Challenges of formulation of mRNA products

Gerrit Borchard, PharmD, PhD

Online conference

CASSS CMC Strategy Forum Europe 2021, October 2021

Last 5-years hands-on experience...

- Development of a pandemic H5N1 vaccine in cooperation with University of Surabaya, Indonesia – R4D project
- Development of a polyvalent pDNA vaccine against Dengue fever in cooperation with Chulalongkorn University Bangkok, Thailand
- Formulation and testing of novel adjuvant – pandemic flu vaccine combinations, COST/SNF project

Development of a SARS-CoV-2-S mRNA/DNA vaccine by ISPSO and Chulalongkorn, Bangkok

March – July 2020

- Development of liposomal formulations of mRNA and DNA vaccines
- Phys.-chem. characterization
- Tests *in vitro*
- Tech transfer

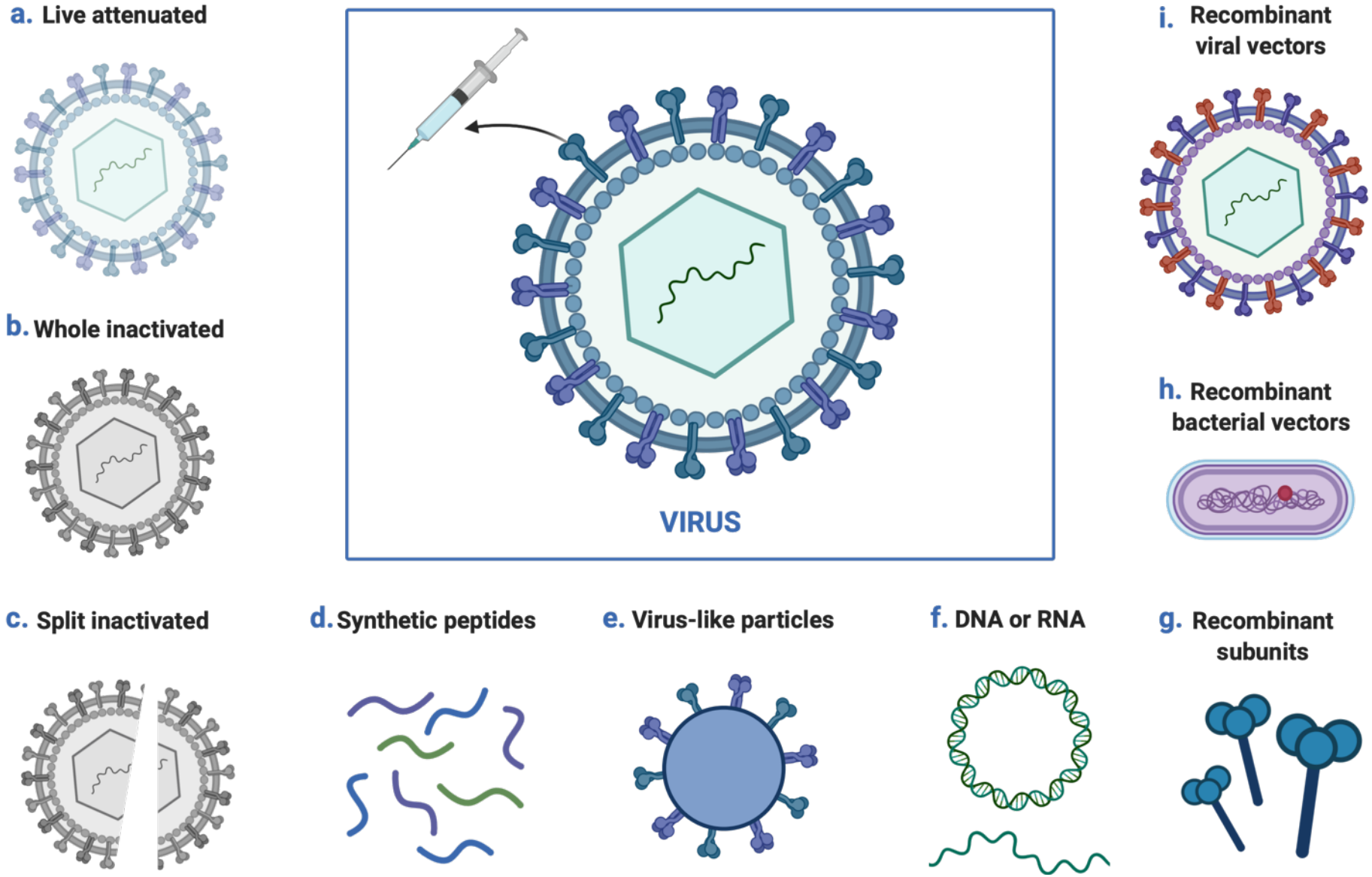
August 2020 – January 2021

- *In vivo* tests (mice)

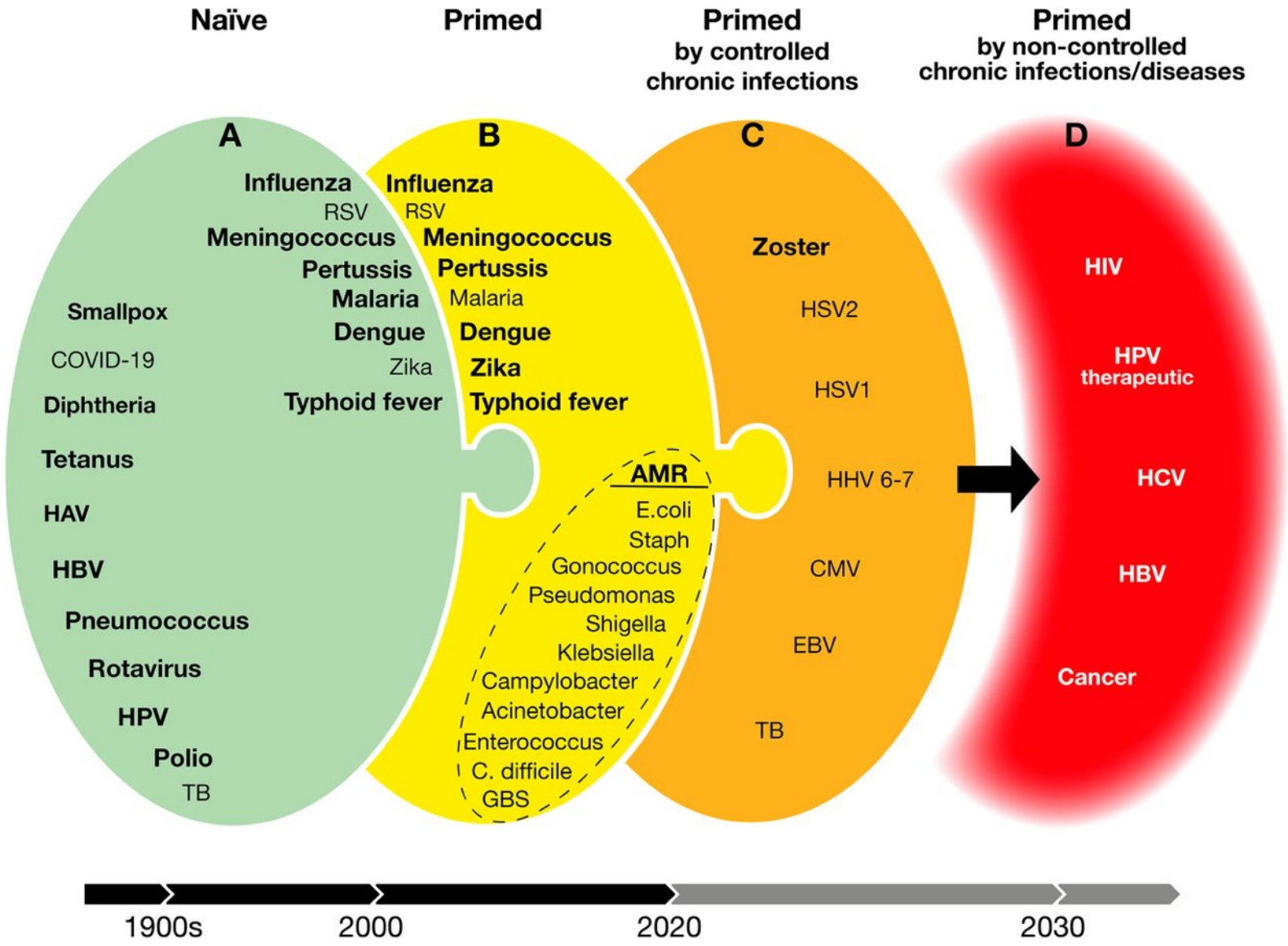
February 2021 -

- Translation to microfluidic production
- *In vivo* tests (non-human primates)
- Clinical phase I studies

Vaccine types



Technological advances that merged to develop a COVID-19 vaccine



Green: available or doable with existing technologies.

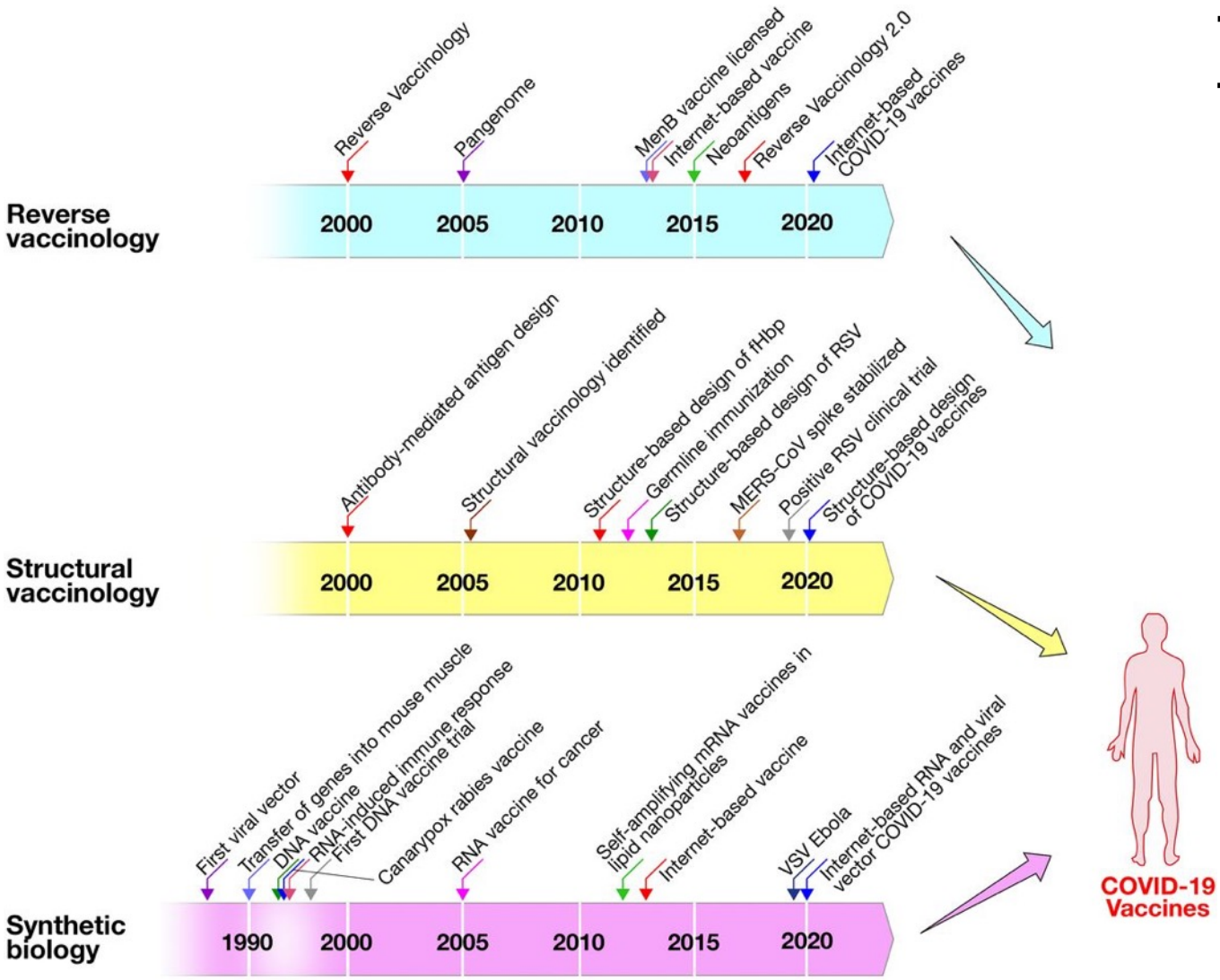
Yellow and orange: doable vaccines with increasing challenges for today's technologies.

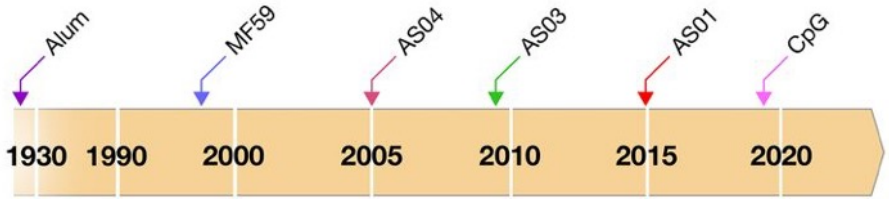
Red : targets for which we do not yet have the scientific knowledge and technologies.

AMR: antimicrobial resistance

Rino Rappuoli et al. PNAS 2021;118:3:e2020368118

Technological advances that merged to develop a COVID-19 vaccine

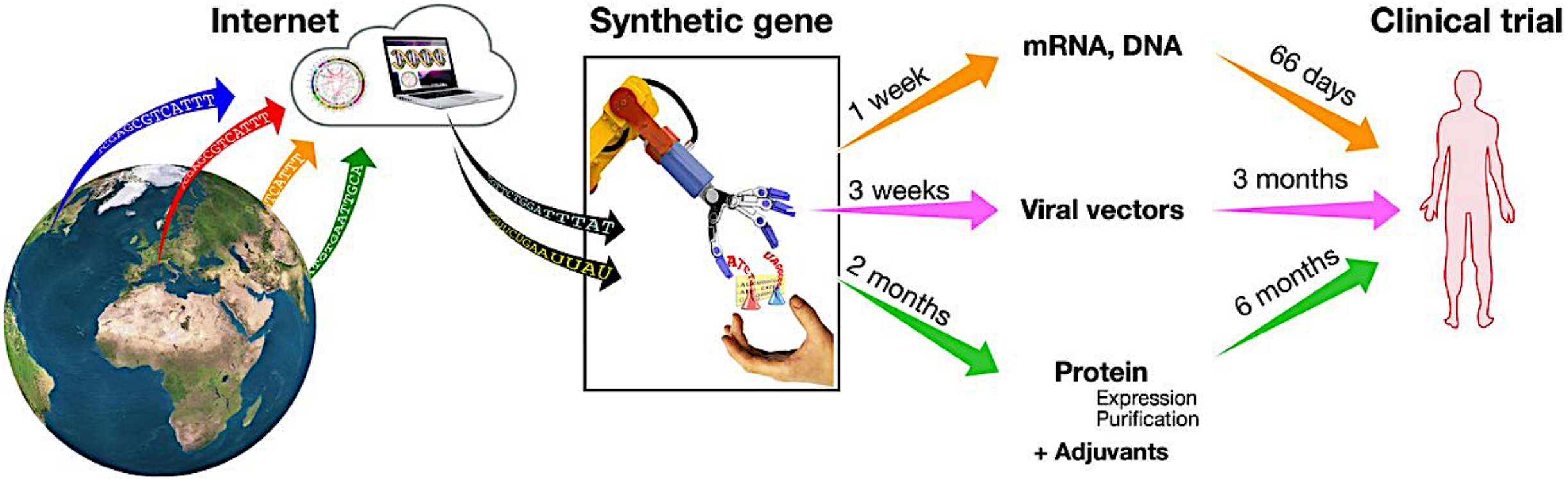




Adjuvants: not that "dirty" anymore

Rino Rappuoli et al. PNAS 2021;118:3:e2020368118

Technological advances that merged to develop a COVID-19 vaccine



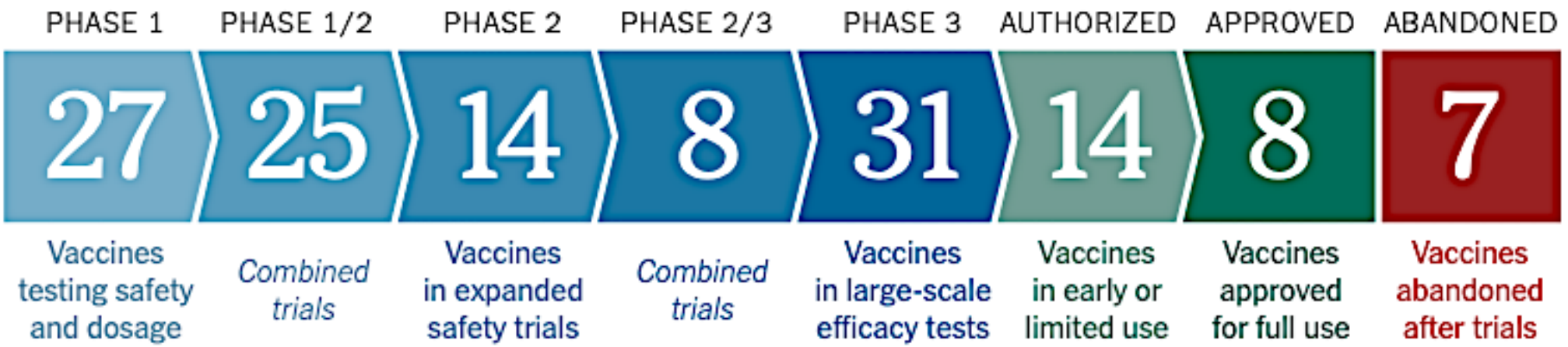
Rino Rappuoli et al. PNAS 2021;118:3:e2020368118

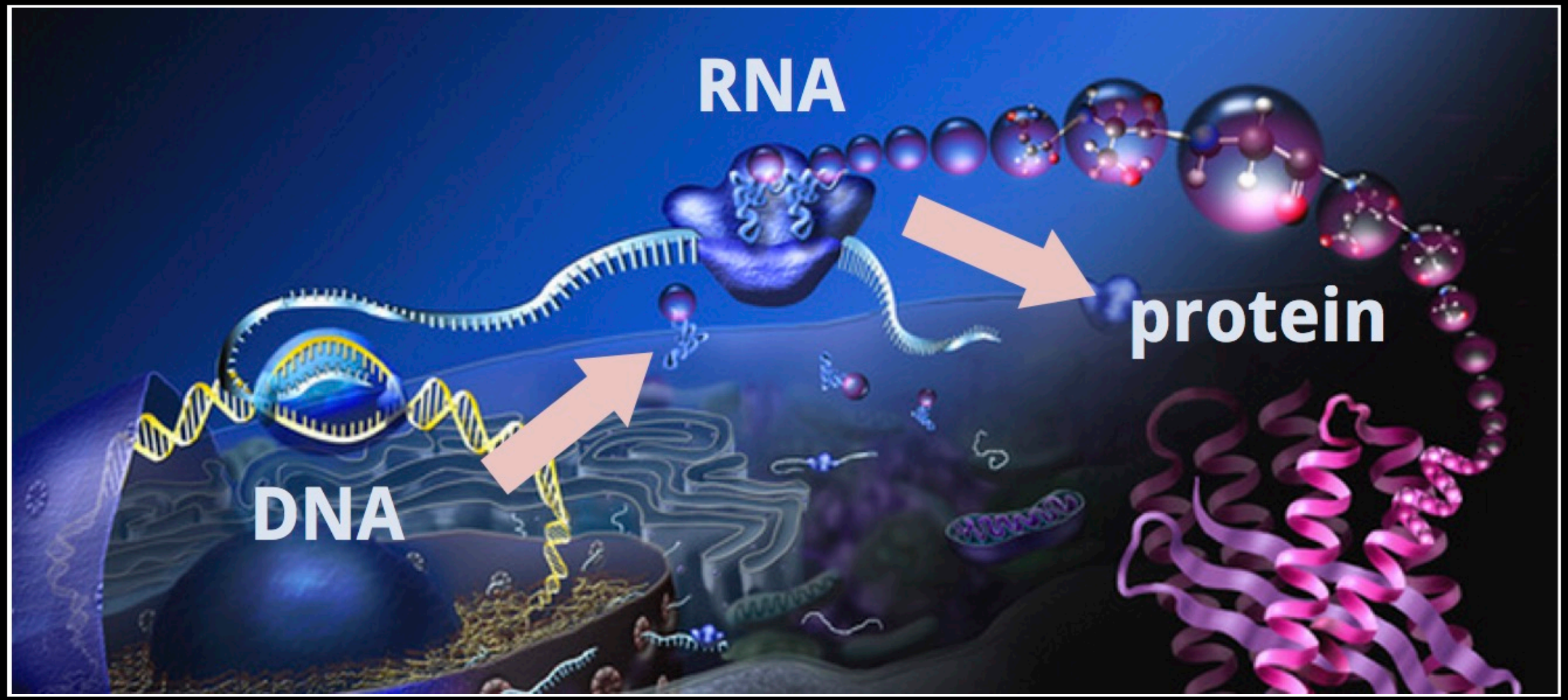
Corona virus vaccine tracker

The New York Times

By Carl Zimmer, Jonathan Corum and Sui-Lee Wee

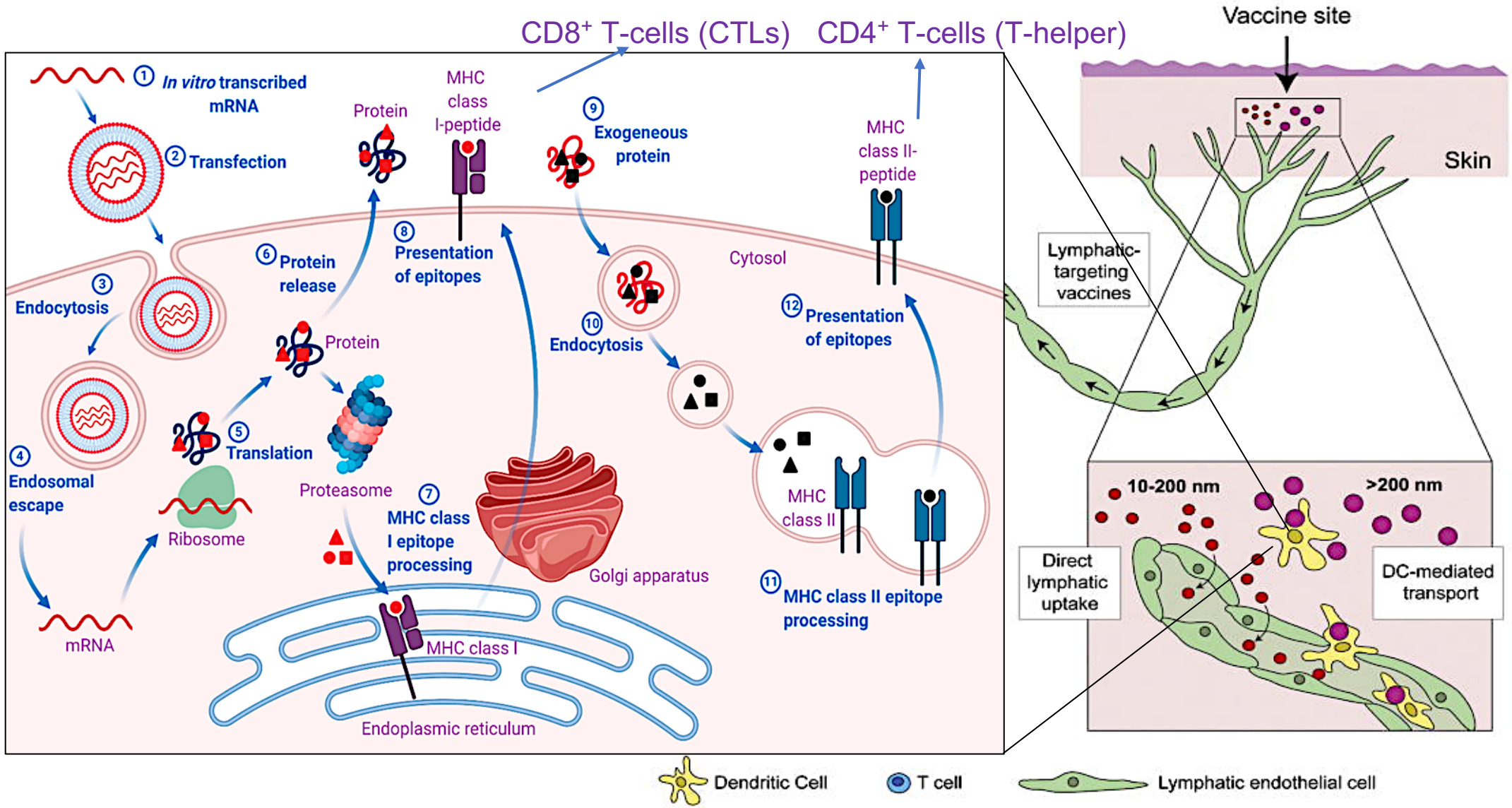
Updated Oct. 13, 2021





Central dogma of molecular biology

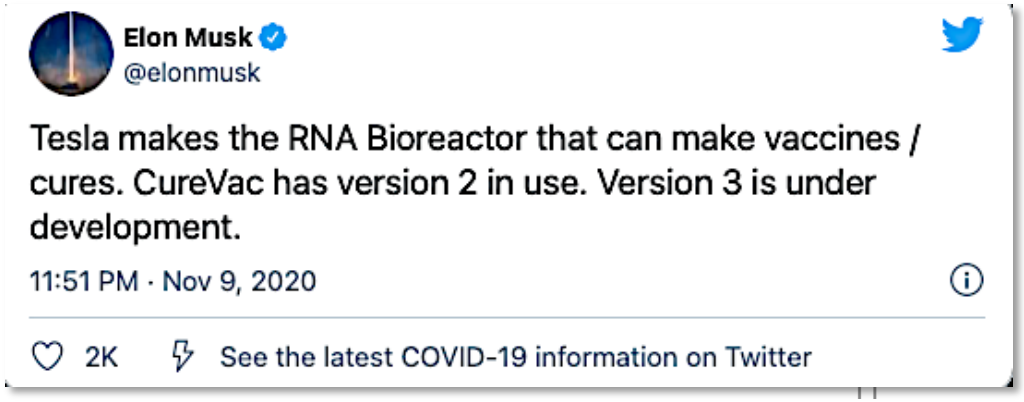
Immune reaction to s.c./i.m. vaccine

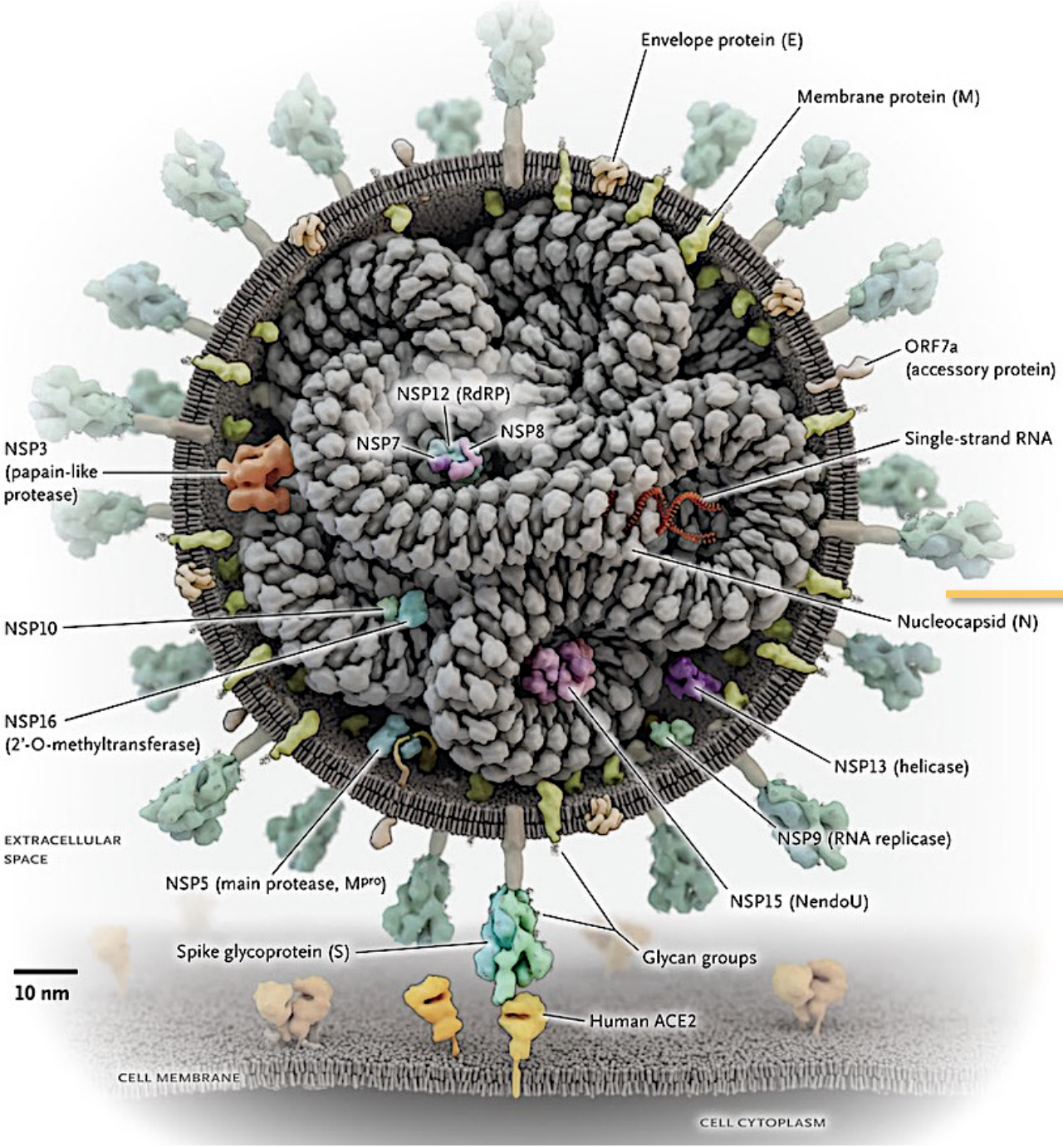


Maisel et al., *Adv Drug Deliv Rev* 2017; 114: 43–59. Ghaffar et al., *Curr Topics Med Chem* 2014, 14, 1194-1208.

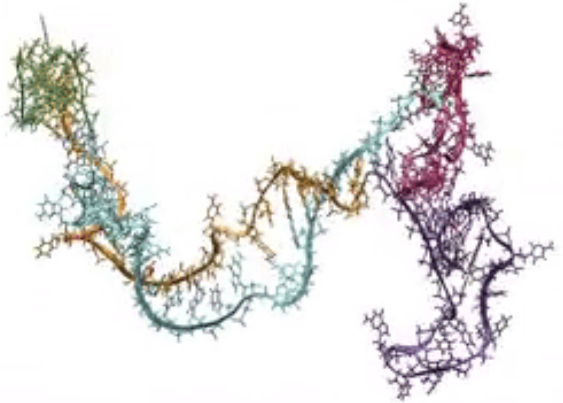
mRNA vaccines

- RNA vaccine: genetic information of the antigen
- Antigen is produced by the cells of the vaccinated person
- Advantages:
- Transcription at ribosomes in the cytosol
- Leads to cellular and humoral immune responses
- No return to virulent form
- Adaptations to new antigens/mutations relatively easy to make
- Rapid production



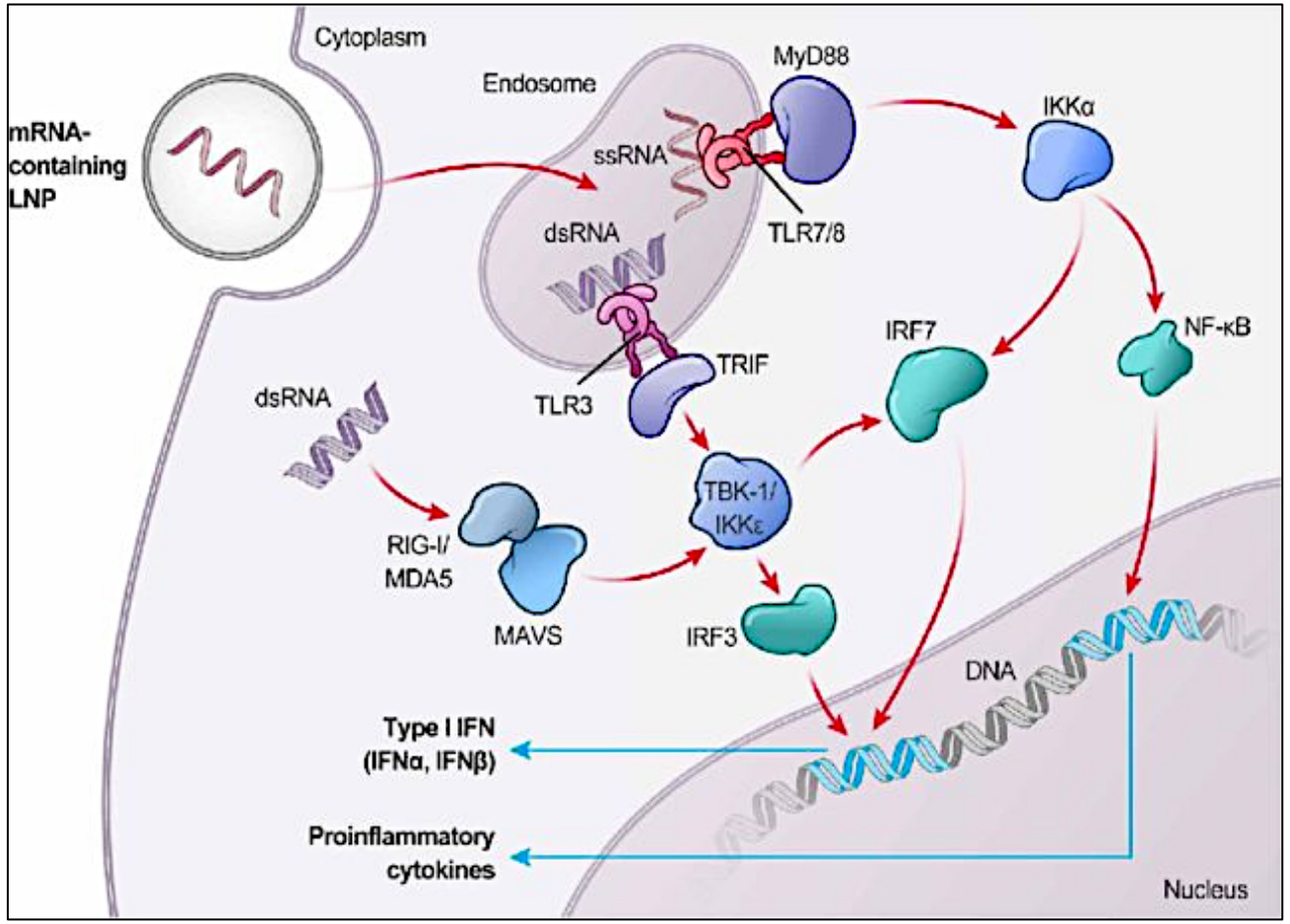


Pfizer/BionTech's S-protein mRNA



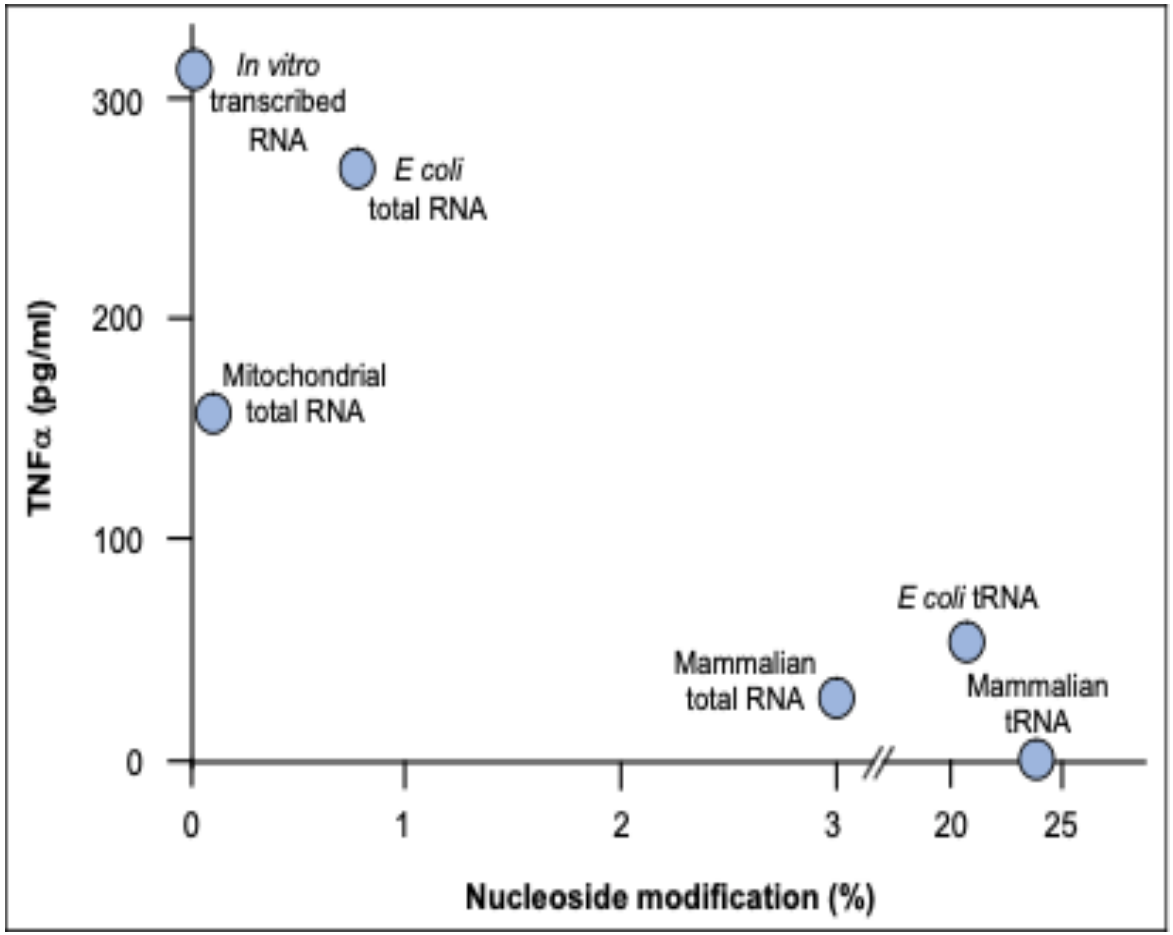
4,284 nucleotides
1388 kDa molecular weight

mRNA interacts with innate immune receptors, causing inflammation



Nelson et al., Sci. Adv. 2020, 6, DOI: 10.1126/sciadv.aaz6893

Naturally occuring nucleoside modifications suppress the immunostimulatory activity of RNA



K. Karikó & D. Weissman, Curr. Opin. Drug Discov. Devel. 2007, 10:523-32.

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

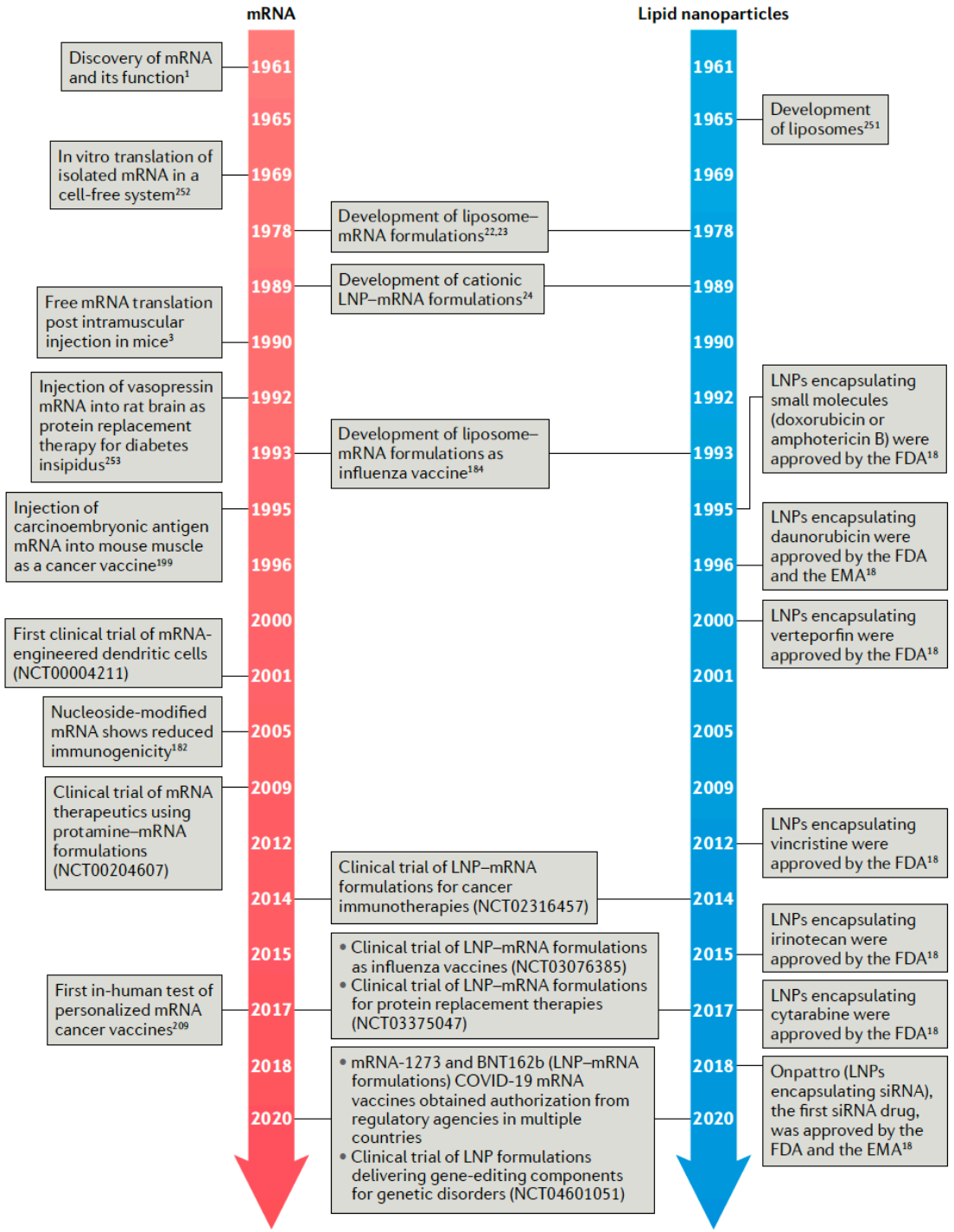
Katalin Karikó[1], Hiromi Muramatsu[1], Frank A Welsh[1], János Ludwig[2], Hiroki Kato[3], Shizuo Akira[3] and Drew Weissman[4]

[1]Department of Neurosurgery, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [2]Laboratory of RNA Molecular Biology, The Rockefeller University, New York, New York, USA; [3]Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, Osaka, Japan; [4]Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

«I felt like a God!»

Mol. Therap. 16, 2008, 1833-1840, doi: 10.1038/mt.2008.200


TAXI

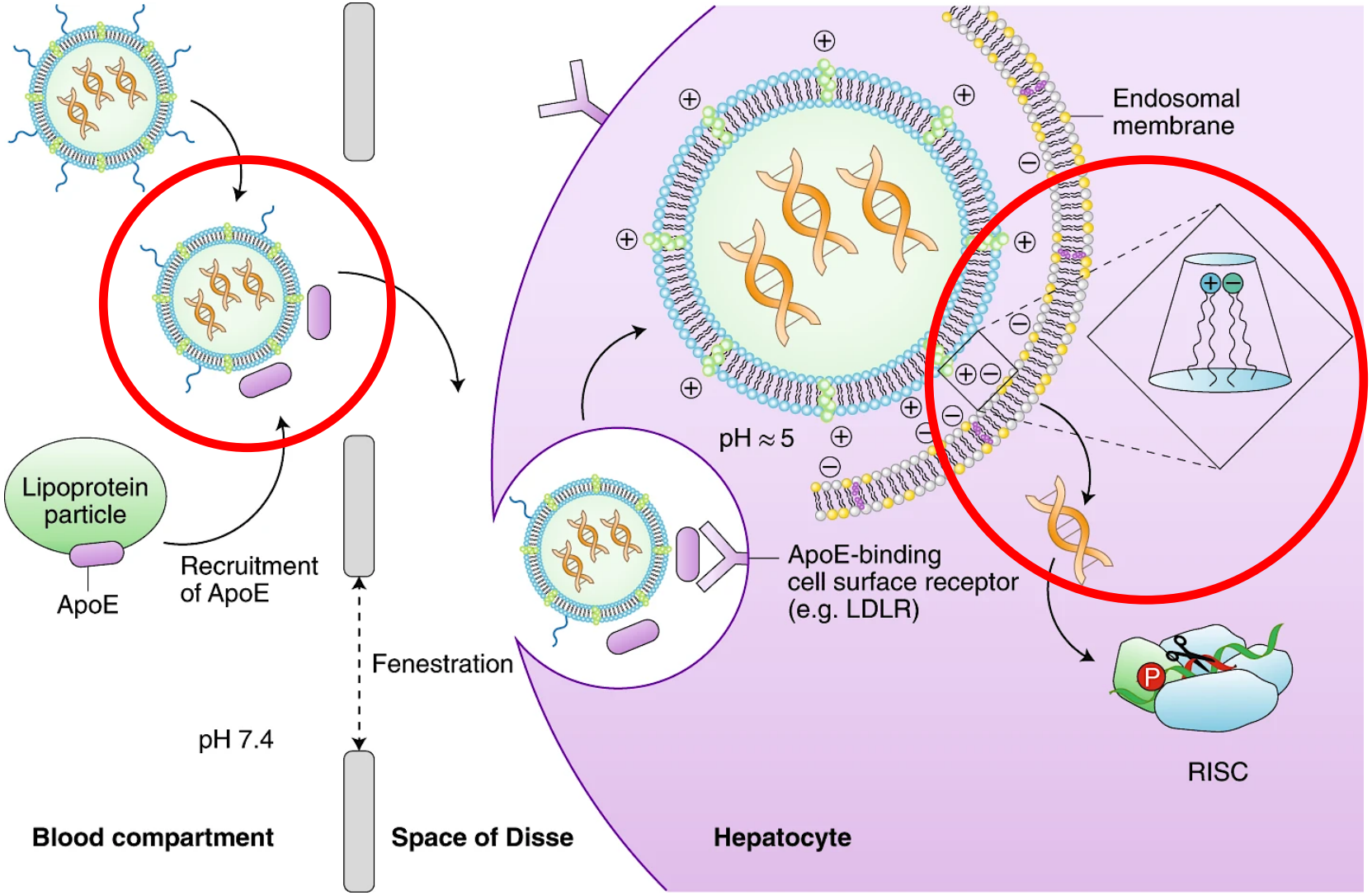


60 years of mRNA...

...and its formulation.

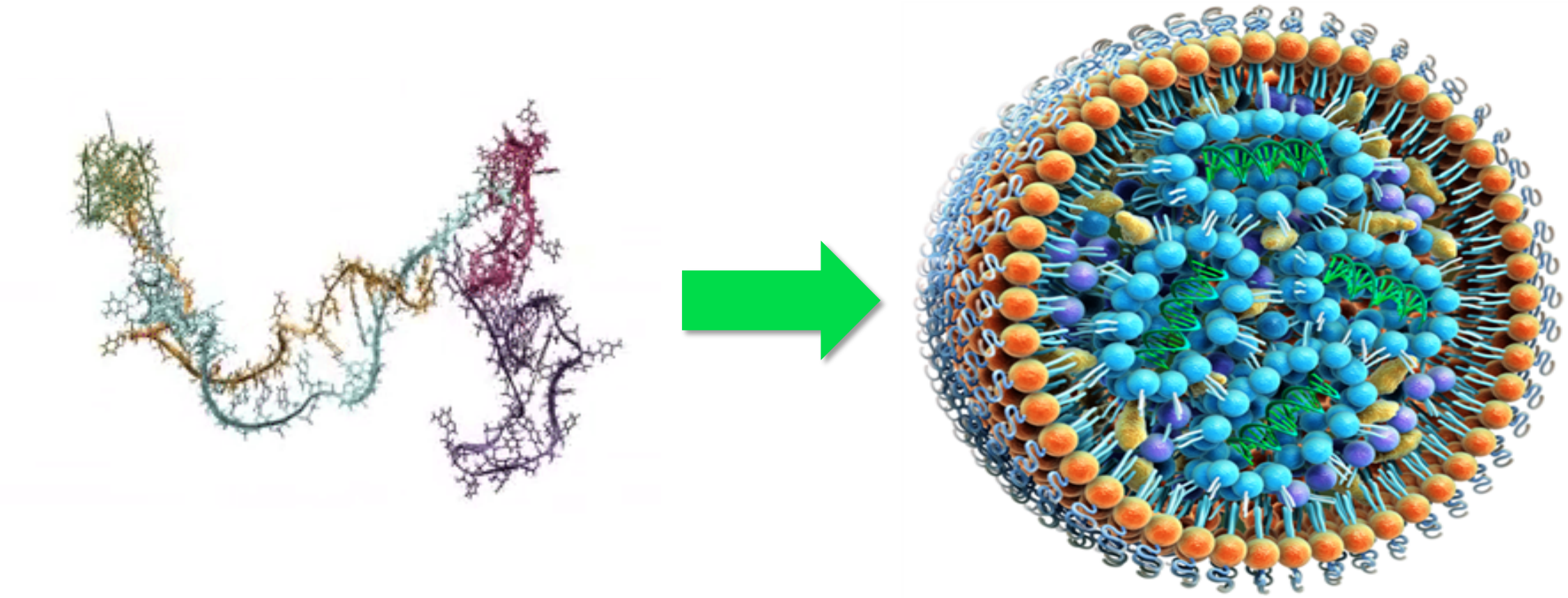
Hou, X., Zaks, T., Langer, R., Dong, Y.
Lipid nanoparticles for mRNA delivery. *Nat Rev Mater* (2021).
https://doi.org/10.1038/s41578-021-00358-0

Onpattro: the first FDA approved RNAi drug (August 2018)

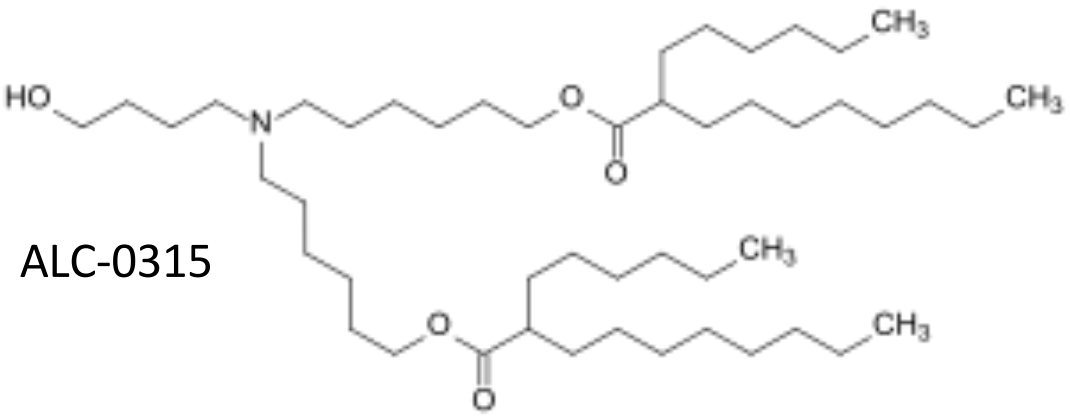


Akinc, *et al. Nat. Nanotechnol.* **14,** 1084–1087 (2019). Kulkarni et al. ACS nano. 2018;12(5):4787-95. Maeki, et al., Adv Drug Deliv Rev. 2018;128:84-100.

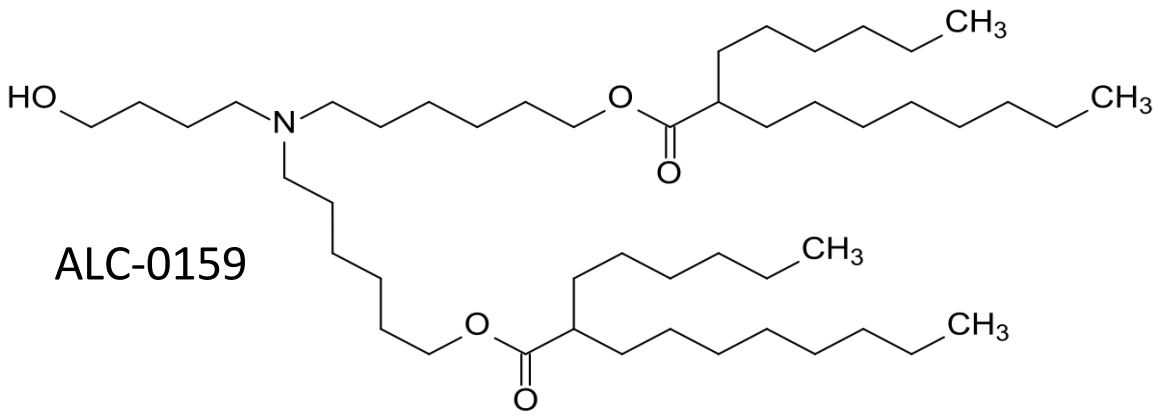
Formulation: lipid nanoparticles (LNPs18)



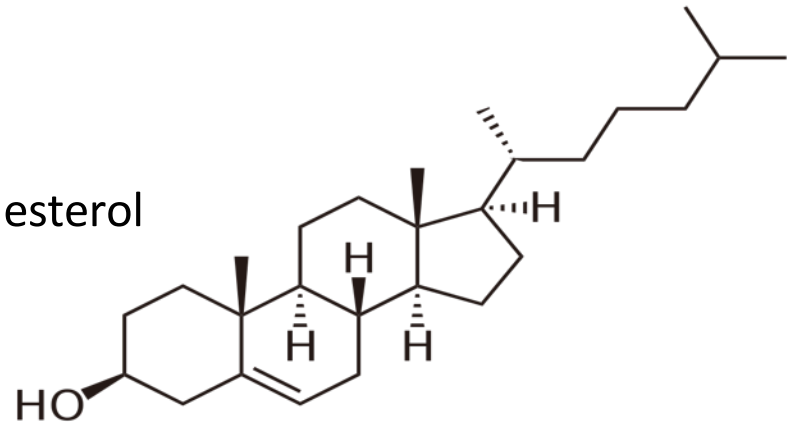
BionTech's formulation



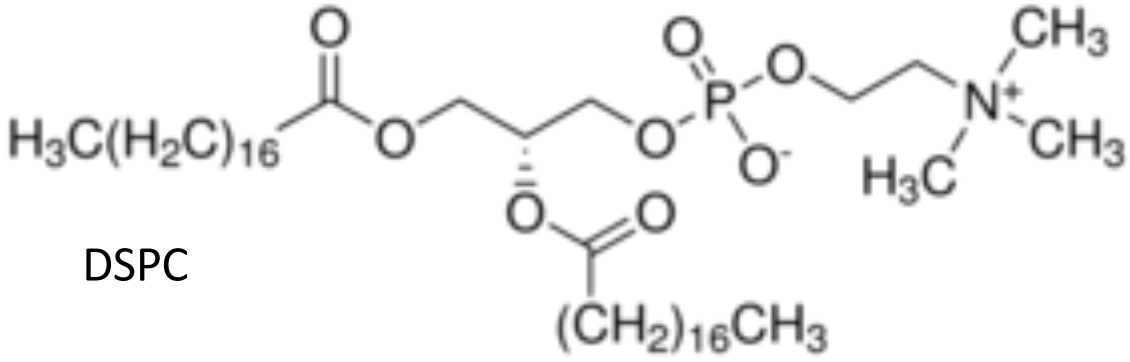
ALC-0315



ALC-0159



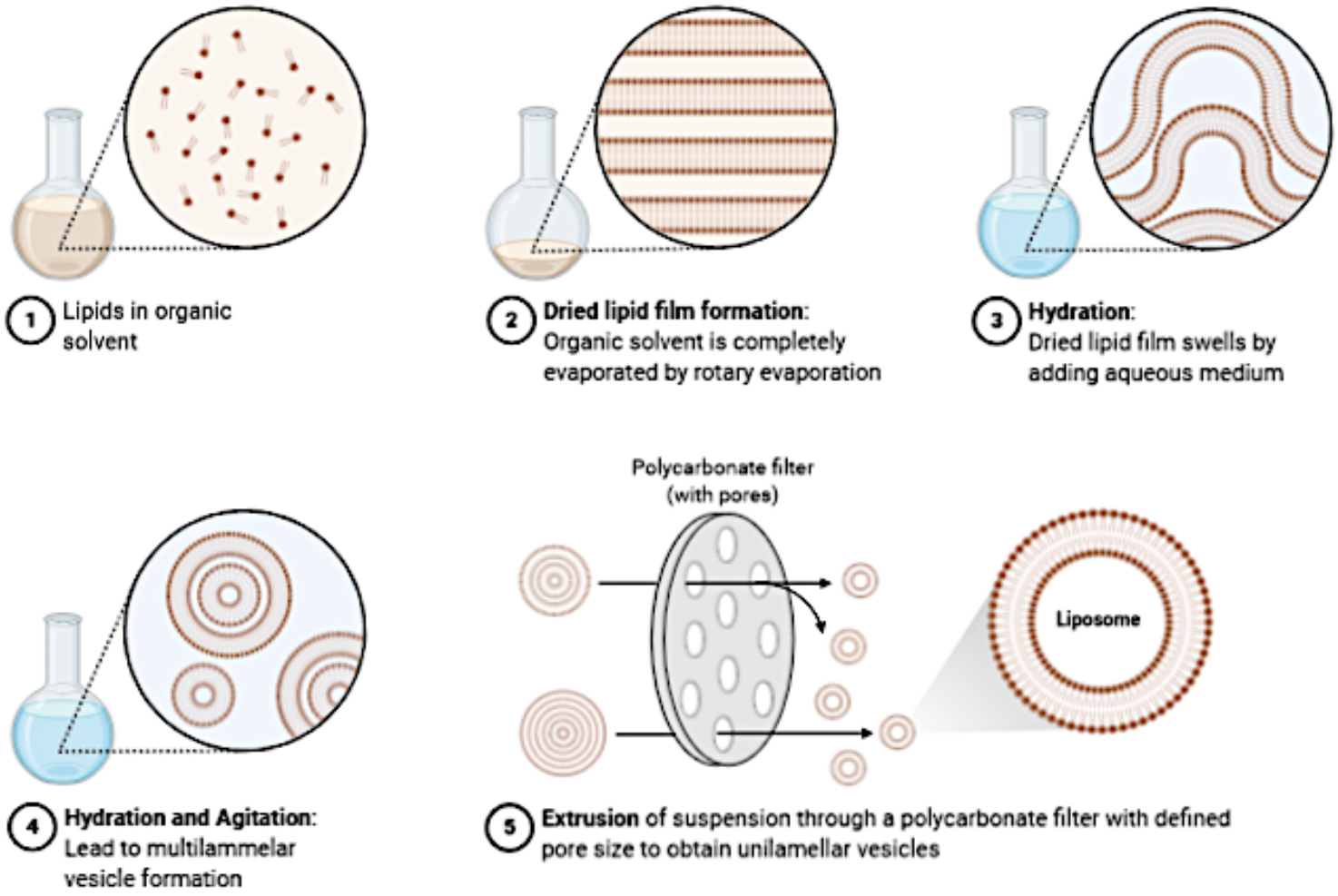
Cholesterol



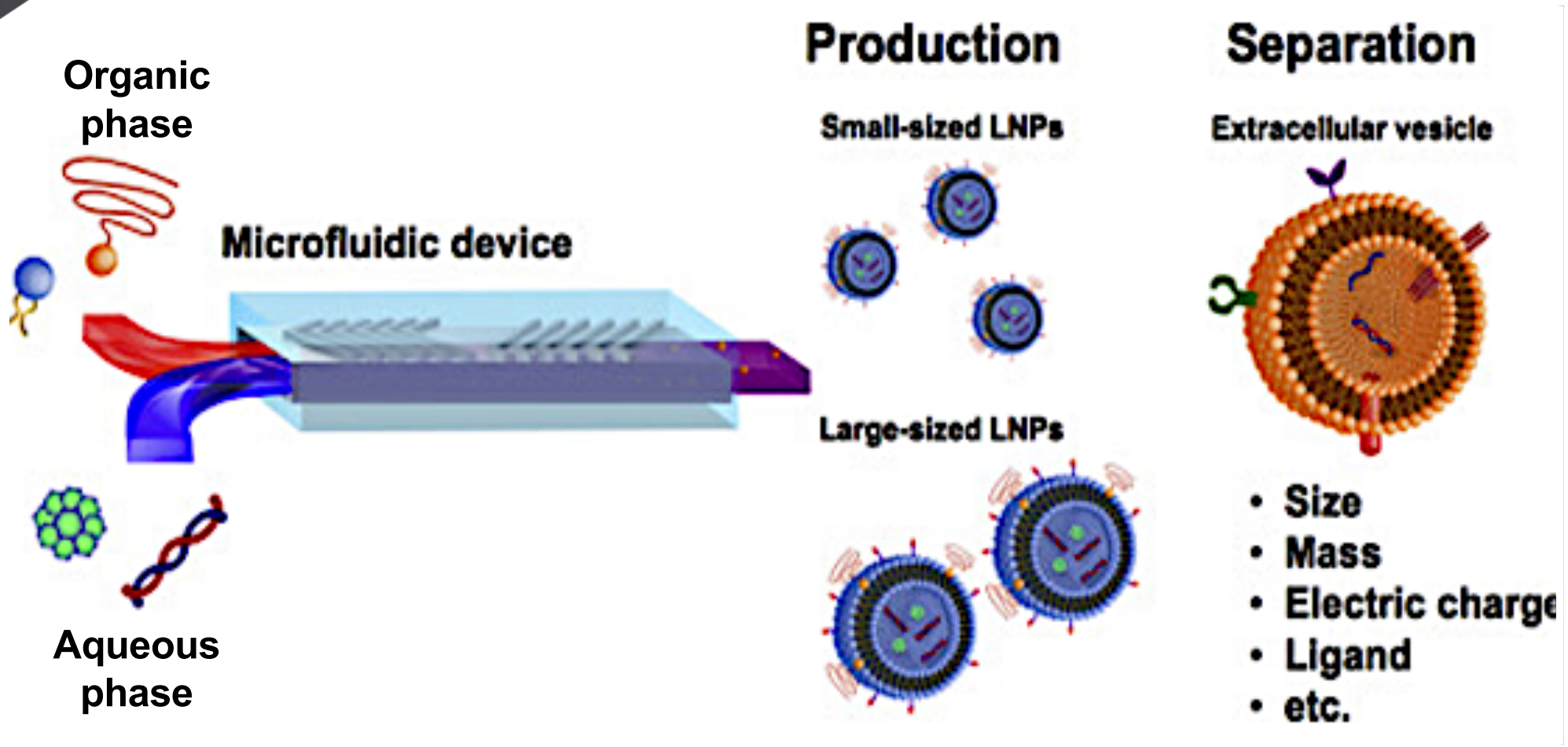
DSPC

KCl, KH_2PO_4, $NaCl$, Na_2HPO_4, Sucrose, aq. ad inj.

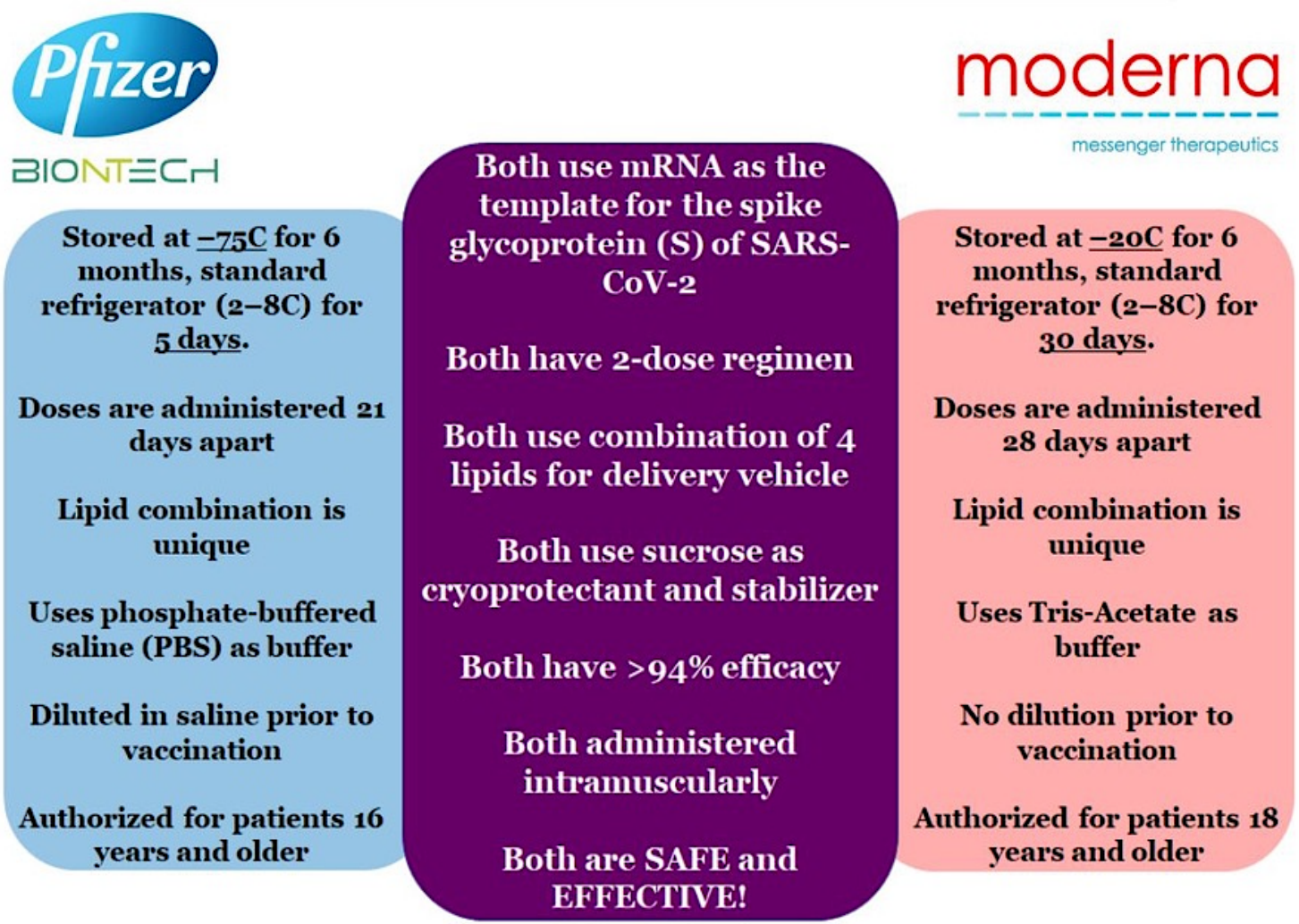
Preparation of liposomes: rehydration of thin lipid films



Preparation of liposomes: microfluidics



How do they compare?



THE UNBIASED SCIENCE PODCAST

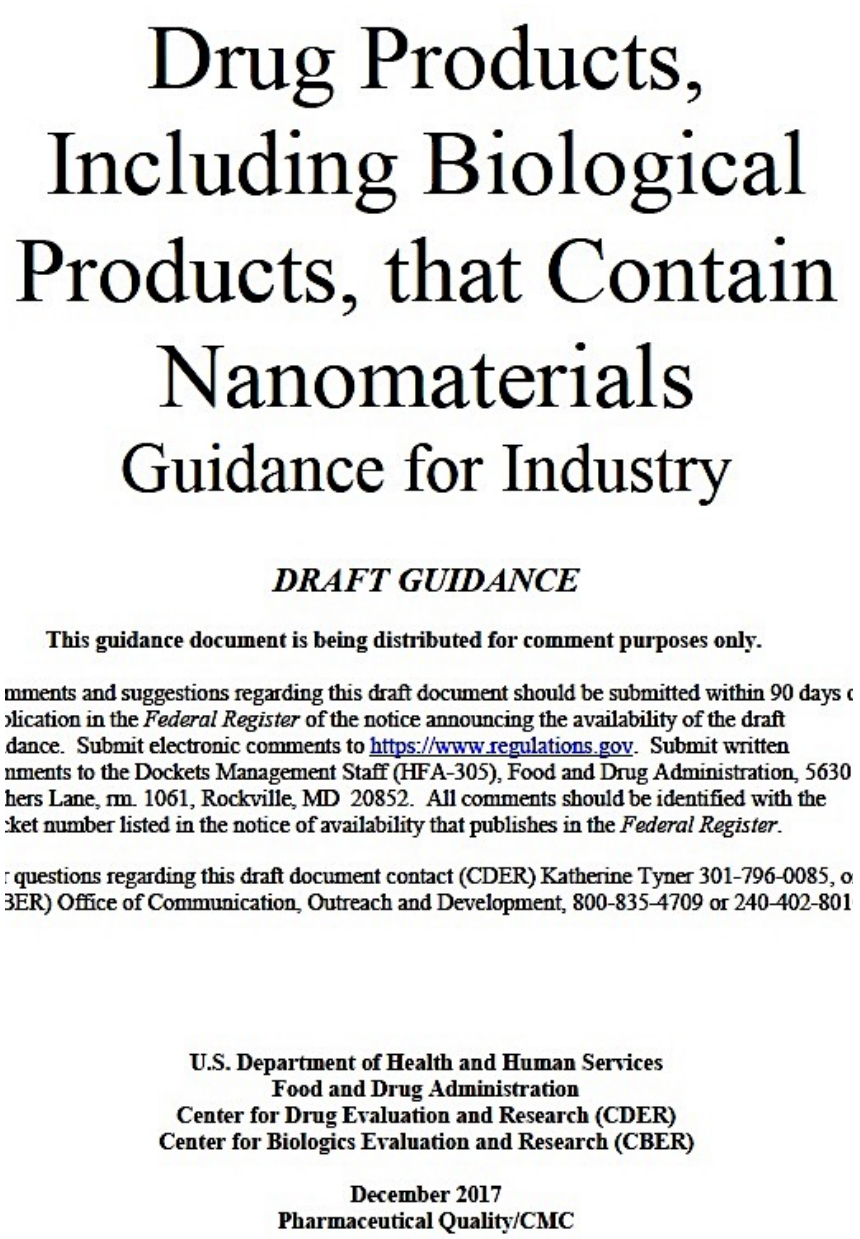
What's next?

Oncology

Drug Class	Platform	Product Candidate	Indication (*Targets*)	Pre-clinical	Phase 1	Phase 2	Phase 3	Rights/Collaborator
mRNA	**FixVac** (fixed combination of shared cancer antigens)	BNT111	Advanced melanoma (Adjuvant & Metastatic)					Global
		BNT112	Prostate cancer					Global
		BNT113	HPV16+ head and neck cancer[1]					Global
		BNT114	Triple negative breast cancer[3]					Global
		BNT115	Ovarian cancer[1]					Global
		BNT116	NSCLC					Global
	iNeST (patient specific cancer antigen therapy)	RO7198457 (BNT122[3])	1L melanoma with CPI[2]					Genentech (global 50:50 profit/loss share)
			Multiple solid tumors					
	Intratumoral Immunotherapy	SAR441000 (BNT131)	Solid tumors (*IL-12sc, IL-15sushi, GM-CSF, IFNα*)					Sanofi (global profit/loss share)
	RiboMabs (mRNA-encoded antibodies)	BNT141	Multiple solid tumors					Global
		BNT142	Multiple solid tumors (*CD3+CLDN6*)					Global
	RiboCytokines (mRNA-encoded cytokines)	BNT151	Multiple solid tumors (*Optimized IL-2*)					Global
		BNT152, BNT153	Multiple solid tumors (*IL-7, IL-2*)					Global

Biontech.de, Sep 3, 2021

FDA draft guidance: Critical Quality Attributes (CQAs)



Drug Products, Including Biological Products, that Contain Nanomaterials

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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olication in the *Federal Register* of the notice announcing the availability of the draft
dance. Submit electronic comments to https://www.regulations.gov. Submit written
nments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630
hers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the
cket number listed in the notice of availability that publishes in the *Federal Register*.

questions regarding this draft document contact (CDER) Katherine Tyner 301-796-0085, o
BER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-801

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2017
Pharmaceutical Quality/CMC

Always:

- Chemical composition
- Average particle size and distribution
- Shape and morphology
- Physical and chemical stability
- Free API, in vitro release kinetics
- Impurities, sterility and endotoxin content.

“Nice” (good) to have:

- Structural attributes related to function.
- Surface properties
- Particle concentration
- Crystal shape


Merci.