Word map reflecting the most cited terms for all the evaluated articles used in the review processes.
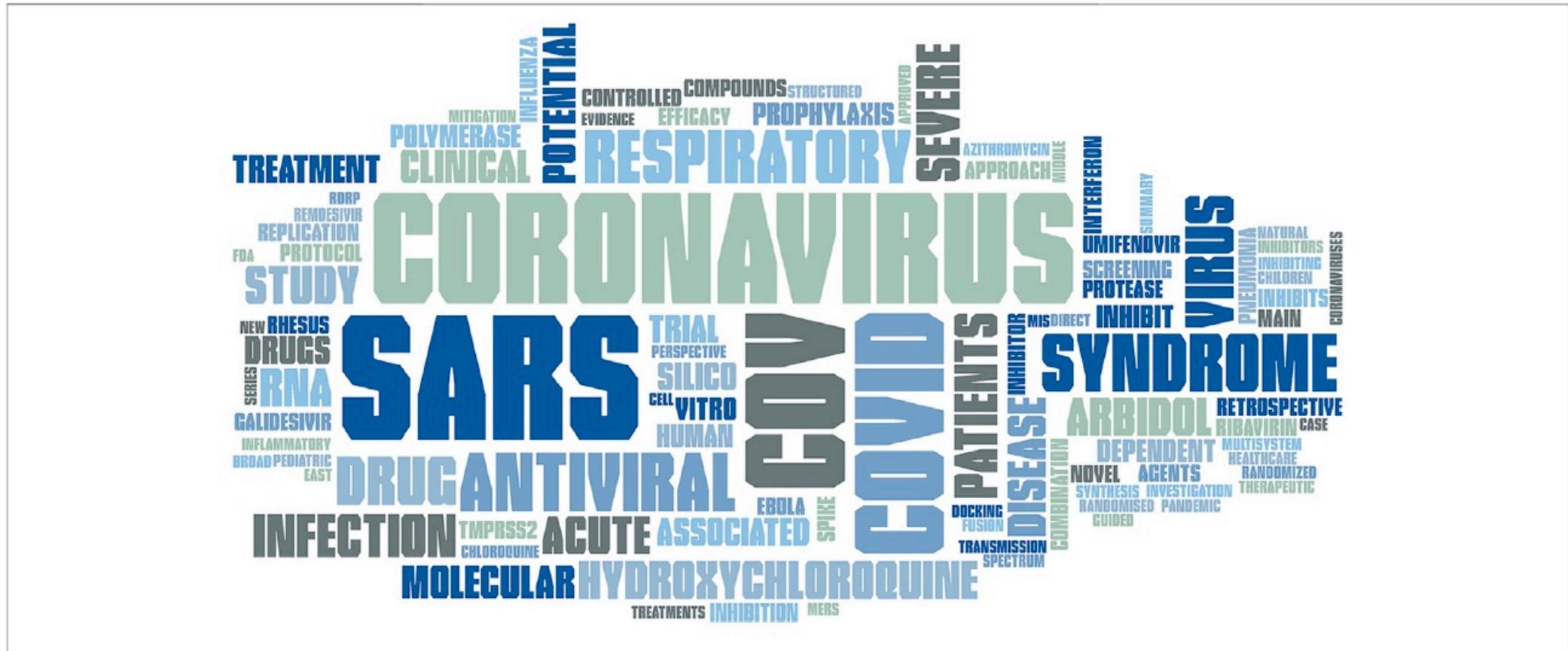
SARS-CoV-2 life cycle in infected cells

Bchetnia M et al., J Infect Public Health. 2020
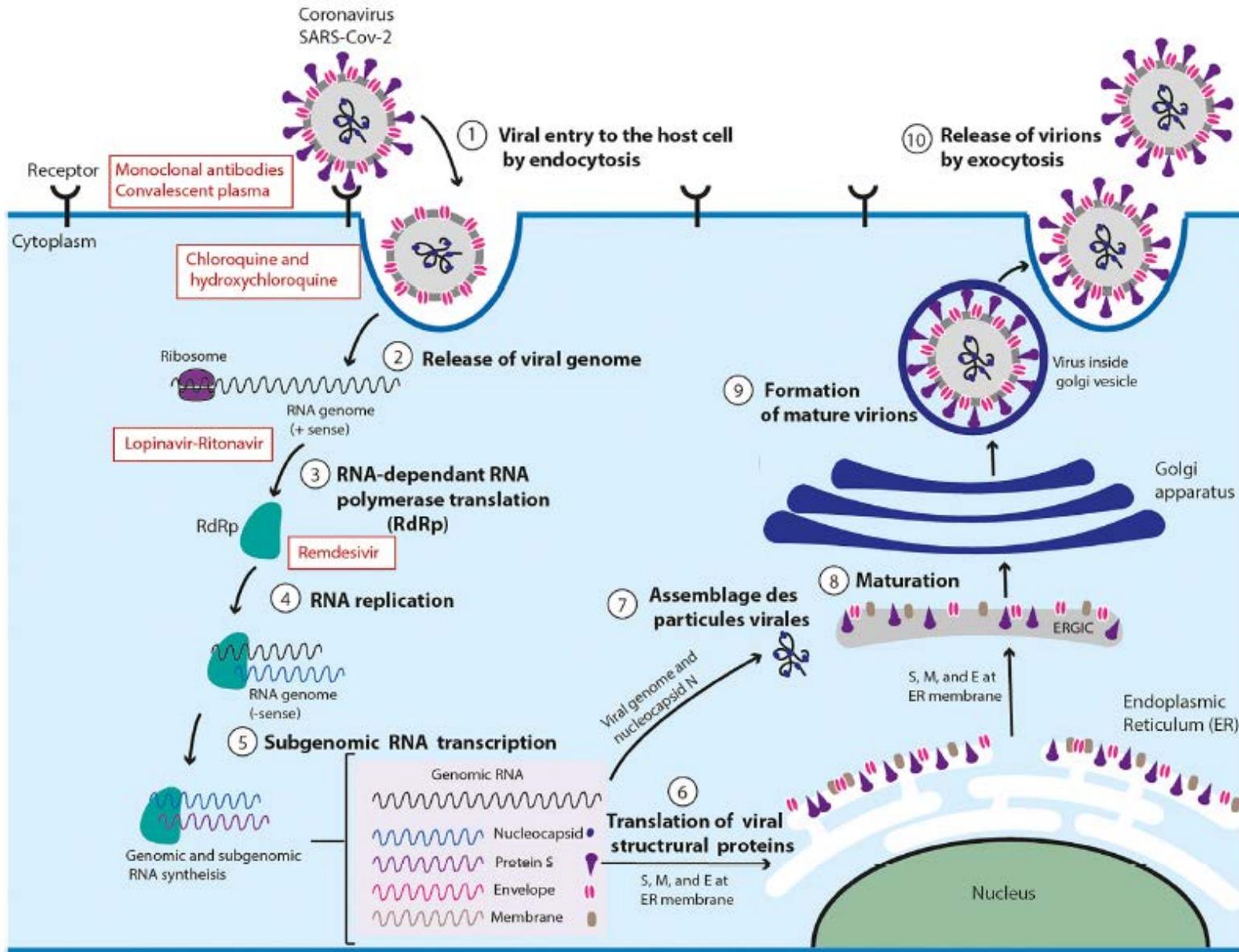
RNA genome organization
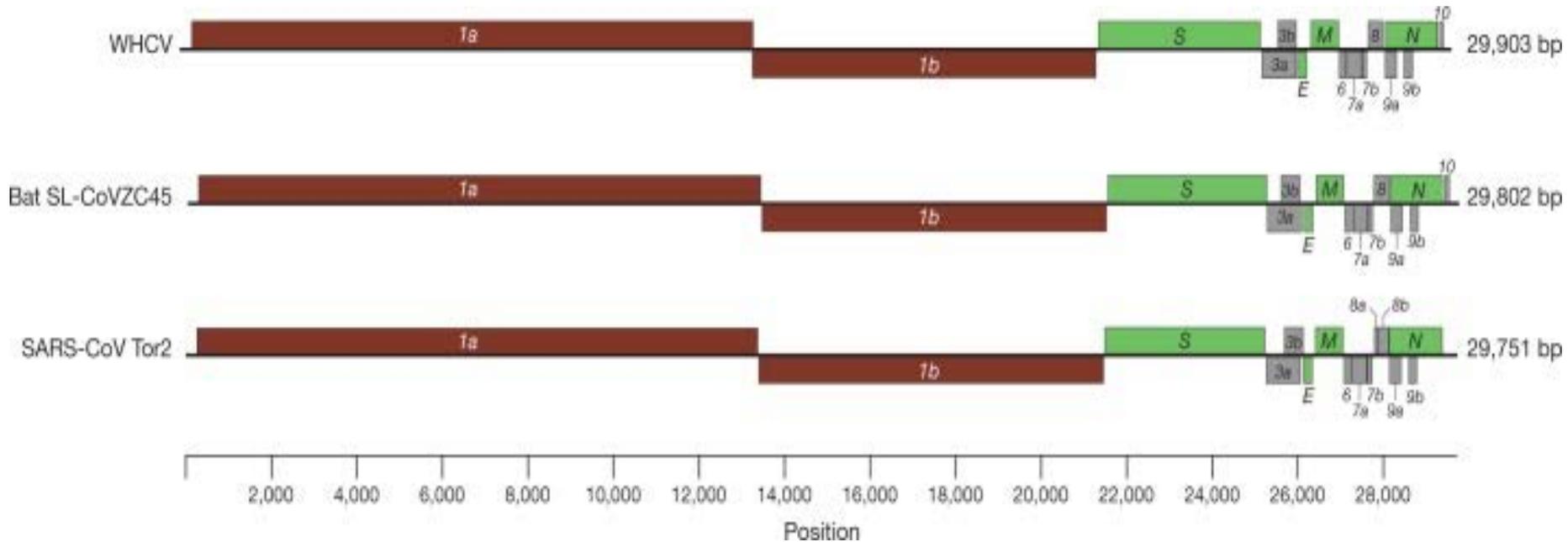
Wu F et al., Nature 2020

- SARS-CoV-2 genome contains 14 openreading frames (ORFs), encoding 27 proteins.
- At the 5'-terminal region of the genome, the ORF1 and ORF2 encode 15 non-structural proteins important for virus replication.
- The 3'-terminal region of the genome encodes functional structural proteins, namely spike (S), envelope protein (E), membrane protein (M) and nucleocapsid(N), plus 8 accessory proteins

Cell Entry

- Phylogenetic and computational genomic analyses suggest that to enter in host's cells, SARS-CoV-2 shares the same human cell receptor with SARS-CoV (ACE2)

- A structure model analysis shows that SARS-CoV-2 binds ACE2 with above 10 folds greater affinity than SARS-CoV, and much higher than the threshold required for viral infection


ACE2 binding to 2019-nCoV S
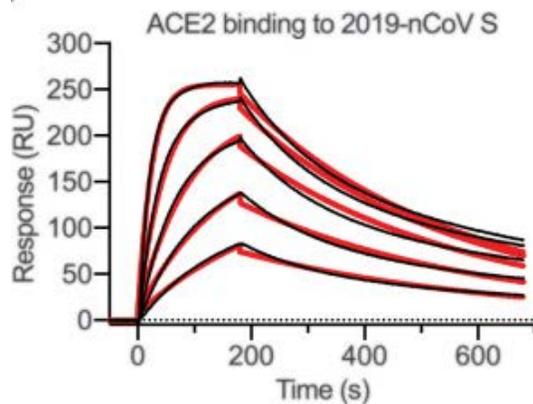
$K_D = 14.7$ nM

$k_a = 1.88 \times 10^5\ M^{-1}s^{-1}$

$k_d = 2.76 \times 10^{-3}\ s^{-1}$
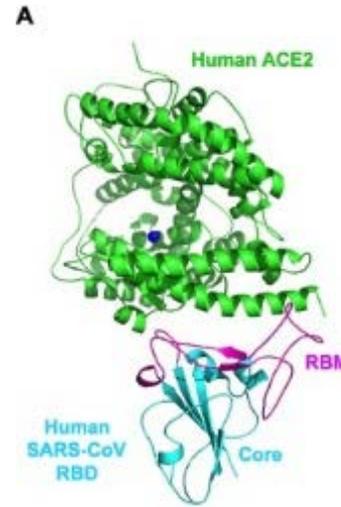
Virus	Year	442	472	479	480	487
SARS - human	2002	Y	L	N	D	T
SARS - civet	2002	Y	L	K	D	S
SARS - human/civet	2003	Y	P	N	G	S
SARS - civet	2005	Y	P	R	G	S
SARS - human	2008	F	F	N	D	S
Viral adaption to human ACE2		F > Y	F > L > P	N = R >>> K	D > G	T >>> S
Optimized - human	In vitro design	F	F	N	D	T
Viral adaptation to civet ACE2		Y > F	P = L > F	R > K = N	G > D	T > S
Optimized - civet	In vitro design	Y	P	R	G	T
SARS - bat	2013	S	F	N	D	N
2019-nCoV – human	2019	L (455)	F (486)	Q (493)	S (494)	N (501)

Wan Y et al., J Virol. 2020
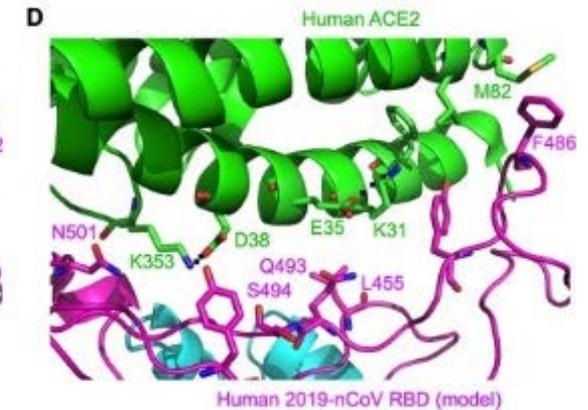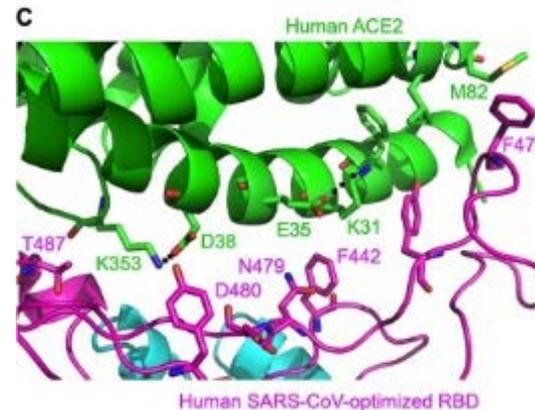
*Wrapp D et al. Science. 2020*

SARS-CoV-2 infectivity

- SARS-CoV-2 shows a gradient infectivity from the proximal to distal respiratory tract

- Ciliated airway cells and AT-2 cells are primary targets for SARS-CoV-2 infection.
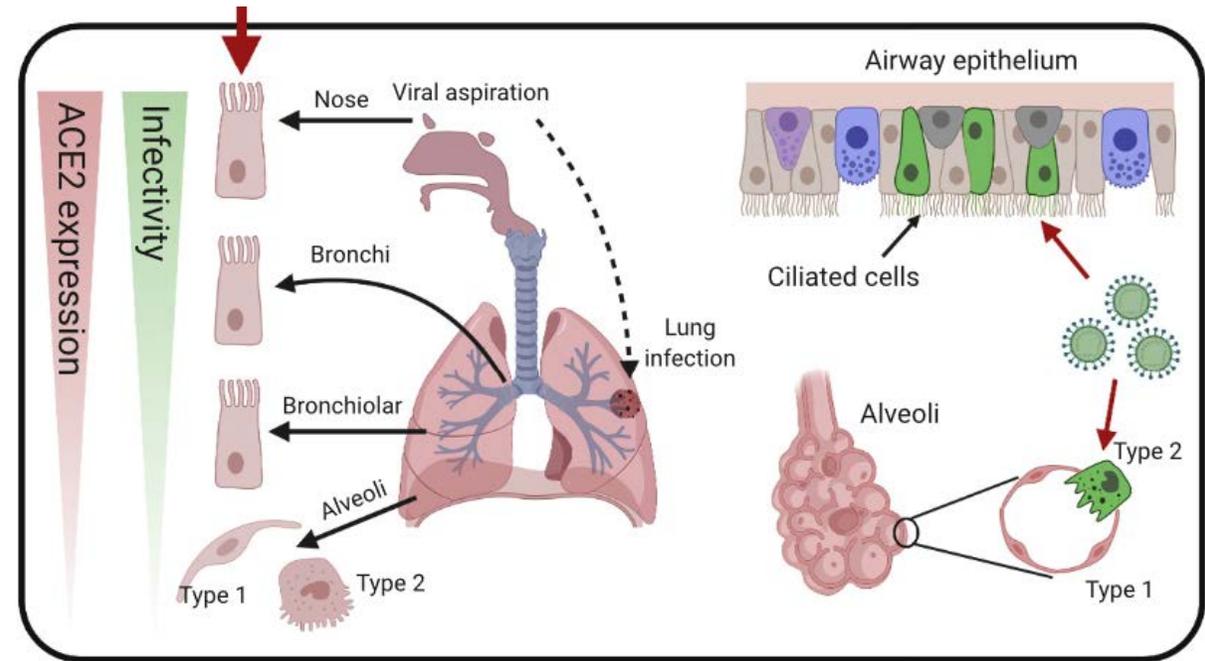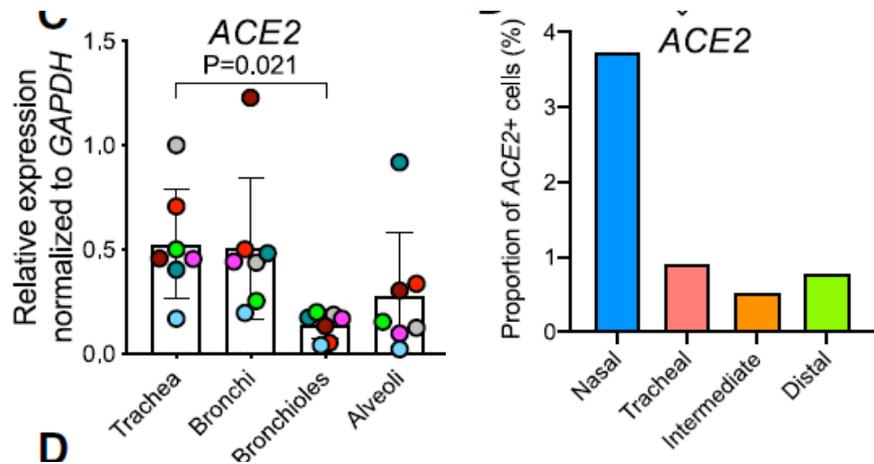
Hou YJ et al., Cell 2020

- No effective drugs targeting 2019-nCoV/SARS-CoV-2.

- Drug repurposing could have been an effective drug discovery strategy from existing drugs, because the shorten time and the reduced cost compared to de novo drug discovery….

- Most of the drugs under clinical trials show effect against SARS-CoV-2 by targeting viral replication or inhibiting viral proteases. Successful druggable targets include RNA dependent RNA polymerase (RdRp), viral proteases like 3-CL pro, PL-pro and endosomal pathway inhibitors
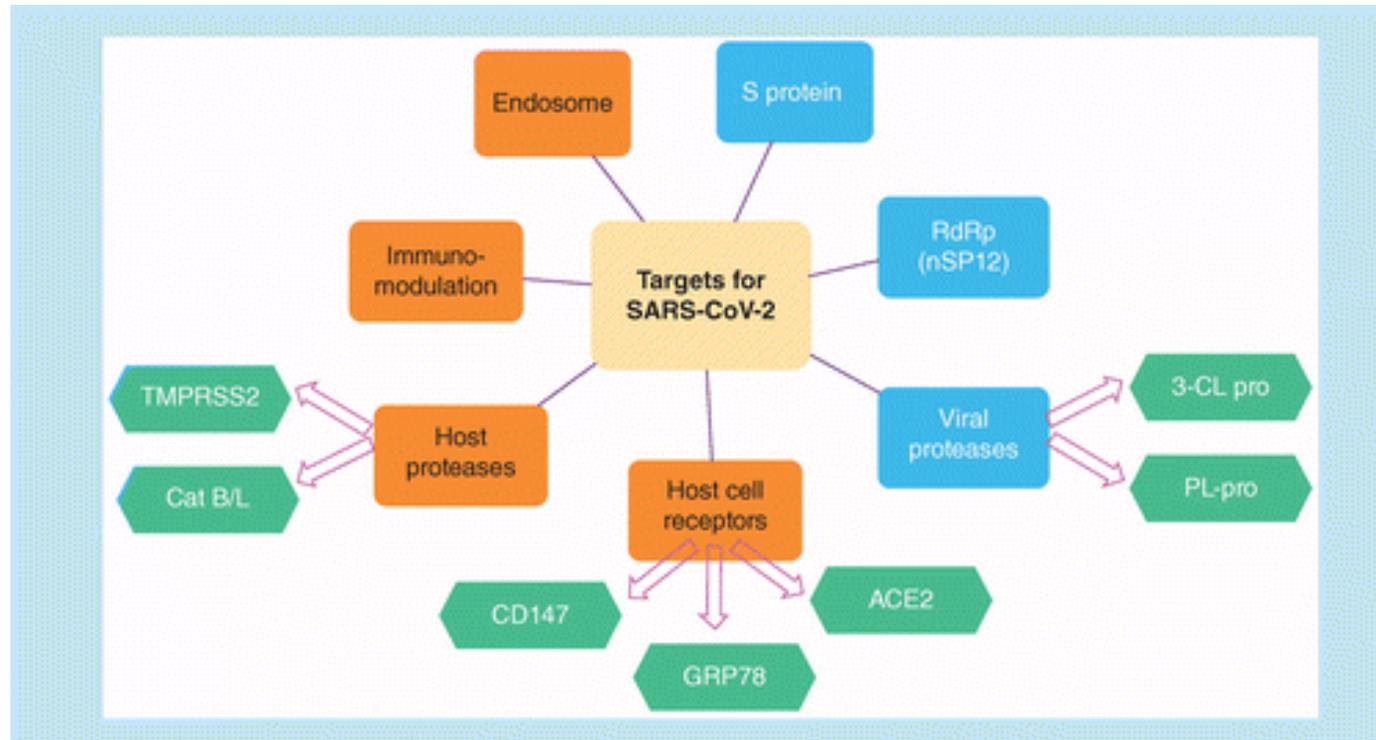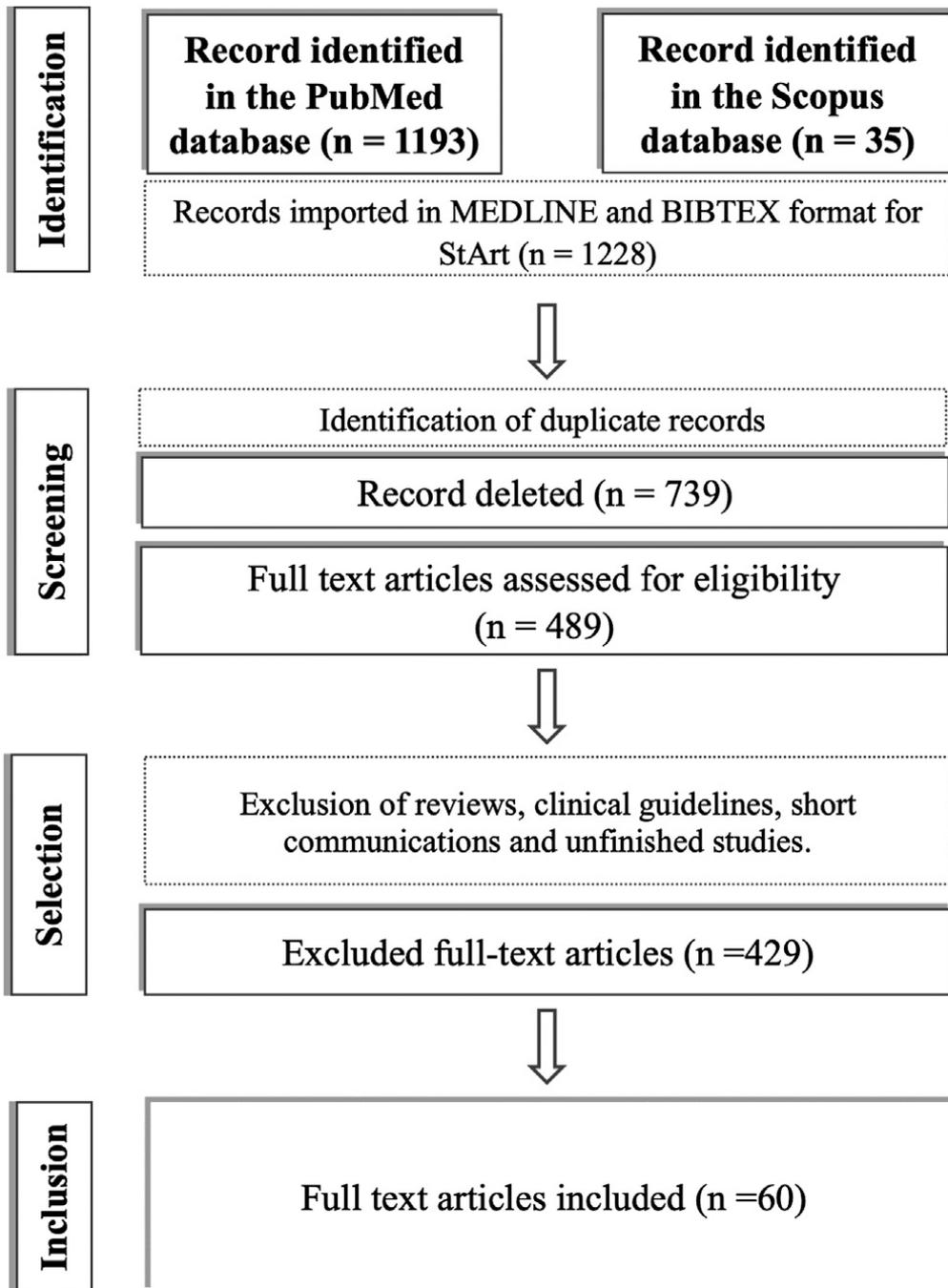
The drug repurposing in the context of COVID-19

Antrade BS et al., Frontiers in Pharmacology
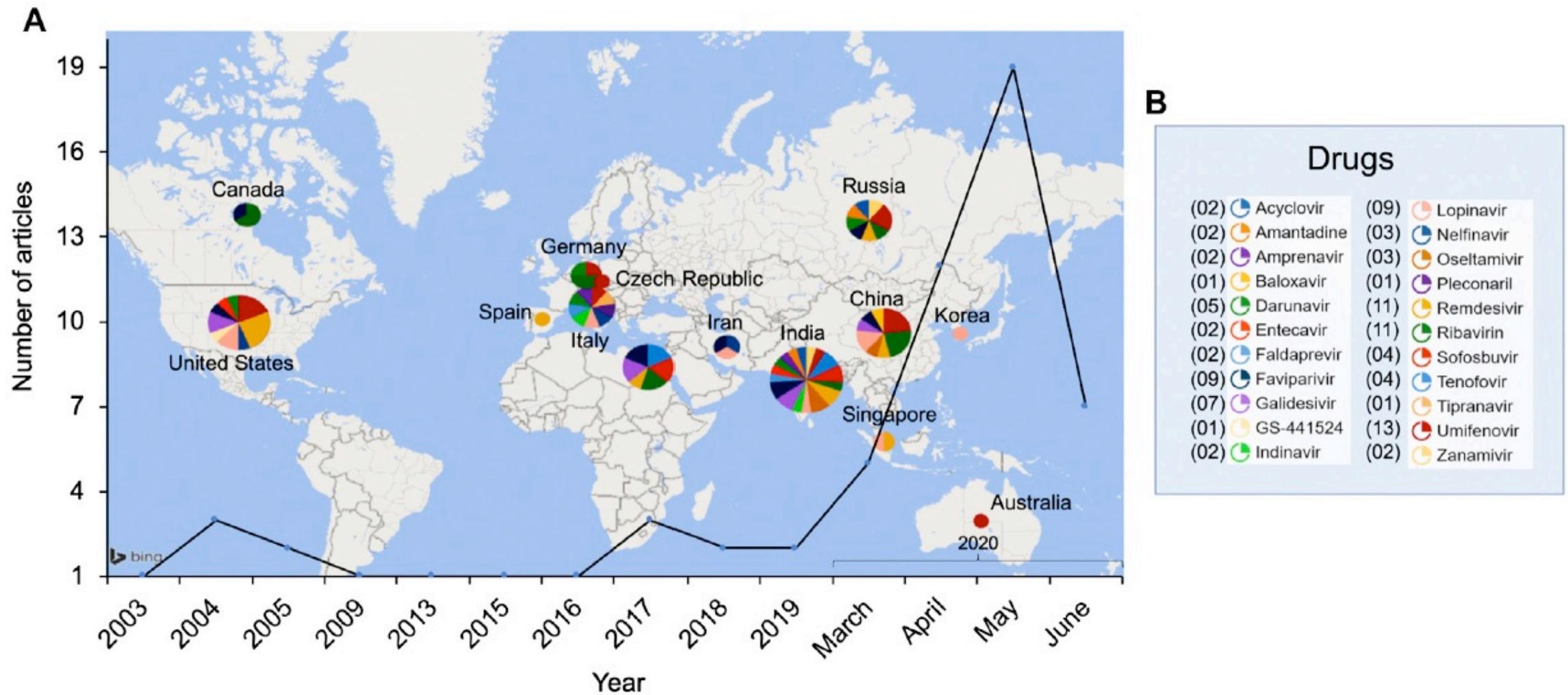
FIGURE 3 | Antiviral research distribution for the 22 selected drugs. **(A)** Most relevant countries for the selected drugs between 2003 and 2020. **(B)** Number of times cited per drug.

TABLE 1 | Screened drugs with potential for prophylaxis studies, and their correspondent number of citations and mechanism of action.

	Drug	Citations	Mechanism of action
1	Aciclovir	World Health Organization (2020)	Nucleoside analog
2	Amantadine	World Health Organization (2020)	Interferes with transmembrane M2 protein
3	Amprenavir	World Health Organization (2020)	Protease inhibitor (HIV)
4	Baloxavir marboxil	Xie et al. (2020)	Endonuclease inhibitor—inhibits the initiation of mRNA synthesis
5	Darunavir	Zhang et al. (2020)	Second generation protease inhibitor
6	Entecavir	World Health Organization (2020)	Guanine analogue (HCV)
7	Faldaprevir	World Health Organization (2020)	HCV protease inhibitor
8	Faviparivir	Beigel et al. (2019)	Prodrug of a purine nucleotide, favipiravir ribofuranosyl-5′-triphosphate—RNA polymerase inhibitor
9	Galidesivir	Mayer et al. (2015)	Protease inhibitor—Adenine analog
10	GS-441524	Xie et al. (2020)	Adenisin nucleoside analog
11	Indinavir	World Health Organization (2020)	HIV protease specific inhibitor
12	Lopinavir	Beigel et al. (2019)	Aspartic acid protease (HIV) inhibitor
13	Nelfinavir	Vellingiri et al. (2020)	Protease inhibitor
14	Oseltamivir	Vellingiri et al. (2020)	Active neuraminidase inhibitor
15	Pleconaril	Xie et al. (2020)	Viral capsid inhibitor
16	Remdesivir	Cheng (2019)	Prodrug—active nucleoside analog C-adenosine triphosphate—(Ebola)
17	Ribavirin	Kang et al. (2020)	Nucleoside analogue (guanine)—inhibits viral RNA-dependent RNA polymerase
18	Sofosbuvir	Glushkov et al. (1999)	Nucleoside analog—hepatitis C virus NS5B polymerase inhibitor
19	Tenofovir	Glushkov et al. (1999)	Acyclic nucleoside analog adenosine monophosphate
20	Tipranavir	Xie et al. (2020)	HIV protease enzyme inhibitor
21	Umifenovir	Zhou et al. (2020)	Hemagglutinin inhibitor (influenza)
22	Zanamivir	World Health Organization (2020)	Neuraminidase inhibitor

Antrade BS et al., Frontiers in Pharmacology 2020

Entecavir
Faviparivir
Remdesivir
Ribavirin

NSP12

Chloroquine
Hydroxychloroquine
Raltegravir

S

Binifibrate
Bamifylline
Ritonavir
Indinavir

3C-L Protease

Ala285   Ala285*

N*

N

C*

C

Cys145*

His41*
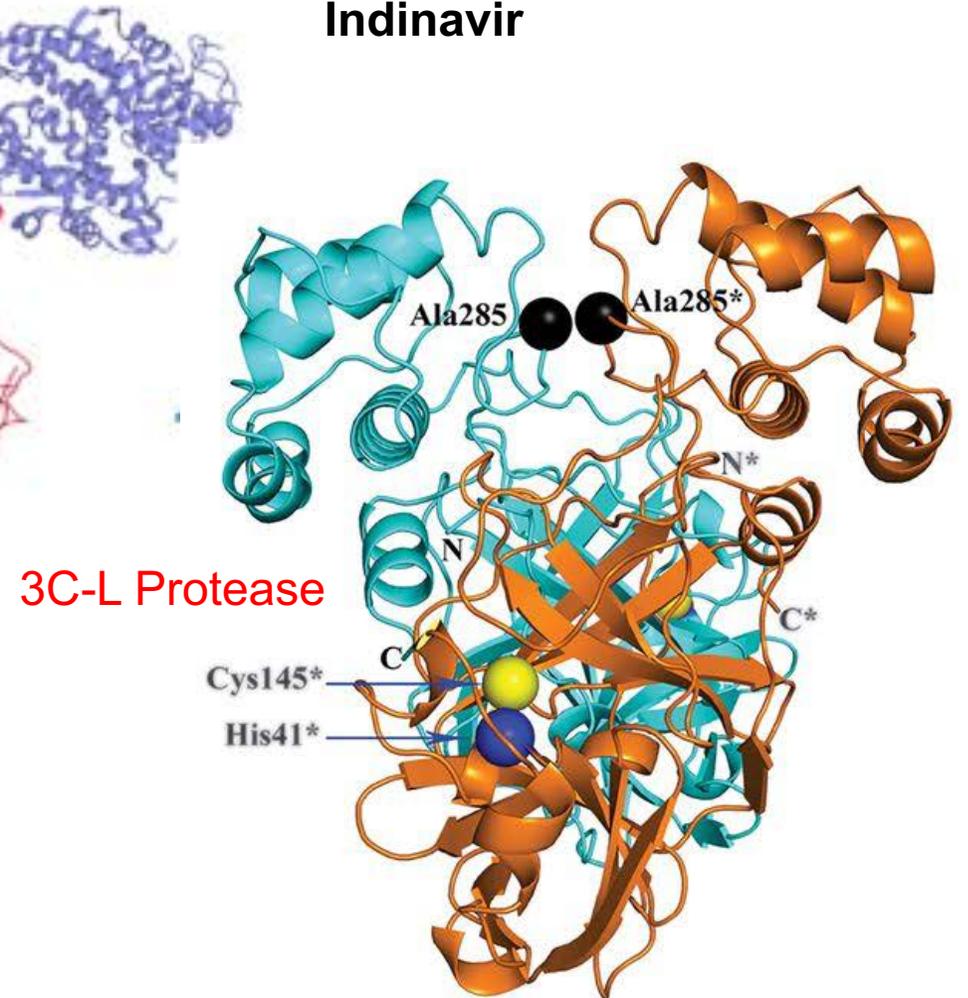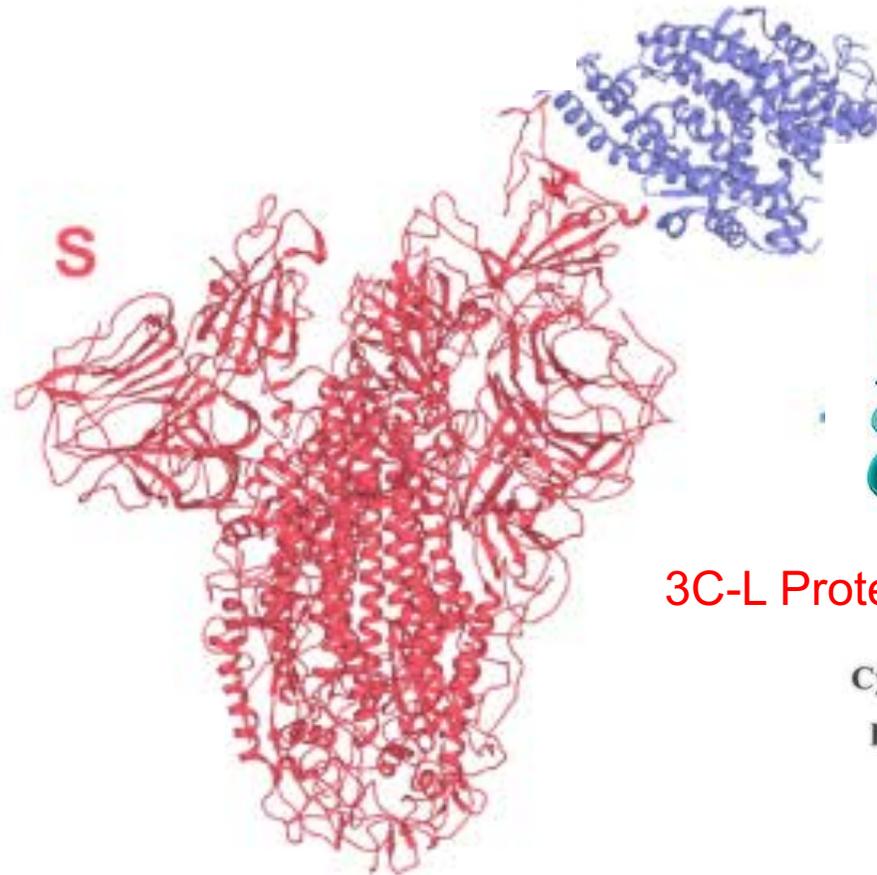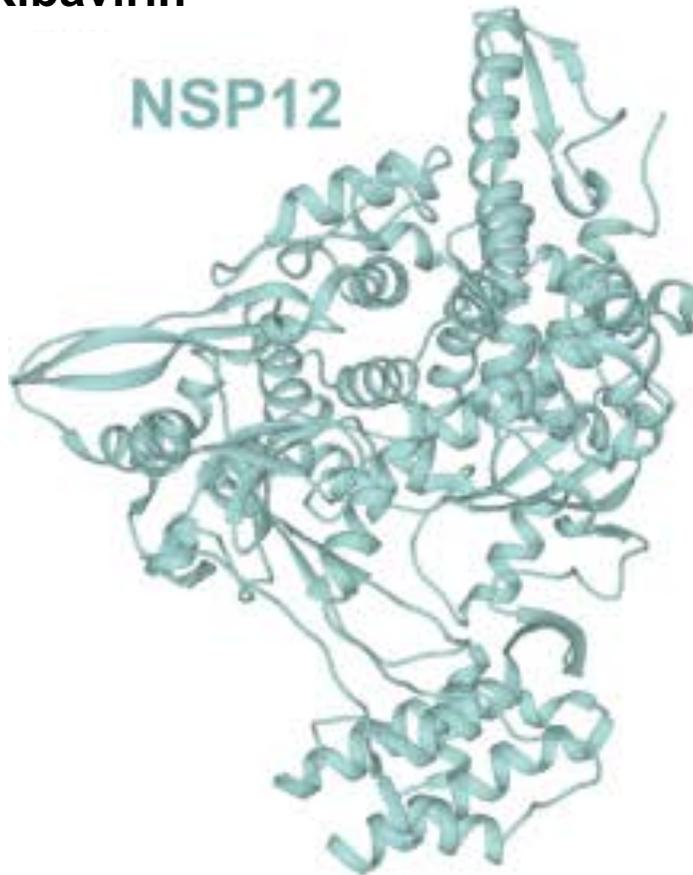
Identifying SARS-CoV-2 Entry Inhibitors through Drug Repurposing Screens of SARS-S and MERS-S Pseudotyped Particles

Catherine Z. Chen,*,# Miao Xu,# Manisha Pradhan, Kirill Gorshkov, Jennifer D. Petersen, Marco R. Straus, Wei Zhu, Paul Shinn, Hui Guo, Min Shen, Carleen Klumpp-Thomas, Samuel G. Michael, Joshua Zimmerberg, Wei Zheng,* and Gary R. Whittaker*

Six compounds (cepharanthine, abemaciclib, osimertinib, trimipramine, colforsin, and ingenol) can be broad spectrum inhibitors for spike-mediated entry.

Anti-SARS-CoV-2 activity of SARS and MERS selected compound

compound name (MOA)	SARS-S PP in Vero E6		VSV-G PP in Vero E6		Vero E6 cytotoxicity		selectivity ratio[b]	SARS-CoV-2 CPE		Vero E6 cytotoxicity		safety ratio[c]
	EC50 (μM)	efficacy (%)	EC50 (μM)	efficacy (%)	CC50 (μM)	cytotox (%)		EC50 (μM)	efficacy (%)	CC50 (μM)	cytotox (%)	
NKH477 (adenylyl cyclase activator)	1.36	71.4	N/A, >57.5	0	N/A, > 57.5	0	42.3	23.06	45.6	25.20	42.0	1.1
trimipramine (tricyclic antidepressant)	4.29	90.9	N/A, >57.5	29.2	N/A, >57.5	16.6	13.4	20.52	48.1	N/A, >20	16.6	1.0
osimertinib (EGFR inhibitor)	2.71	117.5	42.94	118.4	17.1	99.6	15.8	3.98	60.0	10.00	99.7	2.5
ingenol (topical antitumor medication)	0.02	93.3	0.24	76.4	N/A, >57.5	−4.0	12.0	0.06	38.2	N/A, >20	0.0	355.7
cepharanthine (anti-inflammatory, antineoplastic)	1.92	90.9	21.52	76.9	42.94	106.2	11.2	1.41	92.5	11.22	99.0	7.9

compound name (MOA)	MERS-S PP in Huh7		VSV-G PP in Huh7		Huh7 cytotoxicity		selectivity ratio[b]	SARS-CoV-2 CPE		Vero E6 cytotoxicity		safety ratio[c]
	EC50 (μM)	efficacy (%)	EC50 (μM)	efficacy (%)	CC50 (μM)	cytotox (%)		EC50 (μM)	efficacy (%)	CC50 (μM)	cytotox (%)	
abemaciclib (CDK inhibitor)	0.38	82.3	N/A, >57.5	27.1	17.1	90.0	151.3	3.16	68.7	7.08	34.0	6.3
copanlisib (PI3K inhibitor)	3.12	65.8	N/A, >57.5	6.2	N/A, > 57.5	13.6	18.4	N/A, >20	0.0	5.74	42.4	N/D
cepharanthine (anti-inflammatory, antineoplastic)	1.71	108.4	24.15	115.3	38.27	88.9	14.1	1.41	92.5	11.22	99.0	14.2

Cen et al., ASC Science

WHO recommends against the use of remdesivir in COVID-19 patients

20 November 2020

WHO has issued a conditional recommendation against the use of remdesivir in hospitalized patients, regardless of disease severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients.

The place for remdesivir in COVID-19 treatment

*Barnaby Young, Thuan Tong Tan, Yee Sin Leo
barnaby_young@ncid.sg

- The risks and benefits of remdesivir in patients presenting with severe COVID-19 who require high-flow oxygen or mechanical ventilation are uncertain

Humoral immune responses to SARS-CoV-2 are mediated by antibodies that are directed to viral surface glycoproteins, mainly the spike glycoprotein and the nucleocapsid protein

Poland GA et al., The Lancet 2020
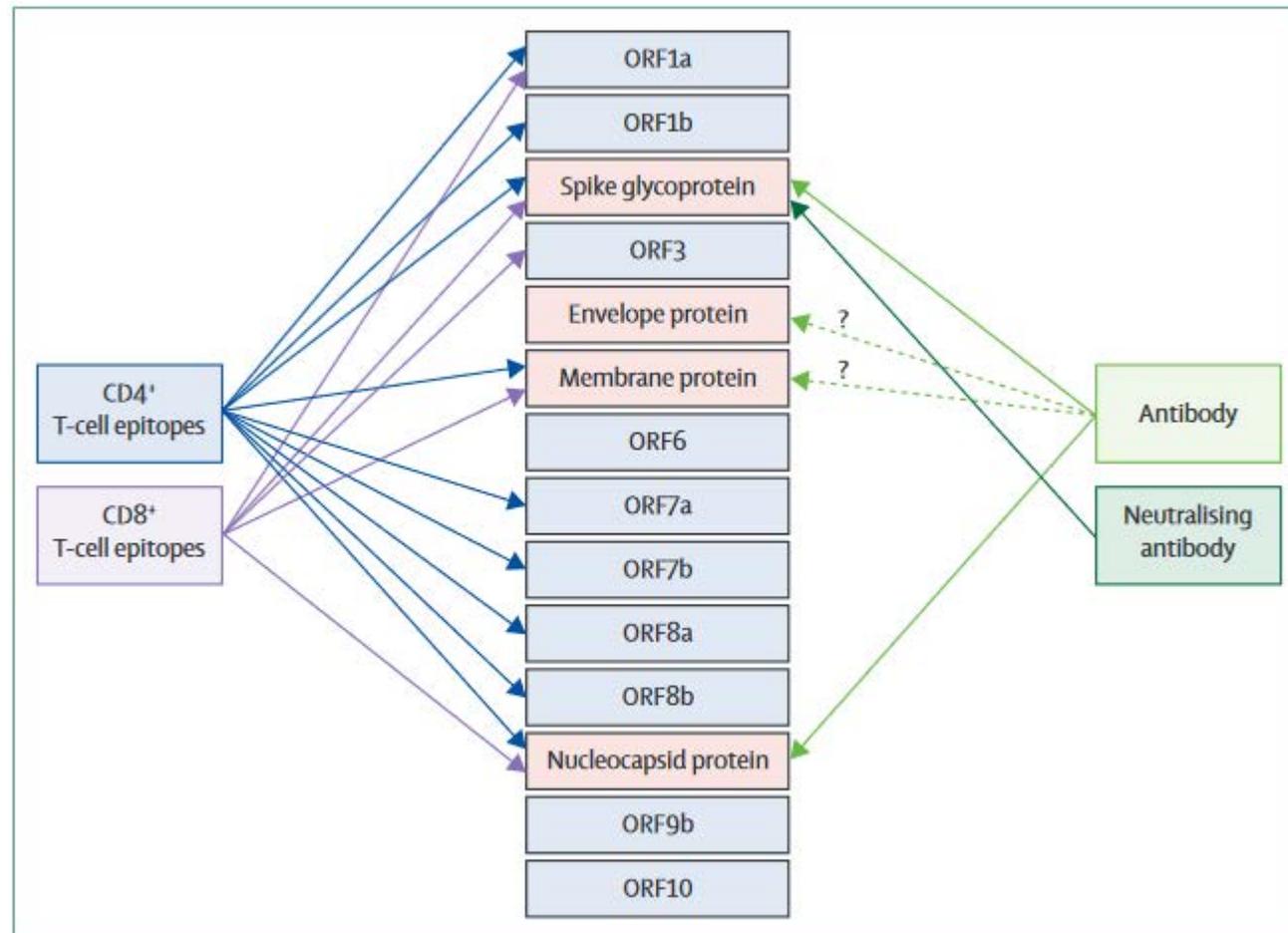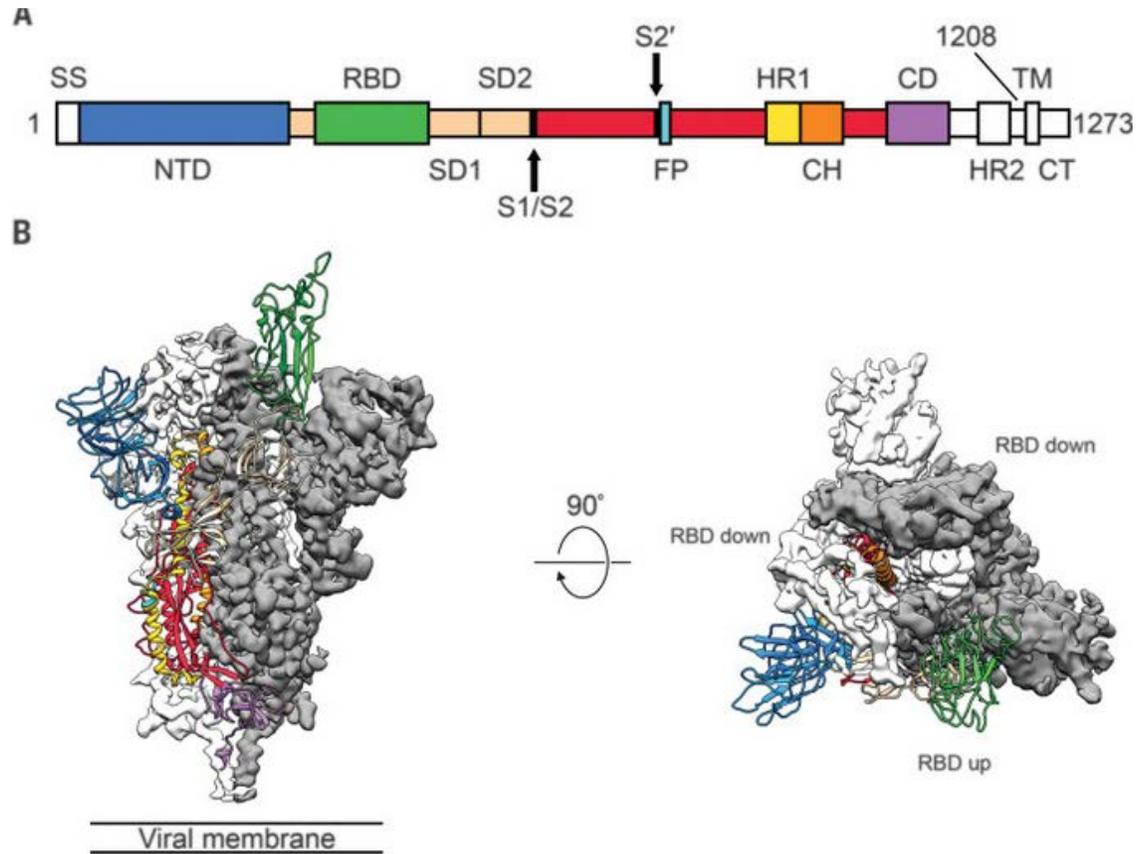
The Spike protein

Wrapp D et al. Science. 2020

- The Spike (S) protein (of about 150kDa) is the major antigen presented on the surface of SARS-CoV-2

- The S protein forms a transmembrane homotrimer protruding from the viral surface to attach to the host cellular receptor ACE2.

- S comprises two functional subunits: subunit S1 responsible for binding to the cell surface receptor ACE2 and subunit S2 responsible viral fusion to the cell membrane

There is little knowledge of post-infection immunity to SARS-CoV-2

Poland GA et al., The Lancet 2020
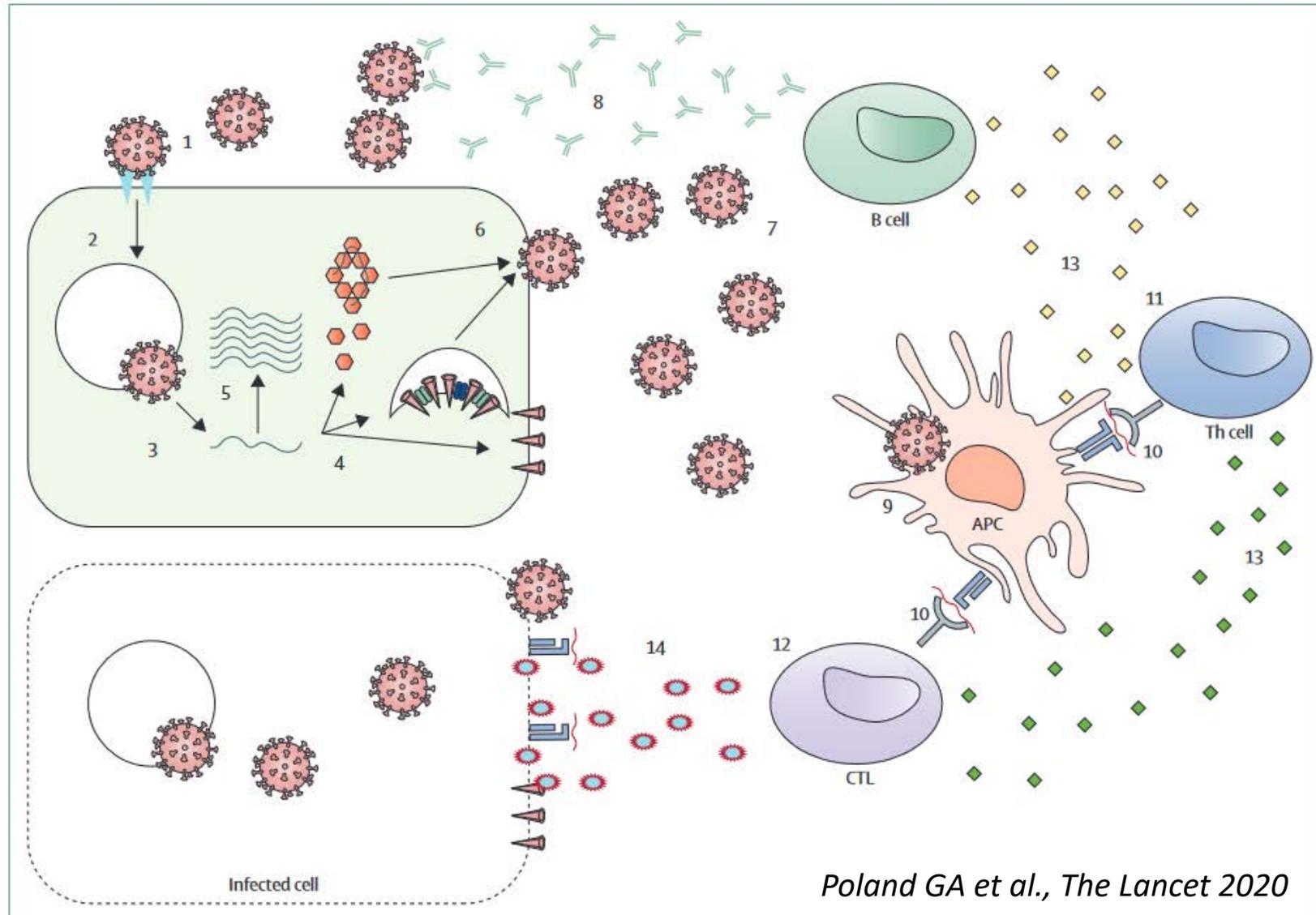
Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies

Wen Shi Lee [1], Adam K. Wheatley [1,2], Stephen J. Kent [1,2,3] ✉ and Brandon J. DeKosky [4,5,6] ✉

Antibody-based drugs and vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are being expedited through preclinical and clinical development. Data from the study of SARS-CoV and other respiratory viruses suggest that anti-SARS-CoV-2 antibodies could exacerbate COVID-19 through antibody-dependent enhancement (ADE). Previous respiratory syncytial virus and dengue virus vaccine studies revealed human clinical safety risks related to ADE, resulting in failed vaccine trials. Here, we describe key ADE mechanisms and discuss mitigation strategies for SARS-CoV-2 vaccines and therapies in development. We also outline recently published data to evaluate the risks and opportunities for antibody-based protection against SARS-CoV-2.

For macrophage-tropic viruses such as dengue virus and FIPV, non-neutralizing or sub-neutralizing antibodies cause increased viral infection of monocytes or macrophages via FcγRIIa-mediated endocytosis, resulting in more severe disease

Macrophage-tropic viruses: dengue virus, FIPV

FcγRIIa

Non-neutralizing antibody

Monocyte/macrophage

Enhanced viral replication
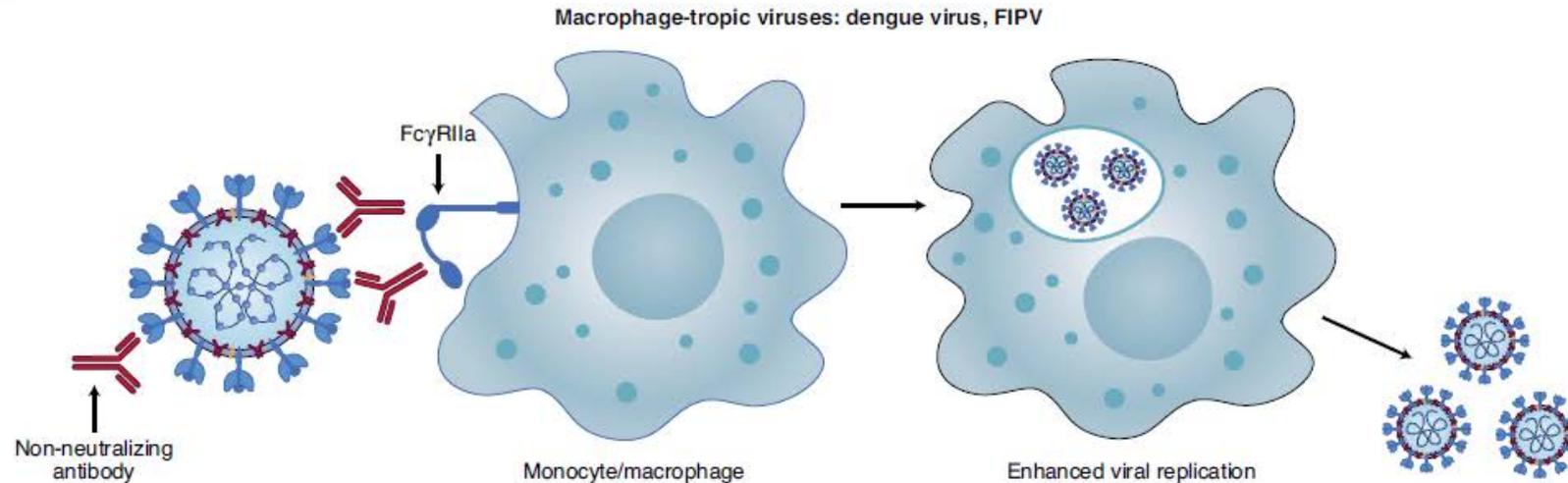
- COVID-19immunopathology studies are still ongoing and the latest available data suggest that human macrophage infection by SARS-CoV-2 is unproductive.

- Existing evidence suggests that immune complex formation, complement deposition and local immune activation present the most likely ADE mechanisms in COVID-19 immunopathology.

Lee et al., Nat Microbiology

Potently neutralizing and protective human antibodies against SARS-CoV-2

Zost et al. , Nature 2020
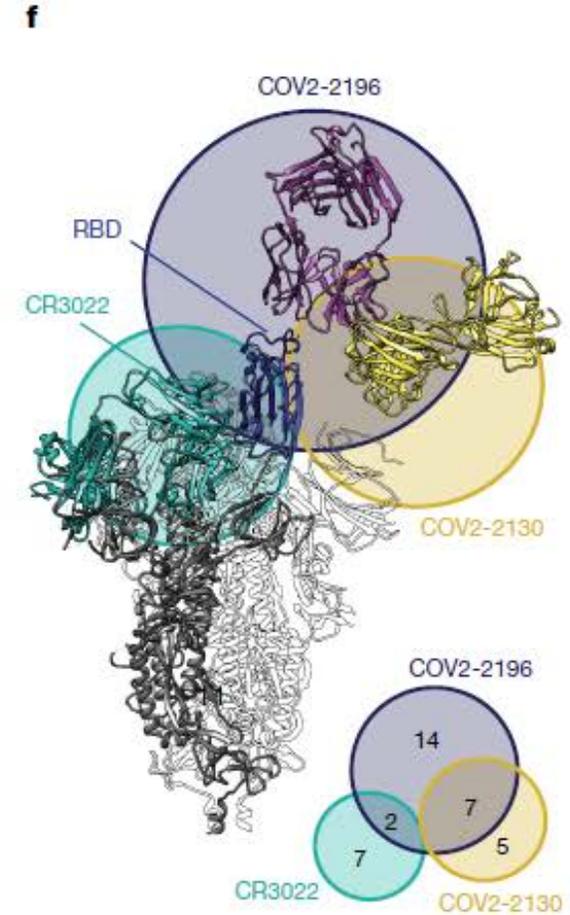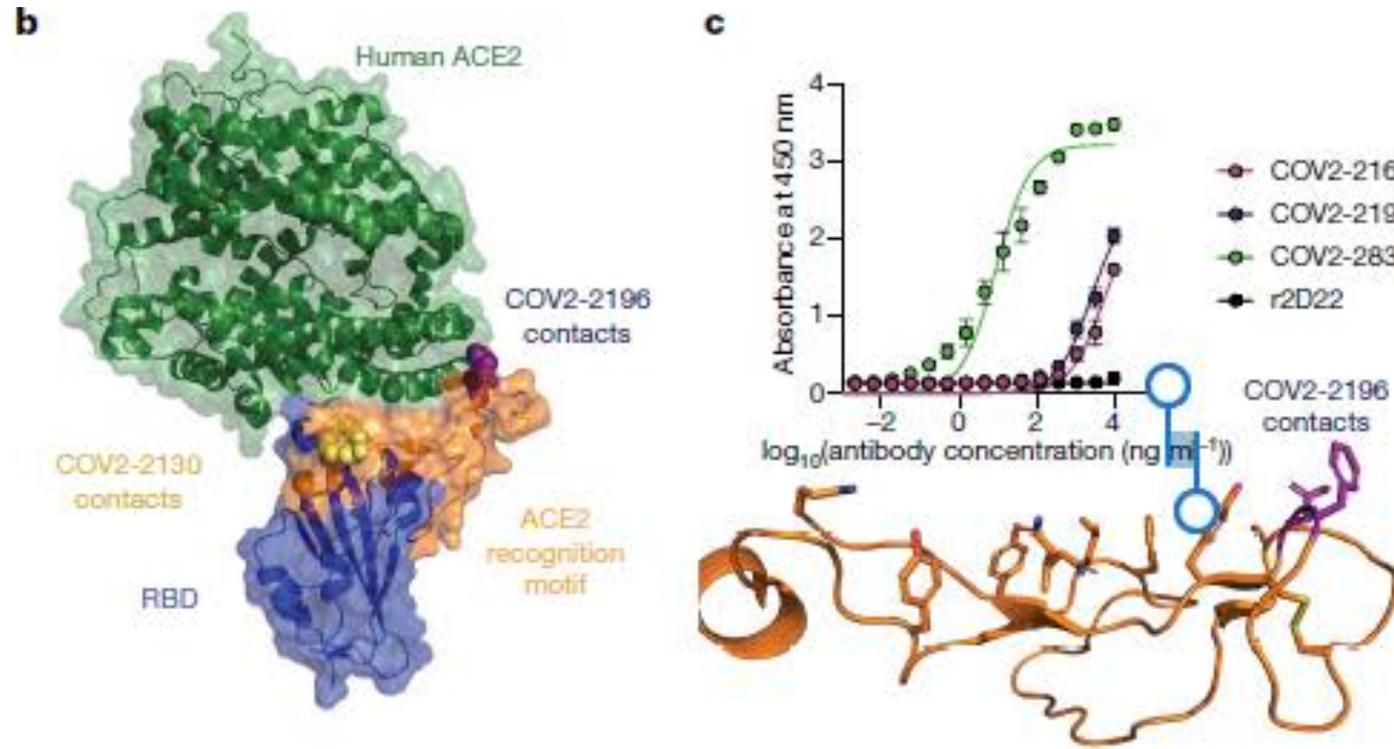
A human monoclonal antibody blocking
SARS-CoV-2 infection

Chunyan Wang[1,6], Wentao Li[1,6], Dubravka Drabek[2,3,6], Nisreen M. A. Okba[4], Rien van Haperen[2,3],
Albert D. M. E. Osterhaus[5], Frank J. M. van Kuppeveld[1], Bart L. Haagmans[4], Frank Grosveld[2,3,7] &
Berend-Jan Bosch[1,7 ✉]
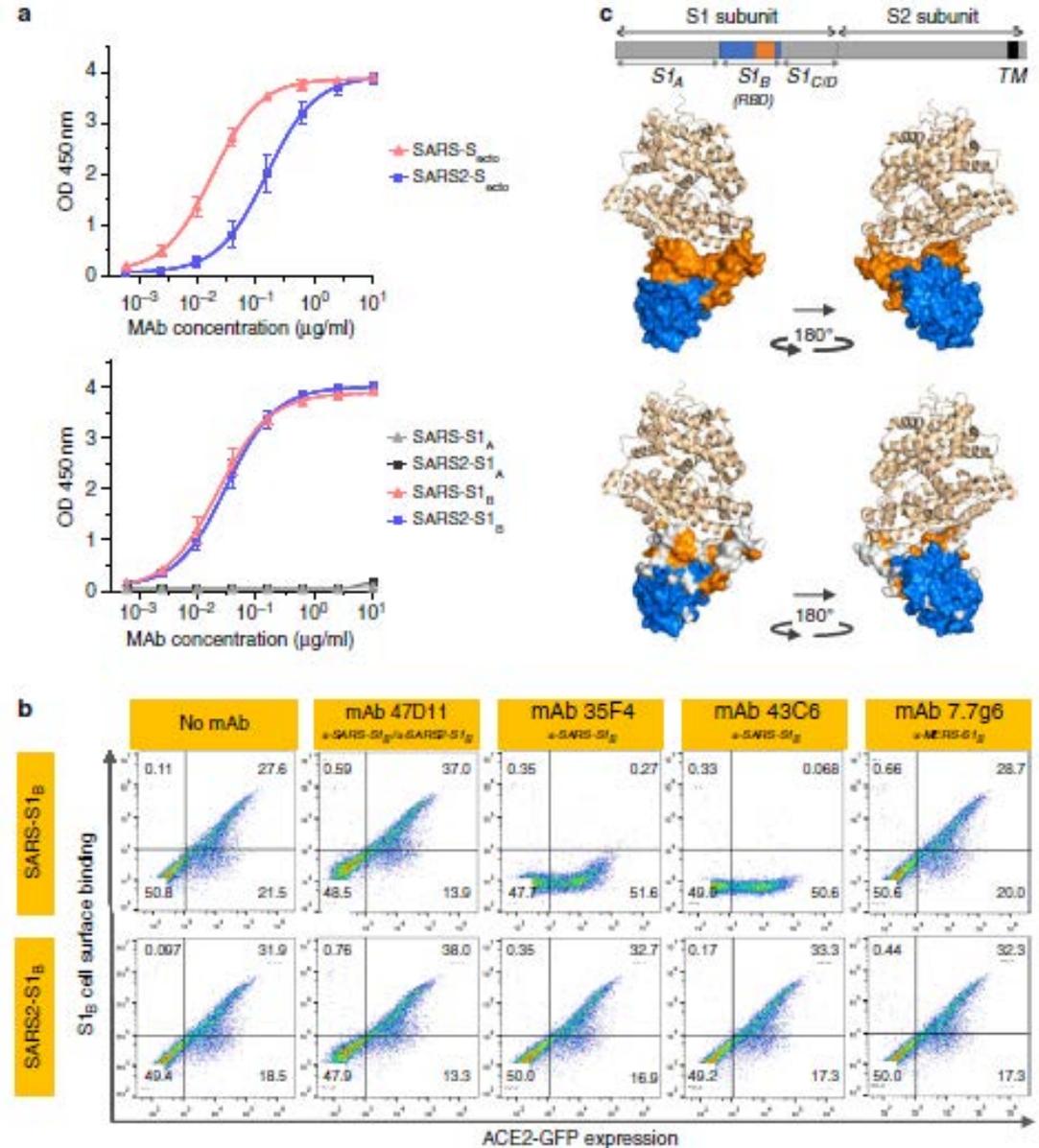
The New York Times

Coronavirus Vaccine Tracker

By Carl Zimmer, Jonathan Corum and Sui-Lee Wee Updated Jan. 5, 2021

PHASE 1	PHASE 2	PHASE 3	LIMITED	APPROVED	ABANDONED
43	20	20	7	3	1
Vaccines testing safety and dosage	Vaccines in expanded safety trials	Vaccines in large-scale efficacy tests	Vaccines in early or limited use	Vaccines approved for full use	Vaccines abandoned after trials
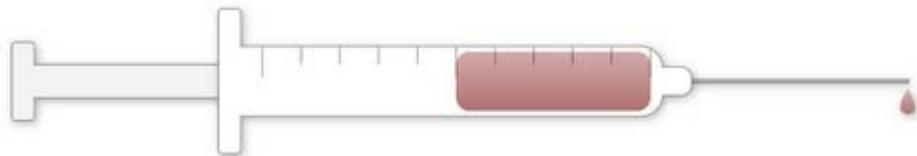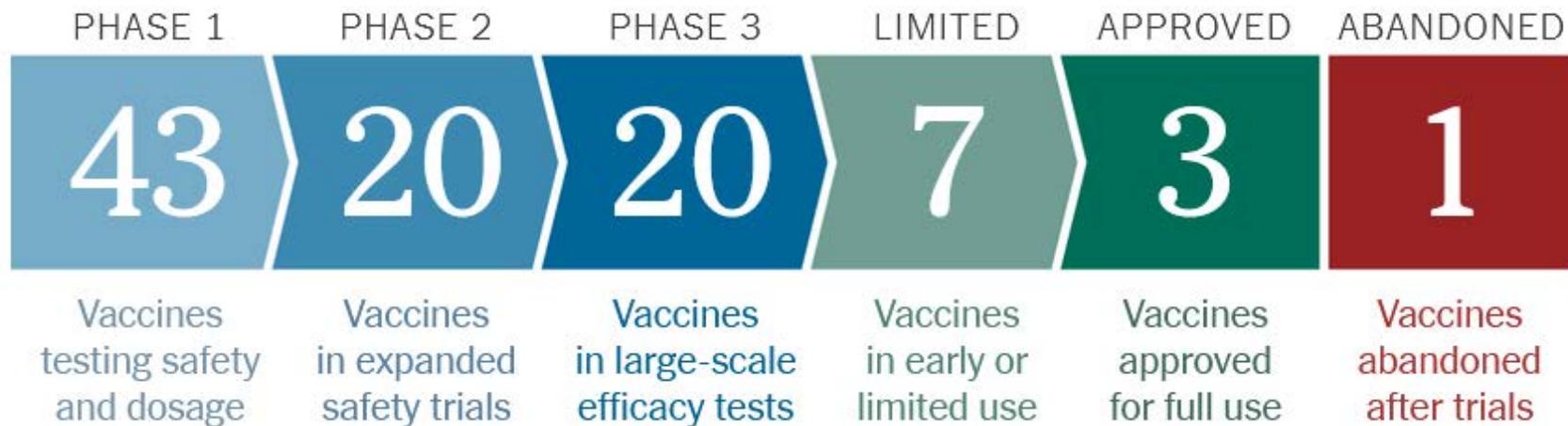
The New York Times

Leading vaccines

Developer	Type	Phase	Status
🇺🇸🇩🇪 Pfizer-BioNTech	mRNA	2 3	Approved in Canada, other countries. Emergency use in U.S., other countries.
🇺🇸 Moderna	mRNA	3	Approved in Canada. Emergency use in U.S., Israel.
🇷🇺 Gamaleya	Adenovirus	3	Early use in Russia. Emergency use in Belarus, Argentina.
🇬🇧🇸🇪 Oxford-AstraZeneca	Adenovirus	2 3	Emergency use in Britain, India, Argentina.
🇨🇳 CanSino	Adenovirus	3	Limited use in China.
🇺🇸🇧🇪 Johnson & Johnson	Adenovirus	3	
🇷🇺 Vector Institute	Protein	3	Early use in Russia.
🇺🇸 Novavax	Protein	3	
🇨🇳 Sinopharm	Inactivated	3	Approved in China, U.A.E., Bahrain. Emergency use in Egypt.
🇨🇳 Sinovac	Inactivated	3	Limited use in China.
🇨🇳 Sinopharm-Wuhan	Inactivated	3	Limited use in China, U.A.E.
🇮🇳 Bharat Biotech	Inactivated	3	Emergency use in India.

How we can stop a pandemic before it starts

- Panviral drugs: hard but not impossible— ones that work broadly within or across virus families — are harder to make than broad-spectrum antibiotics, largely because viruses work by hijacking the machinery of our cells, harnessing their key functions in order to replicate. (i.e. Remdesivir originally developed to treat HCV and later tried agaist Ebola, or Favipiravirs, an influenza drug delevoped in Japan)

- Panviral vaccines are also becoming a real possibility. In recent years, a number of prospective universal flu vaccines have been developed that work by targeting not the virus's capsid or envelope, which mutates easily, but its stem, which barely mutates at all. Another new approach, mRNA vaccines, works by exploiting messenger RNA. The advantages of mRNA vaccines are potentially enormous, in part because they can be made very quickly (one month instead of six for a known strain; two to three months for a novel virus) but also because they can be made on a vast scale (billions of doses, compared with the 100,000 doses that were needed for the Ebola epidemic). They're extremely adaptable too.

Tim Enthoven – NY Times