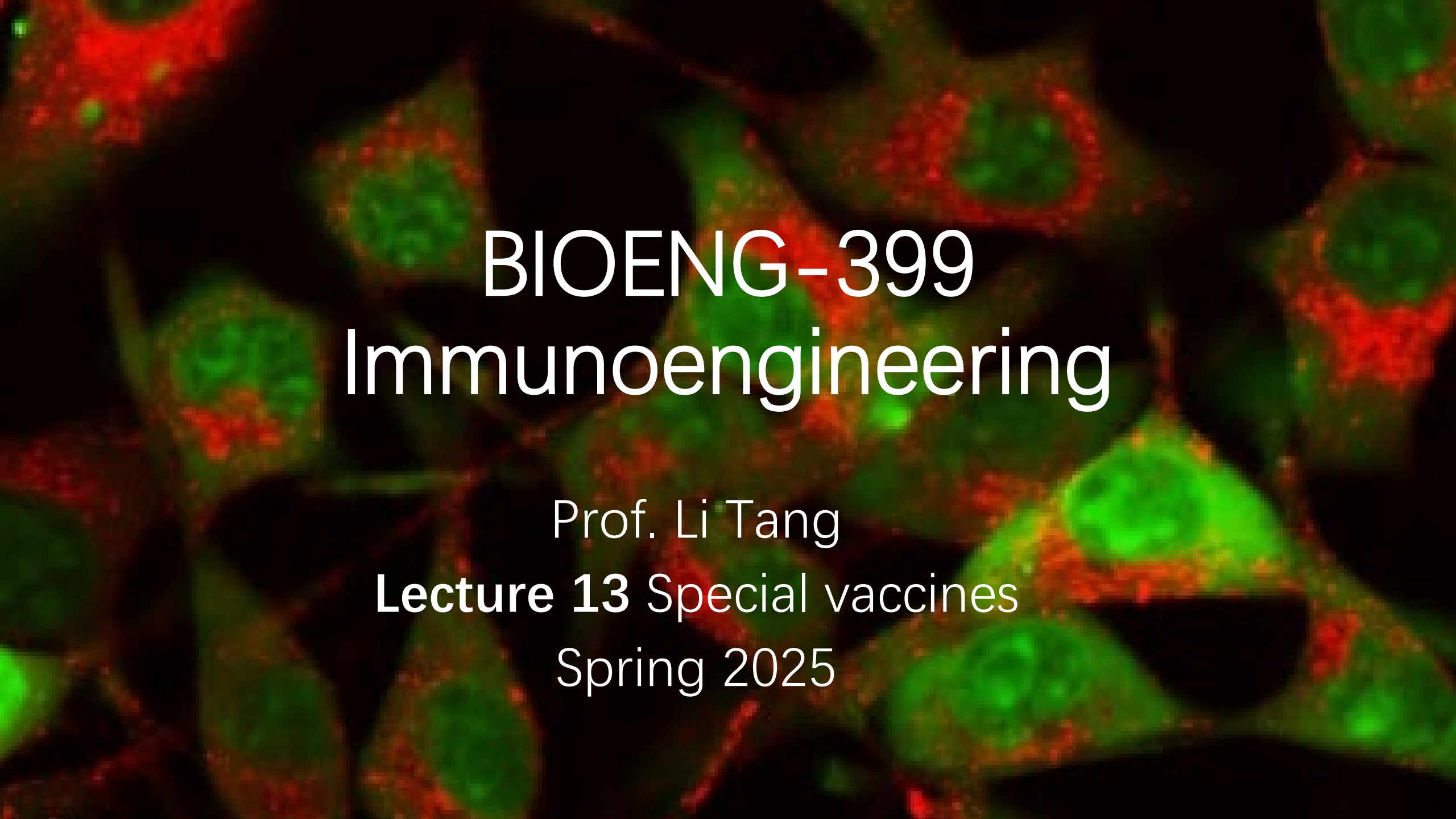


BIOENG-399 Immunoengineering

Prof. Li Tang

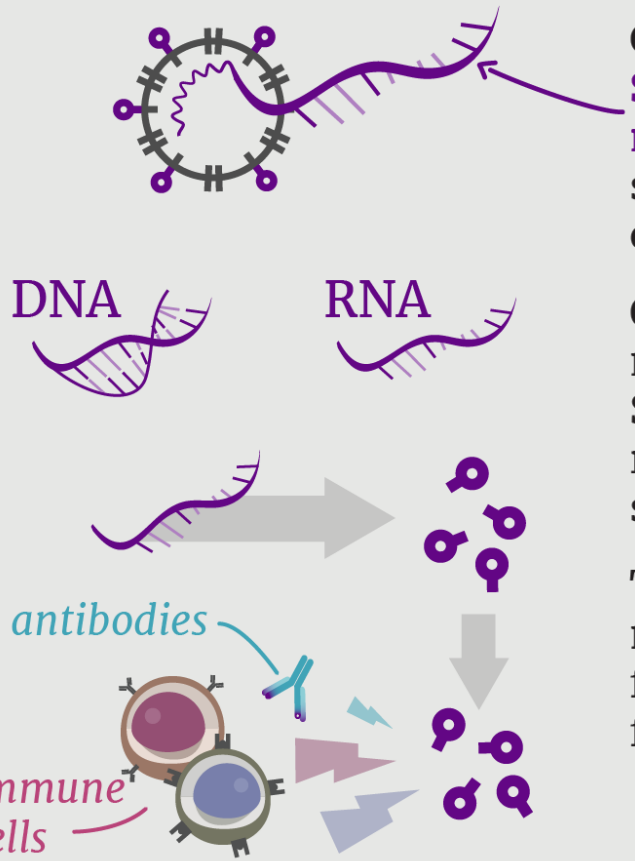
Lecture 13 Special vaccines

Spring 2025

Types of SARS-CoV-2 vaccines for COVID-19

Genetic vaccines
(nucleic acid vaccines)

British Society for immunology
www.immunology.org



Contain a segment of **SARS-CoV-2 virus genetic material** that codes for a specific protein. Can be DNA or RNA.

Our cells use the genetic material to make the SARS-CoV-2 protein, which is recognised by the immune system to trigger a response.

This response builds immune memory, so your body can fight off SARS-CoV-2 in future.

Considerations

Low cost and fast to develop.

May need to be stored at specific low temperatures.

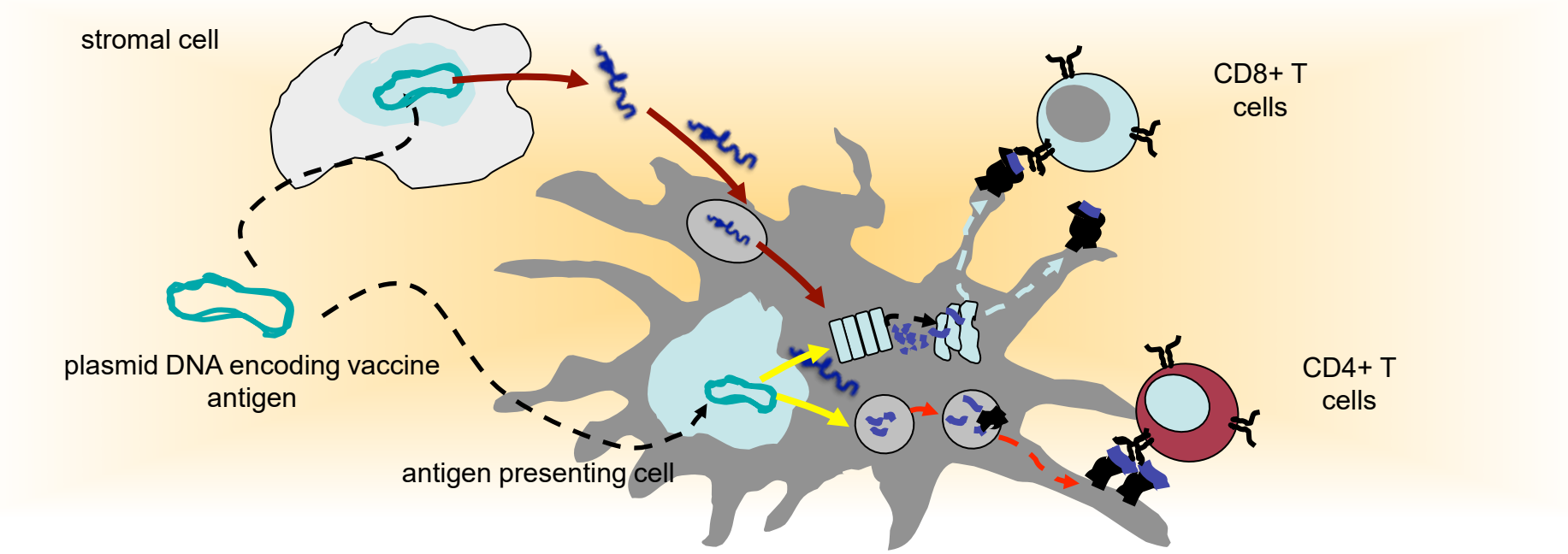
Approved in the UK for COVID-19

Pfizer/BioNTech & Moderna

In clinical trials for COVID-19

CureVac, Inovio Pharmaceuticals

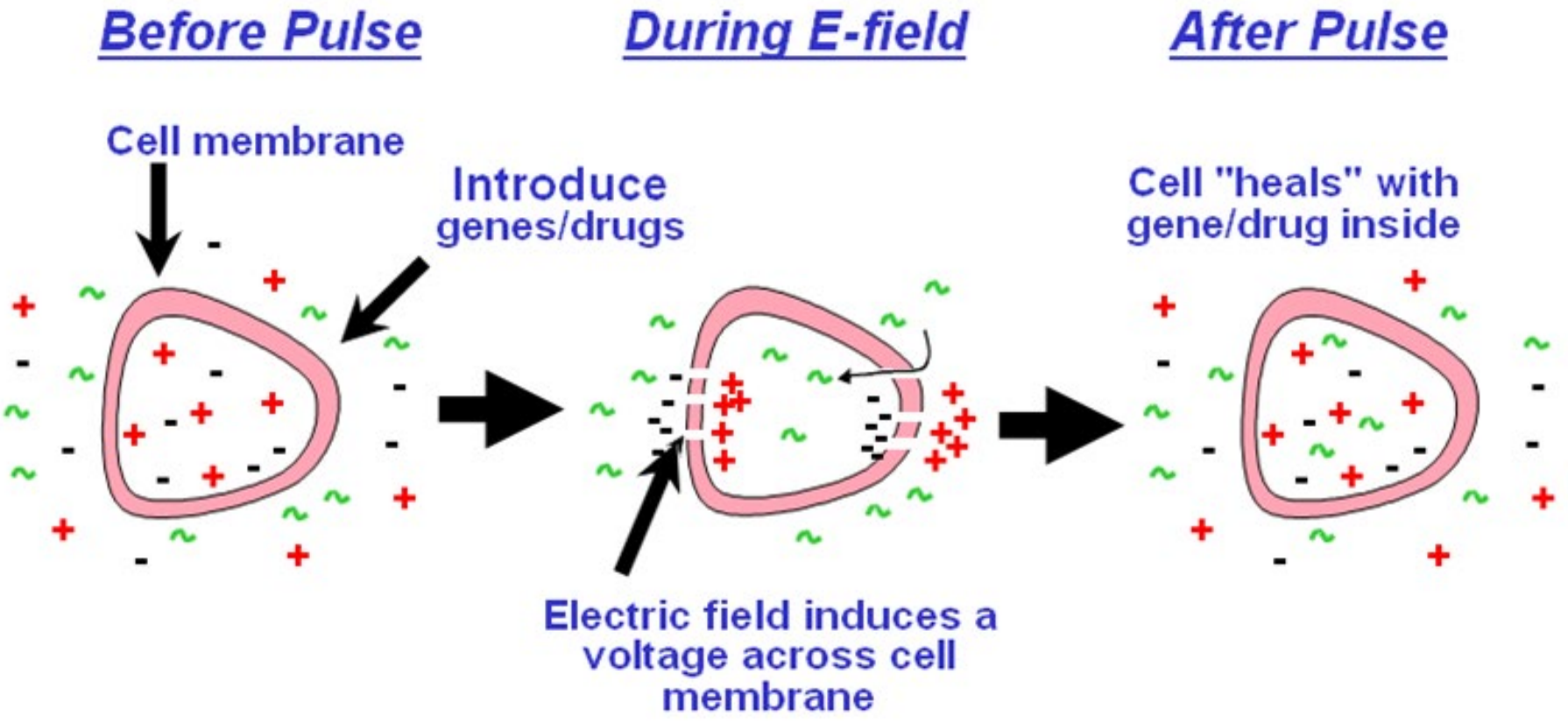
DNA vaccines: a potentially universal vaccine platform, but lacking potency



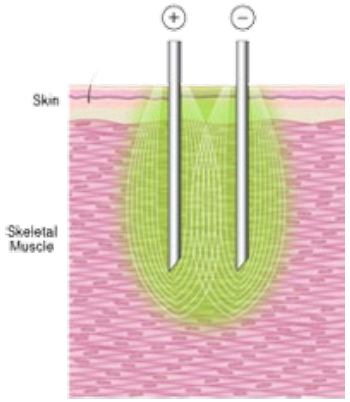
- Naked DNA shown in 1990 to transfect and vaccinate small animals (mice), but much less efficient in non-human primates and humans
- Synthetic transfection agents (lipids, polymers) to date either too toxic or too inefficient

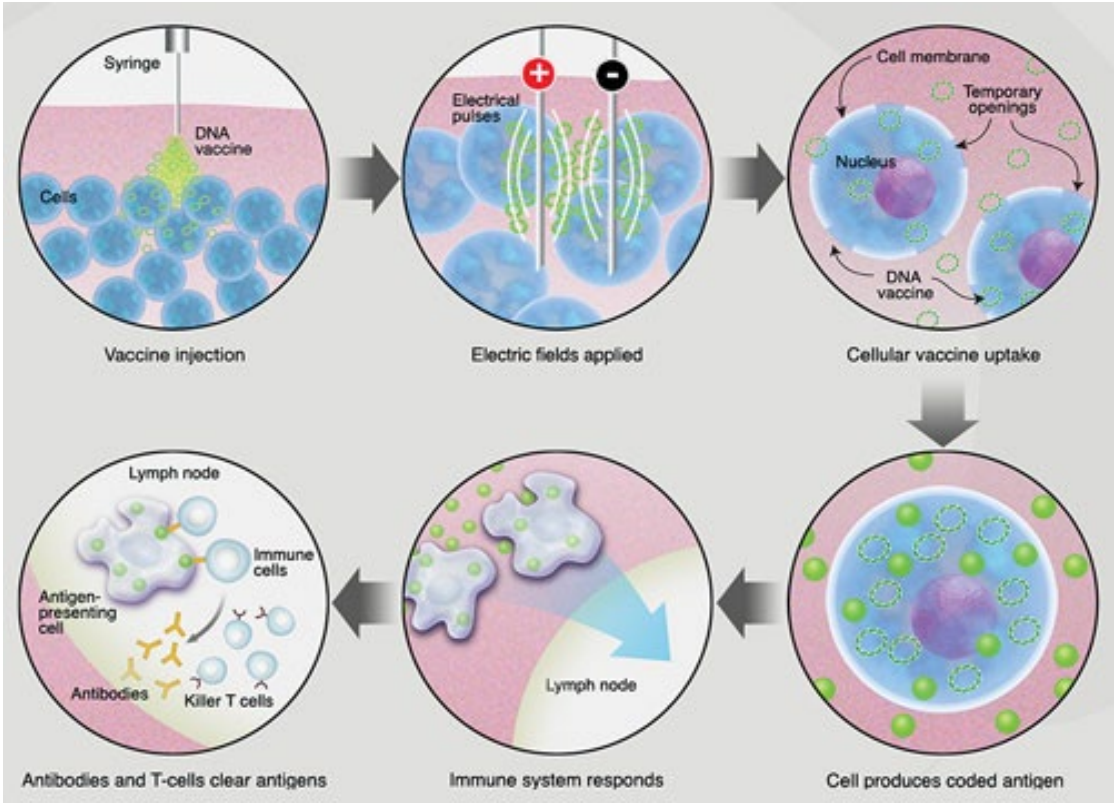
The current golden standard – in vivo electroporation

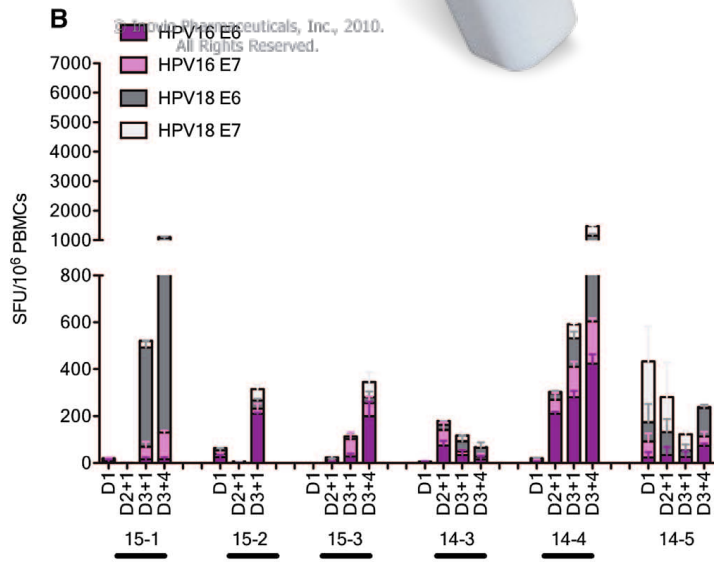
Electroporation:



The current golden standard – in vivo electroporation







Bagarazzi, M. L., Yan, J., Morrow, M. P., Shen, X., Parker, R. L., Lee, J. C., et al. (2012). Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. *Science Translational Medicine*, *4*(155), 155ra138–155ra138.

mRNA-Based Vaccines

The underlying principle is delivery of a transcript that encodes one or more immunogens into the host cell cytoplasm, where translation **generates immunogenic proteins** that are subsequently sequestered intracellularly, incorporated into the cell membrane, or secreted.

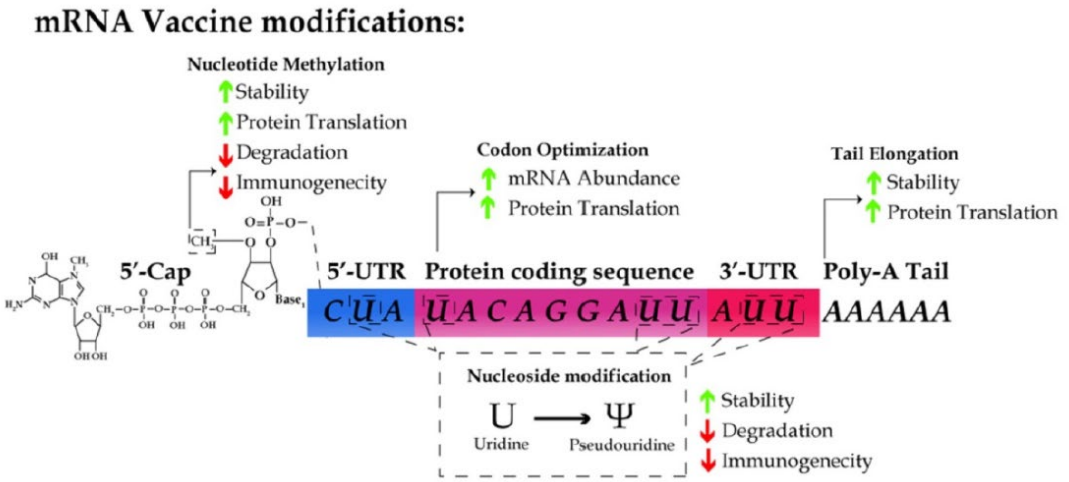
The mRNA is generated by transcribing a DNA template synthesized **once the genetic sequence encoding the immunogen is known** and disseminated globally.

Advantages: high safety, easy and fast manufacturing compared to more conventional approaches, less expensive, easy to be modified, much less possible for the mRNA to integrate into the genome than a DNA-based vaccine.

Disadvantages: a delivery system is necessary, difficulty in storage and transportation, others to be determined

Vaccines **2021**, 9, 390. https:// doi.org/10.3390/vaccines9040390

mRNA-Based Vaccines (mRNA modification)



The 5' 7-methylguanosine (m^7G) cap blocks recognition by the cytoplasmic RNA sensor, RNA helicases retinoic acid-inducible gene I (RIG-I), suppresses exonuclease-mediated degradation, recruits translation initiation factors, and promotes efficient translation

The poly(A) tail and its length are critical for translation and protection of the mRNA vaccine construct from degradation

nonreplicating (a)

2.2 kb

(a)

self-replicating (b)

9.3 kb

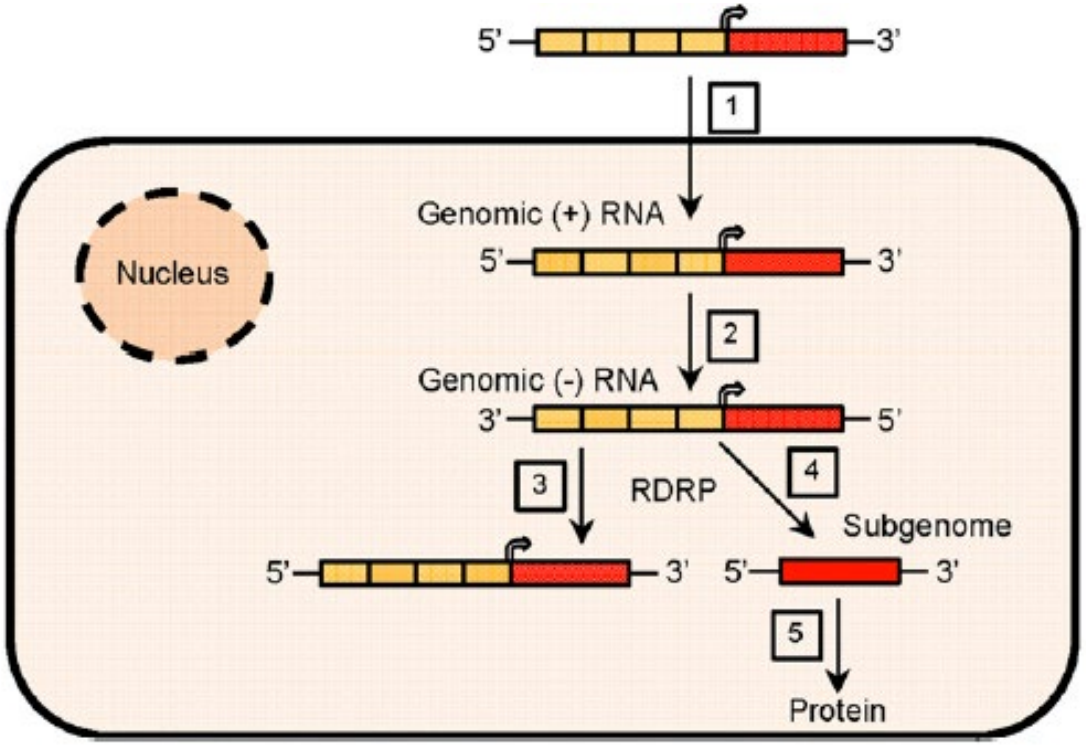
(b)

RNA-dependent RNA polymerase (RDRP) complex required for self-amplification (often derived from alphaviruses, e.g., Sindbis virus)

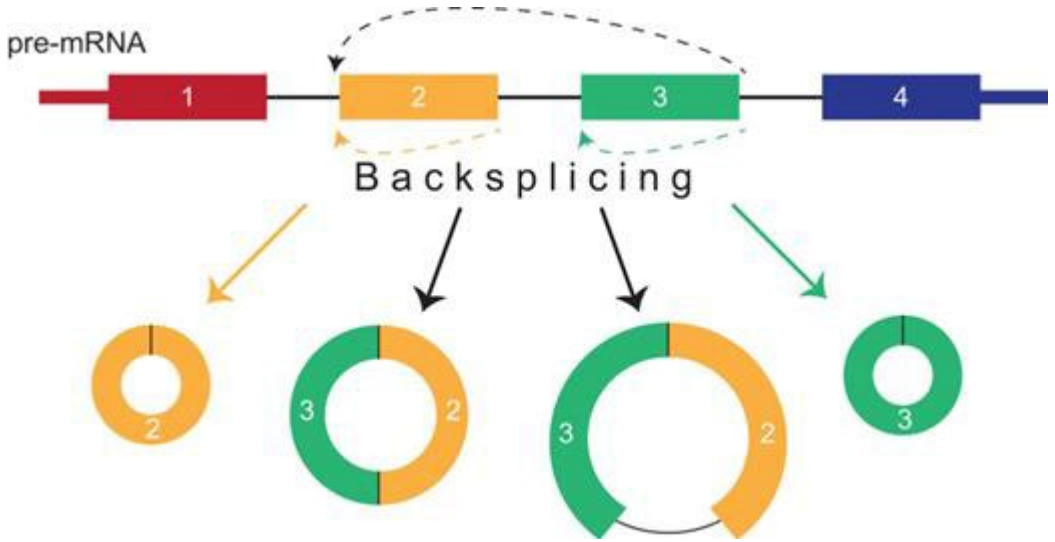
Vaccines **2021**, 9, 390. https:// doi.org/10.3390/vaccines9040390

Self-replicating mRNA vaccines and an alternative

Self-amplification of alphavirus replicon RNA:



An alternative: Circular RNAs (circRNAs) are a class of single-stranded RNAs with a covalently closed loop structure



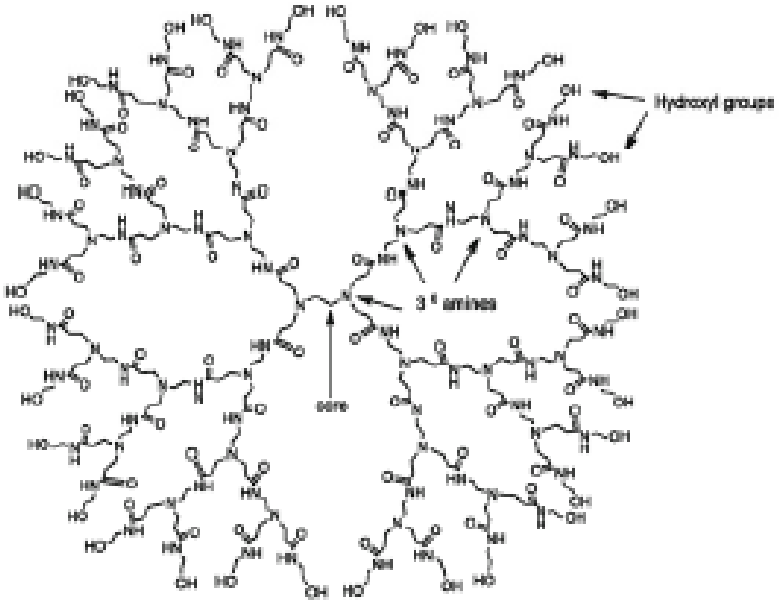
strong intrinsic adjuvant activity of self-replicating mRNA contributes to its higher immunogenicity at lower doses compared to nonreplicating mRNA constructs

Geall et al. *PNAS* 2012

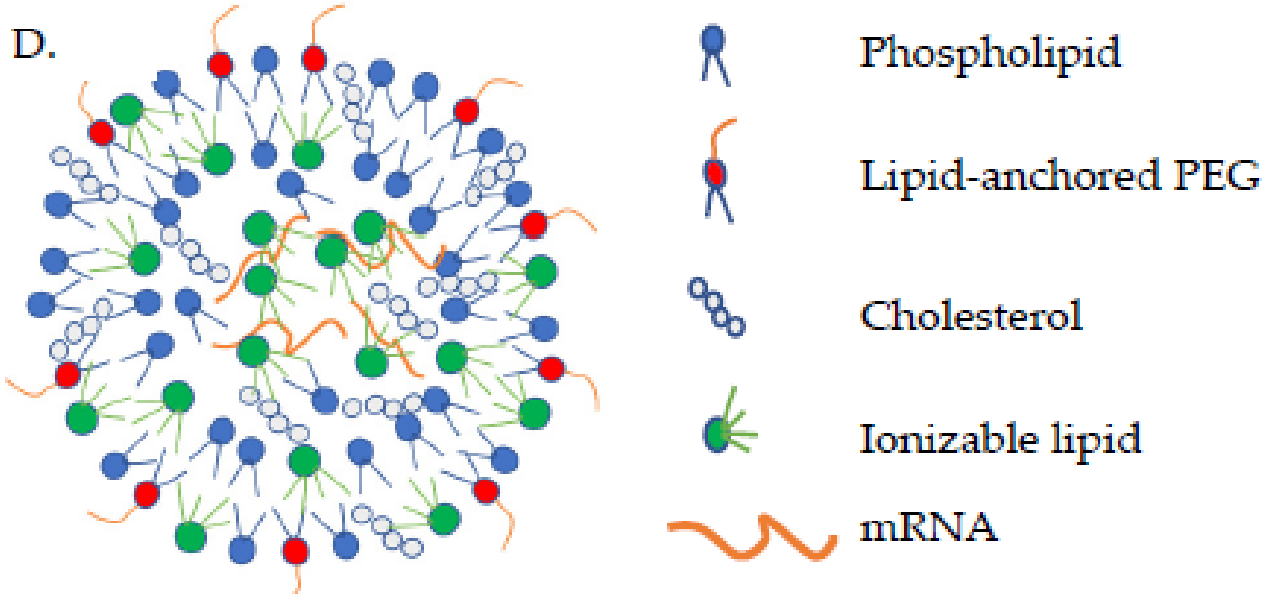
Delivery of mRNA vaccines

- Electroporation
- DCs
- nanoparticles

B.



D.



mRNA vaccines against COVID-19

The Pfizer-BioNTech COVID-19 vaccine has not been approved or licensed by the U.S. Food and Drug Administration (FDA), but has been authorized for emergency use by FDA under an Emergency Use Authorization (EUA) to prevent Coronavirus Disease 2019 (COVID-19) for use in individuals 12 years of age and older.

https://www.pfizer.com/news/hot-topics/the_facts_about_pfizer_and_biontech_s_covid_19_vaccine

The ingredients are mRNA, lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-Distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

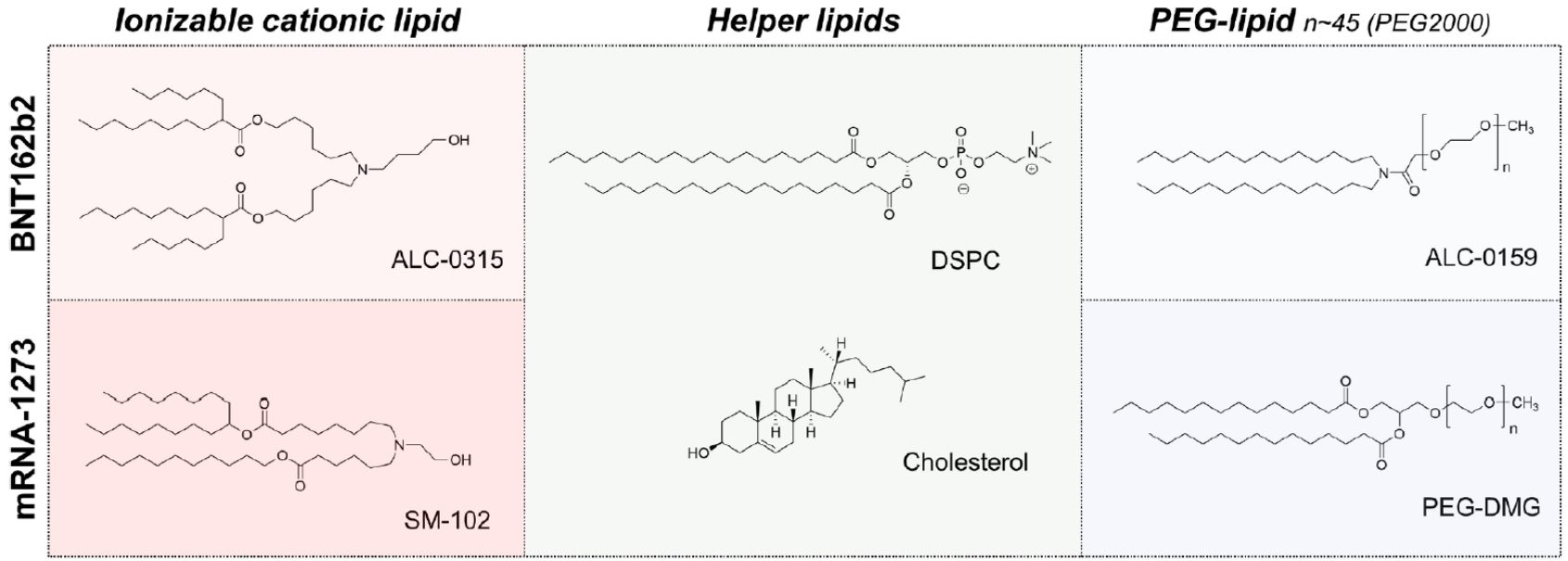
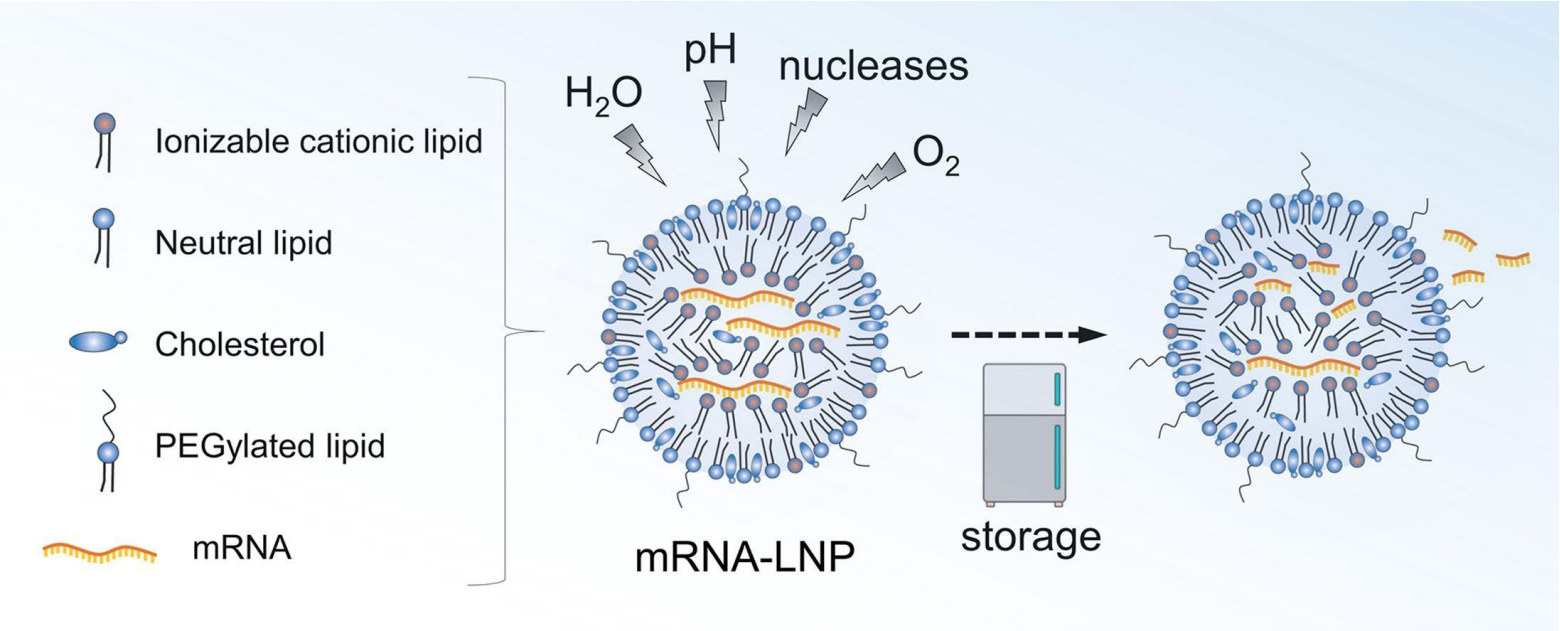
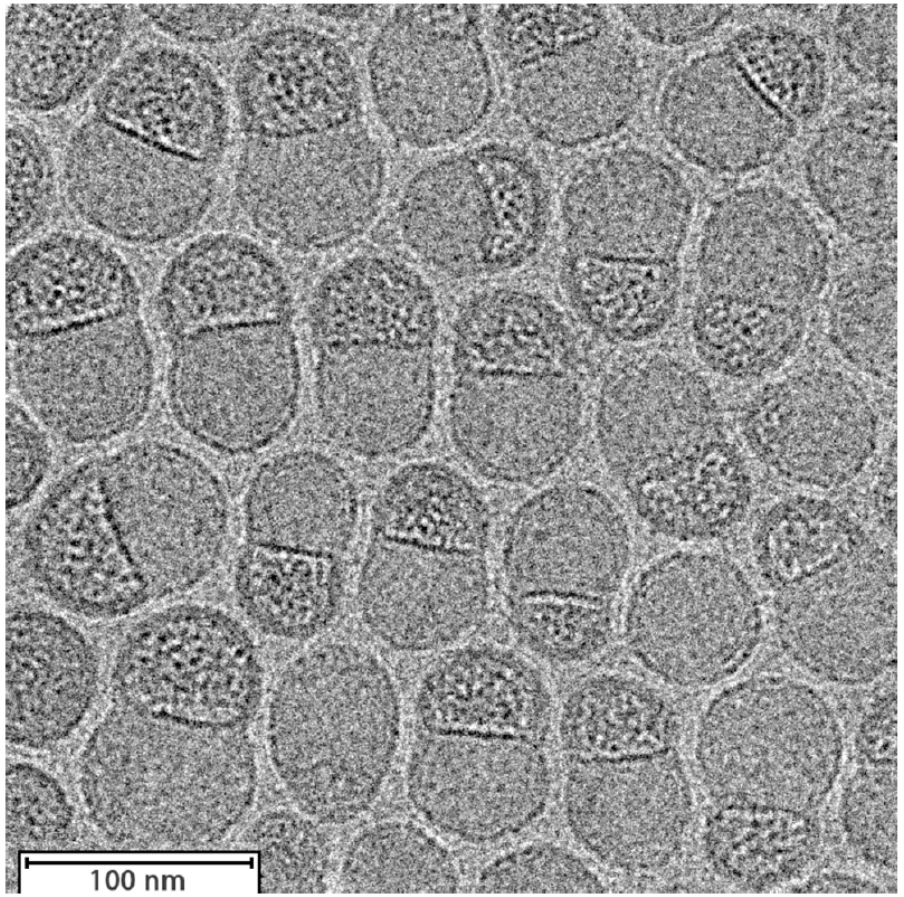


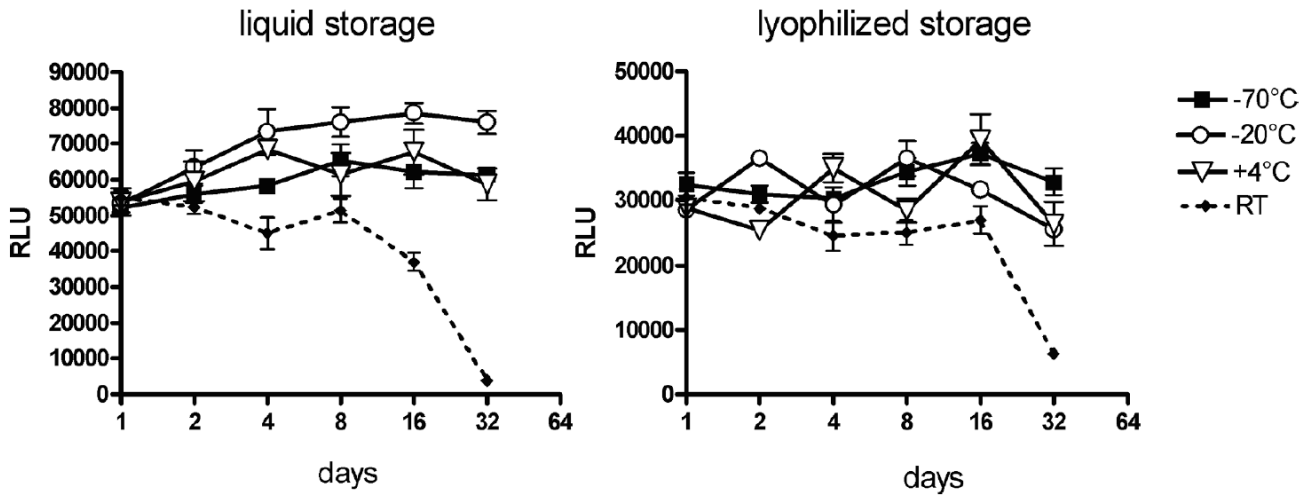
Fig. 6. Lipids used in the mRNA-LNP COVID-19 vaccines BNT162b2 (Comirnaty) and mRNA-1273.

Lipid nanoparticles (LNPs)



60–100 nm in size





International Journal of Pharmaceutics 601 (2021) 120586

Comparison of the mRNA-1273 vaccines by Moderna, BNT162b2/Comirnaty by BioNTech/Pfizer and CVnCoV by CureVac

Information about the three mRNA-LNP drug products that are presently used or in clinical phase III trials. For comparison reasons, drug product information for Onpattro (an siRNA-LNP drug product) has been added.

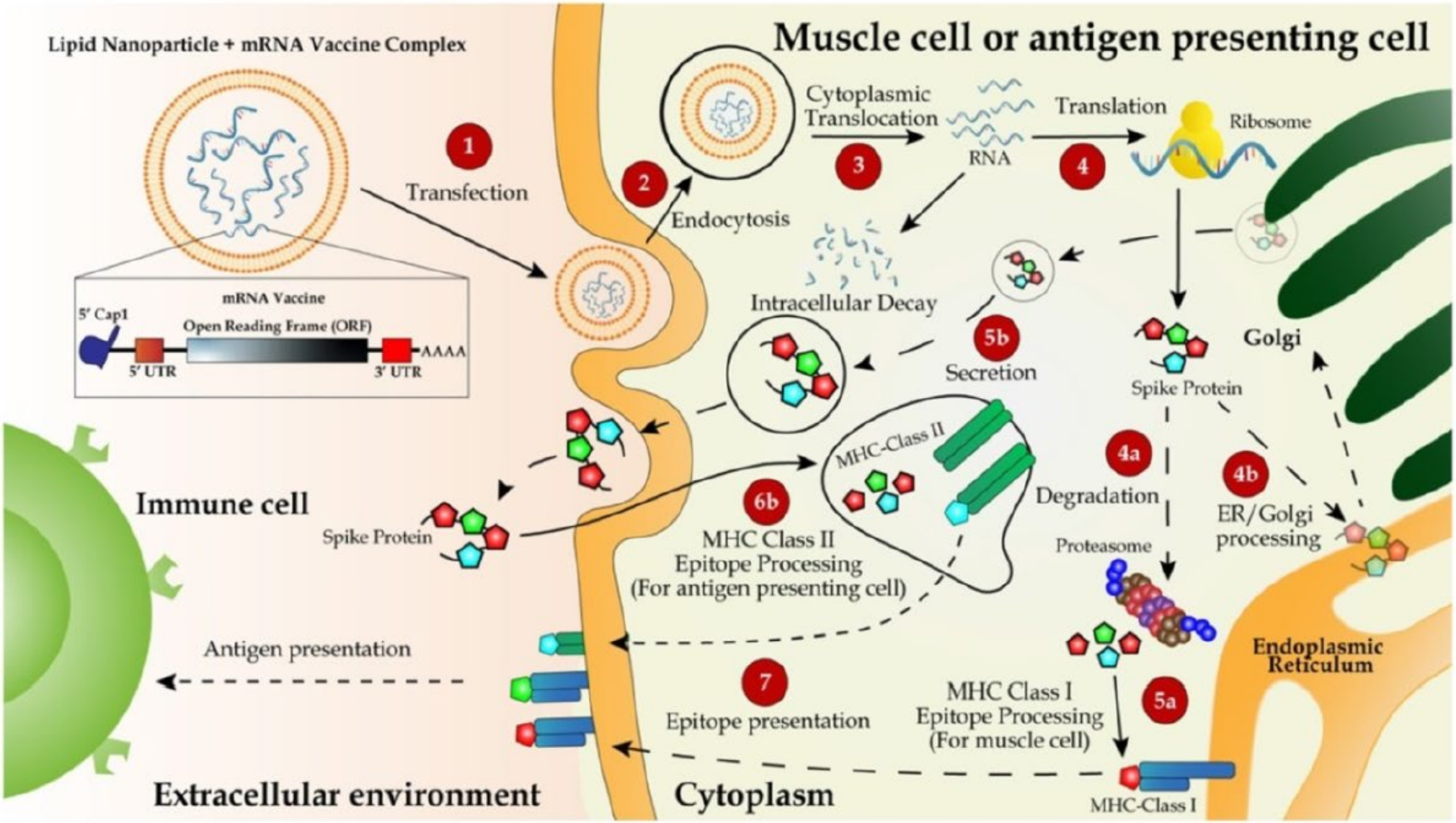
Category	siRNA	Pfizer-BioNTech mRNA vaccine	Moderna mRNA vaccine	Curevac mRNA vaccine candidate
Name product	Onpattro * patisiran	BNT162b2; Comirnaty	mRNA-1273	CVnCoV
mRNA dose; route of administration	0.3 mg/kg, intravenous	30 μg; intramuscular	100 μg; intramuscular	12 μg; intramuscular
Lipid nanoparticle components	DLin-MC3-DMA: (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate 1,2-Distearoyl-*sn*-glycero-3-phosphocholine (DSPC) PEG2000-DMG = Alpha-(3′-{[1,2-di(myristyloxy)propanoxy] carbonylamino}propyl)-ω-methoxy, polyoxyethylene Cholesterol	0.43 mg ALC-0315 = (4-hydroxybutyl) azanediyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate) 0.05 mg ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N ditetradecylacetamide 0.09 mg 1,2-Distearoyl-*sn*-glycero-3-phosphocholine (DSPC) 0.2 mg Cholesterol	SM-102 (heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate} PEG2000-DMG = 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 1,2-Distearoyl-*sn*-glycero-3 phosphocholine (DSPC) Cholesterol	Cationic lipid (Acuitas Therapeutics) Phospholipid Cholesterol PEG-lipid conjugate
Molar lipid ratios (%) ionizable cationic lipid : neutral lipid : cholesterol : PEG-ylated lipid	50:10:38.5:1.5	46.3:9.4:42.7:1.6	50:10:38.5:1.5	50:10:38.5:1.5
Molar N/P ratios[a]	3	6	6[b]	6[b]
Buffer	Potassium phosphate, monobasic, anhydrous Sodium phosphate, dibasic, heptahydrate pH ~ 7	0.01 mg Potassium dihydrogen phosphate 0.07 mg Disodium hydrogen phosphate dihydrate pH 7–8	Tris (tromethamine) pH 7–8	? pH
Other excipients	Sodium chloride Water for injection	0.01 mg Potassium chloride 0.36 mg Sodium chloride 6 mg Sucrose Water for injection	Sodium acetate Sucrose Water for injection	Saline

*NDA 210922 ONPATTRO (patisiran) Lipid Complex Injection; Addendum to Drug Product Quality Review (FDA, 2017).

[a] N = ionizable cationic lipid (nitrogen), P = nucleotide (phosphate).

[b] Estimate.

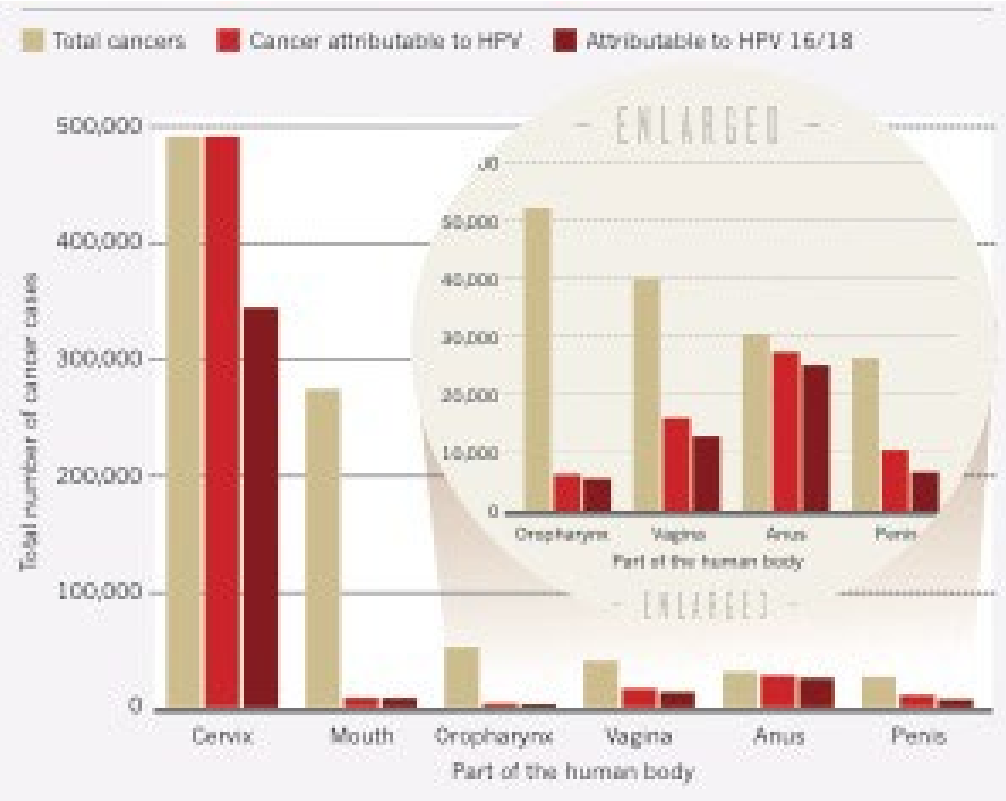
Cellular fates of mRNA vaccines



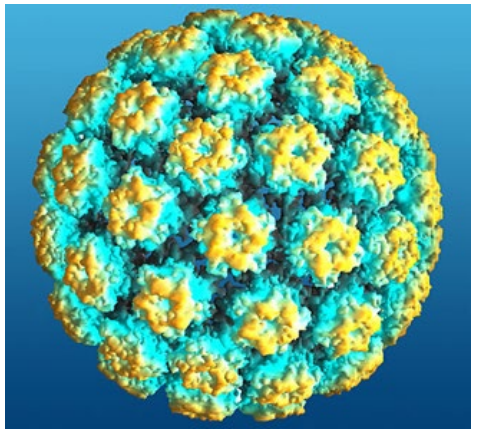
Int. J. Biol. Sci. 2021, Vol. 17, 2021; 17(6): 1446-1460. doi: 10.7150/ijbs.59233

Preventative (prophylactic) cancer vaccines?

- A first target: virus-induced cancers- 20% of all cancers
- Gardasil and cervarix: two example prophylactic cancer vaccines blocking HPV-induced cervical cancer



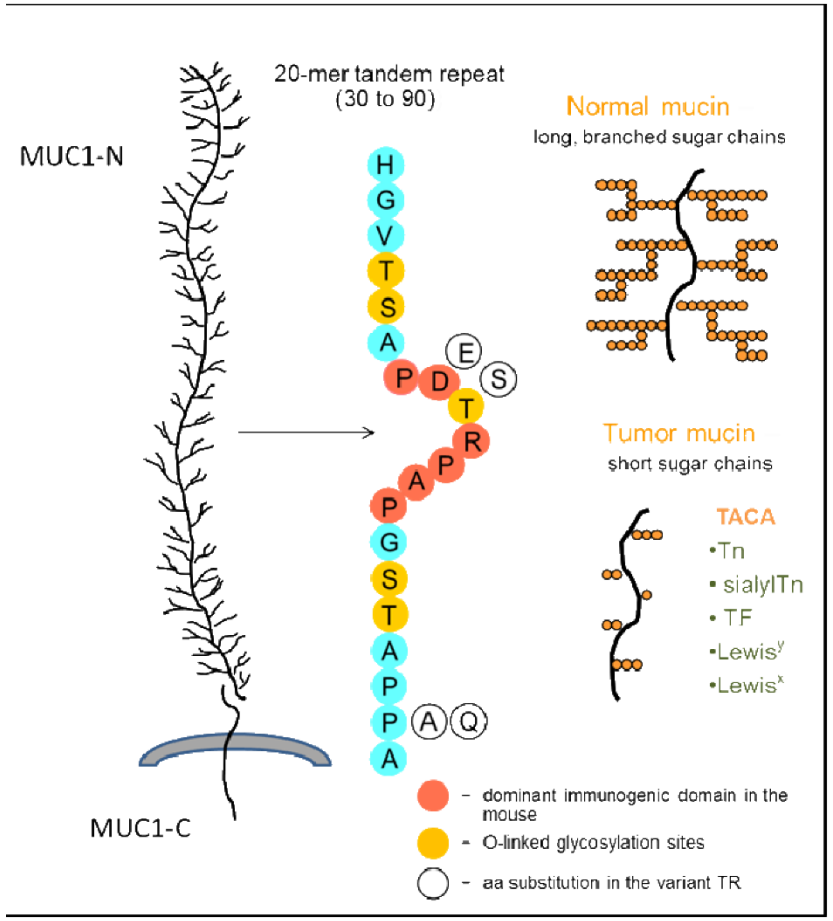
Crow, J. M. (2012). *Nature*, *488*(7413), S2–S3.



HPV virus-like particle

http://www.clinsci.org/cs/110/0525/cs1100525f02.htm

First preventative non-viral cancer vaccine trial



Patients who had colon cancer resected

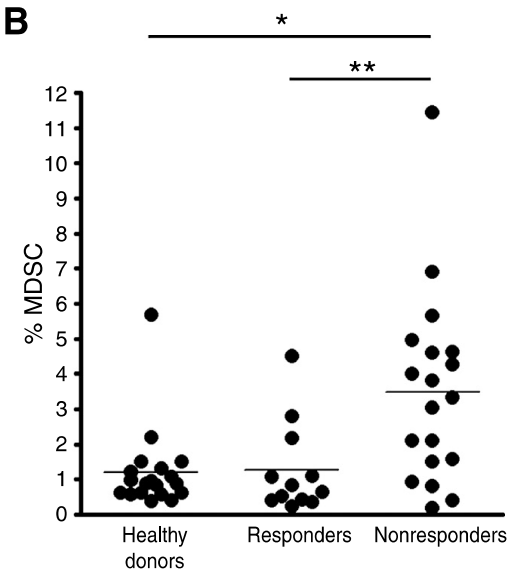
↓

Vaccinated 3X with MUC-1 “long peptide”

↓

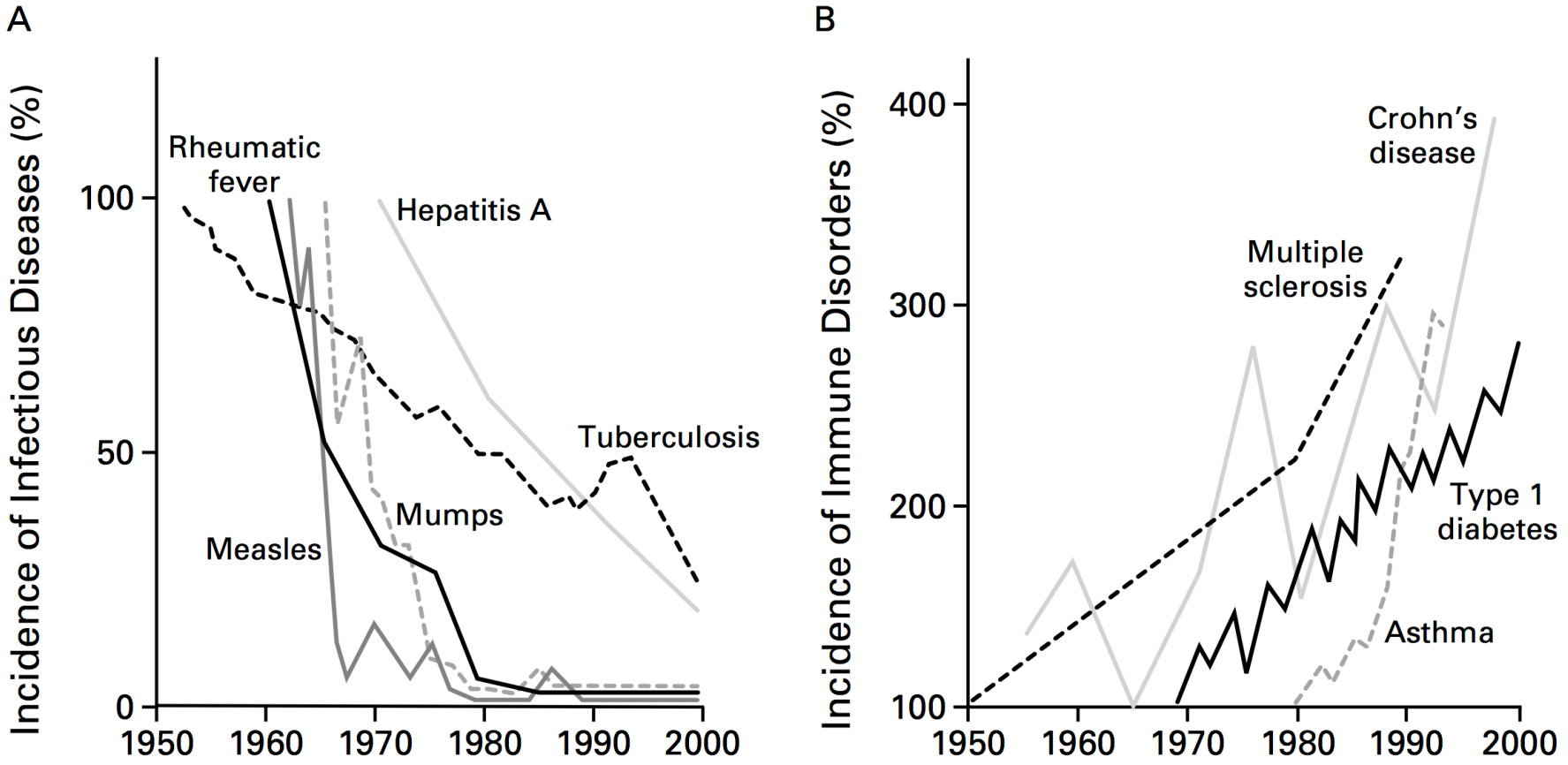
Monitor for recurrence (ongoing)

Nonresponders to the vaccine had higher MDSC levels:



Mensdorff-Pouilly, von, S., Moreno, M., & Verheijen, R. H. M. (2011). *Cancers*, *3*(4), 3073–3103. Kimura, T., McKolanis, J. R., Dzubinski, L. A., Islam, K., Potter, D. M., Salazar, A. M., et al. (2013). *Cancer Prevention Research 6*(1), 18–26. http://doi.org/10.1158/1940-6207.CAPR-12-0275

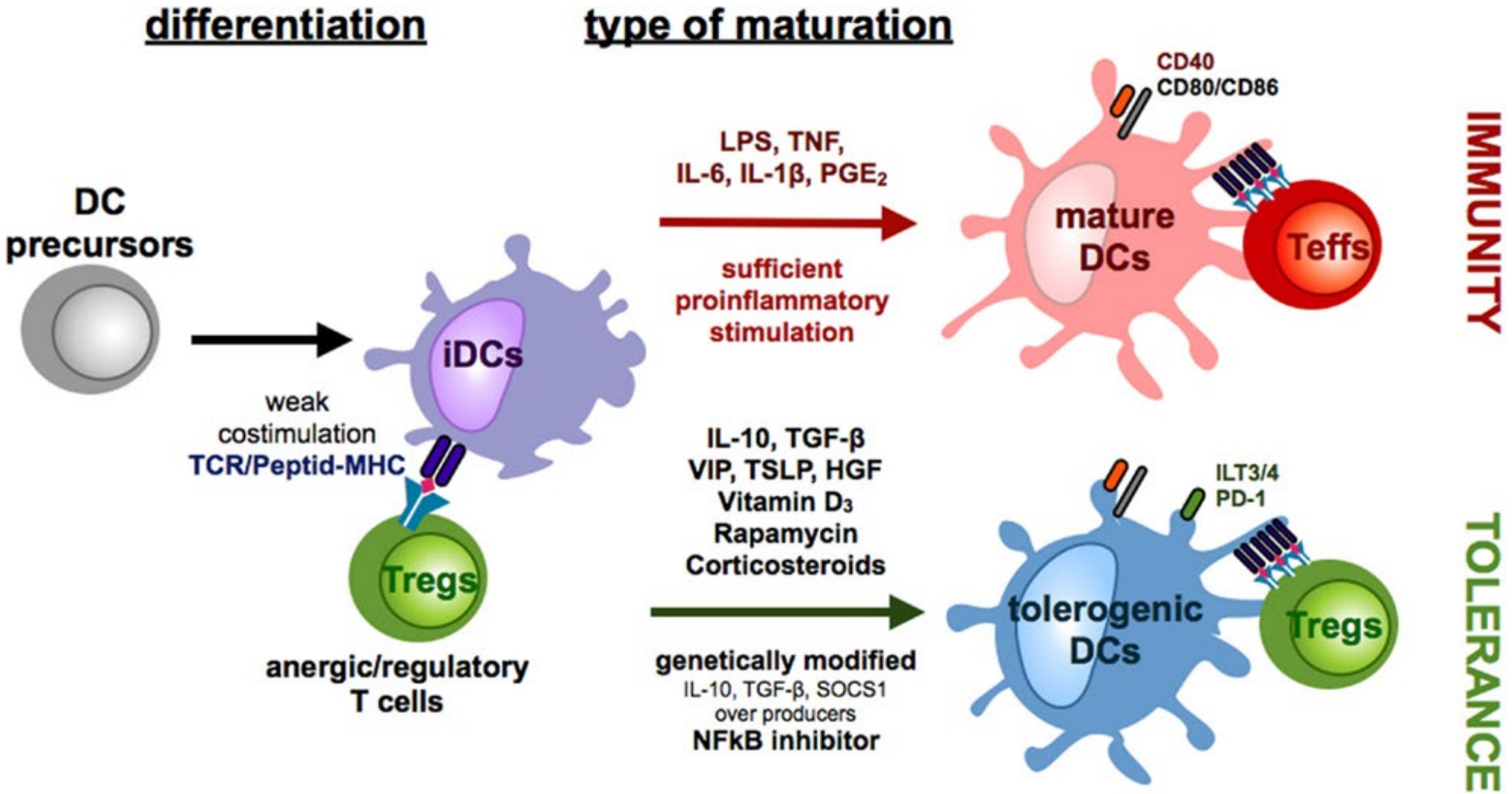
Incidence of autoimmune diseases is on the rise in the world



As infectious diseases have been contained,
more incidences of autoimmune diseases

Bach NEJM 2002

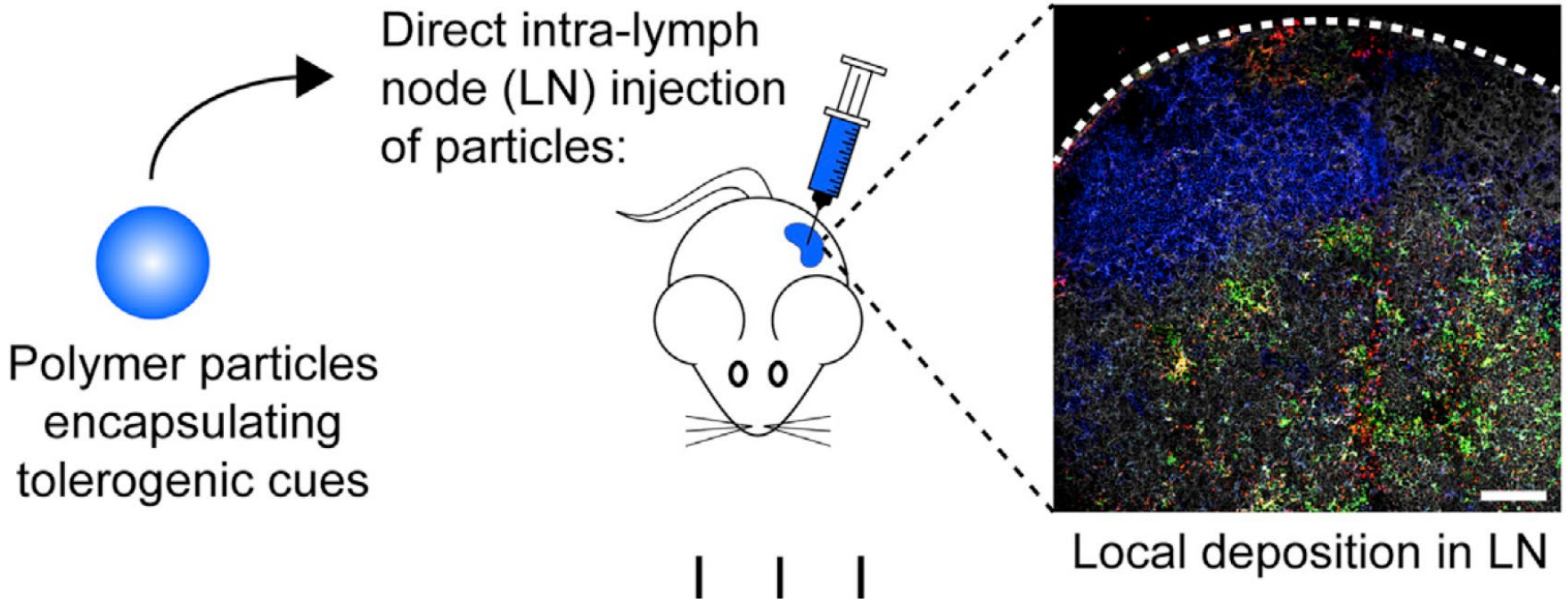
Tolerogenic vaccination for antigen-specific modulation



Raker et al Front Immunol 2015

Antigen-specific tolerogenic vaccines

multiple sclerosis (MS)



Microparticles containing:

- a peptide fragment of myelin oligodendrocyte glycoprotein (MOG)
- rapamycin (Rapa): a regulatory signal

Cell Reports **16**, 2940-2952 (2016).

Images of the cortical ridge of LNs

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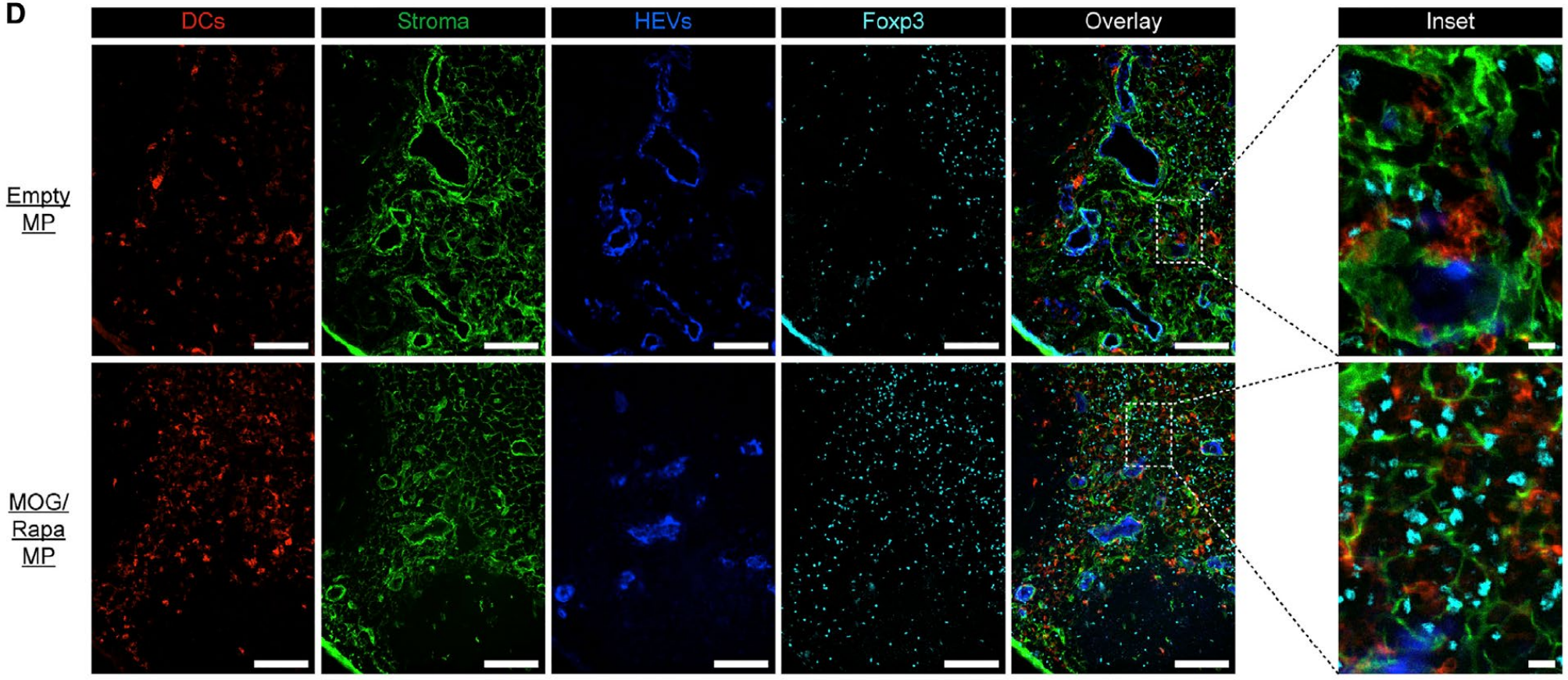
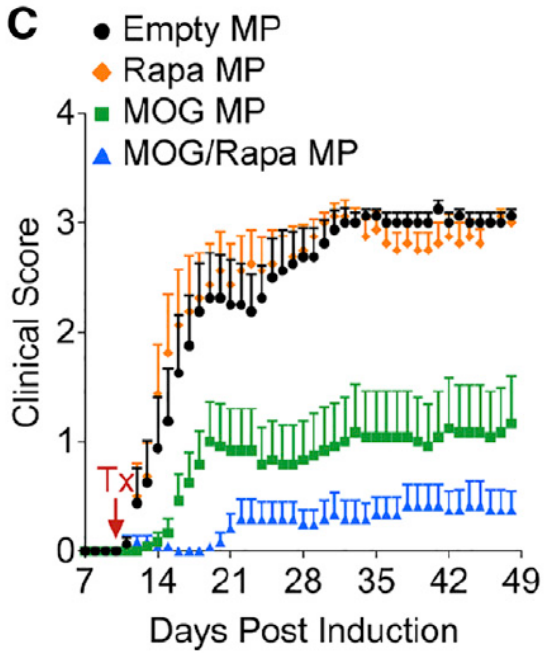
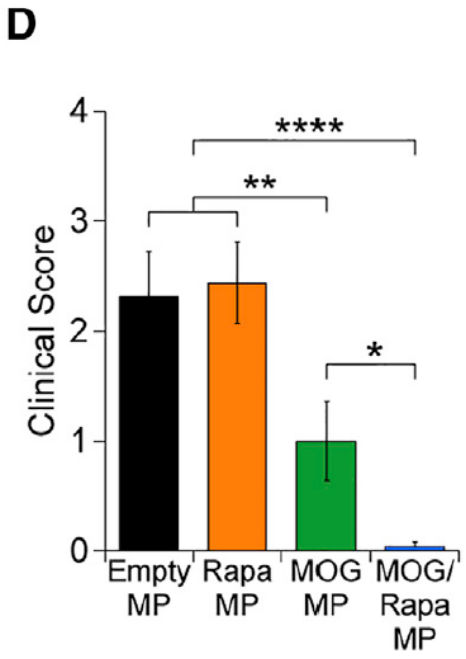
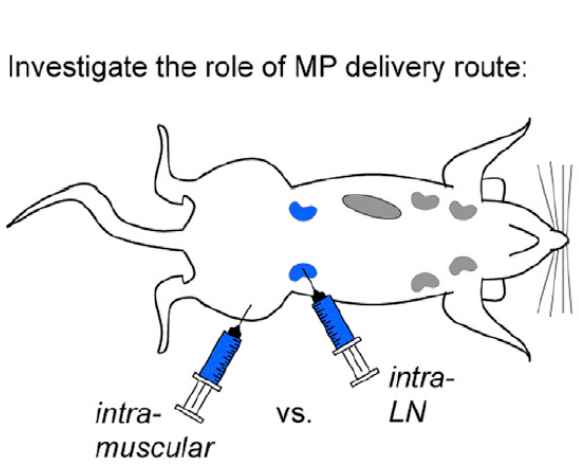
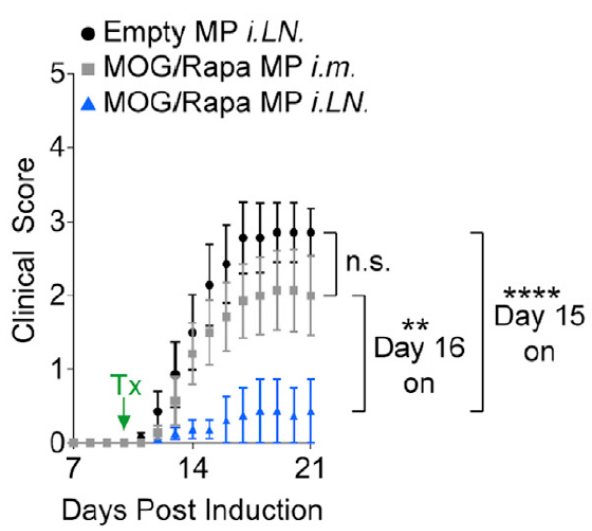


A model of MS: experimental autoimmune encephalomyelitis (EAE)









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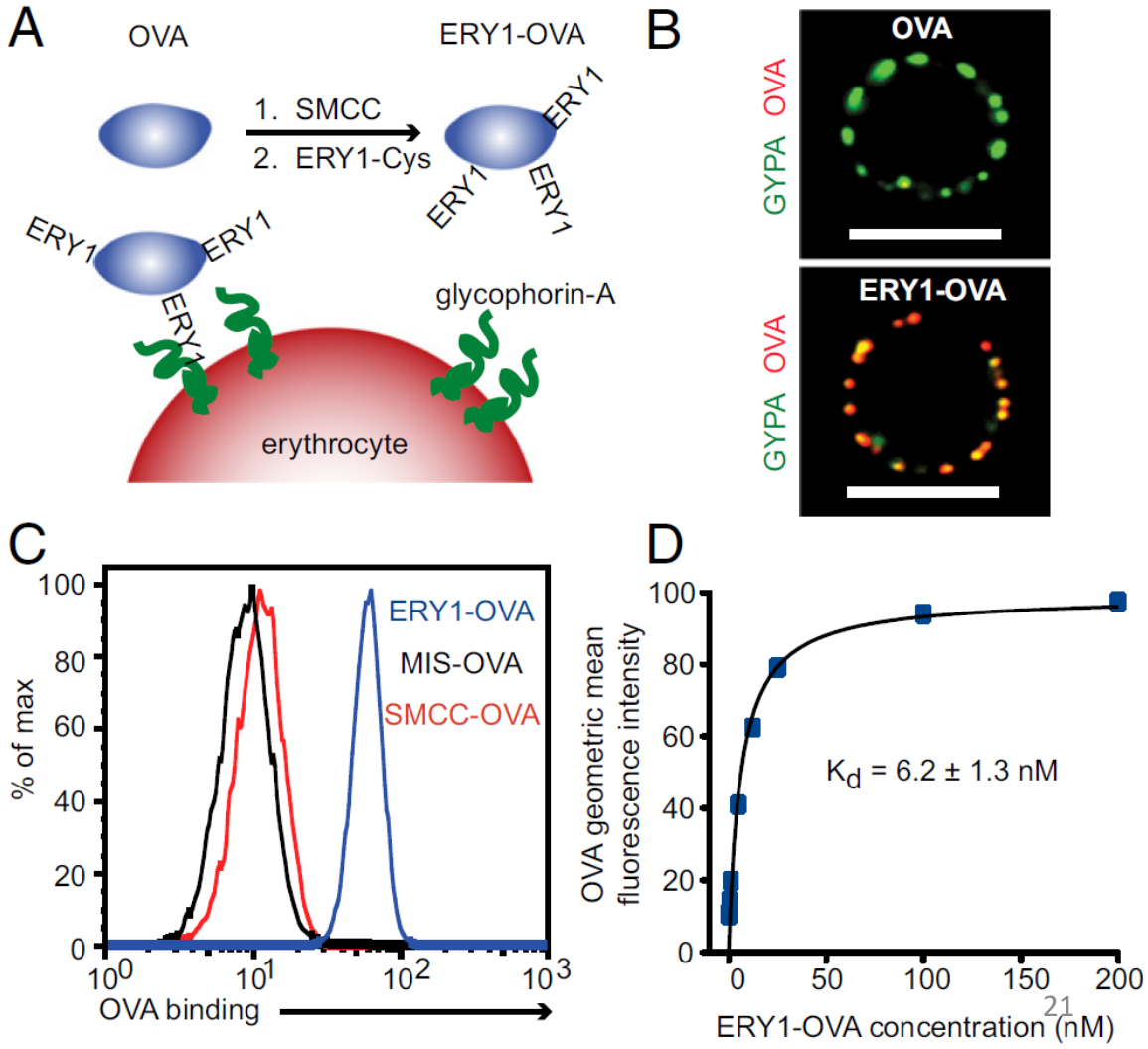
Erythrocyte binding tolerogenic vaccines

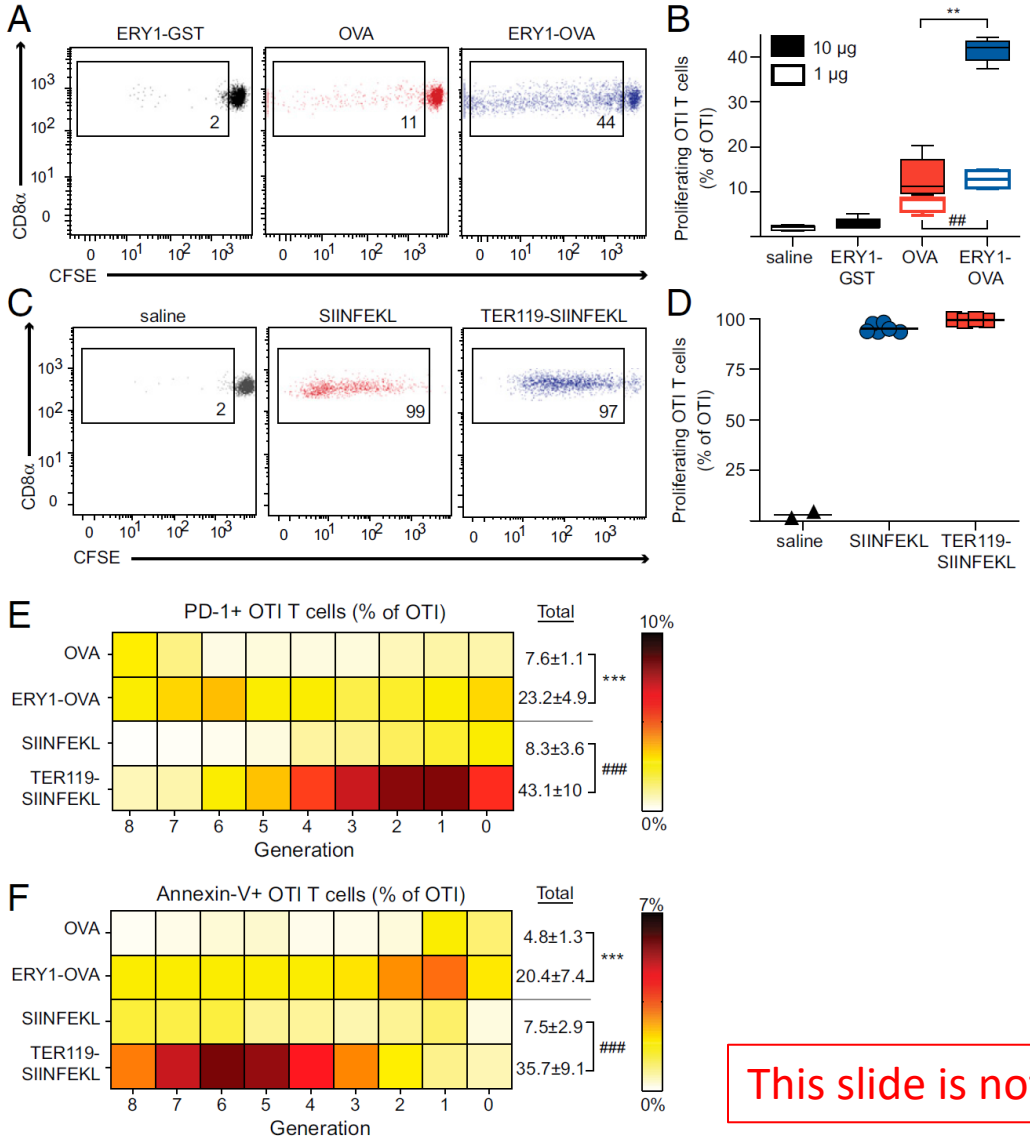
- **Antigens derived from apoptotic cell debris** can drive clonal T-cell deletion or anergy
- antigens chemically coupled ex vivo to apoptotic cell surfaces have been shown correspondingly to induce tolerance on infusion
- a large number of erythrocytes become apoptotic (eryptotic) and are cleared each day

ERY1-OVA binds the equatorial periphery of mouse erythrocytes



Proceedings of the National Academy of Sciences **110**, E60–E68 (2013).

Erythrocyte-binding antigen formulations enhance cross-priming and **apoptotic fate deletional proliferation** of antigen-specific OTI CD8+ T cells in vivo.



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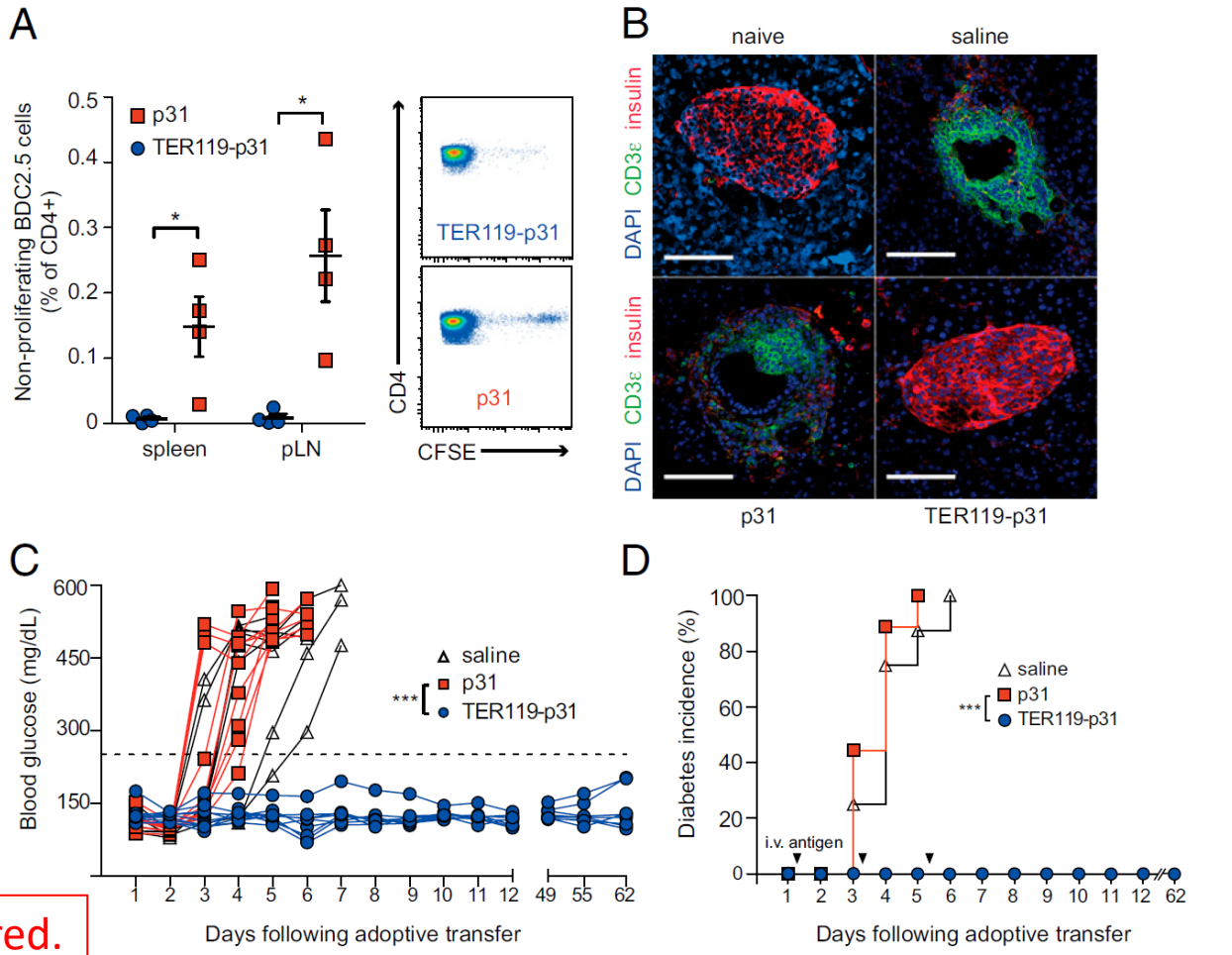
Erythrocyte-binding autoantigen protects mice from T cell-induced autoimmune type 1 diabetes (adoptively transferred transgenic diabetogenic CD4+ T cells from BDC2.5 mouse activated ex vivo with the p31 mimetope peptide to induce rapid diabetes onset)



Resulting in a spin-off from EPFL

Anokion harnesses the power of natural immune equilibrium to develop solutions for antigen-specific immune tolerance

http://anokion.com/