The CoVIC Consortium
Where we are, changes in the virus, immune defense

February 4, 2021
for Bernstein

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erica@lji.org

La Jolla Institute FOR IMMUNOLOGY | Life Without Disease.®

North Denmark in lockdown over mutated virus in mink farms

By JAN M. OLSEN November 6, 2020

COPENHAGEN, Denmark (AP) — More than a quarter million Danes went into lockdown Friday in a northern region of the country where a mutated variation of the coronavirus has infected minks being farmed for their f leading to an order to kill millions of the animals.

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RELATED TOPICS

Virus enters new host adapts to new cell new selection pressures

First Case of Covid-19 in a Wild Animal Found in a Utah Mink

The U.S. Department of Agriculture detected the infection while testing wild animals around a mink farm with a Covid-19 outbreak

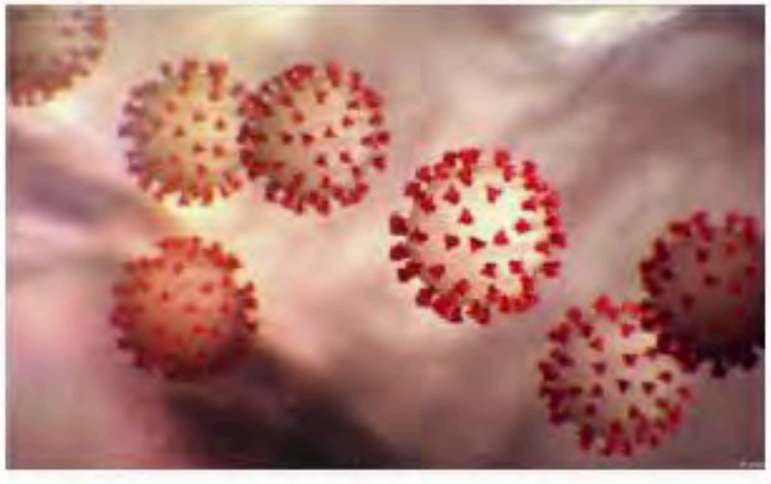
Variation develops in human-to-human transmission as well

As U.K. variant spreads in U.S ...
nbcnews.com

New York State: More cases of UK ...
newsday.com

U.K. Variant Could Drive A New Surge In ...
kpbs.org

South Africa's new Covid-19 variant ...
qz.com



South African COVID variant found in ...
dw.com

South Africa coronavirus variant: What ...
bbc.com

HIV-1, tuberculosis

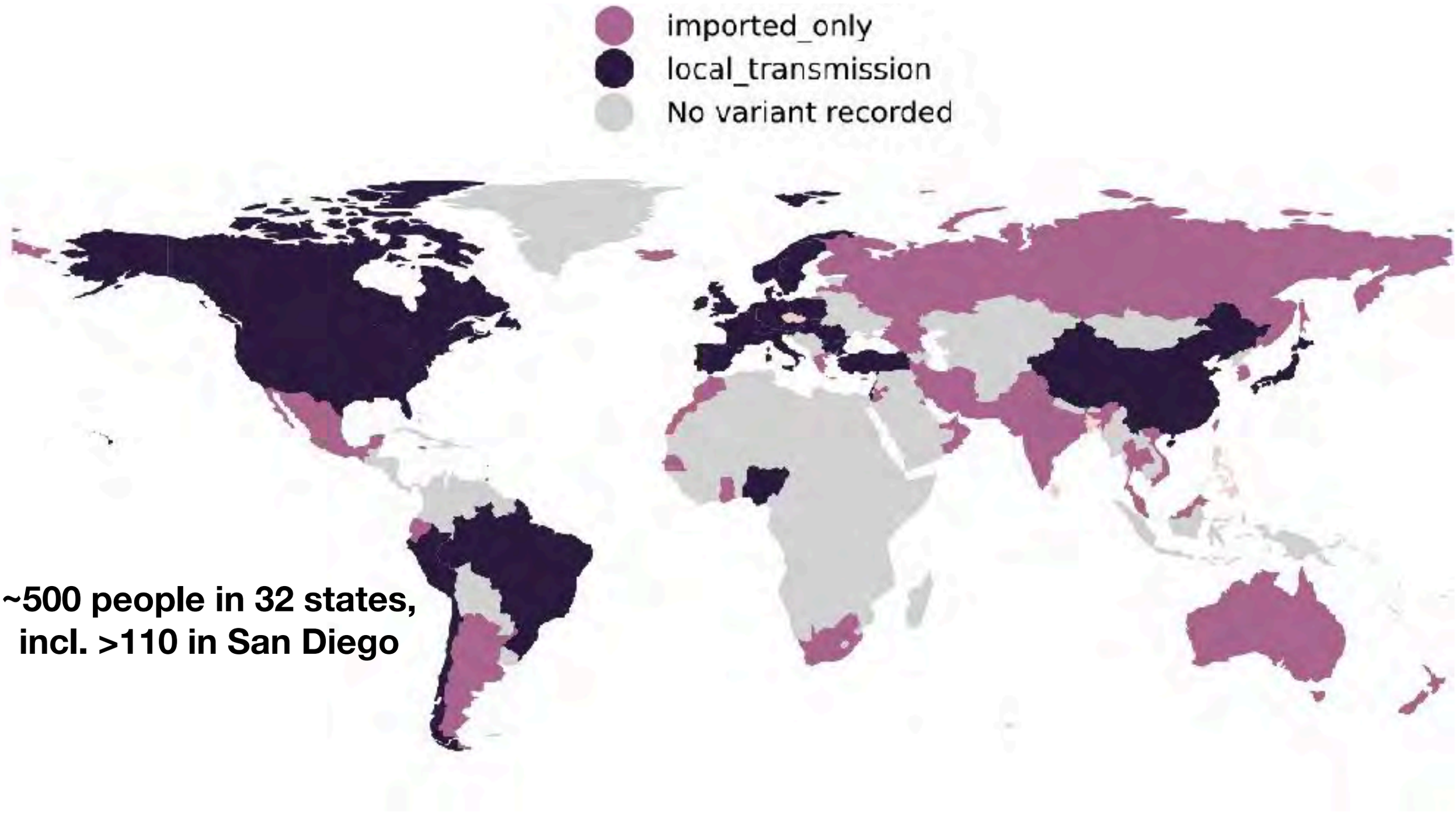
Chronic infection > more mutation > spillover into other humans

UK variant B.1.1.7

cov-lineages.org

Rambaut et al. Nature Microbiol. 2020

B.1.1.7
“UK” variant



~500 people in 32 states,
incl. >110 in San Diego

cov-lineages.org

Rambaut et al. Nature Microbiol. 2020

South African variant B.1.351

cov-lineages.org

B.1.351
“South African” variant

cov-lineages.org

Brazil variant appeared early December

UK: B.1.1.7

deletion 69-70
deletion 144
N501Y
A570D
D614G
P681H
T716I
S982A
D1118H

California: Cal.20C

S13I
W152C
L452R

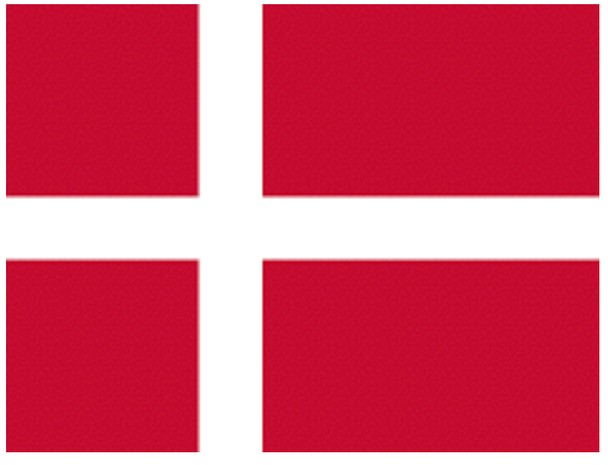
Brazil: P.1, B.1.148

L18F
T20N
P26S
D138Y
R190S
K417N/T
E484K
N501Y
H655Y
T1027I

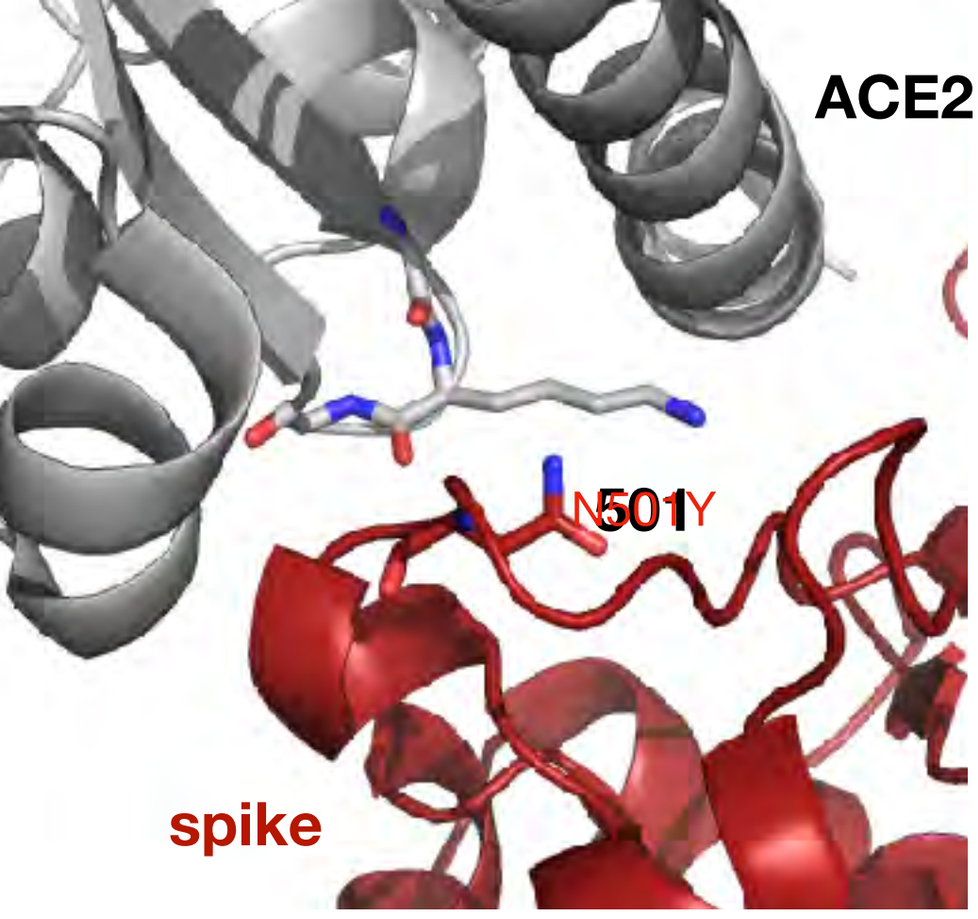
South Africa: B.1.351

L18F
D80A
D215G
K417N
E484K
N501Y
D614G
A701V

Denmark: cluster 5



deletion 69-70
G261D
V367F
N439K
Y453F
N501T
D614G
I692V
M1229I



position 501

multiple independent mutations

501Y in mice
501Y in UK
501Y in South Africa
501T in mink
501T in Denmark

Affords better binding of virus to ACE2 receptor
Greater infectivity
Could escape or outcompete some antibodies
Others will remain effective

H. Gu et al., Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. Science 369, 1603-1607 (2020).
T. N. Starr et al., Deep Mutational Scanning of SARS-CoV-2 Receptor Binding Domain Reveals Constraints on Folding and ACE2 Binding. Cell 182, 1295-1310 e1220 (2020).
Zhu et al., Cryo-EM Structure of the N501Y SARS-CoV-2 Spike Protein in Complex with a Potent Neutralizing Antibody. BioRxiv. (2020)

Which antibodies still work?

Q: Status of antibody consortium?

Coronavirus Immunotherapeutic Consortium

CoVIC

Global Collaboration
Antibody treatments against SARS-CoV2

Antibody therapy: immediate immune protection
prevent progression to severe disease
Good for: those not vaccinated, not yet vaccinated,
can't be vaccinated, in whom vaccines didn't "take"

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250+ therapeutic candidates and growing

Study antibodies contributed by:

Multinational corporations, Large and small biotechs, academics and nonprofits

Asia, Australia, North America, Europe

Data coordination with Operation Warp Speed, NIH, Gates

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CoVIC

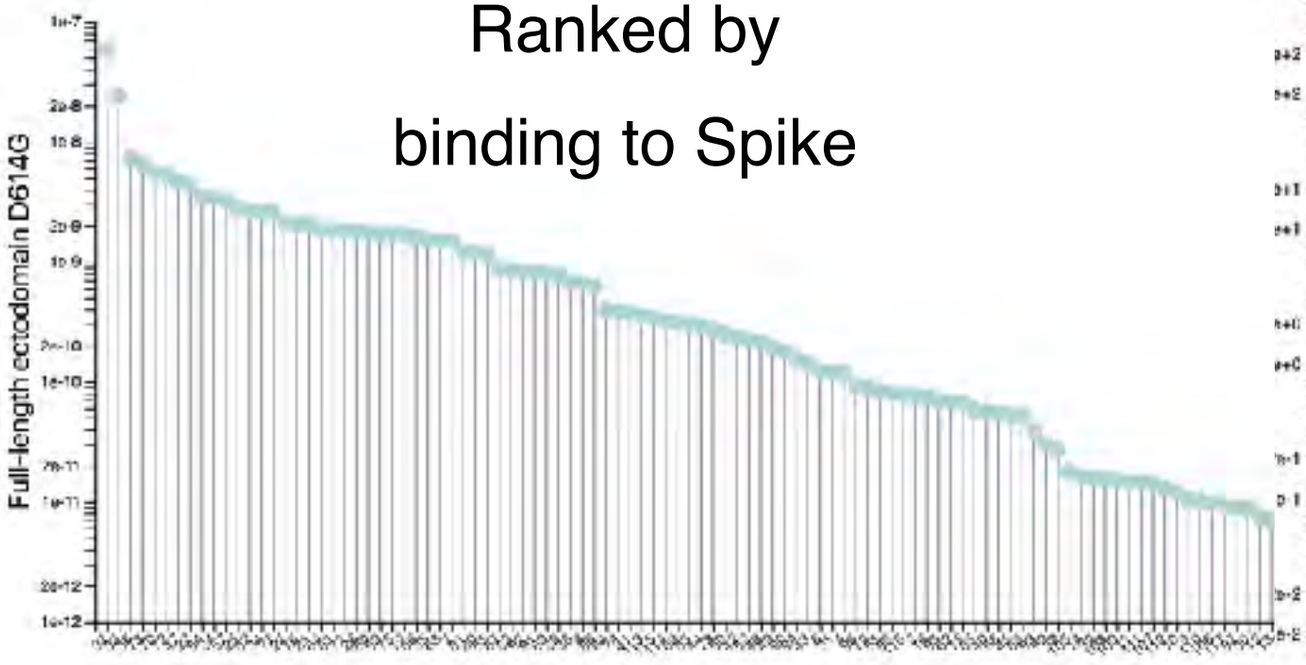
About · Partners Contribute mAbs **CoVIC-DB Database** News Support CoVIC Contact

CoVIC-DB Database

Welcome to the CoVIC Database. Here you'll find data collected by the partner reference labs for the antibodies in the CoVIC panel. New data will be uploaded on a rolling basis, so please check in frequently.

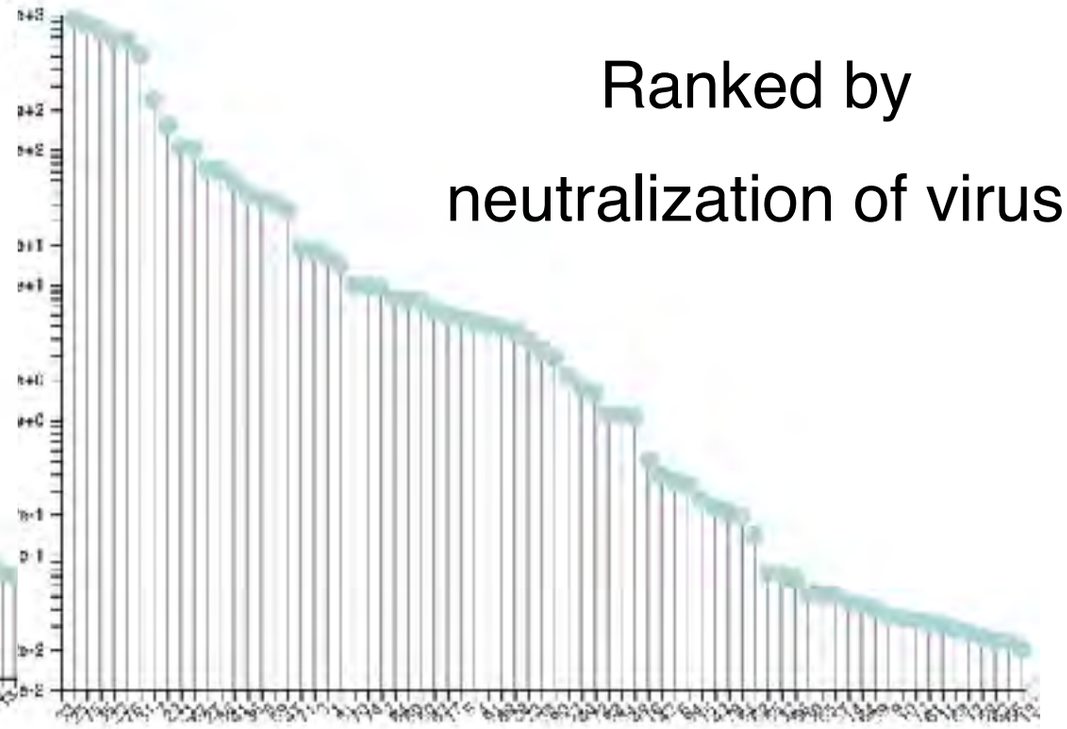
View data in the interactive graph and filter based on features of interest. The data are also available for download as a .csv file. Interactive tools will also be available in the coming weeks.

Contribute Data



Ranked by binding to Spike

Georgia Tomaras, Duke



Ranked by neutralization of virus

Luc Gagnon, Nexelis

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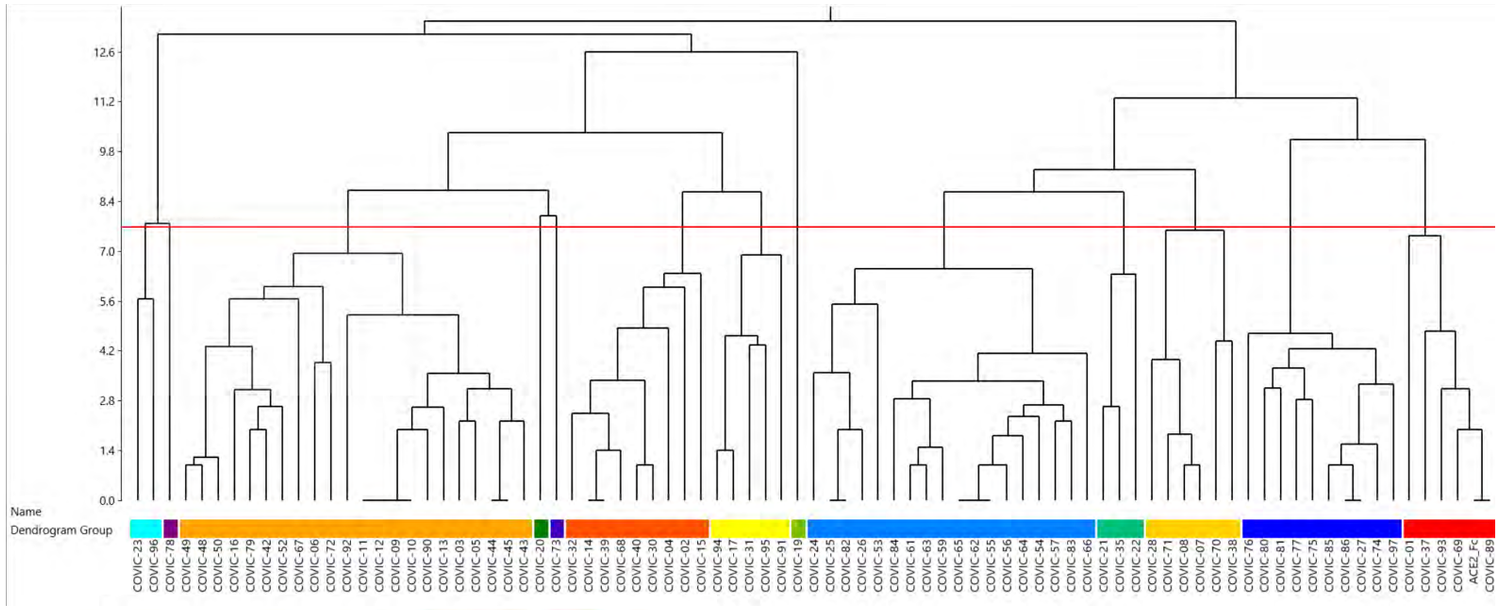
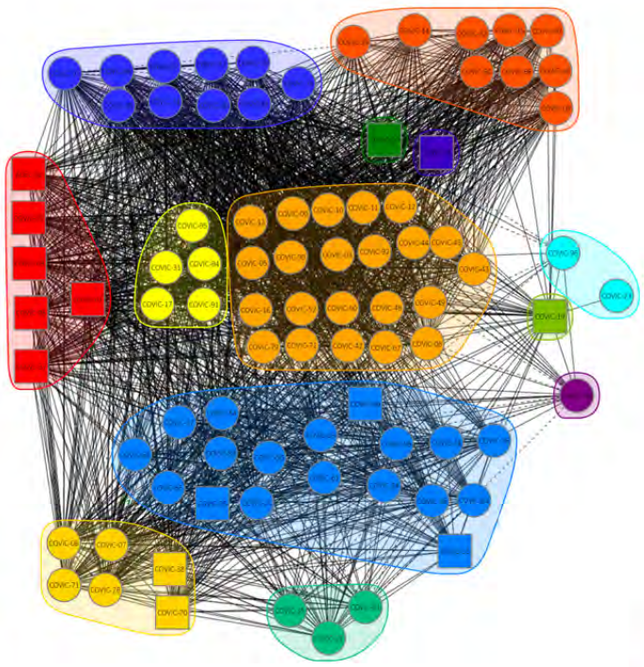
Database, LJI: Bjoern Peters, Randi Vita, Mari Kojima, Brendan Ha

Sorted by “footprint” on coronavirus spike





Carterra: Dan Bedinger

Saphire Lab: Haoyang Li

Xiaoying Yu, Tierra Buck

Adrian Enriquez

Sean Hui, Mike Norris

Sharon Schendel

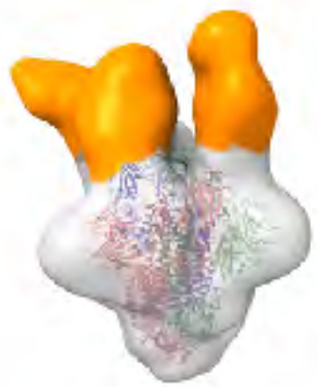
Eduardo Olmedillas

Vamsee Rayaprolu

Colin Mann, Ruben Diaz

Bin 1

Bin 2



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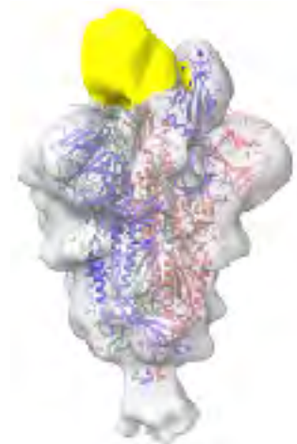
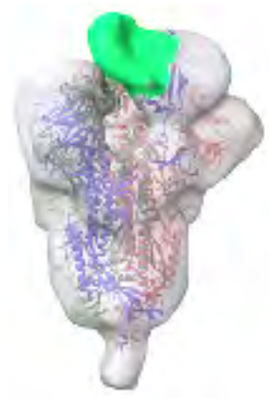
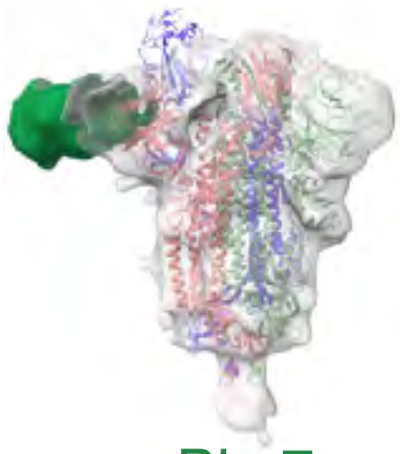


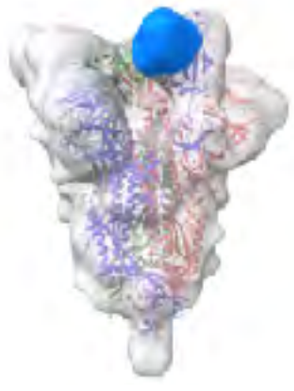
Bin 5



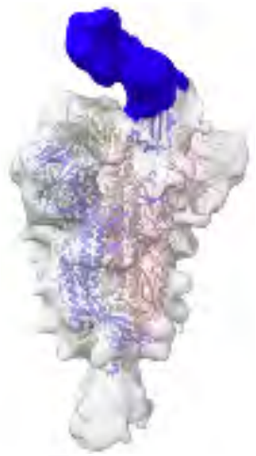
Bin 8



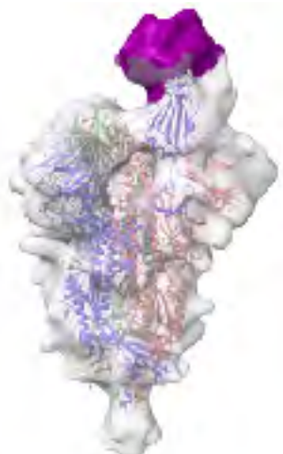
Bin 7



Bin 10



Bin 11



Bin 12

CoVIC

Framework to map which therapeutics to deploy

← Each individual mutation → combination

Epitope bin								
1	0.77	0.23	0.33	0.21	3.43	0.18	0.16	0.16
2	1.87	0.41	1.94	1.63	No Neut	1.68	0.58	No Neut
2	1.62	0.30	1.97	1.39	10.87	1.13	0.53	7.51
3a	1.02	1.00	1.16	1.55	4.99	1.13	1.00	133.01
3b	1.26	0.23	1.29	4.50	4.65	1.07	3.06	12.27
3b	1.57	0.28	1.19	2.80	No Neut	1.95	1.55	No Neut
4	1.49	32.30	60.60	3.42	0.83	3.83	0.96	2.75
5	0.87	0.33	4.68	2.36	0.43	0.45	0.90	0.40
5	1.20	0.69	1.18	1.35	0.92	1.00	0.75	0.66
7	3.97	1.33	1.77	1.83	1.45	1.85	2.24	2.28
8	*70%*	*90%*	*80%*	*70%*	*80%*	*70%*	*80%*	*80%* *
8	*30%*	*80%*	*40%*	*20%*	*30%*	*40%*	*40%*	*50%*
9	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*30%*
9	3.39	3.77	7.17	6.72	2.81	2.25	2.52	4.25
10	1.61	1.00	0.29	1.71	0.71	1.09	1.00	1.00
10	1.19	0.37	0.11	1.45	0.68	0.73	1.18	0.86
10a	NN	NN	NN	NN	NN	NN	NN	NN #
11	1.55	0.79	0.62	2.08	0.77	6.68	1.29	14.05
11	1.16	0.41	2.34	2.49	0.69	29.40	1.31	60.91
12	1.33	0.25	12.14	19.67	0.76	0.18	39.89	72.53
EOS-1A7 (RBD)	2.29	0.81	3.97	0.80	6.91	4.08	0.80	0.56
EOS 6C5 (RBD)	1.62	1.04	1.72	0.95	1.11	1.48	0.95	0.64
EOS-6A7 (NTD)	11.53	0.73	1.31	11.56	0.88	1.13	11.56	11.19

*Calculated IC50 value (μg/mL) is shown except when 100% neutralization was not achieved for wild-type or any mutant. For these entries, the maximal percentage neutralized achieved is shown.

NN= No neutralization of wild type

Antibody diminished/lost

Antibody activity improved

CoVIC

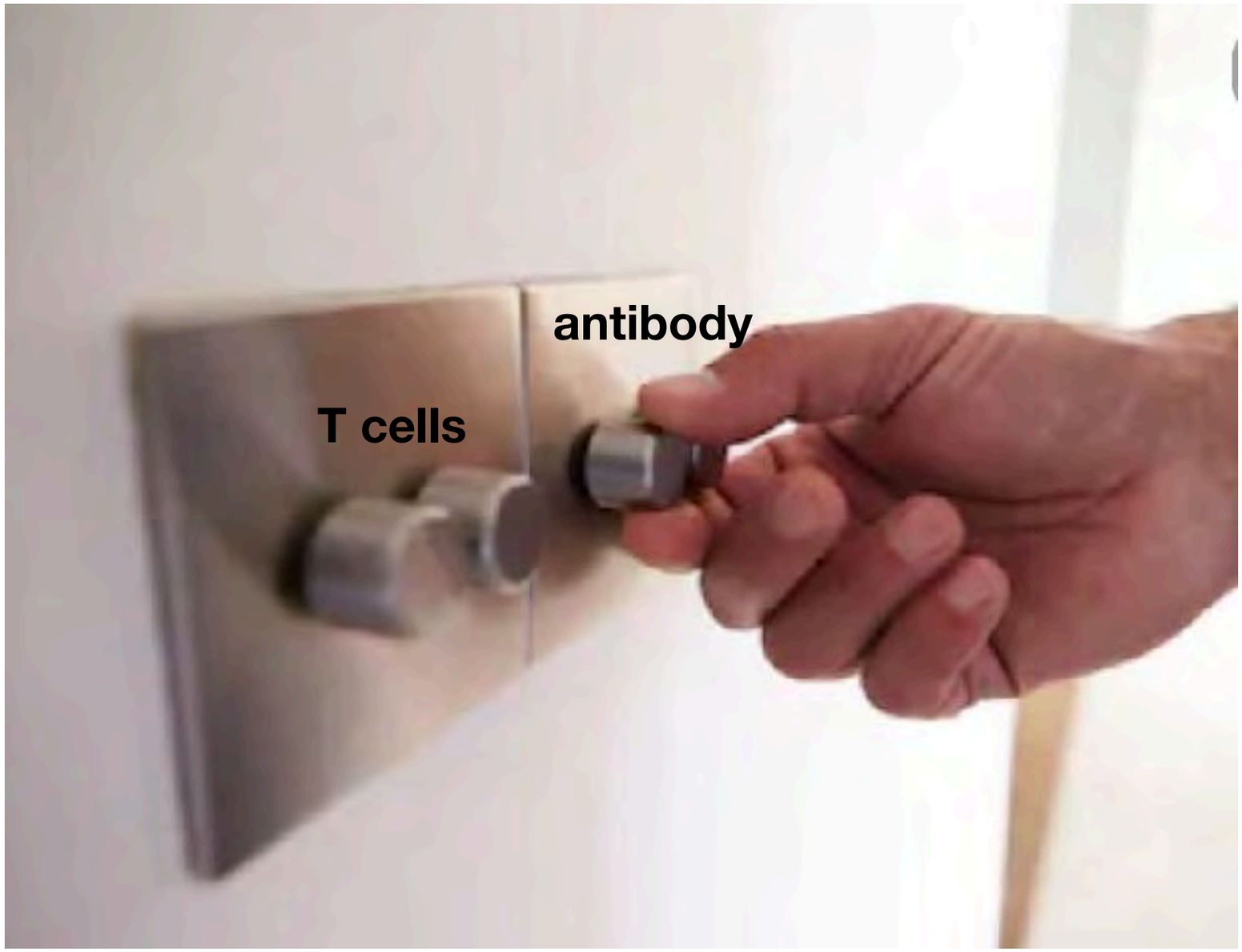
Q: Will vaccines still work?

Quintillion possible antibodies in sera.
Therapy: 1 or 2 super-potent antibodies. One or two footprints.
Vaccine: Thousands of antibodies of low-med-high, thousands of footprints.

Antibody response to infection/vaccination is not ON/OFF

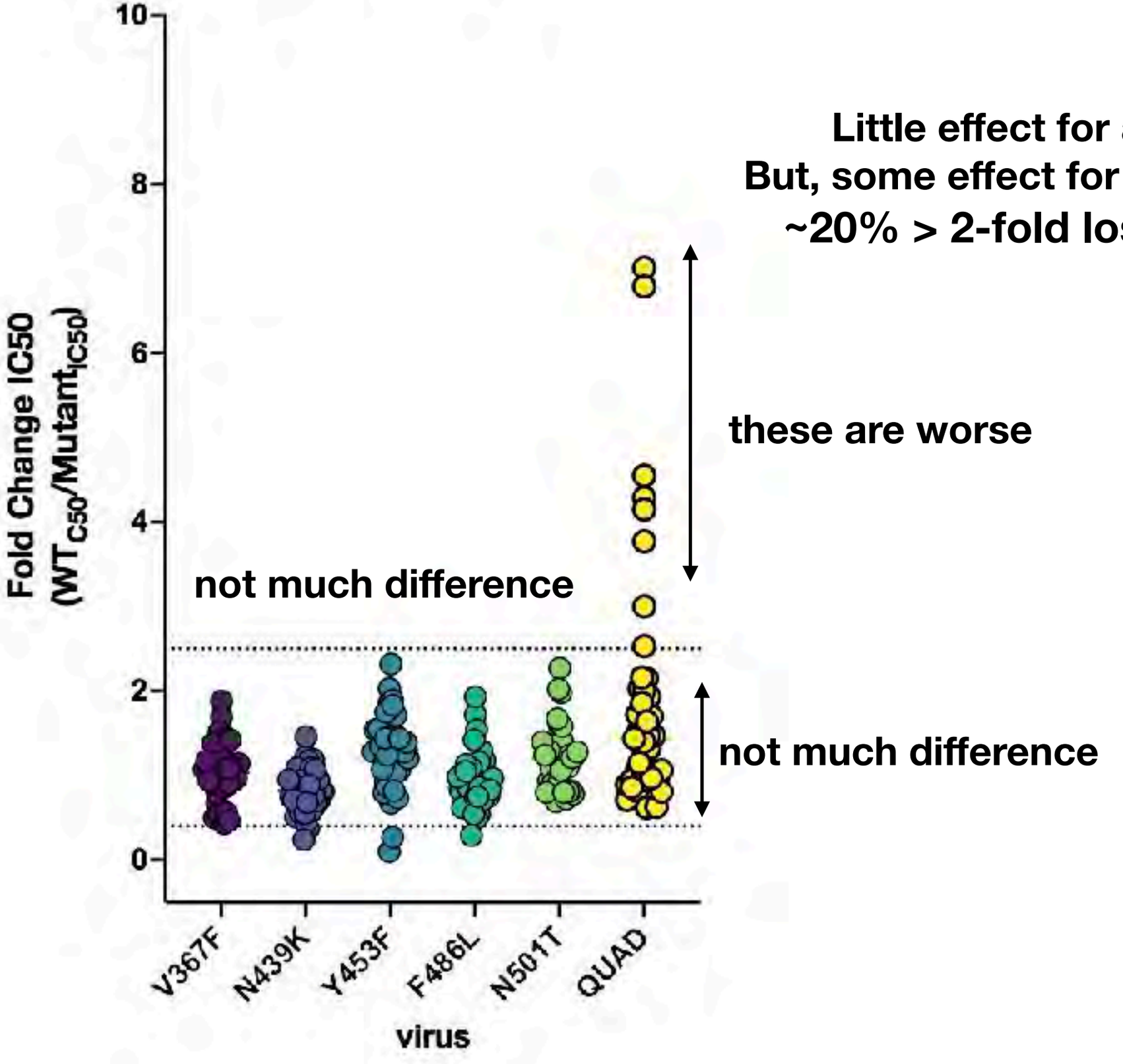
More like a dimmer switch

Or a panel of dimmer switches



**48 convalescent sera from San Diego,
of which 40 are neutralizing.**

**Little effect for any one mutation.
But, some effect for cumulative mutations.
~20% > 2-fold loss of neutralization**



CoVIC

Q: Should I get a vaccine if the virus is changing?

No vaccine

The switch is “off”

With vaccine

Perfect match

No vaccine

With vaccine

The switch is “off”

Perfect match

Mutation cluster

Moderna: “No reduction with UK. 6-fold reduction for South African, but still above level expected to be effective.”

Q: Side effects? = effects

You want to have an immune response.

(Sore arm, some fatigue, etc.)

Q: Allergic reactions?

2 cases out of a million for Moderna

6 cases out of a million for Pfizer

Q: If you have been infected before, can be re-infected?

Q: If you have been infected before, can you still spread it?

Study among UK health care workers:
44/6614 got re-infected in 5 months
0.7%
(might increase with new variants)

Study among 18-20 yr old Marines:
Tested them all, quarantined two weeks, negative upon release to boot camp.
48% of seronegative new recruits became infected in 6 weeks
10% of seropositive recruits got re-infected

The re-infected people resolved disease faster than first-time infections.
Those with initial lower level of antibody were more like to be re-infected.
https://www.medrxiv.org/content/10.1101/2021.01.26.21250535v1.full.pdf

Q: Should you be vaccinated if you've already had COVID-19?

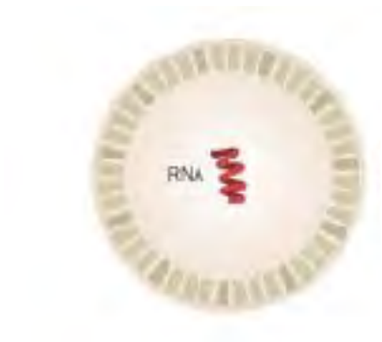
Q: Which vaccine should I get?

Pfizer/BioNTech
95% effective.
30 micrograms.
2 shots, 21 days apart

Moderna
94% effective.
100 micrograms
2 shots, 28 days apart.
Efficacy slightly lower in older people, but small statistical sample

Both need extensive cold chain.

Moderna and Pfizer are RNA vaccines.



Only the RNA encoding spike (and only spike) is delivered, in a lipid particle for stability.

- **Not the other 28 components of the virus. Just the most important one. Not possible to make a virus or establish an infection from it.**

- **RNA is transient:**
  Snapchat message. Vanishes after a while. This is not gene therapy.

- **DNA makes up your genes. RNA makes up temporary messages.**
  Adding DNA: adding a new ingredient in a recipe.
  Adding RNA: adding a temporary page into your cookbook.
  Doesn't change the other recipes.

- **Cheaper than other kinds of vaccines.**
- **Faster to make - more responsive.**
  Year-long process for flu vaccines can lead to poor matches.
- **The main worry was that it wouldn't work.**
- **New advances: lipid packaging, modifications to limit immune stimulation.**

Johnson and Johnson
one shot, viral vector

Gene encoding spike,
delivered by a harmless viral carrier (adenovirus)

Overall:
66% effective against infection
85% effective against disease

Note: Multicountry study (different variants)
72% effective against infection in the US
57% effective against infection in South Africa

testing a two-shot regimen with results expected in May

Q: Which vaccine should I get?

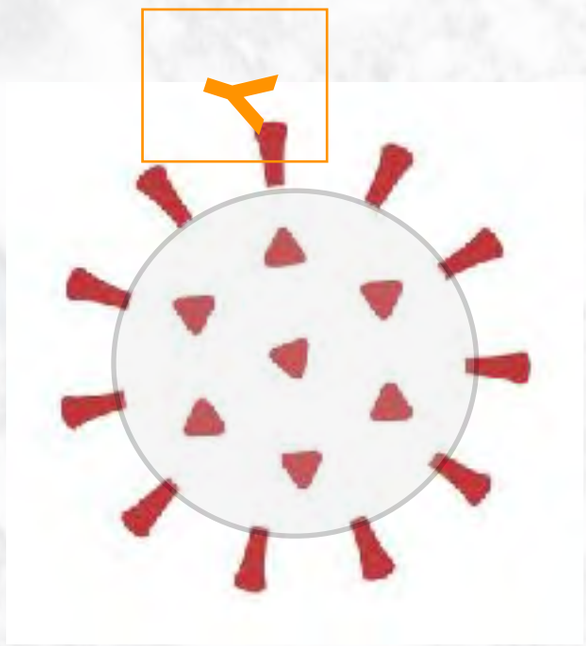
Q: Which vaccine should I not get?

Q: Tell me about the Chinese/Russian inactivated vaccines.

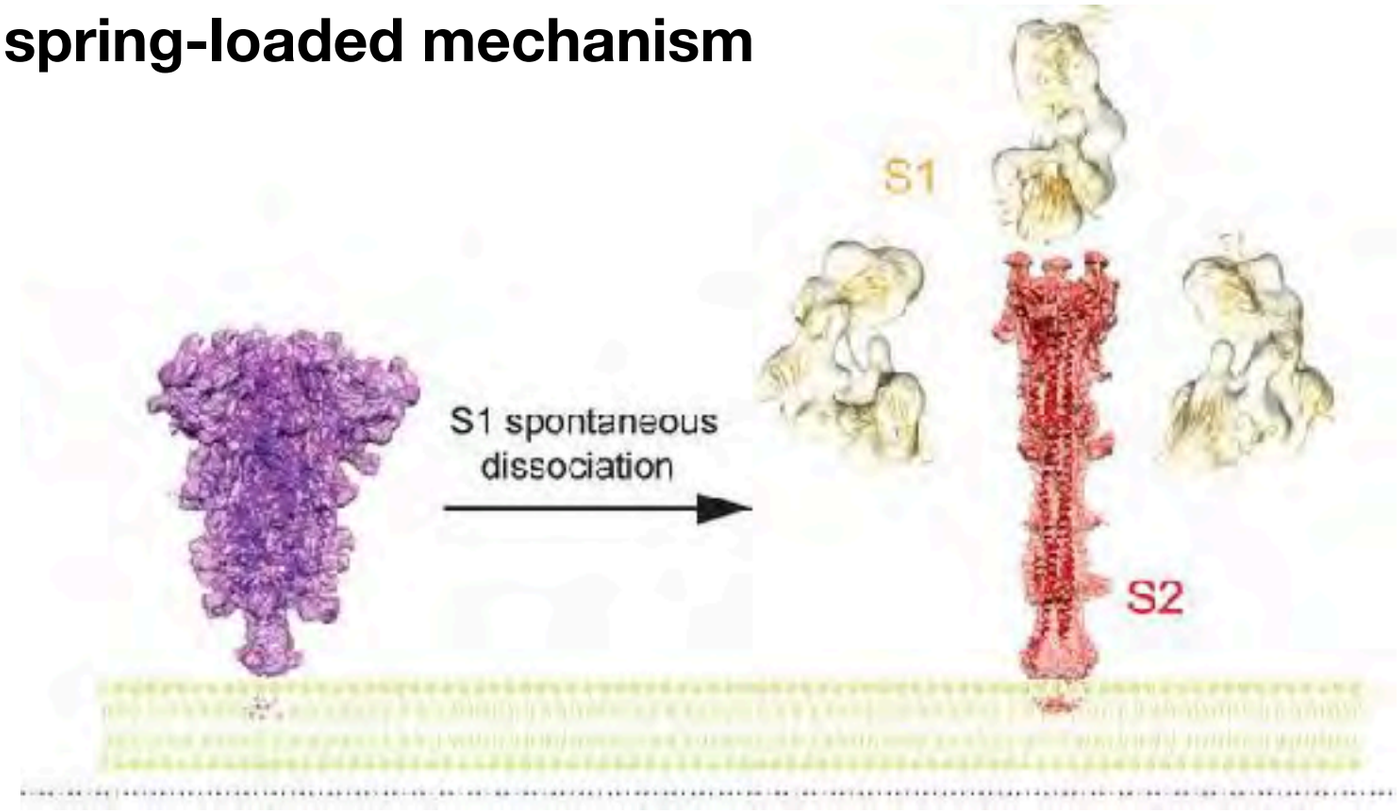
What happens in inactivation?
Shape changes in the surface spike.

Antibody recognizes particular shape and chemistry

wrong shape = no recognition, no neutralization



Spike protein is a spring-loaded mechanism



“pre”-fusion **“post”-fusion**

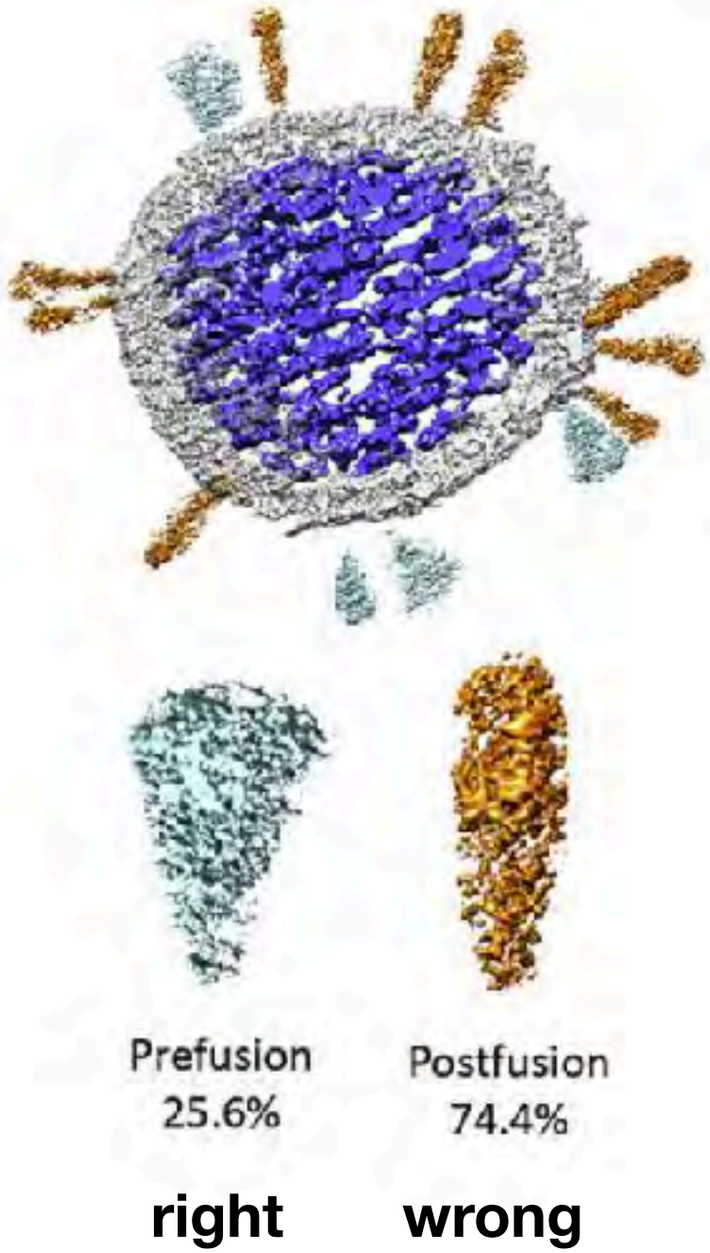
before **after**

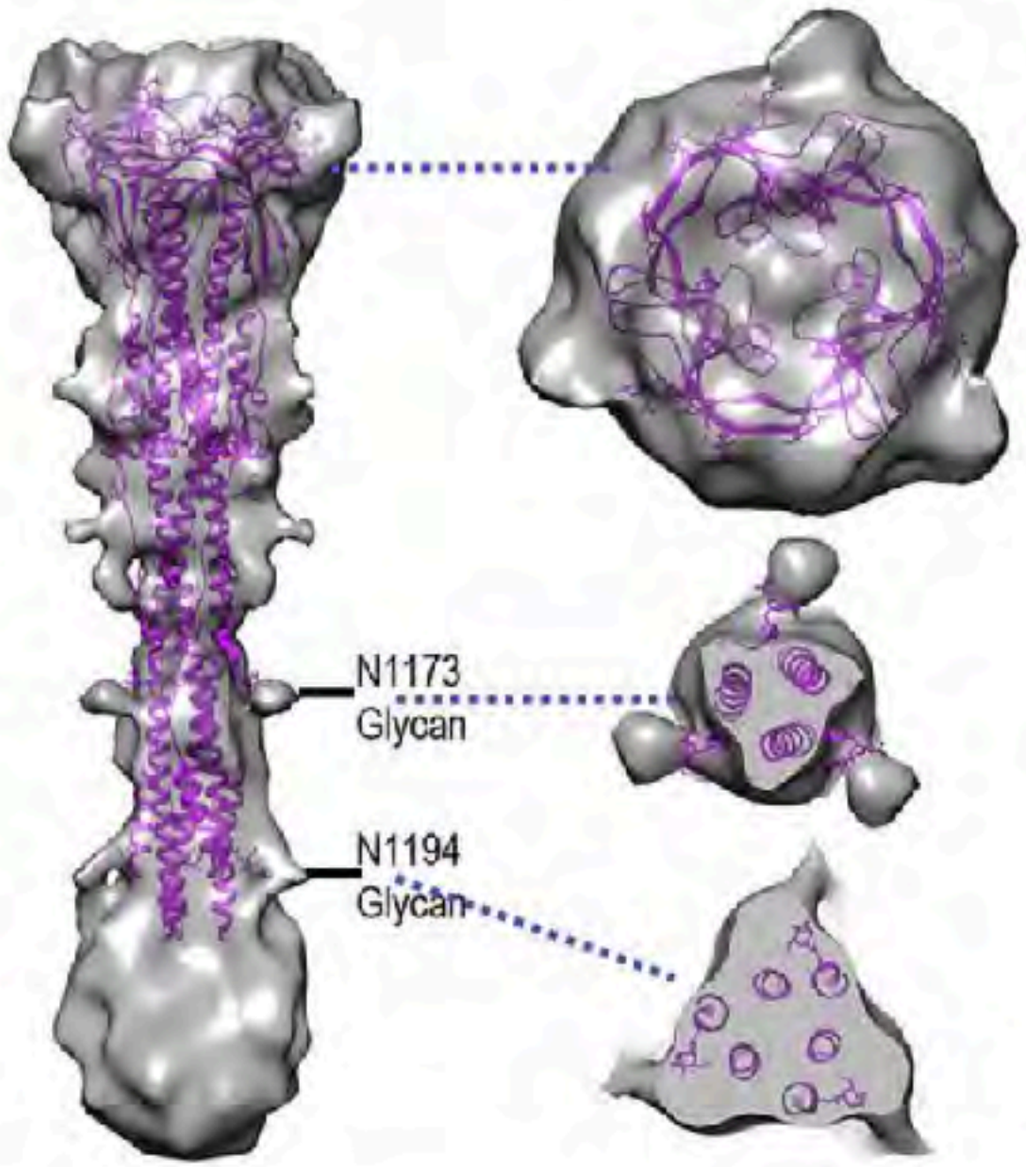
neutralizing antibody would lock the mechanism

right shape for antibodies

wrong shape

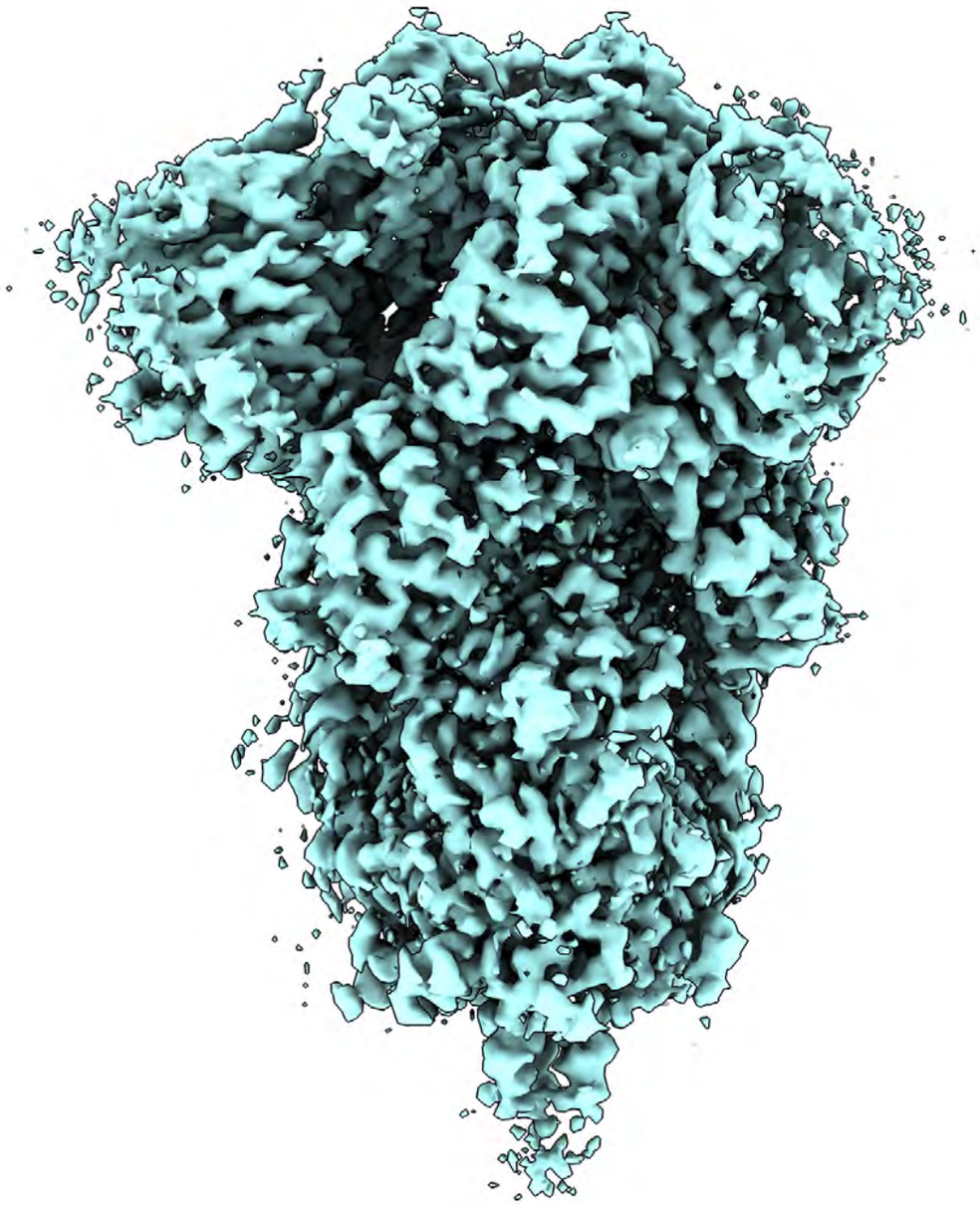
Inactivation process springs the spikes



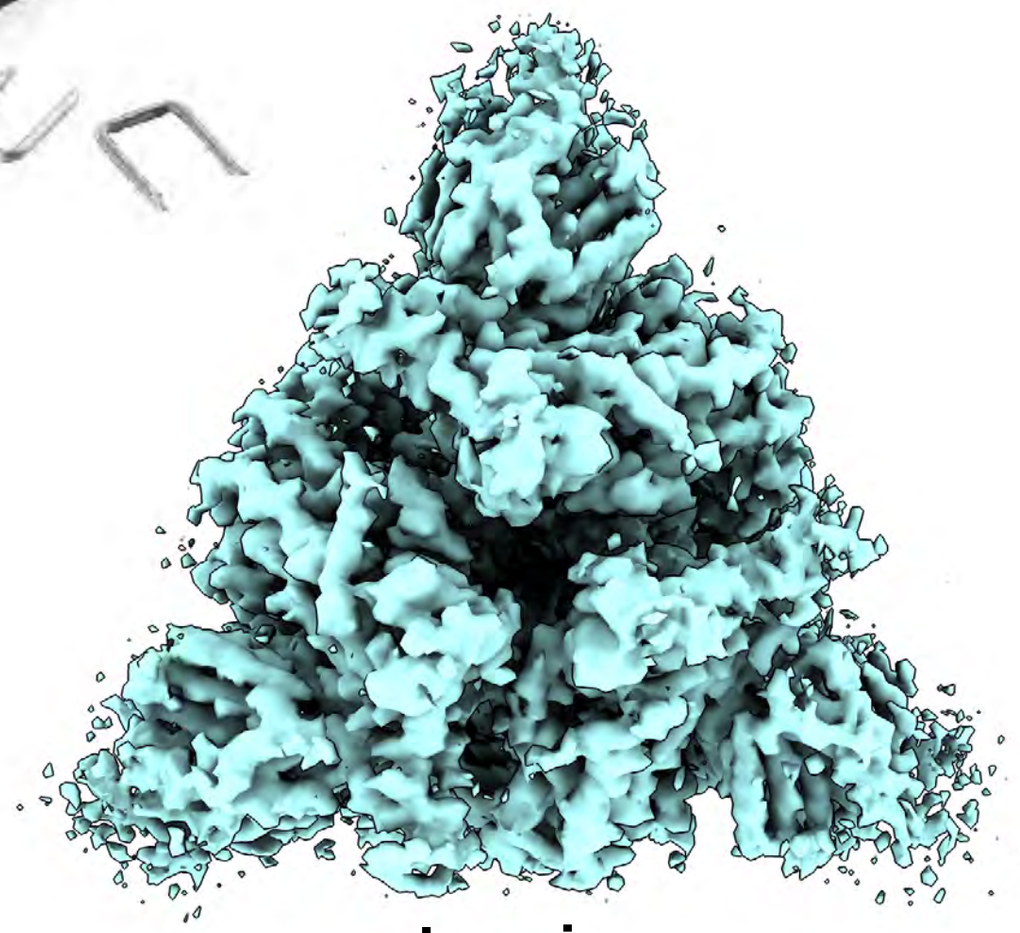


Liu et al Structure 2020
“The architecture of inactivated SARS-CoV-2 with postfusion spikes revealed by cryoEM and cryoET”

Spike stability is a problem



side view



top view

My lab: Third-generation vaccine candidate
Better presents proper structure, especially of the unchanging regions
Better presents the correct carbohydrate cloak.

Stable at room temperature.

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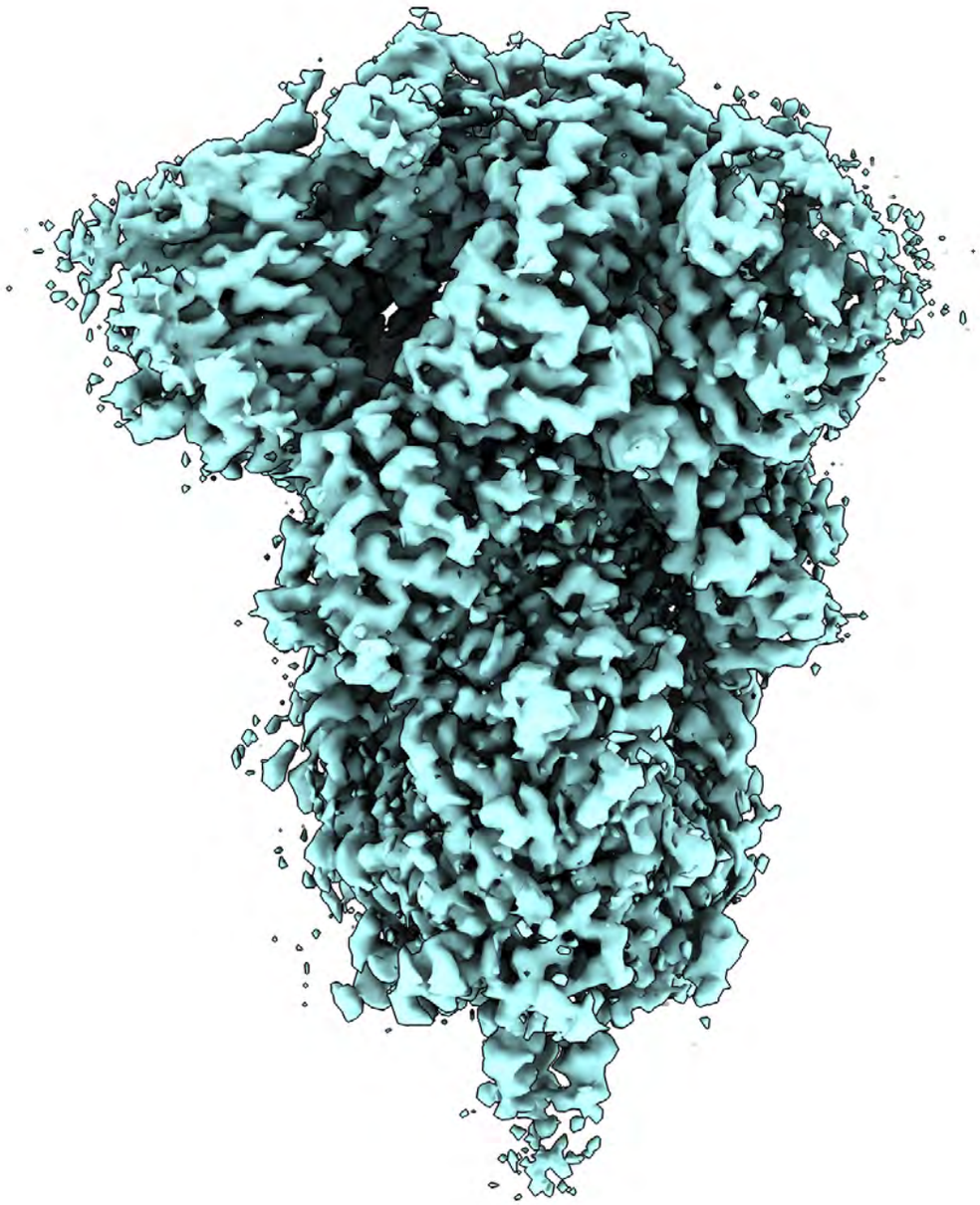
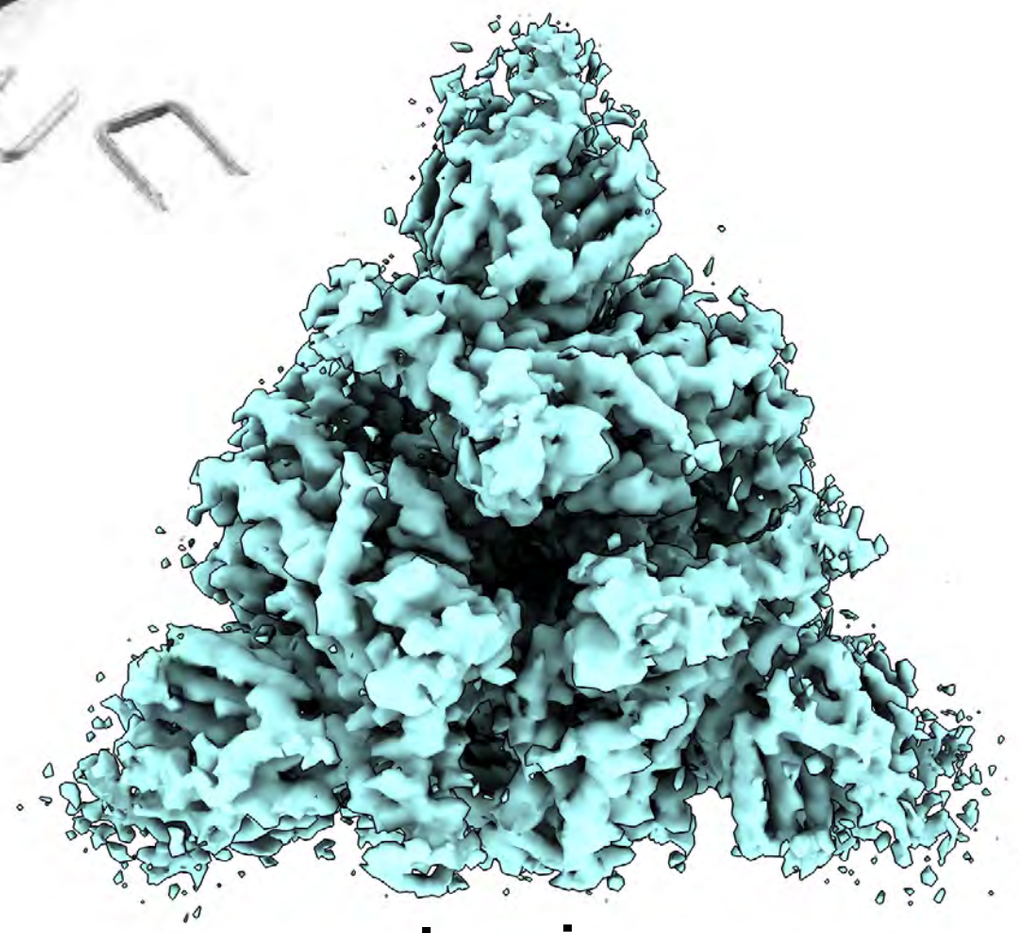


side view



top view

My lab: <u>Third-generation</u> vaccine candidate
Better presents proper structure, especially of the unchanging regions
Better presents the correct carbohydrate cloak.

Use as a tool to find better antibodies.

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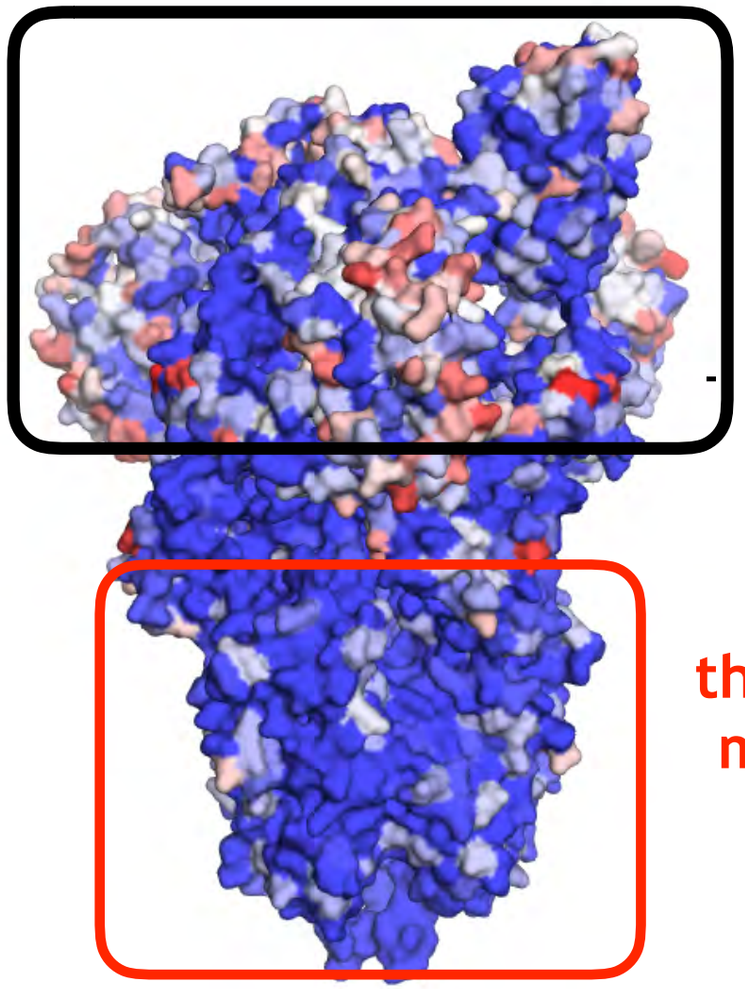
Spike sequence diversity, sarbecovirus group

susceptible to mutations

Epitope bin	del19-G614/G261D	del19-G614/V367F	del19-G614/N439K	del19-G614/Y453F	del19-G614/F486L	del19-G614/N501T	del19-G614/G261D+Y453F	del19-G614/QUAD
1	0.77	0.23	0.33	0.21	3.43	0.18	0.16	0.16
2	1.87	0.41	1.94	1.63	No Neut	1.63	0.58	No Neut
2	1.62	0.30	1.97	1.39	10.87	1.13	0.53	7.51
3a	1.02	1.00	1.16	1.55	4.99	1.13	1.00	133.01
3b	1.26	0.23	1.29	4.50	4.65	1.07	3.06	12.27
3b	1.57	0.28	1.19	2.80	No Neut	1.95	1.55	No Neut
4	1.49	32.30	60.60	3.42	0.83	3.83	0.96	2.75
5	0.87	0.33	4.68	2.36	0.43	0.45	0.90	0.40
5	1.20	0.69	1.18	1.35	0.97	1.00	0.75	0.66
7	3.97	1.33	1.77	1.83	1.45	1.85	2.24	2.28
8	70%	90%	80%	70%	80%	70%	80%	80%
8	50%	80%	40%	20%	30%	40%	40%	50%
9	20%	20%	20%	20%	20%	20%	20%	30%
9	3.36	3.77	7.17	6.72	2.81	2.25	2.52	4.25
10	1.61	1.00	0.29	1.71	0.71	1.09	1.00	1.00
10	1.19	0.37	0.11	1.45	0.68	0.73	1.18	0.86
10a	NN	NN	NN	NN	NN	NN	NN	NN
11	1.55	0.79	0.62	2.08	0.77	6.68	1.29	14.05
11	1.16	0.41	2.34	2.49	0.69	79.40	1.31	60.91
12	1.33	0.25	12.14	19.67	0.76	0.18	39.89	72.53
EOS-1A7 (RBD)	7.25	0.81	3.97	0.80	6.91	4.08	0.80	0.56
EOS 6C5 (RBD)	1.62	1.04	1.72	0.95	1.11	1.48	0.95	0.64
EOS-6A7 (NTD)	11.53	0.73	1.31	11.56	0.88	1.13	11.56	11.19



Current therapeutics target here

An antibody that bound here might be more resistant to mutation

unchanging variable

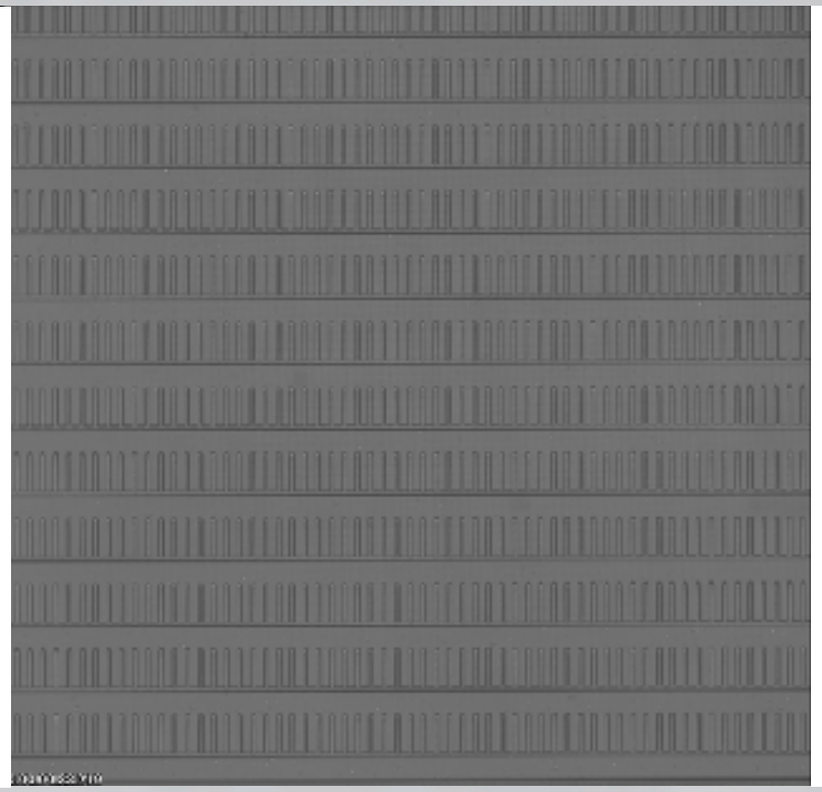
Sequence entropy (bits)

0 1.0 ≥2.0*

Kshitij Wagh, Bette Korber, LANL

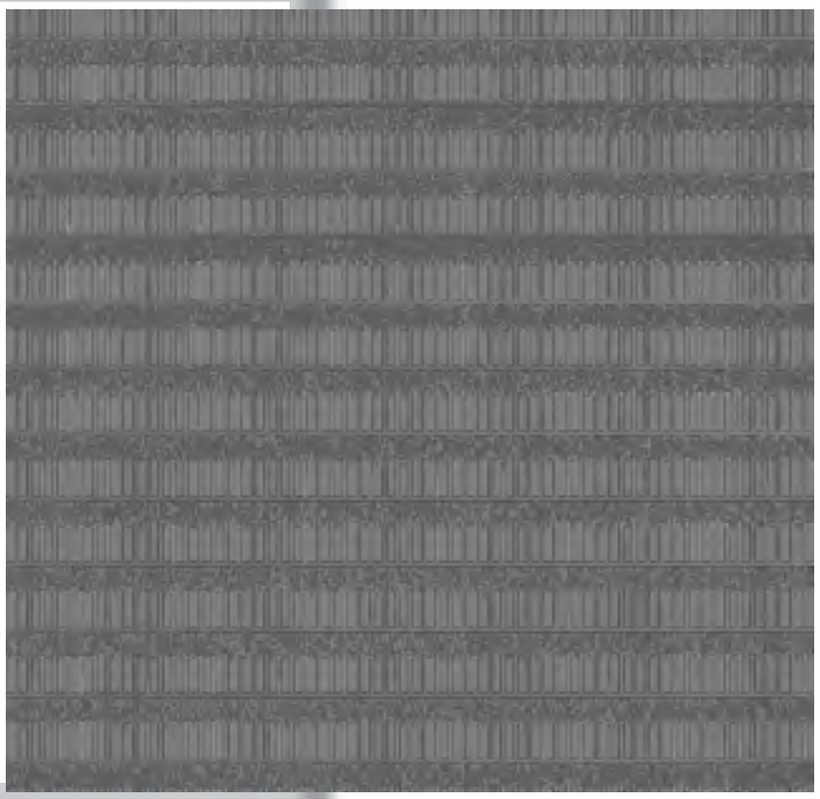
In my lab:

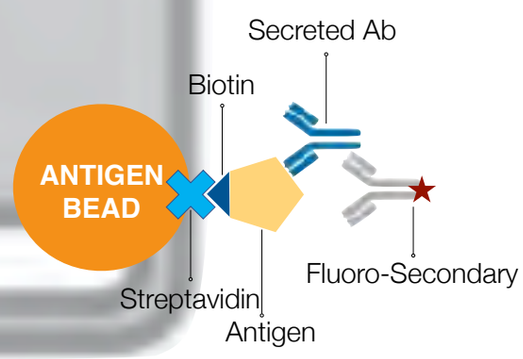
Import individual B cells



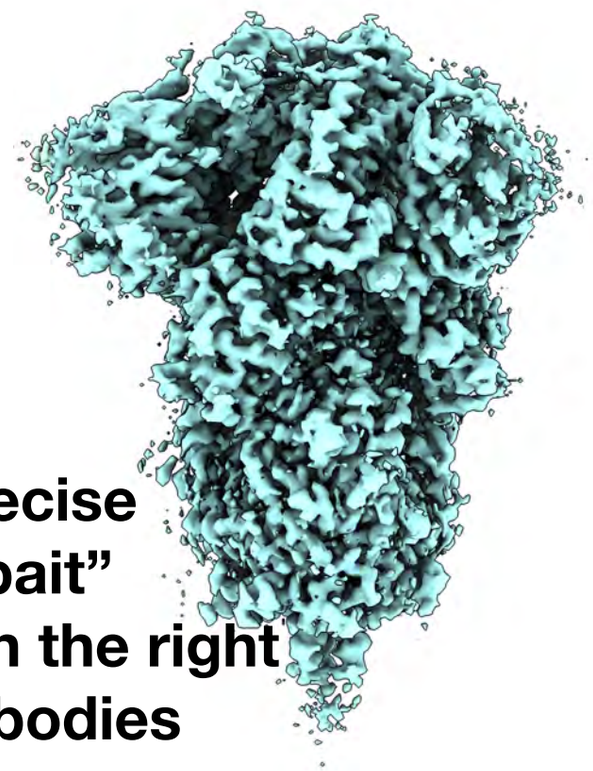
use light to sort individual B cells into holding pens

Assay



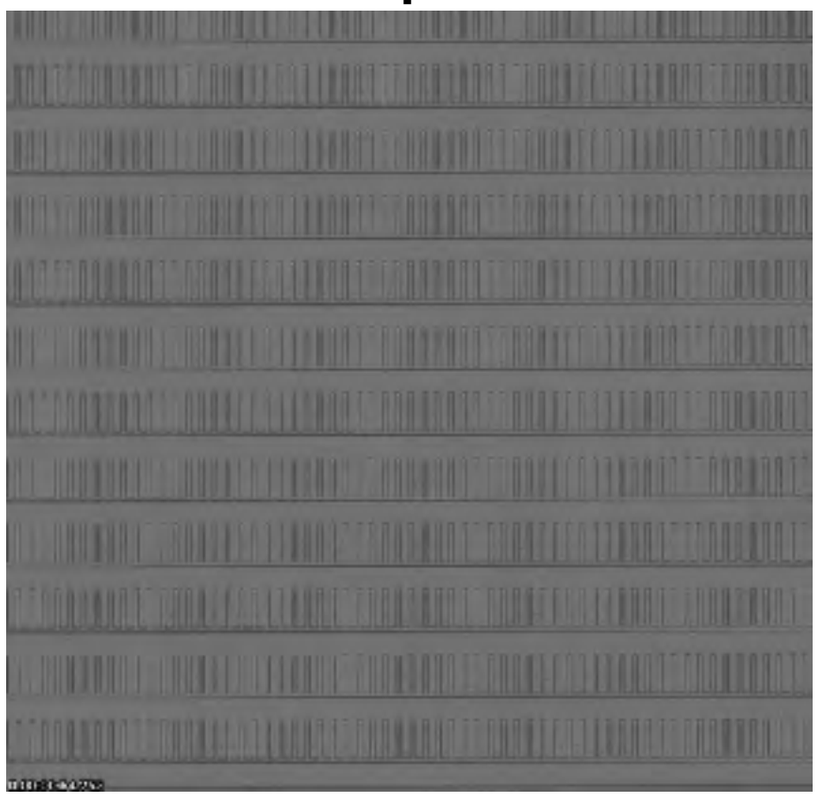


ask each individual cell if it makes the antibody we want

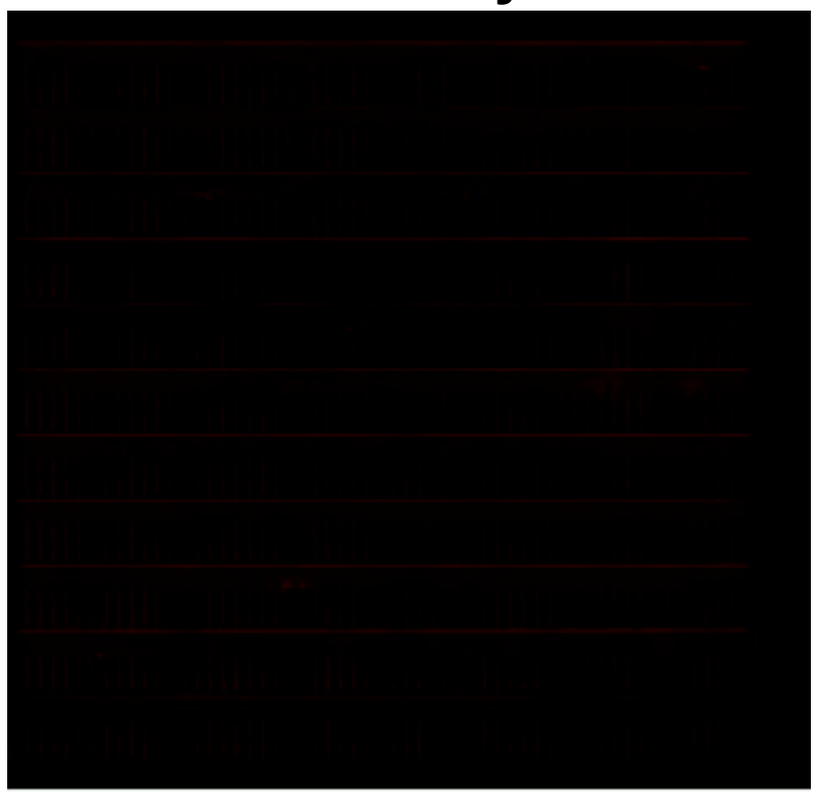


precise “bait” to catch the right antibodies

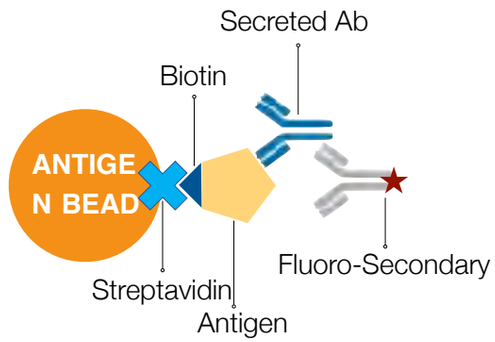
Import



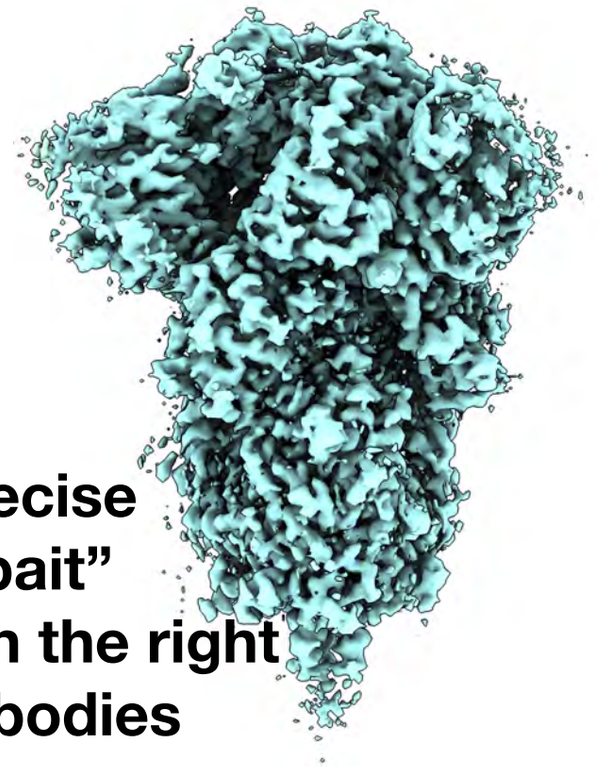
Assay



use light to sort individual B cells into holding pens

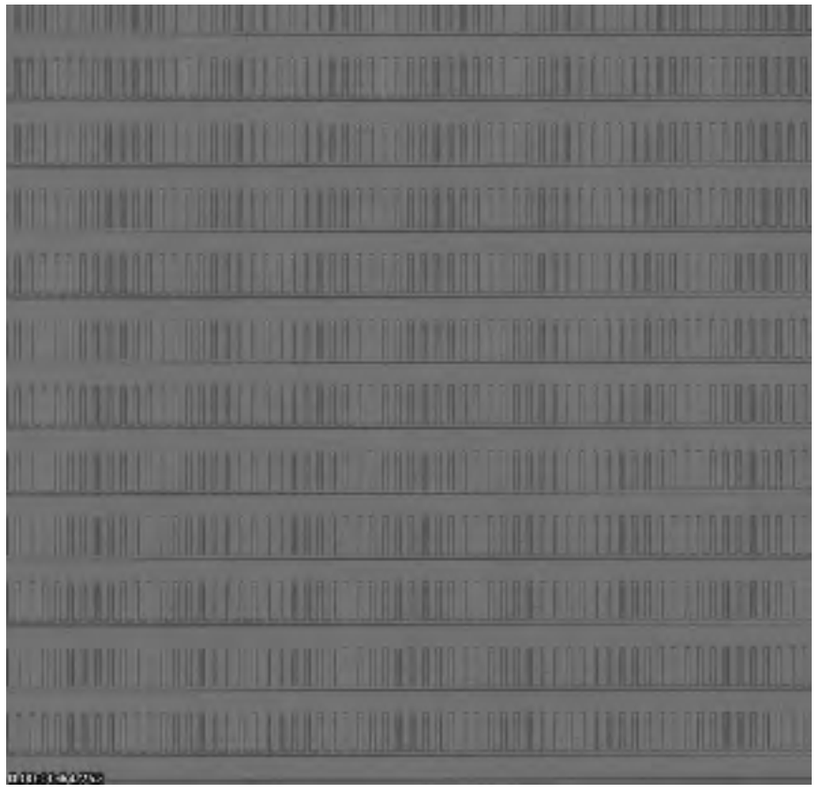


ask each individual cell if it makes the antibody we want

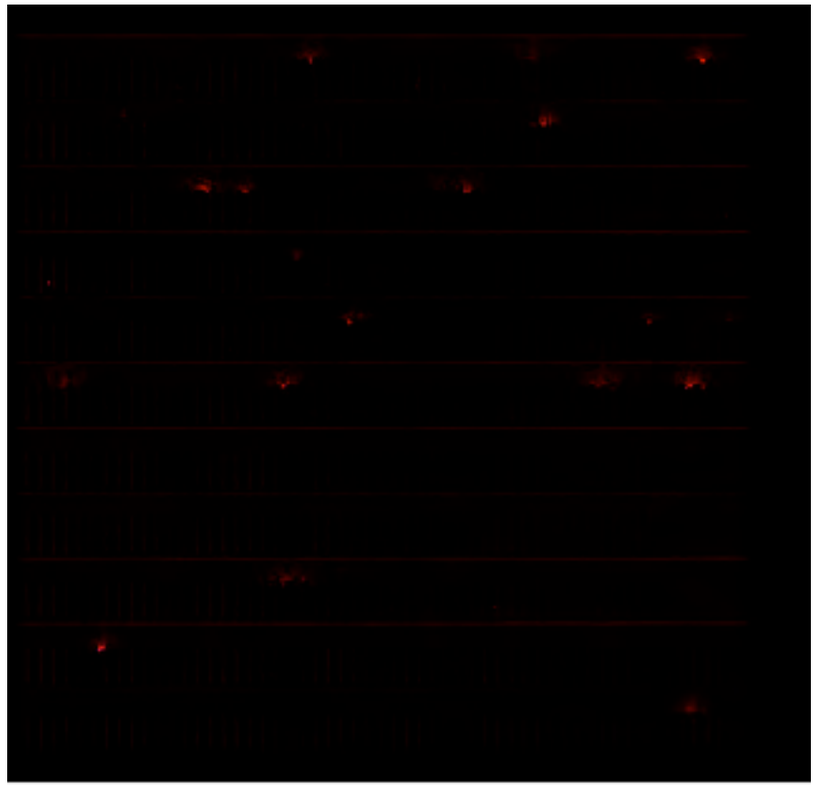


precise “bait” to catch the right antibodies

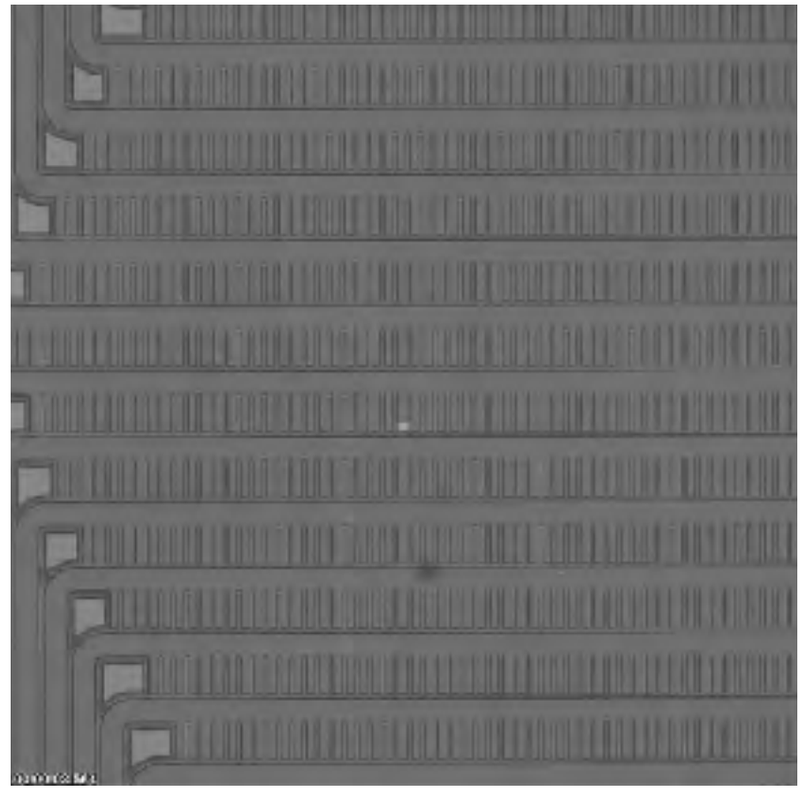
Import

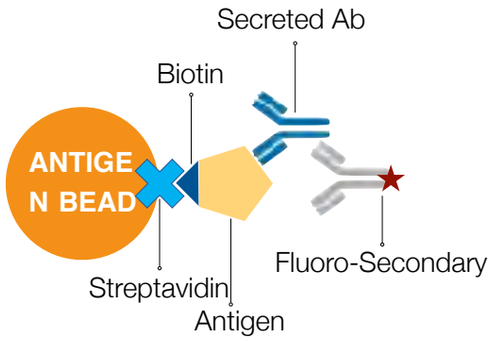


Assay



Export





use light to retrieve the single B cell we want

cDNA synthesis
IgG seq. recovery
Functional assays

CoVIC

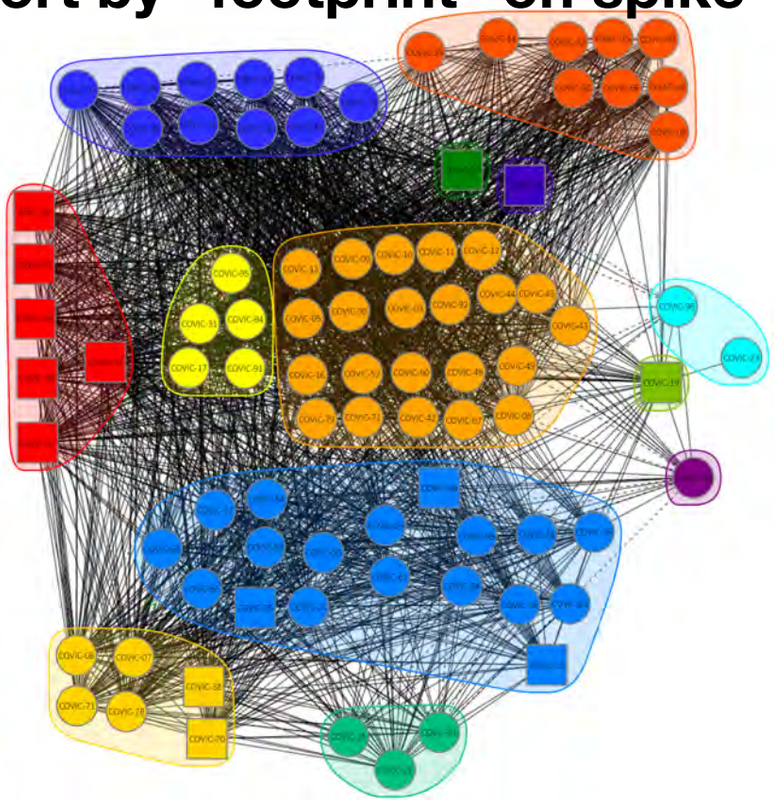
250+ therapeutics from four continents

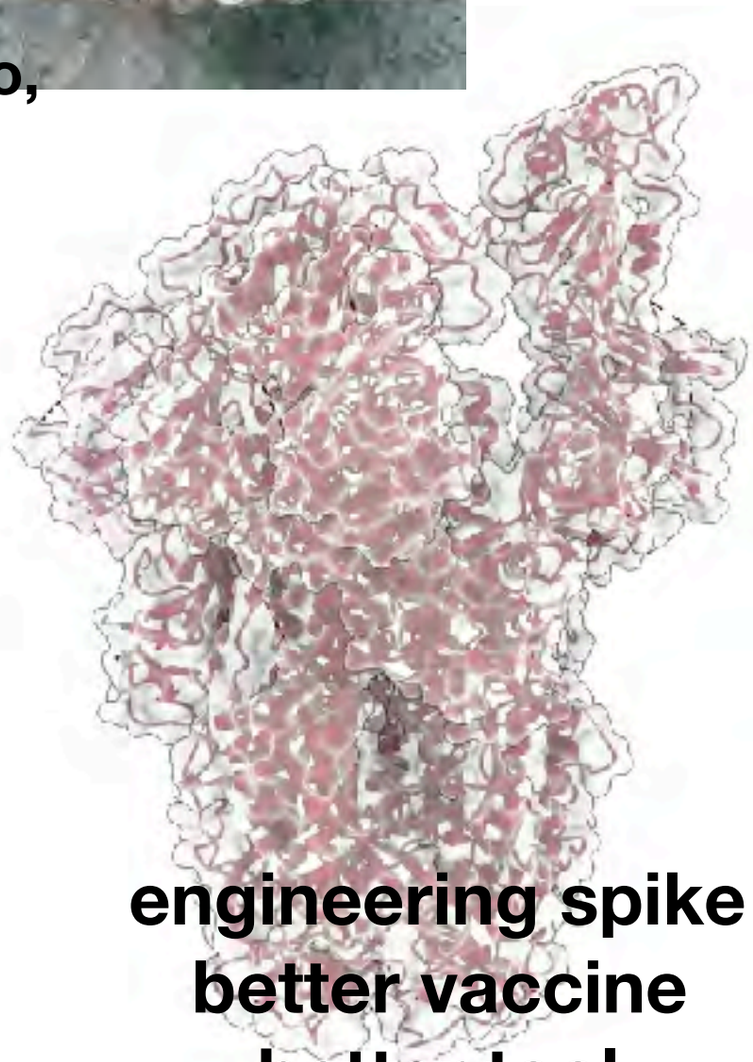
which are susceptible to, or resistant to emerging mutations

del19-G614/Y453F	del19-G614/F486L	del19-G614/N501T
0.21	3.43	0.18
1.63	No Neut	1.63
1.39	10.87	1.13
1.55	4.99	1.13
4.50	4.65	1.07
2.80	No Neut	1.95
3.42	0.83	3.83
2.36	0.43	0.45
1.35	0.92	1.00
1.83	1.45	1.85
70%	*80%*	*70%*
20%	*30%*	*40%*
20%	*20%*	*20%*
6.72	2.81	2.25
1.71	0.71	1.09
1.45	0.68	0.73
NN	NN	NN
2.08	0.77	6.68
2.49	0.69	29.40
19.67	0.76	0.18
0.80	6.91	4.08
0.95	1.11	1.48
11.56	0.88	1.13

arsenal of appropriate therapeutic options

sort by “footprint” on spike





engineering spike better vaccine better tool

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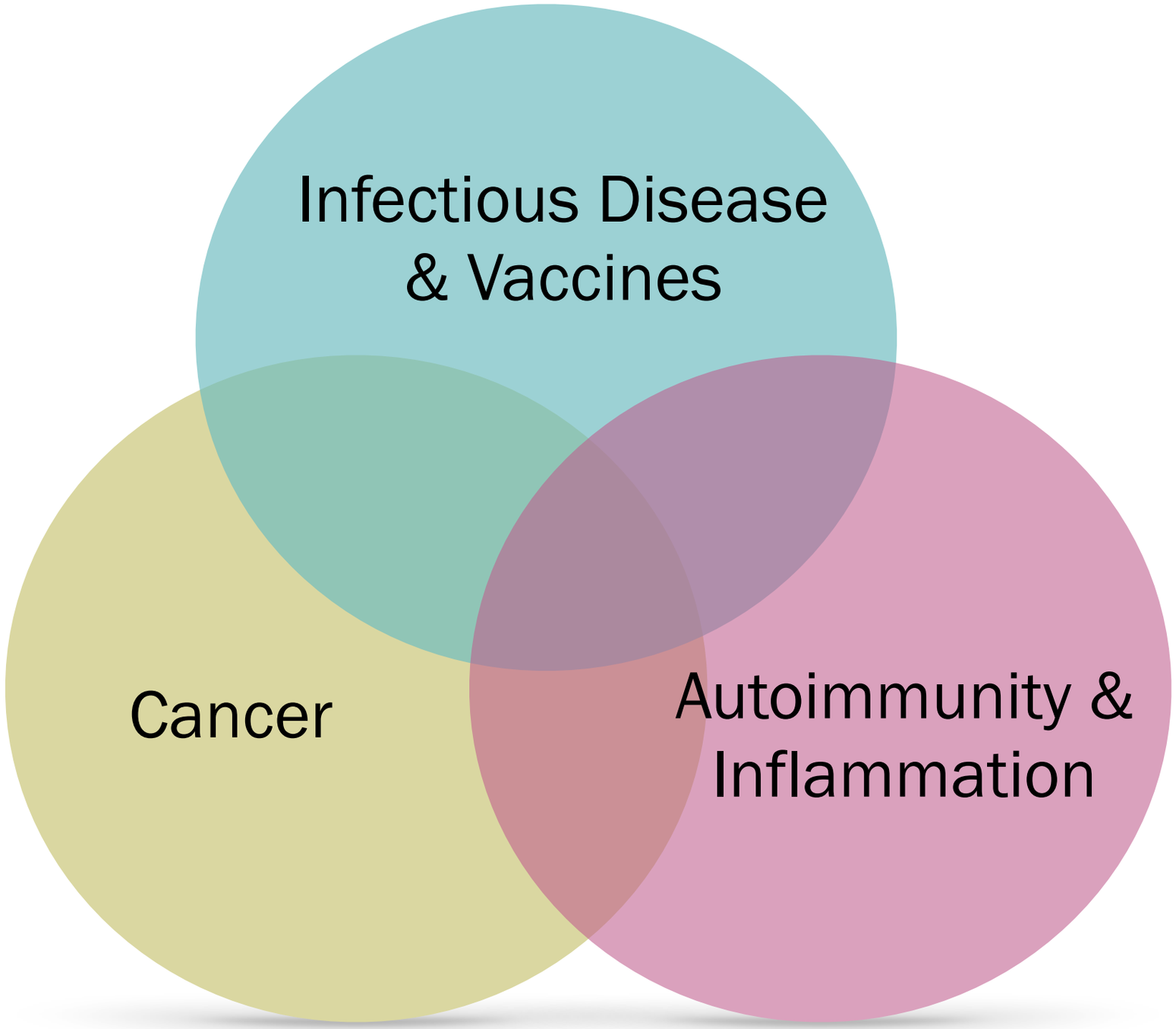
Human Immunology



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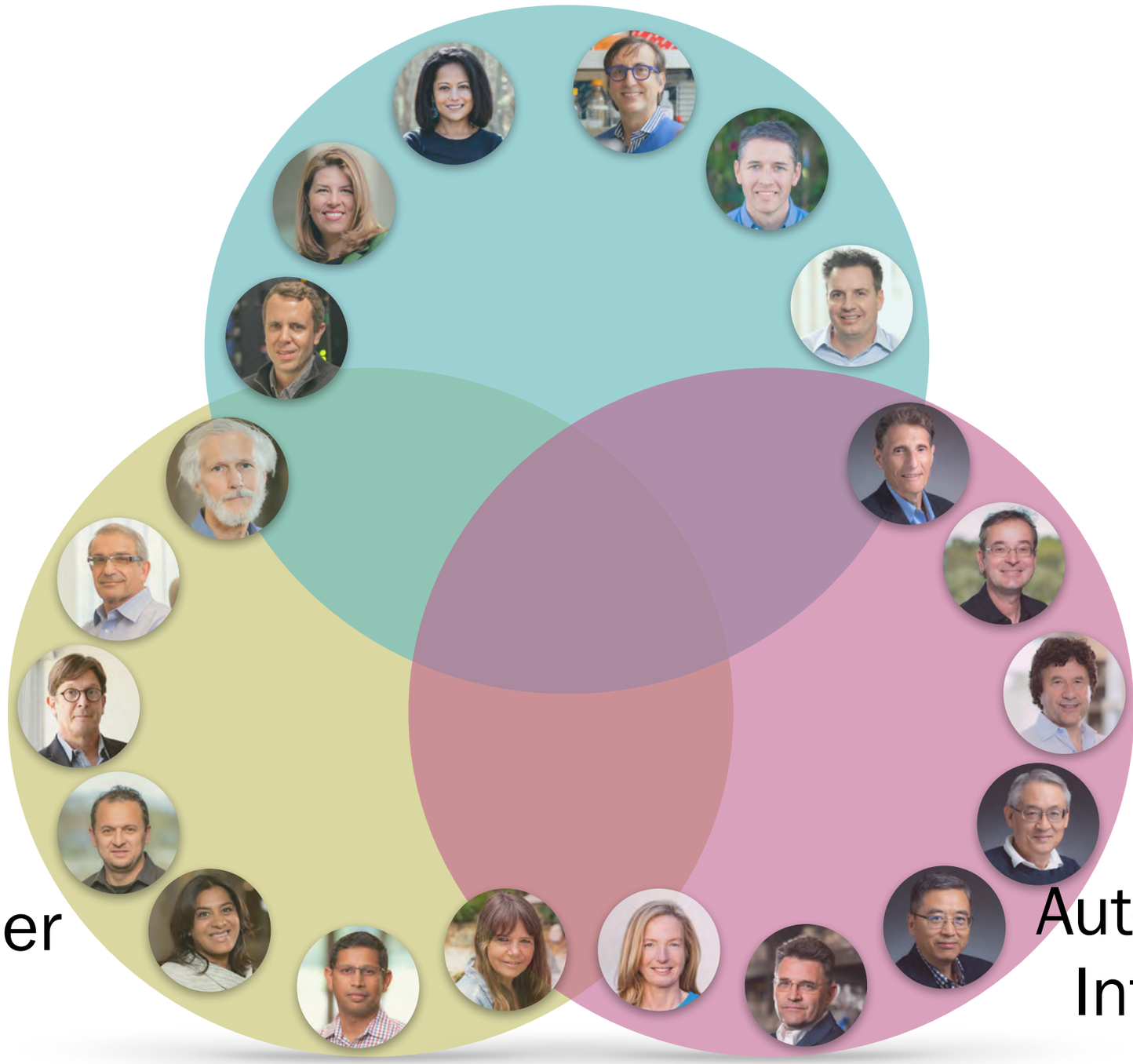
Infectious Disease & Vaccines



Cancer

Autoimmunity & Inflammation

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30
Years
life without
disease.
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My team:
particularly
Sharon Schendel
Kathryn Hastie
Eduardo Olmedillas
Colin Mann
Haoyang Li
Vamsee Rayaprolu
Dawid Zyla

CoVIC labs
and contributors

The Overton Family
for enabling the
urgent study
on the emerging
mutations