



SARS-CoV-2 RBD与hACE2的 互作结构以及中和抗体的应用

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from David S. Goodsell

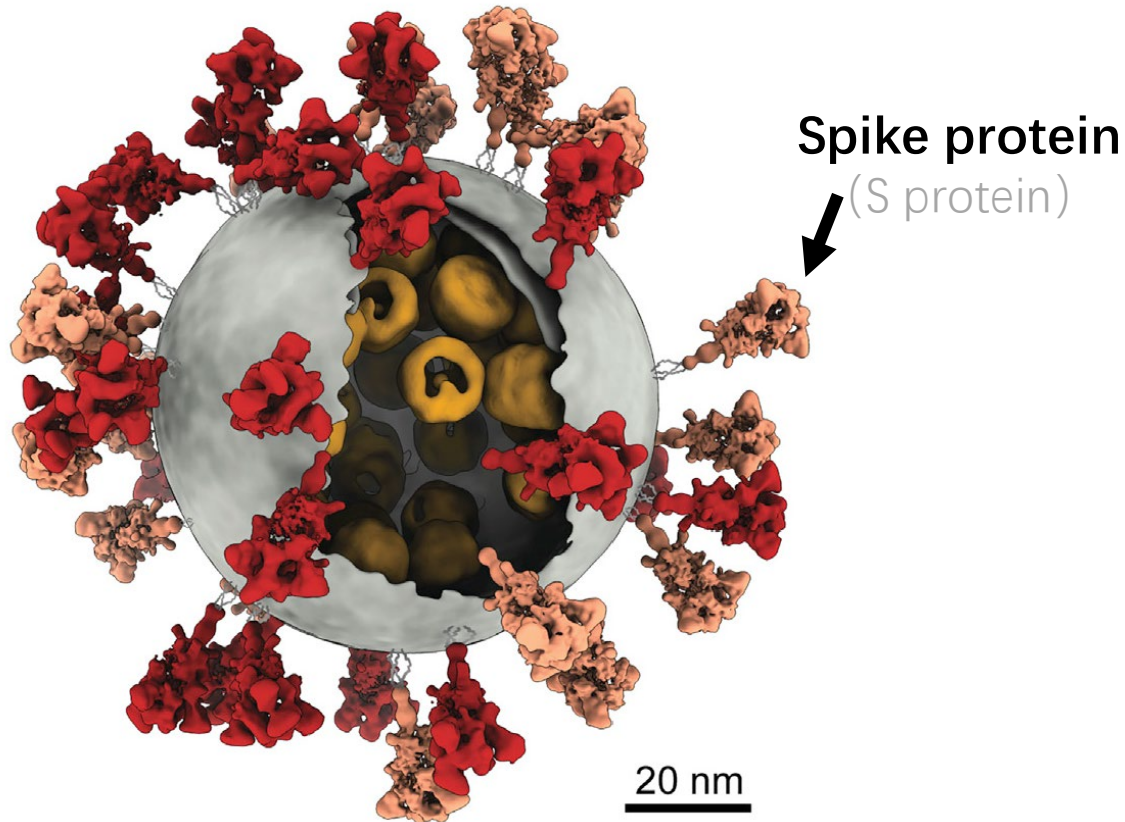
ccsb.scripps.edu/goodsell/cellspace/

SARS-CoV-2

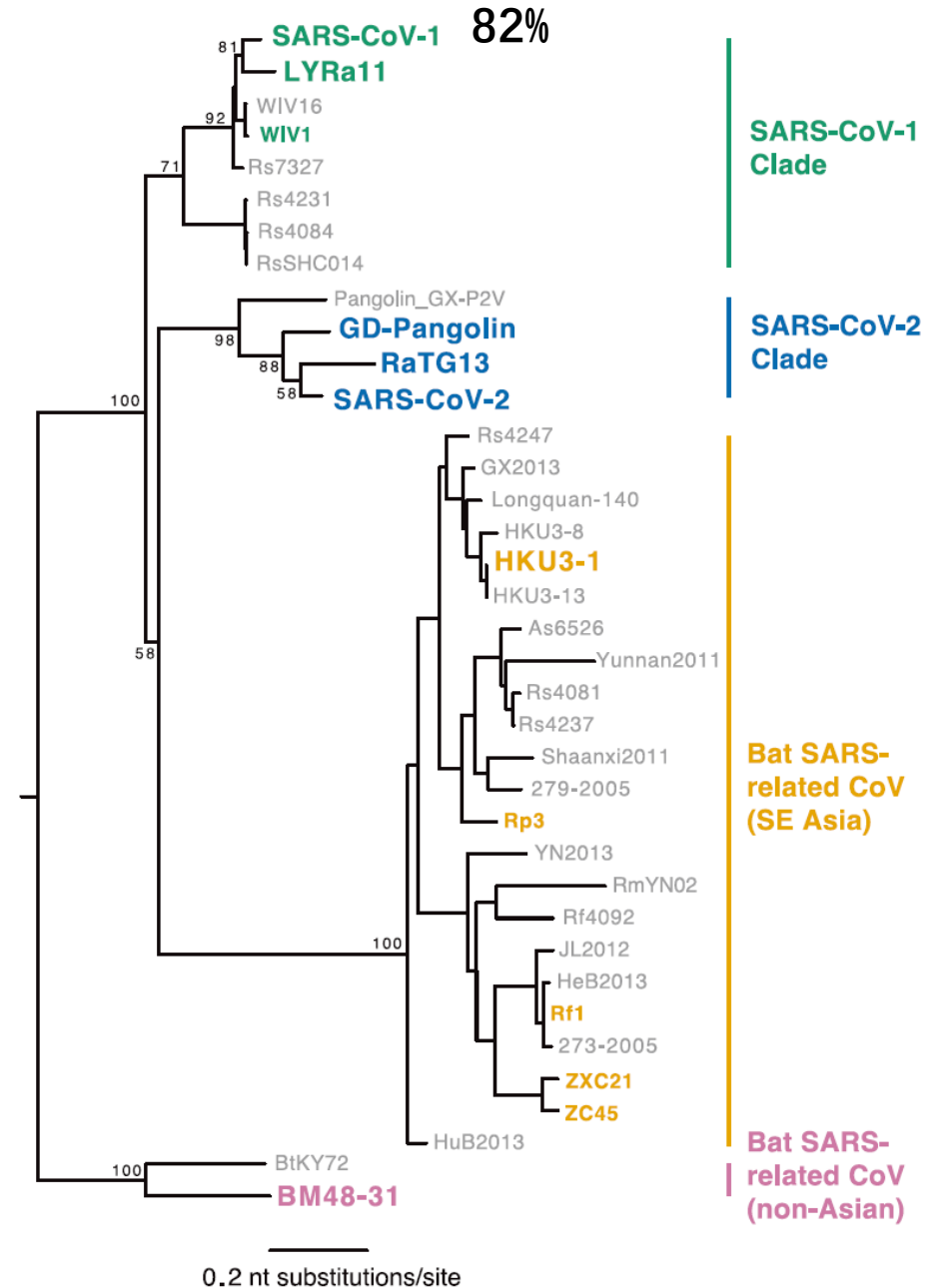
(Severe Acute Respiratory Syndrome-CoronaVirus-2)

Enveloped, positive-sense, single-stranded RNA viruses

Responsible for the **COVID-19** pandemic



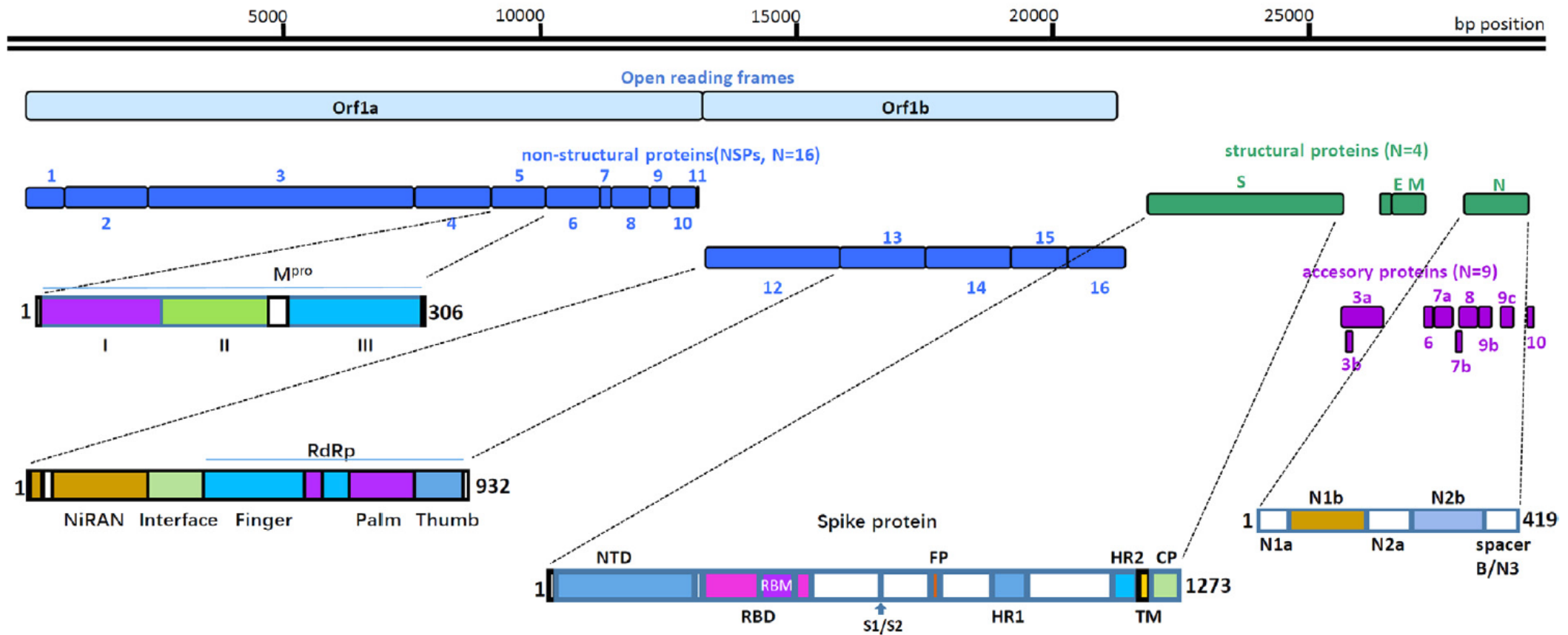
doi.org/10.1016/j.cell.2020.09.018



doi.org/10.1016/j.cell.2020.08.012

SARS-CoV-2 Genome

~30kb positive-sense, single-stranded RNA



RBD: receptor binding domain

RBM: receptor binding motif

NTD: N-terminal domain

Infection mechanism

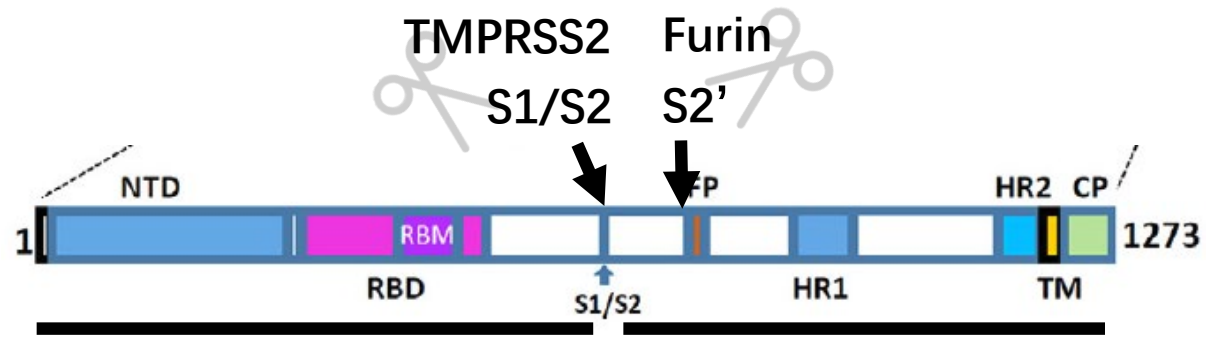
ACE2 血管紧张素转换酶
Angiotensin-**Converting Enzyme 2**

Expressed on major viral target cells,
type II pneumocytes and enterocytes
II型肺泡上皮细胞

Requires the concerted action of **receptor-binding**
and **proteolytic processing** of the S protein to
promote virus-cell fusion

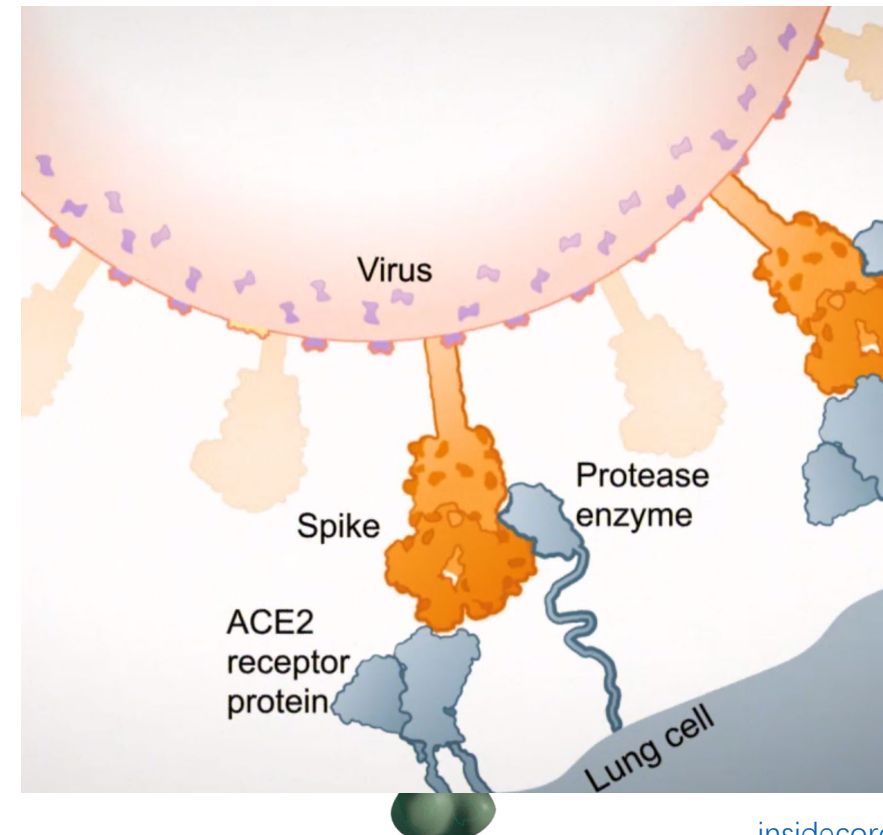
TMPRSS2
Transmembrane **Protease, Serine 2**

Furin
a subtilisin-like peptidase
枯草杆菌蛋白酶样



Attachment
S1 Subunit

Fusion
S2 Subunit



insidecorona.net/protein/spike/

scientificamerican.com/interactive/inside-the-coronavirus/

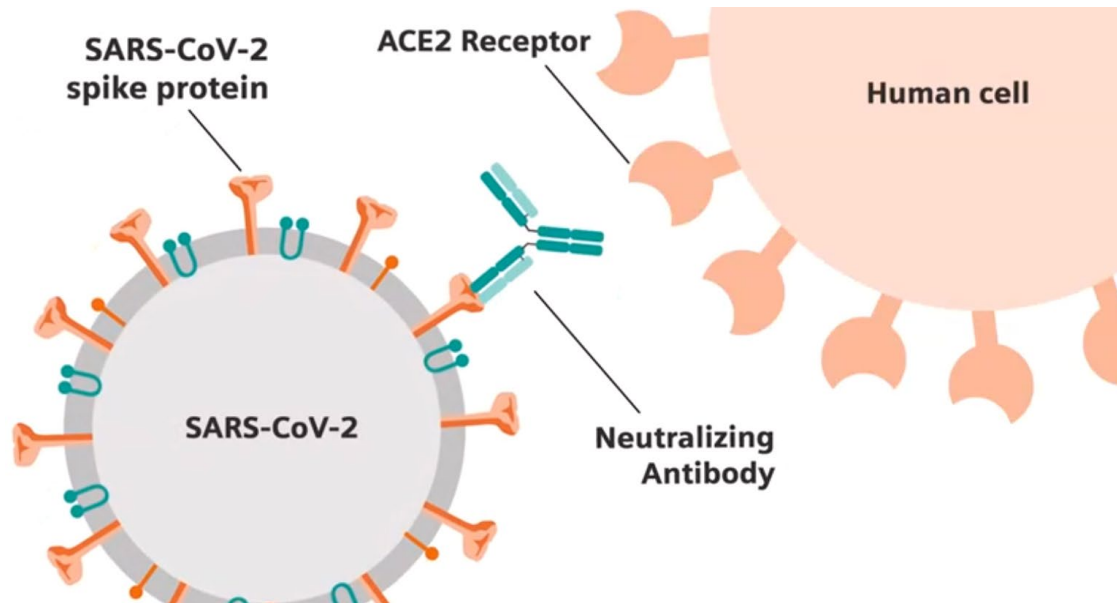
Structural biology in the fight against COVID-19

SARS-CoV-2 proteins	Protein Data Bank entry	Method	Resolution/ Å	Ligands
NSP12/NSP7/NSP8 RdRp Complex	6M71/7BTF (Gao et al., 2020a)	Cryo-EM	2.9/2.95	ZN
	7BV1/7BV2 (Yin et al., 2020)	Cryo-EM	2.8/2.5	F86, POP et al.
	7BZF/7C2K (Wang et al., 2020c)	Cryo-EM	3.26/2.93	ZN
	6YYT (Walls et al., 2019)	Cryo-EM	2.90	ZN
NSP15	6VWW/6W01 (Callaway, 2020)	X-RAY	2.2/1.9	ACY et al.
M ^{PRO}	6Y2G/6Y2F/6Y2E (Zhang et al., 2020)	X-RAY	2.2/1.95/1.75	GLY, O6K, DMS
	6LU7/6M03/7BQY (Jin et al., 2020b)	X-RAY	2.16/2/1.7	N3
	6LZE/6M0K (Dai et al., 2020)	X-RAY	1.5/1.5	11a/11b
S protein	6VSB (Wrapp et al., 2020)	Cryo-EM	3.46	NAG
	6VYB/6VXX (Walls et al., 2020)	Cryo-EM	3.2/2.8	NAG
S protein S2 subunit	6LXT (Xia et al., 2020b)	X-RAY	2.9	PG4, ZN
S protein RBD-ACE2	6M17/6M18/6M1D (Yan et al., 2020)	Cryo-EM	2.9/2.9/4.5	NAG, ZN
	6VW1 (Shang et al., 2020)	X-RAY	2.68	BMA, NAG et al.
	6M0J (Lan et al., 2020)	X-RAY	2.45	NAG, ZN, CL
	6LZG (Gao et al., 2020b)	X-RAY	2.5	NAG, ZN

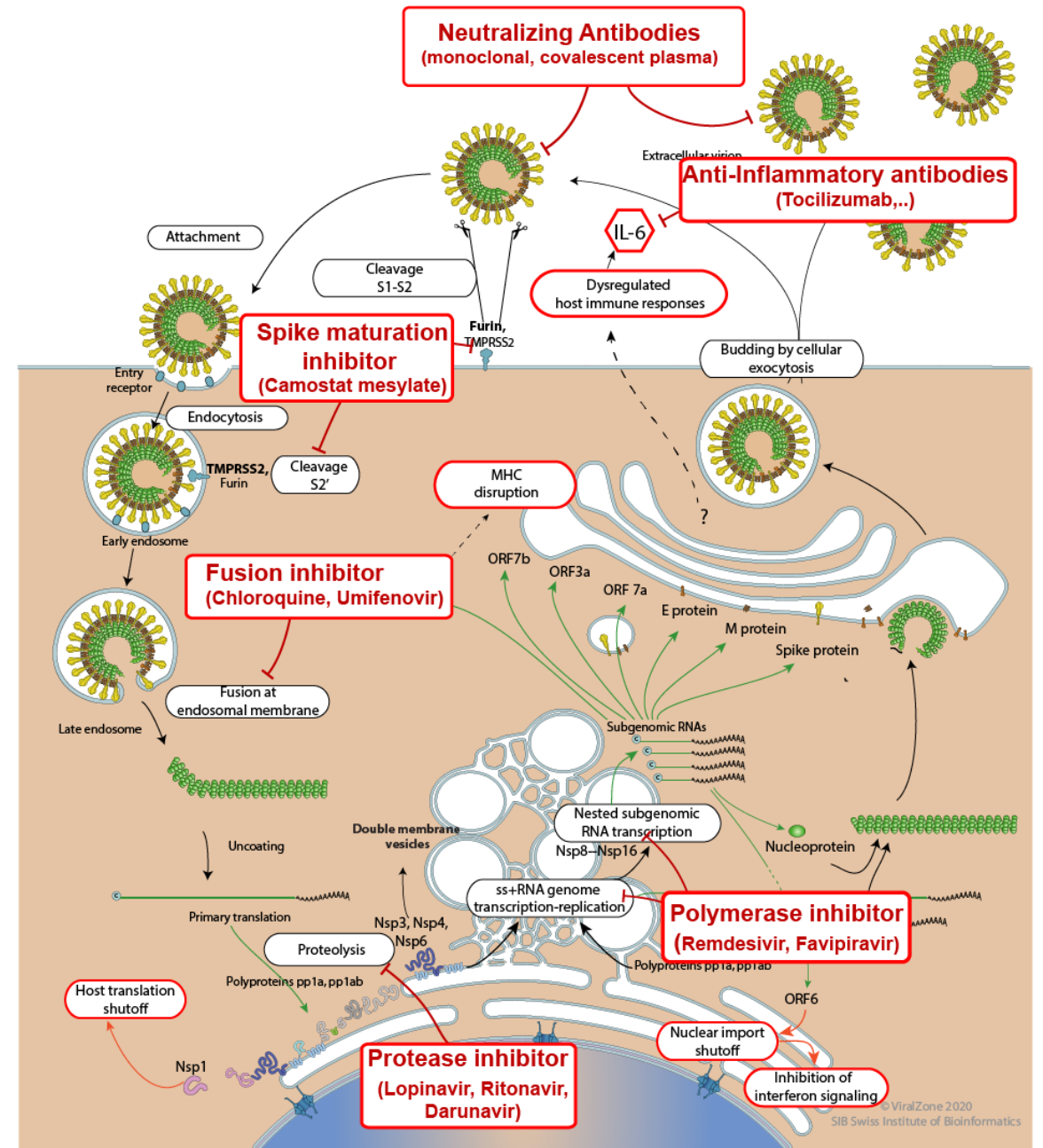
These results provided blueprints of the viral **Infection** and replication machineries, which have been used by thousands of researchers worldwide for the design of vaccines and **Viral Inhibitors**.

Antiviral approach

_ Neutralizing antibody (NAb) 中和抗体



Neutralizing monoclonal antibodies isolated from convalescent patient's memory B cells may serve as a promising intervention to SARS-CoV-2



Neutralizing antibodies for SARS-CoV-2

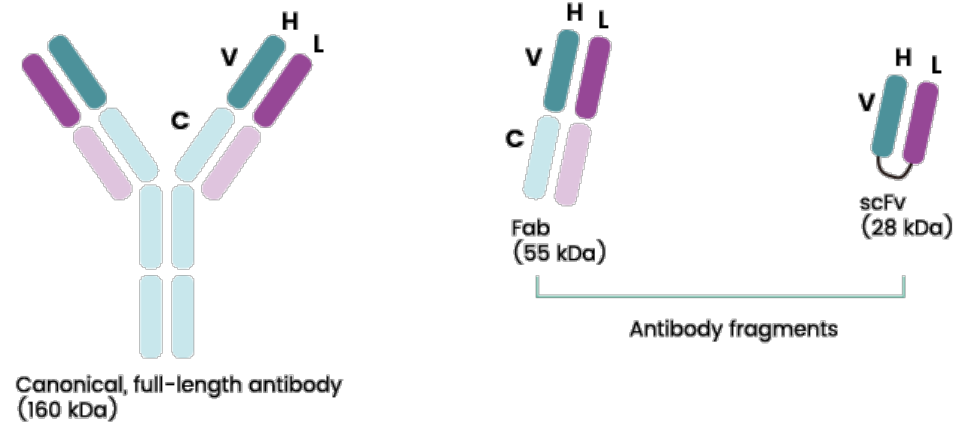
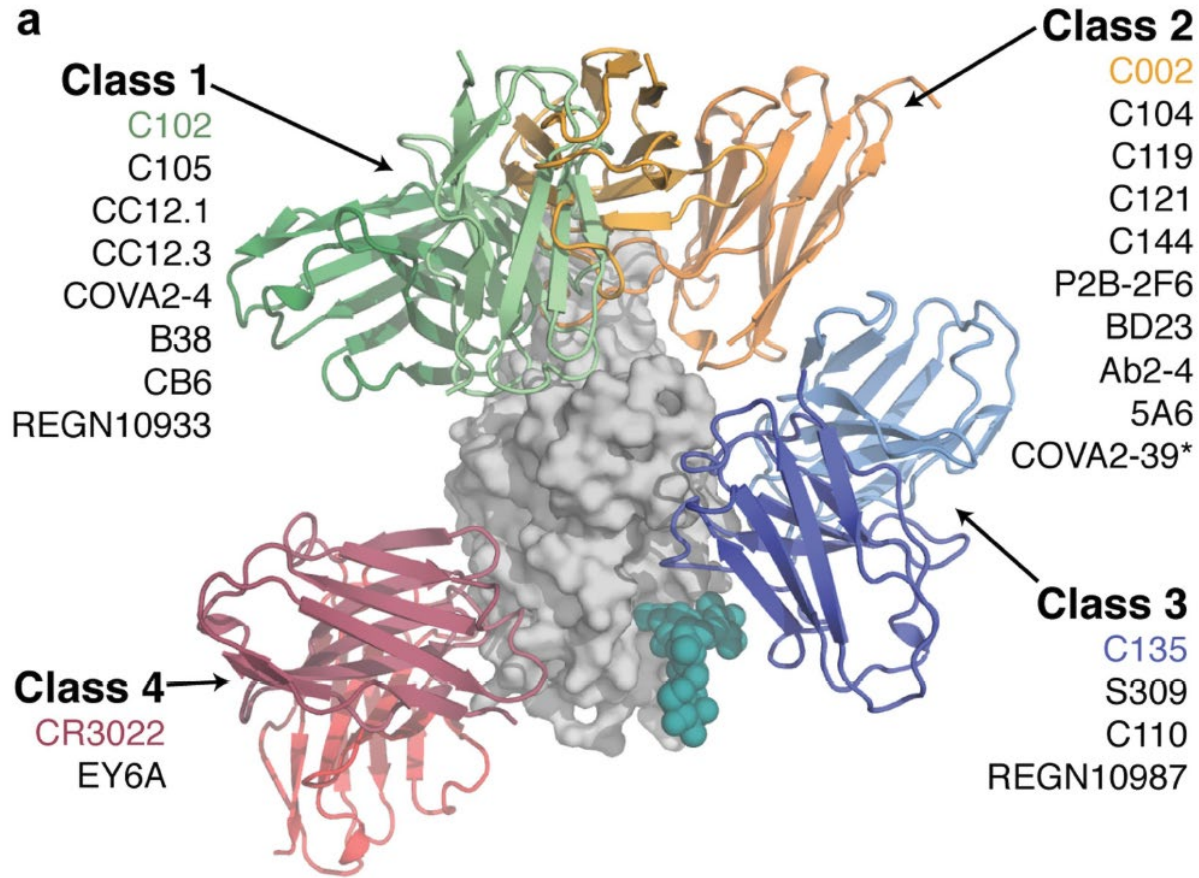
Antibody ID	K _D (nM)		IC ₅₀ (µg/mL)		Epitope	Reference
	Binding to RBD	Binding to S	Pseudovirus	Live virus		
P2C-1F11	2.12	-	0.03 (Huh-7 cell)	0.03 (Vero E6 cell)	-	doi.org/10.1038/s41586-020-2380-z
P2B-2F6	5.14	-	0.05 (Huh-7 cell)	0.41 (Vero E6 cell)	RBD(Class2)	doi.org/10.1038/s41586-020-2380-z
B38	70.1	-	-	0.177 (Vero cell)	RBD(Class1)	doi.org/10.1126/science.abc2241
H4	4.48	-	-	0.896 (Vero cell)	-	doi.org/10.1126/science.abc2241
CA1	4.68(±1.64)	-	-	0.382 (Vero E6 cell)	-	doi.org/10.1038/s41586-020-2381-y
CB6	2.49(±1.65)	-	-	0.036 (Vero E6 cell)	RBD(Class1)	doi.org/10.1038/s41586-020-2381-y
BD-368-2	0.82	-	0.0012 (Huh-7 cell)	0.015 (Vero E6 cell)	-	doi.org/10.1016/j.cell.2020.05.025
BD-23	4.3	-	4.8 (Huh-7 cell)	8.5 (Vero E6 cell)	RBD(Class2)	doi.org/10.1016/j.cell.2020.05.025
H014	0.08	-	0.45 (Vero cell)	5.7 (Vero cell)	RBD(Class4?)	doi.org/10.1126/science.abc5881
4A8	-	0.996	-	0.39 (Vero E6 cell)	NTD	doi.org/10.1126/science.abc6952
REGN10933	●Ligand:nCoV RBD.i○0.0417		0.00642(Vero cell)	0.00632 (VeroE6 cells)	RBD(Class1)	doi.org/10.1126/science.abd0827
REGN10987	●Ligand:nCoV RBD.i○0.0428		0.00609(Vero cell)	0.00561 (VeroE6 cells)	RBD(Class3)	doi.org/10.1126/science.abd0827
47D11	9.56 (±2.68)	10.8 (±2.46)	0.061(Vero E6 cell)	0.57 (VeroE6 cells)	RBD	doi.org/10.1038/s41467-020-16256-y
COVA1-18	0.03*	0.9	0.008(Huh-7 cell)	0.007 (Vero E6 cells)	RBD	doi.org/10.1126/science.abc5902
COVA2-15	0.6*	3.1	0.008(Huh-7 cell)	0.009 (Vero E6 cells)	RBD	doi.org/10.1126/science.abc5902
2B04	-	-	-	0.00146 (Vero E6 cell)	RBD	doi.org/10.1126/science.abc5902
COV2-2196	-	-	0.00007 (293 cells)	0.015 (Vero E6 cell)	RBD	doi.org/10.1038/s41586-020-2548-6
COV2-2130	-	-	0.0016 (293 cells)	0.107 (Vero E6 cell)	RBD	doi.org/10.1038/s41586-020-2548-6
CC12.1	5.92	-	0.019 (HeLa-hACE2 cell)	0.022 (HeLa-ACE2 cell)	RBD(Class1)	doi.org/10.1126/science.abc7520
CC12.3	8.59	-	0.018 (HeLa-hACE2 cell)	0.026 (HeLa-ACE2 cell)	RBD(Class1)	doi.org/10.1126/science.abc7520
S2E12	1.6	2.5	0.0023 for SARS-CoV-2 S-VSV	0.0042 (Vero E6 cell)	RBD	doi.org/10.1126/science.abe3354
S2M11	66	Kd1=68, Kd2=0.2	0.0021 for SARS-CoV-2 S-VSV	0.0012 (Vero E6 cell)	S trimer	doi.org/10.1126/science.abe3354
LY-CoV555			About 0.01 (Vero E6 cell)	0.1-0.01 (Vero E6 cell)	RBD	doi.org/10.1101/2020.09.30.318972

* denotes an apparent KD due to possible avidity effects

● SARS-CoV2 spike protein RBD ectodomain expressed with a C-terminal mycmyc-hexahistidine tag (RBD.mmh), spike protein RBD ectodomain expressed with a C-terminal mouse IgG2a Fc tag (RBD.i)

○ Ligand is the S ecto foldon Trimer expressed with a C-terminal myc-myhexahistidine

Structural of Antibody/RBD Complex



Fab: **A**ntigen-**b**inding **F**ragment

ScFv: **S**ingle-**c**hain **v**ariable **F**ragment

Structural depiction of a representative NAb from each class binding its RBD epitope

Antibody cocktail therapy

抗体“鸡尾酒”疗法

REGENERON

再生元制药

Regeneron

REGN10933 + REGN10987

Eli Lilly and Company

Combination of **LY-CoV555** with **LY-CoV016** (LY3832479)

Lilly 礼来公司

Antibody cocktail therapy

突变逃逸

Can largely prevent **Mutation Escape**, since the possibility of mutations appearing on both epitopes is unlikely



HEALTH • COVID-19

President Trump Has Been Treated With an Experimental COVID-19 Antibody Cocktail. What's That?

Question: Mutation on Spike/RBD

Data Sources



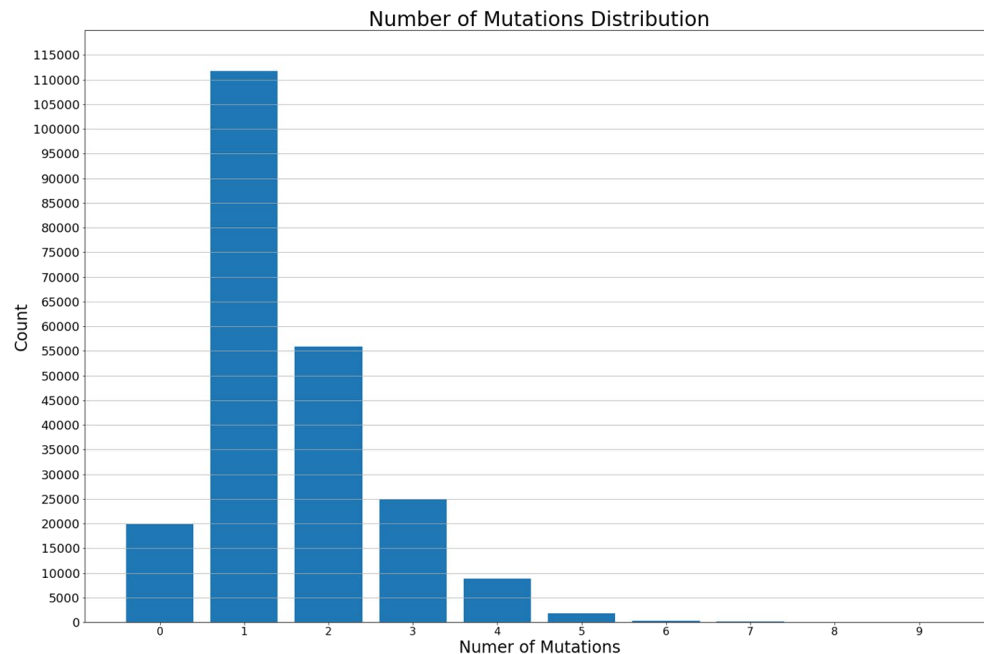
GISAID

NCBI Virus

CNCB

(Global Initiative on Sharing Avian Influenza Data)

(China National Center for Bioinformatics)



- 对ACE2结合能力的影响 → 病毒侵染能力是否提高?
- 对中和抗体的结合效价的影响 → 是否会降低抗体药物的疗效?
- 对一些康复患者体内血清中多克隆抗体结合效价的影响
→ 康复患者会不会二次感染突变后的病毒?
疫苗激活人免疫系统产生的中和抗体会不会因为新冠病毒的突变而失效?

Mutation	Count	Ratio
D614G	200826	0.896761
A222V	35857	0.160114
L18F	17251	0.077032
S477N (RBD)	13529	0.0604119
N439K (RBD)	3875	0.0173033
H69-	3101	0.0138471
V70-	3101	0.0138471
L5F	2707	0.0120877
A262S	1760	0.00785904
R21I	1620	0.00723389

感谢聆听 欢迎提问



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