Go Corona Go

From Shambhunath ki Jadi Buti to mRNA vaccine..

The journey to ultimately check the spread of virus..
And much more..

THE NOBEL PRIZE

MEDICINE PRIZE 2023

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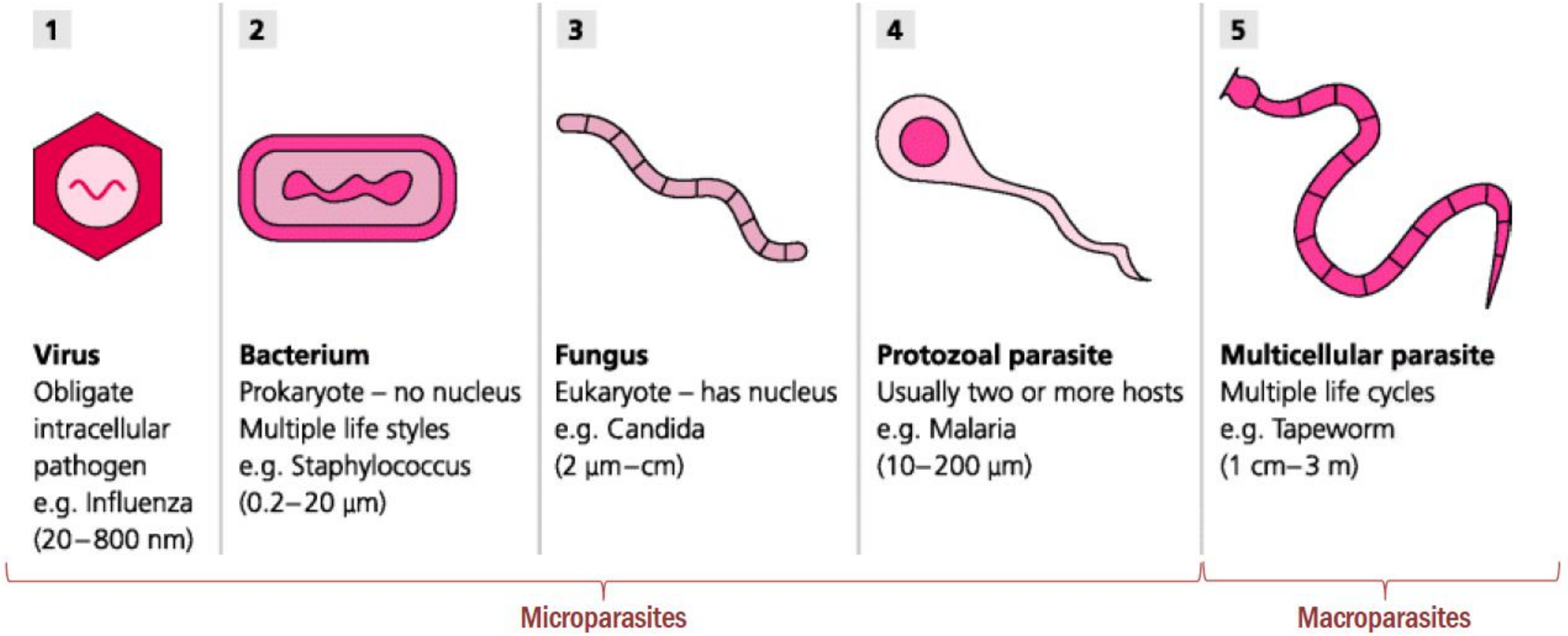
Discoveries that laid the foundation for mRNA vaccines

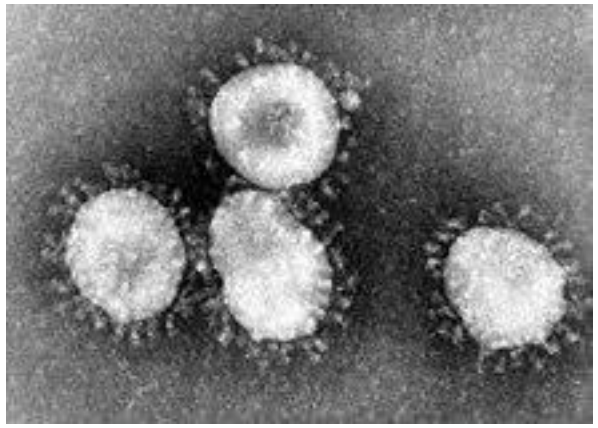
Nobel Prize lessons

Viruses

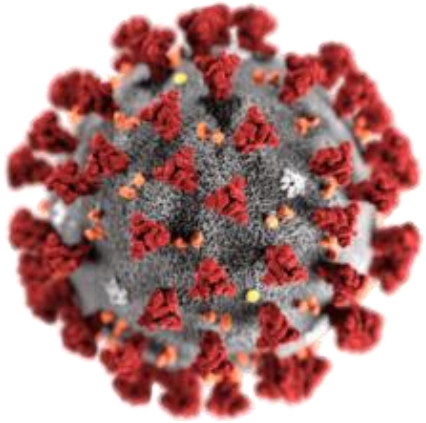
- The smallest known infectious agents
- Replicate in living cells (use the cellular machinery to synthesize new virus particles for the transfer of the viral genomes to uninfected cells)



Coronaviruses



- Coronaviruses are viruses that are causative agent of common colds



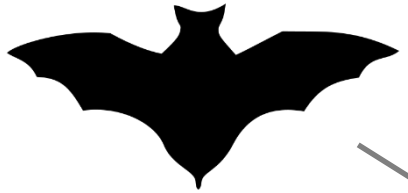
- Two previous recent outbreaks due to coronaviruses:
  - SARS (2002-03) in Asia ~8000 cases & 800 deaths,
  - MERS (2012-2019) in Saudi Arabia and 27 countries: ~2500 cases and ~800 deaths

- COVID-19 is an **emerging viral disease** due to a new strain (SARS-CoV-2)

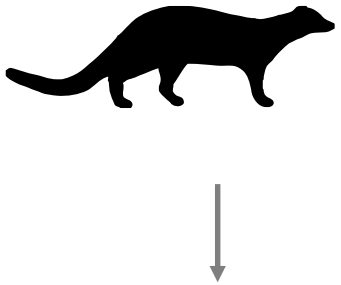
Human Coronaviruses

HCoV- 229E
HCoV- NL63
HCoV- OC43
HCoV- HKU1

URTI



Zoonoses



SARS-CoV

MERS-CoV

SARS-CoV-2

COVID19 Pandemic

- Originated in Wuhan, Hubei province
- Zoonotic origin
  - **Hypothesis**: animals in Wuhan market?
- Person to person transmission
- **By March 25th**
  - **416,686 confirmed cases**
  - **18,589 deaths**
  - **197 countries or territories**

Ways of contagion

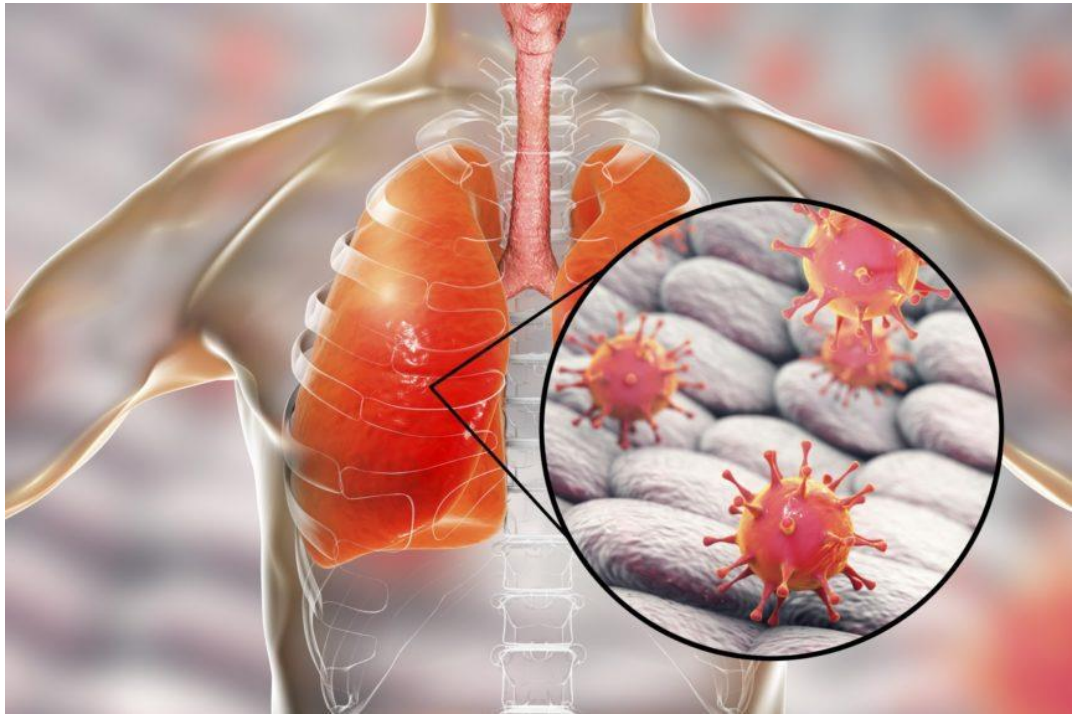
Droplets particles from the nose or mouth which are spread when a person **coughs or exhales.**

These droplets **land on objects and surfaces** around the person.

This is why it is important to stay **more than 1 meter away** from a person who is sick.

Viral respiratory infections

1. The virus enters the respiratory tract (mouth and nose)
2. The virus enters the mucous membrane and starts replicating → the respiratory tract swells and is inflamed
3. The virus enters the lungs and surrounding cells → more symptoms begin to show



How to cure this?

Management of MILD and MODERATE COVID-19

- **Antibiotics should NOT be prescribed unless there is explicit clinical suspicion of a bacterial infection** (in addition to COVID-19). Few patients with COVID-19 experience a secondary bacterial infection.

- Treat symptoms

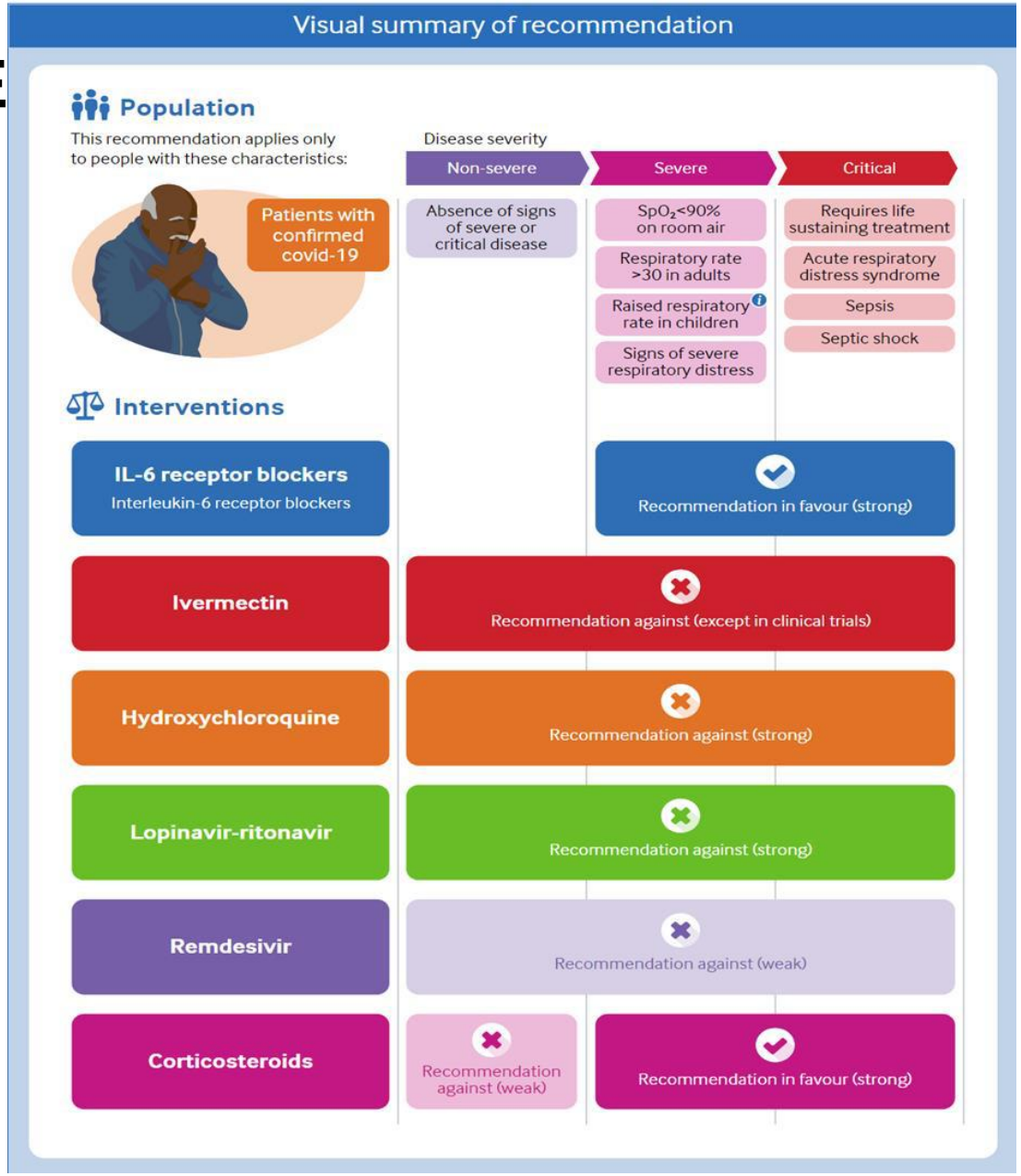
- Give **antipyretics** (paracetamol) for fever
- Ensure adequate **nutrition**
- Ensure adequate **hydration**

- Encourage the patient to take rest when needed but to try to resume activities at appropriate pace.

- Support of patient's psychosocial needs

No specific medication has been approved and recommended against mild and moderate COVID-19

(https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.1)



https://www.bmj.com/content/370/bmj.m3379

Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30423-7/fulltext

Empiric antibacterial therapy and community-onset bacterial coinfection in patients hospitalized with coronavirus disease 2019 (COVID-19): a multi-hospital cohort study. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1239/5895253

WHO does not recommend use of Hydroxychloroquine, Lopinavir / Ritonavir or Remdesivir for treatment of COVID-19

NOT RECOMMENDED FOR ANY LEVEL OF SEVERITY OF DISEASE

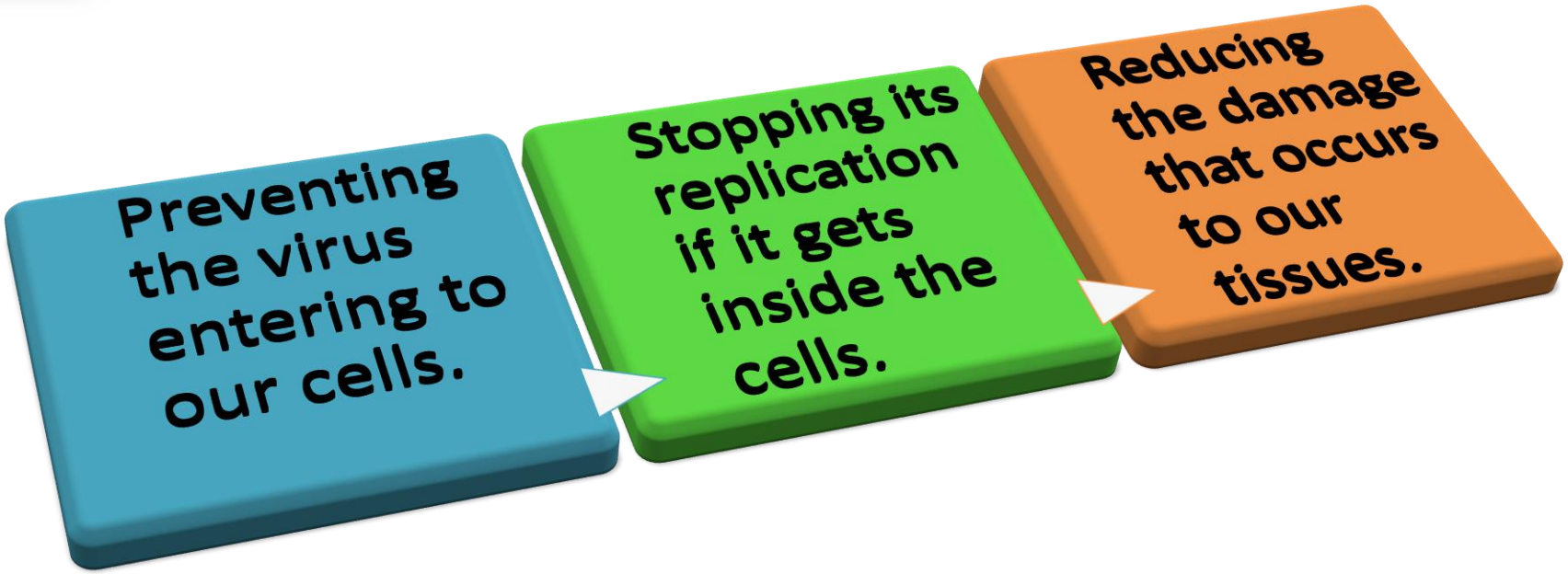
WHO **does not recommend administering Hydroxychloroquine, Lopinavir / Ritonavir or Remdesivir** for treatment of COVID-19 for patients of any disease severity

NOT RECOMMENDED FOR PREVENTION

WHO **does not recommend administering Hydroxychloroquine prophylaxis** to individuals who do not have COVID-19

https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.1
https://www.who.int/publications/i/item/WHO-2019-nCoV-prophylaxes-2021-1

COVID 19 – MANAGEMENT PRINCIPLES



Ayurveda Prophylactic measures

Symptomatic Ayurveda management

Restoration through Rasayana

PROPHYLATIC MEASURES

Ayurvedic Immunity Promoting Measures

1. Take Chyavanprash 10gm (1tsf) in the morning. Diabetics should take sugar free Chyavanprash.
2. Drink herbal tea / decoction (Kadha) made from Tulsi (Basil), Dalchini (Cinnamon), Kalimirch (Black pepper), Shunthi (Dry Ginger) and Munakka (Raisin) - once or twice a day. Add jaggery (natural sugar) and / or fresh lemon juice to your taste, if needed.
3. Golden Milk- Half tea spoon Haldi (turmeric) powder in 150 ml hot milk - once or twice a day.

General Measures

- Drink warm water throughout the day.
- Daily practice of Yogasana, Pranayama and meditation for at least 30 minutes as advised by Ministry of AYUSH
- Spices like Haldi (Turmeric), Jeera (Cumin), Dhaniya (Coriander) and Lahsun (Garlic) are recommended in cooking.

Vaccines


MODERNA 94.5%
PFIZER 95%
IFEBUOY SANITIZER 99.9%
GB
KHOPDI TOD SAALE KA

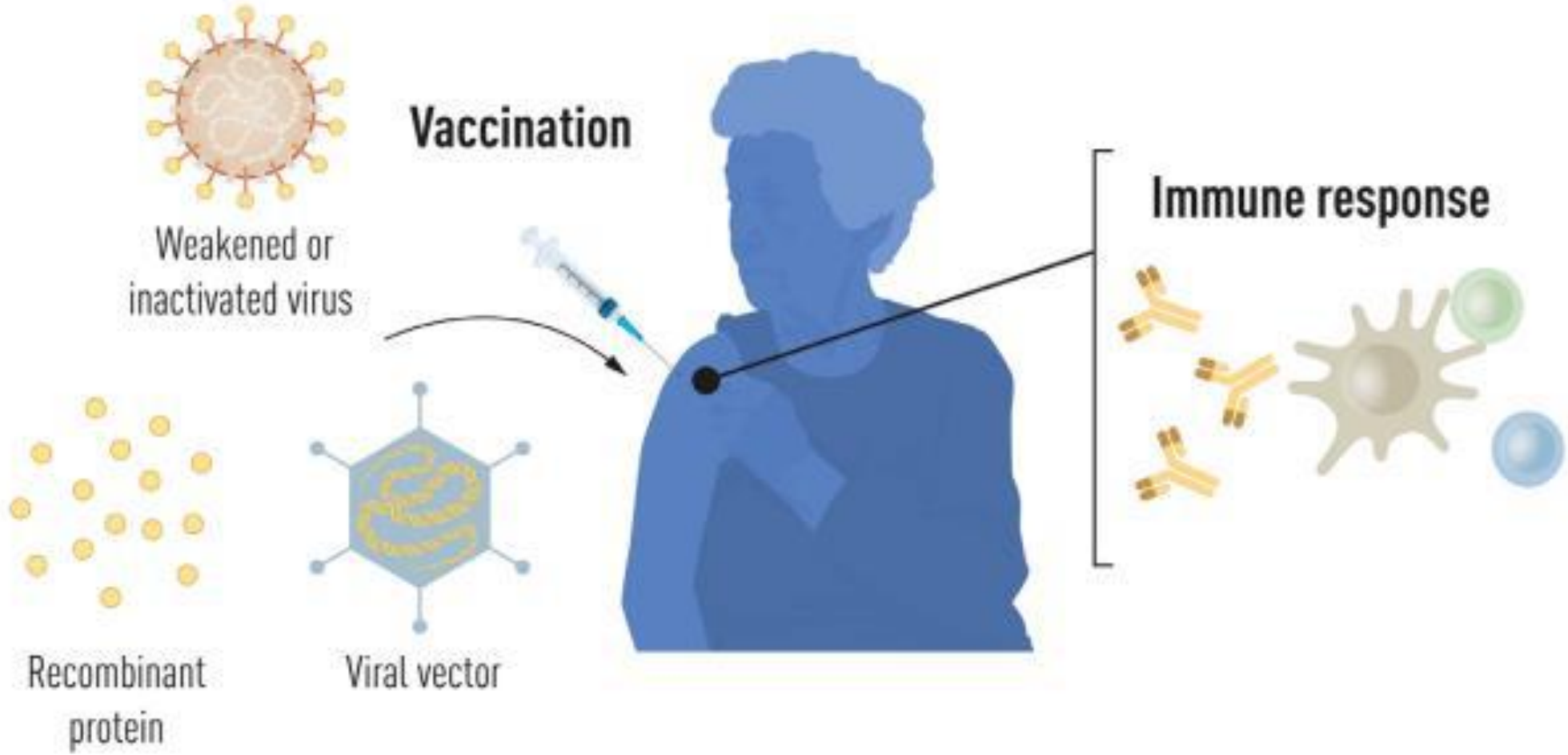
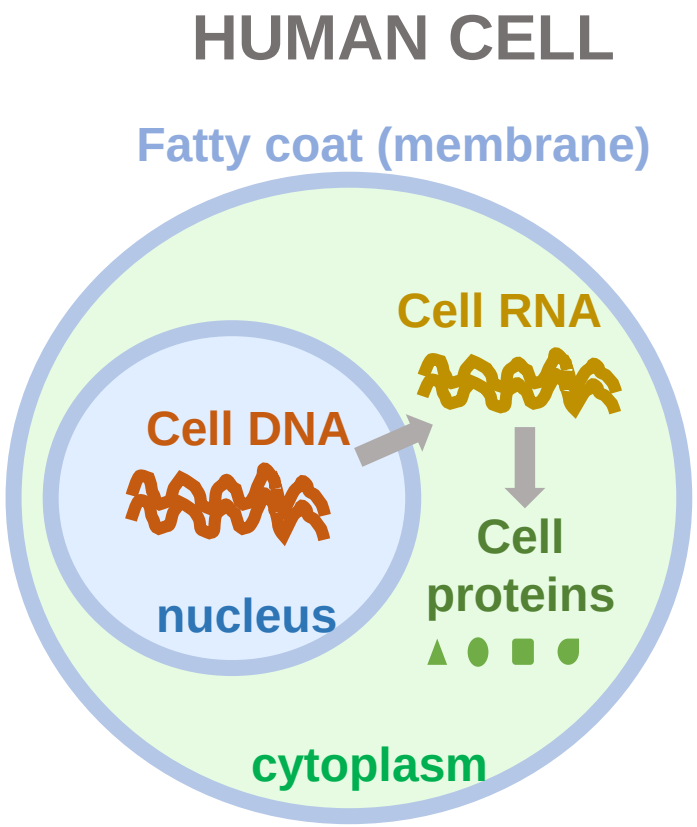
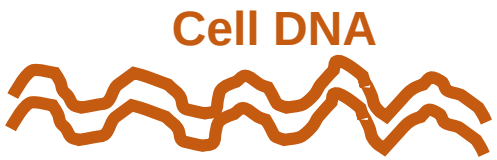


***Fig. 1** Methods for vaccine production before the COVID-19 pandemic.*

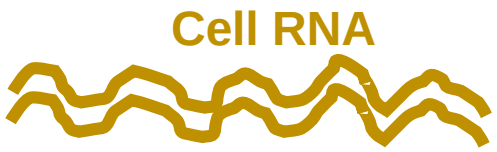
What do nucleic acids (DNA and RNA) do?





- **DNA** is found in the **cell nucleus**
- **DNA** is the code for making **RNA**
- **DNA** in the **nucleus** is stable

codes for



- **RNA** is found in the **cell cytoplasm**
- **RNA** is the code for making **proteins**
- **RNA** is unstable and falls apart in hour

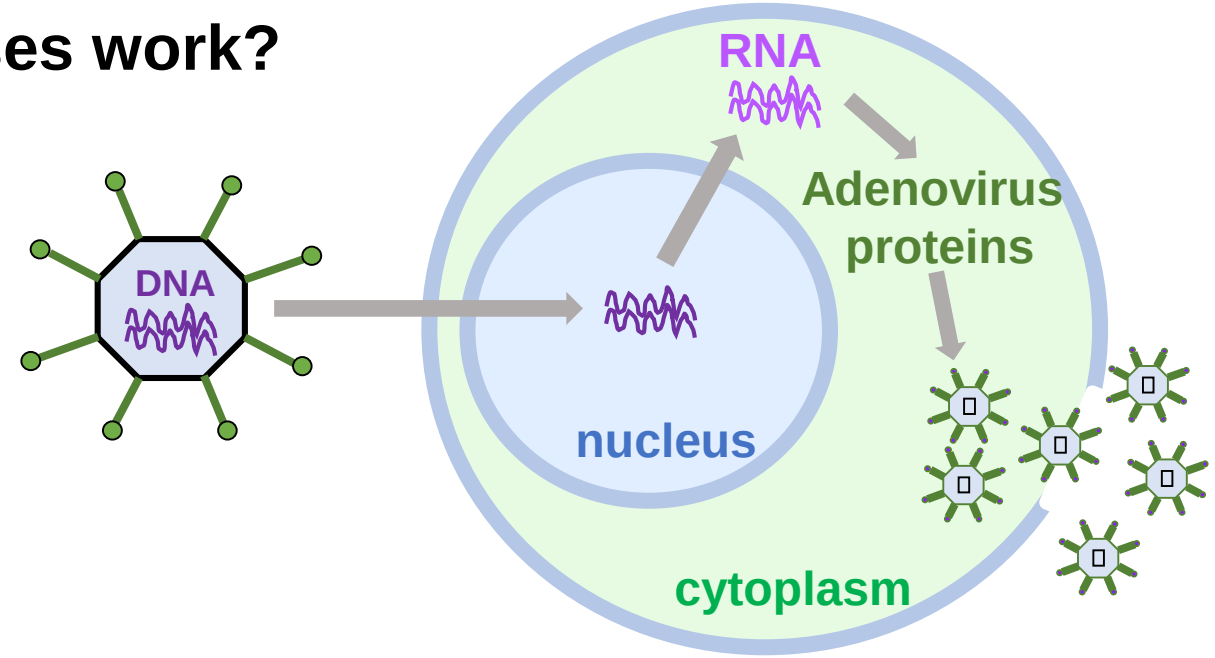
codes for

- **Proteins** are found in the **cell cytoplasr**
- **Proteins** build cell machinery

How do viruses work?

1. DNA virus
(eg. adenovirus)

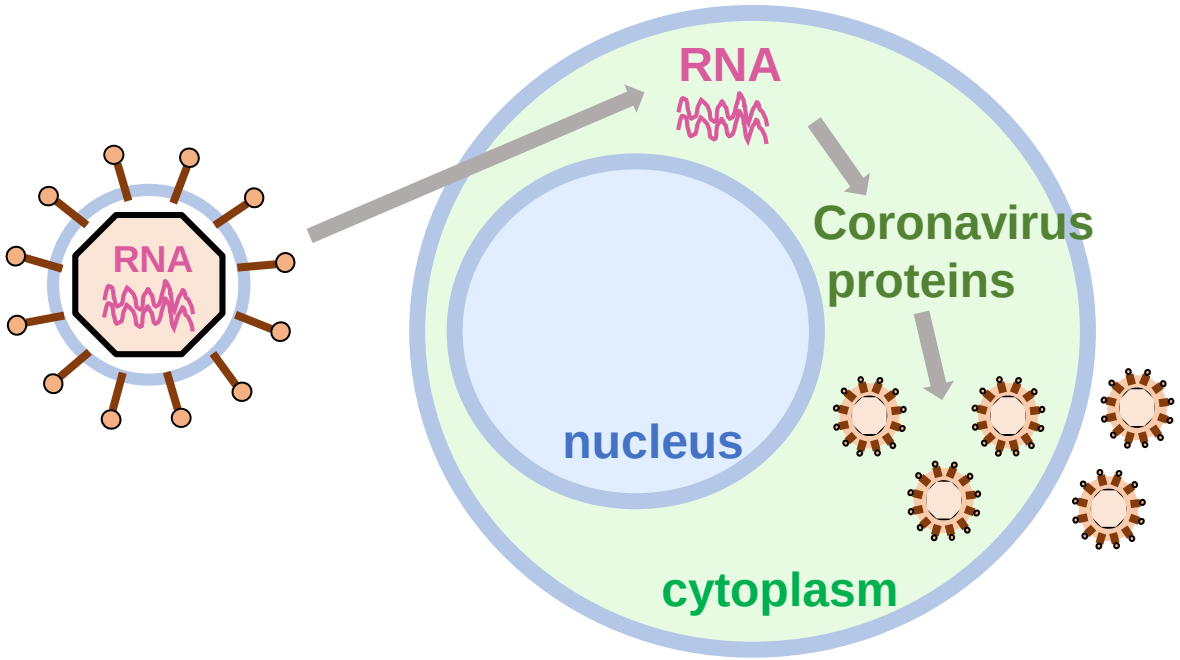
- Protein shell
- Spike protein
- DNA code



1. Virus enters cell
2. Viral DNA enters nucleus
3. Viral DNA makes viral RNA
4. Viral RNA makes proteins
5. Proteins make new viruses
6. Cell bursts releasing viruses
7. Viruses infect new cells
8. Infection eliminated by immune response

2. RNA virus
(eg. coronavirus)

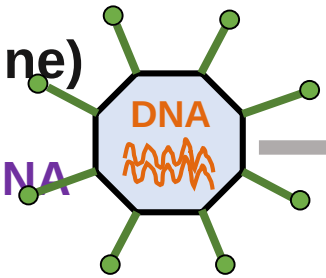
- Fatty coat stolen from infected cell
- Protein shell
- Spike protein
- RNA code

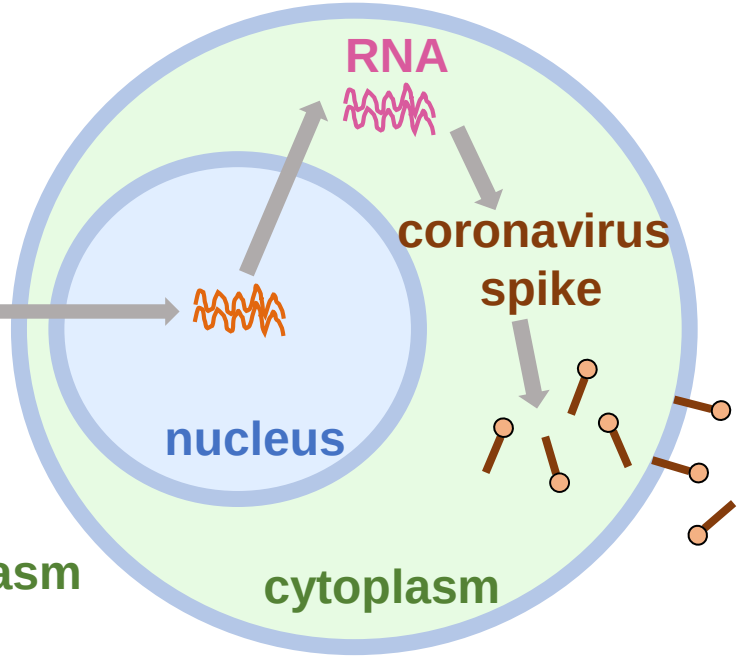


1. Virus enters cell
2. Viral RNA enters cytoplasm
3. Viral RNA makes viral proteir
4. Proteins assemble into virus
5. Cell releases viruses
6. Viruses infect new cells
7. Infection eliminated by immune response

What kind of coronavirus vaccines have we made?

1. Oxford/AstraZeneca vaccine (adenovirus vaccine)



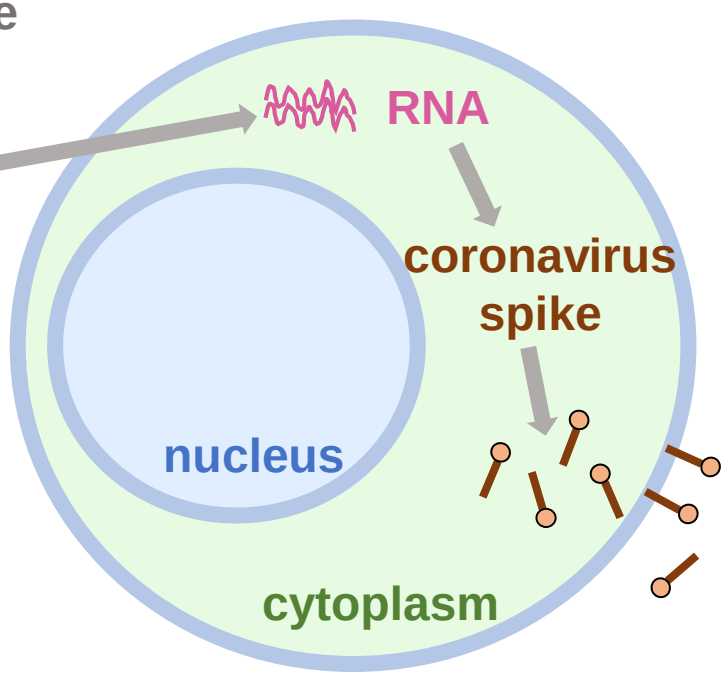


- Has **adenovirus protein shell** empty of **natural virus DNA**
- **Synthetic DNA** coding for **coronavirus spike protein**

is inserted into otherwise empty **adenovirus shell**

- **Virus shell** carries **coronavirus spike DNA** into **cell nucleus**
- **Coronavirus spike DNA** makes **spike RNA** and **spike protein** in **cytoplasm**
- **Spike protein** is released to activate immune system
- Neither **virus shell** nor **coronavirus spike DNA** persist or cause disease

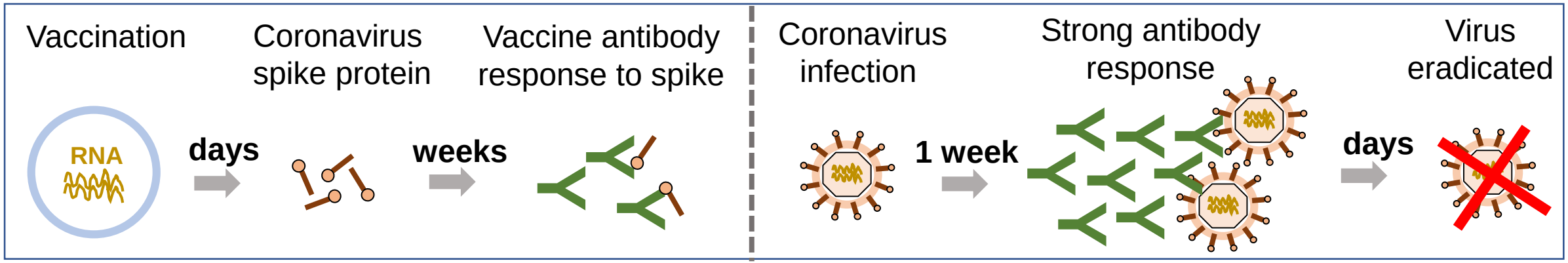
2. BioNTech Pfizer/Moderna vaccines (RNA vaccines)



- Has synthetic **fatty coat** similar to **cell membrane**
- Contains **synthetic RNA** coding for **coronavirus spike proteins**
- **Coronavirus spike RNA** enters **cell cytoplasm**
- **Coronavirus spike RNA** makes **coronavirus spike protein**
- **Spike protein** is released to activate immune system
- Neither **fatty coat** nor **spike RNA** persist or cause disease

How do COVID19 vaccines stimulate an immune response?

- Vaccine makes coronavirus spike protein in cells, which is presented to immune system
- Immune cells detect spike protein and make antibodies specific for spike protein
- During infection, antibodies bind spike protein on real virus and protect against infection and/o
- Antibodies speed up elimination of the coronavirus from the body



Phases of clinical trials

Phase 1
20-100 Healthy Volunteers

Researchers try to answer these questions:

- Is this vaccine safe?
- Are there any serious side effects?
- How does the vaccine dose relate to any side effects?
- Is the vaccine causing an immune response?

Phase 2
Several Hundred Volunteers

Researchers try to answer these questions:

- What are the most common short-term side effects?
- What's the body's immune response?
- Are there signs that the vaccine is protective?

Phase 3
1000+ Volunteers

Researchers try to answer these questions:

- How do disease rates compare between people who get the vaccine and those who do not?
- How well can the vaccine protect people from disease?

Phase 4
Vaccine is Approved

Researchers try to answer these questions:

- FDA approves a vaccine only if it's safe, effective, and benefits outweigh the risks.
- Researchers continue to collect data on the vaccine's long-term benefits and side effects.

Source: https://covid19community.nih.gov/resources/understanding-clinical-trials

COVID-19 vaccines that have received FDA Emergency Use Authorizations

- Two vaccines have received FDA Emergency Use Authorizations (EUAs):
  - **Pfizer/BioNTech (BNT162b2)** – 95% effective (manufacturer data)
  - **Moderna (mRNA-1273)** – 94.5% effective (manufacturer data)
- Both are mRNA vaccines with a 2-dose schedule. People being vaccinated should complete the two-dose series with the same vaccine product.
- Duration of protection is not yet known.

Sources: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-conclude-phase-3-study-covid-19-vaccine
https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy

The Nobel Prize in Physiology or Medicine

“the person who shall have made the most important discovery within the domain of physiology or medicine”

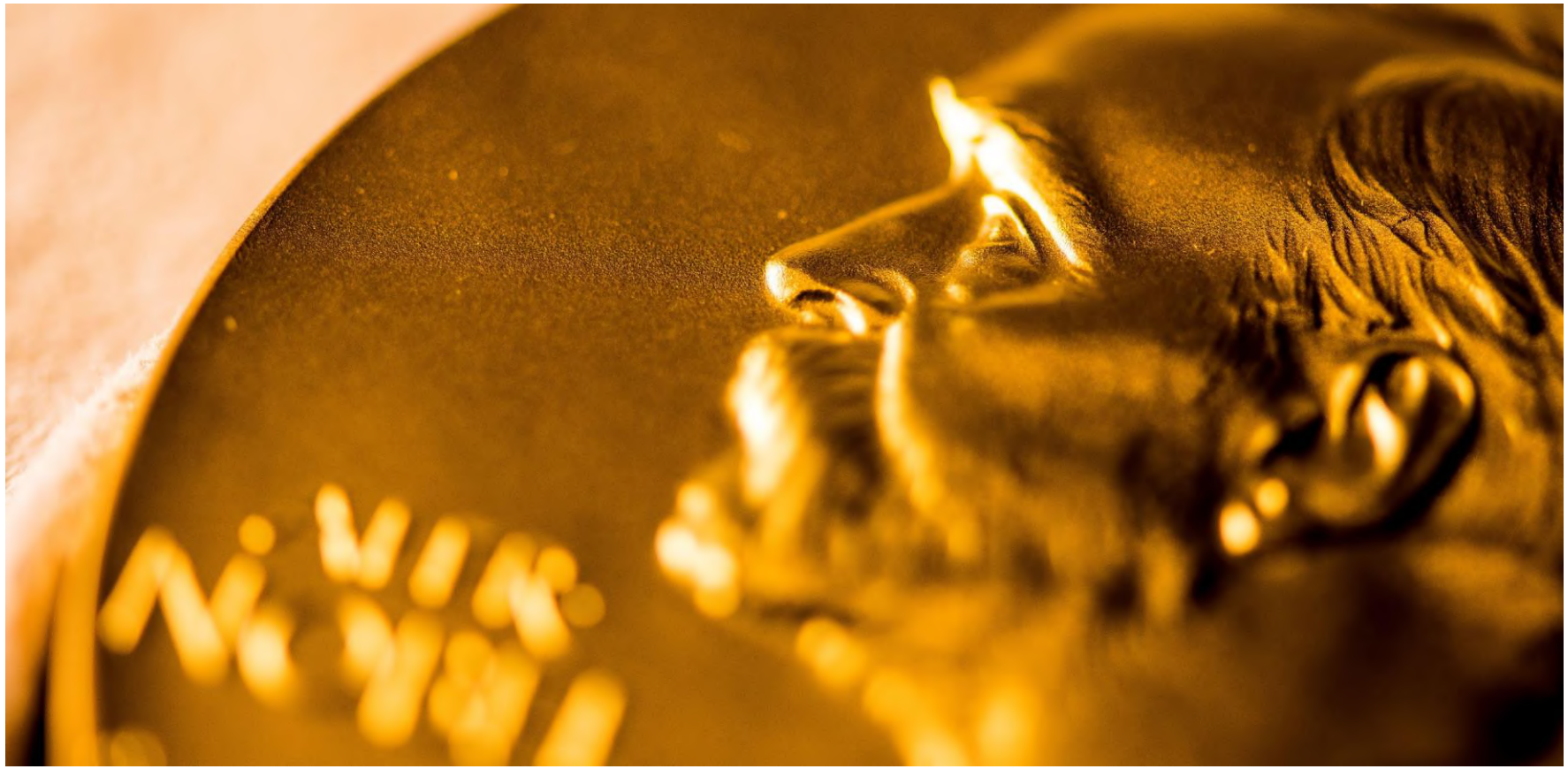


PHOTO: ALEXANDER MAHMOUD

The Nobel Assembly at Karolinska Institutet has today awarded

the 2023 Nobel Prize in Physiology or Medicine

jointly to

Katalin Karikó and Drew Weissman

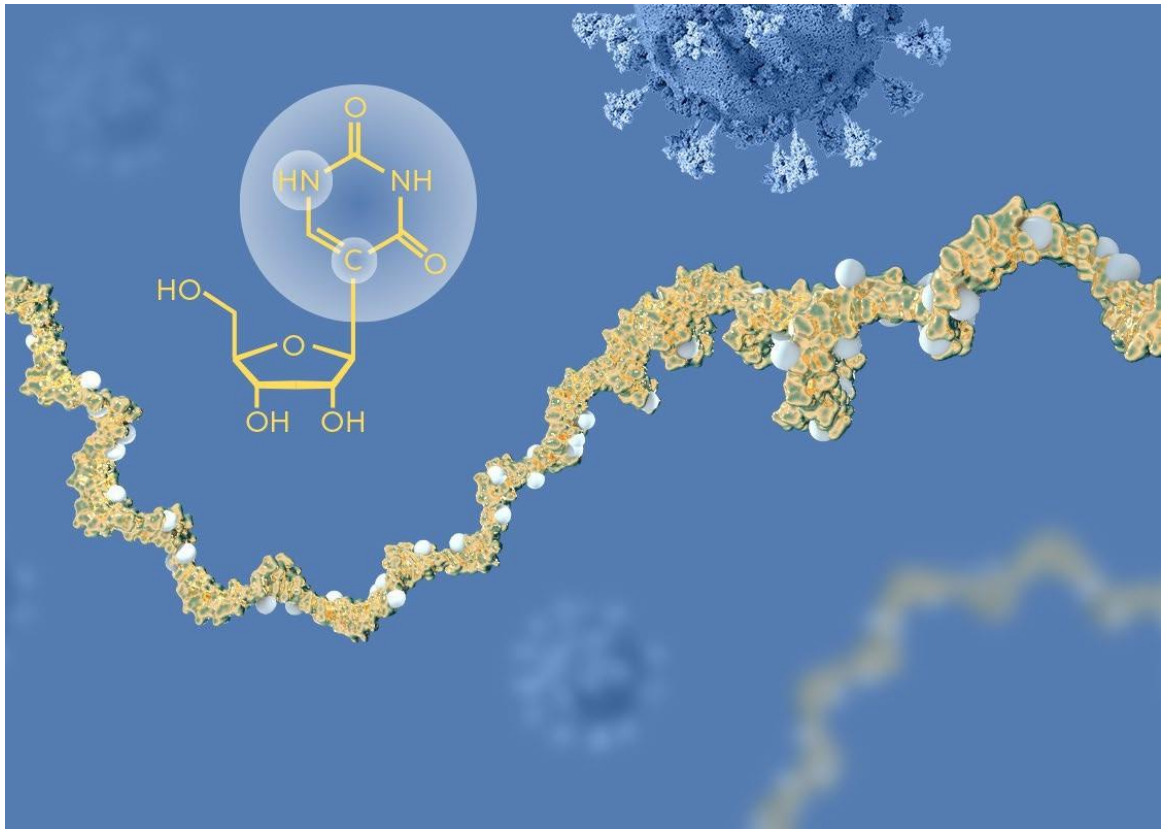
for their discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19

How did it all start? 2005 a small encounter at an xerox machine

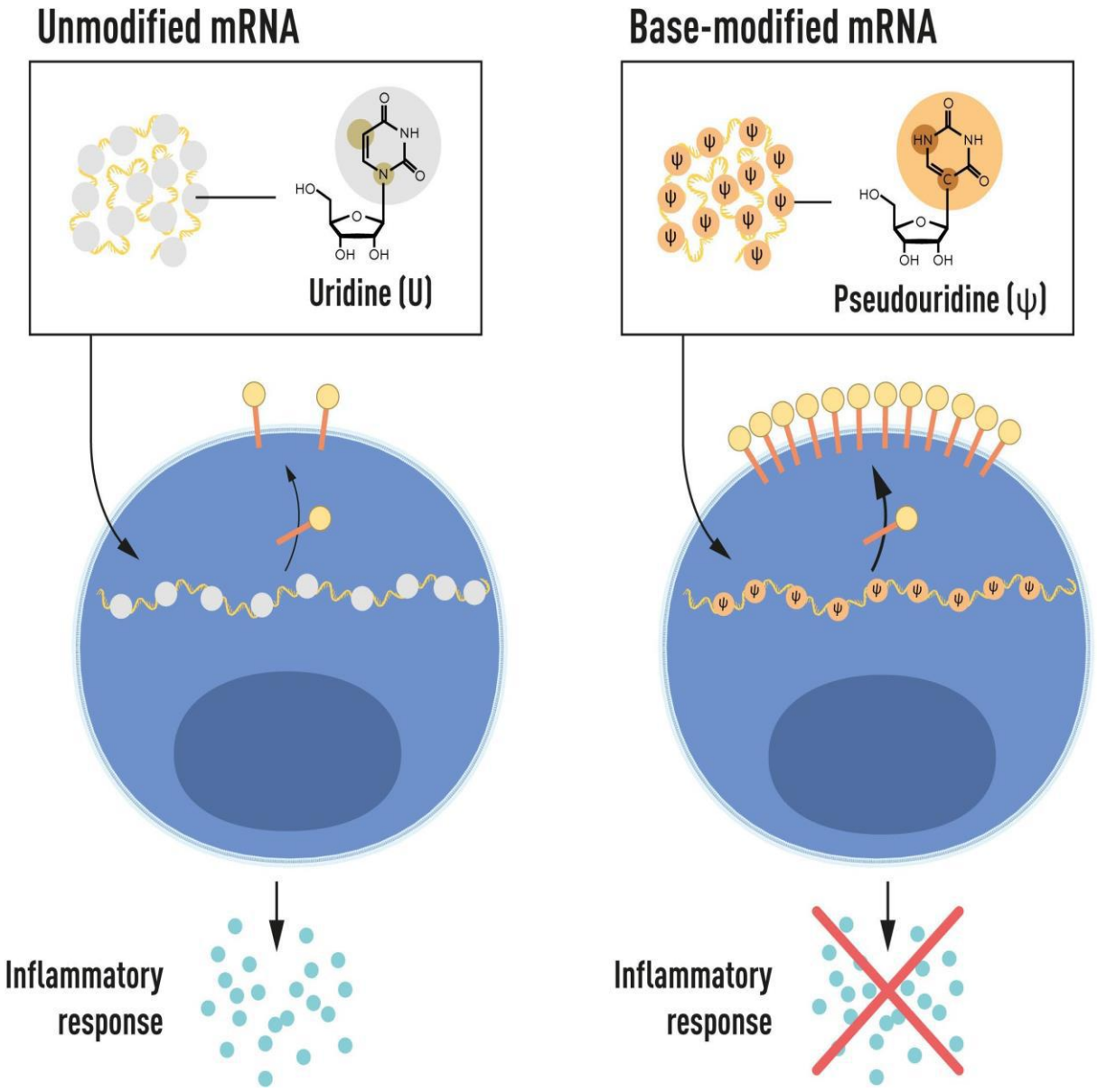
Equivalent to Coffee hours every Tuesday at IITGN ;-)

The 2023 medicine prize

- The 2023 medicine prize honours discoveries that played a decisive role in the fight against the coronavirus pandemic. The laureates' research made it possible for effective vaccines to be developed against COVID-19, an airborne viral infection.



The breakthrough



By modifying mRNA, the inflammatory response is reduced and protein production increased.

Immunity, Vol. 23, 165–175, August, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.immuni.2005.06.008

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

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Summary

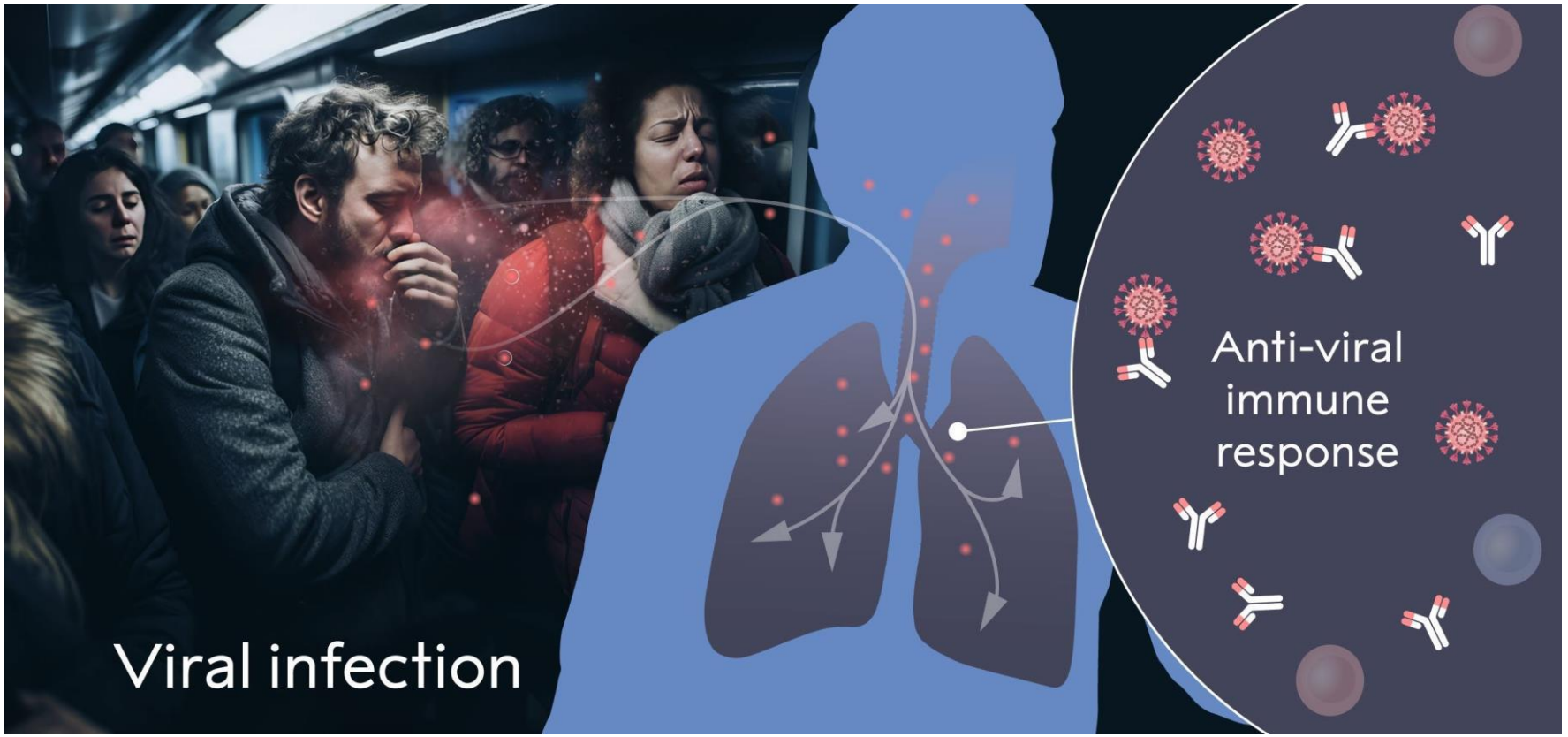
DNA and RNA stimulate the mammalian innate immune system through activation of Toll-like receptors (TLRs). DNA containing methylated CpG motifs, however, is not stimulatory. Selected nucleosides in naturally occurring RNA are also methylated or otherwise modified, but the immunomodulatory effects of these alterations remain untested. We show that RNA signals through human TLR3, TLR7, and TLR8, but incorporation of modified nucleosides m5C, m6A, m5U, s2U, or pseudouridine ablates activity. Dendritic cells (DCs) exposed to such modified RNA express significantly less cytokines and activation markers than those treated with unmodified RNA. DCs and TLR-expressing cells are potently activated by bacterial and mitochondrial RNA, but not by mammalian total RNA, which is abundant in modified nucleosides. We conclude that nucleoside modifications suppress the potential of RNA to activate DCs. The innate immune system may therefore detect RNA lacking nucleoside modification as a means of selectively responding to bacteria or necrotic tissue.

thetic antiviral compound R-848 (Jurk et al., 2002), but a natural ligand has not been identified.

It has been known for decades that selected DNA and RNA molecules have the unique property to activate the immune system. It was discovered only recently that secretion of interferon in response to DNA is mediated by unmethylated CpG motifs acting upon TLR9 present on immune cells (Hemmi et al., 2000). For years, bacterial and mammalian DNA were portrayed as having the same chemical structure, which hampered the understanding of why only bacterial, but not mammalian, DNA is immunogenic. Recently, however, the sequence and structural microheterogeneity of DNA has come to be appreciated. For example, methylated cytidine in CpG motifs of DNA has proven to be the structural basis of recognition for the innate immune system. In light of this finding and given that multiple TLRs respond to RNA, a question emerges as to whether the immunogenicity of RNA is under the control of similar types of modification. This possibility is not unreasonable given that RNA undergoes nearly one hundred different nucleoside modifications (Rozenski et al., 1999). Importantly, the extent and quality of RNA modifications depend on the RNA subtype and correlate directly with the evolutionary level of the organism from which the RNA is isolated. Ribosomal RNA, the major constituent (~80%) of cellular RNA, contains significantly more nucleoside modifications when obtained from mammalian cells versus bacteria. Human rRNA, for example, has ten times more pseudouridine (Ψ) and 25 times more 2′-O-methylated nucleosides

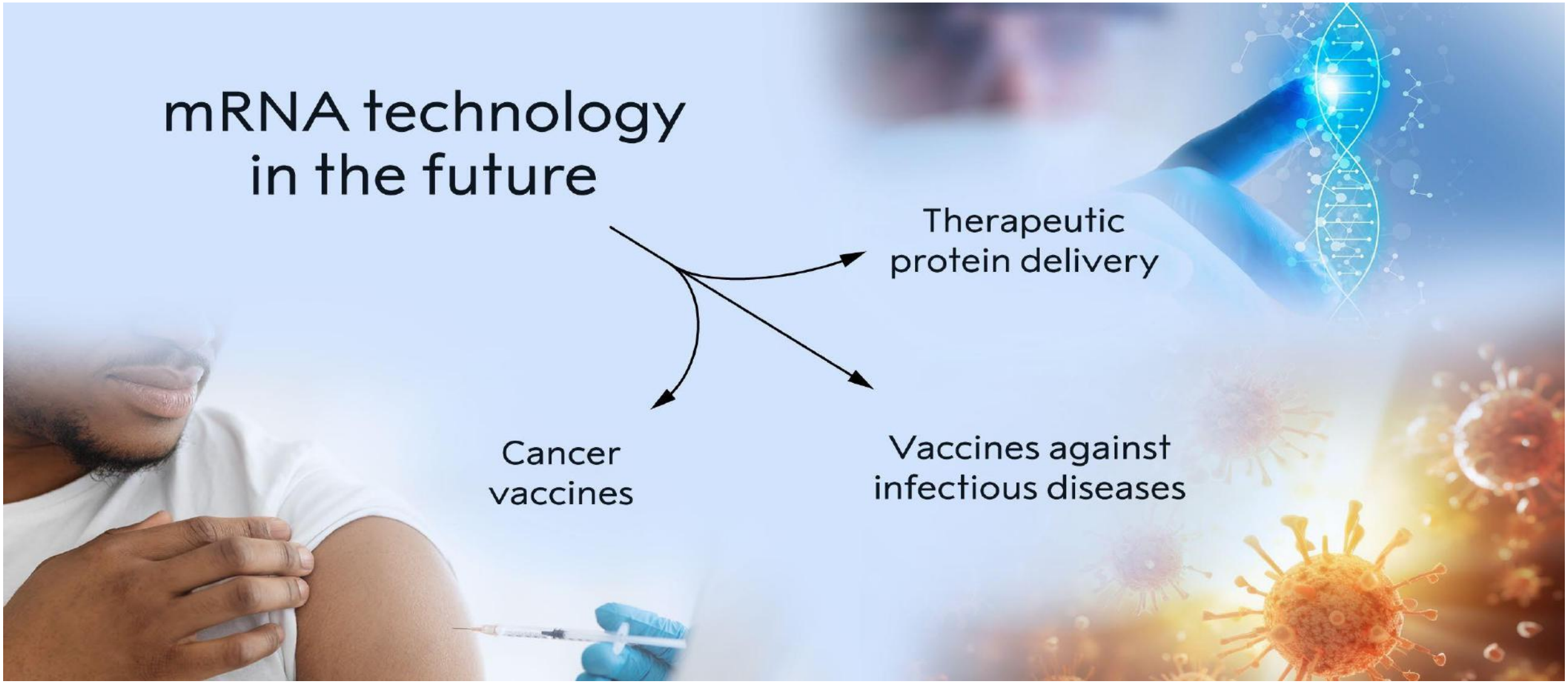
Outbreak of the coronavirus pandemic.

mRNA technology is deployed when the coronavirus pandemic breaks out in early 2020.



For the greatest benefit to humankind

These vaccines have saved millions of people's lives.



COURTESY OF PENN MEDICINE, PHOTO: PEGGY PETERSON

“As important as the vaccine is, if you don’t take it, it doesn’t work!”

Drew Weissman, 2023 medicine laureate