Week 7

SARS-CoV-2

Ed Roy, Marie Roy, Sue Ingels, Mary Kuetemeyer

Dogs presenting

Class

- Hound dogs present rabbit they retrieve
- https://www.youtube.com/watch?v=oMN-1nSQv3U

Antiviral Innate Responses

Natural killer cells (NK cells)

- Invariant receptors activate or inhibit killing by NK cells
- Cellular distress responses activate NK cells
- MHC Class I inhibits NK cell killing
- MHC Class I presents peptides that CD8 cytotoxic T cells bind to, prompting killing
- viruses downregulate MHC Class I, to protect from CD8 T cell killing
- interferonα upregulates MHC Class I, enhancing CD8 T cell ability to kill virally infected cell; another example of Innate/Adaptive interaction

Innate Responses against viruses

Interferons α, β

- viral activation of TLRs prompts interferon secretion
- most cell types have interferon responses (dendritic cells especially strong response)
- secreted interferon binds to interferon receptors on the same cell and neighboring cells (autocrine and paracrine)
- Interferon Stimulated Genes (ISGs), hundreds of them
- most impair virus replication, some decrease all protein synthesis
- viruses in turn inhibit TLR signalling to minimize interferon secretion

Finally, some good news about getting older

- Allergies are NOT worse in the elderly

Summary of immunosenescence features

Cell type	Changes with aging
Neutrophils	Reduced phagocytosis
	Reduced reactive oxygen species production
	Defect in apoptotic cell death
Eosinophils	Reduced degranulation
	Reduced superoxide production
Mast cells	Reduced degranulation
	Dysregulations in function
Monocytes/macrophages	Reduced phagocytosis
	Reduced cytokine and chemokine secretion
	Reduced generation of nitric oxide and superoxide
Dendritic cells	Reduced phagocytosis and pinocytosis
	Increased IL-6 and TNF-alfa production
	Diminished TLR expression and function
	Dysregulations in function

Clin Transl Allergy. 2011; 1: 11.
Published online 2011 Oct 17. doi: 10.1186/2045-7022-1-11
PMCID: PMC3339328
PMID: 22409889

Allergic diseases in the elderly

Victoria Cardona,[1,2] Mar Guilarte,[1,2] Olga Luengo,[1,2] Moises Labrador-Horrillo,[1,2] Anna Sala-Cunill,[1,2] and Teresa Garriga[1]

T cells	Reduced response and proliferation
	Reduced CD28 expression
	Reduced TCR diversity
	Reduced signal transduction
	Dysregulations in function
B cells	Production of low-affinity antibodies
	Increased oligoclonal expansion
	Decline in serum total IgE values
	Reduced surface MHC class II molecule expression
	Dysregulations in function
Epitelial cells	Impaired production of cytokines
	Decreased clearance of particles
NK cells and NKT cells	Reduced numbers or increased in several tissues
	Reduced cytotoxicity and proliferation

Adapted from [4-7]

Clin Transl Allergy. 2011; 1: 11.
Published online 2011 Oct 17. doi: 10.1186/2045-7022-1-11
PMCID: PMC3339328
PMID: 22409889

Allergic diseases in the elderly

Victoria Cardona,[1,2] Mar Guilarte,[1,2] Olga Luengo,[1,2] Moises Labrador-Horrillo,[1,2] Anna Sala-Cunill,[1,2] and Teresa Garriga[1]

may develop symptoms of food allergy during adulthood for the first time. In the Allergy Section at Hospital Vall d'Hebron, we have observed a prevalence of 5% of FA in our outpatients older than 65 years, compared to 26% in patients aged 40 to 65 and 69% in younger patients (16-39 years old) (data not published). The profile of sensitization to

Allergic diseases in the elderly

Victoria Cardona,[1,2] Mar Guilarte,[1,2] Olga Luengo,[1,2] Moises Labrador-Horrillo,[1,2] Anna Sala-Cunill,[1,2] and Teresa Garriga[1]

Author information ▸ Article notes ▸ Copyright and License information Disclaimer

[1]Allergy Section, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Barcelona, Spain

Learning Objectives for Week 7

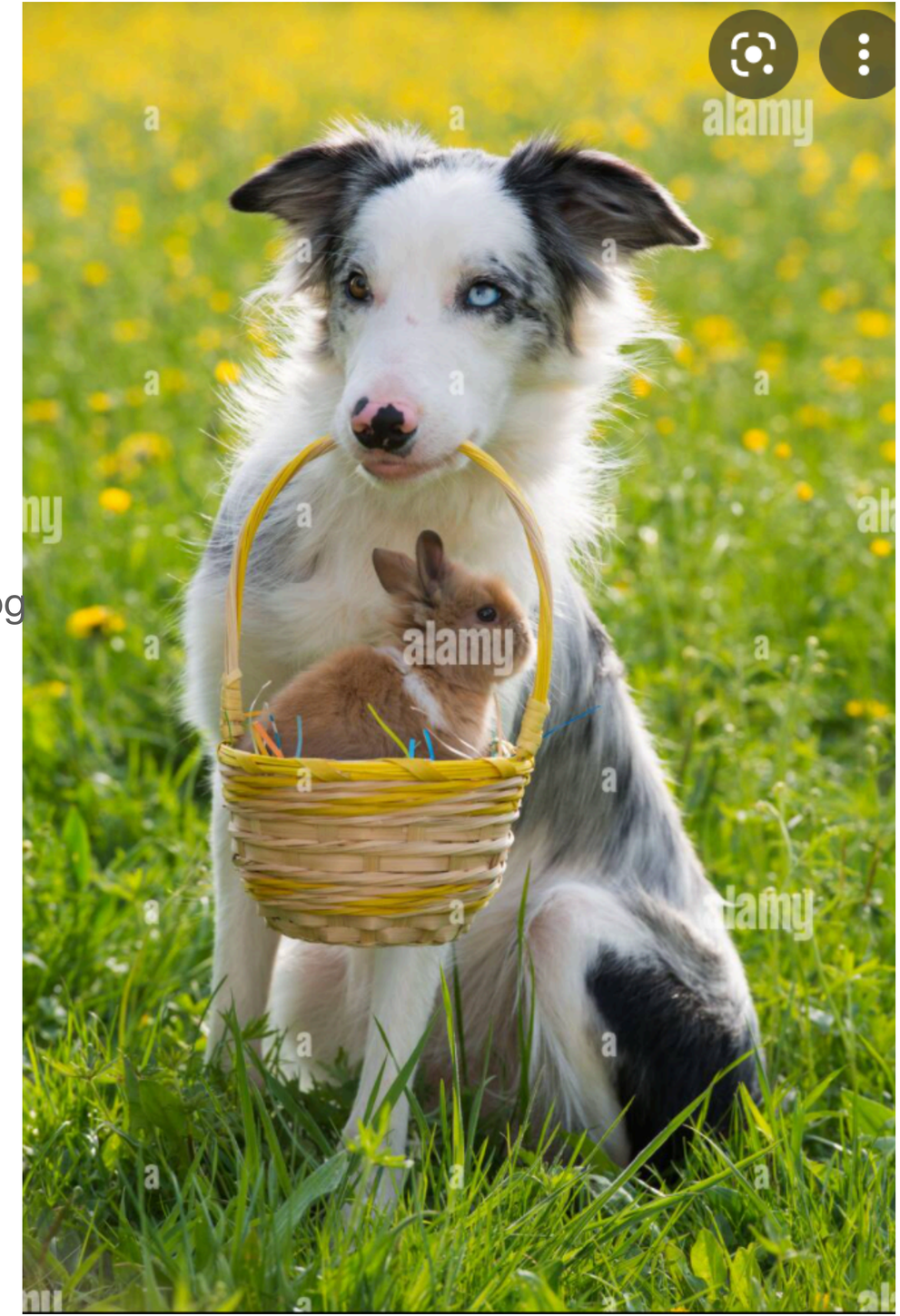
- Antiviral Innate Responses (interferon and NK cells)
- Types of Vaccines against SARS-CoV-2

https://www.youtube.com/watch?v=mvA9gs5gxNY

  - stable form of spike protein: https://www.youtube.com/watch?v=-92HQA0GcI8

- Treatment strategies for COVID-19

There are Different Ways to Present Rabbit Antigens,
some with more class than others, border collie vs hound dog



Different types of COVID-19 vaccines: How they work

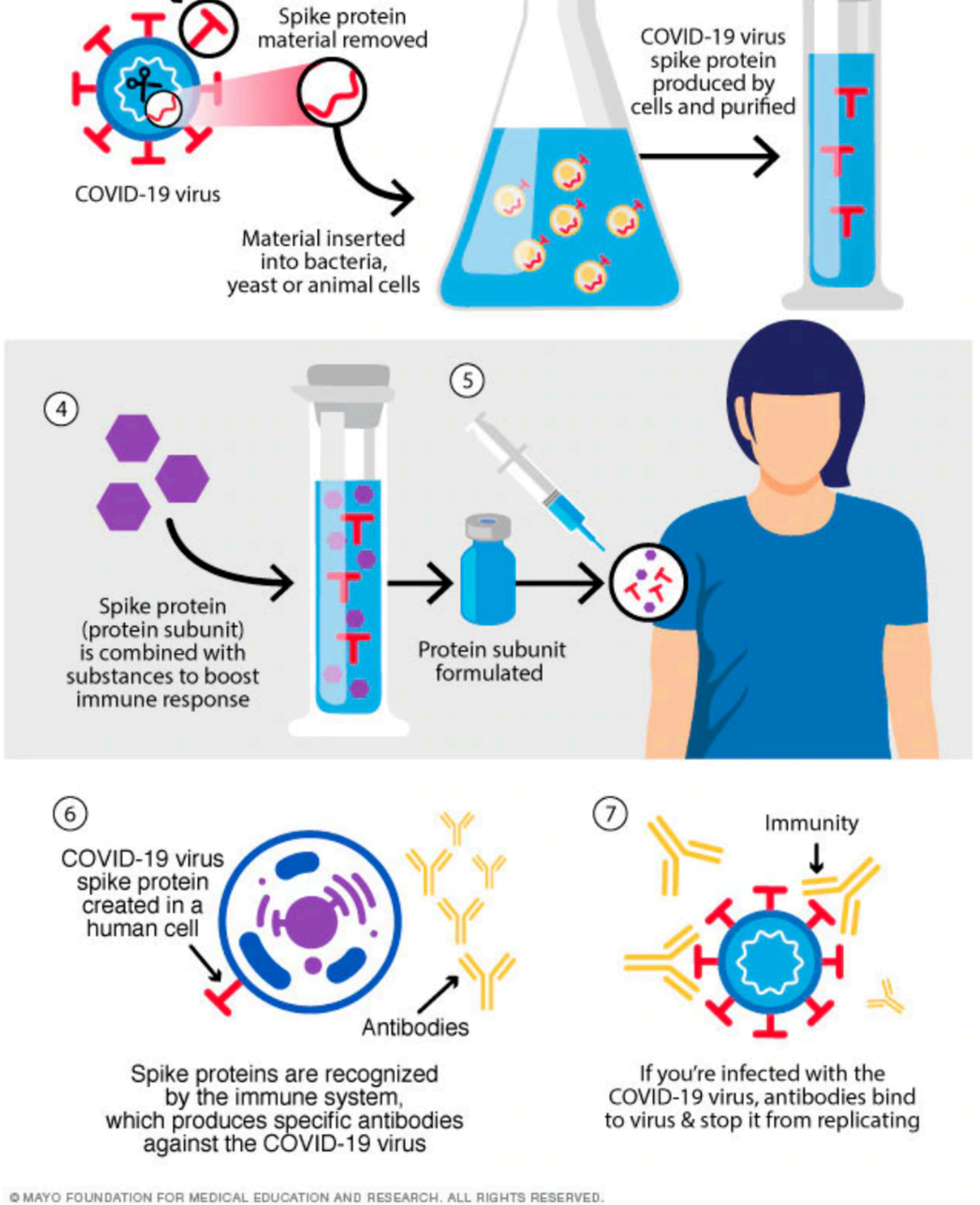
Curious about how mRNA vaccines and other types of COVID-19 vaccines can help you develop immunity to the COVID-19 virus? Understand how different technologies work with the immune system to provide protection.

By Mayo Clinic Staff

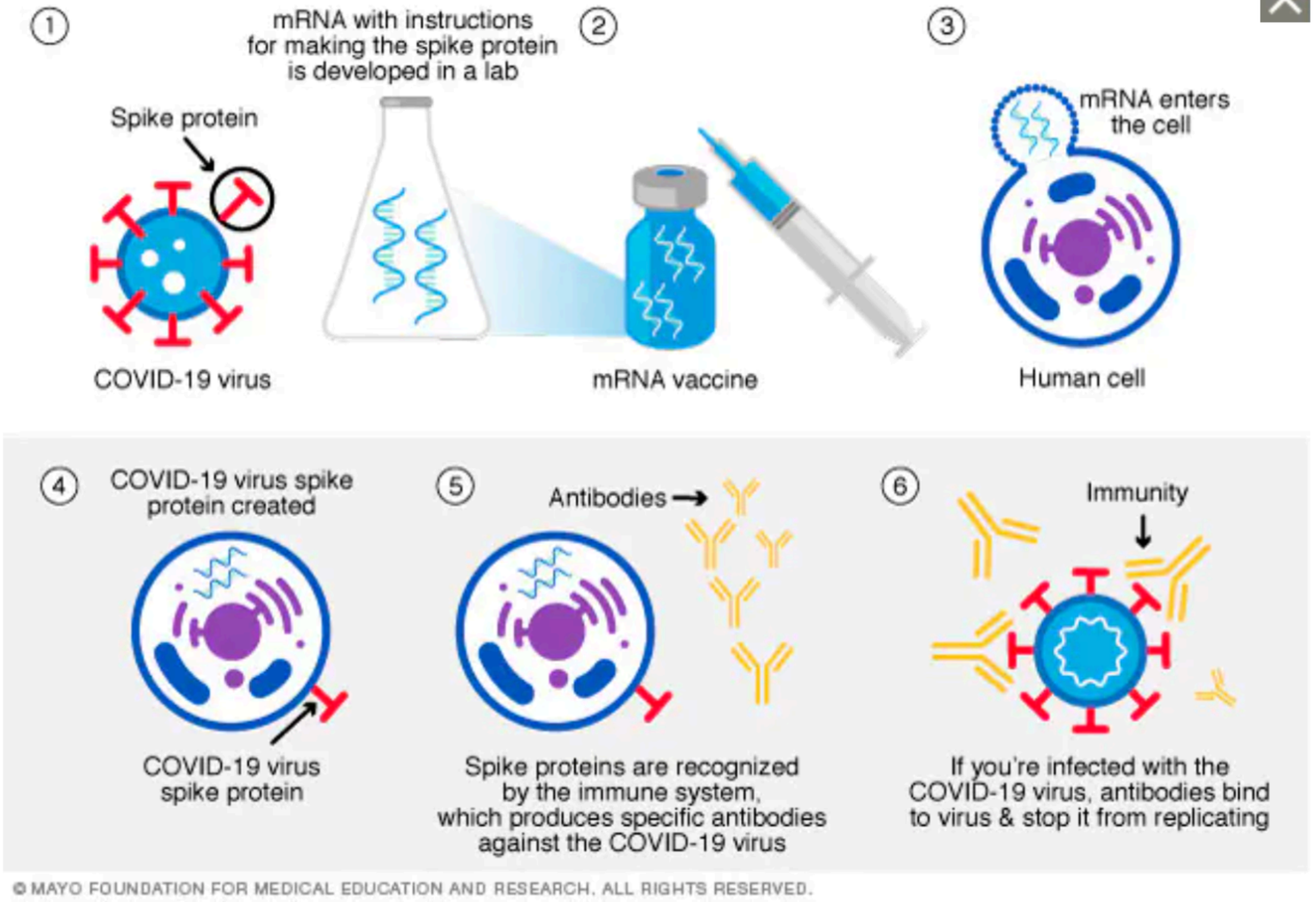
COVID-19 vaccine types in development

Candidates in Clinical Phases I-III

As of 26/01/2021



Protein subunit vaccine



mRNA vaccine

A mRNA vaccine is made using mRNA that gives your cells instructions for how to make the spike protein found on the surface of the COVID-19 virus. After vaccination, your immune cells begin making the spike protein and displaying them on cell surfaces. This causes your body to create antibodies that can fight the COVID-19 virus.

NEWS | 11 October 2021 | Clarification 12 October 2021

mRNA flu shots move into trials

COVID-19 provided an opportunity to show that mRNA vaccines can work. Now, drug companies are racing to apply the technology platform for influenza.

Elie Dolgin

Critical Developments for mRNA vaccine

- The idea of using mRNA rather than delivering proteins
- Development of lipid nanoparticles, liposomes, with charged lipids
- Pseudouridine to reduce TLR stimulation of inflammation by RNA
- Stabilizing spike protein structure

NEWS FEATURE | 14 September 2021 | Correction 22 October 2021

The tangled history of mRNA vaccines

Hundreds of scientists had worked on mRNA vaccines for decades before the coronavirus pandemic brought a breakthrough.

Elie Dolgin

Nature Vol 597, 2021 Sept 16

INSIDE AN MRNA COVID VACCINE

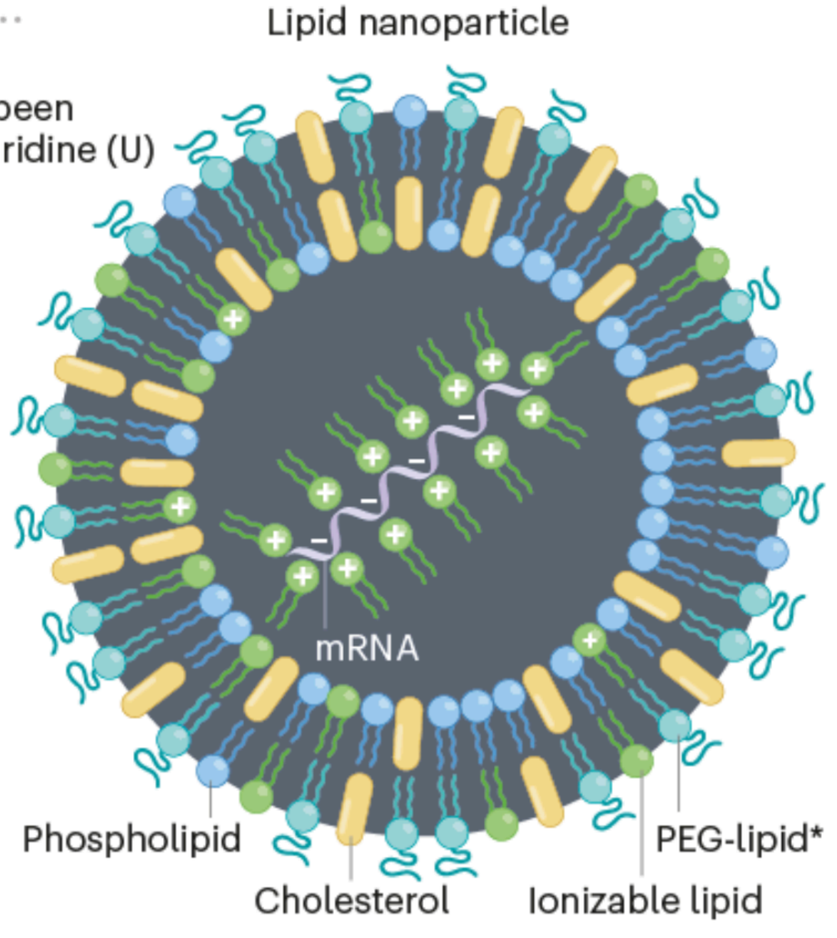
COVID-19 vaccines made from messenger RNA use lipid nanoparticles — bubbles of fats — to carry the molecules into cells. The mRNA contains the code for cells to produce the 'spike' protein that the coronavirus SARS-CoV-2 uses to enter cells. Here are key innovations in the design of these vaccines.

mRNA

...CGAGΨΨCGΨGΨΨΨAA...

The vaccines made by Moderna and Pfizer–BioNTech use mRNA that has been chemically modified to replace the uridine (U) nucleotide with pseudouridine (Ψ). This change is thought to stop the immune system reacting to the introduced mRNA.

To help the body mount an effective immune response to later SARS-CoV-2 infections, the mRNA sequence is adapted to stabilize the spike protein in the shape it uses when fusing with human cells.

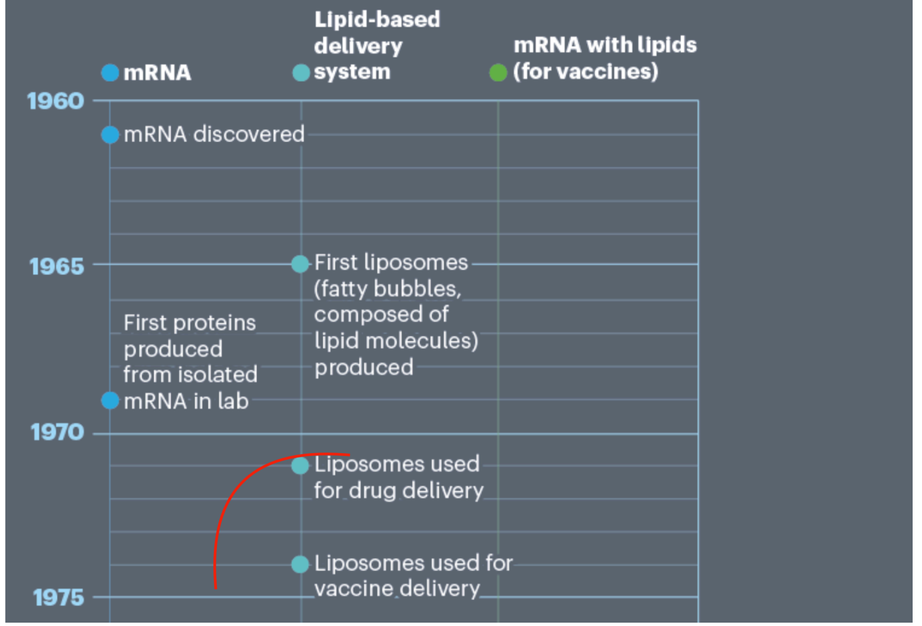


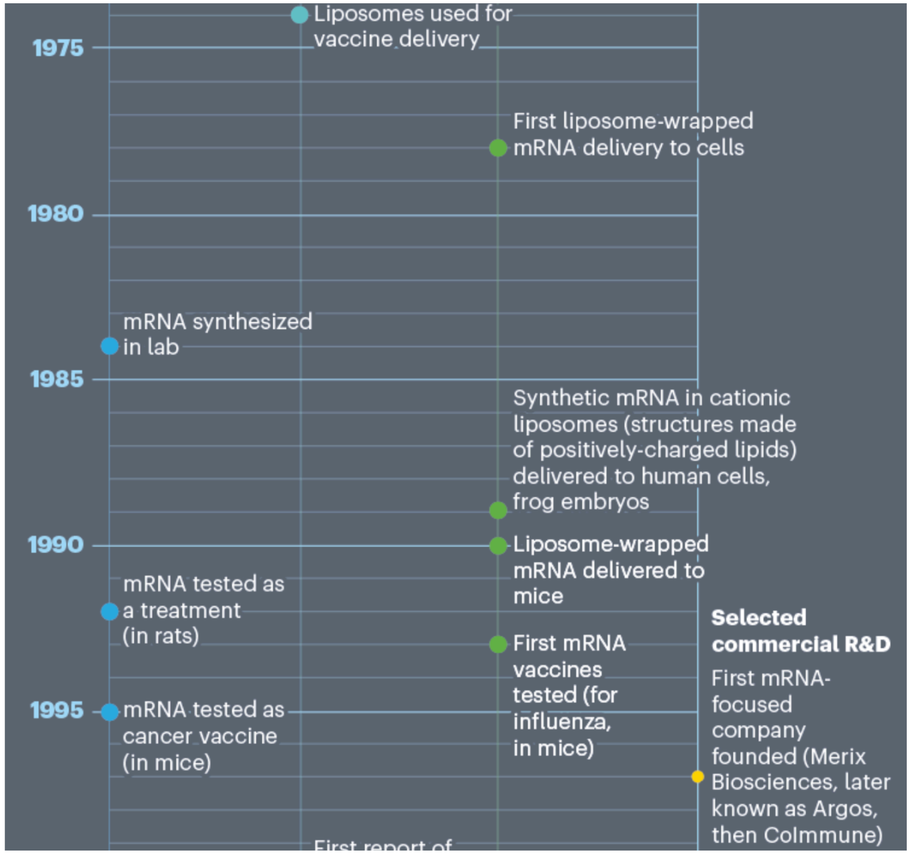
Lipids

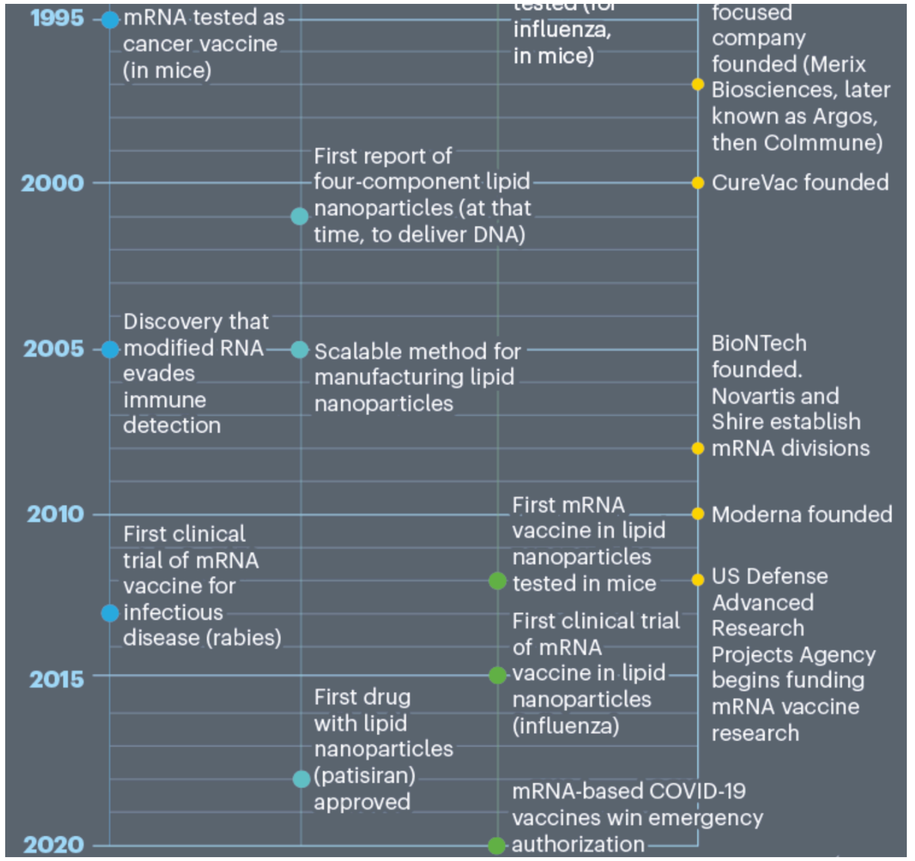
The fatty nanoparticle around the mRNA is made of four

THE HISTORY OF MRNA VACCINES

A long chain of scientific advances led to the first messenger RNA (mRNA) vaccines, released last year to protect people against COVID-19. These vaccines, as well as mRNA drugs, make use of developments in the science of mRNA and in delivery systems, which are made of lipid molecules.

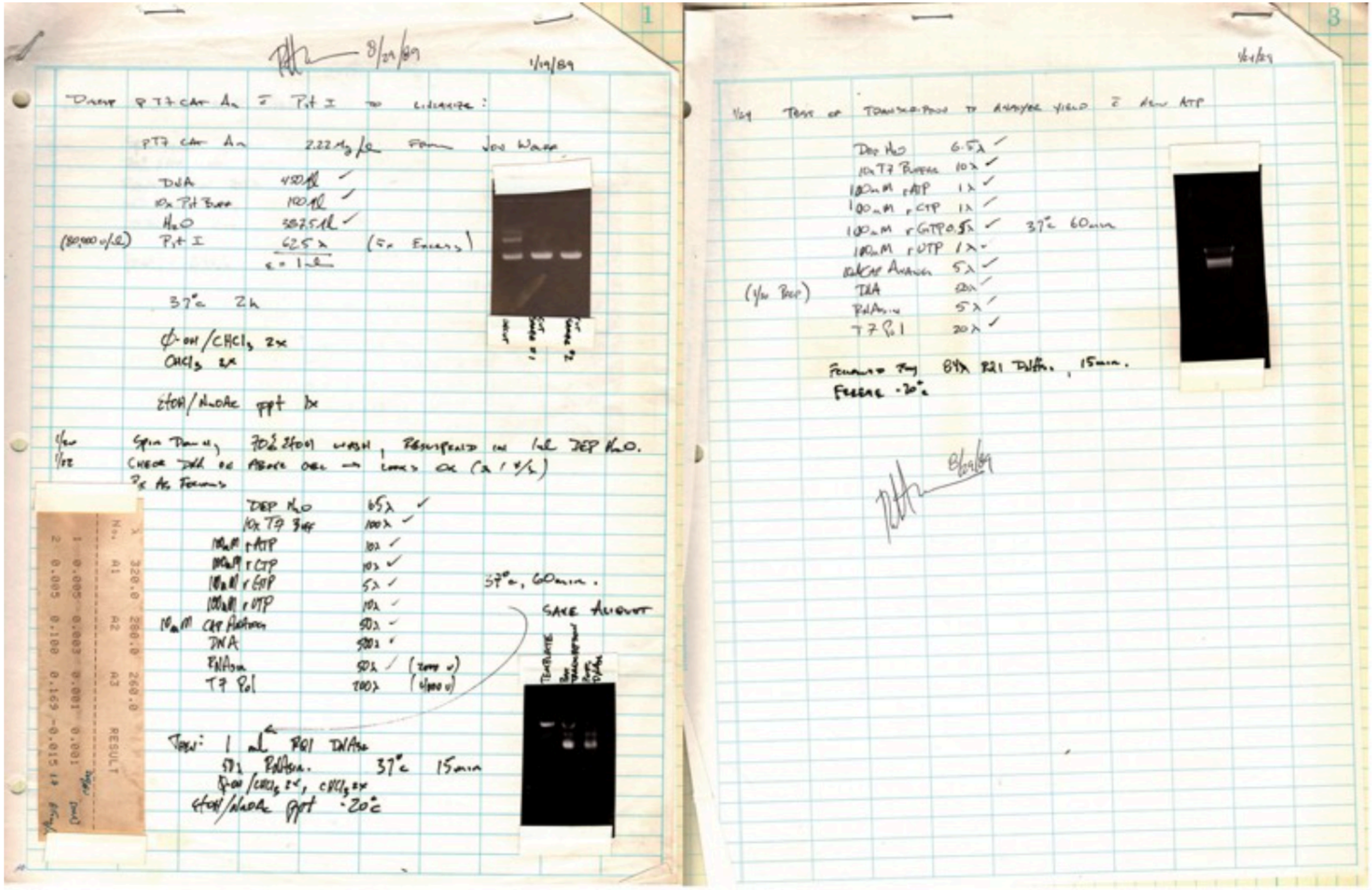





1995
mRNA tested as cancer vaccine (in mice)
influenza, in mice)
focused company founded (Merix Biosciences, later known as Argos, then CoImmune)
2000
First report of four-component lipid nanoparticles (at that time, to deliver DNA)
CureVac founded
2005
Discovery that modified RNA evades immune detection
Scalable method for manufacturing lipid nanoparticles
BioNTech founded. Novartis and Shire establish mRNA divisions
2010
First mRNA vaccine in lipid nanoparticles tested in mice
Moderna founded
First clinical trial of mRNA vaccine for infectious disease (rabies)
US Defense Advanced Research Projects Agency begins funding mRNA vaccine research
First clinical trial of mRNA vaccine in lipid nanoparticles (influenza)
2015
First drug with lipid nanoparticles (patisiran) approved
mRNA-based COVID-19 vaccines win emergency authorization
2020

Philip Felgner (left) and Robert Malone. Credit: Steve Zylius/UCI; Robert Malone

Despite his success using the liposomes to deliver mRNA into human cells and frog embryos, Malone never earned a PhD. He fell out with his supervisor, Salk gene-therapy researcher Inder Verma and, in 1989, left graduate studies early to work for Felgner at Vical, a recently formed start-up in San Diego, California. There, they and collaborators at the University of Wisconsin–Madison showed that the lipid–mRNA complexes could spur protein production in mice[7]. (Malone and his Vical coworkers also explored using mRNA for vaccines: their early patent filings describe injecting mRNA coding for HIV proteins into

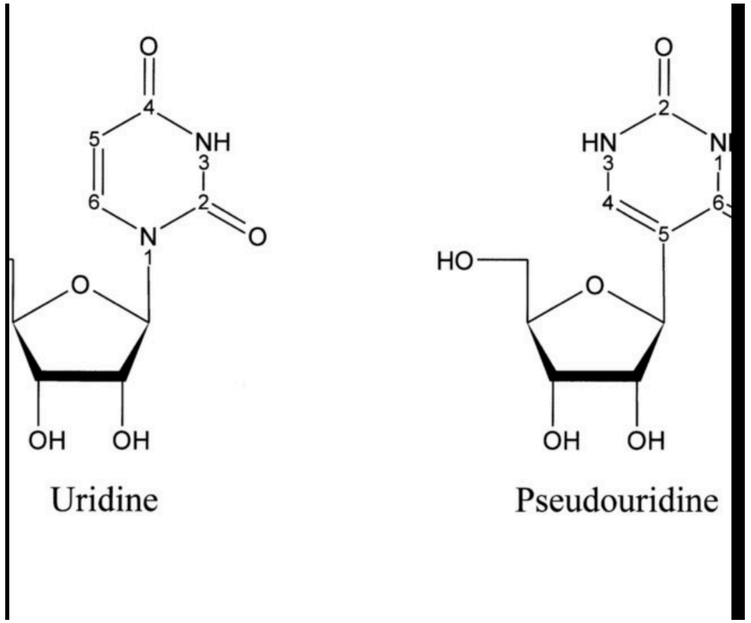


An excerpt from Robert Malone's lab notebooks, describing the 1989 synthesis of mRNA for injection into mice. Credit: Robert Malone

Modified nucleotide improved immunogenicty

while reducing inflammation

- substituted pseudouridine for uridine, reduced inflammatory reactions to the mRNA (reduced interactions with TLRs)

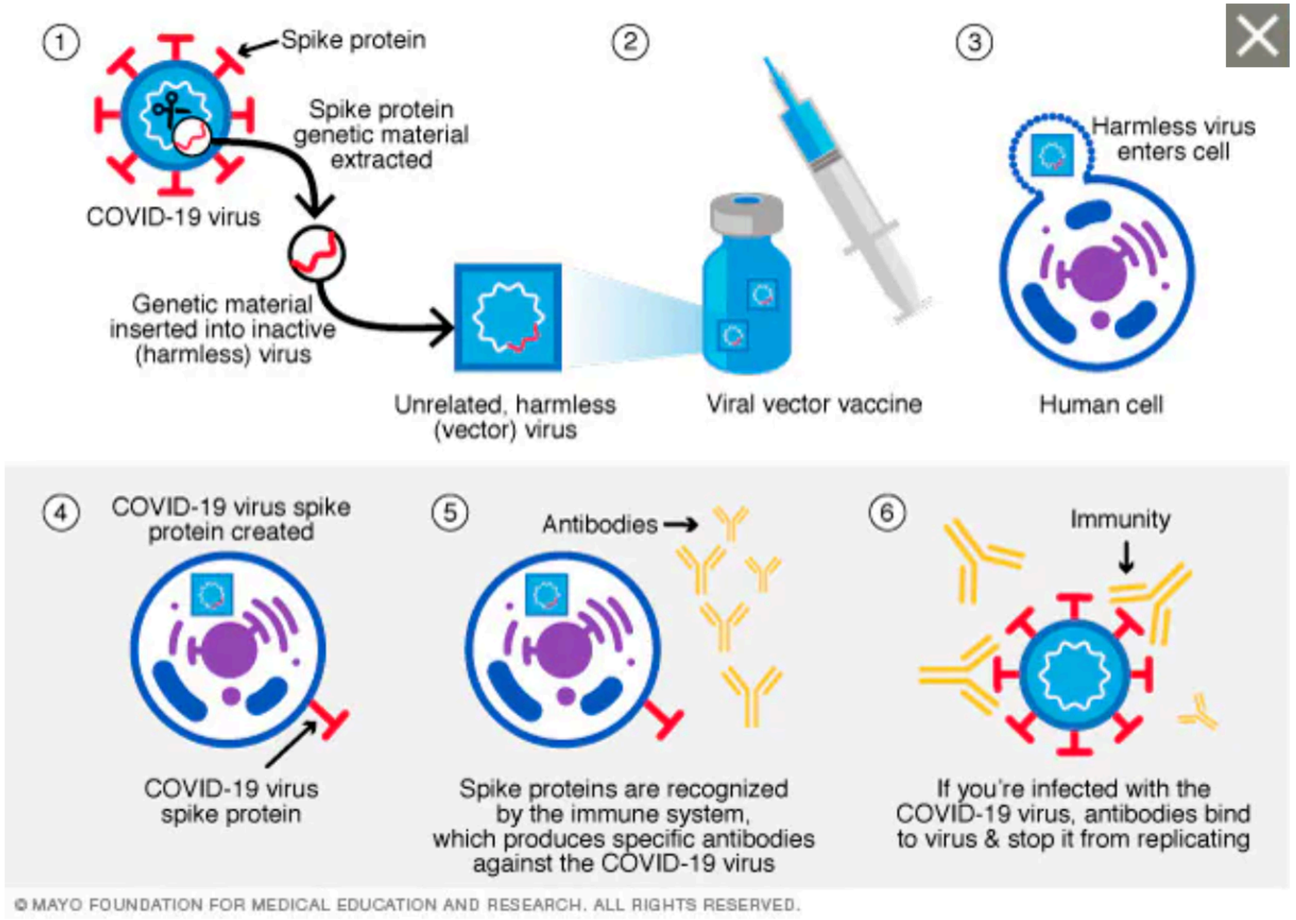


Kariko, coiuldn’t get the work funded

Katalin Karikó helped to show that chemical modifications to RNA can smuggle the molecule past the body’s immune defences. Credit: Hannah Yoon/Bloomberg/Getty

Another important development: a stabilized form of the spike protein

- Took on shape of spike protein as it binds to ACE-2
- https://www.youtube.com/watch?v=-92HQA0GcI8



Viral vector vaccine

A viral vector vaccine is made when genetic material from a COVID-19 virus is inserted into a unrelated, harmless virus. When the viral vector gets into your cells, it delivers genetic material from the COVID-19 virus that gives your cells instructions for how to make the spike protein found on the surface of the COVID-19 virus. Once your cells displace the spike proteins on their surfaces, your immune system creates antibodies that can fight the COVID-19 virus.

frontiers in Immunology

REVIEW
published: 01 October 2021
doi: 10.3389/fimmu.2021.752227

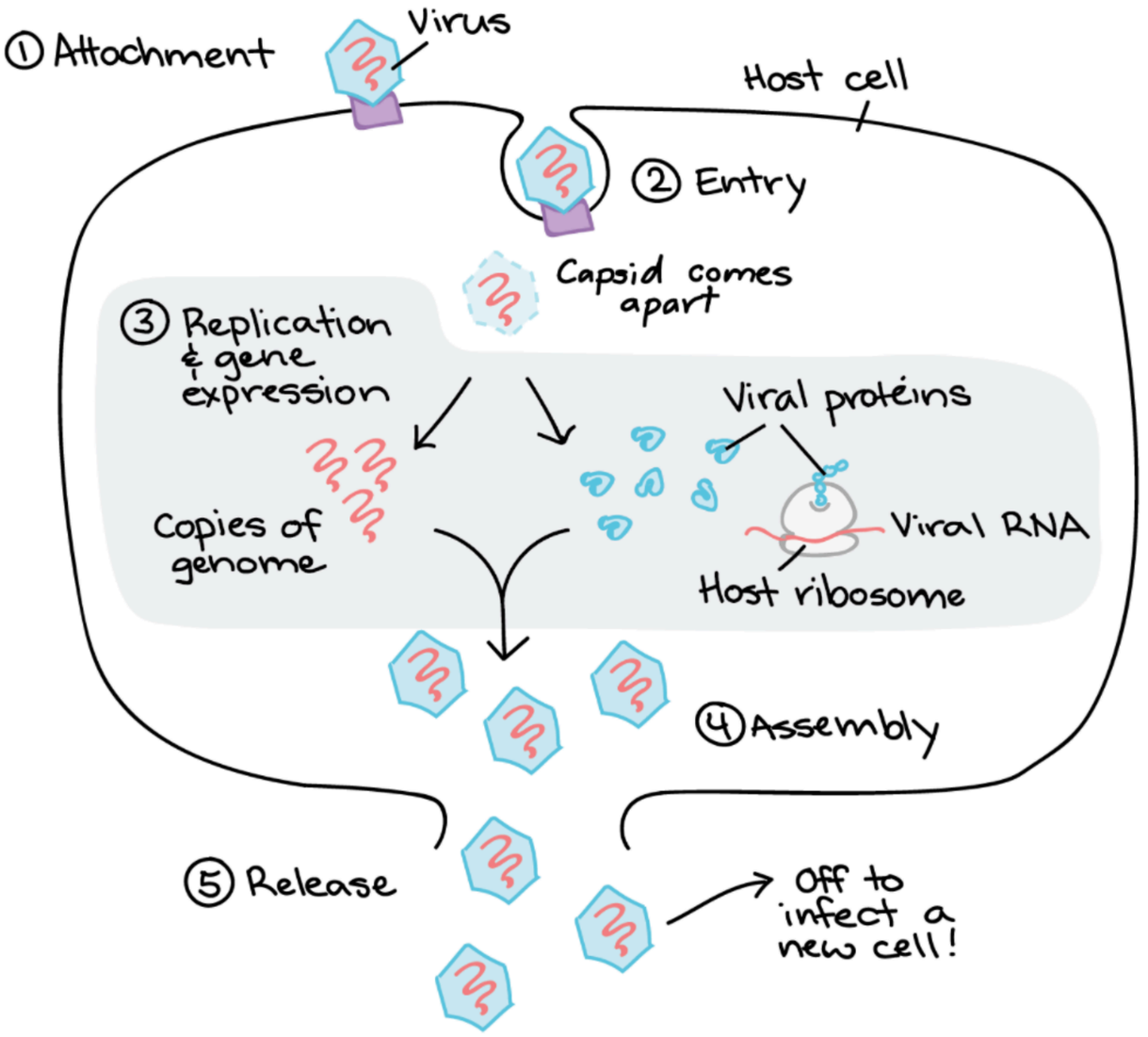
Check for updates

Beyond Vaccines: Clinical Status of Prospective COVID-19 Therapeutics

Sriram Kumar[1,2], *Duygu Merve Çalışkan*[1,2], *Josua Janowski*[1,3], *Aileen Faist*[1,4], *Beate Claudine Gisela Conrad*[1], *Julius Lange*[1], *Stephan Ludwig*[1,2,4,5] *and Linda Brunotte*[1,5*]

[1] Institute of Virology, University of Münster, Münster, Germany, [2] EvoPAD Research Training Group 2220, University of Münster, Münster, Germany, [3] SP BioSciences Graduate Program, University of Münster, Münster, Germany, [4] CiM-IMPRS Graduate Program, University of Münster, Münster, Germany, [5] Interdisciplinary Centre for Medical Research, University of Münster, Münster, Germany

GENERAL DIAGRAM of a VIRUS LIFECYCLE



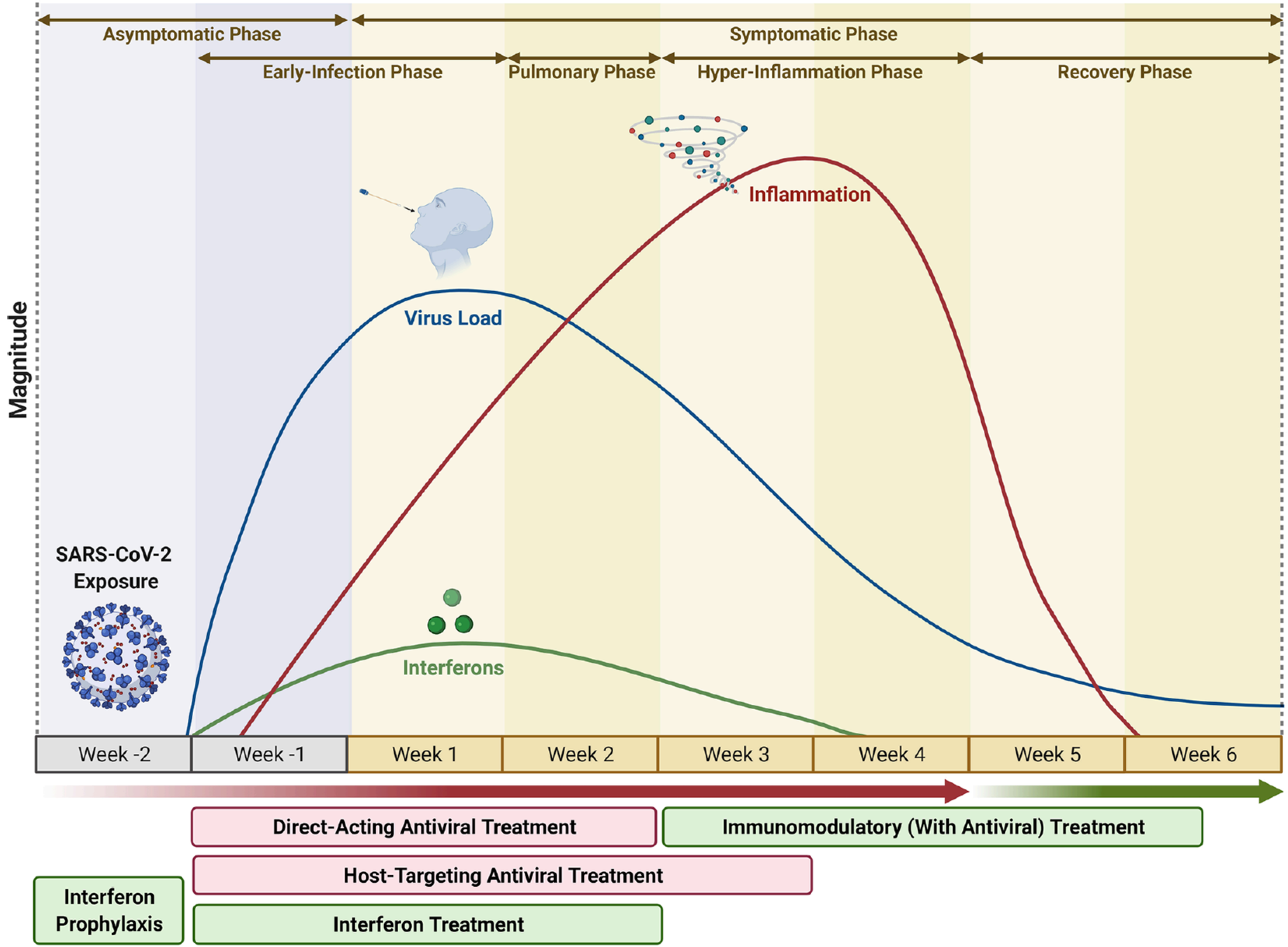


FIGURE 1 | COVID-19 Progression vs Treatment Options. The infection phase of COVID-19 begins 1-week post exposure to SARS-CoV2 (Asymptomatic phase)

COVID-19 Treatment Options

effects depend on stage of the disease

- Mab antibodies (Regeneron and Lilly)
  - Against RBD of Spike protein
  - Against stimuli for cytokine production
  - Against cytokines
- Soluble ACE2 decoys (Procko)
- direct anti-viral drugs
  - Remdesivir, a nucleoside analogue targeting viral polymerase
  - Molnupiravir, Merck nucleoside analogue, tested in hamsters and humans with mild to moderate COVID; reduced risk of hospitalization by 50%; EUA applied for; generic will be manufactured in India
  - Several being combined with interferons;
- Anti-inflammatory drugs
  - Dexamethasone, a synthetic corticosteroid
  - anti-IL6 monoclonal Abs