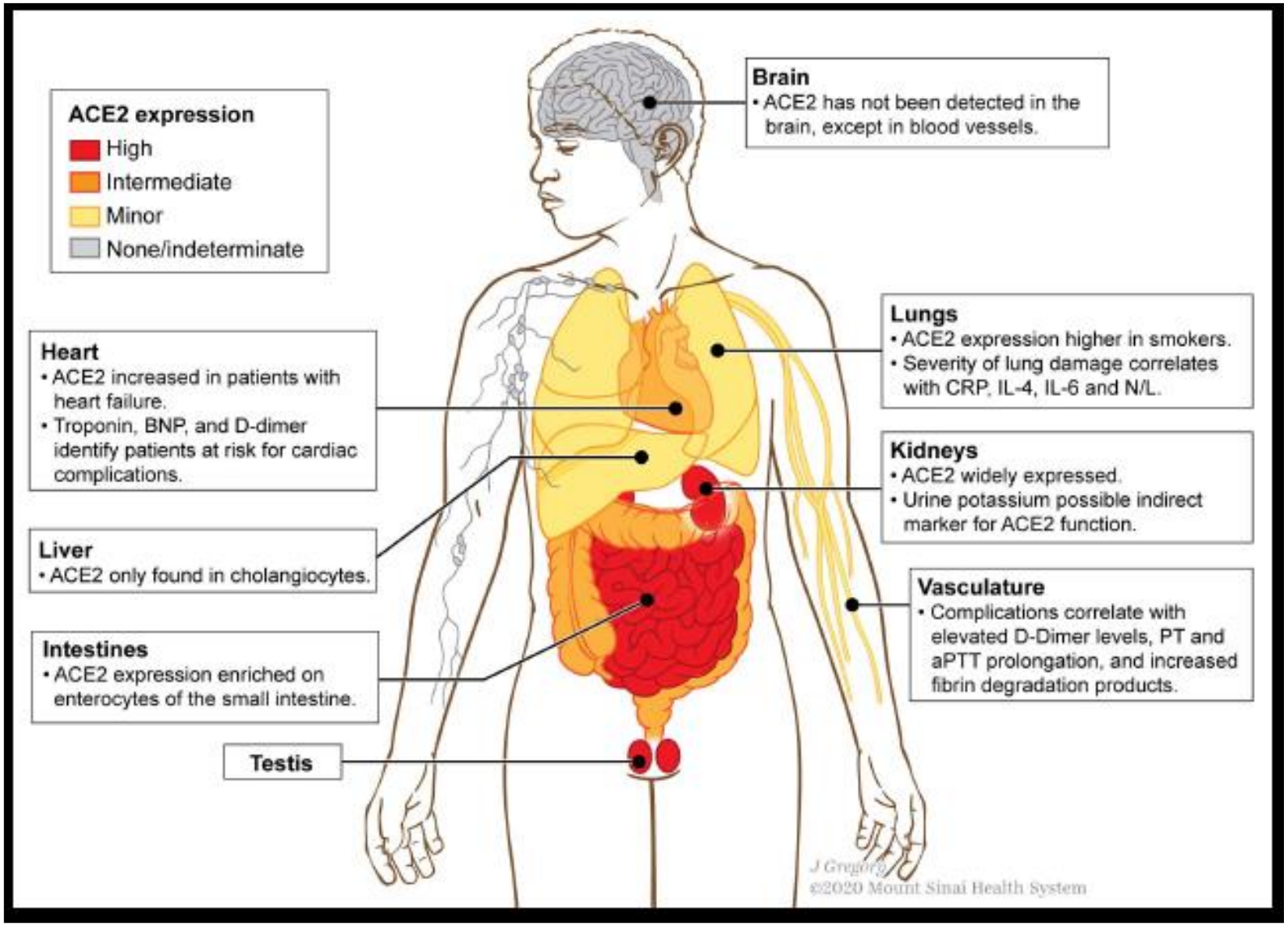
SARS-CoV-2: ANATOMIA VIRAL

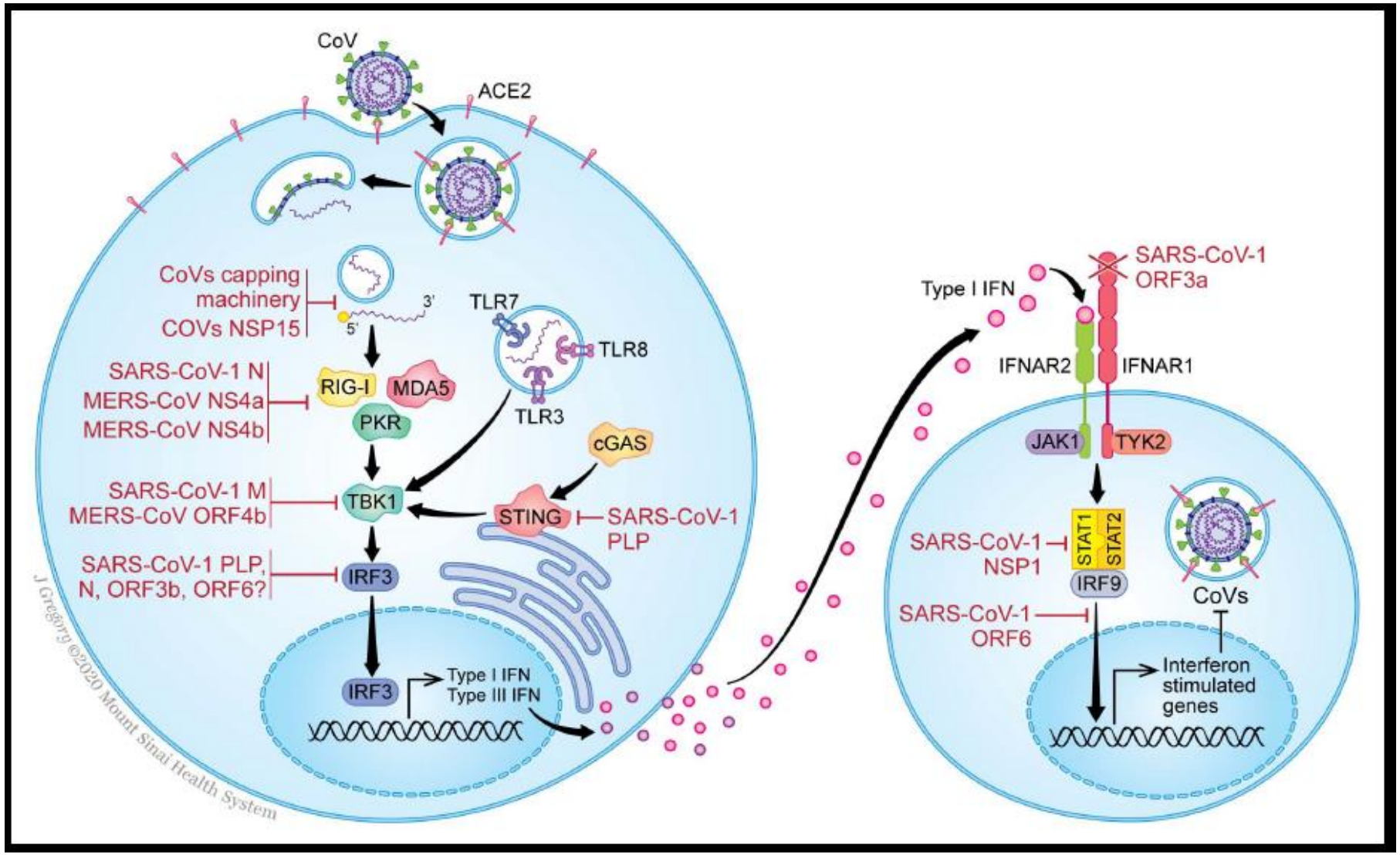


Expressão ACE2 nos diversos órgãos e sistemas



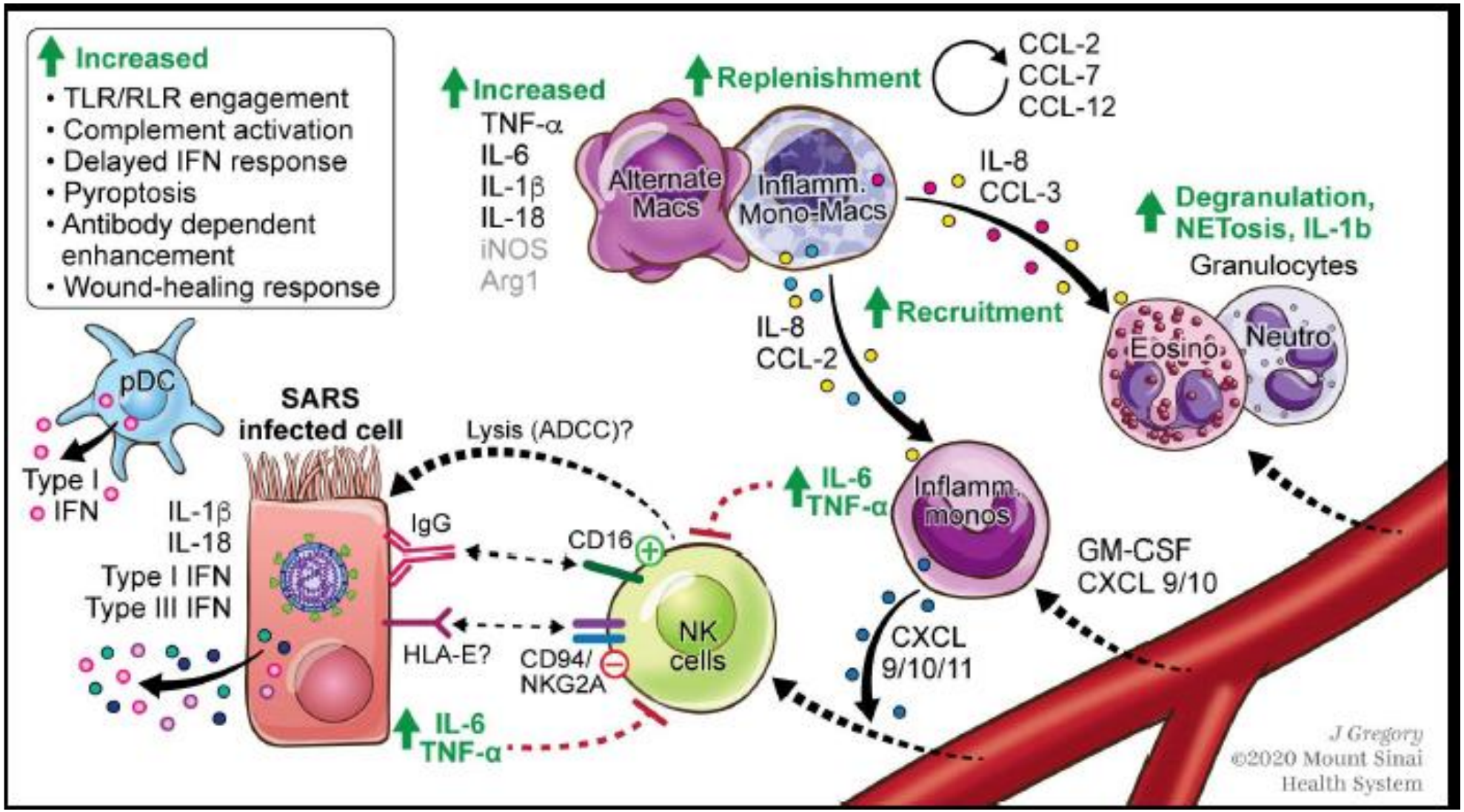
Vabret et al. Immunity, 2020

Imunidade Inata ao Corona Virus



Vabret et al. Immunity, 2020

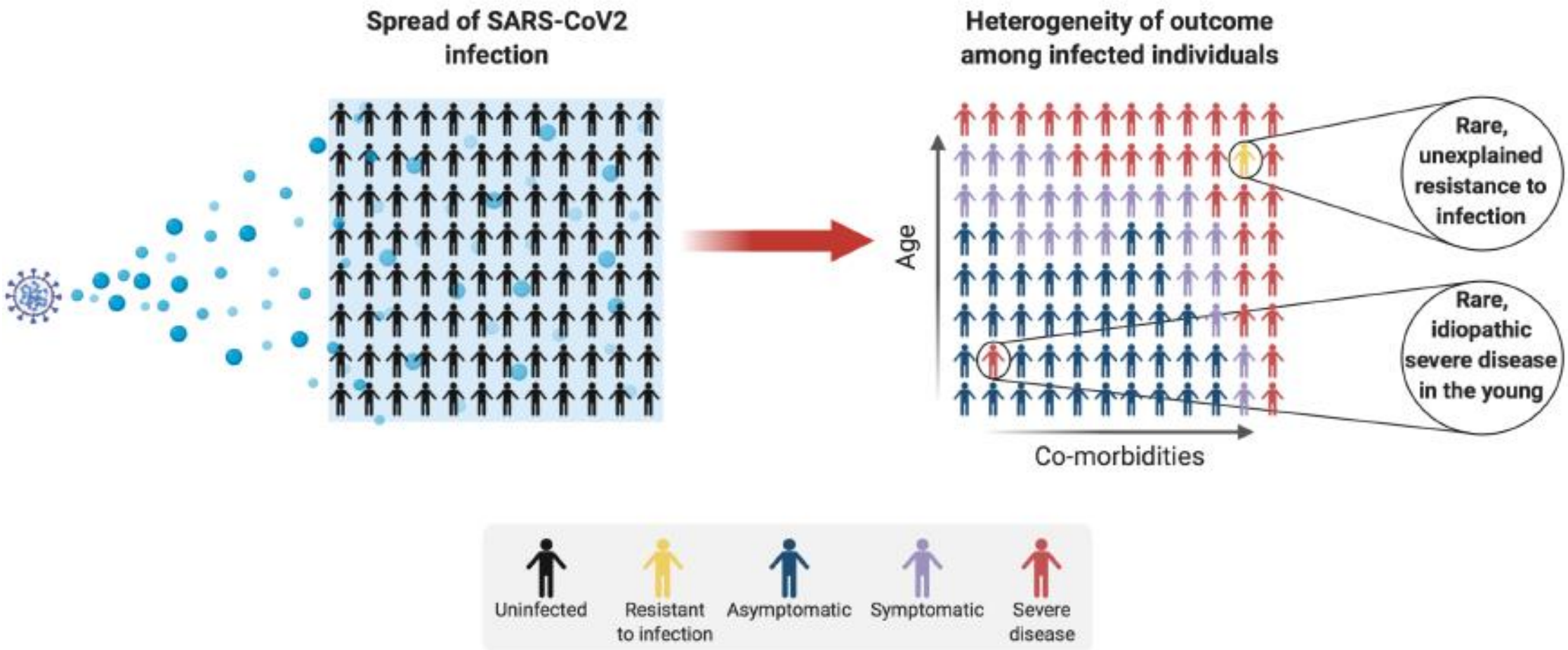
Ativação linhagem mielocítica pelo SARS-Cov2



Vabret et al. Immunity, 2020

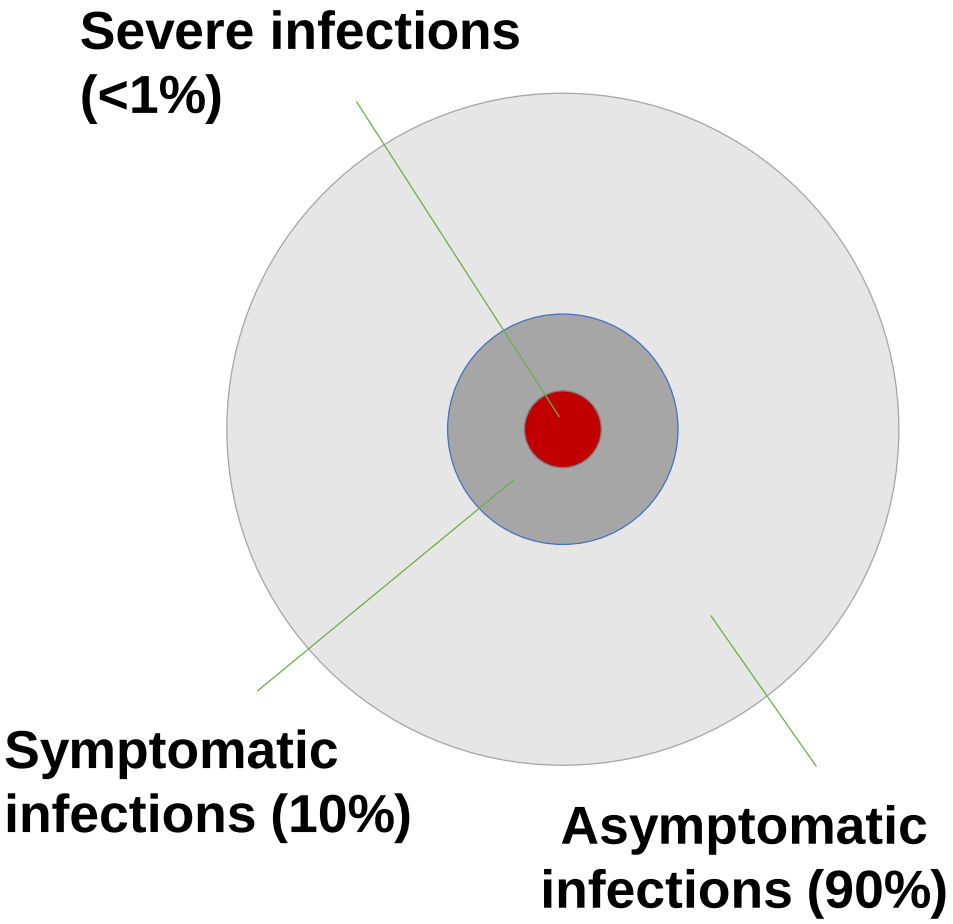
Monogenic causes of COVID-19

SUSCEPTIBILITY or RESISTANCE



Casanova et al. Cell, 2020

Inter-individual clinical variability in the course of SARS-CoV-2 infection



Three epidemiological risk factors:

1. Age. The older the worse.
2. Sex. Being a man is bad.
3. Co-morbidities ?

Yet there remains huge inter-individual clinical variability in each demographic category.

Sick, centenarian men have handled the virus asymptomatically while young healthy women died.

One key question: what is the cause of lethal COVID-19 ?

https://www.covidhge.com/steering-committee

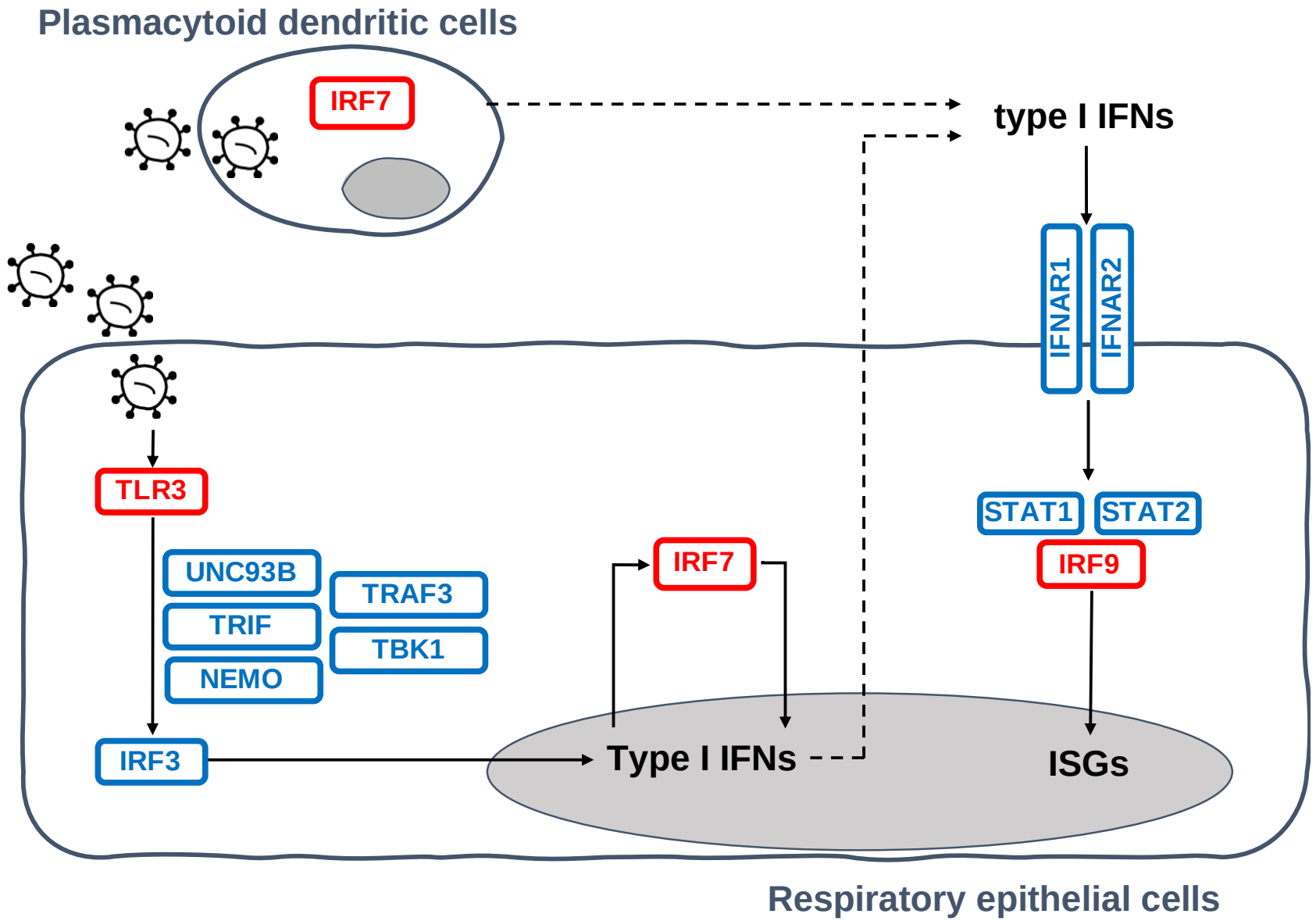
Susceptibilidade genética a doenças virais em humanos

Casanova et al. Cell, 2020

Table 1. Monogenic defects underlying narrow susceptibility to human viral diseases

Outcome	Pathogen (condition)	Gene
Susceptibility	Influenza virus (severe pneumonia)	*IRF7*
		IRF9
		TLR3
	Rhinovirus (severe pneumonia)	*IFIH1*
	Herpes simplex virus 1 (encephalitis)	*UNC93B1*
		TLR3
		TRIF
		TRAF3
		TBK1
		IRF3
		SNORA31
	Herpes simplex virus 1, influenza virus, norovirus (brainstem encephalitis)	*DBR1*
	Beta-papillomavirus (skin warts and cancer)	*TMC6*
		TMC8
		CIB1
	Epstein-Barr virus (hemophagocytosis, lympho-proliferation, lymphoma, hypogammaglobulinemia)	*SH2D1A*
		XIAP
		ITK
		MAGT1
		CD27
		CD70
	Varicella-zoster virus (disseminated disease)	*POLR3A*
		POLR3C
	Human herpes virus-8 (Kaposi sarcoma)	*TNFRSF4*
	Cytomegalovirus (disseminated disease)	*NOS2*
	Hepatitis A virus (fulminant hepatitis)	*IL18BP*
	Live-attenuated measles or yellow fever vaccine (disseminated disease)	*IFNAR1*
		IFNAR2
		STAT2
		IRF9
Resistance	Human immunodeficiency virus	*CCR5*
	Norovirus	*FUT2*

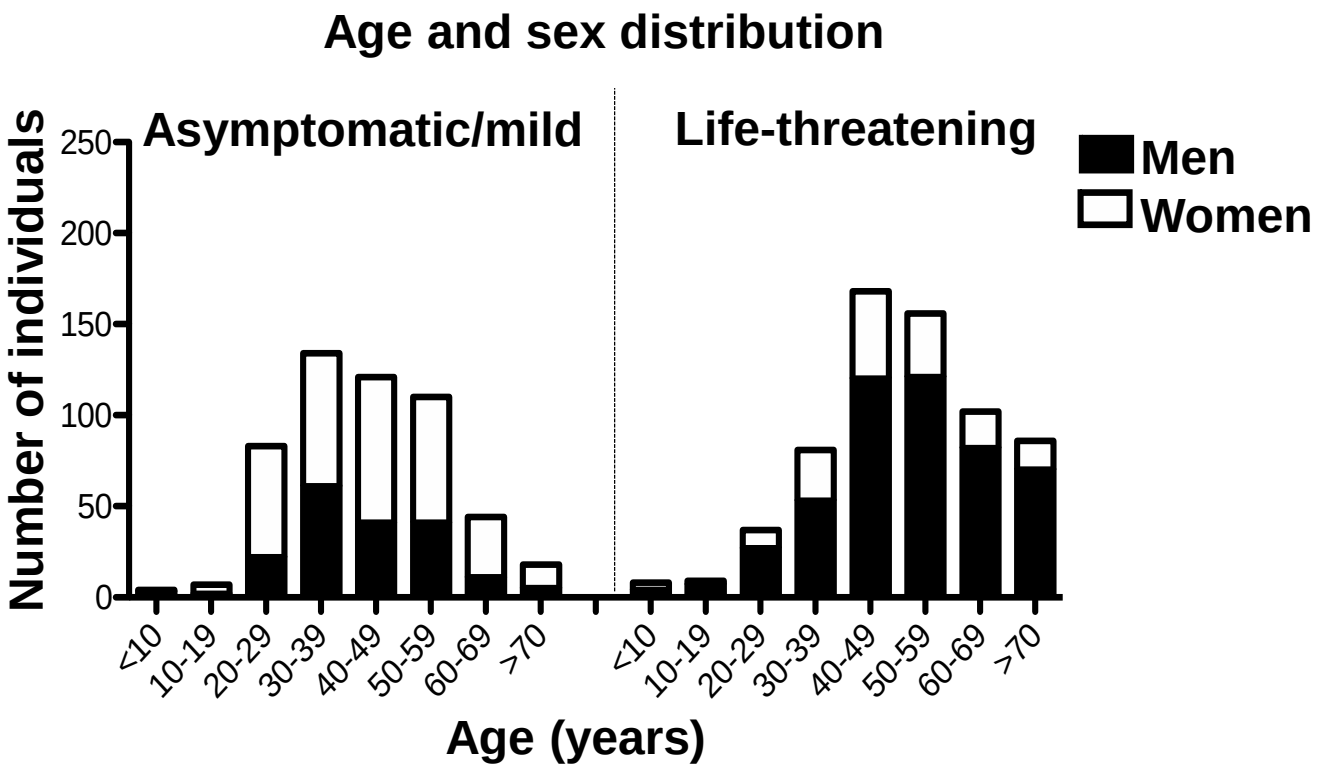
Lethal influenza pneumonia: 13 candidate genes

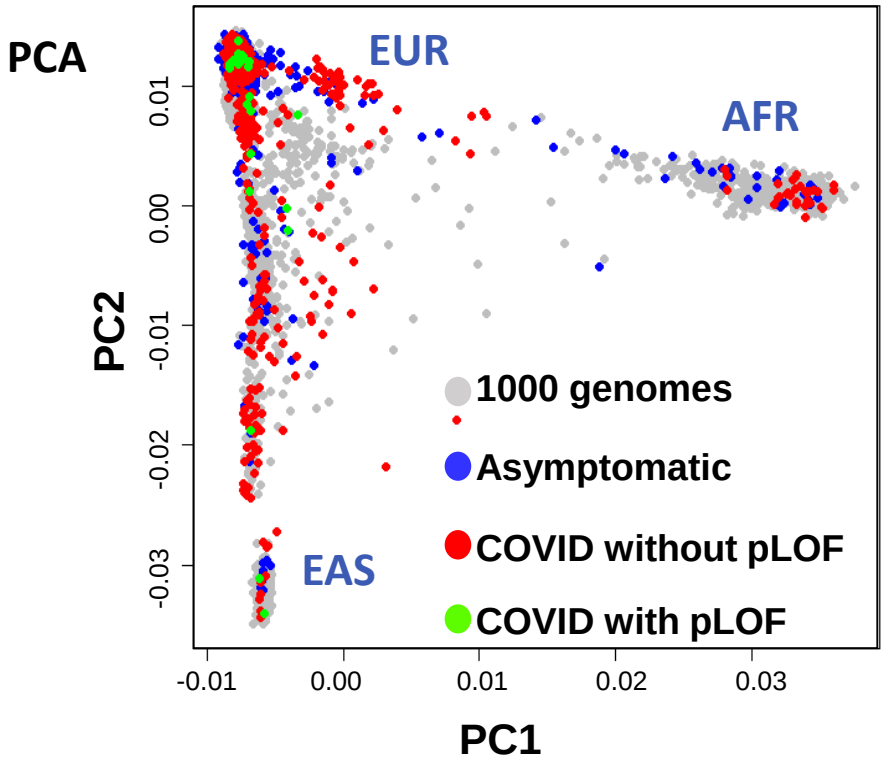


Red: influenza

Blue: other viruses

Enrichment for pLOF variants in critical COVID-19





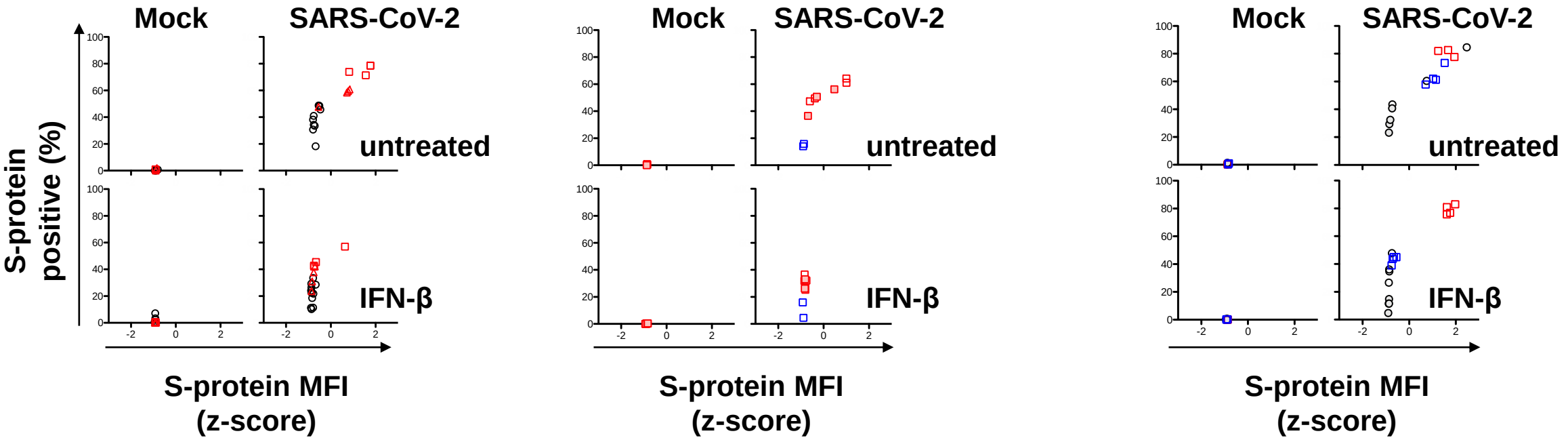
PCA-adjusted burden test pLOF variants MAF < 0.001:
9/659 patients (5 loci), 1/534 controls (OR 8.3, *p* = 0.01)

23 patients (3.5%) with epLOF mutations (8 genes)

Table 1. Disease-causing variants identified in patients with life-threatening COVID-19.

Gene	Inheritance	Genetic form	Genotype	Gender	Age (year)	Ancestry/Residence	Outcome
TLR3	AD	Known	p.Ser339fs/WT	M	40	Spain	Survived
TLR3	AD	Known	p.Pro554Ser/WT	M	68	Italy	Survived
TLR3	AD	Known	p.Trp769*/WT	M	77	Italy	Survived
TLR3	AD	Known	p.Met870Val/WT	M	56	Colombia/Spain	Survived
UNC93B1	AD	New	p.Glu96*/WT	M	48	Venezuela/Spain	Survived
TICAM1	AD	Known	p.Thr4Ile/WT	M	49	Italy	Survived
TICAM1	AD	Known	p.Ser60Cys/WT	F	61	Vietnam/France	Survived
TICAM1	AD	Known	p.Gln392Lys/WT	F	71	Italy	Deceased
TBK1	AD	Known	p.Phe24Ser/WT	F	46	Venezuela/Spain	Survived
TBK1	AD	Known	p.Arg308*/WT	M	17	Turkey	Survived
IRF3	AD	Known	p.Glu49del/WT	F	23	Bolivia/Spain	Survived
IRF3	AD	Known	p.Asn146Lys/WT	F	60	Italy	Survived
IRF7	AR	Known	p.Pro364fs/p.Pro364fs	F	49	Italy/Belgium	Survived
IRF7	AR	Known	p.Met371Val/p.Asp117Asn	M	50	Turkey	Survived
IRF7	AD	New	p.Arg7fs/WT	M	60	Italy	Survived
IRF7	AD	New	p.Gln185*/WT	M	44	France	Survived
IRF7	AD	New	p.Pro246fs/WT	M	41	Spain	Survived
IRF7	AD	New	p.Arg369Gln/WT	M	69	Italy	Survived
IRF7	AD	New	p.Phe95Ser/WT	M	37	Turkey	Survived
IFNAR1	AR	Known	p.Trp73Cys/Trp73Cys	M	38	Turkey	Survived
IFNAR1	AR	Known	p.Ser422Arg/Ser422Arg	M	26	Pakistan/Saudi Arabia	Deceased
IFNAR1	AD	New	p.Pro335del/WT	F	23	China/Italy	Survived
IFNAR2	AD	New	p.Glu140fs/WT	F	54	Belgium	Survived

Impaired intrinsic immunity to SARS-CoV-2



- ○ *TLR3* WT/WT
- △ *TLR3* P554S/WT
- □ *TLR3* P554S/E746*

- □ *IRF7* F410V/Q421*
- □ *IRF7* F410V/Q421* + LUC
- □ *IRF7* F410V/Q421* + WT

- ○ *IFNAR1* WT/WT + EV
- ○ *IFNAR1* WT/WT + WT
- □ *IFNAR1* V225fs/V225fs + EV
- □ *IFNAR1* V225fs/V225fs + WT

Inborn errors of type I IFNs

Zhang Q. et al. *Science* Sept 24

Qian Zhang, Paul Bastard†, Zhiyong Liu†, Jérémie Le Pen†, Marcela Moncada-Velez†, Jie Chen†, Masato Ogishi†, Ira K D Sabli†, Stephanie Hodeib†, Cecili Korol†, Jérémie Rosain†, Kaya Bilguvar†, Junqiang Ye†, Alexandre Bolze†, Benedetta Bigio†, Rui Yang†, Andres Augusto Arias Sierra†, Qinhua Zhou†, Yu Zhang†, Fanny Onodi, Sarantis Korniotis, Léa Karpf, Quentin Philippot, M Chbihi, L Bonnet-Madin, Karim Dorgham, Nikaïa Smith, William M. Schneider, Brandon S. Razooky, Hans-Heinrich Hoffmann, Eleftherios Michailidis, Leen Moens, Ji Eun Han, Lazaro Lorenzo, Lucy Bizien, Philip Meade, Anna-Lena Neehus, Aileen Camille Ugurbil, A Corneau, Gaspard Kerner, Peng Zhang, Franck Rapaport, Yoann Seeleuthner, Jeremy Manry, Cecile Masson, Yohann Schmitt, A Schlüter, Tom Le Voyer, Taushif Khan, J Li, Jacques Fellay, Lucie Roussel, Mohammad Shahrooei, Mohammed F. Alosaimi, Davood Mansouri, Haya Al-Saud, Fahd Al-Mulla, Feras Almourfi, Saleh Zaid Al-Muhsen, Fahad Alsohime, Saeed Al Turki, Rana Hasanato, Diederik van de Beek, Andrea Biondi, Laura Rachele Bettini, Mariella D'Angio', Paolo Bonfanti, Luisa Imberti, Alessandra Sottini, S Paghera, E Quiros-Roldan, Camillo Rossi, Andrew J. Oler, MF. Tompkins, Camille Alba, Isabelle Vandernoot, Jean-Christophe Goffard, Guillaume Smits, Isabelle Migeotte, Filomeen Haerynck, Pere Soler-Palacin, Andrea Martin-Nalda, Roger Colobran, Pierre-Emmanuel Morange, Sevgi Keles, Tayfun Ozcelik, Kadriye Kart Yasar, Sevtap Senoglu, Şemsi Nur Karabela, Carlos Rodríguez Gallego, Giuseppe Novelli, Sami Hraiech, Yacine Tandjaoui-Lambiotte, Xavier Duval, Cédric Laouenan, COVID-STORM Clinicians*, COVID Clinicians**, Imagine COVID group***, French COVID Cohort Study Group****, CoV-Contact Cohort*****, Amsterdam UMC Covid 19 Biobank******, COVID Human Genetic Effort*******, NIAID-USUHS/TAGC COVID Immunity Group********, Andrew L. Snow, Clifton L. Dalgard, J Milner, Donald C. Vinh, Trine H. Mogensen, N Marr, András N. Spaan, B Boisson, S Boisson-Dupuis, Jacinta Bustamante, Anne Puel, Michael Ciancanelli Isabelle Meyts, Tom Maniatis, Vassili Soumelis, Ali Amara, Michel Nussenzweig, Adolfo García-Sastre, Florian Krammer, Aurora Pujol, Darragh Duffy, Richard Lifton§, Shen-Ying Zhang§, Guy Gorochov§, Vivien Béziat§, Emmanuelle Jouanguy§, Vanessa Sancho-Shimizu§, Charles M. Rice§, Laurent Abel§, Luigi D. Notarangelo#, Aurélie Cobat#, Helen C. Su#, Jean-Laurent Casanova#@

Auto-immune phenocopies of inborn errors of cytokines

Auto-Antibodies (Abs) to IFN-γ	**(2003-)**	**Mycobacterial disease**
Inborn errors of IFN-γ (*IFNG*, *IFNGR1*, *IFNGR2*)	**(1996-)**	
Auto-Abs to IL-17A and IL-17F	**(2010-)**	**Mucocutaneous candidiasis**
Inborn errors of IL-17 (*IL17F*, *IL17RA*, *IL17RC*)	**(2011-)**	
Auto-Abs to IL-6	**(2008-)**	**Staphylococcal disease**
Inborn errors of IL-6 (*IL6R*)	**(2019-)**	

These adaptive auto-immune attacks on intrinsic, innate, and/or adaptive immunity are themselves genetically driven (e.g. Auto-Abs to IL-17 in patients with AIRE deficiency)

Auto-Abs to type I IFNs in critical COVID-19 ?

Inborn errors of type I IFN (*IFNAR1*, *IFNAR2*) **(2015-)**

Viral vaccine disease (MMR, YFV)
Herpes simplex virus encephalitis
Critical COVID-19

How about auto-Abs to type I IFNs ?

They are found:

In nearly all patients with APS-1 (*AIRE*) **Clinically silent**
In a minority of patients treated with IFN-α2b or IFN-β
In a small minority of women with SLE

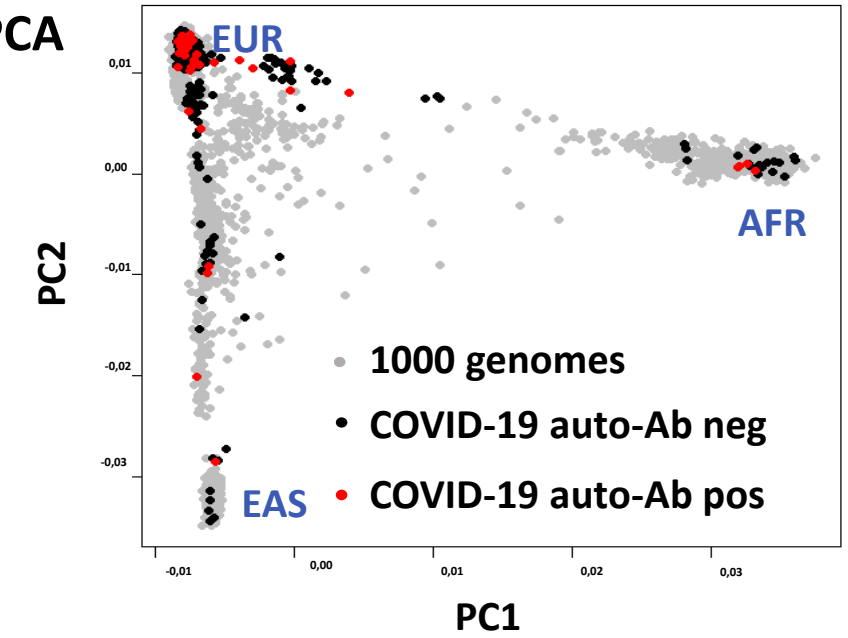
In one patient with severe varicella (Ion Gresser, 1985) **Unusual viral illnesses**
In a few patients with various viral infections (*RAG1*, *RAG2*)

And we found three APS-1 patients … **… with critical COVID-19**

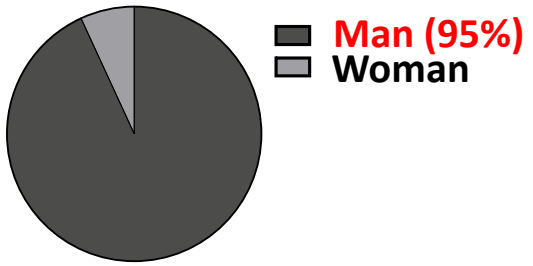
Auto-Abs to type I IFNs in >10% of patients with life-threatening COVID-19

	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	$p < 10^{-16}$

PCA



COVID-19 auto-Ab pos



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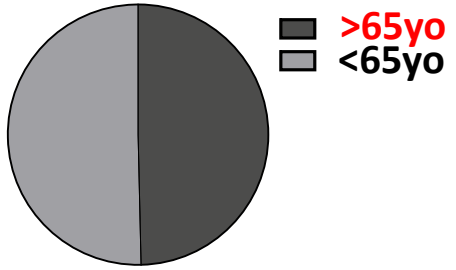
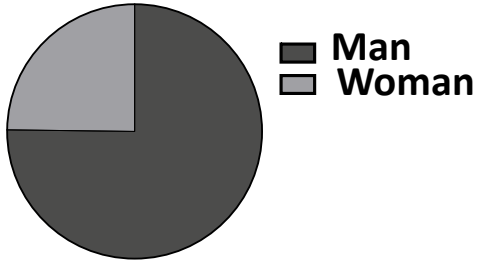
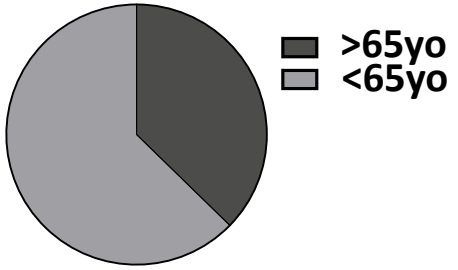


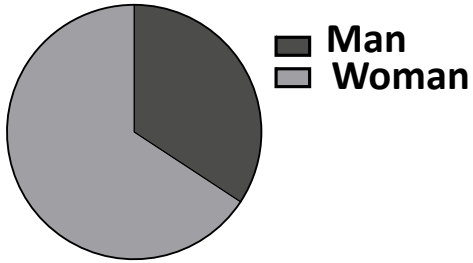
COVID-19 auto-Ab neg



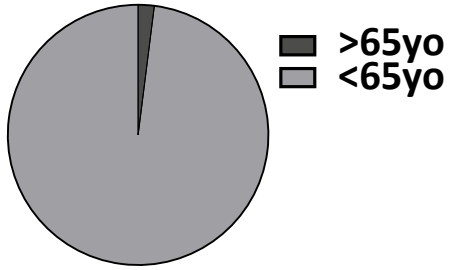
COVID-19 auto-Ab neg



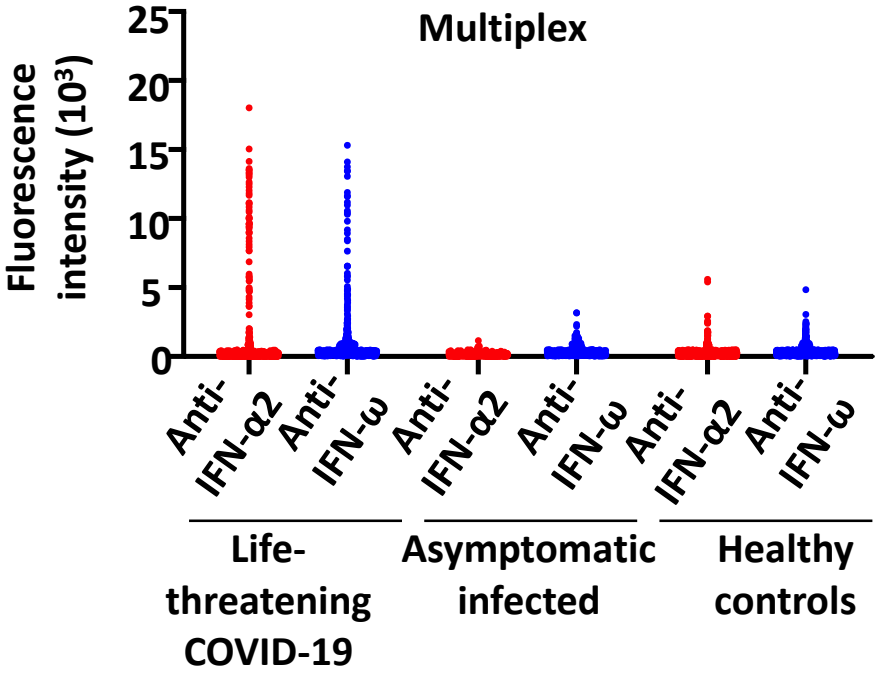
Asymptomatic / auto-Ab neg

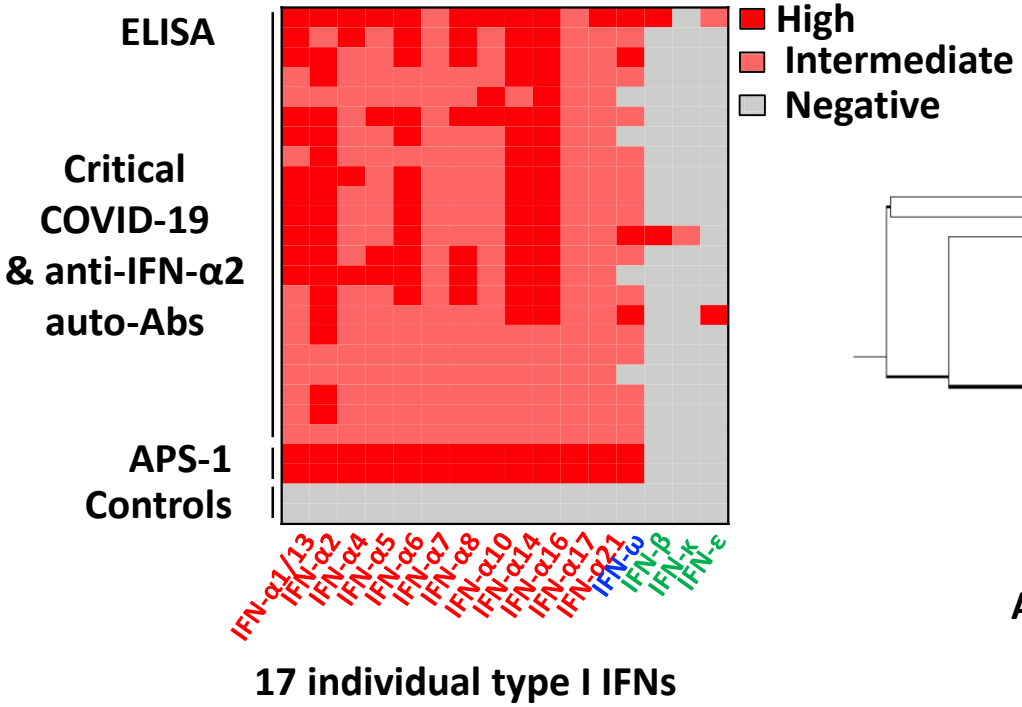


Asymptomatic / auto-Ab neg

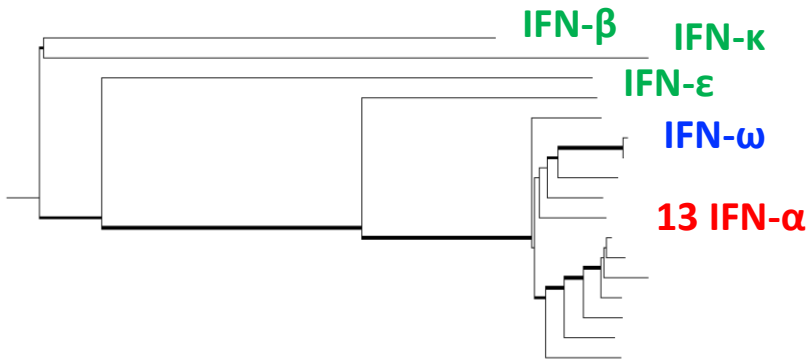


Auto-Abs to ‘systemic’ type I IFNs



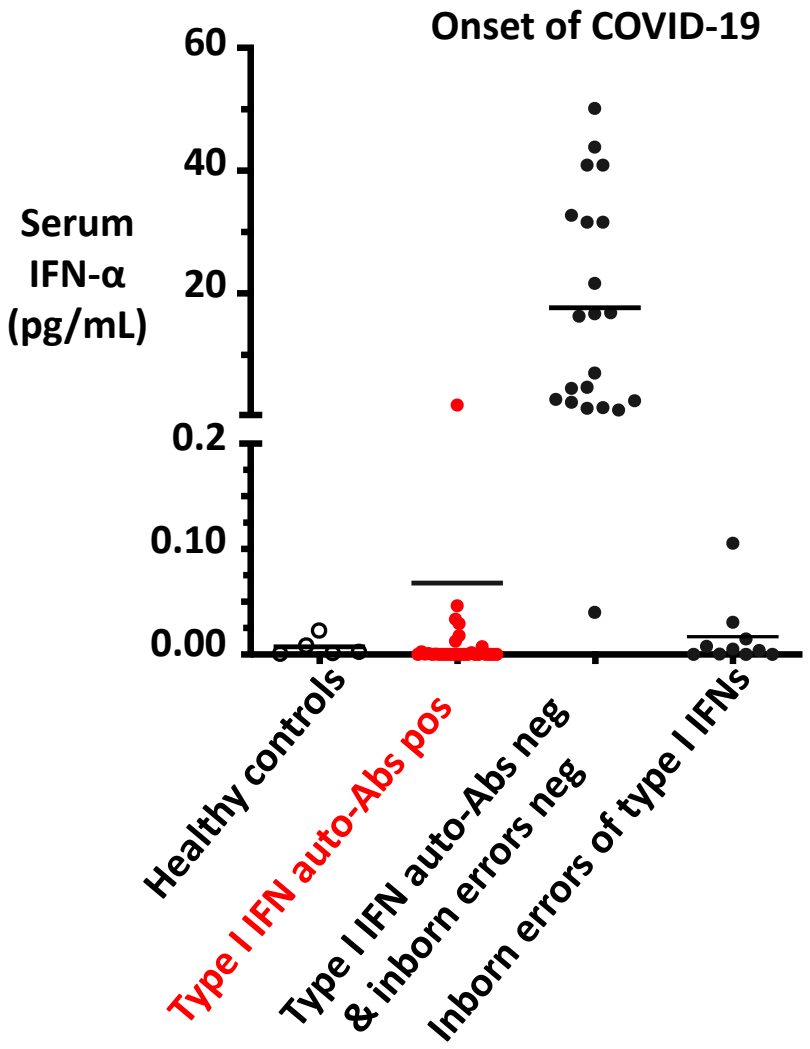


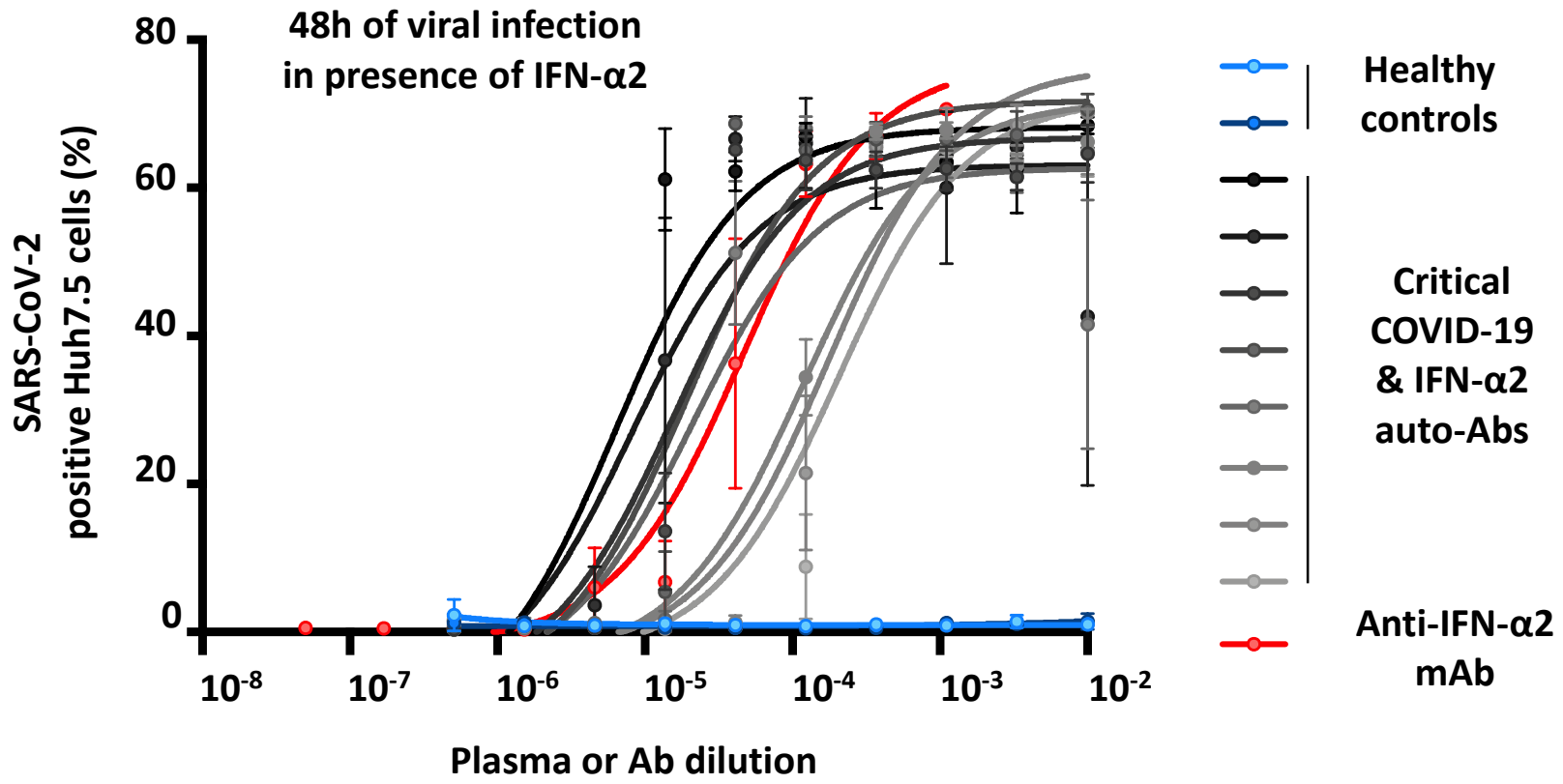
17 individual type I IFNs



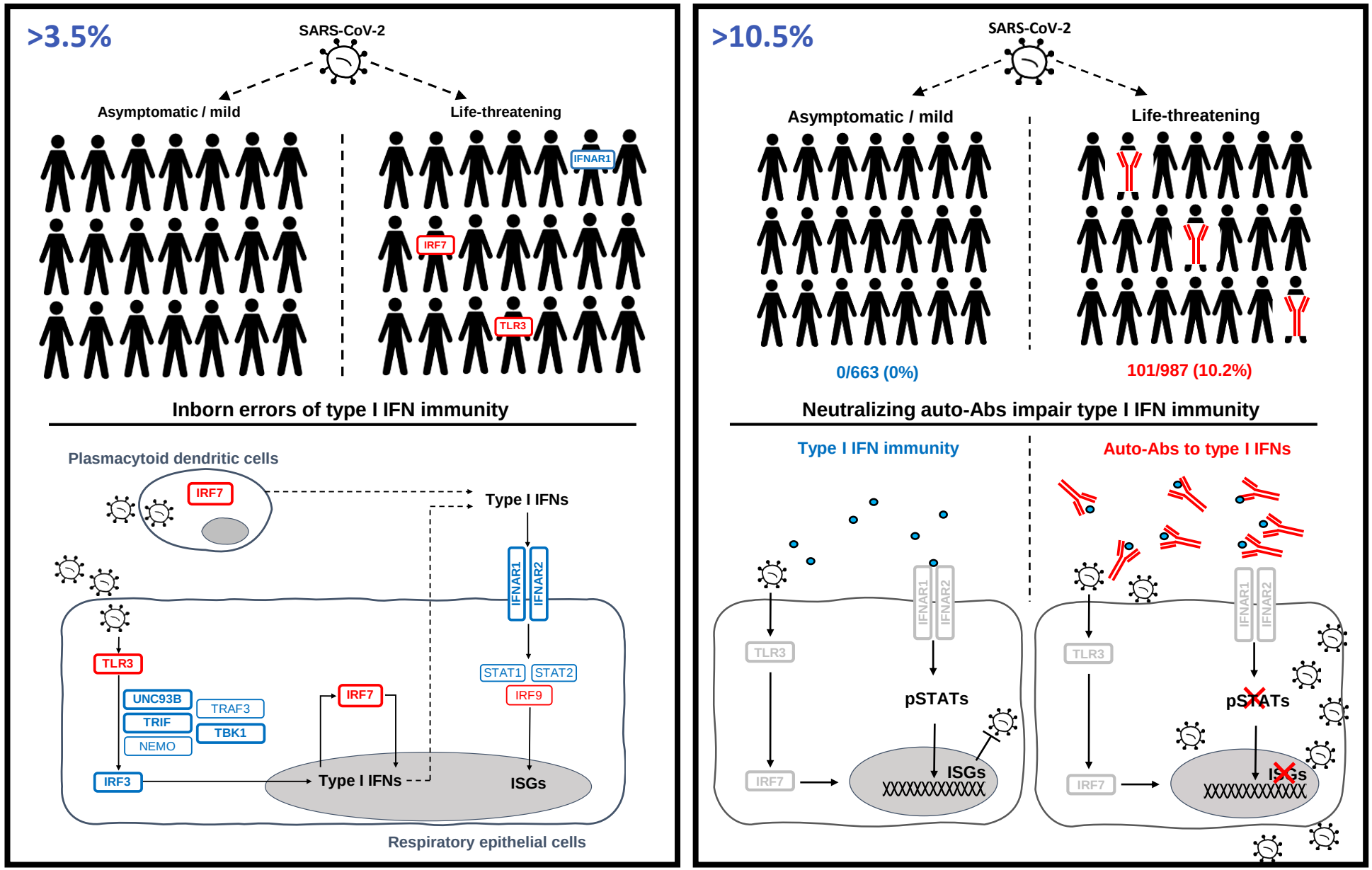
A type I IFN tree

Neutralizing auto-Abs *in vivo* and *in vitro*





Impaired type I IFN immunity in critical COVID-19



Auto-Abs to type I IFNs

Bastard P. et al. *Science* Sept 24

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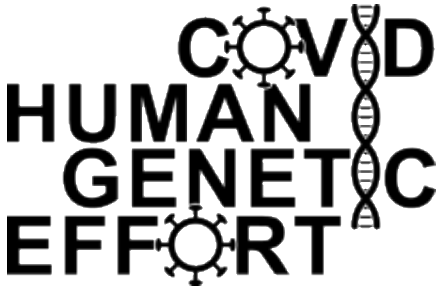
Possíveis implicações terapêuticas

- Corticóide - ok
- Antibióticos – ok
- Terapia com plasma convalescente ??
- Plasmaferese ?
- Reposição Interferon ? Alfa ?? Beta ?
- Reposição imunoglobulinas ?
- Terapia anti-CD20 ?



E as vacinas .... Qual o futuro ? .....

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Zhang Q et al. Inborn errors of type I IFNs in patients with life-threatening COVID-19. *Science* (Online Research Article). 2020, Sept 24

Bastard P. et al. Auto-Abs to type I IFNs in patients with life-threatening COVID-19. *Science* (Online Research Article). 2020, Sept 24