

# New technology, old fears: A walk through the science and myths of mRNA vaccines

---

November 20<sup>th</sup>, 2024

Dan Wilson, PhD

**Disclosure:**

It is the policy of the Minnesota Medical Association (MMA) to ensure balance, independence, objectivity, and scientific rigor in its CME activities. To comply with the Standards for Integrity and Independence of the Accreditation Council for Continuing Medical Education (ACCME), the MMA requires planning committee members and faculty to disclose all financial relationship they have with an ineligible company. The members of the faculty and planning committee for this conference have indicated that they have no financial relationships to disclose related to the content of the CME activity. Faculty members have declared that they will uphold the MMA's standards regarding CME activities and that any clinical recommendations are based on the best available evidence or are consistent with generally accepted medical practice. Please indicate in the comments section of the evaluation form whether you detect any instances of bias toward products manufactured by an ineligible company.

**CME Credit:**

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the Minnesota Medical Association and NDSU. The Minnesota Medical Association (MMA) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Minnesota Medical Association designates this live activity for a maximum of 1 *AMA PRA Category 1 Credit(s)*<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

**Financial Support:**

This project was supported by the Centers for Disease Control and Prevention of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award totaling \$5,755,820 with 100 percent funded by CDC/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by CDC/HHS, or the U.S. Government.

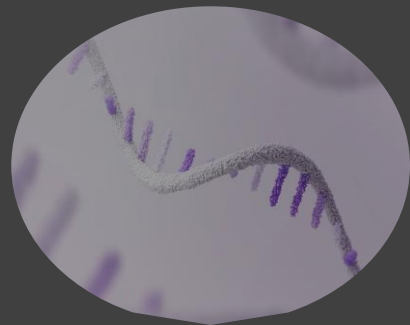
Additionally, the contents do not necessarily represent the official views of, nor an endorsement, by the North Dakota Department of Health and Human Services.

# Disclosure

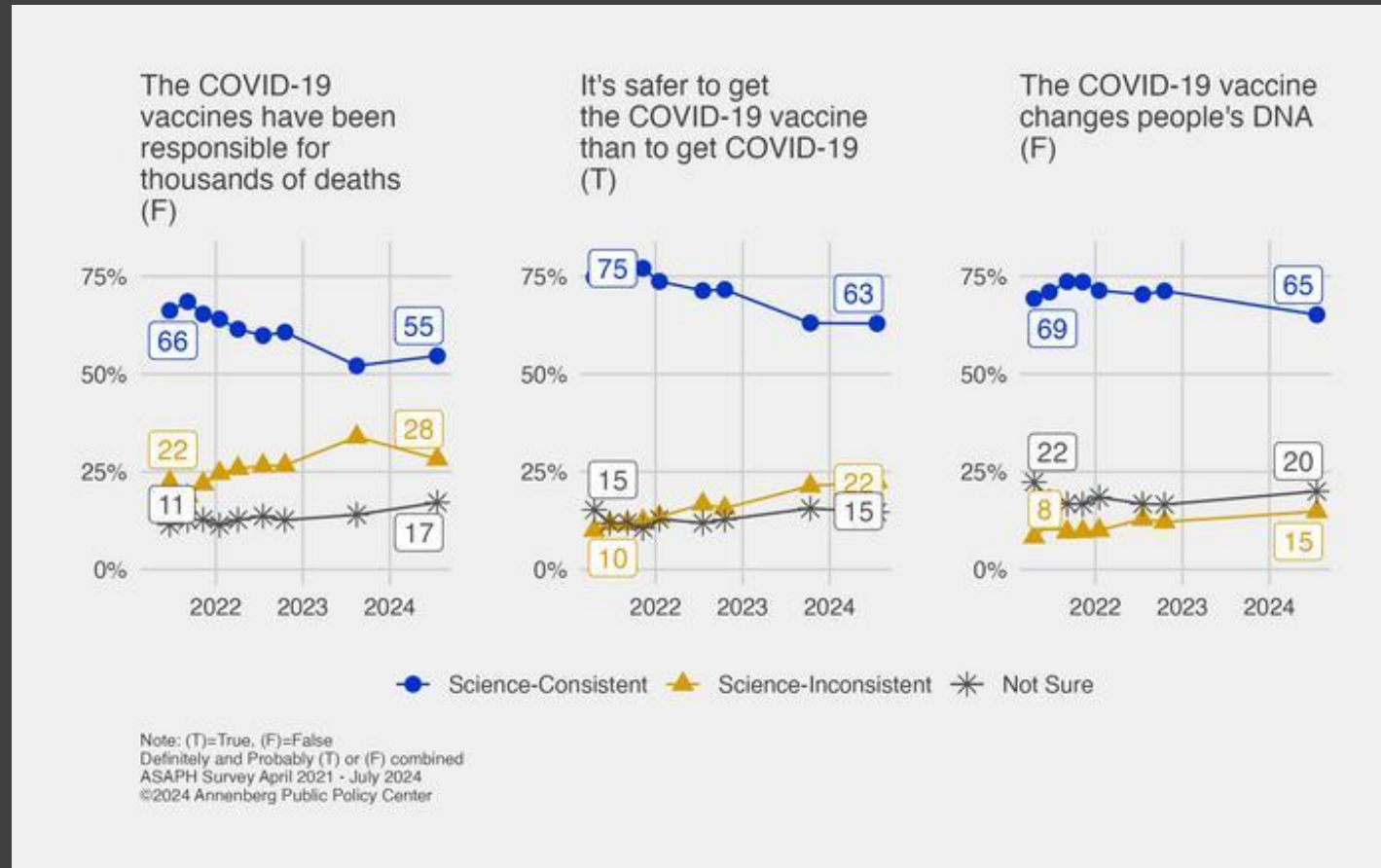
Dr. Dan Wilson has no relevant financial relationships with ineligible companies to disclose.

# Misinformation flourished during COVID, why?

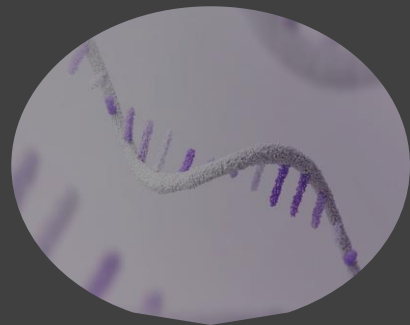
- Uncertainty and fear
- Unprecedented change
- Organized anti-vaccine campaigns




# Misinformation had a measurable impact

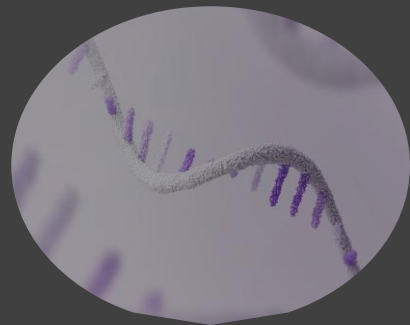


<https://www.asc.upenn.edu/news-events/news/new-appc-survey-finds-belief-covid-19-vaccination-misinformation-has-grown>



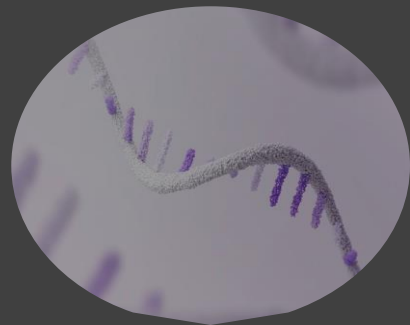
# How can we address misinformation effectively?

- Be willing to have conversations
  - Familiarize yourself with false claims
  - Have the facts on hand
  - Follow up
- 



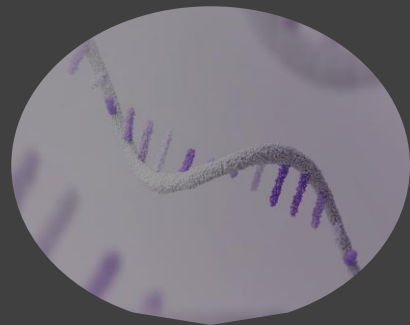
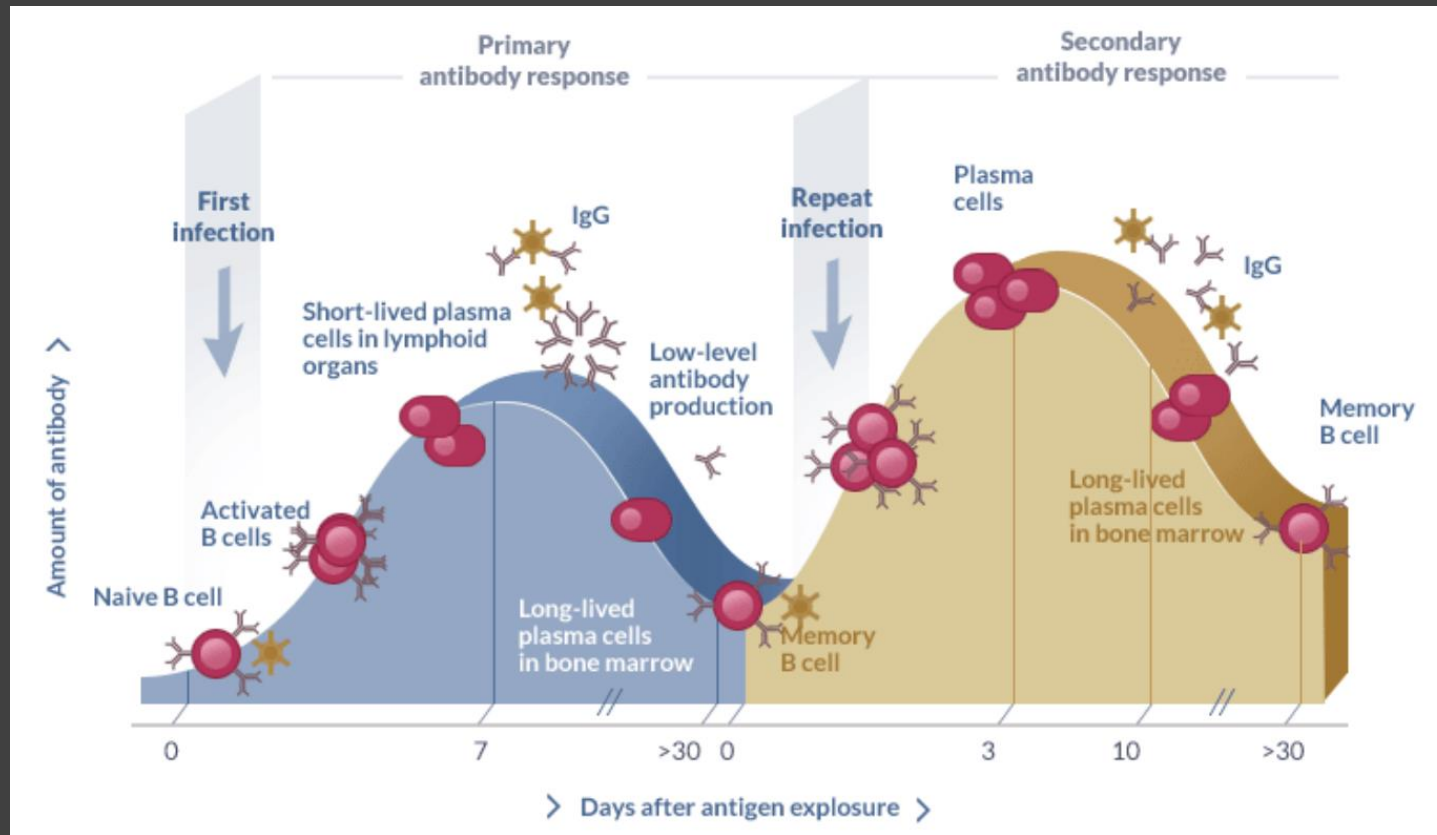
# Objectives for this talk

- Discuss the science of how mRNA vaccines work and are made
- Explore the breakthroughs that made mRNA vaccines possible
- Identify and think through common myths surrounding COVID mRNA vaccines



# How vaccines work

- Vaccines prevent disease, not infections





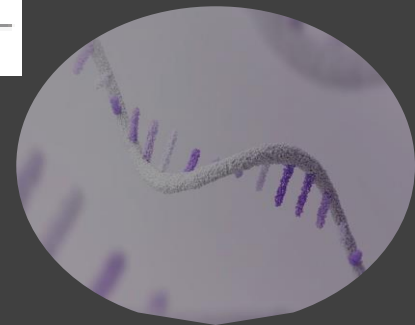
# How vaccines work

- Incubation periods matter
- Antibodies always wane to a baseline
- Immune memory prevents disease
- These concepts were not well communicated

Disease	Incubation period (days) <sup>a</sup>
Influenza	1–2
Common cold	1–3
Bronchiolitis, croup	3–5
Acute respiratory disease (adenoviruses)	5–7
Dengue	5–8
Herpes simplex	5–8
Enterovirus disease	6–12
Poliomyelitis	5–20
Measles	9–12
Smallpox	12–14
Chickenpox	13–17
Mumps	16–20
Rubella	17–20
Mononucleosis	30–50
Hepatitis A	15–40
Hepatitis B and C	50–150
Rabies	30–100
Papilloma (warts)	50–150
AIDS	1–10 yr

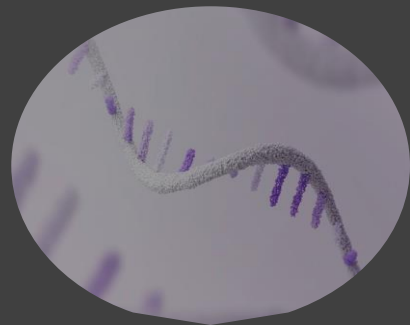
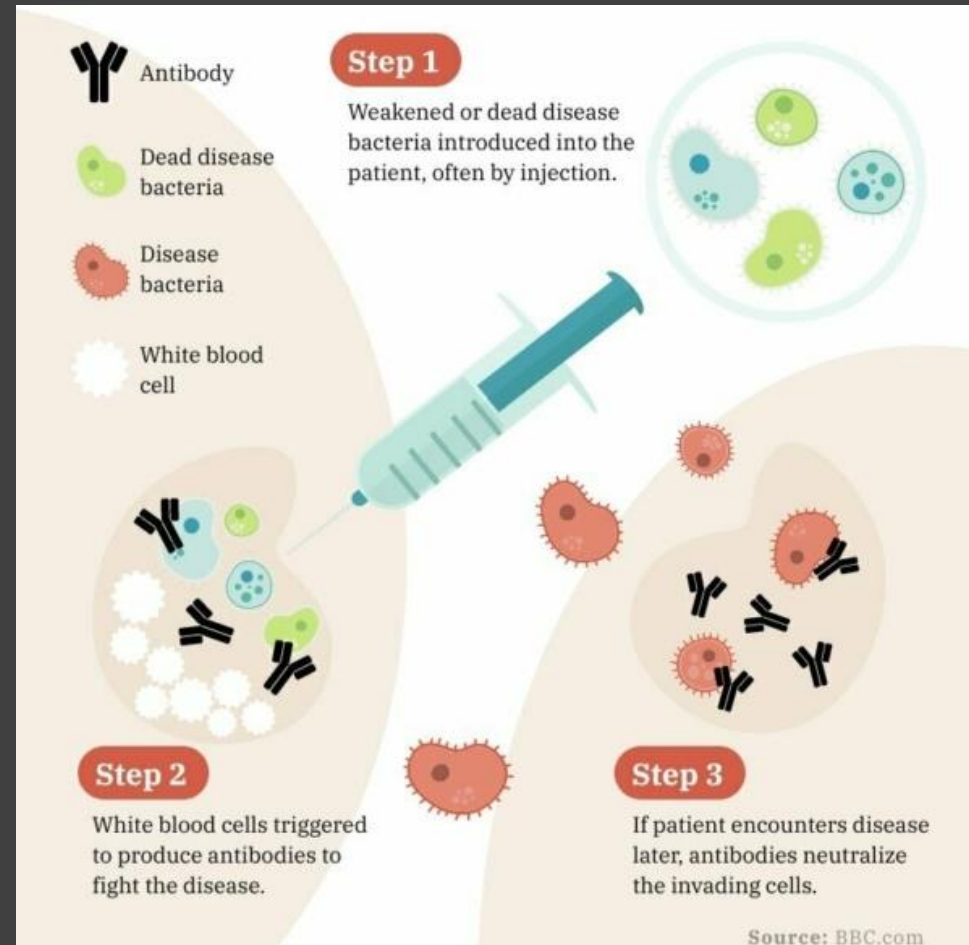
<sup>a</sup>Until first appearance of prodromal symptoms.

<https://virology.ws/2014/10/08/the-incubation-period-of-a-viral-infection/>



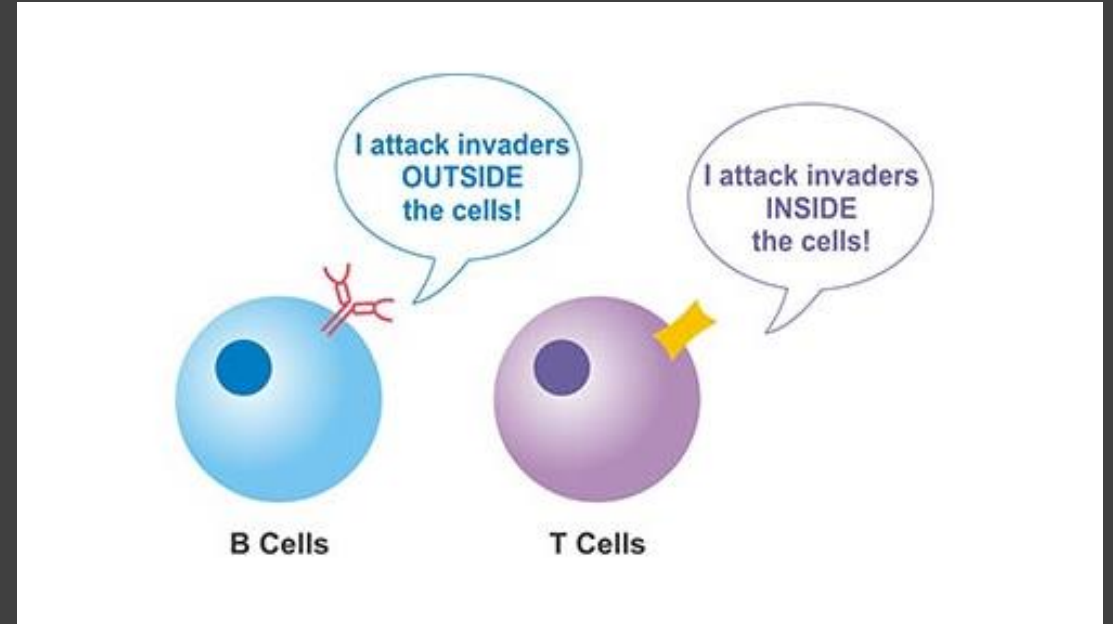
# How vaccines work

- Weakened, killed or pieces of a pathogen
- Immune cells see the foreign proteins
- Immune memory is formed to foreign proteins
- B-cells and T-cells

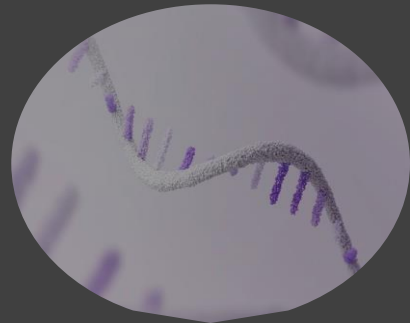


# How vaccines work

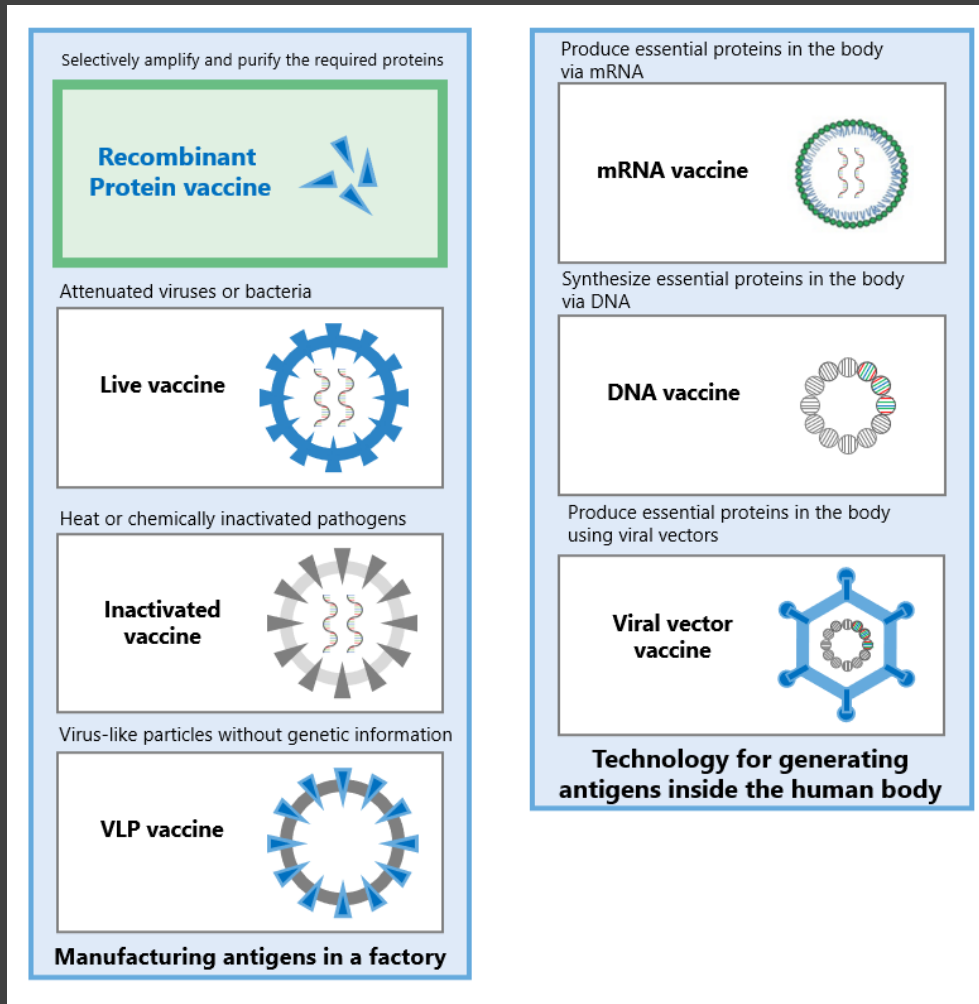
- Antibodies bind epitopes
- T-cells bind peptides on MHC molecules
- Both memory cell types persist post-vaccination



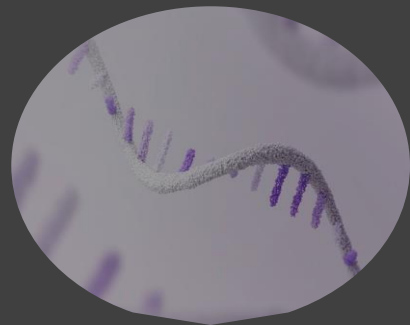
<https://askabiologist.asu.edu/b-cell>



# Types of vaccines

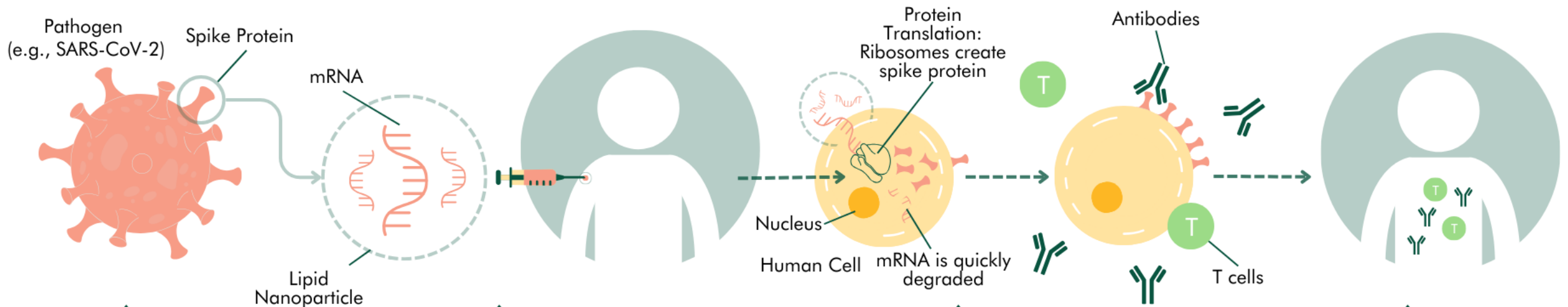


- All vaccine types accomplish the same goals
- Foreign protein → immune response → immune memory



# HOW MRNA VACCINES WORK

mRNA vaccines help the body's immune system build protection against a specific pathogen so that if a person is ever exposed to that pathogen following vaccination, the immune system can quickly recognize and respond to it before it can cause serious illness.



mRNA vaccines give genetic instructions to cells in the body on how to make a piece of a pathogen, usually a protein found on the outer membrane of the pathogen (e.g., the spike protein of SARS-CoV-2, the virus that causes COVID-19.)

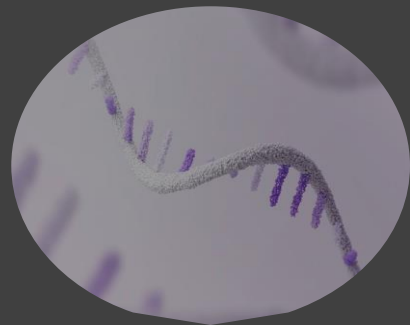
The mRNA vaccine is injected into a muscle, usually on the upper arm or thigh. The vaccine contains mRNA surrounded by a lipid nanoparticle (fatty bubble). Once the vaccine is inside the body, the lipid nanoparticle acts as a vehicle to deliver the instructions (aka the mRNA) to our cells. Without the lipid nanoparticle, the mRNA in the vaccine would degrade quickly and would have difficulty crossing into cells.

Once inside the cell, the mRNA is translated by ribosomes, which make the targeted protein or parts of the targeted protein (e.g., spike protein). After the mRNA is read, it is broken down by the cell. The cell displays the newly made proteins on their surface. As part of a normal immune response, the immune system produces specialized proteins called antibodies and other defenses against the pathogen (ex. T cells).

Vaccination primes the immune system, so if an individual encounters the pathogen in the future, the body is able to recognize and destroy it. mRNA vaccines may prevent disease entirely or it may help to reduce severity of disease if an individual is infected.

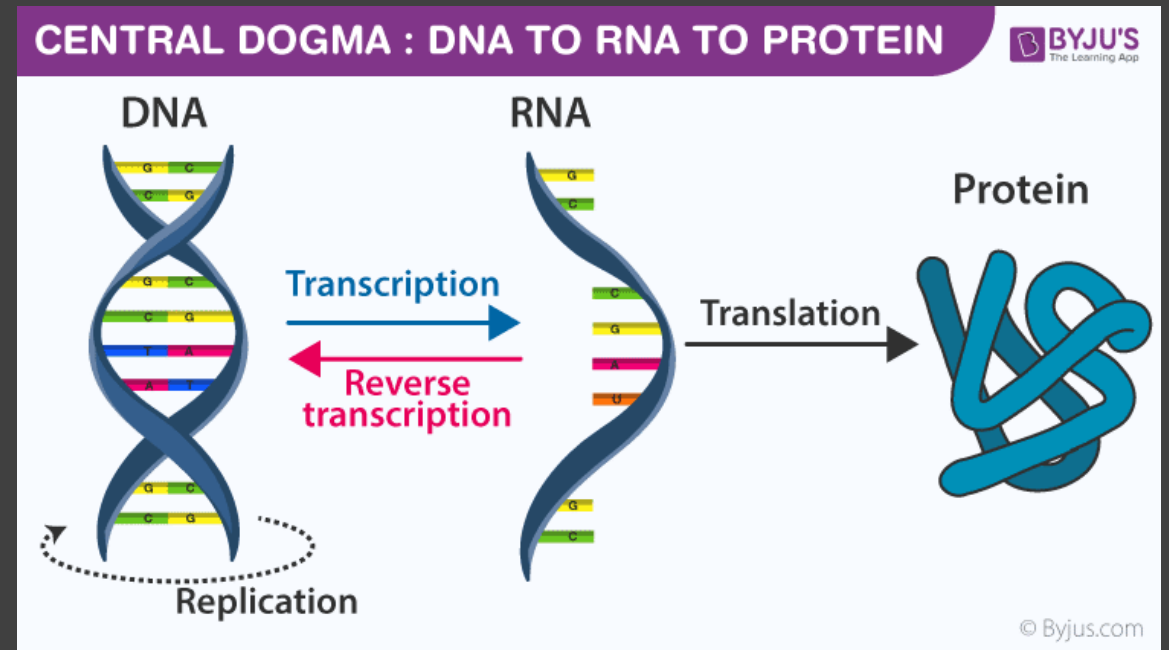
# Pause & recap – Addressing common myths

- Claim: COVID vaccines don't work because you still get COVID
  - It is a short incubation virus, you got symptoms but your immune memory helped prevent bad outcomes
- Question: Why should I get vaccinated if I can still spread the virus?
  - Vaccination reduces risk of transmission but does not eliminate it
  - You should still want to be healthy

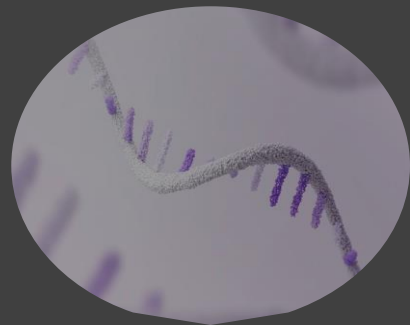


# Refresher – what is mRNA?

- Messenger RNA (mRNA) is transcribed from DNA
- mRNA is translated by ribosomes into protein
- mRNA is much less stable than DNA, and degrades over time



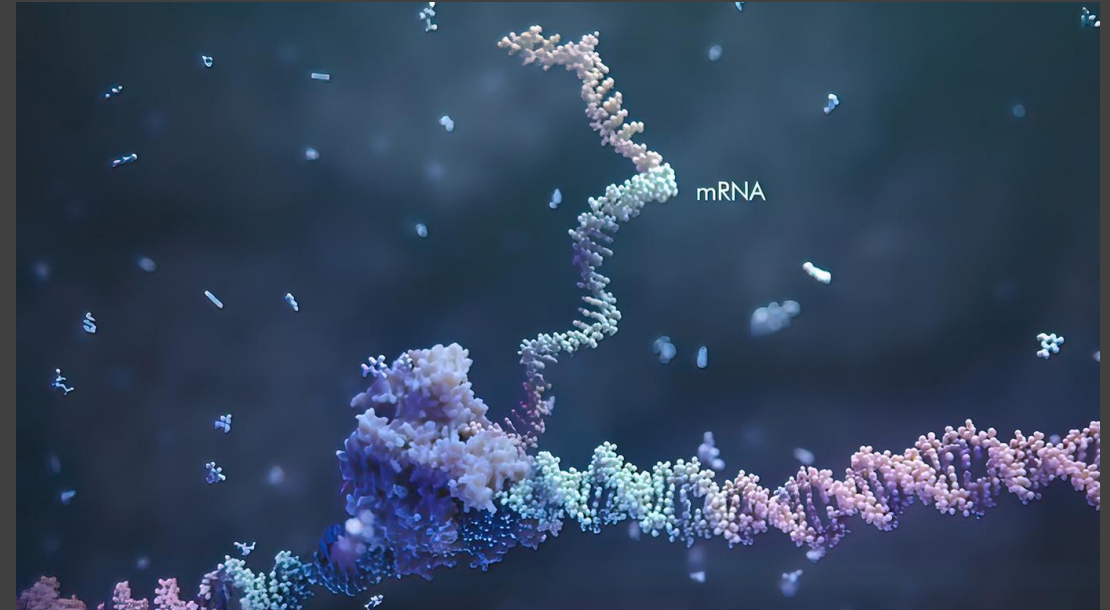
<https://byjus.com/biology/central-dogma-inheritance-mechanism/>



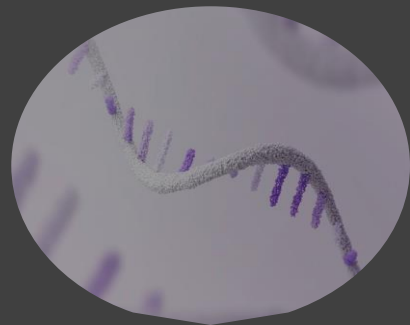


# mRNA is necessary for life

- Different mRNAs are constantly being produced
- A single cell has about 360,000 mRNA molecules at a given time
- Nothing about mRNA should be scary

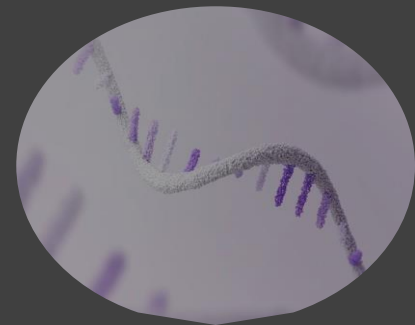
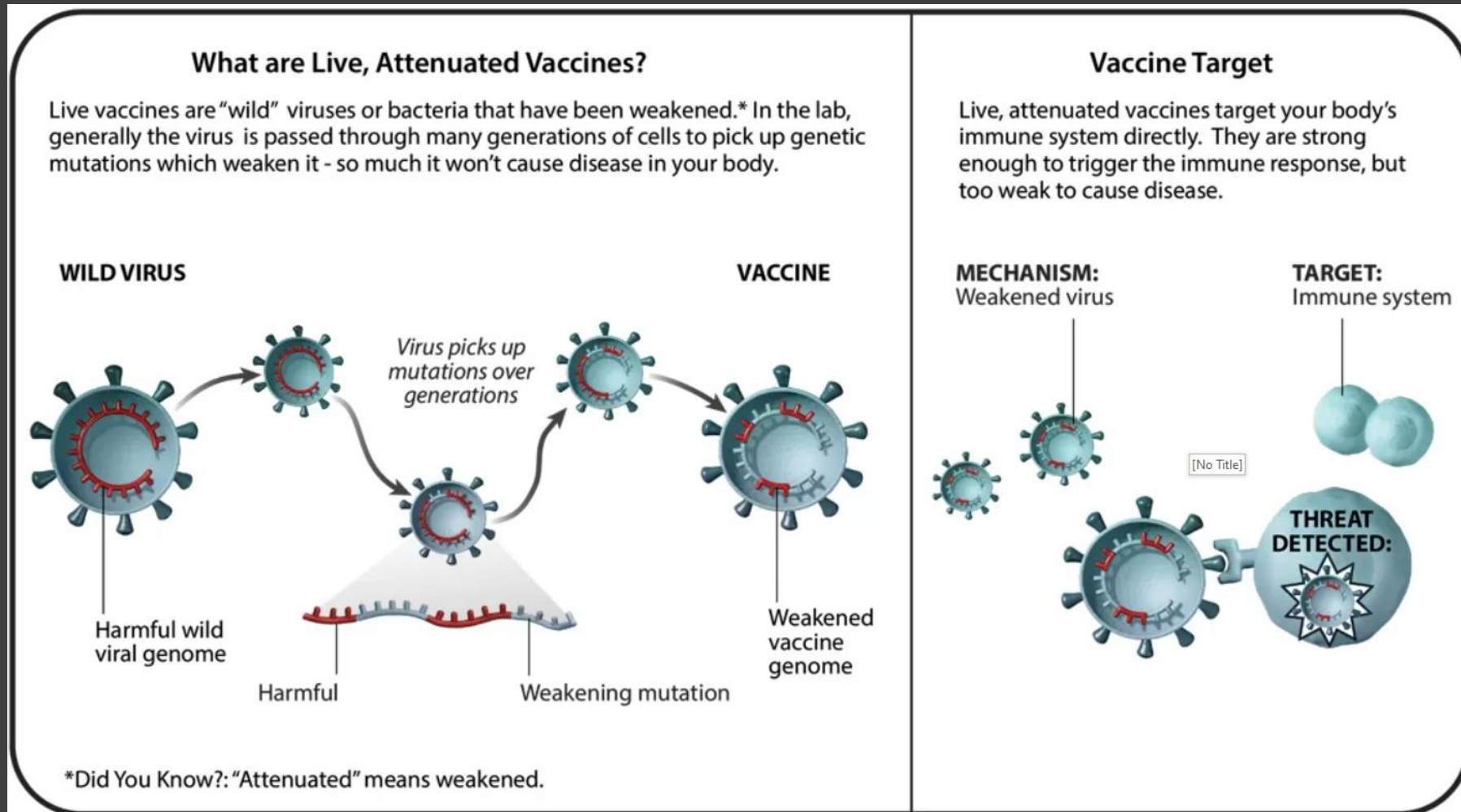


<https://news.uchicago.edu/story/rnas-joints-play-key-role-our-gene-expression-uchicago-scientists-find>



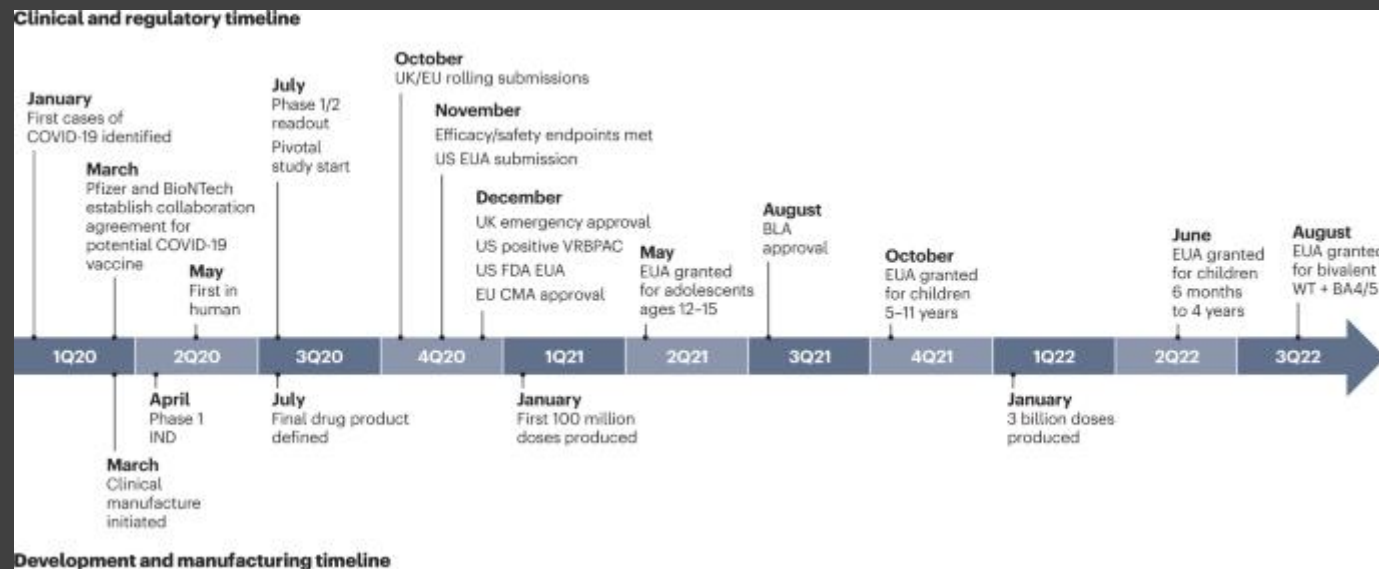


# Live attenuated vaccines are like mRNA vaccines

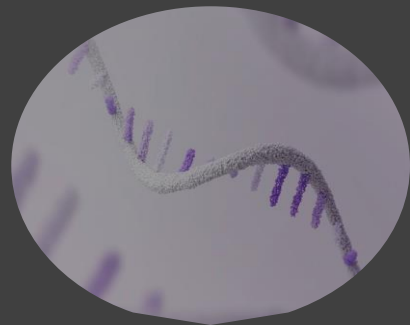


# So, why mRNA vaccines?

- Safety – like an attenuated vaccine but no pathogen
  - Non-infectious
  - Non-integrating
- Manufacturing – speed and flexibility

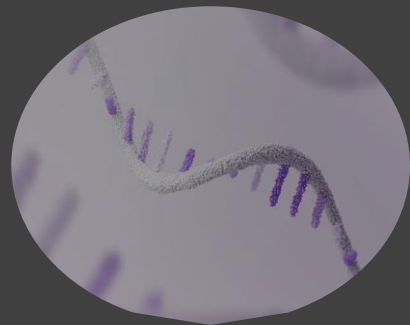


<https://www.nature.com/articles/s41587-022-01643-1>



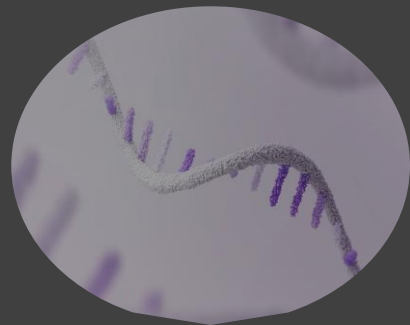
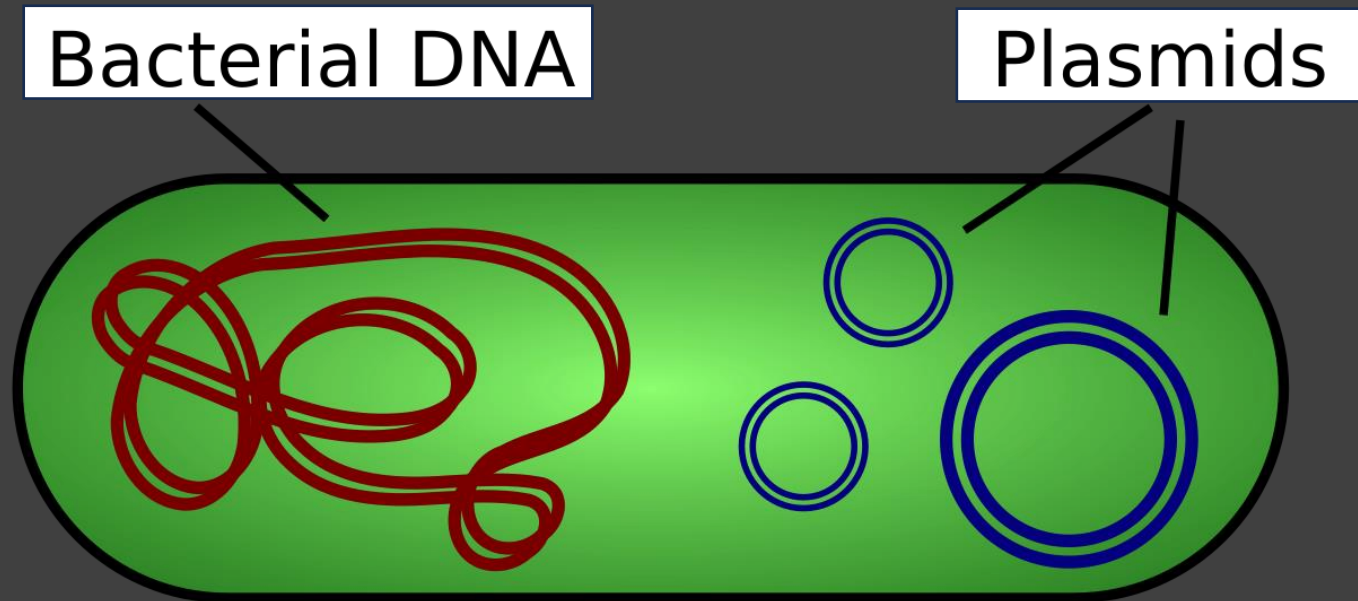
# Pause & recap – Addressing common myths

- Claim: mRNA technology is too new, I don't think it is safe
  - mRNA vaccines function similarly to the longest-used kinds of vaccines in history, but makes them even safer
  - mRNA is not unnatural, your cells make it constantly

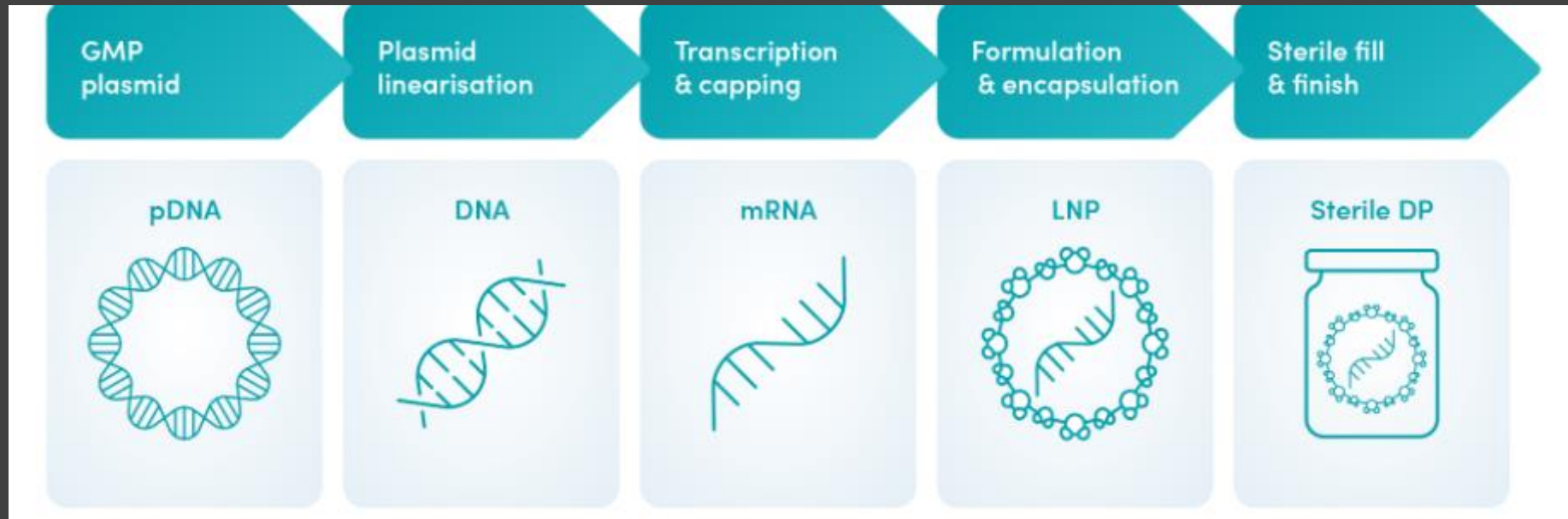


# How mRNA vaccines are made

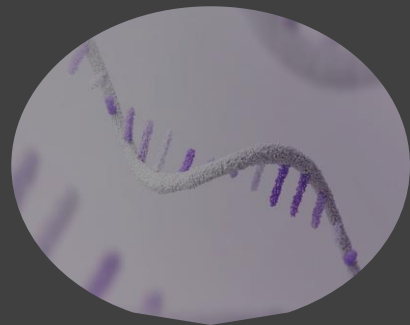
- Plasmid DNA is made in bacteria
  - Plasmids are circular pieces of DNA



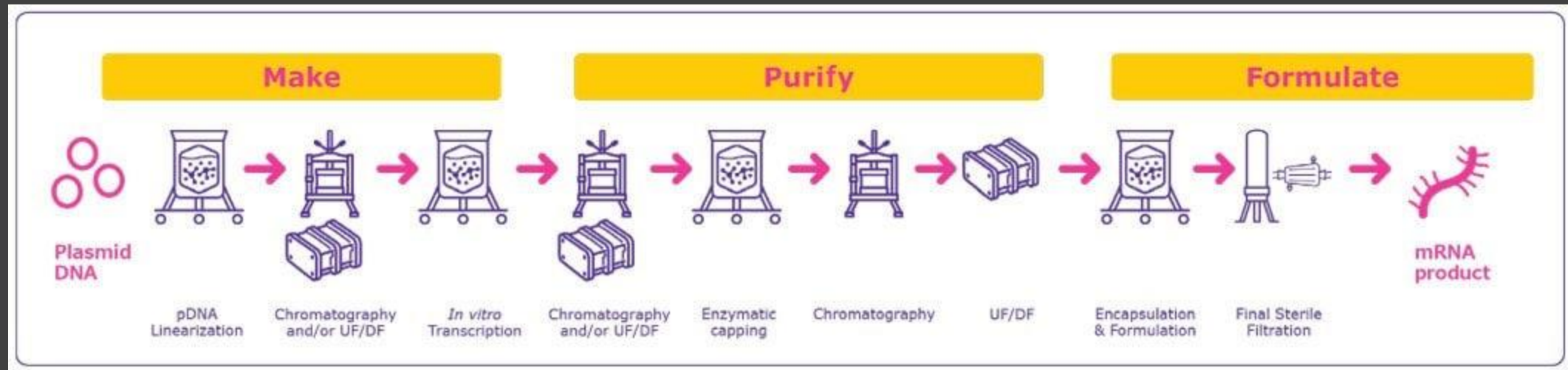
# How mRNA vaccines are made



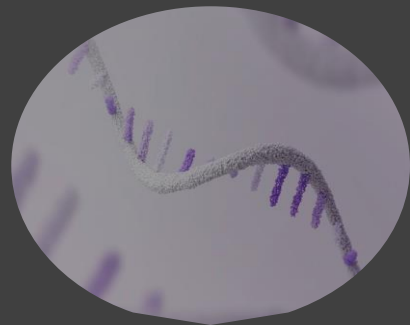
<https://www.recipharm.com/recibiopharm/modalities/rna-therapies/rna-manufacturing>



# How mRNA vaccines are made



<https://www.sigmaaldrich.com/US/en/technical-documents/technical-article/pharmaceutical-and-biopharmaceutical-manufacturing/vaccine-manufacturing/manufacturing-strategies-for-mrna-vaccines>

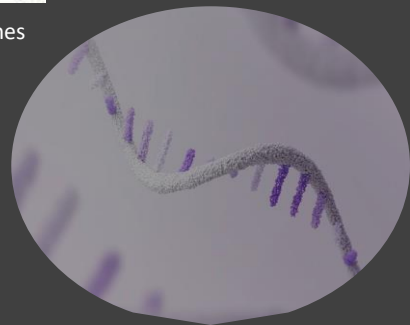




# How mRNA vaccines are made



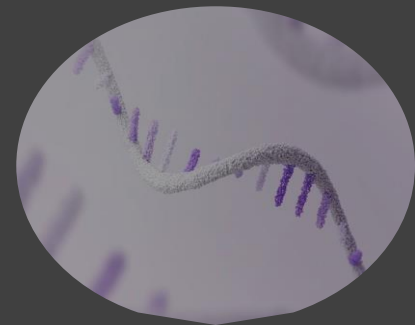
<https://www.sigmaaldrich.com/US/en/technical-documents/technical-article/pharmaceutical-and-biopharmaceutical-manufacturing/vaccine-manufacturing/manufacturing-strategies-for-mrna-vaccines>



# How mRNA vaccines are made

Quality	Attribute	Method
Identity	Sequence confirmation	Next Generation Sequencing (NGS)
		Sanger Sequencing
		Reverse Transcriptase – PCR
Content	RNA content	RT-qPCR and RT-dPCR, Ultraviolet Spectroscopy
Integrity	Percentage of intact mRNA and fragment mRNA	Capillary gel electrophoresis
	5' cap	IP-RP-HPLC
	3' poly(A)	RP-HPLC
	mRNA Integrity	Gel electrophoresis
Purity	Product related impurities - dsRNA	Immunoblot
	Residual DNA template	qPCR
Safety	Endotoxin	USP <85>
	Bioburden	USP <61>, <62>, <1115>
	Sterility	USP <71>
Other	Appearance	USP<1>, <790>
	pH	USP <791>

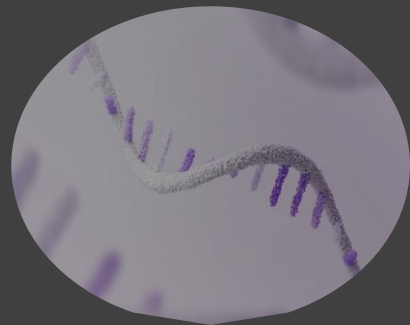
<https://www.uspnf.com/notices/analytical-procedures-mrna-vaccines-20220210>



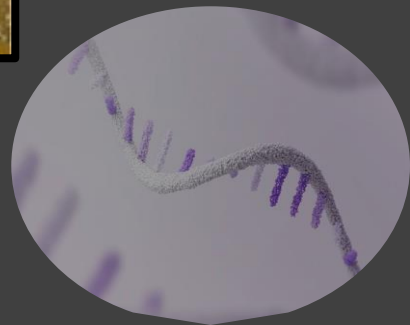
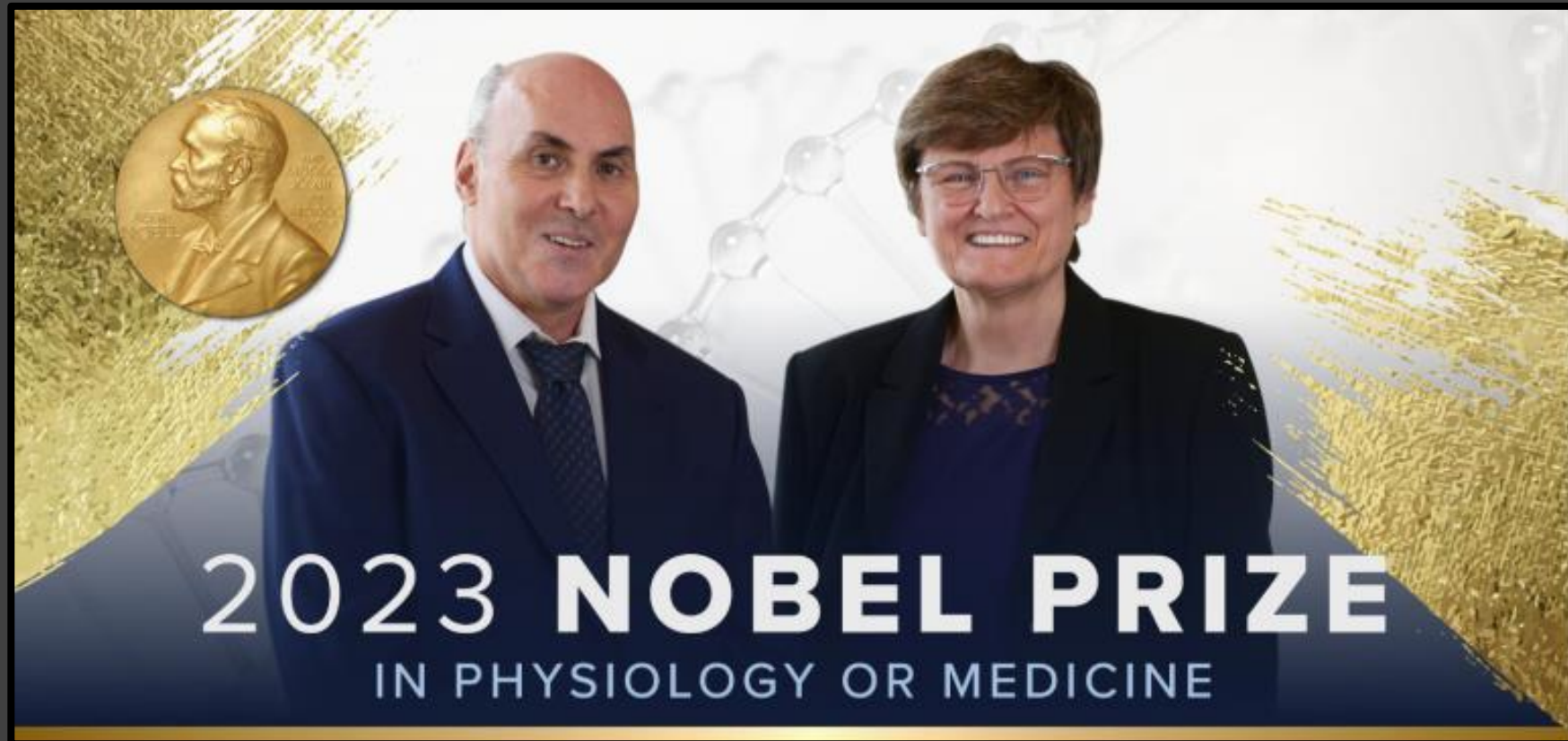


# Pause & recap – Addressing common myths

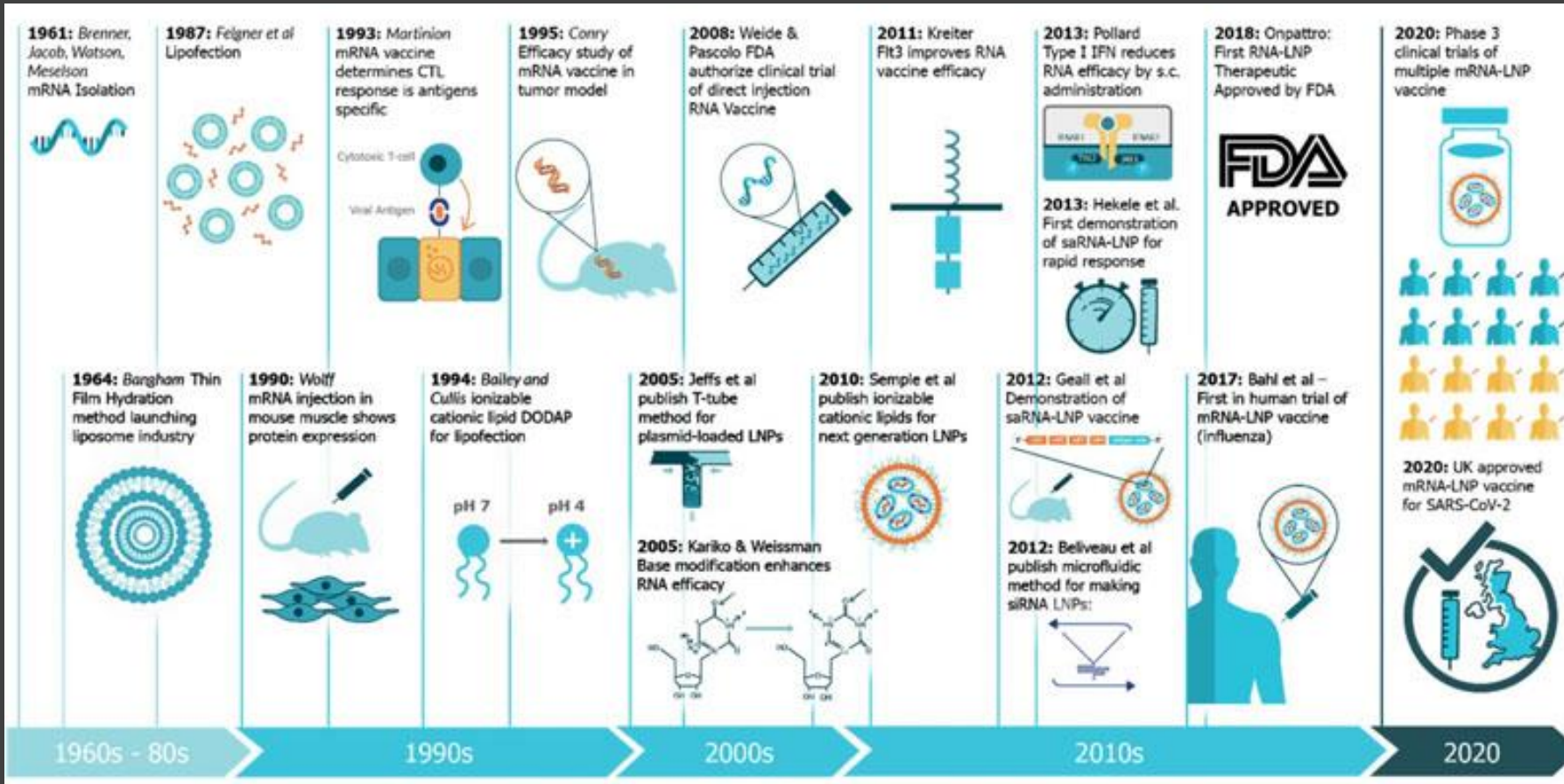
- Claim: mRNA vaccines are contaminated with DNA
  - All batches of mRNA vaccines are tested at multiple steps of manufacturing to ensure that residual contaminants like DNA are being removed
  - Attempts to show contamination have not shown high levels of DNA with proper experiments done to the same standard that pharma is held to



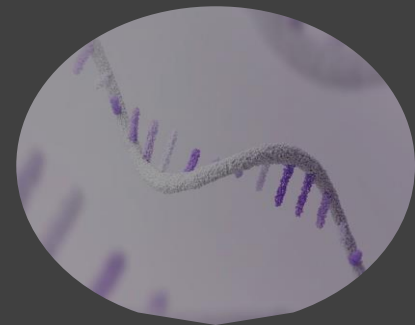
# Breakthroughs in mRNA vaccine technology



# Breakthroughs in mRNA vaccine technology



[https://www.transgenbiotech.com/mrna\\_vaccine\\_products.html](https://www.transgenbiotech.com/mrna_vaccine_products.html)



# Breakthroughs in mRNA vaccine technology

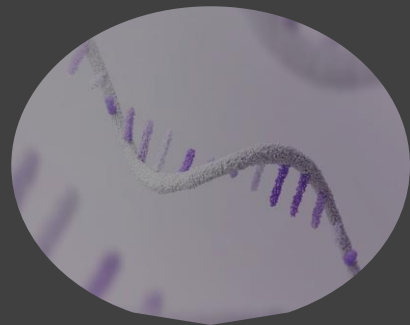
ARTICLE · [Volume 23, Issue 2, P165-175, August 2005](#) · [Open Archive](#)

[Download Full Issue](#)

## Suppression of RNA Recognition by Toll-like Receptors: The Impact of Nucleoside Modification and the Evolutionary Origin of RNA

[Katalin Karikó](#) <sup>1</sup>  · [Michael Buckstein](#)<sup>2</sup> · [Houping Ni](#)<sup>2</sup> · [Drew Weissman](#)<sup>2</sup>

[Affiliations & Notes](#)  [Article Info](#) 

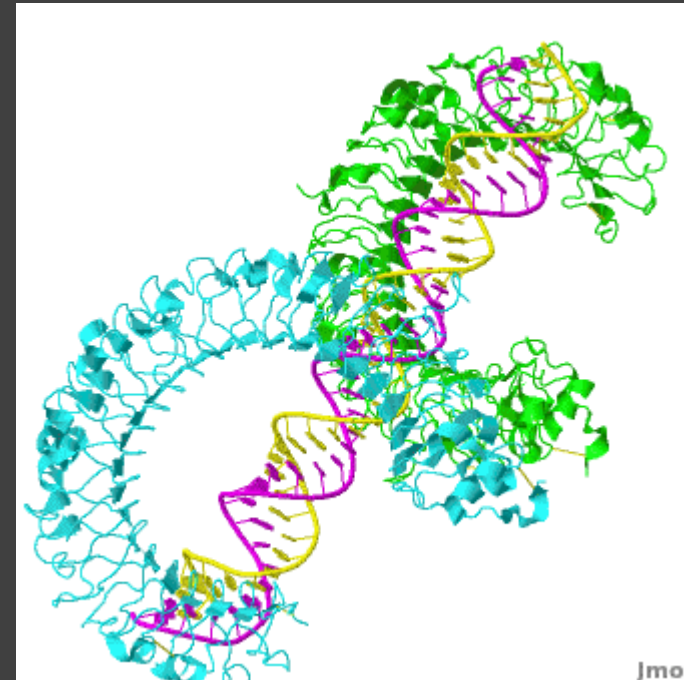


## Suppression of RNA Recognition by Toll-like Receptors: The Impact of Nucleoside Modification and the Evolutionary Origin of RNA

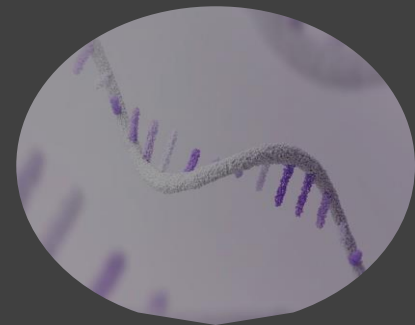
[Katalin Karikó](#) <sup>1</sup>  · [Michael Buckstein](#)<sup>2</sup> · [Houping Ni](#)<sup>2</sup> · [Drew Weissman](#)<sup>2</sup>

[Affiliations & Notes](#)  [Article Info](#) 

- The innate immune system can recognize foreign DNA and RNA
- This is accomplished through proteins called toll-like receptors (TLR's)
- Humans have 10 TLRs



[https://proteopedia.org/wiki/index.php/Toll-like\\_Receptors](https://proteopedia.org/wiki/index.php/Toll-like_Receptors)



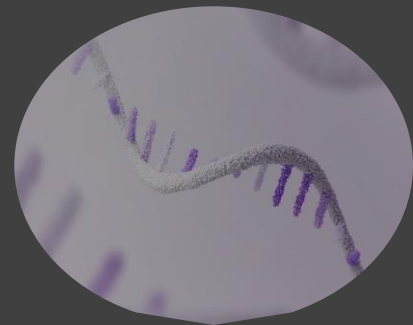
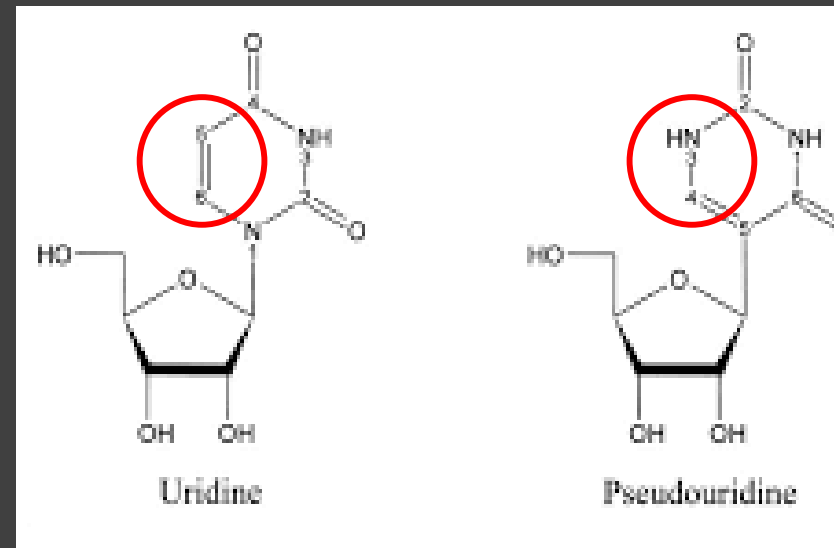


## Suppression of RNA Recognition by Toll-like Receptors: The Impact of Nucleoside Modification and the Evolutionary Origin of RNA

[Katalin Karikó](#) <sup>1</sup>   · [Michael Buckstein](#) <sup>2</sup> · [Houping Ni](#) <sup>2</sup> · [Drew Weissman](#) <sup>2</sup>

[Affiliations & Notes](#)  [Article Info](#) 

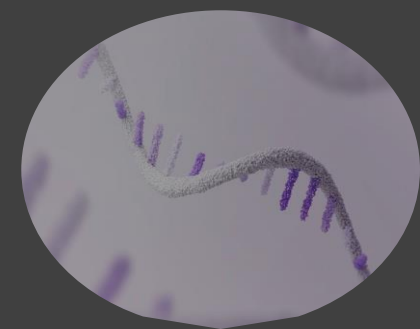
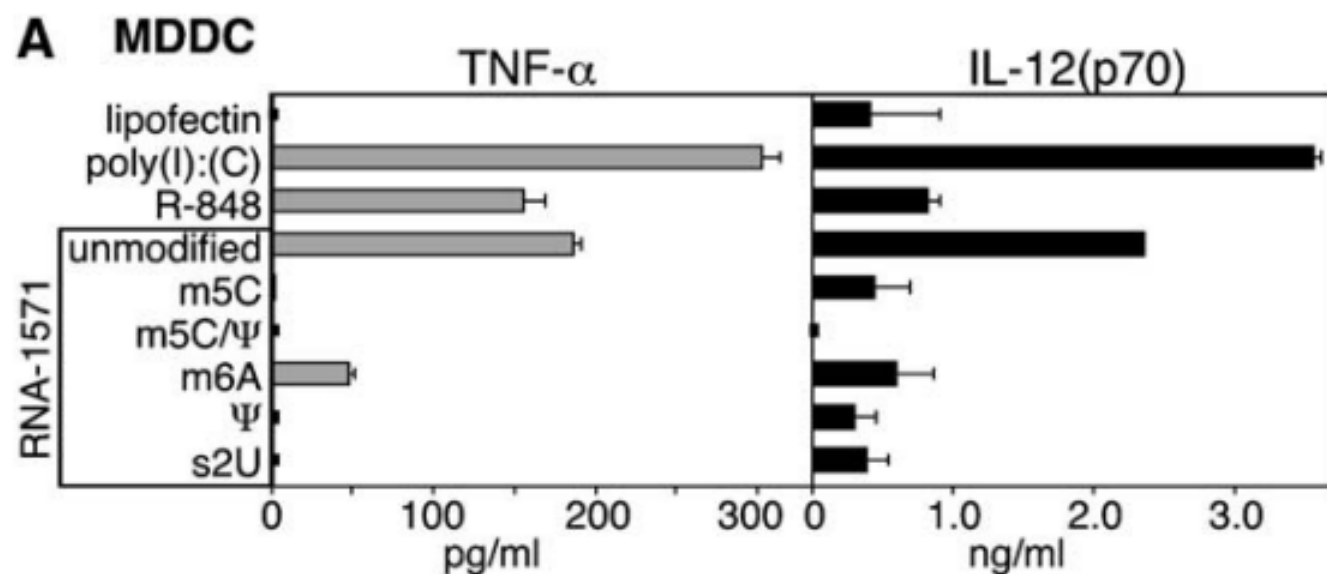
- Small modifications in nucleosides help TLR's tell the difference
- Human RNAs are much more modified than bacteria
- Some RNA virus genomes have more modifications than humans



# Suppression of RNA Recognition by Toll-like Receptors: The Impact of Nucleoside Modification and the Evolutionary Origin of RNA

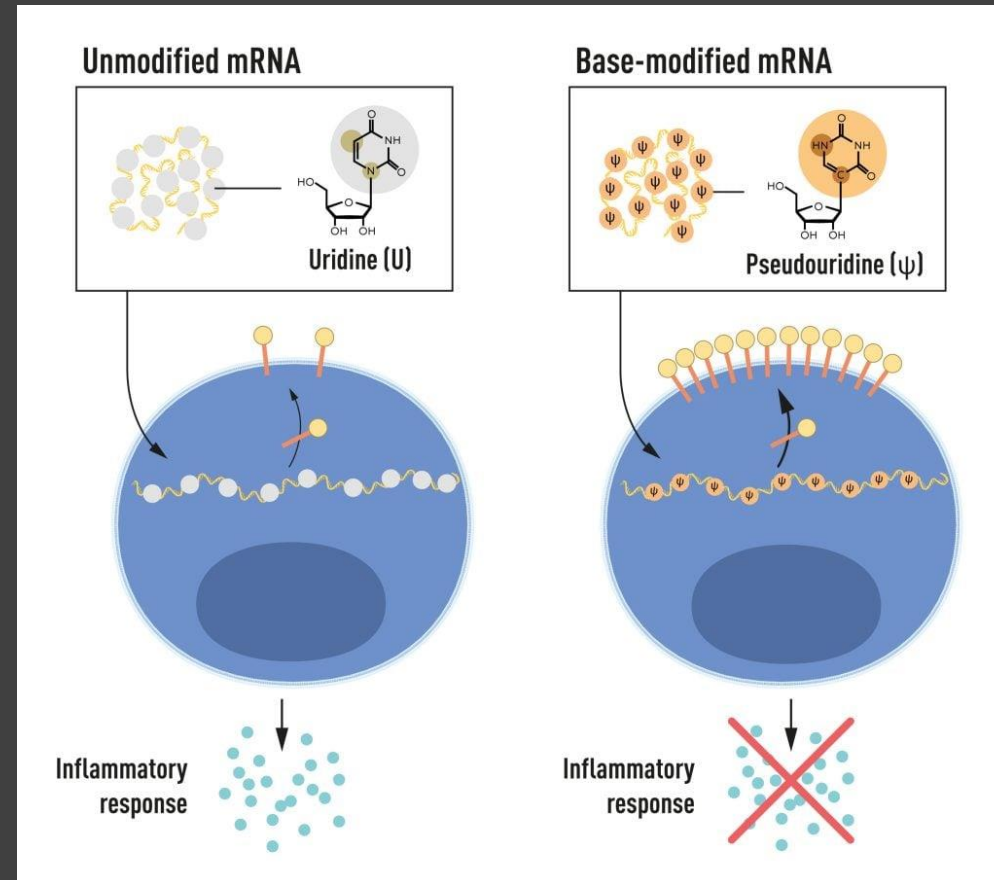
[Katalin Karikó](#) <sup>1</sup> [✉](#) · [Michael Buckstein](#) <sup>2</sup> · [Houping Ni](#) <sup>2</sup> · [Drew Weissman](#) <sup>2</sup>

[Affiliations & Notes](#) [Article Info](#)

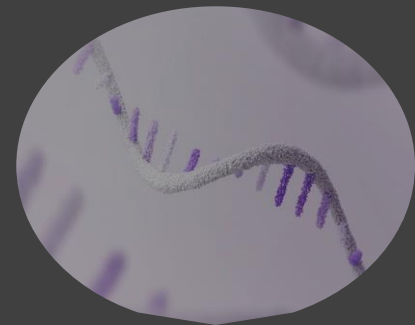


# Tuning the immune system to make mRNA vaccines possible

- Unmodified mRNA gets destroyed too quickly
- Modified mRNA does not, and is able to express protein
- The expressed protein elicits an immune response



<https://www.nobelprize.org/prizes/medicine/2023/advanced-information/>





Article

<https://doi.org/10.1038/s41467-024-51411-9>

# Innate immune responses against mRNA vaccine promote cellular immunity through IFN- $\beta$ at the injection site

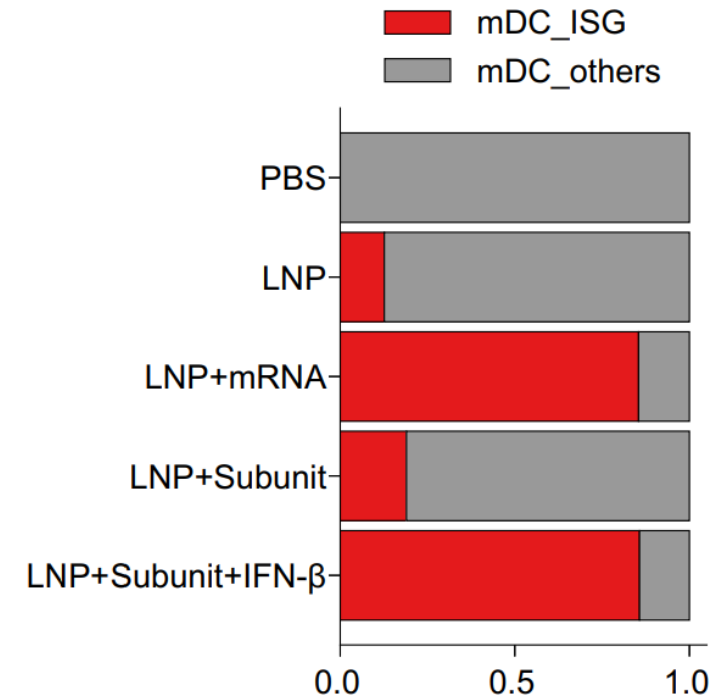
Received: 3 December 2023

Accepted: 6 August 2024

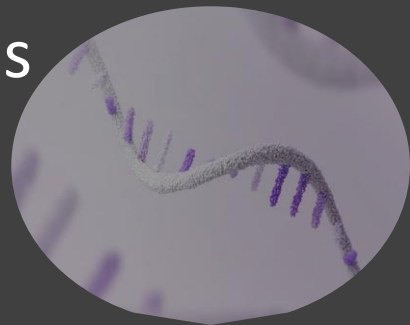
Published online: 27 August 2024

Seongryong Kim<sup>1,6</sup>, Ji Hyang Jeon<sup>2,6</sup>, Myeonghwan Kim<sup>3,4</sup>, Yeji Lee<sup>5</sup>, Yun-Ho Hwang<sup>2</sup>, Myungsun Park<sup>1</sup>, C. Han Li<sup>3,4</sup>, Taeyoung Lee<sup>2</sup>, Jung-Ah Lee<sup>2</sup>, You-Me Kim<sup>1</sup>, Dokeun Kim<sup>2</sup>, Hyukjin Lee<sup>5</sup>, You-Jin Kim<sup>2</sup>, V. Narry Kim<sup>3,4</sup>, Jong-Eun Park<sup>1</sup>✉ & Jinah Yeo<sup>2</sup>✉

d

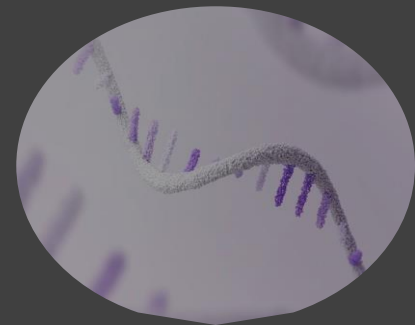


ISG = IFN-stimulated genes



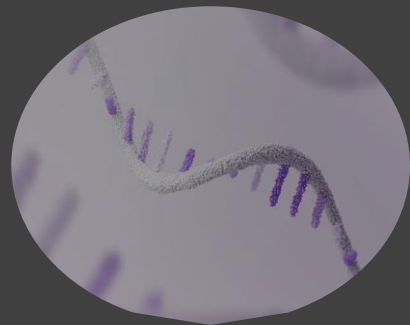
# Tuning the immune system to make mRNA vaccines possible

- Too much innate immune response = no protein
- Too little innate immune response = blunted immune response
- Expression and innate immune cell recruitment

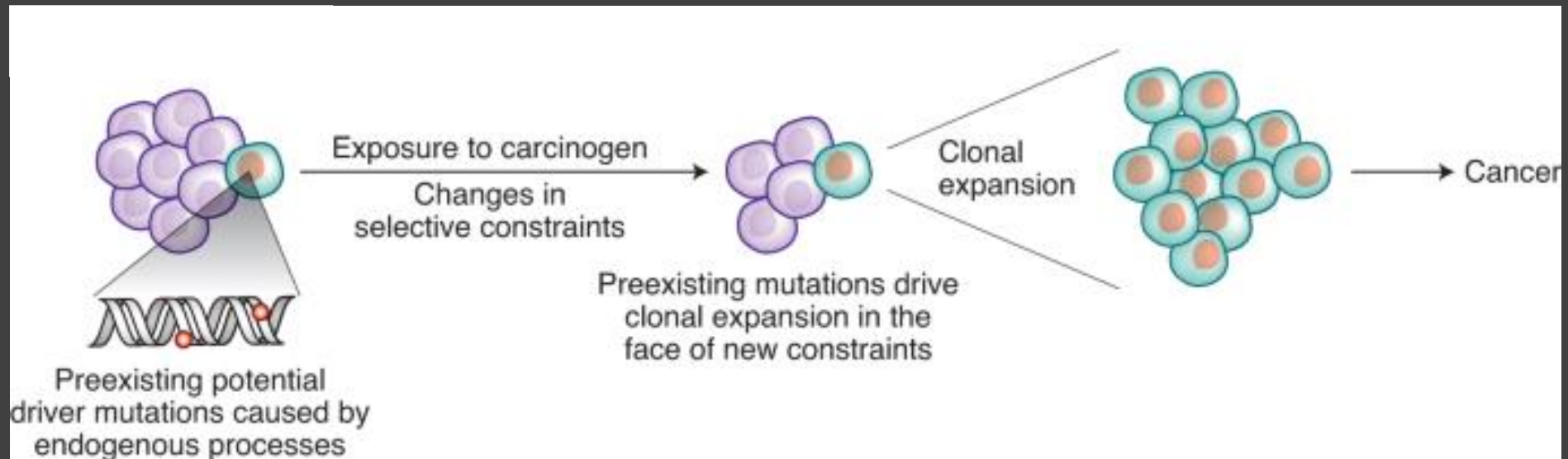


# Pause & recap – Addressing common myths

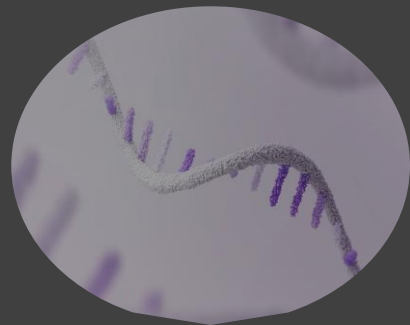
- Claim: mRNA vaccines suppress the immune system
  - They don't, they avoid enough of the innate immune system to achieve a desired adaptive immune response
- Claim: We don't know the dangers of modified mRNA
  - The modifications made to the mRNA are natural, they are found in our own cells and in lots of other organisms



# mRNA vaccines cannot cause cancer



<https://www.nature.com/articles/s41588-020-00730-w>

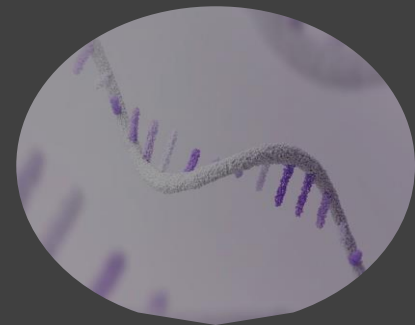
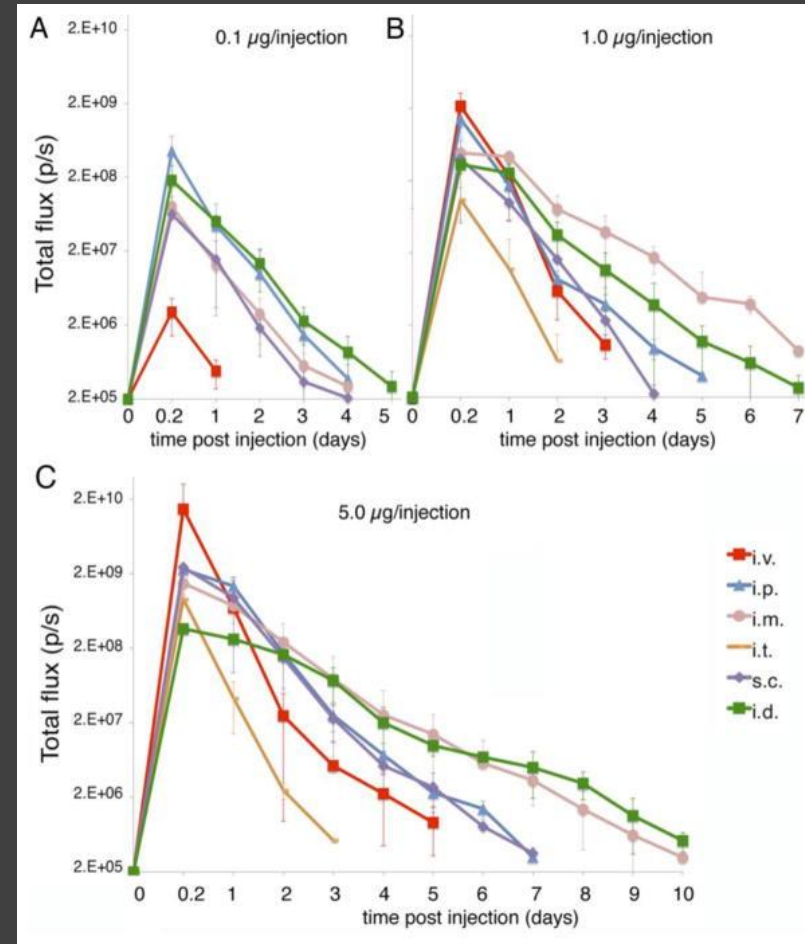


> J Control Release. 2015 Nov 10:217:345-51. doi: 10.1016/j.jconrel.2015.08.007. Epub 2015 Aug 8.


## Expression kinetics of nucleoside-modified mRNA delivered in lipid nanoparticles to mice by various routes

Norbert Pardi<sup>1</sup>, Steven Tuyishime<sup>1</sup>, Hiromi Muramatsu<sup>1</sup>, Katalin Kariko<sup>1</sup>, Barbara L Mui<sup>2</sup>, Ying K Tam<sup>2</sup>, Thomas D Madden<sup>2</sup>, Michael J Hope<sup>2</sup>, Drew Weissman<sup>3</sup>

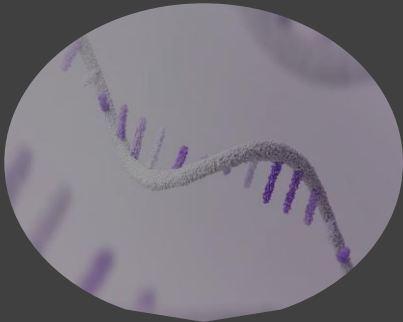
- Neither mRNA nor the protein it produces last very long
- Pharmacokinetics have been tested in animals





# Oncogenicity of DNA *in vivo*: Tumor induction with expression plasmids for activated H-*ras* and c-*myc*

Li Sheng <sup>a</sup>, Fang Cai <sup>a 1</sup>, Yong Zhu <sup>a 2</sup>, Achintya Pal <sup>a 3</sup>, Meropi Athanasiou <sup>b</sup>, Brian Orrison <sup>a</sup>, Donald G. Blair <sup>b 4</sup>, Stephen H. Hughes <sup>b</sup>, John M. Coffin <sup>b c</sup>, Andrew M. Lewis <sup>a</sup>✉, Keith Peden <sup>a</sup>  ✉

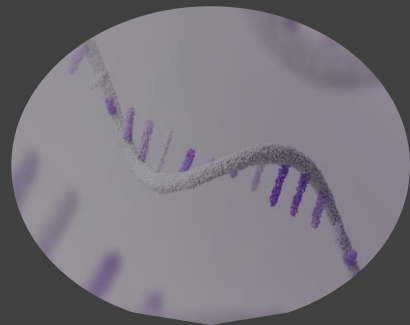
Plasmid	Rat-1				NIH 3T3			
	Number of foci				Number of foci			
	1	2	3	Mean	1	2	3	Mean
pcDNA3.1	0	0	0	0	0	0	0	0
pMSV-T24 H- <i>ras</i>	94	84	109	95.6	167	128	182	159
pMSV-c- <i>myc</i>	0	0	0	0	150 <sup>a</sup>	172 <sup>a</sup>	168 <sup>a</sup>	163.3 <sup>a</sup>
pMSV-c- <i>myc</i> +pMSV-T24-H- <i>ras</i>	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000



# Issues associated with residual cell-substrate DNA in viral vaccines

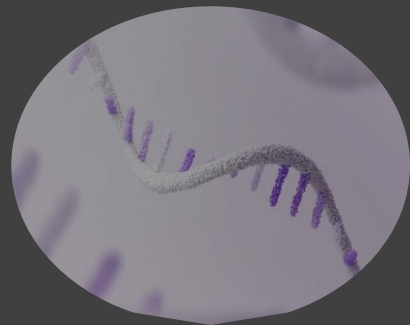
Li Sheng-Fowler, Andrew M. Lewis Jr., Keith Peden  

Clearly, therefore, integration of a retroviral proviral genome can result in oncogenic events. The issue, though, is whether the frequency of integration of exogenous DNA is high enough to be of concern. Although this is not an easy question to answer experimentally with cellular DNA due to its sequence heterogeneity and genomic complexity, data derived from studies with DNA vaccines, which have less complex genomes, suggest that integration of exogenous DNA is an extremely low frequency event [22], [23] and thus the frequency of integration at a particular site will be correspondingly lower. Estimates have been made of the probability of integration of DNA at a site that would result in the activation of a cellular oncogene at approximately  $10^{-10}$  and for two independent events, as would be required to inactivate both alleles of a tumor-suppressor gene in a single cell, at  $10^{-19}$  [24], [25].



# mRNA vaccines and cancer

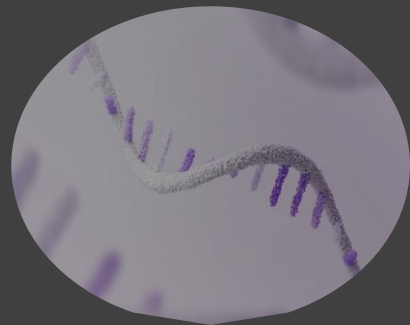
- The misconception that mRNA vaccines cause cancer is widespread in certain online communities
- mRNA cannot cause cancer
- Residual DNA cannot cause cancer when it does not contain oncogenes or present in trace quantities
- There has not been an increase in cancer rates attributable to mRNA vaccines





# Addressing myths with facts

- Misinformation will keep coming
- Lots of specific claims
- Start with the basics then get to the data
- Vaxopedia.org





<https://www.npr.org/sections/goatsandsoda/2015/01/07/375598652/a-cow-head-will-not-erupt-from-your-body-if-you-get-a-smallpox-vaccine>

