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

February 4, 2021
for Bernstein

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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 fur, leading to an order to kill millions of the animals.

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

Chronic infection > more mutation > spillover into other humans

HIV-1, tuberculosis
UK variant B.1.1.7

First known B.1.1.7 sequence

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

First known B.1.351 sequence

cov-lineages.org
B.1.351
“South African” variant

- imported_only
- local_transmission
- No variant recorded

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

South Africa: B.1.351
- L18F
- D80A
- D215G
- K417N
- E484K
- N501Y
- D614G
- A701V

California: Cal.20C
- S13I
- W152C
- L452R

Brazil: P.1, B.1.148
- L18F
- T20N
- P26S
- D138Y
- R190S
- K417N/T
- E484K
- N501Y
- H655Y
- T1027I

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).
Which antibodies still work?

Q: Status of antibody consortium?
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”
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
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

CoVIC-DB Database

Database, LJI: Bjoern Peters, Randi Vita, Mari Kojima, Brendan Ha
Dendrogram and Network Plot

• Competition profiles are compared for similarity and a clustering dendrogram is created.
• A cut-off can be applied to create clusters with highly related profiles and generate a network plot.

Sorted by “footprint” on coronavirus spike

Carterra: Dan Bedinger
Sapphire 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
Bin 3
Bin 4
Bin 5
Bin 6
Bin 7
Bin 8
Bin 9
Bin 10
Bin 11
Bin 12

CoVIC
*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

Framework to map which therapeutics to deploy

<table>
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<th>Epitope bin</th>
<th>Antibody diminished/lost</th>
<th>Antibody activity improved</th>
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# NN= No neutralization of wild type
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

not much difference

these are worse

not much difference
Q: Should I get a vaccine if the virus is changing?

**No vaccine**

The switch is “off”

**With vaccine**

Perfect match
No vaccine  

The switch is “off”

With vaccine  

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 you still spread it?

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

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.

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.
Modern 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
before

“post”-fusion
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
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.
My lab: Third-generation 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.
Spike sequence diversity, sarbecovirus group

susceptible to mutations

Current therapeutics target here

An antibody that bound here might be more resistant to mutation

unchanging variable

Sequence entropy (bits)

Kshitij Wagh, Bette Korber, LANL
In my lab:

Import individual B cells

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
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
Competition profiles are compared for similarity and a clustering dendrogram is created. A cut-off can be applied to create clusters with highly related profiles and generate a network plot.

250+ therapeutics from four continents which are susceptible to, or resistant to, emerging mutations. Sorting by “footprint” on spike can produce an arsenal of appropriate therapeutic options. Engineering the spike can lead to a better vaccine and better tool.
Human Immunology

Infectious Disease & Vaccines

Cancer

Autoimmunity & Inflammation
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