Humoral Immunity and Monoclonal Antibodies

NCOH webinar on COVID-19 and Immunity

October 1st 2020

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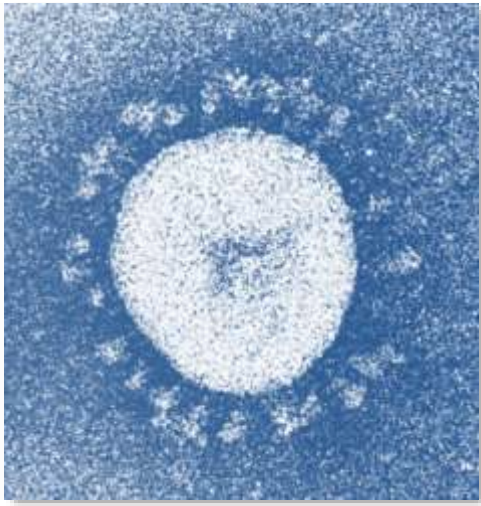

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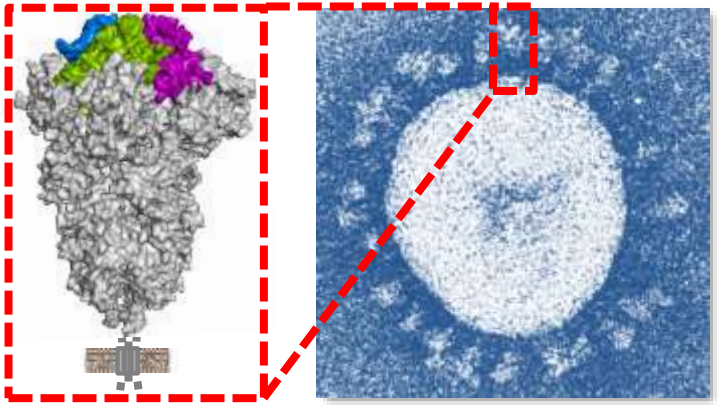
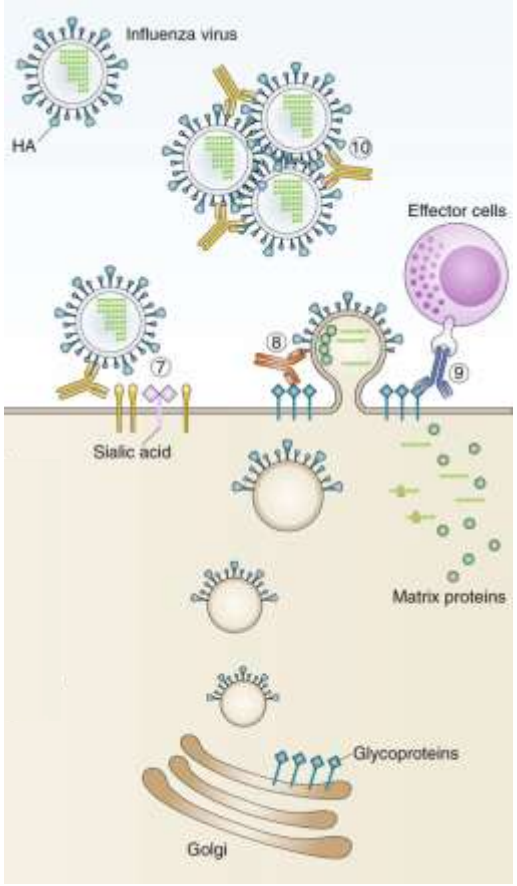
The spike protein: target of neutralizing antibodies



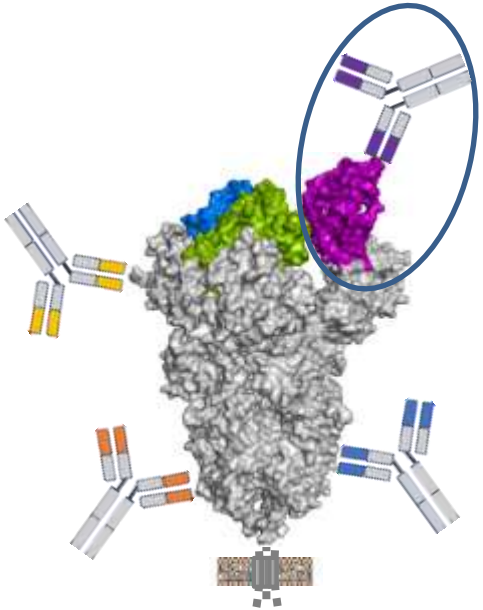
All COVID-19 vaccine approaches target the spike protein of SARS CoV-2, being the **key protein for cell entry and the main target of neutralizing antibodies.**



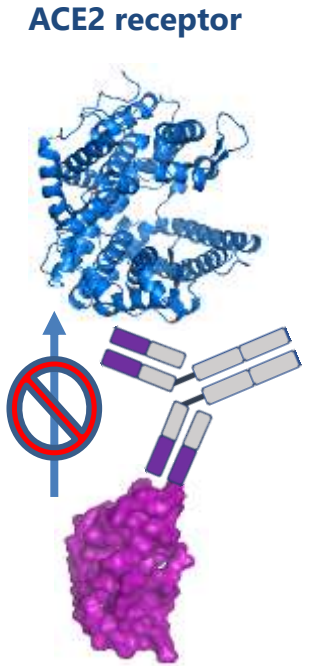
Adapted from Murin et al., Nat.Micr. 2019

The RBD: ‘Achilles heel’ of the spike protein

Analyses of the antibody repertoire of infected patients show that the vast majority of (potent) neutralizing antibodies target the **receptor binding domain**.



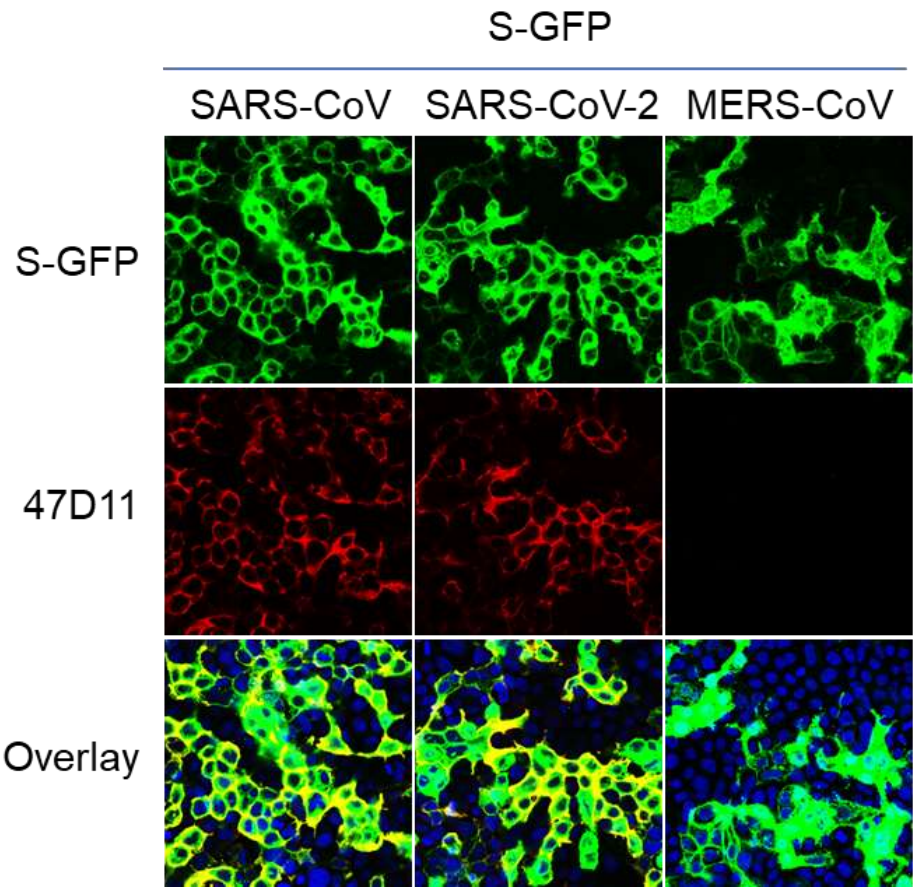
RBD-targeting antibodies are so potent, as their binding prevents virus interaction with the host cell, thereby blocking virus infection.



Widjaja *et al.,* (2018) EMI; Wang *et al.,* (2020) Nat.Comm.; Brouwer *et al.,* (2020) Science; Rogers *et al.,* (2020) Science; Wec *et al.,* (2020) Science; Wu *et al.,* (2020) Science; Hansen *et al.,* (2020) Science; Zost *et al.,* (2020) Nature; Liu *et al.,* (2020) Nature; Pinto *et al.,* (2020) Nature; Shi *et al.,* (2020) Nature; Ju *et al.,* (2020) Nature; Robbiani *et al.,* (2020) Nature; Barnes *et al.,* (2020) Cell; Cao *et al.,* (2020) Cell and others..

Neutralizing mAb targeting a conserved site on SARS-CoV-2

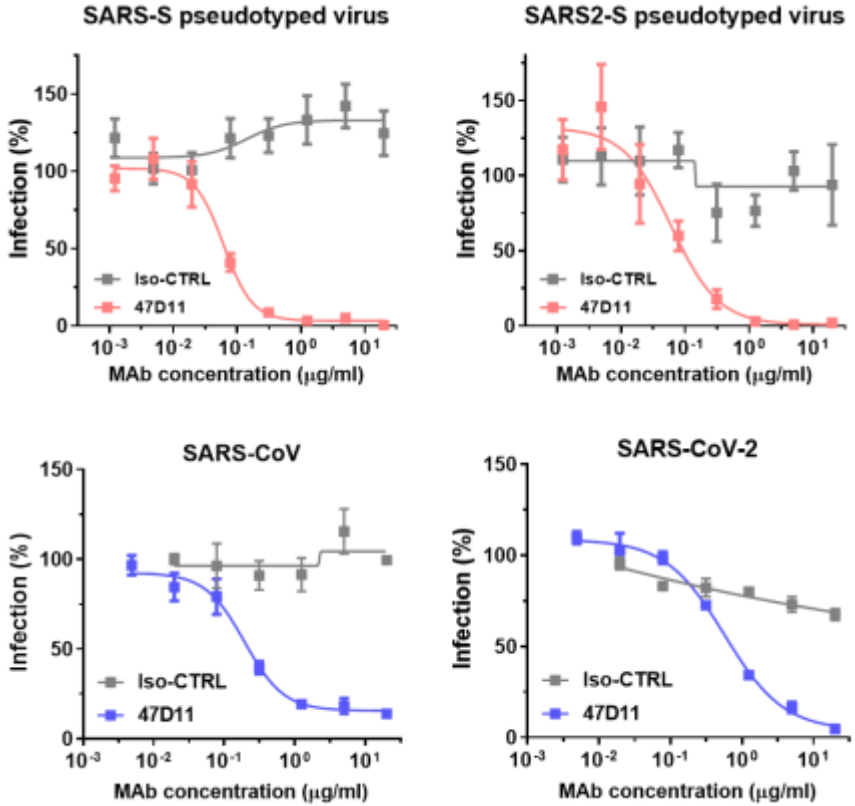
Hybridoma	SARS-S_{ecto}	SARS-S1	SARS-$S1_A$	SARS2-S1
44B3	2,5	2,7	3,3	0,1
45E10	3,0	0,8	1,7	0,0
46F11	2,4	2,7	3,3	0,0
39F9	2,9	3,3	3,5	0,0
41A7	2,6	1,0	1,9	0,0
28 E3	2,4	2,3	3,2	0,0
34C10	1,3	1,0	1,9	0,0
16C10	2,4	0,6	1,7	0,1
14B1	2,6	2,9	3,3	0,1
30B1	0,6	0,5	1,1	0,0
28G10	1,0	1,3	2,6	0,0
28F6	2,4	2,9	3,0	0,0
40H10	1,2	0,7	1,9	0,0
39A4	1,7	1,5	2,8	0,0
37G1	1,3	0,9	1,7	0,0
44E11	2,8	3,3	3,5	0,1
19C1	1,9	0,4	1,2	0,1
58D2	2,6	2,8	3,4	0,1
14C1	2,8	1,2	2,6	0,0
45H1	2,3	3,1	3,6	0,0
24F5	3,3	3,4	3,6	0,0
52D9	1,5	1,6	2,3	1,3
45E6	2,4	2,6	3,3	0,0
47D11	3,4	3,0	0,0	1,5
47G10	2,6	2,8	0,1	0,0
48G1	3,3	3,4	0,1	0,0
49F1	1,8	2,0	0,0	1,3
43C6	3,1	3,4	0,1	0,1
22E10	3,2	3,4	0,1	0,0
28D11	2,7	3,1	0,1	0,0
28H3	2,8	1,8	0,0	0,0
25E7	3,1	3,3	0,1	0,1
22E8	1,2	1,2	0,1	0,0
35F4	3,2	3,6	0,1	0,0
43G5	3,2	3,3	0,1	0,1
47F8	1,4	1,4	0,0	0,0
43B4	3,2	3,3	0,1	0,0
49B10	1,1	0,6	0,0	0,2
51C11	1,9	1,9	0,0	0,0
36F6	1,7	2,7	0,1	0,3
65H8	3,2	3,3	0,1	0,1
65H9	1,6	1,7	0,1	2,5
48D5	3,3	3,5	0,1	0,0
35E2	2,5	3,3	0,2	0,0
44G3	2,4	2,8	0,1	0,0
9H9	1,8	0,1	0,0	0,1
25C3	3,0	0,1	0,1	0,1
29E6	1,1	0,1	0,1	0,0
43F11	2,8	0,1	0,1	0,0
47C4	1,5	0,0	0,1	0,0
13F11	3,0	0,0	0,0	0,0



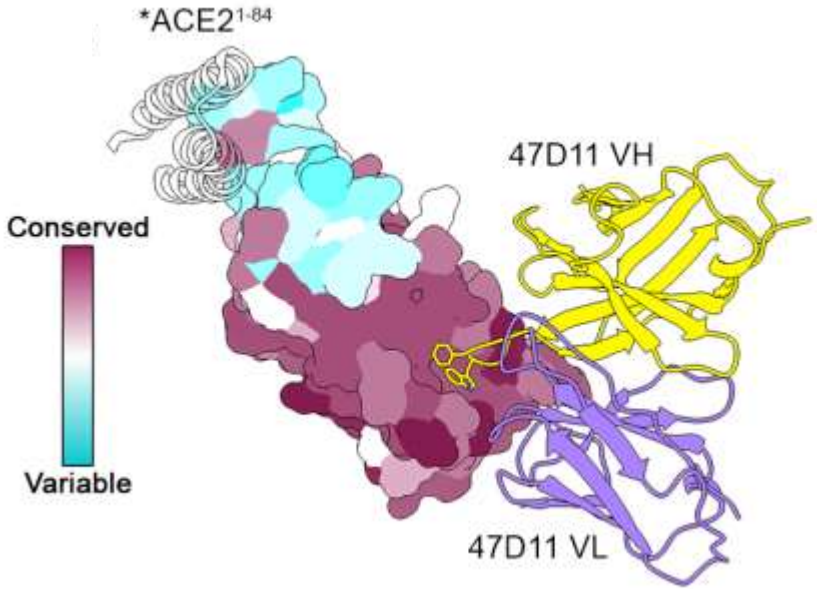
Wang *et al.,* (2020) Nat.Comm.

Similar mAbs reported by: Pinto et al., (2020) Nature; Brouwer et al., (2020) Science; Rogers et al., (2020) Science; Lv et al., (2020) Cell Rep.

Neutralizing mAb targeting a conserved site on SARS-CoV-2

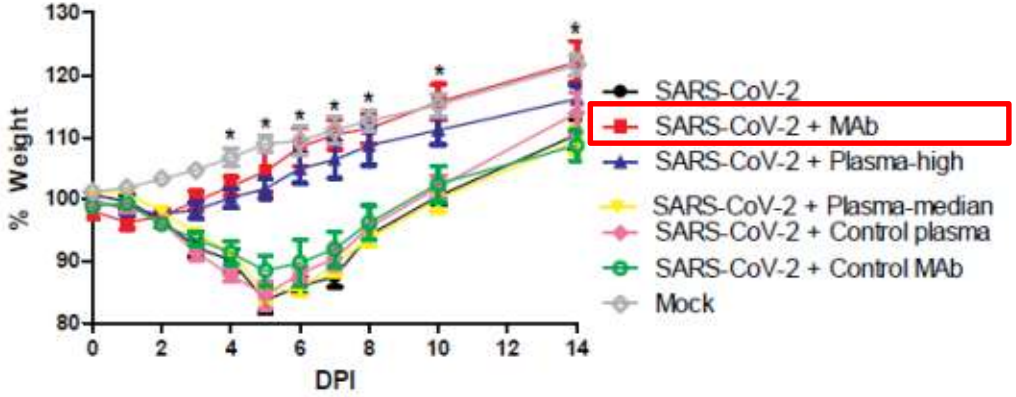


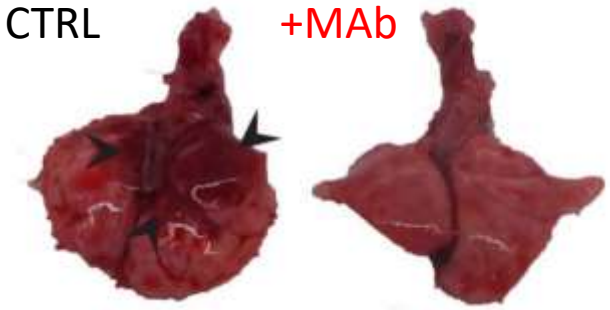
Wang *et al.,* (2020) Nat.Comm.

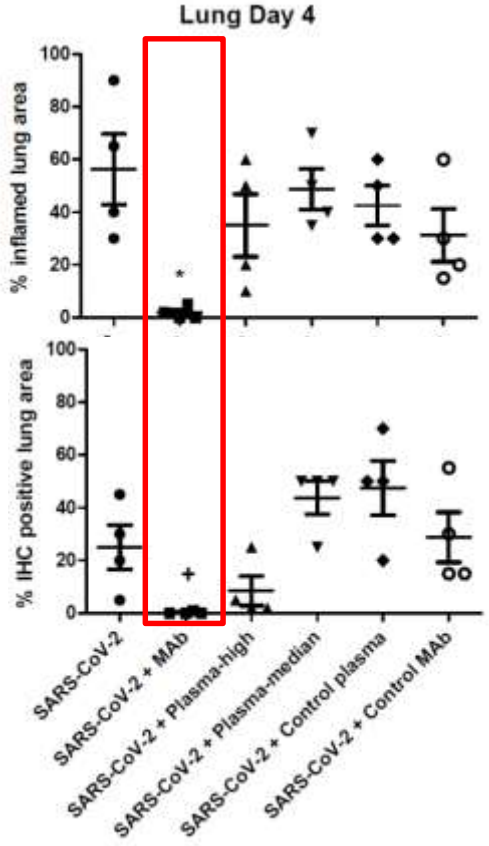


Fedry, Hurdiss, Wang, Li *et al.,* (2020) BioRxives

Ab mediated protection from disease in hamster model







Haagmans *et al.,* (2020) BioRxives

Monoclonal Antibody-Based Prophylaxis / Therapeutics

Pharma	Antibody	Development stage
Regeneron	REGN-COV2 (10933 + 10987)	Phase II/III
li Lilly (Abcellera, Junshi, NIAID)	LY3819253 (LY-CoV555)	Phase III
Junshi Biosciences and Eli Lilly	CB6 (JS016)	?
Vir and GSK	VIR-7831 (S309)	Phase II/III
AstraZenica (VUMC, Parexel)	AZD7442 (COV2-2196, COV2-2130)	Phase I
Abbvie (UU/EMC/HBM)	47D11	Preclinical

Antibody-Based Drug May Reduce COVID-19 Hospitalizations

Lilly announces proof of concept data for neutralizing antibody LY-CoV555 in the COVID-19 outpatient setting

September 16, 2020

- **Primary endpoint of viral load change from baseline at day 11 was met for one of three doses; consistent effects of viral reduction seen at earlier time points**

- **Rate of hospitalizations and ER visits was 1.7 percent (5/302) for LY-CoV555 versus 6 percent (9/150) for placebo--a 72 percent risk reduction in this limited population**

- **LY-CoV555 was well-tolerated across all doses with no drug-related serious adverse events reported**

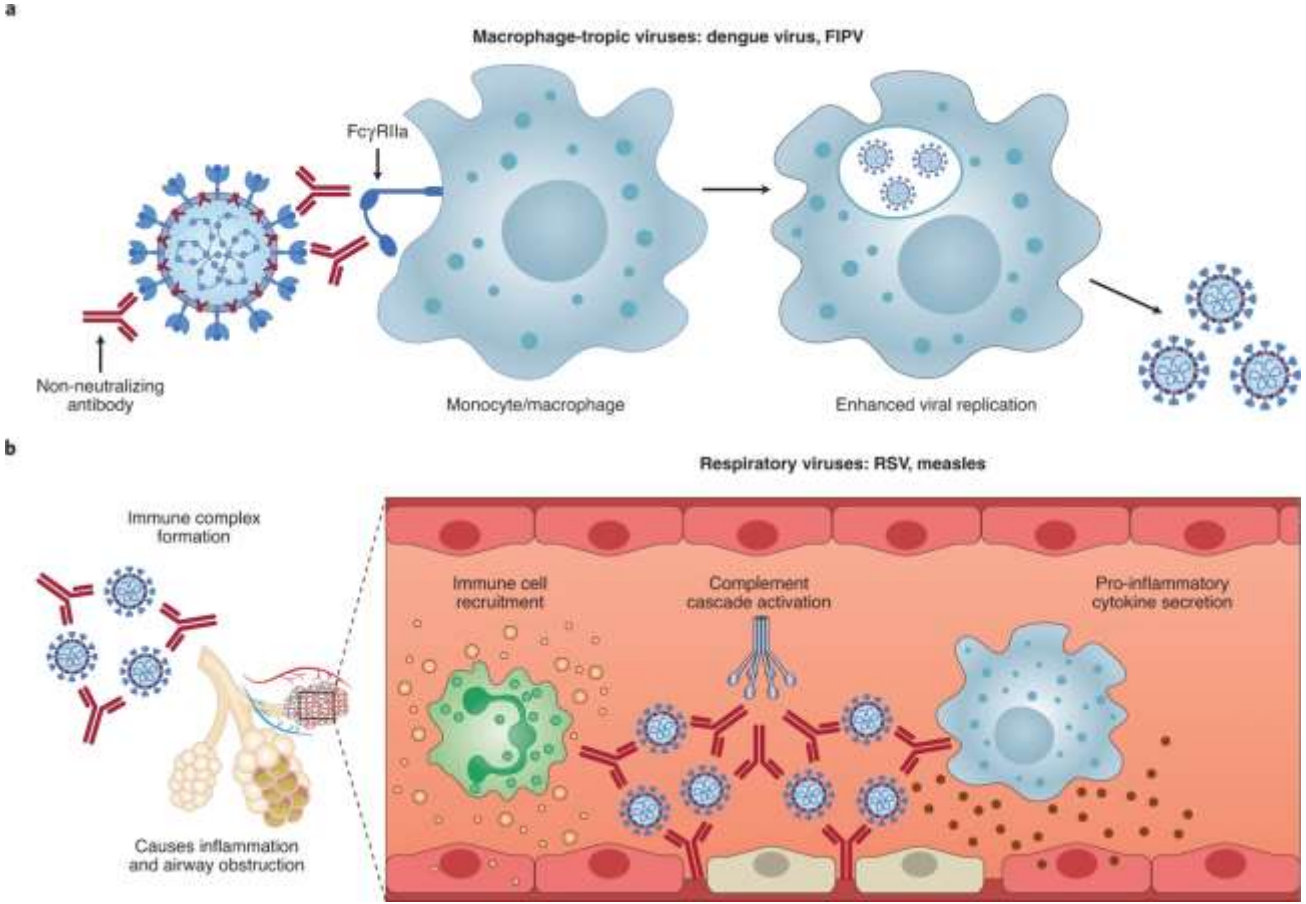
Antibody responses in COVID-19 patients

- Antibodies detectable between 7-14 days post exposure
- Overall level of serum neutralizing activity is generally low
- Neutralizing Ab levels correlate with anti-RBD IgG antibodies
- Neutralizing activity correlates with age, and with duration and severity of symptoms

- How does the presence of antibodies impact the clinical course and severity of the disease?
- What level of antibodies provide protection against infection/disease?
- How do antibodies from natural infection interfere with vaccination?
- Impact of persistence of serum Ab levels on serosurveillance studies?

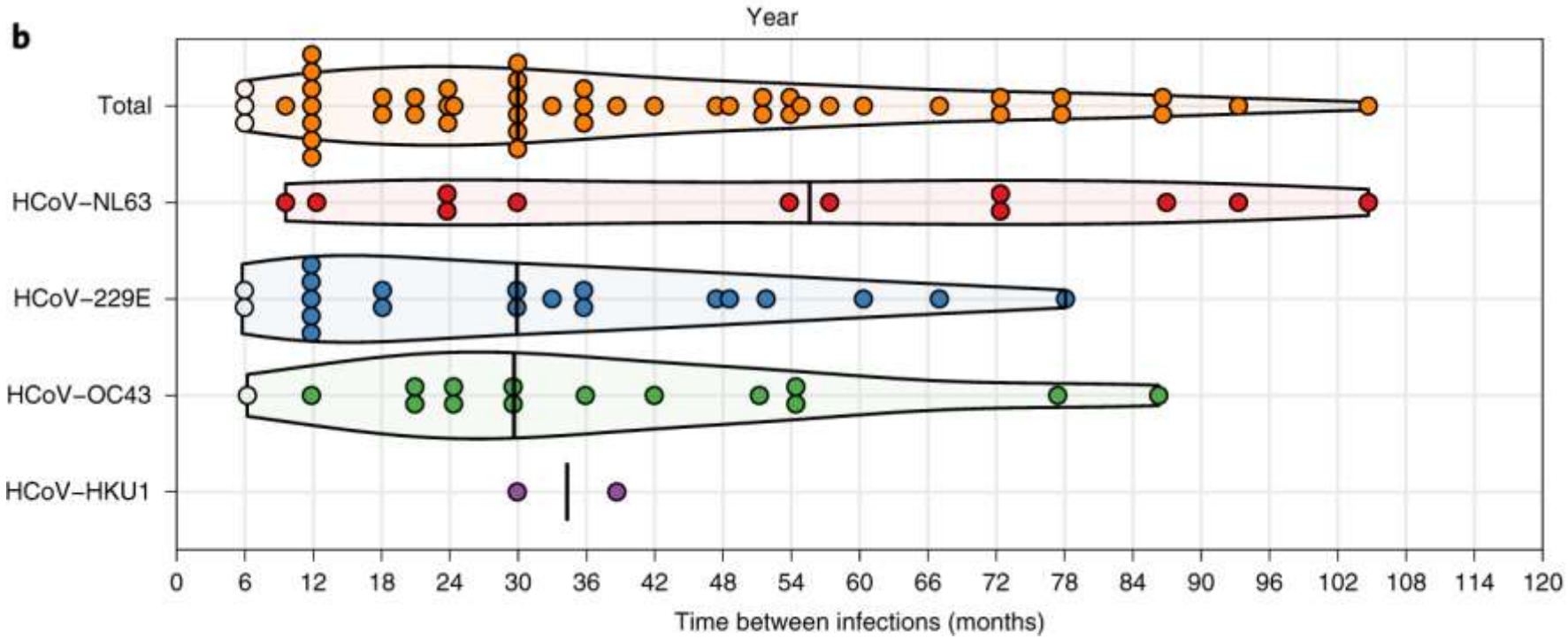
Robbiani *et al.,* (2020) Nature, Huang *et al.,* (2020), Nat.Comm.

Can antibodies do harm?



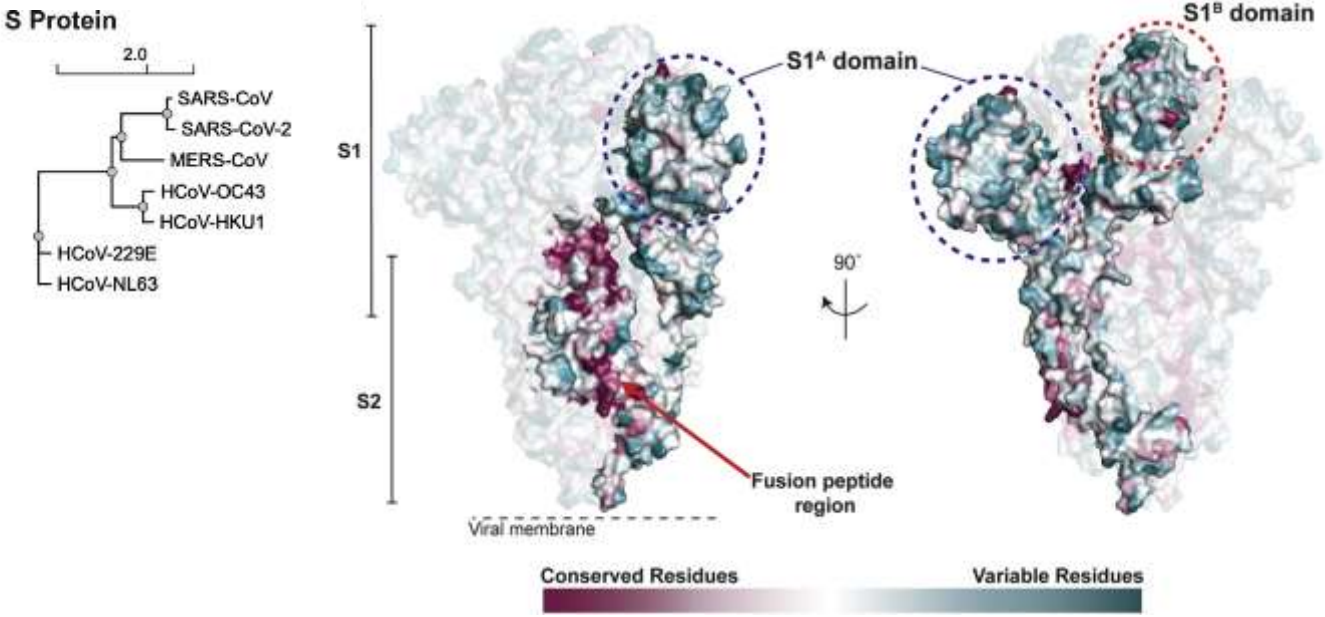
Lee *et al.,* (2020) Nat.Micr.

Protective immunity against endemic coronaviruses is short-lived

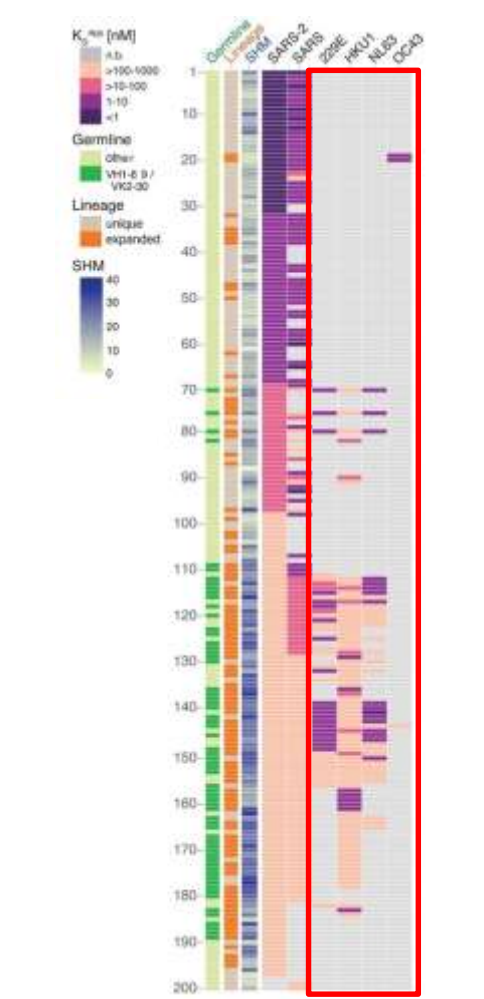


Edridge *et al.,* (2020) Nat.Med.

How ‘new’ is the novel SARS-CoV-2?



Barnes *et al.,* (2020) Cell



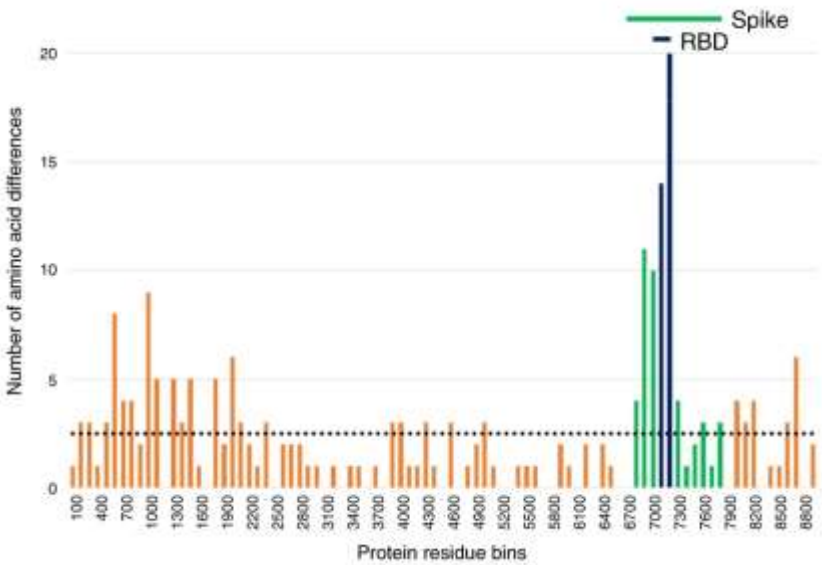
Wec *et al.,* (2020) Science

Can we expect antigenic variation?

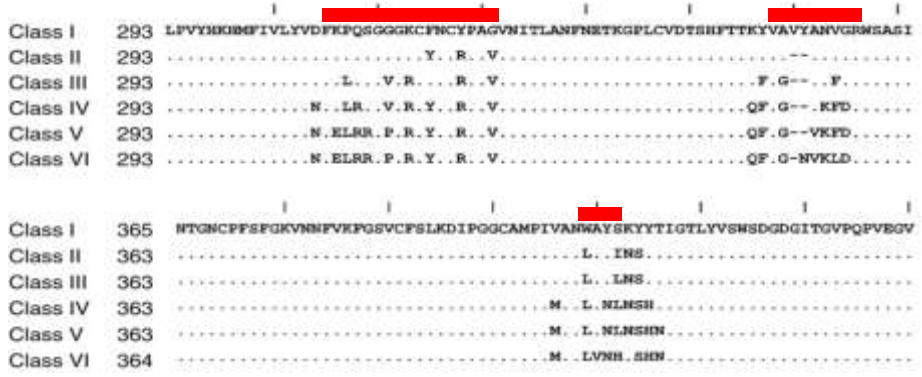
- Current genetic/antigenic variation is low in SARS-CoV-2
- How will it respond when population immunity builds up?

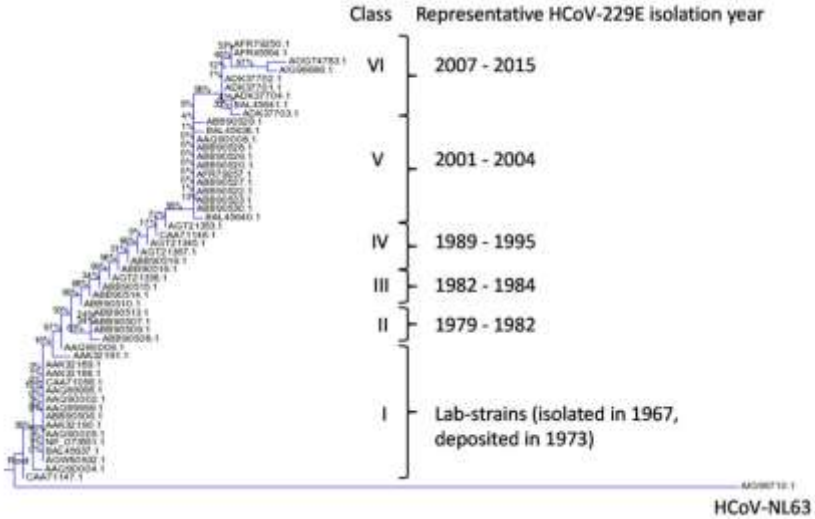
Genetic drift in HCoV-229E

Amino-acid sequence variation in 229E spike



229E RBD sequence variation in ~50 years





Wong *et al.,* (2017) Nat. Comm

Acknowledgements

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Frank Grosveld

ManCo Monoclonal Antibodies against Covid-19

ACZI
IN-ATAC

Health~Holland

ZAPI Zoonoses Anticipation and Preparedness Initiative

imi innovative medicines initiative

efpia European Federation of Pharmaceutical Industries and Associations

NCOH PhD Programme *'Innovative antibody-based strategies to combat future emergence of zoonotic viral infections'*

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