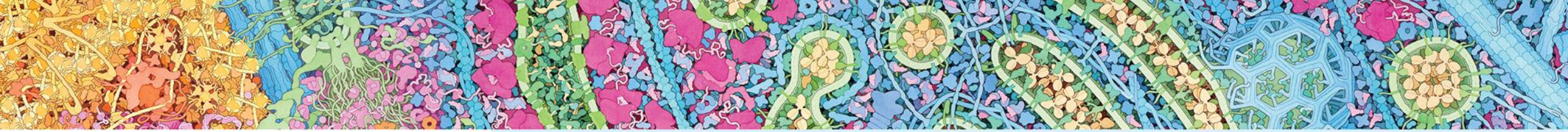
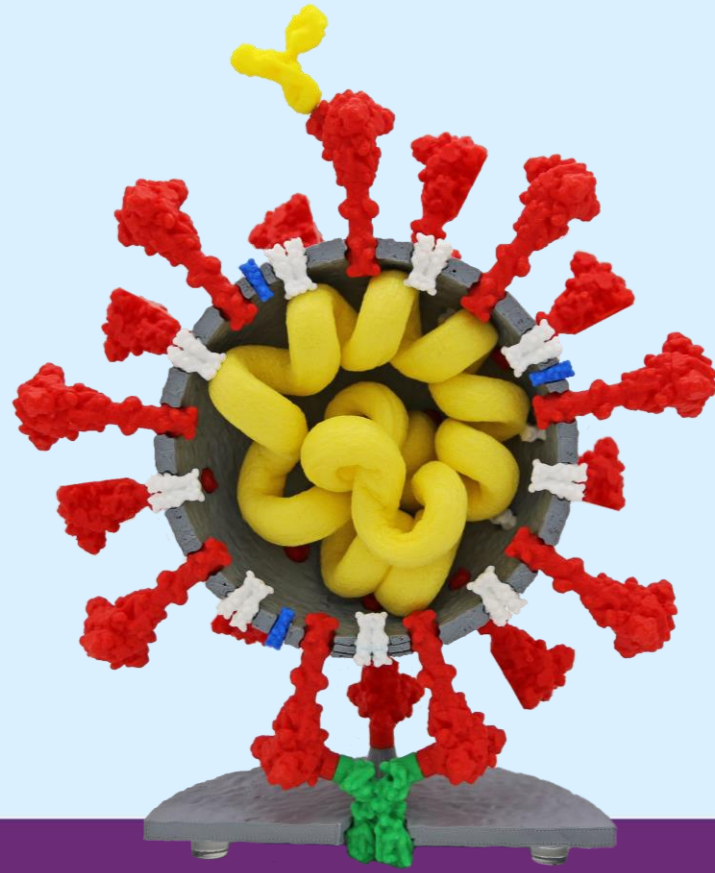


3d molecular designs
Transforming Science Learning

Coronavirus…

…from genome sequence…
…to an mRNA vaccine…
…in less than a year.

Science to the rescue!



Tim Herman, Founding Partner & Science Officer

The Coronavirus Pandemic....

....from tragedy..... to opportunity!

Influenza

CoV-2

Viruses

Mutations

Immune System

RNA genomes

Vaccines

Bacteriophages

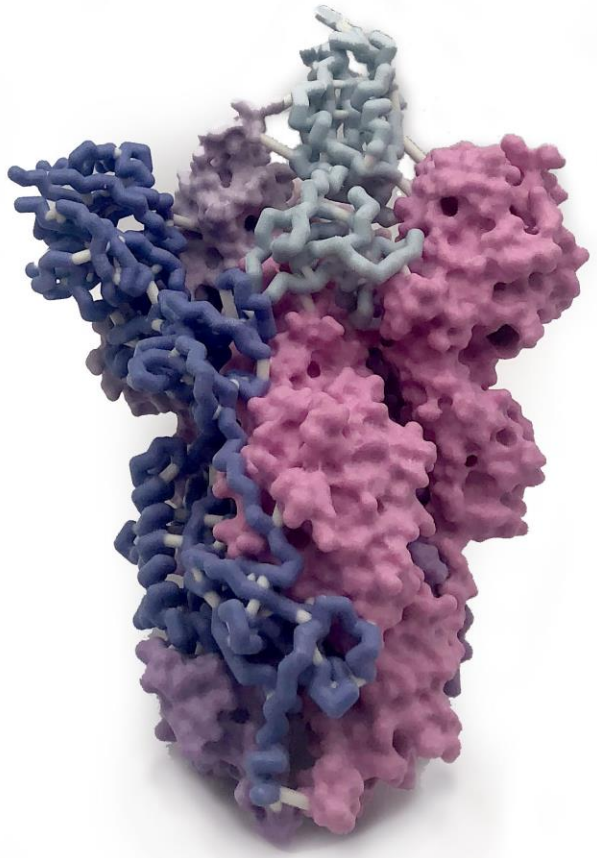
Attenuated Virus

Antibodies

Protein Structure/Function

DNA → RNA → Protein

Coronavirus …and the Spike protein



The magic of models…

Models make words meaningful!

<u>Interactive physical models</u> provide students with a way to understand a description (written or verbal) of a complex molecular process – such as how a vaccine protects us from coronavirus infection.

And now, physical models can be enhanced with Augmented Reality technology.

2022 is a great time to be a biology teacher!!

- **Great science happening all around us**

  …many stories to tell.

- **Google is our friend…**

- **All we are missing is …TIME**

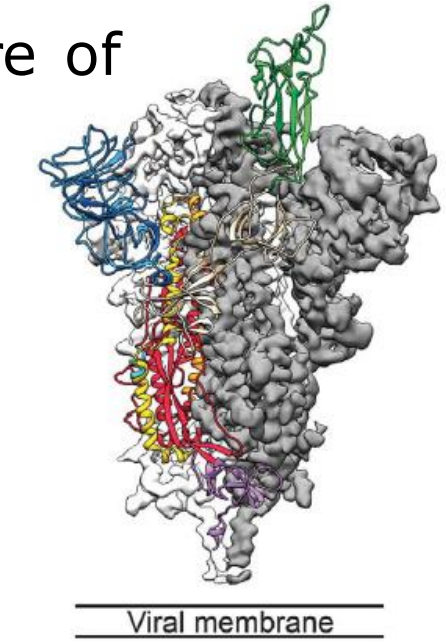
Here's the story....SCIENCE *to the rescue……*

December 2019, new coronavirus (CoV-2) reported in China

January 10, 2020, nucleotide sequence of CoV-2 reported…and shared with the world.

January 13, 2020, optimized version of the spike gene sent to Moderna.

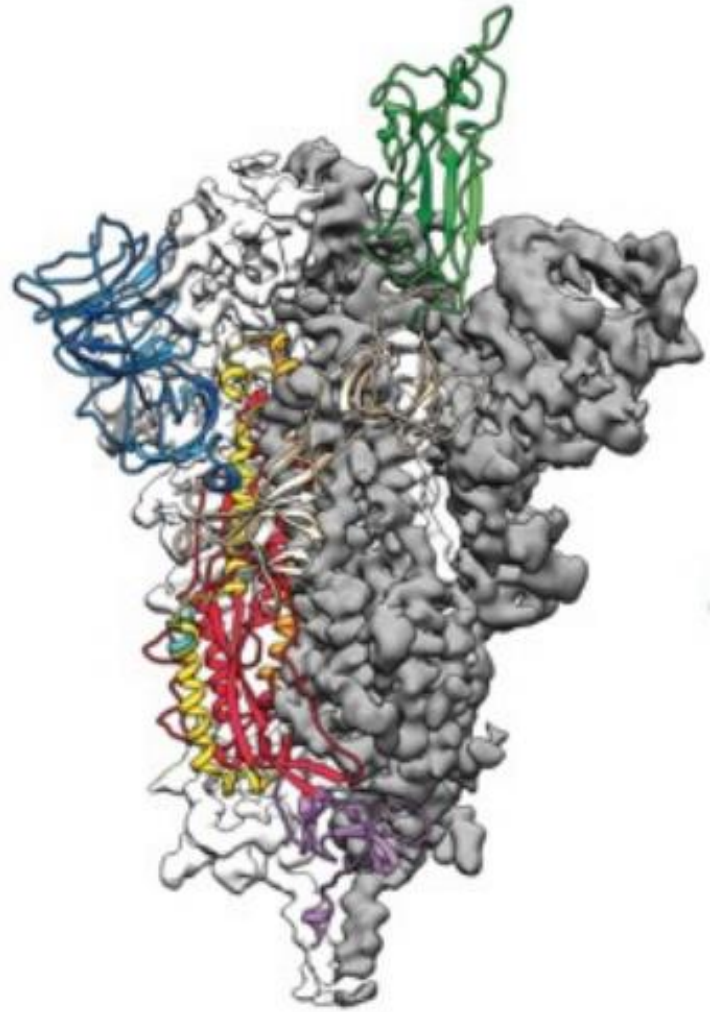
March 20, 2020, Jason McLellan publishes 3D structure of CoV-2 spike protein.



Clinical Trials……

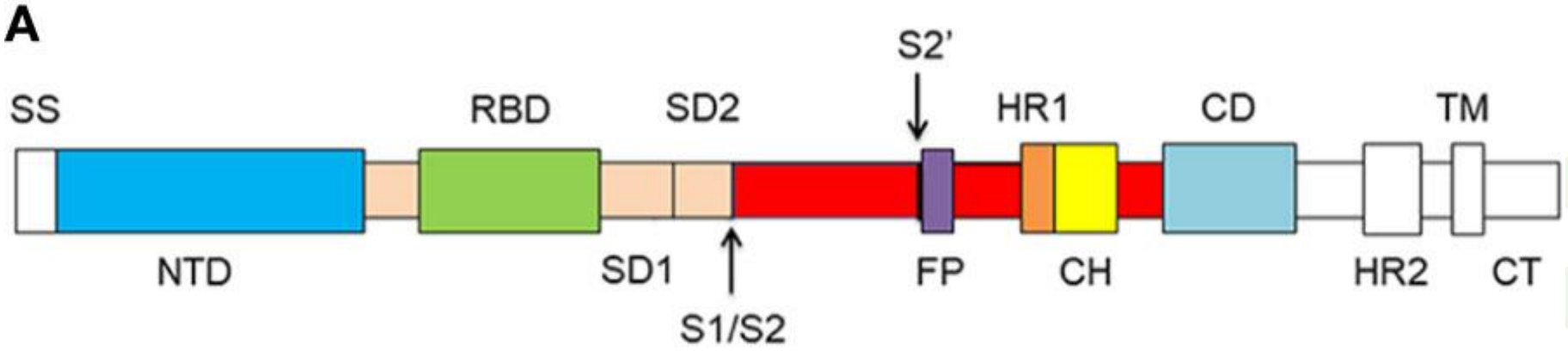
December 18, 2020, Moderna mRNA vaccine EUA.

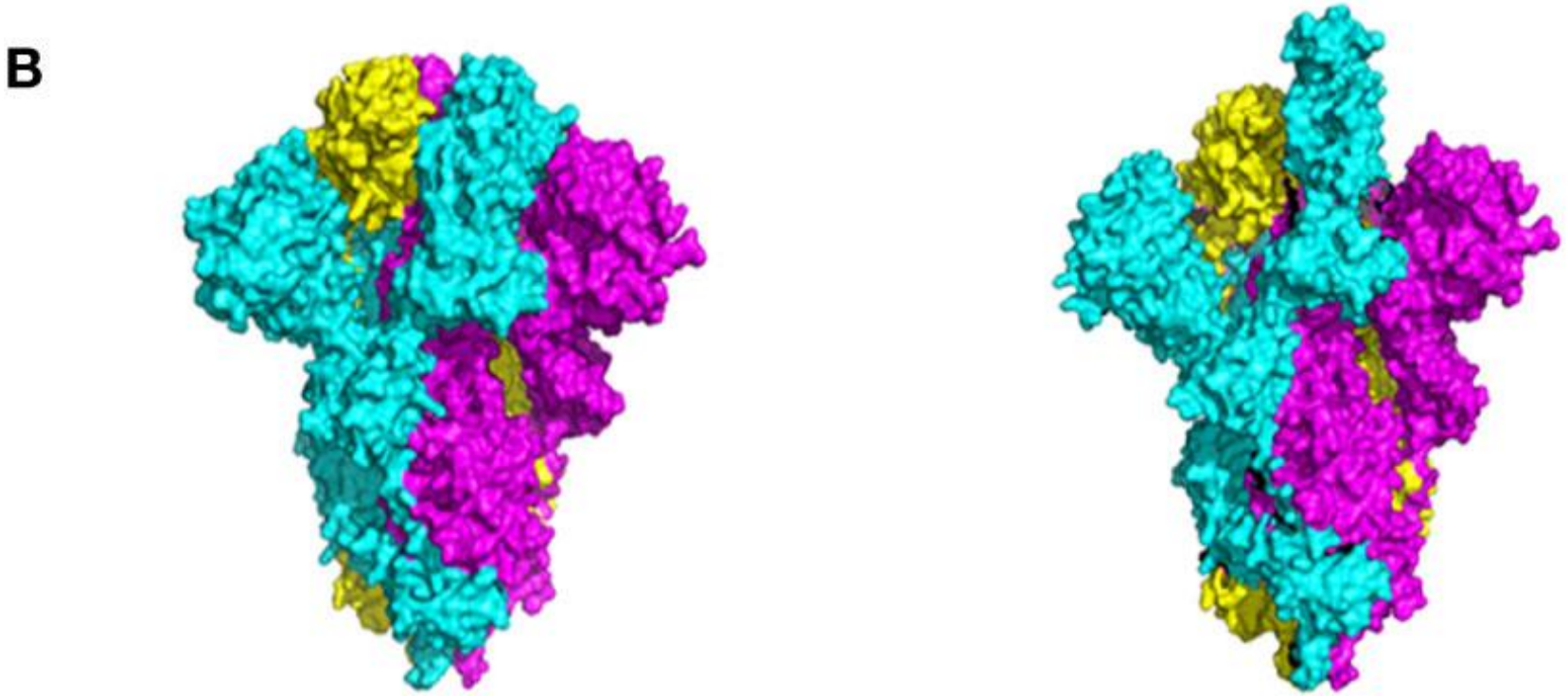
…within 3 months of the CoV-2 genome being sequenced



[Key Innovations from UT Austin's McLellan Lab Powers COVID-19 Vaccines]

[UT-Austin researcher explains lab's key role in coronavirus vaccine development]



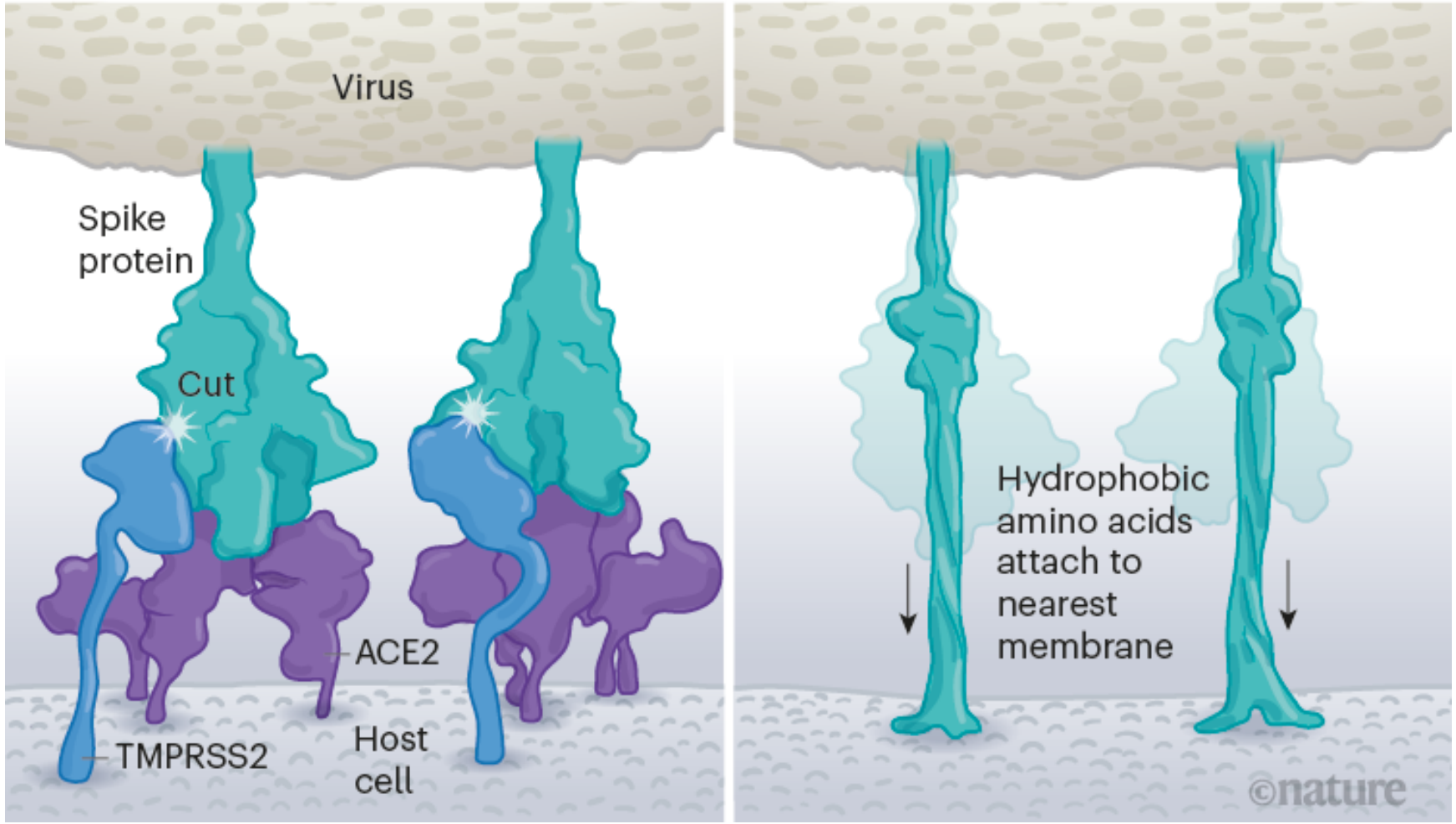


closed state of SARS-CoV-2 spike protein

open state of SARS-CoV-2 spike protein

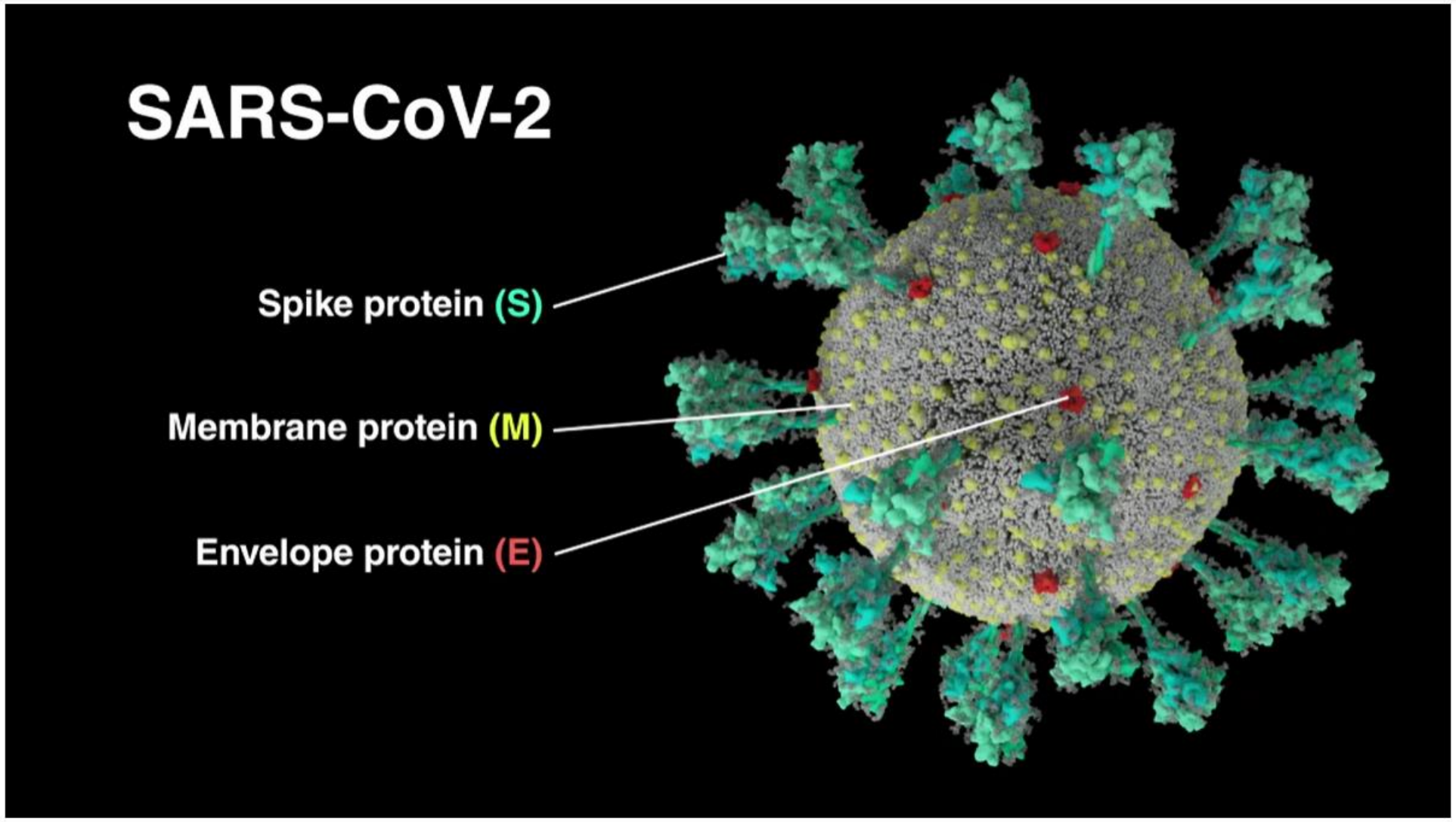
VIRAL ENTRY UP CLOSE

Virus and host-cell membranes fuse after the TMPRSS2 enzyme cuts a SARS-CoV-2 spike protein. This exposes hydrophobic amino acids in the spike that rapidly embed themselves into the nearest membrane — that of the host cell.

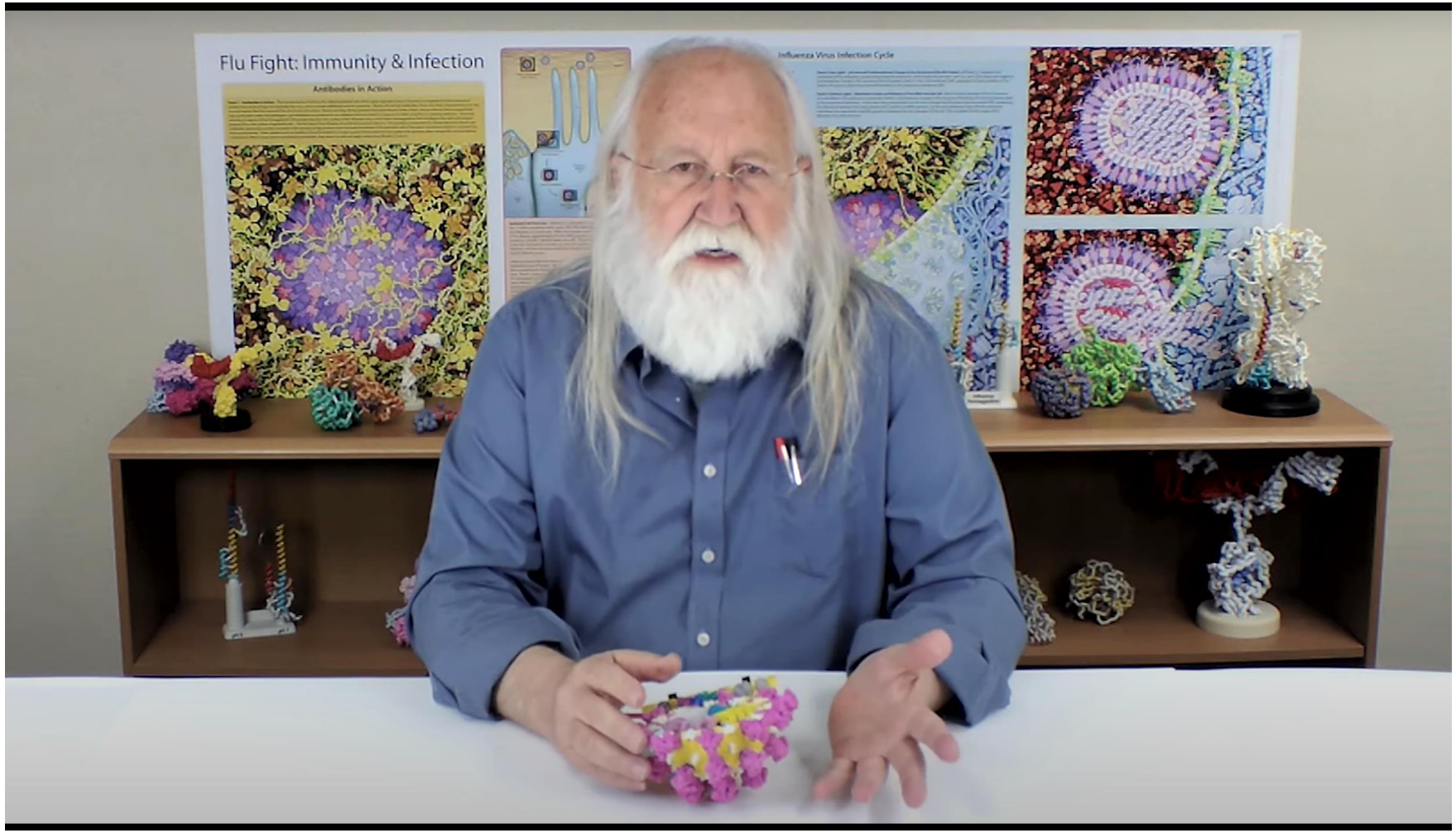


An animation of the SAARS CoV-2 infection process

……from THE ANIMATION LAB at the University of Utah



The Science of Coronavirus... a video series



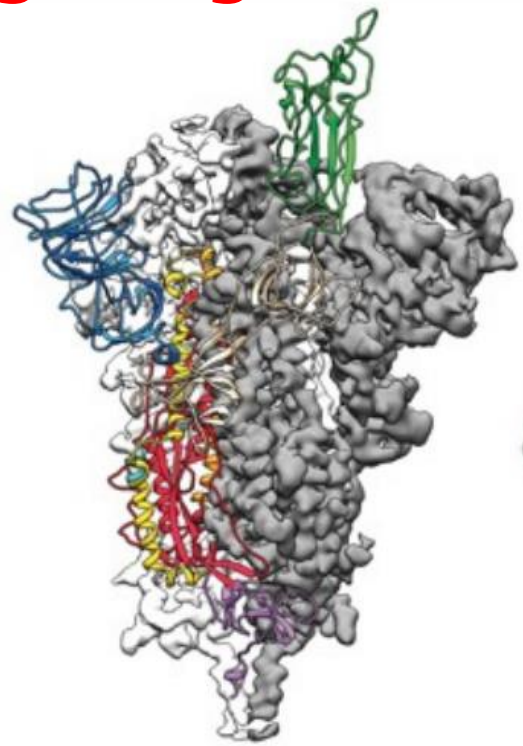
https://www.3dmoleculardesigns.com/The-Science-of-Coronaviruses.htm

Two strategies to STOP CoV-2

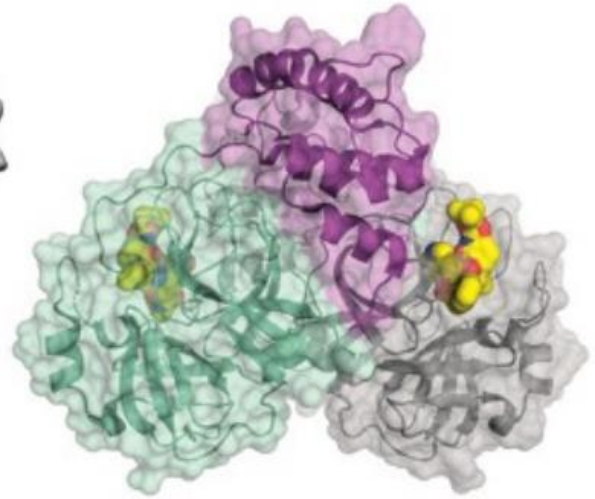
1. **Vaccines,** from new vaccine platforms
   mRNA vaccines
   ultra-potent, multi-valent vaccines

2. **Antivirals**
   Remdesovir
   Paxlovid

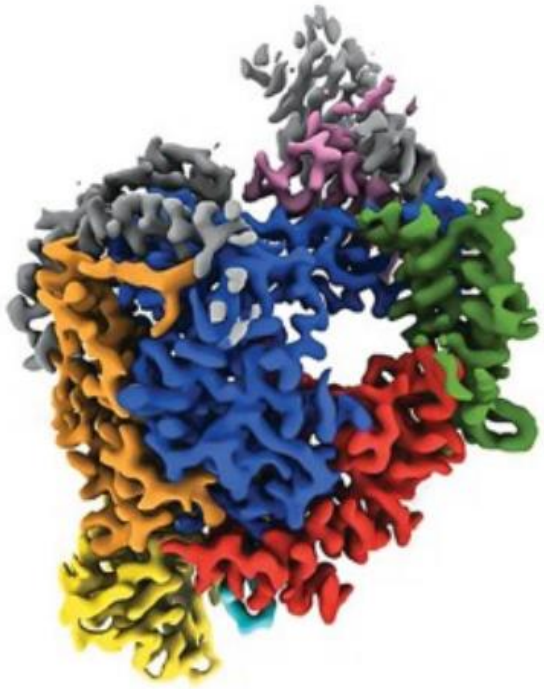
Drug Targets



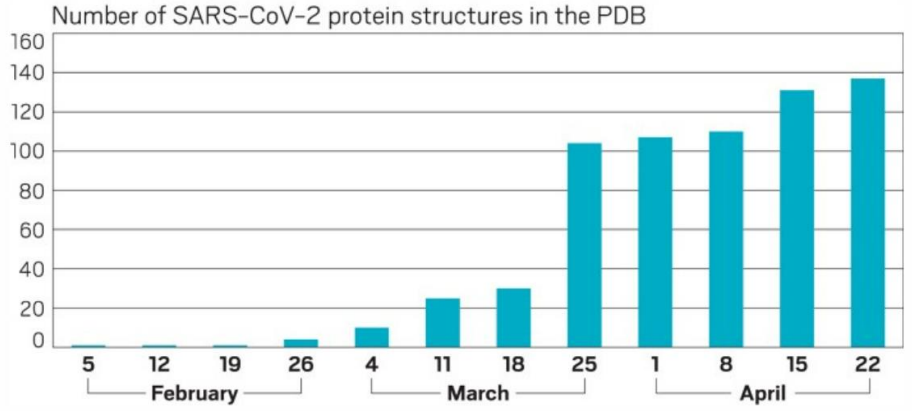
Spike



Main Protease



RNA Polymerase



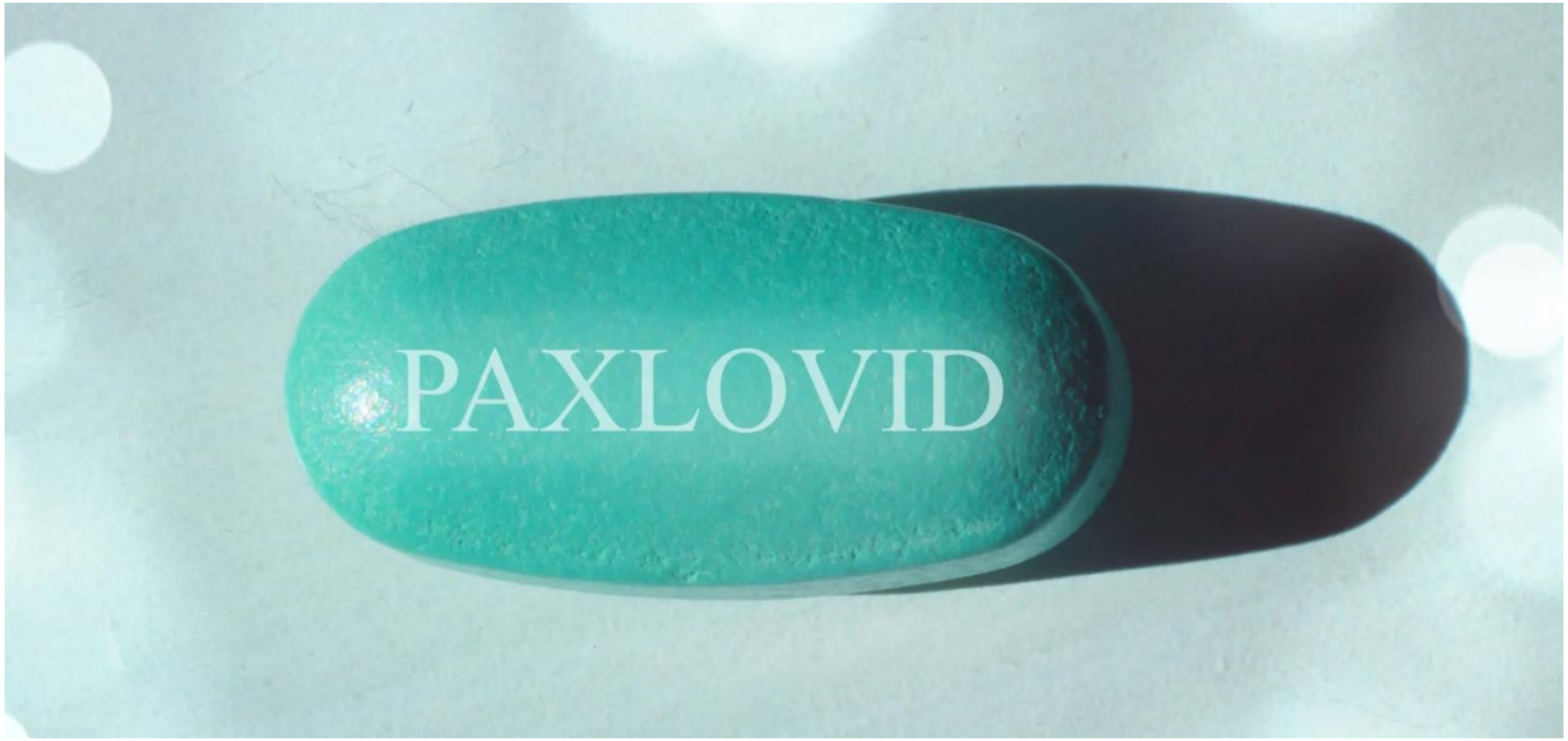
Oral Antivirals….

What we need to really make a dent in the pandemic is to be able to treat people very early in the course of their illness, right when they're diagnosed: give them a safe, oral antiviral they can start immediately and prevent them winding up in the hospital, prevent them from dying, and prevent those strains on the health-care system.

— ***Sarah Read,*** *deputy director of the Division of AIDS, US National Institute of Allergy and Infectious Diseases*

https://cen.acs.org/pharmaceuticals/drug-discovery/covid-19-oral-antiviral-pill-candidates/99/i19?ref=search_results

Paxlovid… an oral antiviral pill



Paxlovid is an antiviral therapy consisting of two antiviral medications nirmatrelvir, and ritonavir.

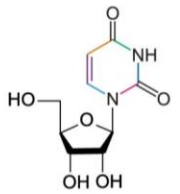
New Approaches to Vaccine Developments: *a preview….*

Katalin Karikó

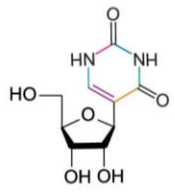
for mRNA vaccines - and more!

photo: Jessica Kourkounis for the Boston Globe

despite a lack of support, she figured out how to modify synthetic mRNA to make it less "generically" immunogenic, paving the way for mRNA therapeutics and vaccines



uridine (U)
immunogenic



pseudouridine (Ψ)
non-immunogenic

David Baker

and ultra-potent, multivalent nanoparticle flu vaccines

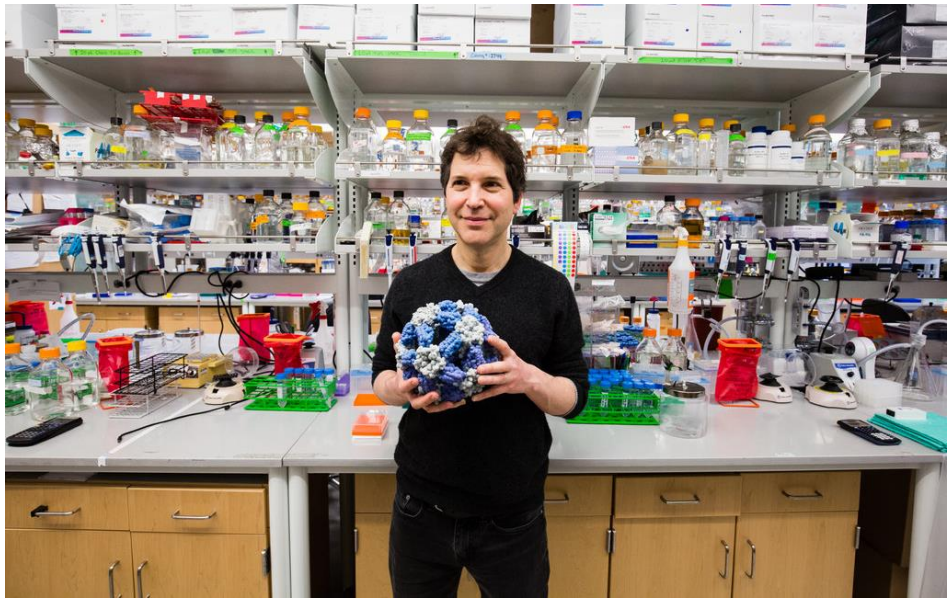


photo: Evan McGlinn for The New York Times

Kati Karikó… and the perseverance of women research associates…..

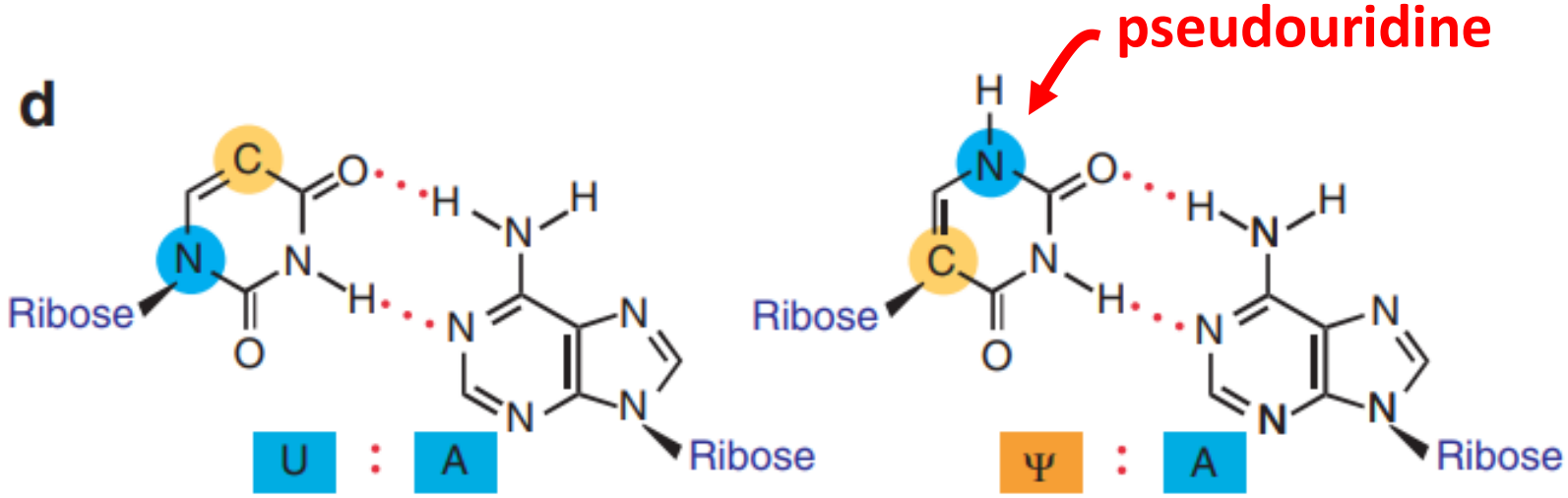
https://www.nytimes.com/2021/04/08/health/coronavirus-mrna-kariko.html

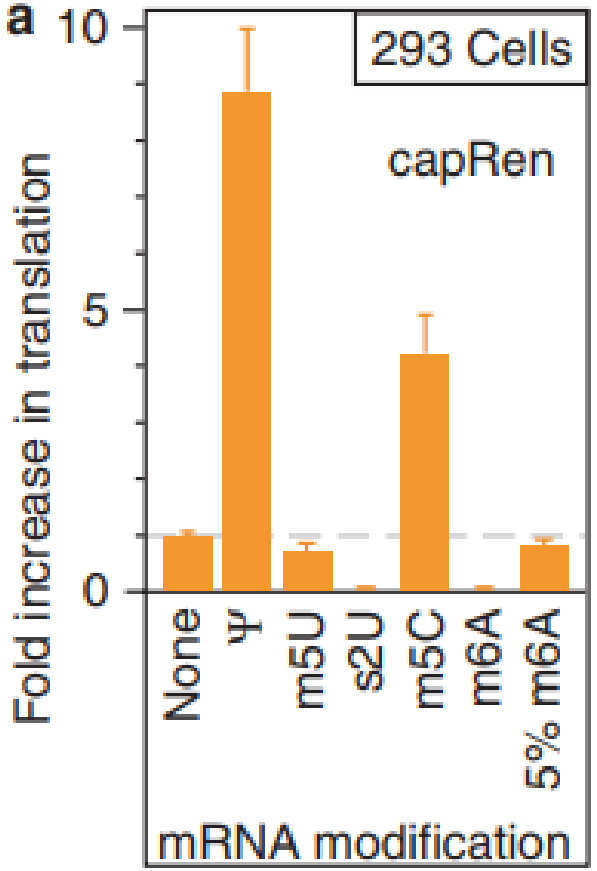
https://www.cnn.com/2020/12/16/us/katalin-kariko-covid-19-vaccine-scientist-trnd/index.html

Incorporation of Pseudouridine Into mRNA Yields Superior Nonimmunogenic Vector With Increased Translational Capacity and Biological Stability

Katalin Karikó[1], Hiromi Muramatsu[1], Frank A Welsh[1], János Ludwig[2], Hiroki Kato[3], Shizuo Akira[3] and Drew Weissman[4]

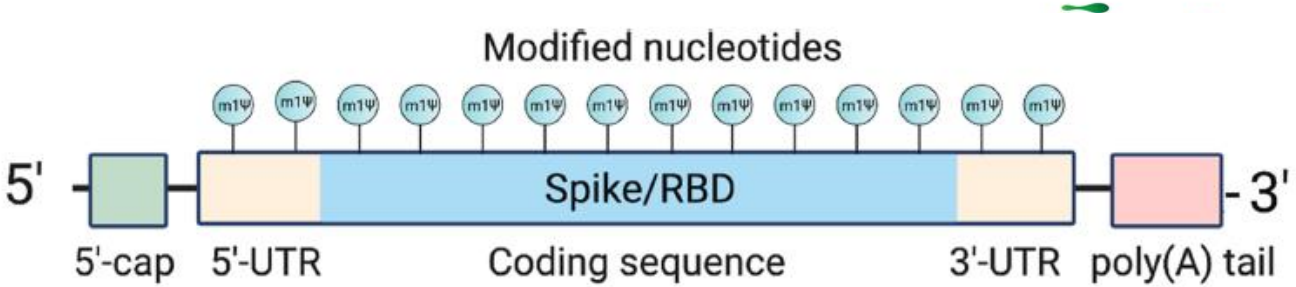
Molecular Therapy vol. 16 no. 11, 1833–1840 Nov. 2008





Coming soon……

An mRNA Vaccine Design Activity



BNT162b2 sequence (U = m1Ψ)


```
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CUCUACCCAG GACCUGUUCC UGCCUUUCUU CAGCAACGUG ACCUGGUUCC ACGCCAUCCA CGUGUCCGGC ACCAAUGGCA CCAAGAGAUU CGACAACCCC   300
GUGCUGCCCU UCAACGACGG GGUGUACUUU GCCAGCACCG AGAAGUCCAA CAUCAUCAGA GGCUGGAUCU UCGGCACCAC ACUGGACAGC AAGACCCAGA   400
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CAAGAGCUGG AUGGAAAGCG AGUUCCGGGU GUACAGCAGC GCCAACAACU GCACCUUCGA GUACGUGUCC CAGCCUUUCC UGAUGGACCU GGAAGGCAAG   600
CAGGGCAACU UCAAGAACCU GCGCGAGUUC GUGUUUAAGA ACAUCGACGG CUACUUCAAG AUCUACAGCA AGCACACCCC UAUCAACCUC GUGCGGGAUC   700
UGCCUCAGGG CUUCUCUGCU CUGGAACCCC UGGUGGAUCU GCCCAUCGGC AUCAACAUCA CCCGGUUUCA GACACUGCUG GCCCUGCACA GAAGCUACCU   800
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AGAGCCAGAA GCGUGGCCAG CCAGAGCAUC AUUGCCUACA CAAUGUCUCU GGGCGCCGAG AACAGCGUGG CCUACUCCAA CAACUCUAUC GCUAUCCCCA   2200
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AAAAGCAUAU GACUAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAA                             4284
```

STEM….

Engineering…delivered to us a design for an effective mRNA vaccine for CoV-2

Science…delivered to us the nucleotide sequence encoding the spike protein of CoV-2

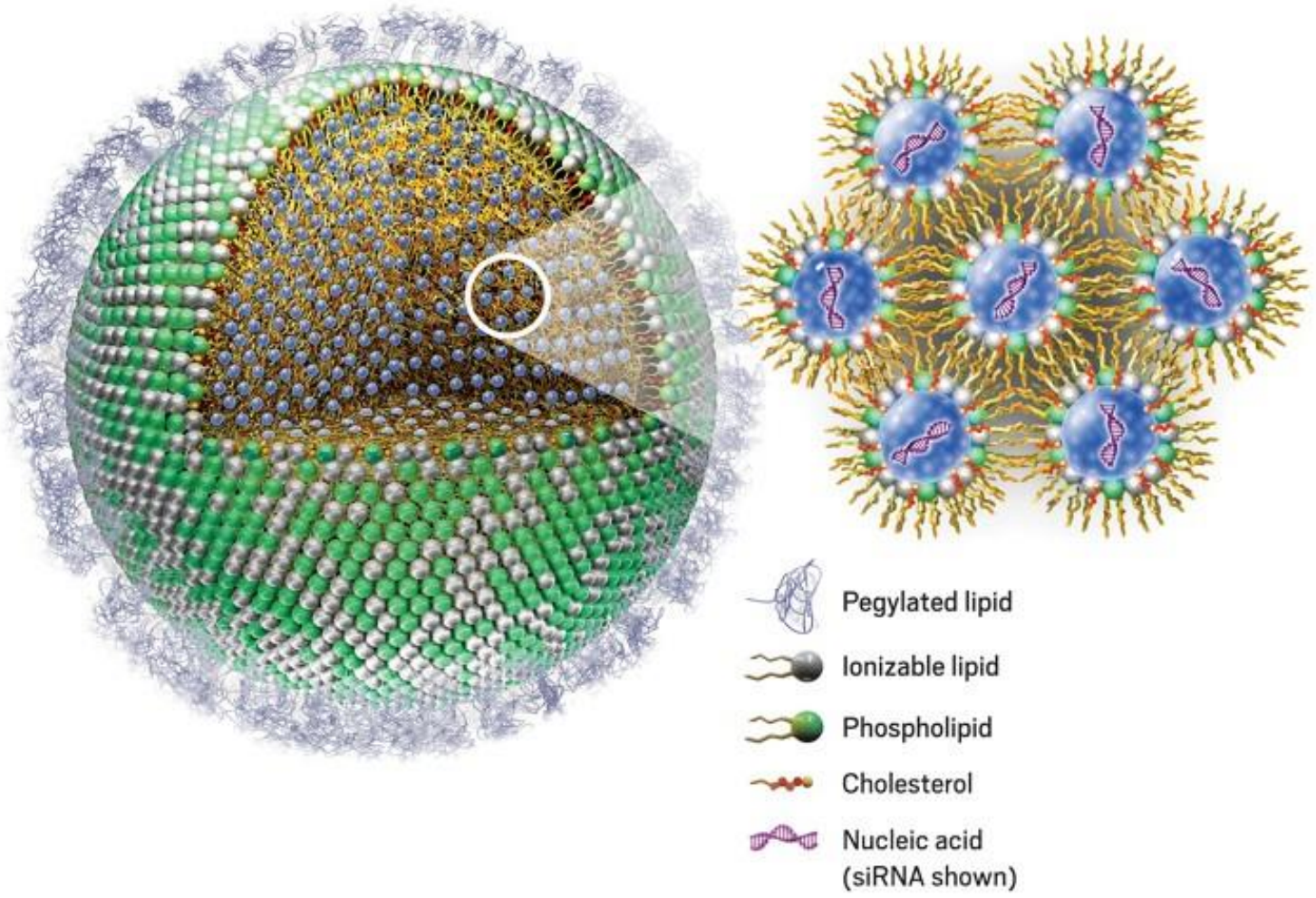
The modRNA sequence of the vaccine is 4,284 nucleotides long and encodes the full-length spike protein of SARS CoV-2.

In addition to a 5′-cap and a 3′-poly-A sequence, the coding sequence was engineered to contain:

- **A signal sequence**…to insure trafficking of the spike protein to the outside surface of an immune cell.
- **Codons were "optimized"** for better expression in human cells
- All uridine bases were replaced with **pseudouridine bases**
- **Two proline mutations** were added to stabilize an immunogenic form of spike

The modRNA sequence of the vaccine is 4,284 nucleotides long. It encodes the full-length spike protein of Sars CoV-2. It consists of a five-prime cap; a five prime untranslated region derived from the sequence of human alpha globin; a signal peptide (bases 55–102) and two proline substitutions (K986P and V987P, designated "2P") that cause the spike to adopt a prefusion-stabilized conformation ….a codon-optimized gene of the full-length spike protein of SARS-CoV-2 (bases 103–3879); followed by a 3'untranslated region (bases 3880–4174) for increased protein expression and mRNA stability and a poly(A) tail. The sequence contains no uridine residues; they are replaced by 1-methyl-3'-pseudouridylyl.

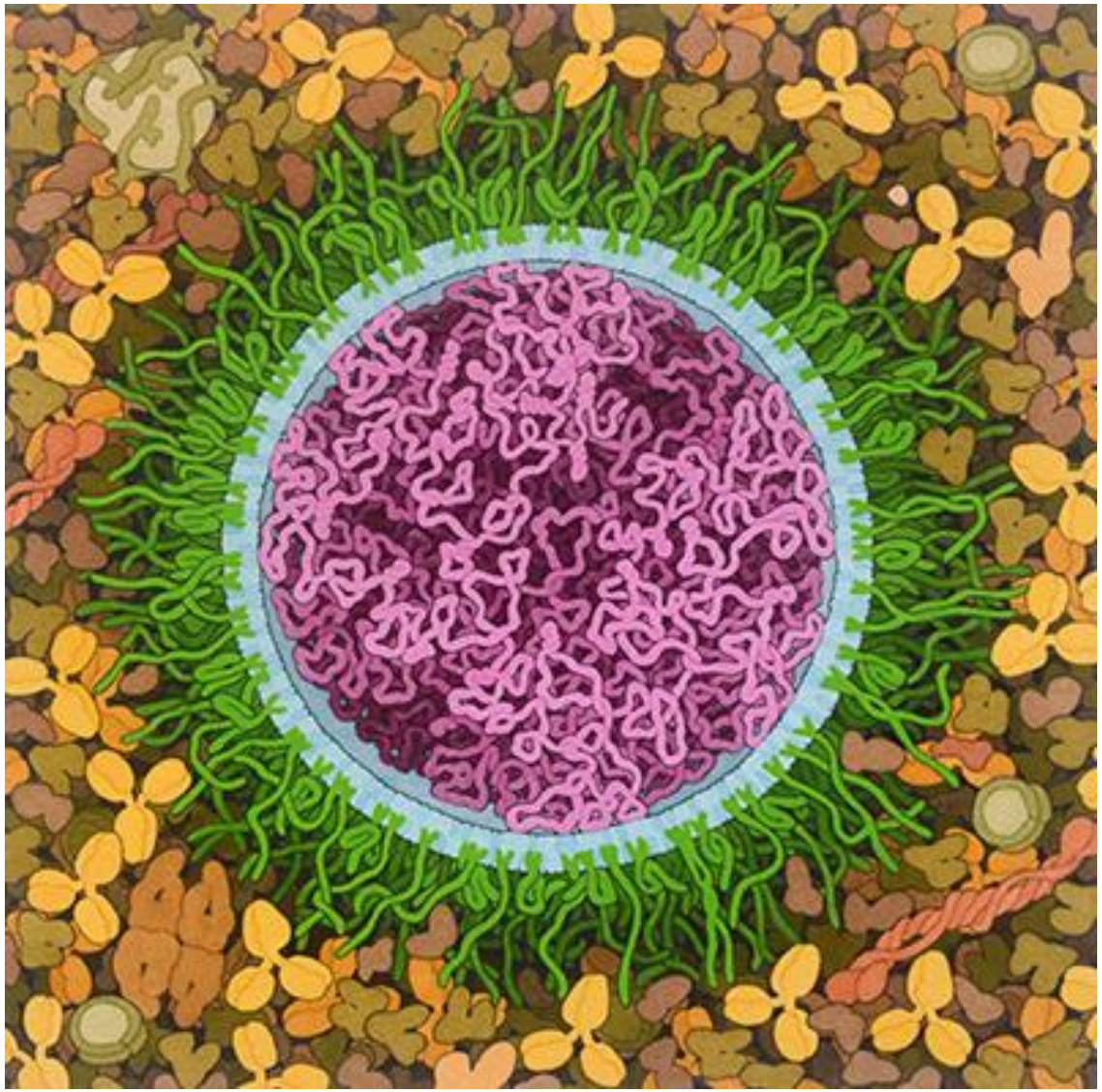
LNPs: Lipid Nano Particles



https://cen.acs.org/pharmaceuticals/drug-delivery/Without-lipid-shells-mRNA-vaccines/99/i8?ref=search_results

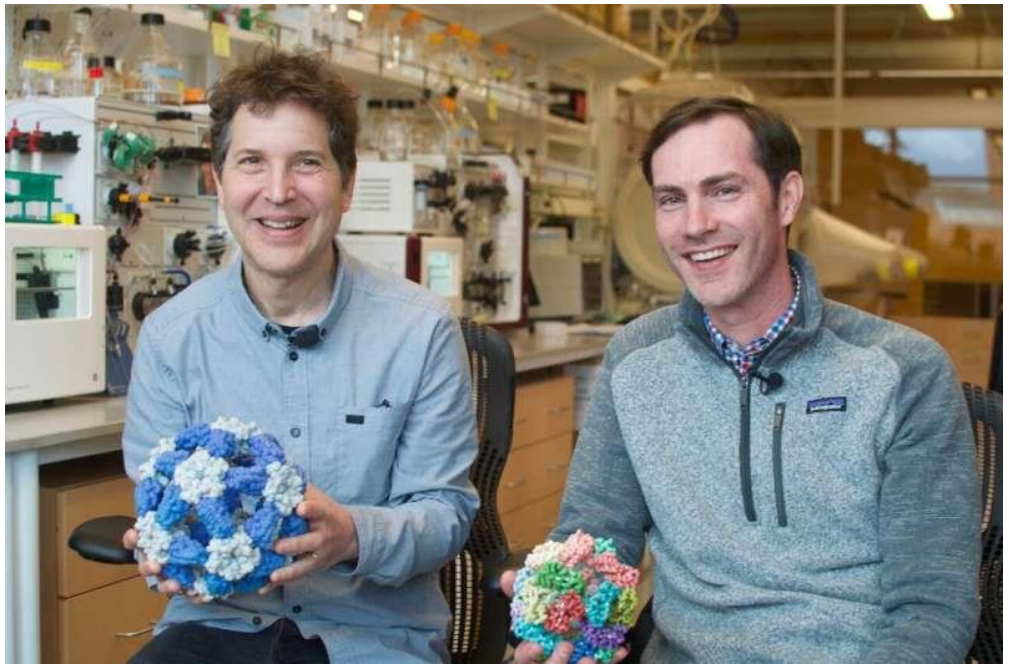
Molecular Landscapes by David S. Goodsell

SARS-CoV-2 mRNA Vaccine, 2020



David Baker, founder of the Institute for Protein Design

David Baker shows off models of some of the unnatural proteins his team has designed and made. © RICH FRISHMAN



David Baker,PhD, Director of the Institute for Protein Design with Dr. Neil King. Credit: Ian C Haydon/UW Institute for Protein Design

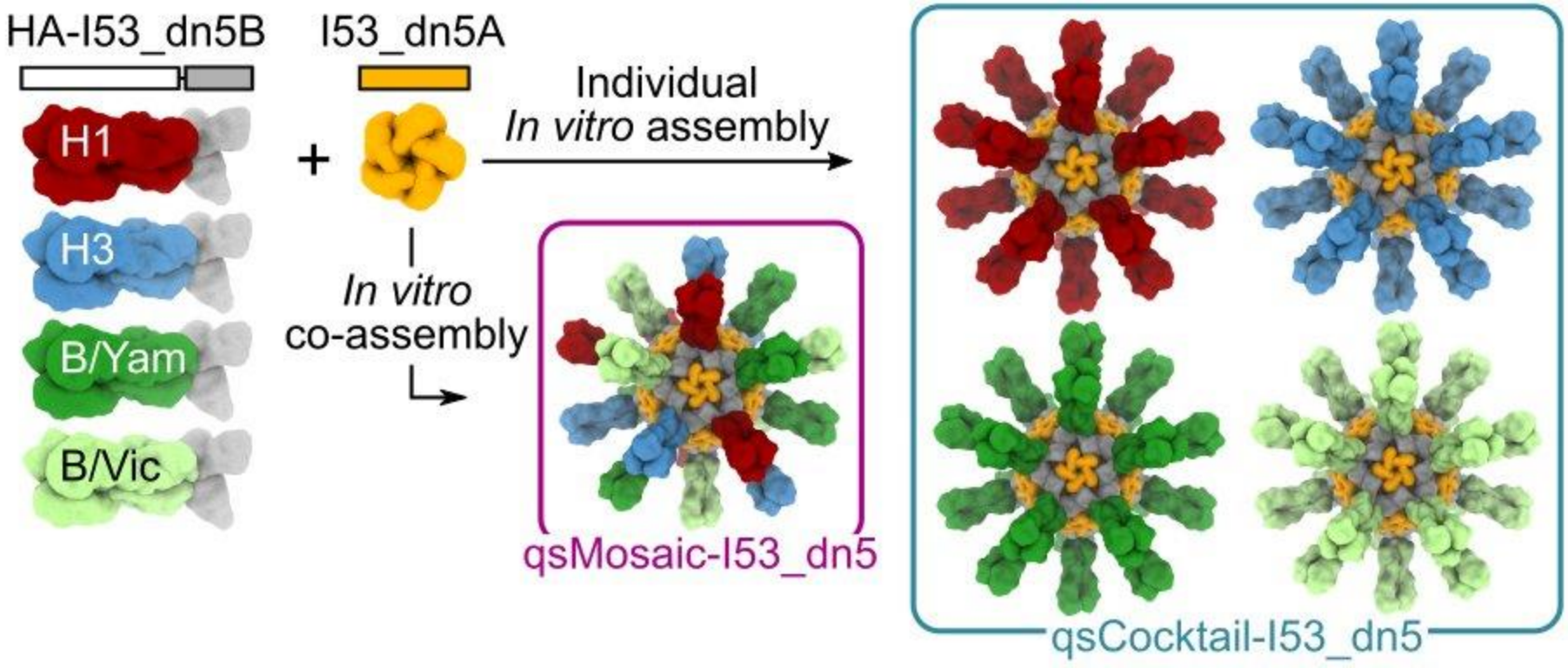
Self-Assembling Nanomaterials and Vaccines

David's TedTalk…. Audacious Project – Institute for Protein Design (uw.edu)

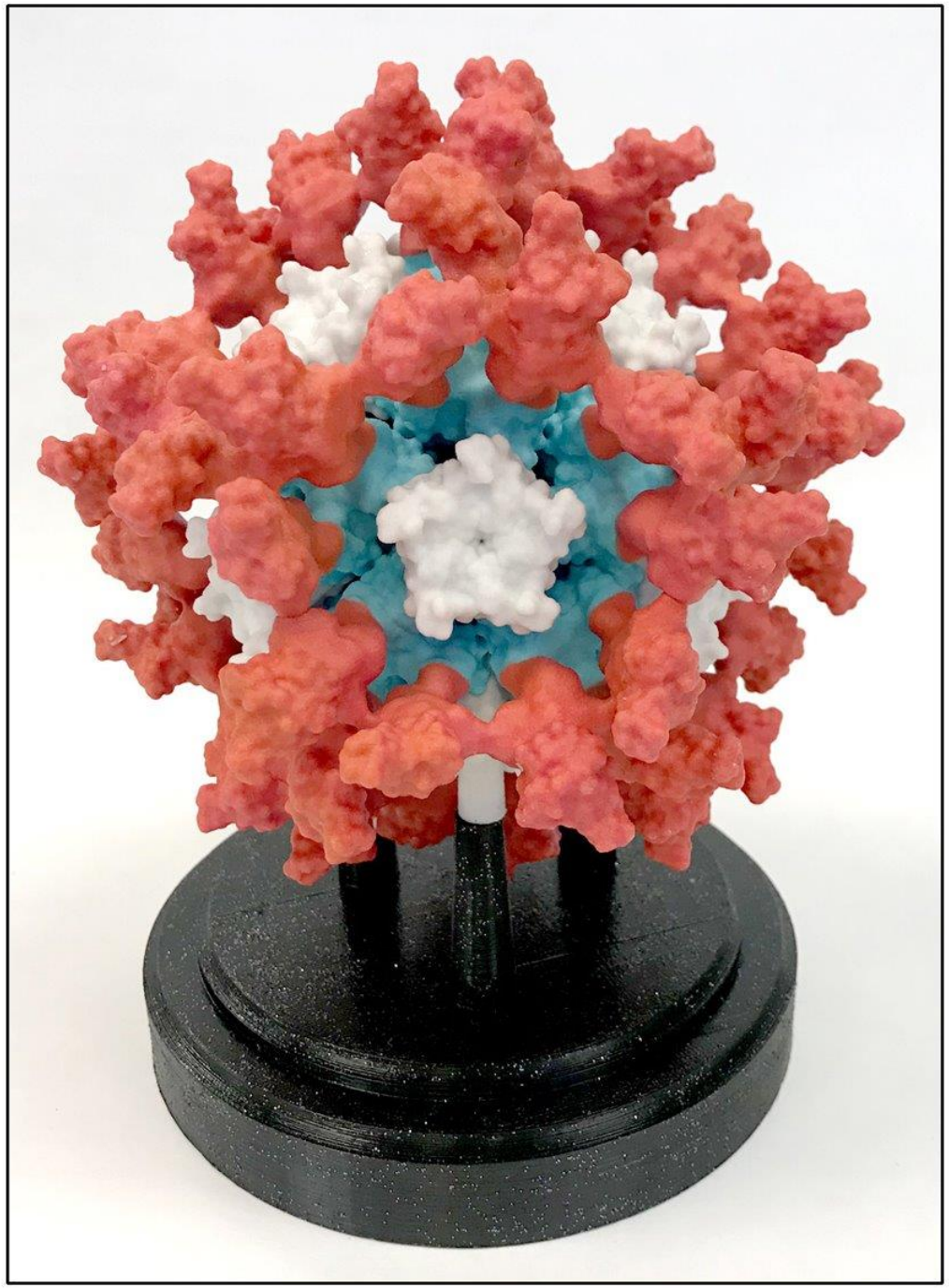
Elicitation of Potent Neutralizing Antibody Responses by Designed Protein Nanoparticle Vaccines for SARS-CoV-2

Quadrivalent influenza nanoparticle vaccines induce broad protection

https://www.nature.com/articles/s41586-021-03365-x



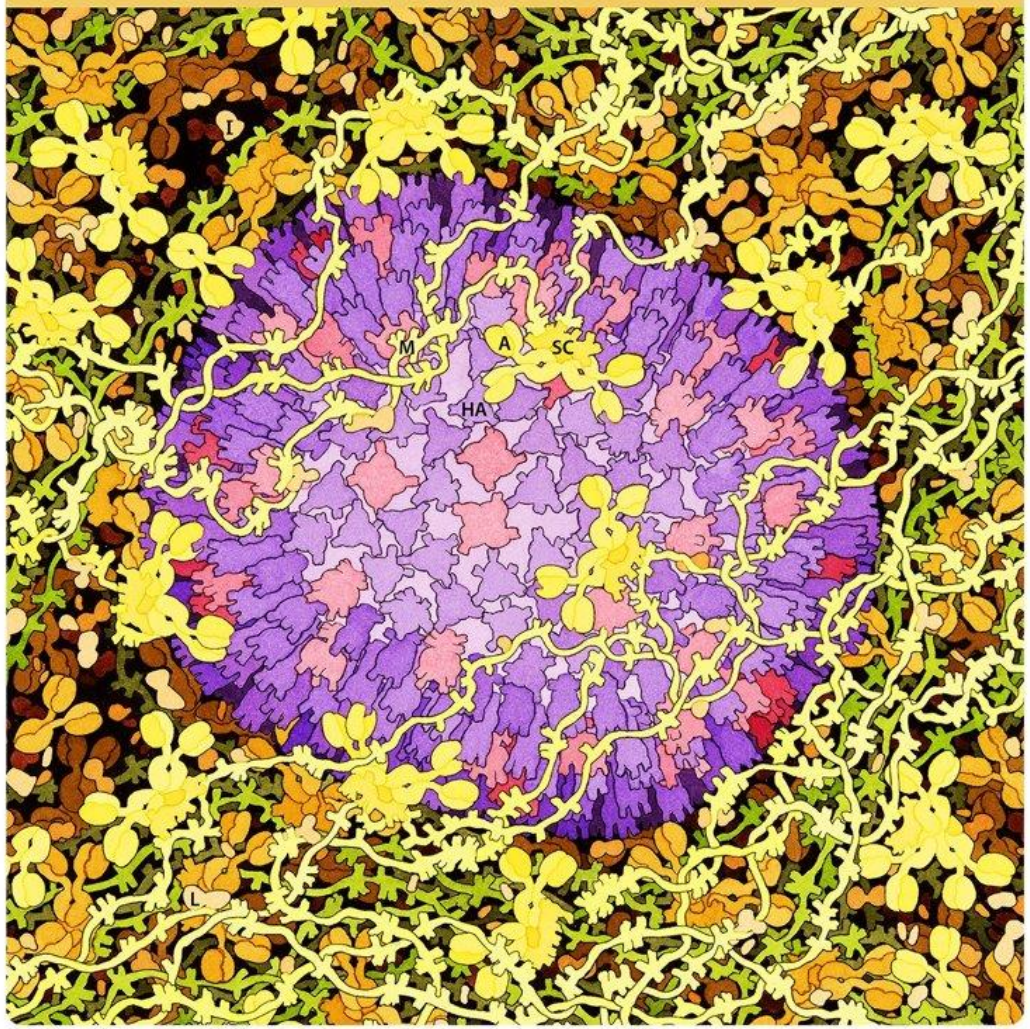
Design and characterization of HA nanoparticle immunogens.

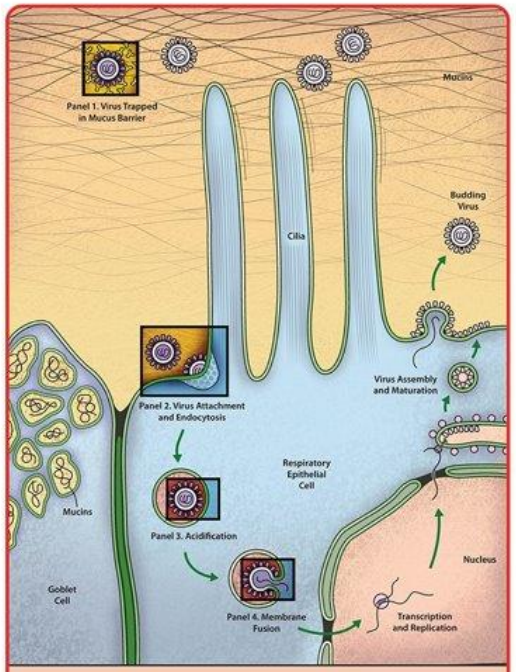


Flu Fight: Immunity & Infection

Antibodies in Action

Panel 1 - Antibodies in Action. The mucosal barrier that lines the ciliated epithelial cells of the upper respiratory tract in humans is composed of a thick network of proteins that works to trap and neutralize the virus, and to activate additional antiviral responses. Mucins (M) and IgA antibodies (A) are two kinds of proteins found in the mucosal barrier that limit access of the virus to the cell surface. Mucins are long, fibrous proteins that intertwine to create a thick, viscous network that nonspecifically traps particulate matter and pathogens. IgA antibodies are produced in our adaptive immune system in response to either a vaccine or a previous infection. They bind primarily to regions of the hemagglutinin (HA) protein found on the surface of the influenza virus, which blocks hemagglutinin from binding to the sialic acid receptor proteins (R) on the surface of epithelial cells – the first step in the influenza virus infection process (Panel 2). The secretory component (SC) shown bound to dimeric IgA antibodies represents a protein involved in the transport of IgA proteins from the basal membrane of the epithelial cells to the apical membrane where it is secreted into the mucosal barrier. Other proteins such as interferon (I) and lactoferrin (L) make up part of the innate immune system that activates other nonspecific antiviral defense mechanisms. When viruses aren't neutralized by antibodies, they attach to cells and begin endocytosis (Panels 2, 3 and 4).





Epithelial Cell Overview. Influenza is a persistent human health threat. Of the 7.4 billion people on earth, up to 10% (740 million people) are infected by the influenza virus each year. While most people experience only a mild form of the disease, approximately 4% (30 million people) develop serious disease, leading to 250,000 - 500,000 deaths annually. These landscapes highlight the molecular mechanisms whereby our immune system protects us from infection, and the molecular events that transpire when those defenses fail and an infection occurs.

Influenza viruses infect the ciliated epithelial cells that line the upper respiratory tract of humans. When the virus is inhaled, it is initially trapped in the mucosal barrier that protects the ciliated epithelial cells in the respiratory tract. Panel 1 shows an influenza virus trapped in this mucosal barrier – where it is neutralized by antibodies that are present due to a vaccine or a previous virus infection. Panel 2 illustrates what happens if the mucosal barrier is breached and the virus reaches the surface of an epithelial cell. The virus binds to glycoproteins embedded in the membrane of the cell, triggering uptake of the virus by receptor-mediated endocytosis. Panel 3 shows how the lower pH of the endosome containing the virus induces a conformational change in the structure of the hemagglutinin (HA) protein of the virus – leading ultimately to the fusion of the viral and endosomal membranes (Panel 4) and the release of the segmented viral RNA genome into the cytoplasm of the cell.

Influenza Virus | Mucosal Barrier | Endosome | Respiratory Epithelial Cell Cytoplasm

Scientist, author and artist David S. Goodsell, PhD, creates cellular landscapes that accurately illustrate the size, shape and distribution of proteins in their natural environment of the cell. His unique watercolor images connect the molecular world, inferred by X-ray crystallography and NMR spectroscopy, with the cellular world, observed by light and electron microscopy. Since 2009 3D Molecular Designs has made several of Dr. Goodsell's cellular landscapes available as large posters for classroom use. Dr. Goodsell's books, *The Machinery of Life* (2010) and *Atomic Evidence: Seeing the Molecular Basis of Life* (2016), are available from major booksellers.

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