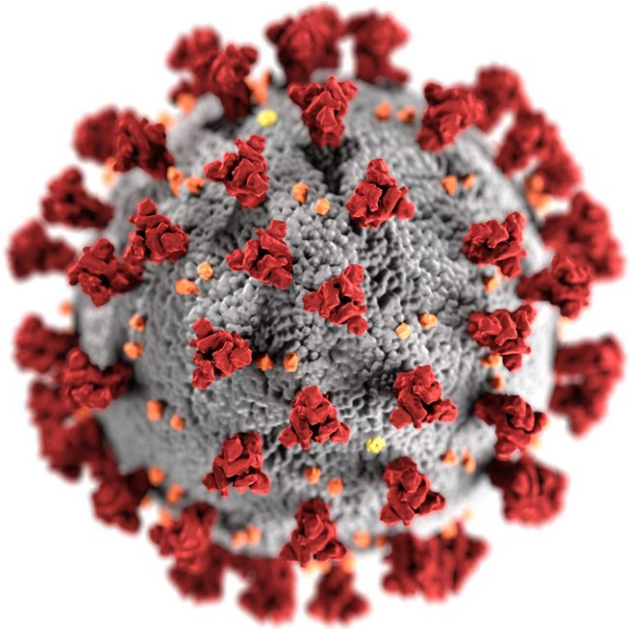
Addressing the Coronavirus Challenge

Front Row Lecture:

Mike Farzan
The Scripps Research Institute
April 22, 2020



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Addressing the Coronavirus Challenge

The big picture

(apologies to Shepard Fairey)

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Hope?

If HIV is a genius and flu is an honors student…

SARS-CoV-2 (the COVID-19 virus) flunked Immunology 101.

We have all the knowledge and scientific tools we need to defeat it.

Our bottlenecks are testing, manufacture, and distribution.

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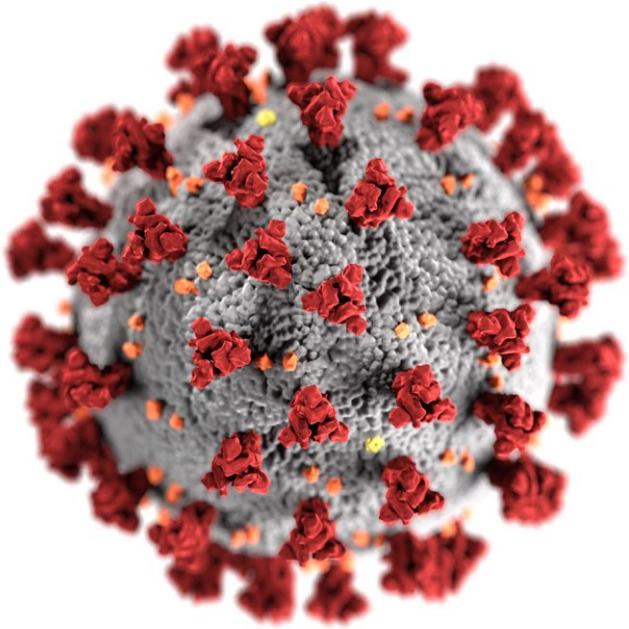
Why is SARS-CoV-2 so stupid? (1)

A strategy of moving from host to host before an adaptive immune response emerges

It chooses transmission efficiency over resistance to our immune systems

It exposes, rather than hides, its key antibody recognition sites

Very vulnerable to conventional vaccines and passive immunization strategies



A dunce

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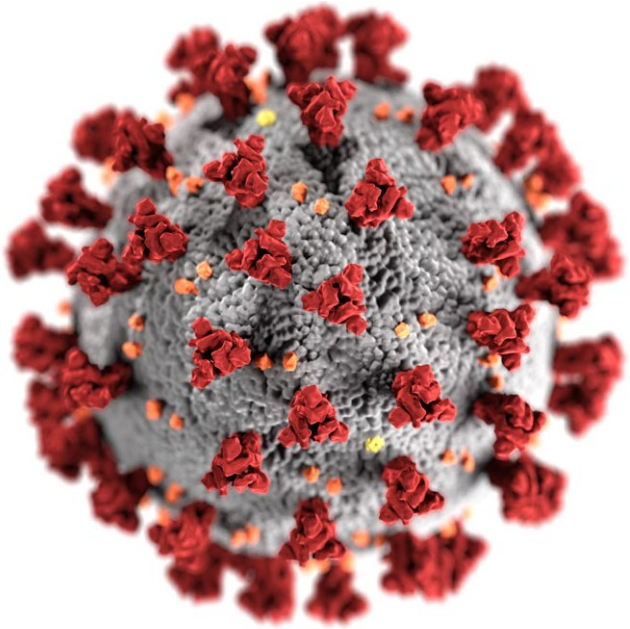
Why is SARS-CoV-2 so stupid? (2)

A huge genome for an RNA virus

Requires a high-fidelity polymerase, otherwise it mutates itself out of business

It therefore evolves slowly

That means a vaccine or antibody cocktail that works in 2021 will work in 2022



A dunce

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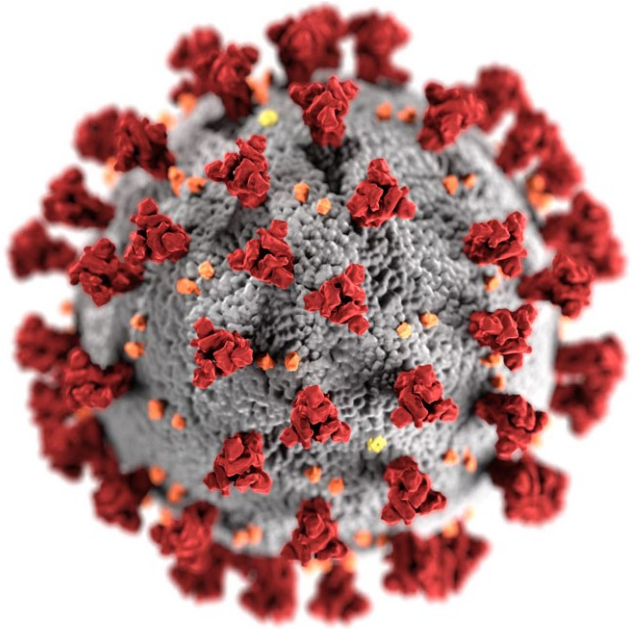
All the tools at our disposal

1. Drugs
2. Biologics
3. Vaccines
4. Convalecent Sera



Front Row Lecture: Mike Farzan, The Scripps Research Institute, April 22, 2020

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Too much to talk about…

Drugs

remdesivir, chloroquine, EIDD-2801, favipiravir…

Biologics

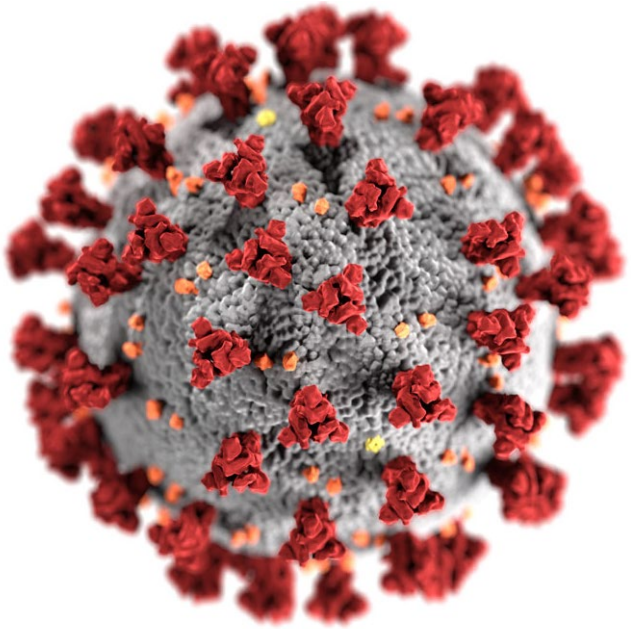
recombinant antibodies, ACE2-Ig

Vaccines

subunit, mRNA, adenvovirus, VSV…

Convalescent sera

efficacy, safety



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…but antibodies are critical to most of these.

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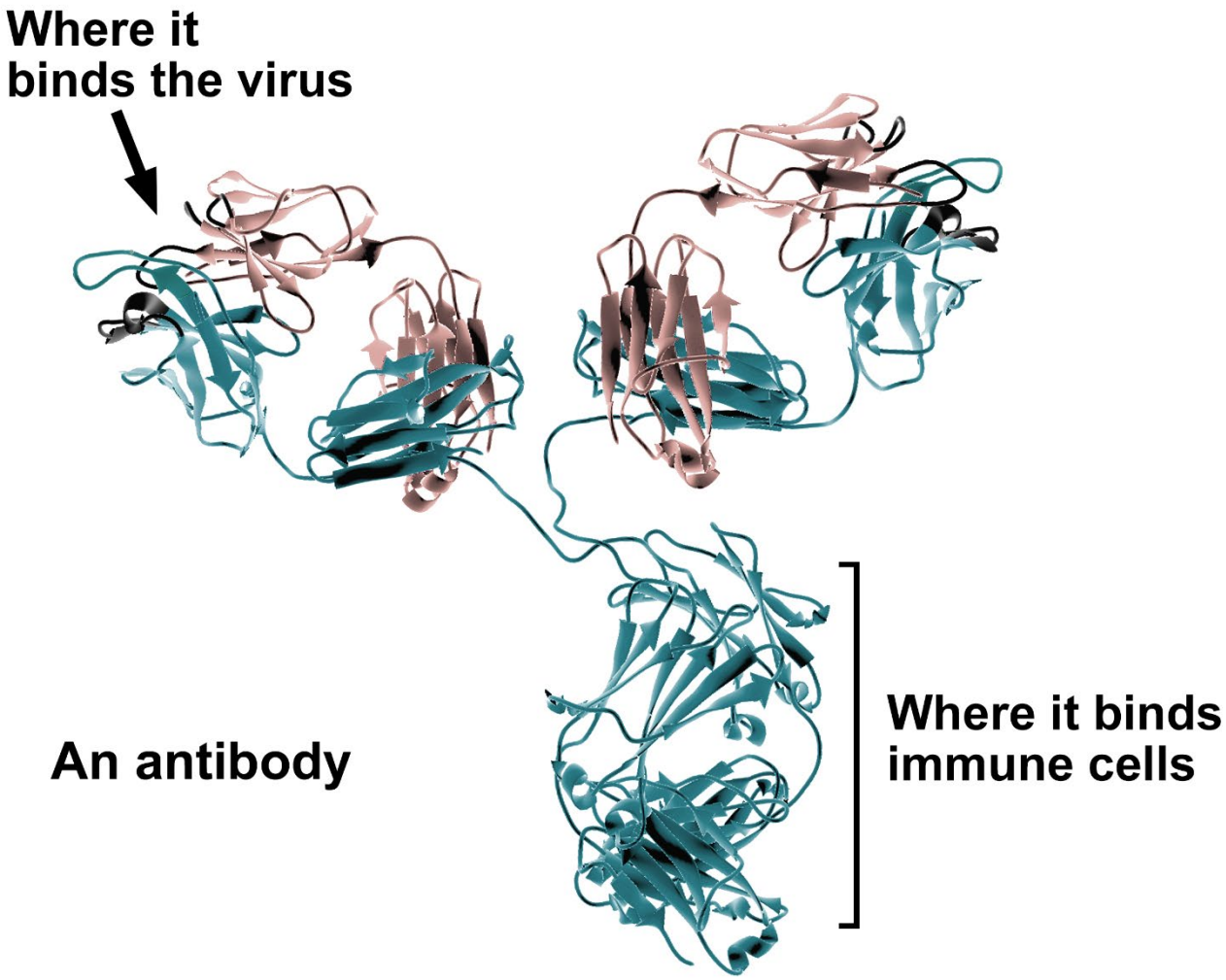

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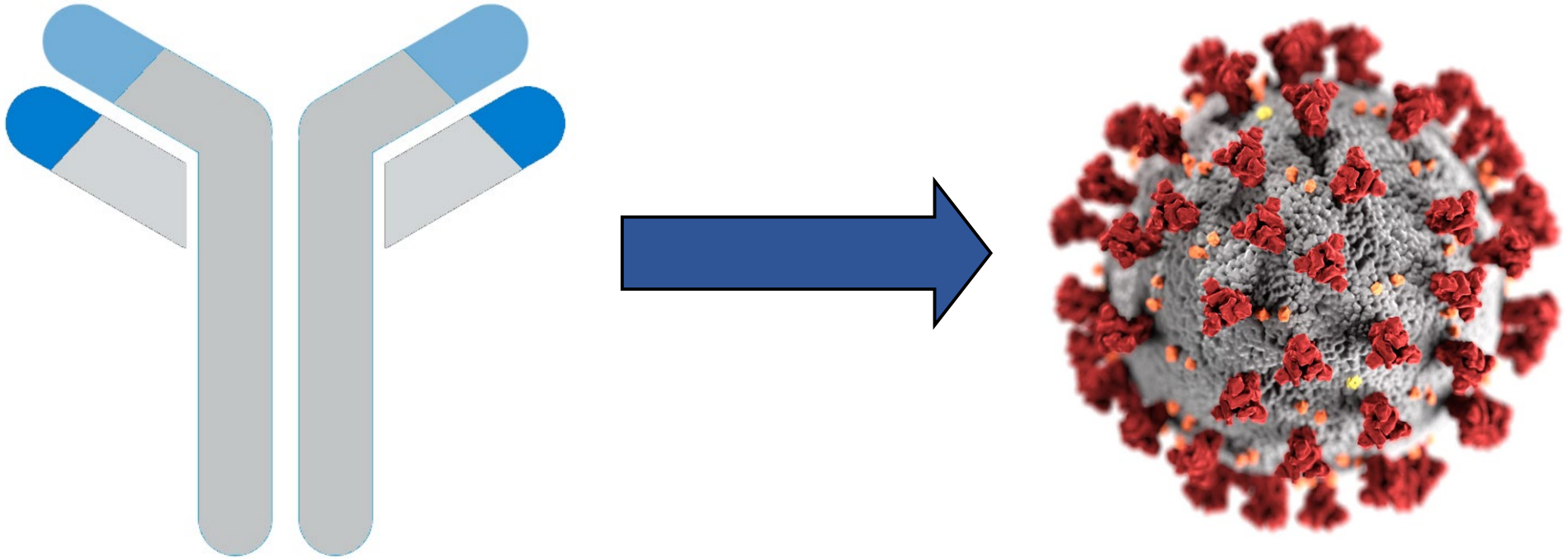
So, how do we make antibodies?
How do they stop the virus?



And how will this end the pandemic????

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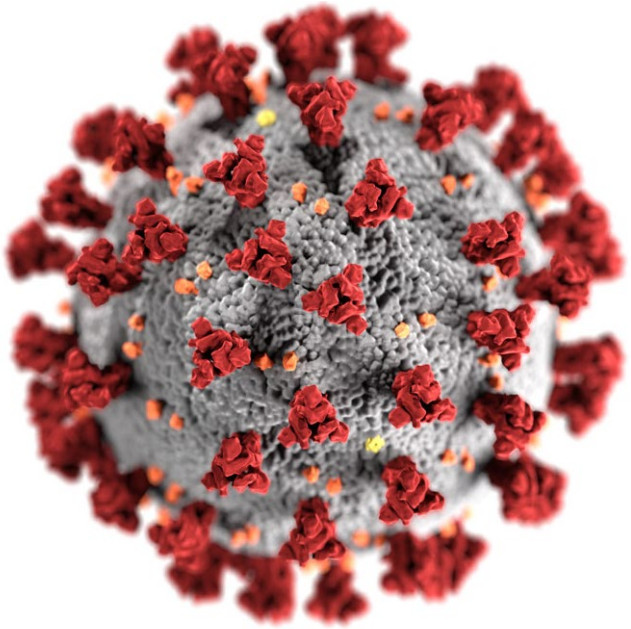

And how will this end the pandemic????

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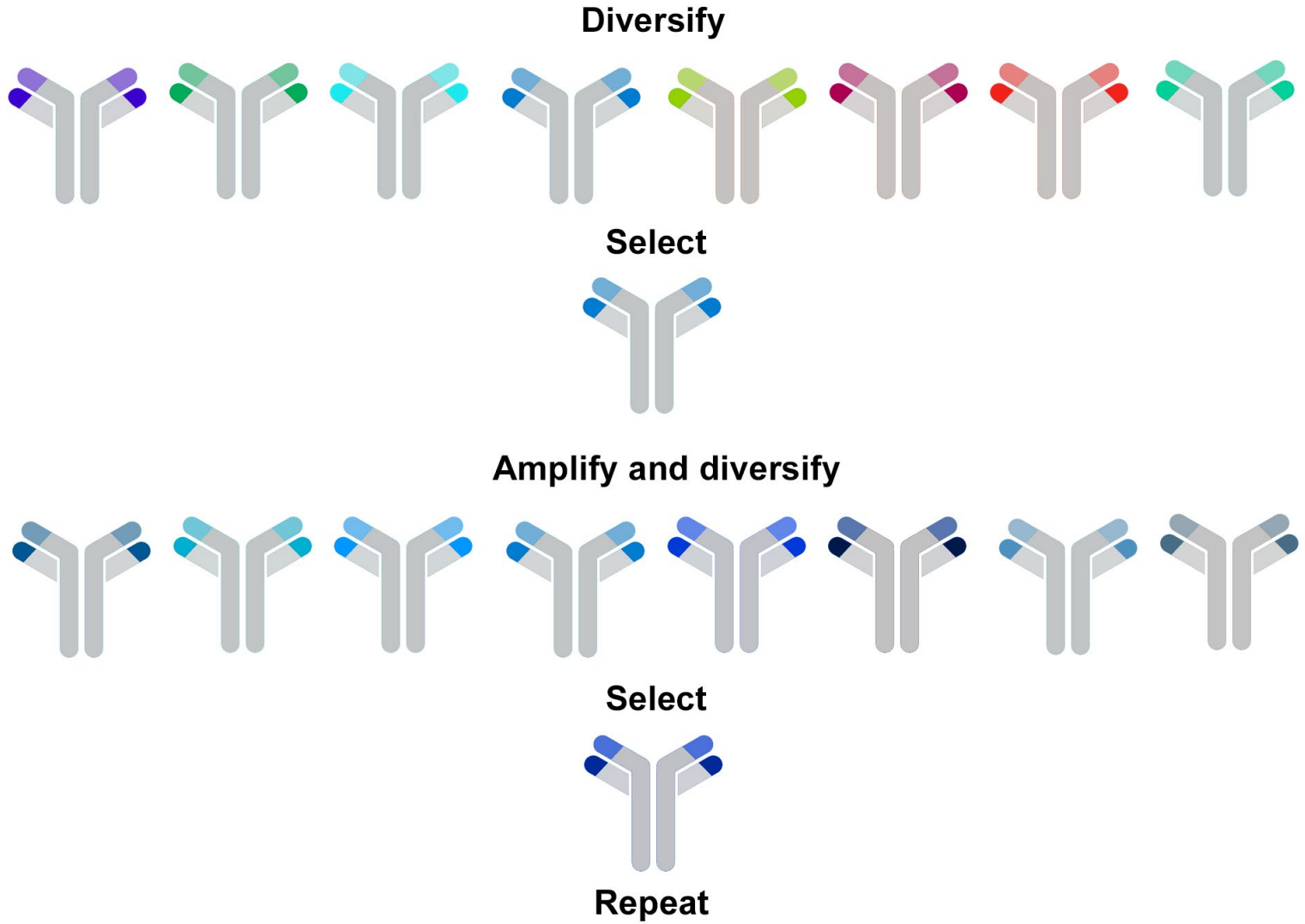
So, how do we make antibodies?

Our immune system uses basic evolutionary principles:

multiply and diversify,
select,
multiple and diversify,
select

Selection based on ability to bind tighter and tighter to a pathogen that appears dangerous.



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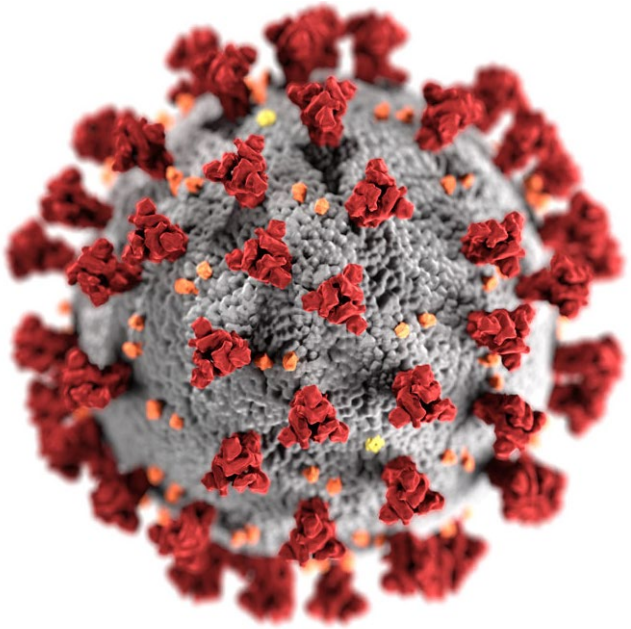

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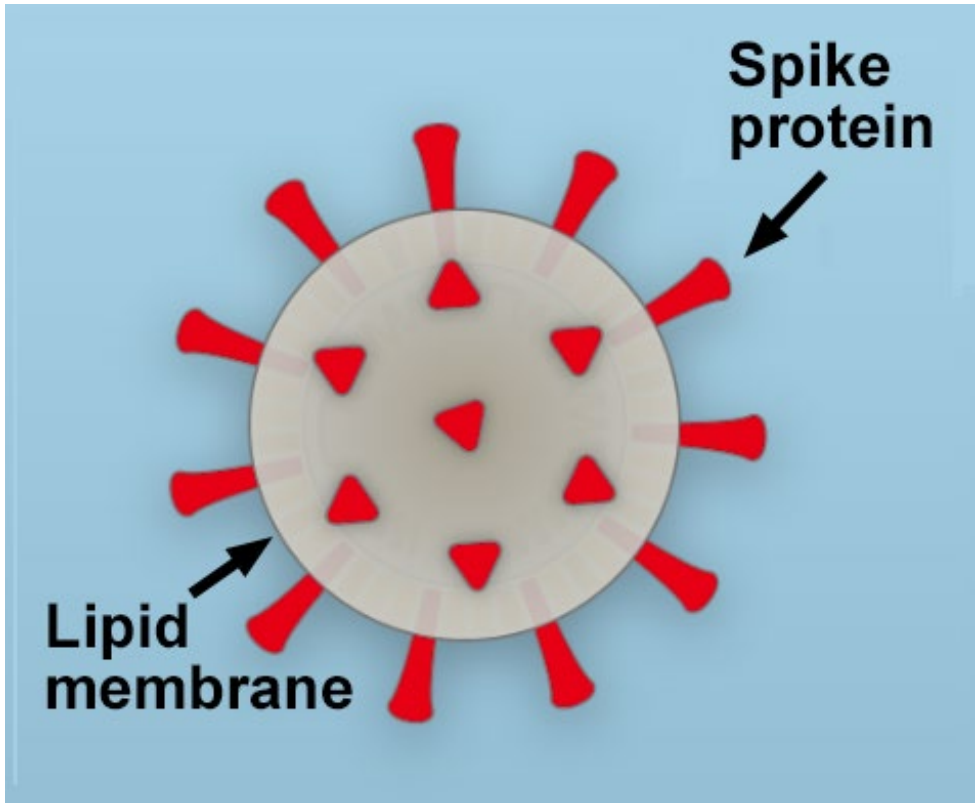

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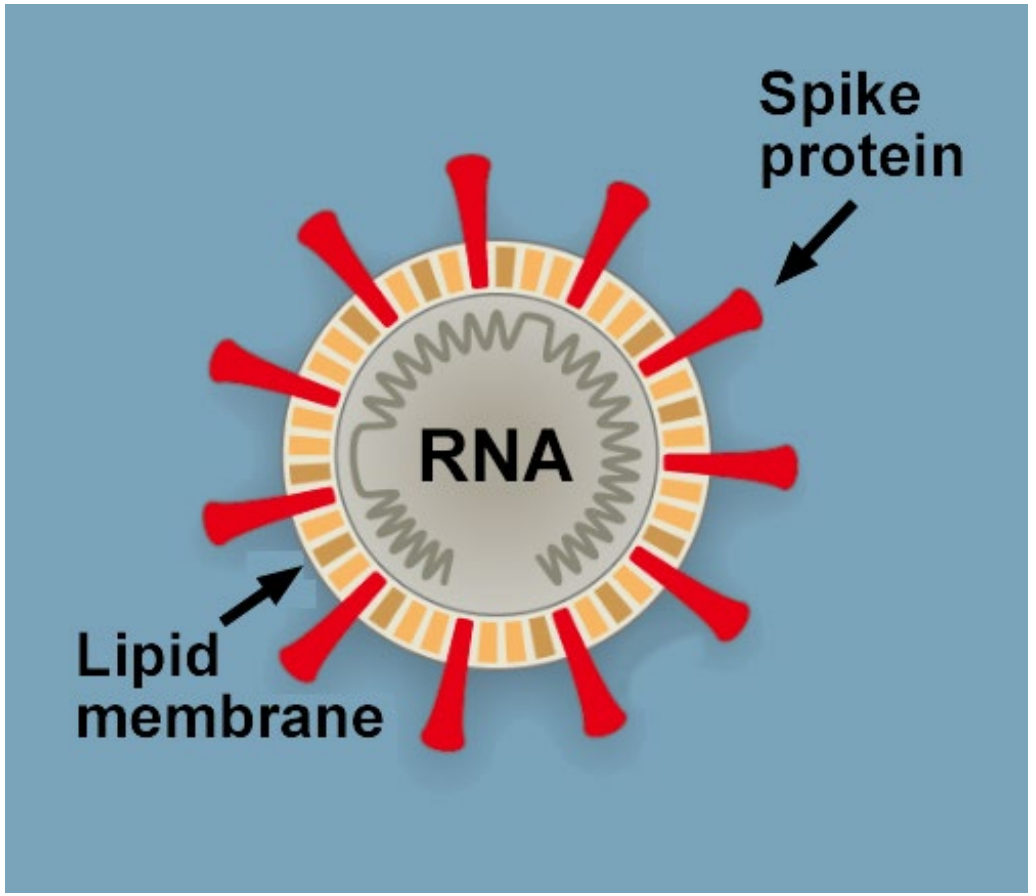

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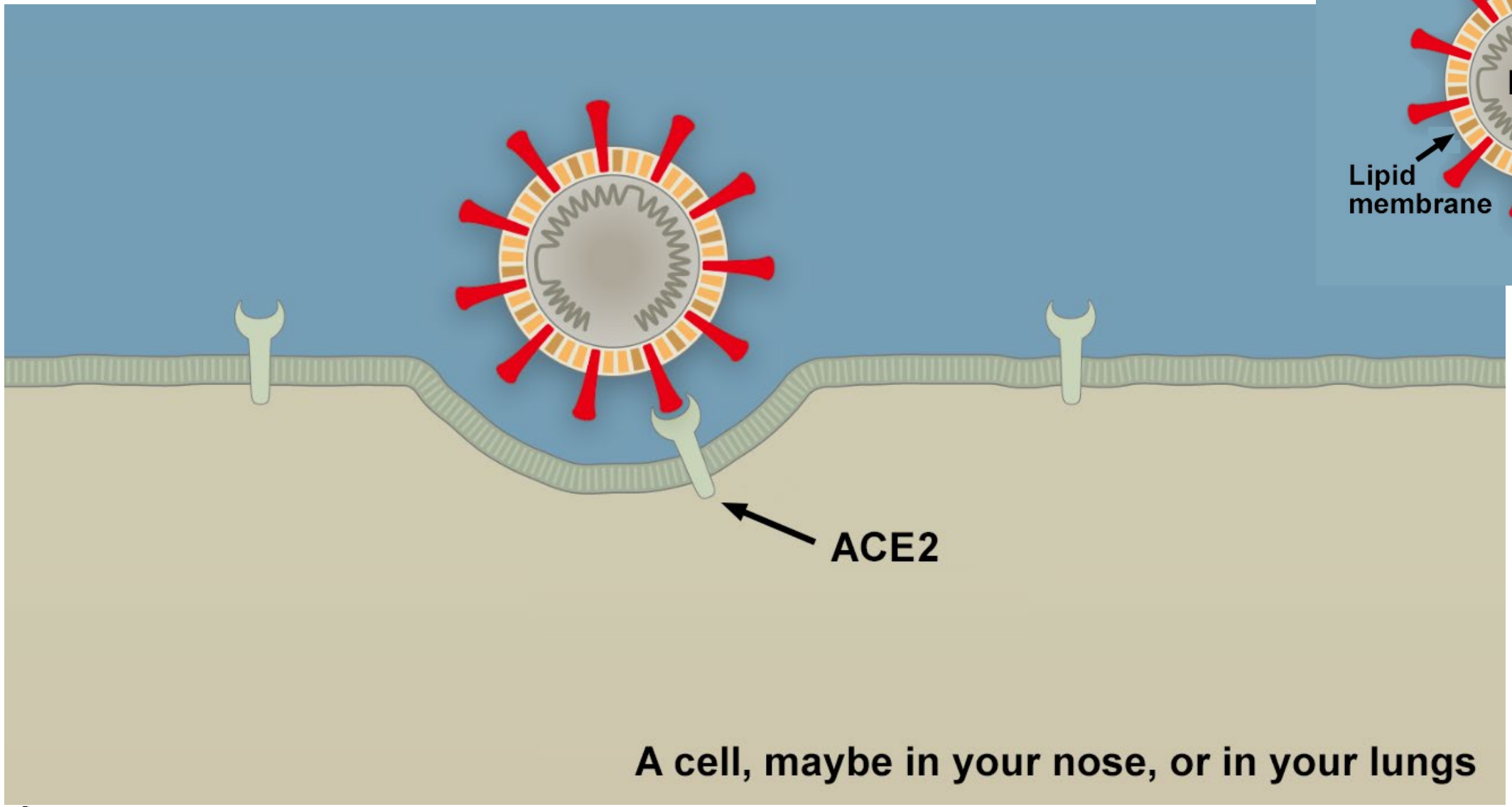

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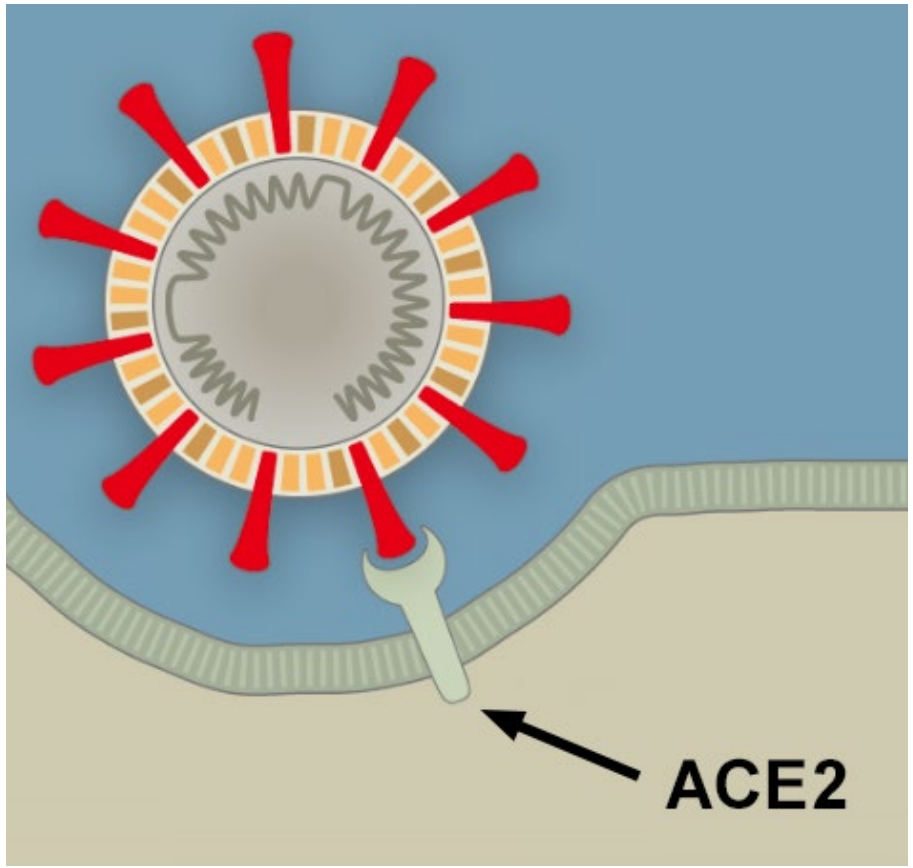
The spike protein latches onto the **ACE2** receptor, necessary for the virus to enter the cell and start replicating.

What is ACE2?



Angiotensin-converting enzyme 2

Necessary for SARS-CoV-1 and SARS-CoV-2 to replicate

Critical for regulating you blood pressure

Counteracts the vasoconstrictive activities of ACE1
(ACE1 is the target of ACE-inhibitors that control high blood pressure)

Expressed in upper-respiratory tract (nasal epithelium) and lower respiratory tract (type II pneumocytes), also in your gut, heart, and kidney.

Expressed more when lungs are insulted.

In smokers, more broadly distributed in lower respiratory tract

In children, very little in lower respiratory tract.

It's expression is induced by type I interferons (a potentially dangerous feedback loop).

ACE2 utilization predicts whether a animal species will be susceptible to SARS-CoV-1 and SARS-CoV-2.

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ACE2 primes the spike to change its shape.

This shape change provides energy.

This energy is used merge the viral membrane and the cell membrane

This is how the viral RNA gets into the cell.

So we show it as a stick but…
the spike is a complicated and delicate machine that can be easily blocked

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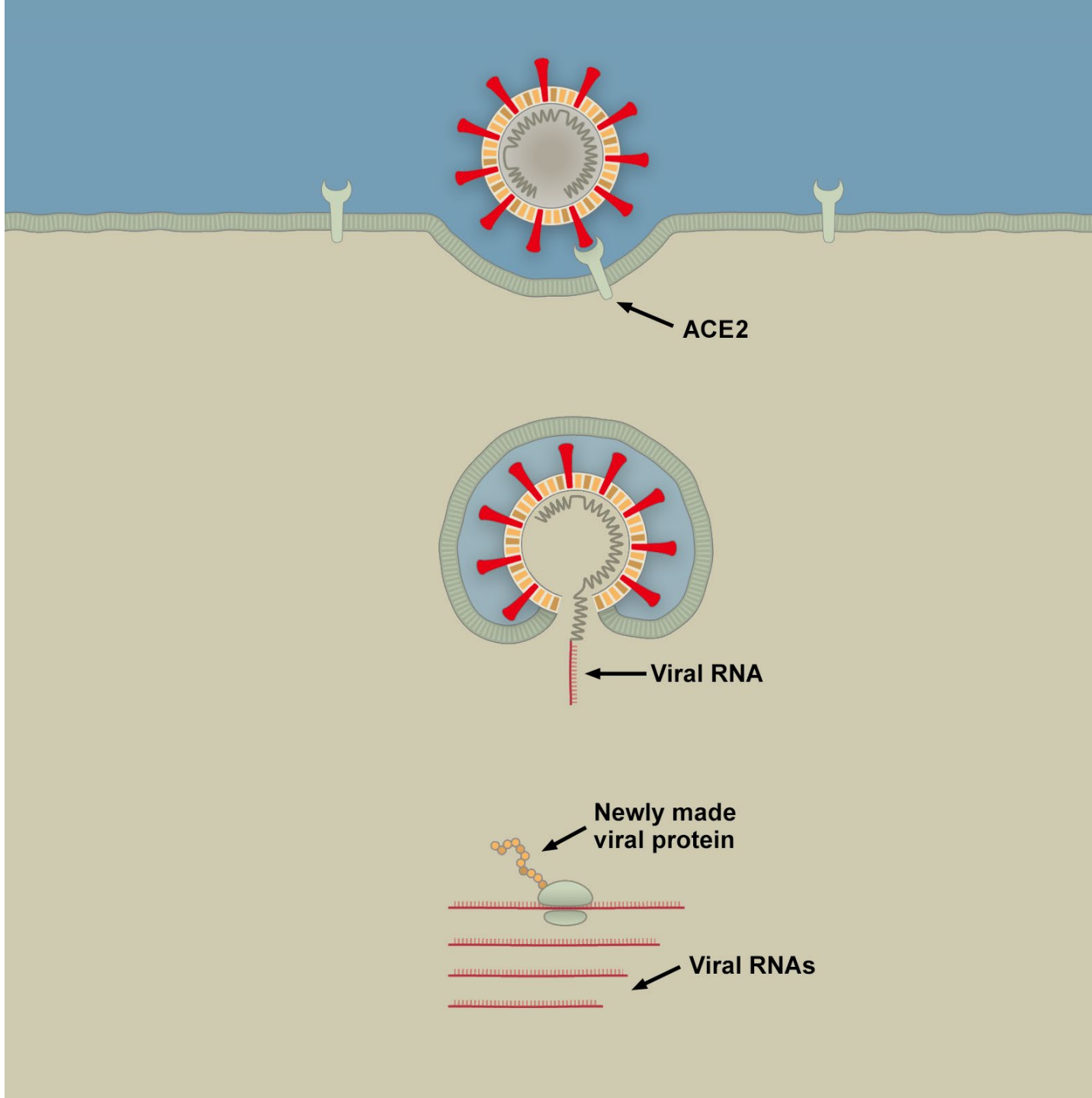


When your immune system sees the virus or a vaccine, it makes antibodies

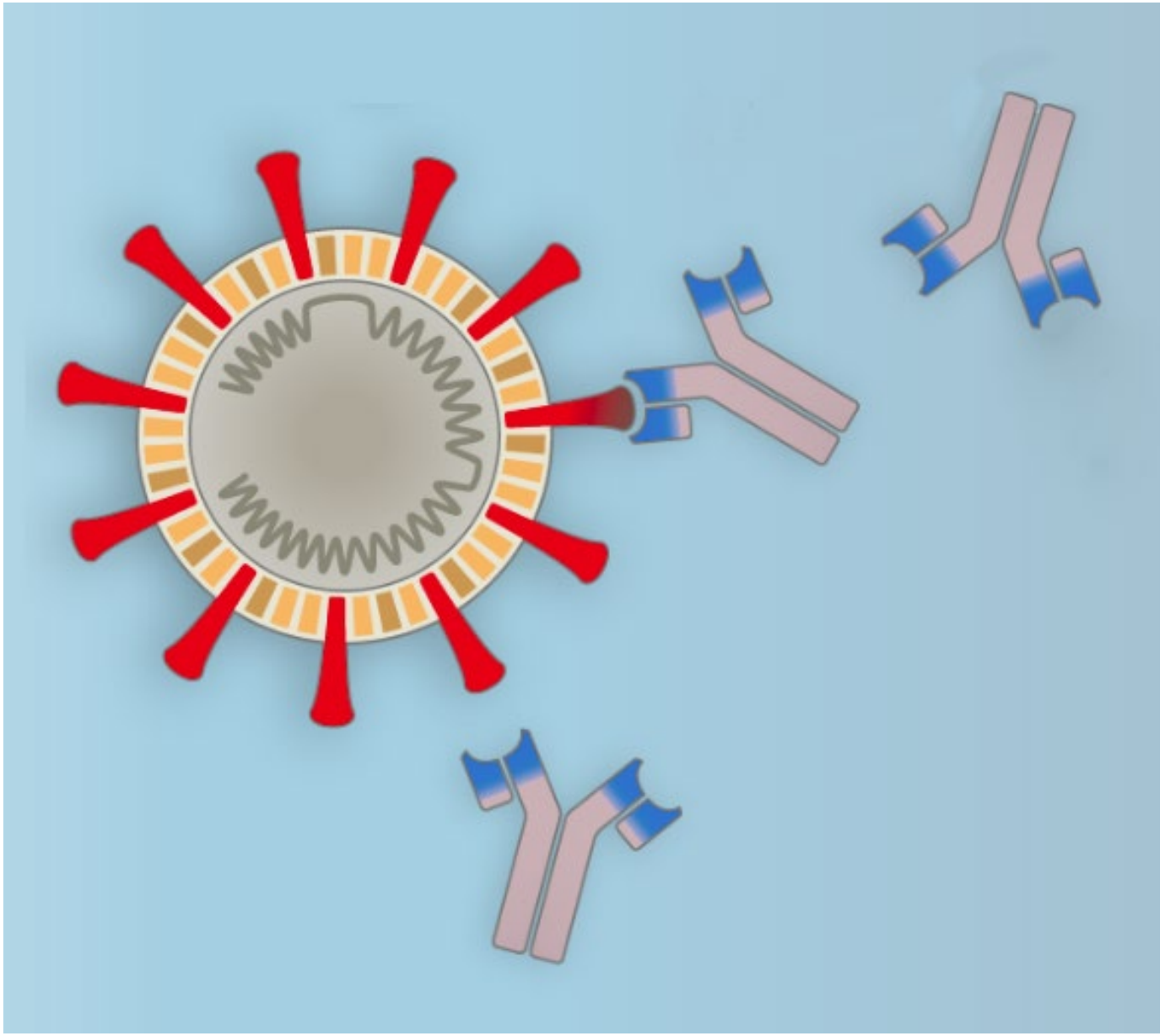
Some of these block the Spike protein, preventing it from working

We call this “neutralization”

Notice blue end of the antibody binds the spike.

The other end also works by recruiting immune cells that
- clear the virus
- kill infected cells

We call these “effector functions”



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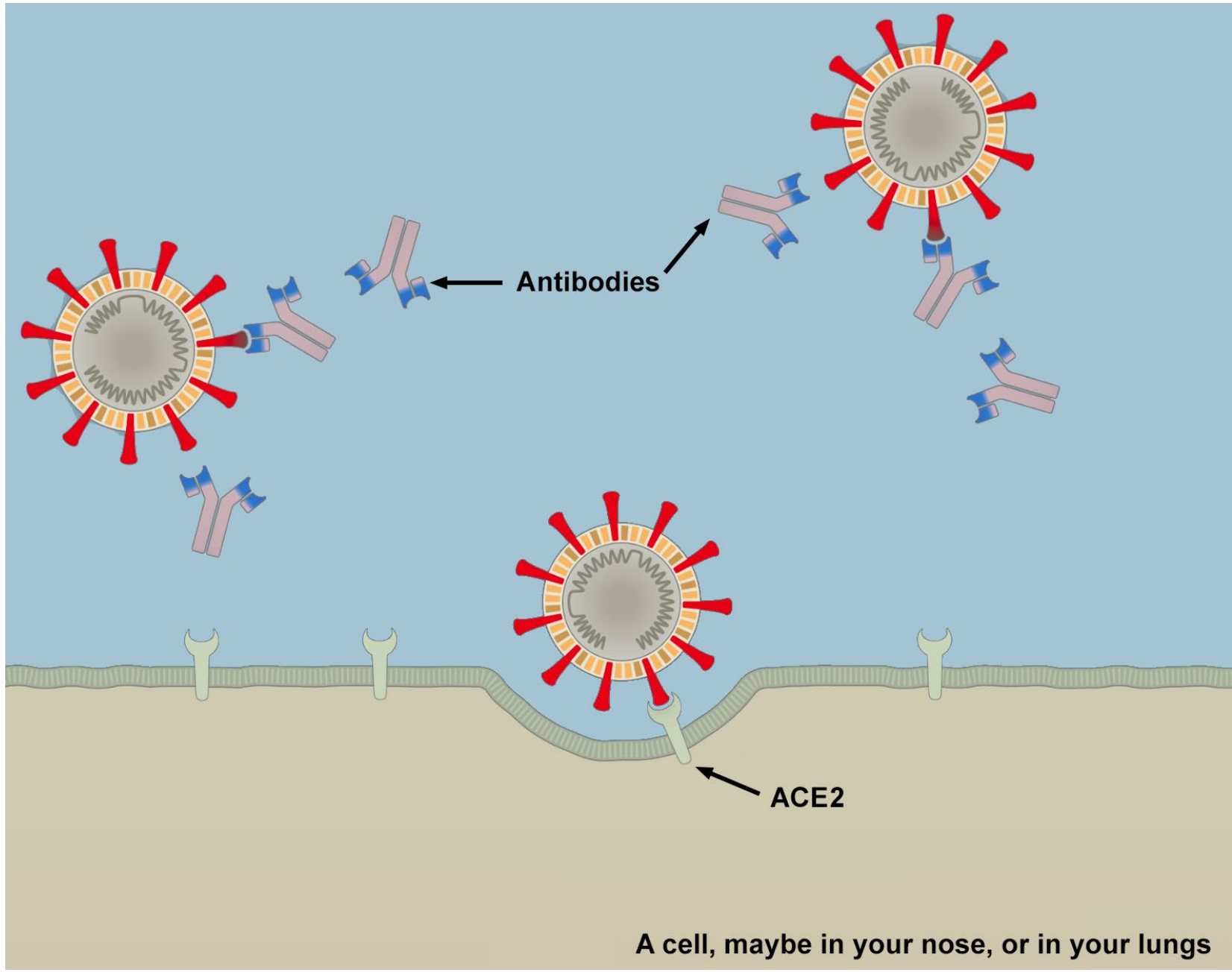
So lets divide antibodies in three groups

1. Antibodies that directly interfere with binding to ACE2 and neutralize the virus. The best ones.

2. Antibodies that bind elsewhere on the spike. These might be useful, maybe signaling immune cells to remove the virus.

3. Useless antibodies that bind other viral proteins, for example nucleocapsid (infected people make lots of these)



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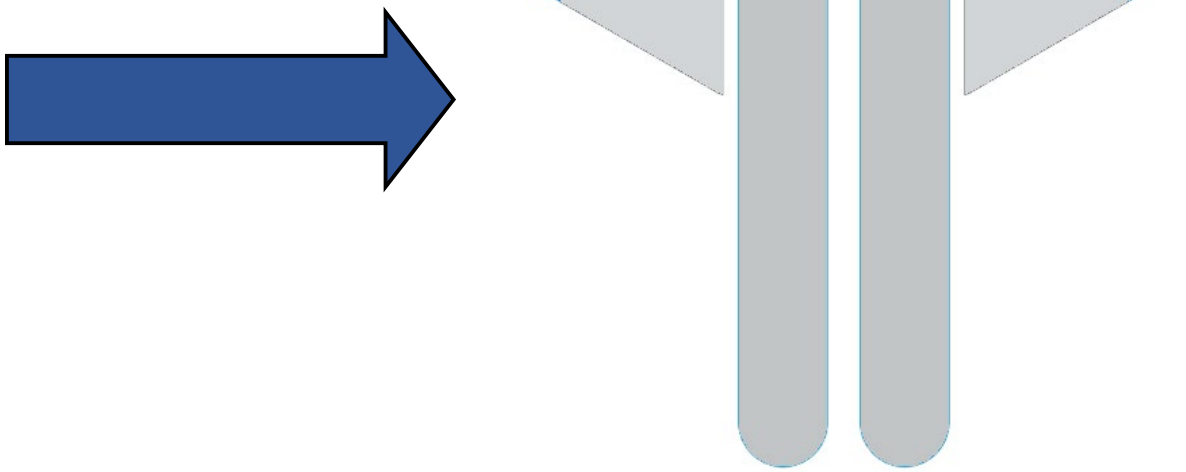
Convalescent Sera

efficacy, safety



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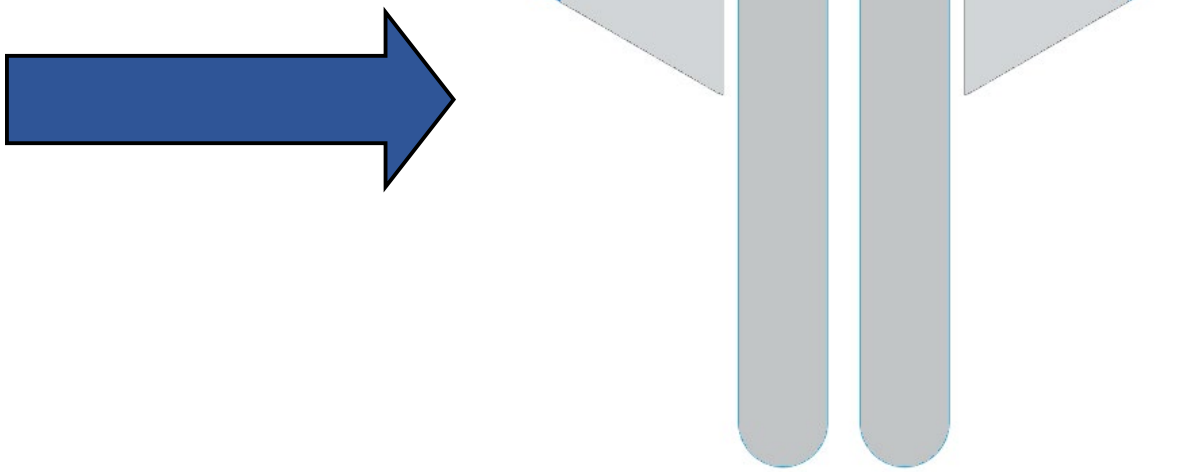

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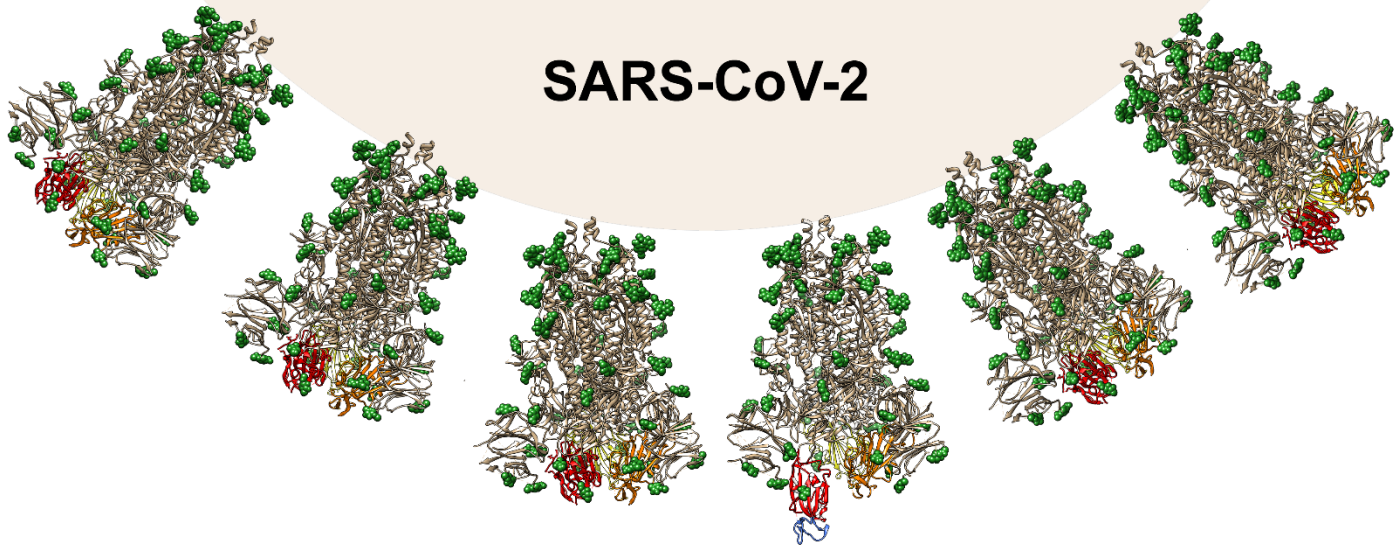
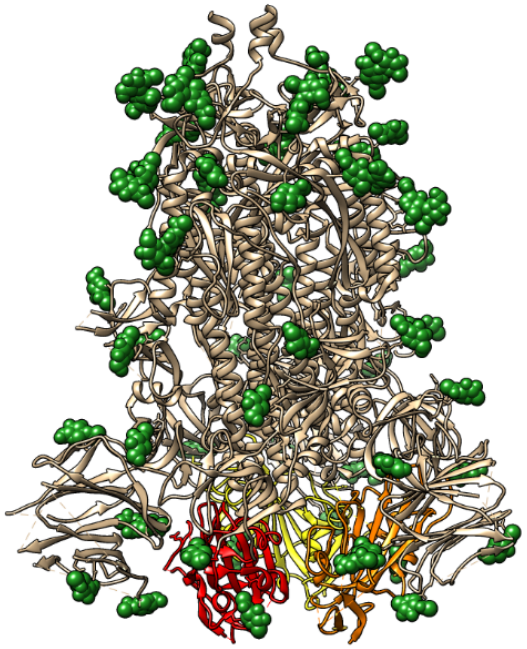
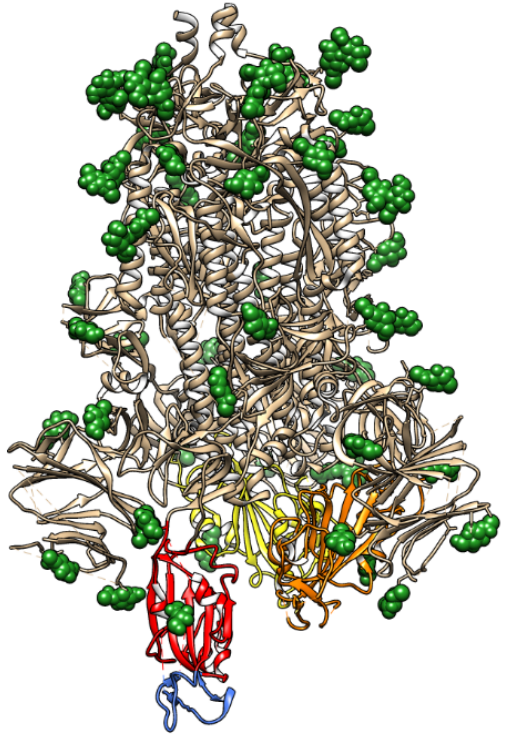
SARS-CoV-2

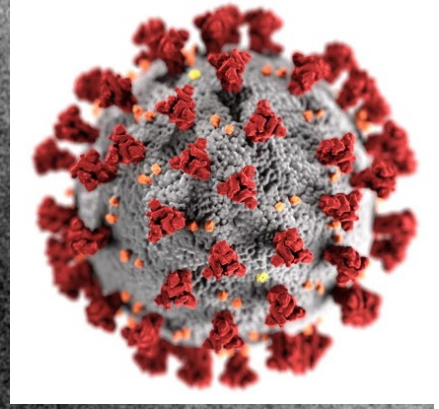


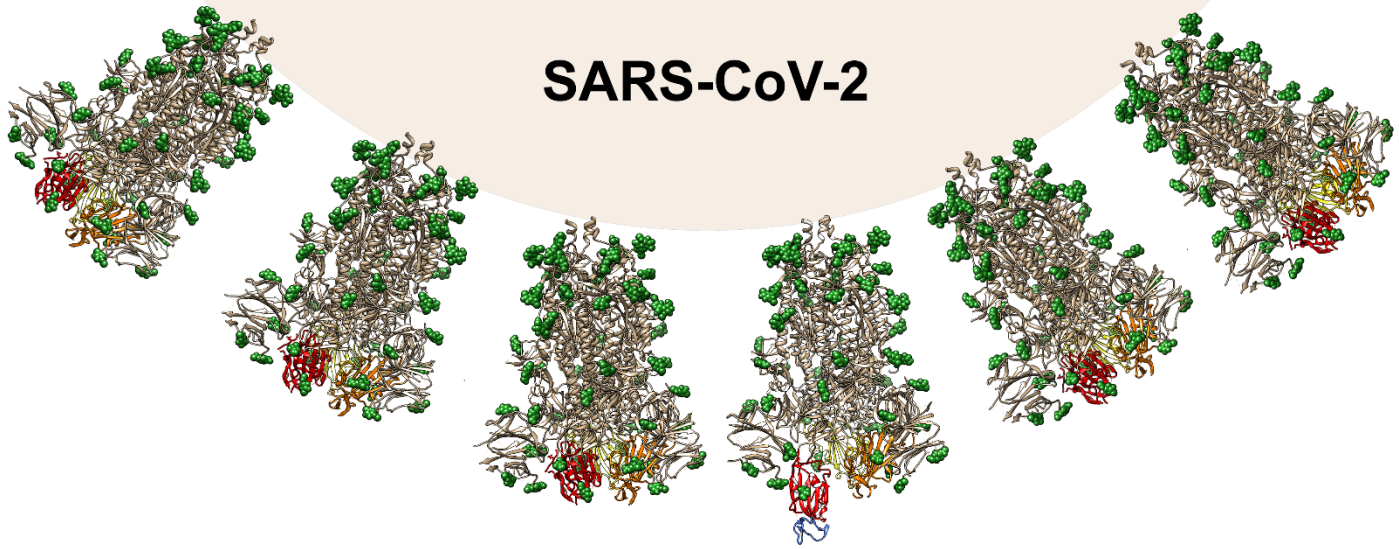


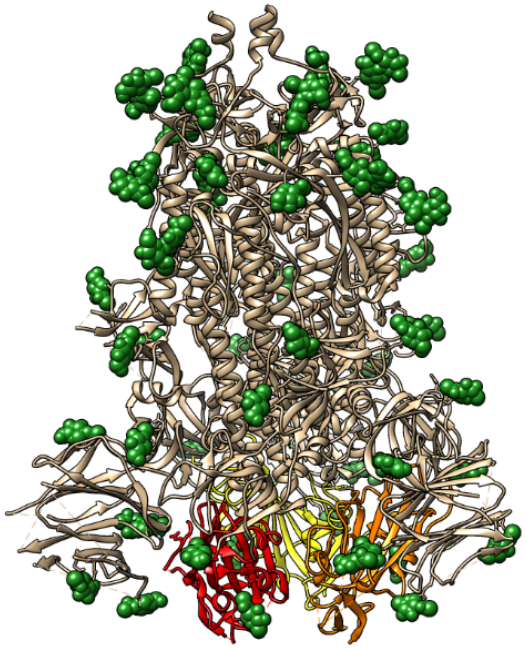
Closed spike



RBD exposed







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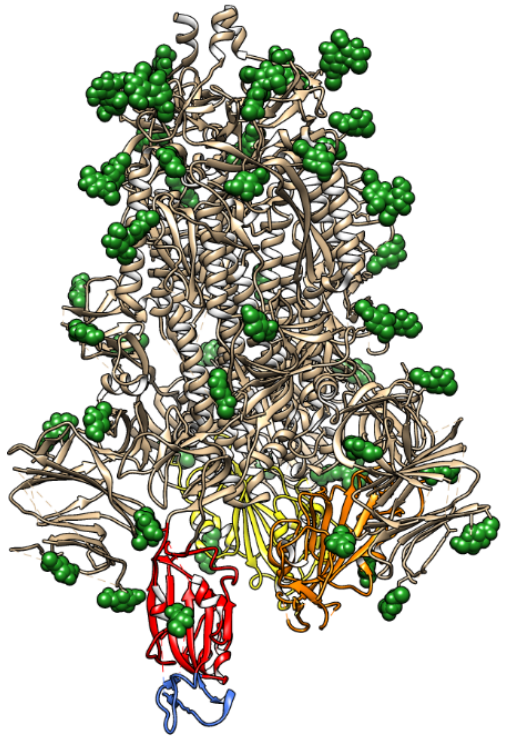

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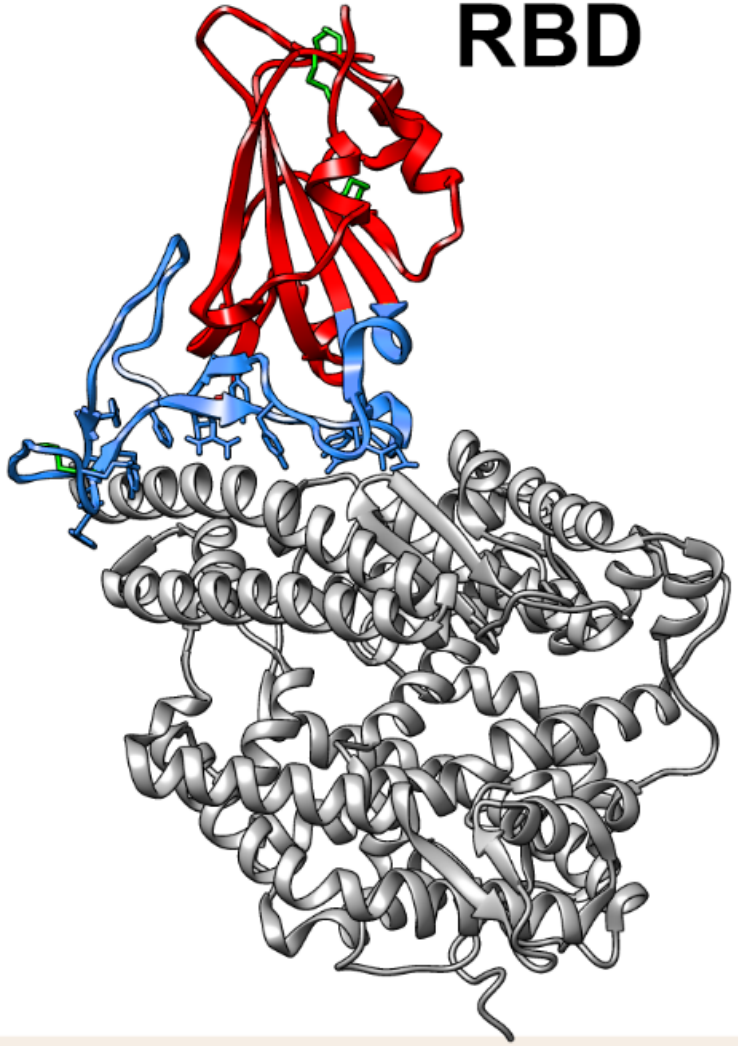
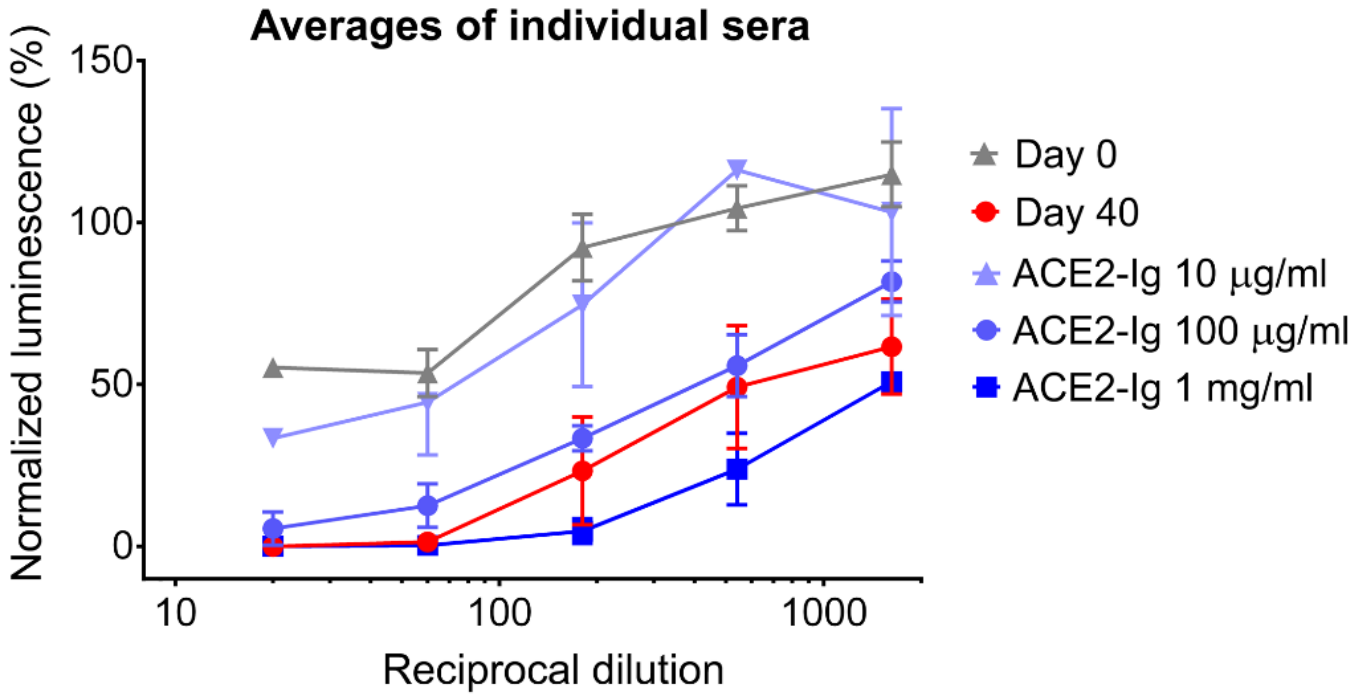


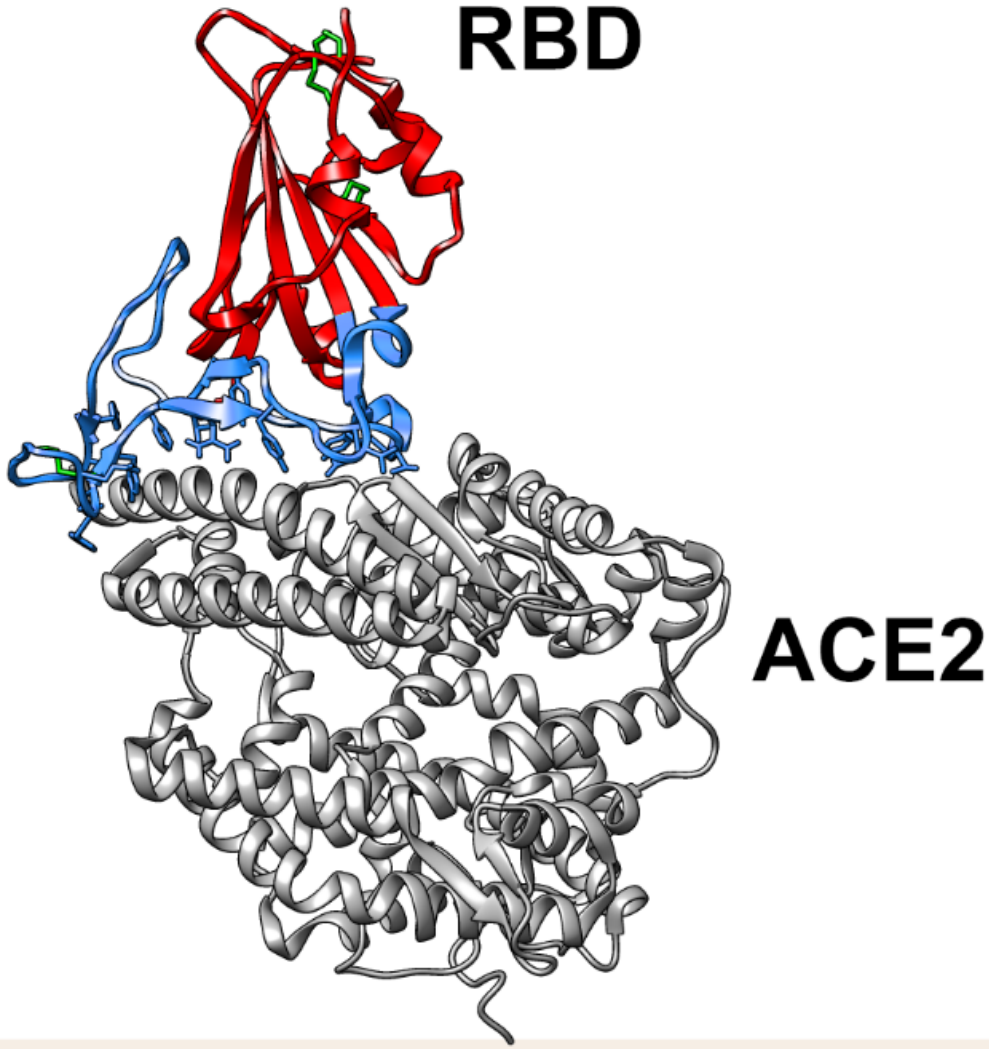
Cell membrane

Is the RBD sufficient as a vaccine? (apparently, and no ADE)



Data from Quinlan et al., submitted

https://www.biorxiv.org/content/10.1101/2020.04.10.036418v1



Cell membrane

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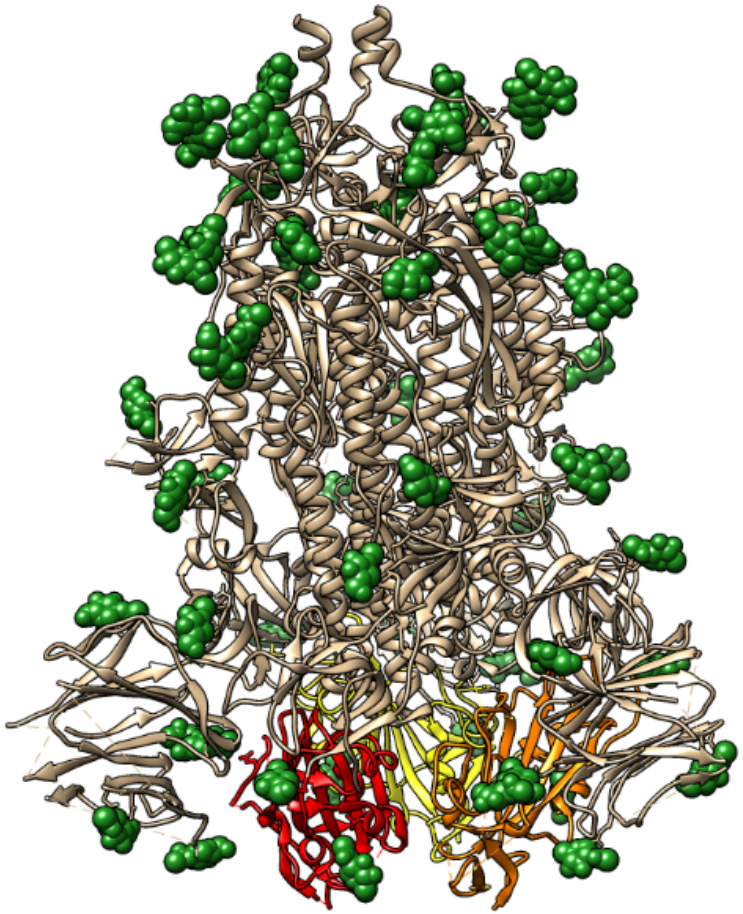
But what's the best antigen?



Soluble trimer?

The RBD is much easier to produce.

The trimer has more antibody-binding regions.

This is a double-edged sword.

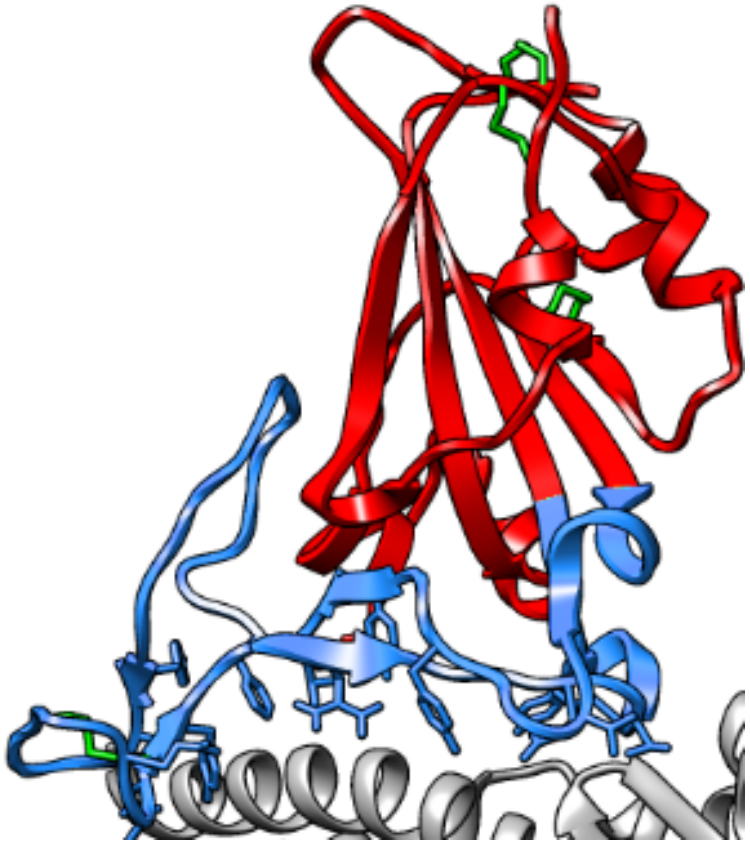
Some are regions immunogenic but distracting and useless.

But antibody effector response are stronger when multiple antibodies bind the same target at once.

However if you think neutralization is more important, focus on the RBD.

Trimer prime/RBD boost?

Necessary if early vaccines don't protect the elderly, immune-compromised.



The RBD alone?

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Biologics

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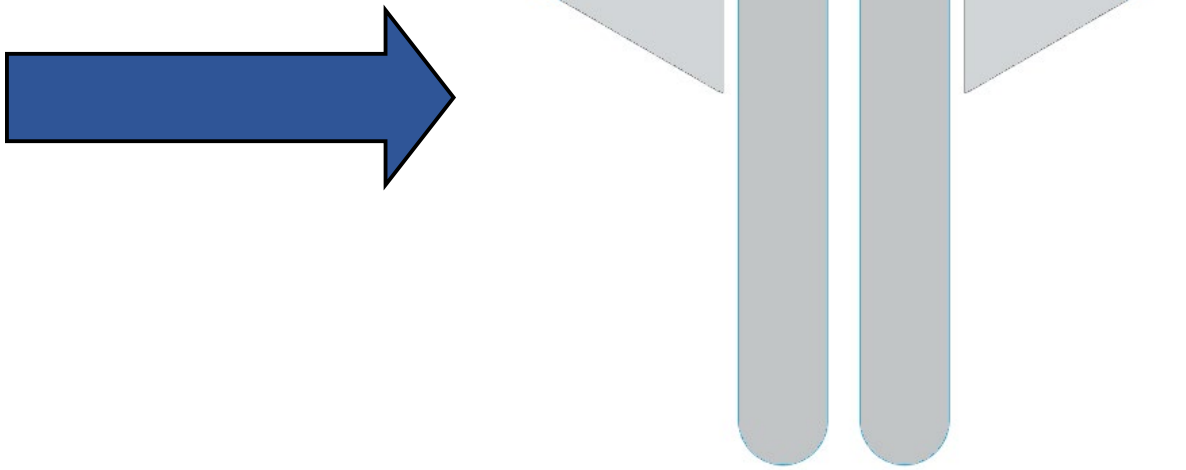
Convalescent Sera

efficacy, safety

Testing

PCR, serological



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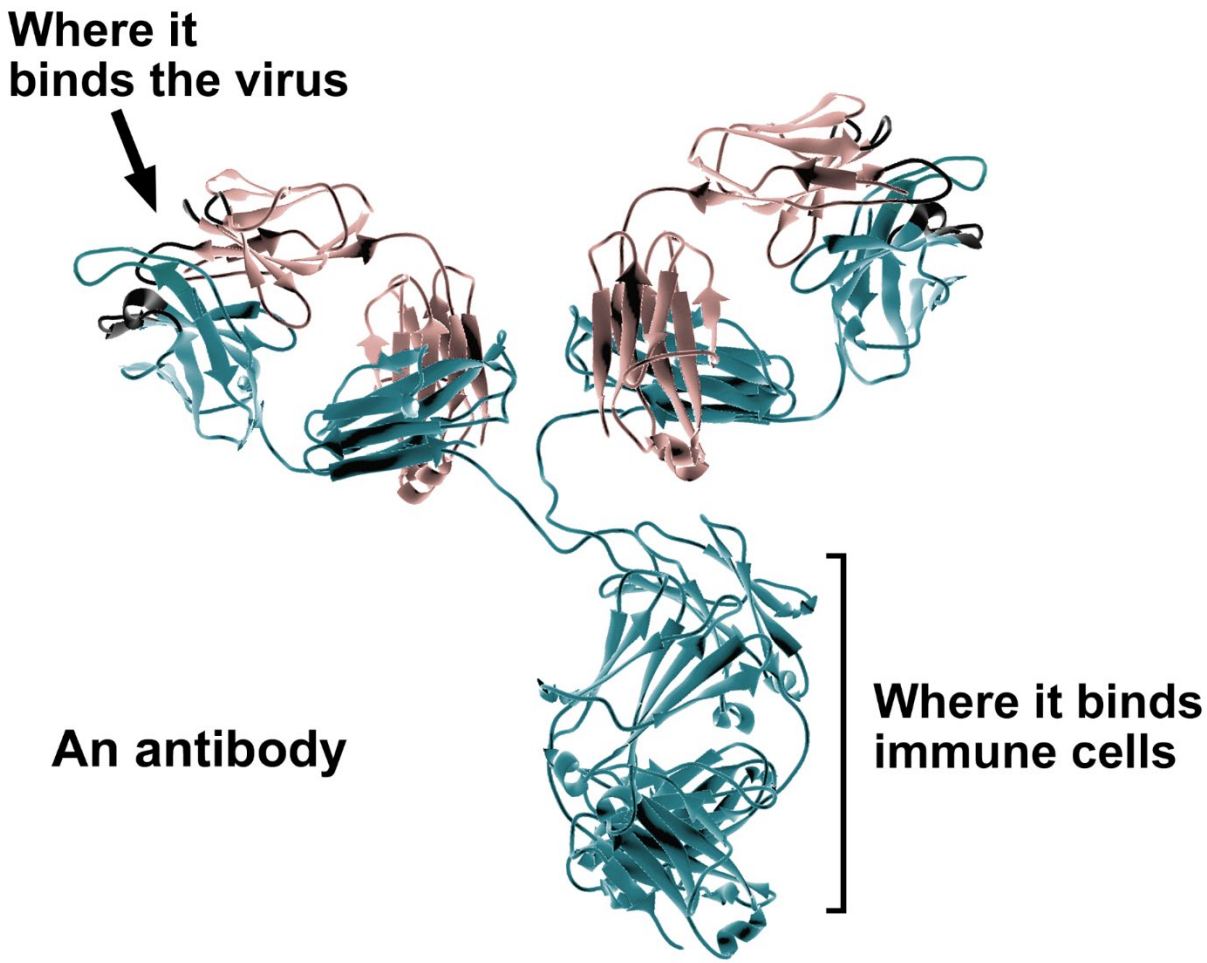
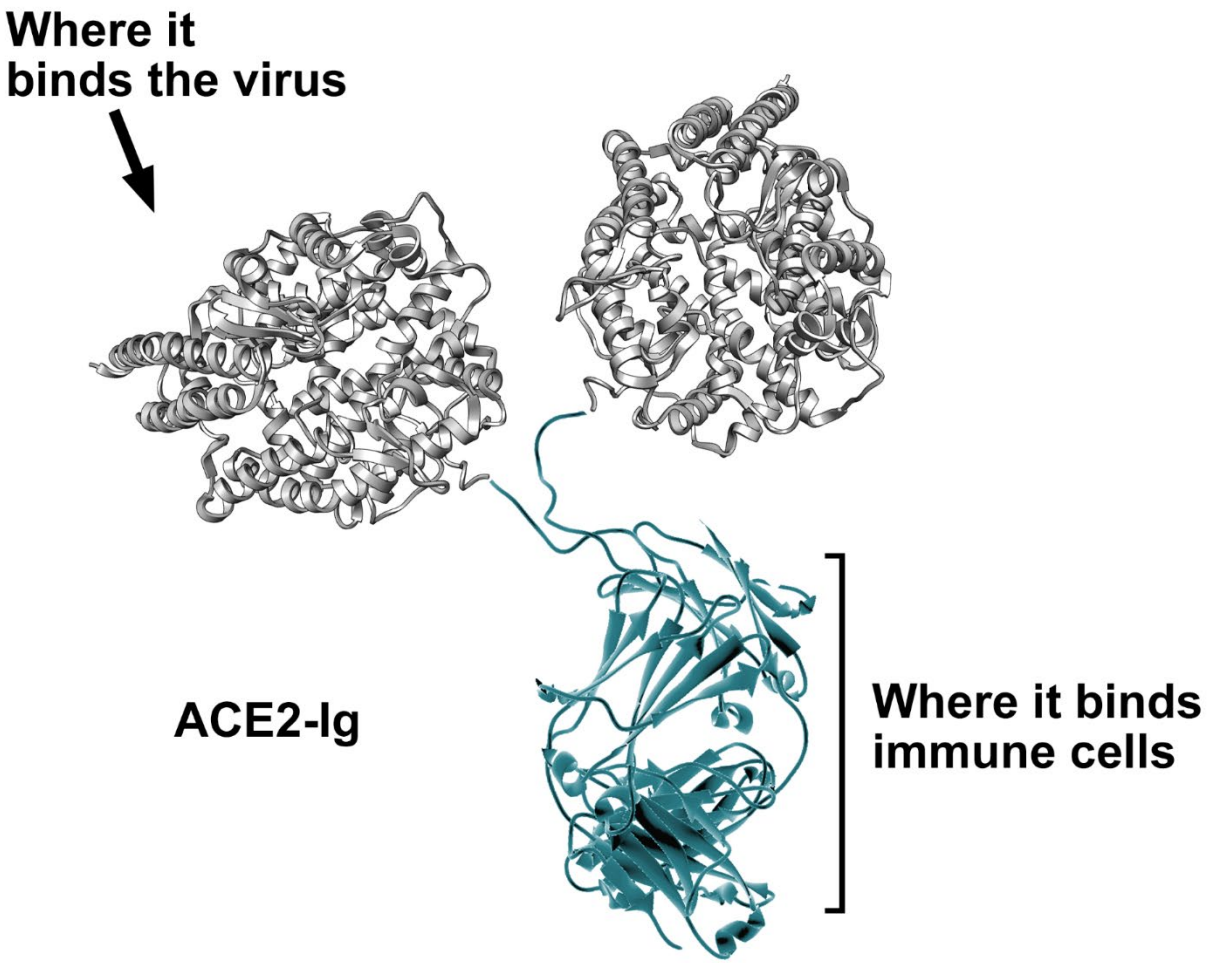
ACE2-Ig can work like an antibody





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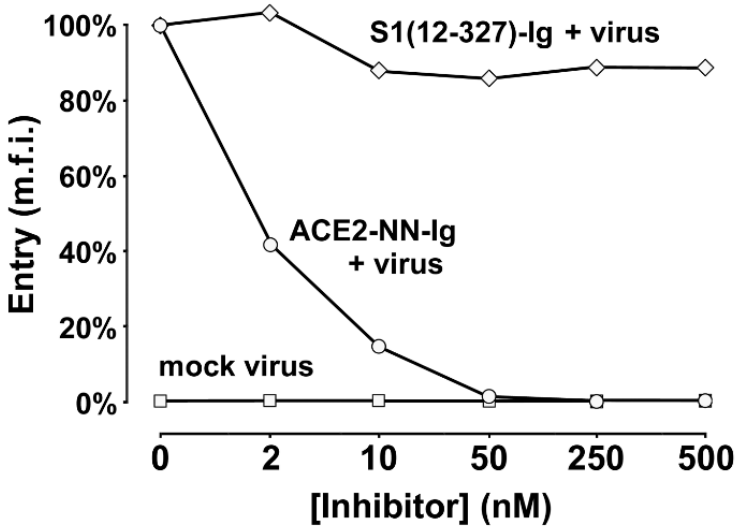

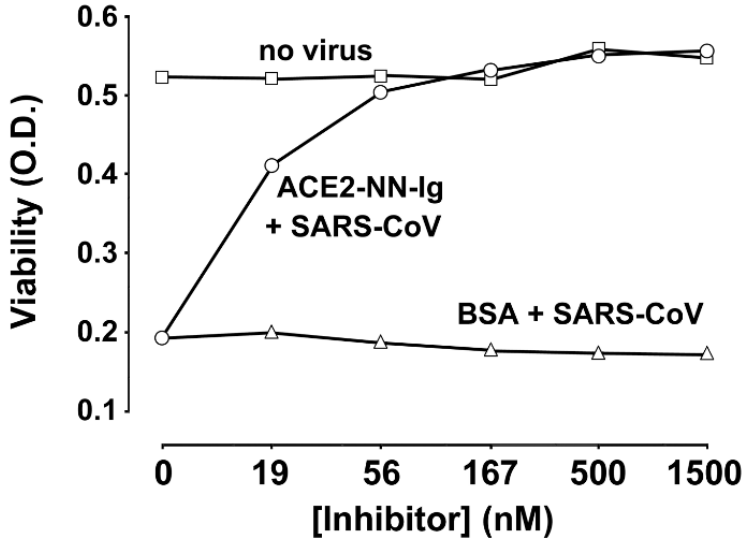

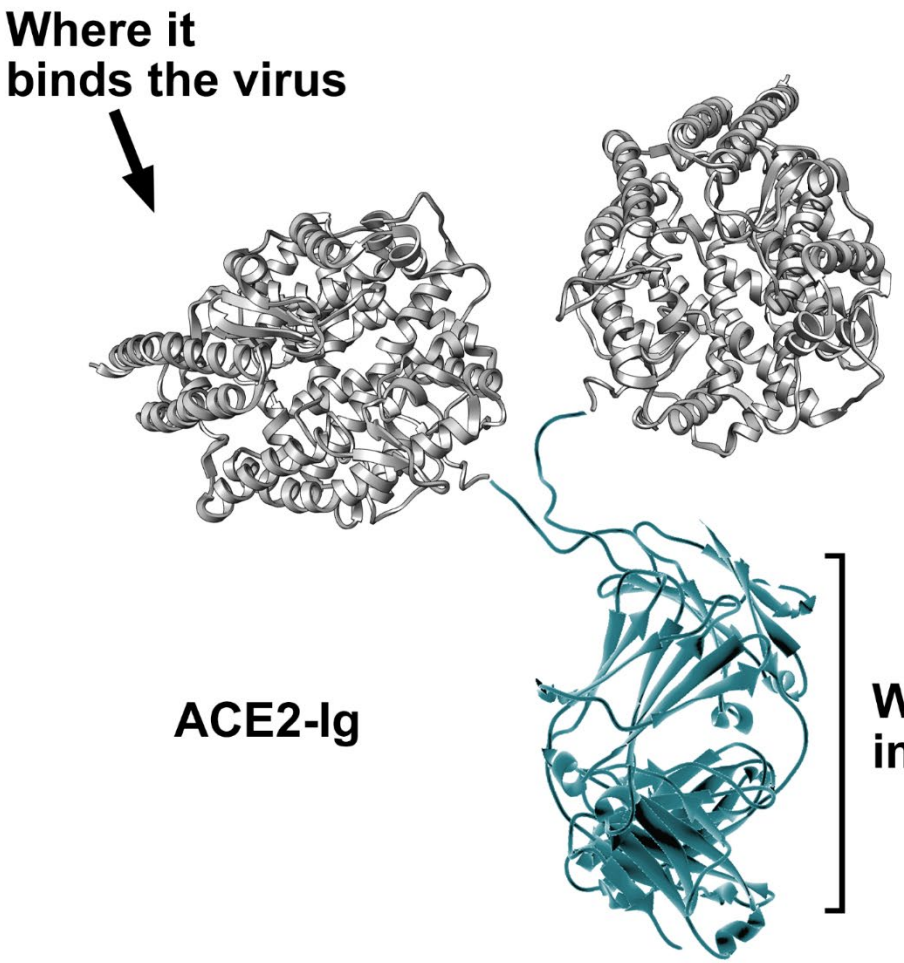

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ACE2-Ig can work like an antibody

Advantages over antibodies

Neutralizes SARS-CoV-1, SARS-CoV-2, SARS-CoV-3, and especially SARS-CoV-2.1

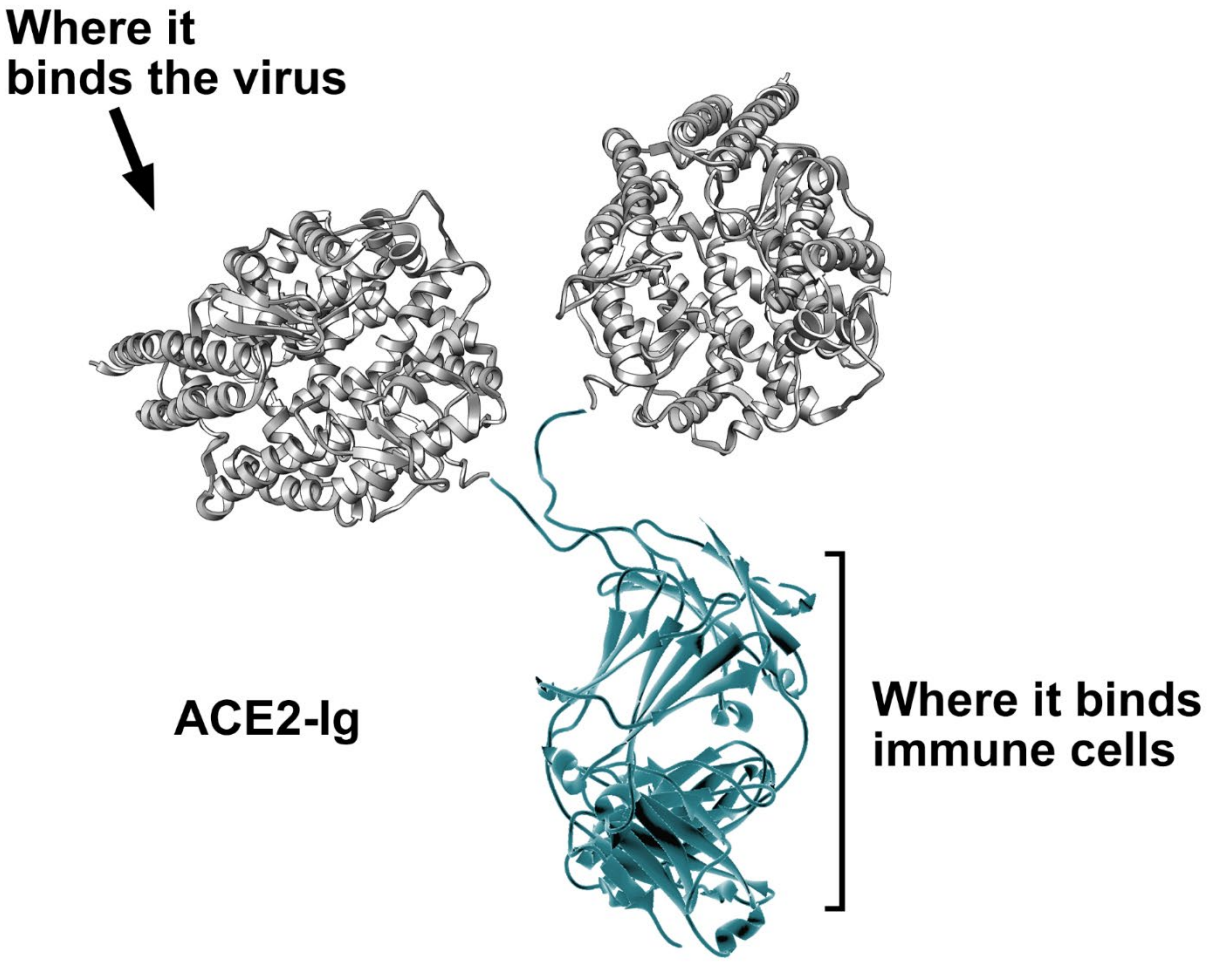
Very potent, and – as shown with SARS-CoV-1 – transfer of elements from reservoir species can increase potency further

Only need one

Disadvantages

Shorter half-life

Therefore better for therapy
than for prophylaxis



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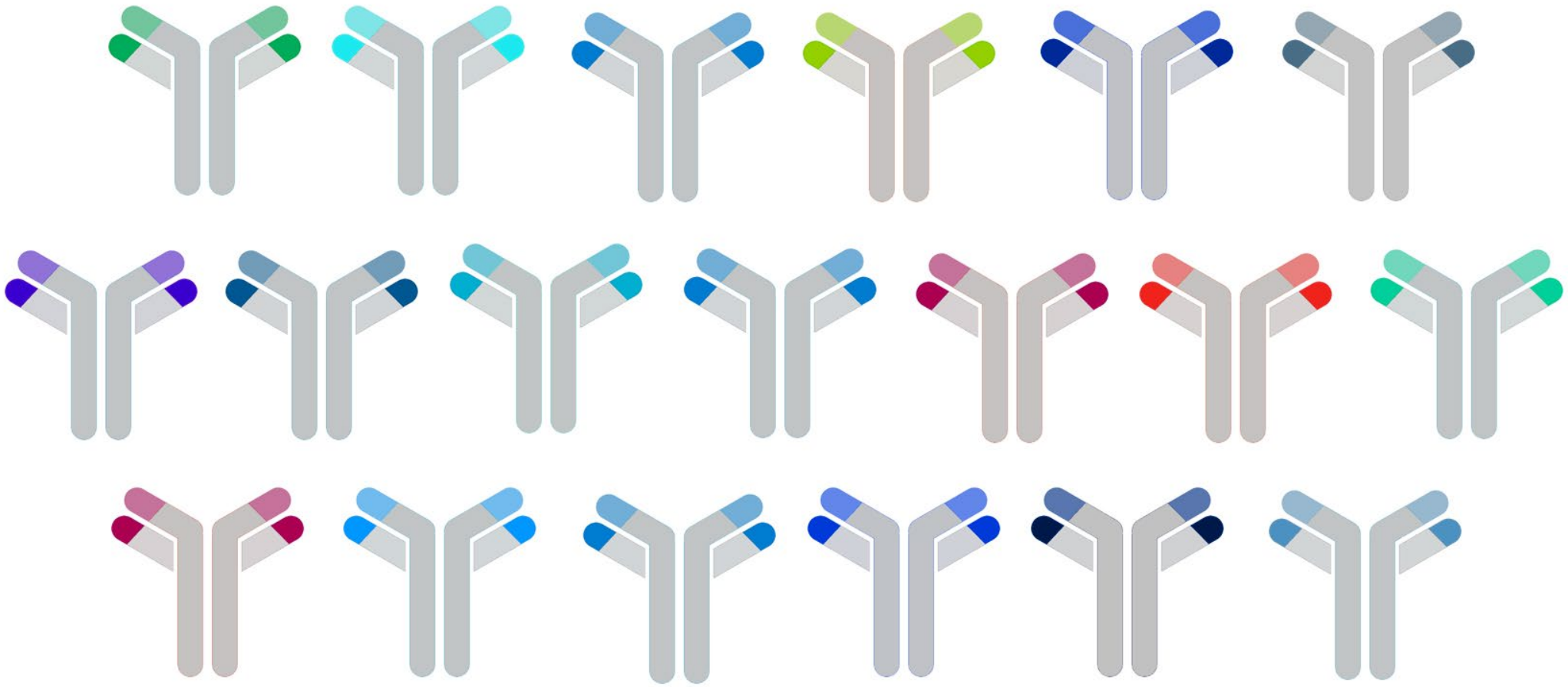
Convalescent serum, an important stop-gap



But which sera is good (neutralizing), which sera is less good, and can any sera cause harm?
Also, expensive, not scalable.

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So where are we?

Convalescent Sera – *A high immediate priority that will save lives.*

We need to be smarter about what sera is most effective.

Biologics – *Straightforward path and real hope.*

A cocktail of two or three antibodies (one against the RBD) would protect our first-responders for > month or two.

A high-potency ACE2-Ig with an antibody-like half-life could replace the cocktail.

Vaccines – *Easier than for most viruses.*

Most approaches will work at least partially in healthy individuals.

A vaccine will ultimately replace an antibody cocktail.

Early vaccines will be inadequate for older, immunocompromised persons.

An RBD vaccine is effective, easier to make, and may be best for world-wide use.

Bottom line – *The science is nearly done.*

Testing, manufacture, distribution are what keep us at home.

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Thank you

Brian D. Quinlan
Huihui Mou
Lizhou Zhang
Yan Guo
Wenhui He
Wenhui Li
Michael Moore
Michael Alpert
Charles Bailey
Guocai Zhong
Hyeryun Choe
BMGF
NIAID/NIH

Your questions…

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