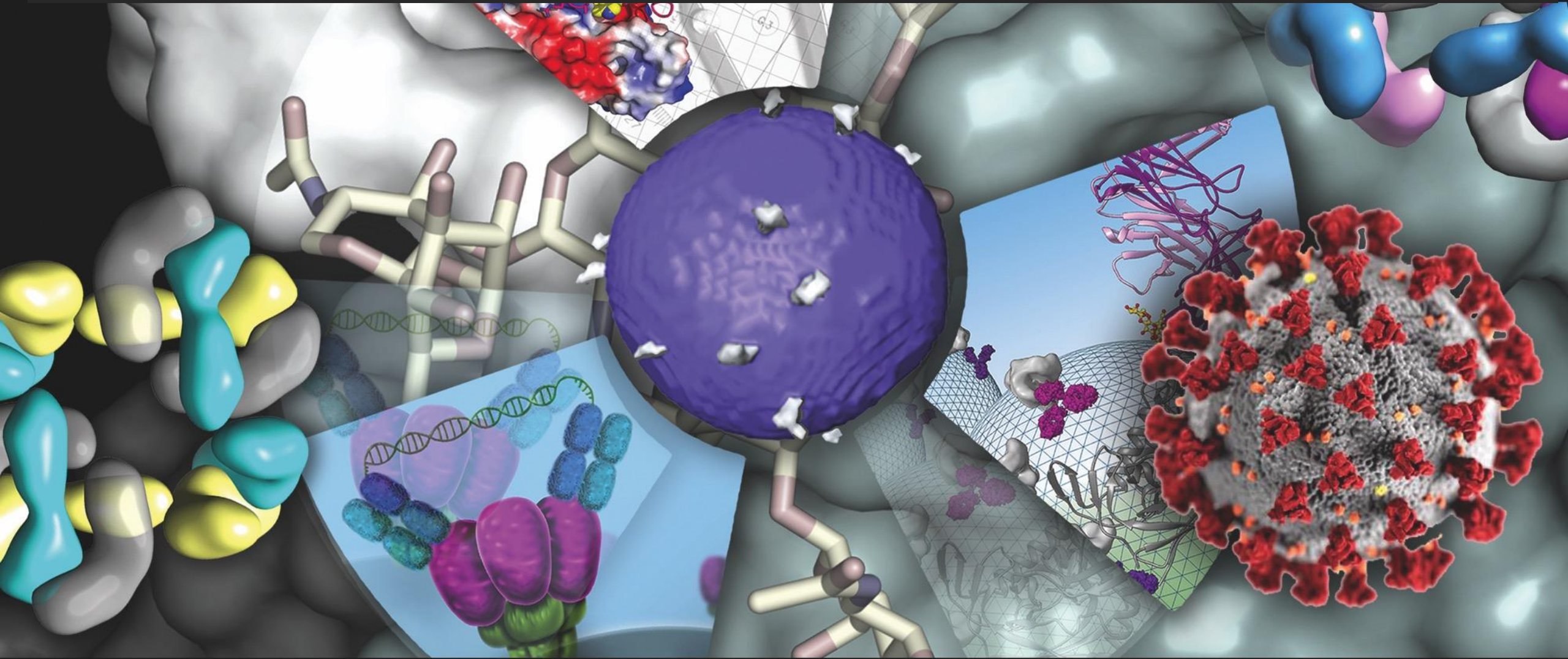


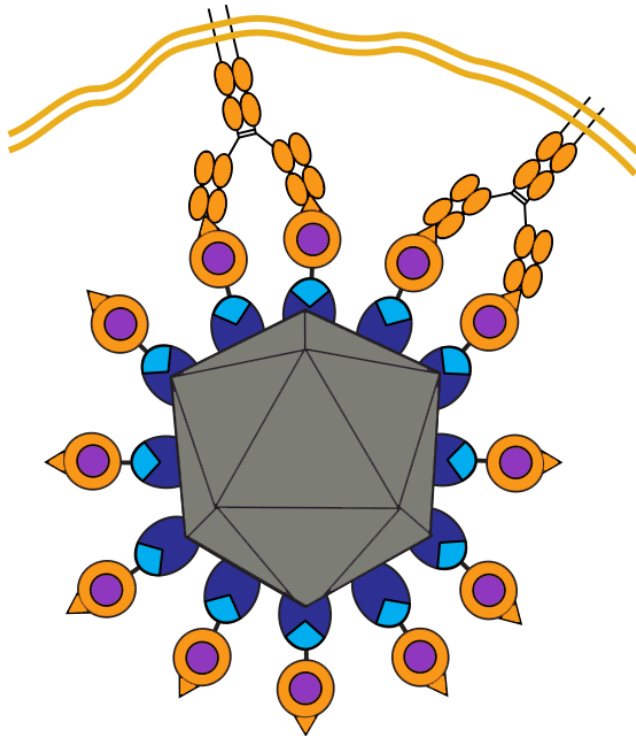
# Mosaic RBD nanoparticles protect against multiple sarbecovirus challenges in animal models



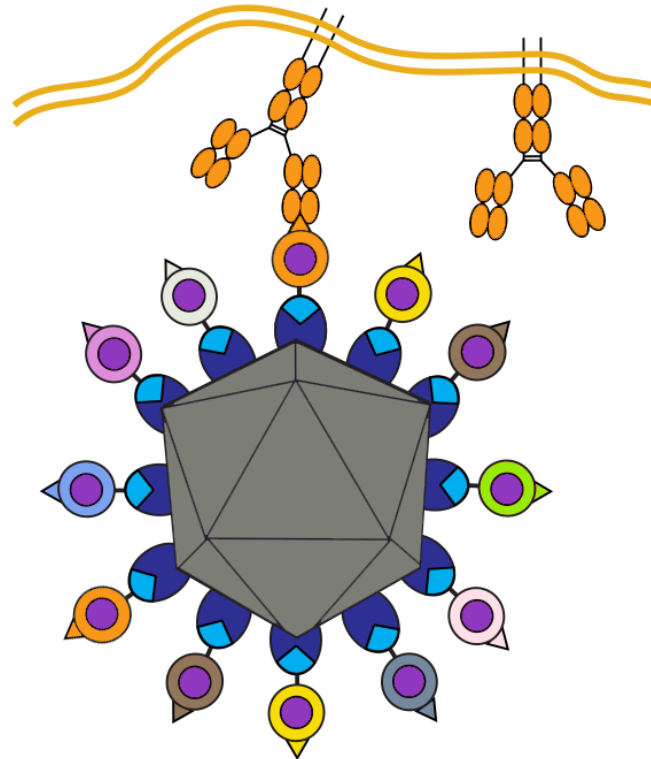
Pamela J. Bjorkman, Division of Biology and Biological Engineering, Caltech  
David Baltimore Professor of Biology & Biological Engineering; Merkin Institute Professor

**Mosaic Strategy:** Preferentially stimulate B-cells whose BCRs avidly bind to conserved epitopes shared by variable antigens. Spycatcher003-mi3 architecture displays diverse antigens randomly to promote avid binding to adjacent conserved epitopes.

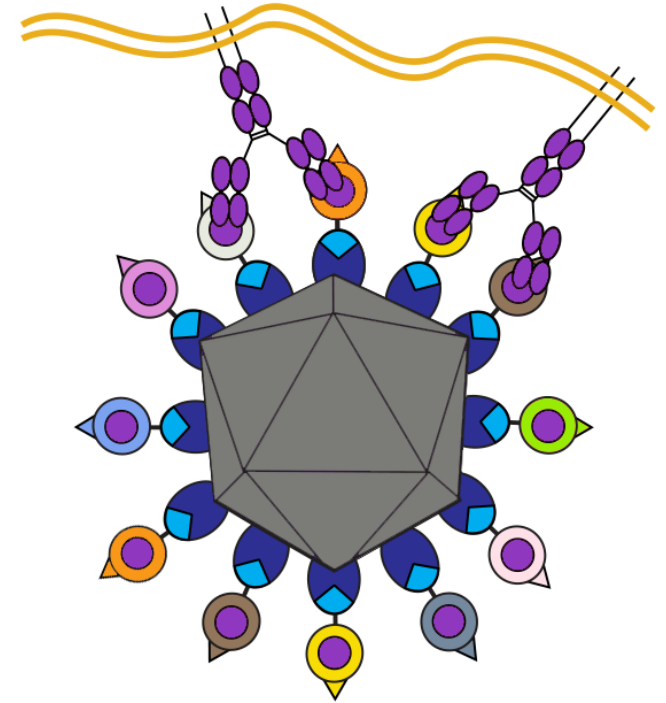
Clustered **orange BCRs** bind with avidity to a **strain-specific distracting epitope** (▲) on **orange antigens**. This B cell is stimulated to proliferate and make **strain-specific Abs**.



**Orange BCRs** cannot bind with avidity to **strain-specific distracting epitope** (▲) on **orange antigens**. This B cell will not be stimulated to proliferate to make **strain-specific Abs**.

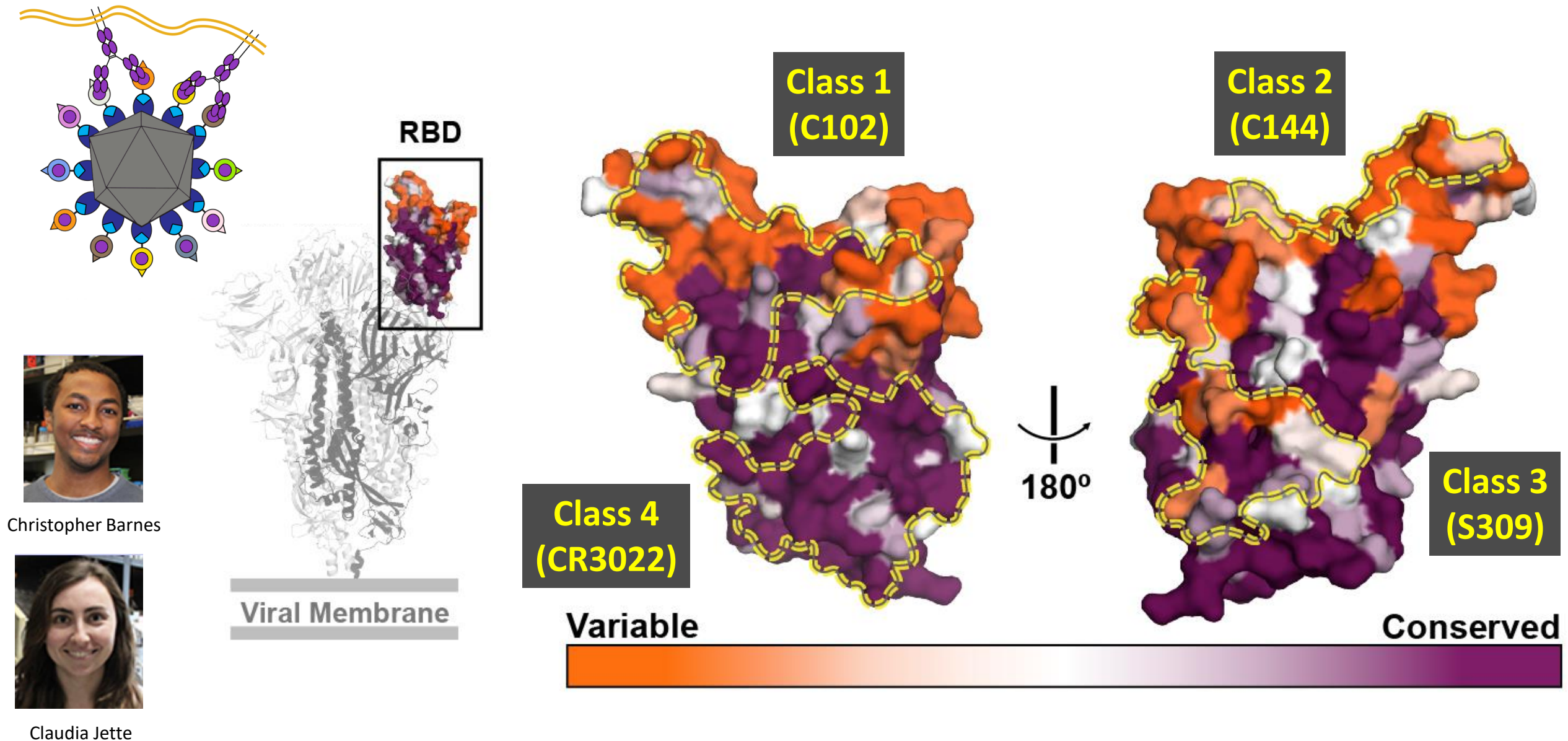


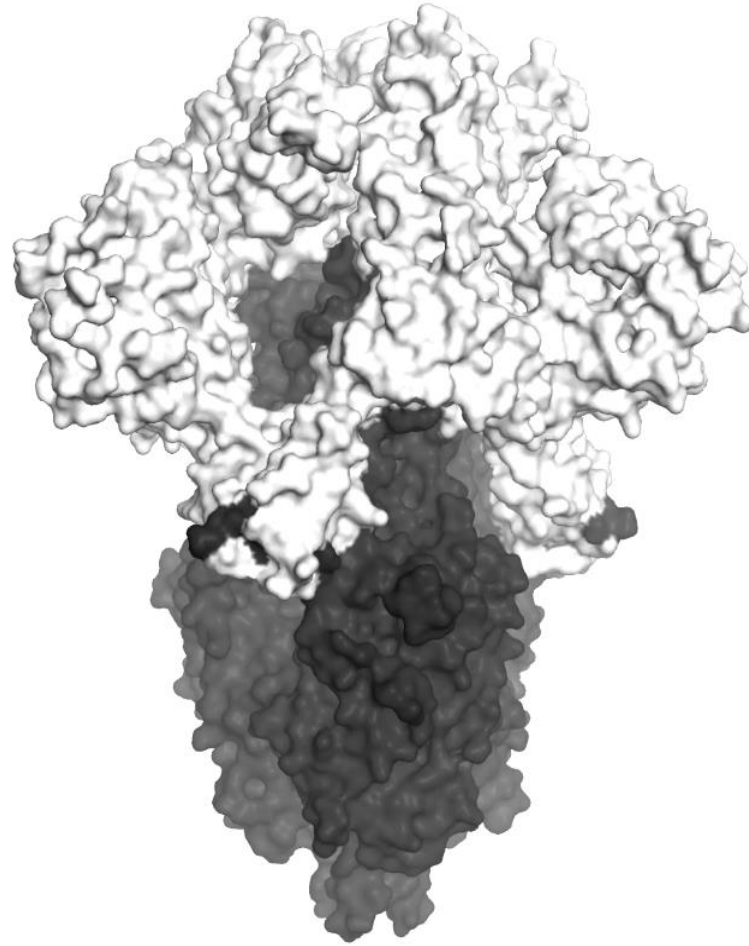
**Purple BCRs** can bind with avidity to desired epitope presented on multiple different antigens (●), but not to distracting epitopes (▲▲) This B cell will be stimulated to proliferate and produce **cross-reactive Abs**.





# Class 4 anti-RBD are more conserved than other Ab-binding regions





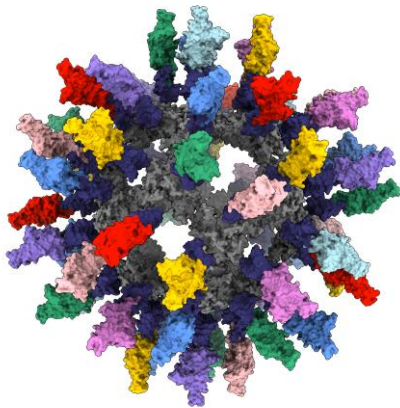
We are trying to target the base of the RBD (class 3 and class 4 anti-RBD antibody epitopes) that is more conserved than the immunodominant class 1 and class 2 epitopes overlapping with the ACE2 binding site that are less conserved and also accumulate mutations in SARS-CoV-2 variants.

# We chose RBDs from 8 sarbecovirus spike proteins for making nanoparticles, including RBDs from viruses with spillover potential

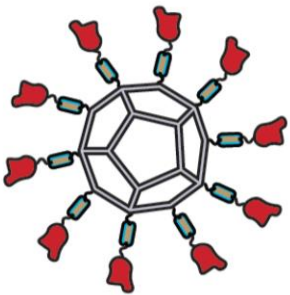
(from Letko et al., 2020, *Nature Microbiology*)

		Virus	Accession	Residue number	Clade	Host species
8	4a	SARS-CoV-2	MN985325.1	319-539	1b	human
		RaTG13	QHR63300	319-541	1b	<i>Rhinolophus affinis</i> (bat)
		SHC014	KC881005	307-524	1a	<i>Rhinolophus sinicus</i> (bat)
		Rs4081	KY417143	310-515	2	<i>Rhinolophus sinicus</i> (bat)
	4b	Pang17	QIA48632	317-539	1b	<i>Manis javanica</i> (pangolin)
		RmYN02	EPI_ISL_412977	298-503	2	<i>Rhinolophus malayanus</i> (bat)
		Rf1	DQ412042	310-515	2	<i>Rhinolophus ferrumequium</i> (bat)
		WIV1	KF367457	307-528	1a	<i>Rhinolophus sinicus</i> (bat)
Not included	Mismatched	SARS-CoV	AAP13441.1	318-510	1a	human
		LyRa3	AHX37569.1	318-511	1a	<i>Rhinolophus affinis</i>
		Yun11	JX993988	310-515	2	<i>chaerephon plicata</i> (bat)
		BM-4831	NC014470	310-530	3	<i>Rhinolophus blasii</i> (bat)
		BtKY72	KY352407	309-530	3	<i>Rhinolophus</i> sp. (bat)
		Khosta-2	QVN46569.1	309-531	4	<i>Rhinolophus</i> spp. (bat)
		RshSTT200	EPI_ISL_852605	317-539	1b	<i>Rhinolophus shameli</i>

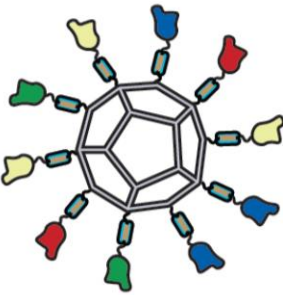
Amino acid sequence identity between these RBDs: 67-95%



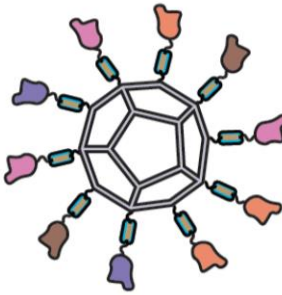
Alex Cohen  
Cohen et al., 2021, *Science*



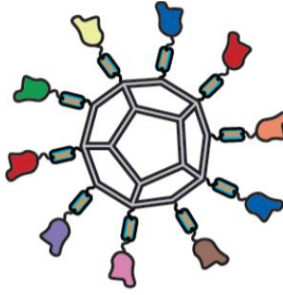
Homotypic



mosaic-4a



mosaic-4b

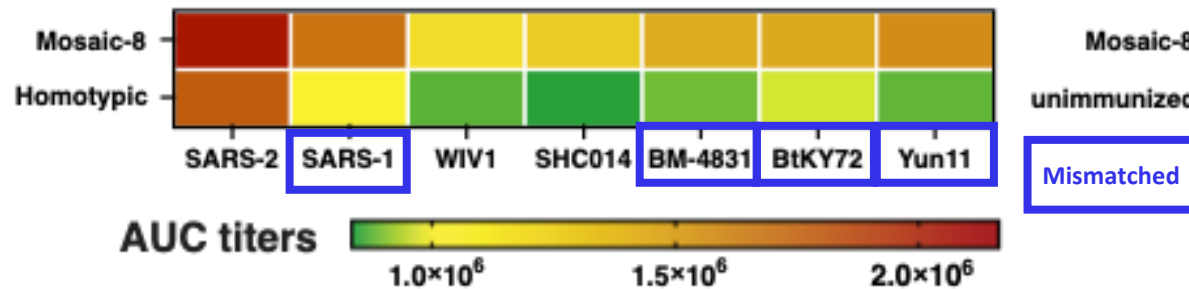


mosaic-8

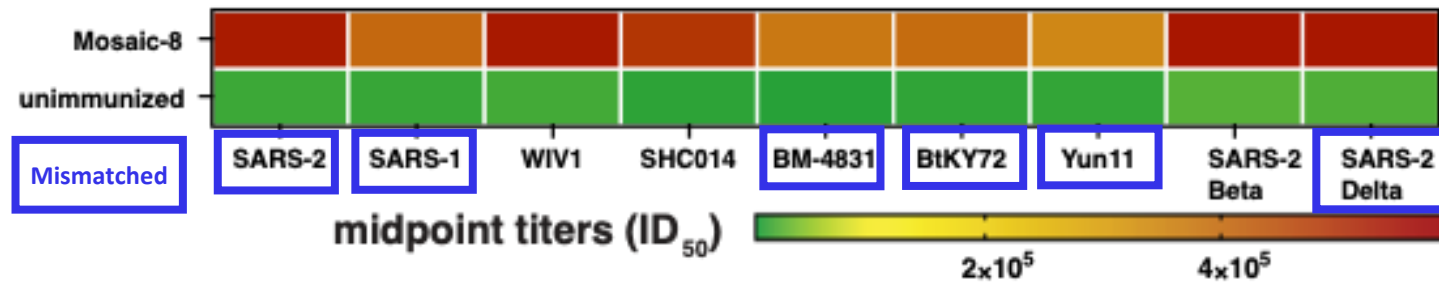
Look for “matched”  
and “mismatched”  
binding and  
neutralization  
responses.

# Mosaic immunizations in mice and NHPs elicit broad recognition of sarbecoviruses

Mean (n=10) AUC titer of mouse sera 28 days after boost 1



Mean (n=8) midpoint titer (ED<sub>50</sub>) of NHP sera 8 days after boost 1



Mean (n=10) neutralization ID<sub>50</sub> of mouse sera 28 days after boost 1

Vaccine Immunogen	SARS-2 D614G	SARS-1	WIV1	SHC014	SARS-2 Beta	SARS-2 Delta
Mosaic-8	5,400	1,800	2,600	15,000	2,400	1,130
Homotypic	5,600	410	370	340	3,300	1,680

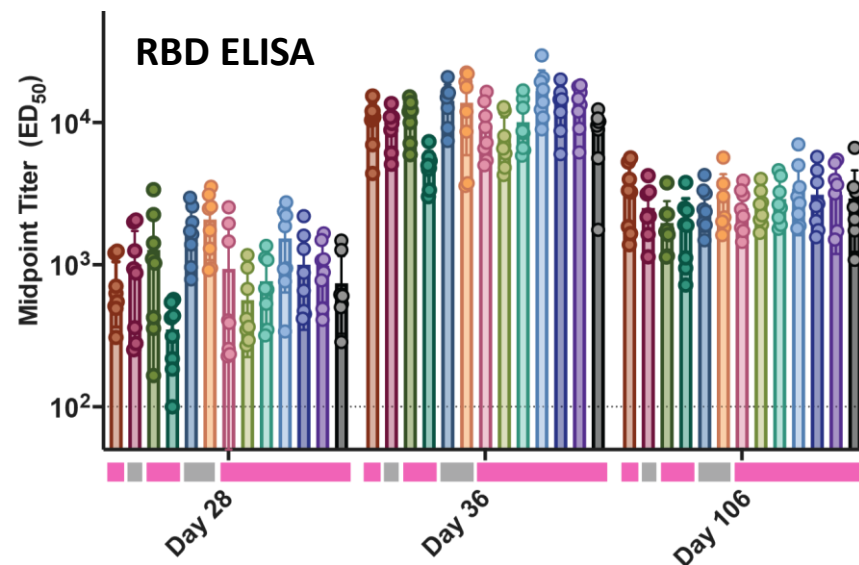
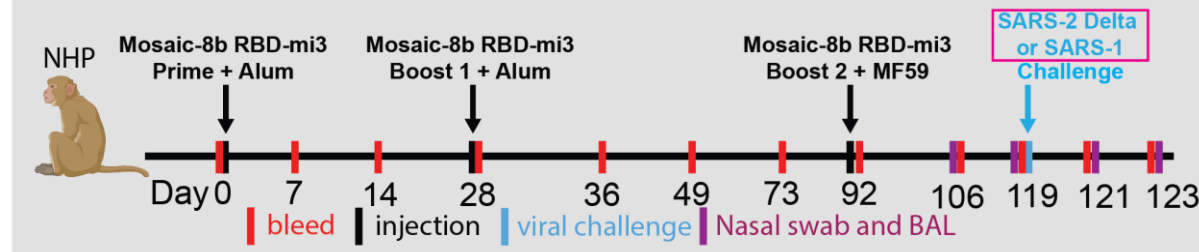
Mean (n=8) neutralization ID<sub>50</sub> of NHP plasma 8 days after boost 1

Vaccine Immunogen	SARS-2 D614G	SARS-1	WIV1	SHC014	SARS-2 Beta	SARS-2 Delta
Mosaic-8	320	2,200	4,490	12,000	680	500

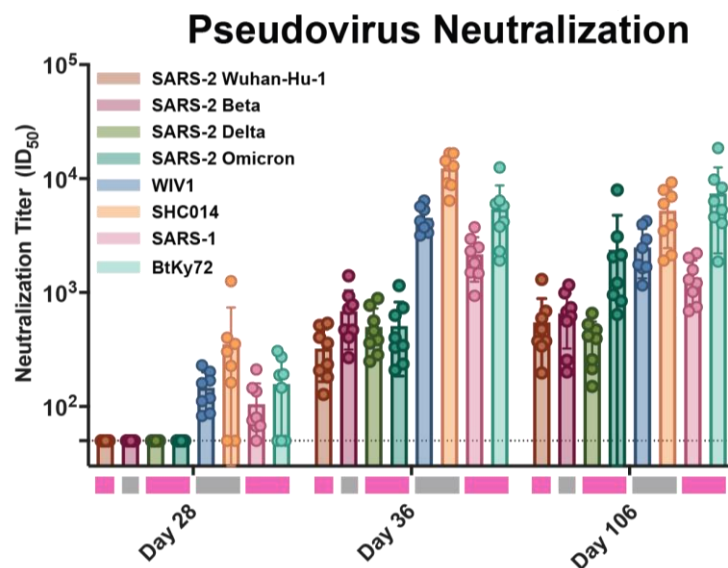
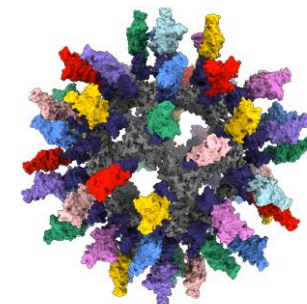
Neutralization ID<sub>50</sub> >10000 1000-10000 500-1000 100-500 <100



Mosaic-8 RBD-nanoparticle immunized NHPs raise cross-reactive binding and neutralizing antibodies that react with both matched and mismatched sarbecoviruses across different clades

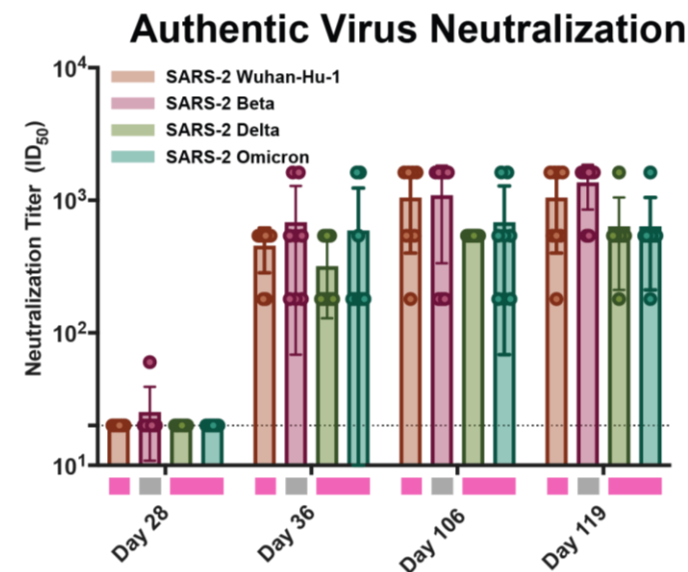


SARS-2 Wuhan-Hu-1	mismatched	1b
SARS-2 Beta	matched	1b
SARS-2 Delta	mismatched	1b
SARS-2 Omicron	mismatched	1b
WIV1	matched	1a
SHC014	matched	1a
SARS-1	mismatched	1a
BM-4831	mismatched	3
BtKy72	mismatched	3
Yun11	mismatched	2
RshSTT200	mismatched	1b
LyRa3	mismatched	1a
Khosta-2	mismatched	4



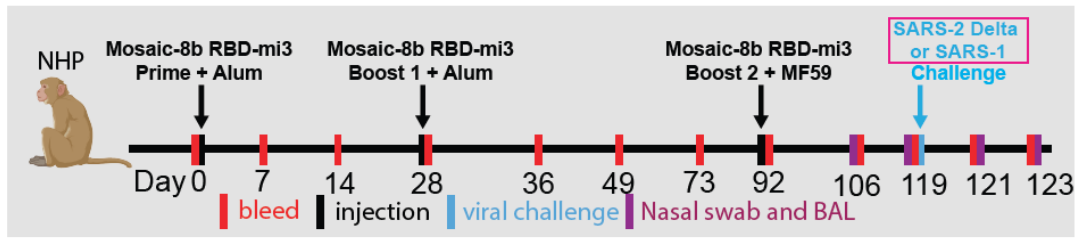
mismatched

matched

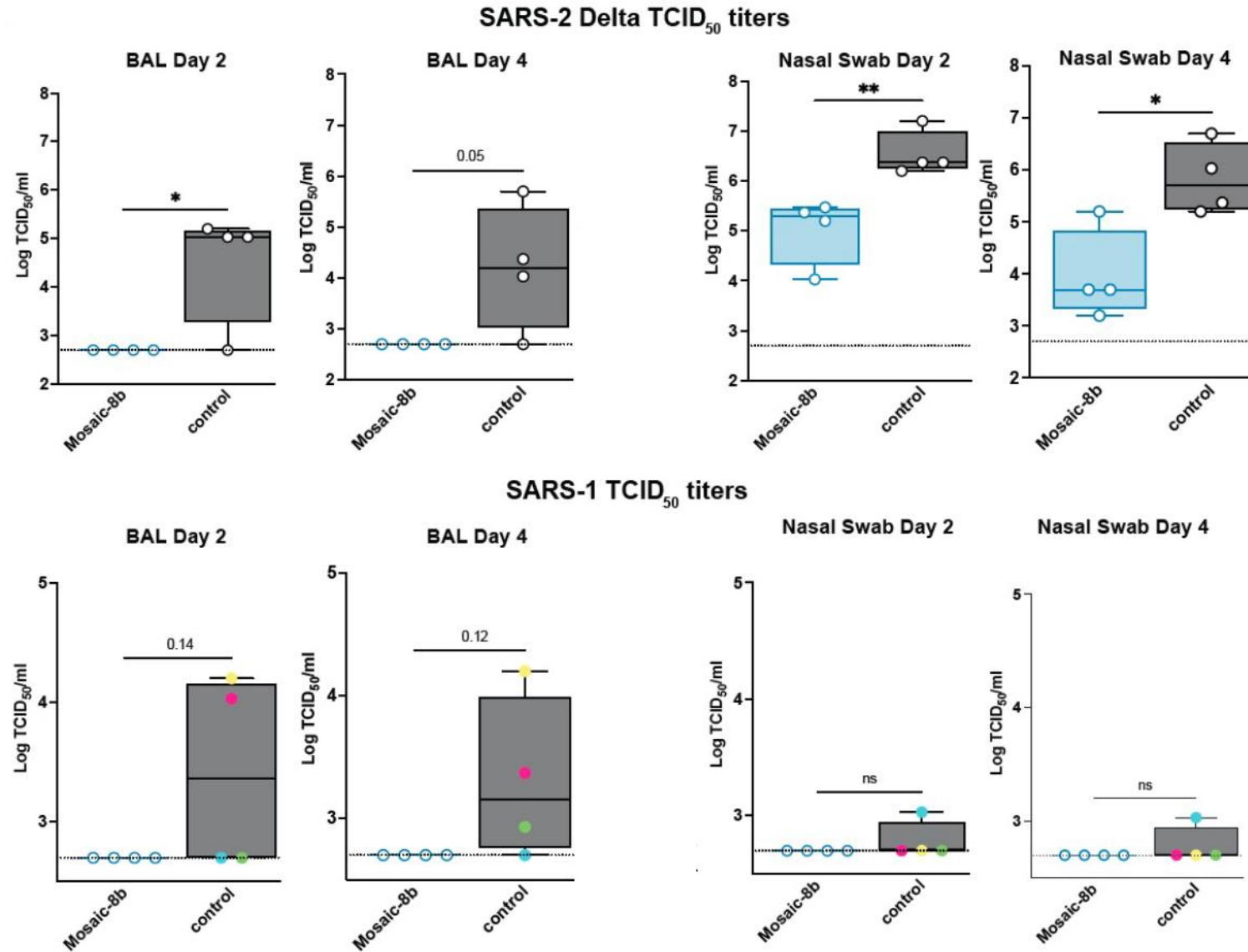


Alex Cohen

BIOQUAL  
Mark Lewis  
Hanne Andersen  
Ankur Sharma



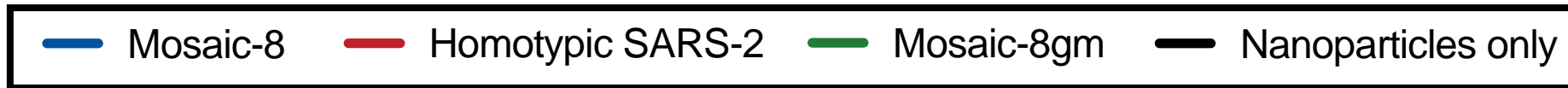
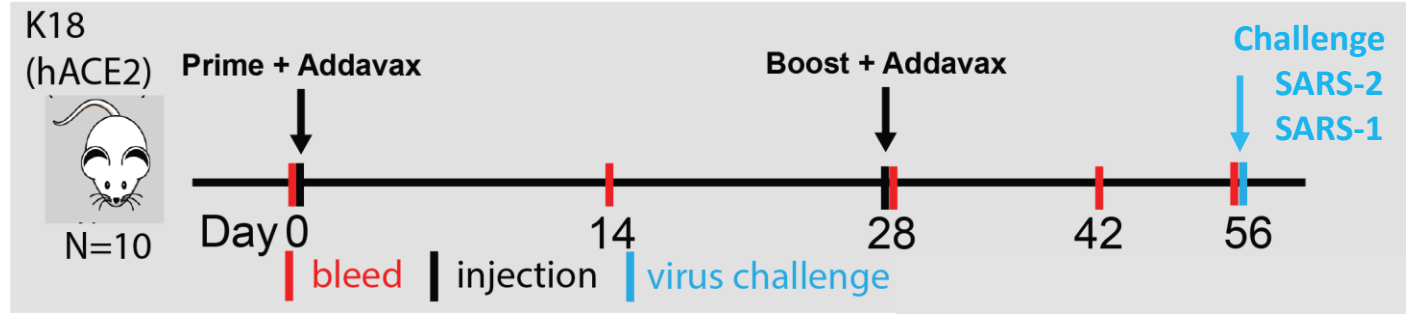
# Mosaic-8 nanoparticles protect against SARS-CoV-2 and SARS-CoV infections



Hanne Andersen  
Ankur Sharma  
Mark Lewis  
(BIOQUAL)



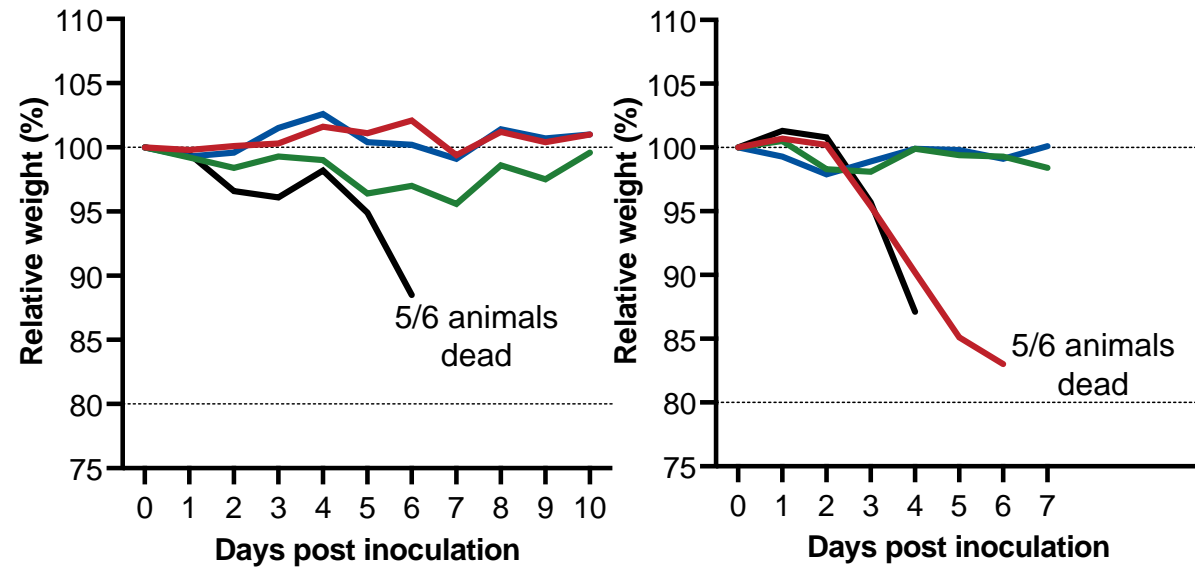
# Mosaic-8 nanoparticles protect against SARS-CoV-2 and SARS-1 infections



Relative weight post challenge

SARS-2 Beta

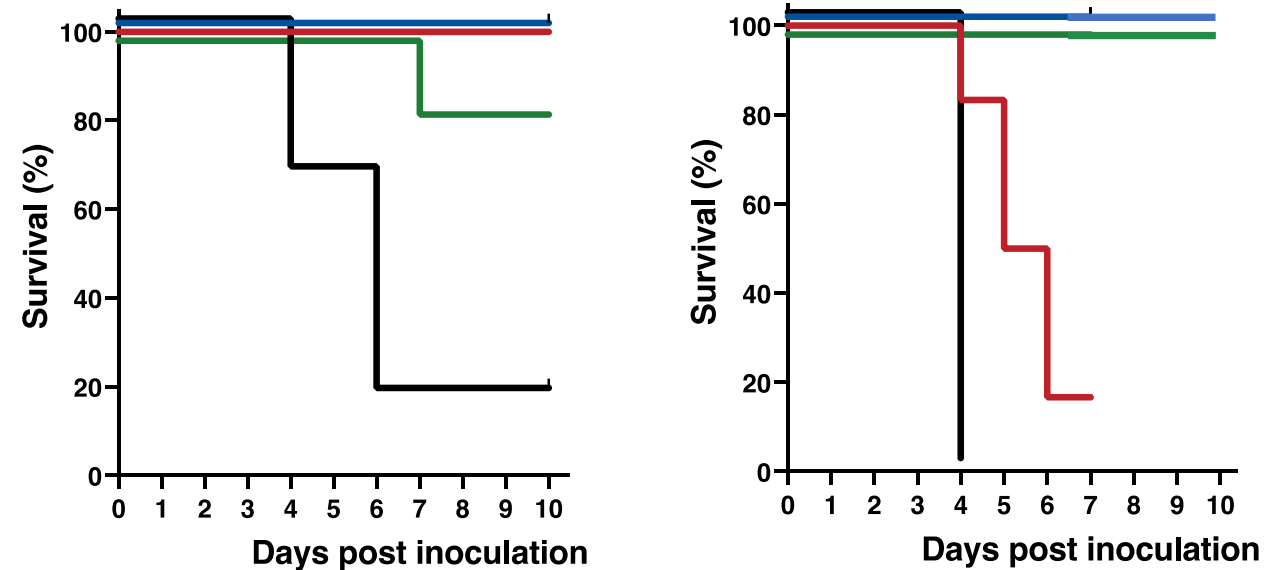
SARS-1



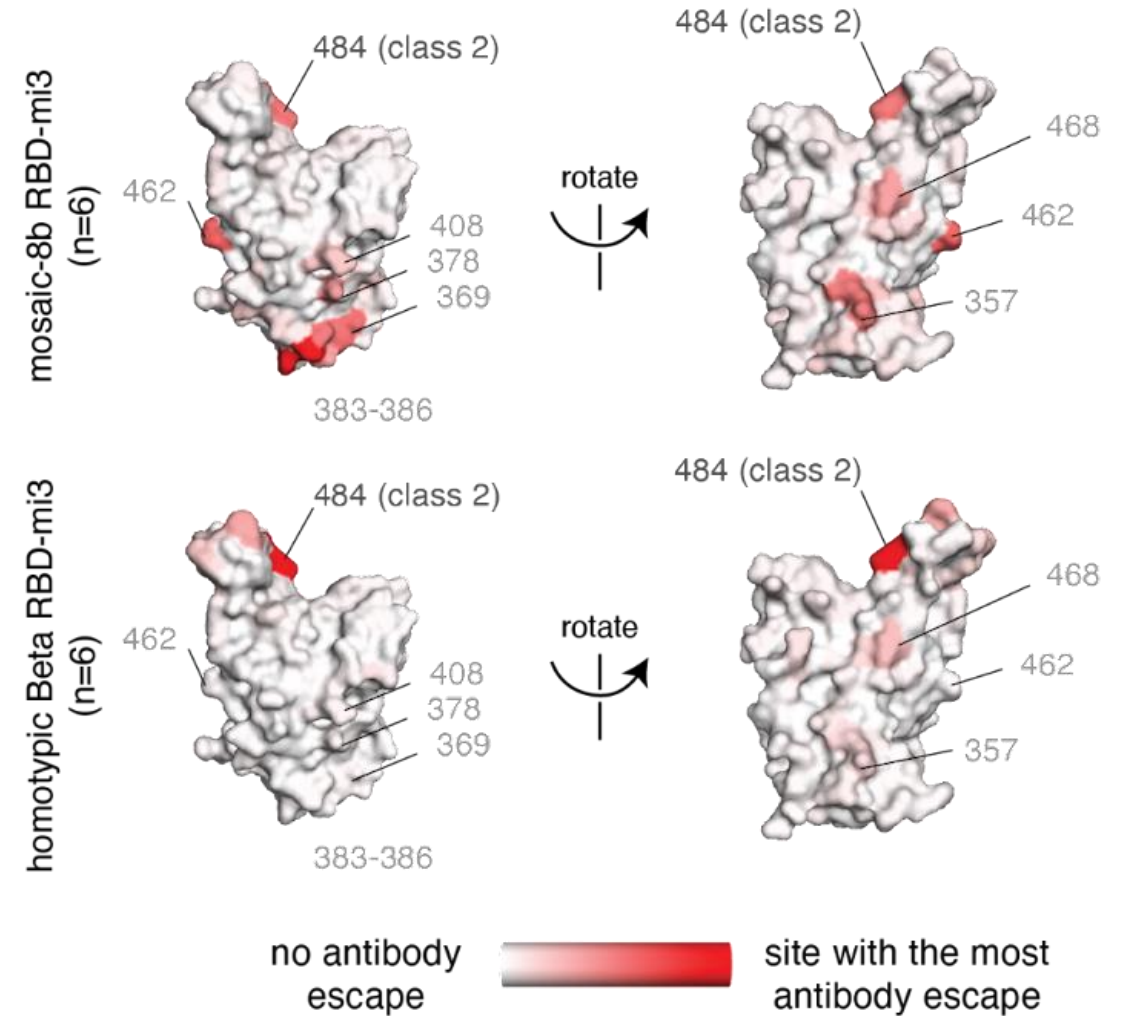
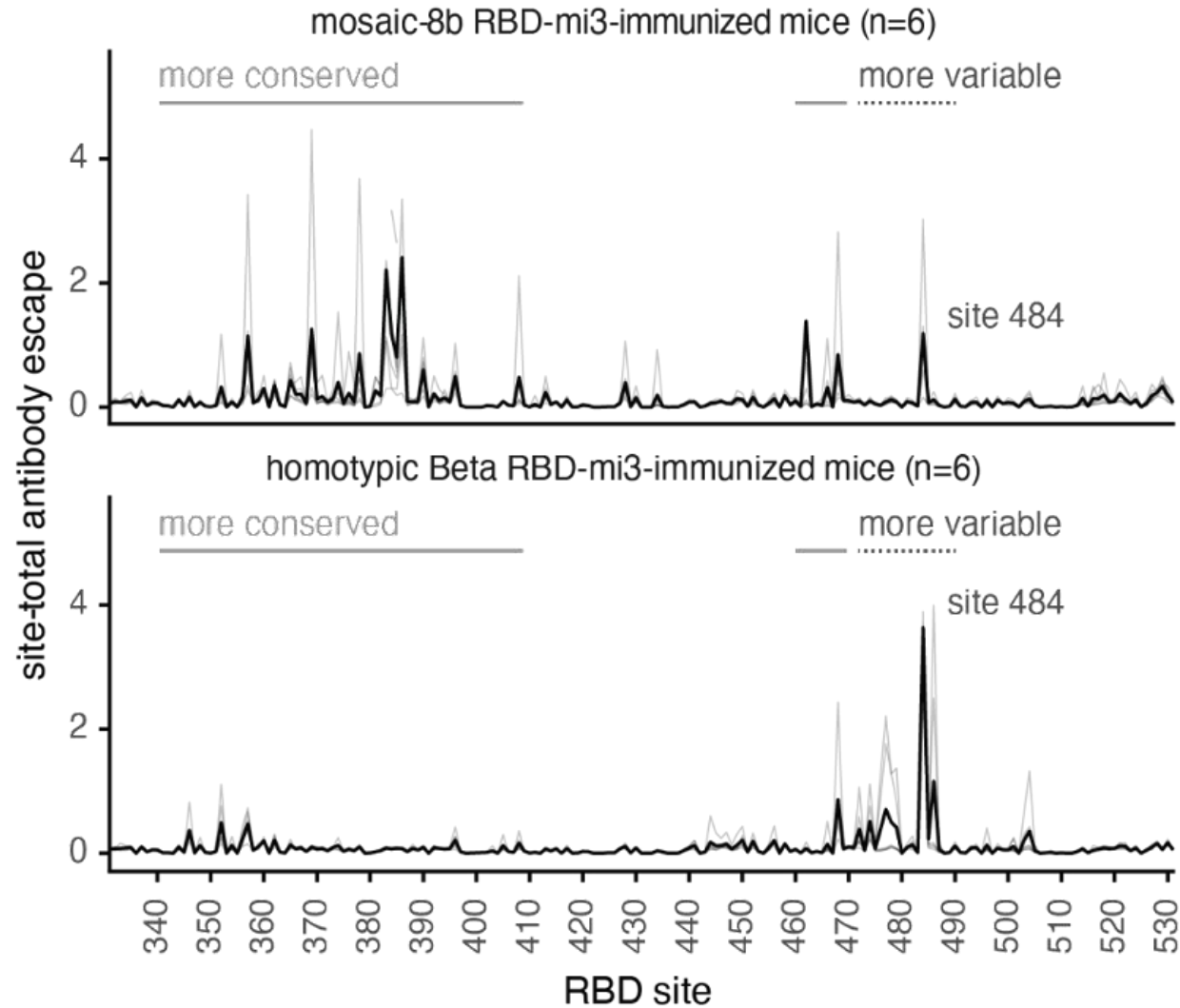
Survival post challenge

SARS-2 Beta

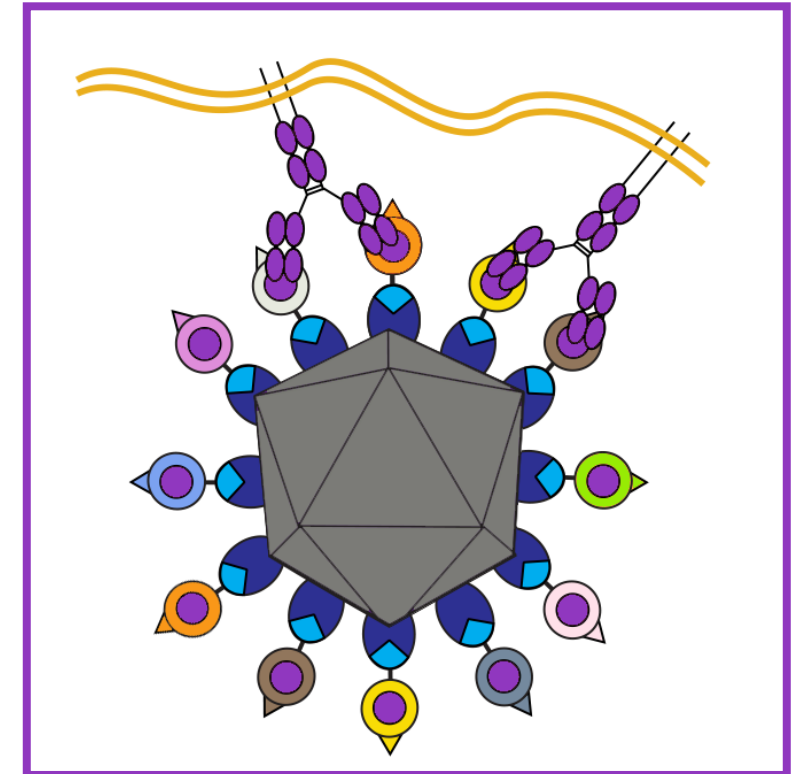
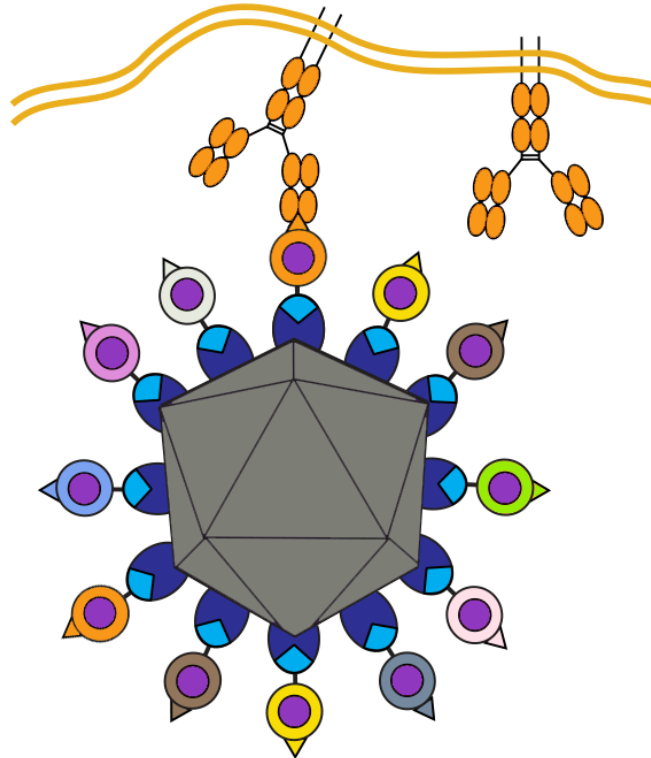
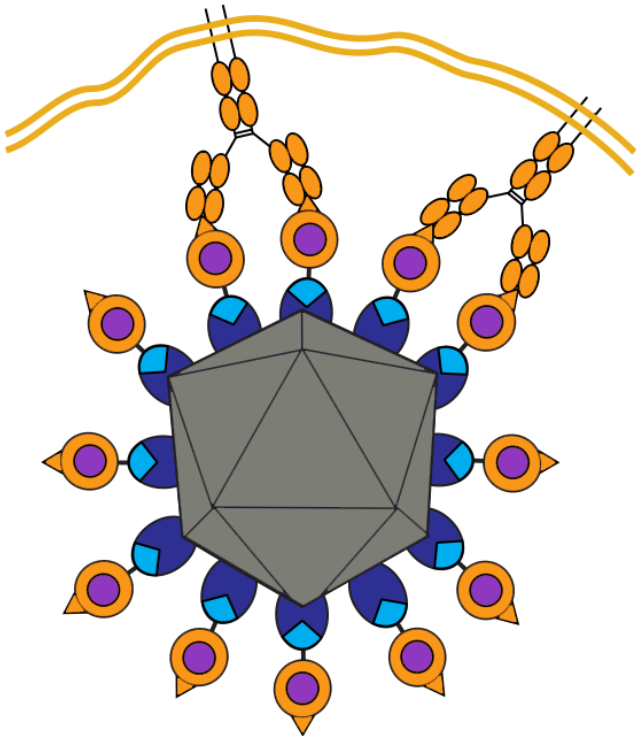
SARS-1



# Mosaic-8b and homotypic SARS-2 RBD-mi3 nanoparticles elicit Abs against different RBD epitopes

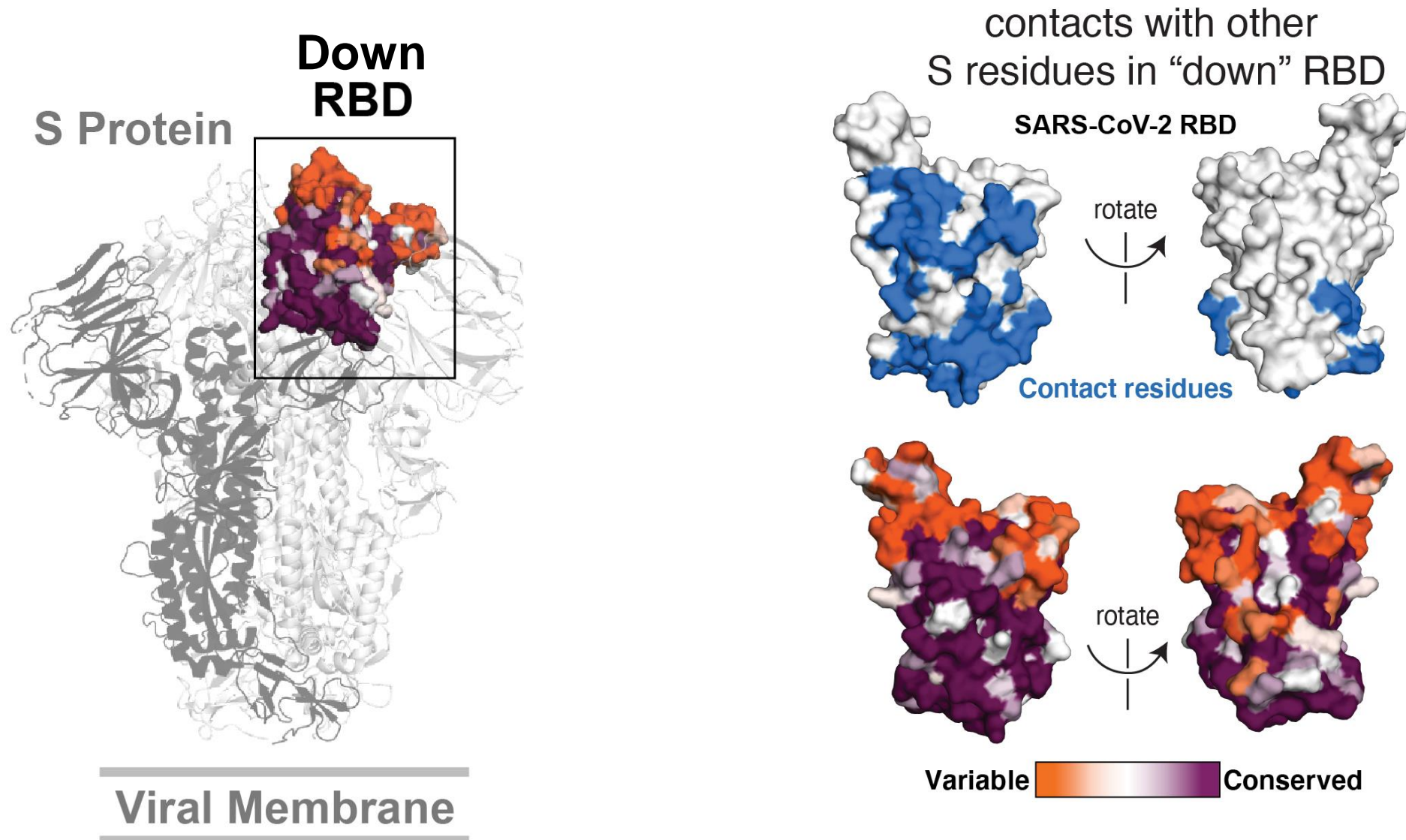


If you target the conserved (“purple”) RBD regions,  
will conserved regions begin to mutate?





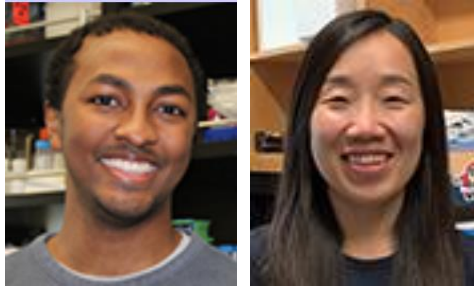
RBD regions conserved between sarbecoviruses and SARS-CoV-2 variants are involved in contacts within S trimer – they “should” remain conserved



# Acknowledgements

<https://twitter.com/bjorkmanlab>;

<http://www.its.caltech.edu/~bjorker/>



## CoV structural studies

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Hanne Andersen

Ankur Sharma

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