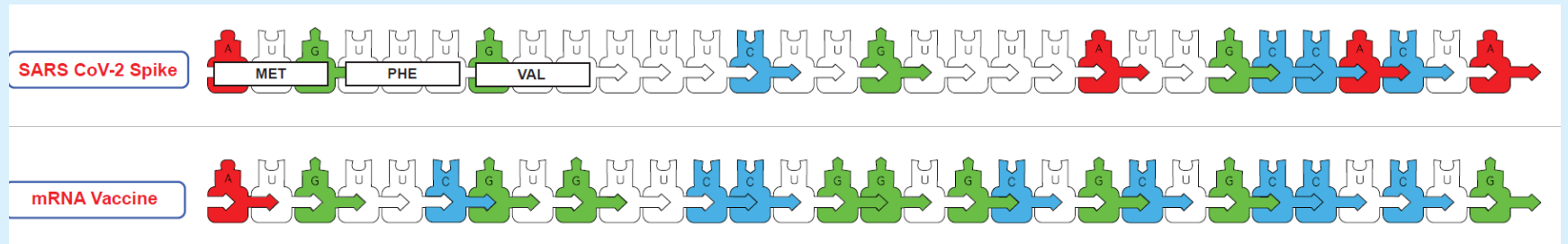


Teaching mRNA Vaccines...

...and the future of therapeutic RNAs



Tim Herman
3D Molecular Designs

Workshop Outline

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

A story about the process of science...

- **Coming Soon....*Tomorrow's Science Today***

An NIH SEPA project focused on infectious diseases

- **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.

Tomorrow's Science Today: *preparing for the next pandemic.*

An NIH SEPA project.

- **New Instructional Materials**
 - Models, models and more models....
A Virus 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 Professional Learning Experience**...beginning in the summer of 2024

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

Session 1 -- June 26–30, or

Session 2 -- July 17 – 21

Teaching the Molecular Biosciences in a post-pandemic era

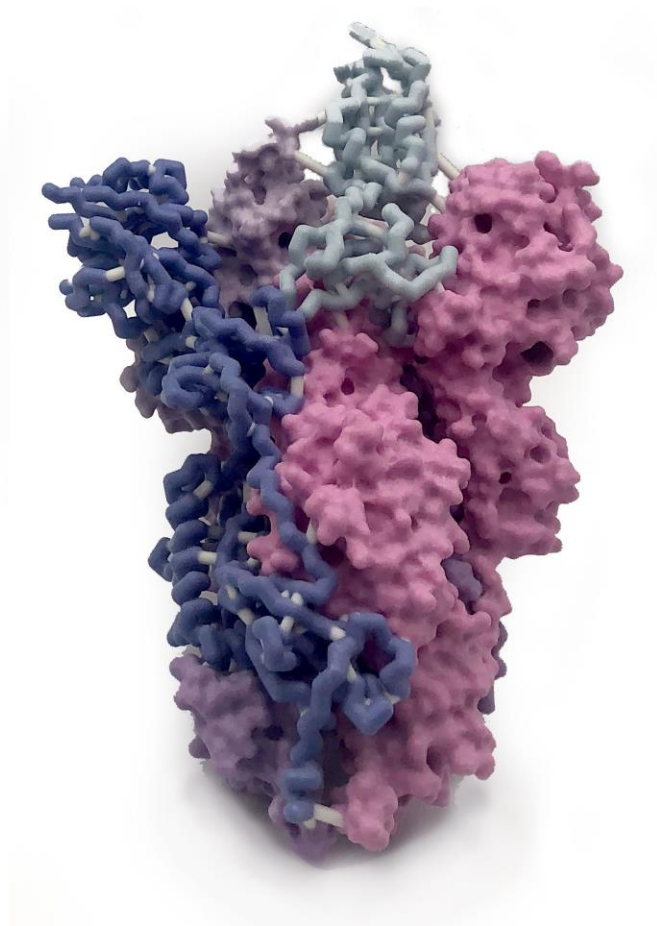
It has been the best of times,... it has been the worst of times.

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



The magic of models...

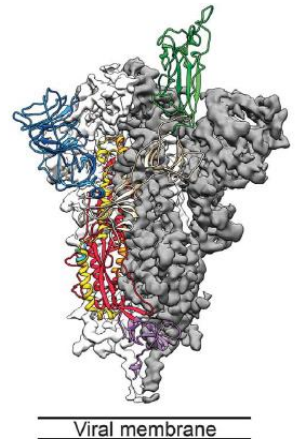
Here's the story....**SCIENCE to the rescue.....**

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.

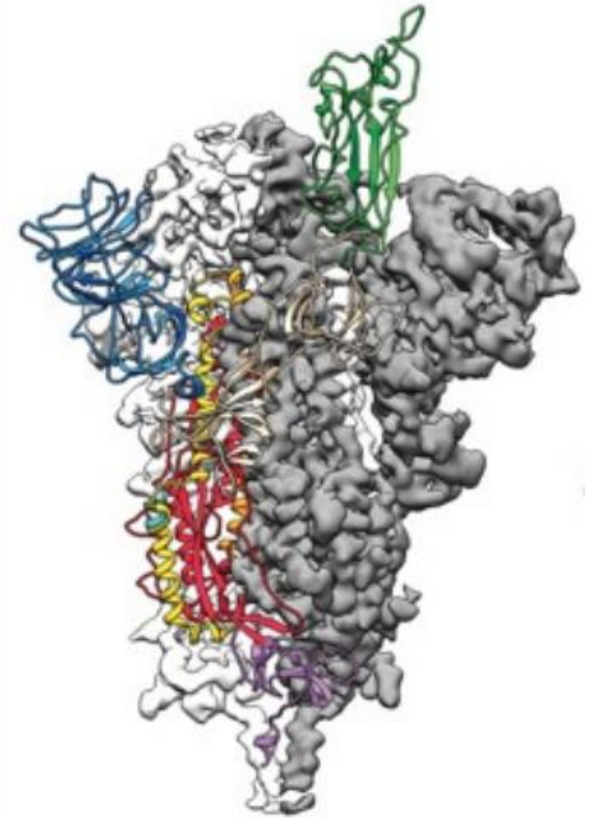
March 20, 2020, Jason McLellan publishes 3D structure
of CoV-2 spike protein.



Clinical Trials.....

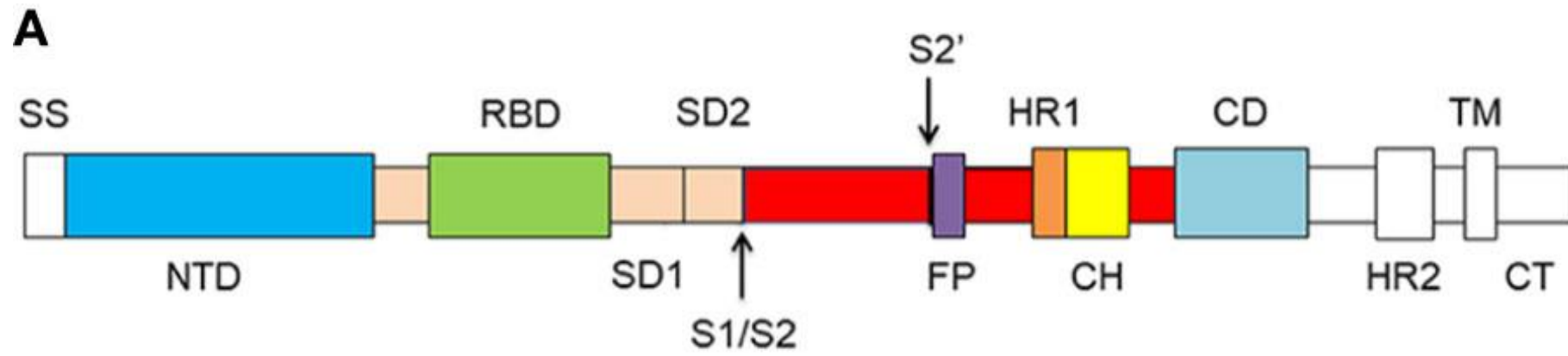
December 18, 2020, Moderna mRNA vaccine EUA.

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

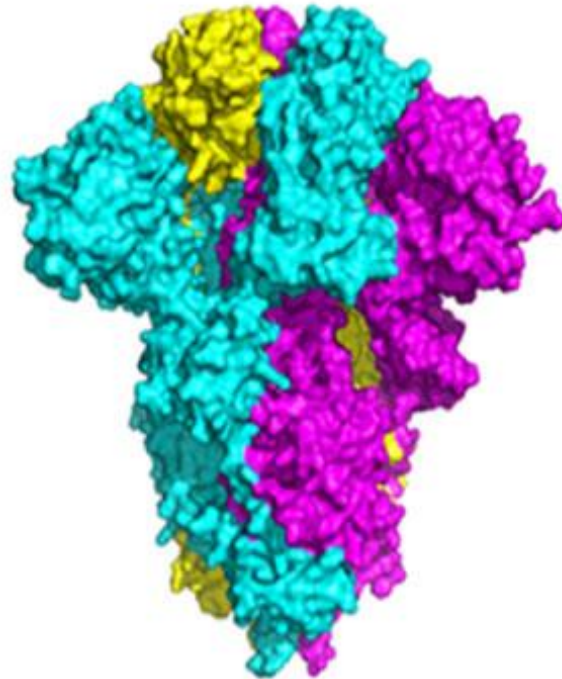


[Key Innovations from UT Austin's McLellan Lab Powers COVID-19 Vaccines](#)

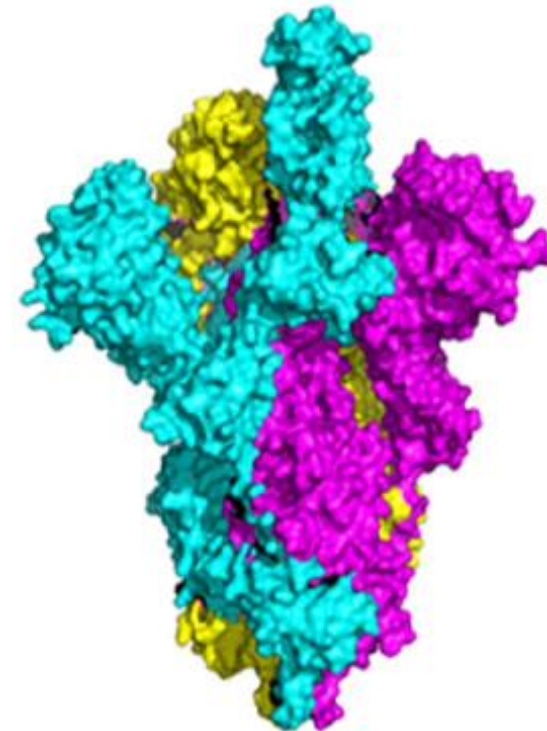
[UT-Austin researcher explains lab's key role in coronavirus vaccine development](#)



B



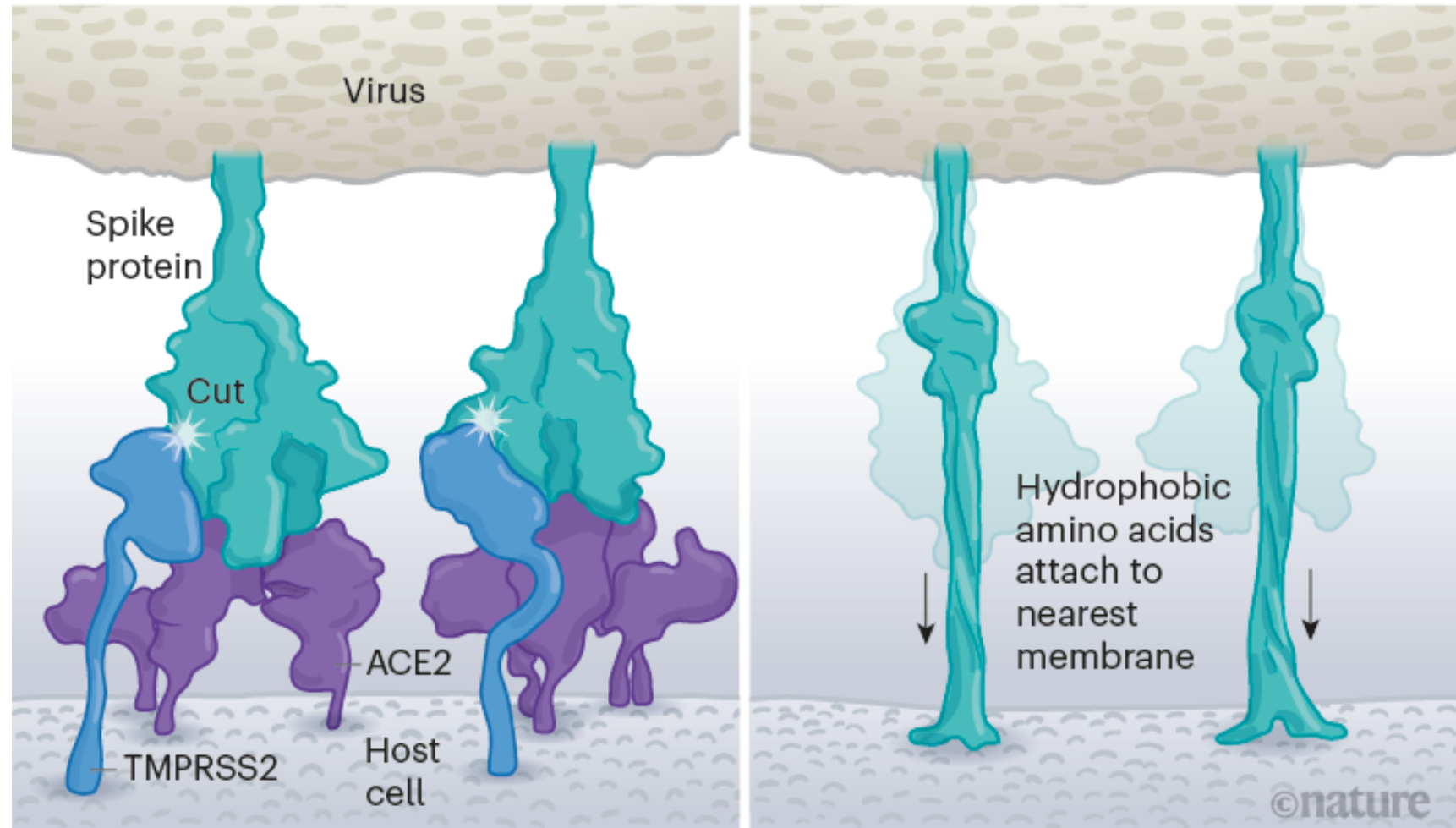
closed state of SARS-CoV-2 spike protein



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.



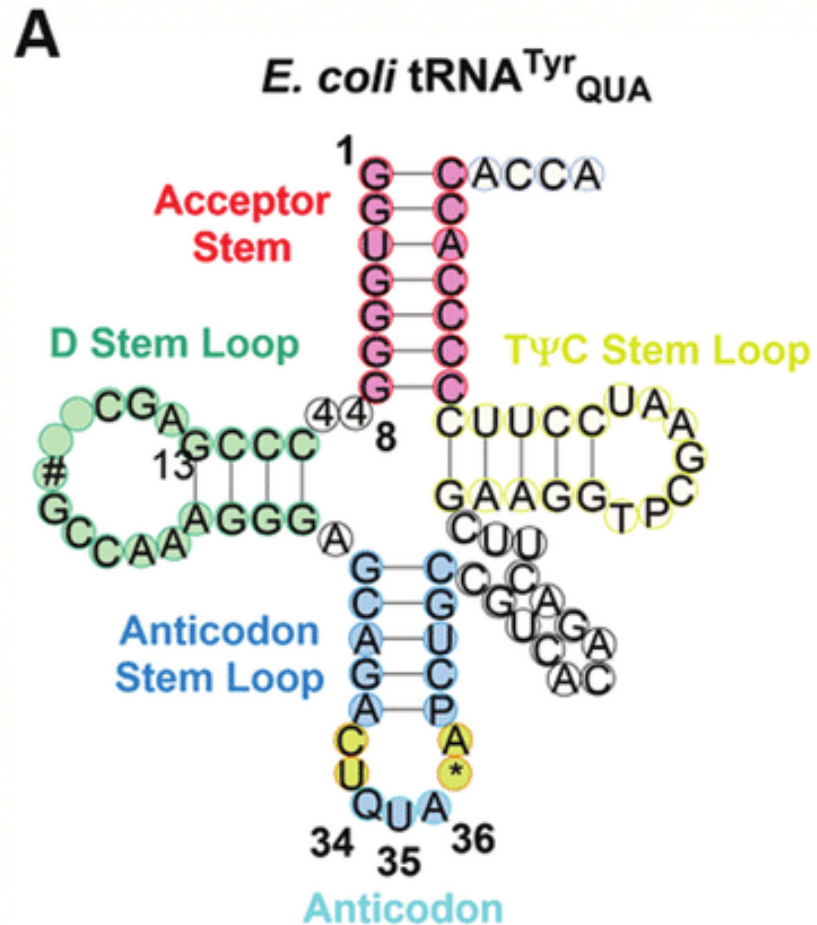


The Science of Coronavirus... a video series



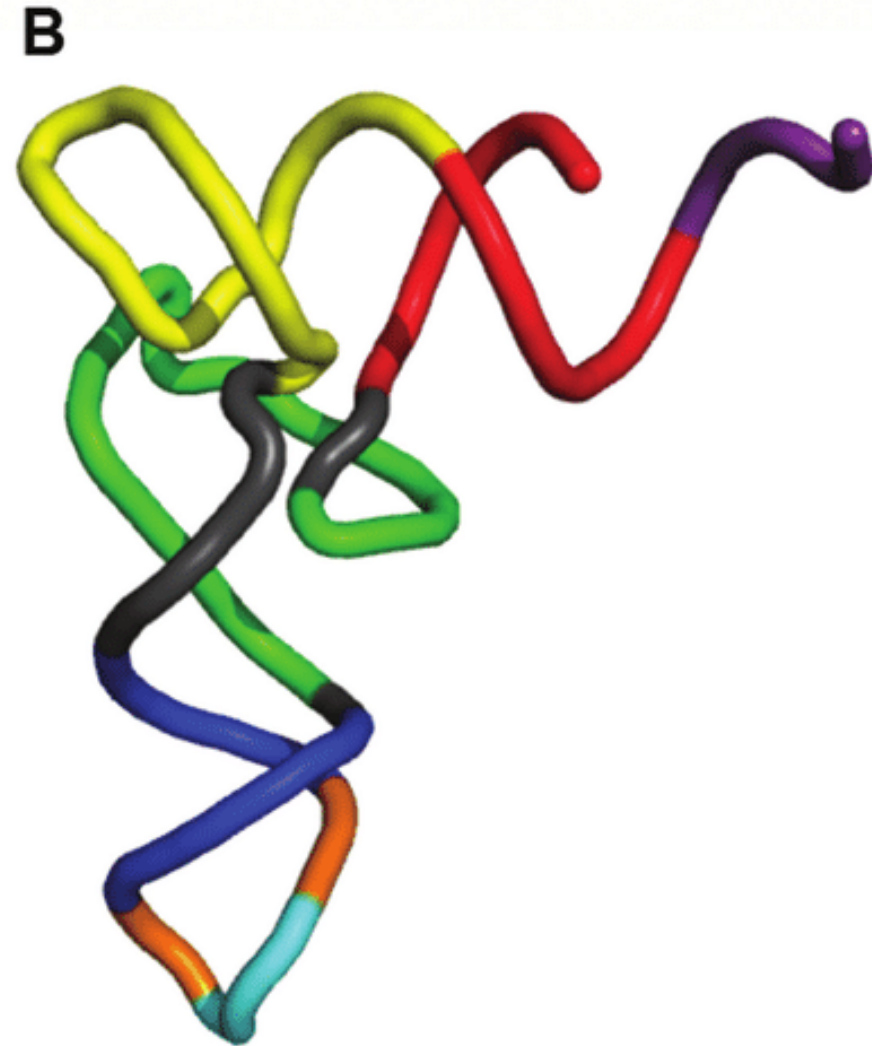
<https://www.3dmoleculardesigns.com/The-Science-of-Coronaviruses.htm>

tRNA ModificationsWHY?



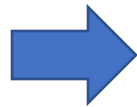
Legend of tRNA modifications:

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



mRNA Vaccines, ...*yesterday's science today!*

- CoV2 RNA genome published in December of 2020....
- mRNA vaccine for CoV2 approved for emergency use in less than 1 year.

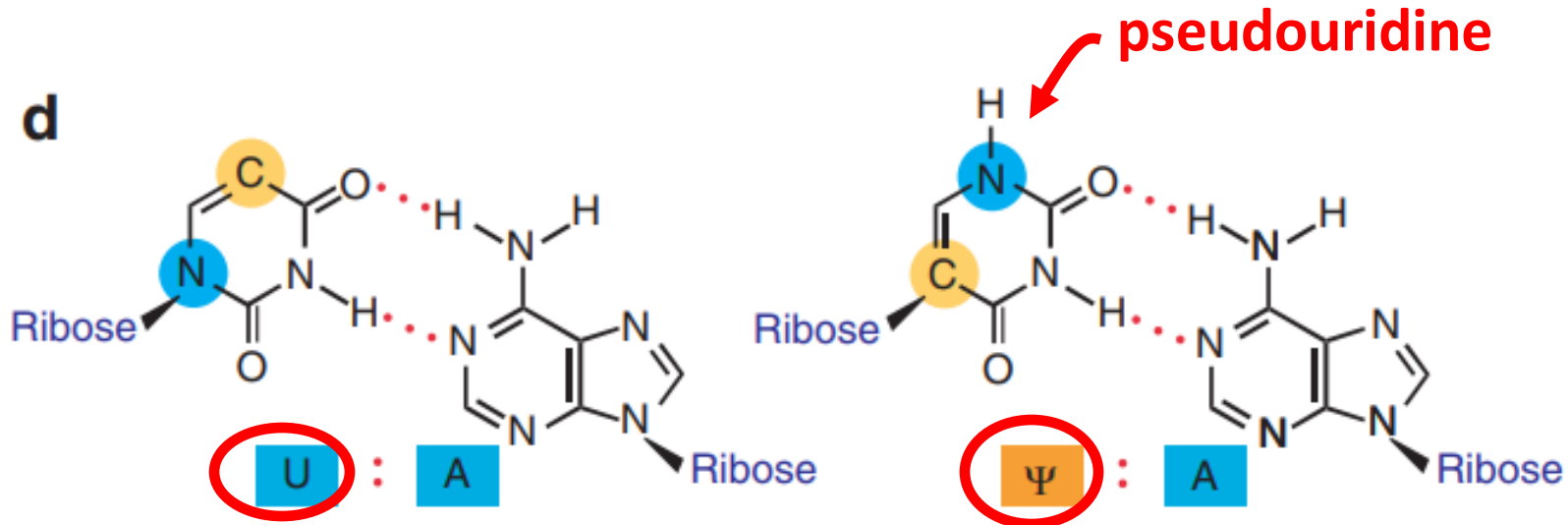


Kati Kariko... *persistence rewarded.*

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

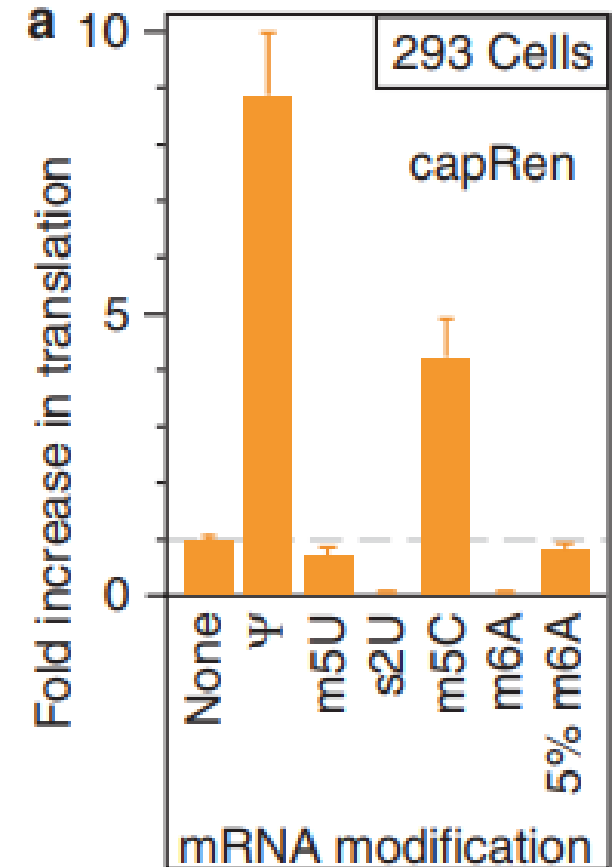
Katalin Karikó¹, Hiromi Muramatsu¹, Frank A Welsh¹, János Ludwig², Hiroki Kato³, Shizuo Akira³
and Drew Weissman⁴

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



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

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



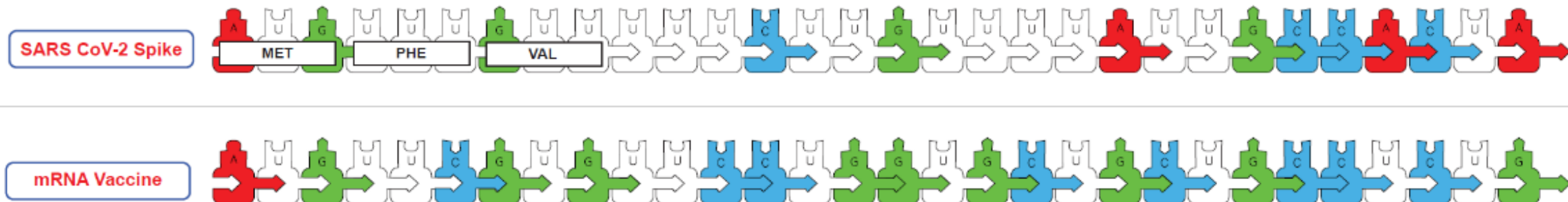
STEM....

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

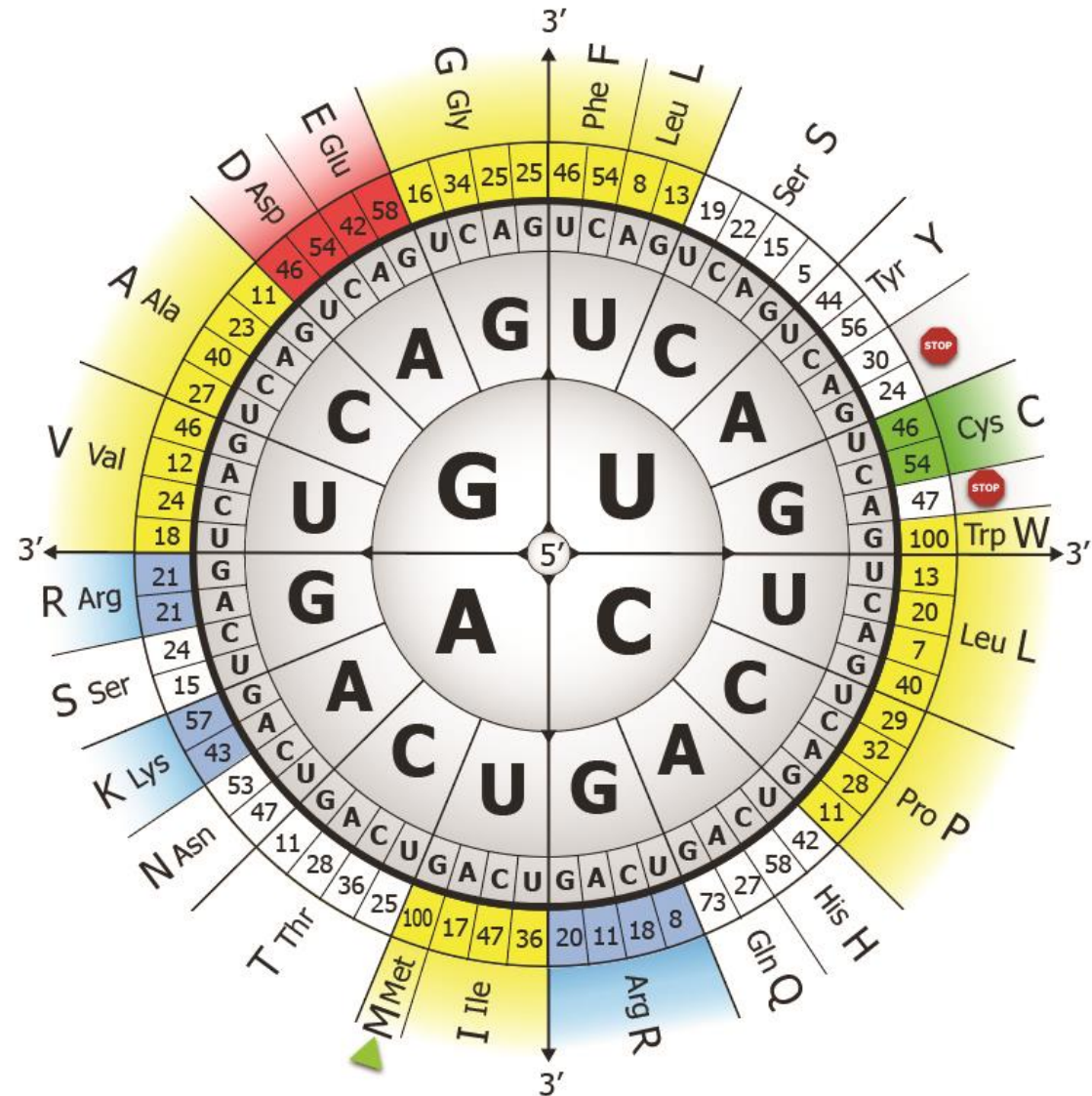
How can you incorporate principles of engineering design into our science classes?

...a vaccine design activity



A Table of Genetic Codons....

... *with human codon preferences*



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

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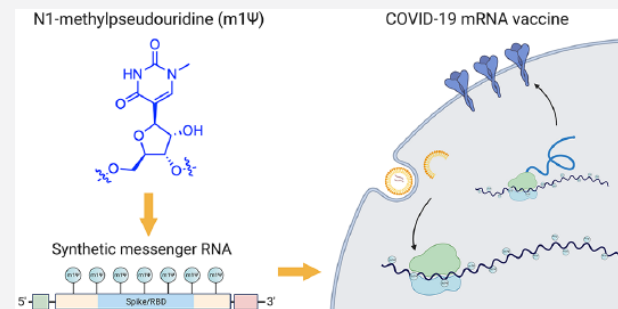
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Supporting Information

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

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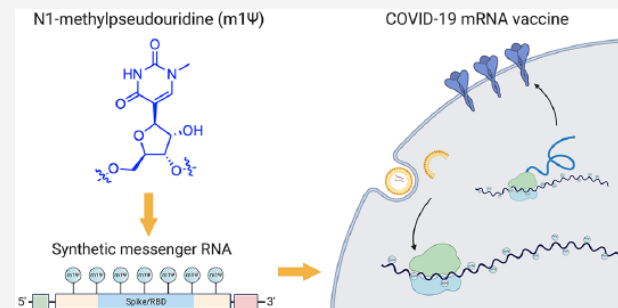
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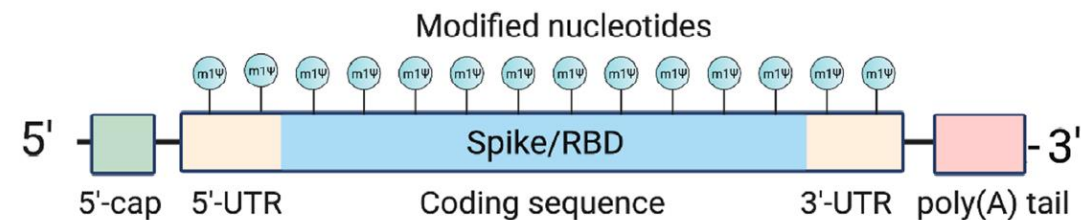


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BNT162b2 sequence (U = m1Ψ)

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

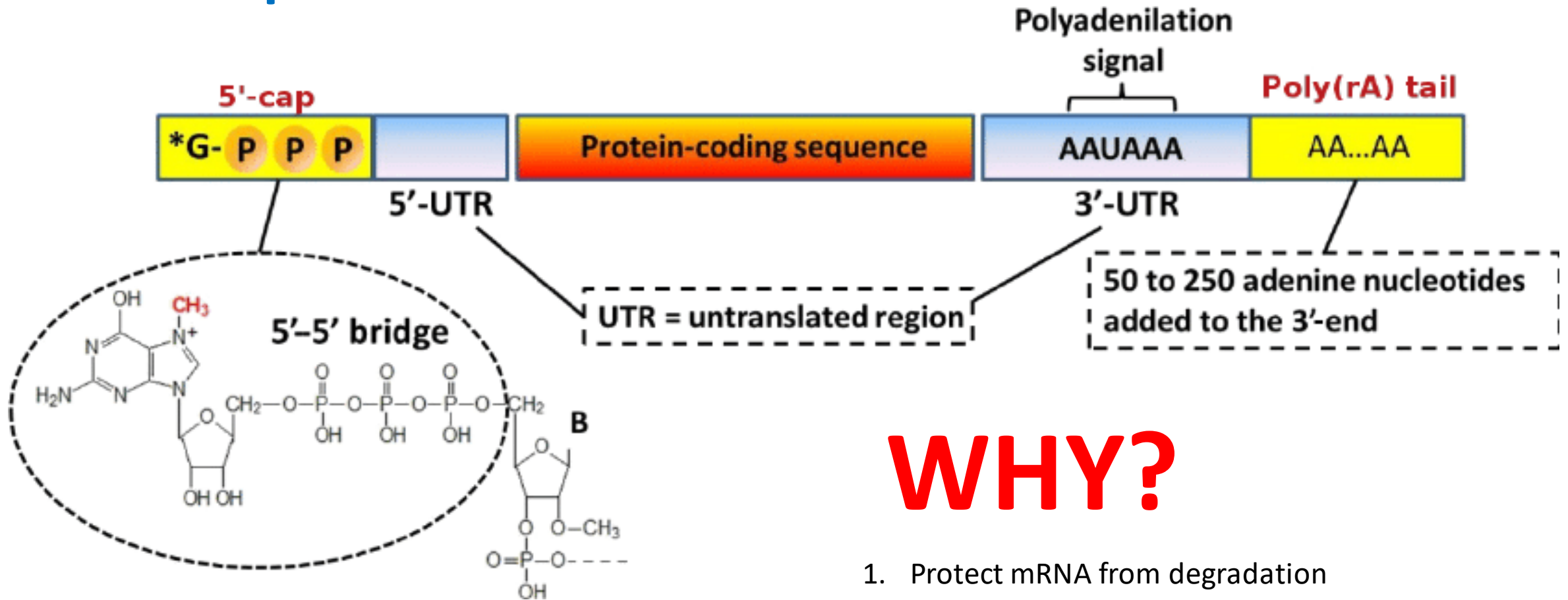
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CUCUACCCAG GACCUGUUCU UGCCUUUCUU CAGCAACUGU ACCUGGUUCC ACCGCAUCCA CGUGUCCGCG ACCAAUGGCA CCAAGAGAUU CGACAACCCC 300
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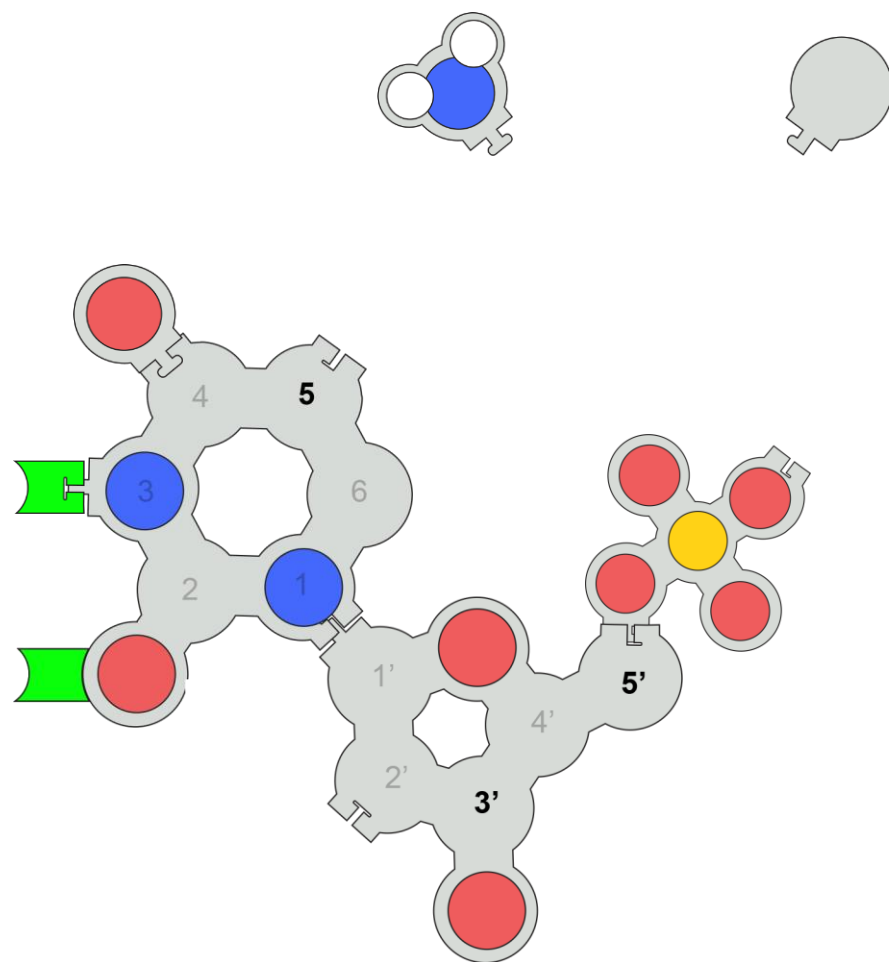
Figure 2. Top: Design elements found in synthetic mRNA therapeutics. Bottom: Sequence of the COVID-19 mRNA vaccine tozinameran (BNT162b2).

The Components of mRNA

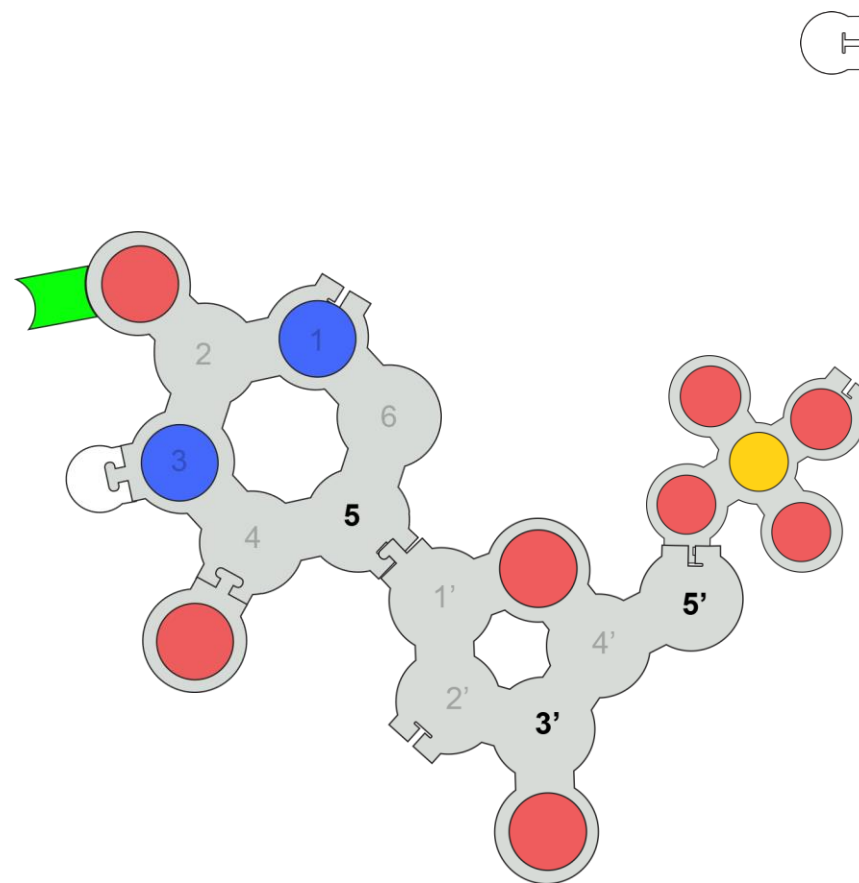


WHY?

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



Uridine



Pseudo-Uridine

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

Tomorrow's Science Today: *preparing for the next pandemic.*

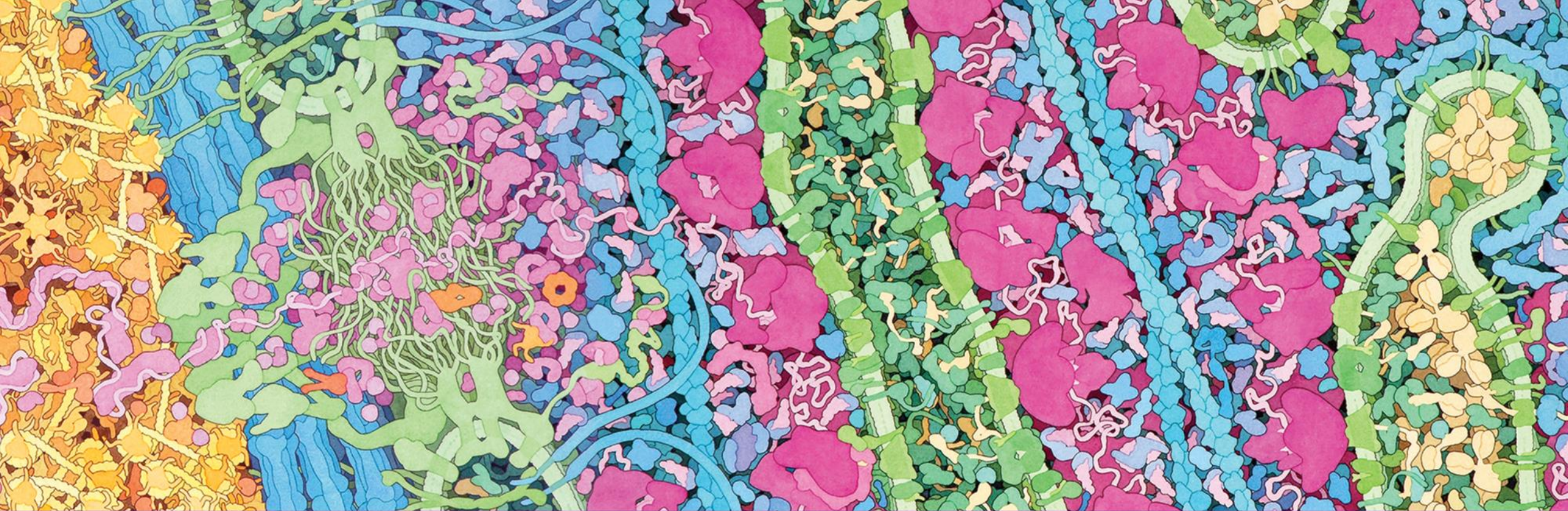
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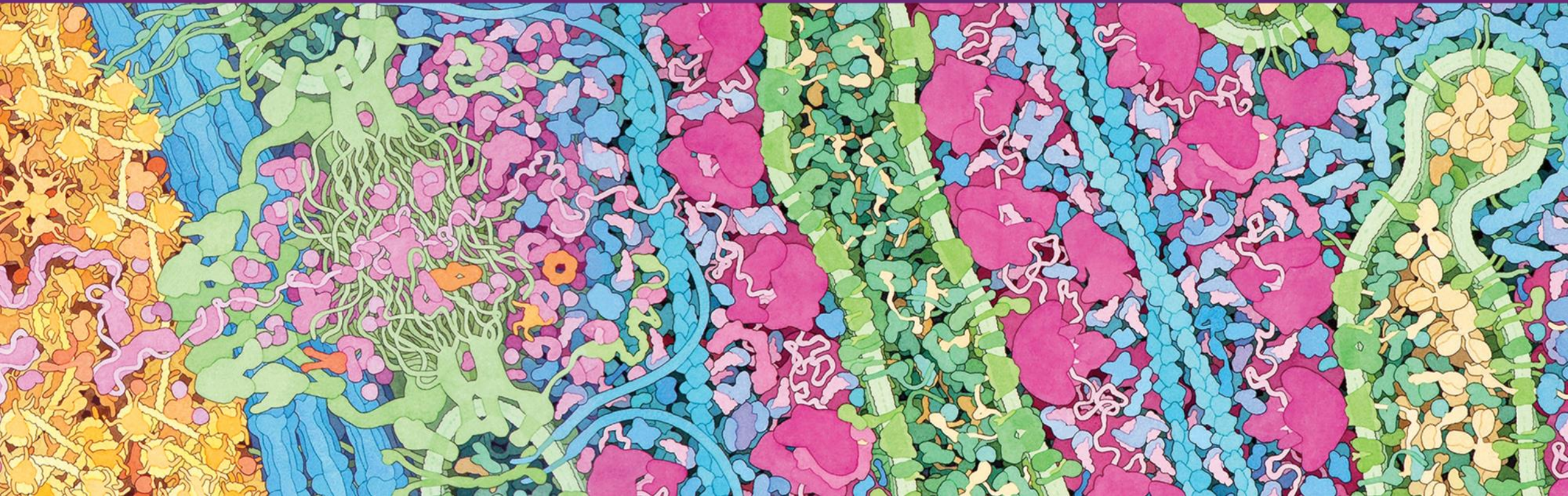
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3d molecular
designs

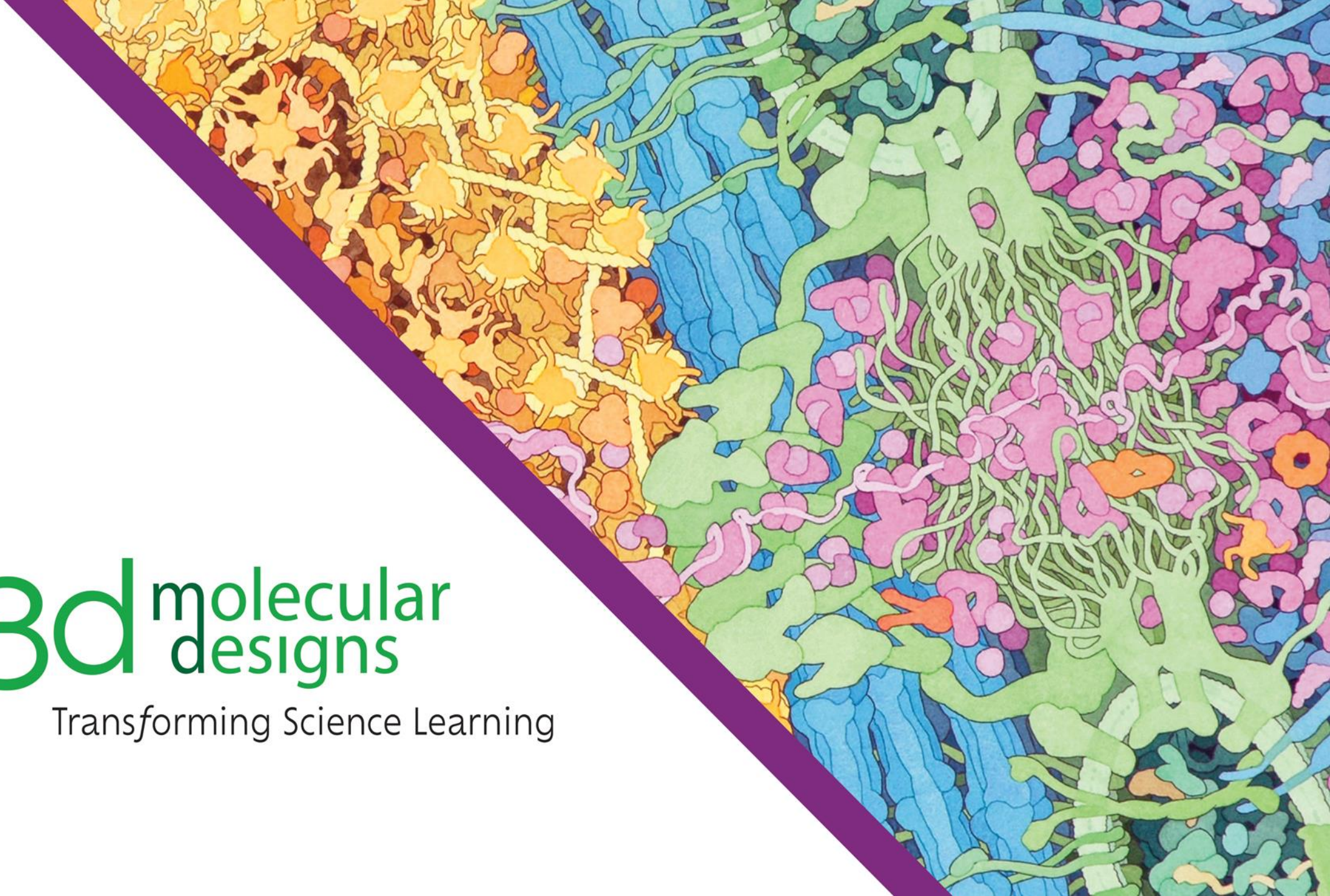
Transforming Science Learning

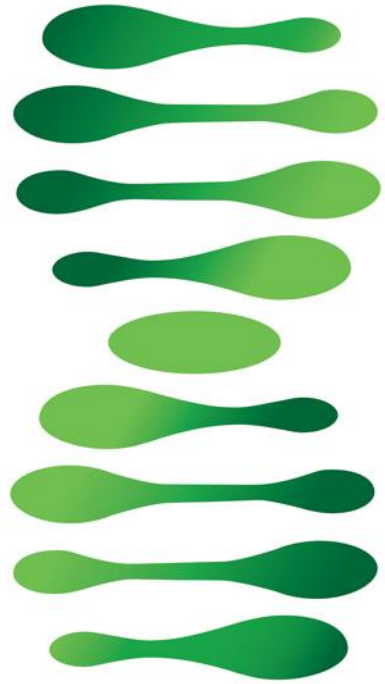




3d molecular
designs

Transforming Science Learning





Transforming Science Learning



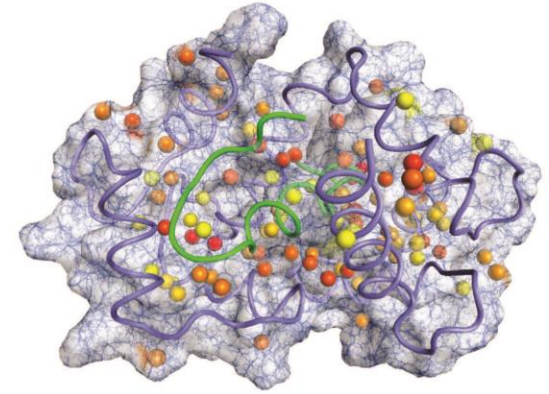


The Importance of Being Modified...

Its not just A's and T's and G' and C's....

Life as we know it only works because of many critical modifications of our 4 (5) nucleotides.

We will consider several of these modifications here....



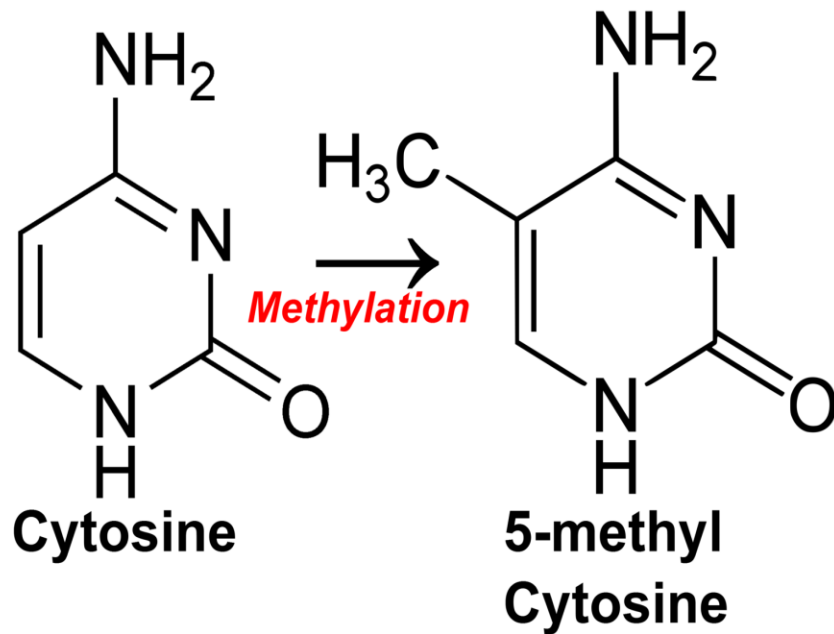
*Life is
Complicated*
Let's deal with it. . .

Epigenetics,... *the methylation of Cytidine*

Epigenetics is the study of how your behaviors and environment can cause changes that affect the way your genes work. Unlike genetic changes, epigenetic changes are reversible and do not change your DNA sequence, but they can change how your body reads a DNA sequence.



In epigenetics, the Cytosine of the dinucleotide sequence CpG ...
....is methylated at the #5 carbon.



WHY?

Four Base Modifications... *that make life even more interesting.*

- **tRNA Modifications.....pseudouridine**
- **5' Cap on mRNA**
- **Epigenetics methylation of CpGs**
- **mRNA vaccines**