A little more Scientific Prognosis for the Current Crisis

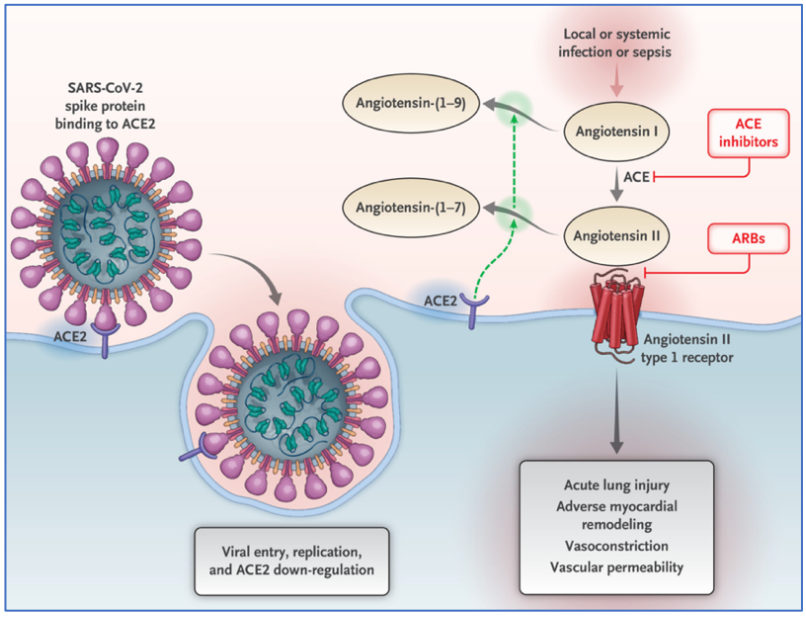
SARS-CoV-2 (the name of the virus) causes COVID-19 (the name of the disease). Sep. 19, 2020

After Wuhan Municipal Health Commission in China reported a cluster of cases of pneumonia in Wuhan, Hubei Province, and a novel coronavirus was eventually identified on Dec. 31, 2019, WHO made the assessment that COVID-19 can be characterized as a pandemic on March 11, 2020. Since then, it drew almost all countries' desperate attention on this planet hoping to find an urgent, eventual solution to get it over with. While medical professionals and researchers have published nearly 60,000 studies through the National Heath Institute (NIH) in mid-September, 2020, people are literally overwhelmed by news or rumors on the pandemic, which is now called info-demic. It seems to make people more perplexed and even depressed because it distracts the entire society from seeing the right exit in a dark tunnel. Evidence based understanding of the virus is the only way for one not to go astray.

Is there an established treatment protocol for COVID-19 yet?

Currently there are no FDA-approved drugs specifically for COVID-19. The FDA has granted emergency use authorizations for some medicines to be used only for certain patients hospitalized with COVID-19 such as convalescent plasma. Instead, FDA posts a guideline saying that they recommend *against* the use of chloroquine or hydroxychloroquine but recommend *for* the use of remdesivir only for Patients with COVID-19 *who require supplemental oxygen*.

Nonetheless, Yale researchers began a controlled clinical trial of a drug called ibudilast (MN-166) for treating acute respiratory distress syndrome (ARDS), a life-threatening lung condition developed by some of the most seriously ill COVID-19 patients in July, 2020. Ibudilast has been used for the treatment of asthma and shown positive results for reducing inflammation associated with ARDS.



As a matter of fact, another pre-existing drug is in a clinical trial phase 3, and some basic mechanism of COVID-19 needs to be covered to fully understand how the drug is supposed to help.

ACE2 is a protein on the surface of many cell types - oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, vessels, and brain, which the virus could eventually attack. It is an enzyme that generates small proteins – by cutting up the larger protein angiotensinogen – that then go on to regulate functions in the cell. Using the spike-like protein on its surface, the SARS-CoV-2 virus binds itself to ACE2 prior to entry and infection of cells. Hence, ACE2 acts as a cellular gateway – a receptor – for the virus that causes COVID-19.

ACE2 is a vital element in a biochemical pathway that is critical to regulating processes such as blood pressure, wound healing and inflammation, called the renin-angiotensin-aldosterone system (RAAS) pathway. ACE2 helps modulate the many activities of a protein called angiotensin II (ANG II) that increases blood pressure and inflammation, increasing damage to blood vessel linings and various types of tissue injury. ACE2 converts ANG II to other molecules that counteract the effects of ANG II.

When the SARS-CoV-2 virus binds itself to ACE2, it prevents ACE2 from performing its normal function to regulate ANG II signaling. Thus, ACE2 action is “inhibited,” removing the brakes from ANG II signaling and making more ANG II available to injure tissues. This “decreased braking” likely contributes to injury, especially to the lungs and heart, in COVID-19 patients.

ANG II is converted from ANG I by ACE(Angiotensin-1 Converting Enzyme), which is totally different from ACE2, used as a door of corona virus. Thus, the medication that inhibits ACE(ACE inhibitors) and blocks ANG II receptor(ARBs) reduces tissue injuries. This kind of medication has been mainly prescribed for hypertension or heart failure, and indeed, it shows a promising result for COVID-19 patients.

Is any effective vaccine for COVID-19 coming out sooner or later?

It takes eight to fifteen years to complete all the clinical trials and get ready to apply for a final FDA approval. Here is a general outline of a vaccine developing process.

+Preclinical Testing: Scientists test a new vaccine on cells and then give it to animals such as mice or monkeys to see if it produces an immune response.

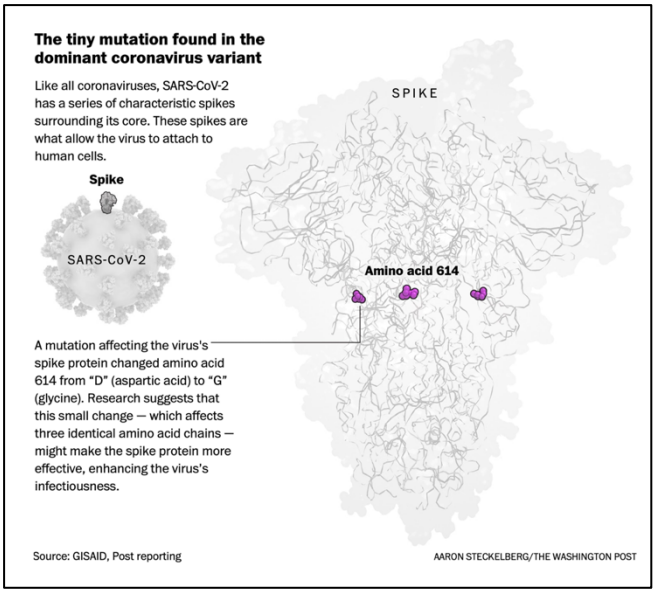
+Phase1 Safety Trial: Scientists give the vaccine to a small number of people to test safety and dosage as well as to confirm that it stimulates the immune system.

✚**Phase2 Expanded Trial**: Scientists give the vaccine to hundreds of people split into groups, such as children and the elderly, to see if the vaccine acts differently in them. These trials further test the vaccine's safety and ability to stimulate the immune system.

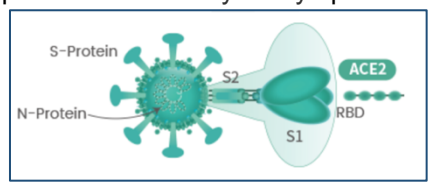
✚**Phase3 Efficacy Trial**: Scientists give the vaccine to thousands of people and wait to see how many become infected, compared with volunteers who received a placebo.

Surprisingly, only 6% of them are approved after this long process. More surprisingly, some of approved vaccines are re-called administered to great number of humans. In fact, side effects or adverse reactions usually appear after two years of vaccination.

SARS-CoV-2 spread to 210 countries within four months, and the only thing the community could do was just 'staying home.' In June 2020, the government declared war to this invisible enemy and initiated Operation Warp Speed(OWS) to accelerate the development, manufacturing, and distribution of COVID-19 vaccines by January, 2021.



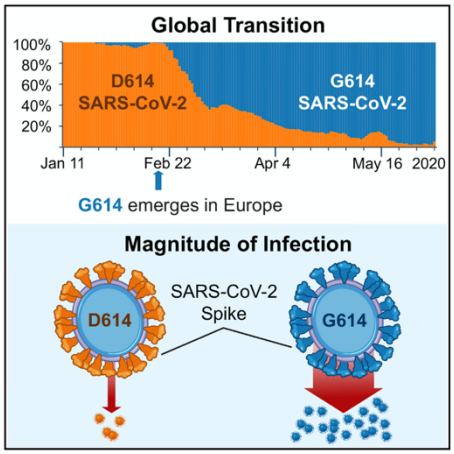
The US government has chosen three vaccine candidates among 231 candidates worldwide to fund for Phase 3 trials under Operation Warp Speed: Moderna's mRNA-1273, The University of Oxford and AstraZeneca's AZD1222, and Pfizer and BioNTech's BNT162. Especially, **Moderna** develops vaccines based on messenger RNA (mRNA-1273) to produce viral proteins in the body. They operate an efficient drug delivery system using lipid nanoparticles, so that mRNA vaccines can be delivered into the target cells, which is key for their success.



Their vaccine has progressed into Phase 3 testing, which began on July 27 after showing the promising results in phase 2. If they provide data indicating their vaccine is at least 50% effective against COVID-19, FDA will grant an approval according to their guidance issued and effective on June 30.

Is the vaccine going to be effective for mutated SARS-CoV-2?

Over 100,000 viral genomic sequences of SARS-CoV-2 have been submitted to GISAID (Global Initiative on Sharing All Influenza Data consortium) and shared by researches all over the world. Among them, two strains have been dominant throughout the world even though more than 30,000 samples have genomic mutations.



At the surface of the virus, a spike is a clove-shaped trimer with three protomers consisting of the S1 and S2 subunits. The S1 has a receptor binding domain, and open conformation is expected to be necessary for binding to the ACE2 receptor at the surface of host target cells. The S2 subunit forms a trimeric stalk. It contains a fusion peptide (FP) and two heptad repeats (HR1 and HR2), which operate the fusion of viral and host membranes.

A mutation in the spike protein of the SARS-CoV-2 virus changes just one amino acid, number 614 which was switched in the new variant from a "D" (shorthand for aspartic acid) to a "G" (short for glycine) in a chain of about 1,300, so called point mutation. The mutation (called D614G), which first appeared in January, is found in what has become the dominant variant of the coronavirus. 614G has made the virus more contagious at least 10 times of the original 614D because the affected location is at the junction of S1 and S2, which broke the hydrogen bond of the trimer and made wider binding surfaces with target cells. As a result of that, the viral loads of the infected body has increased, and the prevention/intervention has been more challenging although the virulence of the virus has decreased - *natural selection*: the process whereby organisms better adapted to their environment tend to survive and produce more offspring (Oxford).

Since D614G is not in the receptor-binding domain (RBD) of the spike protein, it would not drastically alter the immunogenicity of RBD epitopes. Furthermore, the antibodies generated from natural infection with viruses containing D614 or G614 could cross-neutralize. Therefore, the D614G mutation is unlikely to have a major impact on the efficacy of vaccines, some of which exclusively target the RBD although it merely suggests that the locus is not critical for antibody-mediated immunity *this time.*

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A human is like a small universe. I see a smaller universe in the virus, and I also witness His Will, Grace, and Mercy in this journey. So I am grateful humbling myself and listening to His Voice. Stay Gold and Stay Connected!