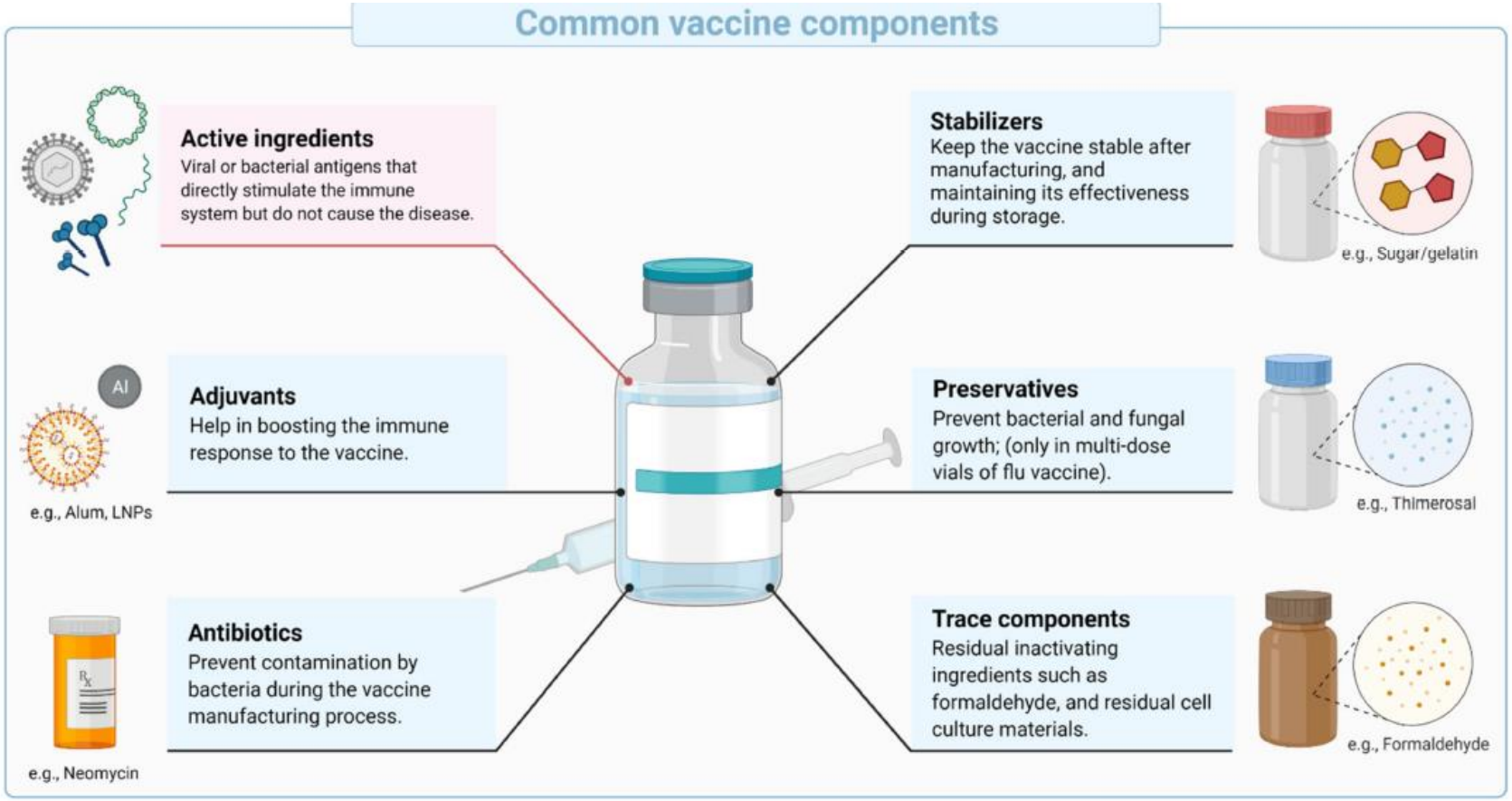
Plataformas de fabricación de vacunas

Las clásicas y las nuevas

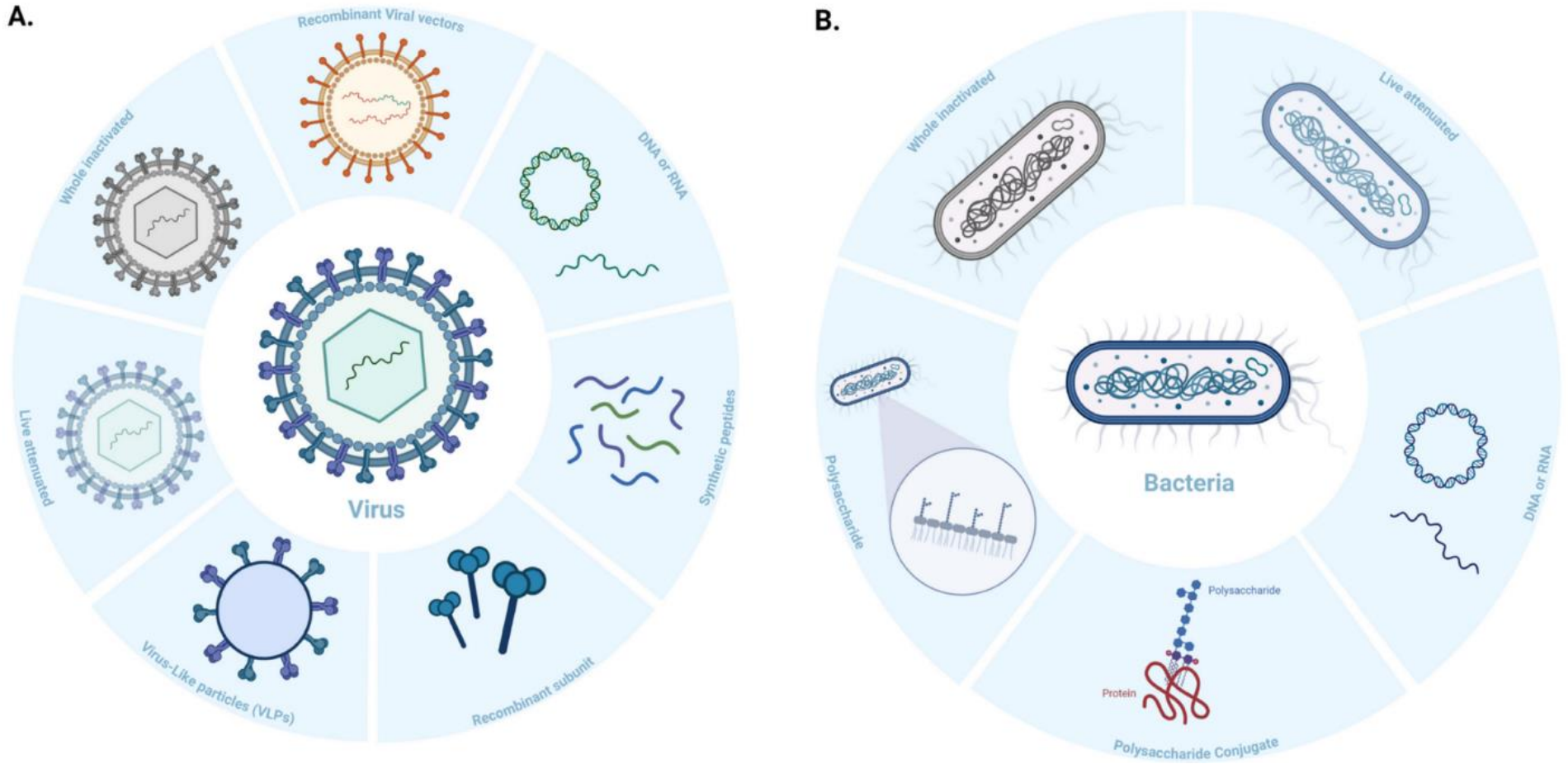
Jesús Ruiz Contreras

Componentes de las vacunas



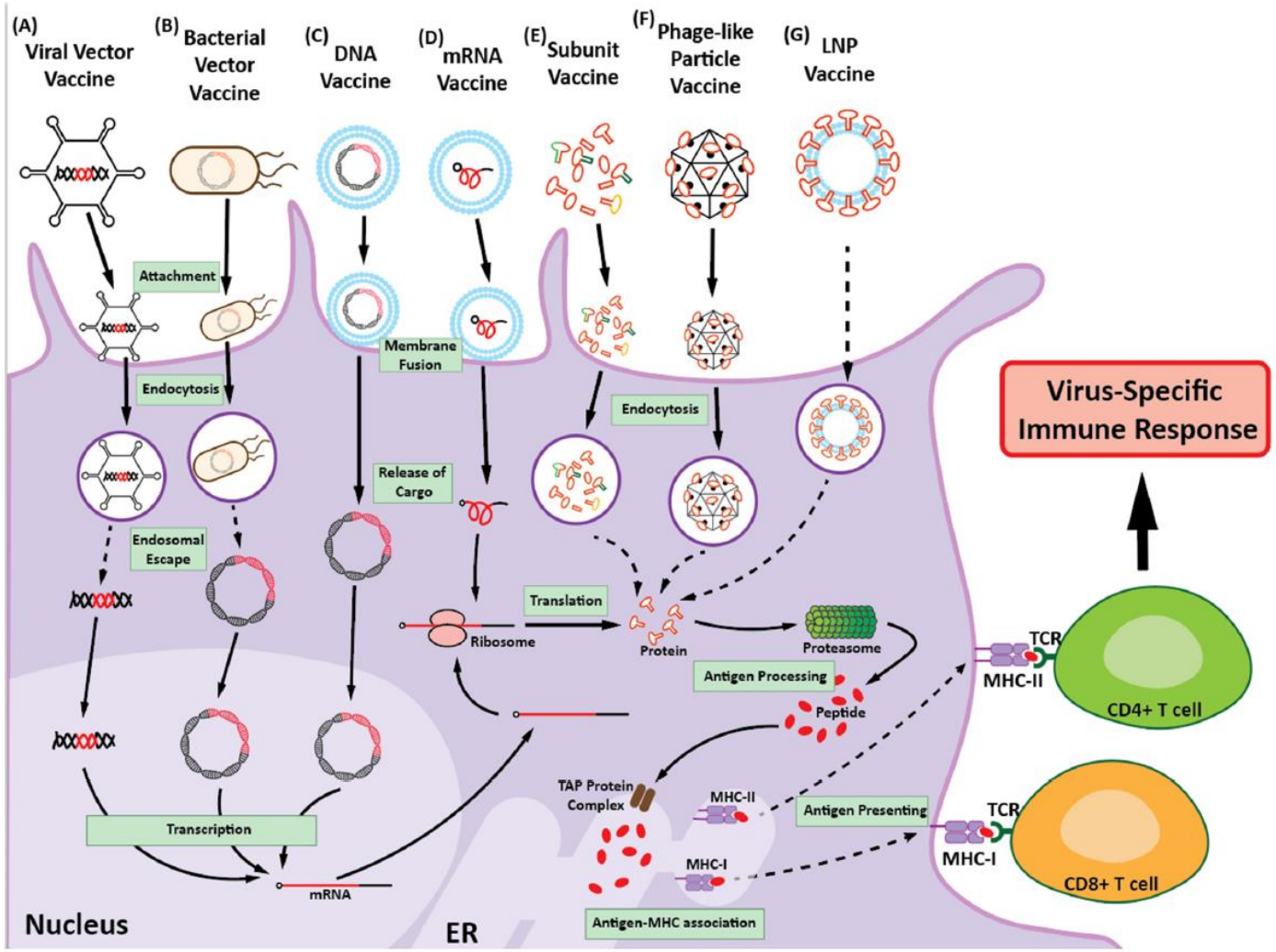
Gatthas M et al. Vaccines 2021; 9: 1490

Plataformas vacunales

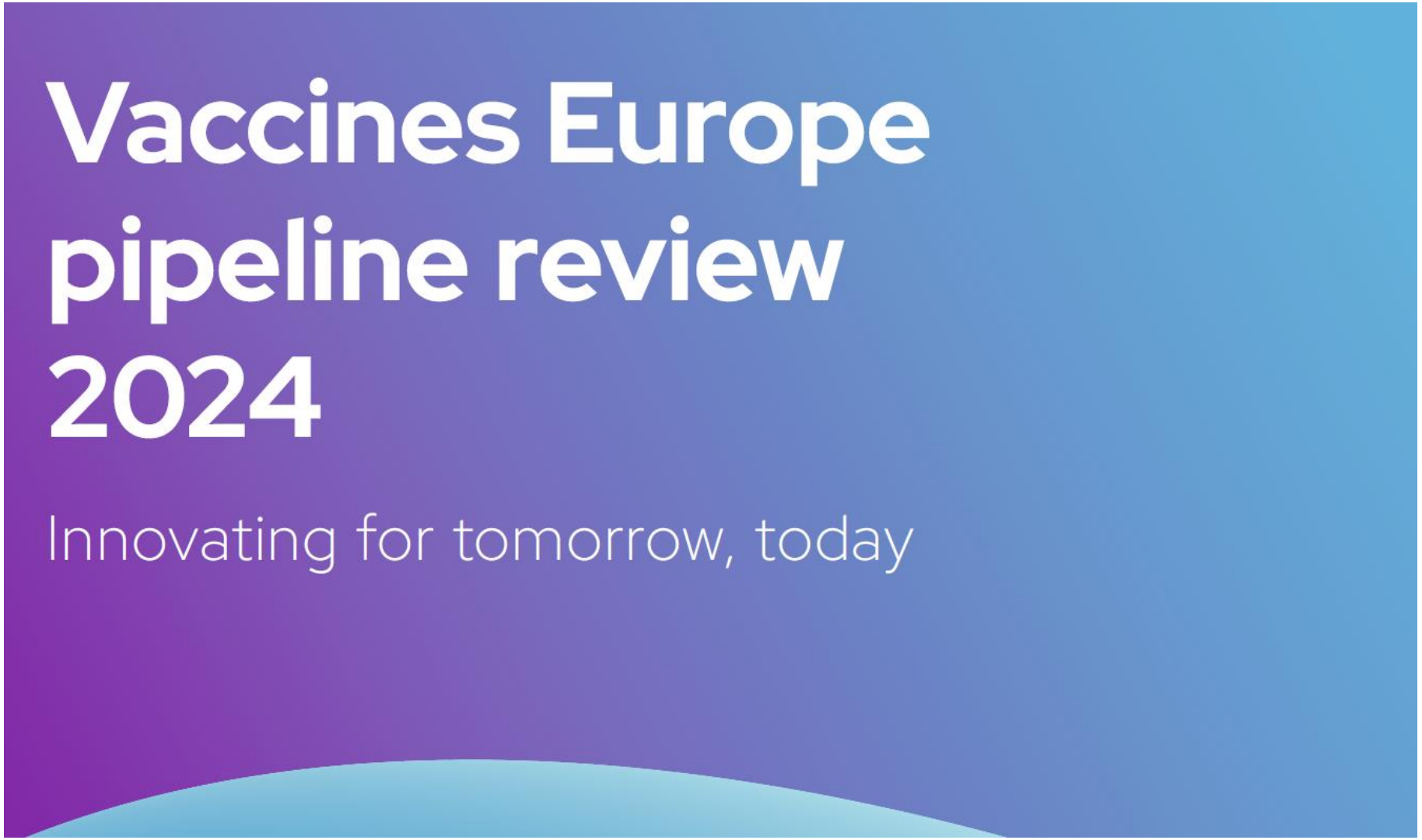


Gatthas M, et al. Vaccines 2021, 9,1490. https://doi.org/10.3390/vaccines9211490

Nuevas plataformas vacunales



Hsiung KC et al. *Vaccines* **2024**, *12*, 1345. https://doi.org/10.3390/vaccines12121345



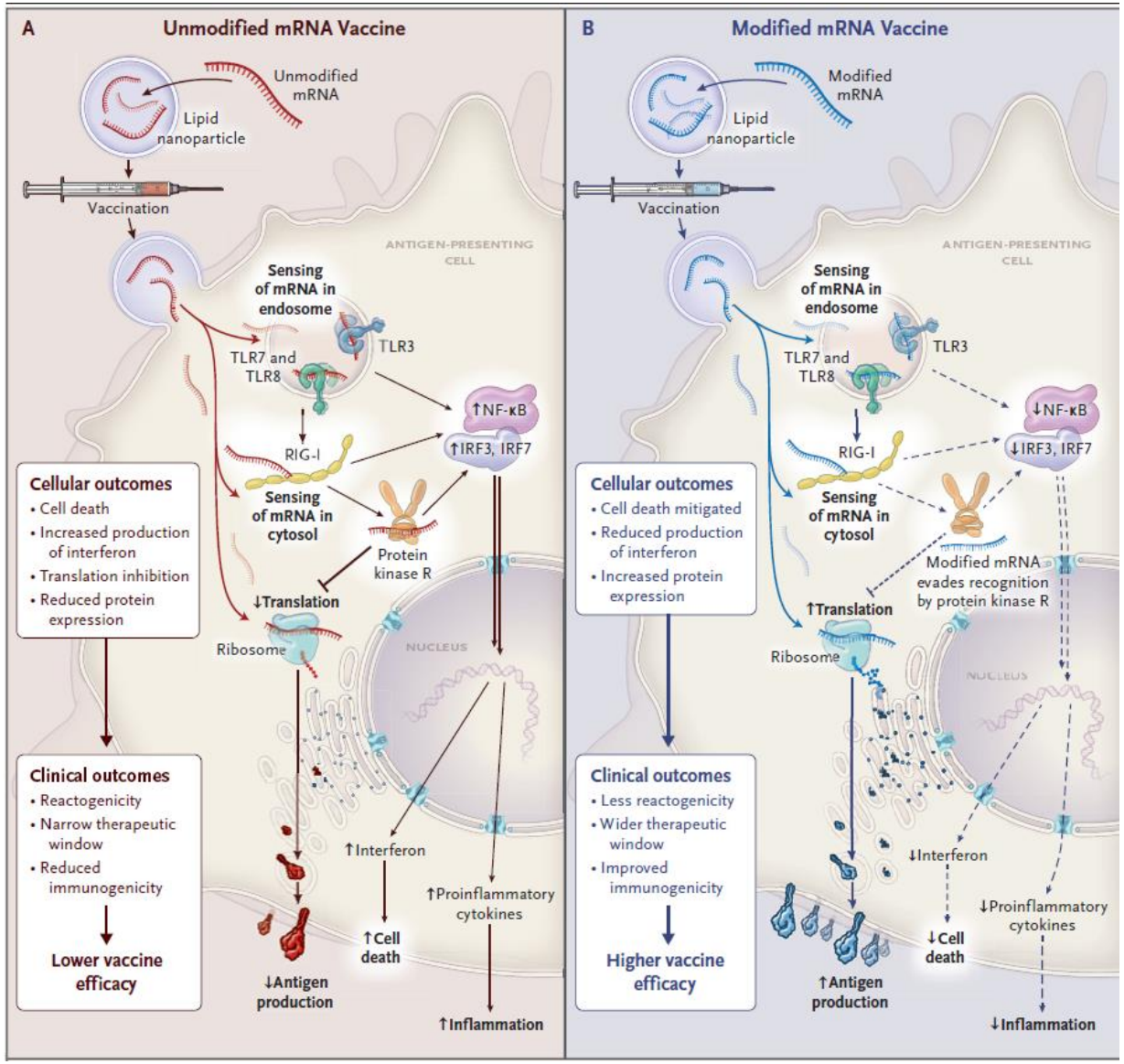
https://ufukavrupa.org.tr/sites/default/files/users/user20790/VaccinesEurope-PipelineReview2024.pdf

Vacunas ARNm

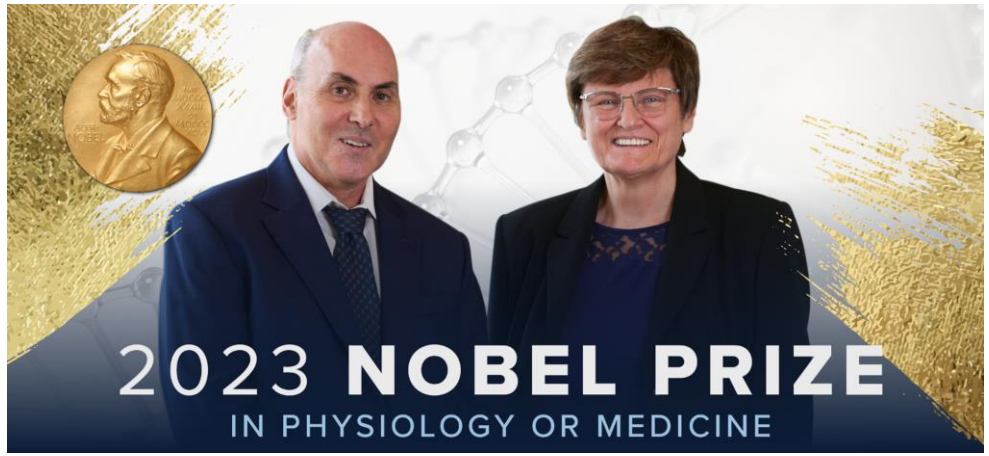
Entrega del antígeno (nanopartículas)

Vacunas e IA

Vacunas de RNA



Stuart LM. N Engl J Med 2021; 385: 1436-1438



Immunity, Vol. 23, 165–175, August, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.immuni.2005.06.008

Suppression of RNA Recognition by Toll-like Receptors: The Impact of Nucleoside Modification and the Evolutionary Origin of RNA

Katalin Karikó,[1,*] Michael Buckstein,[2] Houping Ni,[2] and Drew Weissman[2]
[1]Department of Neurosurgery
[2]Department of Medicine
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania 19104

thetic antiviral compound R-848 (Jurk et al., 2002), but a natural ligand has not been identified.

It has been known for decades that selected DNA and RNA molecules have the unique property to activate the immune system. It was discovered only recently that secretion of interferon in response to DNA is mediated by unmethylated CpG motifs acting upon

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

KATALIN KARIKÓ, DREW WEISSMAN, PHILIP FELGNER, UĞUR ŞAHIN, ÖZLEM TÜRECI, DERRICK ROSSI Y SARAH GILBER Y PIETER CULLIS

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

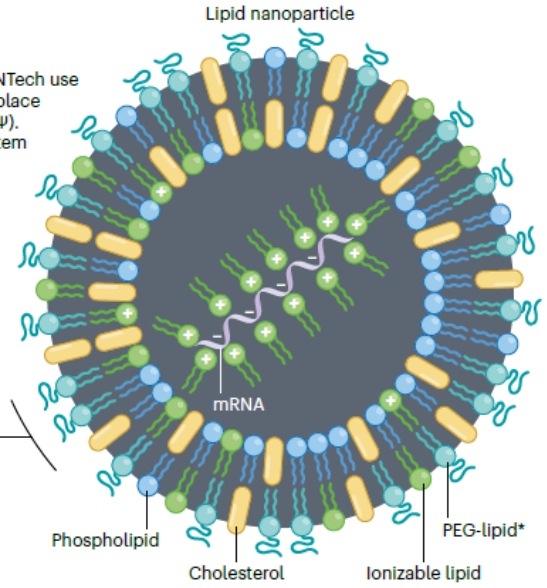
...CGAGΨΨCGΨGΨΨΨAA...

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 types of lipid molecule. One of these is 'ionizable': in the vaccine, many of these molecules have a positive charge and cling to negatively charged mRNA, but they lose that charge in the more alkaline conditions of the bloodstream, reducing toxicity in the body.



*Lipid attached to polyethylene glycol

| Nature | Vol 597 | 16 September 2021

Pieter Cullis

INSIDE AN MRNA COVID VACCINE

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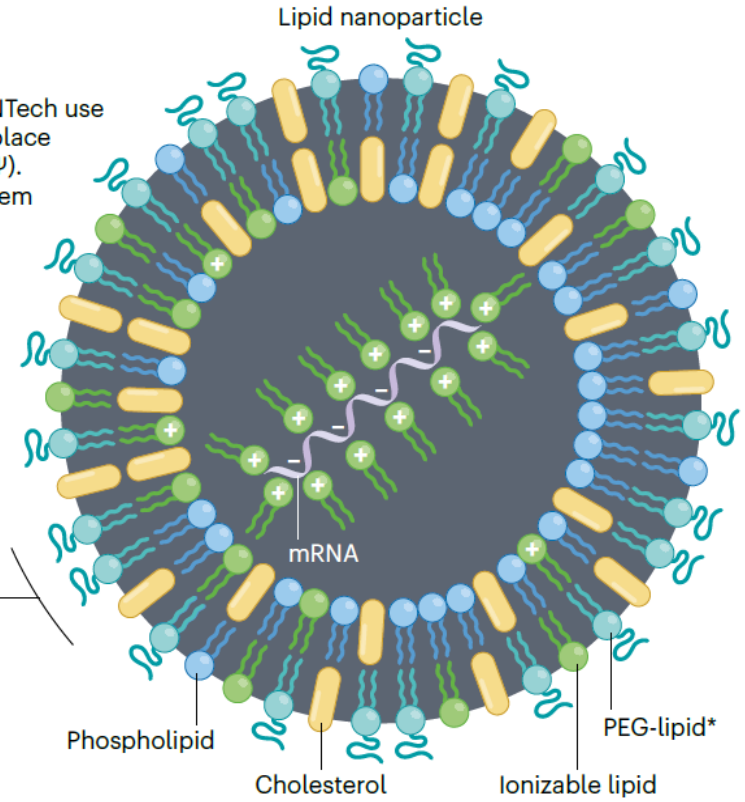
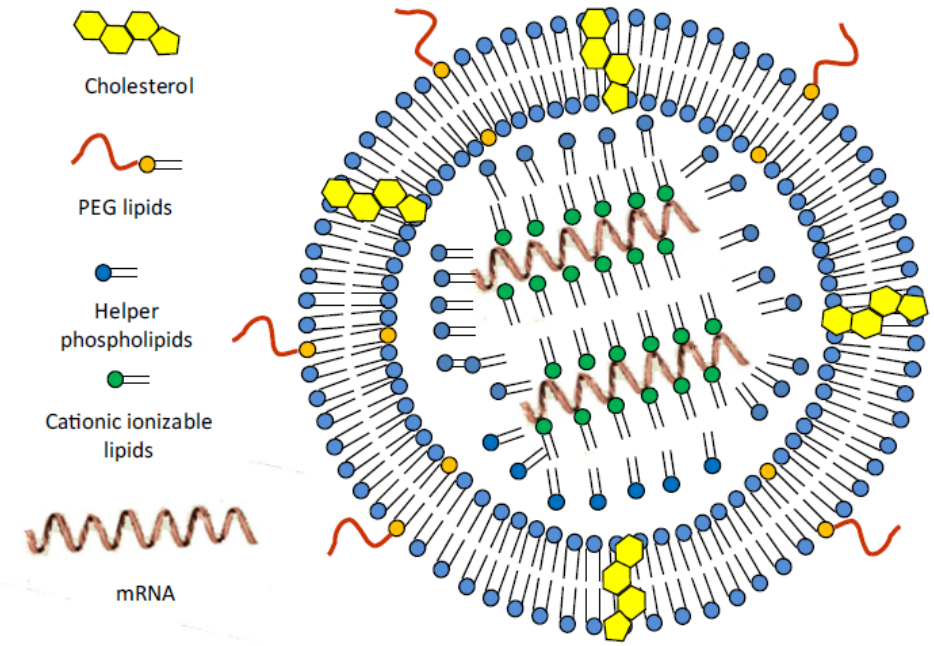
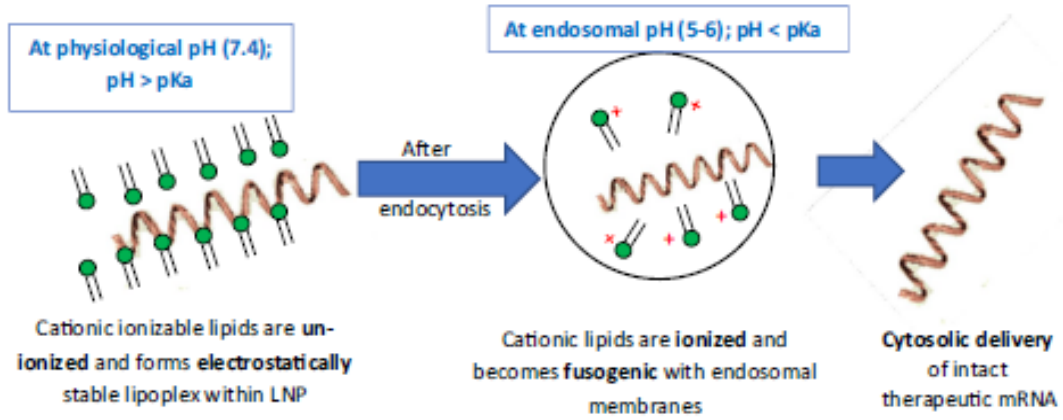


*Lipid attached to polyethylene glycol

| Nature | Vol 597 | 16 September 2021

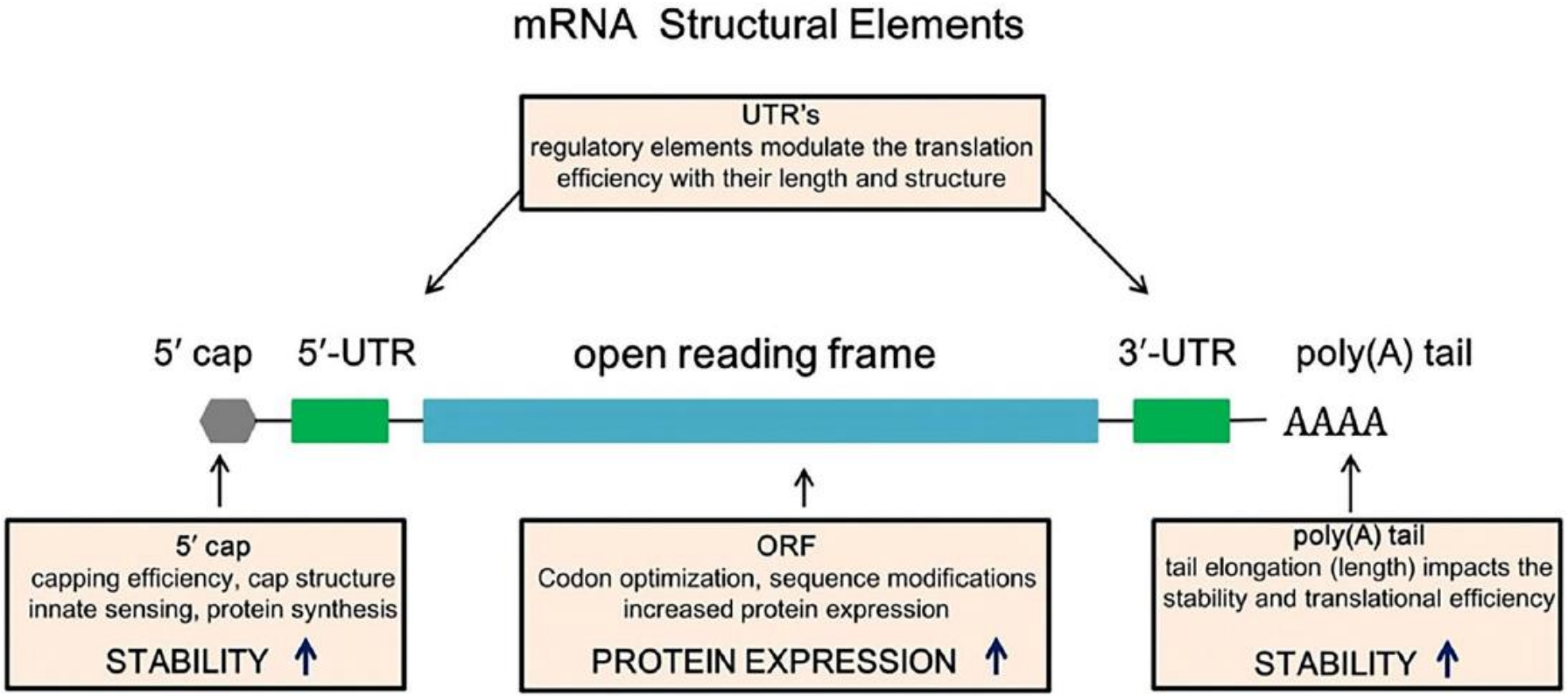
Nanopartículas lipídicas





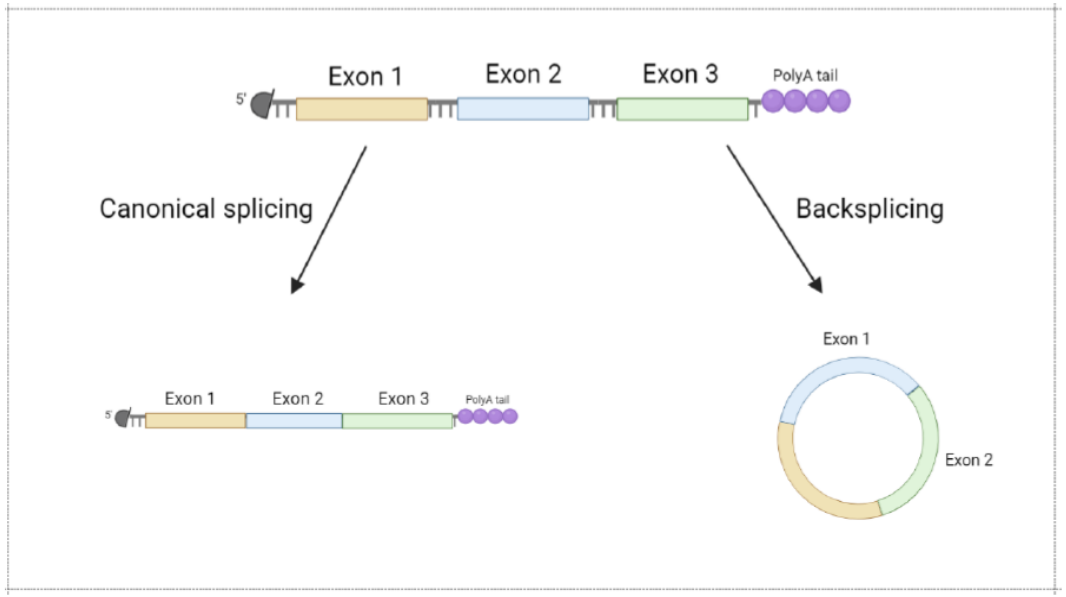
Deviatkin A, et al. Vaccines 2022; 10: 709

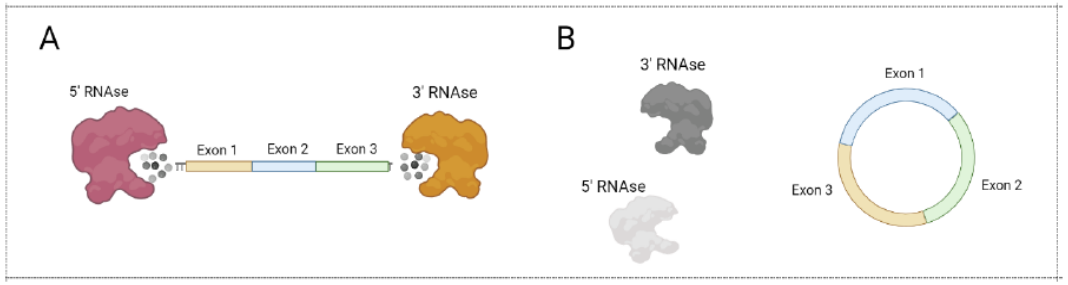
Vacunas de ARNm



Wang J, et al. Nano-Micro Lett 2025; 17: 155

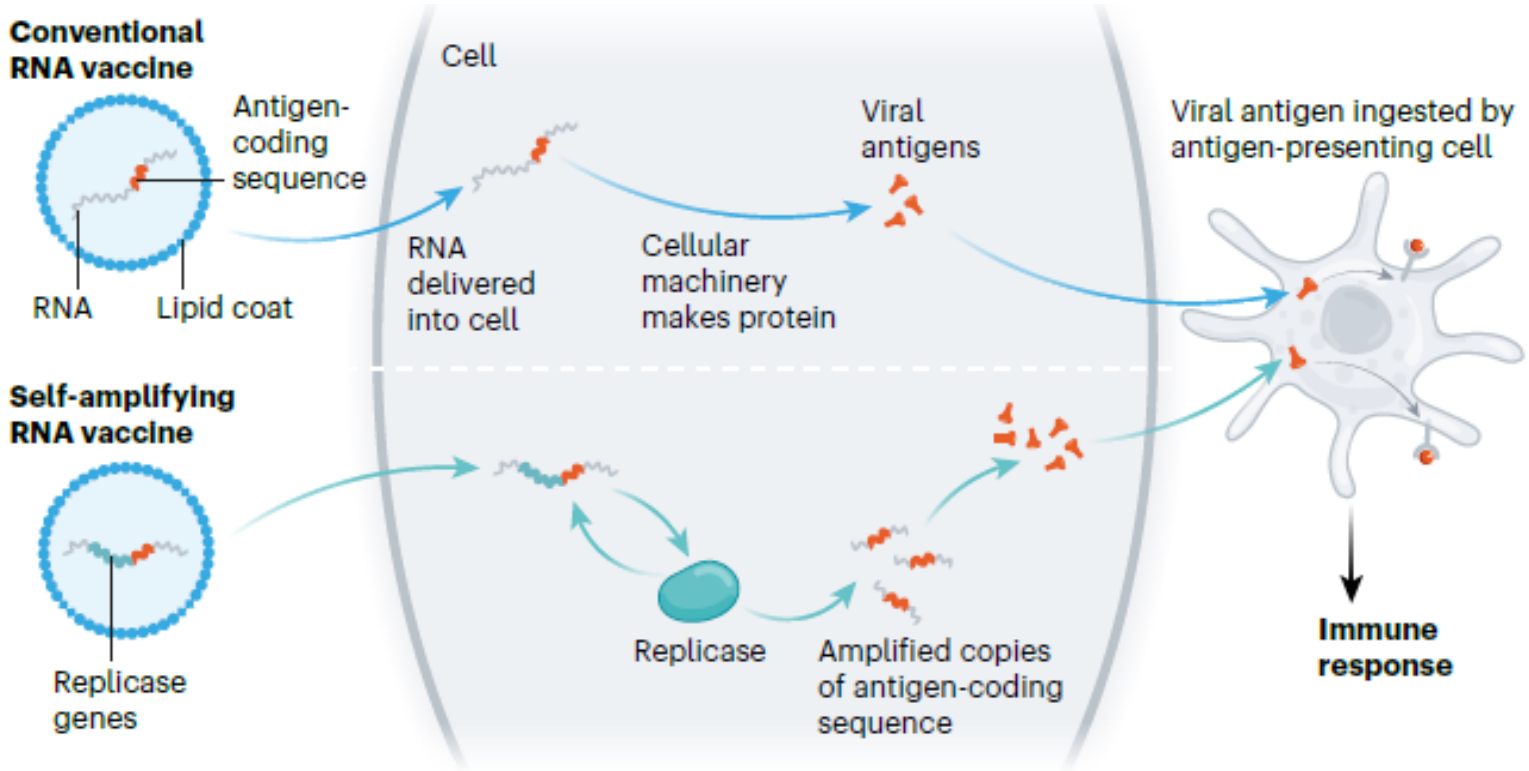
Vacunas de ARNm





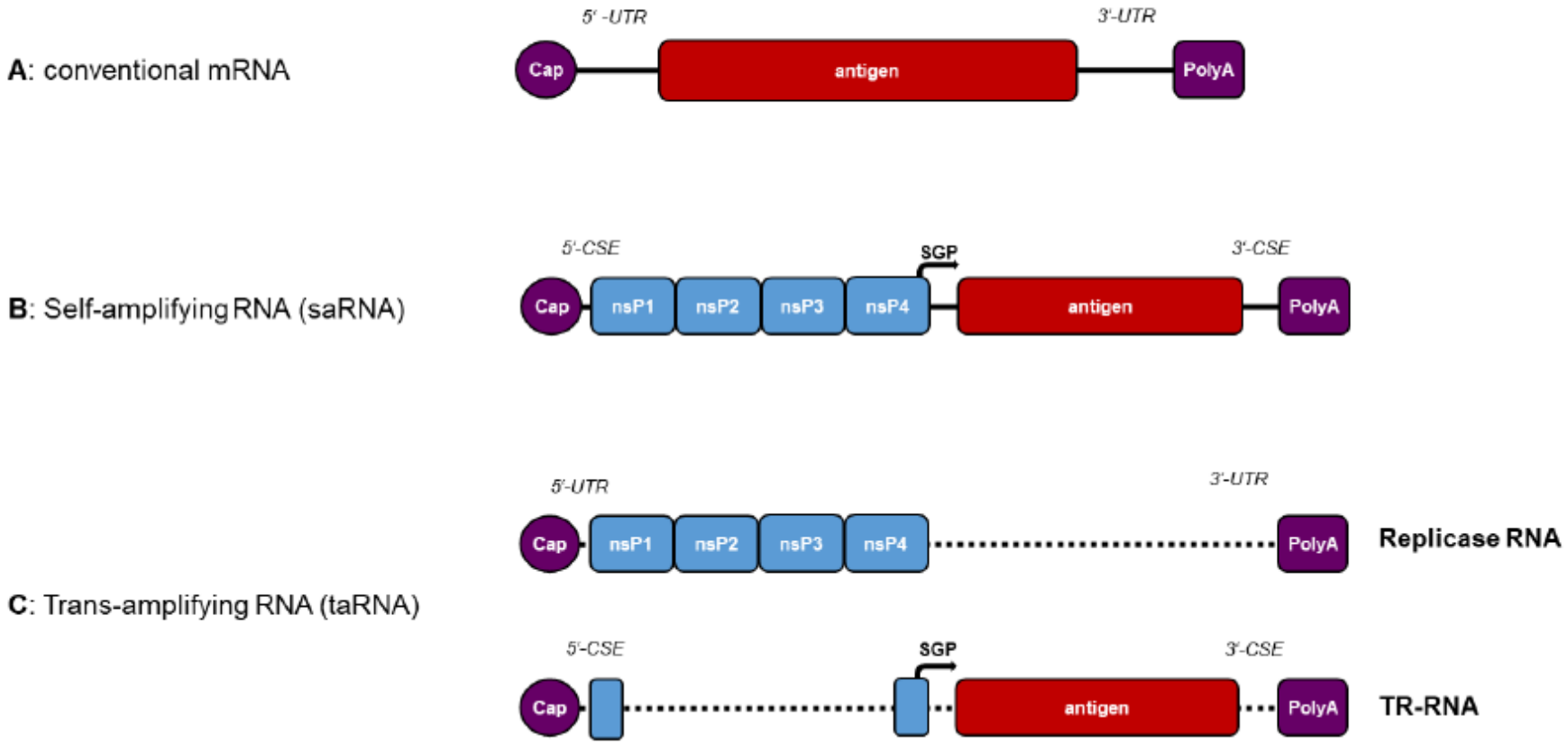
Deviatkin A, et al. Vaccines 2022; 10: 709

Vacunas ARNm autorreplicantes



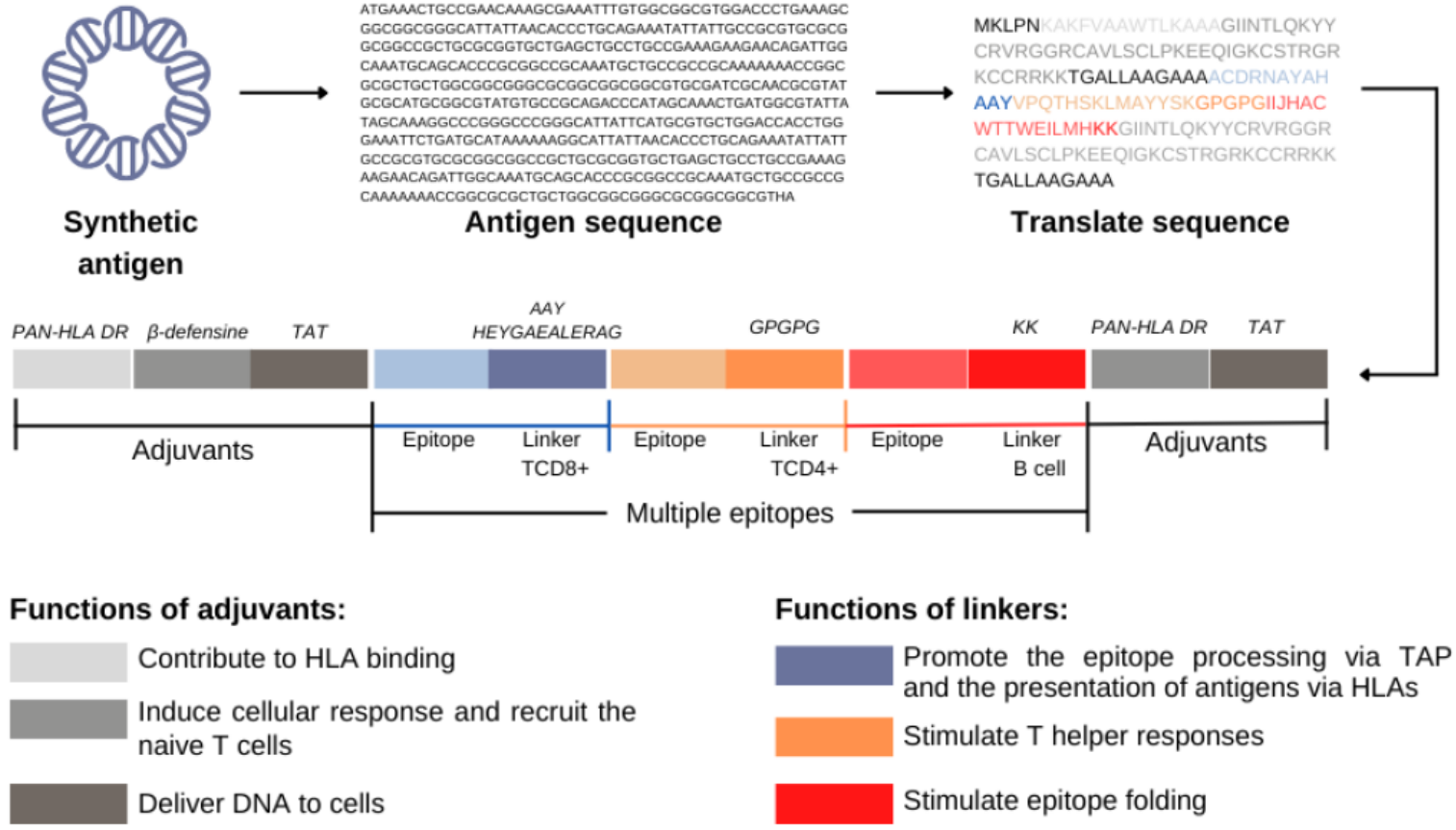
Dolgin BE. Nature 2021; 589: 189-191

Vacunas de ARNm



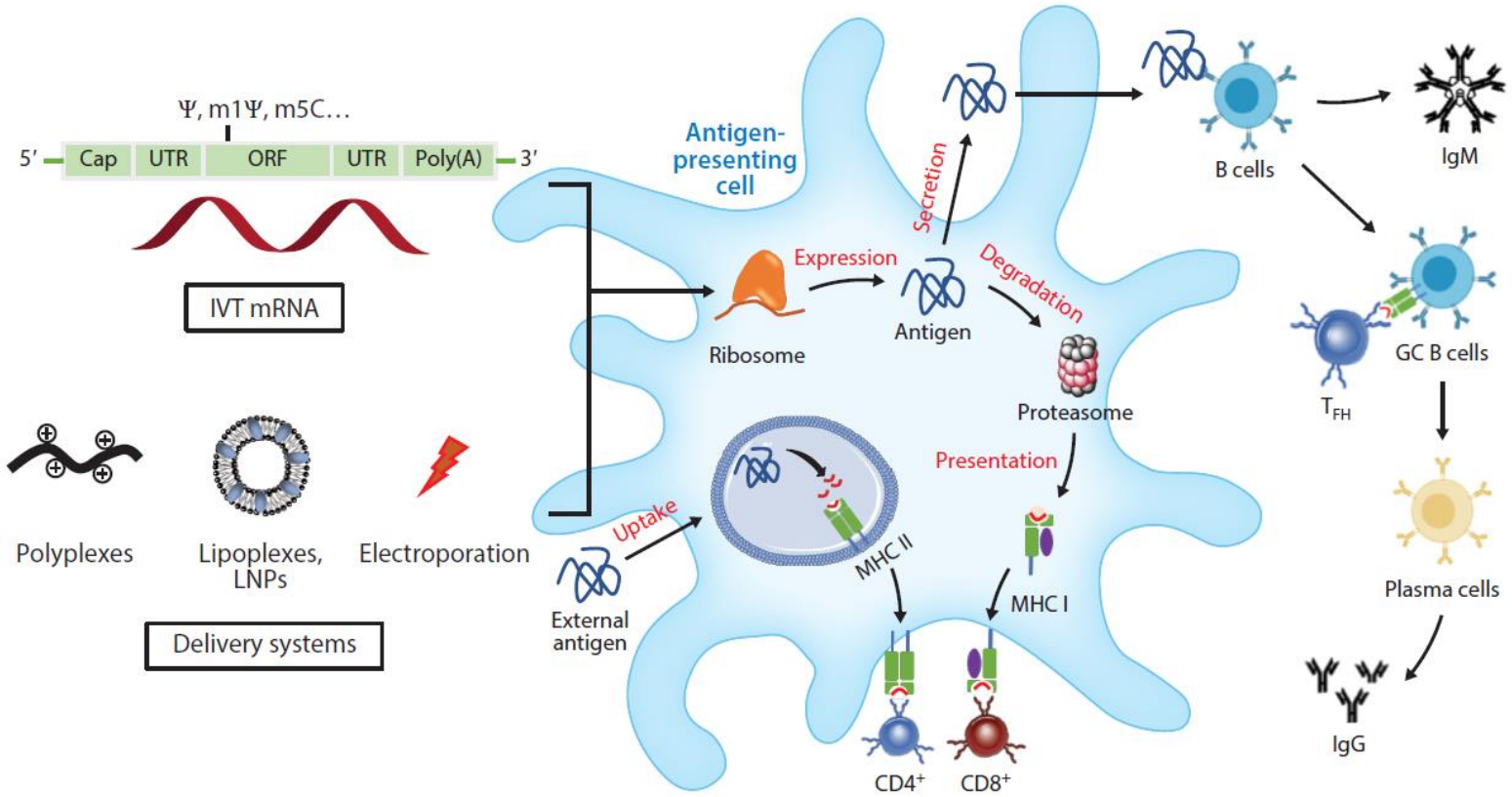
Schmidt T, et al. Pathogens 2023; 12, 138

Vacunas ARNm con adyuvantes y otros epitopos



Silva Melo AR et al. Genes 2022; 13: 2287

Respuesta inmune a las vacunas ARNm



Chen J, et al. Ann Rev Biomed Enginn 2022; 24: 85-109

Vacunas RNAm

Entrega del antígeno (nanopartículas)

Vacunas e IA

Sistemas de liberación: Tipos de nanopartículas

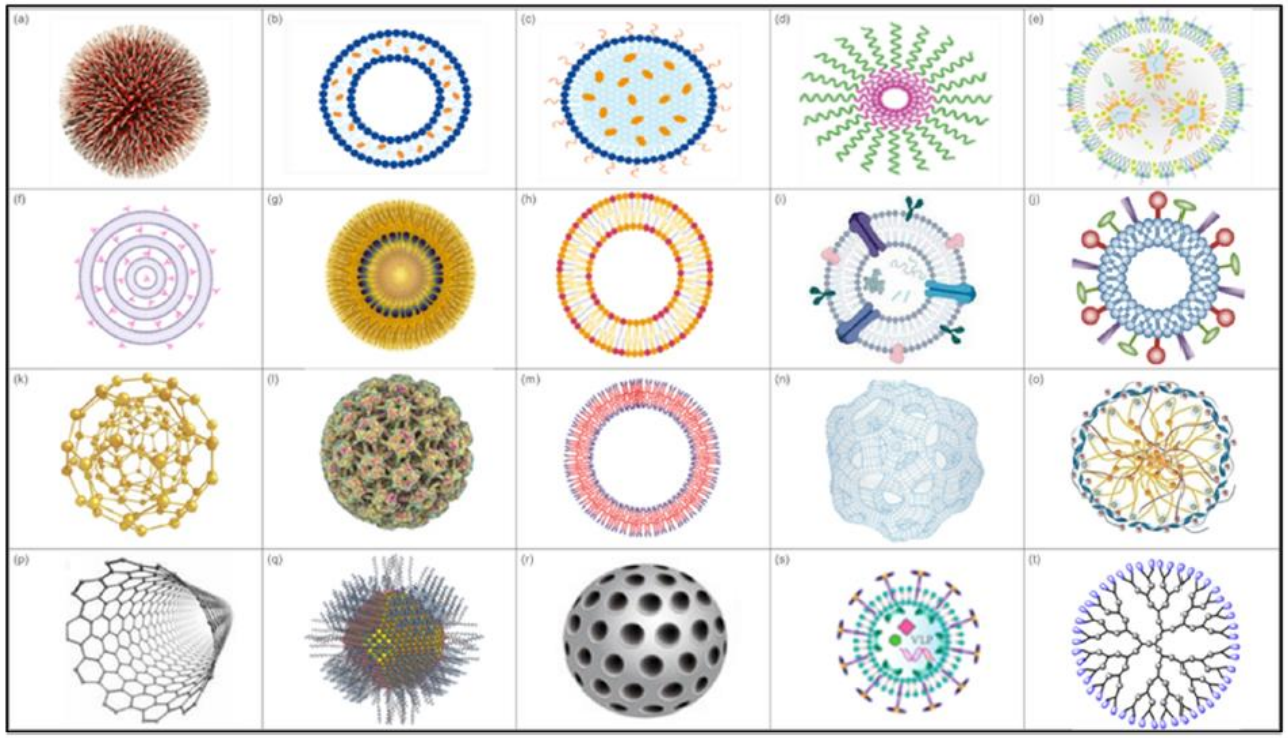


Figure 3. Types of NPs. (**a**) Polymeric nanoparticle, (**b**) liposome, (**c**) solid lipid NP, (**d**) polymeric micelle, (**e**) lipid NP, (**f**) multilamellar lipid vesicles, (**g**) lipid nanoemulsion, (**h**) lipoprotein, (**i**) exosomes, (**j**) virosomes, (**k**) gold NP, (**l**) protein-based NP, (**m**) polymersomes, (**n**) polymeric nanosphere, (**o**) chitosan NP, (**p**) carbon nanotubes, (**q**) quantum dots, (**r**) mesorphous silica NP, (**s**) virus-like particle (VLP), and (**t**) dendrimer.

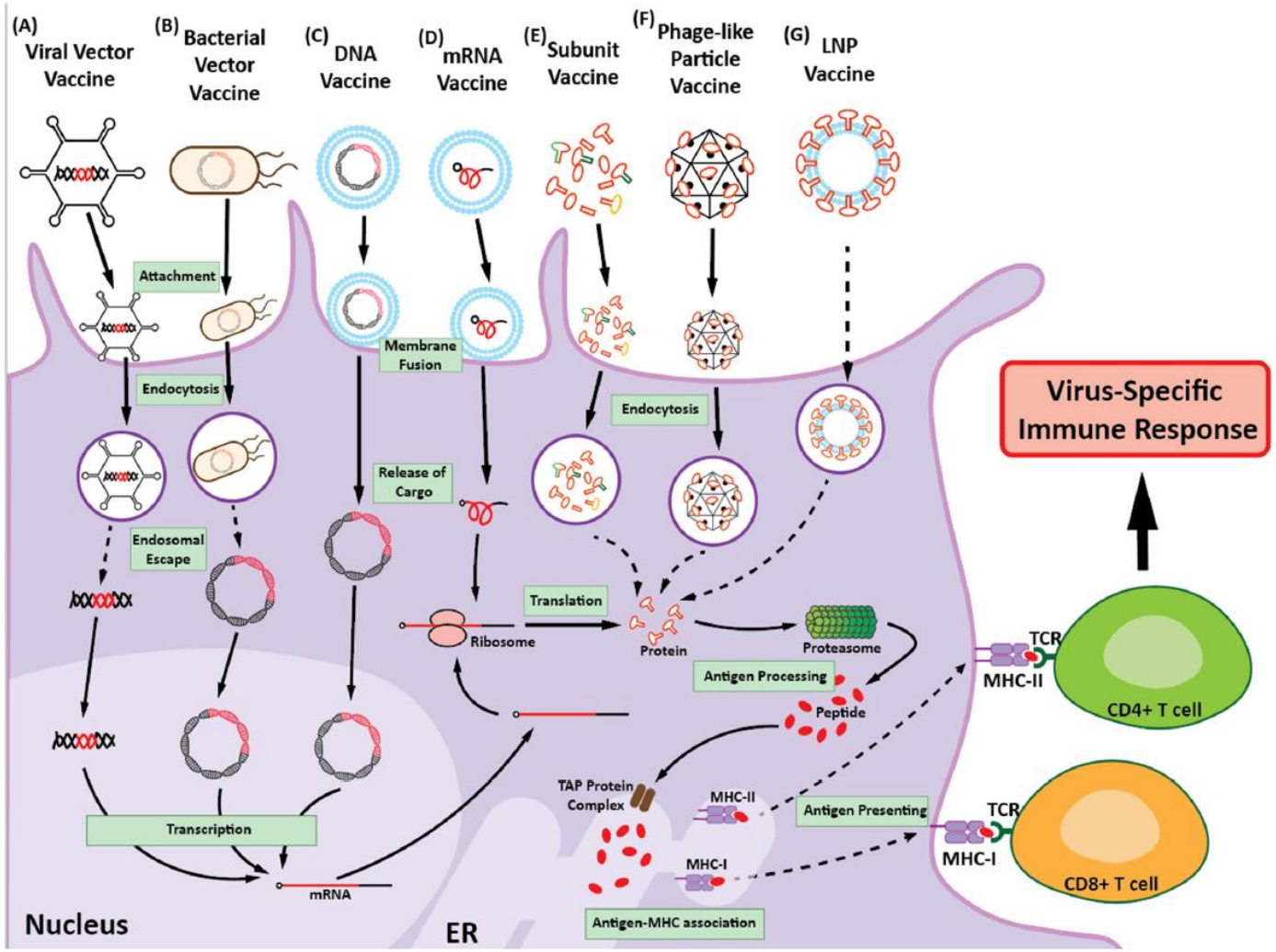
Saleh M, et al. Vaccines. Enero 2025

Ventajas y desventajas de las vacunas ARNm

Ventajas	Desventajas
Generan respuestas TH1 y TH2 Respuestas robustas y duraderas No necesitan adyuvante (auto-adyuvantes RNA y NPL) Pueden incorporar secuencias de adyuvantes Rapidez de adaptación a la epidemiología (pandemias) Pueden contener mútiples antígenos (del mismo o diferente patógeno) No pasan al núcleo y se aclaran en poco tiempo después de la expresión del antígeno No hay inmunidad pre-existentes como con las vacunas de vectores	Mayor frecuencia de efectos secundarios Necesidad de cadena del frío Incidencia más elevada de anafilaxia (posiblemente el PEG)

Chen J, et al. Ann Rev Biomed Enginn 2022; 24: 85-109

Plataformas vacunales



Hsiung KC et al. *Vaccines* **2024**, *12*, 1345. https://doi.org/10.3390/vaccines12121345

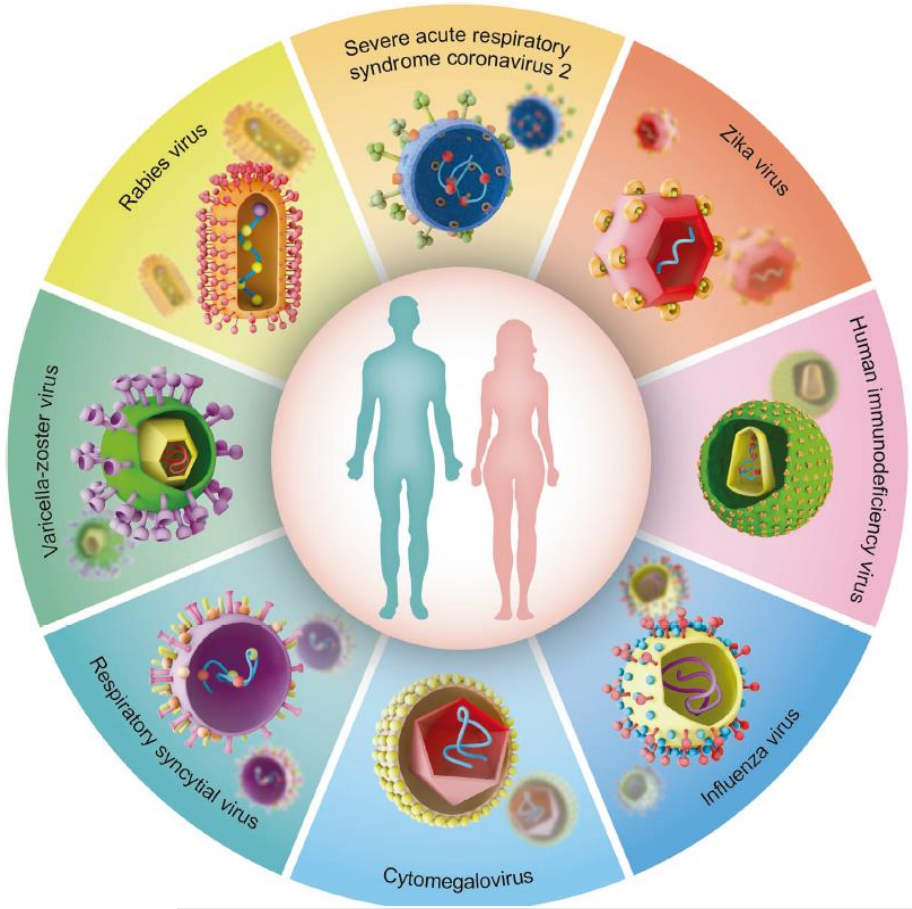
Have mRNA vaccines sentenced DNA vaccines to death?

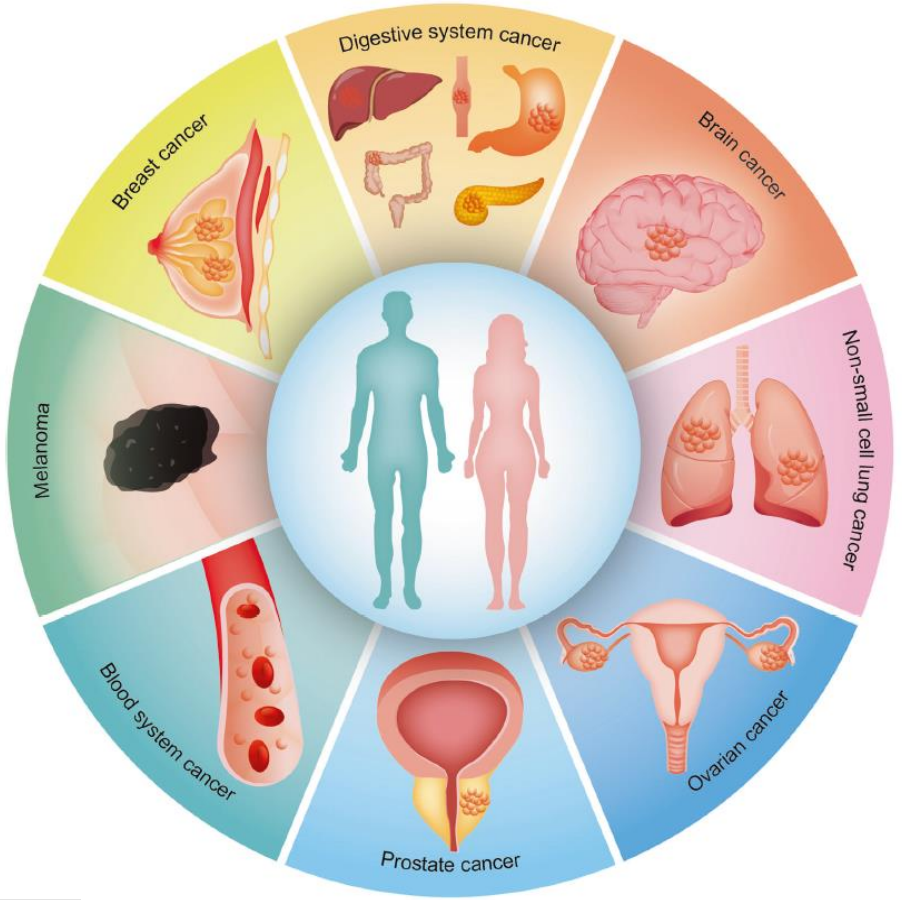
Alberto Cagigi & Bruno Douradinha

	Vacunas ADN	Vacunas ARN
Respuesta inmune	Menos potente	Más potente
Duración de la respuesta inmune	Larga	Corta
Seguridad	Segura (muy remota capacidad e integración)	Segura
Capacidad de multivalencia	Alta	Alta
Estabilidad	Alta	Inestable
Cadena del frío	No	Sí
Administración	Plásmido	Nanopartículas

Cagigi A, et al. Expert Rev Vacc 22:1, 1154-67.

Vacunas de ARNm en enfermedades infecciosas y cáncer





Zhang T, et al. *Signal Transduction and Targeted Therapy* (2023)8:365

npj | vaccines

Article

Published in partnership with the Sealy Institute for Vaccine Sciences

https://doi.org/10.1038/s41541-024-00890-4

Multivalent mRNA-DTP vaccines are immunogenic and provide protection from *Bordetella pertussis* challenge in mice

Wolf MA et al. NPJ Vaccines

Vacunas ARNm frente a tosferina

Table 1 | Description of antigens selected for mRNA vaccines

mRNA antigen acronym	Description of mRNA construct	Role in pathogenesis
PTX-S1	Consists of the PTX S1 subunit of *Bp* Tohama I strain, truncated at residue 180 to remove the hydrophobic C-terminal tail and increase expression[90]. The native signal peptide was removed, and the construct was detoxified by mutating residue 9 from an arginine to lysine and residue 129 from a glutamic acid to a glycine[48].	PT is a secreted exotoxin involved in the colonization and respiratory tract and induces leuko- and lymphocytosis
FHA3	Encodes filamentous hemagglutinin representing residues 1655-2111 of full-length Tohama I hemagglutinin. This fragment was previously published as MAL85[91].	Cell surface or secreted protein that mediates adherence to epithelial and immune cells
FIMD/2/3	Encodes a mammalian mimetic containing segments of both fimbrae-2 and fimbrae-3. Consists of FimD tip protein with its native signal peptide removed (residues 38-376), a GGGS linker, the Fim2 protein with its native signal peptide removed (residues 30-210) a second GGGSGGGS linker, the Fim3 protein with its native signal peptide removed (residues 26-204), a third GGGS linker, and then amino acids 26-44 of Fim3. Five mutations were introduced to avoid putative N-linked glycosylation sites.	Role in attachment to respiratory epithelial cells
PRN	Consists of the passenger domain of pertactin (residues 35-636) of the Tohama I strain. One mutation was introduced to avoid a putative N-linked glycosylation site.	Adhesin involved in attachment to epithelial cells, specifically the trachea epithelial cells
DT	Consists of the full-length diphtheria toxin from *Corynebacterium diphtheriae*, with two mutations (K51E/E148K) to eliminate its enzymatic activity. Three N-glycosylation modifications were introduced to avoid N-glycosylation events.	Essential toxin for *Corynebacterium diphtheriae* which kills cells by inhibiting protein synthesis
TT	Consists of fragment C receptor domain from tetanus toxin from *Clostridium tetani*. Five N-glycosylation modifications were introduced to avoid N-glycosylation events.	Essential toxin for *Clostridium tetani* and inhibits nerve terminals leading to muscle rigidity and spasm
RTX	Consists of residues 1006 to 1600 of the C-terminal repeats in toxin domain (RTX) of adenylate cyclase toxin (ACT) from *Bp* Tohama I strain. Four mutations were introduced to avoid putative N-linked glycosylation sites.	ACT is a secreted toxin that binds to phagocytic cells and generates cAMP upon activation, which leads to cellular intoxication
TCFA	Consists of the passenger domain of the *Bp* Tohama I strain tracheal colonization factor (residues 40-362).	TCFA is an autotransporter and in a murine model, deletion of this protein decreased colonization
SPHB1	Consists of the passenger domain of subtilisin-like protease B1 from the Tohama I strain (residues 50-752).	Cleaves FhaB to generate FHA
BRKA	Consists of the passenger domain of BrkA (residues 42-732) of the Tohama I strain. One mutation was introduced to avoid a putative N-linked glycosylation site.	Inhibits complement activation

Wolf MA et al. NPJ Vaccines

https://doi.org/10.1038/s41541-024-00890-4

nature communications

Article

https://doi.org/10.1038/s41467-022-32149-8

Development of a pentavalent broadly protective nucleoside-modified mRNA vaccine against influenza B viruses

Received: 29 November 2021

Accepted: 20 July 2022

Published online: 09 August 2022

Norbert Pardi[1], Juan Manuel Carreño[2,3], George O'Dell[2], Jessica Tan[2,4], Csaba Bajusz[1,5], Hiromi Muramatsu[1], Willemijn Rijnink[2], Shirin Strohmeier[2], Madhumathi Loganathan[2,3], Dominika Bielak[2,3], Molly M. H. Sung[6], Ying K. Tam[6], Florian Krammer[2,7] & Meagan McMahon[2]

strains. Therefore, we utilized mRNA-encoded HAs from both lineages (B/Phuket/3073/2013 (Y) and B/Colorado/06/2017 (V)) and NA, NP, and M2 from the B/Colorado/06/2017 strain. Before the mRNA-LNP vaccines were made, protein production from mRNA

vaccines

MDPI

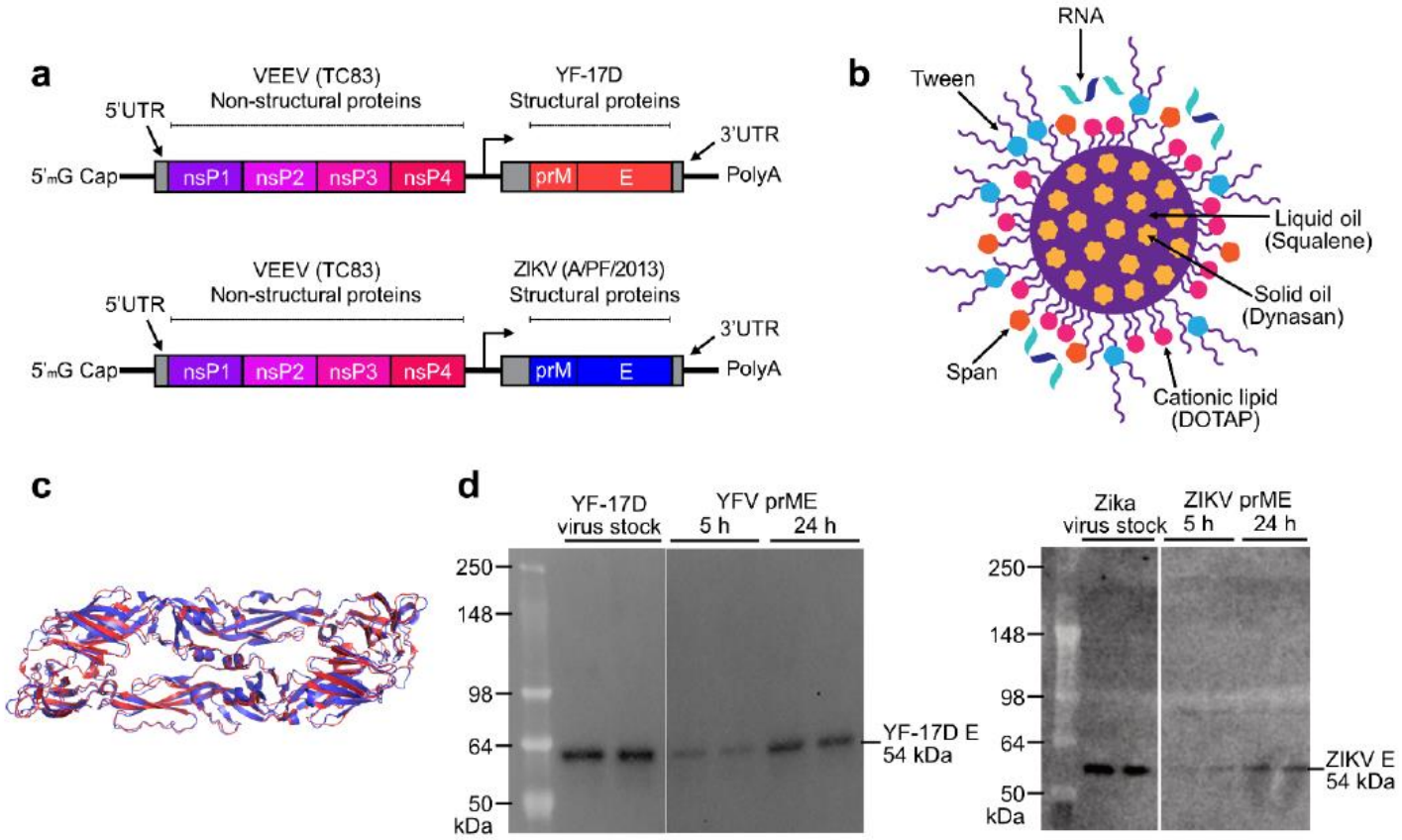
Review

The Integrated Consideration of Vaccine Platforms, Adjuvants, and Delivery Routes for Successful Vaccine Development

Michael Kozak [1,2,*] and Jiafen Hu [1,2,*]

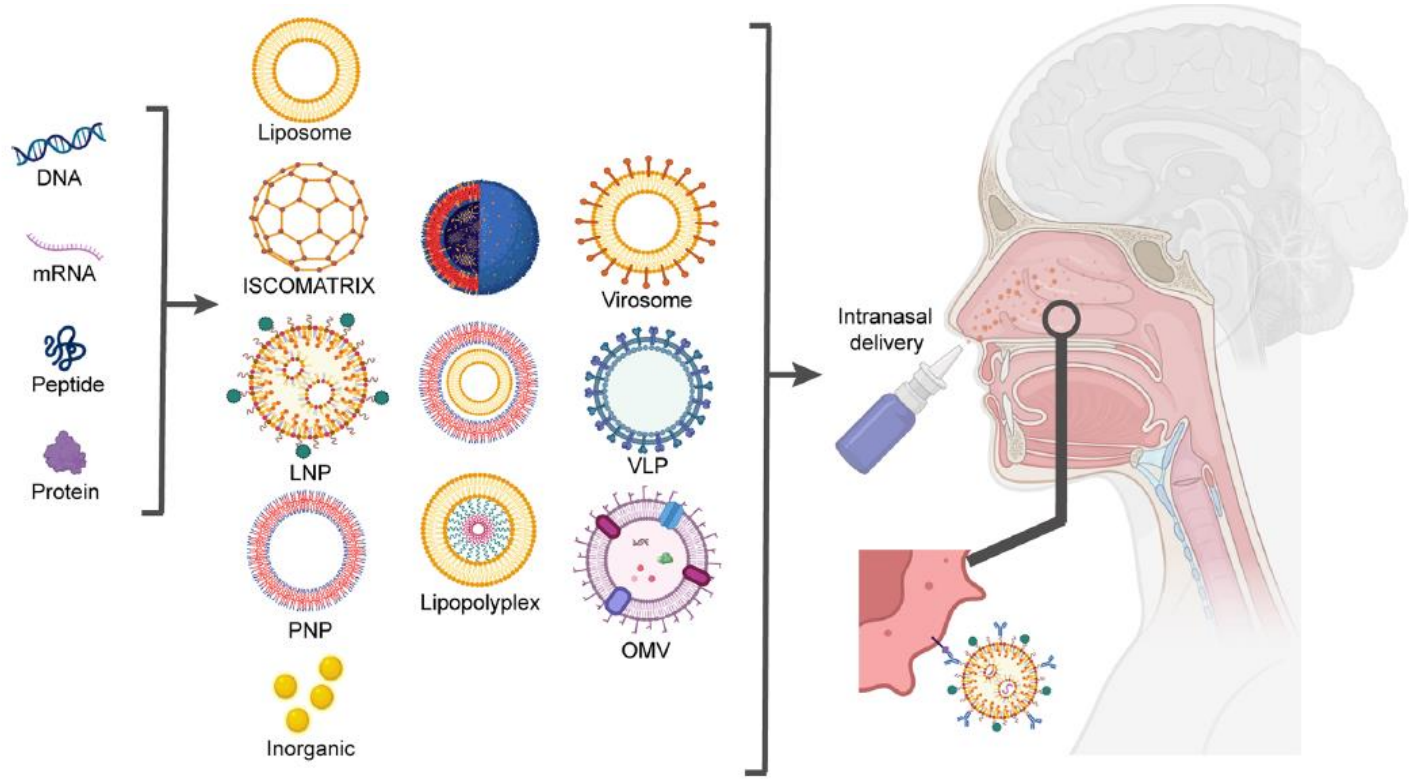
Kozak M, et al. Vaccines 2023; 11: 695

Vacuna autoamplificante de de fiebre amarilla y Zika expresado en NPL



Battisti P, et al. bioRxiv preprint doi: https://doi.org/10.1101/2025.01.31.635934

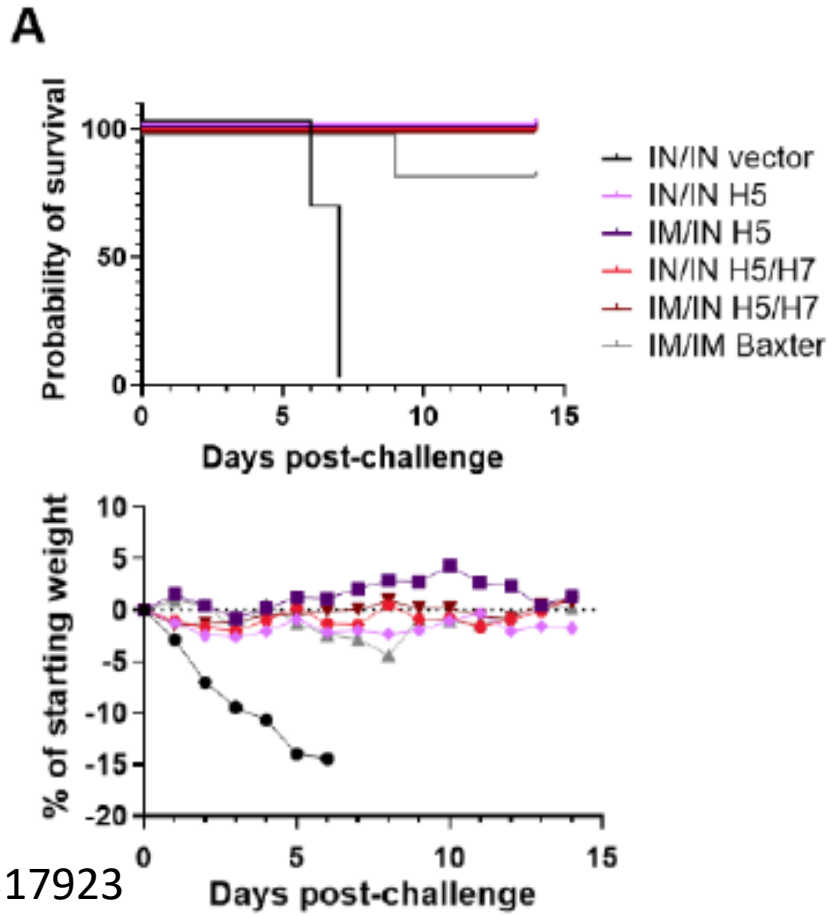
Vacunas intranasales basadas en nanoplataformas



Bai Z, et al. *ACS Nano* 2024, 18, 24650–24681

Vacuna intranasal monovalente y bivalente frente a la gripe H5N1 y H7N9 vehiculizadas en NPL

- IM o intranasal
  - IM: respuestas sistémicas pero no de mucosas
  - Intranasal: respuestas de mucosas y sistémicas
  - La vacuna intranasal evita la muerte y los síntomas en hurones



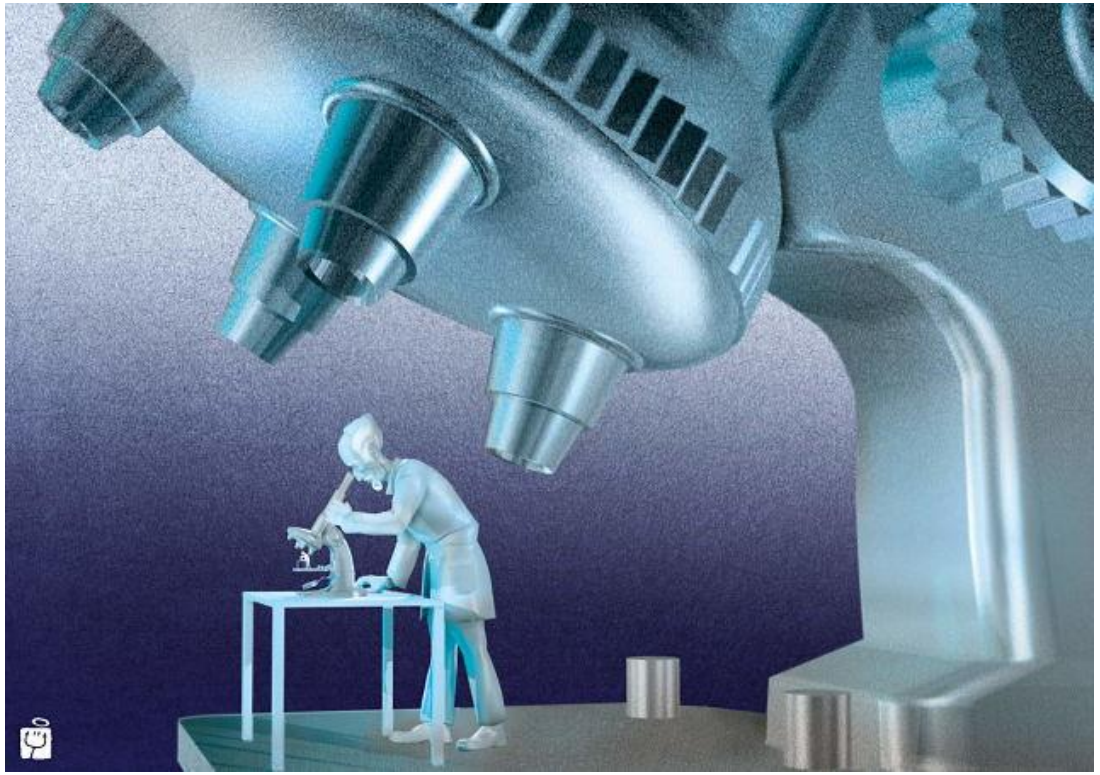
Ykema MR, et al. bioRxiv preprint doi: https://doi.org/10.1101/2025.01.07.6317923

Vacunas RNAm

Entrega del antígeno (nanopartículas)

Vacunas e IA

Inteligencia artificial y vacunas



- Selección de antígenos
- Identificación de epítopos
- Identificación de adyuvantes
- Optimización de estrategias
- Acelerar el diseño de vacunas

https://infomudi.blogspot.com/2018/10/humor-grafico-sobre-inteligencia.html
Olawade DB, et al. J Microbiol Meth 224 2024; 106998

Inteligencia artificial y vacunas (Deep Seek)

- **Diseño y desarrollo de vacunas**
  - Descubrimiento de antígenos: (grandes cantidades de datos biológicos para identificar proteínas o antígenos)
  - Modelado de proteínas: Herramientas como AlphaFold, desarrollada por DeepMind, utilizan IA para predecir la estructura tridimensional de las proteínas..
  - Optimización de formulaciones: La IA puede ayudar a determinar la combinación óptima de ingredientes en una vacuna para maximizar su eficacia y minimizar efectos secundarios.
- **Aceleración de ensayos clínicos** (selección de candidatos, diseño, monitorización en tiempo real)
- **Producción y control de calidad (**Optimización de procesos, detección de defectos, anomalías en la producción
- **Distribución y logística (**Predicción de la demanda, optimización de la cadena de frío)
- **Vigilancia post-comercialización**6. Personalización de vacunas: En el futuro, la IA podría permitir el desarrollo de vacunas personalizadas basadas en el perfil genético o inmunológico de cada individuo.

Scientific Background to the Nobel Prize in Chemistry 2024

COMPUTATIONAL PROTEIN DESIGN AND PROTEIN STRUCTURE PREDICTION

This year's Nobel Prize in Chemistry recognizes decisive breakthroughs in solving both of these problems – structure prediction from sequence and sequence prediction from structure – and the implications are truly profound. Most monomeric protein structures can now be predicted with high fidelity, and large databases of hundreds of millions of structures have thus been created, with huge impact on biochemical and biological research. Likewise, completely new protein structures, not found in nature, can now be created by computational design and used in various biotechnological and biomedical applications.

Nobel Prize in Chemistry 2024

© Nobel Prize Outreach. Photo: Clément Morin

David Baker

Prize share: 1/2

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Demis Hassabis

Prize share: 1/4

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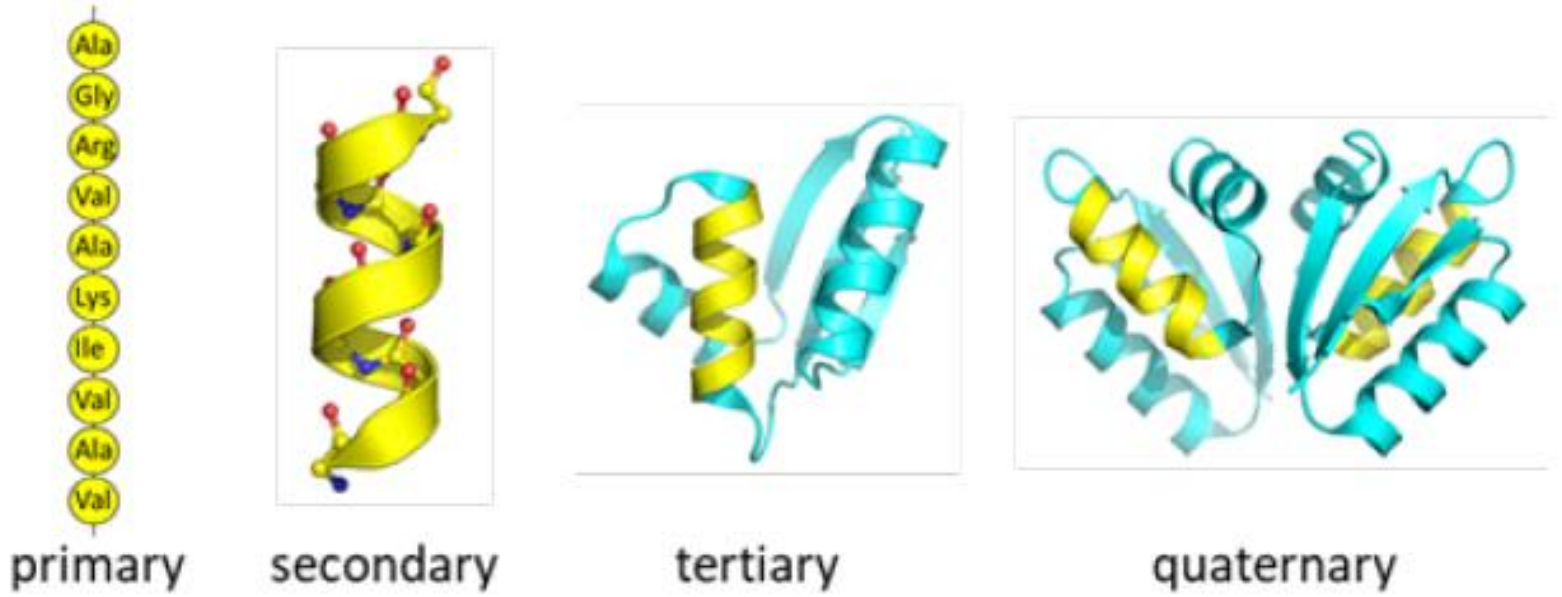
John Jumper

Prize share: 1/4

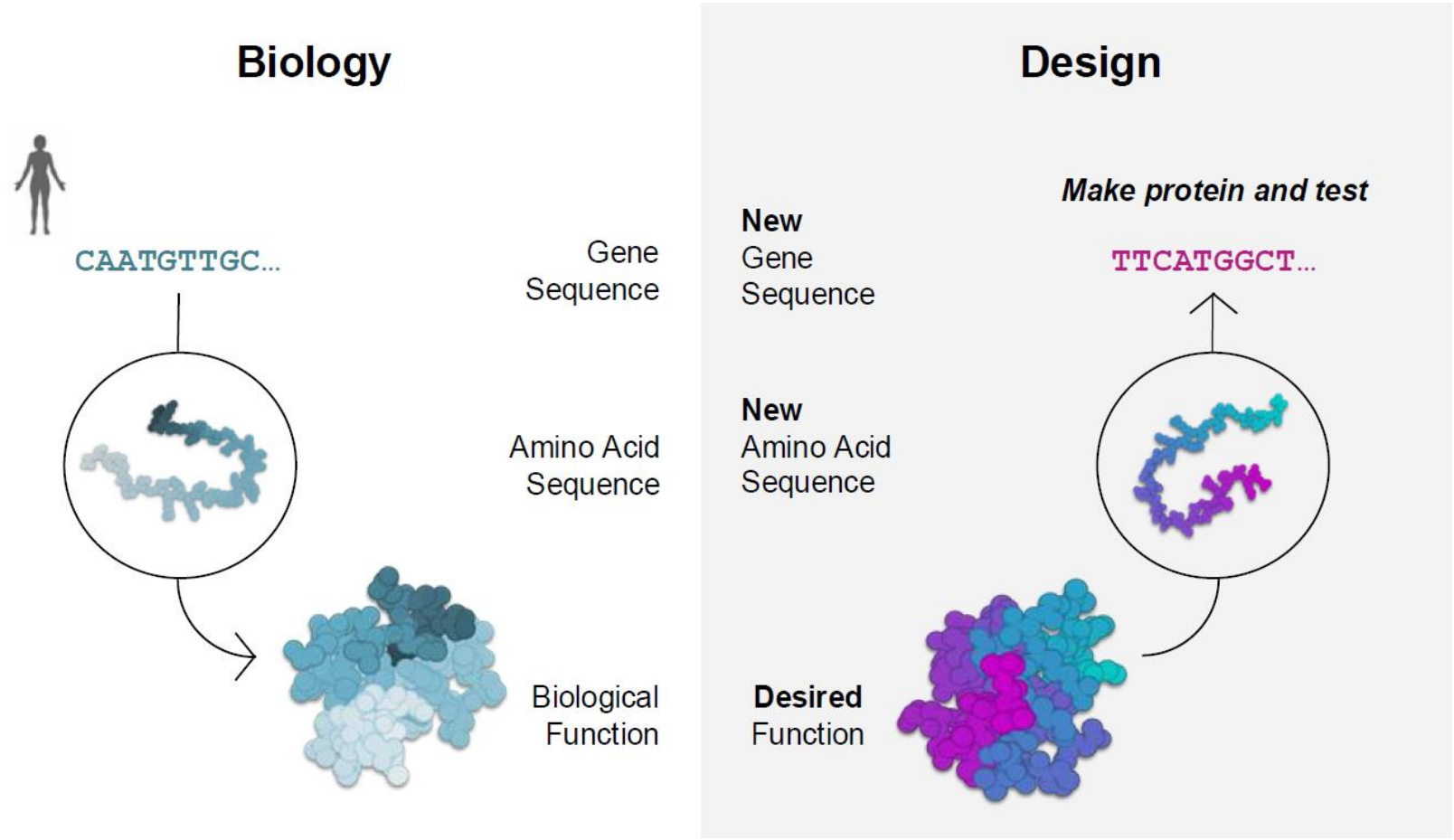
https://www.nobelprize.org/prizes/chemistry/2024/summary/

Breve recuerdo de la estructura de las proteínas



https://www.nobelprize.org/uploads/2024/10/advanced-chemistryprize2024.pdf

Discurso del Nobel de David Baker

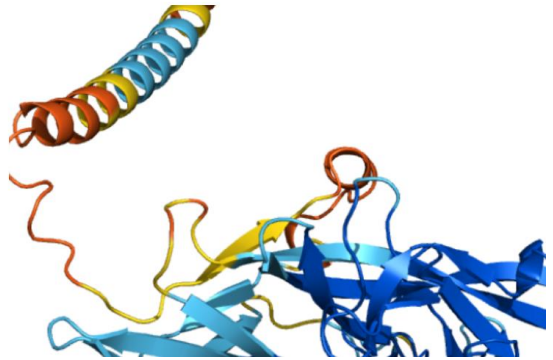


https://www.nobelprize.org/uploads/2024/12/baker-lecture.pdf

La historia de la IA, Google DeepMind y AlfaFold

Background

AlphaFold is an AI system developed by Google DeepMind that predicts a protein's 3D structure from its amino acid sequence. It regularly achieves accuracy competitive with experiment.



https://alphafold.ebi.ac.uk/

Article

Highly accurate protein structure prediction with AlphaFold

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Check for updates

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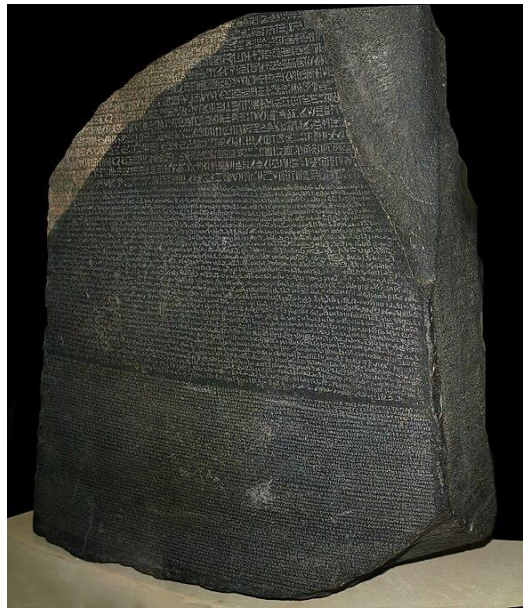
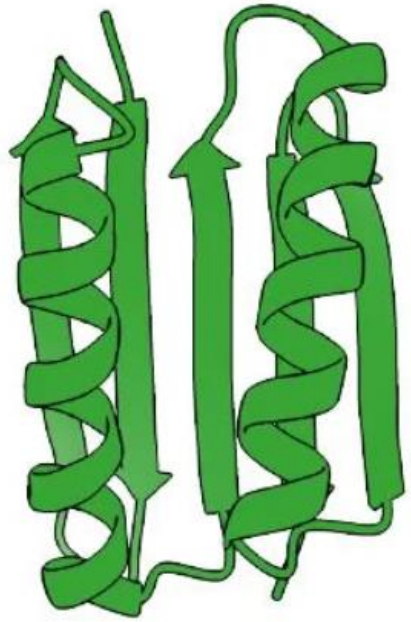
Jumper J, et al. Nature 15 de julio de 2021

Baker made his debut in the CASP competition in 1998 using Rosetta and, in comparison to other participants, it did really well. This success led to a new idea – that David Baker's team could use the software in reverse. Instead of entering amino acid sequences in Rosetta and getting protein structures out, they should be able to enter a desired protein structure and obtain suggestions for its amino acid sequence, which would allow them to create entirely new proteins.





David Baker

Proteína top 7

RESEARCH ARTICLE

PROTEIN DESIGN

Scaffolding protein functional sites using deep learning

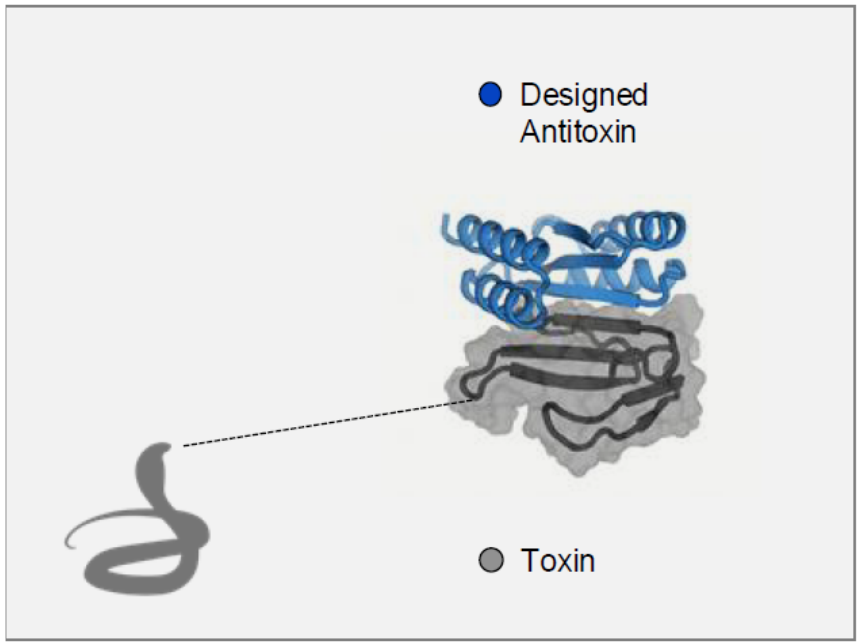
Jue Wang[1,2]†, Sidney Lisanza[1,2,3]†, David Juergens[1,2,4]†, Doug Tischer[1,2]†, Joseph L. Watson[1,2]†, Karla M. Castro[5], Robert Ragotte[1,2], Amijai Saragovi[1,2], Lukas F. Milles[1,2], Minkyung Baek[1,2], Ivan Anishchenko[1,2], Wei Yang[1,2], Derrick R. Hicks[1,2], Marc Expòsit[1,2,4], Thomas Schlichthaerle[1,2], Jung-Ho Chun[1,2,3], Justas Dauparas[1,2], Nathaniel Bennett[1,2,4], Basile I. M. Wicky[1,2], Andrew Muenks[1,2], Frank DiMaio[1,2], Bruno Correia[5], Sergey Ovchinnikov[6,7]*, David Baker[1,2,8]*

The binding and catalytic functions of proteins are generally mediated by a small number of functional residues held in place by the overall protein structure. Here, we describe deep learning approaches for scaffolding such functional sites without needing to prespecify the fold or secondary structure of the scaffold. The first approach, "constrained hallucination," optimizes sequences such that their predicted structures contain the desired functional site. The second approach, "inpainting," starts from the functional site and fills in additional sequence and structure to create a

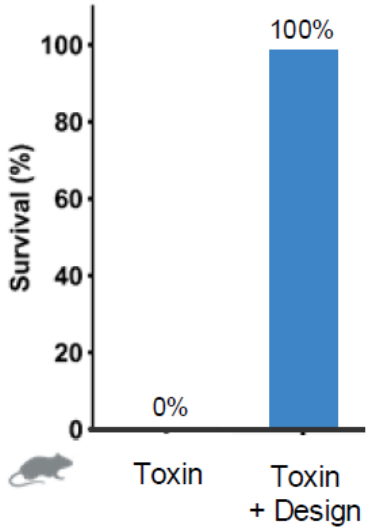
Partially constrained hallucination using a multiobjective loss function

To extend existing trRosetta-based design methods to scaffold functional sites (Fig. 1A), we optimized amino acid sequences for folding to a structure containing the desired functional site using a composite loss function that combines the previously used hallucination loss with a motif reconstruction loss over the functional motif [rather than the entire structure, as in (*13*)] (Fig. 1B; see materials and methods in the supplementary materials). Although we succeeded in generating structures with segments closely recapitulating functional sites, Rosetta structure predictions suggested that the sequences poorly encoded the structures (fig. S1A), and hence we used Rosetta design calculations to generate more-optimal sequences (*14*). Several designs targeting programmed cell death ligand 1 (PD-L1) generated by constrained hallucination with binding

Neutralizing snake toxin



Protects animals from
lethal doses of cobratoxin.

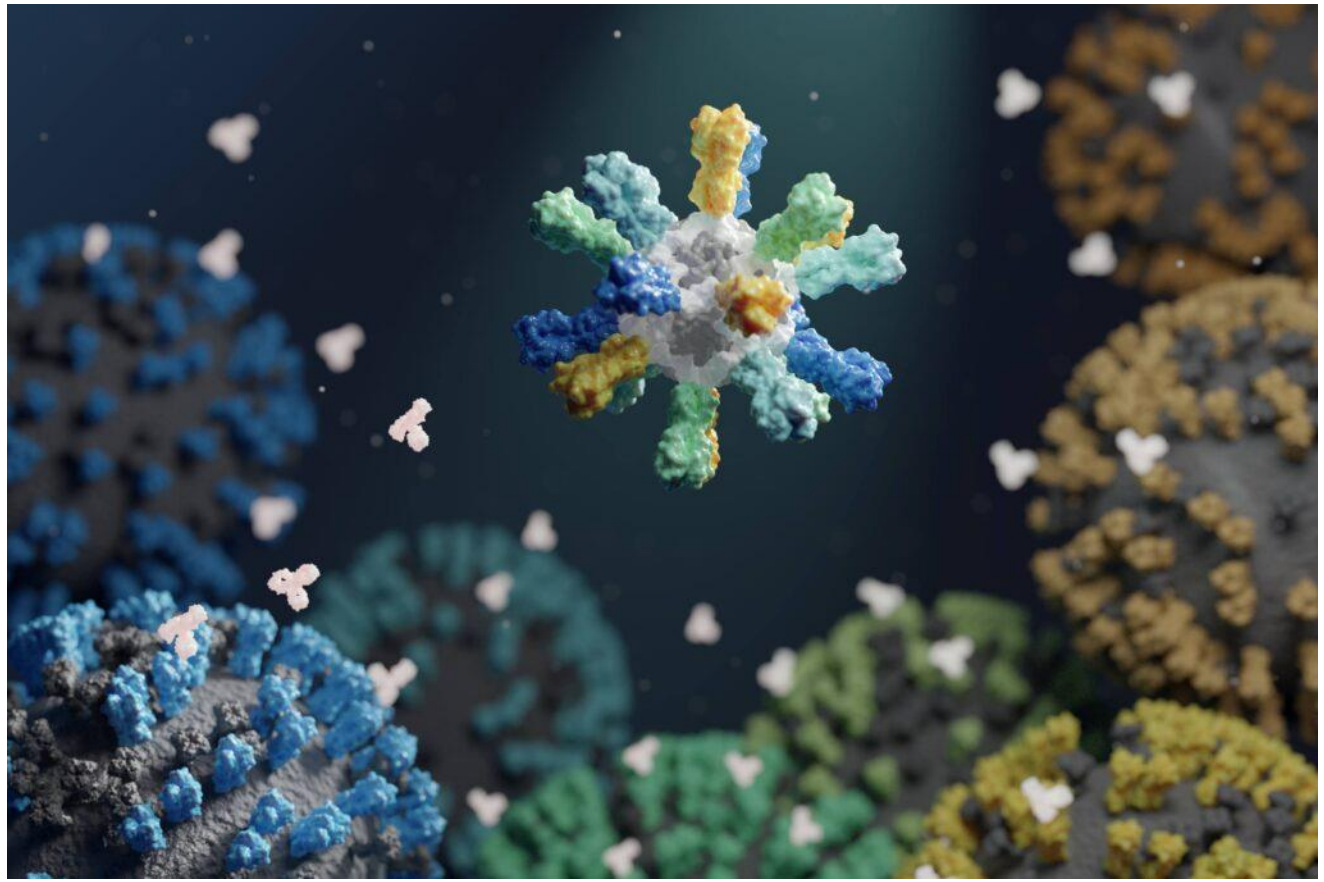


with Jenkins Lab (Technical University of Denmark)

Susana Vázquez Torres et al. Research Square (preprint), 2024

David Baker y Neil King (Universidad de Washington)

Vacunas frente a la gripe creadas por diseño computacional de proteínas



https://www.openphilanthropy.org/research/how-neil-king-and-david-baker-are-using-ai-to-create-more-effective-vaccines/

Article

Algorithm for optimized mRNA design improves stability and immunogenicity

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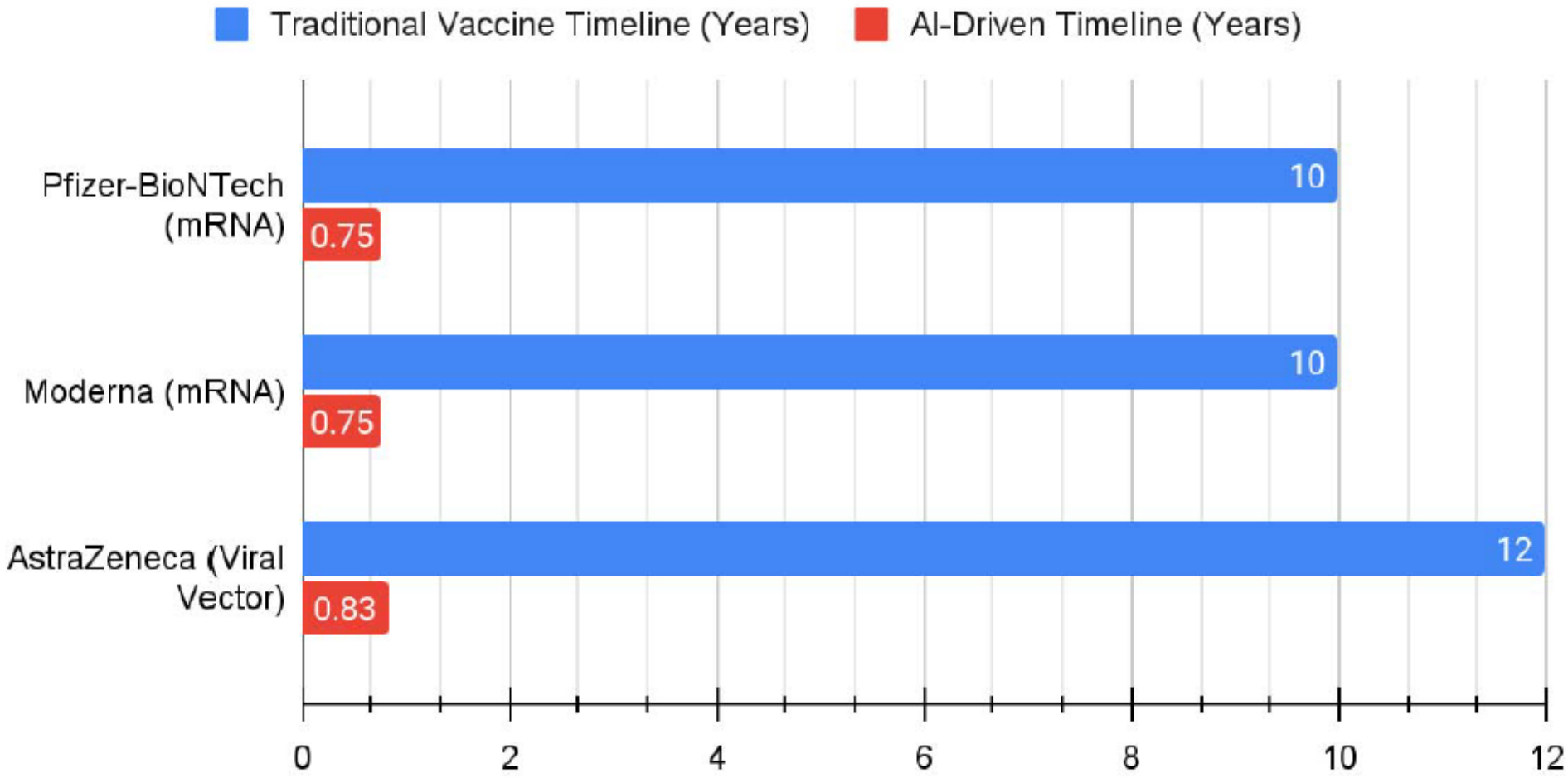
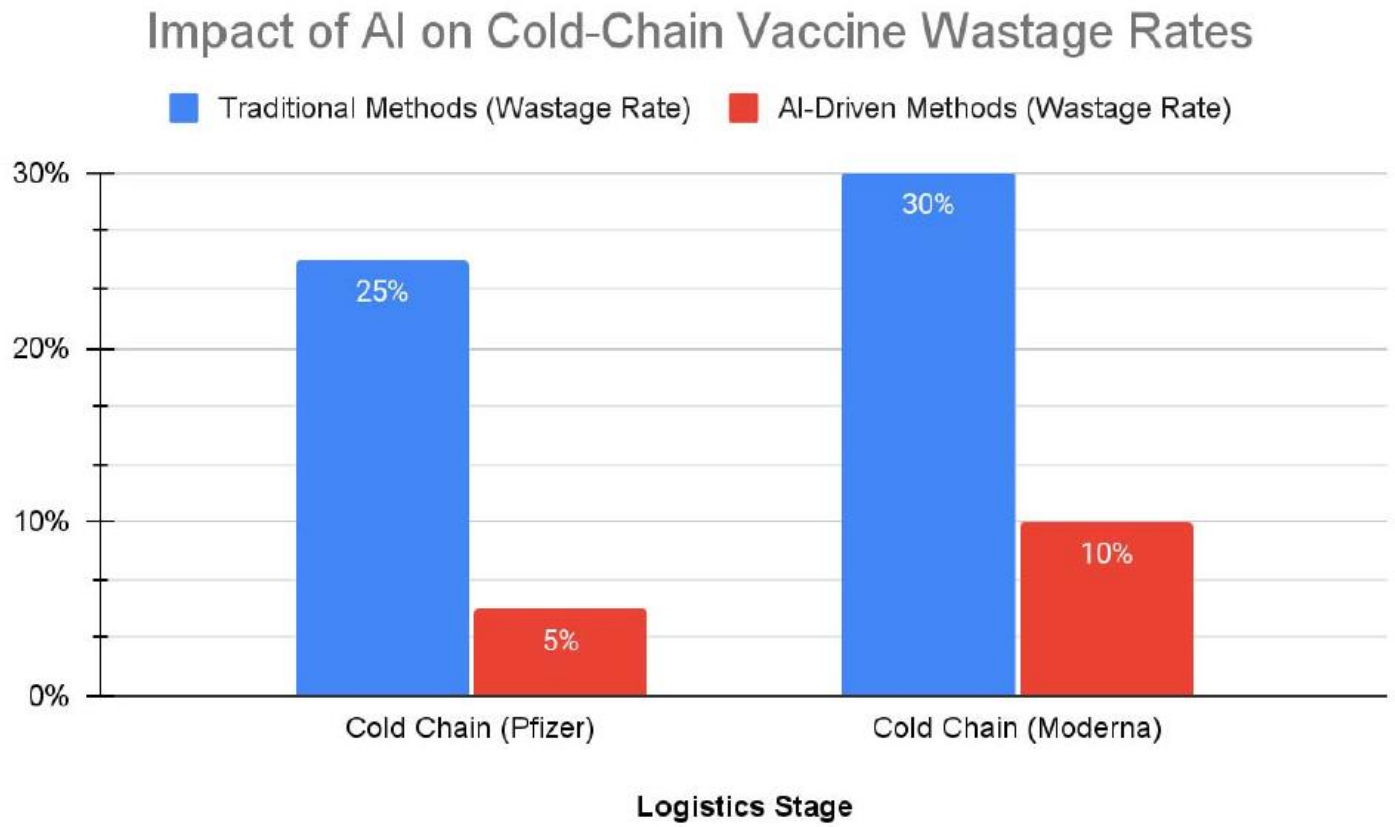
He Zhang[1,2,11], Liang Zhang[1,2,8,11], Ang Lin[3,8,11], Congcong Xu[3,11], Ziyu Li[1], Kaibo Liu[1,2], Boxiang Liu[1,9], Xiaopin Ma[3], Fanfan Zhao[3], Huiling Jiang[3], Chunxiu Chen[3], Haifa Shen[3], Hangwen Li[3]✉, David H. Mathews[4,5,6,7]✉, Yujian Zhang[3,10]✉ & Liang Huang[1,2,7,11]✉

is analogous to identifying the most likely sentence among similar-sounding alternatives[6]. Our algorithm LinearDesign finds an optimal mRNA design for the spike protein in just 11 minutes, and can concurrently optimize stability and codon usage. LinearDesign substantially improves mRNA half-life and protein expression, and profoundly increases antibody titre by up to 128 times in mice compared to the codon-optimization benchmark on mRNA vaccines for COVID-19 and varicella-zoster virus. This result reveals the great potential of principled mRNA design and enables

Comparison of Traditional and AI-Driven Vaccine Development Timelines



Farahani AF, et l. medRxiv preprint doi: https://doi.org/10.1101/2024.10.23.24315991



Farahani AF, et l. medRxiv preprint doi: https://doi.org/10.1101/2024.10.23.24315991

Conclusiones: el futuro de las vacunas

- Vacunas ARN
- Vacunas personalizadas
- Vacunas ADN
- Vacunas universales
- Vacunas terapéuticas
- Tecnologías de administración
- IA y diseño de vacunas
- Enfoque de enfermedades emergentes
- Equidad
- Vacunas comestibles

Muchas gracias