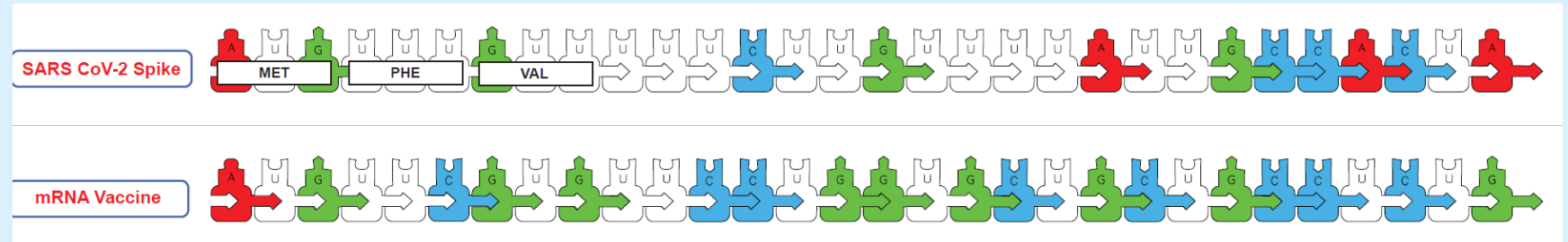


Modeling...

Infectious Diseases & Immunity



Tim Herman
3D Molecular Designs

The Nobel Prize in Physiology or Medicine 2023

Prize Announcement

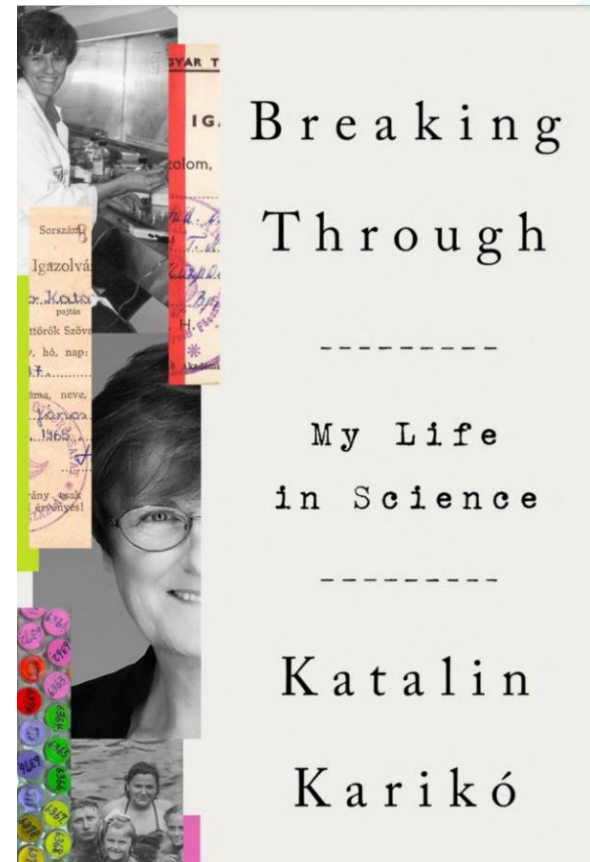


<https://www.nobelprize.org/prizes/medicine/2023/prize-announcement/>

And yet she persisted.....

“...nature rarely replies to questions unless they are put to her in the form of experiments, ... to which she can say yes or no.”

Katie Kariko, F



If you torture the data long enough, nature will confess.

Workshop Outline

- **Coming Soon....*Modeling Infectious Diseases and Immunity***

An NIH SEPA project focused on infectious diseases

- **COVID-19.... and mRNA vaccines**

A story about the process of science,...

...and Katie Kariko,... and pseudouridine

- **An mRNA Vaccine Design Activity....**

Why did it take so long?... and why did it happen so fast?

Student Challenge... *Can you engineer an mRNA vaccine?*

Coming soon,... to a workshop near you.

Modeling Infectious Diseases & Immunity

An NIH SEPA project.

- **New Instructional Materials**
 - Models, models and more models....
A Virus and Cell Modeling Collection,..
Antibodies/vaccines /and your immune system
mRNA vaccines and multi-valent, ultra-potent vaccines...from synthetic biology.
 - Stories, stories and more stories....
- **A Professional Learning Experience**...beginning June 24-28, 2024

But first,...enroll now in **Modeling the Molecular World, 2023**

Session 1 -- July 29 – Aug 2, or

Session 2 -- Aug 5 – Aug 9

Teaching the Molecular Biosciences in a post-pandemic era

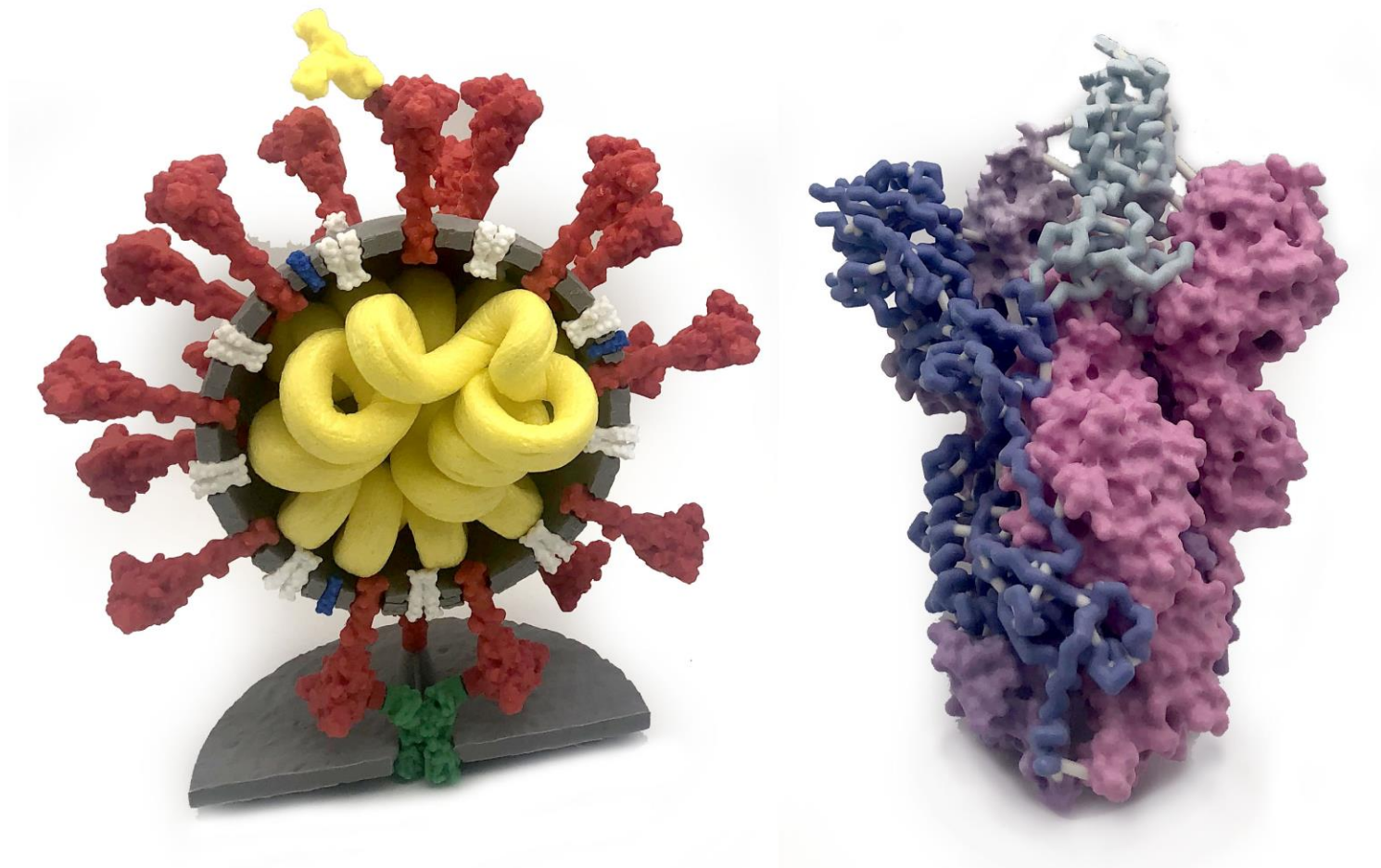
It has been the best of times,... it has been the worst of times.

The biosciences have demonstrated their considerable power and maturity by delivering an effective vaccine to protect the public from CoV-2 ... in less than 1 year.

The public has been reluctant to embrace this new technology, choosing instead to question the validity of the science and the motives of big pharma.

But let's not lose this opportunity to tell this amazing story of *the process of science*.

Coronavirus ...and the Spike protein



Models give meaning to words....

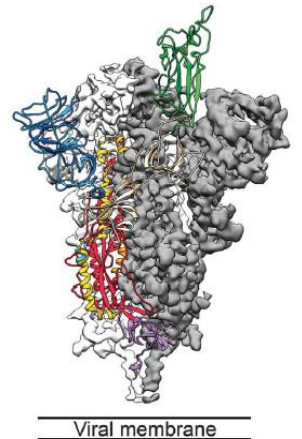
Here's the story....**SCIENCE to the rescue.....**

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.

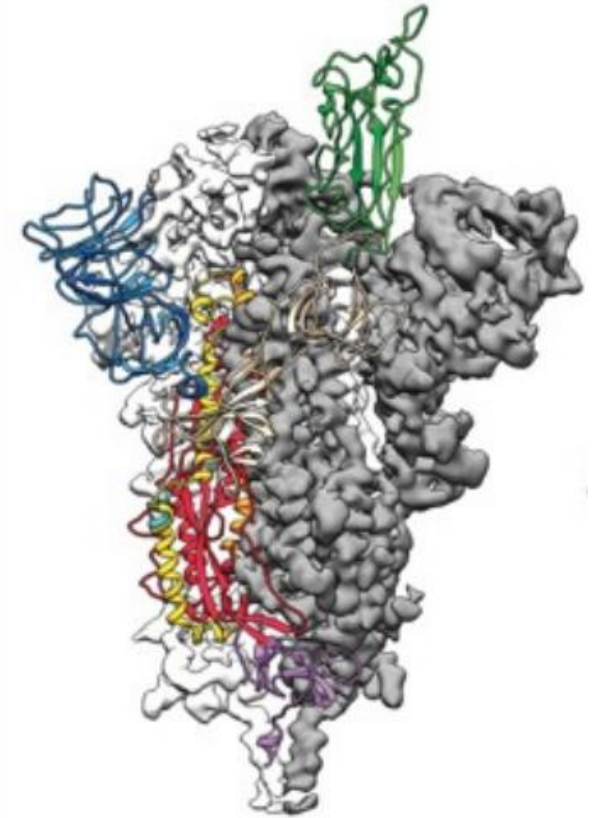
March 20, 2020, Jason McLellan publishes 3D structure
of CoV-2 spike protein.



Clinical Trials.....

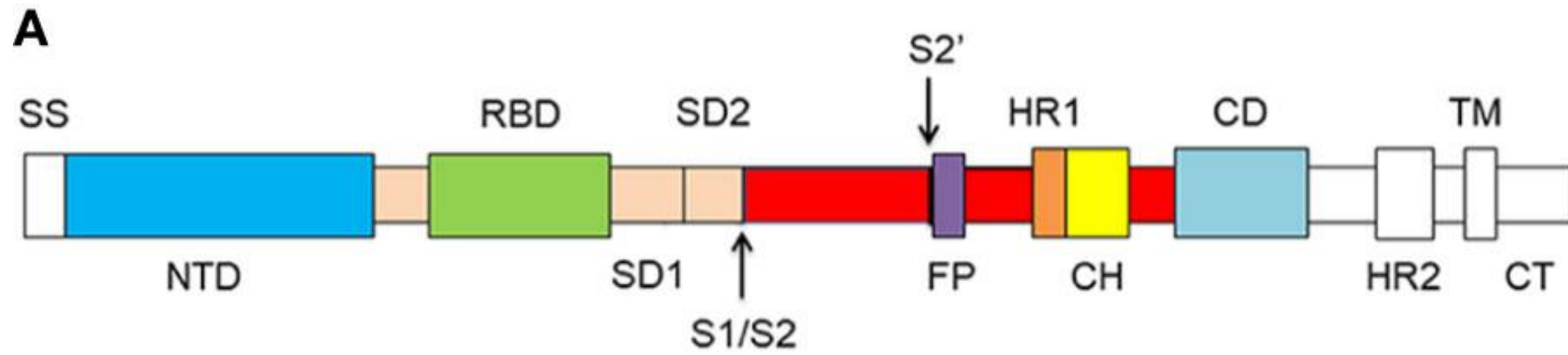
December 18, 2020, Moderna mRNA vaccine EUA.

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

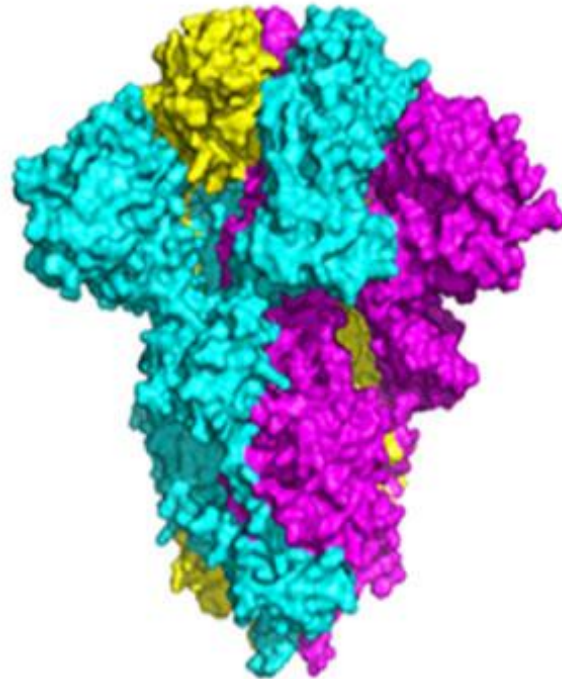


[Key Innovations from UT Austin's McLellan Lab Powers COVID-19 Vaccines](#)

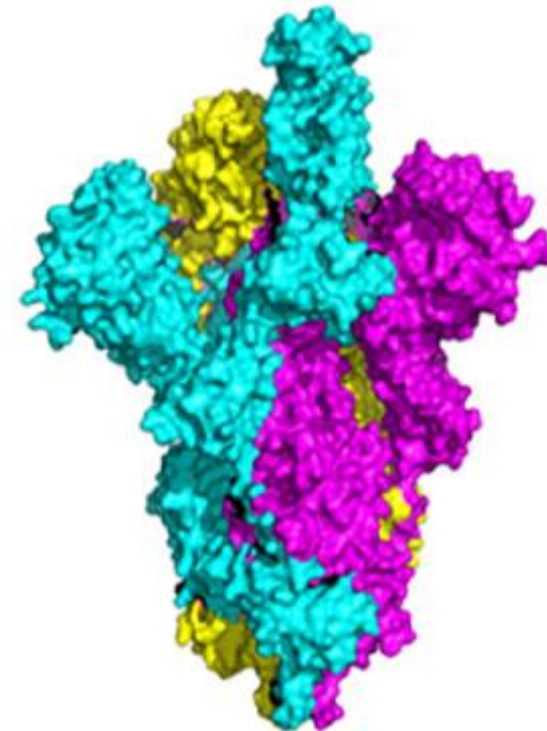
[UT-Austin researcher explains lab's key role in coronavirus vaccine development](#)



B



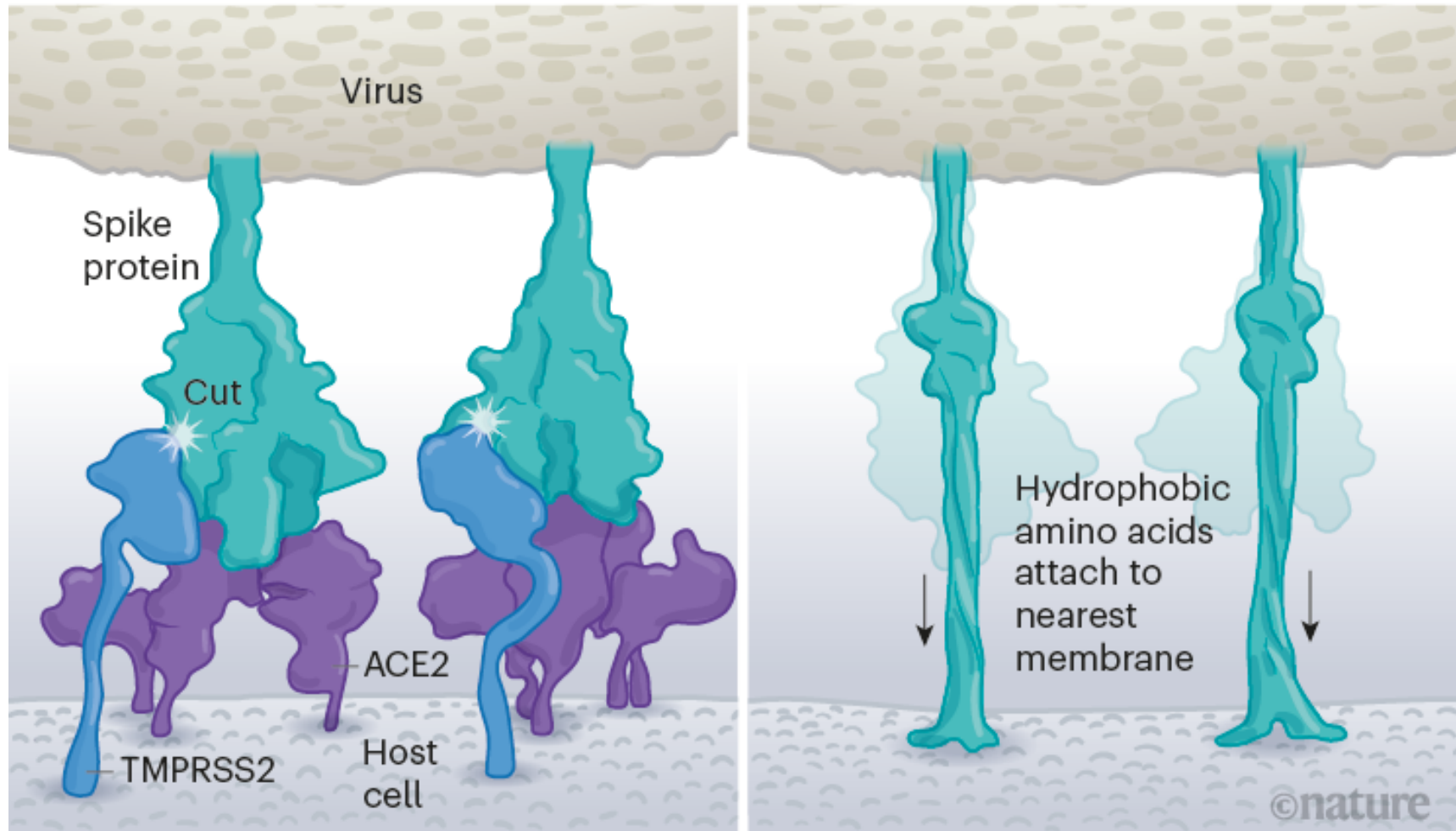
closed state of SARS-CoV-2 spike protein



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.



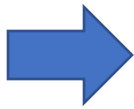
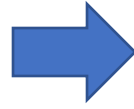


The Science of Coronavirus... a video series



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

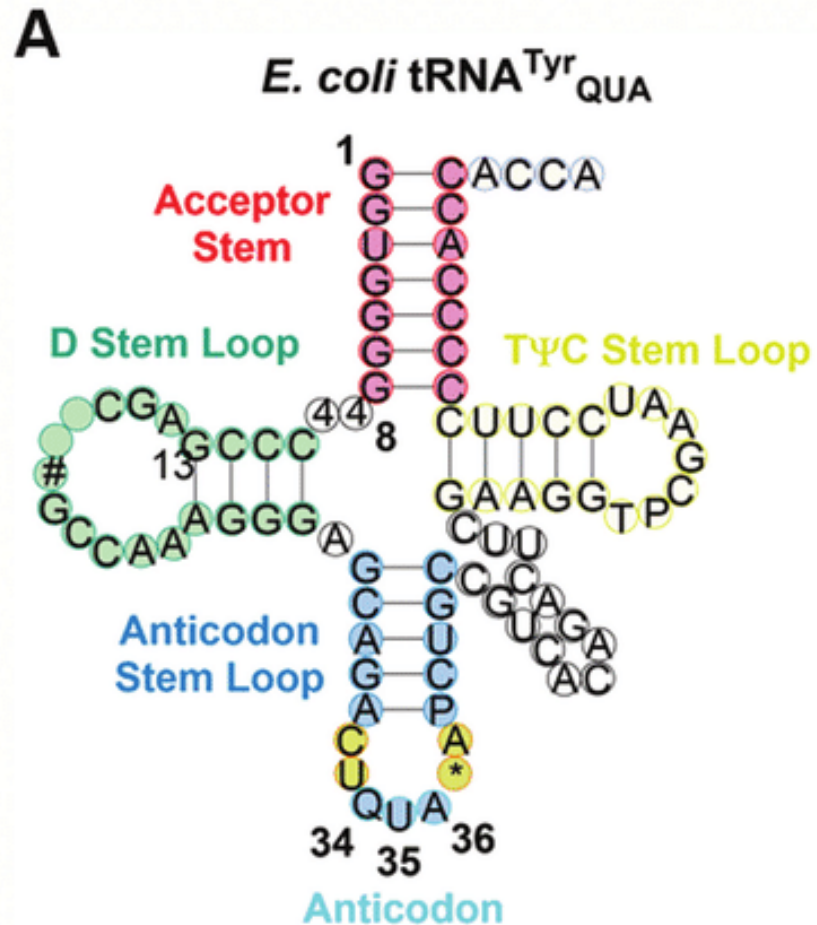
Kati Kariko,.. and the perseverance of women research associates.....



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

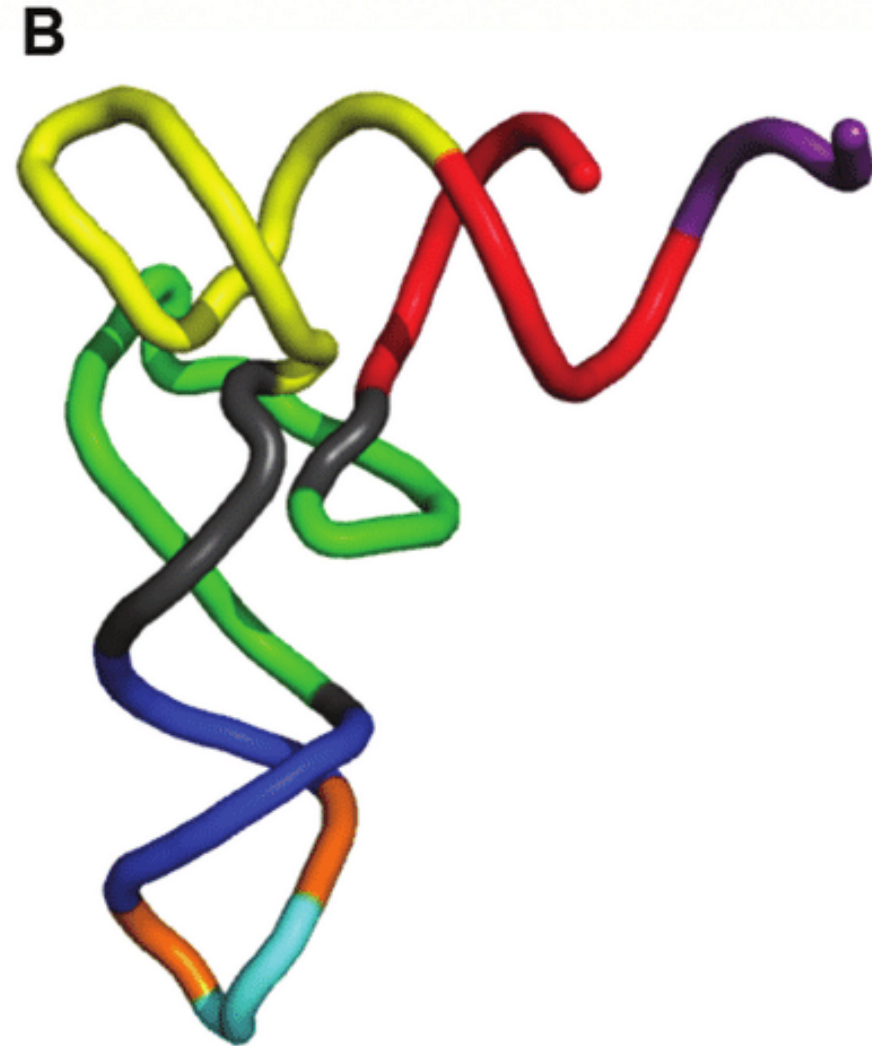
<https://www.cnn.com/2020/12/16/us/katalin-kariko-covid-19-vaccine-scientist-trnd/index.html>

tRNA ModificationsWHY?



Legend of tRNA modifications:

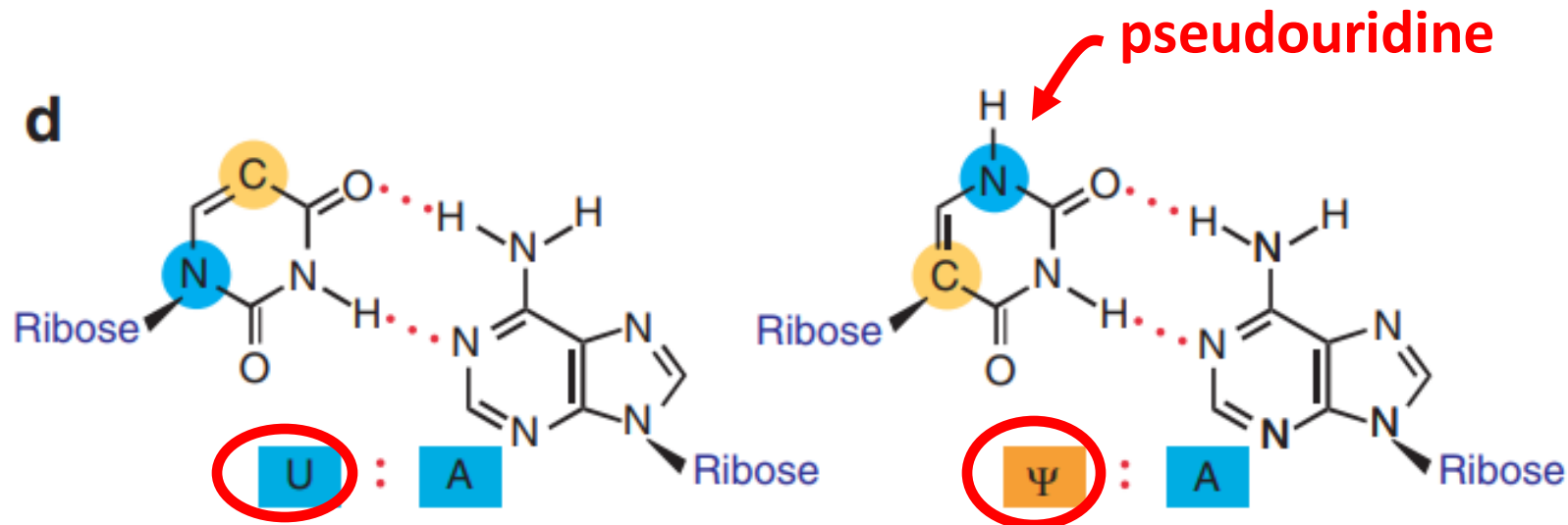
T: m5U	D: dihydrouridine	\: m5Um
P: pseudouridine	4: s4U	#: Gm
Q: queosine	7: m7G	*: ms2i6A



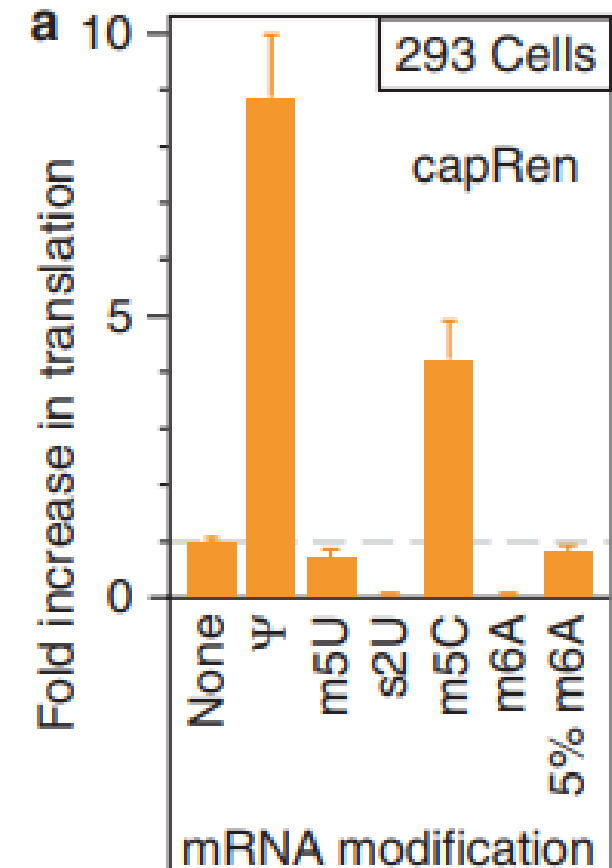
Incorporation of Pseudouridine Into mRNA Yields Superior Nonimmunogenic Vector With Increased Translational Capacity and Biological Stability

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

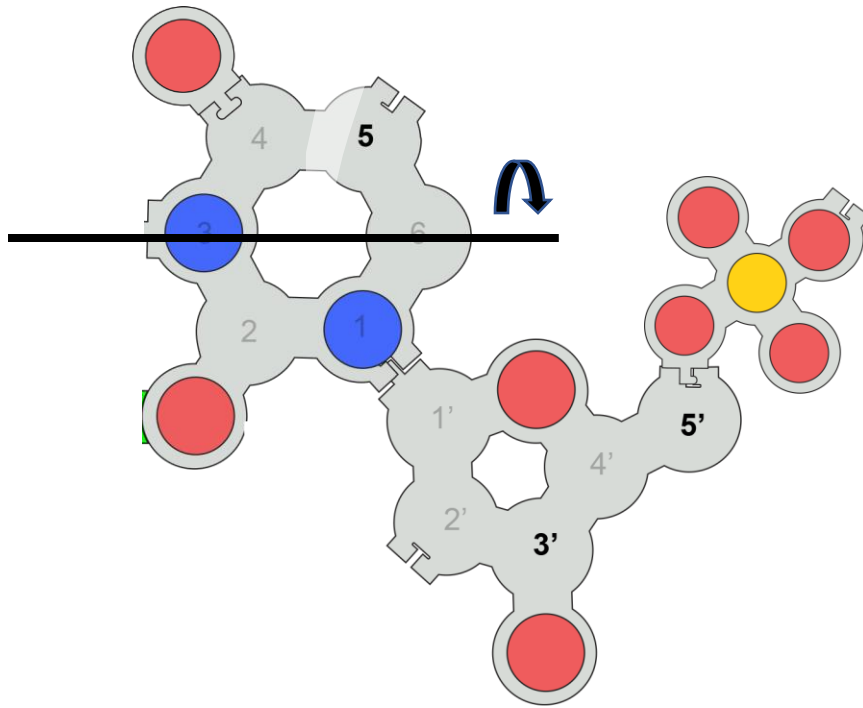
Molecular Therapy vol. 16 no. 11, 1833–1840 nov. 2008



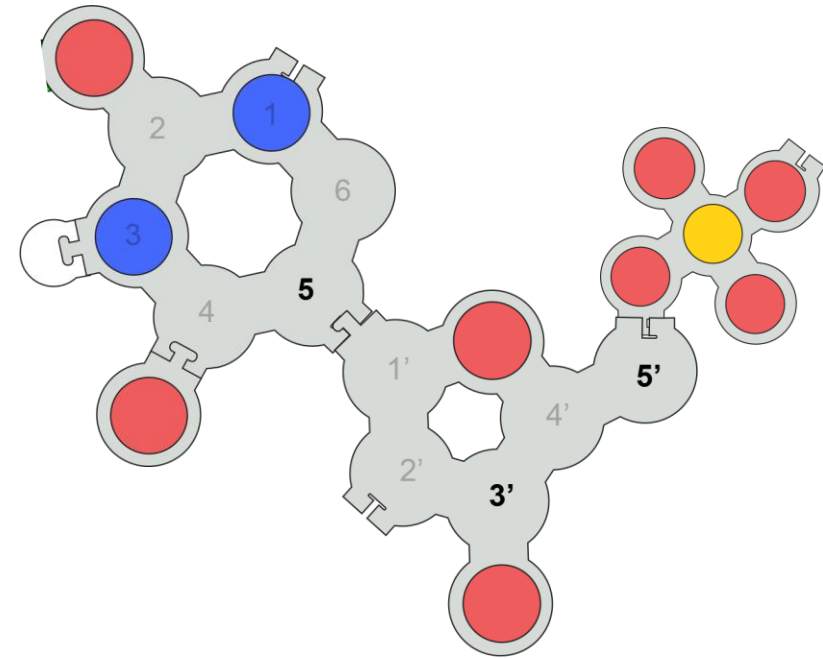
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G Ψ A A C Ψ G C A U G C Ψ A G C Ψ A G C Ψ A G C Ψ C A G Ψ G C Ψ G C Ψ G C Ψ G Ψ A Ψ Ψ Ψ G C Ψ Ψ G A



Tactile Base Pairs



Uridine



Pseudo-Uridine

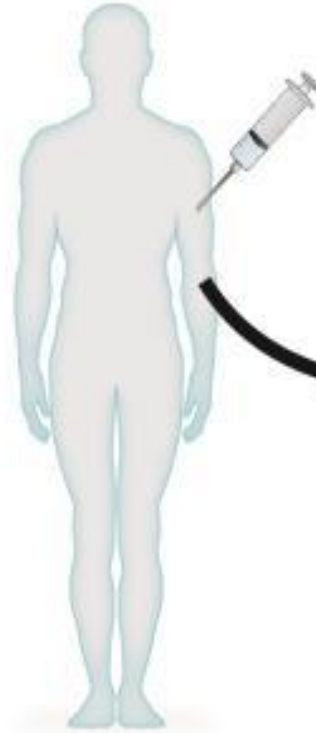
Formulation

mRNA modifications → translation **vs** (self)-adjuvancy



naked mRNA
vs
mRNA (lipid)
nanoparticles

mRNA vaccination

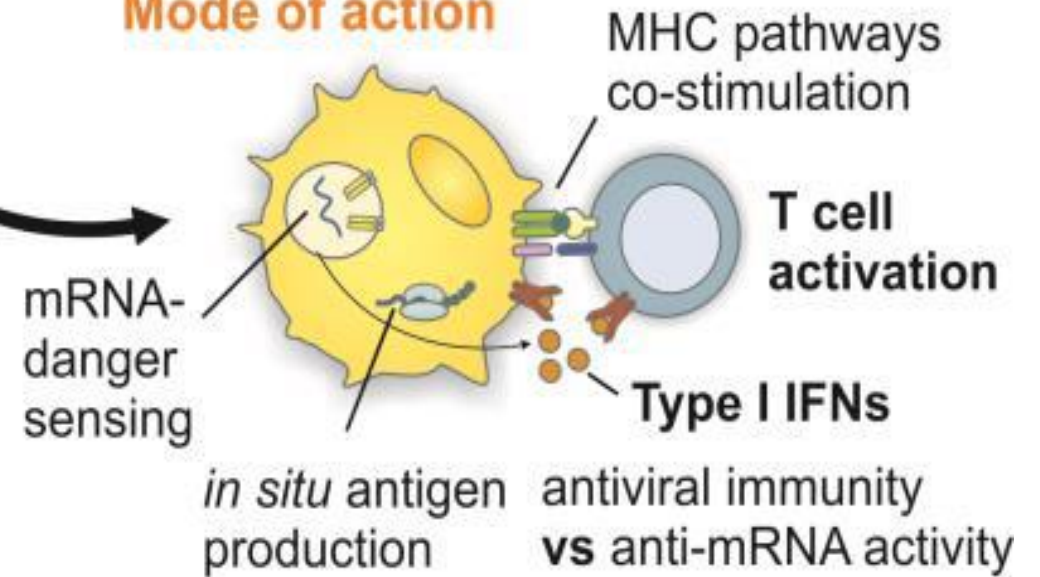


In vivo delivery

local **vs** systemic

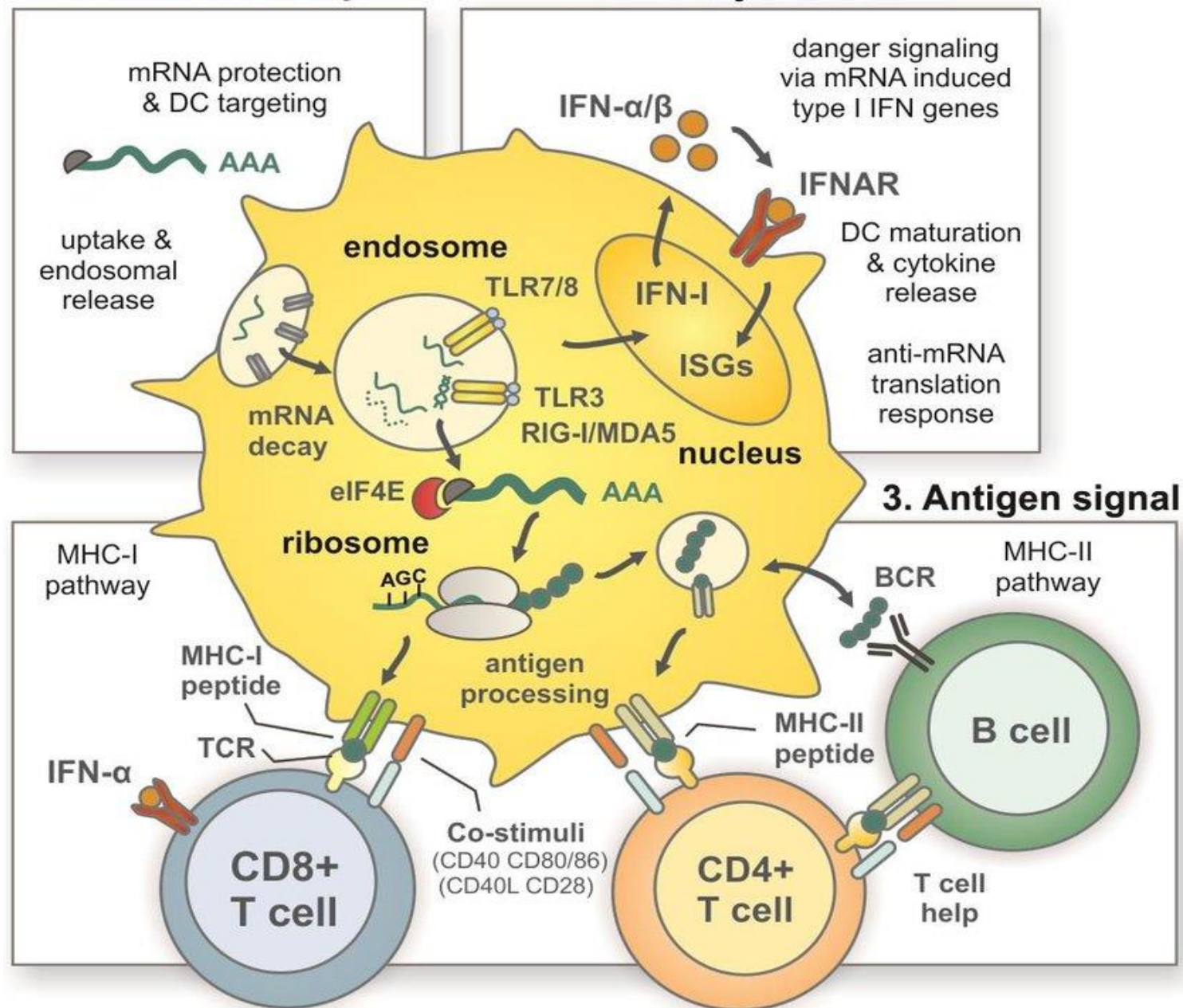
extra- & intracellular
barriers

Mode of action



1. mRNA delivery

2. Self-adjuvant effect



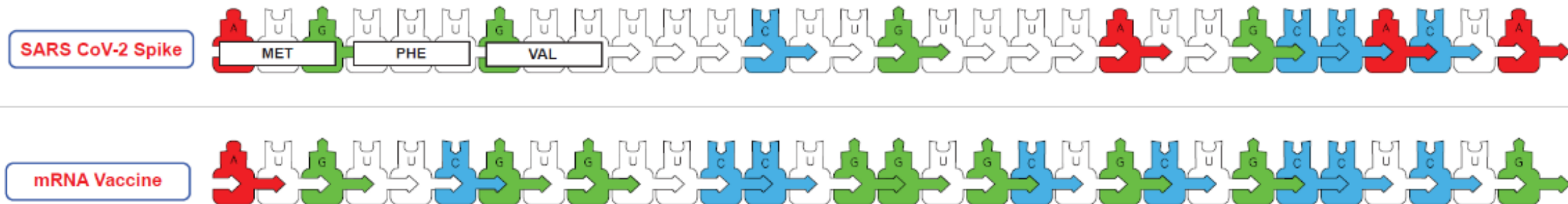
STEM....

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

How can you incorporate principles of engineering design into your science classes?

...an mRNA vaccine design activity



Modifications in an Emergency: The Role of N1-Methylpseudouridine in COVID-19 Vaccines

Kellie D. Nance and Jordan L. Meier*

Cite This: *ACS Cent. Sci.* 2021, 7, 748–756

Read Online

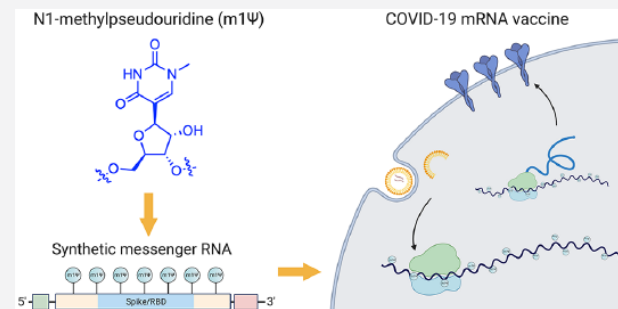
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Supporting Information

ABSTRACT: The novel coronavirus SARS-CoV-2, the cause of the COVID-19 pandemic, has inspired one of the most efficient vaccine development campaigns in human history. A key aspect of COVID-19 mRNA vaccines is the use of the modified nucleobase N1-methylpseudouridine (m1Ψ) to increase their effectiveness. In this Outlook, we summarize the development and function of m1Ψ in synthetic mRNAs. By demystifying how a novel element within these medicines works, we aim to foster understanding and highlight future opportunities for chemical innovation.

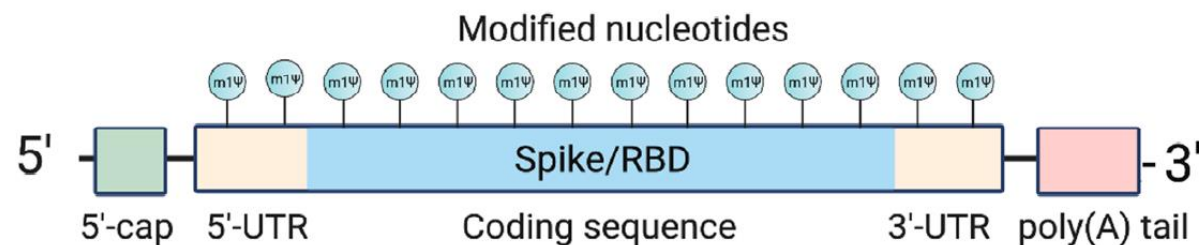


INTRODUCTION

On December 11, 2020, the U.S. Food and Drug Administration (FDA) issued the first emergency use authorization (EUA) for a vaccine to prevent COVID-19, a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹

vaccines can be found in the primary literature reporting them as well as several excellent reviews.^{3,6–8}

The chemical components of mRNA vaccines are pleasantly unremarkable, consisting primarily of RNA plus “water, salt, sugar, and fat,” with two notable exceptions. The first is the lipid



BNT162b2 sequence (U = m1Ψ)

<https://pubs.acs.org/doi/10.1021/acscentsci.1c00197?fig=fig2&ref=pdf>

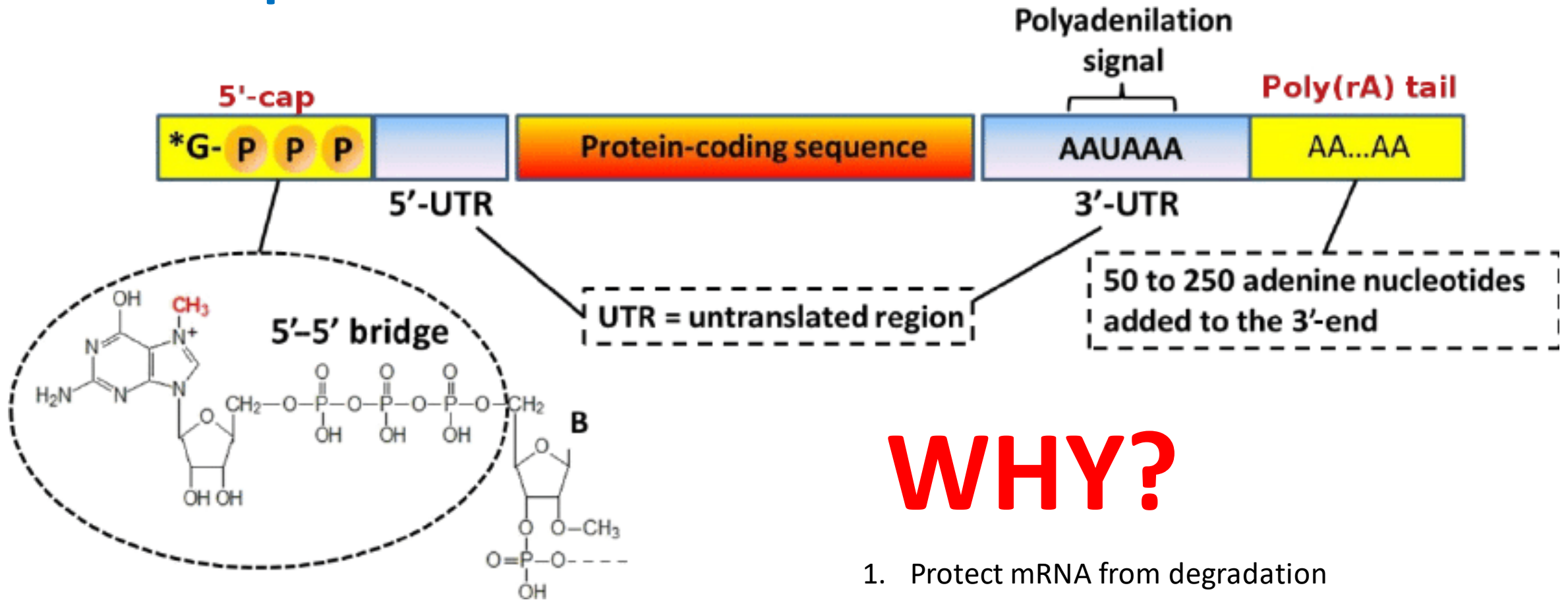
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Figure 2. Top: Design elements found in synthetic mRNA therapeutics. Bottom: Sequence of the COVID-19 mRNA vaccine tozinameran

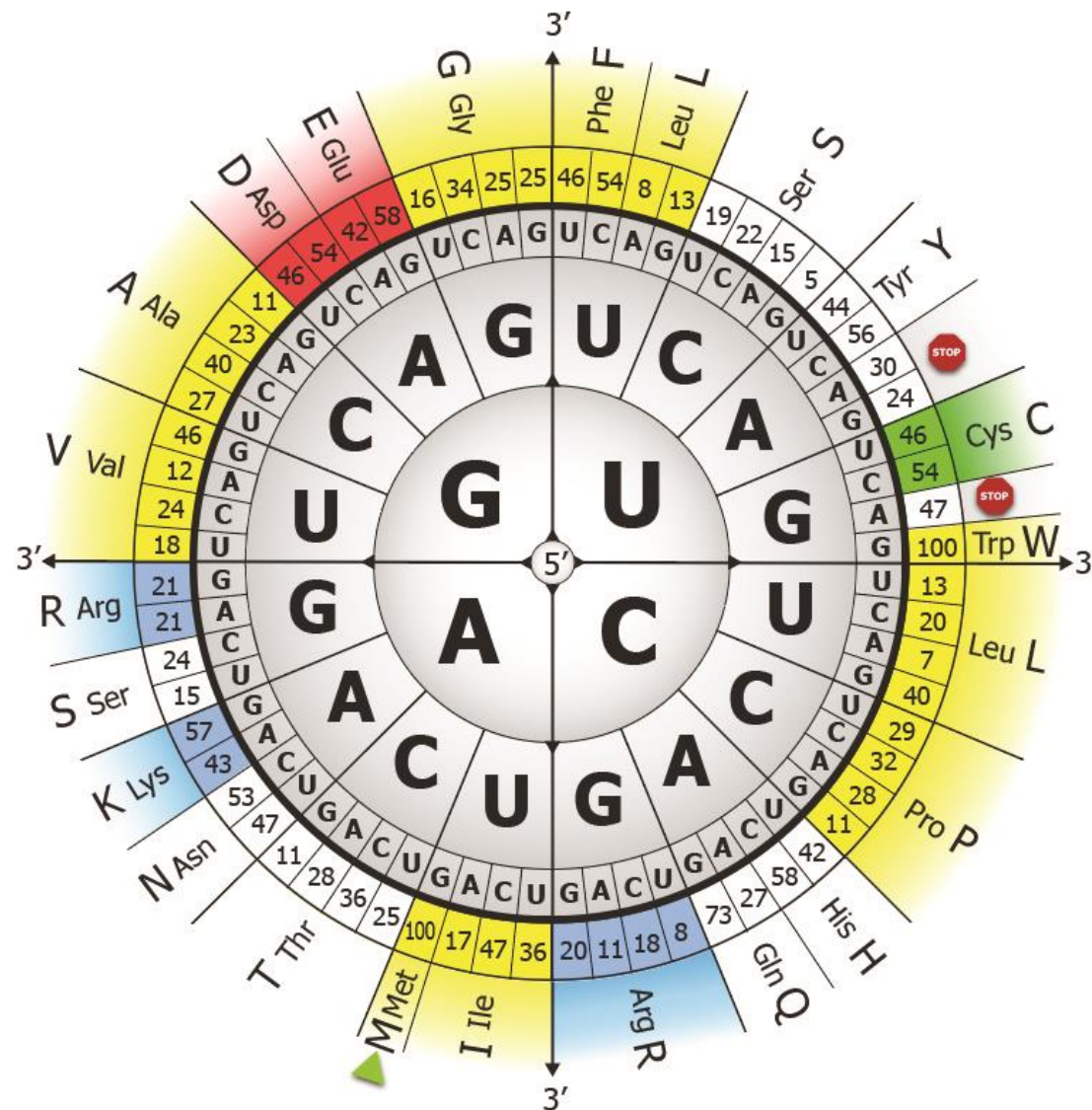
The Components of mRNA



WHY?

1. Protect mRNA from degradation
2. Ribosome engagement site...
3. Distinguish between viral RNA and endogenous mRNA

... *with human codon preferences*



Coming soon,...
Modeling Infectious Diseases and Immunity

June 24-28

An NIH SEPA project.

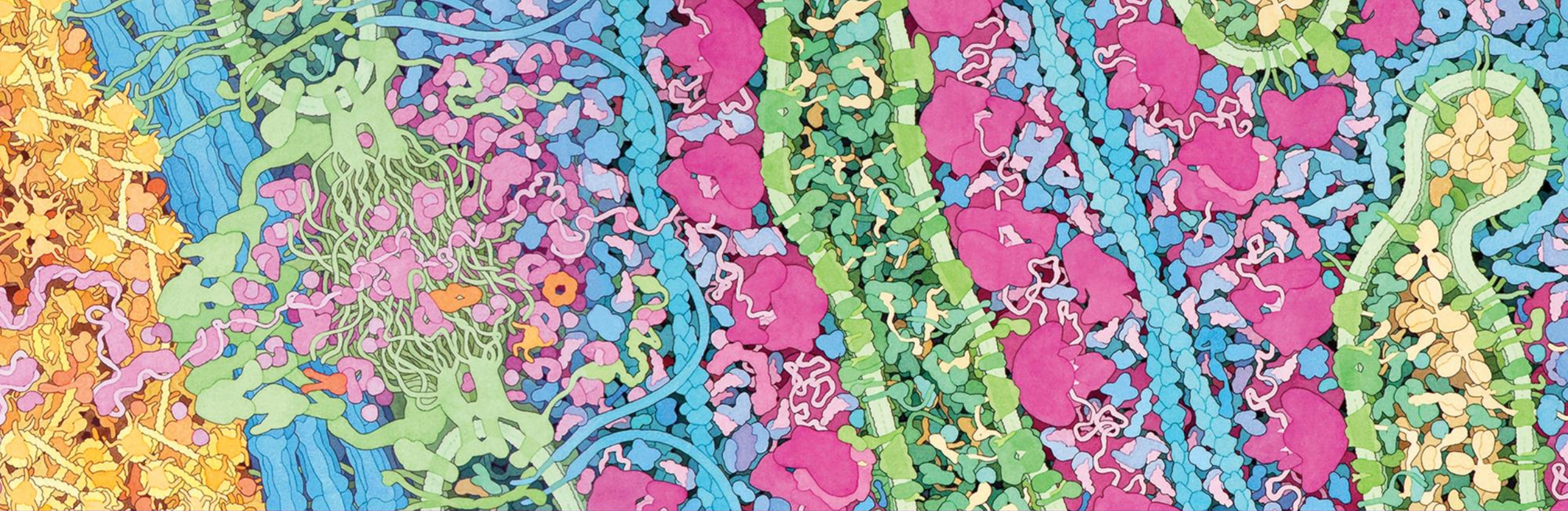
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- **New Instructional Materials**
 - Models, models and more models....
A Virus and Cell Modeling Collection,.. including CoV-2
Antibodies/vaccines /and your immune system
mRNA vaccines and multi-valent, ultra-potent vaccines...from synthetic biology.
 - Stories, stories and more stories....

A Pre-requisite for this advanced course is...

Modeling the Molecular World

Session 1 -- July 29 – Aug 2,

Session 2 -- Aug 5 – 9



3d molecular
designs

Transforming Science Learning