

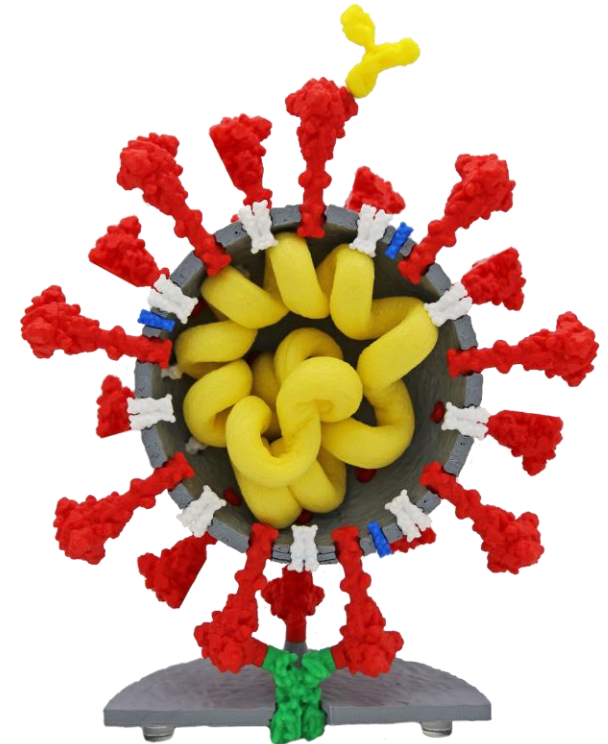
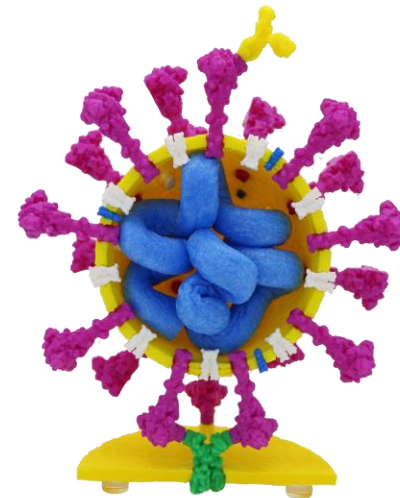
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Coronavirus

From Genome Sequencing to mRNA
Vaccine Production, in Less than One Year!



Coronavirus....

...from genome sequence...

...to an mRNA vaccine...

...in less than a year.

Science to the rescue!

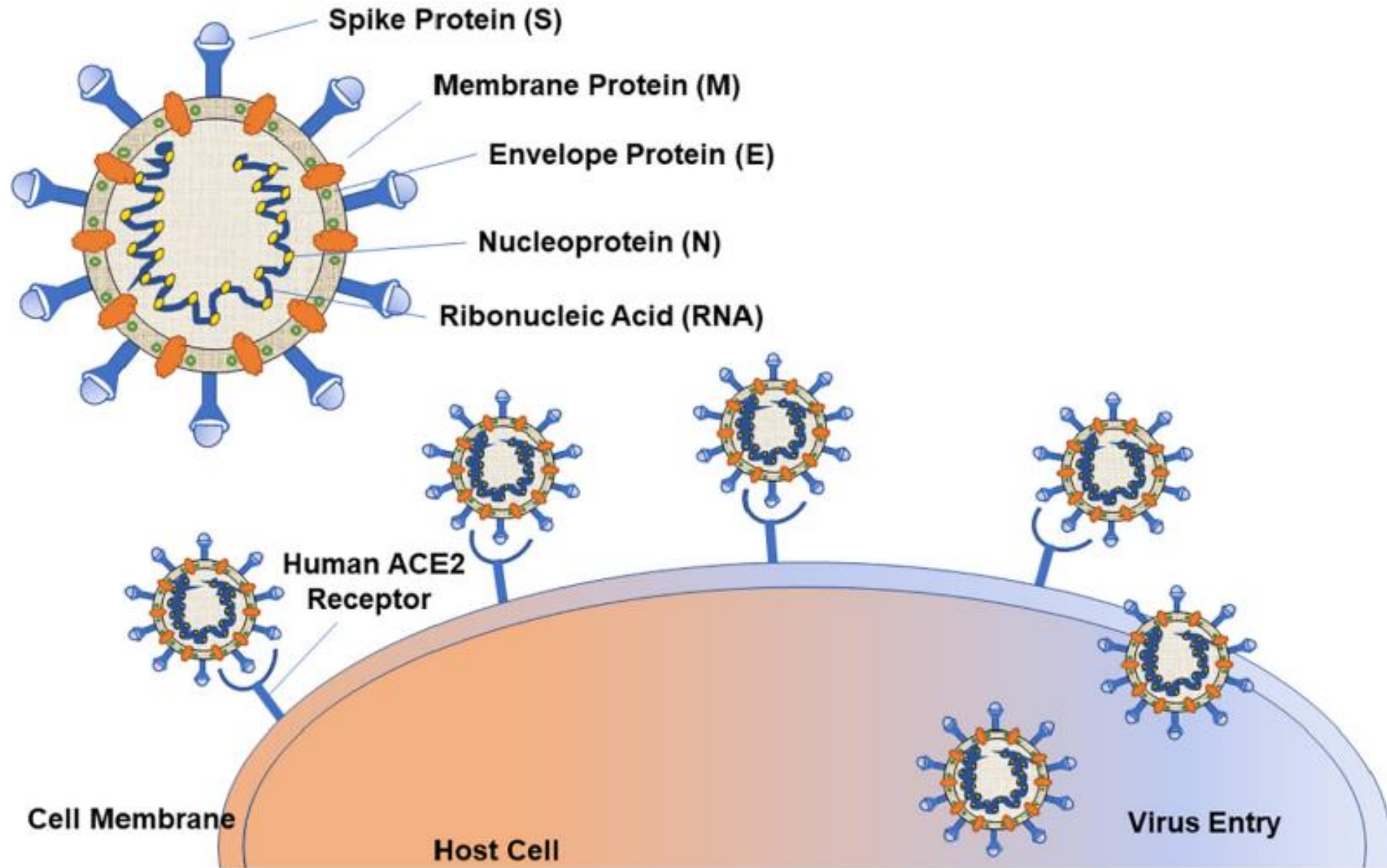
COVID 19

A Tragedy...

...and...

An Opportunity

...to tell an incredible story -- of the process of science.

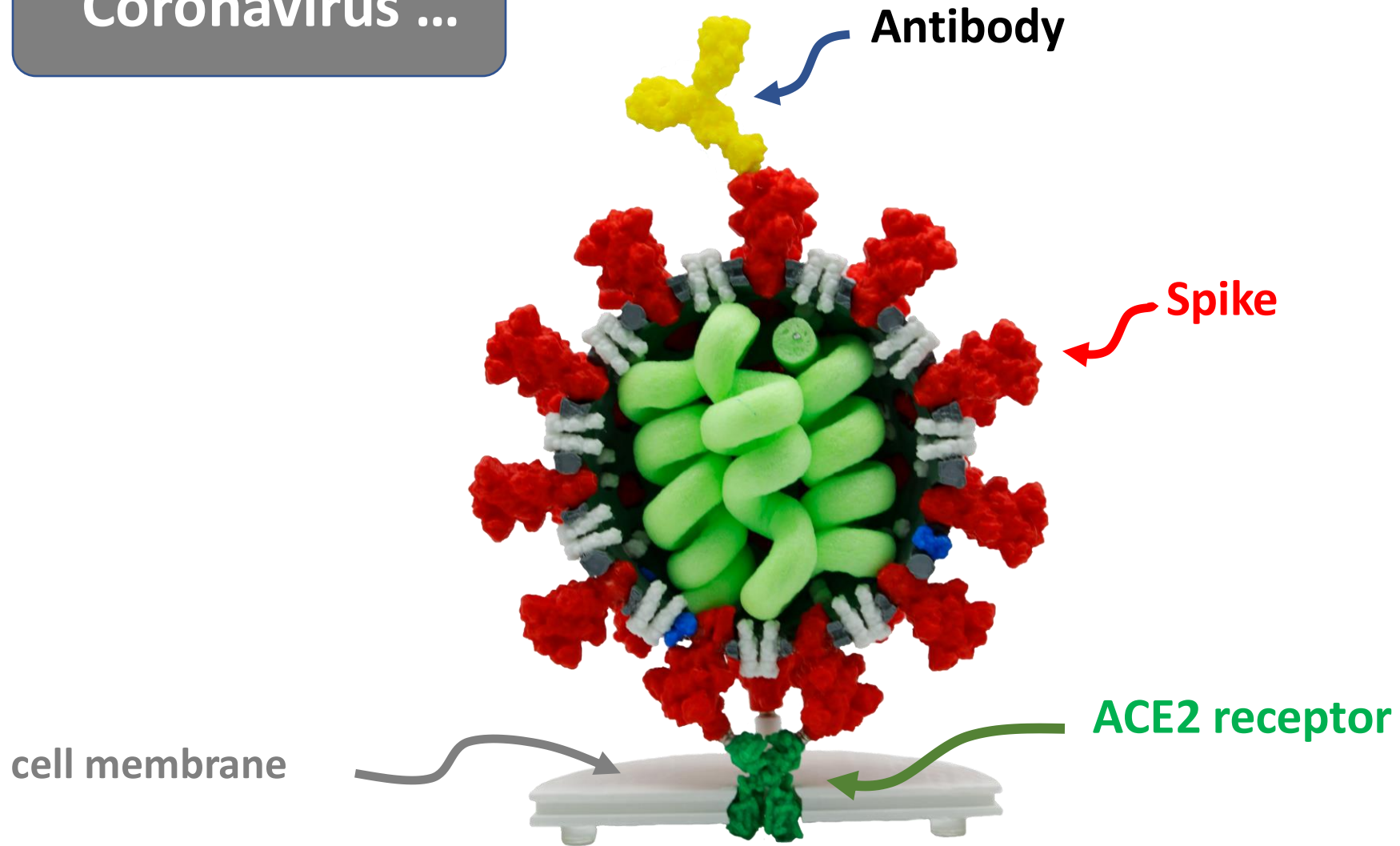


The magic of models....

Models make words meaningful!

Interactive physical models 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.

Coronavirus ...



•NEWS FEATURE

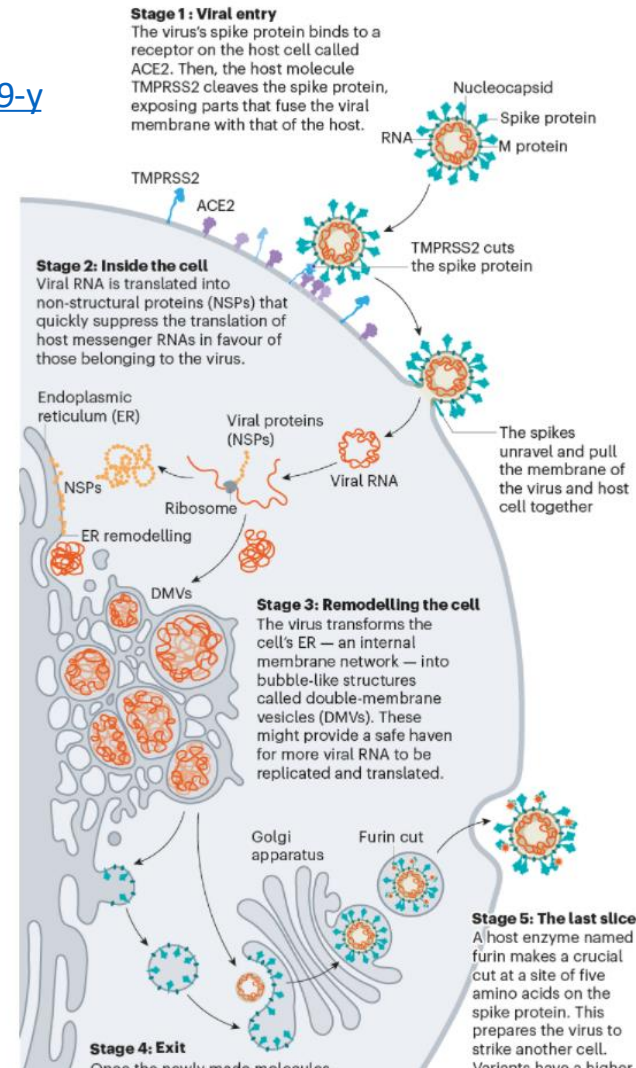
•28 July 2021

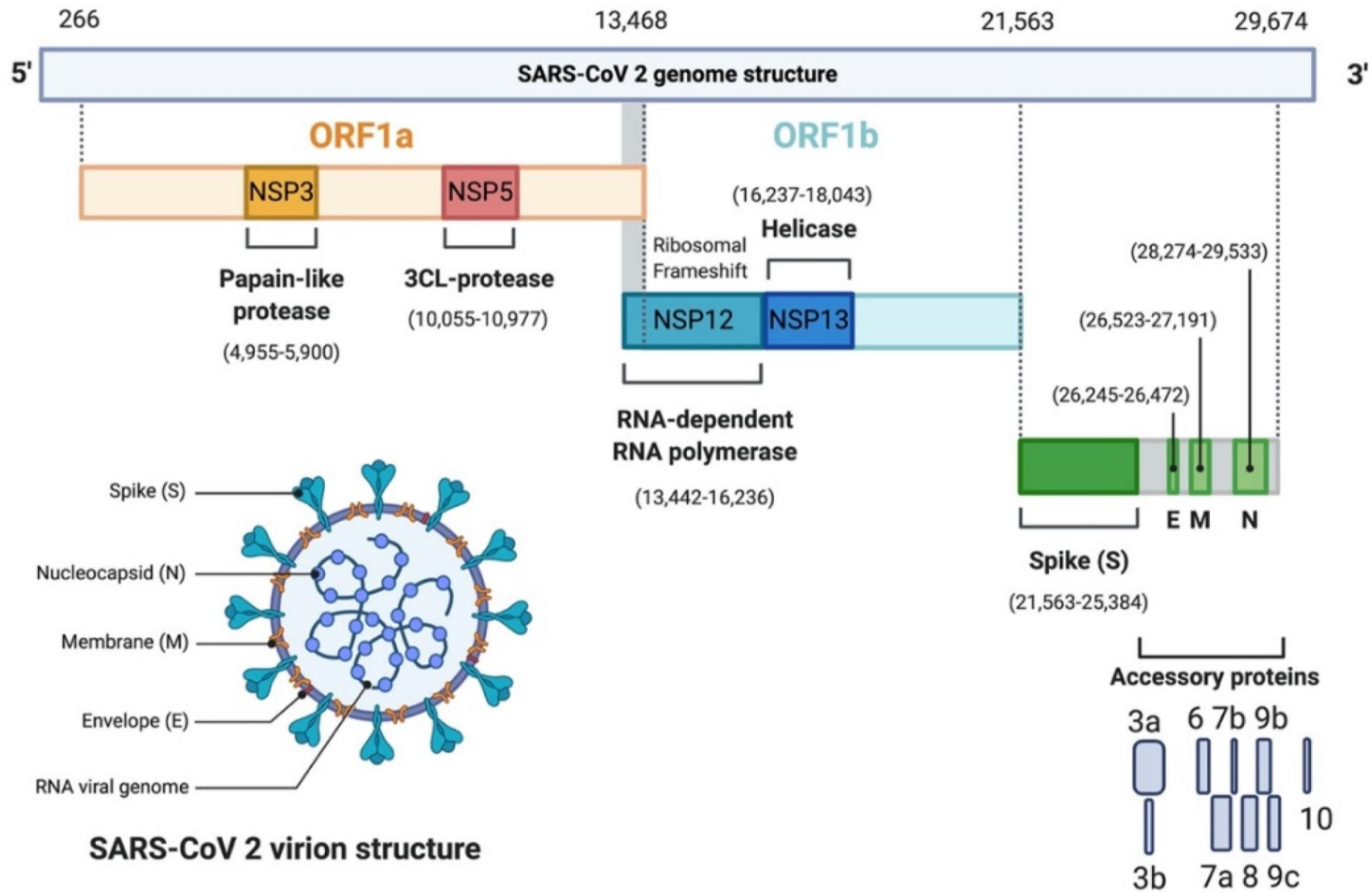
How the coronavirus infects cells

<https://www.nature.com/articles/d41586-021-02039-y>

LIFE CYCLE OF THE PANDEMIC CORONAVIRUS

A simplified account of how SARS-CoV-2 enters and exits cells.





SCIENCE,... to the rescue.....

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

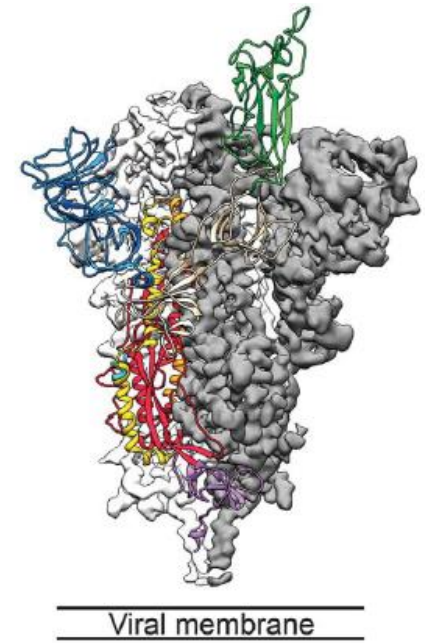
January 10, 2020,... nucleotide sequence of CoV-2 reported,...and shared with the world.

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

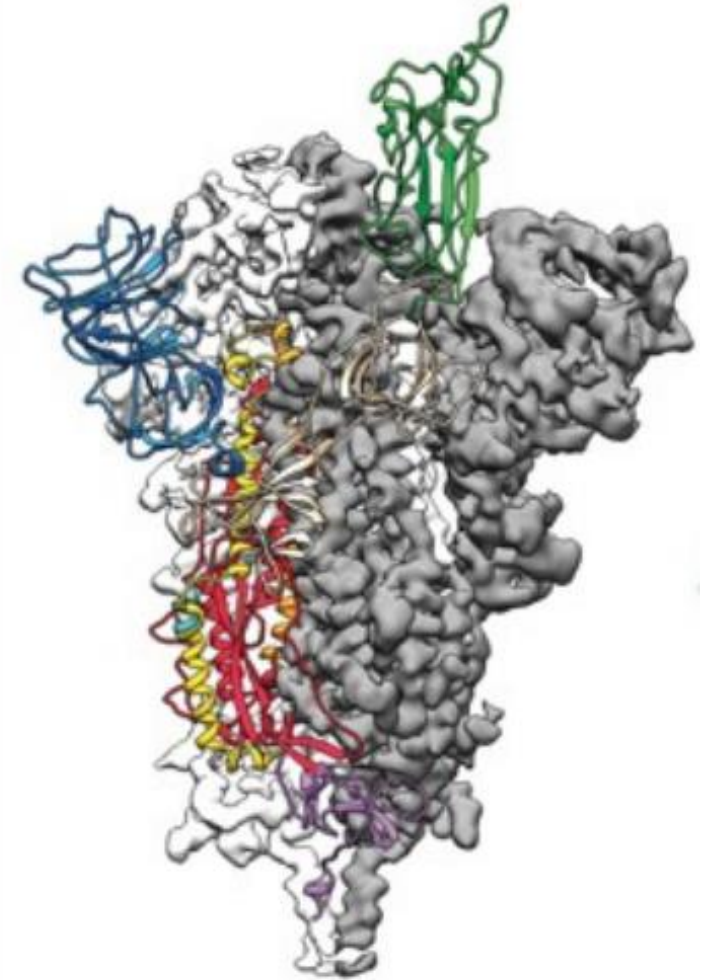
March 20, 2020,... Jason McLellan publishes 3D structure of CoV-2 spike protein.

Clinical Trials,.....

Dec. 18, 2020,... Moderna mRNA vaccine EUA.

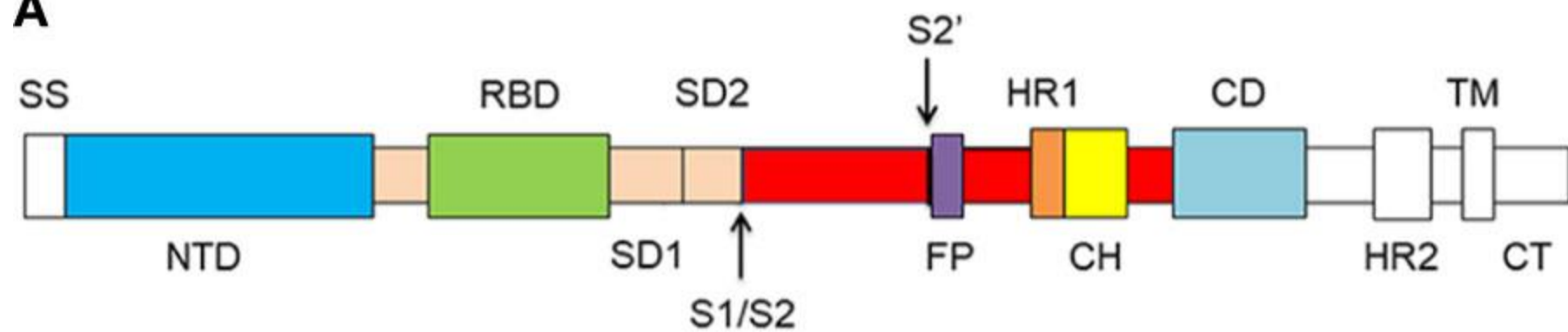
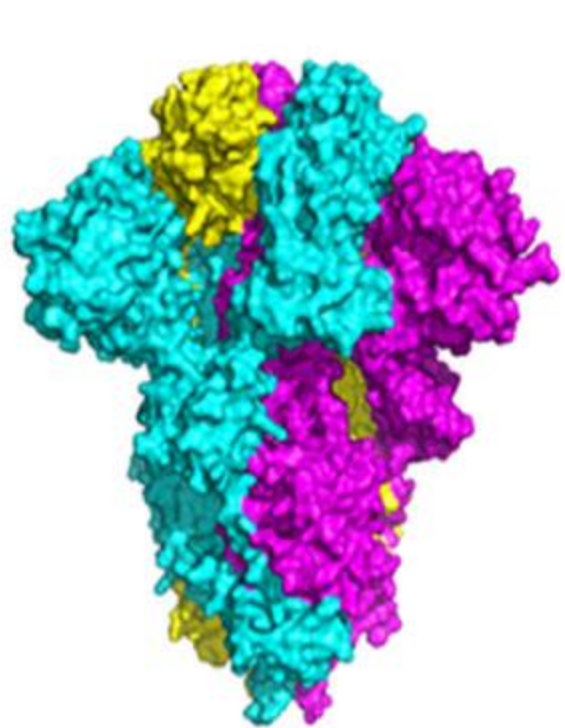


...within 3 months of the CoV-2 genome being sequenced

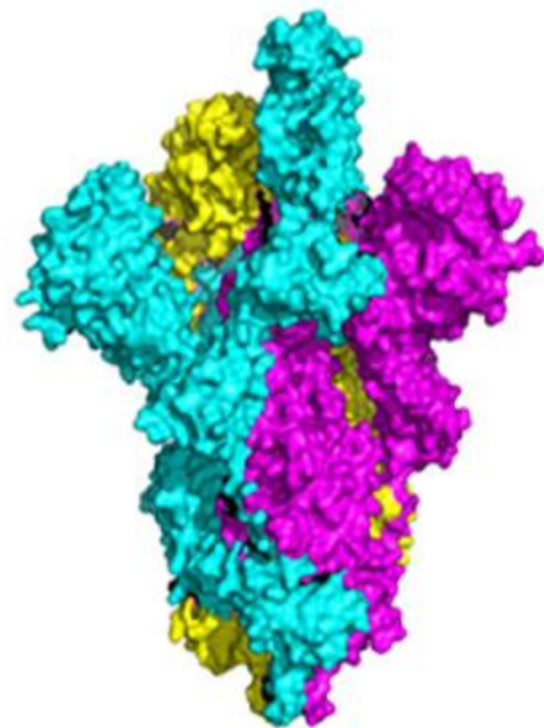


<https://youtu.be/7wMa06xhgWg>

<https://www.youtube.com/watch?v=uM61BGIbiiU>

A**B**

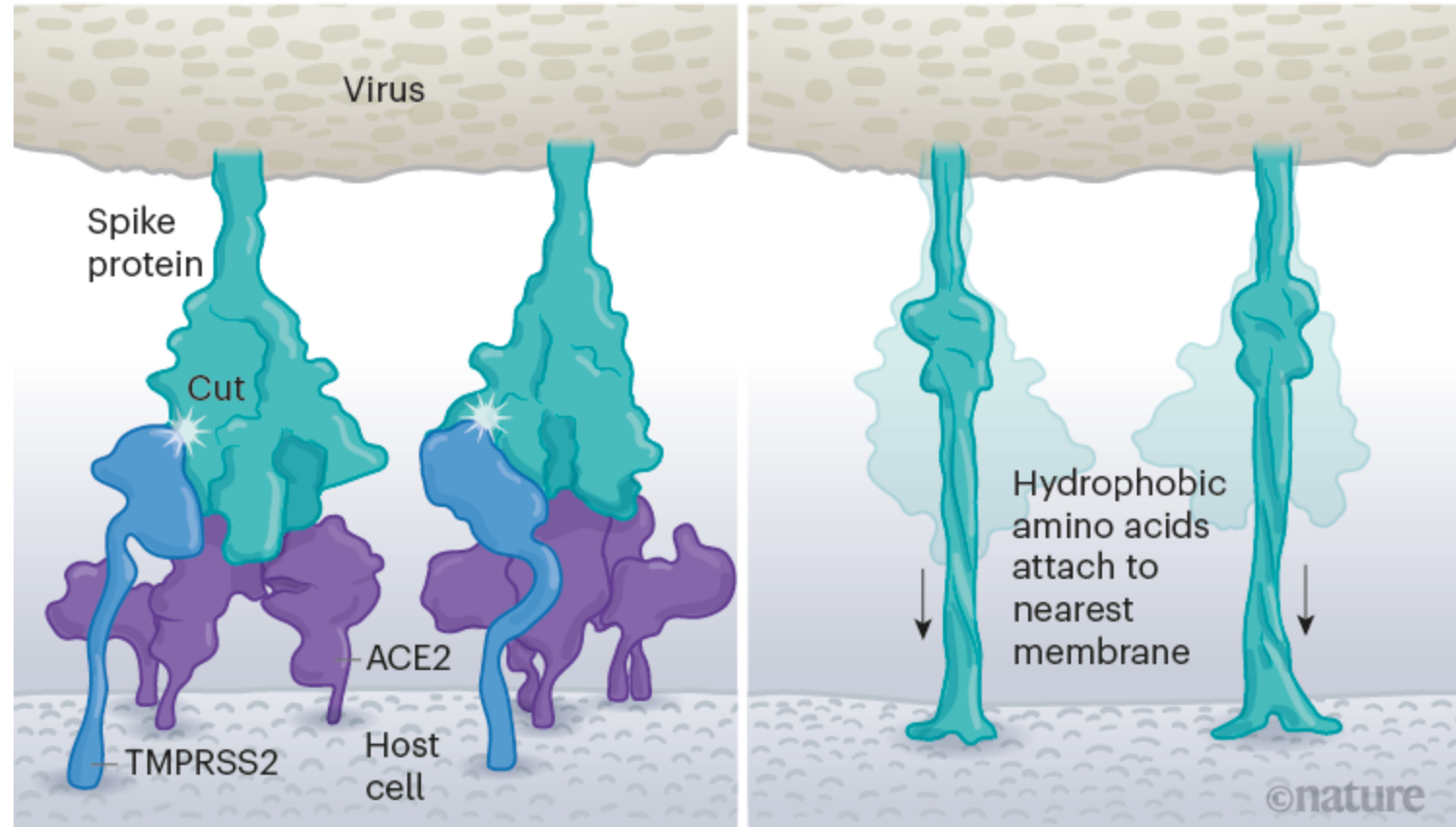
closed state of SARS-CoV-2 spike protein



open state of SARS-CoV-2 spike protein

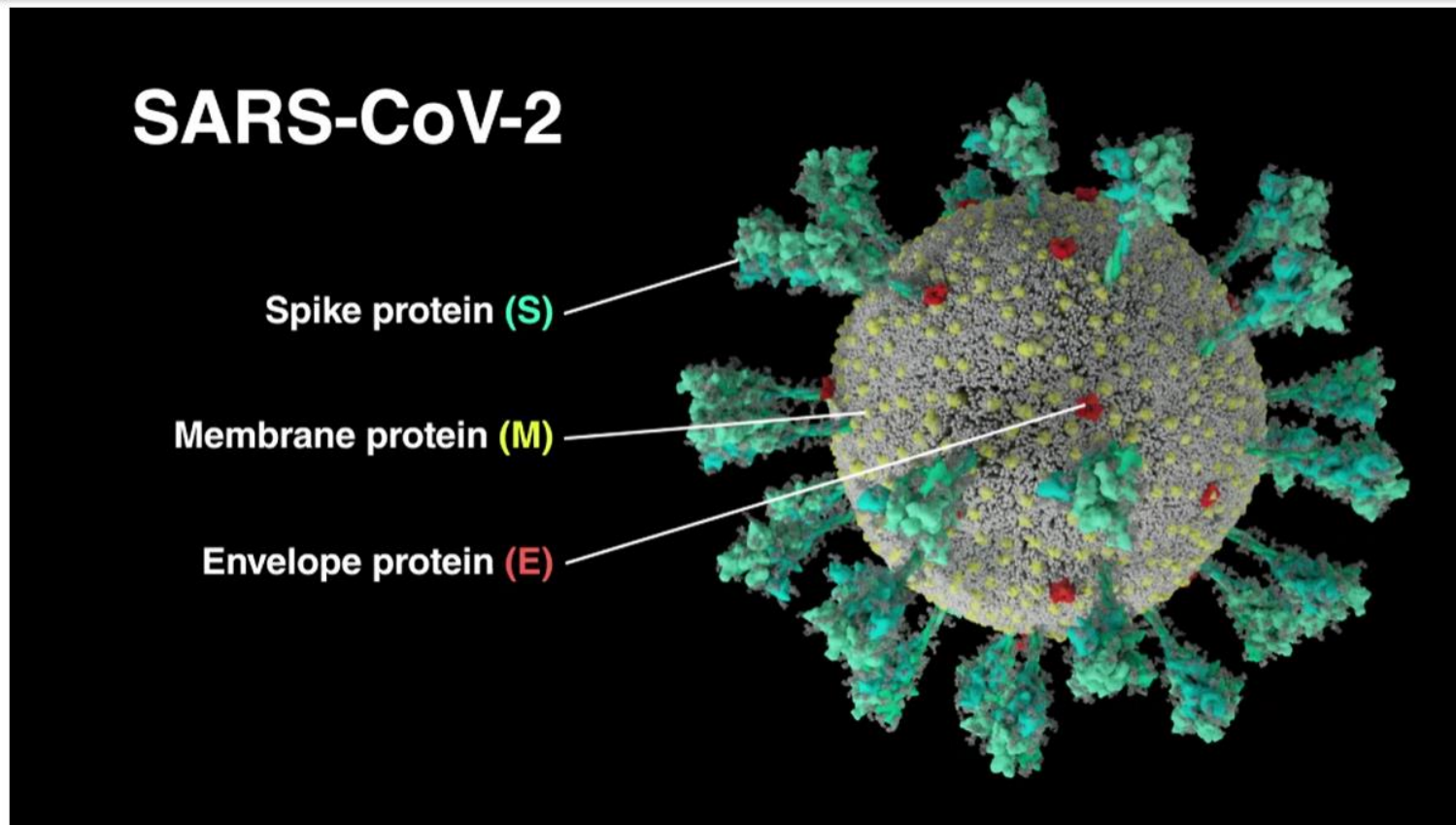
VIRAL ENTRY UP CLOSE

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



<https://coronavirus-annotation-3.sci.utah.edu/>

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

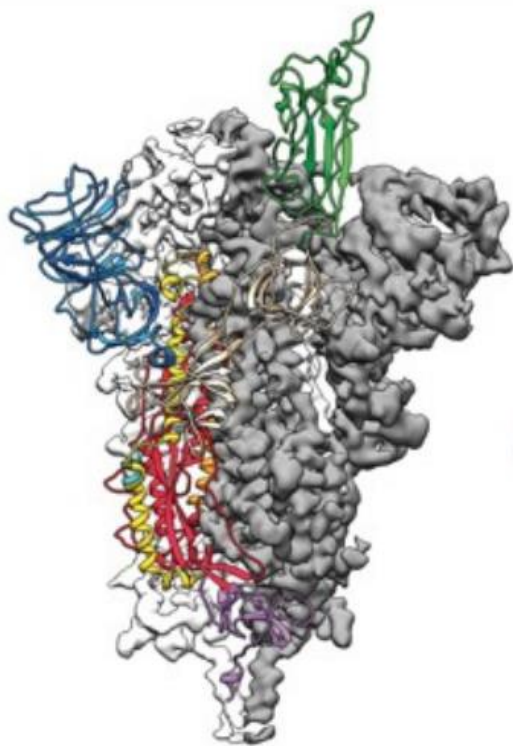
mRNA vaccines

ultrapotent, multivalent vaccines

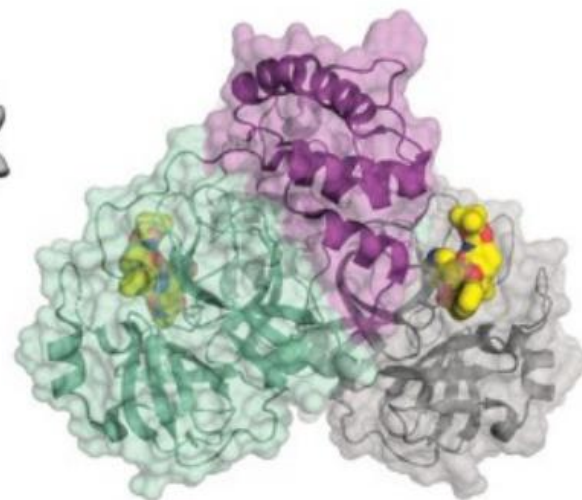
2. **Antivirals**

Remdesovir

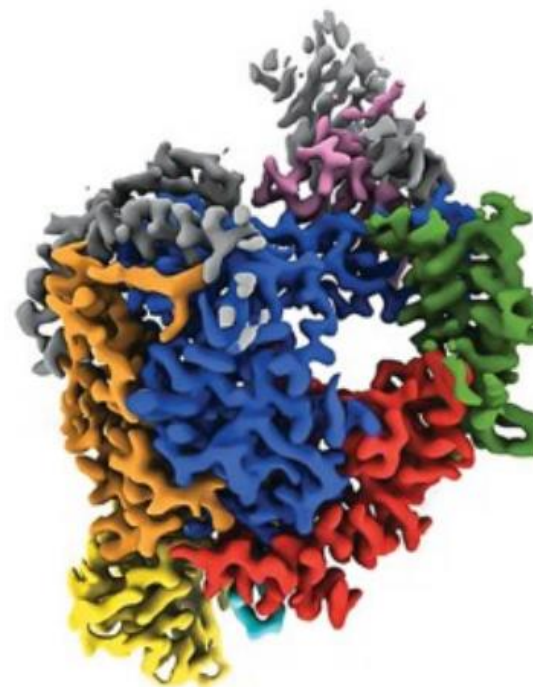
Paxlovid



Spike

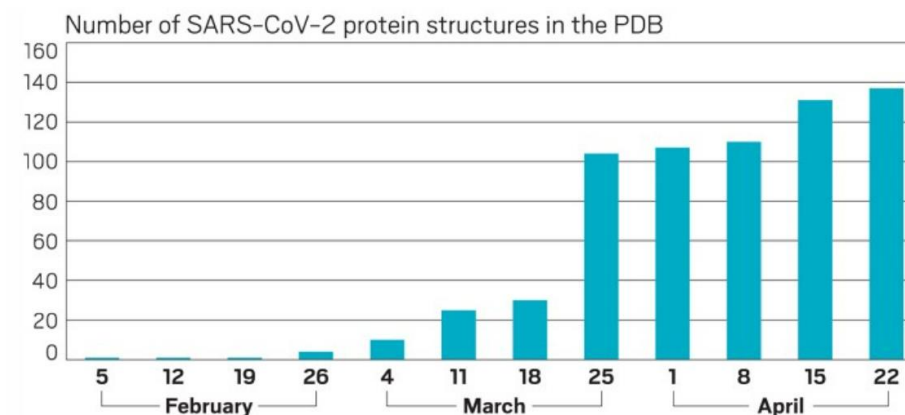


Main Protease



RNA Polymerase

Drug Targets



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



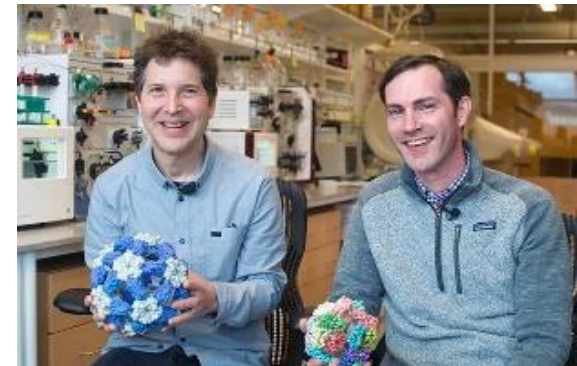
Paxlovid is an antiviral therapy consisting of two antiviral medications.... nirmatrelvir, and ritonavir,

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

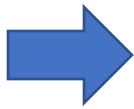
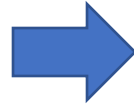
1. Katalin Kariko,... and mRNA vaccines



2. David Baker,... and ultra-potent, multivalent nanoparticle flu vaccines.



Kati Kariko,.. and the perseverance of women research associates.....



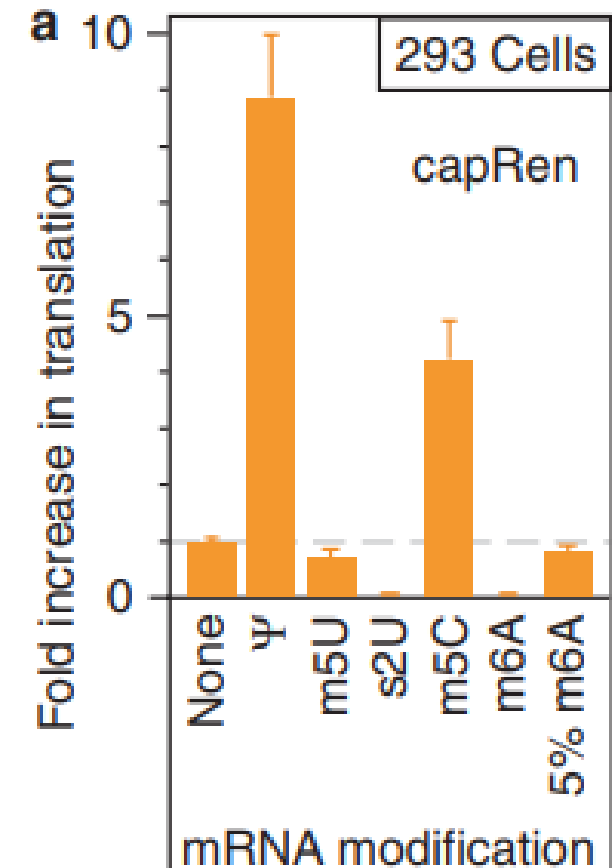
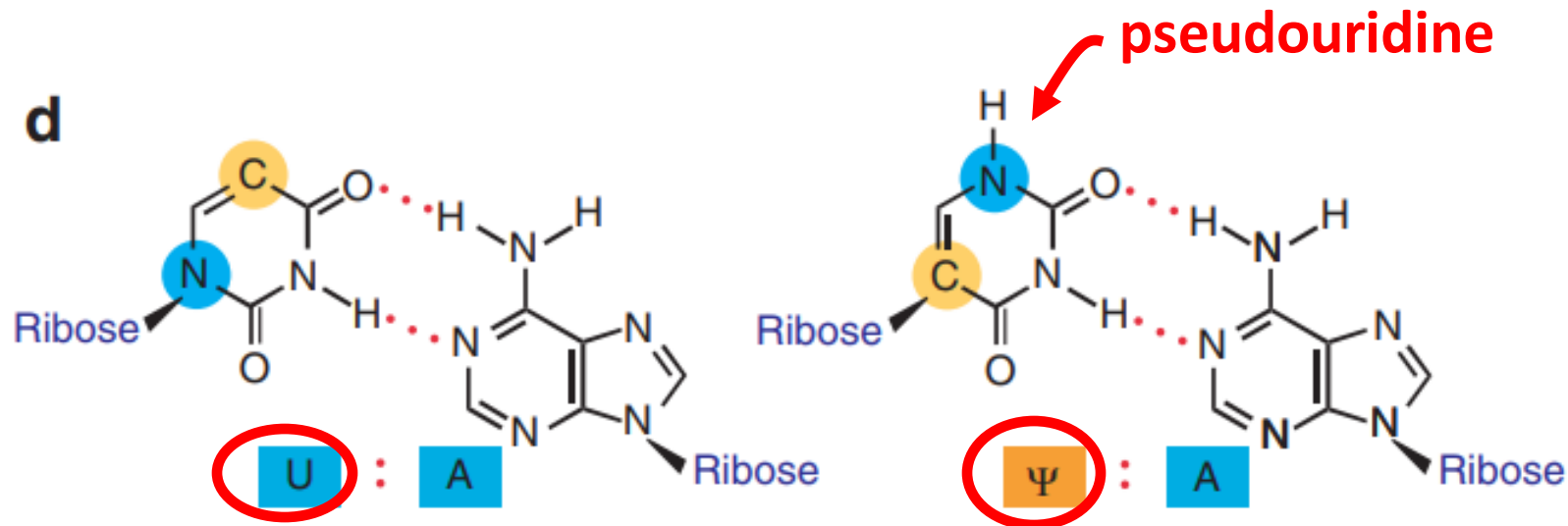
<https://www.nytimes.com/2021/04/08/health/coronavirus-mrna-kariko.html>

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

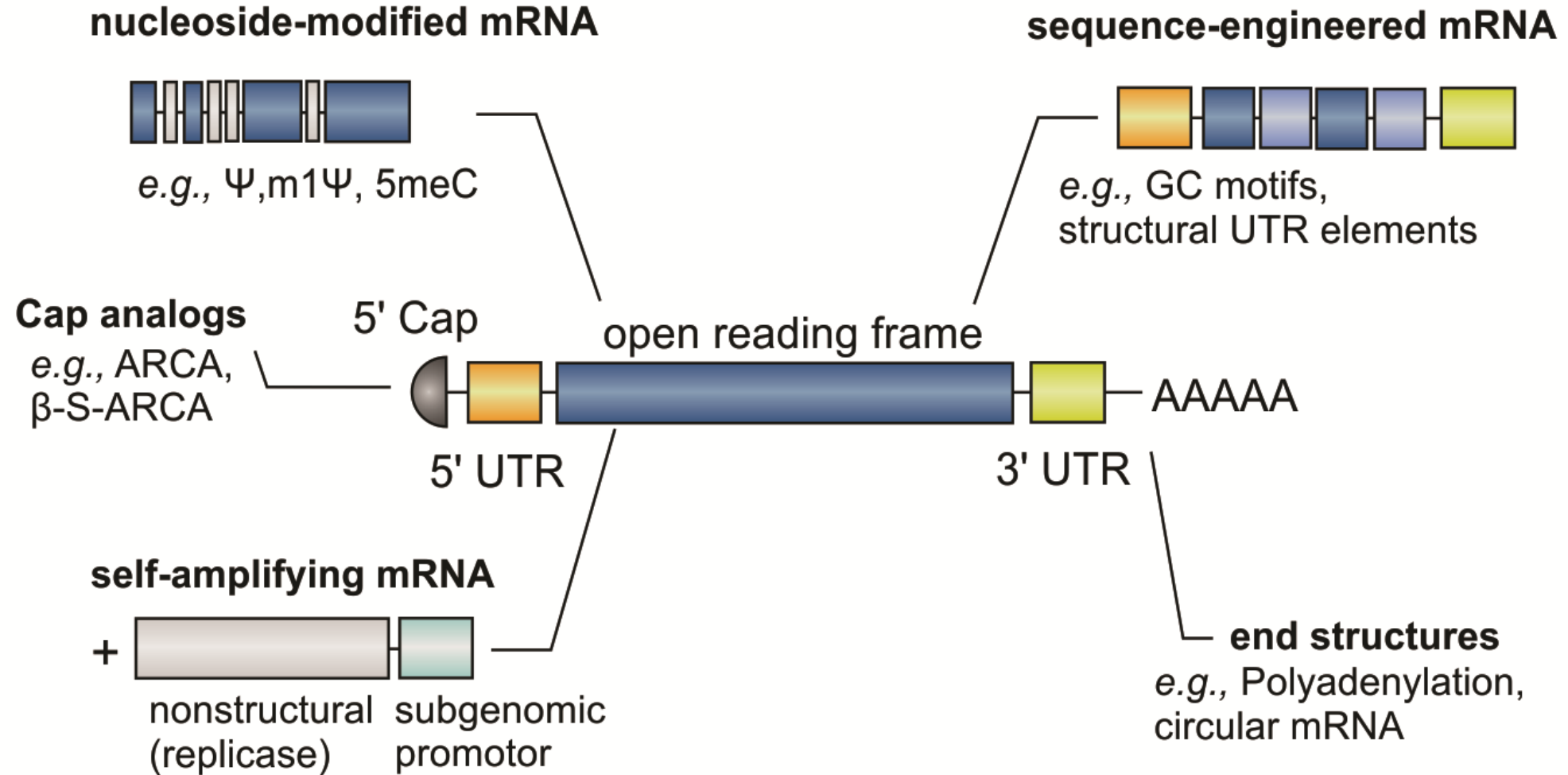
Incorporation of Pseudouridine Into mRNA Yields Superior Nonimmunogenic Vector With Increased Translational Capacity and Biological Stability

Katalin Karikó¹, Hiromi Muramatsu¹, Frank A Welsh¹, János Ludwig², Hiroki Kato³, Shizuo Akira³ and Drew Weissman⁴

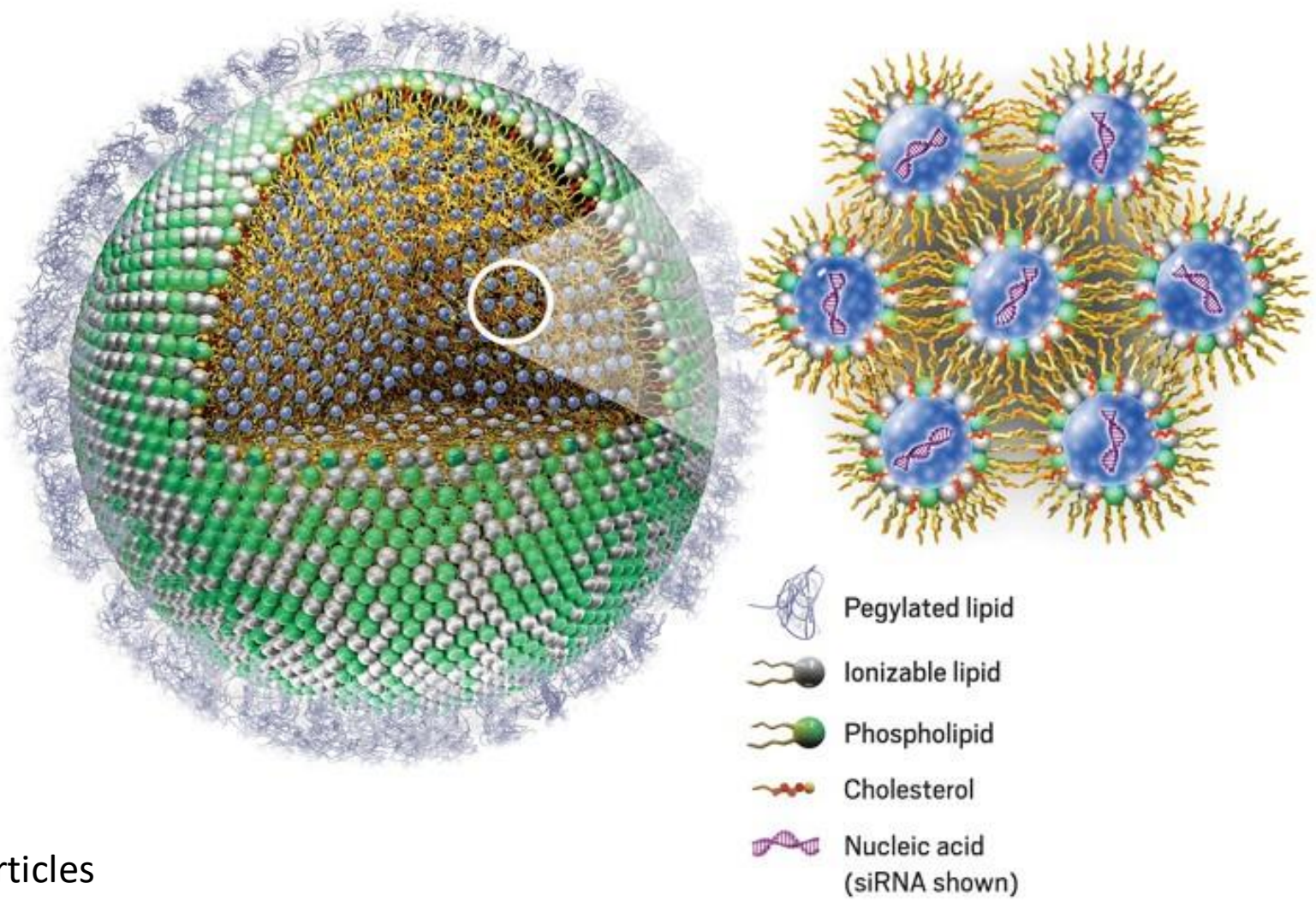
Molecular Therapy vol. 16 no. 11, 1833–1840 nov. 2008



IVT mRNA & modifications



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.**

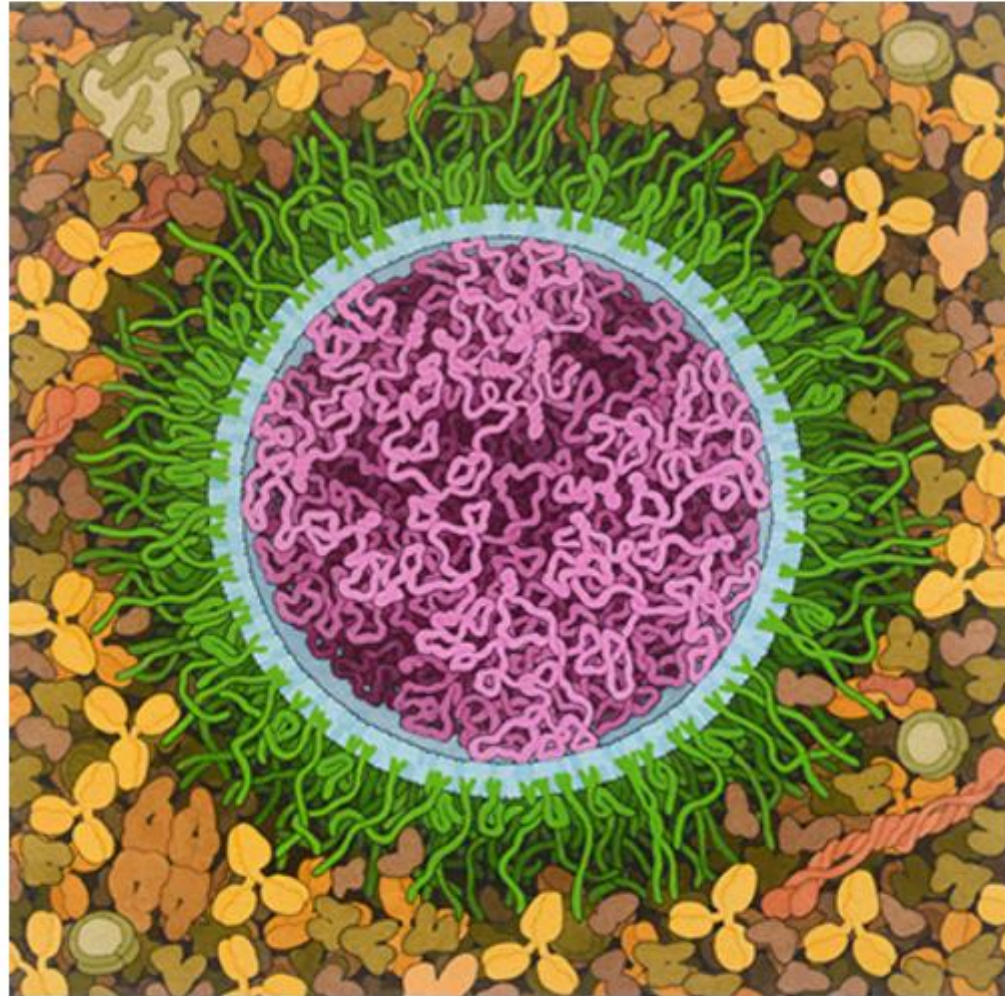


LNPs

Lipid Nano Particles

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

SARS-CoV-2 mRNA Vaccine, 2020



[Download high quality TIFF image](#) 

David Baker,...founder of the Institute for Protein Design



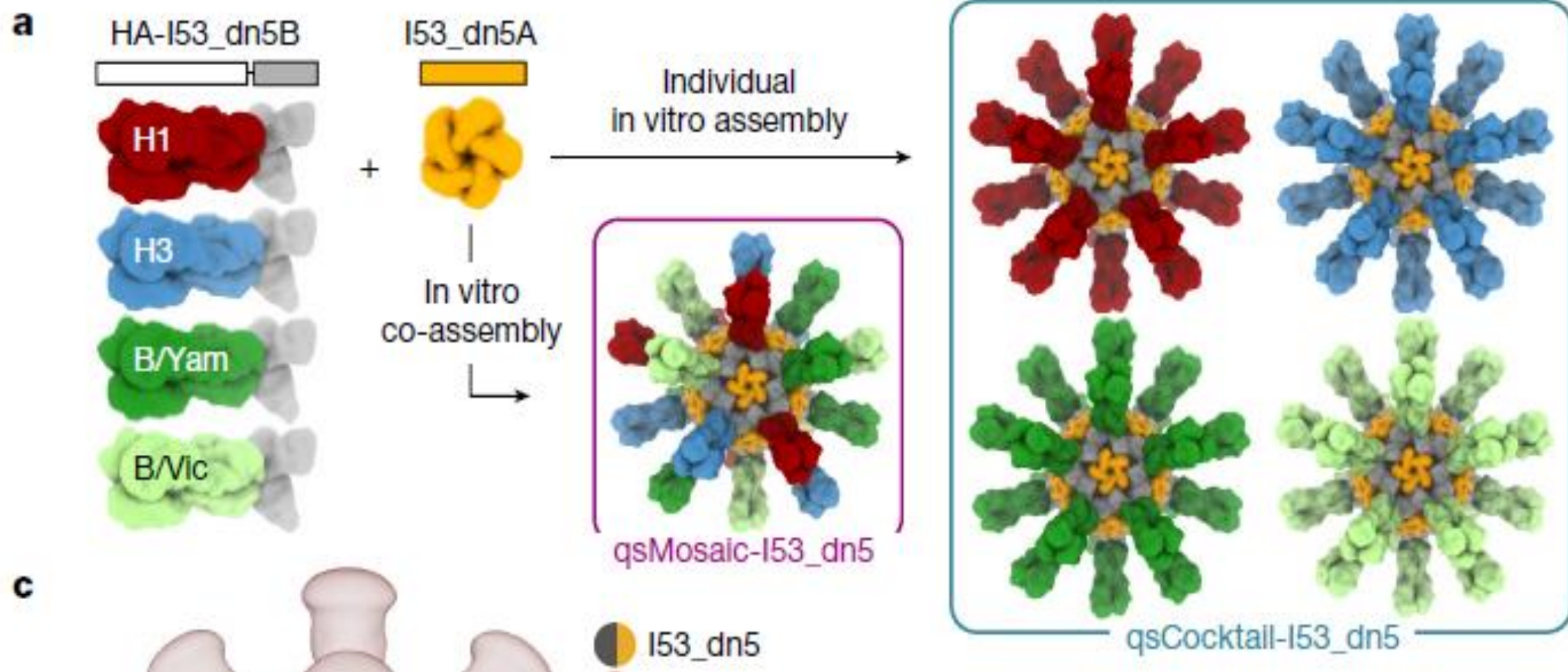
Self-Assembling Nanomaterials and Vaccines

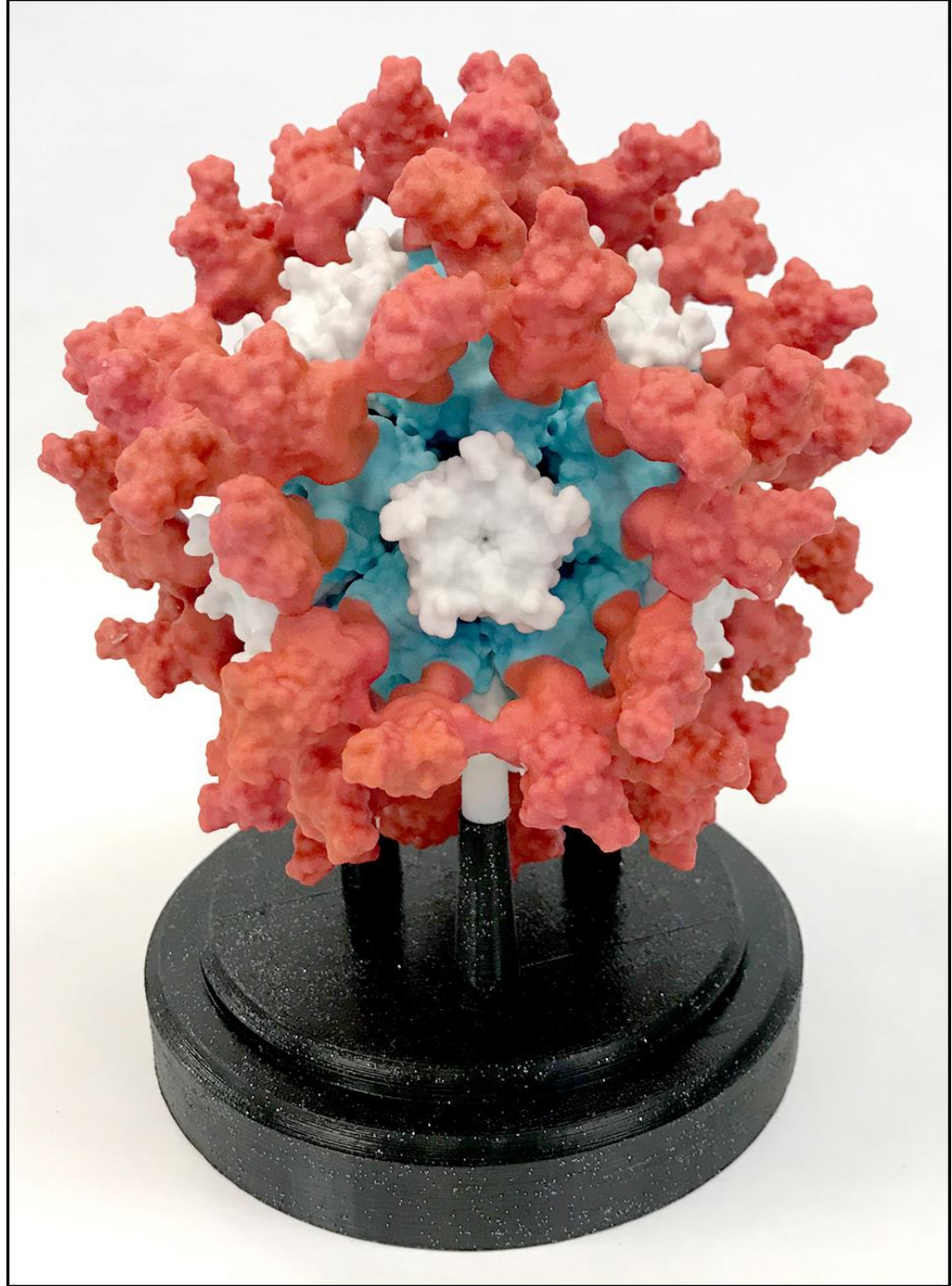
David's TedTalk.... <https://www.ipd.uw.edu/audacious/>

Quadrivalent **influenza nanoparticle vaccines induce broad protection**

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

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

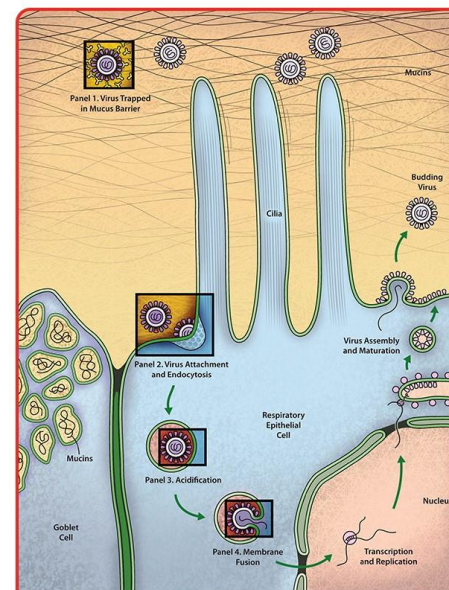
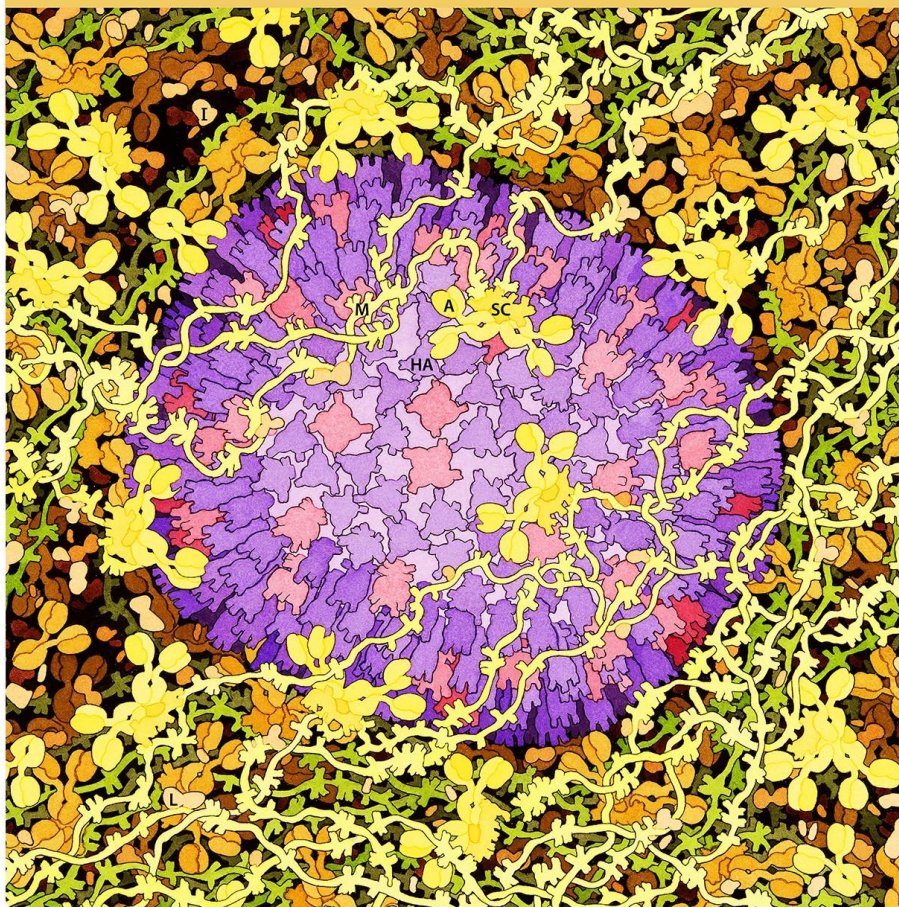




Flu Fight: Immunity & Infection

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.



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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The AeroNab Story



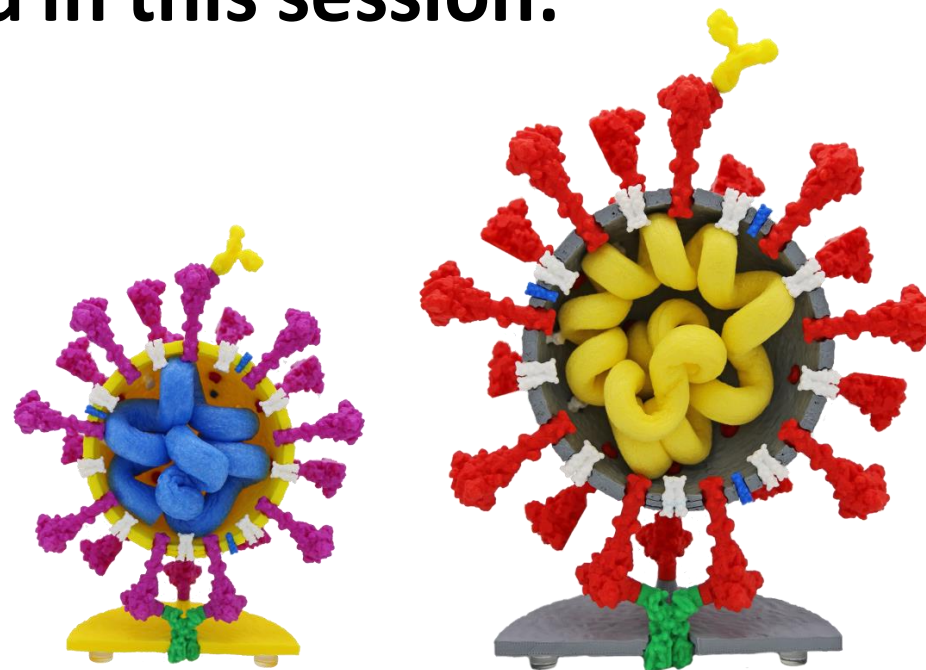
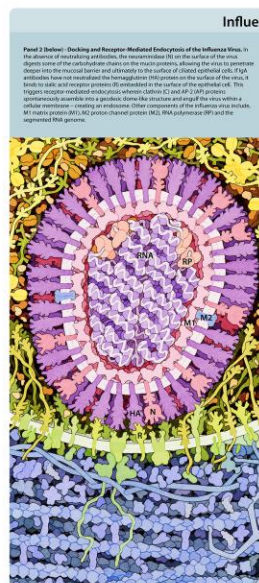
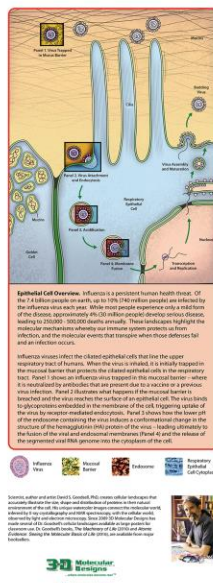
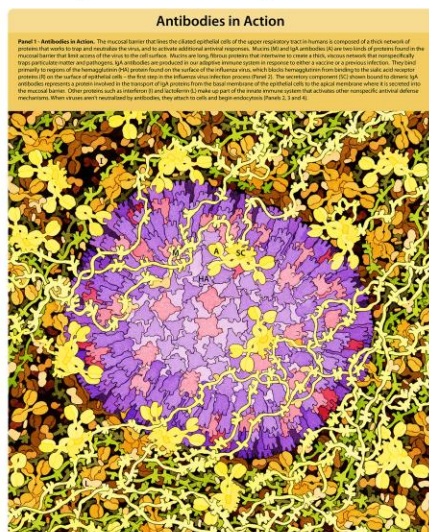
MAPS Teams,... Modeling A Protein Story

<https://cbm.msoe.edu/mapsTeams/antibodies.php>

THANK YOU FOR ATTENDING!

Models and posters used in this session:

Flu Fight: Immunity & Infection



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