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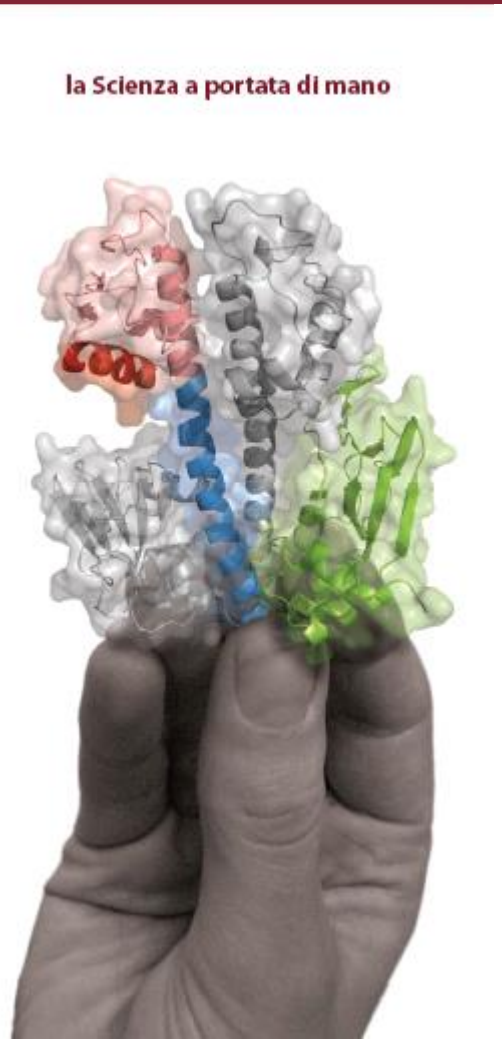

Comunicazione delle Scienze Biomediche

Prof.ssa Cristina Cerboni

SARS-CoV-2

Anno Accademico 2023-2024

Cenni «storici»

Cell *182*, September 3, 2020

Perspective

Emerging Pandemic Diseases: How We Got to COVID-19

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SUMMARY

Infectious diseases prevalent in humans and animals are caused by pathogens that once emerged from other animal hosts. In addition to these established infections, new infectious diseases periodically emerge. In extreme cases they may cause pandemics such as COVID-19; in other cases, dead-end infections or smaller epidemics result. Established diseases may also re-emerge, for example by extending geographically or by becoming more transmissible or more pathogenic. Disease emergence reflects dynamic balances and imbalances, within complex globally distributed ecosystems comprising humans, animals, pathogens, and the environment. Understanding these variables is a necessary step in controlling future devastating disease emergences.

Table 1. Emerging Infectious Diseases in History

Year	Name	Deaths	Comments
430 BCE	"Plague of Athens"	~100,000	First identified trans-regional pandemic
541	Justinian plague (*Yersinia pestis*)	30–50 million	Pandemic; killed half of world population
1340s	"Black Death" (*Yersinia pestis*)	~50 million	Pandemic; killed at least a quarter of world population
1494	Syphilis (*Treponema pallidum*)	>50,000	Pandemic brought to Europe from the Americas
c. 1500	Tuberculosis	High millions	Ancient disease; became pandemic in Middle Ages
1520	*Hueyzahuatl* (*Variola major*)	3.5 million	Pandemic brought to New World by Europeans
1793–1798	"The American plague"	~25,000	Yellow fever terrorized colonial America
1832	2nd cholera pandemic (Paris)	18,402	Spread from India to Europe/Western Hemisphere
1918	"Spanish" influenza	~50 million	Led to additional pandemics in 1957, 1968, 2009
1976–2020	Ebola	15,258	First recognized in 1976; 29 regional epidemics to 2020
1981	Acute hemorrhagic conjunctivitis	rare deaths	First recognized in 1969; pandemic in 1981
1981	HIV/AIDS	~37 million	First recognized 1981; ongoing pandemic
2002	SARS	813	Near-pandemic
2009	H1N1 "swine flu"	284,000	5th influenza pandemic of century
2014	Chikungunya	uncommon	Pandemic, mosquito-borne
2015	Zika	~1,000?*	Pandemic, mosquito-borne

Selected important emerging and re-emerging infectious diseases of the past and present, 430 BCE–2020 CE. Mortality estimates are in most cases imprecise; see text.
*Zika mortality has not been fully established. Most deaths are fetal or related to outcomes of severe congenital infections.

Year(s)	Disease	Geography	Deaths
1899–23	Cholera (6th)	Europe, Asia, Africa	80,000
1910–12	China Bubonic Plague	China	40,000
1918–20	Spanish Flu	Worldwide	50,000,000
1957–58	Asian Flu	Worldwide	2,000,000
1968–69	Hong Kong Flu	Worldwide	1,000,000
1960–	HIV/AIDS	Worldwide	30,000,000
2002–04	SARS (Coronavirus)	Asia, Canada	<1,000
2009	Flu Pandemic	Worldwide	203,000
2019	Coronavirus (COVID-19)	Worldwide	>3,000

SOURCE: Ruthven Institute 03/0

24 October 2023: 771.679.618 confirmed cases, including **6.977.023 deaths**, and a total of **13.534.457.273 vaccine doses** administered.

World Health Organization

CoV phylogenetic tree

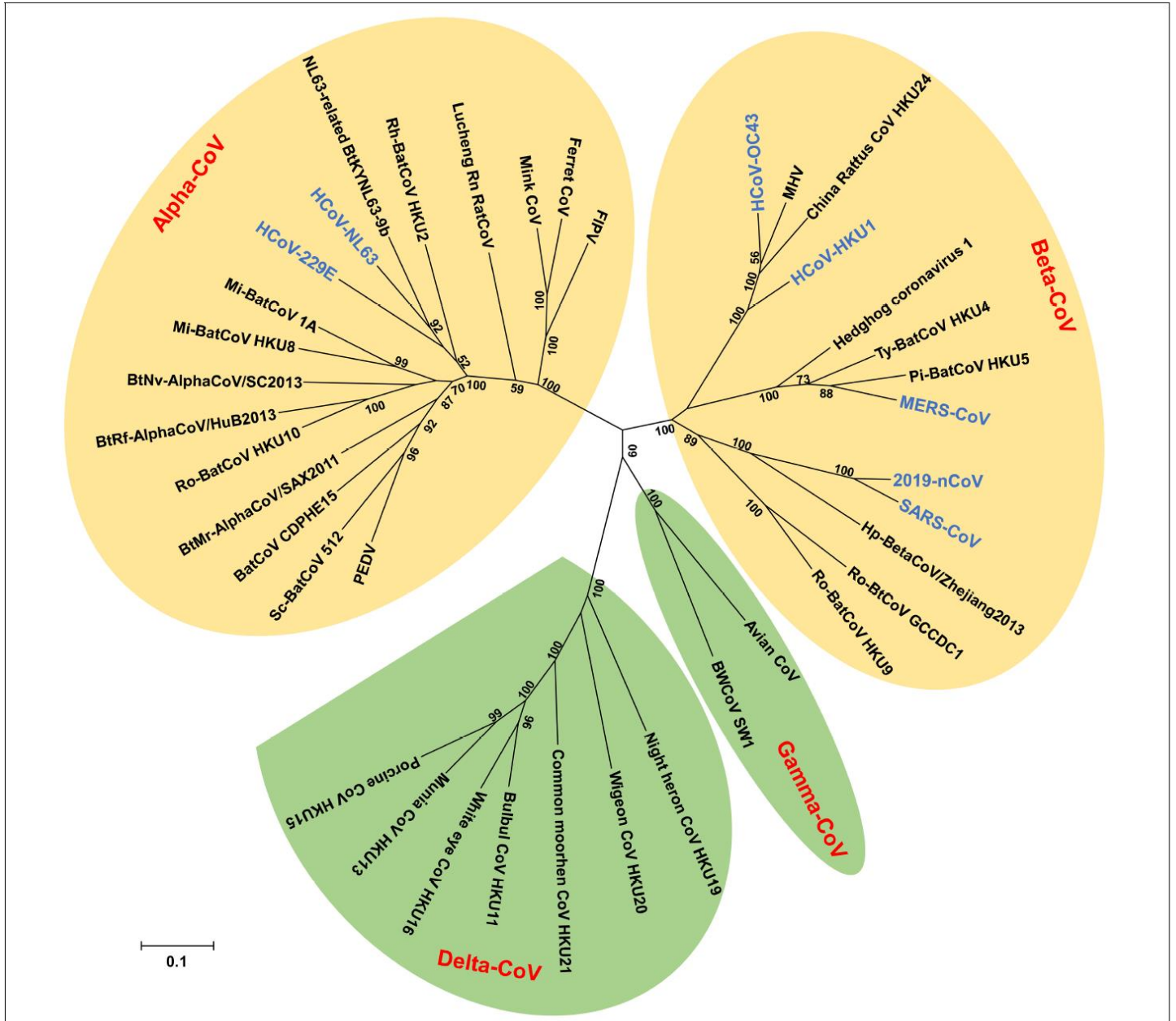
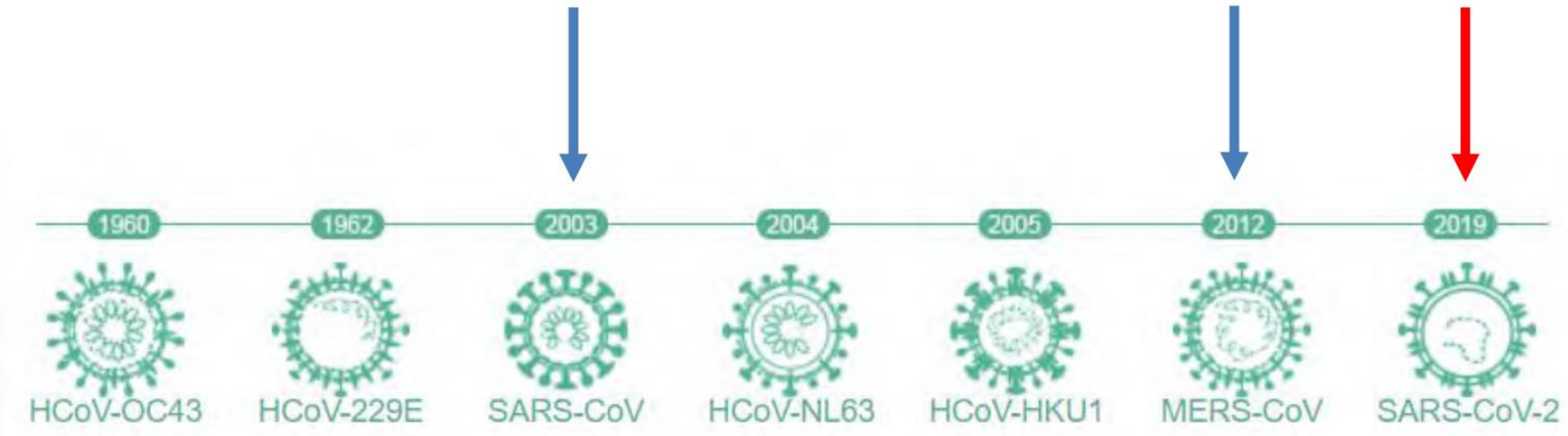


FIGURE 1 | Phylogenetic tree of coronaviruses (CoVs) based on the nucleotide sequences of RNA dependent RNA polymerase (RdRp). The Tree, with 1,000 bootstrap values, was constructed by the maximum likelihood method using MEGA 6. The four main phylogenetic clusters correspond to genera alpha-CoV, beta-CoV, gamma-CoV, and delta-CoV. Each CoV genus contains different subgenera. The letters in blue indicate human CoVs.

(breve) cronistoria dei CoV umani



Mortality rate:			9%			>30%	3-5%?

(breve) descrizione dei CoV umani

Types	Genera	Disease
 SARS-CoV-2 (2019-nCoV)	Betacoronavirus	Coronavirus disease 2019 (COVID-19). Up to 20th Feb, >2100 deaths
 SARS-CoV	Betacoronavirus	Severe acute respiratory syndrome(SARS), mortality rate 9%
 MERS-CoV	Betacoronavirus	Middle East respiratory syndrome(MERS), mortality rate >30%
 HCoV-HKU1	Betacoronavirus	Upper and lower respiratory tract disease
 HCoV-NL63	Alphacoronavirus	Common cold
 HCoV-OC43	Betacoronavirus	Common cold
 HCoV-229E	Alphacoronavirus	Common cold

Carlo Urbani

nature medicine

A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence

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2015!

The emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS)-CoV underscores the threat of cross-species transmission events leading to outbreaks in humans. Here we examine the disease potential of a SARS-like virus, SHC014-CoV, which is currently circulating in Chinese horseshoe bat populations[1]. Using the SARS-CoV reverse genetics system[2], we generated and characterized a chimeric virus expressing the spike of bat coronavirus SHC014 in a mouse-adapted SARS-CoV backbone. The results indicate that group 2b viruses encoding the SHC014 spike in a wild-type backbone can efficiently use multiple orthologs of the SARS receptor human angiotensin converting enzyme II (ACE2), replicate efficiently in primary human airway cells and achieve *in vitro* titers equivalent to epidemic strains of SARS-CoV. Additionally, *in vivo* experiments demonstrate replication of the chimeric virus in mouse lung with notable pathogenesis. Evaluation of available SARS-based immune-therapeutic and prophylactic modalities revealed poor efficacy; both monoclonal antibody and vaccine approaches failed to neutralize and protect from infection with CoVs using the novel spike protein. On the basis of these findings, we synthetically re-derived an infectious full-length SHC014 recombinant virus and demonstrate robust viral replication both *in vitro* and *in vivo*. Our work suggests a potential risk of SARS-CoV re-emergence from viruses currently circulating in bat populations.

The emergence of SARS-CoV heralded a new era in the cross-species transmission of severe respiratory illness with globalization leading to rapid spread around the world and massive economic impact[3,4]. Since then, several strains—including influenza A strains H5N1, H1N1 and H7N9 and MERS-CoV—have emerged from animal populations, causing considerable disease, mortality and economic hardship for the afflicted regions[5]. Although public health measures were able to stop the SARS-CoV outbreak[4], recent metagenomics studies have identified sequences of closely related SARS-like viruses circulating in Chinese bat populations that may pose a future threat[1,6]. However, sequence data alone provides minimal insights to identify and prepare for future prepandemic viruses. Therefore, to examine the emergence potential (that is, the potential to infect humans) of circulating bat CoVs, we built a chimeric virus encoding a novel, zoonotic CoV spike protein—from the RsSHC014-CoV sequence that was isolated from Chinese horseshoe bats[1]—in the context of the SARS-CoV mouse-adapted backbone. The hybrid virus allowed us to evaluate the ability of the novel spike protein to cause disease independently of other necessary adaptive mutations in its natural backbone. Using this approach, we characterized CoV infection mediated by the SHC014 spike protein in primary human airway cells and *in vivo*, and tested the efficacy of available immune therapeutics against SHC014-CoV. Together, the strategy translates metagenomics data to help predict and prepare for future emergent viruses.

The sequences of SHC014 and the related RsWIV1-CoV show that these CoVs are the closest relatives to the epidemic SARS-CoV strains (**Fig. 1a,b**); however, there are important differences in the 14 residues that bind human ACE2, the receptor for SARS-CoV, including the five that are critical for host range: Y442, L472, N479, T487 and Y491 (ref. 7). In WIV1, three of these residues vary from the epidemic SARS-CoV Urbani strain, but they were not expected to alter binding to ACE2 (**Supplementary Fig. 1a,b** and **Supplementary Table 1**). This fact is confirmed by both pseudotyping experiments that measured the ability of lentiviruses encoding WIV1 spike proteins to enter cells expressing human ACE2 (**Supplementary Fig. 1**) and by *in vitro* replication assays of WIV1-CoV (ref. 1). In contrast, 7 of 14 ACE2-interaction residues in SHC014 are different from those in SARS-CoV, including all five residues critical for host range (**Supplementary Fig. 1c** and **Supplementary Table 1**). These changes, coupled with

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Nature | Article

A pneumonia outbreak associated with a new coronavirus of probable bat origin

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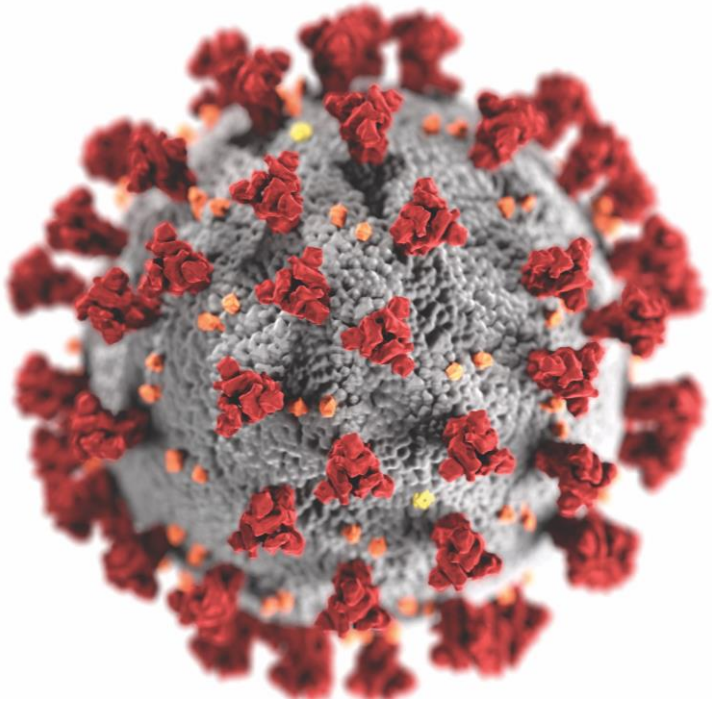
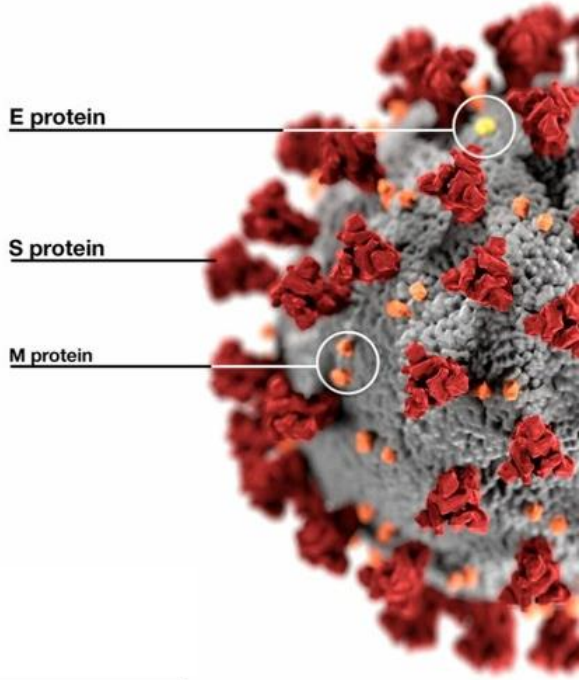
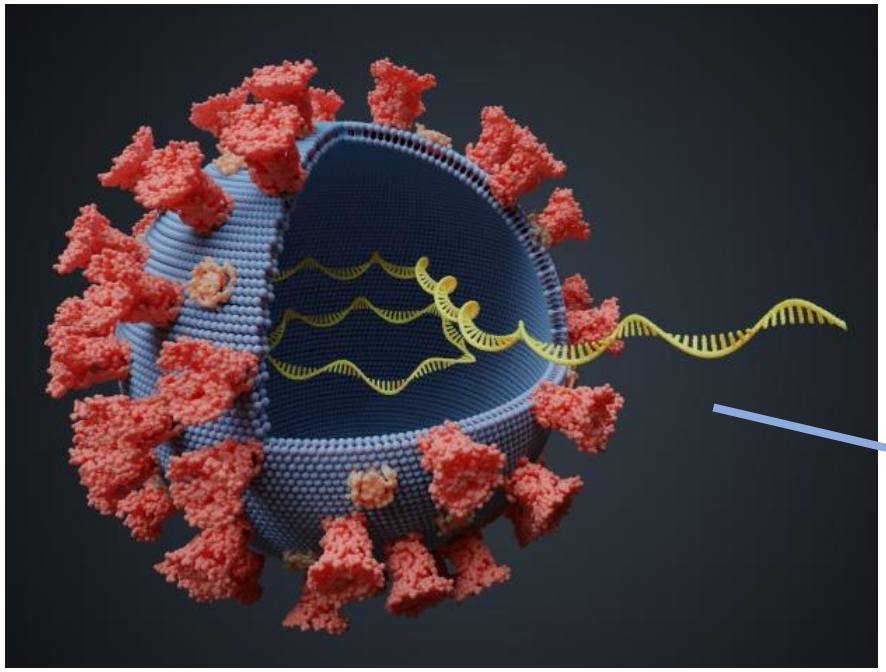
Peng Zhou[1,5], Xing-Lou Yang[1,5], Xian-Guang Wang[2,5], Ben Hu[1], Lei Zhang[1], Wei Zhang[1], Hao-Rui Si[1,3], Yan Zhu[1], Bei Li[1], Chao-Lin Huang[2], Hui-Dong Chen[2], Jing Chen[1,3], Yun Luo[1,3], Hua Guo[1,3], Ren-Di Jiang[1,3], Mei-Qin Liu[1,3], Ying Chen[1,3], Xu-Rui Shen[1,3], Xi Wang[1,3], Xiao-Shuang Zheng[1,3], Kai Zhao[1,3], Quan-Jiao Chen[1], Fei Deng[1], Lin-Lin Liu[4], Bing Yan[1], Fa-Xian Zhan[4], Yan-Yi Wang[1], Geng-Fu Xiao[1] & Zheng-Li Shi[1]✉

Since the outbreak of severe acute respiratory syndrome (SARS) 18 years ago, a large number of SARS-related coronaviruses (SARSr-CoVs) have been discovered in their natural reservoir host, bats[1–4]. Previous studies have shown that some bat SARSr-CoVs have the potential to infect humans[5–7]. Here we report the identification and characterization of a new coronavirus (2019-nCoV), which caused an epidemic of acute respiratory syndrome in humans in Wuhan, China. The epidemic, which started on 12 December 2019, had caused 2,794 laboratory-confirmed infections including 80 deaths by 26 January 2020. Full-length genome sequences were obtained from five patients at an early stage of the outbreak. The sequences are almost identical and share 79.6% sequence identity to SARS-CoV. Furthermore, we show that 2019-nCoV is 96% identical at the whole-genome level to a bat coronavirus. Pairwise protein sequence analysis of seven conserved non-structural proteins domains show that this virus belongs to the species of *SARSr-CoV*. In addition, 2019-nCoV virus isolated from the bronchoalveolar lavage fluid of a critically ill patient could be neutralized by sera from several patients. Notably, we confirmed that 2019-nCoV uses the same cell entry receptor—angiotensin converting enzyme II (ACE2)—as SARS-CoV.

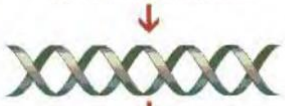
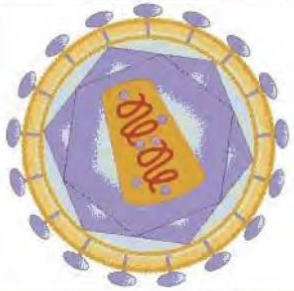
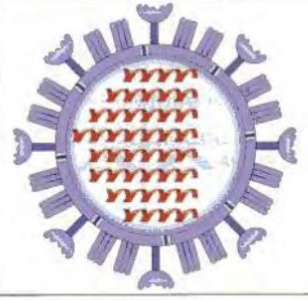
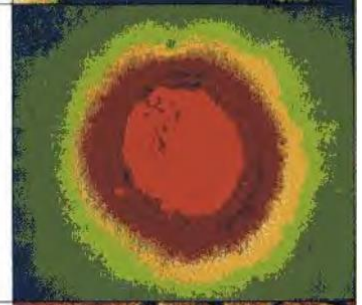
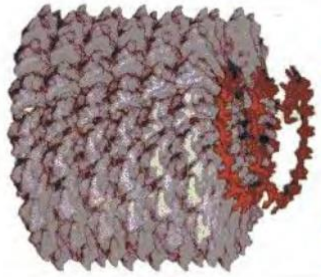
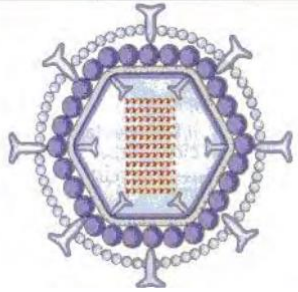
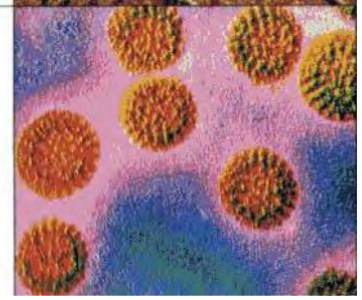
SARS-CoV-2





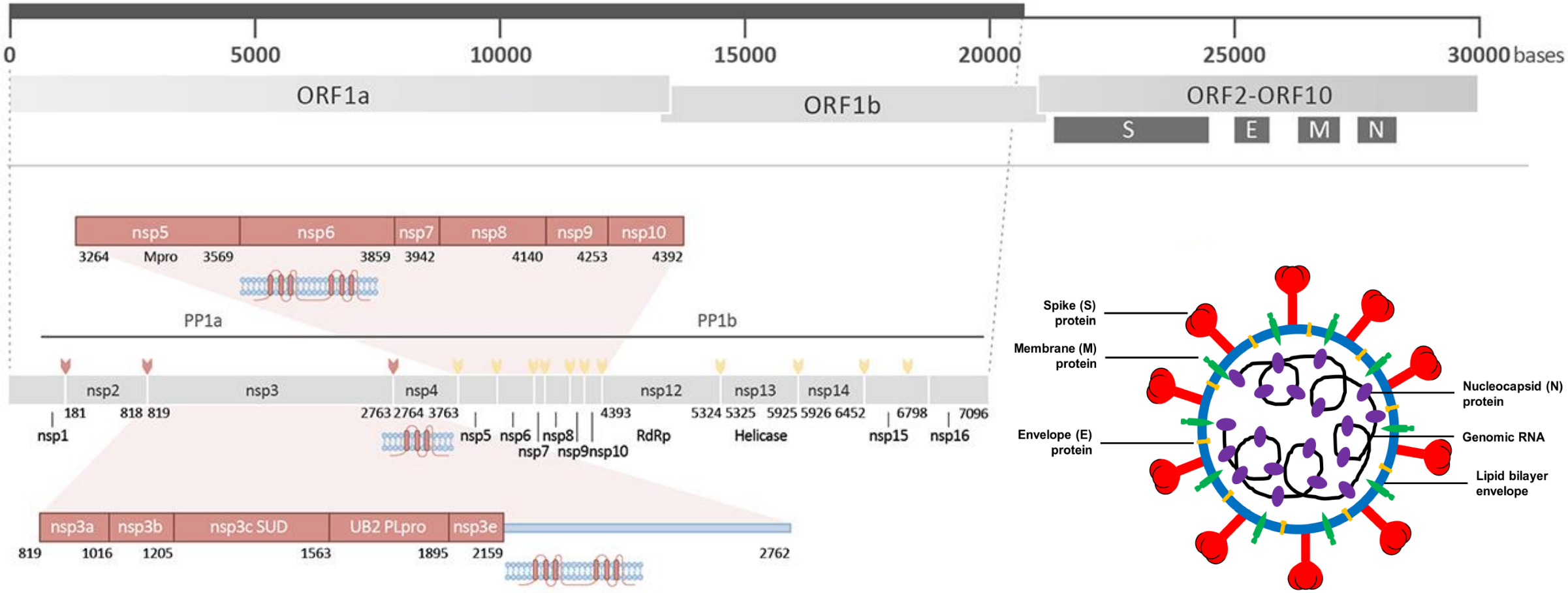


Virus a RNA

Tipo di genoma	Passaggi necessari per la produzione di mRNA virale	Esempi		
 RNA retrovirus	Trascrizione inversa  Trascrizione ↓ mRNA	HIV		
 RNA a filamento negativo	Produzione di RNA complementare ↓  Il nuovo filamento prodotto è l'mRNA	Virus dell'influenza		
 RNA a filamento positivo	Il filamento è usato come mRNA	Virus del mosaico del tabacco		
 RNA a doppio filamento	Un filamento è usato come mRNA	Rotavirus		

SARS CoV2

SARS-CoV-2



MERS-CoV
SARS-CoV
SARS-CoV-2

- ~29.9 kilobase positive-sense RNA genome that contains as many as 29 ORFs.
- Though the exact number of functional proteins remains to be established, there are at least:

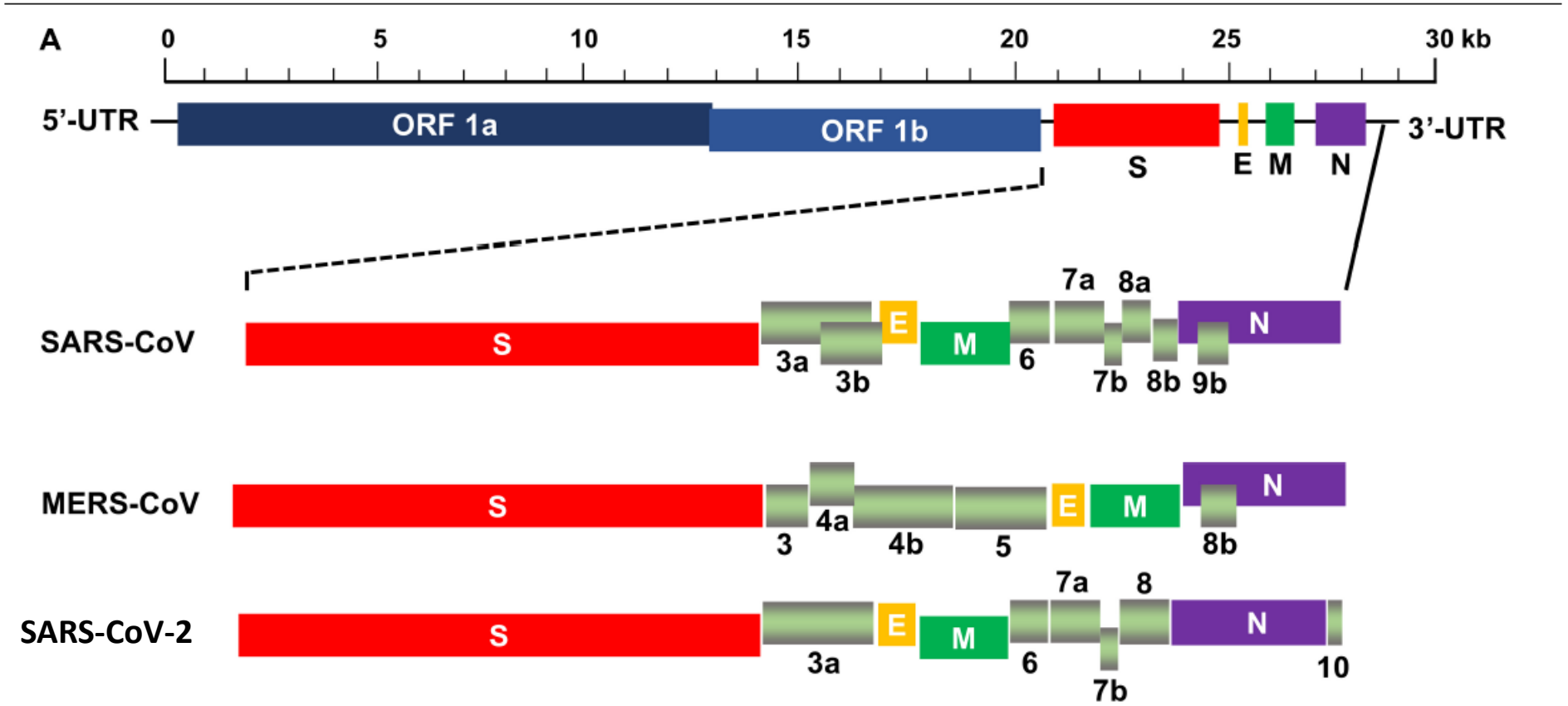
✓ 16 nonstructural proteins (nsp),
✓ 4 structural proteins, (S, E, M, N)
✓ at least 6-7 accessory proteins

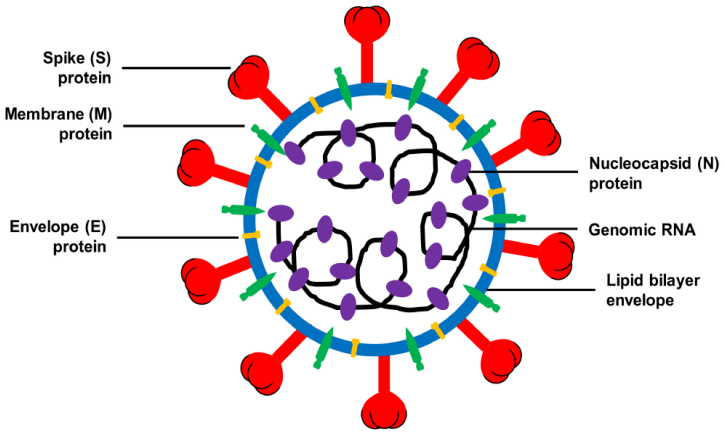
Based on previous work with SARS-CoV and other CoVs, scientists have quickly identified functions for the majority of these factors, though the work is still ongoing.

Putative functions of SARS-CoV-2 proteins

Protein	Functions
Spike (S)	Spike full-length (~1273 a.a. in SARS-CoV-2) protein precursor is cleaved into glycosylated subunits, S1 and S2 (S2'). S1 binds to the host's receptor, ACE2, while S2 mediates viral and host membrane fusion.
Nucleocapsid (N)	Nucleocapsid (~419 a.a. in SARS-CoV-2) binds viral genomic RNA and forms a helical ribonucleocapsid. Involved in genome protection, viral RNA replication, virion assembly, and immune evasion. Interacts with M and nsp3 proteins.
Membrane (M)	Membrane/matrix protein (~222 a.a. in SARS-CoV-2) is the most abundant structural component of the virion, and very conserved. Mediates assembly and budding of viral particles through recruitment of other structural proteins to "ER-Golgi-intermediate compartment (ERGIC)". Interaction with N for RNA packaging into virion. Interacts with accessory proteins 3a and 7a. Mitigation of immune response?
Envelope (E)	Envelope small membrane protein (~75 a.a. in SARS-CoV-2) is a single-pass type III membrane protein involved in viral assembly, budding, and pathogenesis. Localizes to ERGIC. Forms a homopentameric ion channel and is a viroporin. Interacts with M, N, 3a, and 7a.
nsp1	Nonstructural protein 1 (nsp1; ~180 a.a. in SARS-CoV-2) likely inhibits host translation by interacting with 40S ribosomal subunit, leading to host mRNA degradation through cleavage near their 5'UTRs. Promotes viral gene expression and immunoevasion in part by interfering with interferon-mediated signaling.
nsp2	nsp2 (~638 a.a. in SARS-CoV-2) interacts with host factors prohibitin 1 and prohibitin 2, which are involved in many cellular processes including mitochondrial biogenesis. It appears that nsp2 may change the intracellular milieu and perturb host intracellular signaling.
nsp3	nsp3 (~1945 a.a. in SARS-CoV-2) is a papain-like protease (PLpro) and multi-pass membrane protein that processes the viral polyprotein to release nsp1, nsp2, and nsp3. It also exhibits deubiquitinating and deISGylating activities. Interacts with nsp4 and nsp6.
nsp4	nsp4 (~500 a.a. in SARS-CoV-2) is required for viral replication by inducing (with nsp3) assembly of, and localizing to, double-membrane cytoplasmic vesicles. Multi-pass membrane protein.
nsp5	nsp5 (3CLpro; ~306 a.a. in SARS-CoV-2) cleaves at 11 sites in the polyprotein to release nsp4-nsp16. It is also responsible for nsp maturation.
nsp6	nsp6 (~290 a.a. in SARS-CoV-2) is a multi-pass membrane protein that induces double-membrane vesicles in infected cells with nsp 3 and nsp4. It also limits autophagosome expansion and interferes with autophagosome delivery of viral factors to lysosomes for destruction.
nsp7	nsp7 (~83 a.a. in SARS-CoV-2) forms a hexadecamer with nsp8 as a cofactor for the RNA-dependent RNA polymerase nsp12. May have processivity or RNA primase function.
nsp8	nsp8 (~198 a.a. in SARS-CoV-2) forms a hexadecamer with nsp7 as a cofactor for the RNA-dependent RNA polymerase nsp12. May have processivity or RNA primase function. Mutation of certain residues in nsp8 is lethal to SARS-CoV by impacting RNA synthesis.
nsp9	nsp9 (~113 a.a. in SARS-CoV-2) functions in viral replication as a dimeric ssRNA-binding protein.
nsp10	nsp10 (~139 a.a. in SARS-CoV-2) forms a dodecamer and interacts with both nsp14 and nsp16 to stimulate their respective 3'-5' exoribonuclease and 2'-O-methyltransferase activities in the formation of the viral mRNA capping machinery.
nsp11	nsp11 (~13-23 a.a., depending on the CoV species) is a pp1a cleavage product at the nsp10/11 boundary. For pp1ab, it is a frameshift product that becomes the N-terminal of nsp12. Its function, if any, is unknown.
nsp12	nsp12 (~932 a.a. in SARS-CoV-2) is the RNA-dependent RNA polymerase (RdRp) performing both replication and transcription of the viral genome. It has >95% identity to the SARS-CoV polymerase and is inhibited by the nucleoside analogue Remdesivir.
nsp13	nsp13 (~601 a.a. in SARS-CoV-2) is a multifunctional superfamily 1 helicase capable of using both dsDNA and dsRNA as substrates with 5'-3' polarity. In addition to working with nsp12 in viral genome replication, it is also involved in viral mRNA capping. It associates with nucleoprotein in membranous complexes.
nsp14	nsp14 (~527 a.a. in SARS-CoV-2) has both 3'-5' exoribonuclease (proofreading during RNA replication) and N7-guanine methyltransferase (viral mRNA capping) activities. Interacts with nsp10.
nsp15	nsp15 (~346 a.a. in SARS-CoV-2) is an endoribonuclease that favors cleavage of RNA at the 3'-ends of uridylates. Loss of nsp15 affects both viral replication and pathogenesis. It is also required for evasion of host cell dsRNA sensors.
nsp16	nsp16 (~298 a.a. in SARS-CoV-2) interacts with and is activated by nsp10. Its 2'-O-methyltransferase activity is essential for viral mRNA capping. It may also work against host cell antiviral sensors.
ORF3a	ORF3a (~275 a.a. in SARS-CoV-2) is a multi-pass membrane protein that forms a homotetrameric viroporin in SARS-CoV. It interacts with accessory protein 7a, M, S and E. May be involved in viral release. Importantly, it also activates both NF-kB and NLRP3 inflammasome and contributes to the generation of cytokine storm.
ORF6	ORF6 (~61 a.a. in SARS-CoV-2) appears to be a virulence factor in SARS-CoV. It was shown to be an antagonist of type I interferons (IFNs) and is involved in viral escape from the host innate immune system.
ORF7a	ORF7a (~121 a.a. in SARS-CoV-2) is a type I membrane protein that interacts with bone marrow stromal antigen 2 (BST-2) in SARS-CoV. BST-2 tethers virions to the host's plasma membrane. ORF7a binding inhibits BST-2 glycosylation and interferes with this restriction activity. ORF7a also interacts with S, M, E, and ORF3a in SARS-CoV.
ORF7b	ORF7b (~43 a.a. in SARS-CoV-2) is a type III integral transmembrane protein in the Golgi apparatus. In SARS-CoV, it appears to be a viral attenuation factor.
ORF8	ORF8 (~121 a.a. in SARS-CoV-2) has only 30% identity to the intact ORF8 of SARS-CoV and might be a luminal ER membrane-associated protein. It may trigger ATF6 activation and affect the unfolded protein response (UPR).
ORF9b	ORF9b (~97 a.a. in SARS-CoV-2) is coded for in an alternative ORF within the N gene. No function is known, though the SARS-CoV protein interacts with nsp5, nsp14, and ORF6. There is limited evidence it may bind to lipids.
ORF10	ORF10 (~38 a.a. in SARS-CoV-2) has no known function but might have a regulatory role involving interaction with another factor(s).

Confronto tra l'organizzazione genomica di SARS-CoV-2, SARS-CoV e MERS-CoV





MERS-CoV
SARS-CoV
SARS-CoV-2

frontiers in Microbiology
REVIEW
published: 28 February 2020
doi: 10.3389/fmicb.2020.00298

Cell Host & Microbe

A Sequence Homology and Bioinformatic Approach Can Predict Candidate Targets for Immune Responses to SARS-CoV-2

Grifoni et al., 2020, Cell Host & Microbe *27*, 1–10
April 8, 2020
https://doi.org/10.1016/j.chom.2020.03.002

Confronto tra le sequenze genomiche di SARS-CoV-2, Bat-CoV, SARS-CoV e MERS-CoV

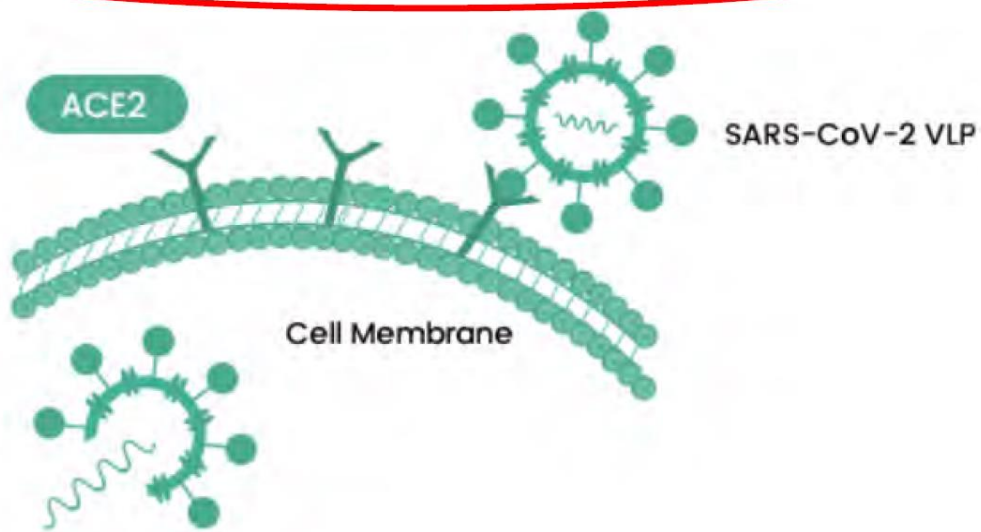
SARS-CoV-2	orf1ab	S	ORF3a	E	M	ORF6	ORF7a	ORF8	N	ORF10
Bat-SL-CoV	95%	80%	91%	100%	98%	93%	88%	94%	94%	-
SARS-CoV	86%	76%	72%	94%	90%	68%	85%	40%	90%	-
MERS-CoV	50%	35%	-	36%	42%	-		-	48%	-

Human Coronavirus Antigens

CoV Antigens	Description
Spike	Receptor binding and membrane fusion Target for antiviral treatment and vaccines
Nucleocapsid	Genome replication and cell signaling regulation A diagnostic marker
HE	Receptor interaction
Plpro	Viral polyprotein cleavage and host innate immune response blockage; Target for drugs development
3CLPro	Polypeptides cleavage and IFN signaling inhibition Target for drugs development
E	Assembly and release of the virus Vaccine candidates; Target for drugs development
M	Membrane and virion structure

Host Receptor of Human Coronavirus

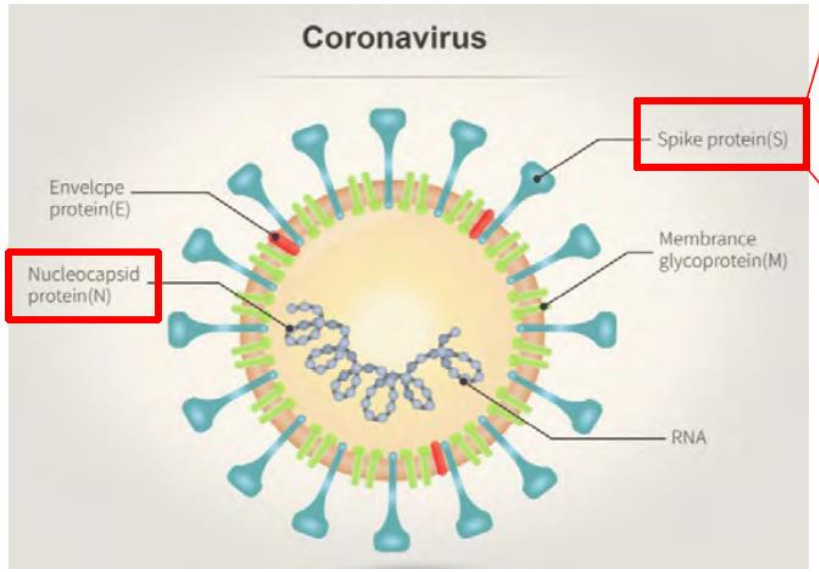
HCoV Types	Host receptors
HCoV-229E	APN (aminopeptidase N, CD13)
HCoV-NL63	ACE2 (angiotensin-converting enzyme 2)
HCoV-HKU1	O-ac Sia
HCoV-OC43	O-ac Sia
MERS-CoV	DPP4 (dipeptidyl peptidase 4)
SARS-CoV	ACE2 (angiotensin-converting enzyme 2)
SARS-CoV-2	ACE2 (angiotensin-converting enzyme 2)

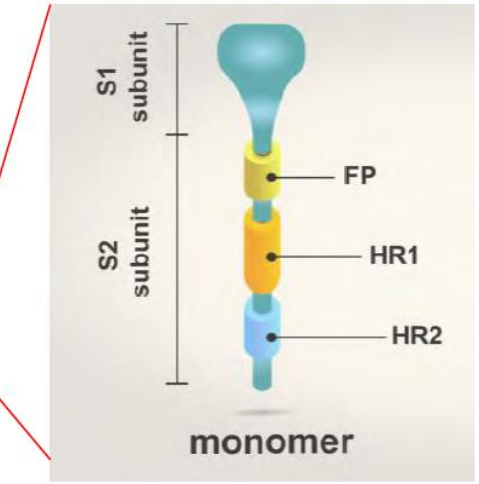


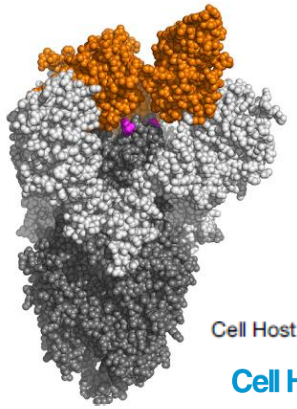
Proteina S (Spike)

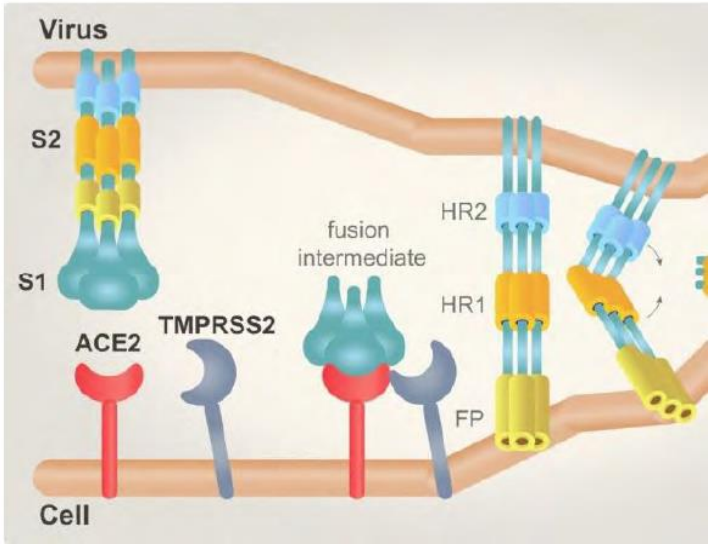
- Come tutti i Coronavirus, il SARS CoV2 ha proteine spike (S), proteine dell'envelope (E), proteine di membrana (M) e proteine del nucleocapside (N)
- La proteina spike riconosce il recettore dell'ospite (ACE2)
- La proteina S è composta dalle subunità S1 e S2. S1 è la RBD che riconosce e lega il recettore dell'ospite

Target per anticorpi terapeutici e vaccini





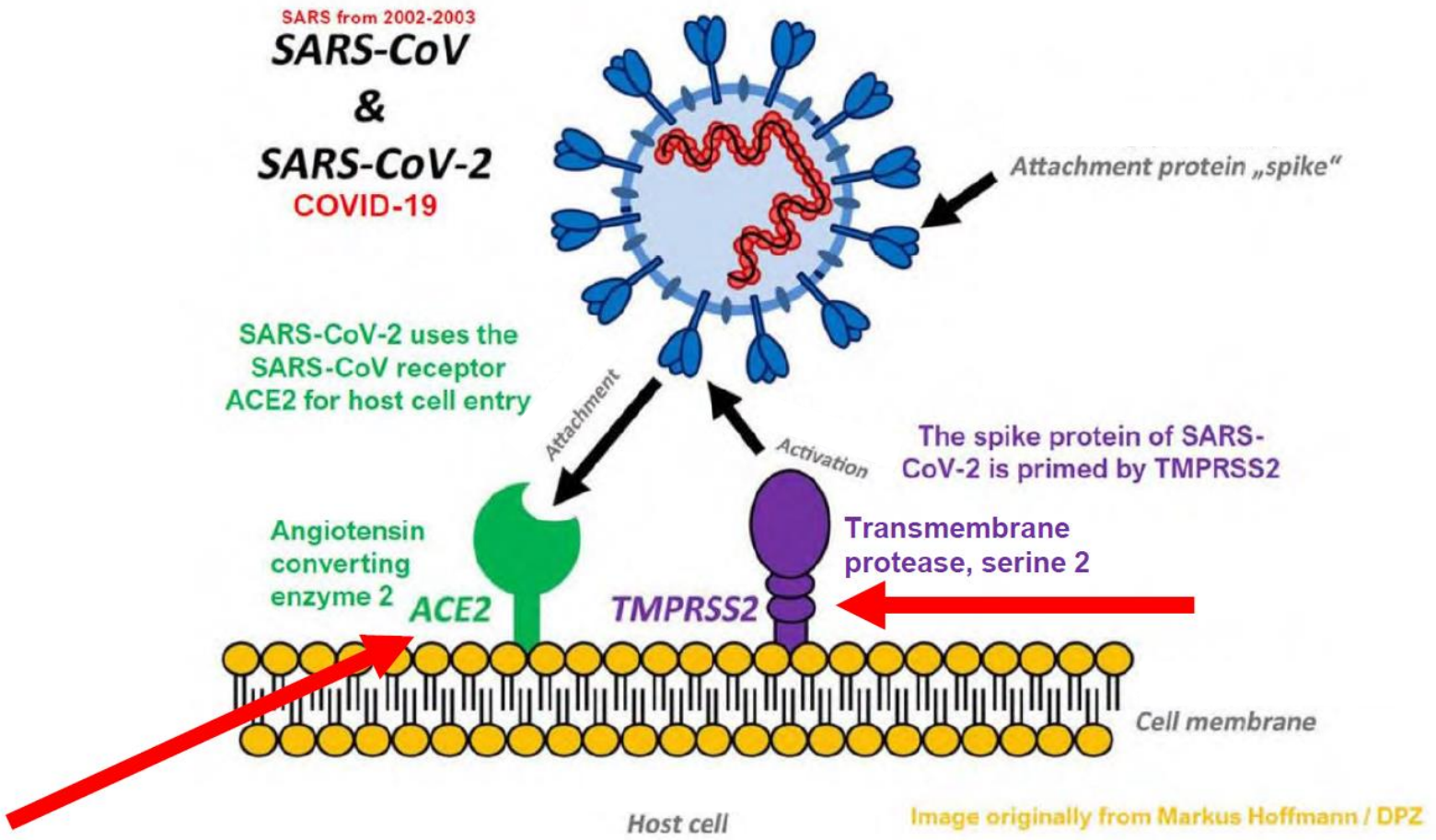




Cell Host & Microbe 28, September 9, 2020

Cell Host & Microbe
Perspective

Altri attori coinvolti: TMPRSS2



Review

Immunology of COVID-19: Current State of the Science

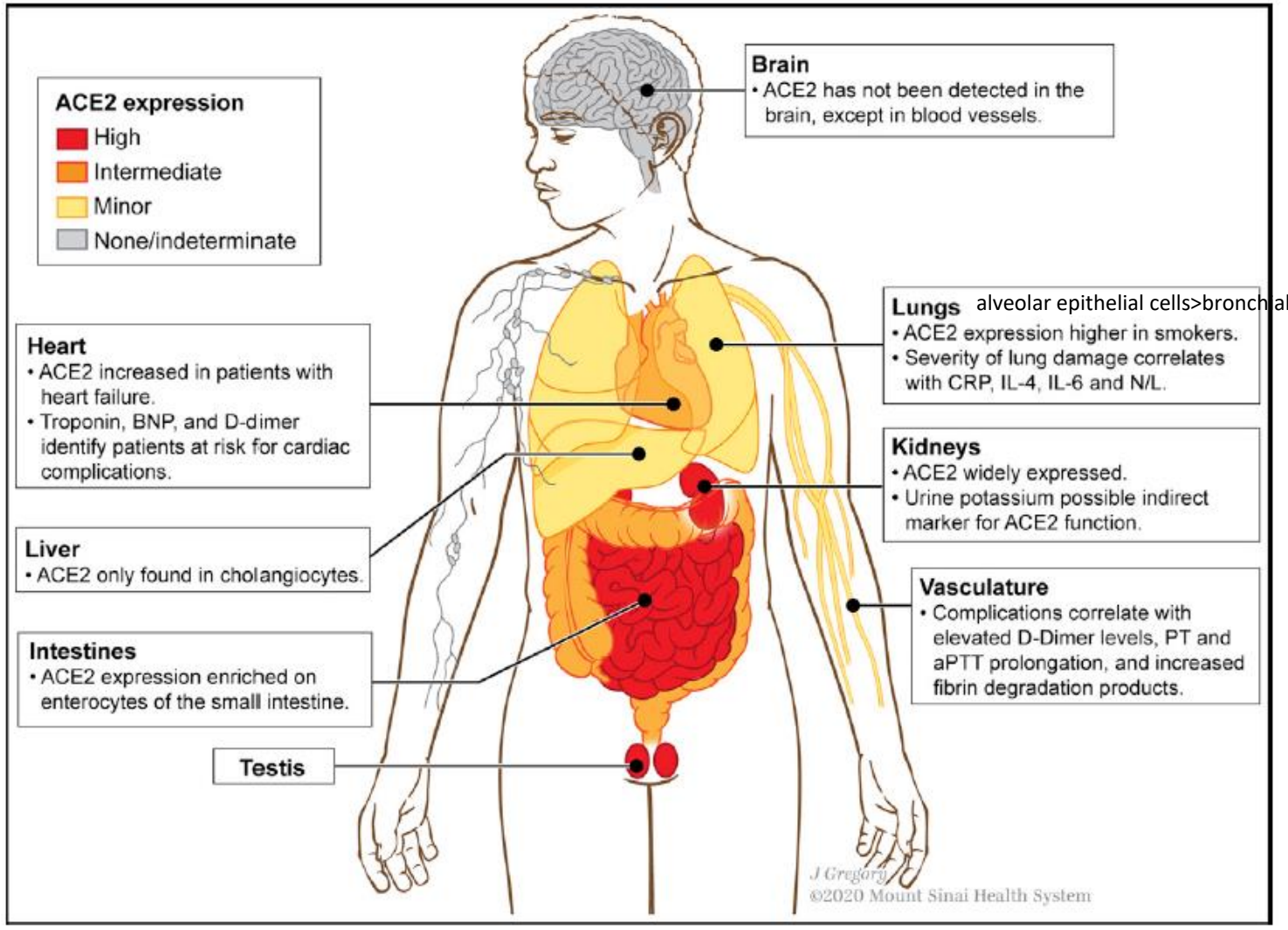
Nicolas Vabret,[1,*] Graham J. Britton,[1] Conor Gruber,[1] Samarth Hegde,[1] Joel Kim,[1] Maria Kuksin,[1] Rachel Levantovsky,[1] Louise Malle,[1] Alvaro Moreira,[1] Matthew D. Park,[1] Luisanna Pia,[1] Emma Risson,[1] Miriam Saffern,[1] Bérengère Salomé,[1] Myvizhi Esai Selvan,[1] Matthew P. Spindler,[1] Jessica Tan,[1] Verena van der Heide,[1] Jill K. Gregory,[1] Konstantina Alexandropoulos,[1] Nina Bhardwaj,[1] Brian D. Brown,[1] Benjamin Greenbaum,[1] Zeynep H. Gümüş,[1] Dirk Homann,[1] Amir Horowitz,[1] Alice O. Kamphorst,[1] Maria A. Curotto de Lafaille,[1] Saurabh Mehandru,[1] Miriam Merad,[1,*] Robert M. Samstein,[1,*] and The Sinai Immunology Review Project

[1]Precision Immunology Institute at the Icahn School of Medicine at Mount Sinai, New York, NY, USA

*Correspondence: nicolas.vabret@mssm.edu (N.V.), miriam.merad@mssm.edu (M.M.), robert.samstein@mountsinai.org (R.M.S.)

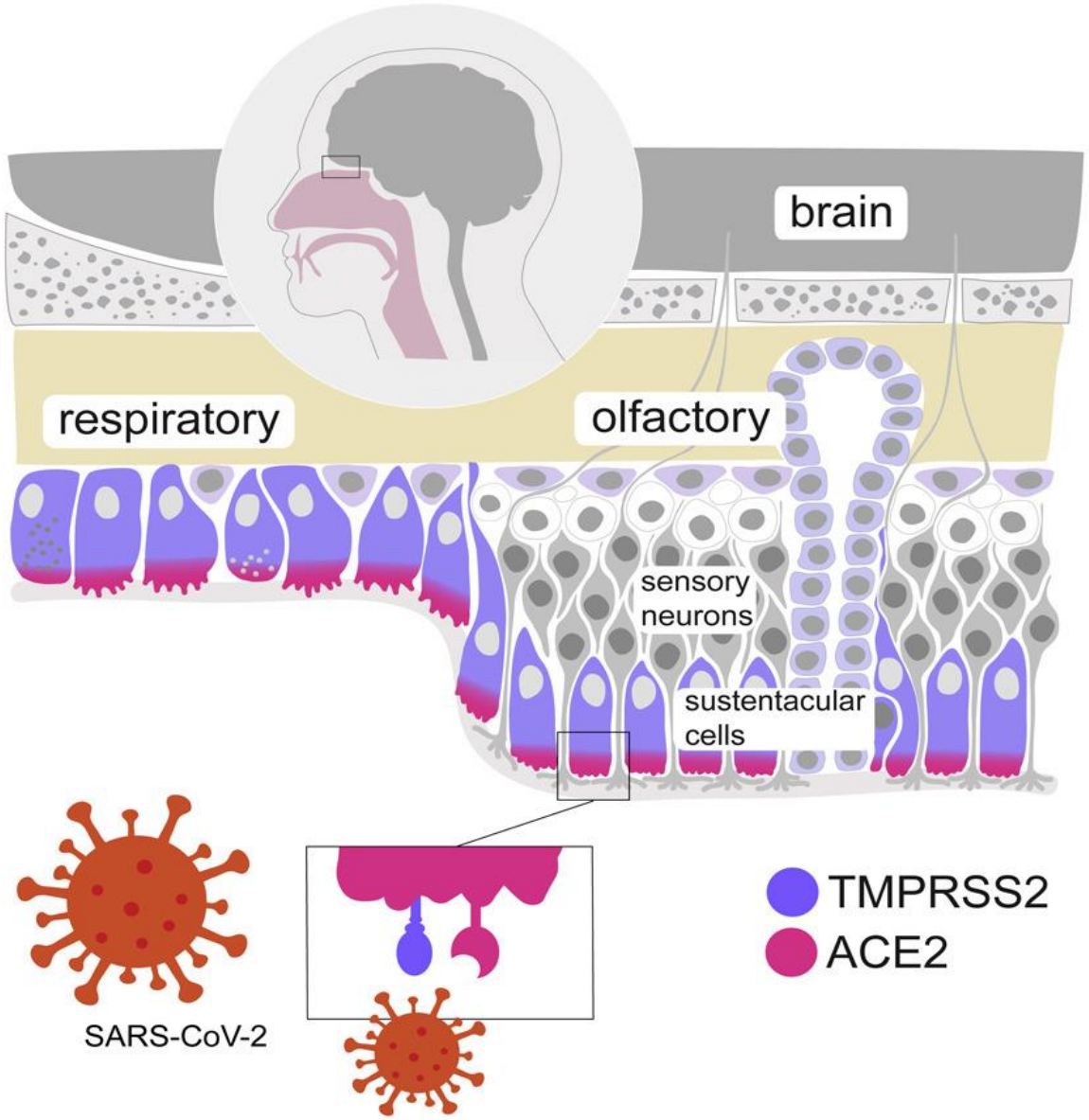
https://doi.org/10.1016/j.immuni.2020.05.002

ACE2 expression



alveolar epithelial cells>bronchial epithelial cells

SARS-CoV-2 receptors and entry genes are expressed in the human olfactory neuroepithelium and brain



Highlights

- SARS-CoV-2 receptors ACE2 and TMPRSS2 are expressed in olfactory neuroepithelia
- ACE2 and TMPRSS2 are co-expressed in supporting sustentacular cells
- A subset of neuronal and non-neuronal cells in the brain transcribe *ACE2*

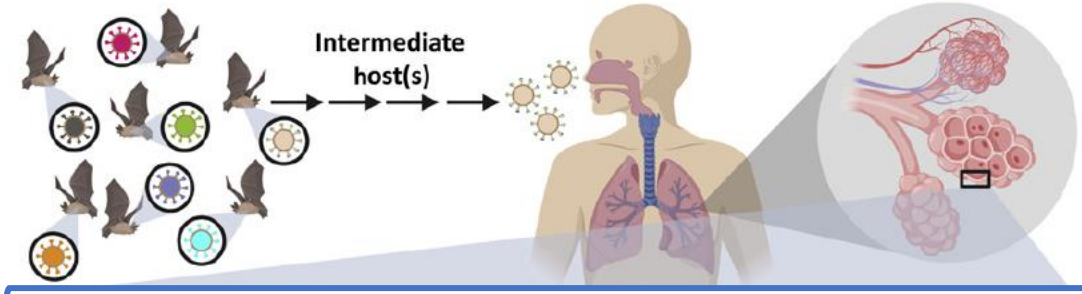
Fodoulian L et al , iScience, December 2020

Trends in Immunology 2020

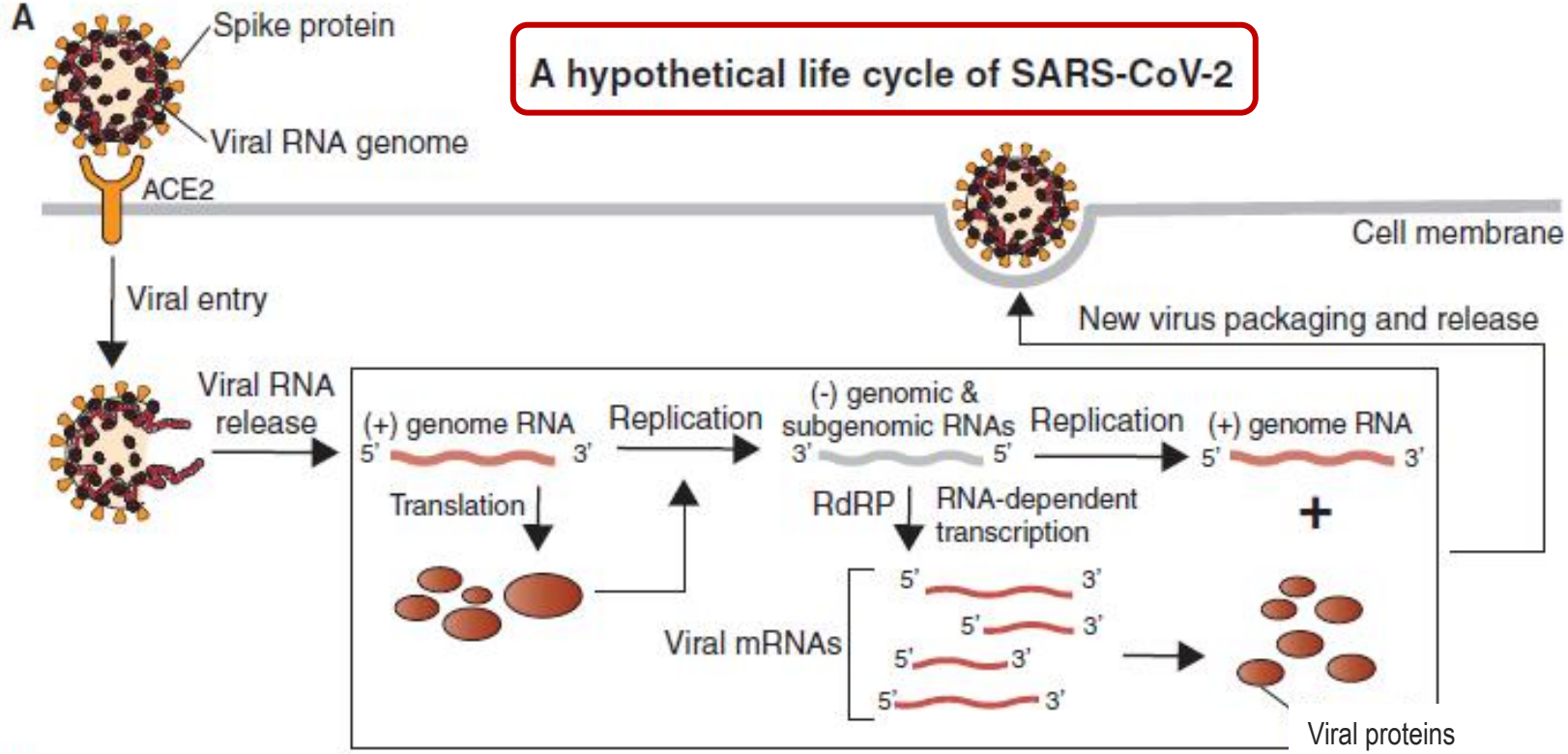
Spotlight

SARS Coronavirus Redux

Enya Qing[1] and Tom Gallagher[1,*]

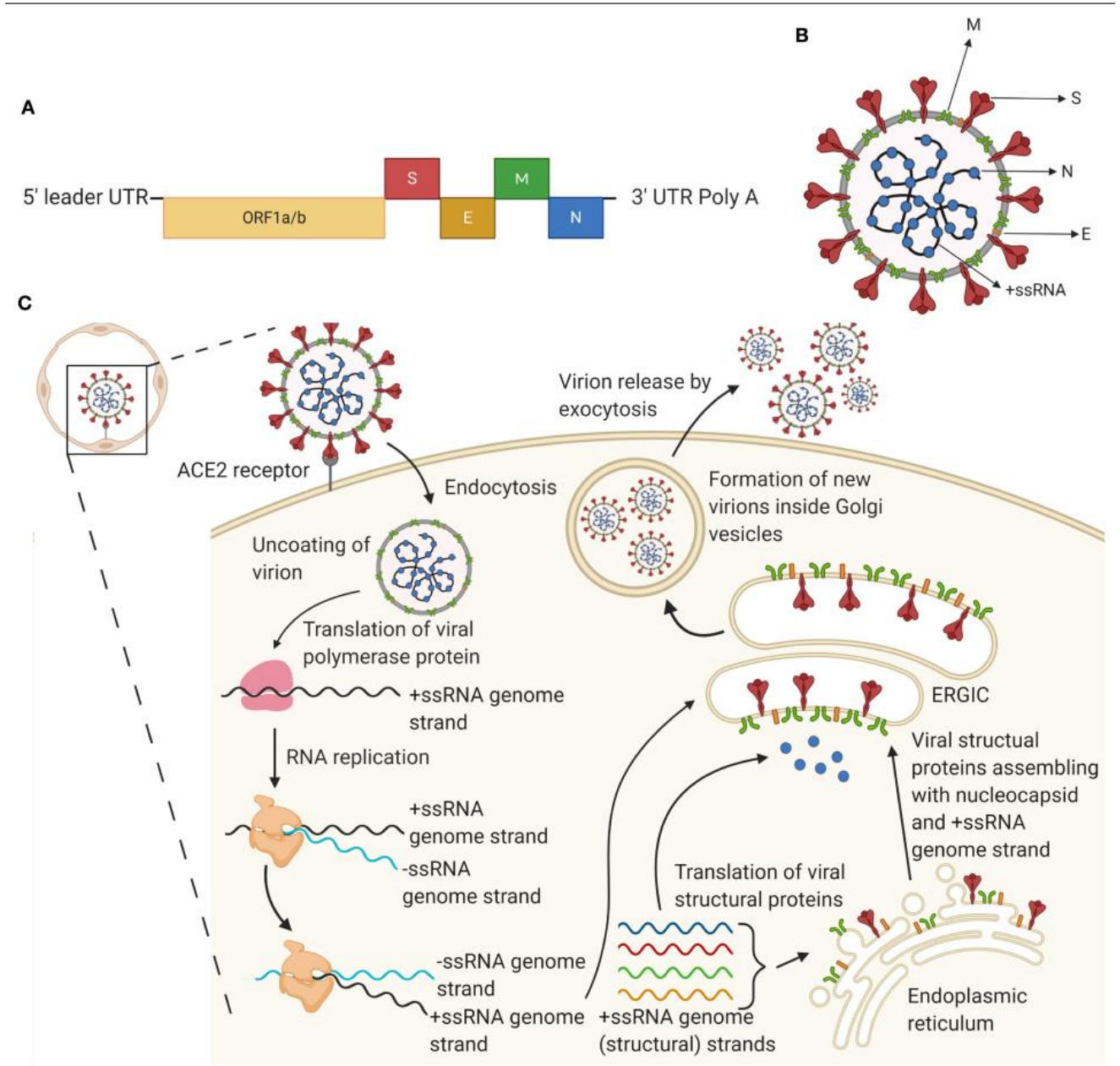


Cell Article

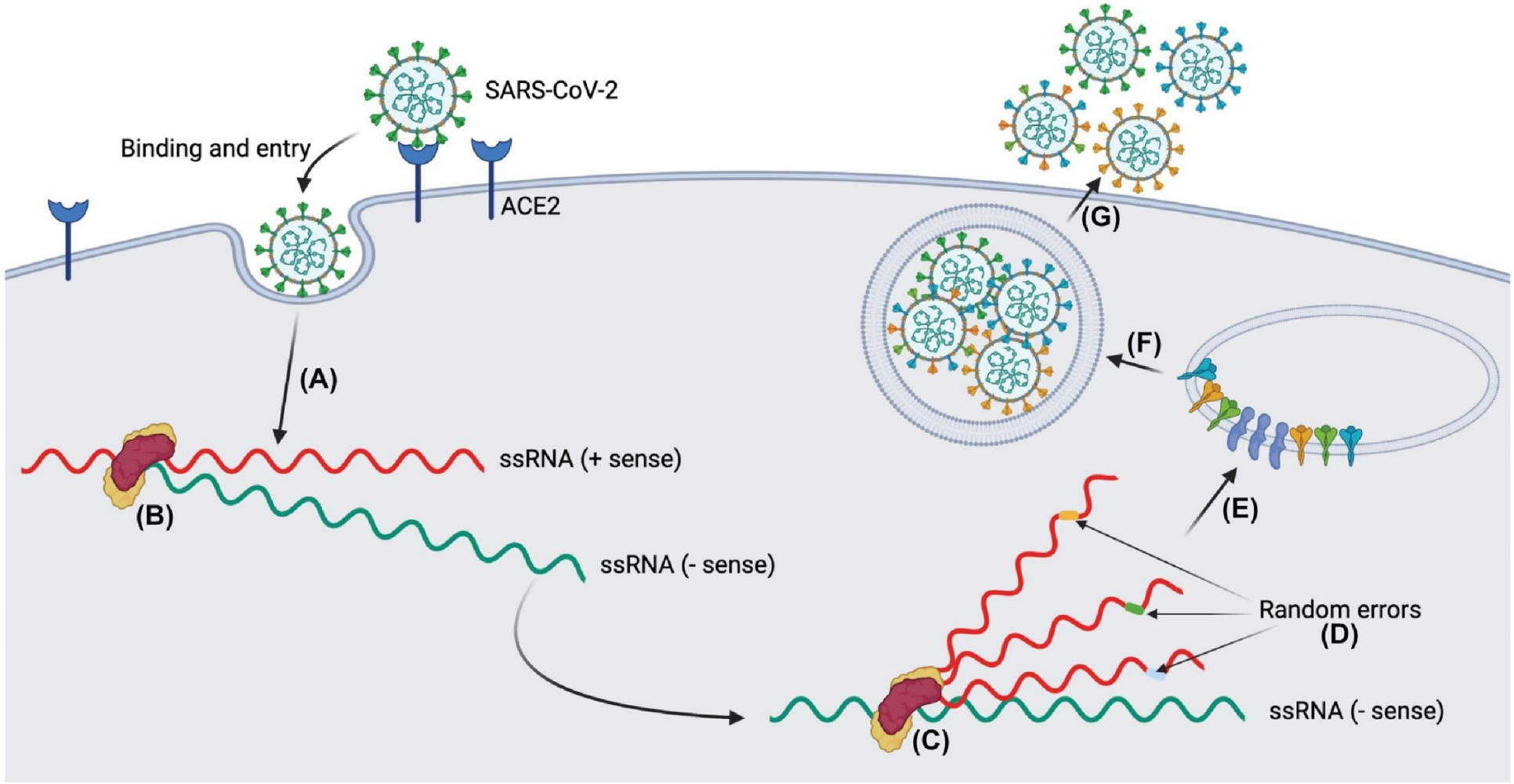


RdRp: RNA-dependent RNA polymerase

SARS-CoV-2 lyfe cycle



SARS-CoV-2 lyfe cycle and generation of mutants



Trends in Microbiology 2021

SARS-CoV-2 variants

Naming SARS-CoV-2 variants

The established nomenclature systems for naming and tracking SARS-CoV-2 genetic lineages by GISAID, Nextstrain and Pango are currently and will remain in use by scientists and in scientific research. To assist with public discussions of variants, WHO convened a group of scientists from the WHO Virus Evolution Working Group (now called the Technical Advisory Group on Virus Evolution), the WHO COVID-19 reference laboratory network, representatives from GISAID, Nextstrain, Pango and additional experts in virological, microbial nomenclature and communication from several countries and agencies to consider easy-to-pronounce and non-stigmatising labels for VOI and VOC. At the present time, this expert group convened by WHO has recommended using letters of the Greek Alphabet, i.e., Alpha, Beta, Gamma, Delta which will be easier and more practical to be discussed by non-scientific audiences.

Variants of Concern (VOC)

Working definition:

A SARS-CoV-2 variant that meets the definition of a VOI (see below) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:

- Increase in transmissibility or detrimental change in COVID-19 epidemiology; OR
- Increase in virulence or change in clinical disease presentation; OR
- Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.

Currently designated Variants of Concern (VOCs):

WHO label	Pango lineage*	GISAID clade	Nextstrain clade	Additional amino acid changes monitored°	Earliest documented samples	Date of designation
Alpha	B.1.1.7	GRY	20I (V1)	+S:484K +S:452R	United Kingdom, Sep-2020	18-Dec-2020
Beta	B.1.351	GH/501Y.V2	20H (V2)	+S:L18F	South Africa, May-2020	18-Dec-2020
Gamma	P.1	GR/501Y.V3	20J (V3)	+S:681H	Brazil, Nov-2020	11-Jan-2021
Delta	B.1.617.2	G/478K.V1	21A, 21I, 21J	+S:417N	India, Oct-2020	VOI: 4-Apr-2021 VOC: 11-May-2021

*Includes all descendent lineages. See the cov-lineages.org and the Pango network websites for further details.

° only found in a subset of sequences

Variant of Interest (VOI)

A variant with specific genetic markers associated with changes to receptor binding, reduced neutralization by Abs generated against previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity.

Possible attributes of a VOI:

•Specific genetic markers that are predicted to affect transmission, diagnostics, therapeutics, or immune escape.

•Evidence that it is the cause of an increased proportion of cases or unique outbreak clusters.

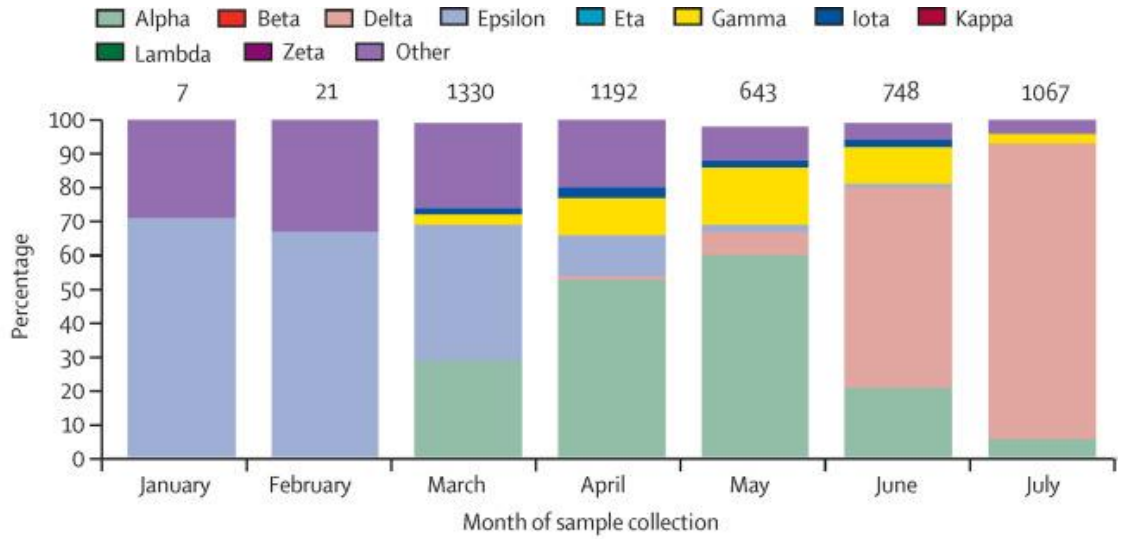
•Limited prevalence or expansion in the US or in other countries.

VOI might require one or more appropriate public health actions, including enhanced sequence surveillance, laboratory characterization, or epidemiological investigations to assess how easily the virus spreads to others, the severity of disease, the efficacy of therapeutics and whether currently approved or authorized vaccines offer protection.

World Health Organization

WHO, 16/11/2021

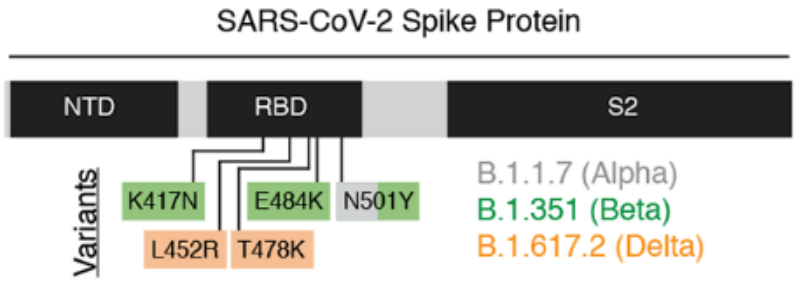
Distribution of variants from January to July 2021



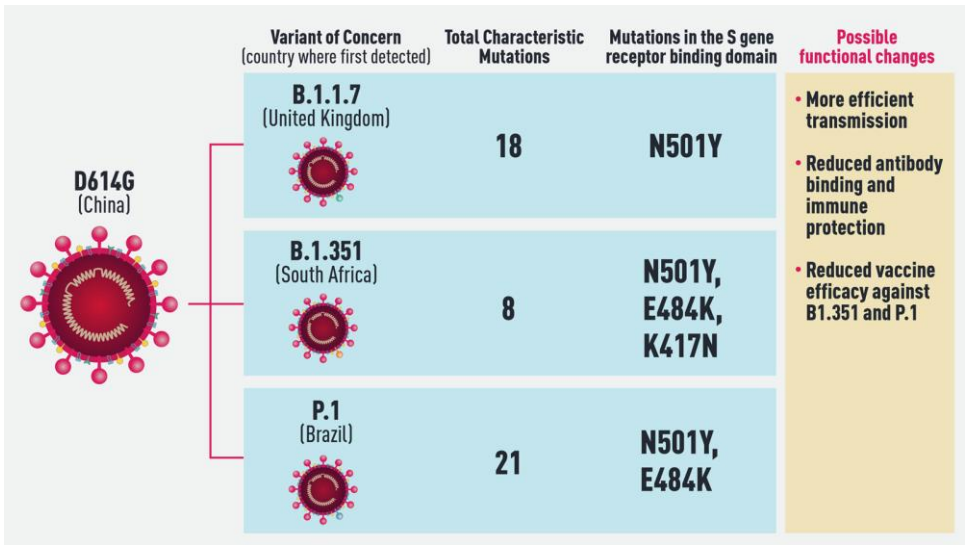
	January	February	March	April	May	June	July
Alpha	0	0	383 (28·8%)	632 (53·0%)	389 (60·5%)	158 (21·1%)	60 (5·6%)
Beta	0	0	2 (0·2%)	5 (0·4%)	2 (0·3%)	1 (0·1%)	1 (0·1%)
Delta	0	0	0	7 (0·6%)	47 (7·3%)	445 (59·5%)	923 (86·5%)
Epsilon	5 (71·4%)	14 (66·7%)	532 (40·0%)	139 (11·7%)	11 (1·7%)	4 (0·5%)	0
Eta	0	0	2 (0·2%)	2 (0·2%)	1 (0·2%)	1 (0·1%)	0
Gamma	0	0	40 (3·0%)	131 (11·0%)	107 (16·6%)	82 (11·0%)	33 (3·1%)
Iota	0	0	25 (1·9%)	33 (2·8%)	16 (2·5%)	17 (2·3%)	1 (0·1%)
Kappa	0	0	1 (0·1%)	1 (0·1%)	0	0	0
Lambda	0	0	1 (0·1%)	4 (0·3%)	3 (0·5%)	0	1 (0·1%)
Zeta	0	0	6 (0·5%)	0	0	0	0
Other	2 (28·6%)	7 (33·3%)	338 (25·4%)	238 (20·0%)	67 (10·4%)	40 (5·3%)	48 (4·5%)
All	7 (100%)	21 (100%)	1330 (100%)	1192 (100%)	643 (100%)	748 (100%)	1067 (100%)

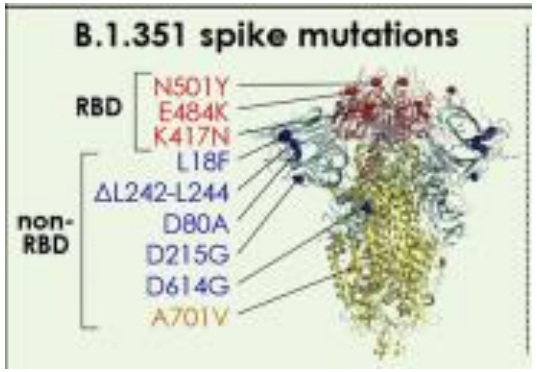
Failed sequence	9/16 (56·3%)	13/34 (38·2%)	993/2323 (42·7%)	882/2074 (42·5%)	648/1291 (50·2%)	720/1468 (49·0%)	638/1705 (37·4%)

Tartof SY, The Lancet 2021

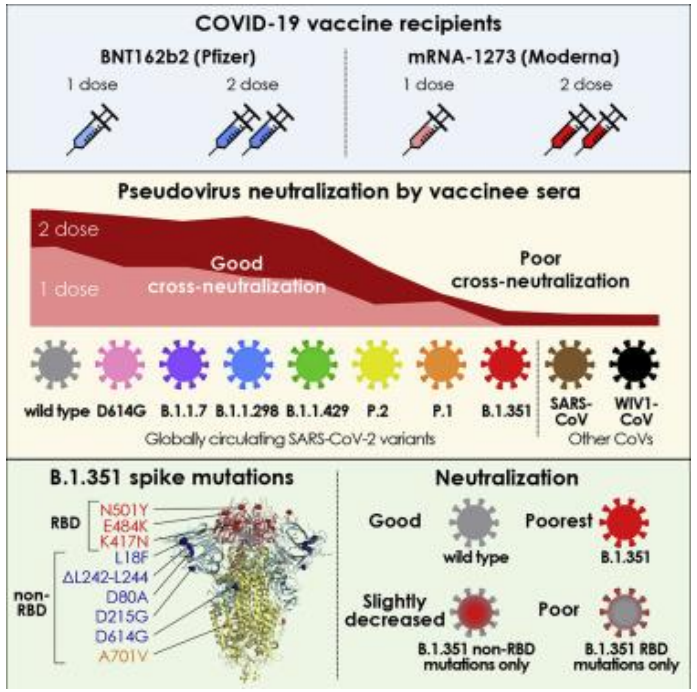


Goel RR, Science 2021



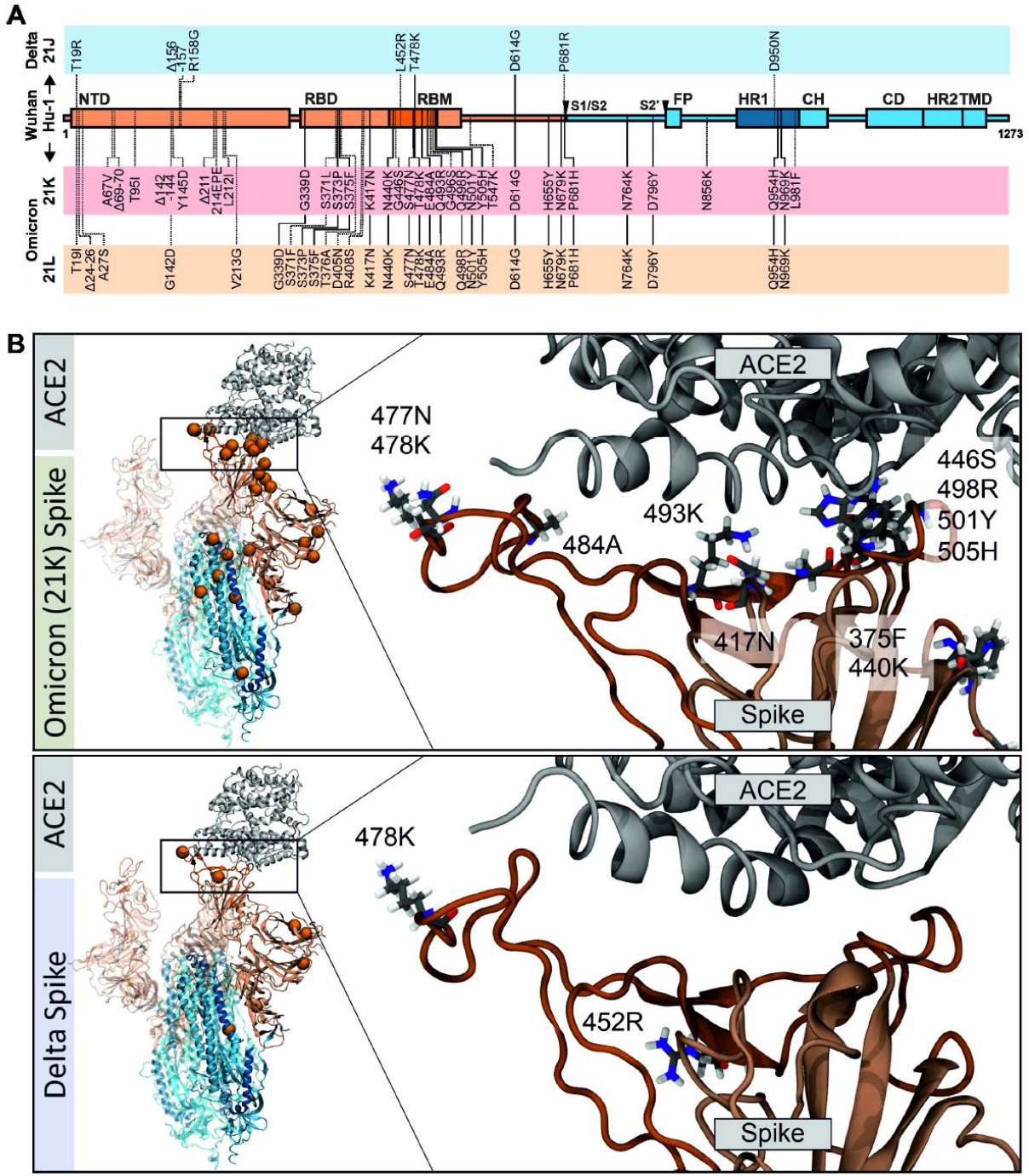


Garcia-Beltran WF, Cell 2021



Garcia-Beltran WF, Cell 2021

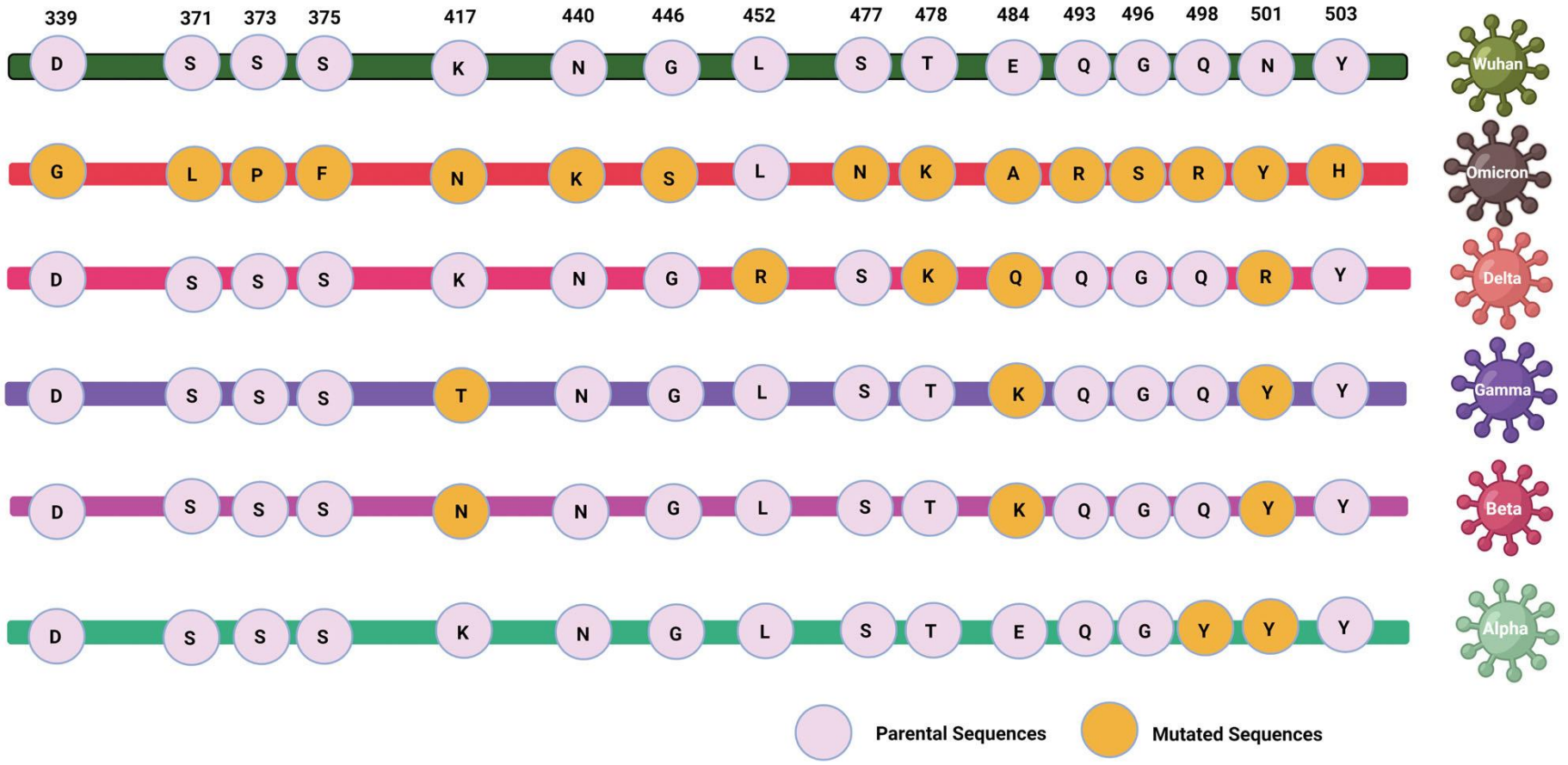
Omicron: what makes the latest SARS-CoV-2 variant of concern so concerning?



Position of changes in the 3D structure of the Spike/ACE2 complex based on the CoV-RDB

C. Jung et al., JVI 2022

Mutazioni aminoacidi nella regione RBD



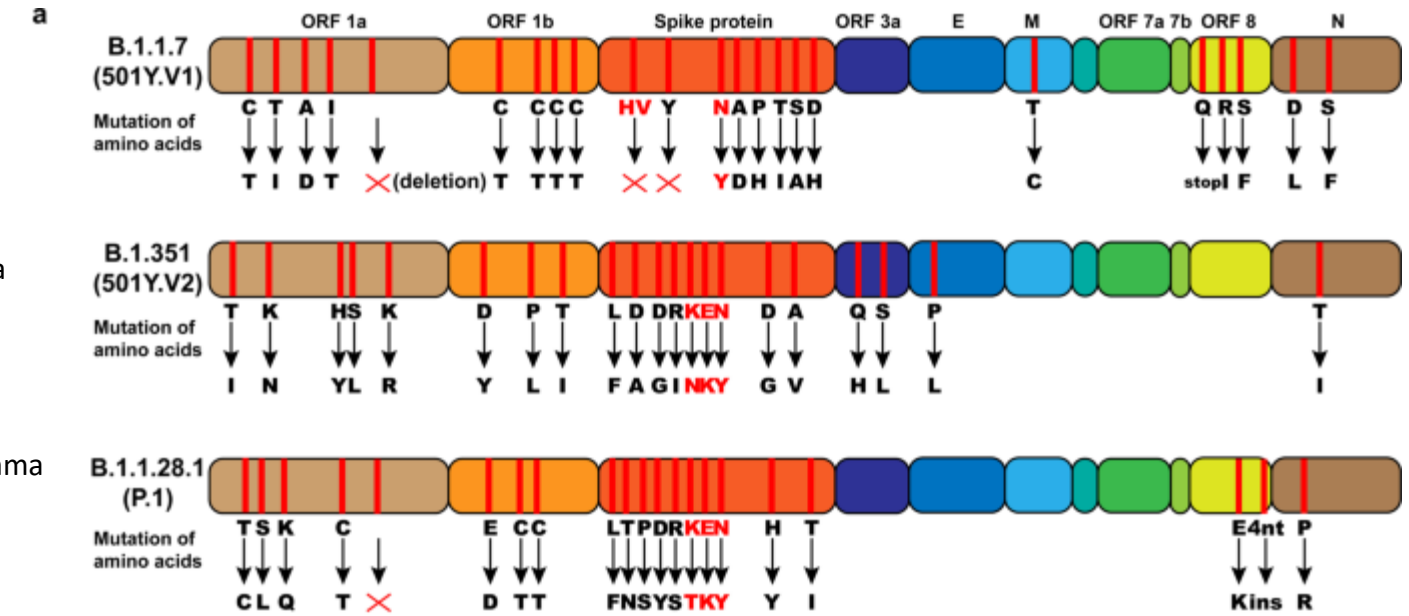
Fonte: https://doi.org/10.1080/07853890.2022.2031274

SARS-CoV-2 variants: not only in the spike protein!

Variante alfa

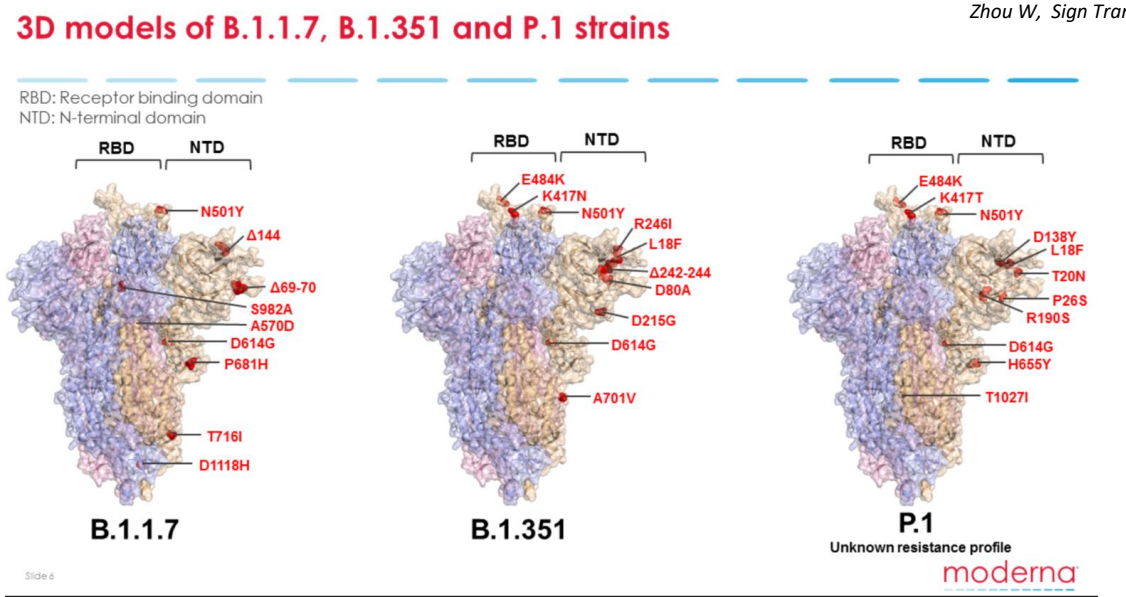
Variante beta

Variante gamma

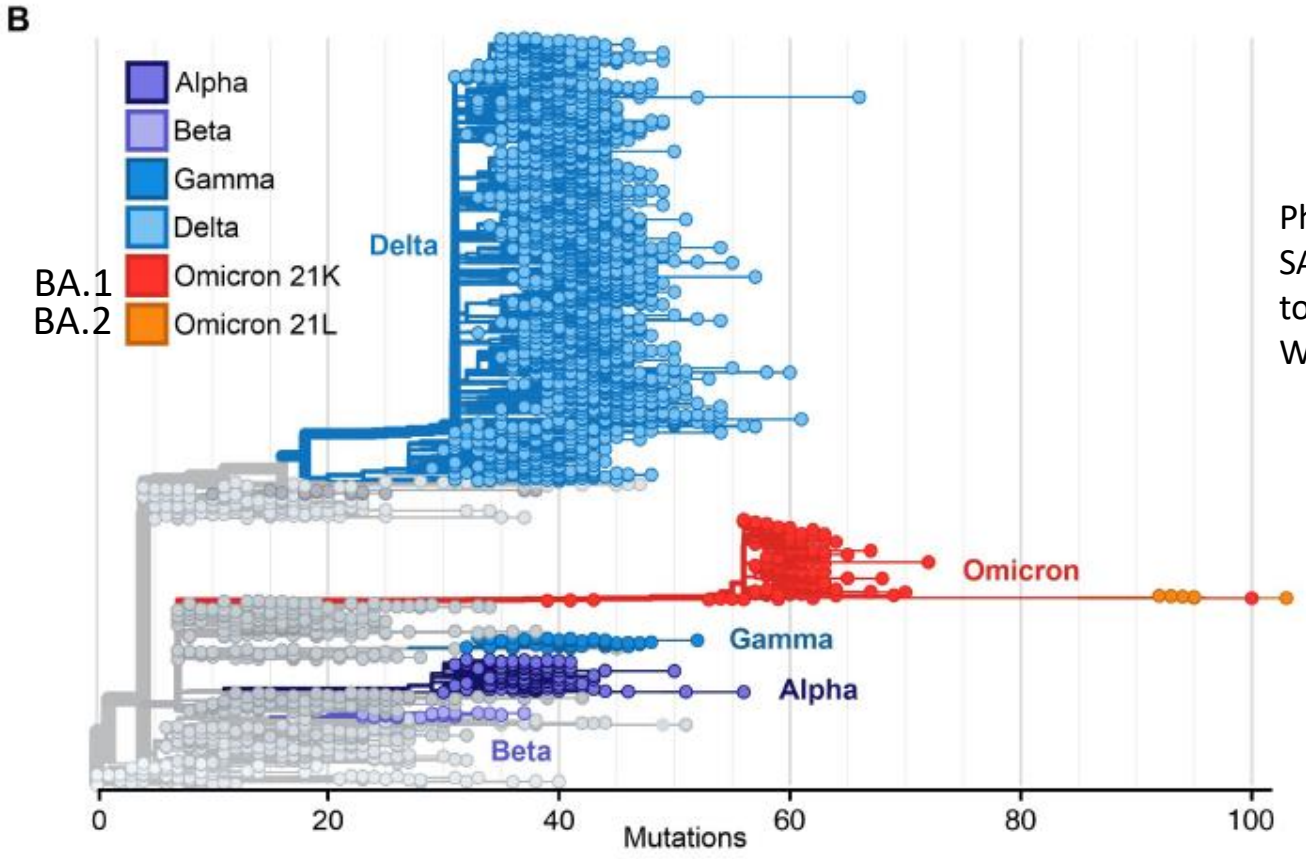


in red: key mutations

Zhou W, Sign Transd and Target Therapy, 2021

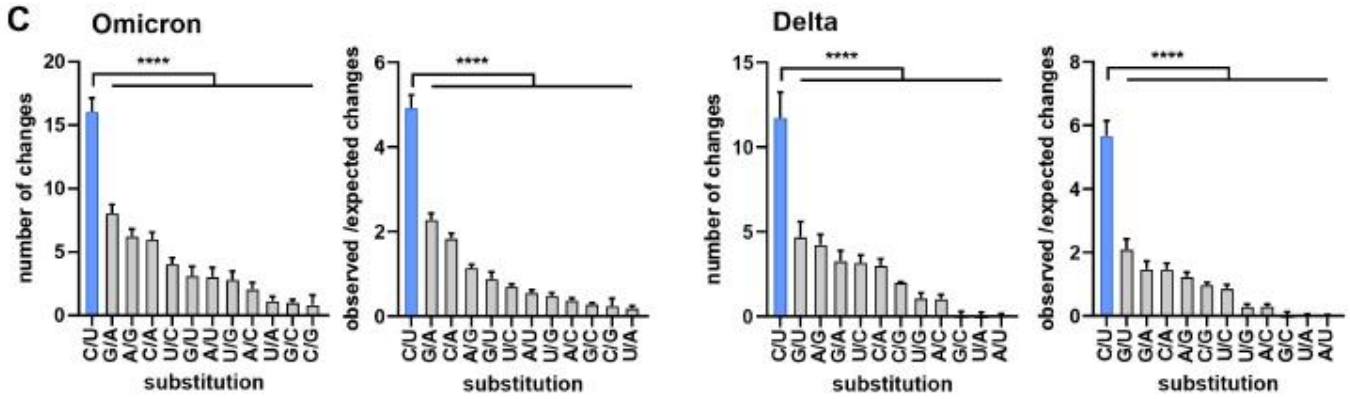


SARS-CoV-2 mutations and escape from immune control



Phylogenetic analysis of representative SARS-CoV-2 isolates scaled according to their divergence compared to the Wuhan Hu-1 sequence

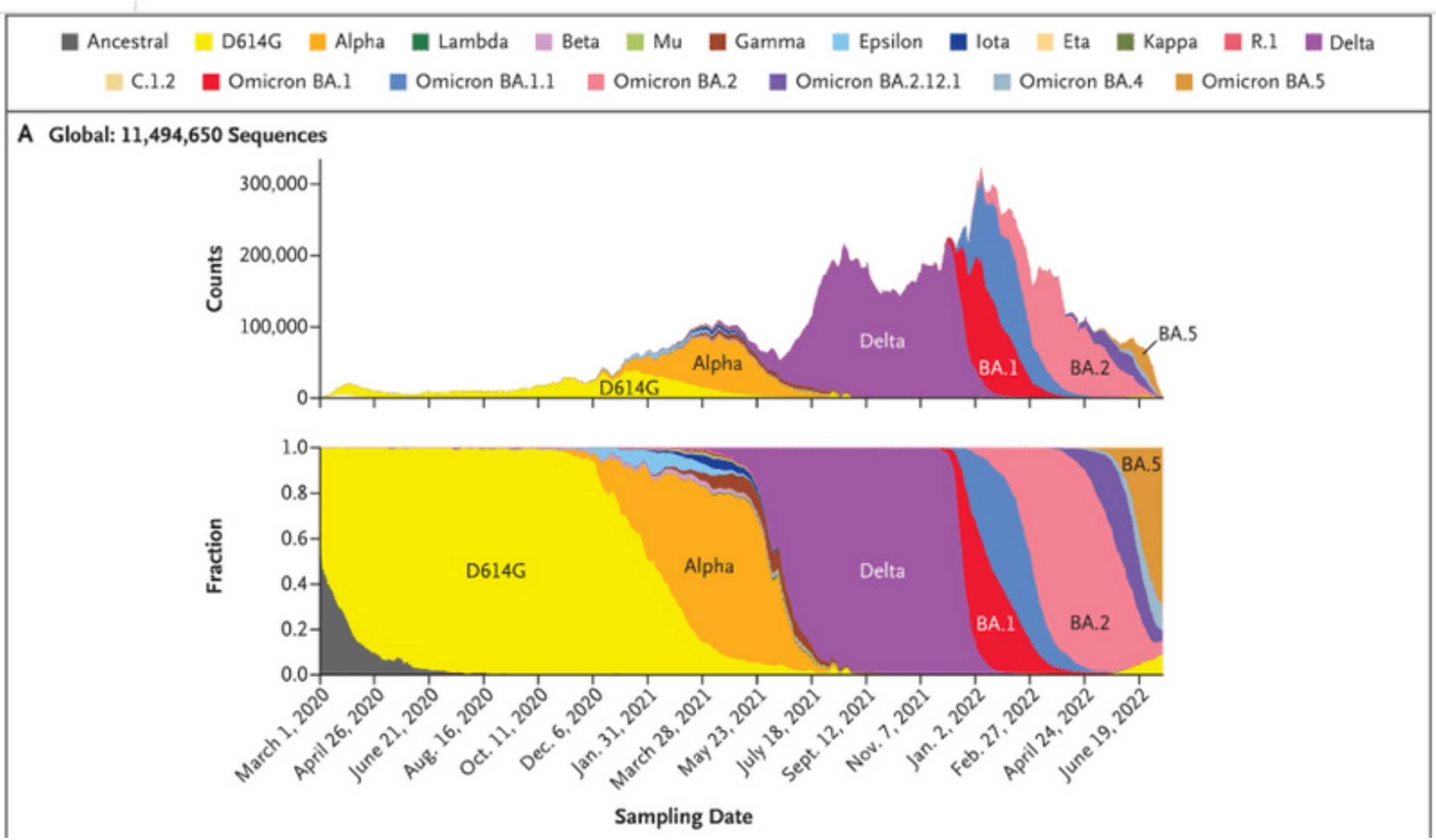
Types of single nucleotide substitutions in SARS-CoV-2 Omicron and Delta VOCs compared to Wuhan Hu-1 reference strain



N of isolates= 475 (Delta); 77 (Omicron)

C. Jung et al., JVI 2022

Varianti di SARS-CoV-2 (marzo 2020-giugno 2022)



OMS: "sottovarianti di Omicron sotto monitoraggio"

"CENTAURUS" (BA.2.75)

India - maggio 2022

Si è diffusa in altri Paesi: Regno Unito, USA, Germania, Giappone, Canada, Nepal, Indonesia, Nuova Zelanda.

É considerata una variante della sottovariante Omicron 2 (BA.2)

"GRYPHON (XBB)"

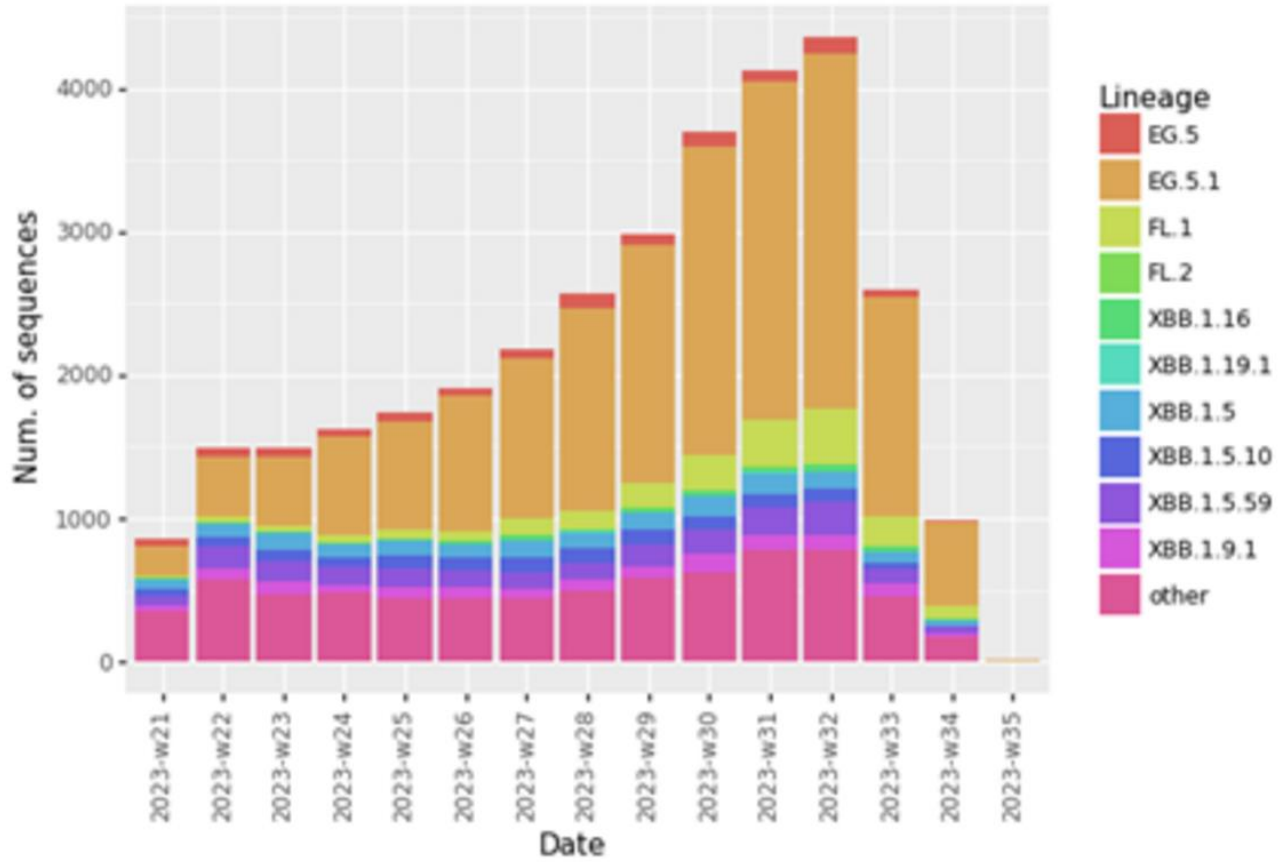
Si tratta di una variante ricombinante di BA.2.10.1 e BA.2.75
É stata segnalata in 35 Paesi, fra cui l'Italia (in particolare, i primi due casi sono stati segnalati in Abruzzo e in Friuli Venezia Giulia).

Varianti di SARS-CoV-2 (9 marzo 2023)

Variants of Concern (VOC) As of 3 March 2023, ECDC has de-escalated BA.2, BA.4 and BA.5 from its list of SARS-CoV-2 VOC, as these parental lineages are no longer circulating. ECDC will continue to categorize and report on specific SARS-CoV-2 sub-lineages in circulation that are relevant to the epidemiological situation

Variants of Interest (VOI)

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Transmission in EU/EEA
Omicron	BA.2.75 (x)	India	(y)	May 2022	Unclear (9)	Similar to Baseline (10-12)	No evidence	Community
Omicron	BQ.1	n/a	K444T, N460K	n/a	Baseline (13)	Baseline (10, 11, 14-16)	Baseline (17)	Dominant
Omicron	XBB (z)	n/a	N460K, F490S	n/a	Similar to Baseline (13,18)	Increased (v) (10, 11, 15, 19)	No evidence	Community
Omicron	XBB.1.5	United States	N460K, S486P, F490S	n/a	Increased (13, 20)	Increased (v) (13, 21)	Similar to Baseline (22)	Community

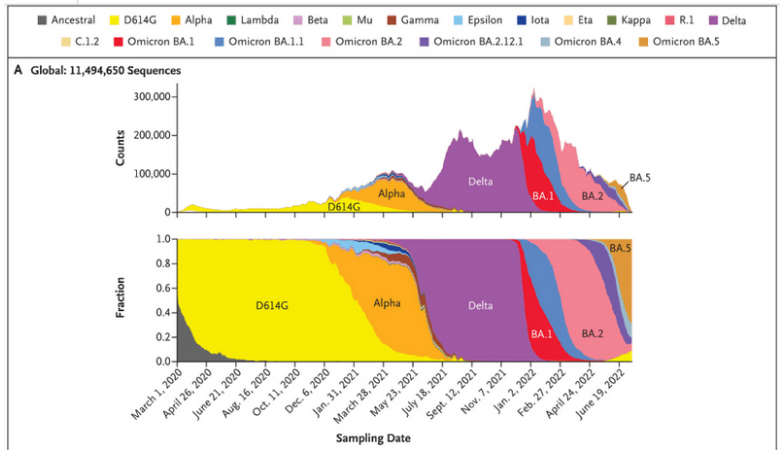


Distribution of the SARS-CoV-2 lineages assigned within XBB.1.5-like + F456L, per sample collection week (globally) as of 4 September 2023

De-escalated variants

These additional variants of SARS-CoV-2 have been de-escalated based on at least one the following criteria: (1) the variant is no longer circulating, (2) the variant has been circulating for a long time without any impact on the overall epidemiological situation, (3) scientific evidence demonstrates that the variant is not associated with any concerning properties.

								the EU/EEA
Omicron	BA.2	South Africa	(y)	November 2021	Increased (v) (1, 2)	Increased (v) (3)	Reduced (v) (4, 5)	Parental lineages are no longer circulating, ECDC monitoring sub-lineages in circulation
Omicron	BA.4	South Africa	L452R, F486V, R493Q	January 2022	No evidence	Increased (6, 7)	No evidence	Parental lineages are no longer circulating, ECDC monitoring sub-lineages in circulation
Omicron	BA.5	South Africa	L452R, F486V, R493Q	February 2022	No evidence	Increased (6, 7)	Unclear (8)	Parental lineages are no longer circulating, ECDC monitoring sub-lineages in circulation



SARS-Cov-2 e risposta immunitaria:

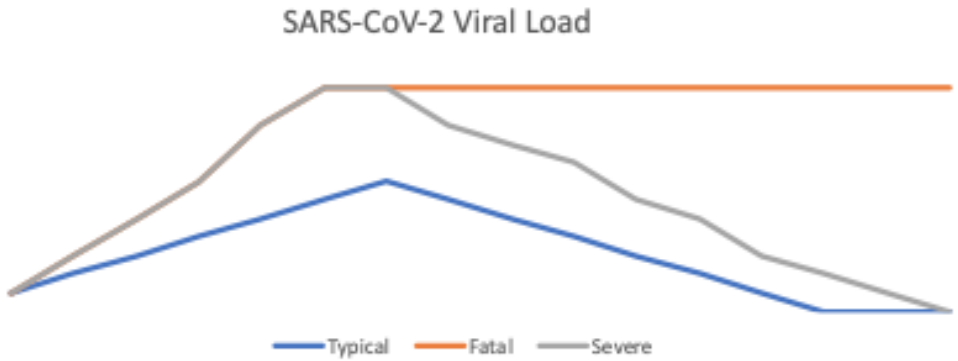
Immunità innata, infiammazione, IFN, linfociti T e B…
e la malattia

SARS-Cov-2 e risposta immunitaria:

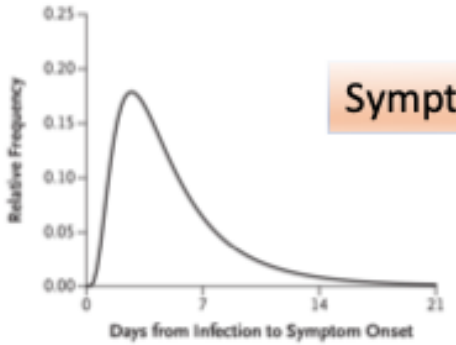
Immunità innata, infiammazione, IFN, linfociti T e B…

e la malattia

COVID-19 Disease Course



5.1 days (median)	5-10 days	Days - weeks	
Incubation Period	**Acute Mild Phase ***	**ARDS/Pro-inflammatory Phase**	**Recovery**



Symptom onset

Hallmarks: dyspnea, tachypnea, hypoxemia

* Acute Mild Phase: nonspecific symptoms. Most commonly fevers, cough, myalgias, fatigue. Nausea, diarrhea reported <50% of the time

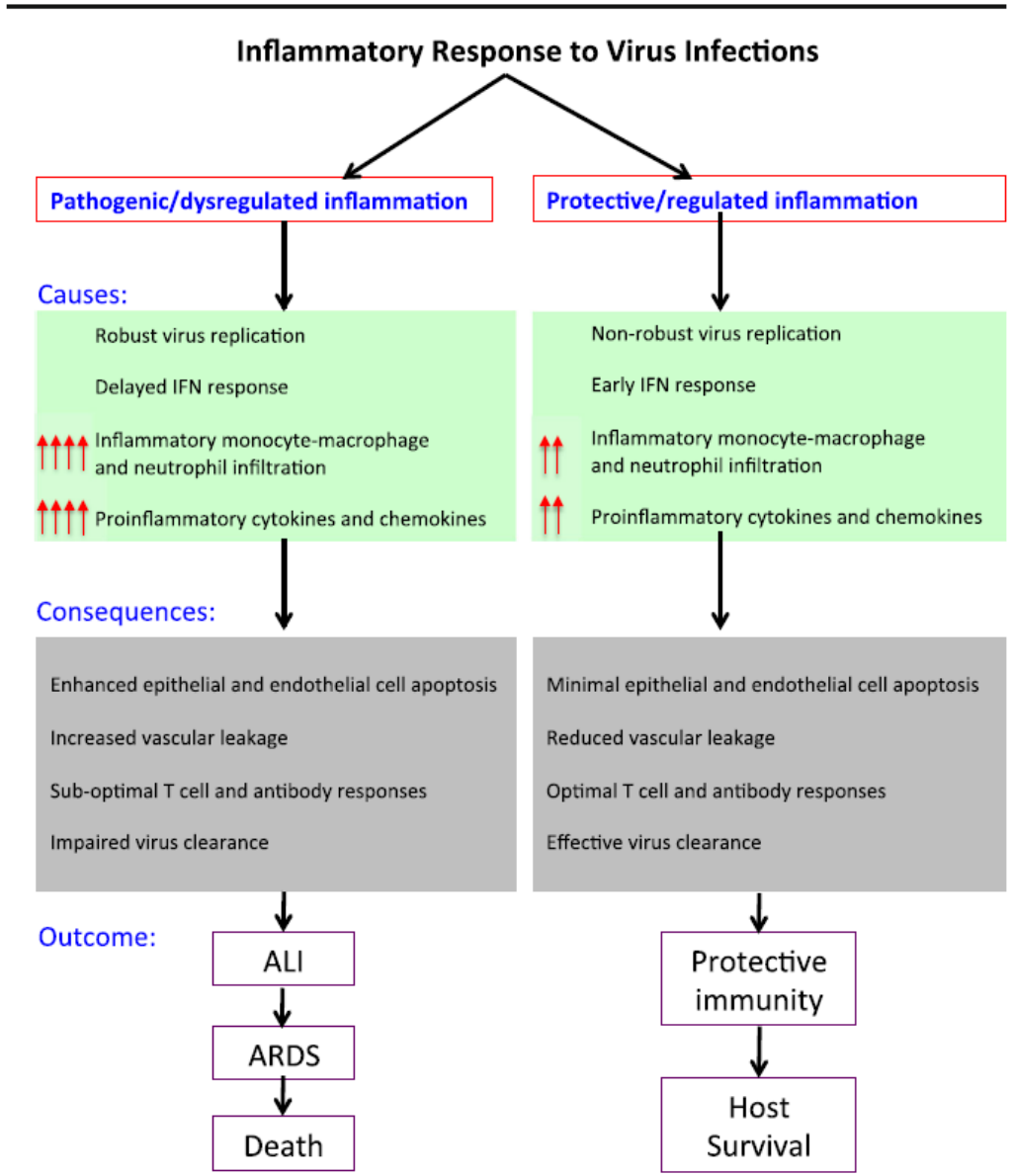
Pan Lancet ID 2020 https://doi.org/10.1016/S1473-3099(20)30113-4
Zou NEJM 2020 DOI: 10.1056/NEJMc2001737
Zhou Lancet 2020 https://doi.org/10.1016/S0140-6736(20)30566-3
Li NEJM 2020 DOI: 10.1056/NEJMoa2001316
Wang JAMA 2020 doi:10.1001/jama.2020.1585
Siddiqi JHLT 2020 doi:10.1016/j.healun.2020.03.012

Semin Immunopathol (2017) 39:529–539
DOI 10.1007/s00281-017-0629-x

REVIEW

Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology

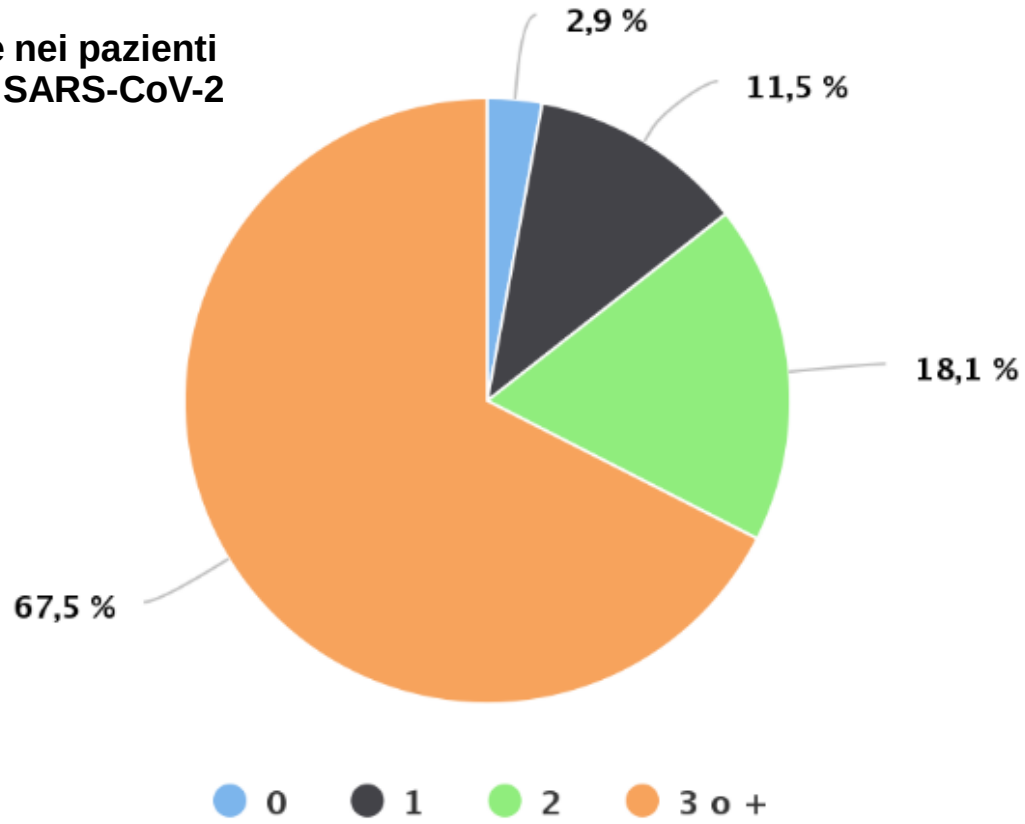
Rudragouda Channappanavar[1] · Stanley Perlman[1]



Infezioni da CoVs (2017!)

COVID-19 E COMORBIDITÀ

Numero di patologie nei pazienti deceduti e positivi a SARS-CoV-2



Report dell'Istituto Superiore di Sanità del 5 ottobre 2021

- Numero di decessi per Covid-19: 130.468
- Età media: 80 anni
- Campione: 7.910 persone decedute positive al Covid-19

Bellotti Azevedo et al. Journal of Human Hypertension, 2021

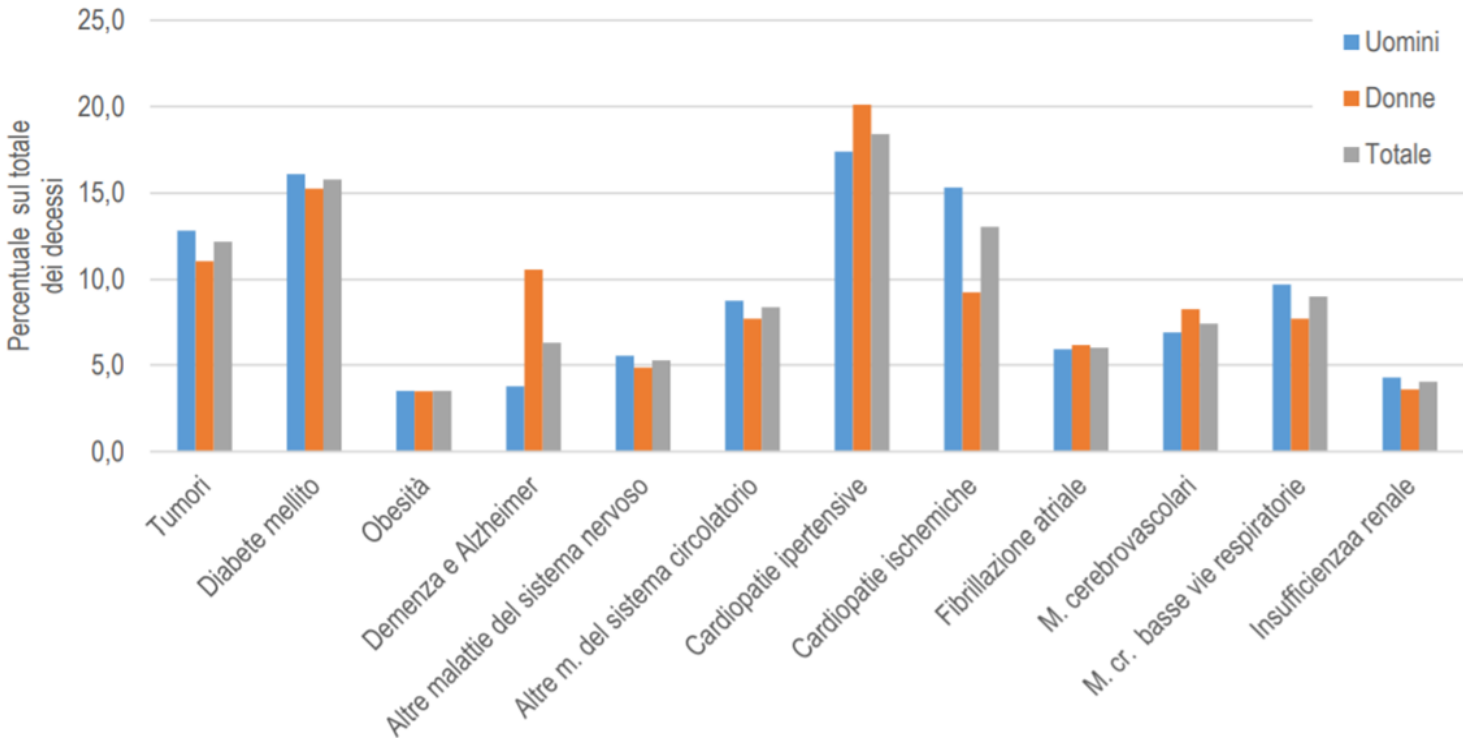
Report prodotto dal Gruppo della Sorveglianza dei Decessi SARS-CoV-2: Luigi Palmieri et al.

COVID-19 E COMORBIDITÀ

Concausa: malattia o circostanza esterna
in grado di avviare sequenze di eventi morbosi indipendenti tra loro che contribuiscono al decesso

- Covid-19 principale causa di morte nell'89% dei casi
- Comorbidità più frequenti: cardiopatie ipertensive (18%), diabete mellito (16%), cardiopatie ischemiche (13%) e tumori (12%)

Concause presenti nelle cartelle di morte

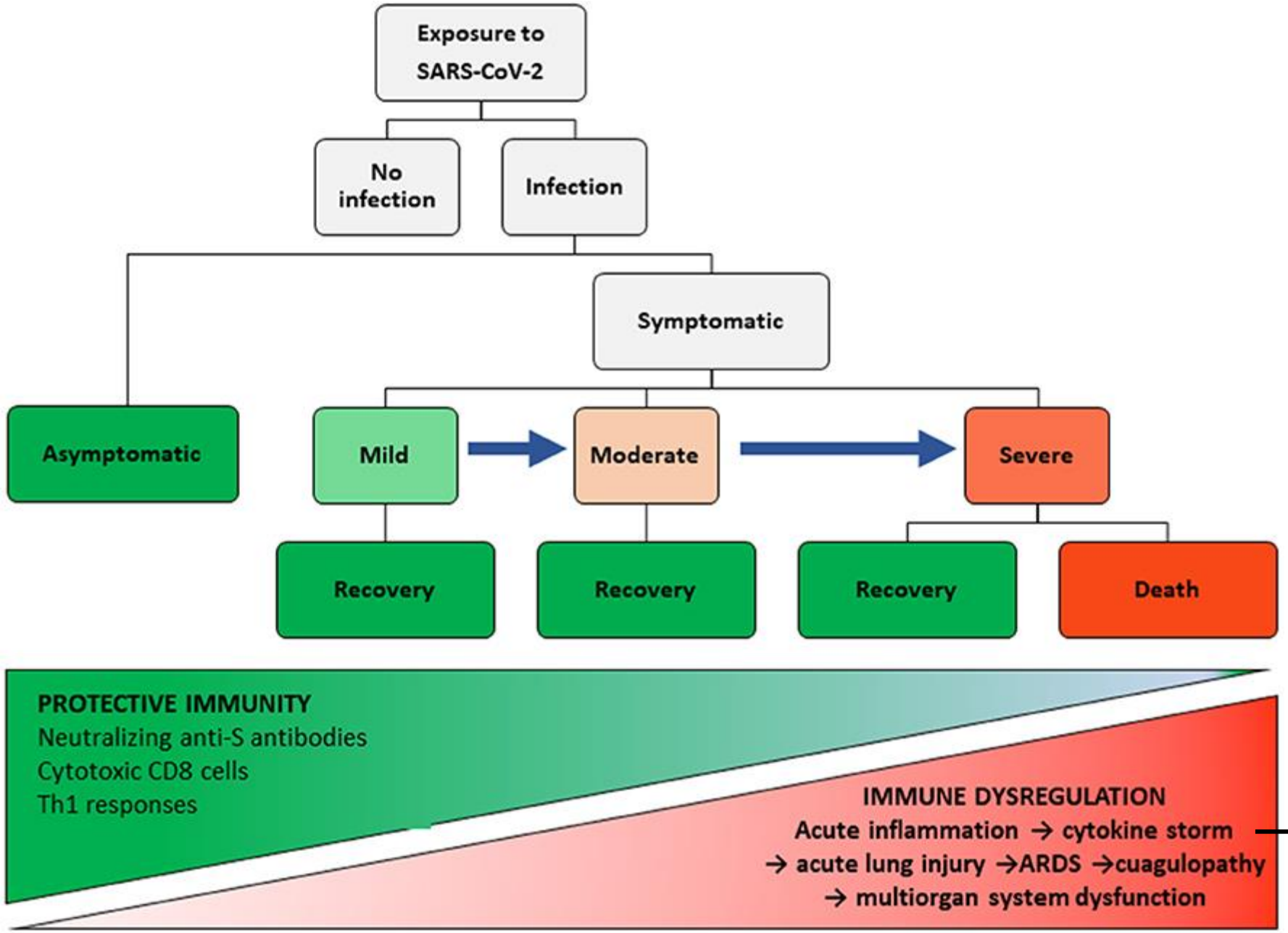


Analisi ISTAT di 4.942 schede di morte di pazienti positivi al 25 maggio 2020

Il ruolo delle patologie croniche pregresse nella prognosi dei pazienti COVID-19. Maria Masocco et al.
https://www.epicentro.iss.it/coronavirus/sars-cov-2-flussi-dati-confronto-patologie-croniche-pregresse

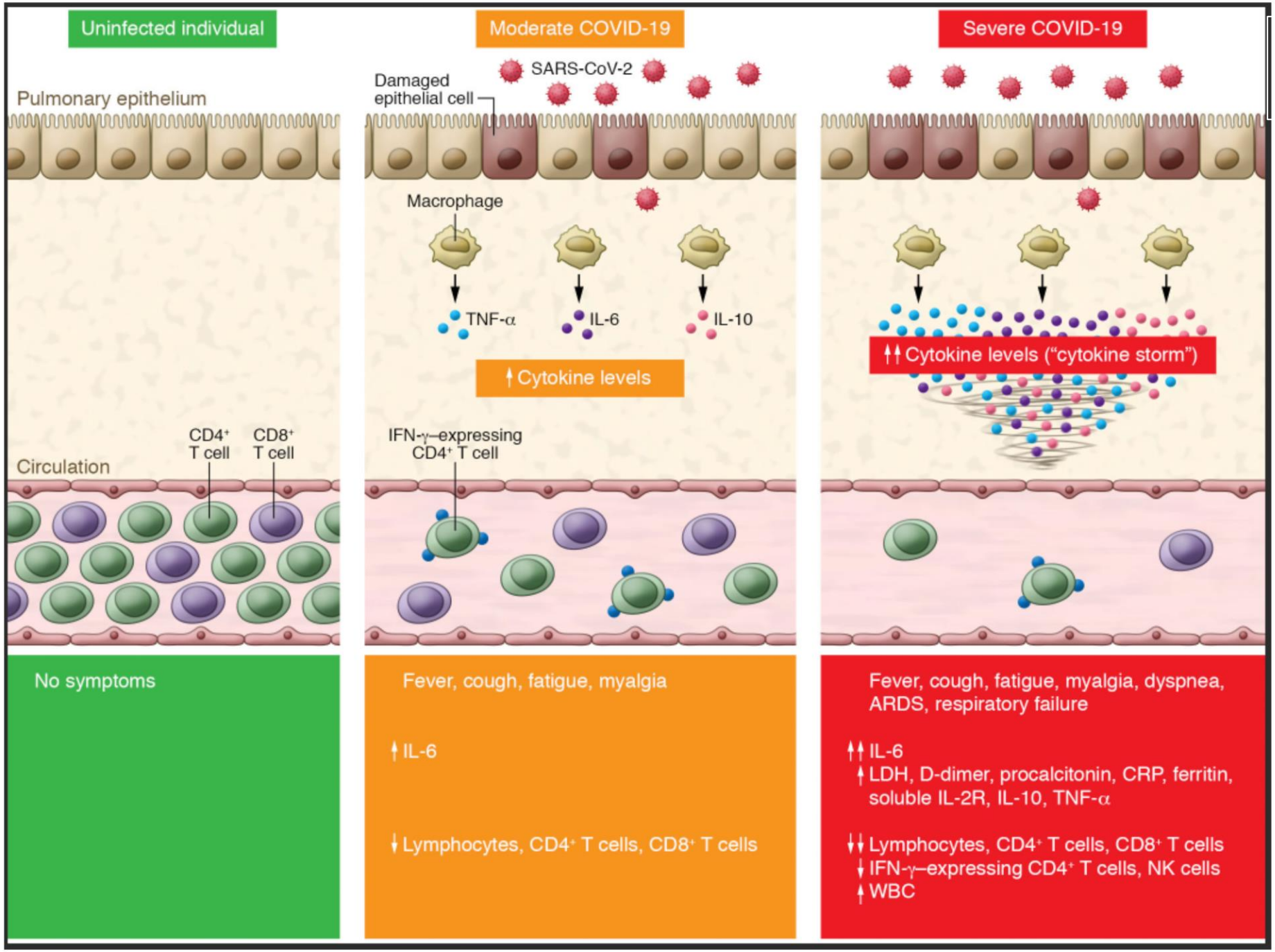
Elaborazione Istat su dati Iss: IMPATTO DELL'EPIDEMIA COVID-19 SULLA MORTALITÀ: CAUSE DI MORTE NEI DECEDUTI POSITIVI A SARS-COV-2

Risposta immunitaria, infiammazione e spettro dei sintomi clinici da infezione con SARS-CoV-2



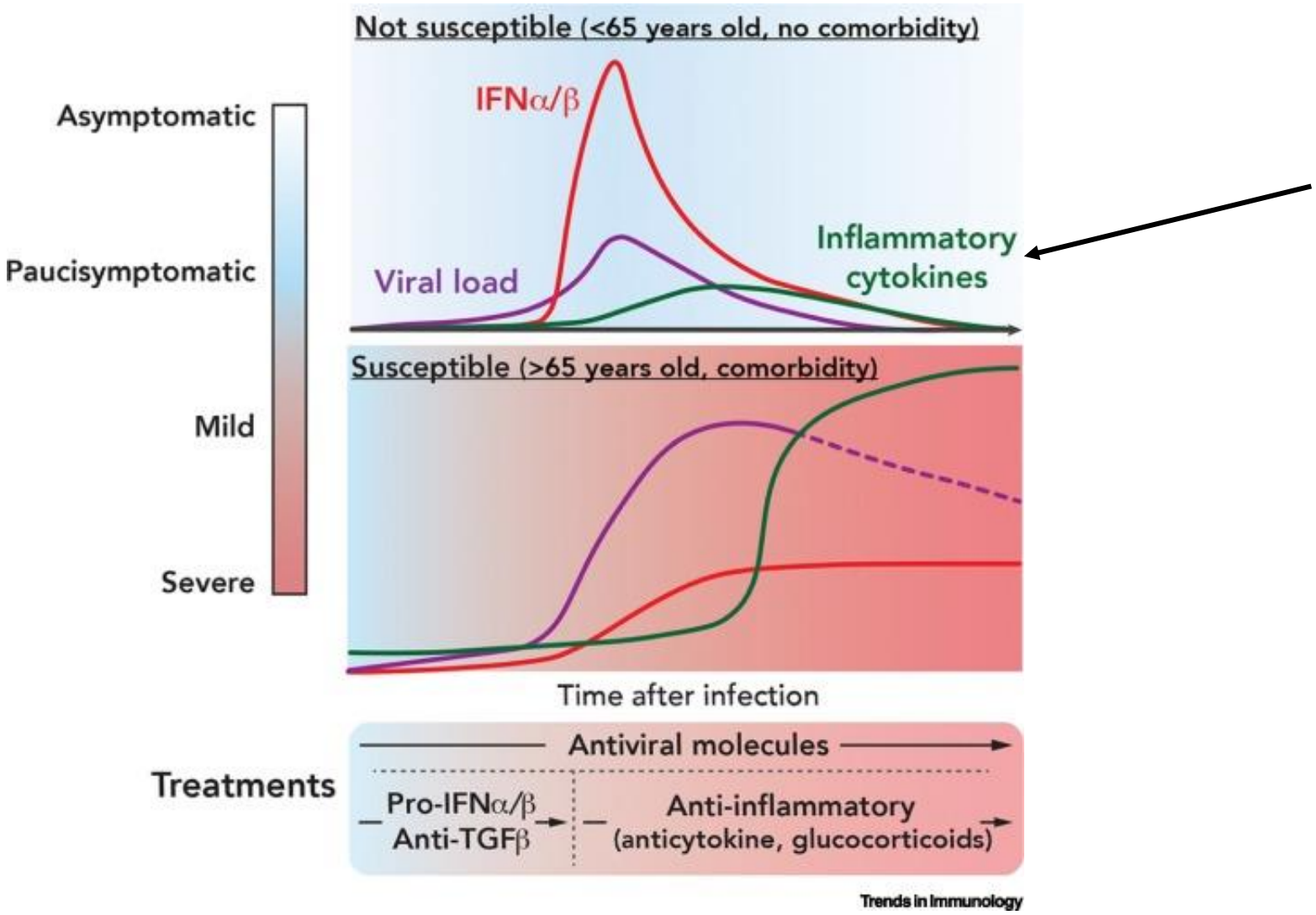
Frontiers Immunol, 2020

L'immunopatologia: una visione d'insieme



JCI The Journal of Clinical Investigation
SARS-CoV-2: A Storm is Raging
Savannah F. Pedersen, Ya-Chi Ho
J Clin Invest. 2020. https://doi.org/10.1172/JCI137647.

Cinetica della carica virale, IFN-I , e le citochine infiammatorie



Please cite this article as: V. Feuillet, B. Canard and A. Trautmann, Combining Antivirals and Immunomodulators to Fight COVID-19, *Trends in Immunology* (2020),

SARS-Cov-2 e risposta immunitaria:

Immunità innata, infiammazione, **IFN,** linfociti T e B…
e la malattia

La famiglia degli IFN può essere classificata in 3 tipi principali di citochine

Type	Subtype	Receptor	Chromosome	Number of aminoacids	Molecular weight (kilodaltons)	Area of expression
I	IFN-α*	IFNR-1/IFNR2	9p21	165-166	15-23	Ubiquitously expressed
	IFN-β	IFNR-1/IFNR2	9p21	166	15-23	Ubiquitously expressed
	IFN-ε	IFNR-1/IFNR2	9p21	208	24.4	Uterus, ovary
	IFN-κ	IFNR-1/IFNR2	9p21	180	24.5	Skin keratinocytes
	IFN-ω	IFNR-1/IFNR2	9p21	172	20-23	Leukocytes
II	IFN-γ	IFNGR-1/IFNGR2	12q24.1	146	34	T lymphocytes, NK cells
III	IFN-λ1(IL-29)	IL-28Rα/IL-10Rβ	19q13.13	200	20-33	Epithelial cells Some leukocytes
	IFN-λ2(IL-28A)	IL-28Rα/IL-10Rβ	19q13.13	200	22	
	IFN-λ3(IL-28B)	IL-28Rα/IL-10R2	19q13.13	196	22	

*** 13 subtypes**

Interferon biological activities

- 1. Antiviral
- 2. Antiproliferative
- 3. Immunomodulatory
- 4. Proapoptotic
- 5. Proinflammatory

3 main functions of type I IFNs

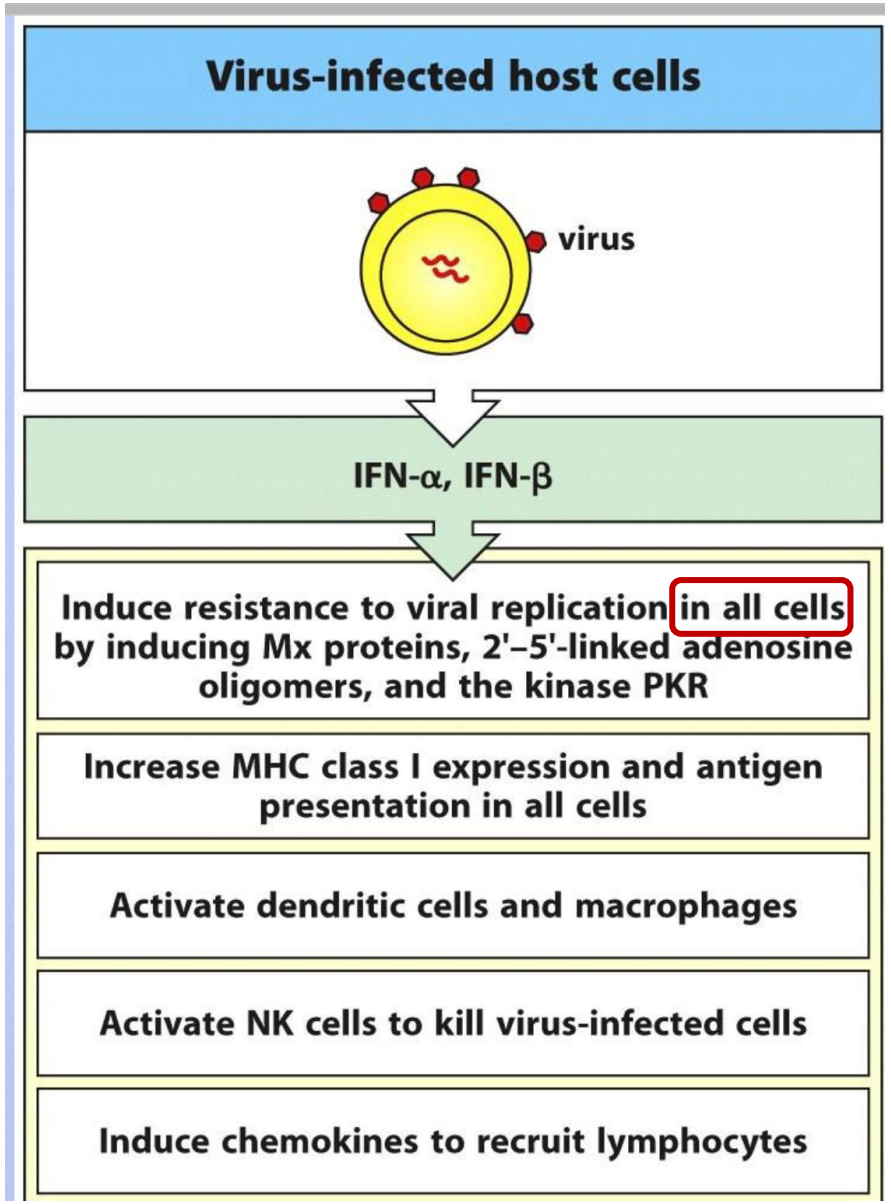
- Induction of cell-intrinsic antimicrobial states in infected and neighbouring cells that limit the spread of infectious agents, particularly viral pathogens.

- Modulation of innate immune responses in a balanced manner that promotes antigen presentation and NK cell functions while restraining pro-inflammatory pathways and cytokine production.

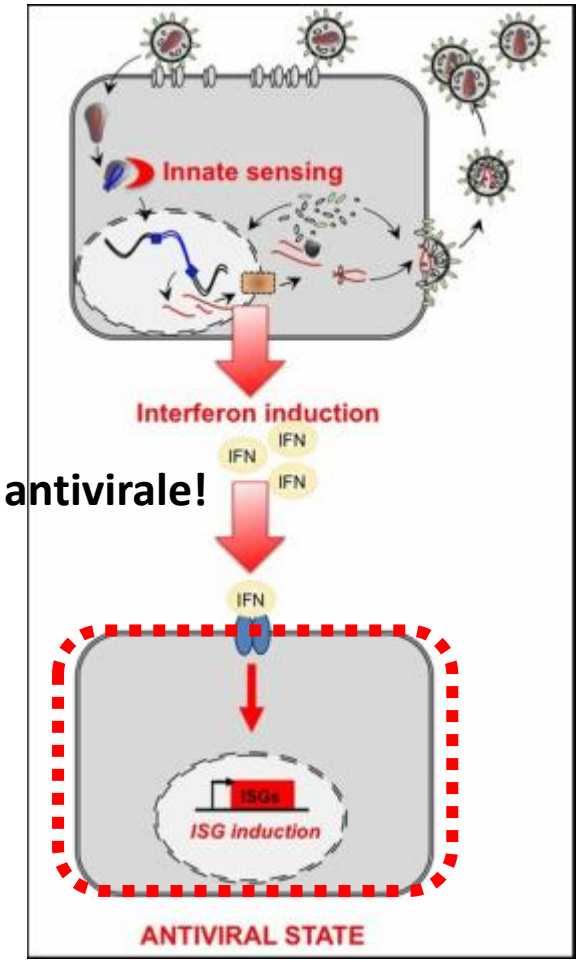
- Activation of the adaptive immune system, thus promoting the development of high-affinity antigen-specific T and B cell responses and immunological memory.

Type I IFNs can be produced by almost every cell type

Attività antivirale e immunoregolatoria dell'IFN di tipo I



lo stato antivirale!



ISGs: IFN-stimulated genes

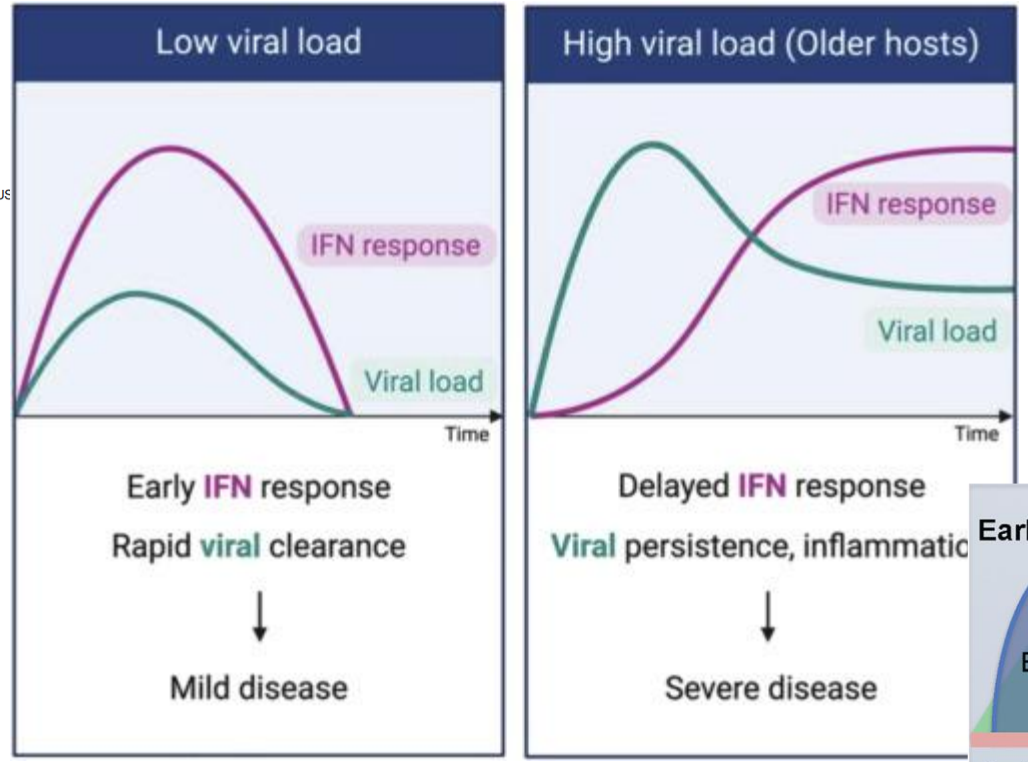
CellPress

Cell Host & Microbe

Review

Type I and Type III Interferons – Induction, Signaling, Evasion, and Application to Combat COVID-19

Annsea Park[1] and Akiko Iwasaki[1,2,3,*]
[1]Department of Immunobiology, Yale University School of Medicine, New Haven, CT, USA
[2]Department of Molecular Cellular and Developmental Biology, Yale University School of Medicine, New Haven, CT, US
[3]Howard Hughes Medical Institute, Chevy Chase, MD, USA
*Correspondence: akiko.iwasaki@yale.edu
https://doi.org/10.1016/j.chom.2020.05.008

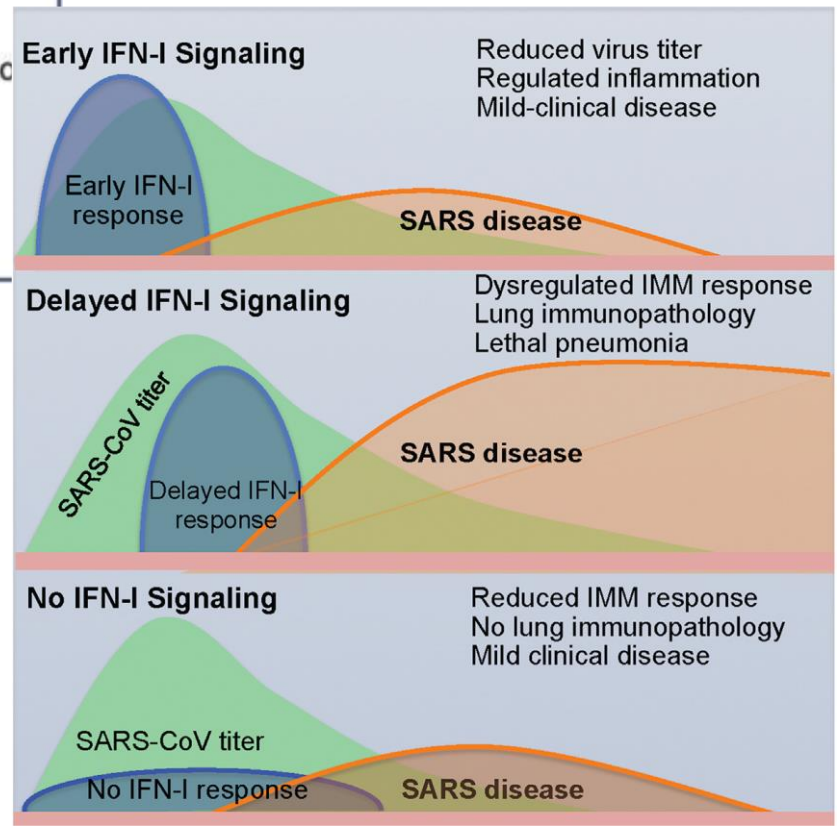


2016!

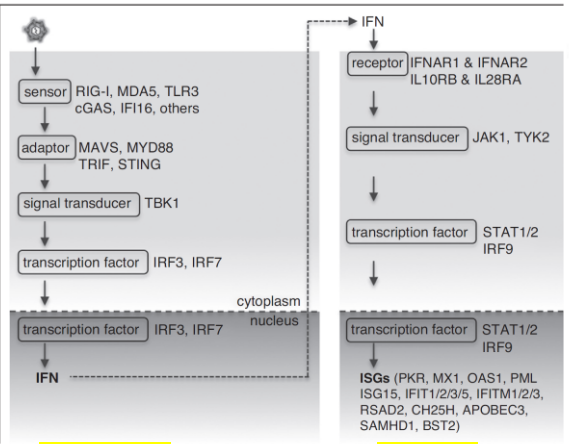
Cell Host & Microbe

Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice

Channappanavar et al., 2016, Cell Host & Microbe *19*, 181–193
February 10, 2016 ©2016 Elsevier Inc.

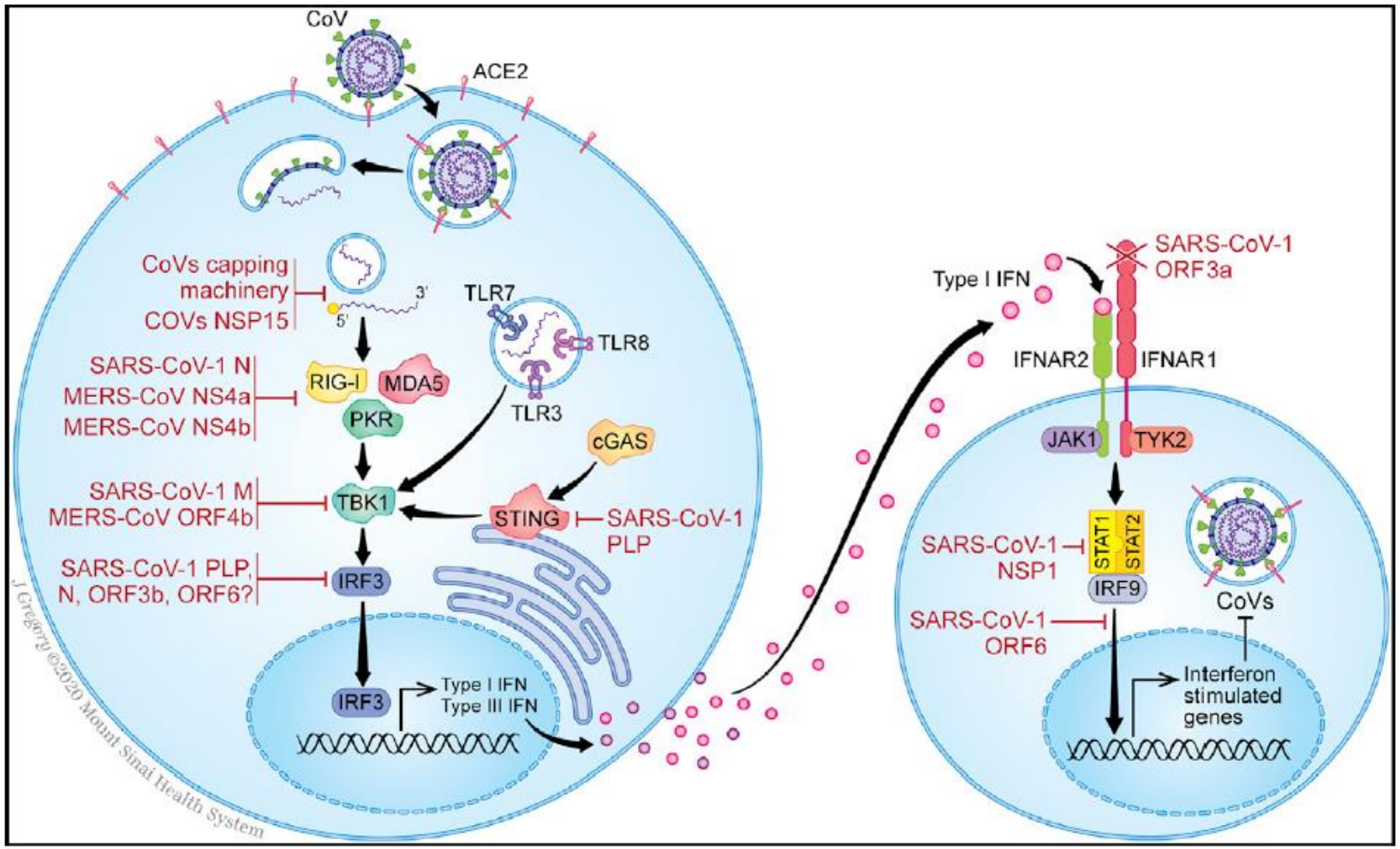


Immunità innata e immunoevasione da parte dei Coronavirus



Recognition (immune sensing)

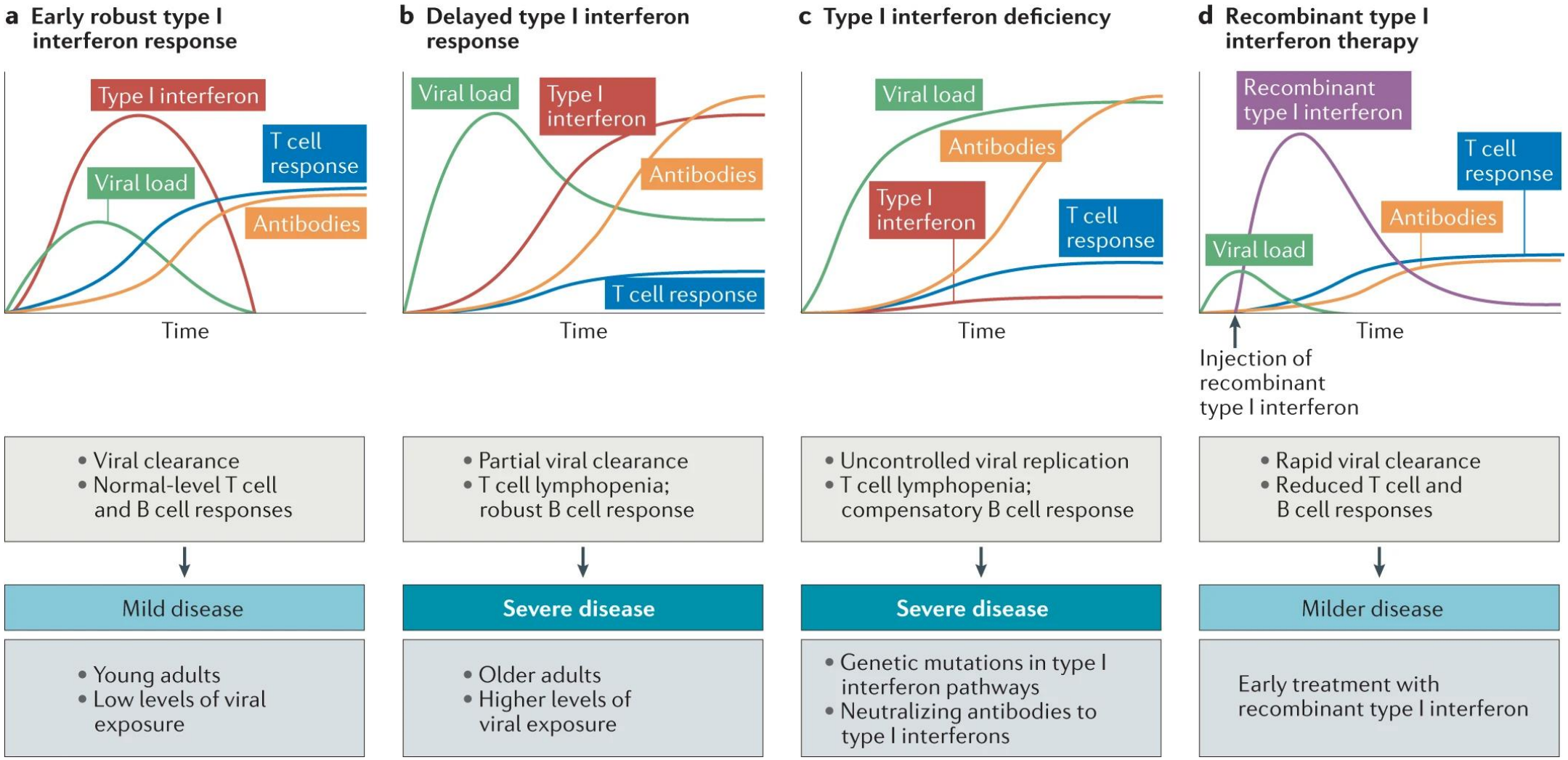
Outcome (IFN signaling)



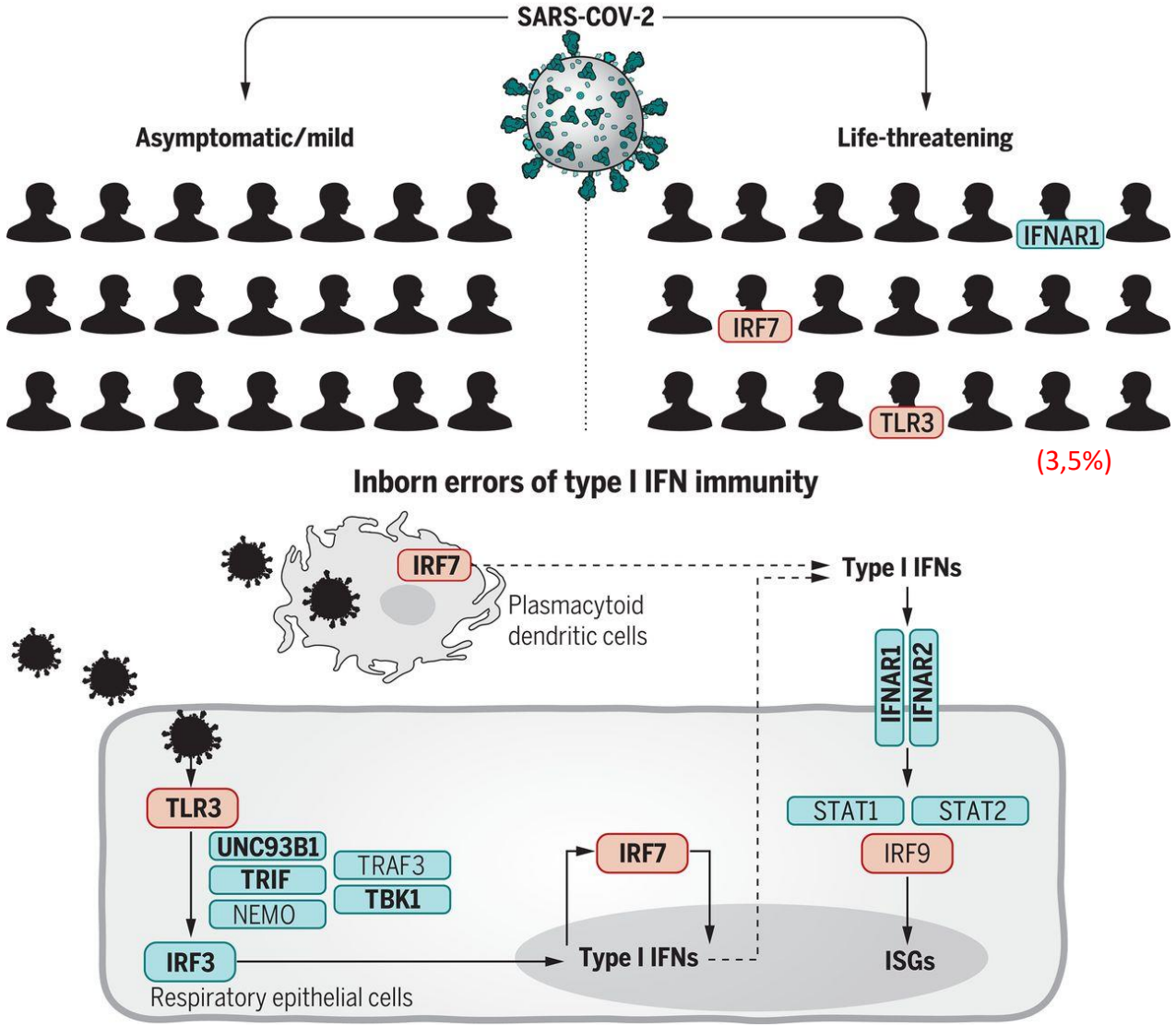
Recognition (immune sensing)

Outcome (IFN signaling)

CellPress
Review
Immunology of COVID-19: Current State of the Science
Immunity 52, June 16, 2020


a Early robust type I interferon response
Type I interferon
T cell response
Viral load
Antibodies
Time
• Viral clearance
• Normal-level T cell and B cell responses
Mild disease
• Young adults
• Low levels of viral exposure
b Delayed type I interferon response
Viral load
Type I interferon
Antibodies
T cell response
Time
• Partial viral clearance
• T cell lymphopenia; robust B cell response
Severe disease
• Older adults
• Higher levels of viral exposure
c Type I interferon deficiency
Viral load
Antibodies
Type I interferon
T cell response
Time
• Uncontrolled viral replication
• T cell lymphopenia; compensatory B cell response
Severe disease
• Genetic mutations in type I interferon pathways
• Neutralizing antibodies to type I interferons
d Recombinant type I interferon therapy
Recombinant type I interferon
T cell response
Antibodies
Viral load
Time
Injection of recombinant type I interferon
• Rapid viral clearance
• Reduced T cell and B cell responses
Milder disease
Early treatment with recombinant type I interferon

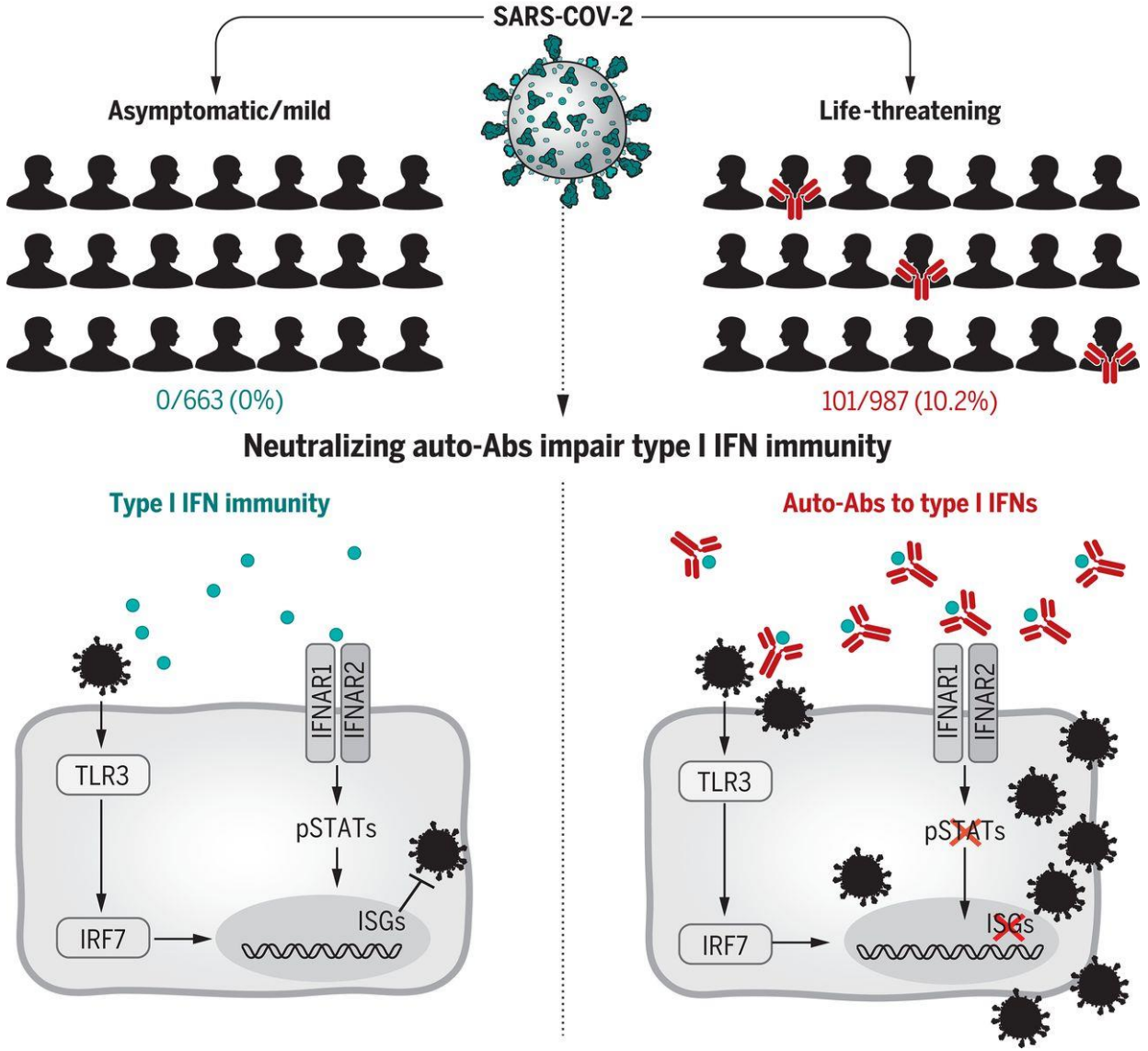
Inborn errors of TLR3- and IRF7-dependent type I IFN production and amplification underlie life-threatening COVID-19 pneumonia



Science AAAS

Zhang Q et al. Science 2020

Neutralizing auto-Abs to type I IFNs underlie life-threatening COVID-19 pneumonia



In these patients, adaptive autoimmunity impairs innate and intrinsic antiviral immunity

Science AAAS

Bastard P et al. Science 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genomewide Association Study of Severe Covid-19 with Respiratory Failure

The Severe Covid-19 GWAS Group*

N ENGL J MED 383;16 NEJM.ORG OCTOBER 15, 2020

La genetica: associazioni tra geni e COVID-19

The red dashed line indicates the genomewide significance threshold of a P value less than 5×10^{-8}.

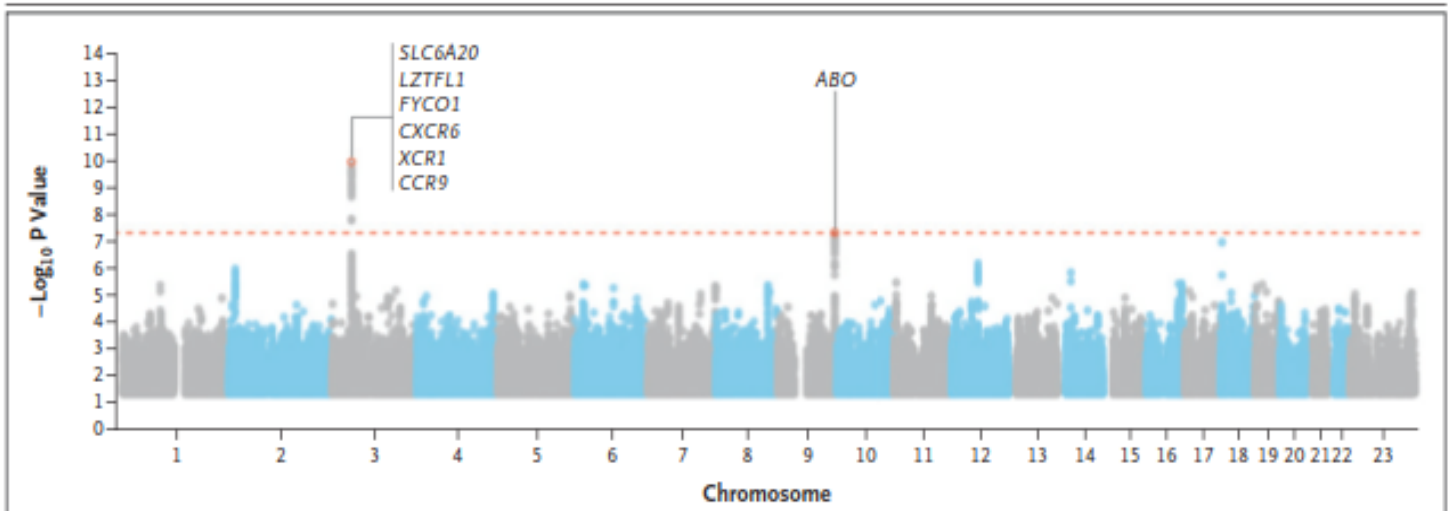


Figure 2. GWAS Summary (Manhattan) Plot of the Meta-analysis Association Statistics Highlighting Two Susceptibility Loci with Genomewide Significance for Severe Covid-19 with Respiratory Failure.

Shown is a Manhattan plot of the association statistics from the main meta-analysis (controlled for potential population stratification). The red dashed line indicates the genomewide significance threshold of a P value less than 5×10^{-8}. Figure S6 in Supplementary Appendix 1 shows Manhattan plots that include hits passing a suggestive significance threshold of a P value less than 1×10^{-5} (total of 24 additional suggestive genomic loci) (see the Supplementary Methods section and Supplementary Appendix 4).

CONCLUSIONS

We identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with Covid-19 with respiratory failure and confirmed a potential involvement of the ABO blood-group system. (Funded by Stein Erik Hagen and others.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Anastassopoulou *et al. Human Genomics* (2020)

Genomewide Association Study of Severe Covid-19 with Respiratory Failure

The Severe Covid-19 GWAS Group*

N ENGL J MED 383;16 NEJM.ORG OCTOBER 15, 2020

La genetica: associazioni tra geni e COVID-19

Gene(s)	Polymorphism(s)	Chromosome location	Reported COVID-19 associations
ABO	rs657152	9q34.2	Higher risk of infection for blood group A vs. non-A (OR 1.45, 95% CI 1.20–1.75, $P = 1.48 \times 10^{-4}$) and lower risk of infection for blood group O vs. non-O (OR 0.65, 95% CI 0.53–0.79, $P = 1.06 \times 10^{-5}$)
ACE2	p.Arg514-Gly	Xp22.2	Cardiovascular and pulmonary conditions in the African/ African-American population by altering AGT-ACE2 pathway
ApoE	rs429358-C-C (e4e4)	19q13.32	Severe disease independently of pre-existing dementia, cardiovascular disease, and type 2 diabetes
HLA	B*46:01 and B*15:03	6p21.33	Vulnerable to disease for *HLA-B*46:01* and cross-protective T cell-based immunity for *HLA-B*15:03*
IFITM3	rs12252-C/C	11p15.5	Mild-to-moderate disease requiring hospitalization
SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, XCR1	rs11385942-GA	3p21.31	Severe disease (respiratory failure) (OR 1.77, 95% CI 1.48–2.11, $P = 1.15 \times 10^{-10}$)
TLR7	g.12905756_12905759del and g.12906010G>T	Xp22.2	Severe disease
TMEM189-UBE2V1	rs6020298-A	20q13.13	Severe disease
TMPRSS2	p.Val160Met (rs12329760)	21q22.3	Increased susceptibility to disease and for risk factors, e.g., cancer

Article

The major genetic risk factor for severe COVID-19 is inherited from Neanderthals

https://doi.org/10.1038/s41586-020-2818-3

Received: 3 July 2020

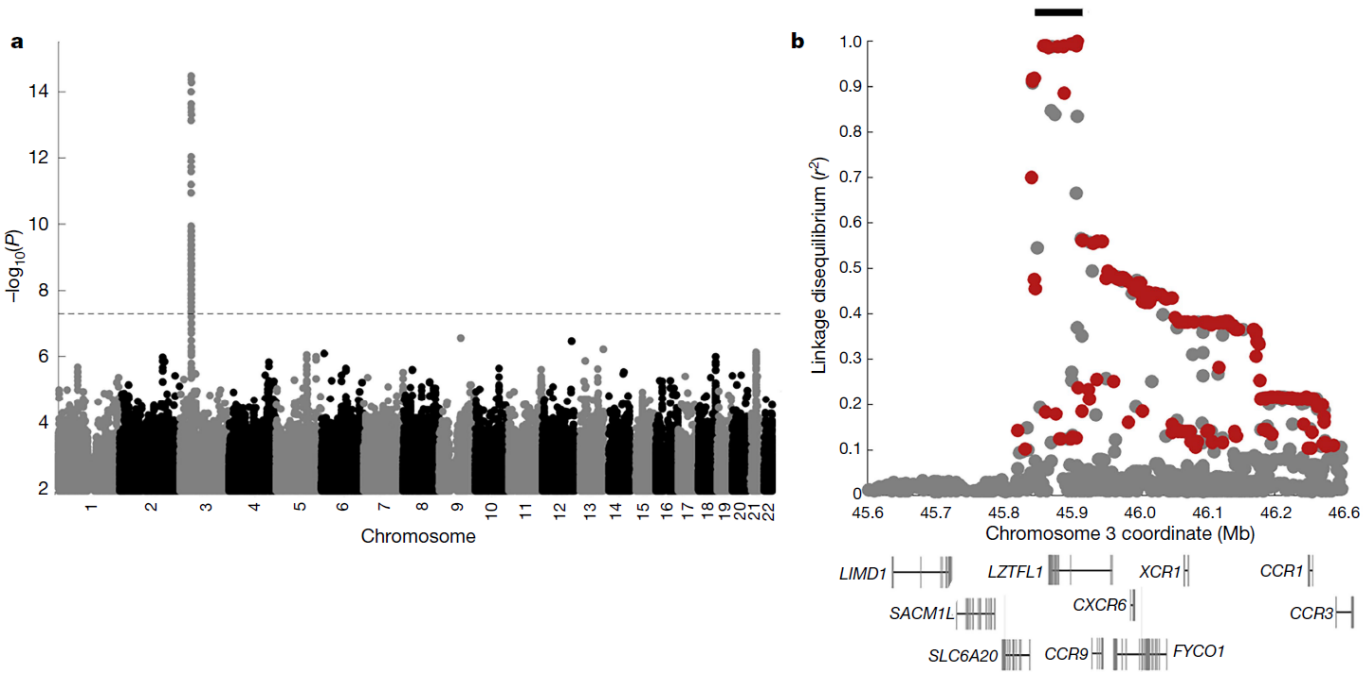
Accepted: 22 September 2020

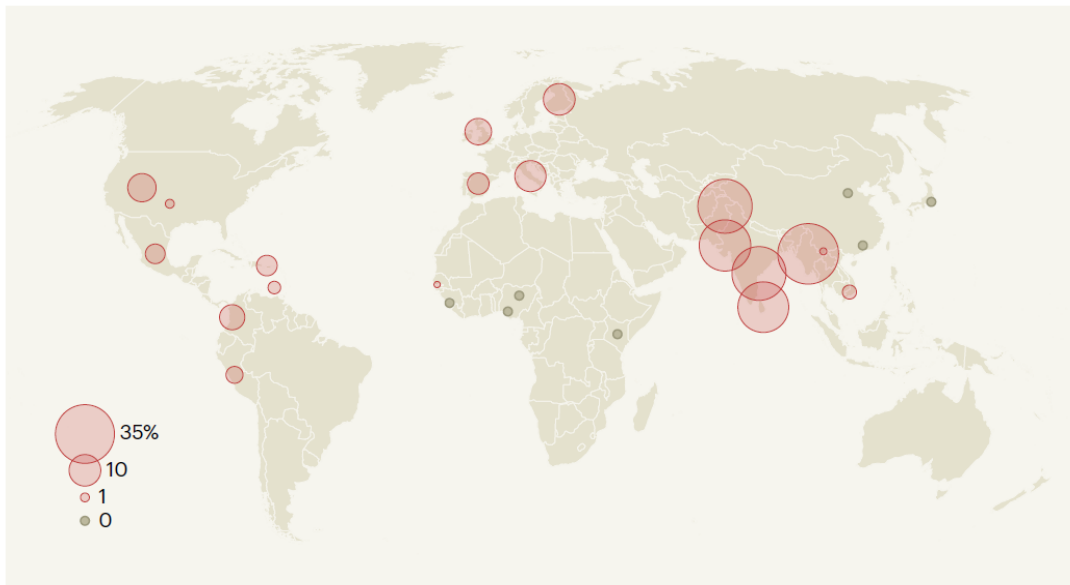
Published online: 30 September 2020

Check for updates

Hugo Zeberg[1,2] ✉ & Svante Pääbo[1,3] ✉

A recent genetic association study[1] identified a gene cluster on chromosome 3 as a risk locus for respiratory failure after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A separate study (COVID-19 Host Genetics Initiative)[2] comprising 3,199 hospitalized patients with coronavirus disease 2019 (COVID-19) and control individuals showed that this cluster is the major genetic risk factor for severe symptoms after SARS-CoV-2 infection and hospitalization. Here we show that the risk is conferred by a genomic segment of around 50 kilobases in size that is inherited from Neanderthals and is carried by around 50% of people in south Asia and around 16% of people in Europe.





nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01281-1

A Neanderthal OAS1 isoform protects individuals of European ancestry against COVID-19 susceptibility and severity

Sirui Zhou[1,2,23], Guillaume Butler-Laporte[1,2,23], Tomoko Nakanishi[1,3,4,5,23], David R. Morrison[1], Jonathan Afilalo[1,2,6], Marc Afilalo[1,7], Laetitia Laurent[1], Maik Pietzner[8], Nicola Kerrison[8], Kaiqiong Zhao[1,2], Elsa Brunet-Ratnasingham[9,10], Danielle Henry[1], Nofar Kimchi[1], Zaman Afrasiabi[1], Nardin Rezk[1], Meriem Bouab[1], Louis Petitjean[1], Charlotte Guzman[1], Xiaoqing Xue[1], Chris Tselios[1], Branka Vulesevic[1], Olumide Adeleye[1], Tala Abdullah[1], Noor Almamlouk[1], Yiheng Chen[1,3], Michaël Chassé[9], Madeleine Durand[9], Clare Paterson[11], Johan Normark[12], Robert Frithiof[13], Miklós Lipcsey[13,14], Michael Hultström[13,15], Celia M. T. Greenwood[1,2,16], Hugo Zeberg[17], Claudia Langenberg[8,18], Elin Thysell[19], Michael Pollak[1,20], Vincent Mooser[3], Vincenzo Forgetta[1], Daniel E. Kaufmann[9,21] and J. Brent Richards[1,2,3,22] ✉

To identify circulating proteins influencing Coronavirus Disease 2019 (COVID-19) susceptibility and severity, we undertook a two-sample Mendelian randomization (MR) study, rapidly scanning hundreds of circulating proteins while reducing bias due to reverse causation and confounding. In up to 14,134 cases and 1.2 million controls, we found that an s.d. increase in OAS1 levels was associated with reduced COVID-19 death or ventilation (odds ratio (OR) = 0.54, $P = 7 \times 10^{-8}$), hospitalization (OR = 0.61, $P = 8 \times 10^{-8}$) and susceptibility (OR = 0.78, $P = 8 \times 10^{-6}$). Measuring OAS1 levels in 504 individuals, we found that higher plasma OAS1 levels in a non-infectious state were associated with reduced COVID-19 susceptibility and severity. Further analyses suggested that a Neanderthal isoform of OAS1 in individuals of European ancestry affords this protection. Thus, evidence from MR and a case–control study support a protective role for OAS1 in COVID-19 adverse outcomes. Available pharmacological agents that increase OAS1 levels could be prioritized for drug development.

OAS1 is on Chr 12

Published online: 25 February 2021

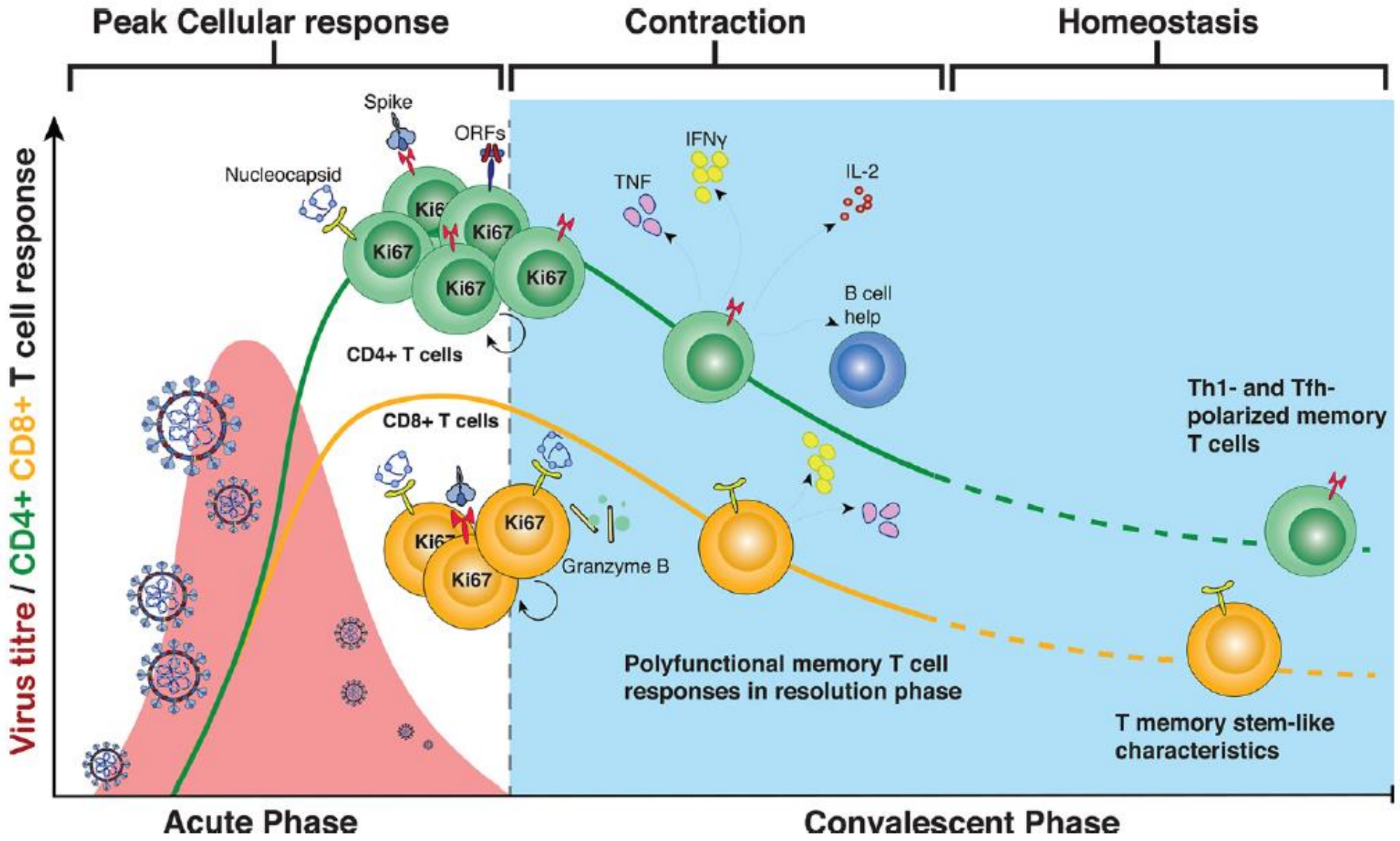
SARS-Cov-2 e risposta immunitaria:

Immunità innata, infiammazione, IFN,

linfociti T e B…

e la malattia

Phenotype and kinetics of SARS-Cov-2-specific T cell responses after natural infection



Niessl J, Seminars in Immunol, 2021

Review

Immunology of COVID-19: Current State of the Science

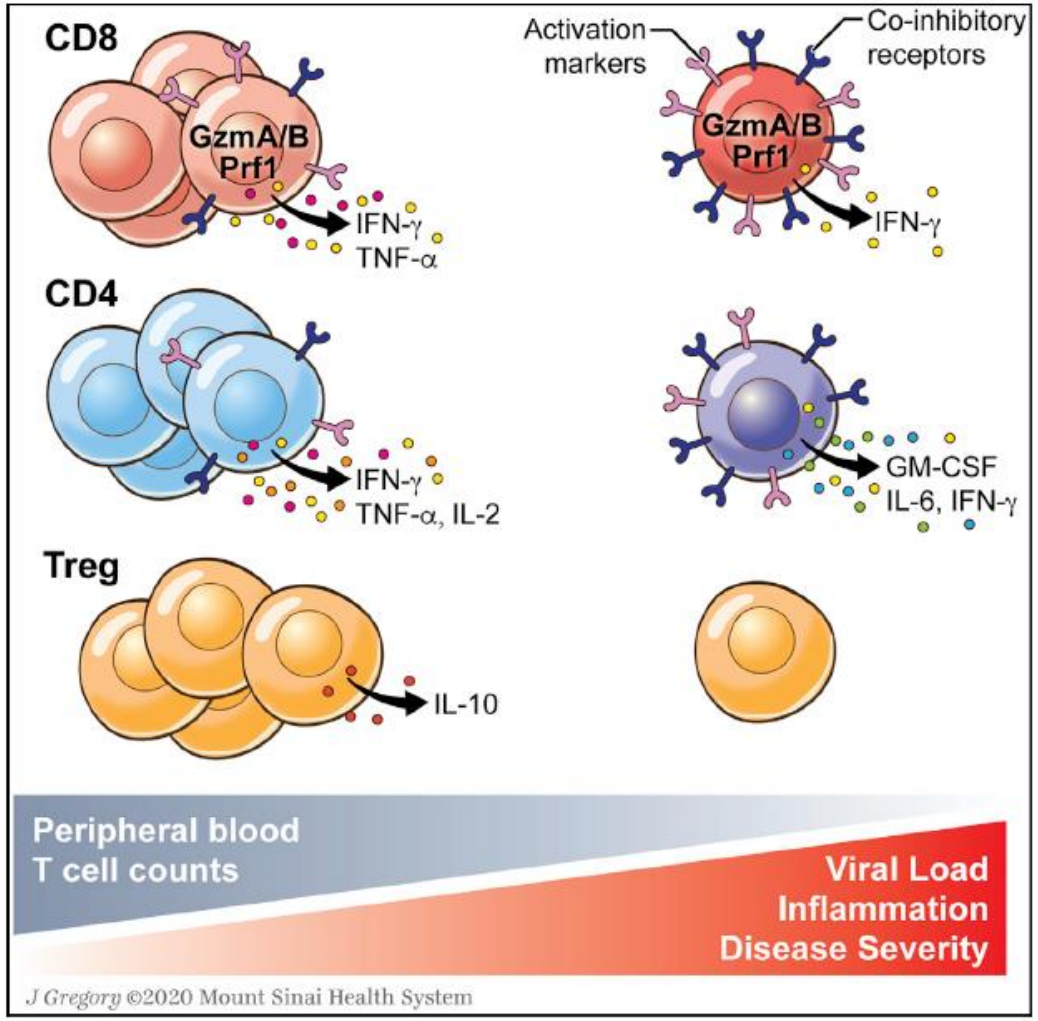
Nicolas Vabret,[1,*] Graham J. Britton,[1] Conor Gruber,[1] Samarth Hegde,[1] Joel Kim,[1] Maria Kuksin,[1] Rachel Levantovsky,[1] Louise Malle,[1] Alvaro Moreira,[1] Matthew D. Park,[1] Luisanna Pia,[1] Emma Risson,[1] Miriam Saffern,[1] Bérengère Salomé,[1] Myvizhi Esai Selvan,[1] Matthew P. Spindler,[1] Jessica Tan,[1] Verena van der Heide,[1] Jill K. Gregory,[1] Konstantina Alexandropoulos,[1] Nina Bhardwaj,[1] Brian D. Brown,[1] Benjamin Greenbaum,[1] Zeynep H. Gümüş,[1] Dirk Homann,[1] Amir Horowitz,[1] Alice O. Kamphorst,[1] Maria A. Curotto de Lafaille,[1] Saurabh Mehandru,[1] Miriam Merad,[1,*] Robert M. Samstein,[1,*] and The Sinai Immunology Review Project

[1]Precision Immunology Institute at the Icahn School of Medicine at Mount Sinai, New York, NY, USA

*Correspondence: nicolas.vabret@mssm.edu (N.V.), miriam.merad@mssm.edu (M.M.), robert.samstein@mountsinai.org (R.M.S.)

https://doi.org/10.1016/j.immuni.2020.05.002

Linfociti T



1. Diminuzione numero (leucopenia)
2. Aumento numero cellule T attivate con fenotipo «exhausted» (recettori inibitori, ridotta polifunzionalità e ctx)

- Linfociti T virus-specifici?
- Correlazione tra quadro clinico severo e risposta/fenotipo T?
- Presenza linfociti T anti-SARSCov2 in individui non esposti? →

Table 1. Spike-specific immune responses detected in 25-μg mRNA-1273 vaccinees. ELISA, enzyme-linked immunosorbent assay; AIM, activation-induced markers; ICS, intracellular cytokine staining.

Component	Assay	Days after vaccination			
		1	15 ± 2	43 ± 2	209 ± 7
	Antibodies				
Anti-spike IgG	ELISA	0	86%	100%	100%
Anti-RBD IgG	ELISA	3%	94%	100%	100%
Neutralizing	Neutralization	0	29%	100%	88%
	T cells				
Spike-specific $CD4^+$ T cells	AIM*	49%	97%	100%	97%
	ICS†	34%	94%	100%	97%
	Total‡	49%	97%	100%	97%
Spike-specific $CD8^+$ T cells	AIM*	0	34%	53%	34%
	ICS†	0	51%	70%	54%
	Total‡	0	69%	88%	67%

*Antigen-specific T cells using AIM were measured as a percentage $CD4^+$ T expressing $OX40^+CD137^+$ and $CD8^+$ T cells expressing $CD69^+CD137^+$ after stimulation of PBMC with spike overlapping peptides spanning the entire protein. †Antigen-specific T cells using ICS were measured as a percentage $CD4^+$ T expressing CD40L or producing IFNγ, TNFα, IL-2, or GzB; and $CD8^+$ T cells producing IFNγ, TNFα, IL-2, or GzB after stimulation of PBMC with spike overlapping peptides spanning the entire protein. ‡The overall spike-specific T cell response was calculated on the basis of the AIM and ICS results per donor and time point.

Mateus J et al. Science 2021

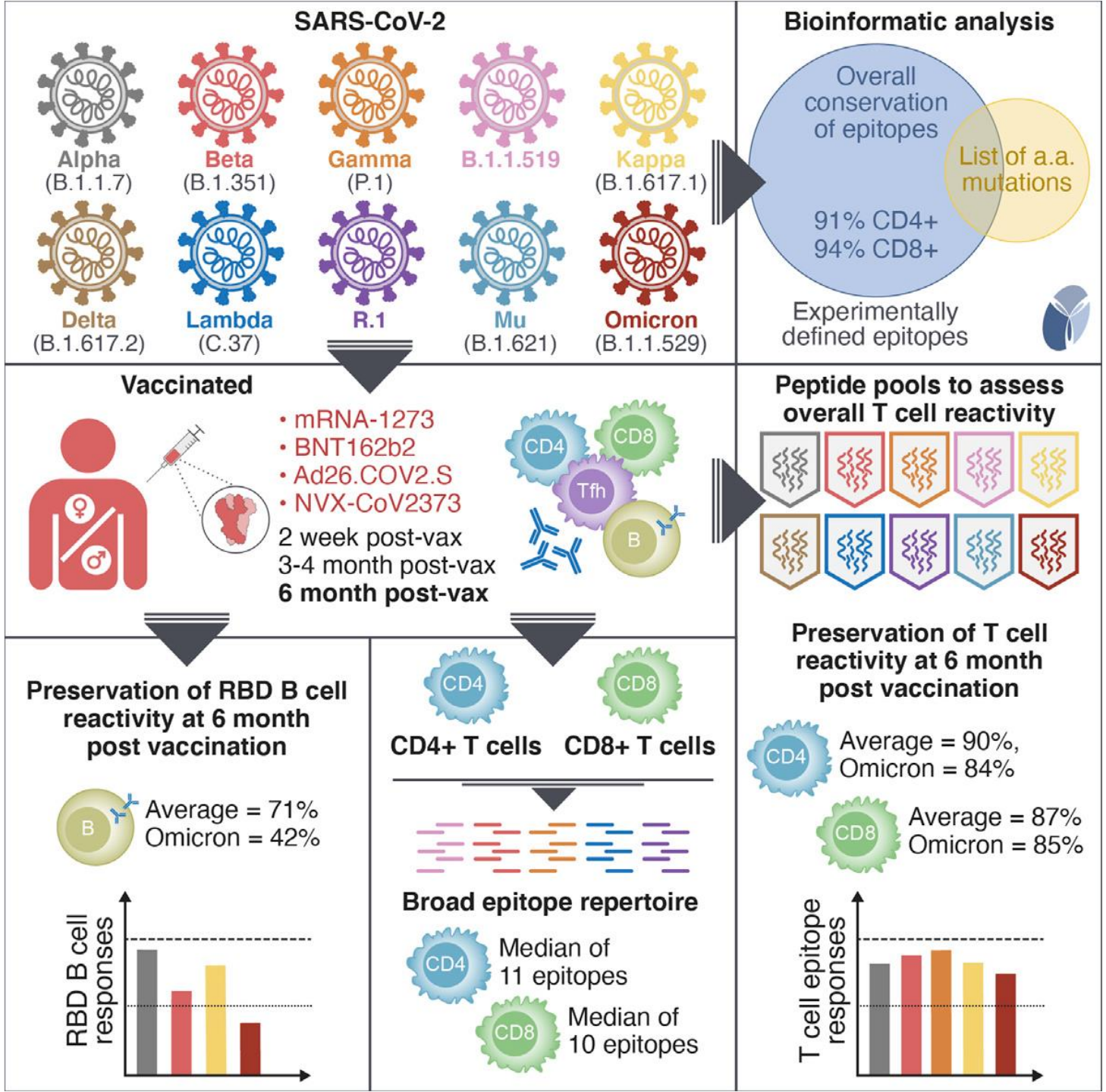
Highlights

- T cells of vaccinees recognize SARS-CoV-2 variants, including Omicron.
- RBD memory B cells' recognition of Omicron is reduced
- A median of 11 CD4 and 10 CD8 spike epitopes are recognized in vaccinees.
- Average preservation > 80% for Omicron at the epitope level.

In brief:

Human memory T cells induced by SARSCoV-2 vaccines maintain the ability to recognize viral variants, including the Omicron variant.

Not so good…



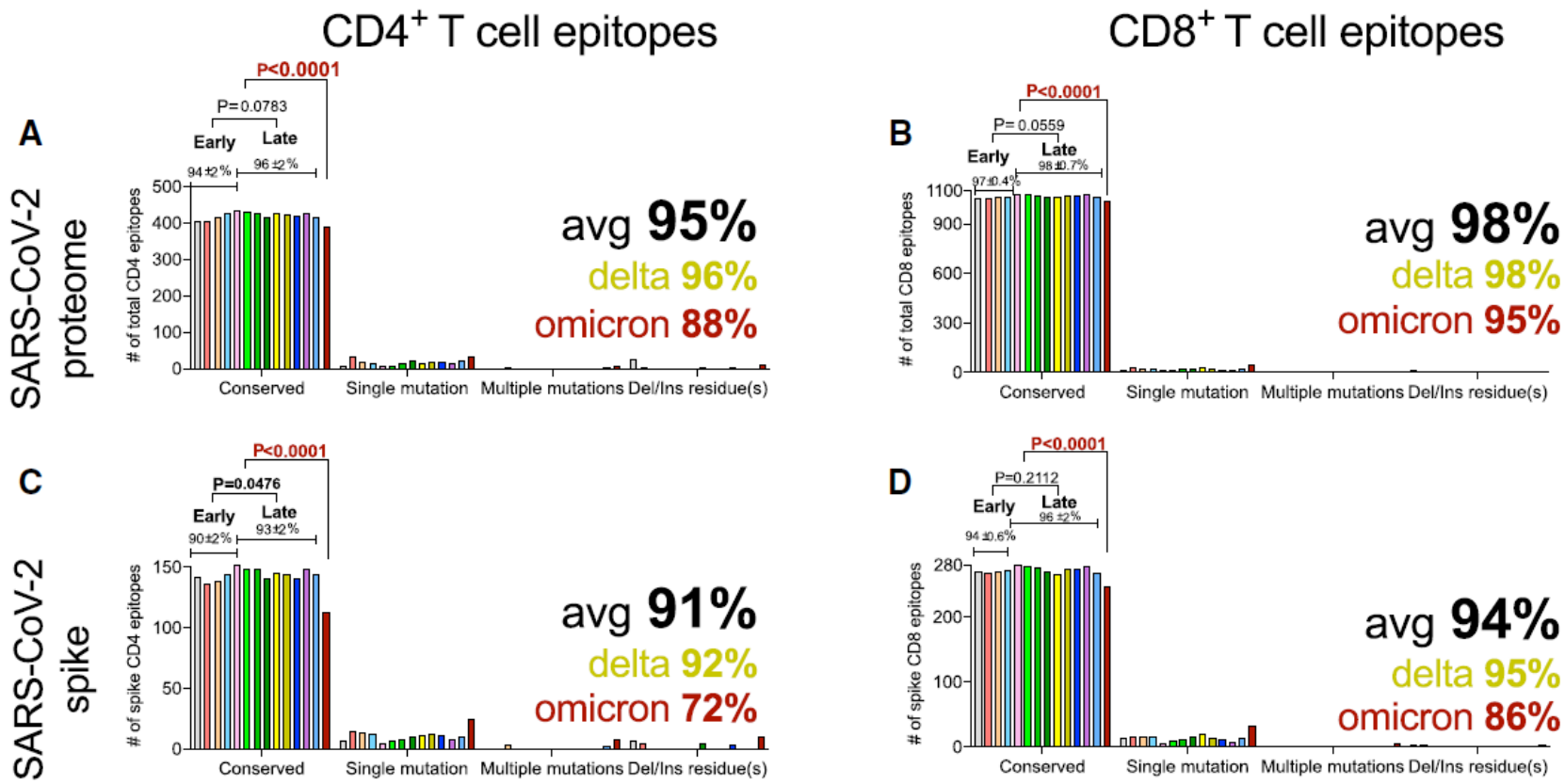
SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from Alpha to Omicron

Good!

Tarke, …Sette, Cell 2022

Che impatto hanno le varianti sulle risposte mediate dai linfociti T?

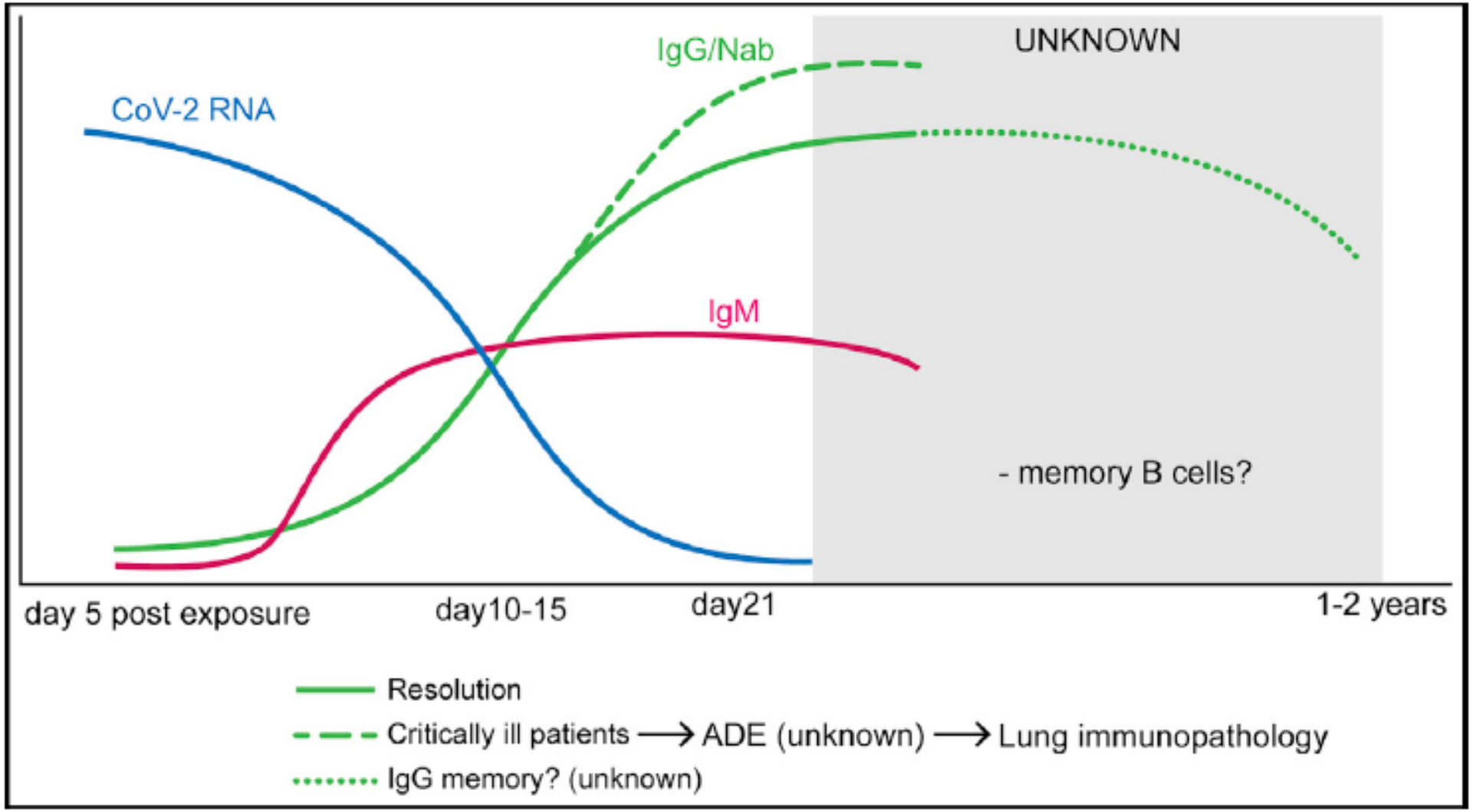
Sequence conservation of SARS-CoV-2 T cell epitopes in variants



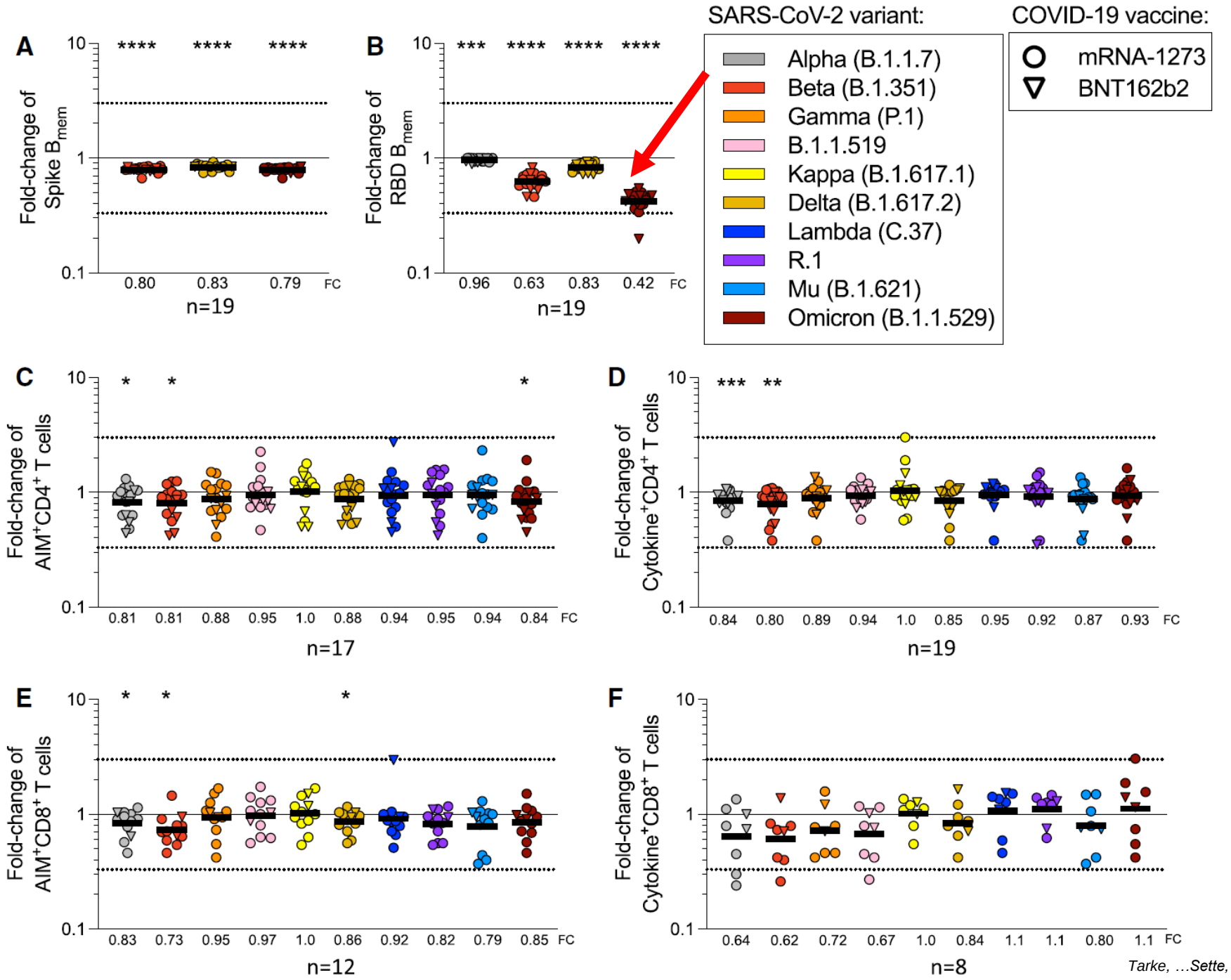
Alpha (B.1.1.7)	Beta (B.1.351)	Gamma (P.1)	Epsilon (B.1.427/429)		Early
B.1.1.519	Eta (B.1.525)	Iota (B.1.526)	B.1.526.1	Mu (B.1.621)	Late
Kappa (B.1.617.1)	Delta (B.1.617.2)	Lambda (C.37)	R.1		
Omicron (B.1.1.529)					Omicron

Tarke, …Sette, Cell 2022

Linfociti B e anticorpi

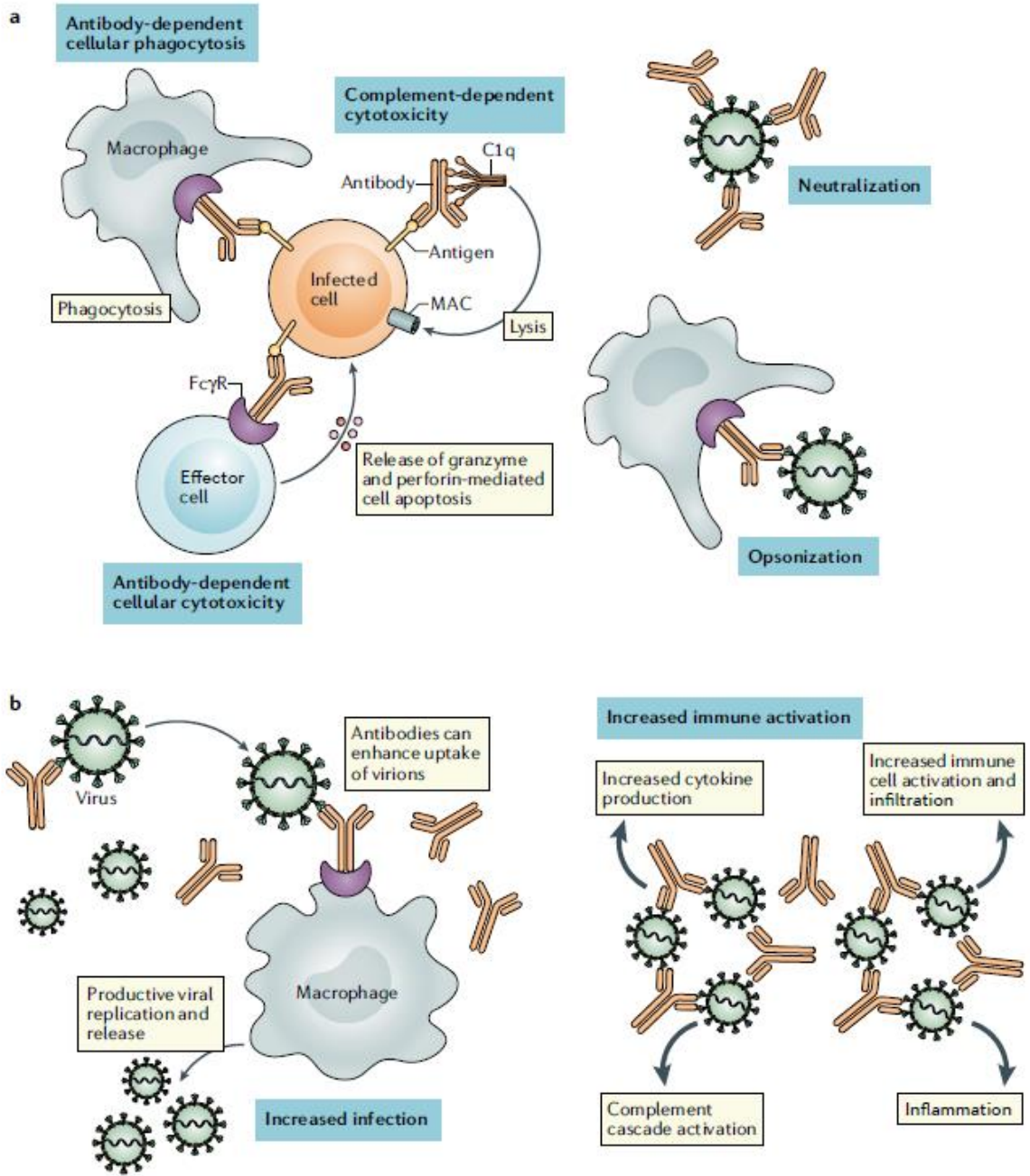


Impact of Omicron and other variants on memory T cell and B cell recognition



Tarke, …Sette, Cell 2022

Mechanisms of action of monoclonal antibodies in a viral infection and antibody-dependent enhancement (ADE)

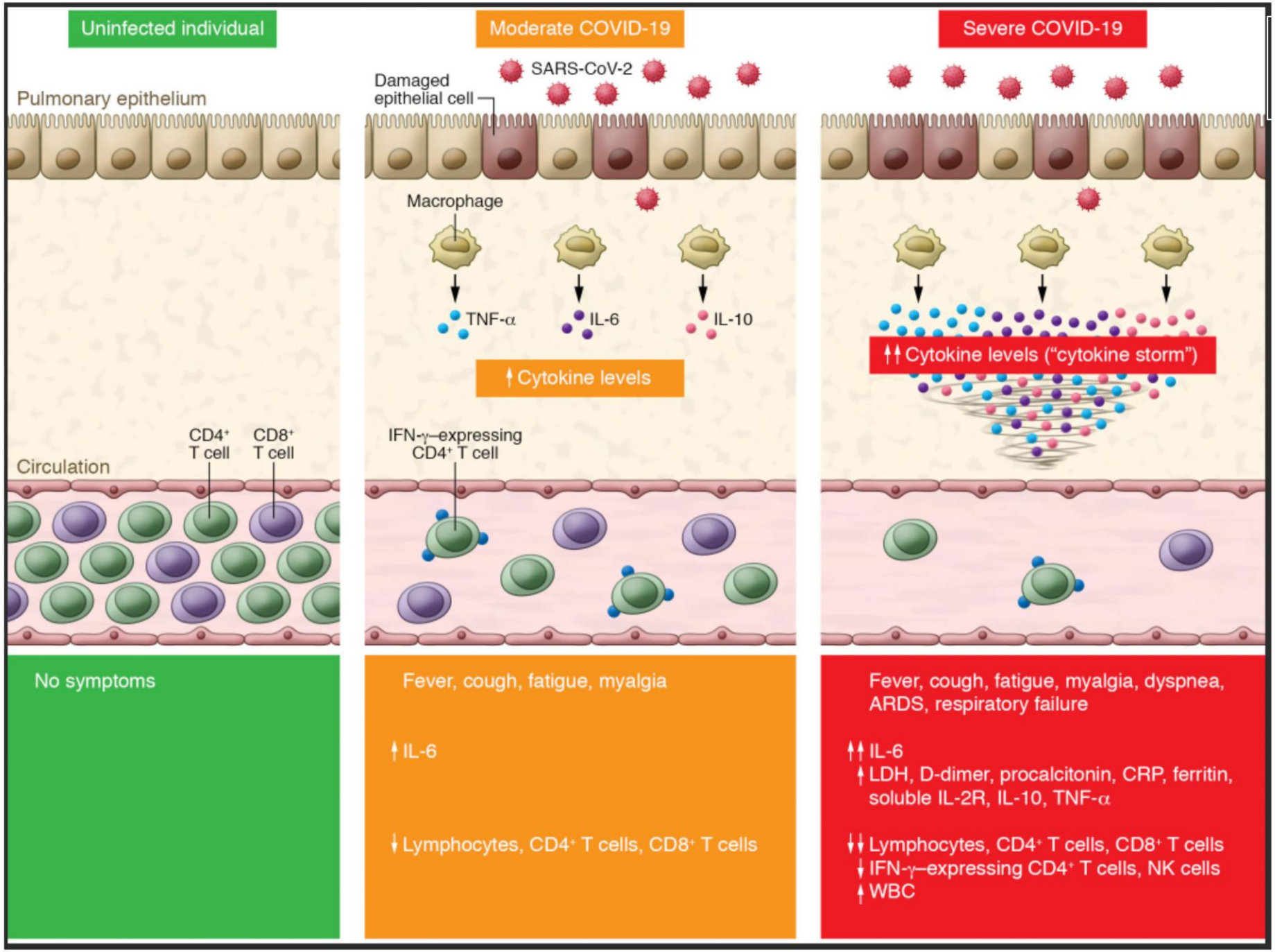


Taylor PC, Nat Rev Imm, 2021

SARS-Cov-2 e risposta immunitaria:

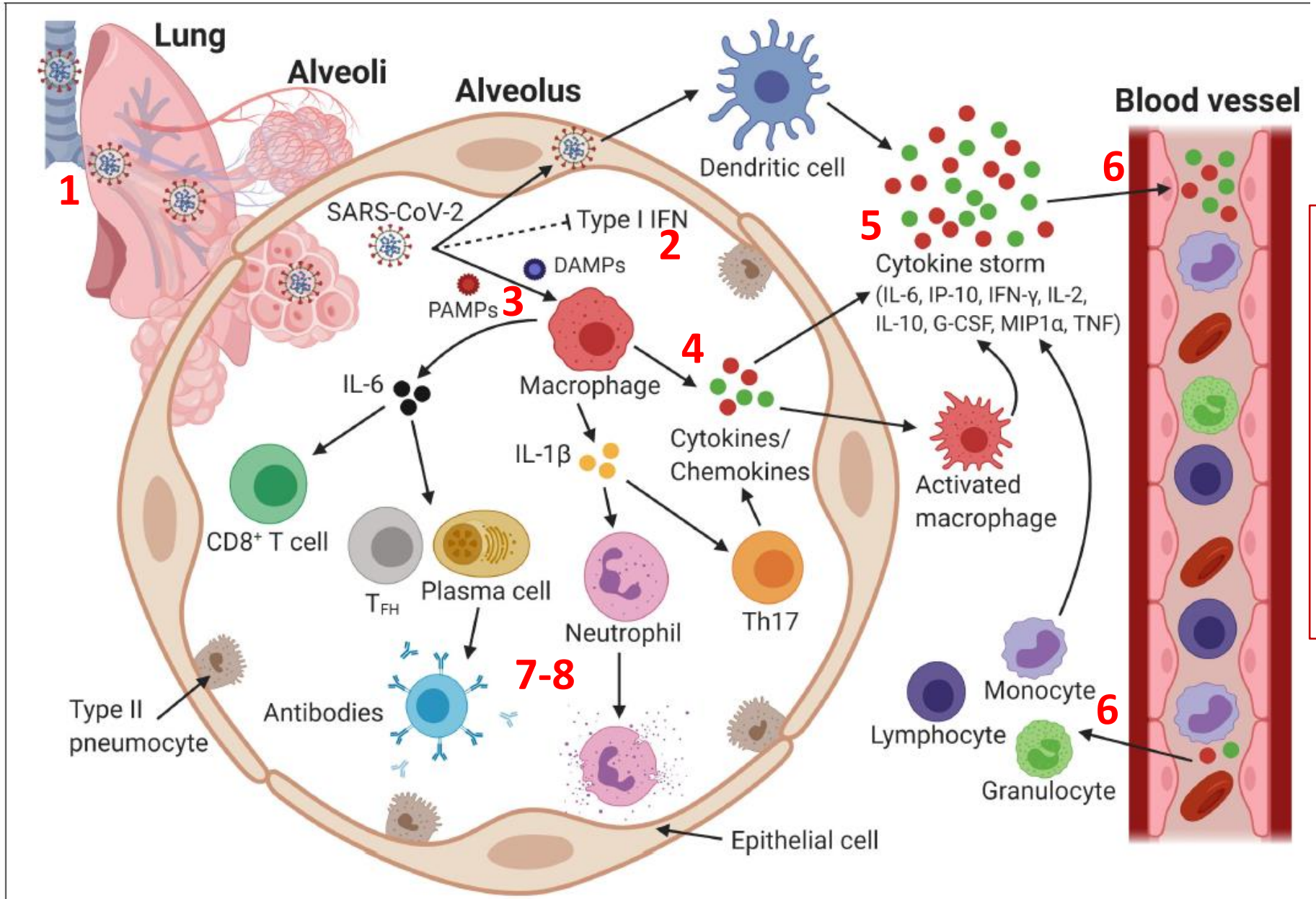
conclusioni

L'immunopatologia: una visione d'insieme



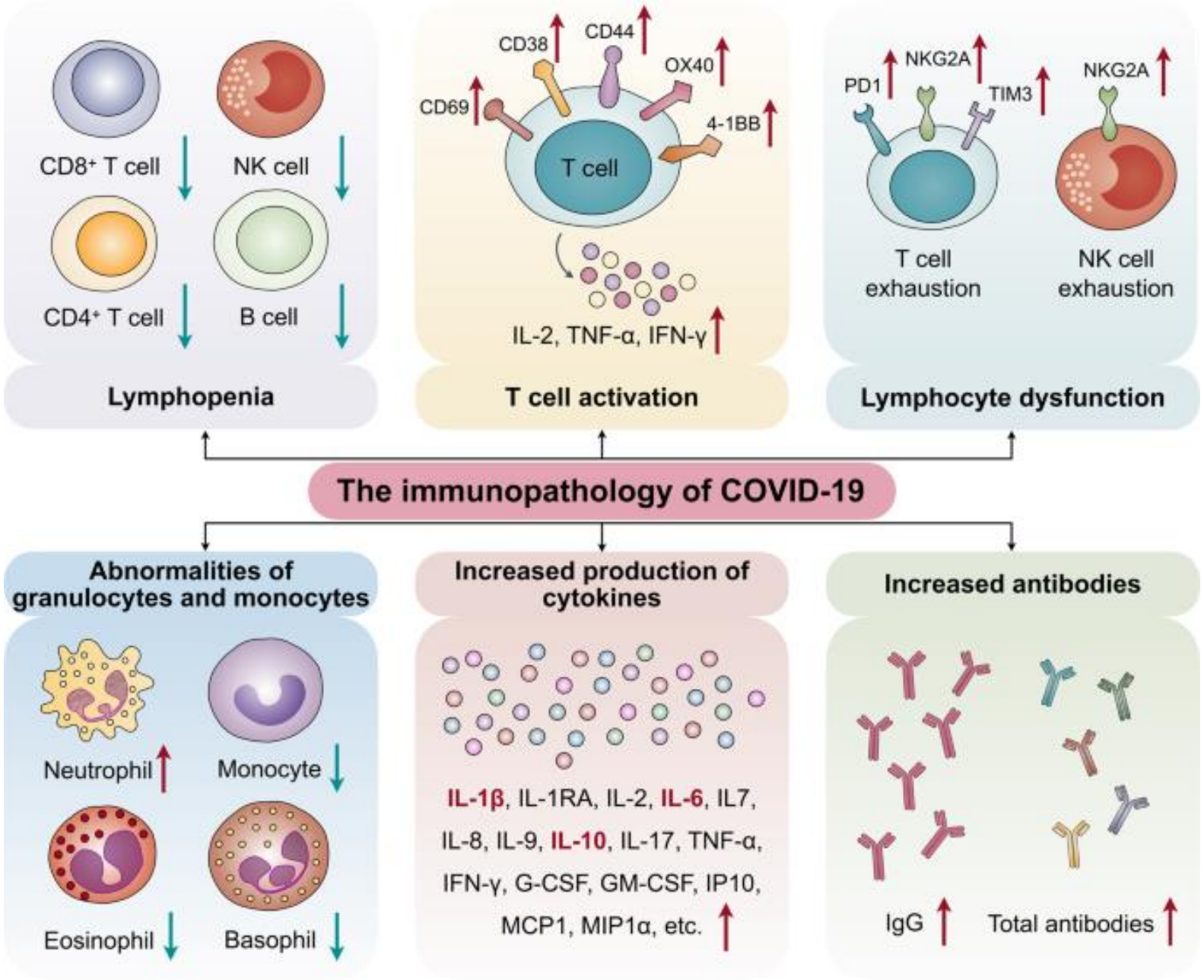
JCI The Journal of Clinical Investigation
SARS-CoV-2: A Storm is Raging
Savannah F. Pedersen, Ya-Chi Ho
J Clin Invest. 2020. https://doi.org/10.1172/JCI137647.

L'immunopatologia: una visione d'insieme



1. Infezione delle cellule ACE2/TMPRSS2+
2. Soppressione IFN-I e aumento replicazione virale
3. PAMPs/DAMPs attivano cellule epiteliali, endoteliali e macrofagi
4. Rilascio citochine
5. Tempesta citochinica
6. Richiamo leucociti dal sangue e amplificazione tempesta citochinica (feedback positivo)
7. Danno da cellule infiammatorie e da anticorpi non-neutralizzanti (Antibody-Dependent Enhancement, ADE)
8. Danno multi-organo (nei polmoni: ARDS)

L'immunopatologia



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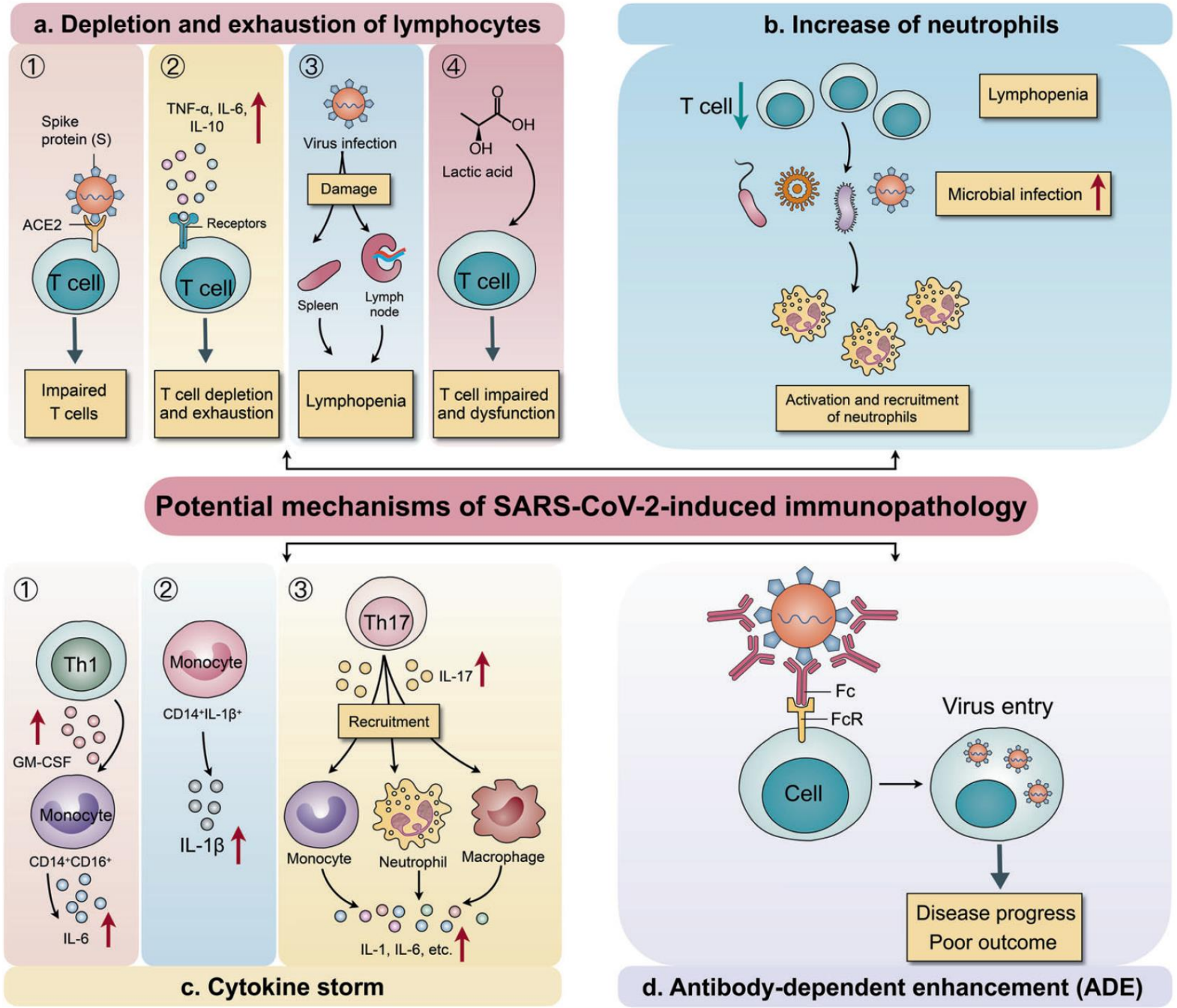
L'immunopatologia: i meccanismi



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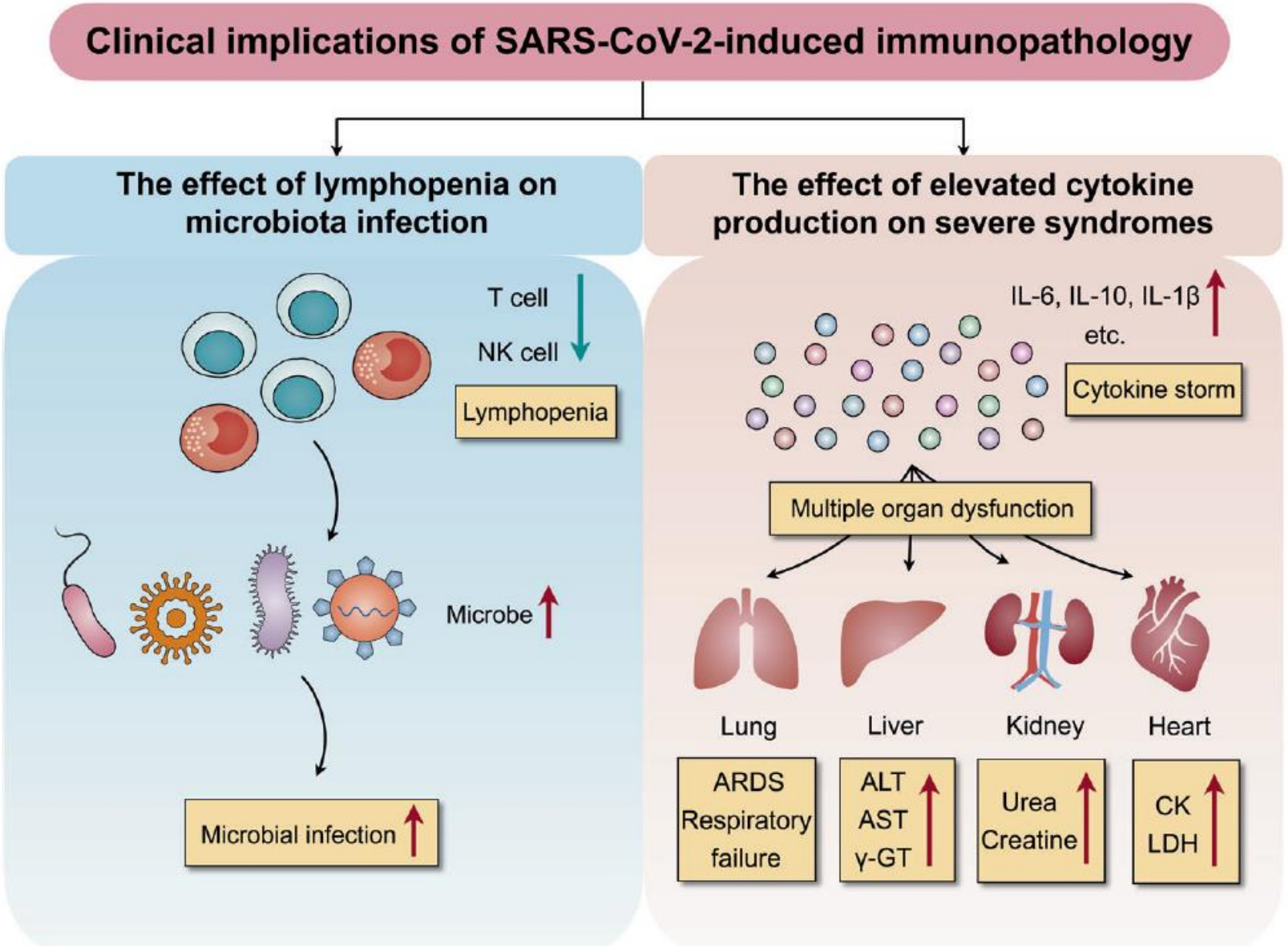
L'immunopatologia: le implicazioni cliniche



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