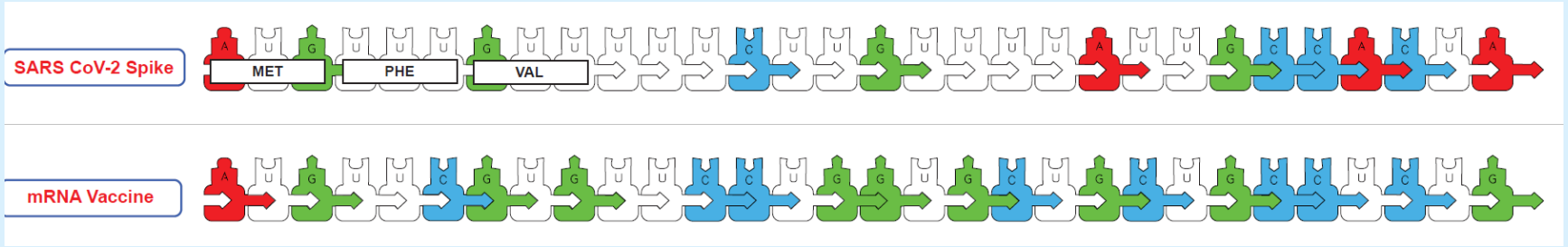
3d molecular designs
Transforming Science Learning

Modeling…
Infectious Diseases & Immunity



Tim Herman
3D Molecular Designs

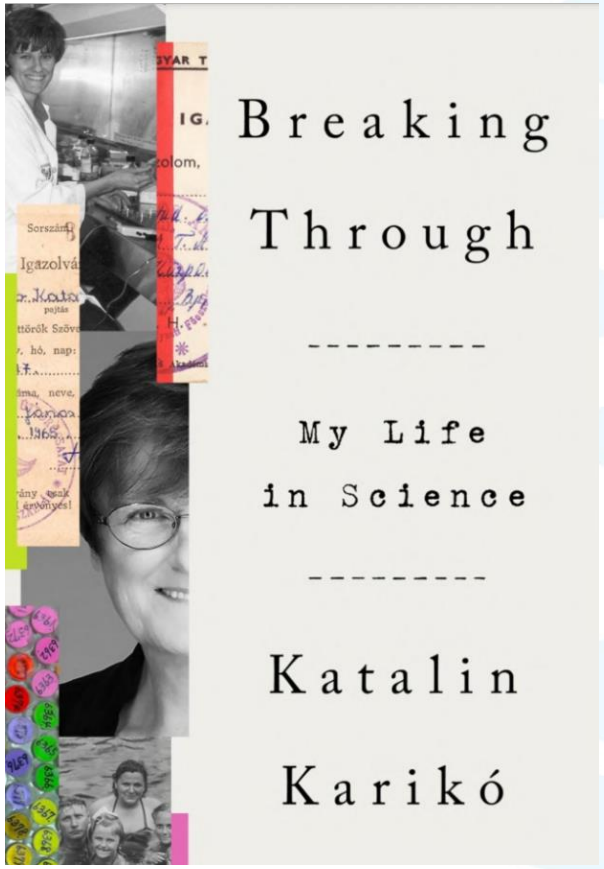
The Nobel Prize in Physiology or Medicine 2023 | Prize Announcement

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

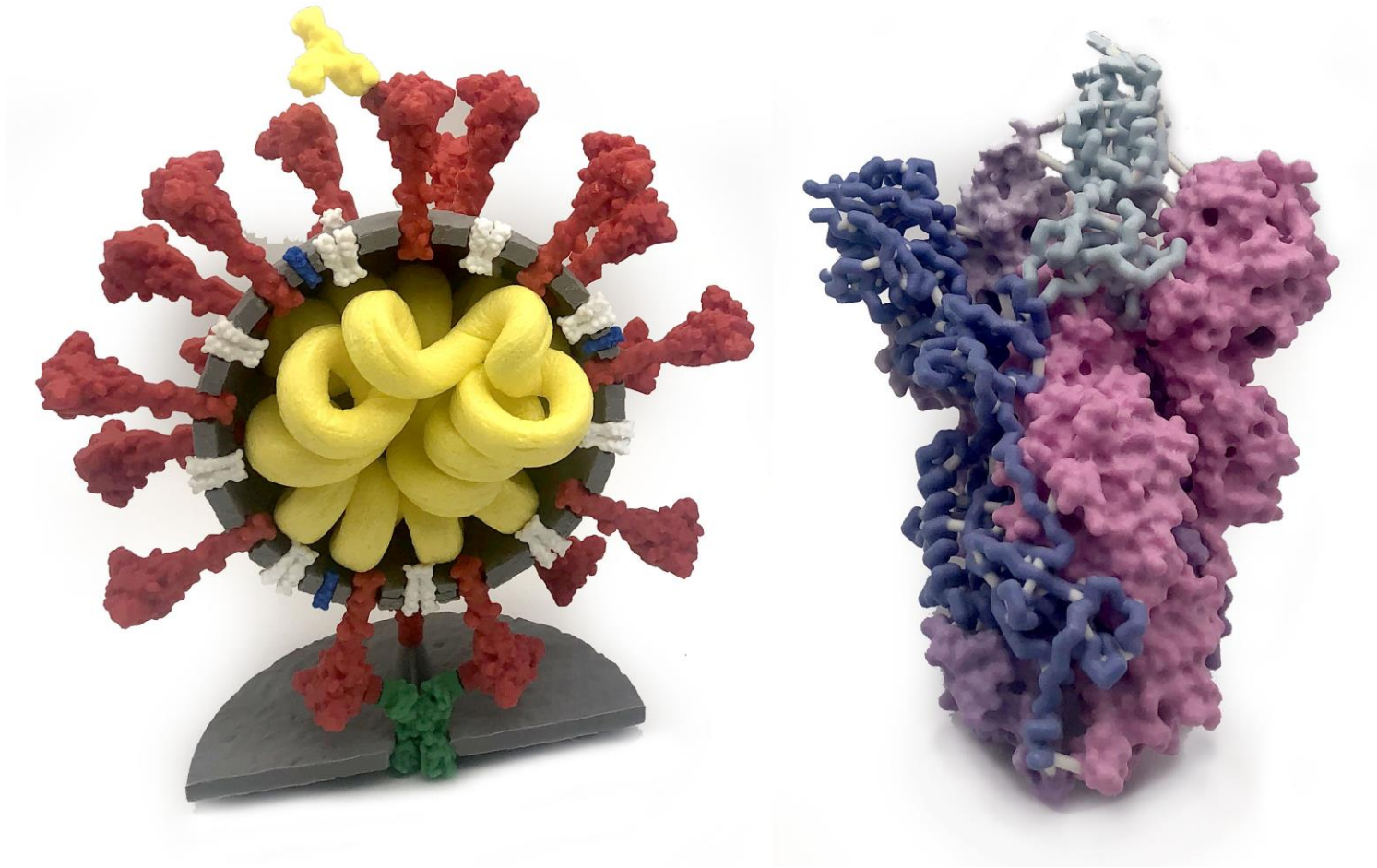
It has been the best of times,… it has been the worst of times.

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.....*

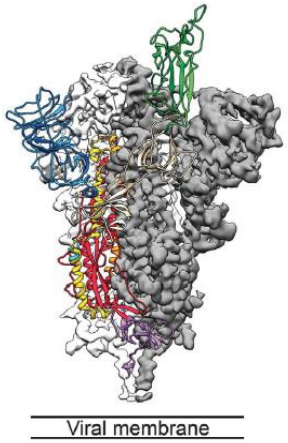
December 2019, new coronavirus (CoV-2) reported in China

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.

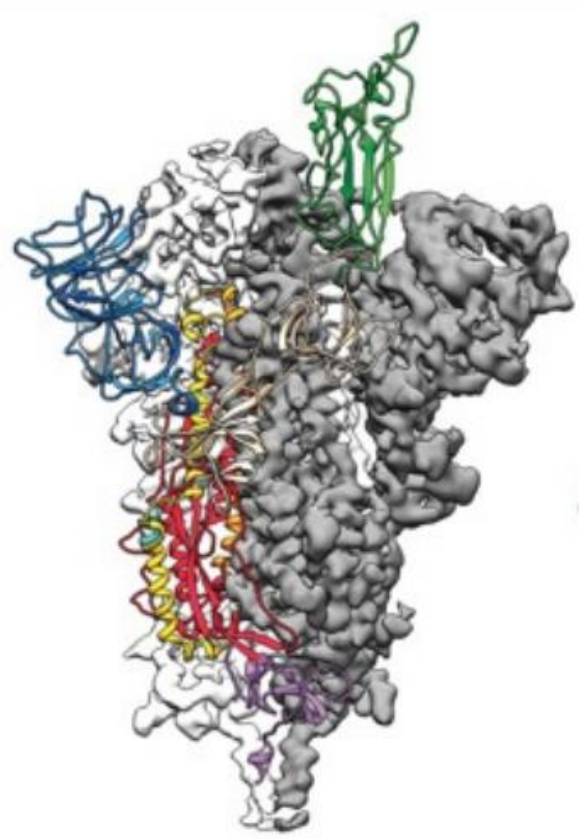
March 20, 2020, Jason McLellan publishes 3D structure of CoV-2 spike protein.



Clinical Trials.....

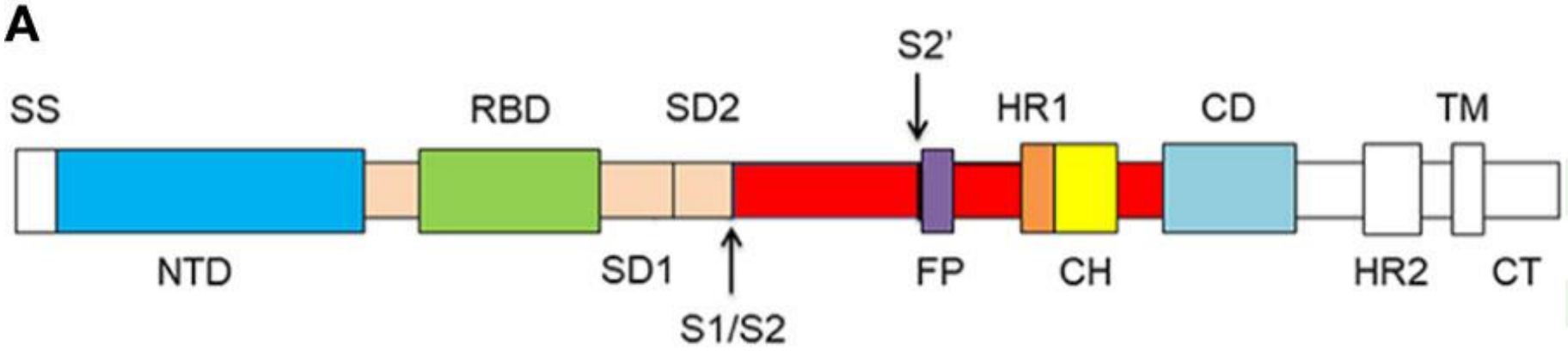
December 18, 2020, Moderna mRNA vaccine EUA.

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

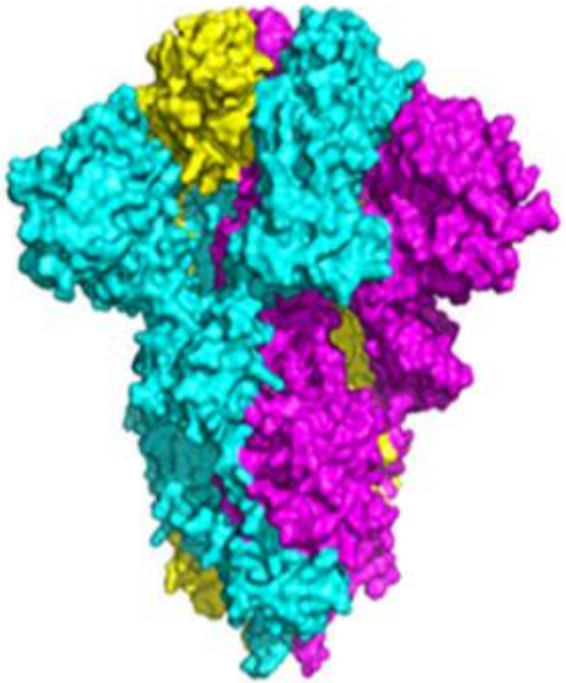


[Key Innovations from UT Austin's McLellan Lab Powers COVID-19 Vaccines]

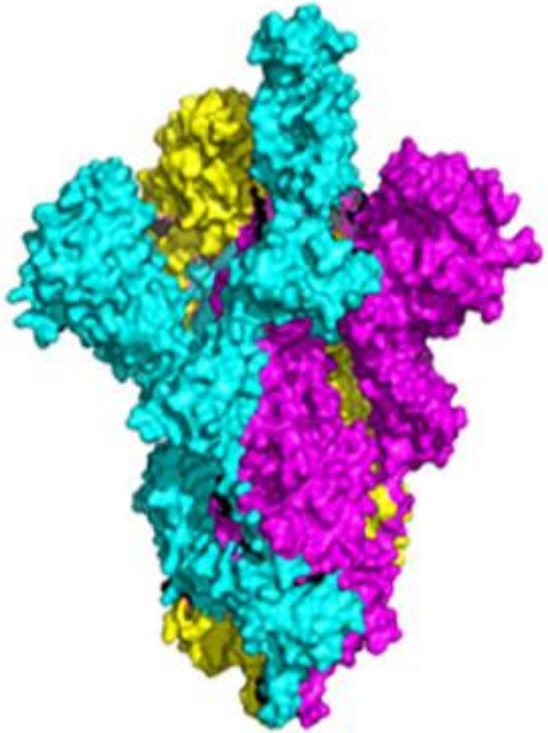
[UT-Austin researcher explains lab's key role in coronavirus vaccine development]



B



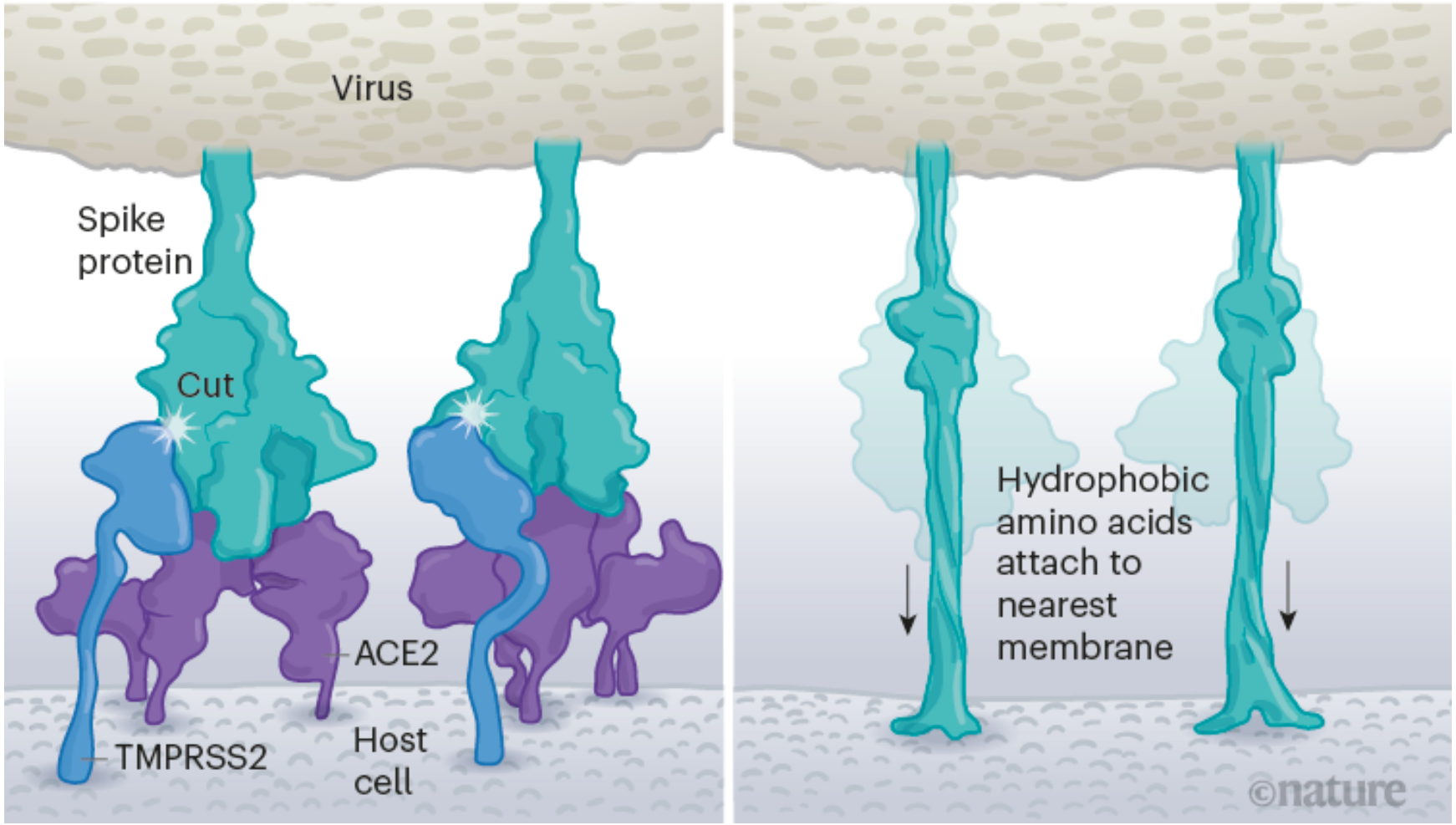
closed state of SARS-CoV-2 spike protein



open state of SARS-CoV-2 spike protein

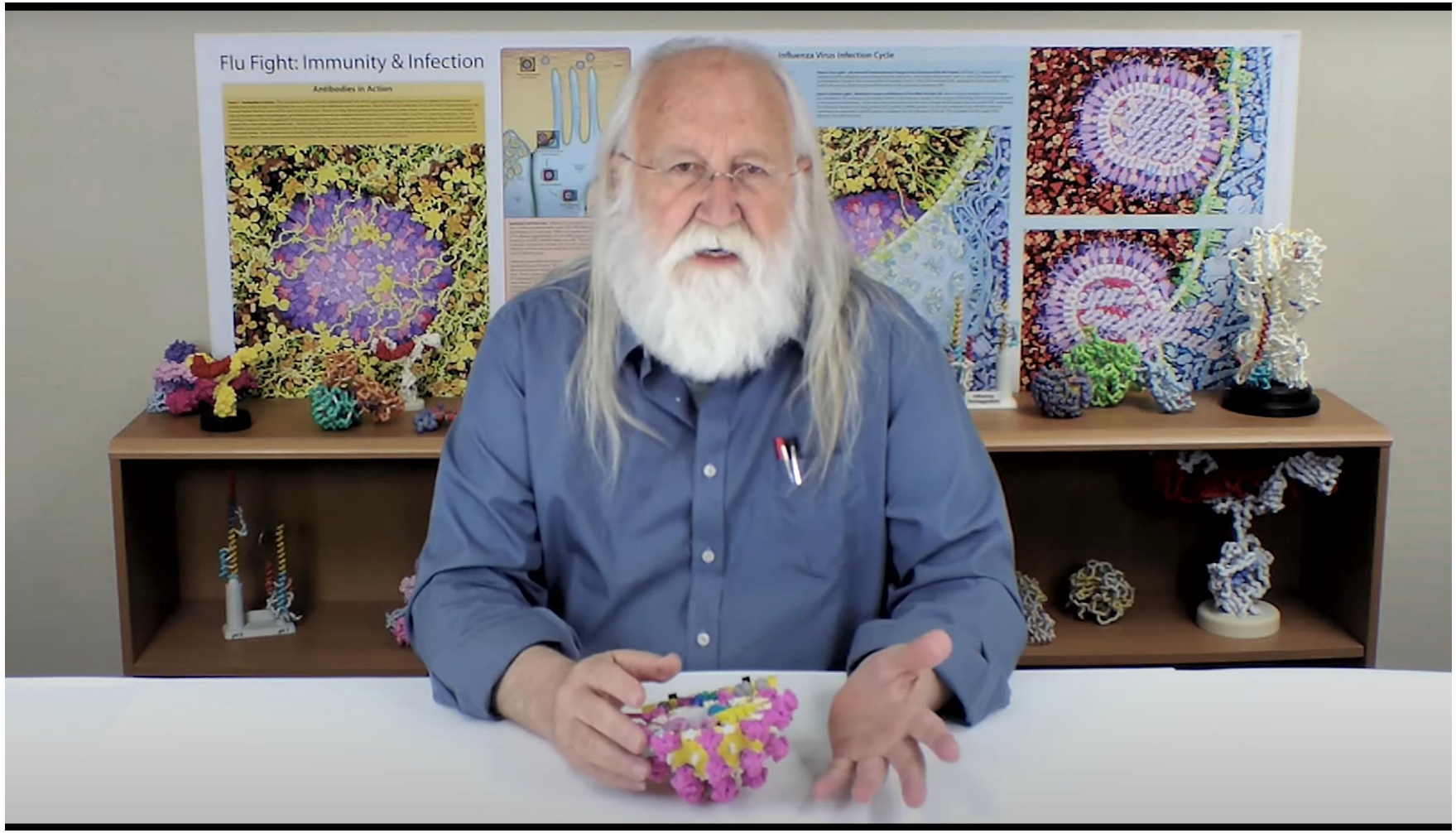
VIRAL ENTRY UP CLOSE

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.



Janet Iwasa, The Animation Lab…at https://animationlab.utah.edu/cova

The Science of Coronavirus... a video series



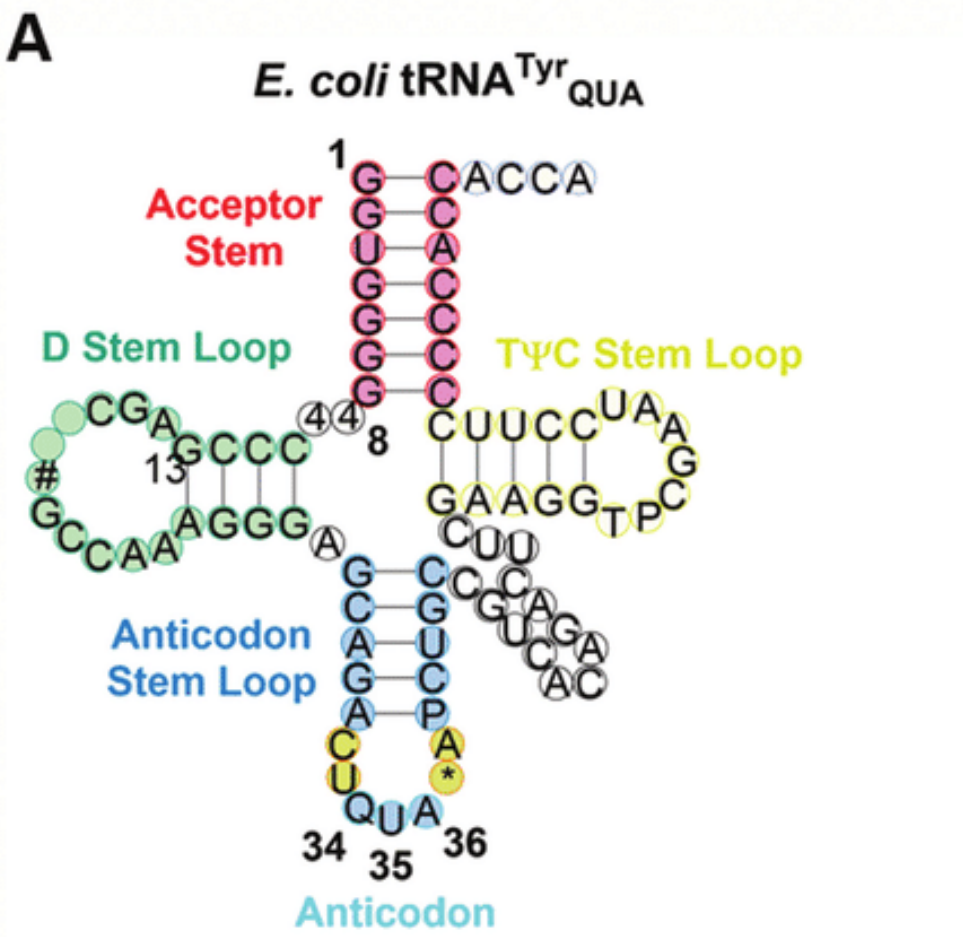
https://www.3dmoleculardesigns.com/The-Science-of-Coronaviruses.htm

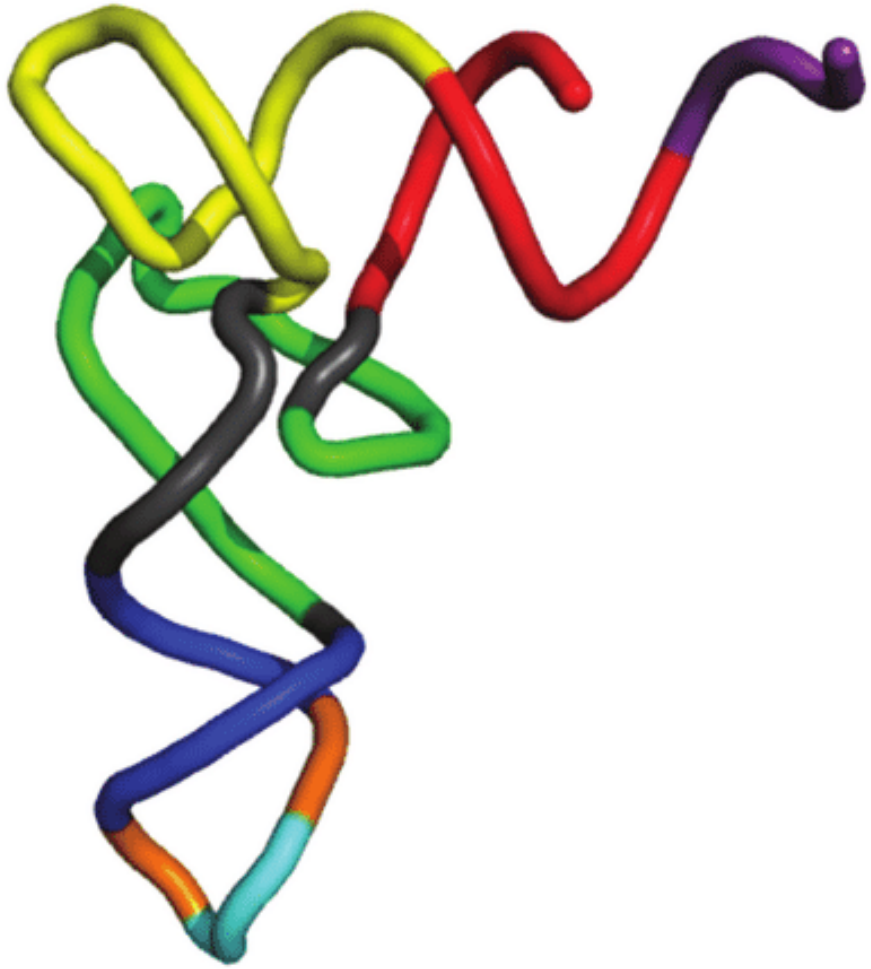
Kati Kariko,.. and the perseverance of women research associates…..

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 Modifications .....WHY?



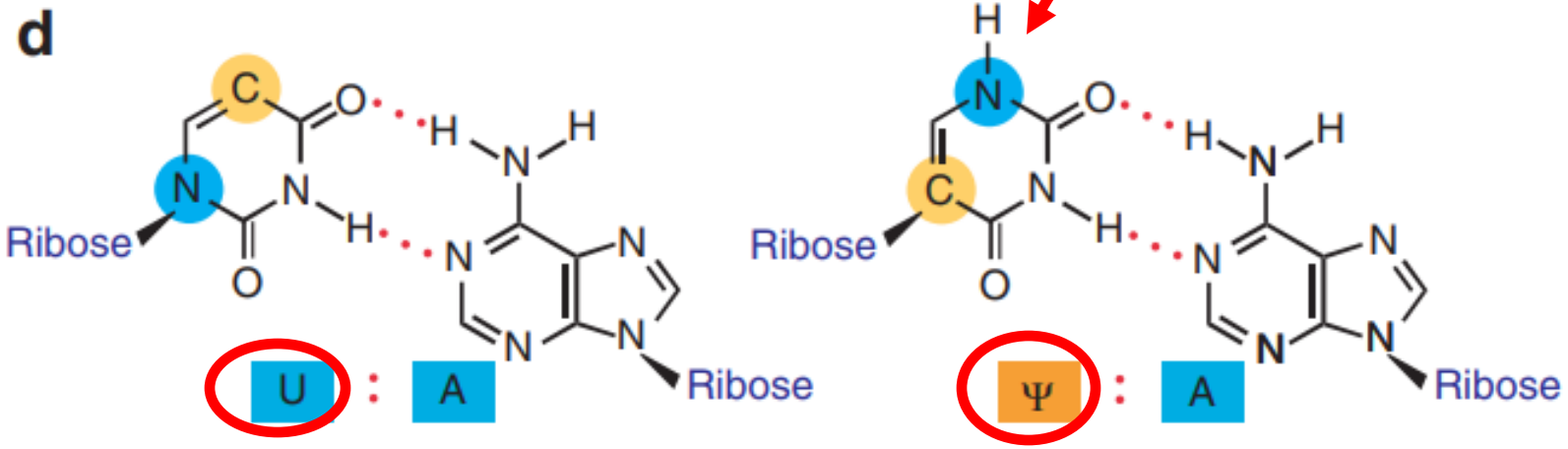


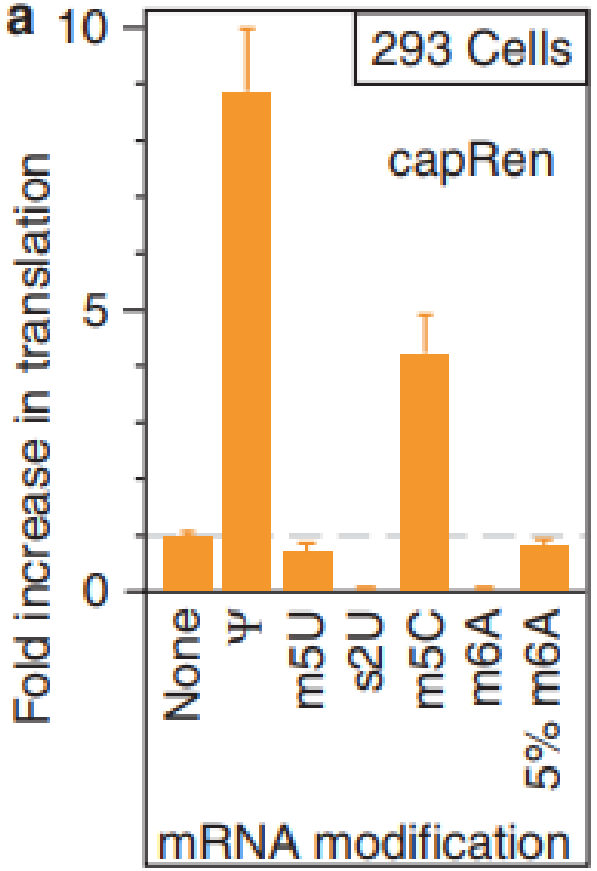
Incorporation of Pseudouridine Into mRNA Yields Superior Nonimmunogenic Vector With Increased Translational Capacity and Biological Stability

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

pseudouridine

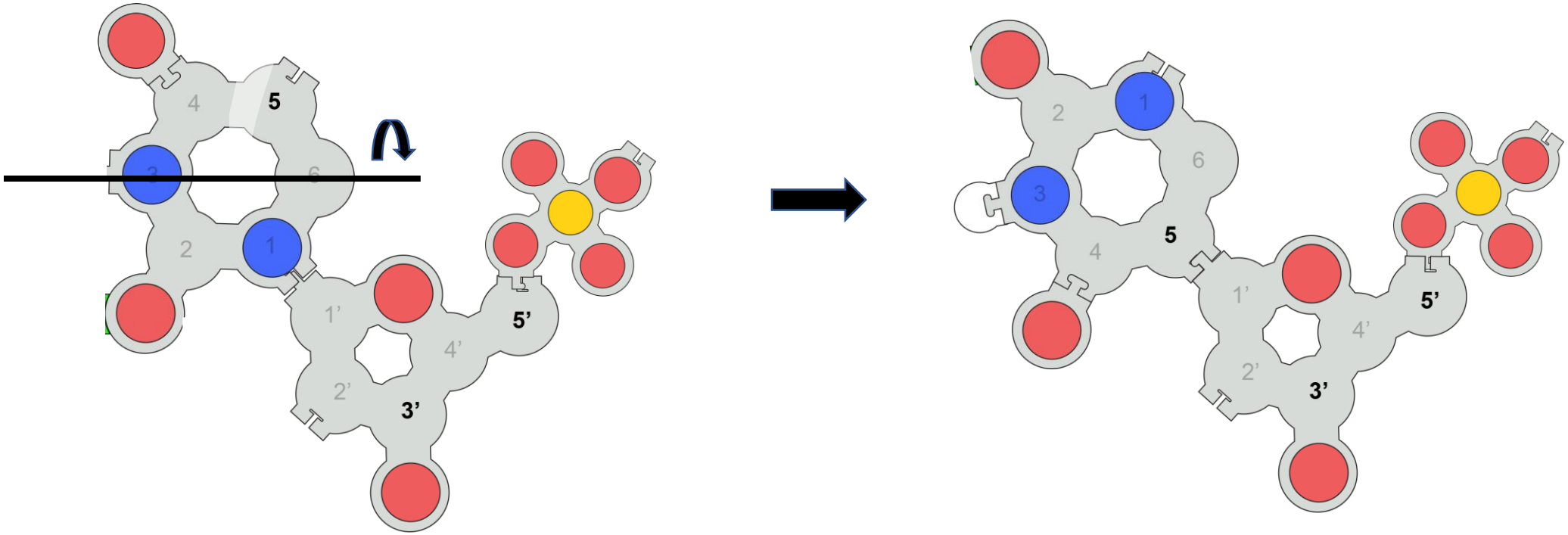




GUAACUGCAUGCUAGCUAGCUAGCUCAGUGCUGCUGCUGUAUUUGCUUGA

GΨAACΨGCAUGCΨAGCΨAGCΨAGCΨCAGΨGCΨGCΨGCΨGΨAΨΨΨGCΨΨGA

Tactile Base Pairs



Uridine

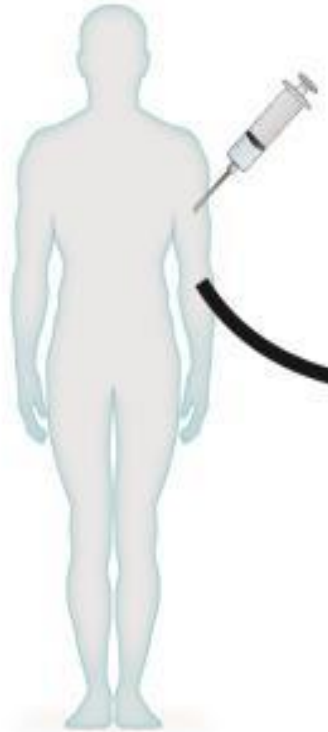
Pseudo-Uridine

Formulation

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

naked mRNA **vs** mRNA (lipid) nanoparticles

mRNA vaccination

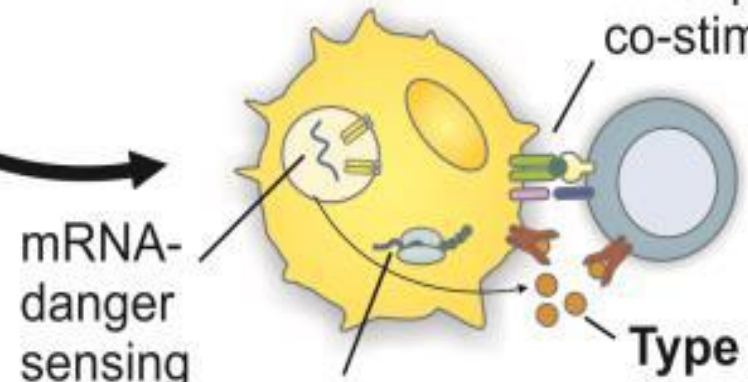


In vivo delivery

local **vs** systemic

extra- & intracellular barriers

Mode of action



MHC pathways co-stimulation

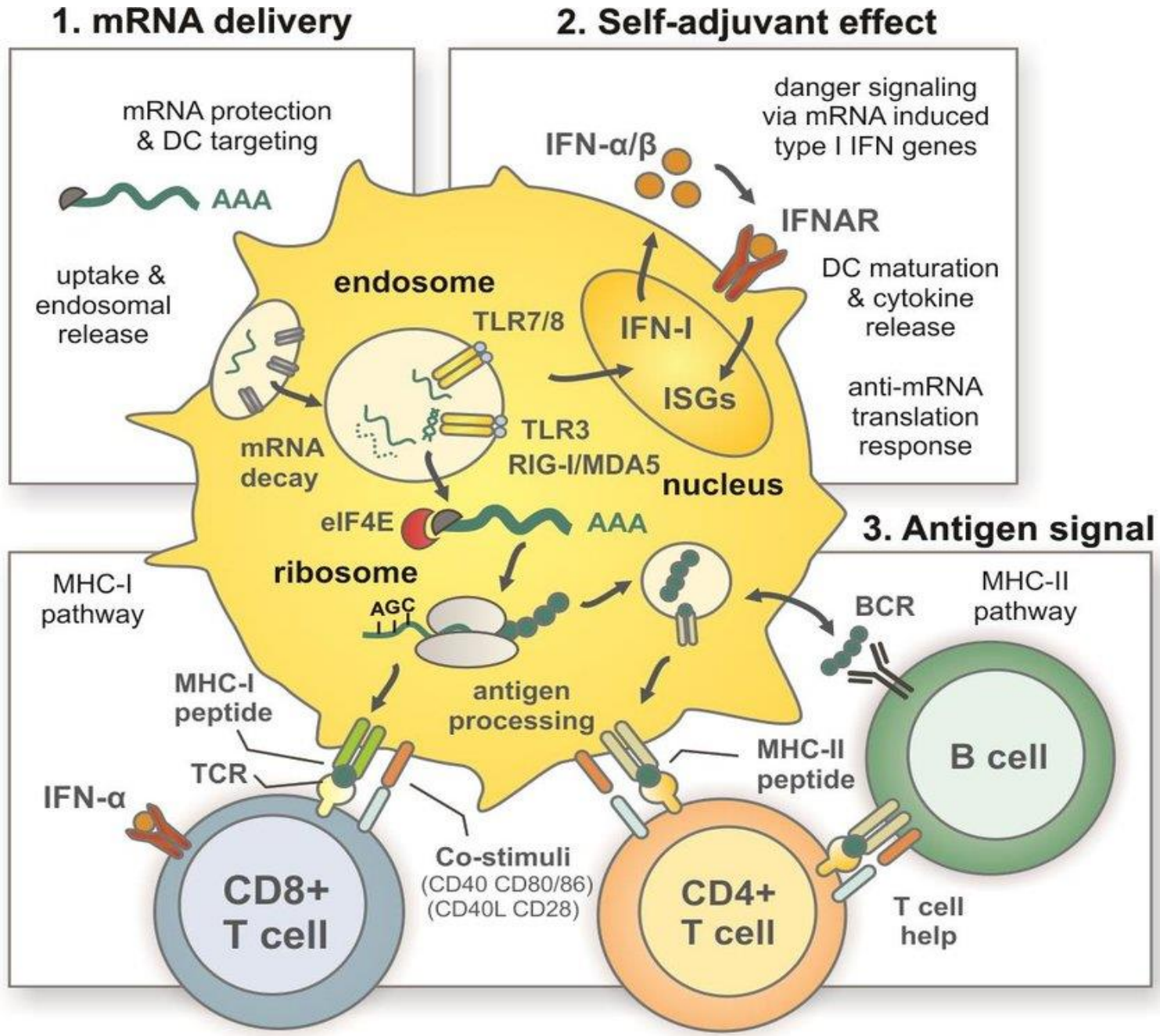
T cell activation

Type I IFNs

mRNA-danger sensing

in situ antigen production

antiviral immunity **vs** anti-mRNA activity


1. mRNA delivery
2. Self-adjuvant effect
3. Antigen signal
mRNA protection
& DC targeting
AAA
uptake &
endosomal
release
endosome
TLR7/8
TLR3
RIG-I/MDA5
mRNA
decay
eIF4E
AAA
ribosome
AGC
nucleus
IFN-α/β
danger signaling
via mRNA induced
type I IFN genes
IFNAR
IFN-I
ISGs
DC maturation
& cytokine
release
anti-mRNA
translation
response
MHC-I
pathway
MHC-I
peptide
TCR
IFN-α
antigen
processing
Co-stimuli
(CD40 CD80/86)
(CD40L CD28)
CD8+
T cell
BCR
MHC-II
pathway
MHC-II
peptide
B cell
CD4+
T cell
T cell
help

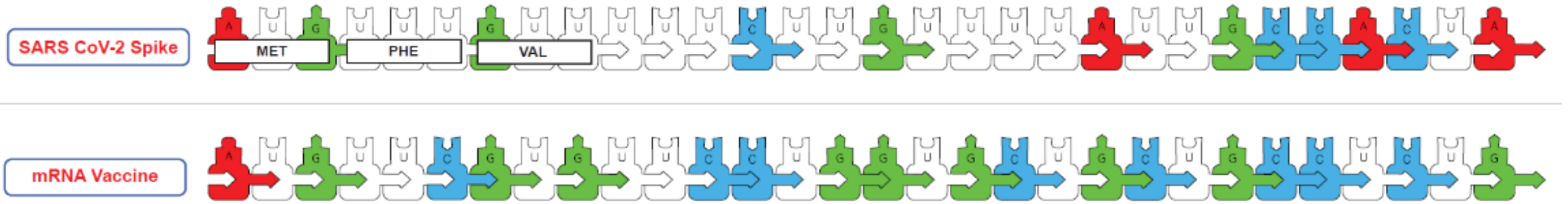
STEM….

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



ACS central science

http://pubs.acs.org/journal/acscii

Outlook

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

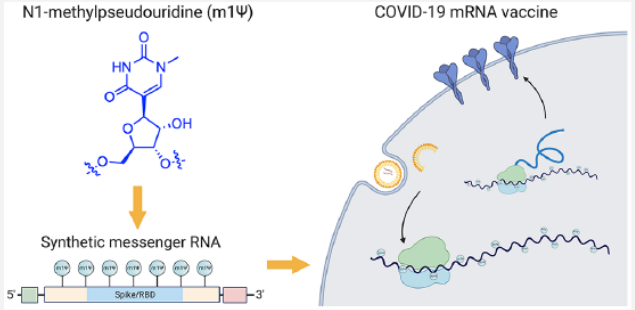
Kellie D. Nance and Jordan L. Meier*

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

Read Online

ACCESS | Metrics & More | Article Recommendations | 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.

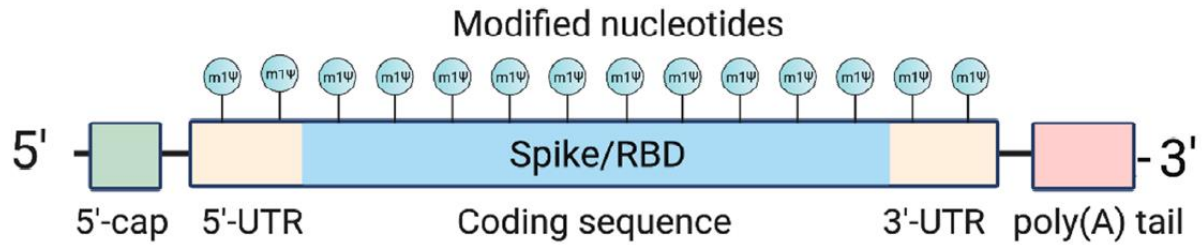


INTRODUCTION

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

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

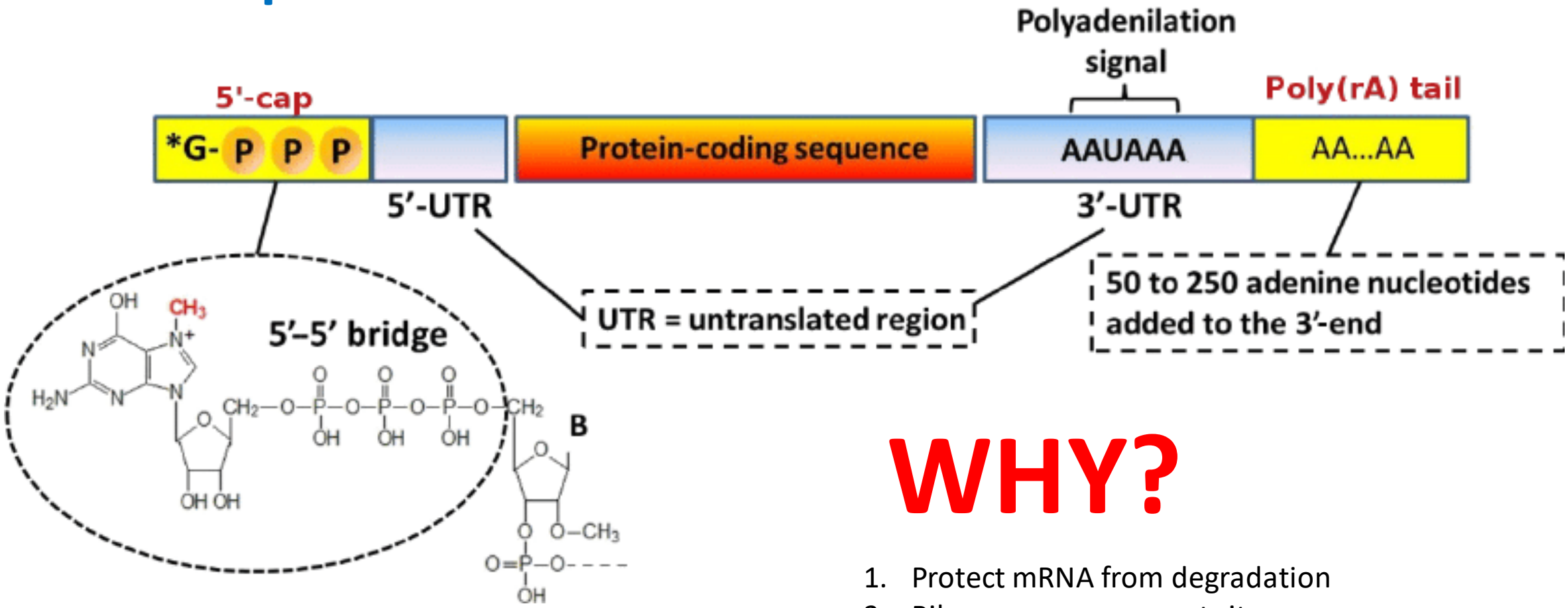


BNT162b2 sequence (U = m1Ψ)

```
GAGAAUAAAC UAGUAUUCUU CUGGUCCCCA CAGACUCAGA GAGAACCCGC CACCAUGUUC GUGUUCCUGG UGCUGCUGCC UCUGGUGUCC AGCCAGUGUG  100
UGAACCUGAC CACCAGAACA CAGCUGCCUC CAGCCUACAC CAACAGCUUU ACCAGAGGCG UGUACUACCC CGACAAGGUG UUCAGAUCCA GCGUGCUGCA  200
CUCUACCCAG GACCUGUUCC UGCCUUUCUU CAGCAACGUG ACCUGGUUCC ACGCCAUCCA CGUGUCCGGC ACCAAUGGCA CCAAGAGAUU CGACAACCCC  300
GUGCUGCCCU UCAACGACGG GGUGUACUUU GCCAGCACCG AGAAGUCCAA CAUCAUCAGA GGCUGGAUCU UCGGCACCAC ACUGGACAGC AAGACCCAGA  400
GCCUGCUGAU CGUGAACAAC GCCACCAACG UGGUCAUCAA AGUGUGCGAG UUCCAGUUCU GCAACGACCC CUUCCUGGGC GUCUACUACC ACAAGAACAA  500
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
GACACCUGGC GAUAGCAGCA GCGGAUGGAC AGCUGGUGCC GCCGCUUACU AUGUGGGCUA CCUGCAGCCU AGAACCUUCC UGCUGAAGUA CAACGAGAAC  900
GGCACCAUCA CCGACGCCGU GGAUUGUGCU CUGGAUCCUC UGAGCGAGAC AAAGUGCACC CUGAAGUCCU UCACCGUGGA AAAGGGCAUC UACCAGACCA 1000
GCAACUUCCG GGUGCAGCCC ACCGAAUCCA UCGUGCGGUU CCCCAAUAUC ACCAAUCUGU GCCCCUUCGG CGAGGUGUUC AAUGCCACCA GAUUCGCCUC 1100
UGUGUACGCC UGGAACCGGA AGCGGAUCAG CAAUUGCGUG GCCGACUACU CCGUGCUGUA CAACUCCGCC AGCUUCAGCA CCUUCAAGUG CUACGGCGUG 1200
UCCCCUACCA AGCUGAACGA CC                                                                  GAUUGCCCCU GGACAGACAG 1300
GCAAGAUCGC CGACUACAAC UA                                                                  UCCAAAGUCG GCGGCAACUA 1400
CAAUUACCUG UACCGGCUGU UC                                                                  GCAGCACCCC UUGUAACGGC 1500
GUGGAAGGCU UCAACUGCUA CU                                                                  AGUGGUGGUG CUGAGCUUCG 1600
AACUGCUGCA UGCCCCUGCC ACAGUGUGCG GCCCUAAGAA AAGCACCAAU CUCGUGAAGA ACAAAUGCGU GAACUUCAAC UUCAACGGCC UGACCGGCAC 1700
CGGCGUGCUG ACAGAGAGCA ACAAGAAGUU CCUGCCAUUC CAGCAGUUUG GCCGGGAUAU CGCCGAUACC ACAGACGCCG UUAGAGAUCC CCAGACACUG 1800
GAAAUCCUGG ACAUCACCCC UUGCAGCUUC GGCGGAGUGU CUGUGAUCAC CCCUGGCACC AACACCAGCA AUCAGGUGGC AGUGCUGUAC CAGGACGUGA 1900
ACUGUACCGA AGUGCCCGUG GCCAUUCACG CCGAUCAGCU GACACCUACA UGGCGGGUGU ACUCCACCGG CAGCAAUGUG UUUCAGACCA GAGCCGGCUG 2000
UCUGAUCGGA GCCGAGCACG UGAACAAUAG CUACGAGUGC GACAUCCCCA UCGGCGCUGG AAUCUGCGCC AGCUACCAGA CACAGACAAA CAGCCCUCGG 2100
AGAGCCAGAA GCGUGGCCAG CCAGAGCAUC AUUGCCUACA CAAUGUCUCU GGGCGCCGAG AACAGCGUGG CCUACUCCAA CAACUCUAUC GCUAUCCCCA 2200
CCAACUUCAC CAUCAGCGUG ACCACAGAGA UCCUGCCUGU GUCCAUGACC AAGACCAGCG UGGACUGCAC CAUGUACAUC UGCGGCGAUU CCACCGAGUG 2300
CUCCAACCUG CUGCUGCAGU ACGGCAGCUU CUGCACCCAG CUGAAUAGAG CCCUGACAGG GAUCGCCGUG GAACAGGACA AGAACACCCA AGAGGUGUUC 2400
GCCCAAGUGA AGCAGAUCUA CAAGACCCCU CCUAUCAAGG ACUUCGGCGG CUUCAAUUUC AGCCAGAUUC UGCCCGAUCC UAGCAAGCCG AGCAAGCGGA 2500
GCUUCAUCGA GGACCUGCUG UUCAACAAAG UGACACUGGC CGACGCCGGC UUCAUCAAGC AGUAUGGCGA UUGUCUGGGC GACAUUGCCG CCAGGGAUCU 2600
GAUUUGCGCC CAGAAGUUUA ACGGACUGAC AGUGCUGCCU CCUCUGCUGA CCGAUGAGAU GAUCGCCCAG UACACAUCUG CCCUGCUGGC CGGCACAAUC 2700
ACAAGCGGCU GGACAUUUGG AGCAGGCGCC GCUCUGCAGA UCCCCUUUGC UAUGCAGAUG GCCUACCGGU UCAACGGCAU CGGAGUGACC CAGAAUGUGC 2800
UGUACGAGAA CCAGAAGCUG AUCGCCAACC AGUUCAACAG CGCCAUCGGC AAGAUCCAGG ACAGCCUGAG CAGCACAGCA AGCGCCCUGG GAAAGCUGCA 2900
GGACGUGGUC AACCAGAAUG CCCAGGCACU GAACACCCUG GUCAAGCAGC UGUCCUCCAA CUUCGGCGCC AUCAGCUCUG UGCUGAACGA UAUCCUGAGC 3000
AGACUGGACC CUCCUGAGGC CGAGGUGCAG AUCGACAGAC UGAUCACAGG CAGACUGCAG AGCCUCCAGA CAUACGUGAC CCAGCAGCUG AUCAGAGCCG 3100
CCGAGAUUAG AGCCUCUGCC AAUCUGGCCG CCACCAAGAU GUCUGAGUGU GUGCUGGGCC AGAGCAAGAG AGUGGACUUU UGCGGCAAGG GCUACCACCU 3200
GAUGAGCUUC CCUCAGUCUG CCCCUCACGG CGUGGUGUUU CUGCACGUGA CAUAUGUGCC CGCUCAAGAG AAGAAUUUCA CCACCGCUCC AGCCAUCUGC 3300
CACGACGGCA AAGCCCACUU UCCUAGAGAA GGCGUGUUCG UGUCCAACGG CACCCAUUGG UUCGUGACAC AGCGGAACUU CUACGAGCCC CAGAUCAUCA 3400
CCACCGACAA CACCUUCGUG UCUGGCAACU GCGACGUCGU GAUCGGCAUU GUGAACAAUA CCGUGUACGA CCCUCUGCAG CCCGAGCUGG ACAGCUUCAA 3500
AGAGGAACUG GACAAGUACU UUAAGAACCA CACAAGCCCC GACGUGGACC UGGGCGAUAU CAGCGGAAUC AAUGCCAGCG UCGUGAACAU CCAGAAAGAG 3600
AUCGACCGGC UGAACGAGGU GGCCAAGAAU CUGAACGAGA GCCUGAUCGA CCUGCAAGAA CUGGGGAAGU ACGAGCAGUA CAUCAAGUGG CCCUGGUACA 3700
UCUGGCUGGG CUUUAUCGCC GGACUGAUUG CCAUCGUGAU GGUCACAAUC AUGCUGUGUU GCAUGACCAG CUGCUGUAGC UGCCUGAAGG GCUGUUGUAG 3800
CUGUGGCAGC UGCUGCAAGU UCGACGAGGA CGAUUCUGAG CCCGUGCUGA AGGGCGUGAA ACUGCACUAC ACAUGAUGAC UCGAGCUGGU ACUGCAUGCA 3900
CGCAAUGCUA GCUGCCCCUU UCCCGUCCUG GGUACCCCGA GUCUCCCCCG ACCUCGGGUC CCAGGUAUGC UCCCACCUCC ACCUGCCCCA CUCACCACCU 4000
CUGCUAGUUC CAGACACCUC CCAAGCACGC AGCAAUGCAG CUCAAAACGC UUAGCCUAGC CACACCCCCA CGGGAAACAG CAGUGAUUAA CCUUUAGCAA 4100
UAAACGAAAG UUUAACUAAG CUAUACUAAC CCCAGGGUUG GUCAAUUUCG UGCCAGCCAC ACCCUGGAGC UAGCAAAAAA AAAAAAAAAA AAAAAAAAAA 4200
AAAAGCAUAU GACUAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAA                          4284
```


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

The Components of mRNA

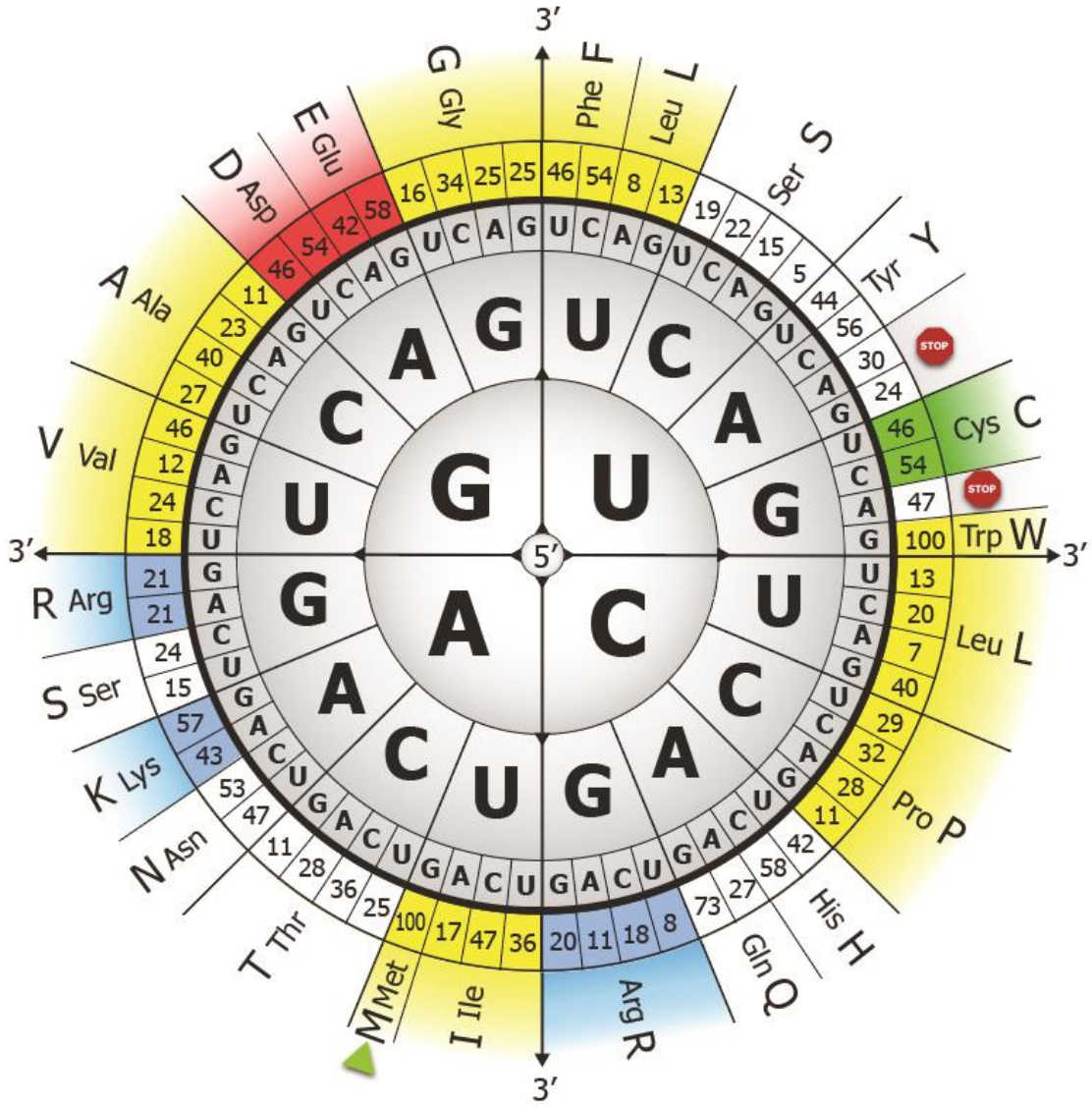


WHY?

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

A Table of Genetic Codons….

… *with human codon preferences*



Coming soon,…

Modeling Infectious Diseases and Immunity

June 24-28

An NIH SEPA project.

- **A Professional Learning Experience**…beginning in the summer of 2024
- **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