Antibodies-COVID-19 | Krammer Laboratory

David R. Kotok

Wed Mar 25, 2020

An Antibodies Test: A Vital Weapon in the Fight Against COVID-19.

While the US continues to struggle without enough diagnostic tests for COVID-19, the quest continues for a different holy grail, a test to tell us who has already been exposed to the virus and now has some immunity.

The exciting news on the serologic testing front this past week is not a test that will come in a package to be shipped around the world, though those are in development. It is an assay developed by a team at the Mount Sinai Health System Translational Science Hub – a procedure that can be replicated in any lab, using a blood sample. On March 19, health policy analyst and writer Laurie Garrett described it on Twitter as “a MAJOR breakthrough in the #COVID19 fight…” (https://twitter.com/laurie_garrett/status/1240823073399586817?s=11).

One of the authors of the March 19 paper published on medRxiv, Florian Krammer of the Krammer Lab of the Icahn School of Medicine at Mount Sinai, explained on Twitter how the results of the new blood test can be utilized: “(A) With this assay we can figure out who was infected and who wasn’t. That means we can determine the true infection rate and infection fatality rate. (B) We can use the assay to screen for people who seroconverted and are now immune, and they can donate their serum, and it can [be] used to treat patients. (C) We can test healthcare workers and ask the ones who are already immune to work with infectious patients. In that way, the virus is not easily spread to colleagues or other patients. And (D) we can now use this assay to better study how our immune response reacts to the virus.”

Beyond those vital uses noted by Dr. Krammer, a serologic can test tell us who, given a measure of immunity, is in the best position to go back to work, to keep society moving and vital services functioning, and to begin to revive the economy after its COVID-19 swoon.

A vitally important study from Imperial College of London’s COVID-19’s Response Team, published on March 16, finds that the world may suffer the rolling impacts of COVID-19 outbreaks for a full 18 months (“Impact of non-pharmaceutical interventions (NPIs) to reduce COVID- 19 mortality and healthcare demand,” https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf), until the human population achieves herd immunity or until people have been vaccinated.

The findings in the Imperial College of London study, headed by epidemiologist Neil Ferguson, Director of J-IDEA and the MRC Centre for Global Infectious Disease Analysis, have now shaped the path of COVID-19 policy in the US and Britain, and their economic implications are challenging. (Dr. Ferguson is currently weathering COVID-19 himself, and we wish him a complete and timely recovery.)

Eighteen months is a long haul. In the meantime, the world needs strategies to choreograph both the physical distancing measures designed to reduce transmission and the vital work of keeping critical production and services going. An antibody test for COVID-19 can help us to find that balance.

For more information about the serologic test developed at Mount Sinai, readers may wish to read Gretchen Vogel’s article, “New blood tests for antibodies could show true scale of coronavirus pandemic,” https://www.sciencemag.org/news/2020/03/new-blood-tests-antibodies-could-show-true-scale-coronavirus-pandemic.

Here is a page on the Krammer Lab's website that summarizes their breakthrough work: https://labs.icahn.mssm.edu/krammerlab/covid-19/.

Finally, here is the Mount Sinai team's paper, "A serological assay to detect SARS-CoV-2 seroconversion in humans," https://www.medrxiv.org/content/10.1101/2020.03.17.20037713v1.

Dr. Krammer's sometimes technical Twitter thread about the assay is appended below (https://twitter.com/florian_krammer/status/1240432285184405505?s=20).

David R. Kotok
Chairman of the Board & Chief Investment Officer
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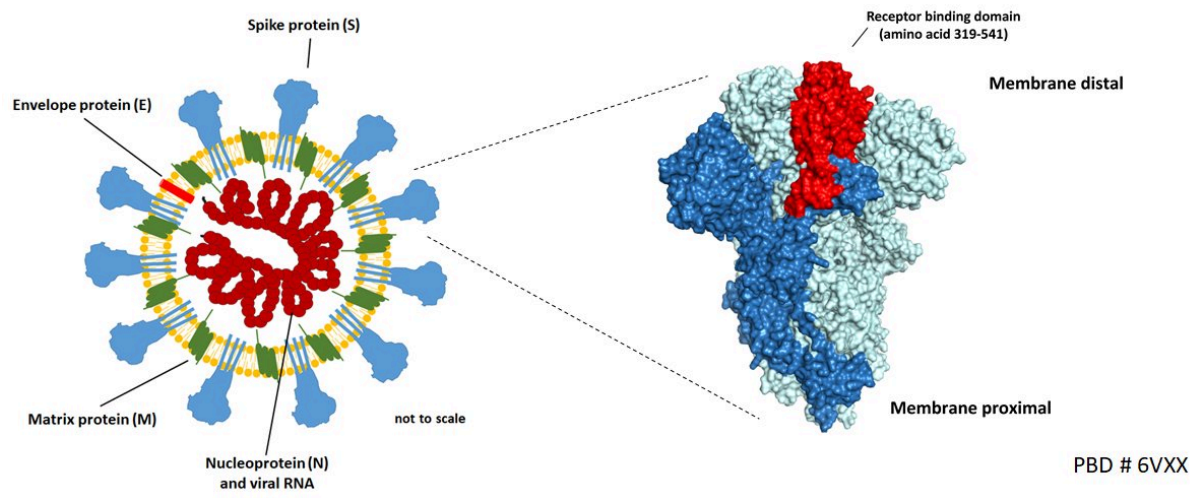
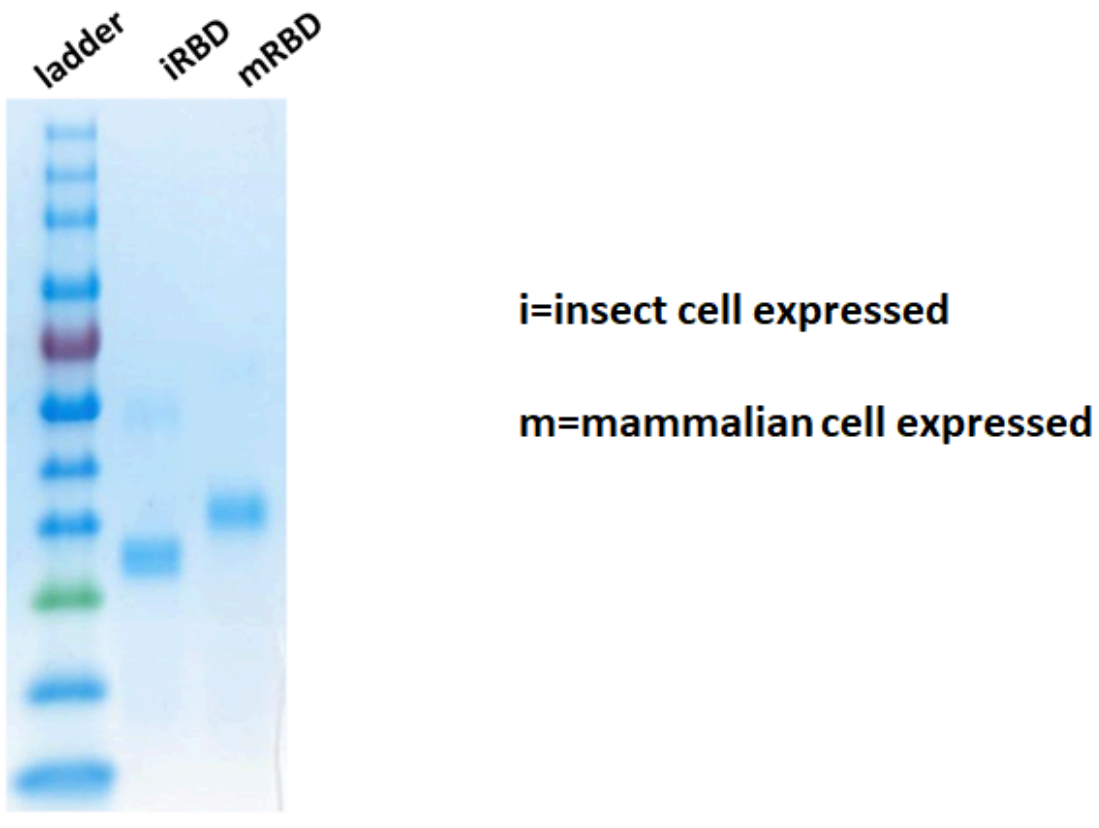
A thread by Florian Krammer

Thread: 1) OK, so I promised to explain the manuscript that we just put on medRxiv (https://www.medrxiv.org/content/10.1101/2020.03.17.20037713v1).

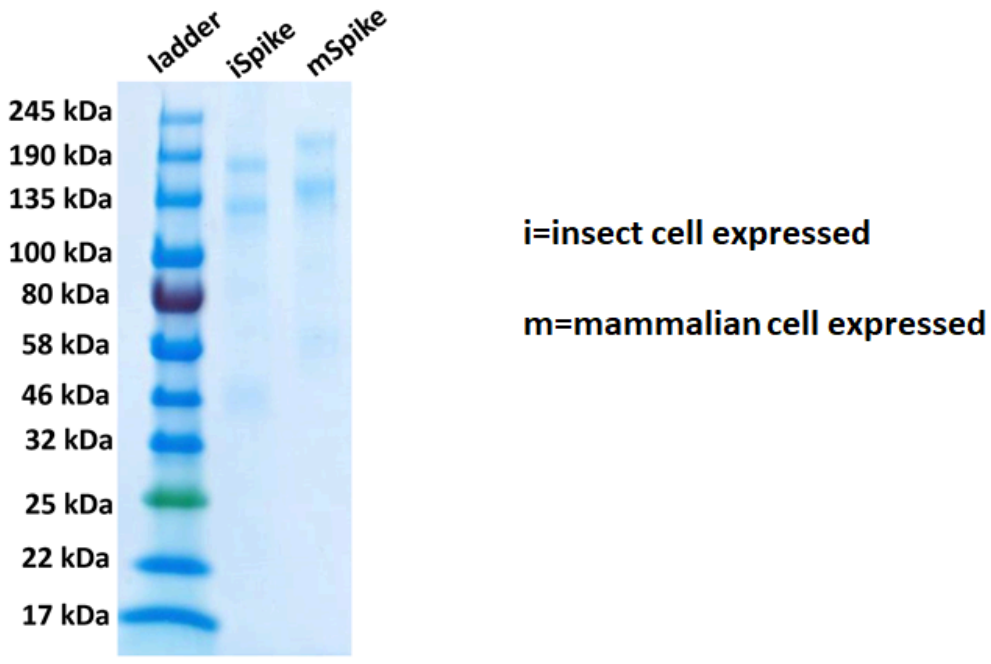
First, I wanted to thank our awesome collaborators @VivianaSimonLab at Sinai, @Olli_Vapalahti @hepojoki at University of Helsinki and @kedzierskalab at University of Melbourne. This would not have been possible without them. Now, typically, when we get infected with a virus, we make antibody responses, especially against proteins on the surface of the virus. Often these antibodies can neutralize the virus and protect us from getting infected again. The main target on the surface of most coronaviruses is the spike protein, or S. below you see a model of the virus and a visualization of a crystal structure of the spike of SARS-CoV-2 (solved by @veeslerlab - heroes!).



Now, in order to detect antibodies, we use an ELISA or enzyme-linked immunosorbent assay. For this, an antigen – in this case the spike protein – is coated on a sticky plastic plate (a miniaturized format). Then we let serum from patients react with it and can detect that. So, first, we needed the spike antigen. We don't want to sue the virus for various reasons. So we make recombinant antigen. We can do that in insect cells or in mammalian cells in cell culture. We made two versions: a soluble version of the full spike trimer and the receptor binding domain (RBD) which is part of the spike on its own (the red part in #4). Then we run them on a gel to see if they look OK and purified. i=insect, m=mammalian. Here are the recombinant RBD proteins. They turned out very nicely.



And here are the full-length proteins. We added several stabilizing mutations. Nevertheless, we got two bands. One full-length version and a degradation product. We don't know why but think this is not important for assay.

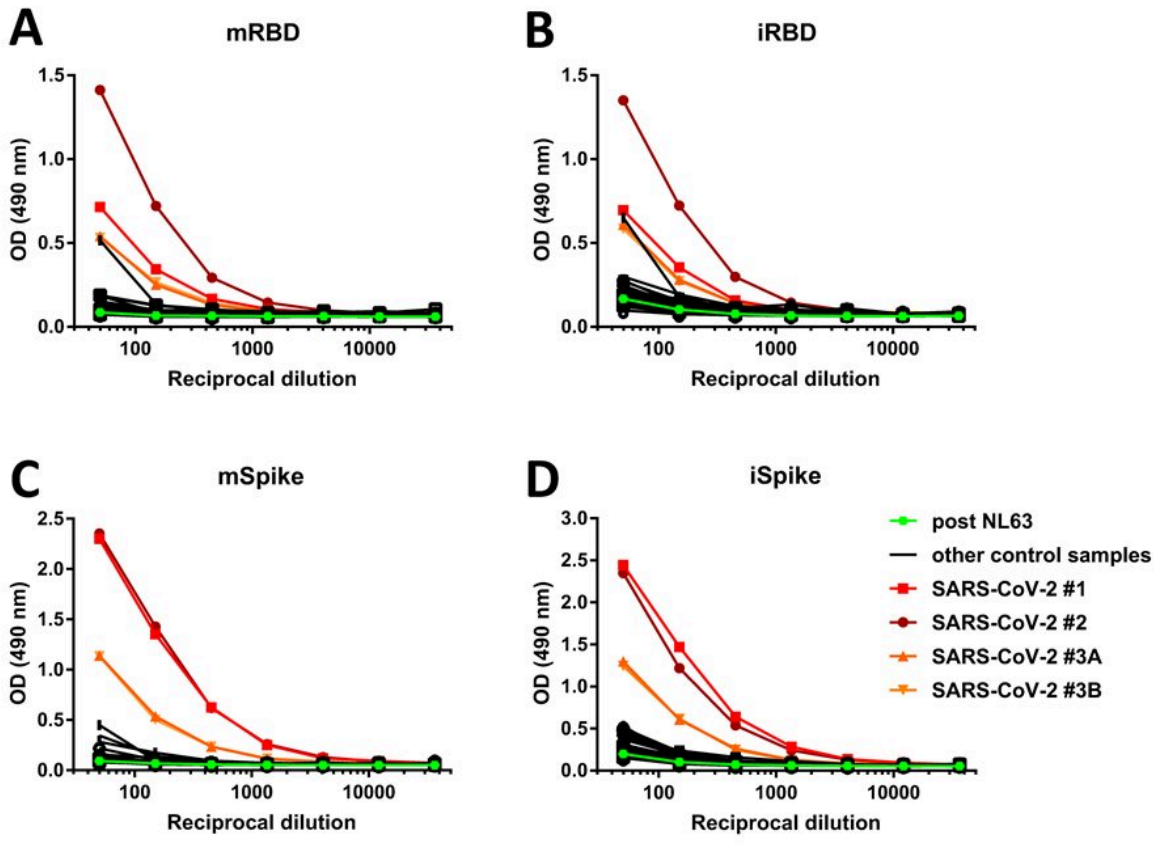


So, we had the following sera from controls (not exposed to COVID19) and from COVID19 patients. The controls are from different age groups. Also, we had serum from a person with a confirmed NL63 infection. NL63 is a human CoV that causes common cold and uses the same receptor as SARS-CoV-2, namely ACE2. We thought if we get any cross-reactivity to the spike of SARS-CoV-2, then with this sample.

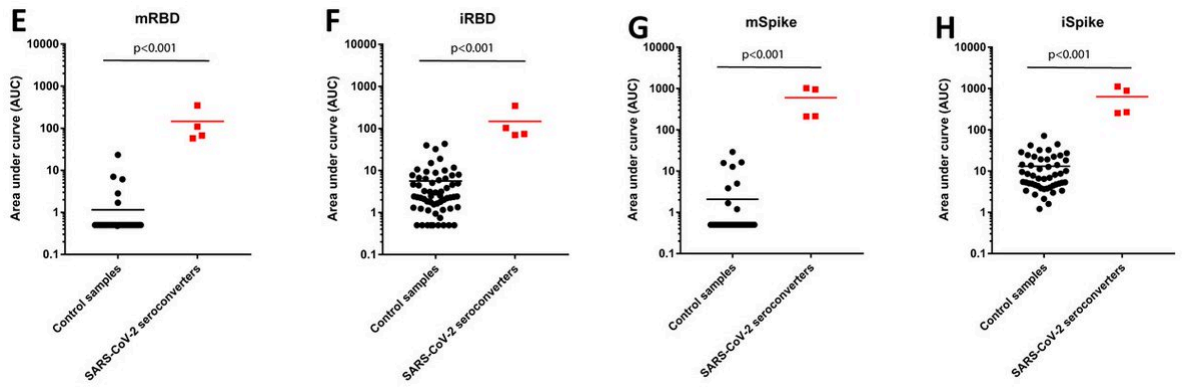
- **Personalized Virology Initiative samples (late 2019/early 2020)**
  - **20-29: n= 6**
  - **30-39: n=19**
  - **40-49: n = 13**
  - **50-59: n = 7**
  - **60 or older: n=6**
  - **Included a sample taken 30 days after confirmed NL63 infection**
- **Samples from patients with COVID19 were obtained from 3 subjects:**
  - **SARS-CoV-2 #1, day 20, 1:160 MN titer**
  - **SARS-CoV-2 #2, day 4**
  - **SARS-CoV-2 #3A and B, days 2 and 6**

  (days are post symptom onset)

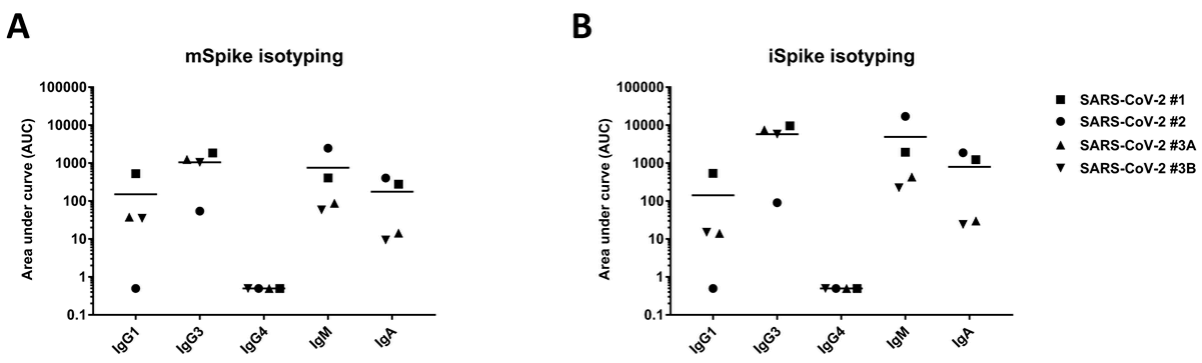
So we ran our ELISAs. For this, the serum is diluted out, and you get these curves. The higher up on the y-axis, the more reactivity. We used all four proteins as substrate to compare. Reactivity was a little lower to RBD than the full-length spike. But it was clearly possible to distinguish sera from COID19 patients (red) and sera from controls (black), including the NL63 serum (green).



We can quantify the area under the curve to make this easier to grasp. Here we saw more background reactivity with the insect-cell-derived proteins than the mammalian-cell-derived ones.



I won’t go into details about isotypes of mAbs we found in the positives, but that was also pretty interesting.



Now, what does this all mean? (A) With this assay we can figure out who was infected and who wasn’t. That means we can determine the true infection rate and infection fatality rate. (B) We can use the assay to screen for people who seroconverted and are now immune, and they can donate their serum, and it can maybe [be] used to treat patients. (C) We can test healthcare workers and ask the ones who are already immune to work with infectious patients. In that way the virus is not easily spread to colleagues or other patients. And (D) we can now use this assay to better study how our immune response reacts to the virus.

And then there are two more take home messages that are important: First, it looks like we are all naive, meaning we have no immunity whatsoever to SARS-CoV-2. That would explain why it spreads so quickly.

And second, it means we make an immune response to the spike. Antibodies to the RBD domain are often neutralizing, and it is likely (but needs to be confirmed) that once the antibody response sets in, we become protected. Please keep in mind that these conclusions are preliminary and based on small numbers. Larger studies to confirm this are needed and ongoing.

We have started to share the reagents globally and hope that this or similar assays can be set up in many places. Finally, I want to thank the student who took the lead on this, Fatima Amanat, as well as my whole group of dedicated students, postdocs, techs and assistant professors who dropped all their beloved influenza work to help out with creating tools to fight SARS-CoV-2.

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