COVID-19 vaccine platforms, pharmaceutical and biopharmaceutical aspects

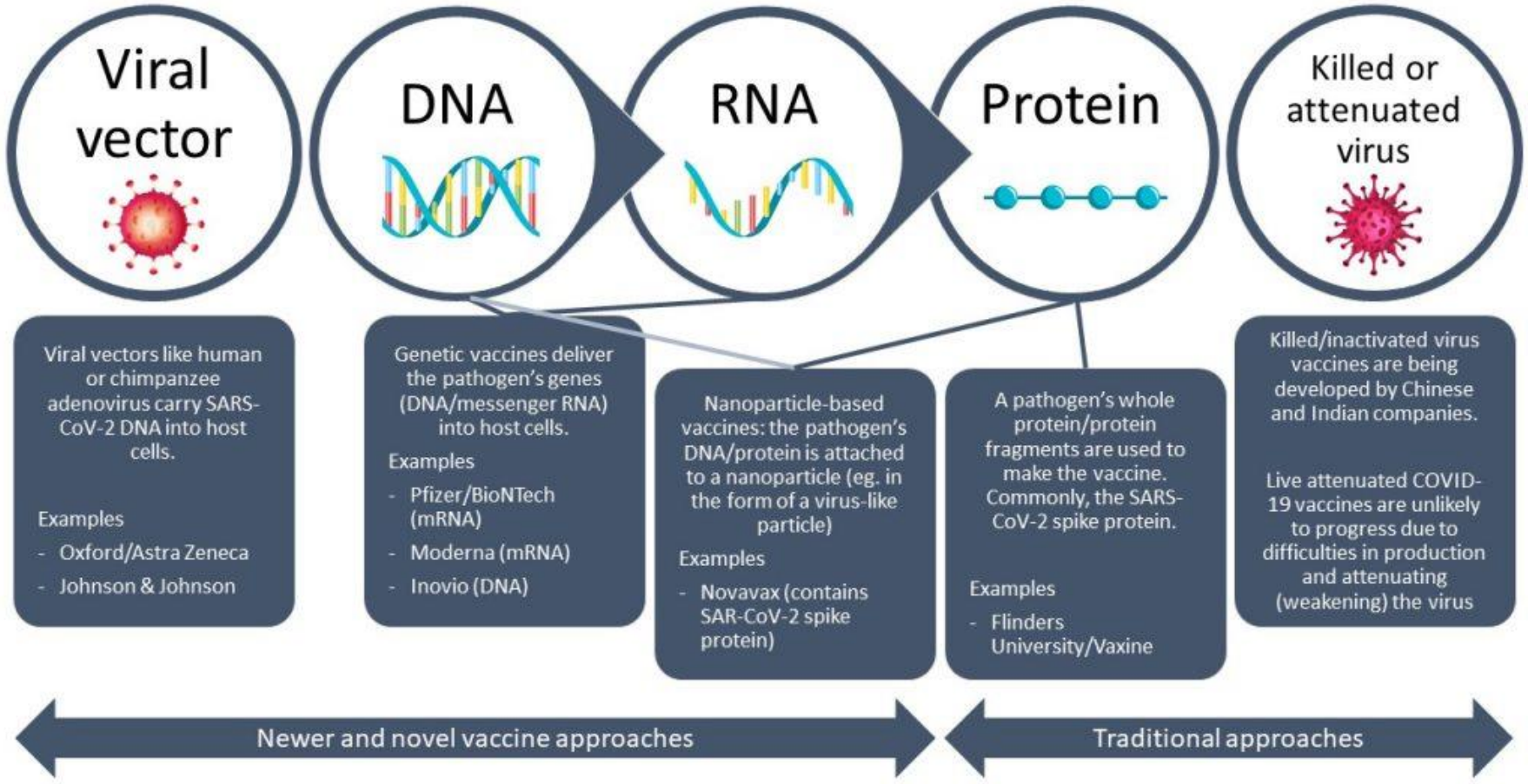
Danish Pharmaceutical Society

Camilla Foged, Professor, Department of Pharmacy, Faculty of Health and Medical Sciences

UNIVERSITY OF COPENHAGEN

Vaccine Design and Delivery

Vaccine platforms – COVID-19



https://mvec.mcri.edu.au/references/covid-19-vaccine-platforms/

COVID-19 vaccines conditionally authorised for use in EU

Vaccine	Producer	Technology	Status for EU approval
Comirnaty	BioNTech/Pfizer	mRNA	Authorised (21/12-2020)
COVID-19 Vaccine Moderna	Moderna	mRNA	Authorised (6/1-2021)
Vaxzevria	AstraZeneca/Oxford University	Adenovirus	Authorised (29/1-2021)
COVID-19 Vaccine Janssen	Johnson & Johnson	Adenovirus	Authorised (11/3-2021)
CVnCoV	CureVac AG	mRNA	Rolling review (start 12/02-2021)
NVX-CoV2373	Novavax CZ AS	Protein subunit	Rolling review (start 03/02-2021)
Sputnik V	Gamaleya National Centre of Epidemiology and Microbiology	Adenovirus	Rolling review (start 04/03-2021)
COVID-19 Vaccine (Vero Cell) Inactivated	Sinovac Life Sciences Co., Ltd	Inactivated	Rolling review (start 04/05-2021)

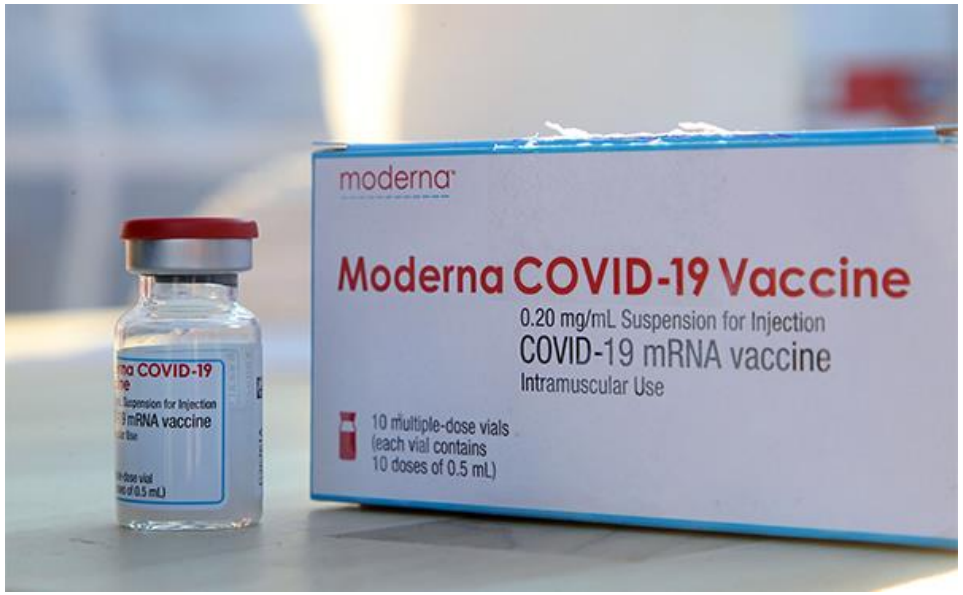
Source: Danish Medicines Agency and EMA

Danish Advance Purchase Agreements

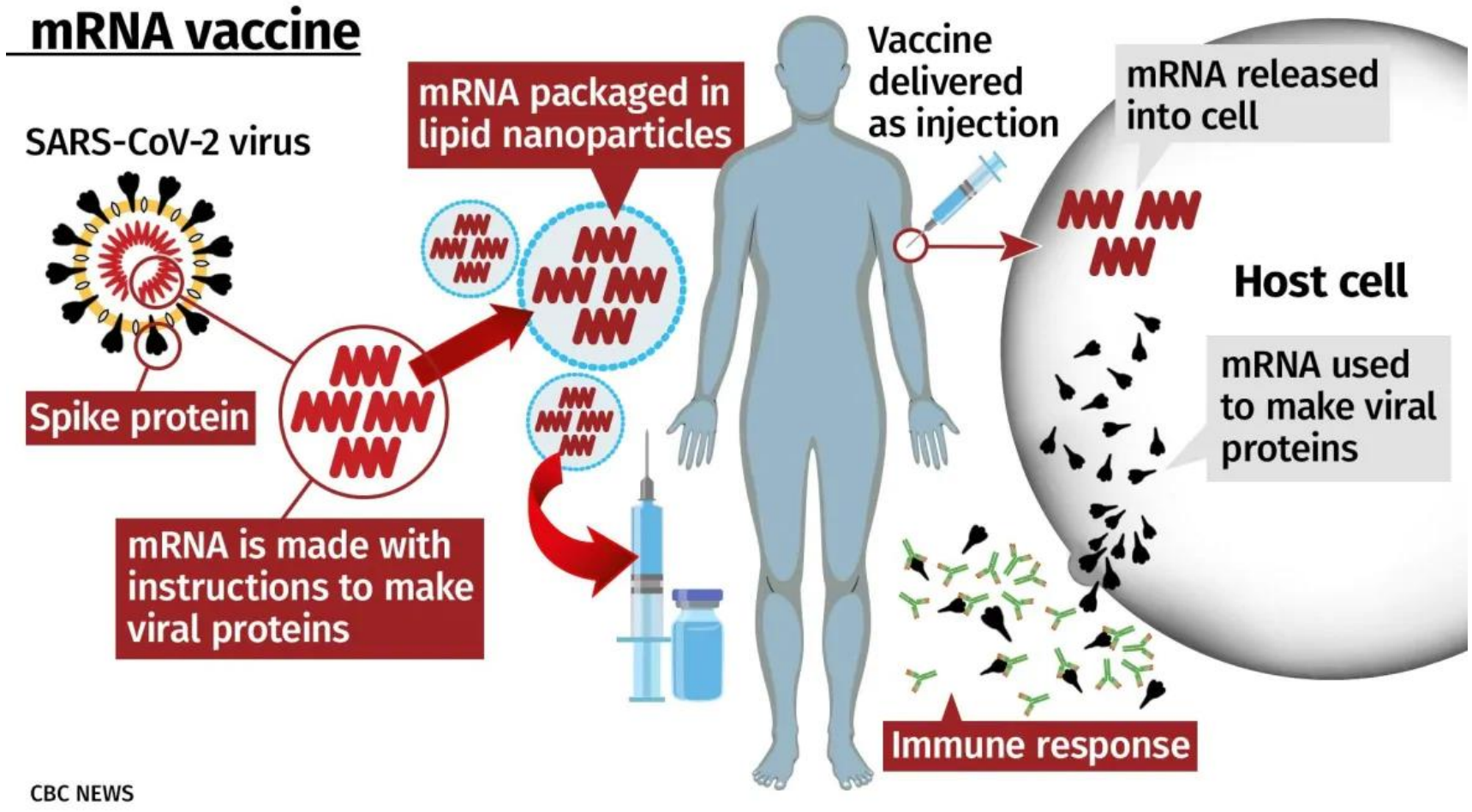
Vaccine	Vaccine doses	Vaccinations
BioNTech/Pfizer	app. 9.2 mio.	app. 4.6 mio.
Moderna	app. 10.8 mio.	app. 5.4 mio.
AstraZeneca	app. 5.2 mio.	app. 2.6 mio.
Johnson & Johnson	app. 7.0 mio.	app. 7.0 mio.
CureVac	app. 9.1 mio.	app. 4.5 mio.
Sanofi-GSK	app. 3.9 mio.	app. 1.9 mio.
Total		app. **26 mio.**

Source: Danish Medicines Agency

mRNA vaccines

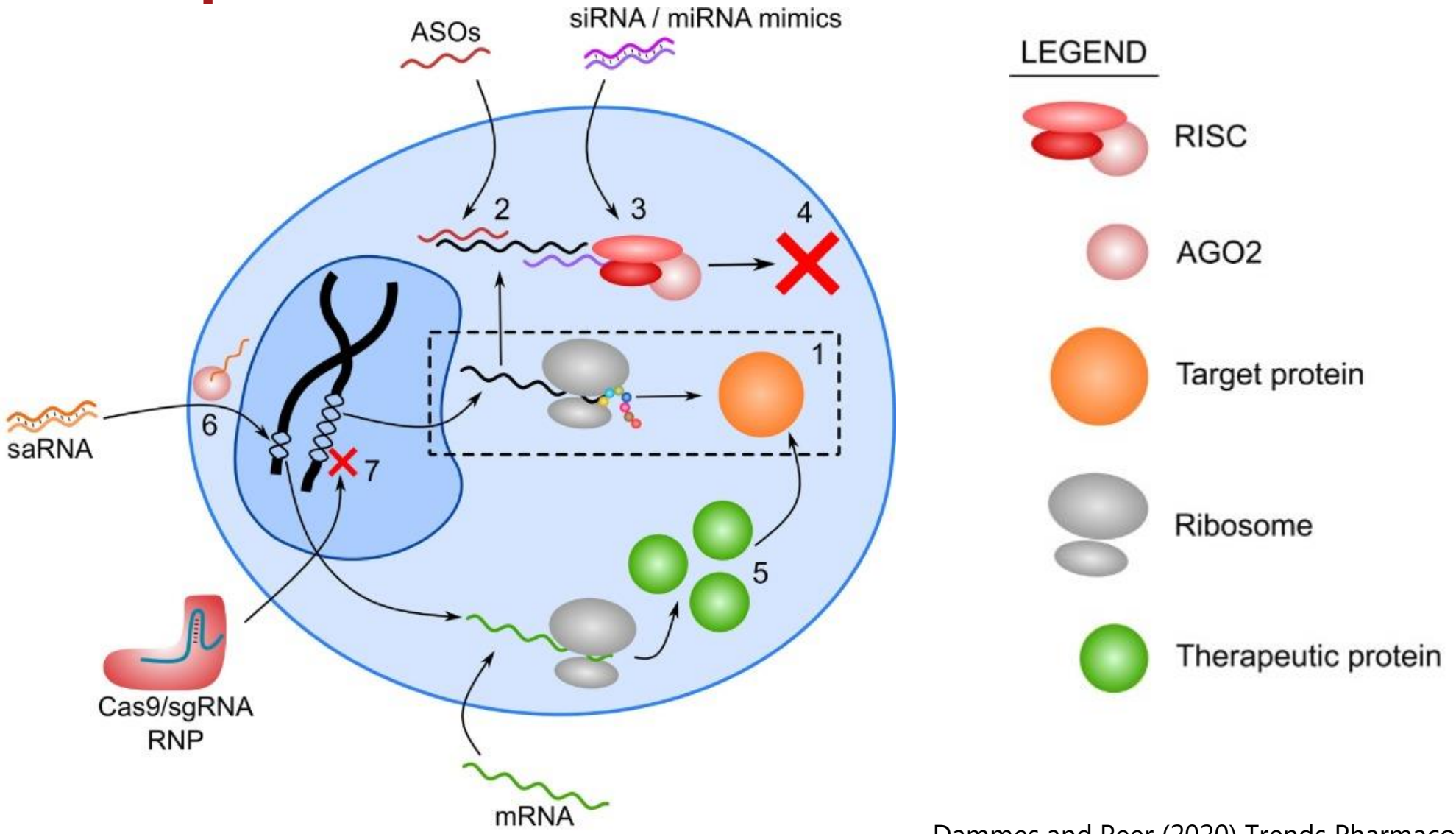


mRNA vaccines



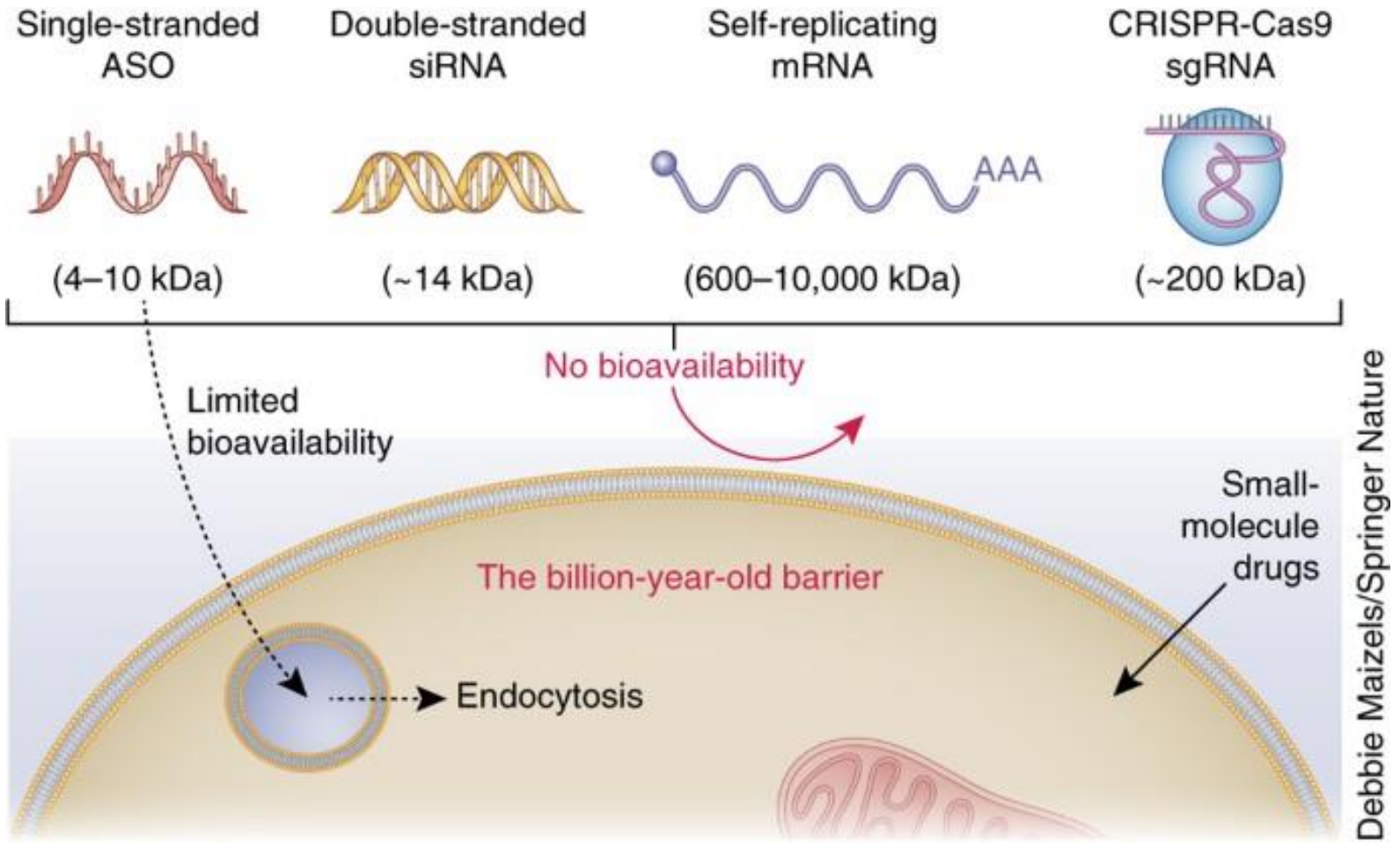
CBC News. https://www.cbc.ca/news/health/covid-vaccines-canada-profiles-1.5708240

RNA therapeutics



Dammes and Peer (2020) Trends Pharmacol Sci

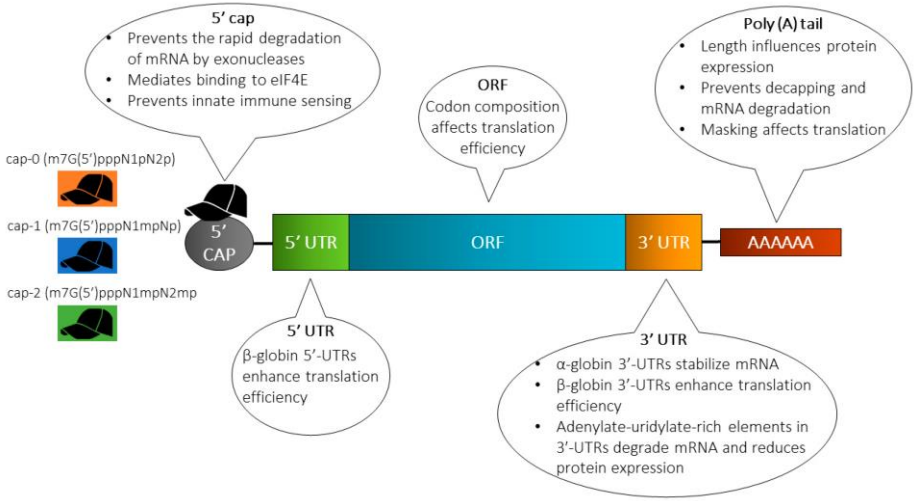
Delivery challenges

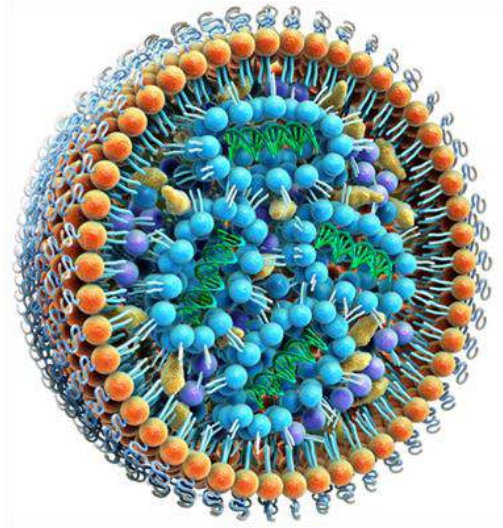


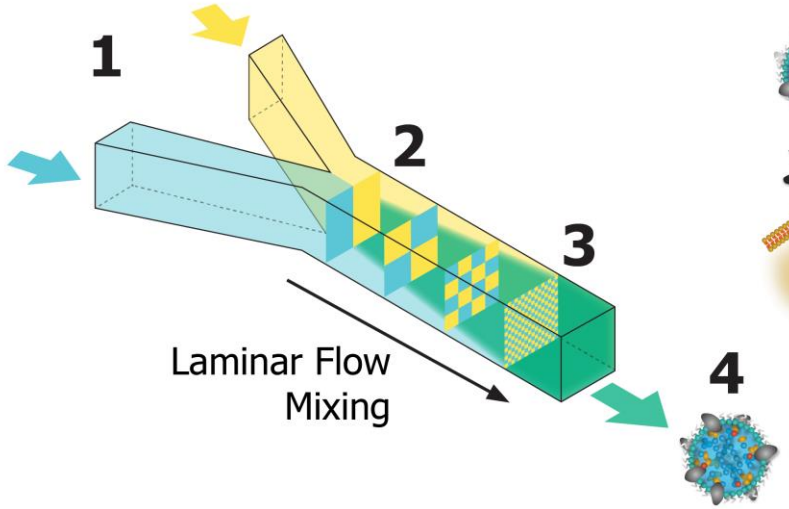
Steven F Dowdy (2017) Nature Biotechnology

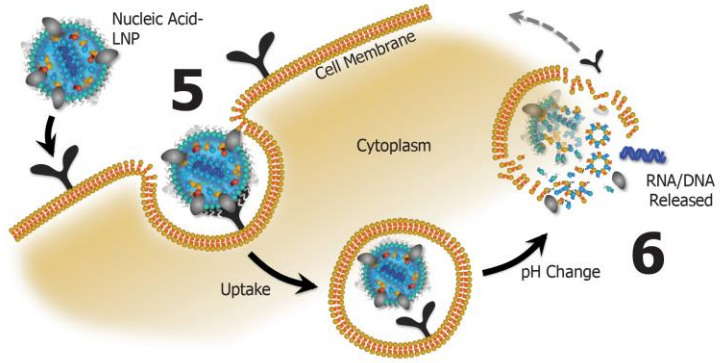
mRNA vaccines - enabling technologies

- mRNA stabilisation
- Delivery system: Lipid nanoparticles (LNPs)
- Scalable LNP manufacturing: Microfluidics

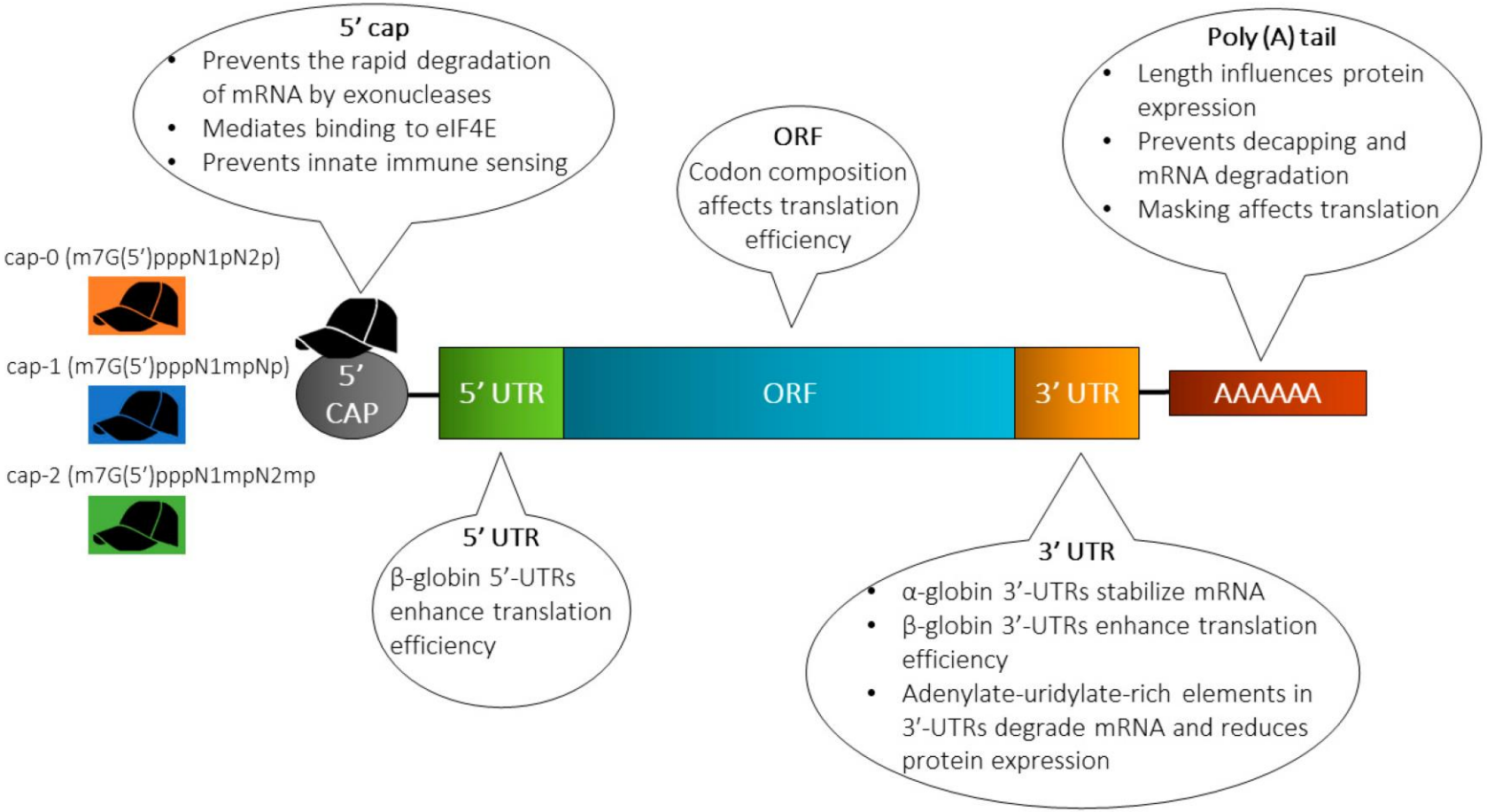






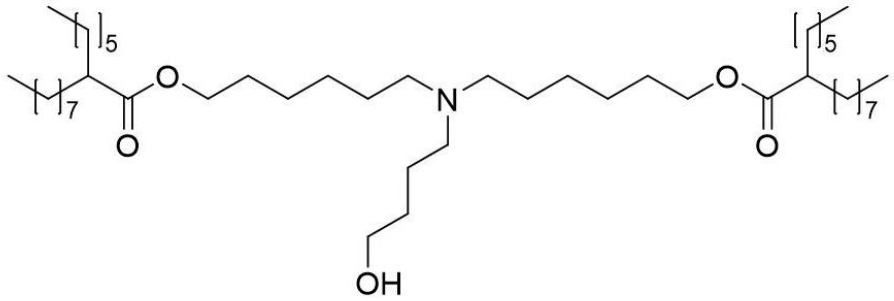


Stabilisation of *in vitro* transcribed (IVT) mRNA



Wadhwa *et al.*, Pharmaceutics 2020

Ionizable cationic lipids



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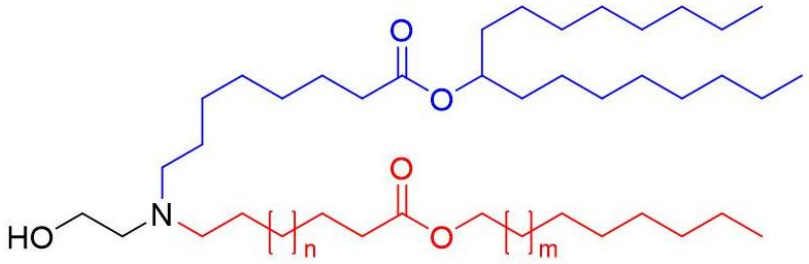
ALC-0315 (Acuitas Therapeutics; used by BioNTech)

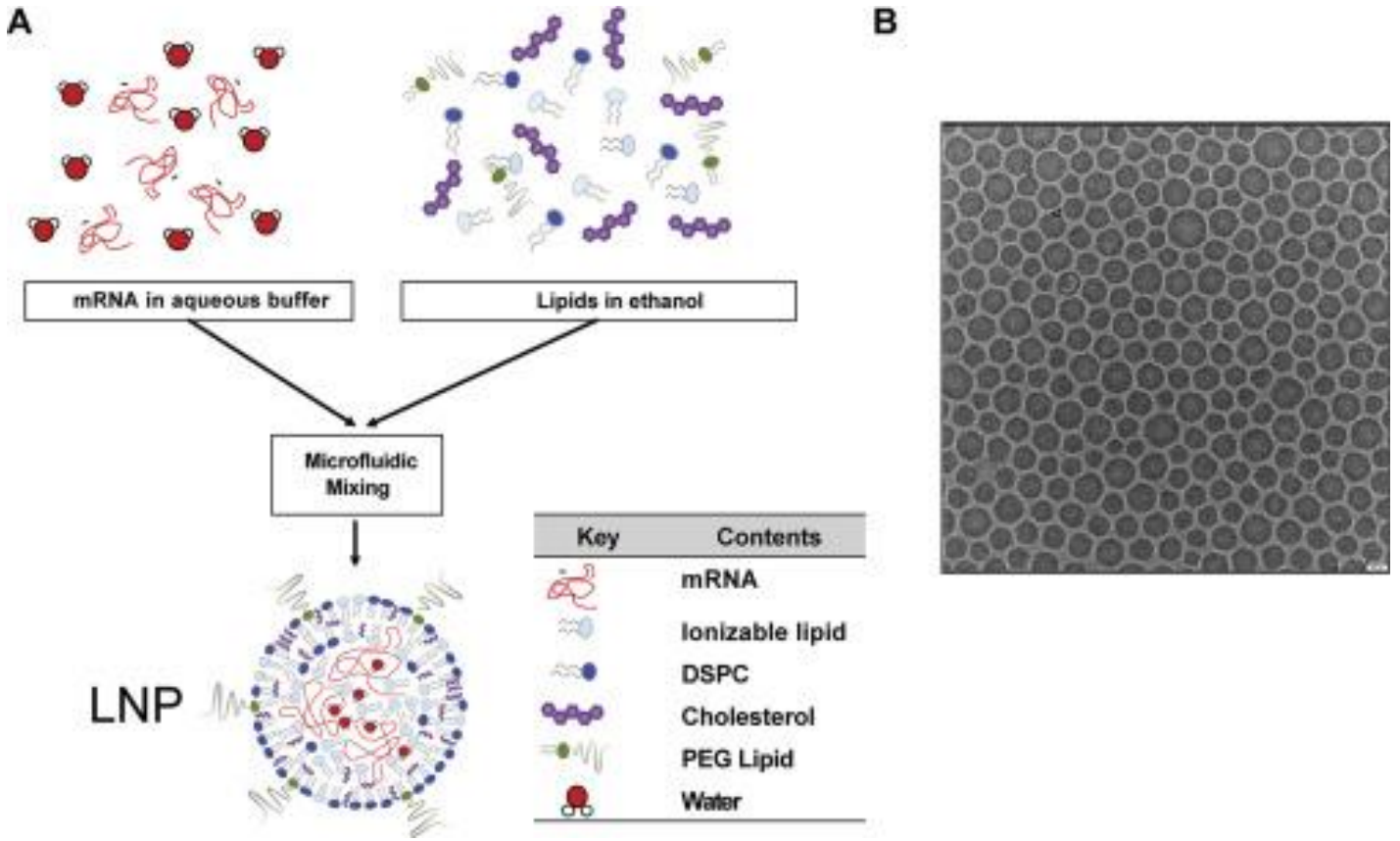


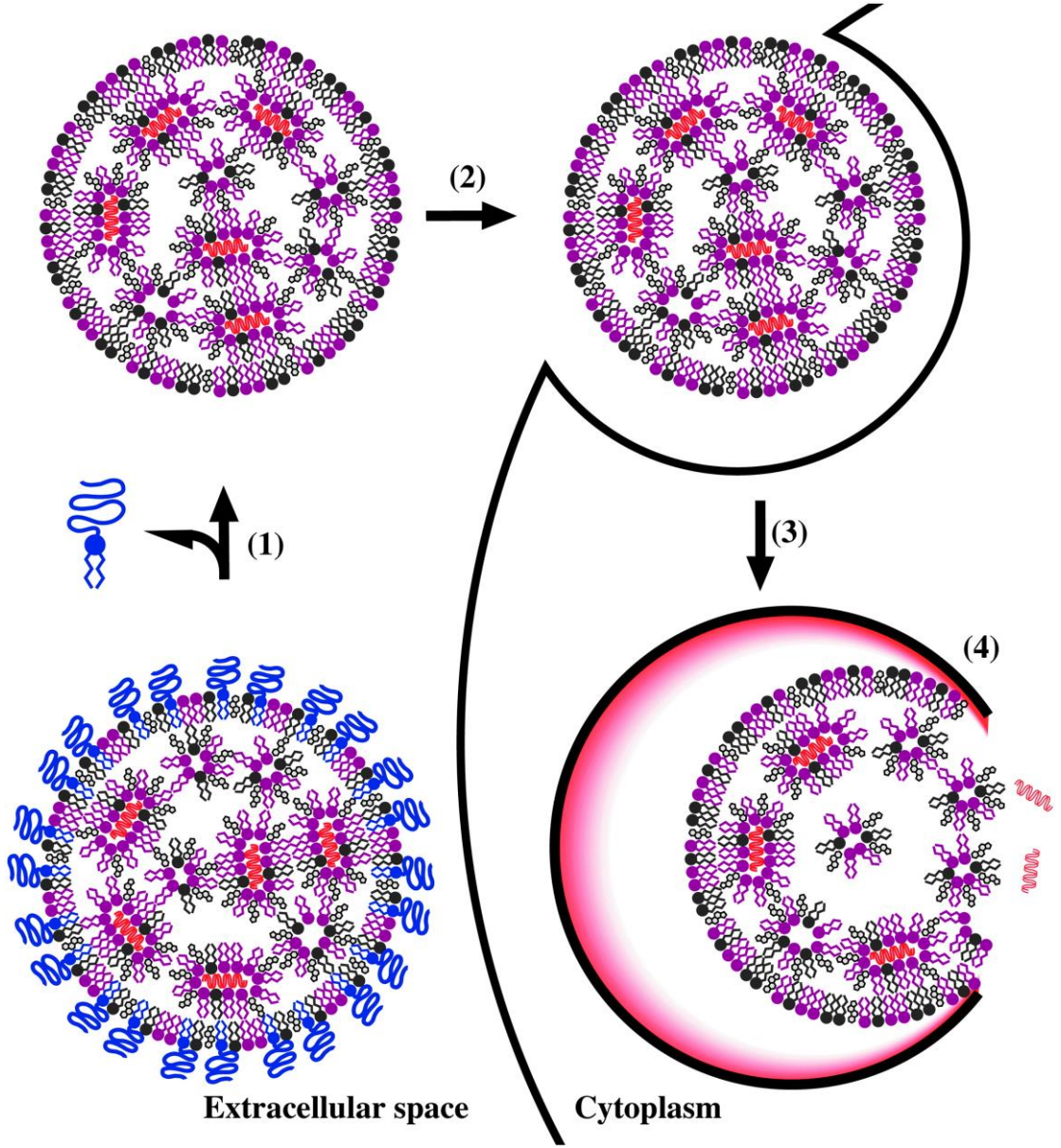
9

n = 1 ; m = 2 : SM-102 (Moderna Lipid H))

n = 3 ; m = 1 : Moderna Lipid 5

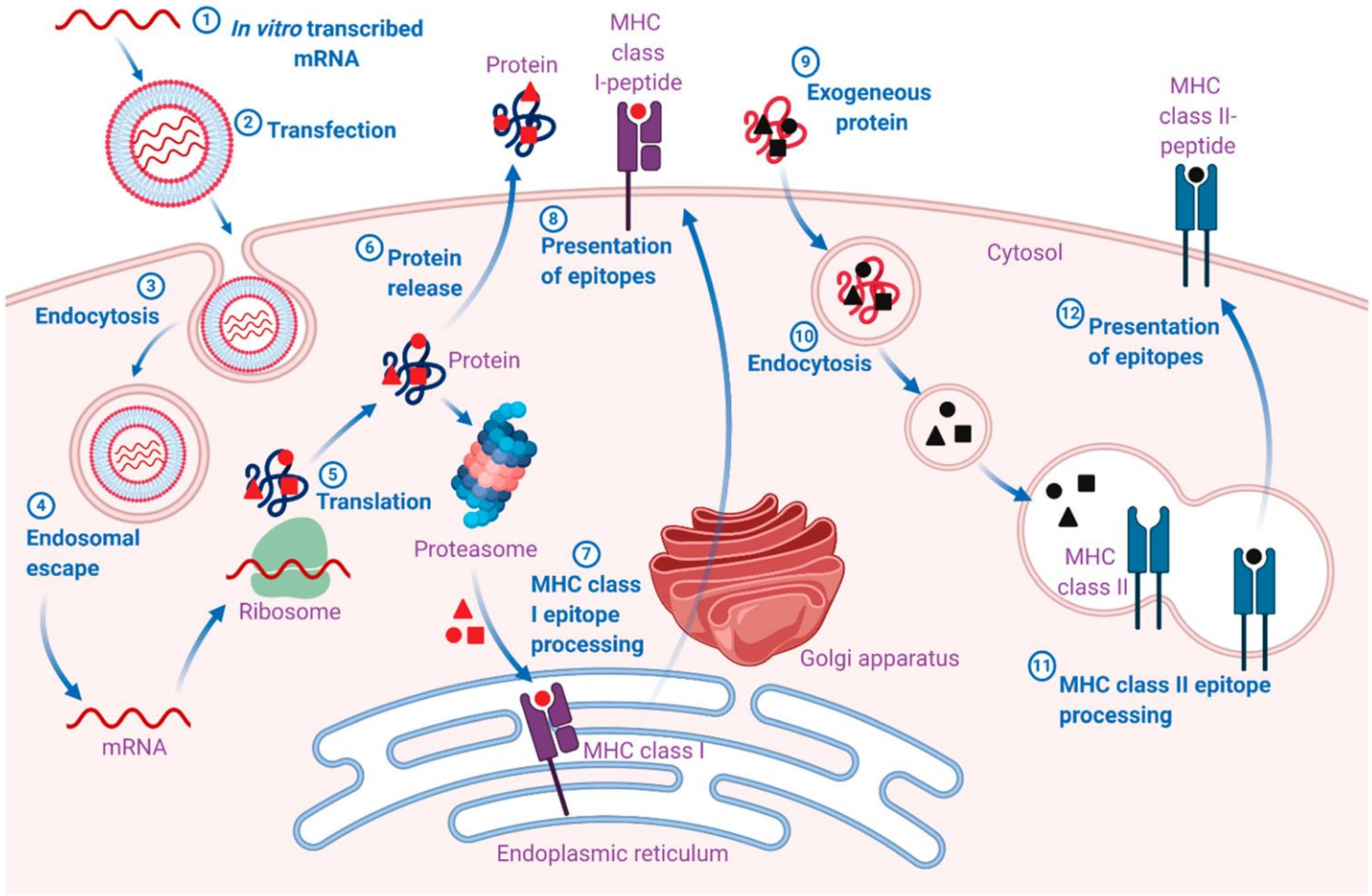
Lipid nanoparticles (LNPs)





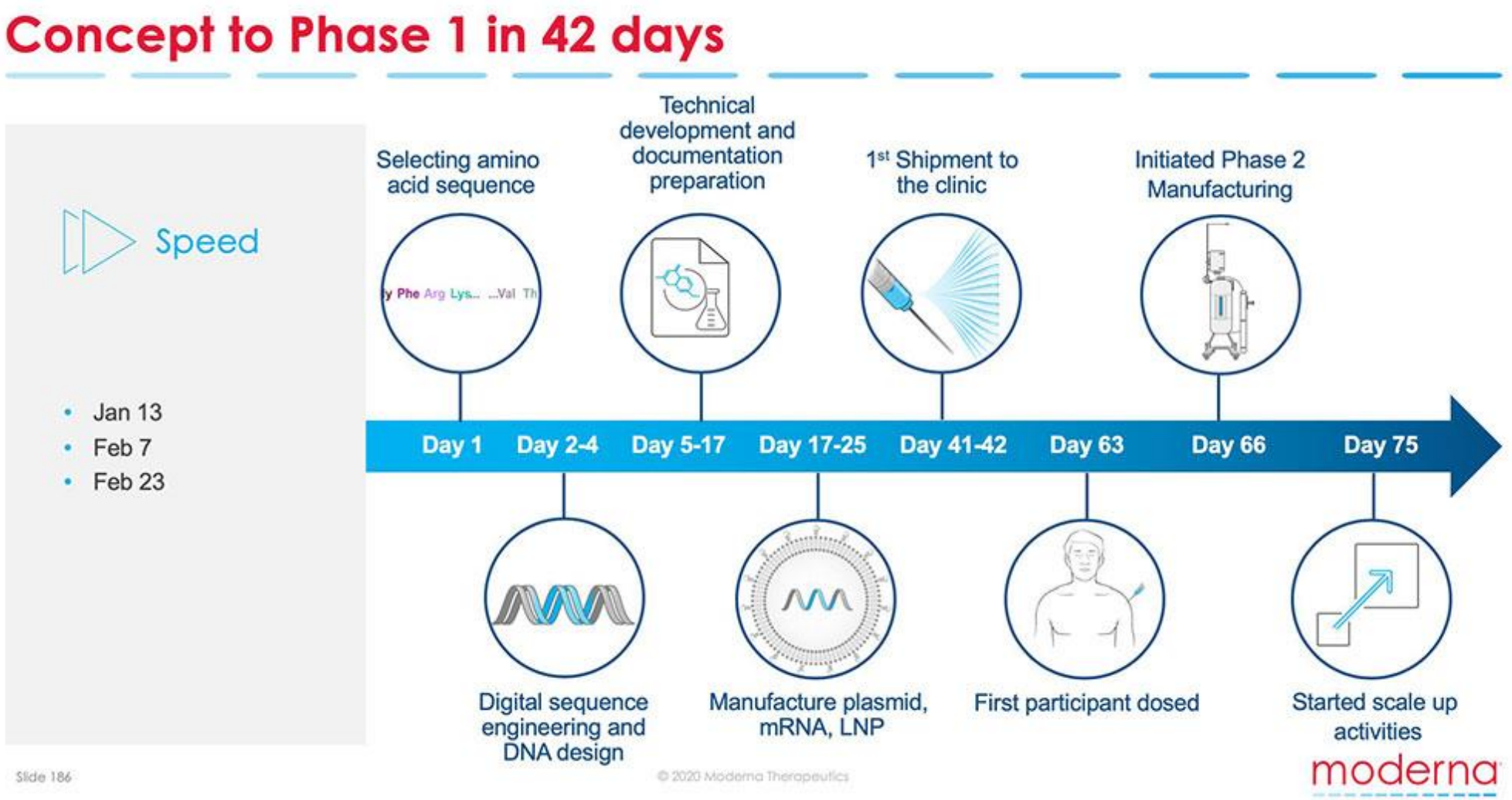
Kulkarni *et al.* 2018. Nucleic Acid Ther

mRNA vaccines – mechanism of action

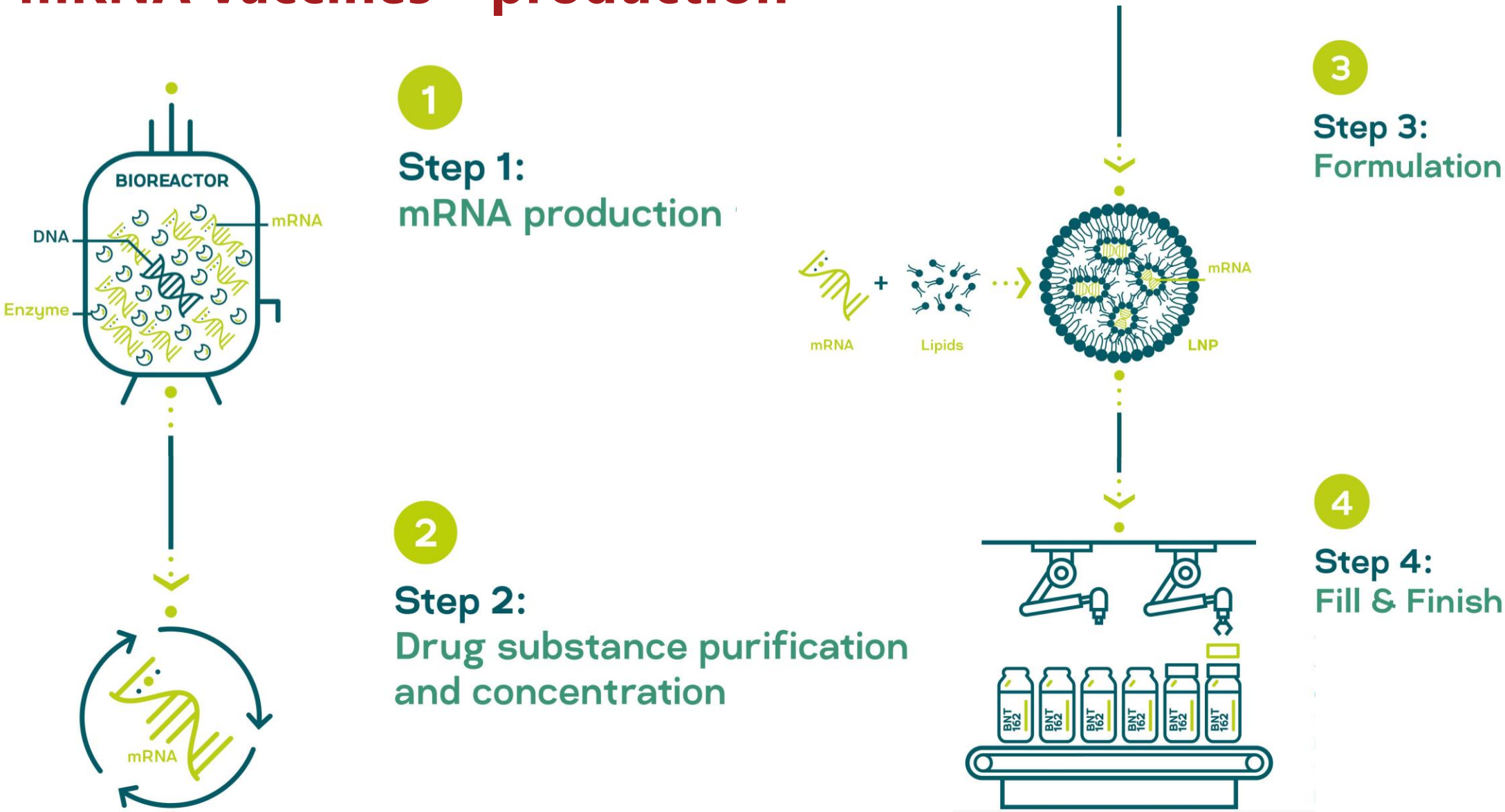


Wadhwa *et al.*, Pharmaceutics 2020

SARS-CoV2 mRNA vaccine (mRNA-1273) - Moderna



mRNA vaccines - production

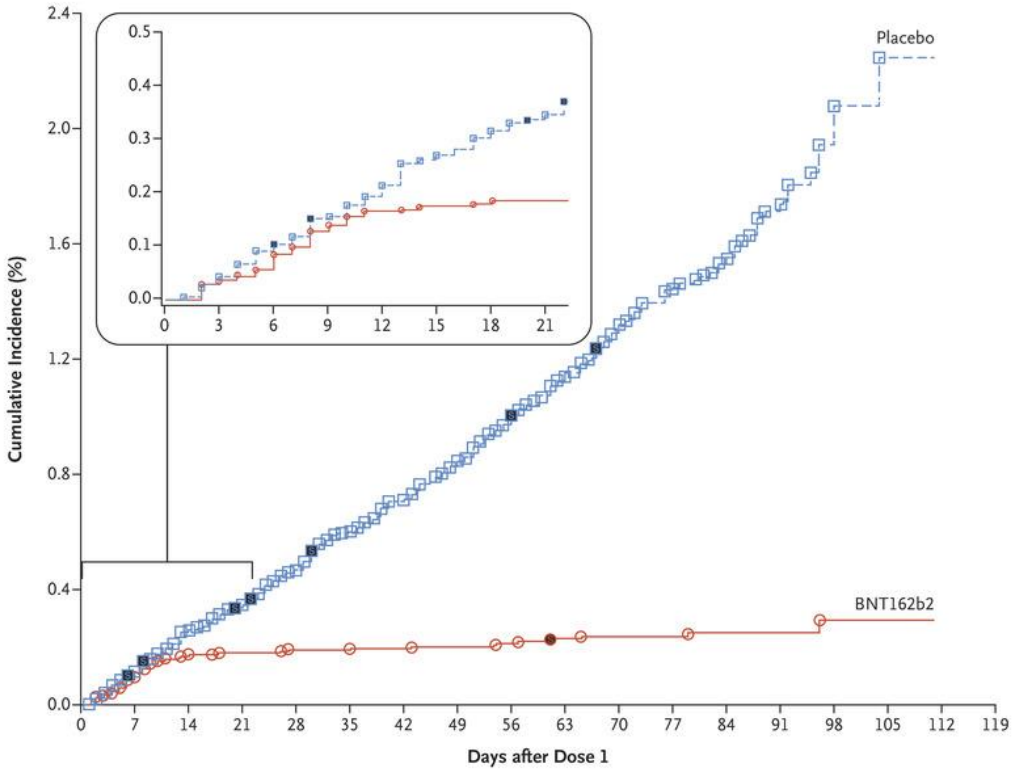


Kilde: https://www.biopharma-reporter.com/Article/2021/02/10/BioNTech-starts-production-at-Marburg-COVID-19-vaccine-site

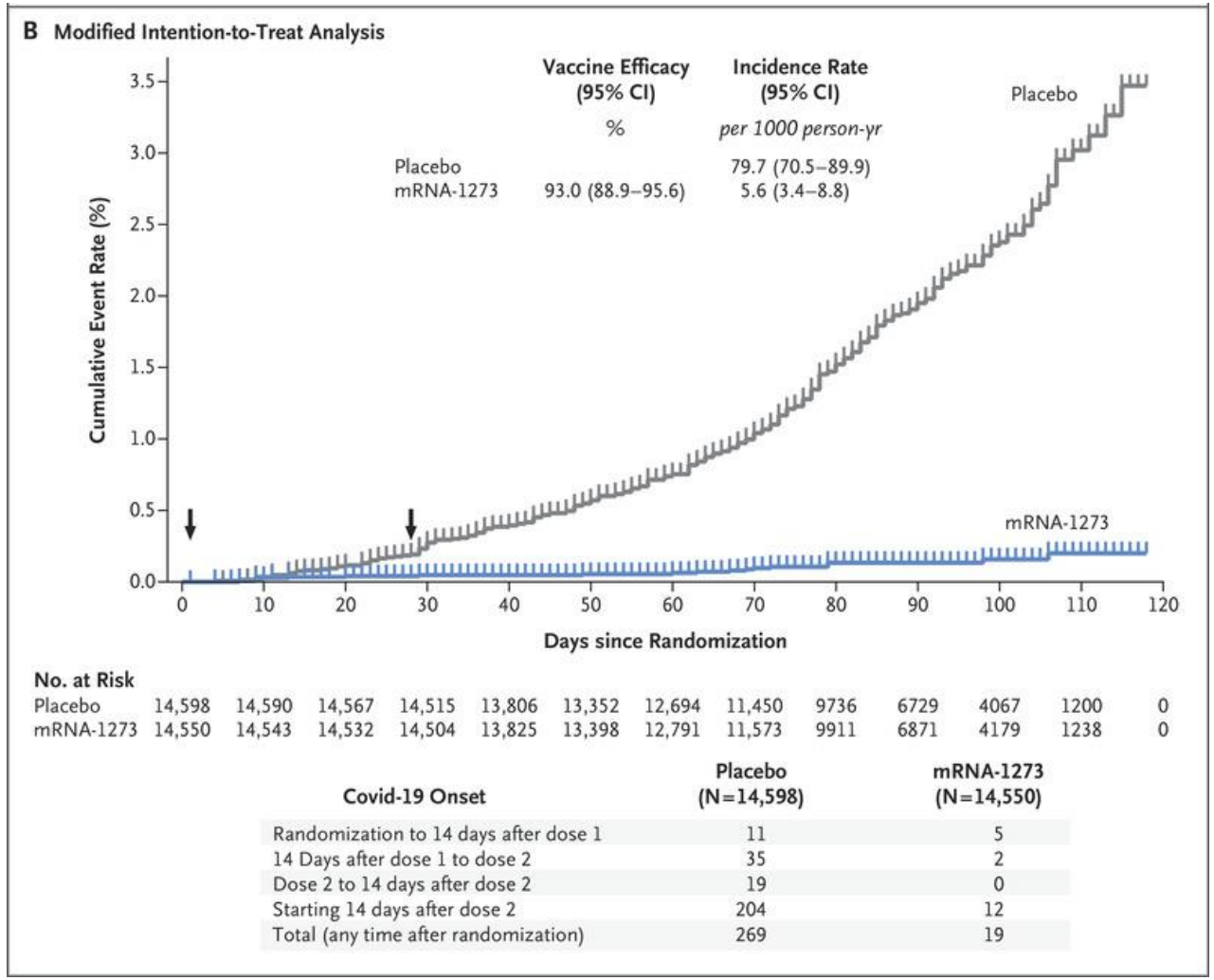
Manufacturing moonshot: How Pfizer makes its millions of Covid-19 vaccine doses

Kilde: https://edition.cnn.com/2021/03/31/health/pfizer-vaccine-manufacturing/index.html

Efficacy – phase III



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)



Covid-19 Onset	Placebo (N=14,598)	mRNA-1273 (N=14,550)
Randomization to 14 days after dose 1	11	5
14 Days after dose 1 to dose 2	35	2
Dose 2 to 14 days after dose 2	19	0
Starting 14 days after dose 2	204	12
Total (any time after randomization)	269	19

Effectiveness - real life data

TABLE 2. COVID-19 vaccine effectiveness among health care personnel case-patients and controls, by number of COVID-19 vaccine doses received before SARS-CoV-2 test date — 33 U.S. sites, January–March 2021

Interval from dose to test date	No. (%) Case-patients* (N = 623)	No. (%) Controls* (N = 1,220)	Vaccine effectiveness† % (95% CI) Unadjusted	Vaccine effectiveness† % (95% CI) Adjusted§
Dose 1				
≥14 days	64 (10)	241 (20)	82.2 (75.1–87.3)	81.7 (74.3–86.9)
Dose 2				
≤2 days	5 (<1)	109 (9)		
3–6 days	16 (3)	85 (7)		
≥7 days	19 (3)	184 (15)	93.4 (86.4–96.8)	93.5 (86.5–96.9)

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 70 May 14, 2021

Interim Estimates of Vaccine Effectiveness of Pfizer-BioNTech and Moderna COVID-19 Vaccines Among Health Care Personnel — 33 U.S. Sites, January–March 2021

Tamara Pilishvili, PhD[1]; Katherine E. Fleming-Dutra, MD[1]; Jennifer L. Farrar, MPH[1]; Ryan Gierke, MPH[1]; Nicholas M. Mohr, MD[2]; David A. Talan, MD[3]; Anusha Krishnadasan, PhD[3]; Karisa K. Harland, PhD[2]; Howard A. Smithline, MD[4]; Peter C. Hou, MD[5]; Lilly C. Lee, MD[6]; Stephen C. Lim, MD[7]; Gregory J. Moran, MD[3]; Elizabeth Krebs, MD[8]; Mark Steele, MD[9]; David G. Beiser, MD[10]; Brett Faine, PharmD[2]; John P. Haran, MD, PhD[11]; Utsav Nandi, MD[12]; Walter A. Schrading, MD[13]; Brian Chinnock, MD[14]; Daniel J. Henning, MD[15]; Frank LoVecchio, DO[16]; Joelle Nadle, MPH[17]; Devra Barter, MSc[18]; Monica Brackney, MS[19]; Amber Britton, MPH[20,21]; Kaytlynn Marceaux-Galli, MPH[22]; Sarah Lim, MBBCh[23]; Erin C. Phipps, DVM[24,25]; Ghinwa Dumyati, MD[26]; Rebecca Pierce, PhD[27]; Tiffanie M. Markus, PhD[28]; Deverick J. Anderson, MD[29]; Amanda K. Debes, PhD[30]; Michael Lin, MD[31]; Jeanmarie Mayer, MD[32]; Hilary M. Babcock, MD[33]; Nasia Safdar, MD, PhD[34,35]; Marc Fischer, MD[1]; Rosalyn Singleton, MD[36]; Nora Chea, MD[1]; Shelley S. Magill, MD, PhD[1]; Jennifer Verani, MD[1]; Stephanie Schrag, DPhil[1]; Vaccine Effectiveness Among Healthcare Personnel Study Team

mRNA vaccines - pros and cons

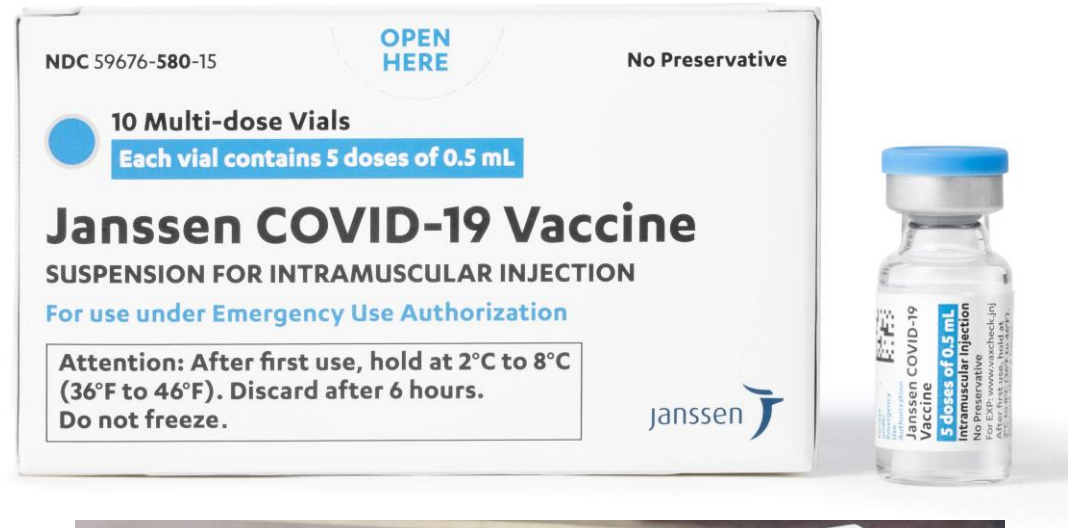
Pros:

- Fast design
- Efficacy approximately 95%
- Safe
- Flexible: mRNA can readily be exchanged (new virus variants)

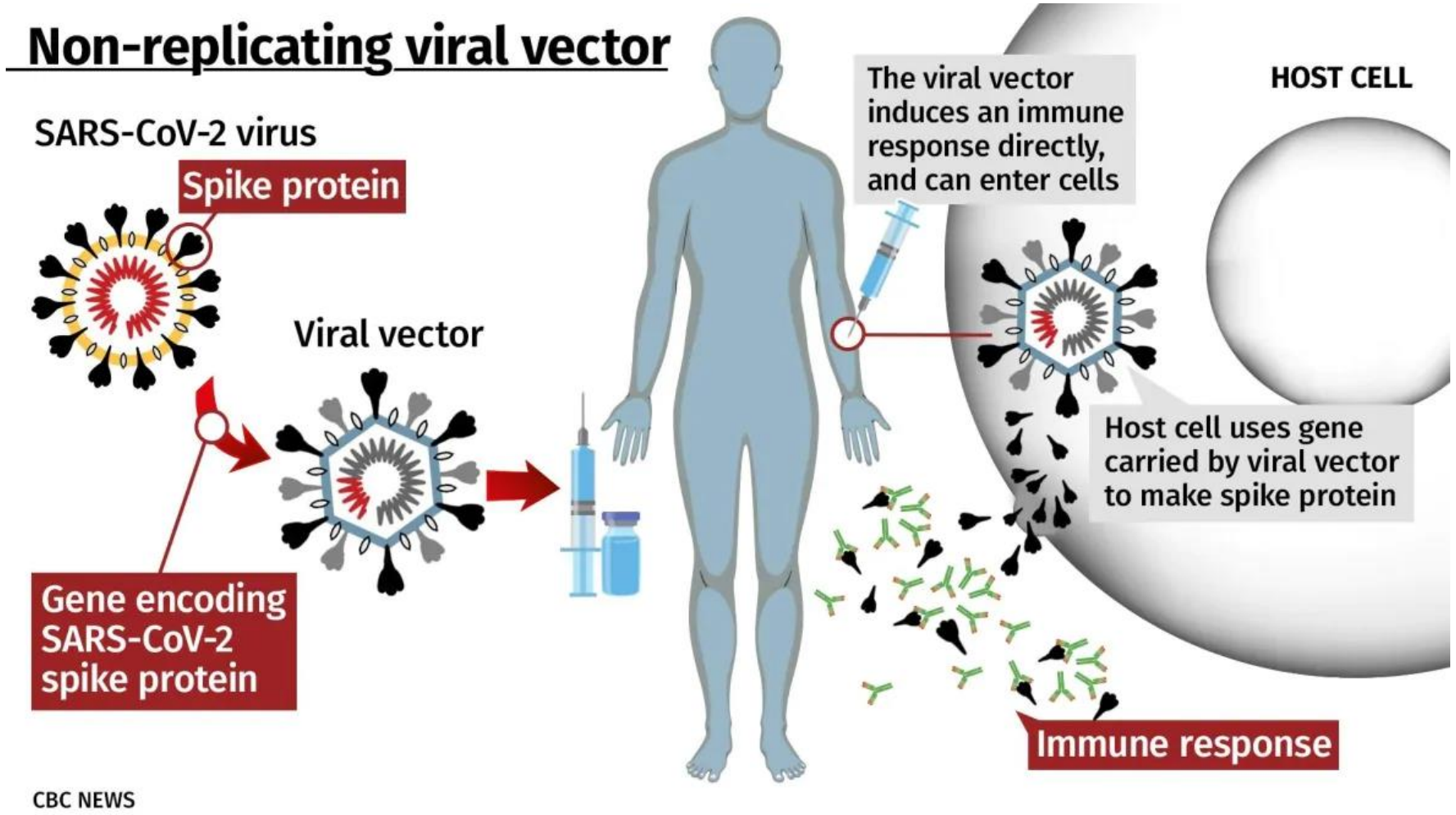
Cons:

- Relatively expensive
- Many raw materials needed for production
- Complex manufacturing process
- Duration of immunity – revaccination will probably be required after 9 months

Adenovirus vaccines

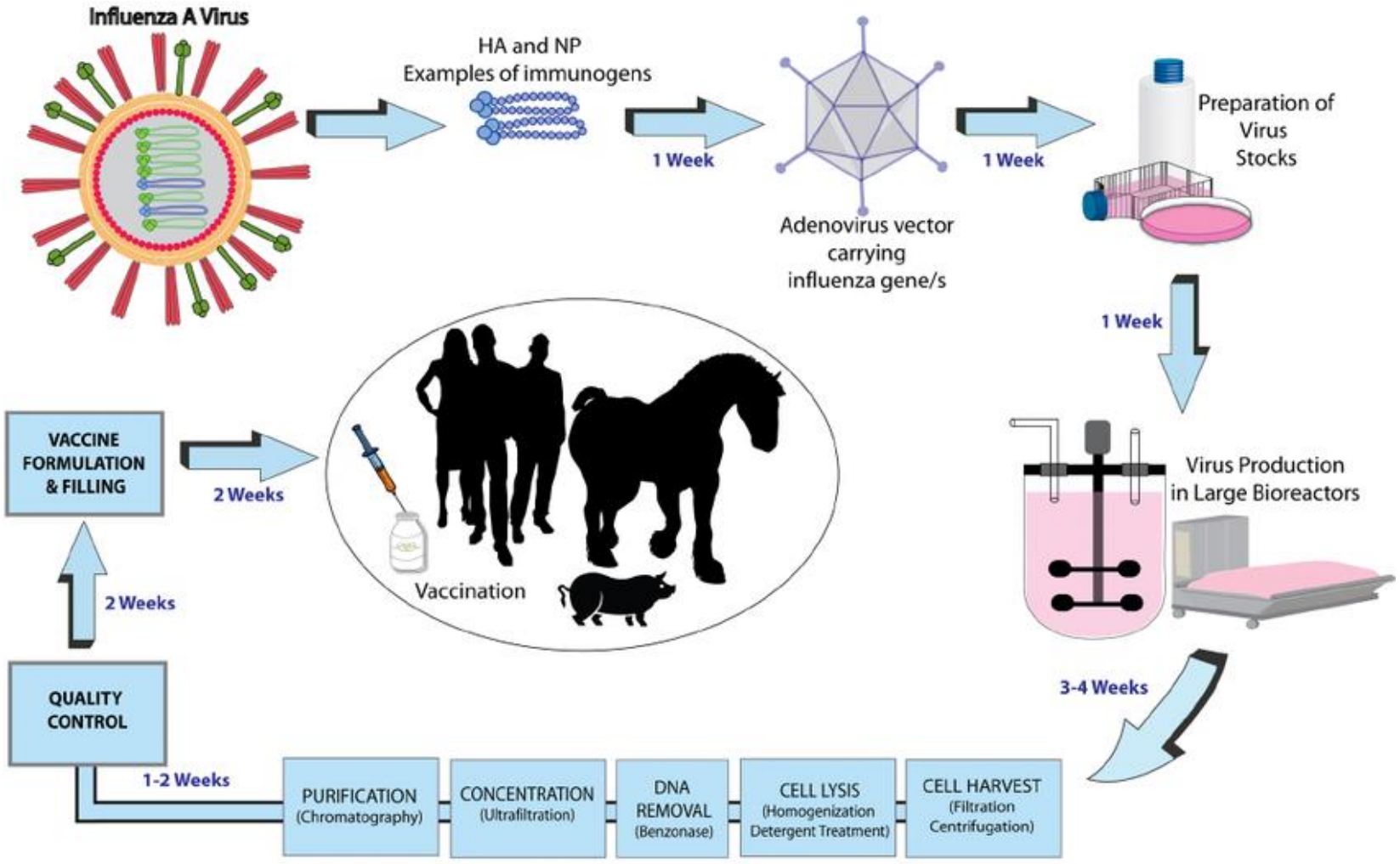


Adenovirus vaccines



Kilde: CBC News. https://www.cbc.ca/news/health/covid-vaccines-canada-profiles-1.5708240

Adenovirus vaccines - production



Vemula and Mittal (2010) Production of adenovirus vectors and their use as a delivery system for influenza vaccines. Expert Opinion on Biological Therapy **10**, 1469-1487

Adenovirus vaccines – pros and cons

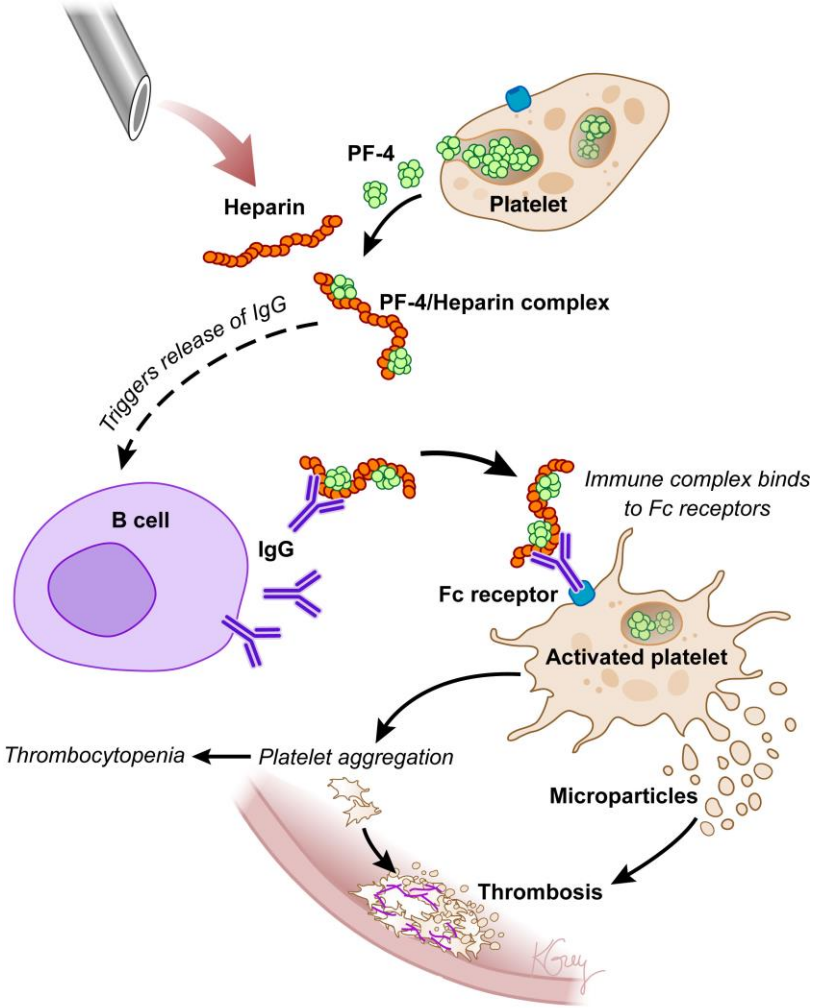
Pros:

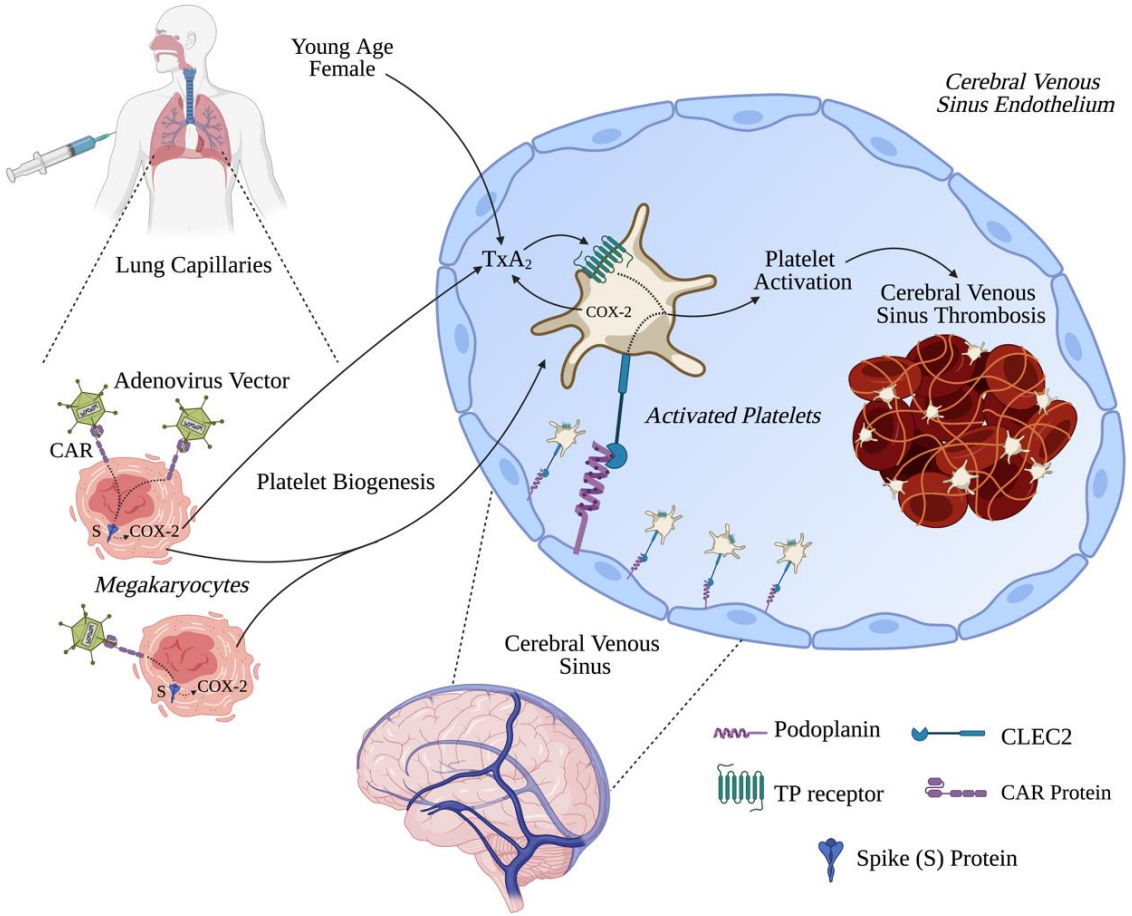
- Rapid design
- Cheap
- Stability
- Easy distribution and storage
- Single dose vaccines

Cons:

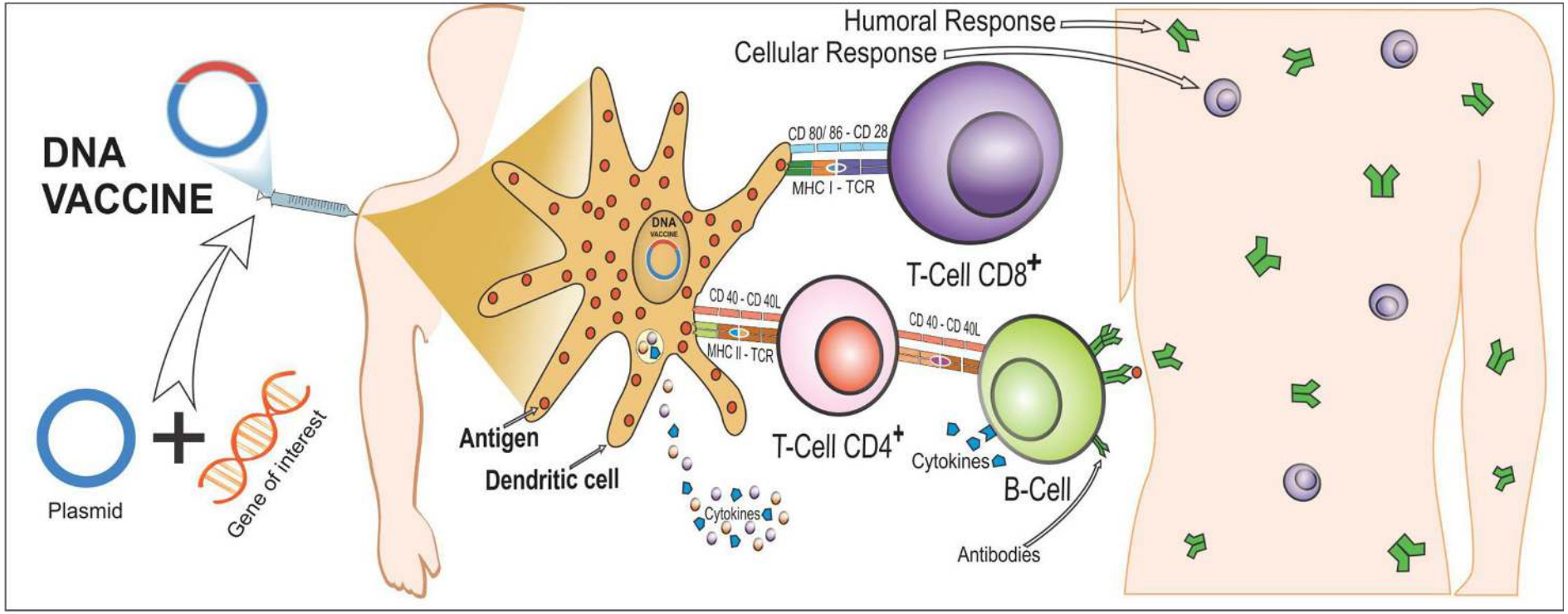
- Efficacy approximately 60%
- Revaccination: Decreased efficacy is expected (emergency vaccine)
- Safety (VITT)

Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)





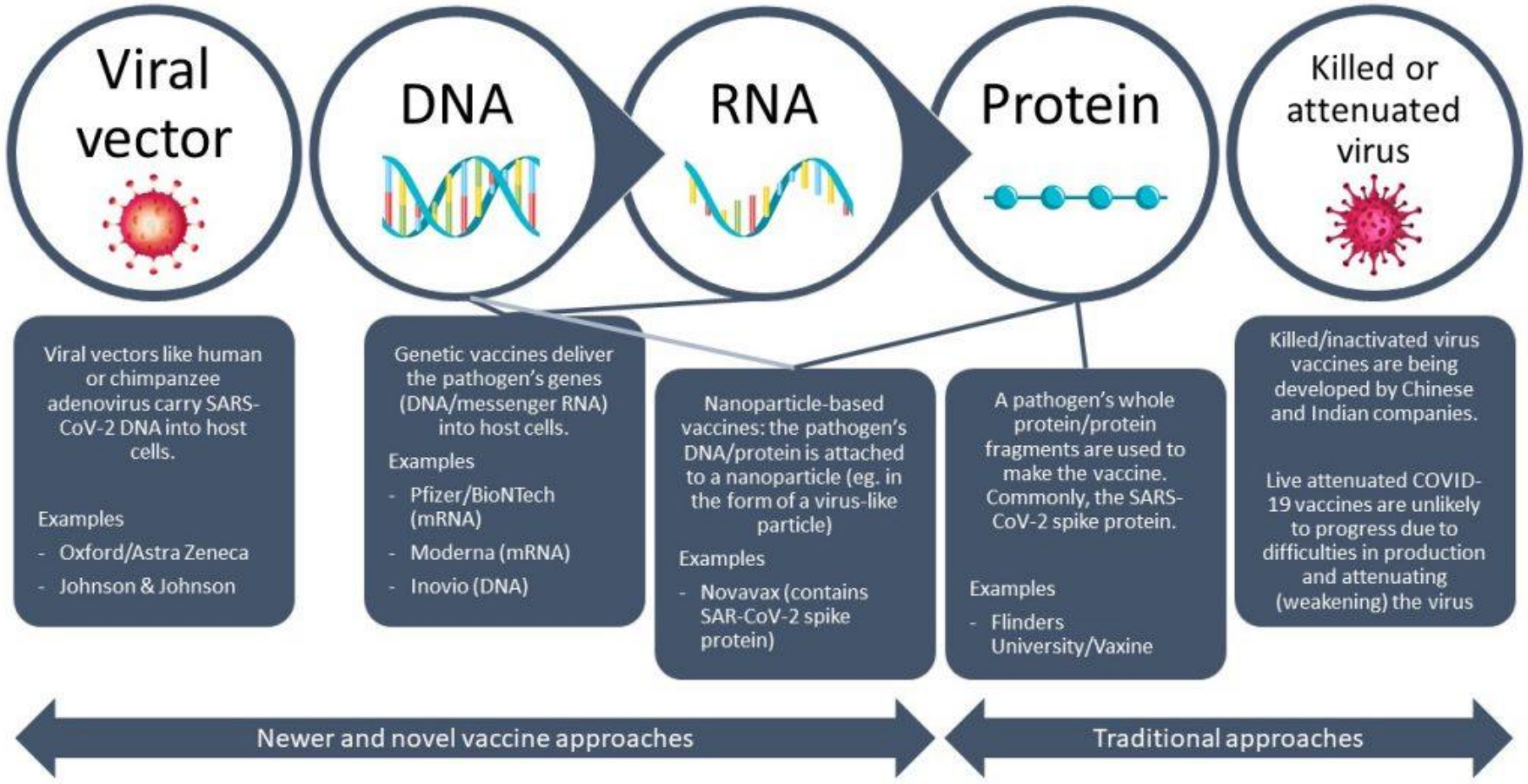
DNA vaccines - CoVaXIX - SSI



Kilde: Silveira *et al.* DNA vaccines against COVID-19: Perspectives and challenges, Life Sciences, Volume 267, 2021, 118919

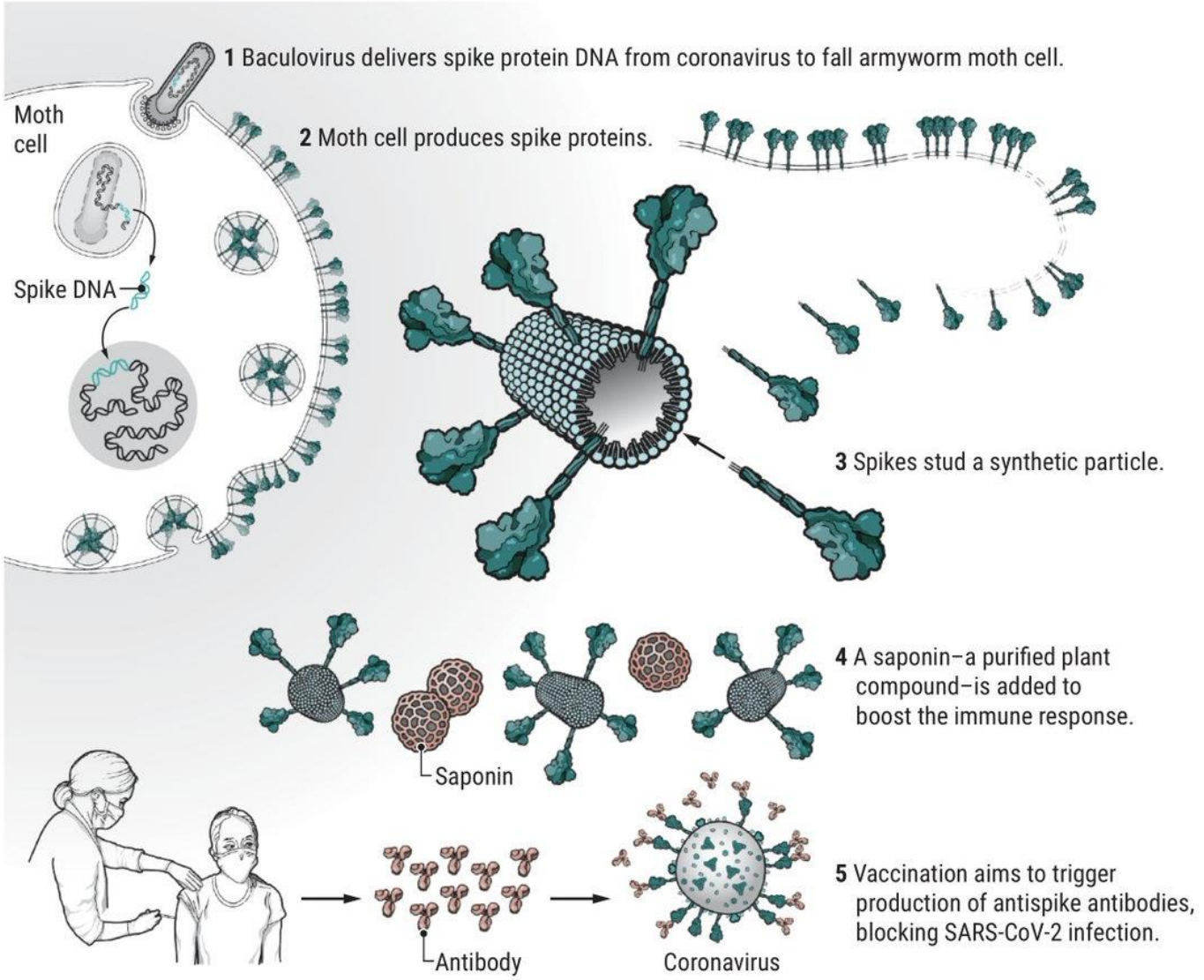
- Stable and can be stored at 4°C. Efficacy?
- Clinical testing not initiated, but is expected to be ready in 2023

Vaccine platforms – COVID-19

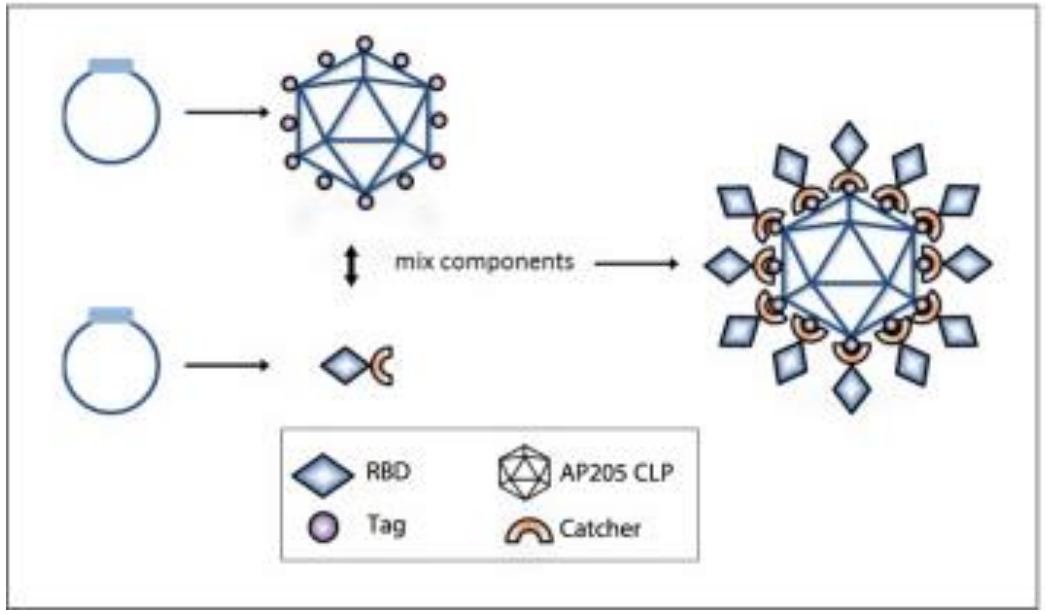


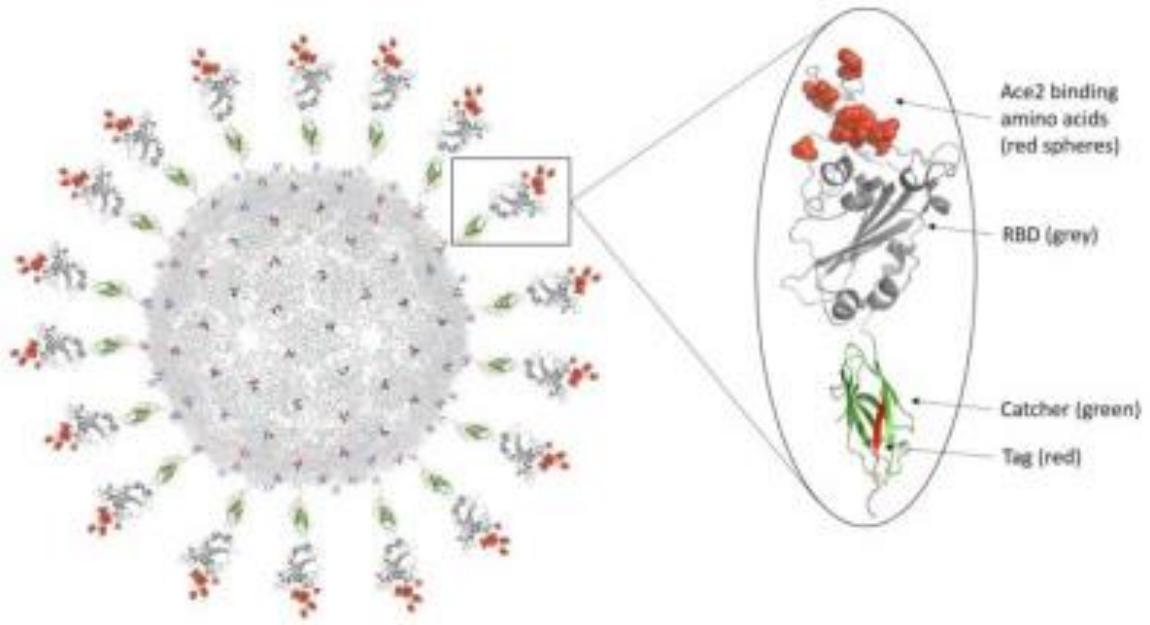
https://mvec.mcri.edu.au/references/covid-19-vaccine-platforms/

Protein subunit vaccines - Novavax



Danish vaccine – ABNCoV2 – Adaptvac/Bavarian Nordic/UCPH





Fougeroux *et al*. Capsid-like particles decorated with the SARS-CoV-2 receptor-binding domain elicit strong virus neutralization activity. Nat Commun. 2021 Jan 12;12(1):324.

- Phase I studies initiated, ready ultimo 2021 or primo 2022
- Safe, efficacious and stable (storage at room temperature)
- Can be produced anywhere

Protein subunit vaccine – Sanofi/GSK

Platform

1 Baculovirus recombinant vaccine approach(1)

Protein Antigen

+

Adjuvant

Advantage

- Licensed recombinant platform(1)
- Existing large scale capacity
- BARDA collaboration
- Collaboration with gsk for proven AS03 adjuvant

Timelines

- Phase I/II study start: Sept 2020
- Earliest potential approval: Jun 2021

Capacity

- Existing capacity for 100-600 million doses
- Capacity for >1 billion doses by 2021

SANOFI PASTEUR

BARDA: Biomedical Advanced Research & Develop
(1) Same as that for Flublok®, manufactured with
(2) In collaboration with

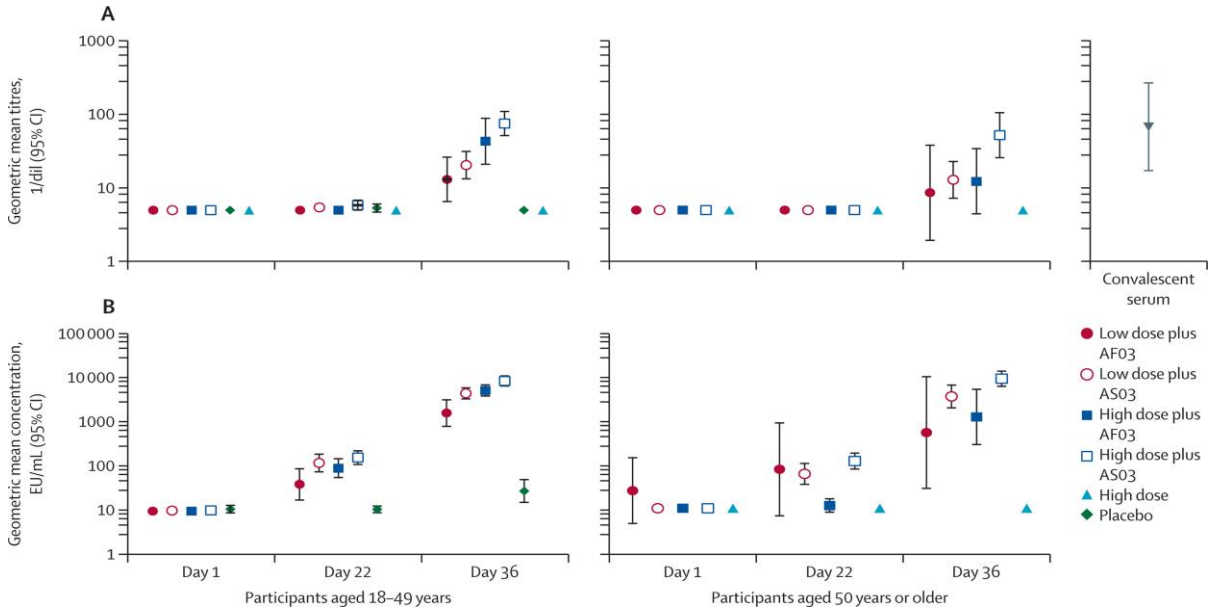
Safety and immunogenicity of SARS-CoV-2 recombinant protein vaccine formulations in healthy adults: interim results of a randomised, placebo-controlled, phase 1–2, dose-ranging study

Paul A Goepfert, Bo Fu, Anne-Laure Chabanon, Matthew I Bonaparte, Matthew G Davis, Brandon J Essink, Ian Frank, Owen Haney, Helene Janosczyk, Michael C Keefer, Marguerite Koutsoukos, Murray A Kimmel, Roger Masotti, Stephen J Savarino, Lode Schuerman, Howard Schwartz, Lawrence D Sher, Jon Smith, Fernanda Tavares-Da-Silva, Sanjay Gurunathan, Carlos A DiazGranados, Guy de Bruyn

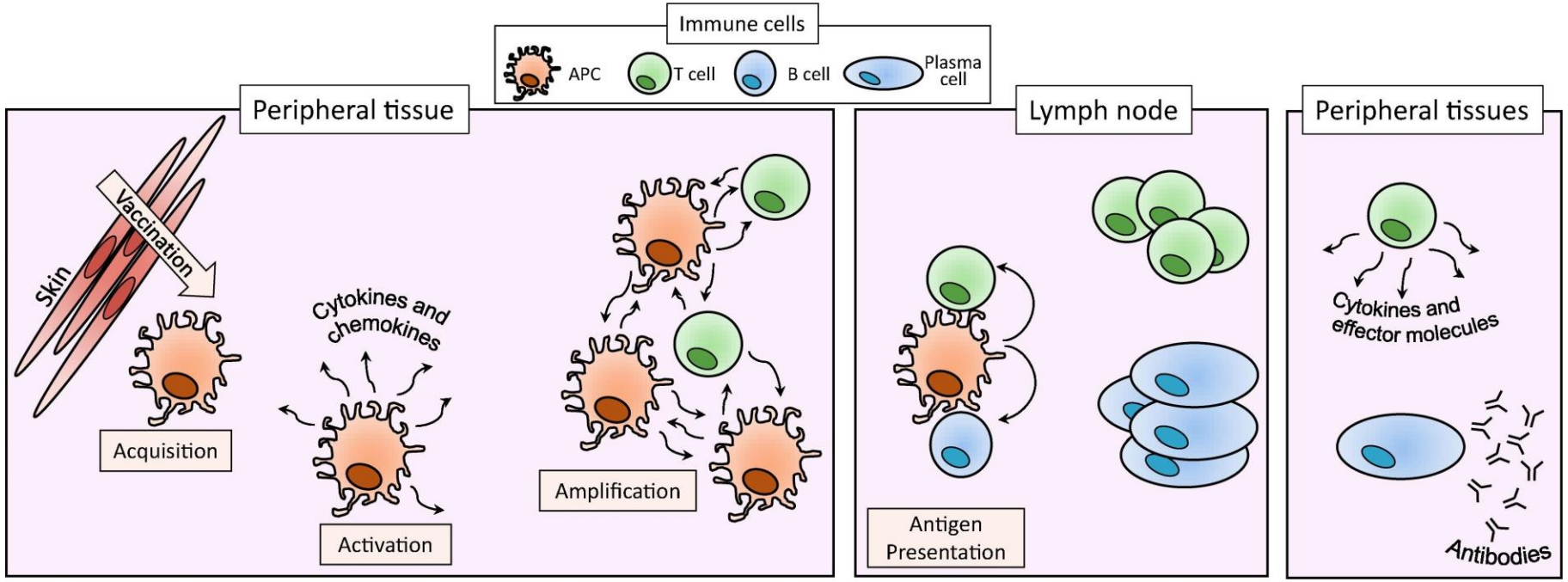
Summary

Background CoV2 preS dTM is a stabilised pre-fusion spike protein vaccine produced in a baculovirus expression system being developed against SARS-CoV-2. We present interim safety and immunogenicity results of the first-in-human study of the CoV2 preS dTM vaccine with two different adjuvant formulations.

Lancet Infect Dis 2021
Published Online
April 19, 2021



AS03 mechanism of action

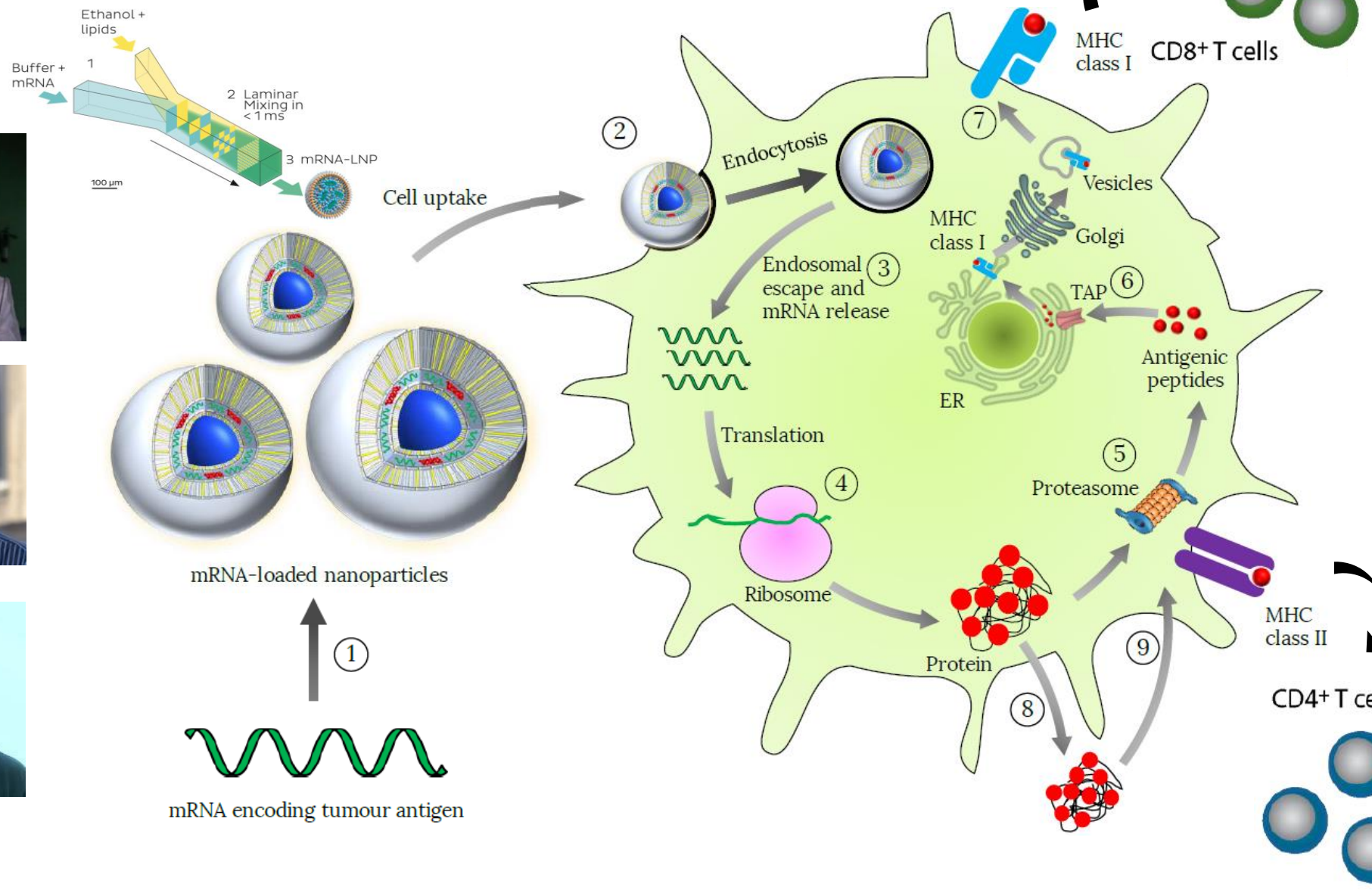


Killed/inactivated virus vaccines

Conclusions

- The corona crisis is the **moon landing of vaccine research**
- COVID-19 vaccines were developed in **record time**!
- **Entirely new vaccine platforms** (mRNA + adenovirus) have been the fastest to develop
- mRNA vaccines are **safe**, **very efficacious**, and **flexibe**
- Adenovirus vaccines are relatively efficacious, but cause **rare, serious side effects** (VITT)
- Other **types** of vaccines are reviewed/in phase III (subunit and inactivated vaccines)
- **Revaccination** will likely be needed in the future (immunity decreases after 9 months)

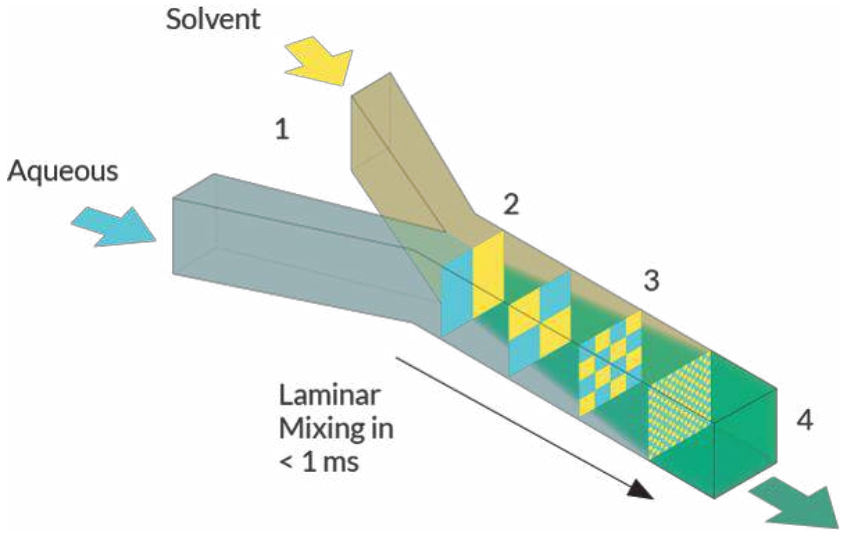
Next-generation mRNA vaccines

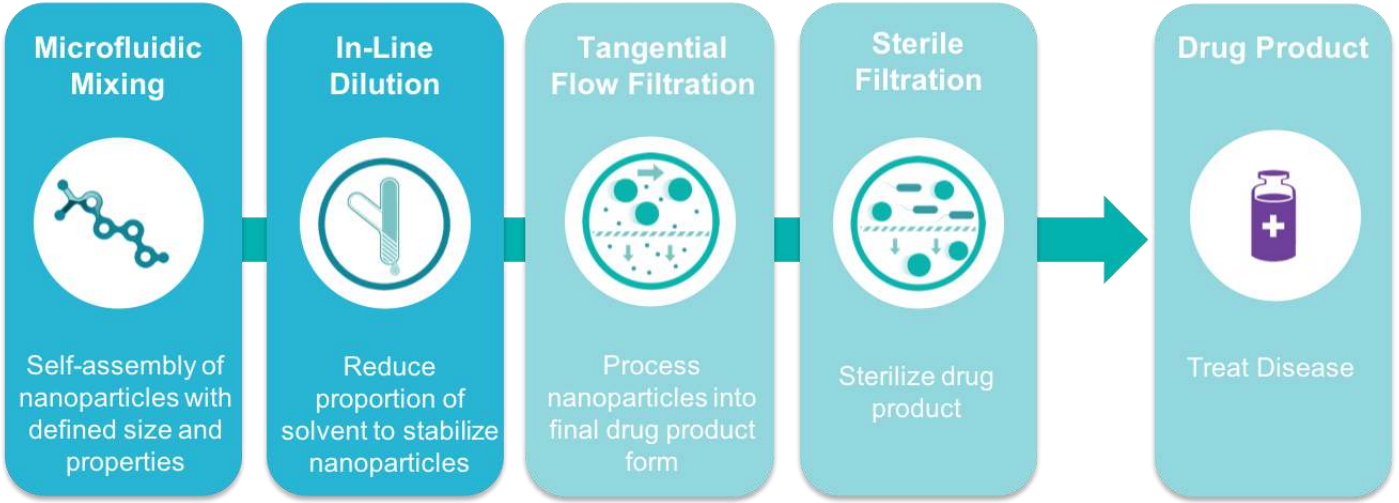


DET FRIE FORSKNINGSRÅD
DANISH COUNCIL FOR INDEPENDENT RESEARCH

STATENS SERUM INSTITUT

NanoAssemblr®Ignite – Precision Nanosystems





Physicochemical characterization of mRNA nanomedicine – an analytical challenge

Nanomaterial Quality Attributes:

- Chemical composition
- Average particle size
- Particle size distribution
- General shape and morphology
- Stability, both physical and chemical

Physicochemical characterization boils down to analytical instrumentation and development of new methods

Additional Quality Attributes:

- Assay and distribution of API
- Structural attributes
- Surface properties
- Coating properties
- Porosity
- *In vitro* release
- Crystal form
- Impurities
- Sterility and endotoxin levels

Conclusions

- RNA therapeutics represent **highly complex products**, and their development should be based on solid science
- Understanding formulations based on nanoparticles represents an **analytical challenge**
- Our focus is to **generate fundamental knowledge** to facilitate the design, development and manufacture of safe and efficacious nanomedicines
- **Scalability is key**