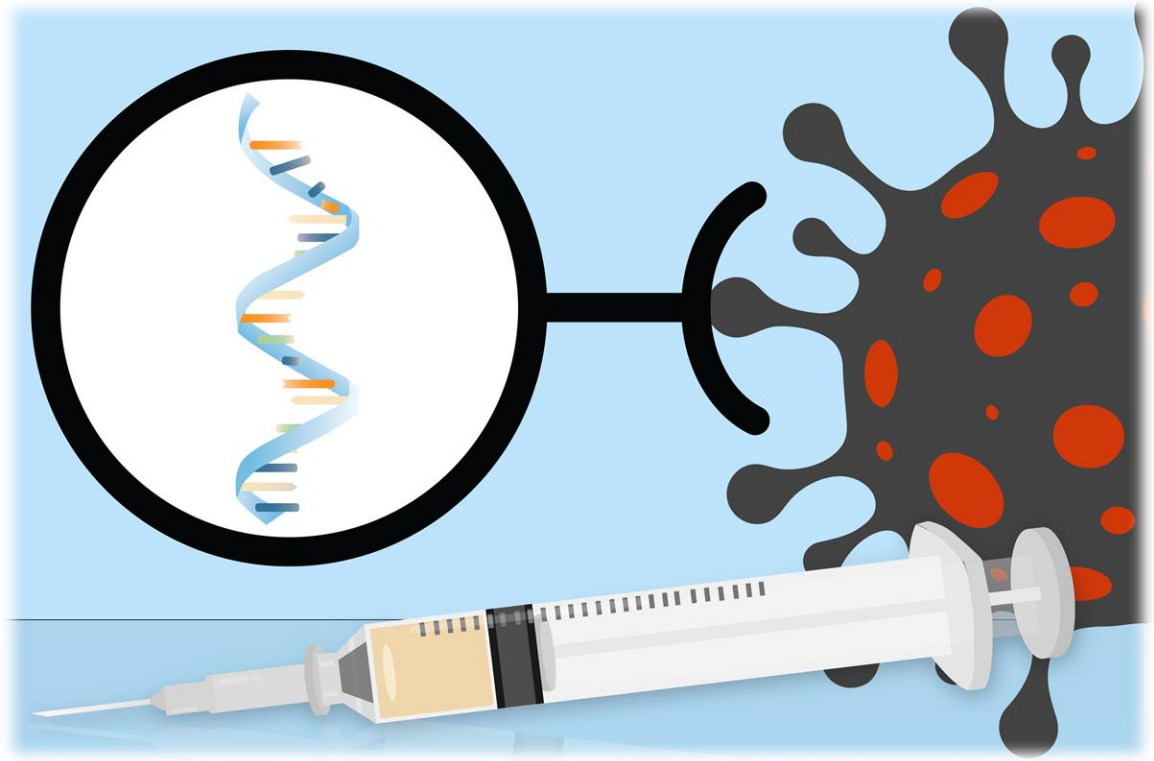
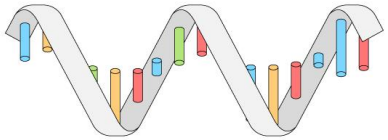


Del antígeno al mensajero



Dr. Fernando Fariñas Guerrero

Instituto de Inmunología Clínica y Enfermedades Infecciosas

GRUPO nmun

VACUNAS ARNm

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¡¡¡No me fío!!! Son demasiado nuevas y no se sabe nada sobre esta tecnología

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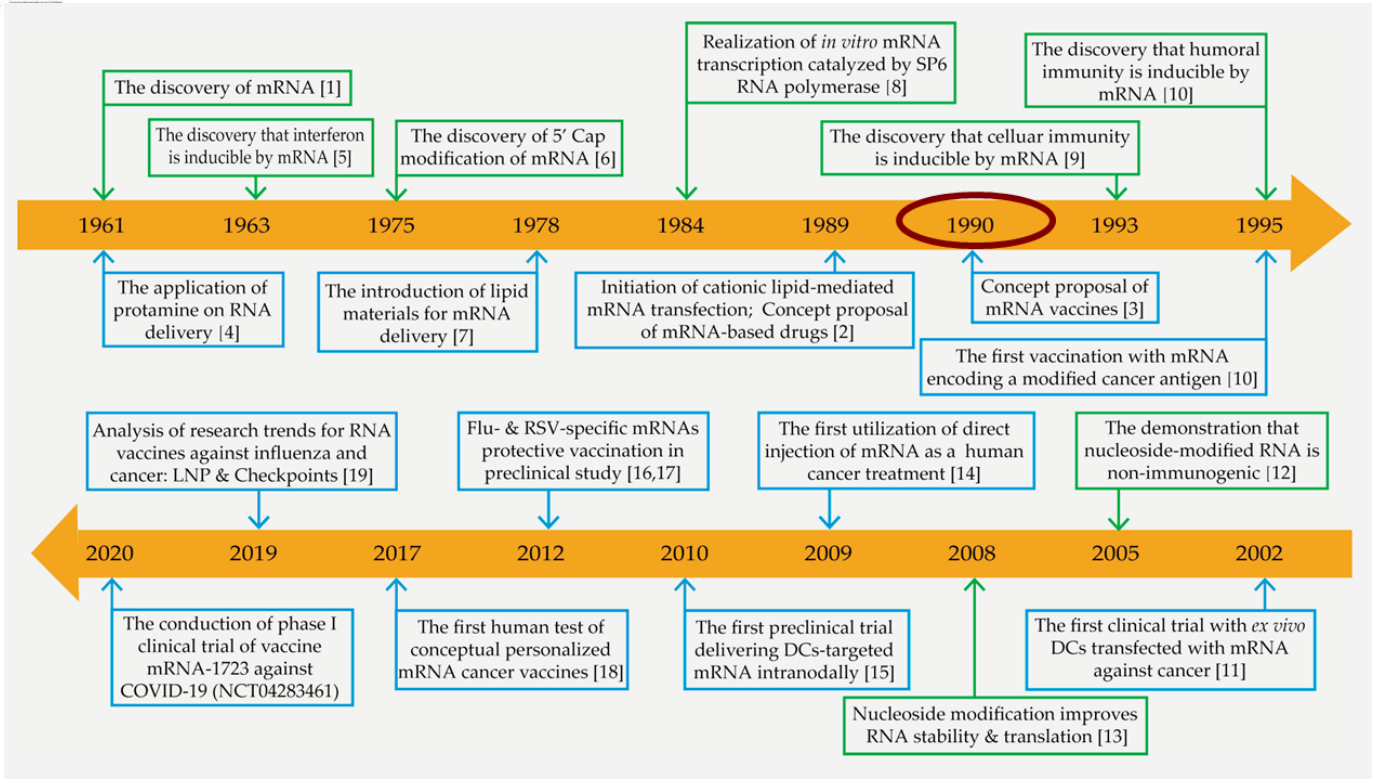

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Safety and immunogenicity of a mRNA rabies vaccine in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial

Martin Alberer, Ulrike Gnad-Vogt, Henoch Sangjoon Hong, Keyvan Tadjalli Mehr, Linus Backert, Greg Finak, Raphael Gottardo, Mihai Alexandru Bica, Aurelio Garofano, Sven Dominik Koch, Mariola Fotin-Mleczek, Ingmar Hoerr, Ralf Clemens, Frank von Sonnenburg

Summary

Background Vaccines based on mRNA coding for antigens have been shown to be safe and immunogenic in preclinical models. We aimed to report results of the first-in-human proof-of-concept clinical trial in healthy adults of a prophylactic mRNA-based vaccine encoding rabies virus glycoprotein (CV7201).

Methods We did an open-label, uncontrolled, prospective, phase 1 clinical trial at one centre in Munich, Germany. Healthy male and female volunteers (aged 18–40 years) with no history of rabies vaccination were sequentially enrolled. They received three doses of CV7201 intradermally or intramuscularly by needle-syringe or one of three needle-free devices. Escalating doses were given to subsequent cohorts, and one cohort received a booster dose after 1 year. The primary endpoint was safety and tolerability. The secondary endpoint was to determine the lowest dose of CV7201 to elicit rabies virus neutralising titres equal to or greater than the WHO-specified protective antibody titre of 0·5 IU/mL. The study is continuing for long-term safety and immunogenicity follow-up. This trial is registered with ClinicalTrials.gov, number NCT02241135.

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http://dx.doi.org/10.1016/S0140-6736(17)31964-5

Department of Infectious Diseases and Tropical Medicine, Medical Centre of the University of Munich, Munich, Germany (M Alberer MD, Prof F von Sonnenburg MD); **CureVac AG, Tübingen,**

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¿De qué están hechas?

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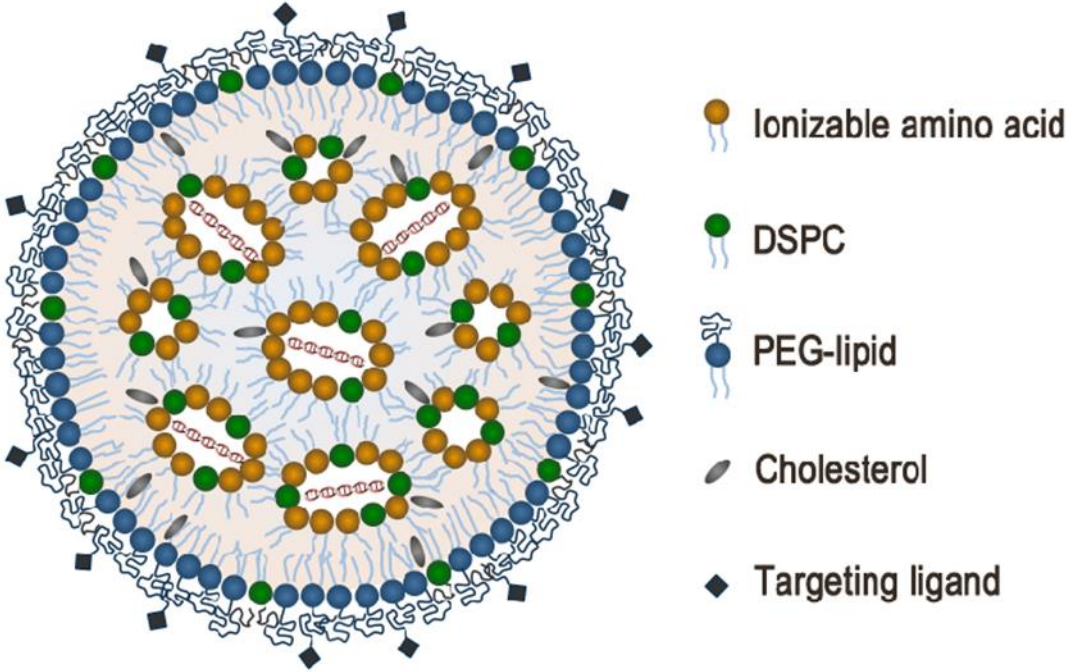
Los LNP (Lipid Nanoparticles) operan en la misma escala de tamaño que los virus



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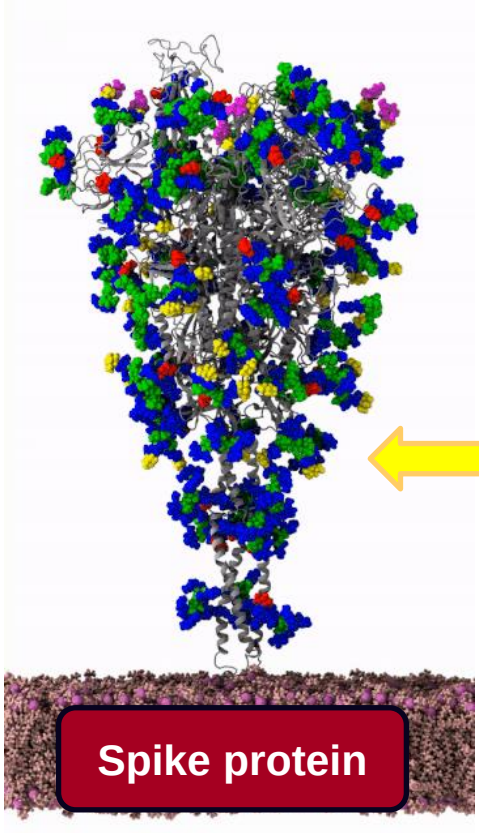

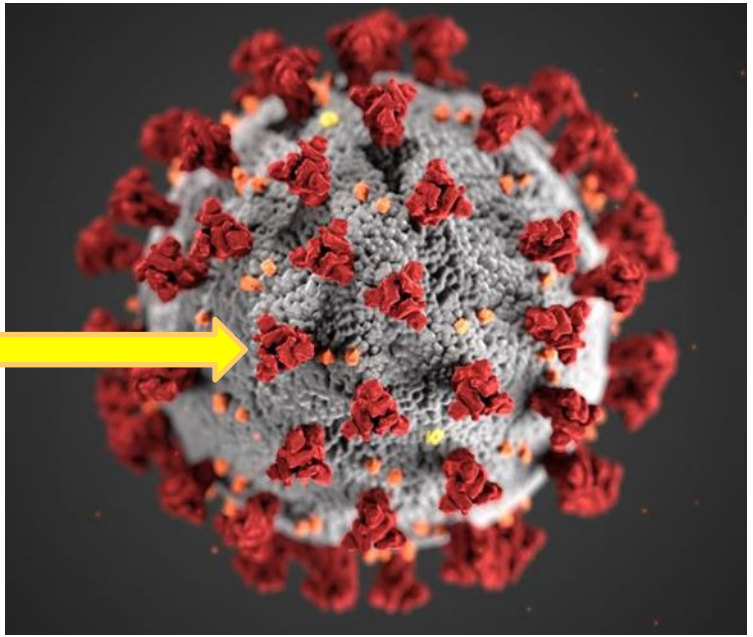

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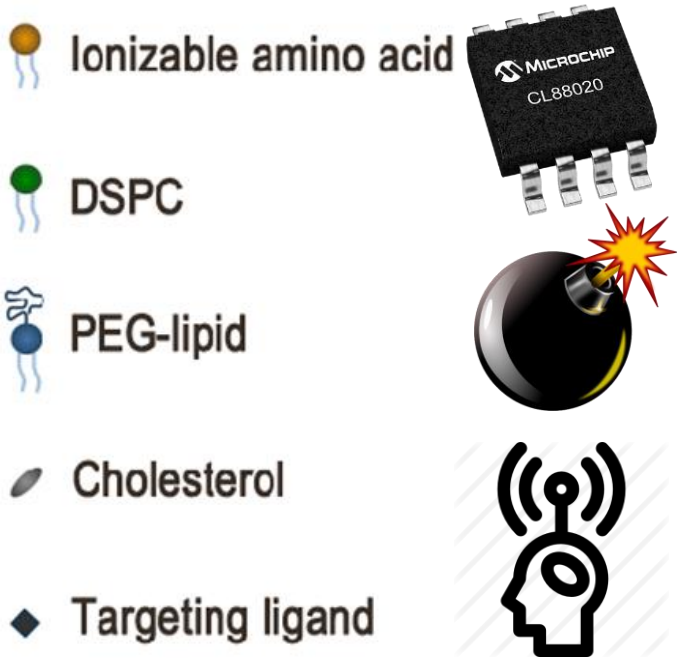

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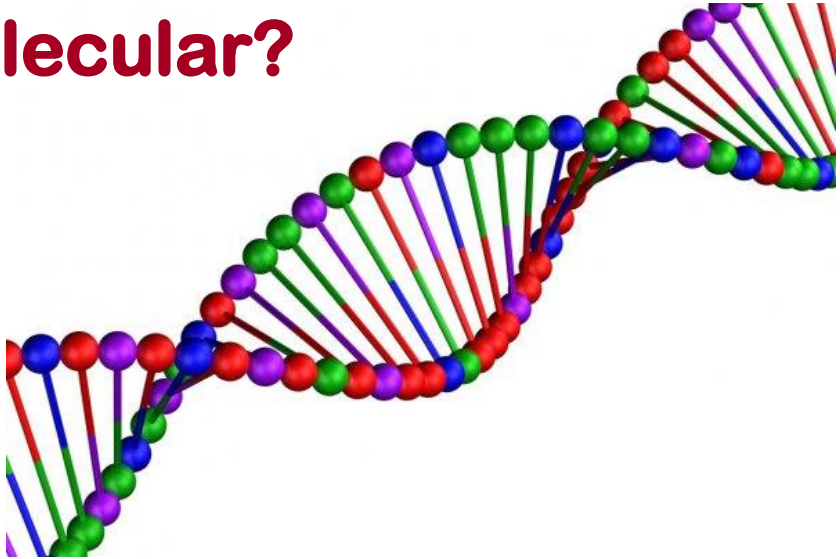
¿Cómo funcionan a nivel molecular?



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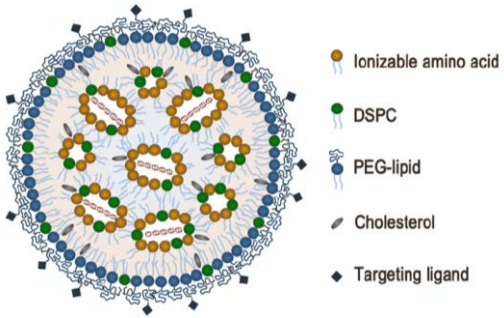

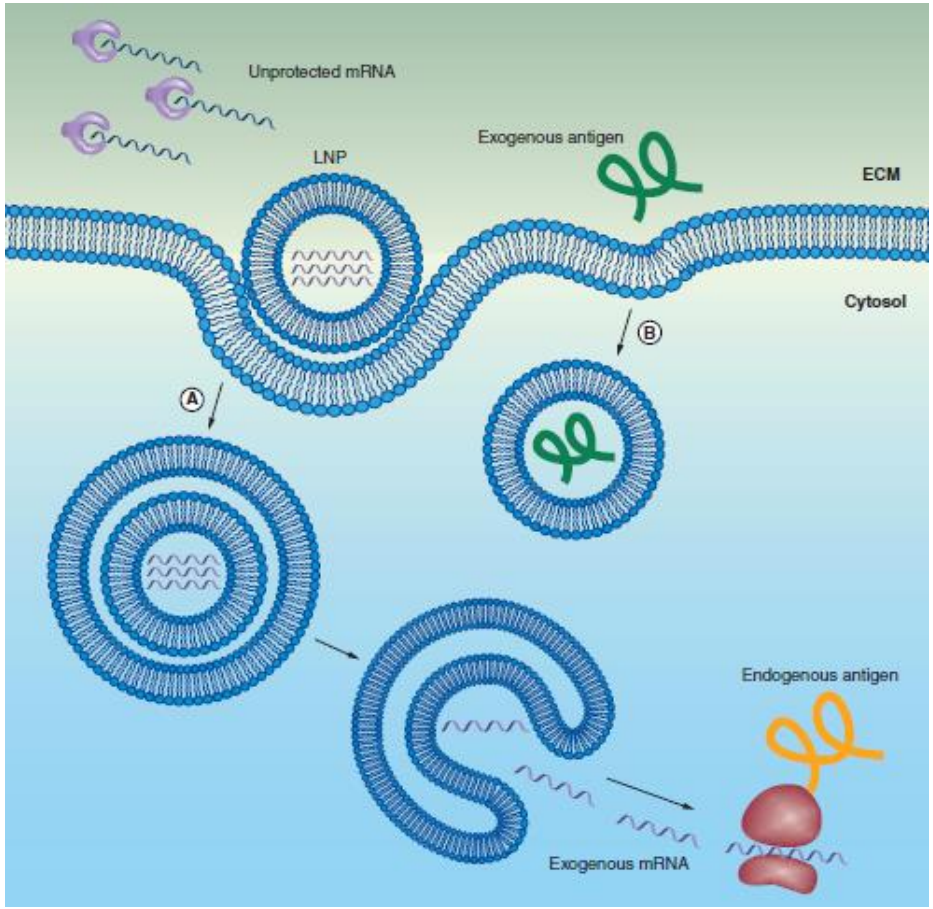

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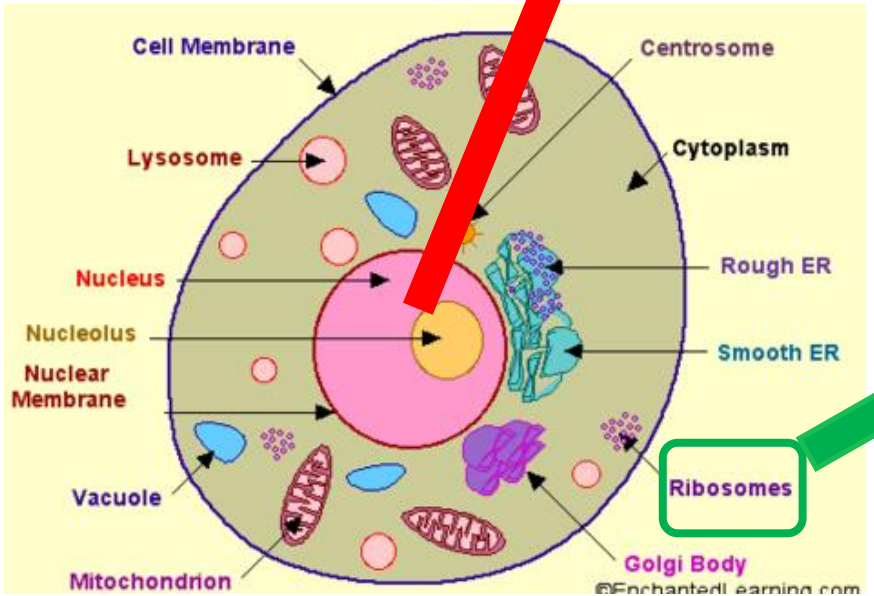

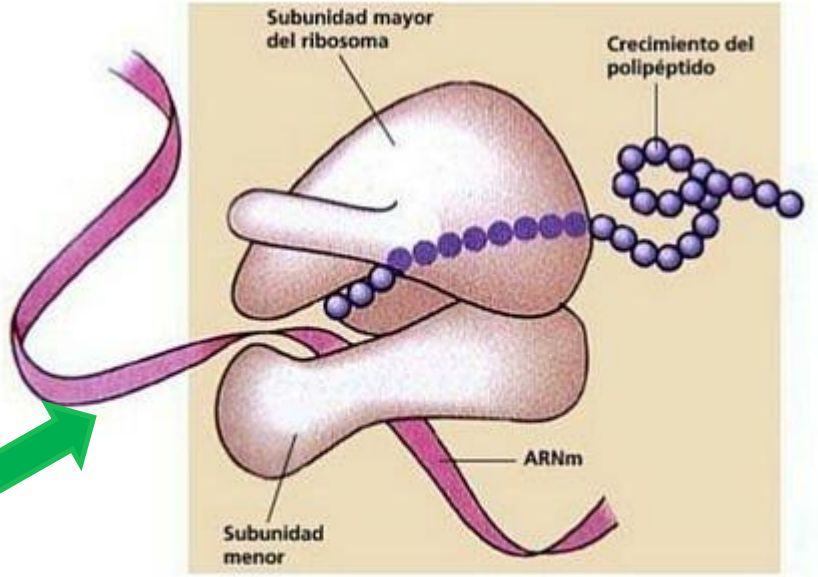

Ribosomas

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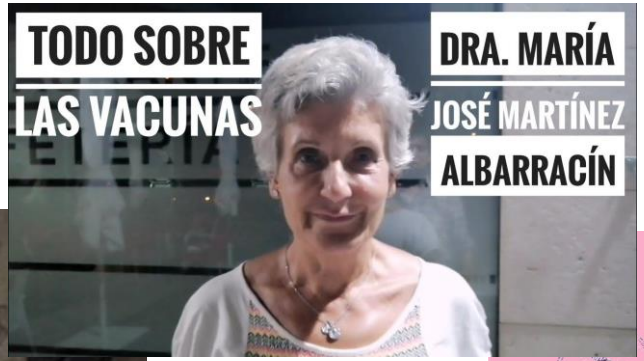

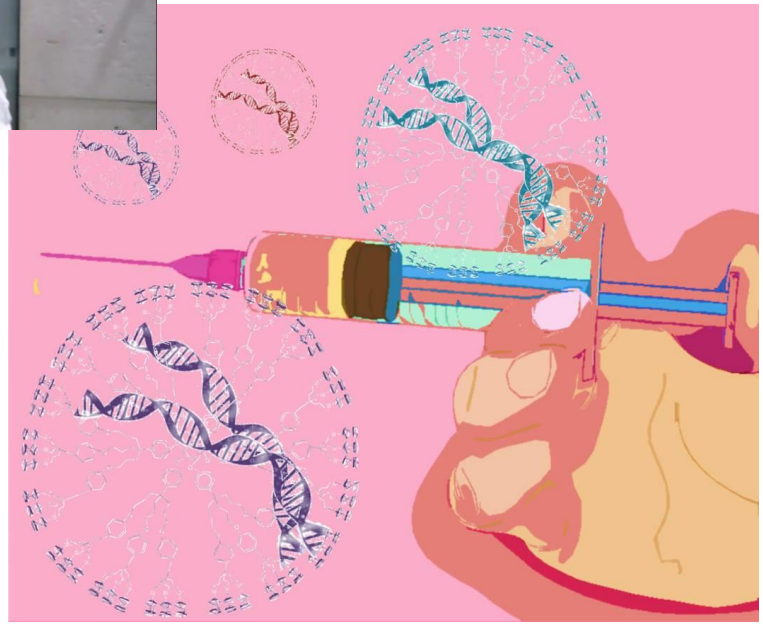

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¿Qué tipos de vacunas ARNm existen?

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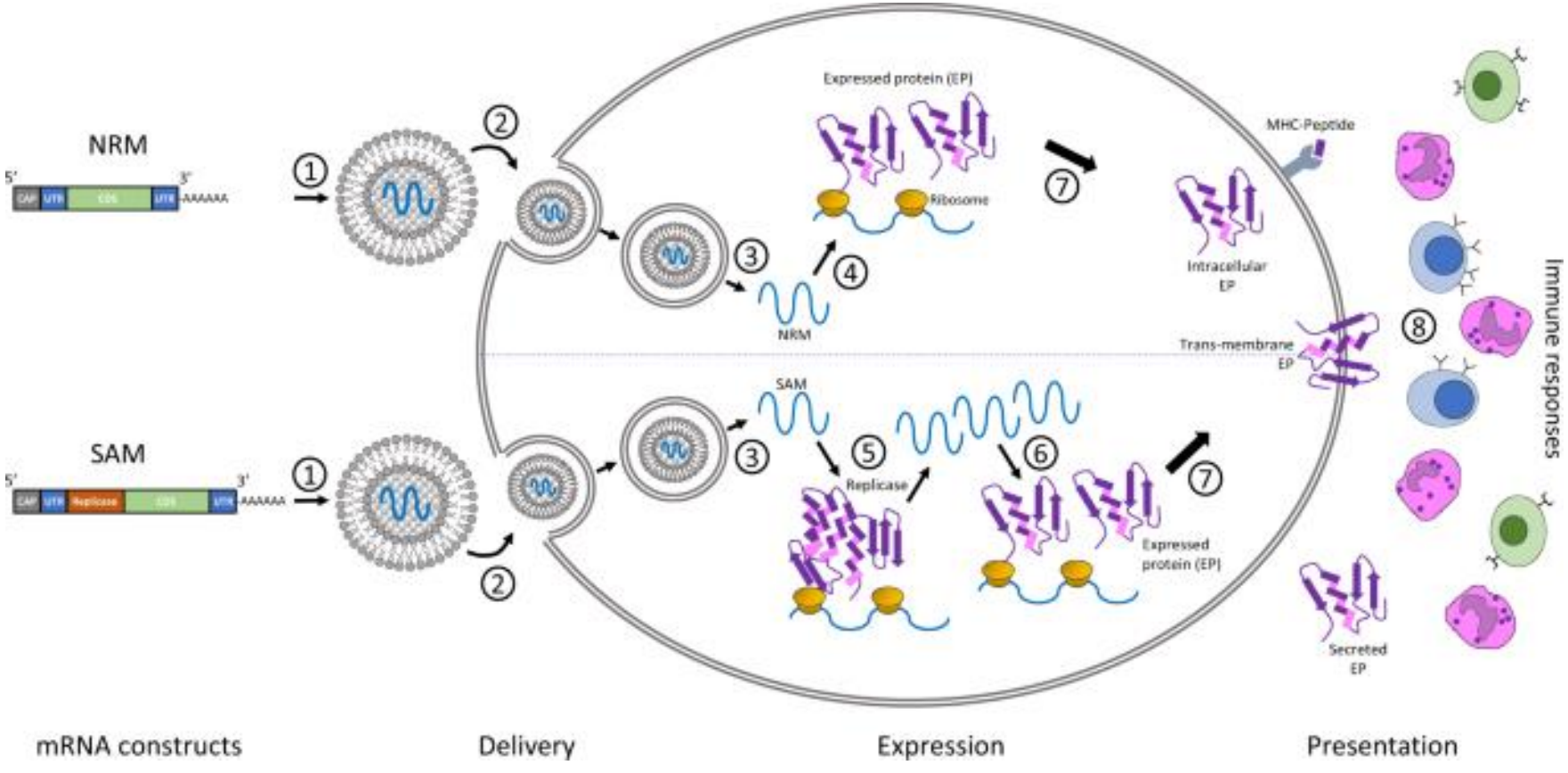

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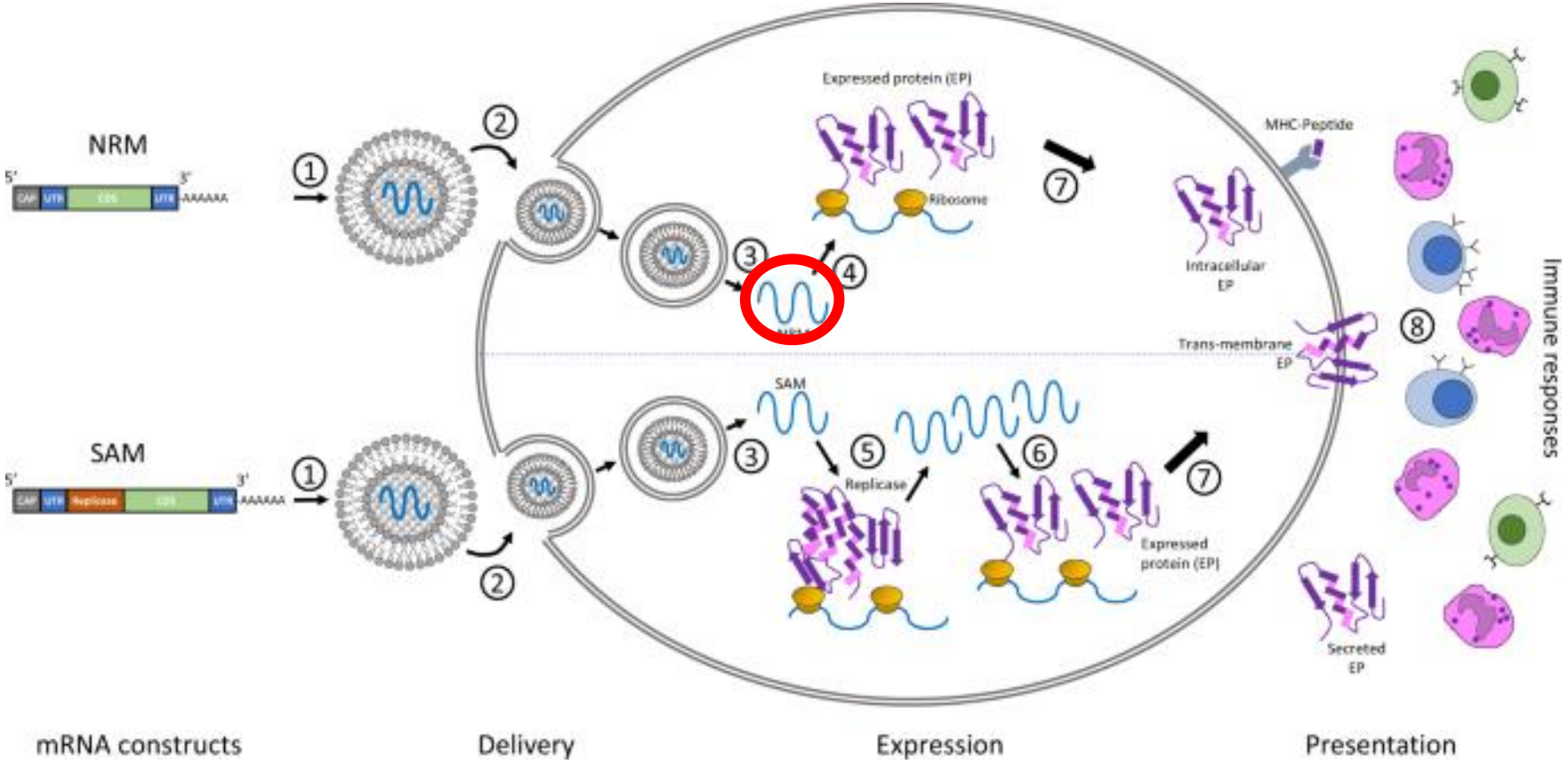

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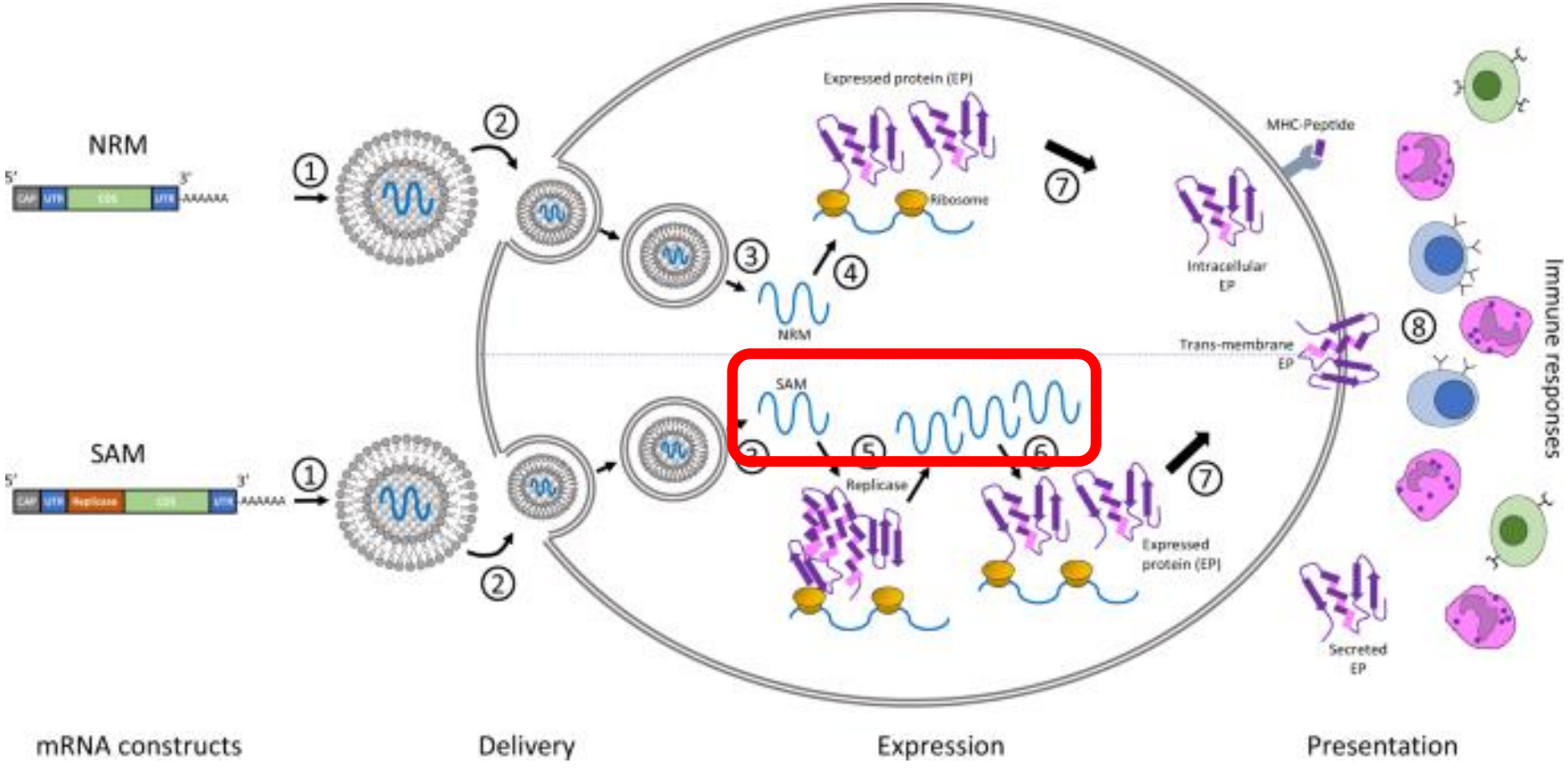

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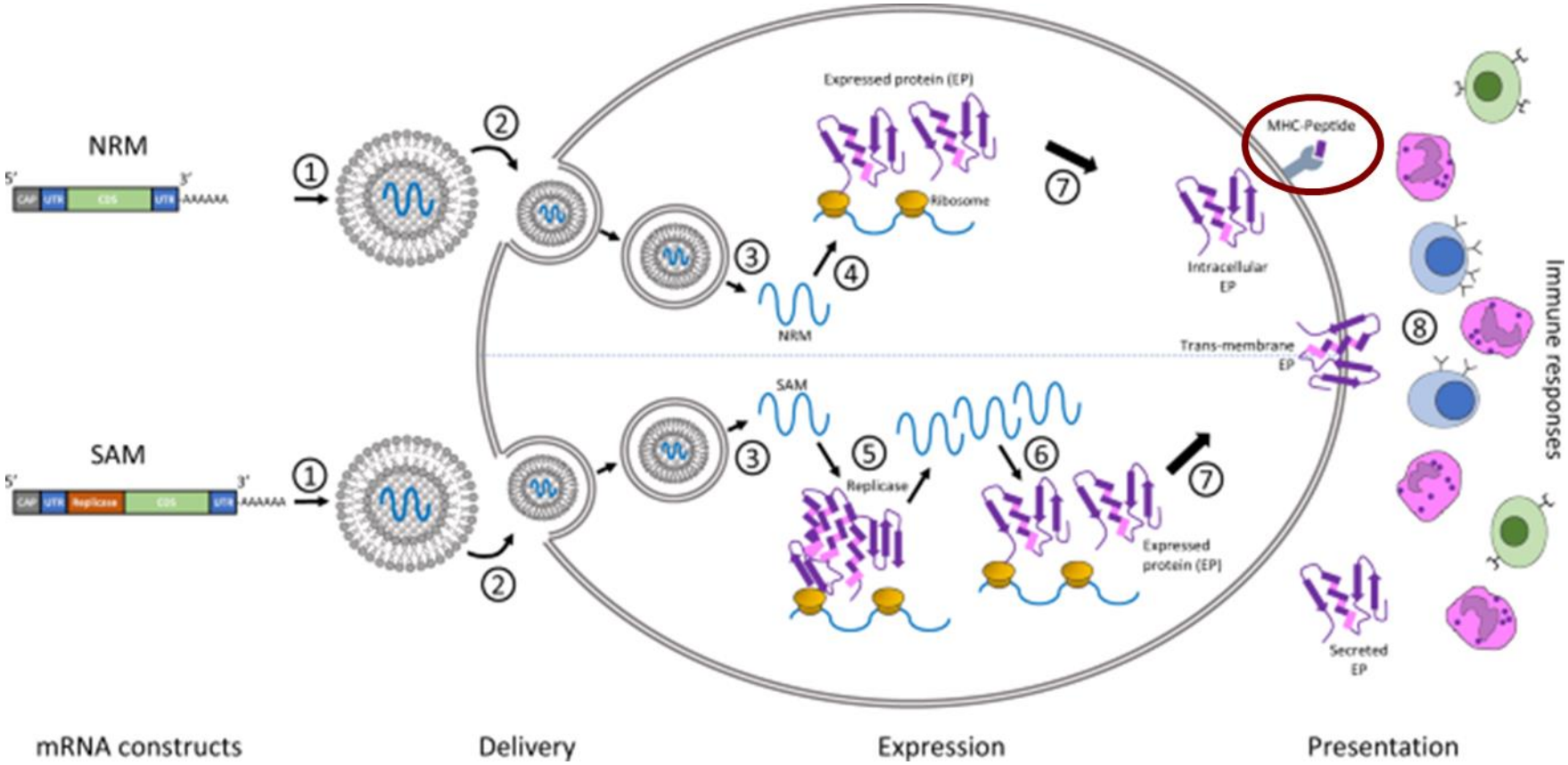

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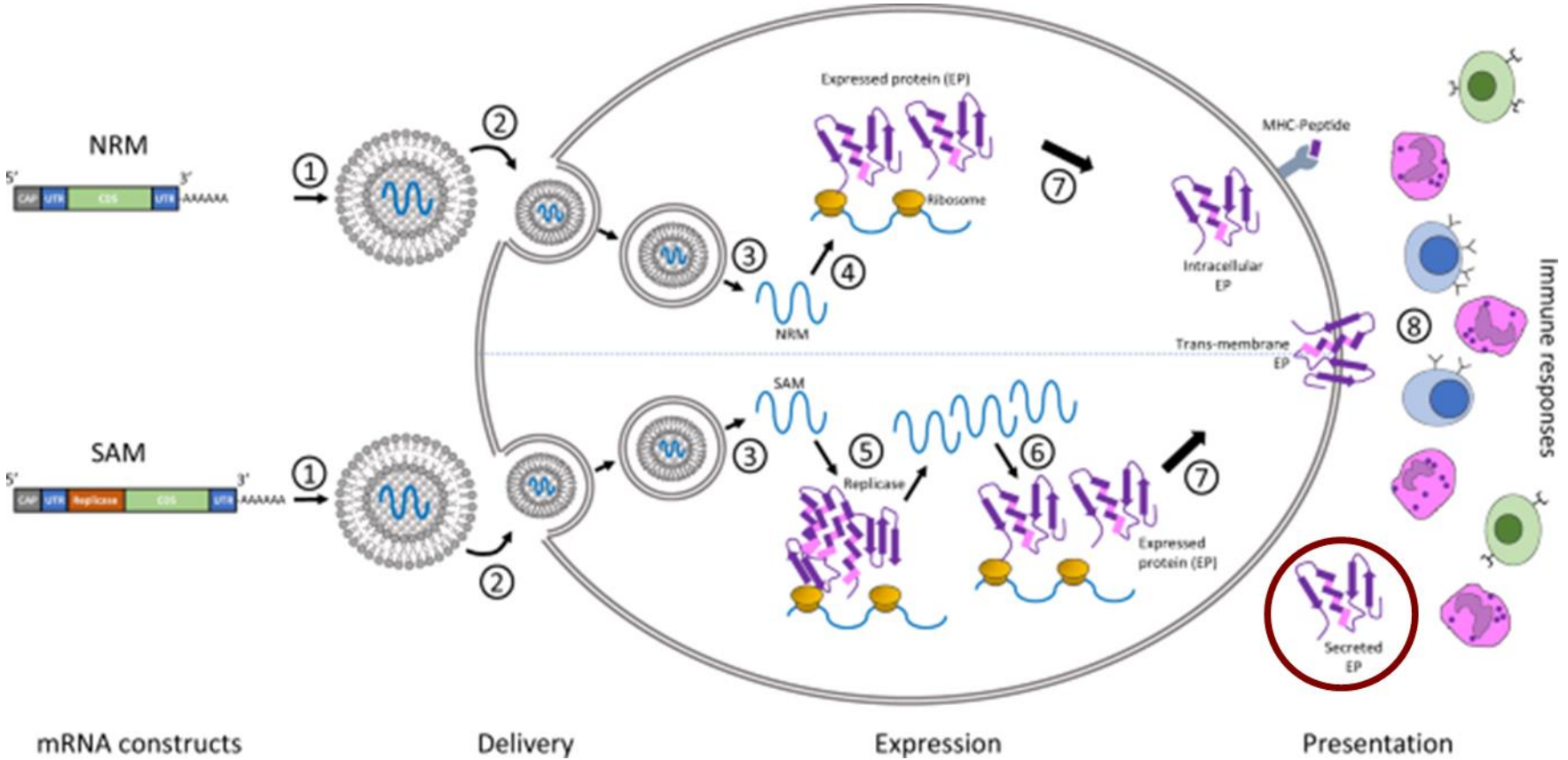

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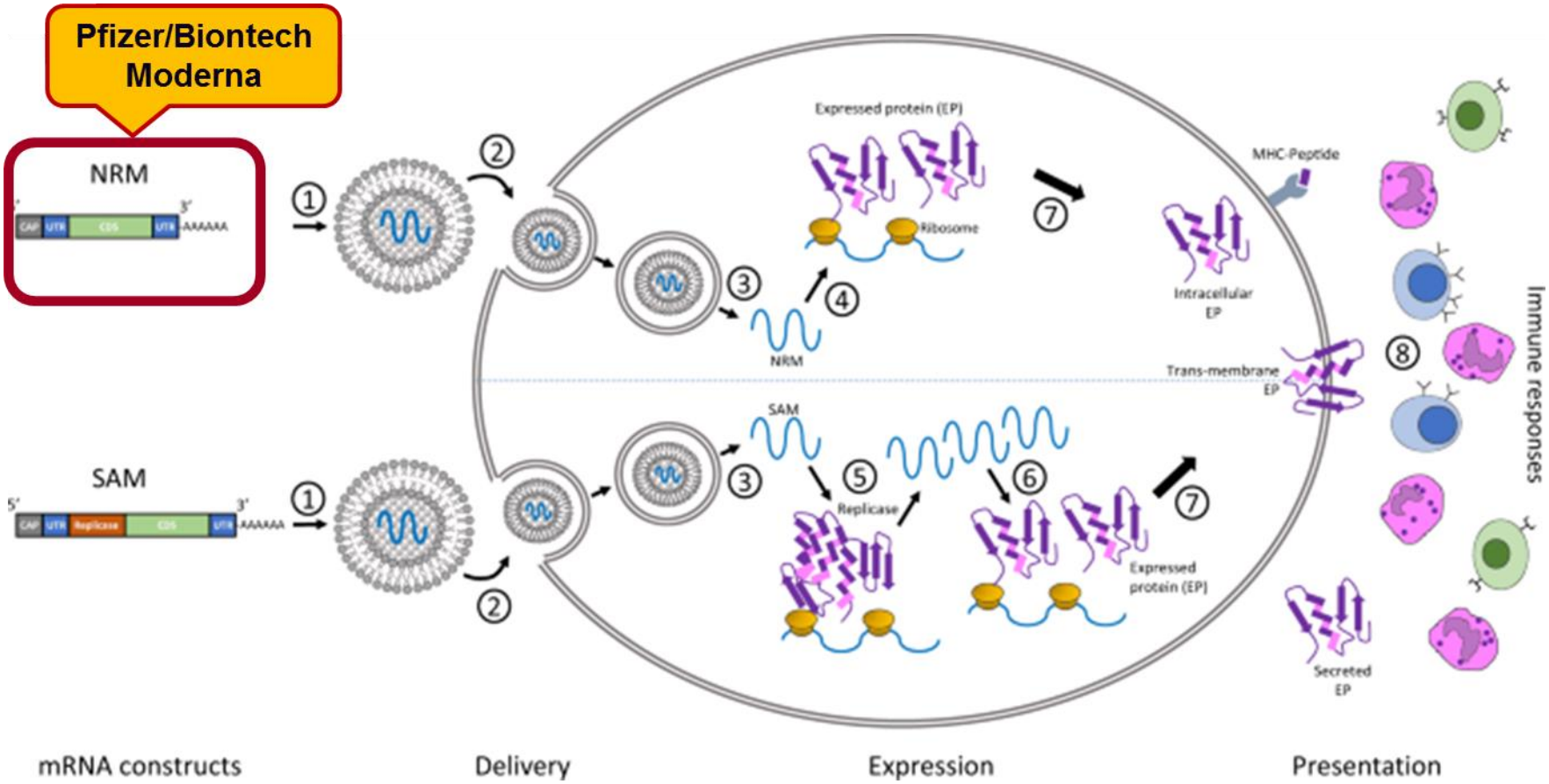

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¡¡¡ Houston, tenemos un problema!!!

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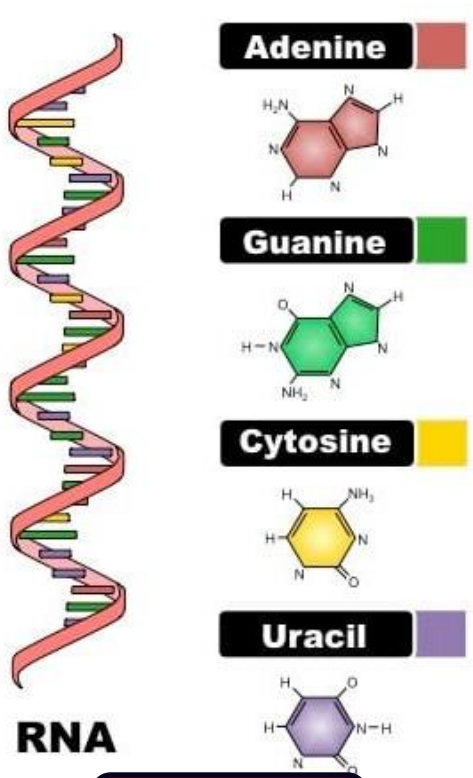
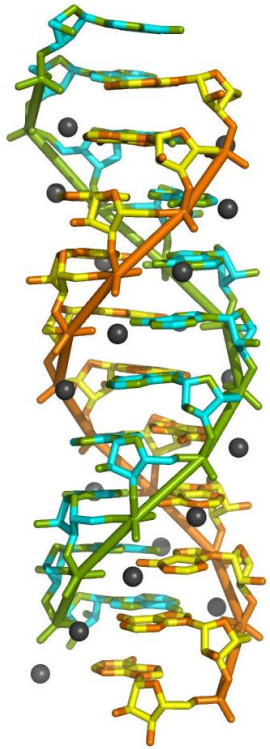
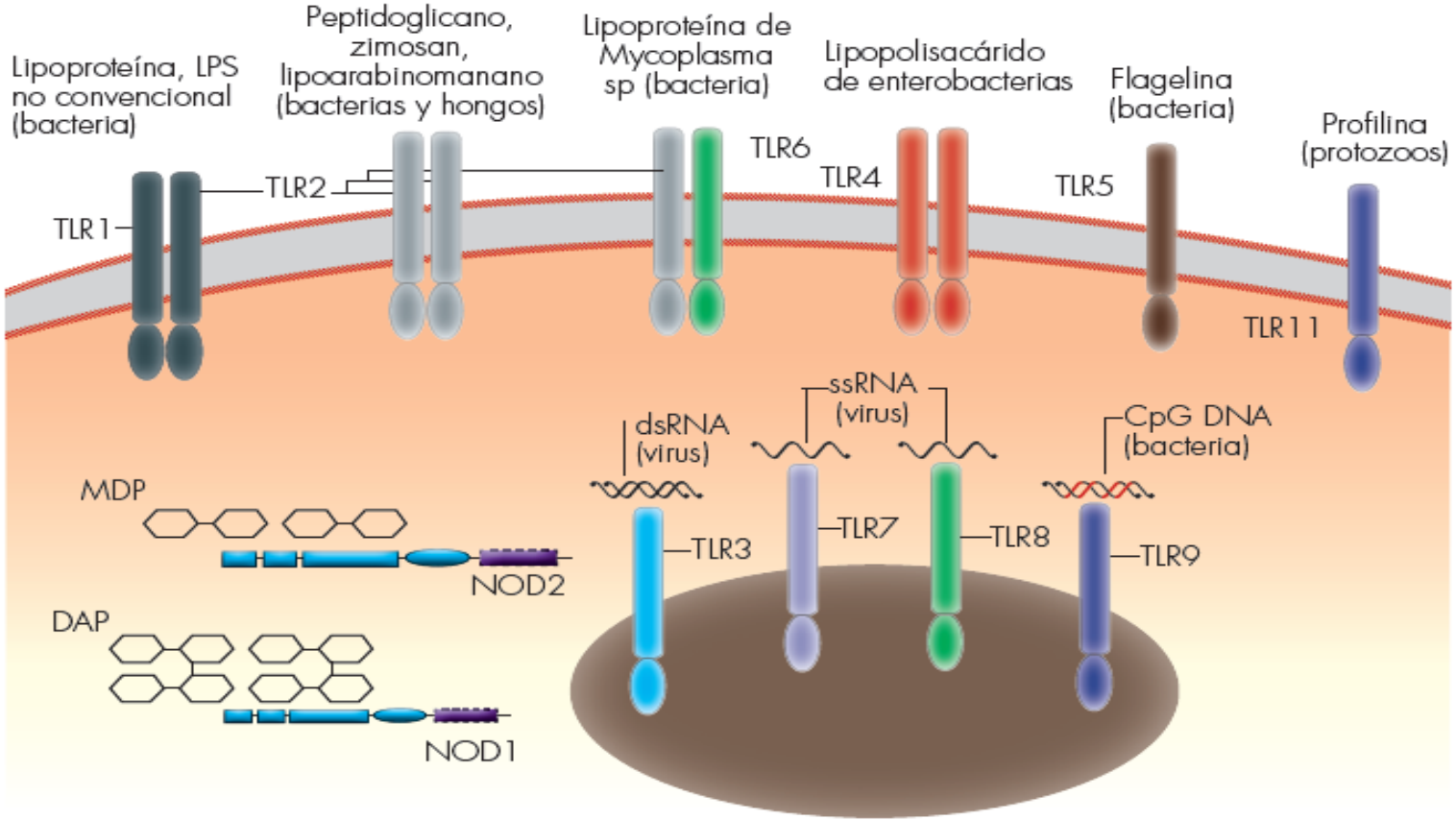


ARNss

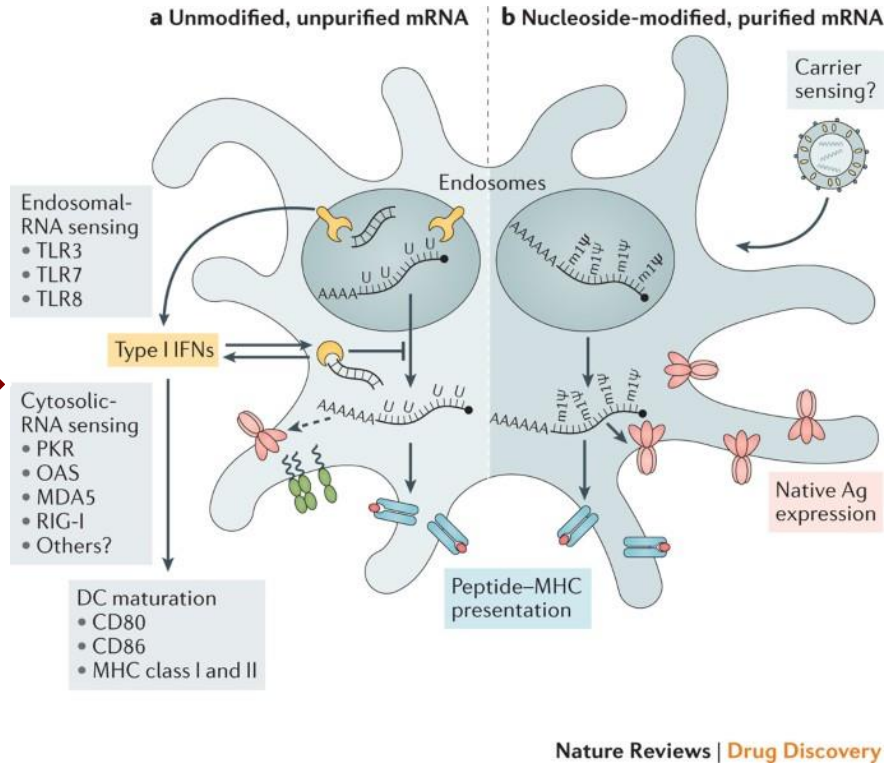


ARNds

VACUNAS ARNm



- Reconocido por **TLR3, TLR7 y TLR8** endosomas.
- Esto produce **IFN-I.**
- **“Parálisis”** de la maquinaria de producción de proteínas.
- **Degradación rápida** del RNAm.
- Una alta producción de **IFN-I induce cascada de citocinas** (IL6, TNFα,..).
- Aunque promueve LTC T8+, una alta cantidad puede inducir un estado de **“exhaustion”** y **pobre expresión de antígeno** asociado a HLA clase I.
- La falta de purificación conlleva **presencia de RNAds** que incrementa aún más todo lo anterior.
- Mayor **reactogenicidad**



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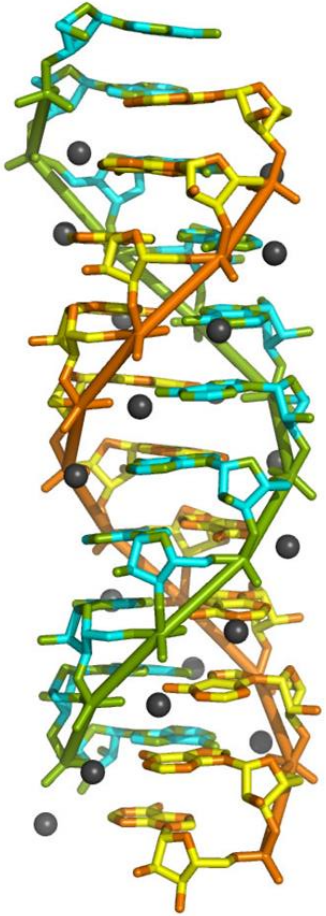

ARNds

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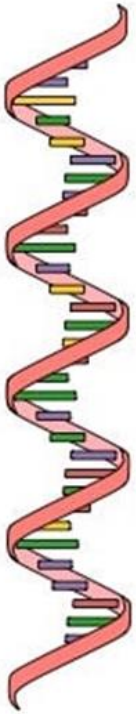
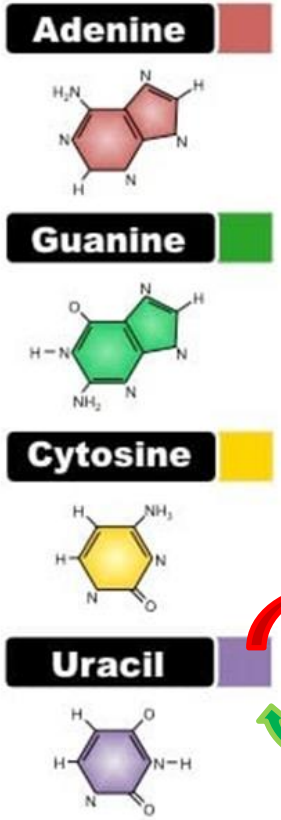
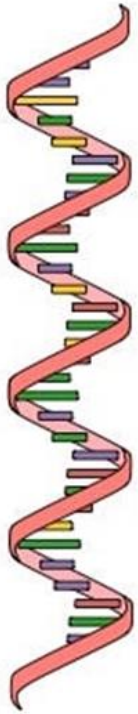


RNA

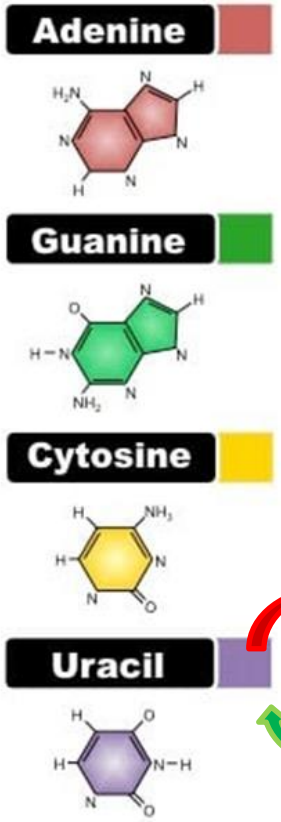


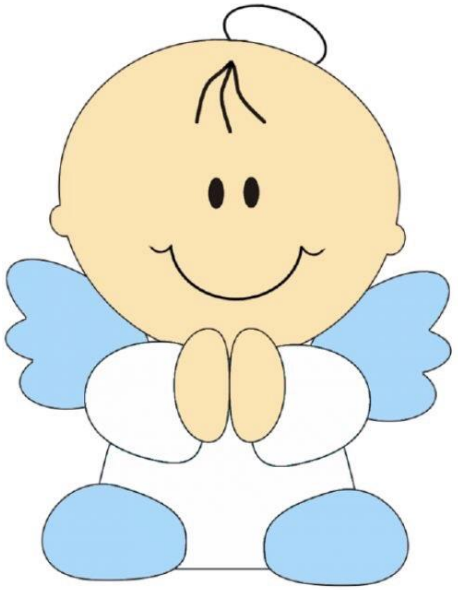
Pseudouridina

VACUNAS ARNm

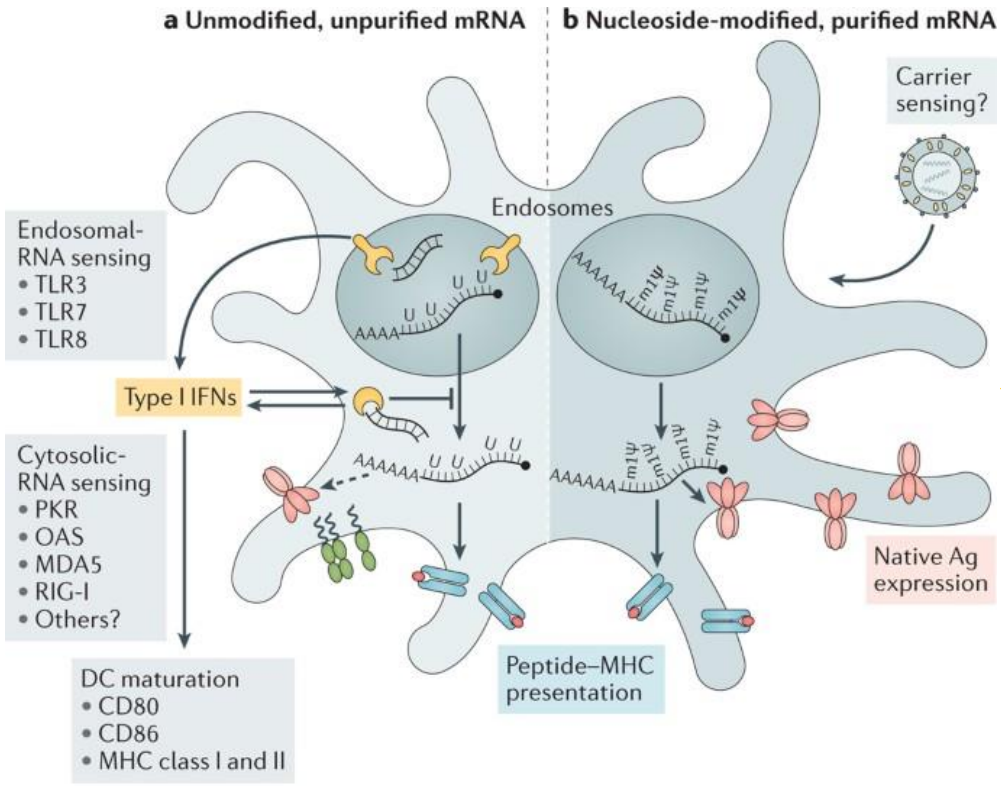


RNA





Pseudouridina



-**Mínima activación** de los TLR3, TLR 7, TLR8, MDA5 y RIG-I

-**Ausencia** de **RNAds**

-Mayor duración en el citoplasma celular.

-Despierta respuestas de **linfocitos B y linfocitos T (CD4+ y CD8+).**

-Incremento de la **estabilidad y de la expresión del antígeno en superficie.**

-Menos inmunógena por lo que requiere a veces un **booster, aunque no siempre….**

-Menor **reactogenicidad**

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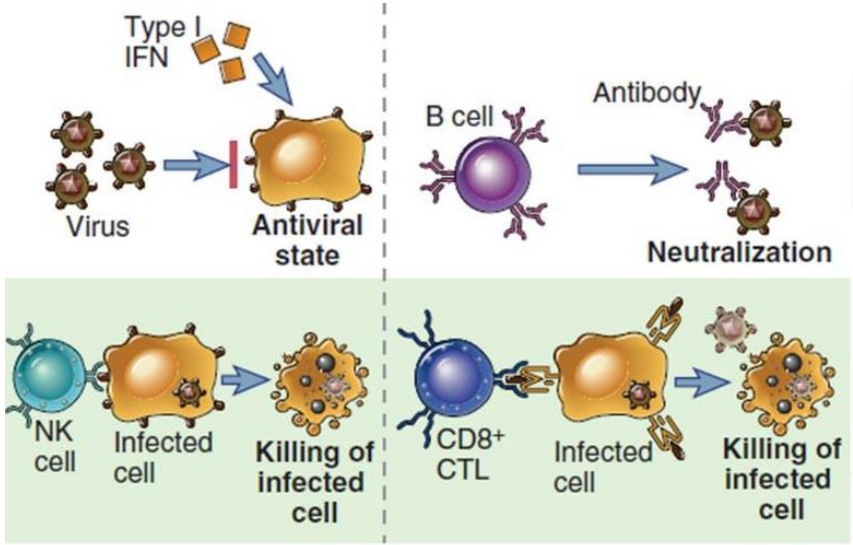
¿Cómo funcionan a nivel inmunitario?



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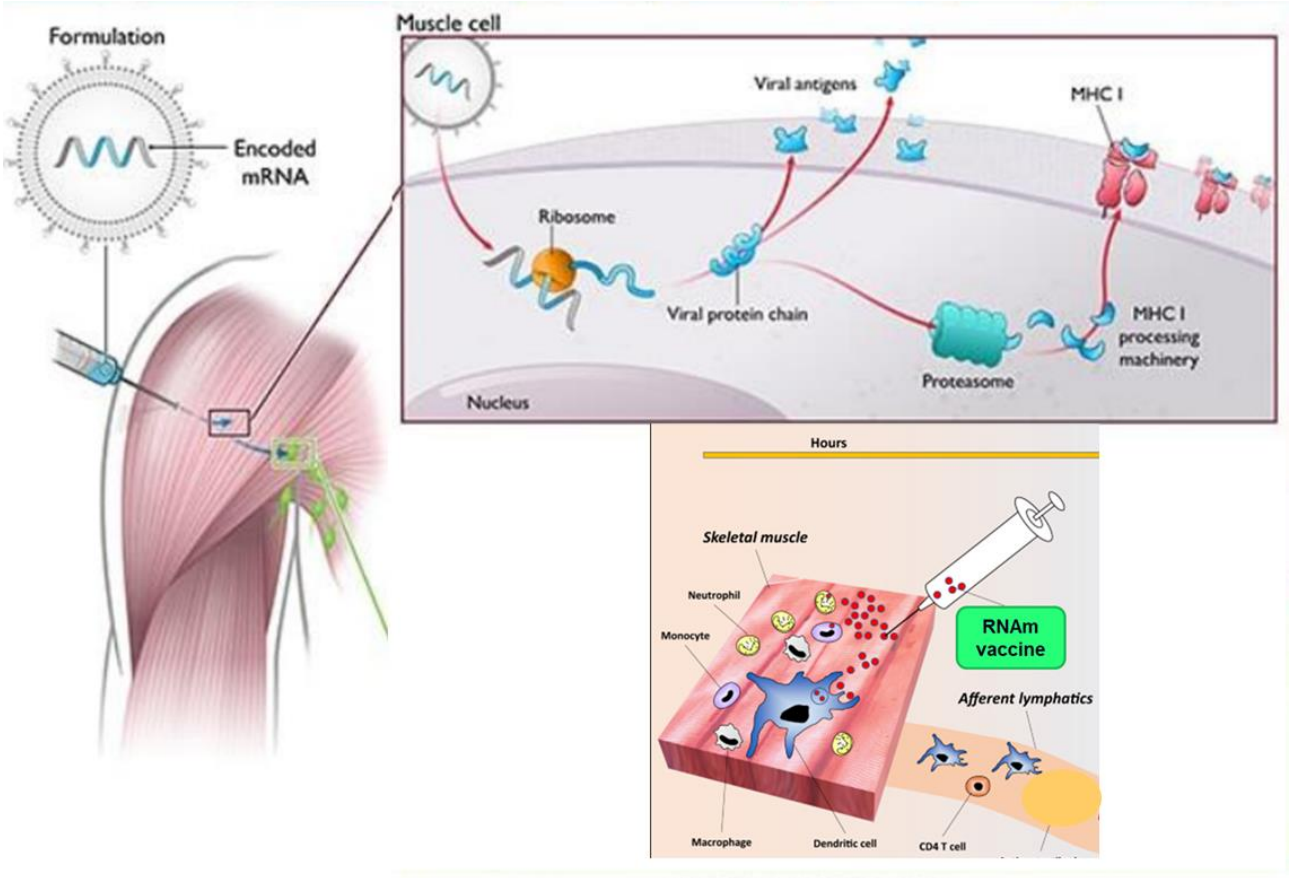
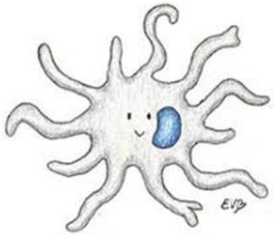


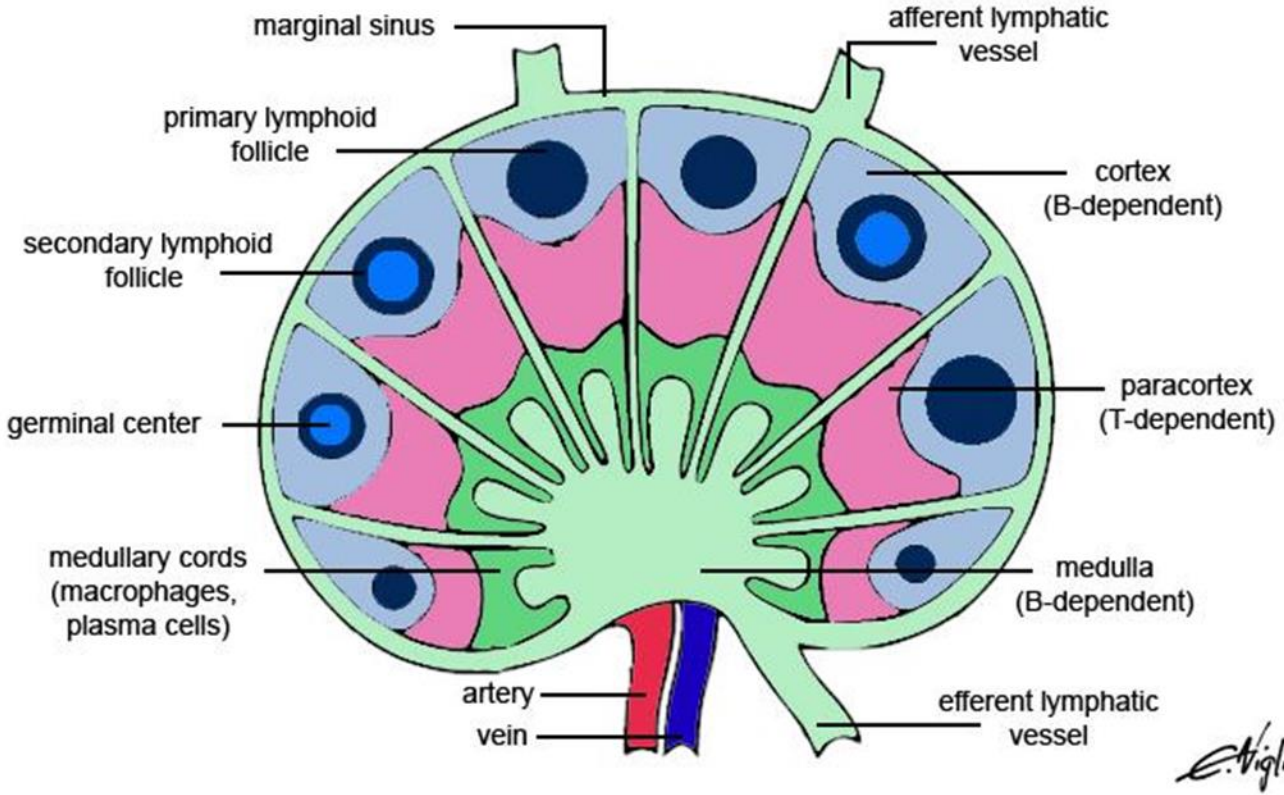


CÉLULA DENDRÍTICA

Spike protein

mRNA Vaccine

Lipid coat



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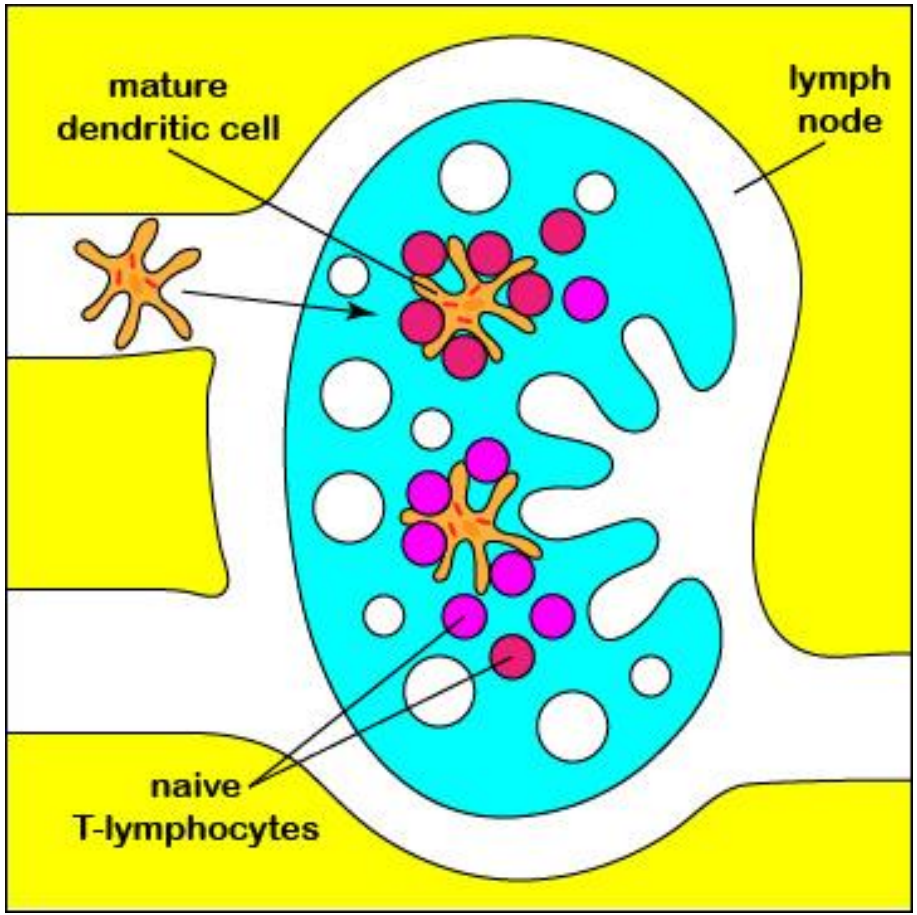

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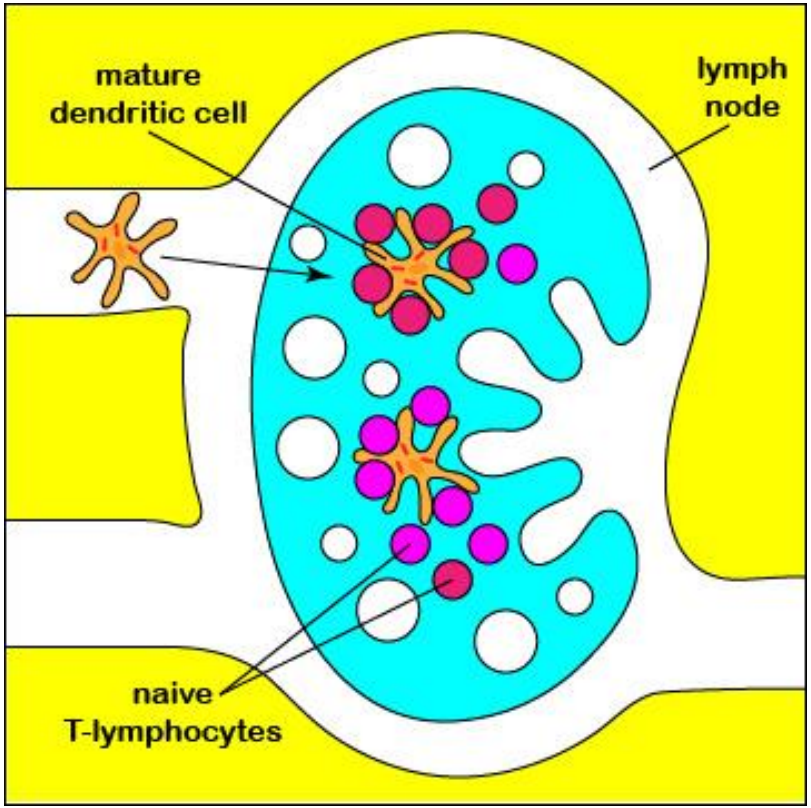

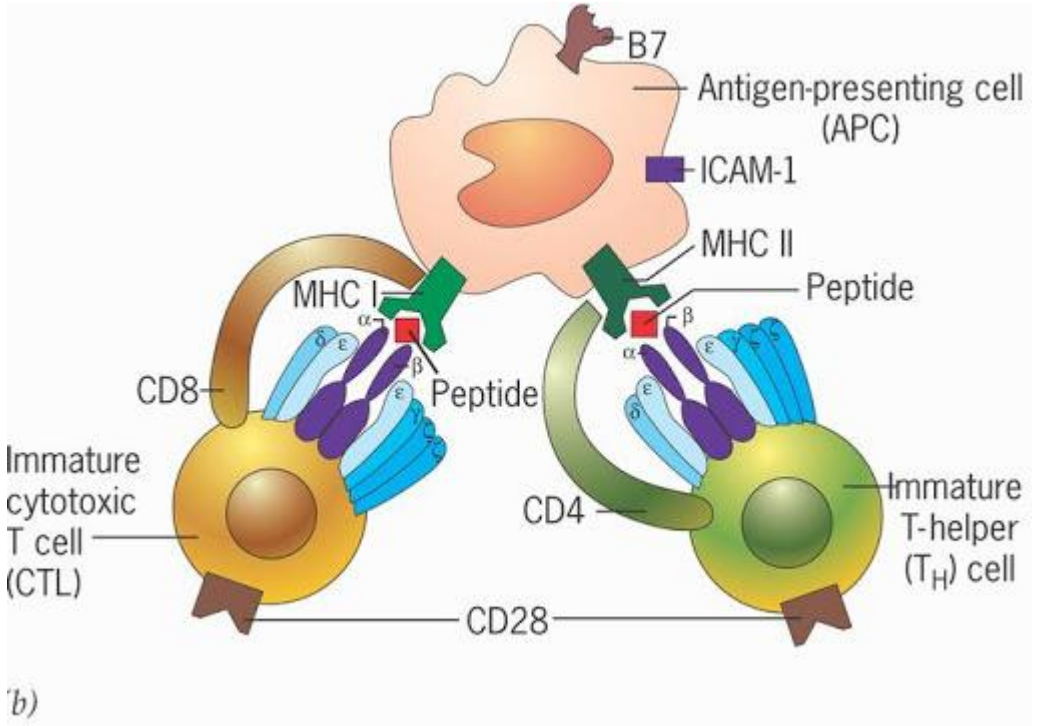

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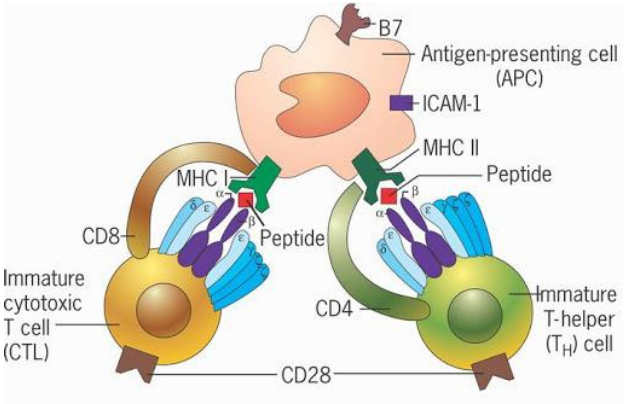

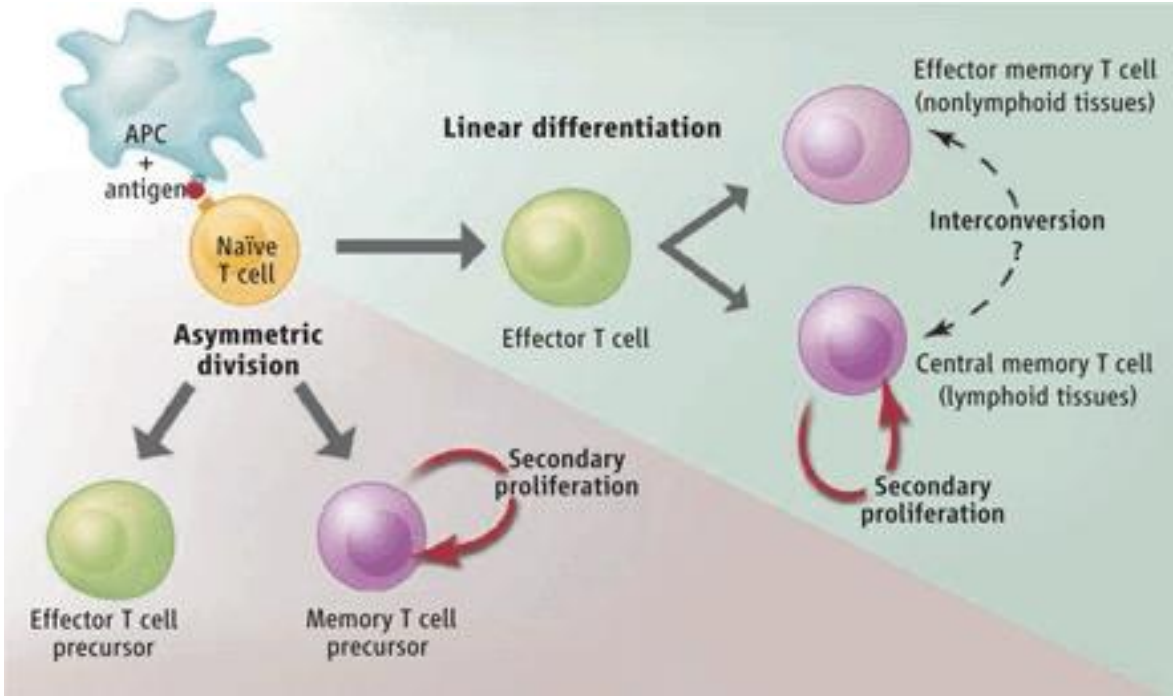

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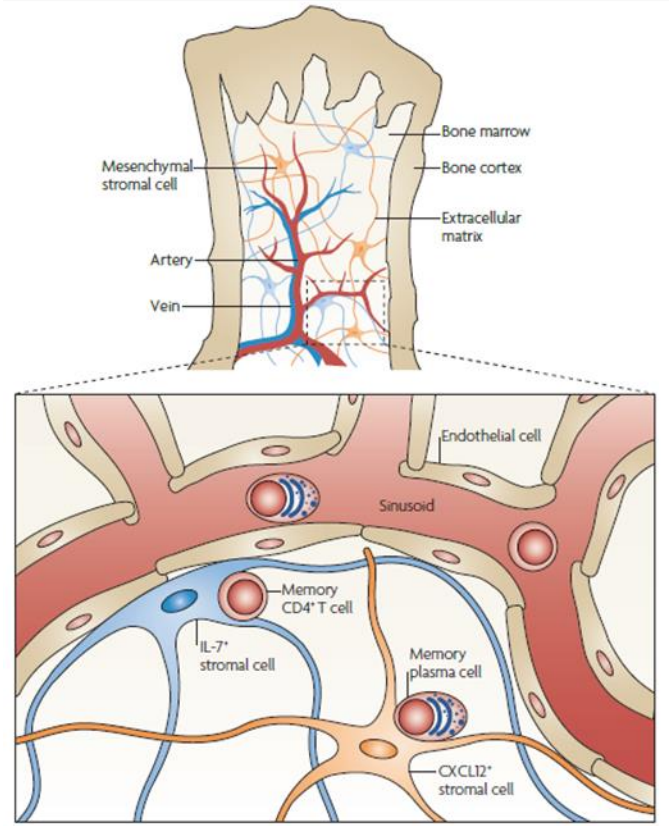

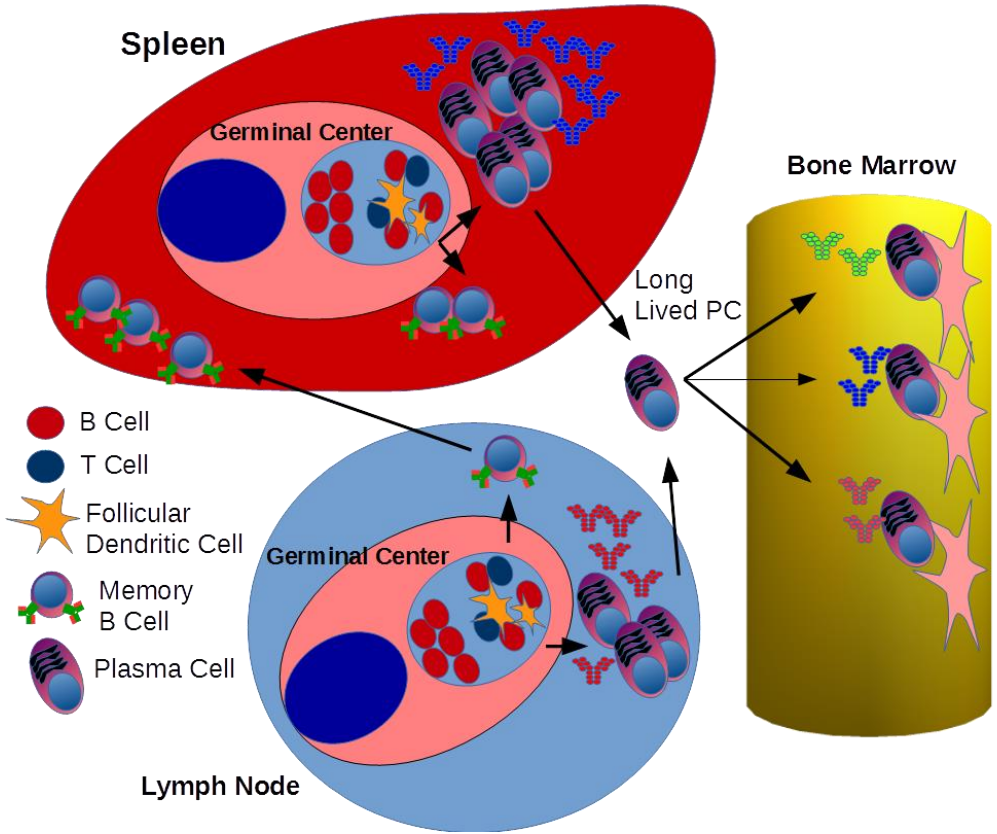

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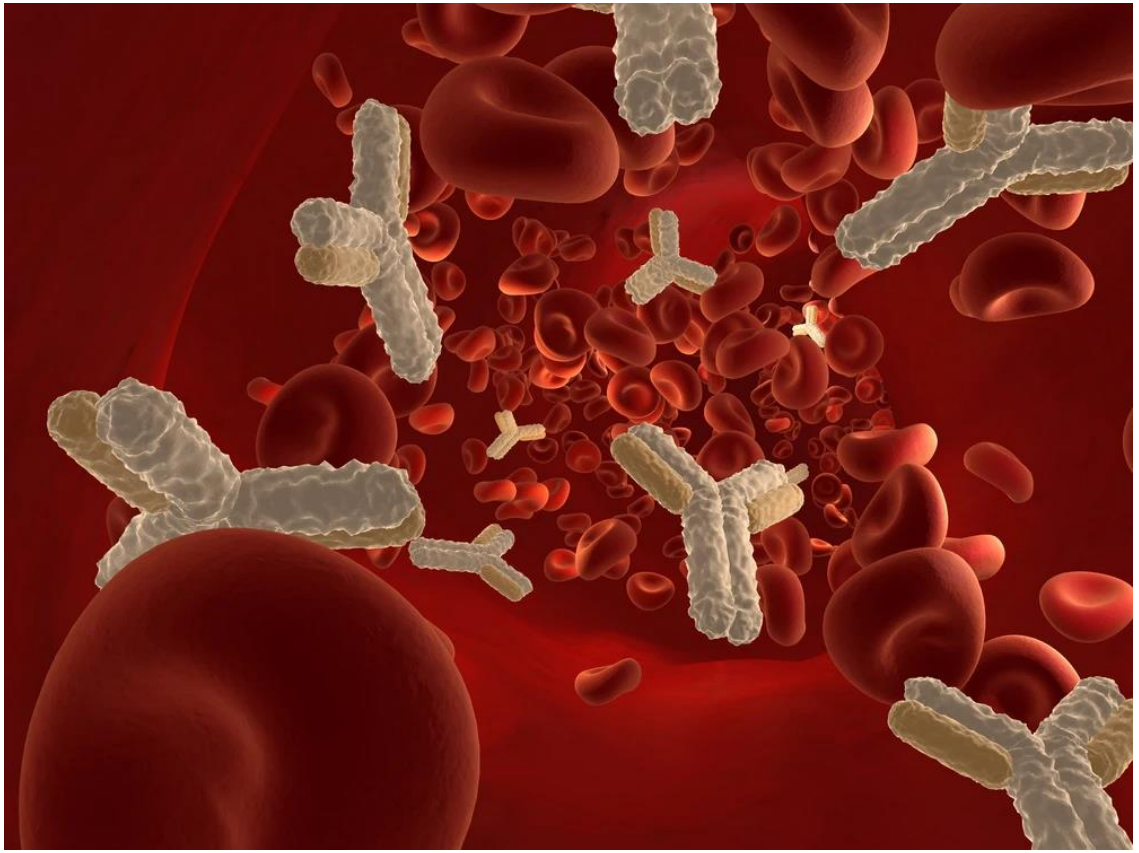
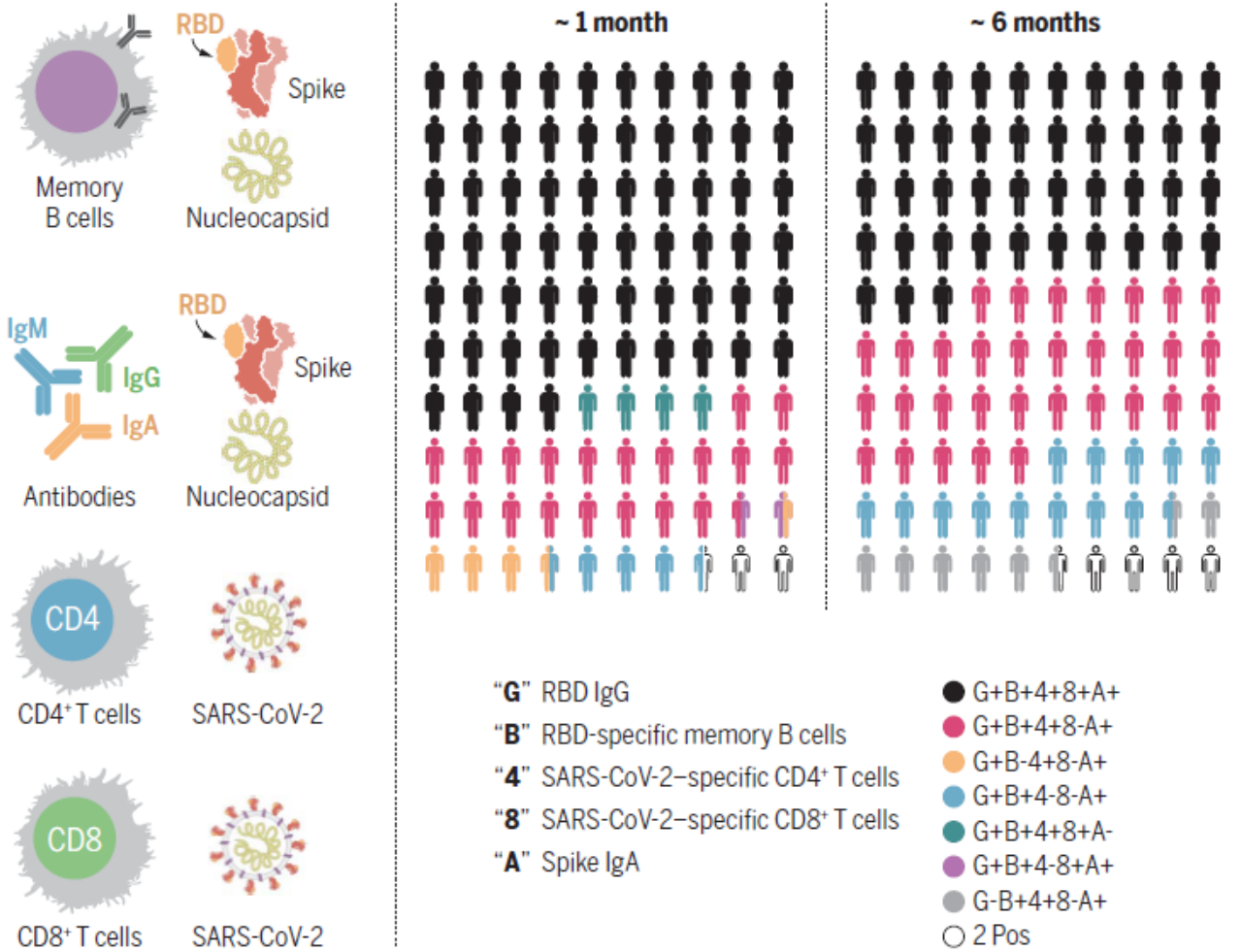


Correlato de protección


RBD
Spike
Memory
B cells
Nucleocapsid
IgM
IgG
IgA
RBD
Spike
Antibodies
Nucleocapsid
CD4
CD4⁺ T cells
SARS-CoV-2
CD8
CD8⁺ T cells
SARS-CoV-2
~ 1 month
~ 6 months
"G" RBD IgG
"B" RBD-specific memory B cells
"4" SARS-CoV-2–specific CD4⁺ T cells
"8" SARS-CoV-2–specific CD8⁺ T cells
"A" Spike IgA
G+B+4+8+A+
G+B+4+8-A+
G+B-4+8-A+
G+B+4-8-A+
G+B+4+8+A-
G+B+4-8+A+
G-B+4+8-A+
2 Pos

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¿Influye la vía de administración?

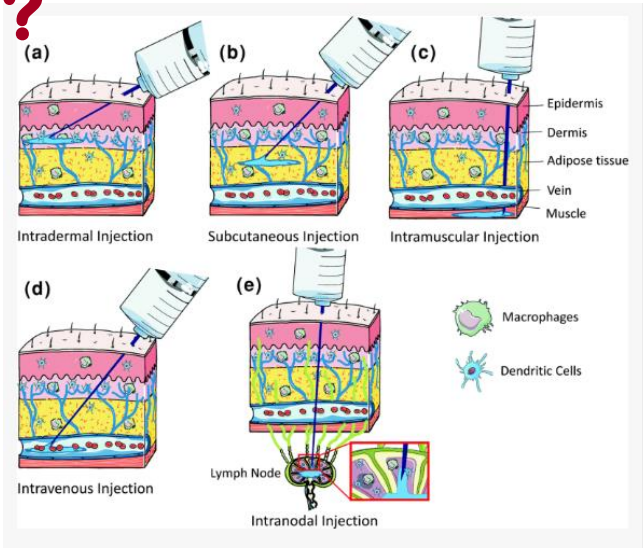

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Table 1 Major delivery routes of mRNA vaccines

Delivery route	Access to APCs and lymphoid organs	Maximum injection volume per site		Advantages[3]	Challenges[4]
		Human[1]	Mouse[2]		
Intradermal	• Dermal DC • Lymph node DC • Lymph node	~0.1 mL	~0.05 mL	• Direct access to APCs	• Local side effect, • Limited injection volume
Subcutaneous	• Dermal DC • Lymph node DC • Lymph node	~1 mL (Adult), ~0.5 mL (Child)	~0.8 mL total at 2–3 sites[a]	• Larger injection volume (than ID) • Less local side effect	• Degradation of mRNA
Intramuscular	• DC • Lymph node	1–3 mL (Adult), 0.5–2 mL (Child)	0.05 mL per site, maximum of 2–4 sites	• Less local side effect • Dense blood networks	• Limited injection volume
Intranodal	• Lymph node DC • Lymph node	~0.2 mL	0.01-0.02 mL	• High delivery efficiency	• Complicated procedures
Intravenous	• Splenic DC • Lymph node DC • Spleen • Lymph node	~20 mL (bolus)	~0.1 mL (bolus)[a] ~0.5 mL (slow)[a]	• Large injection volume • Direct access to APCs and lymphoid organs	• Degradation of mRNA • Risk of systemic side effect

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¿Qué ventajas tiene con respecto a otras vacunas?

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-**Son seguras** ya no que son infecciosas ni se integran en el DNA nuclear (riesgo cero de mutagénesis por inserción).
-Se **degradan normalmente** por procesos celulares normales.
-Producen proteínas con **alta estabilidad conformacional y con estructura nativa.**
-Su **inmunogenicidad y reactogenicidad inherente puede ser modulada** mediante inserción de nucleósidos y purificación.
-Varias modificaciones hacen a este **RNAm más estable y altamente "traducible".**
-RNAm es un vector genético minúsculo, esto implica la **falta de reconocimiento como vector viral** y por lo tanto puede administrarse tantas veces como se quiera sin riesgo de neutralización.
-El RNAm se puede producir de forma **muy rápida, barata y con una producción altamente escalable**.

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Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 70
March 29, 2021

Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021

TABLE 2. Person-days, SARS-CoV-2 infections, and vaccine effectiveness among health care personnel, first responders, and other essential and frontline workers, by messenger RNA immunization status — eight U.S. locations, December 14, 2020–March 13, 2021

		SARS-CoV-2 infections		Unadjusted vaccine effectiveness*	Adjusted vaccine effectiveness*,†
COVID-19 immunization status	Person-days	No.	Incidence rate per 1,000 person-days	% (95% CI)	% (95% CI)
Unvaccinated	116,657	161	1.38	N/A	N/A
Partially immunized	41,856	8	0.19	82 (62–91)	80 (59–90)
≥14 days after receiving first dose only§	15,868	5	0.32		
≥14 days after first dose through receipt of second dose	25,988	3	0.12		
Fully immunized					
≥14 days after second dose	78,902	3	0.04	91 (73–97)	90 (68–97)

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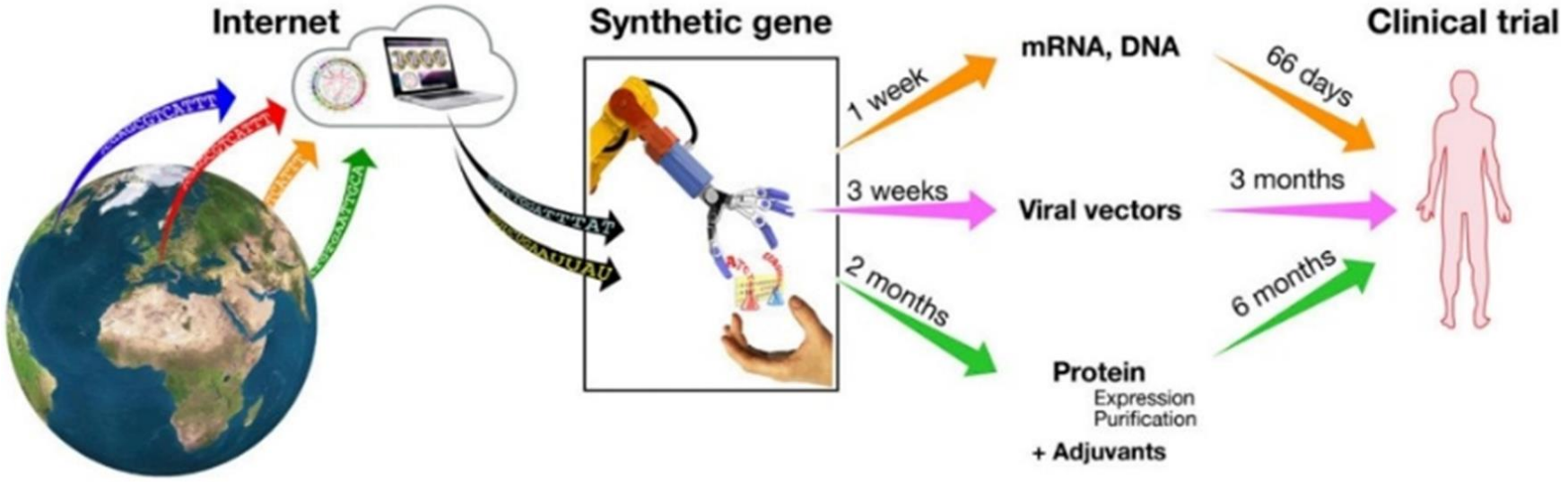

Fig. 2. COVID-19 vaccines in development and their timeline to clinical testing in humans.

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¿Qué nos queda por saber?

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Cuestiones pendientes de respuesta:

¿Bloquean la transmisión?

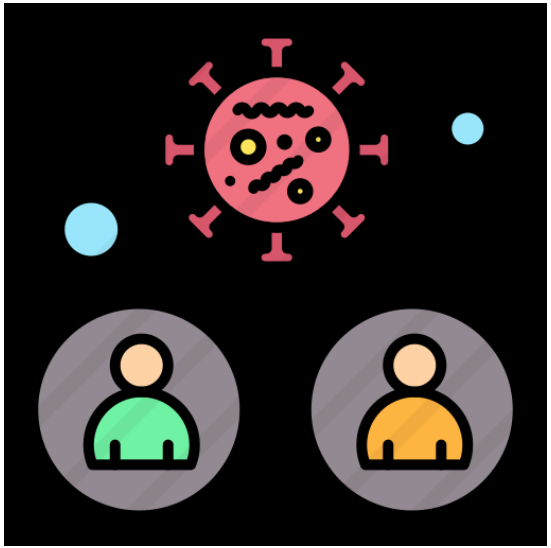
- No sabemos si estas **vacunas evitan la transmisión del virus** en seres humanos.

- Los estudios realizados en **macacos** han mostrado que aunque **no se bloquea por completo la presencia del virus en la tráquea o en la nariz,** hay una gran diferencia entre los animales vacunados y los no vacunados.

- Los no vacunados tienen virus activos en las vías respiratorias superiores durante bastantes días, mientras que en los **animales vacunados el virus desaparece rápidamente.**

- Si esto se cumple también en humanos, estas vacunas **podrían impedir la transmisión, no completamente pero sí en gran medida**.

- No obstante, incluso si estas vacunas no impiden la transmisión**, hay bastantes candidatos en camino** que podrían ser más eficaces, evitar la transmisión y requerir una sola dosis.



El Confidencial

EL CASO DE ISRAEL

Primeros datos del efecto de las vacunas en la pandemia: hay luz al final del túnel

La vacuna de Pfizer puede cortar la transmisión del coronavirus, según datos preliminares recabados en Israel, incluso con solo una dosis 14 días después

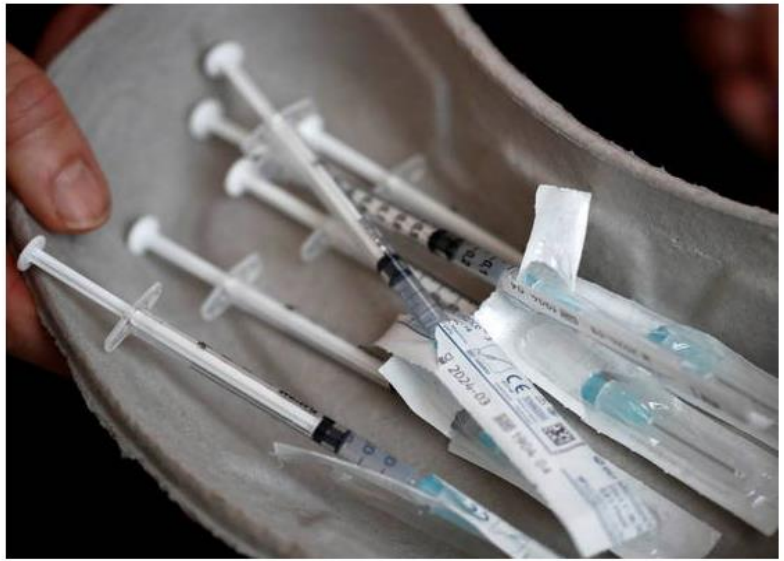
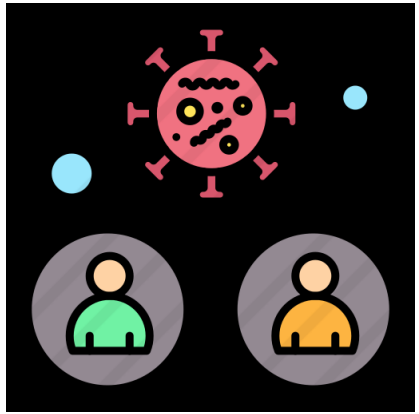


Foto: Reuters.



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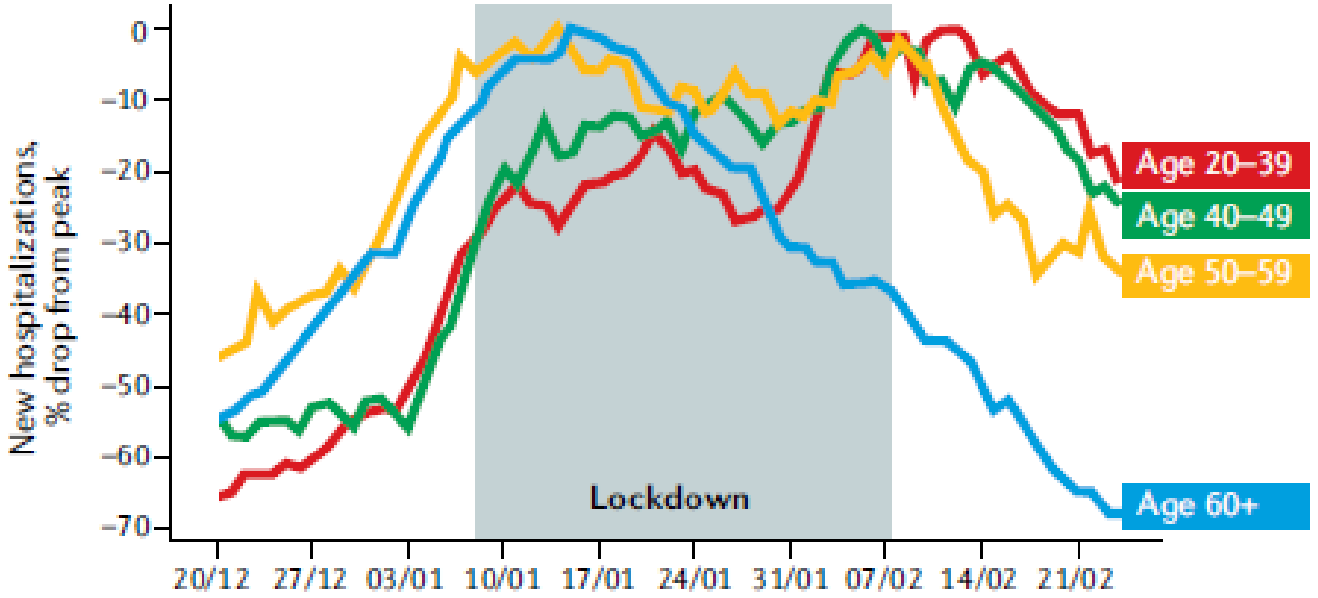
nature
International journal of science

Check for updates

Signals of hope: gauging the impact of a rapid national vaccination campaign

Smadar Shilo[1,2,3,4], Haggai Rossman[1,2,4] and Eran Segal[1,2]



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CDC
Centers for Disease Control and Prevention

Science Brief: Background Rationale and Evidence for Public Health Recommendations for Fully Vaccinated People

Updated Mar. 8, 2021 Languages Print

- A growing body of evidence suggests that fully vaccinated people are less likely to have asymptomatic infection and potentially less likely to transmit SARS-CoV-2 to others. However, further investigation is ongoing.

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nature medicine

BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-021-01316-7

Check for updates

Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine

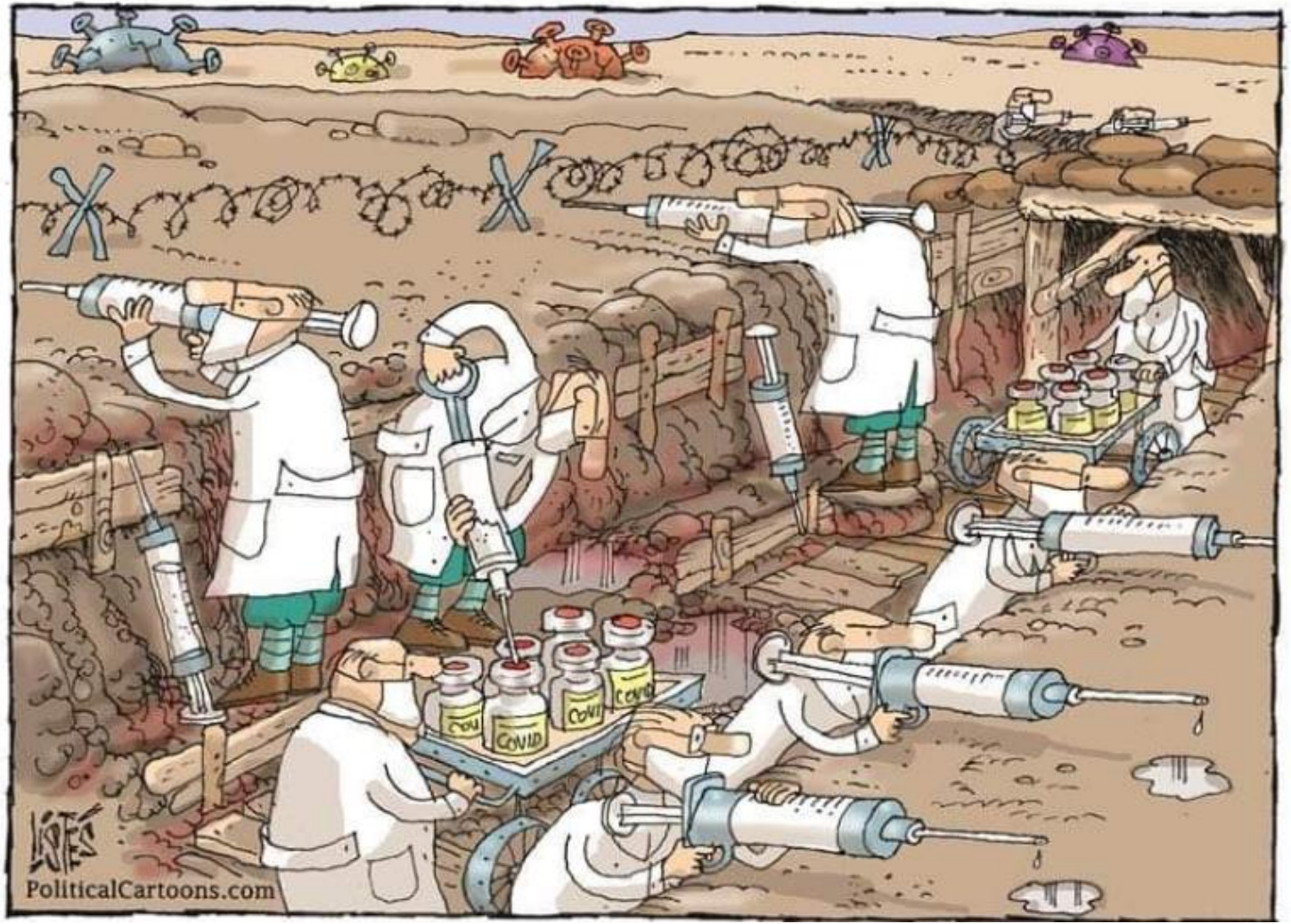
Matan Levine-Tiefenbrun[1,6], Idan Yelin[1,6] ✉, Rachel Katz[2], Esma Herzel[2], Ziv Golan[3], Licita Schreiber[3], Tamar Wolf[3], Varda Nadler[3], Amir Ben-Tov[2,4], Jacob Kuint[2,4], Sivan Gazit[2], Tal Patalon[2], Gabriel Chodick[2,4] and Roy Kishony[1,5] ✉

Beyond their substantial protection of individual vaccinees, coronavirus disease 2019 (COVID-19) vaccines might reduce viral load in breakthrough infection and thereby further suppress onward transmission. In this analysis of a real-world dataset of positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test results after inoculation with the BNT162b2 messenger RNA vaccine, we found that the viral load was substantially reduced for infections occurring 12–37 d after the first dose of vaccine. These reduced viral loads hint at a potentially lower infectiousness, further contributing to vaccine effect on virus spread.

The recently authorized BNT162b2 Coronavirus Disease 2019 (COVID-19) messenger RNA (mRNA) vaccine is approximately 95% efficient in preventing polymerase chain reaction (PCR)-confirmed symptomatic disease from 7 d after the second

Table 1 | Study population

Age group (years)	Total no. of patients	Male	Female
16–19	241	143	98
20–29	425	216	209
30–39	485	277	208
40–49	1,077	513	564
50–59	1,344	708	636
60–69	821	445	376
70–79	422	216	206
80–89	123	53	70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“El más estúpido de los virus, es más listo que el más listo de los virólogos”

Dr. George Klein (1.925-2016)

GRUPO nmun