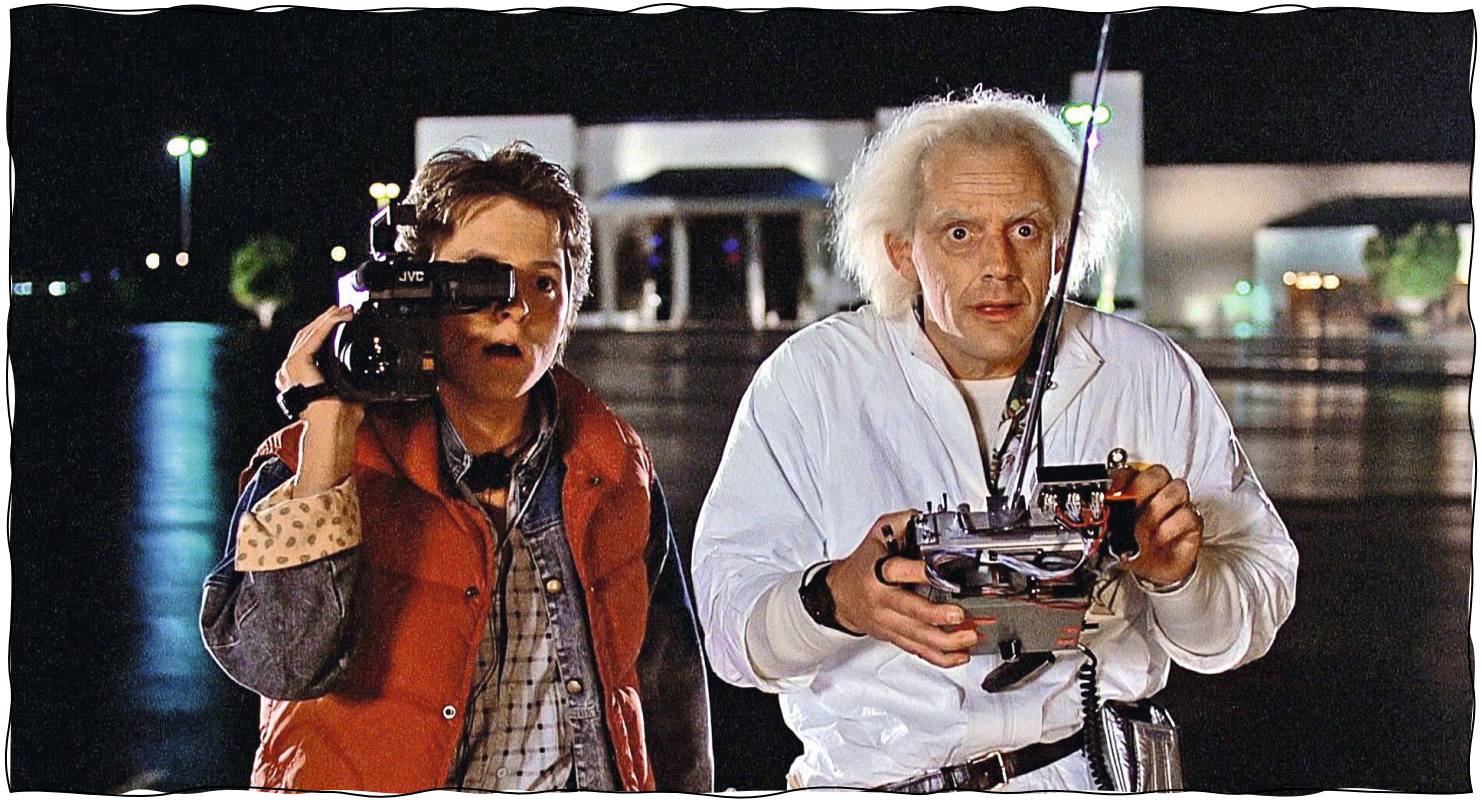


Regreso al futuro
Vacunas del covid

15 de abril de 2021

Vacunas del covid

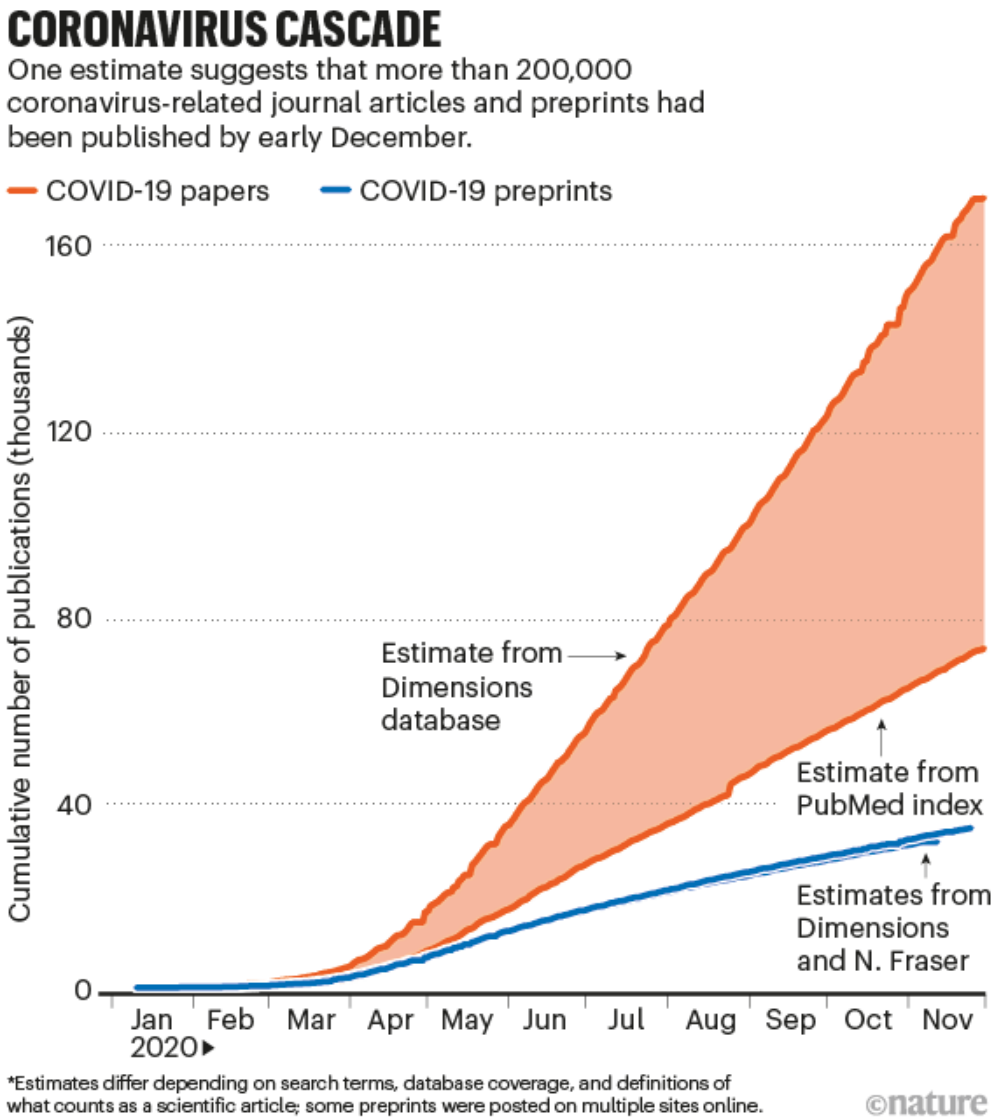
Regreso al futuro

Ángel Hernández Merino
Pediatra de Atención Primaria, Madrid
Vocal del CAV-AEP

15 de abril de 2021

@angel_h_merino

Vacunas del covid: regreso al futuro
Ideas clave



H. Else. Nature. 2020;558:553.

¿Cómo hemos llegado hasta aquí?
"A hombros de gigantes"

Pasado, presente y futuro

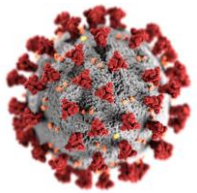
- A hombros de gigantes

1796, Edward Jenner

1885, Louis Pasteur

1937, Max Theiler

1980, R. Mulligan y P. Berg



2020, vacunas del covid de ARN y vectores virales

A. Desmond. N Engl J Med. 2021; 384:1081-3
https://www.nejm.org/doi/full/10.1056/NEJMp2034334

Vacunas del covid
El año 2020, ¿solo un año de suerte?

Las vacunas del covid no son producto de la suerte

- Todo empezó con Kariko

Vacunas del covid
Los antecedentes lejanos

Las vacunas del covid no son producto de la suerte

- Todo empezó con Kariko

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Direct gene transfer into mouse muscle in vivo

JA Wolff, RW Malone, P Williams, W Chong, G Acsadi, A Jani, PL Felgner

+ See all authors and affiliations

Science 23 Mar 1990:
Vol. 247, Issue 4949, pp. 1465-1468
DOI: 10.1126/science.1690918

Article Info & Metrics eLetters PDF

Abstract

RNA and DNA expression vectors containing genes for chloramphenicol acetyltransferase, luciferase, and beta-galactosidase were separately injected into mouse skeletal muscle in vivo. Protein expression was readily detected in all cases, and no special delivery system was required for these effects. The extent of expression from both the RNA and DNA constructs was comparable to that obtained from fibroblasts transfected in vitro under optimal conditions. In situ cytochemical staining for beta-galactosidase activity was localized to muscle cells following injection of the beta-galactosidase DNA vector. After injection of the DNA luciferase expression vector, luciferase activity was present in the muscle for at least 2 months.

Science
Vol 247, Issue 4949
23 March 1990

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Vacunas del covid
Katalin y Drew se encuentran

Las vacunas del covid no son producto de la suerte

- Todo empezó con Kariko

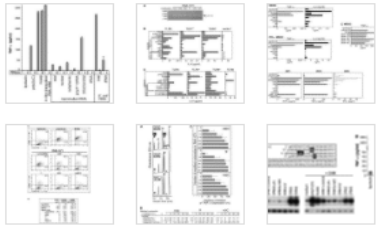
Katalin Kariko

Katalin Kariko y Drew Weissman

Outline

Show full outline

Figures (6)



Extras (1)

Document S1. One figure

Immunity

Volume 23, Issue 2, August 2005, Pages 165-175

Article

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], Drew Weissman [2]

Show more

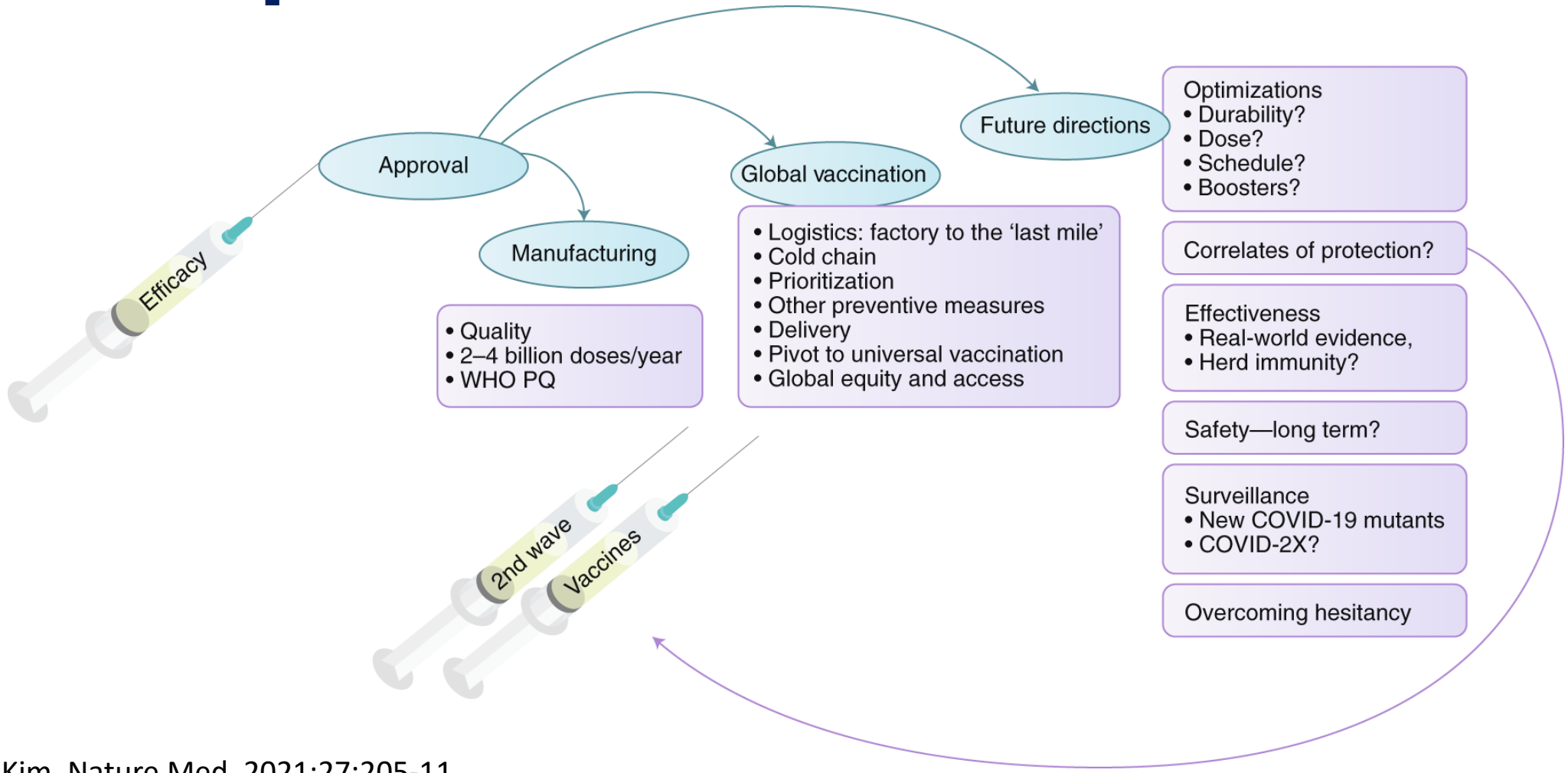
https://doi.org/10.1016/j.immuni.2005.06.008

Summary

DNA and RNA stimulate the mammalian innate immune system through activation of Toll-like receptors (TLRs). DNA containing methylated CpG motifs, however, is not stimulatory. Selected nucleosides in naturally occurring RNA are also methylated or otherwise modified, but the immunomodulatory effects of these alterations remain untested. We show that RNA signals through human TLR3, TLR7, and TLR8, but incorporation of modified nucleosides m5C, m6A, m5U, s2U, or pseudouridine ablates activity. Dendritic cells (DCs) exposed to such modified RNA express significantly less cytokines and activation markers than those treated with unmodified RNA. DCs and TLR-expressing cells are potently activated by bacterial and mitochondrial RNA, but not by mammalian total RNA, which is abundant in modified nucleosides. We conclude that nucleoside modifications suppress the potential of RNA to activate DCs. The innate immune system may therefore detect RNA lacking nucleoside modification as a means of selectively responding to bacteria or necrotic tissue.

https://www.sciencedirect.com/science/article/pii/S1074761305002116

Retos de las vacunas del covid a corto plazo



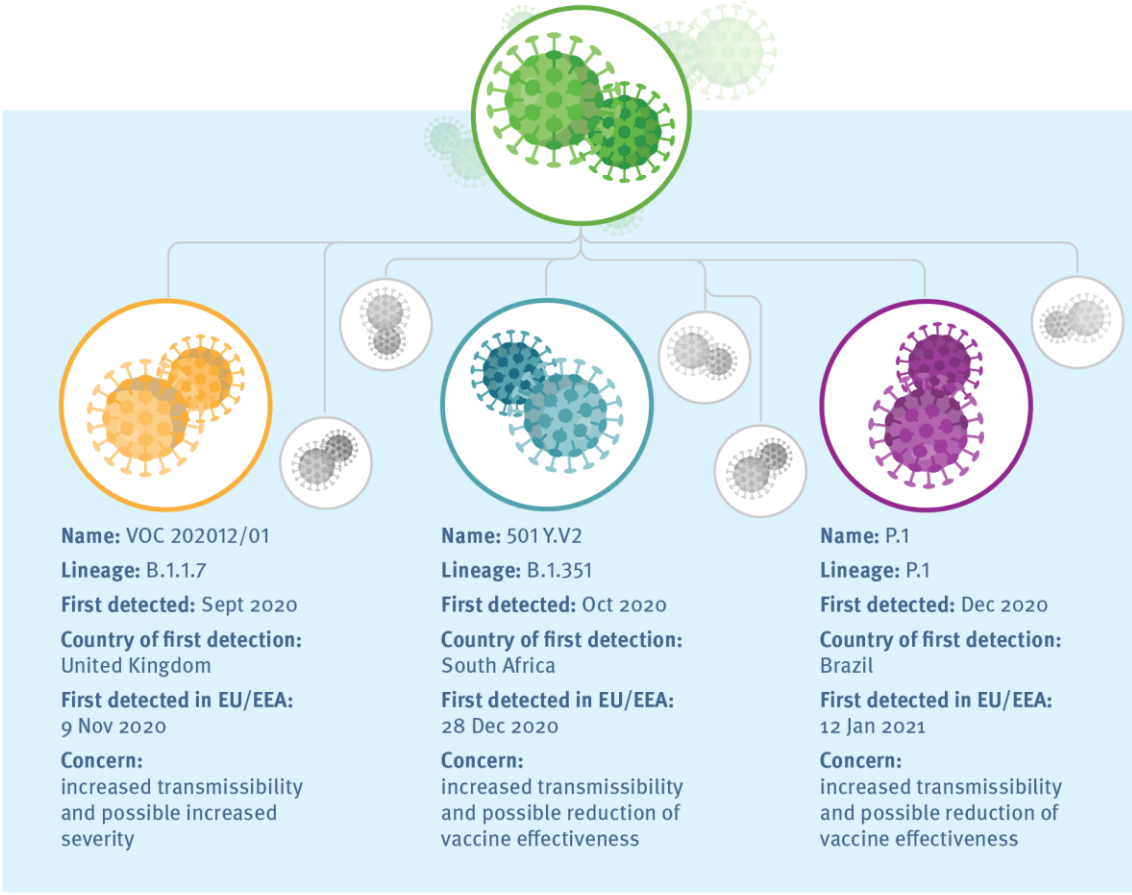
JH. Kim. Nature Med. 2021;27:205-11.
https://www.nature.com/articles/s41591-021-01230-y

¿Cómo afectarán las variantes del SARS-CoV-2 a l[illegible]vidad al?

Mutation of SARS-CoV-2: current variants of concern

8 February 2021

Mutations of SARS-CoV-2 that cause COVID-19 have been observed globally. Viruses, in particular RNA viruses such as coronaviruses, constantly evolve through mutations, and while most will not have a significant impact, some mutations may provide the virus with a selective advantage such as increased transmissibility. Such mutations are cause for concern and need to be monitored closely.



Name: VOC 202012/01
Lineage: B.1.1.7
First detected: Sept 2020
Country of first detection: United Kingdom
First detected in EU/EEA: 9 Nov 2020
Concern: increased transmissibility and possible increased severity

Name: 501 Y.V2
Lineage: B.1.351
First detected: Oct 2020
Country of first detection: South Africa
First detected in EU/EEA: 28 Dec 2020
Concern: increased transmissibility and possible reduction of vaccine effectiveness

Name: P.1
Lineage: P.1
First detected: Dec 2020
Country of first detection: Brazil
First detected in EU/EEA: 12 Jan 2021
Concern: increased transmissibility and possible reduction of vaccine effectiveness

#COVID19

Learn more in the latest risk assessment by ECDC on SARS-CoV-2 variants of concern http://bit.ly/RRAVariants1

ecdc

El futuro de la pandemia

- Retos pendientes

¿Cómo afectará la vacunación a las variantes del SARS-CoV-2

Mutation of SARS-CoV-2: current variants of concern

8 February 2021

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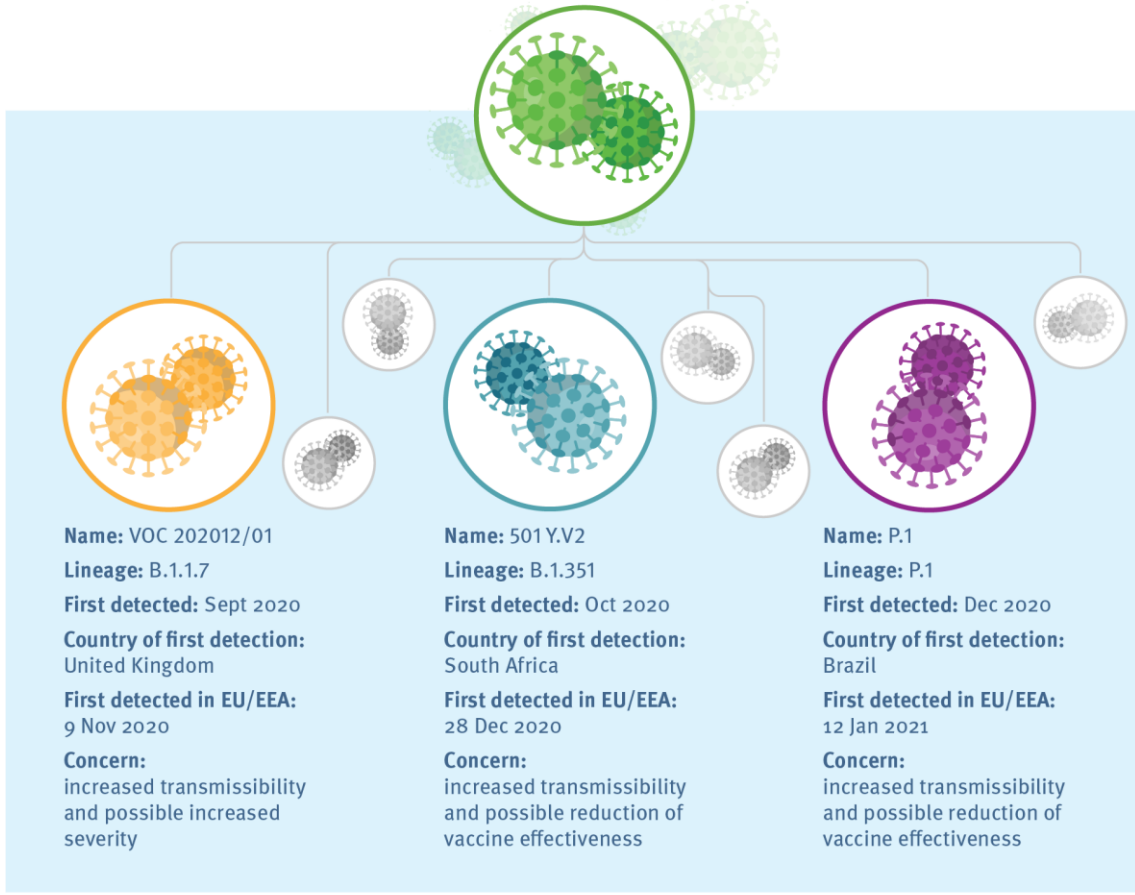

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#COVID19

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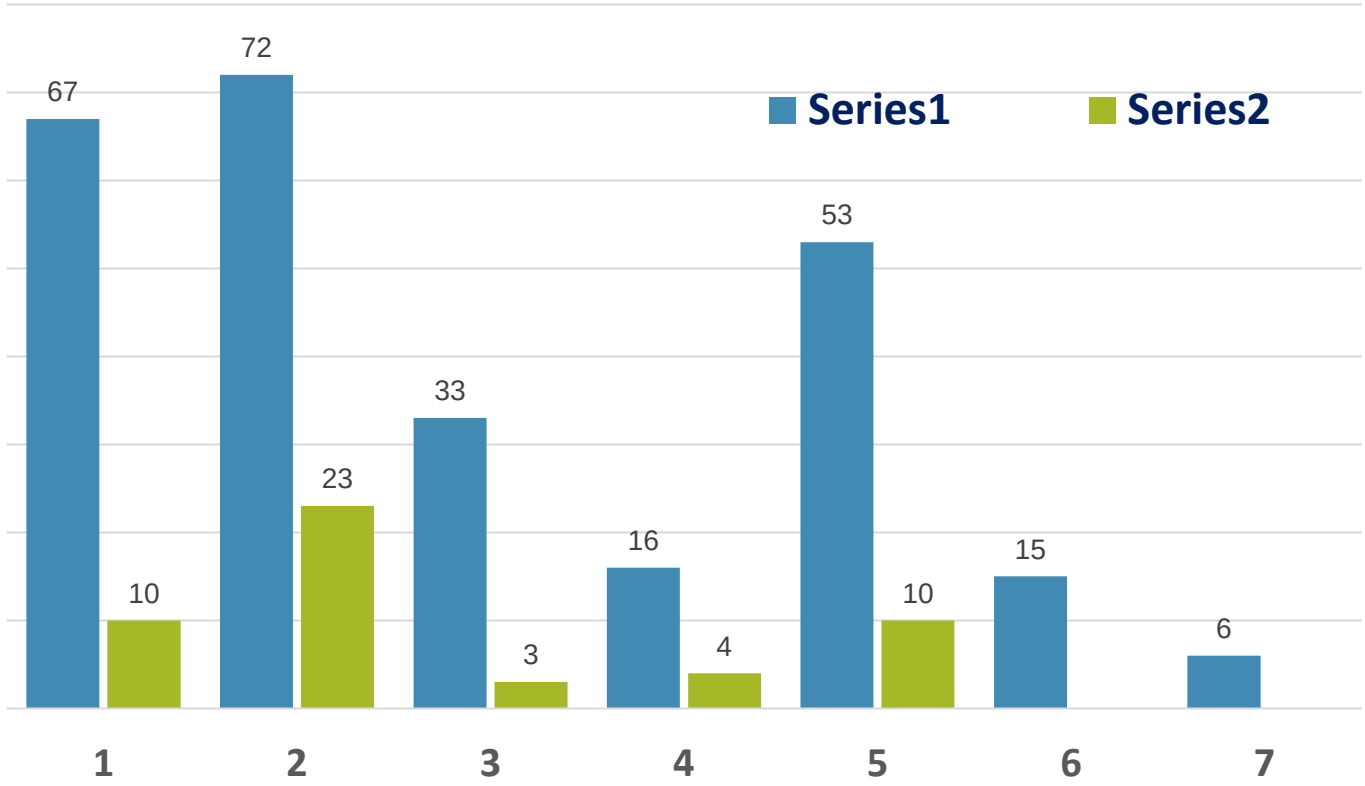
ecdc

Vacunas del covid
Nuevos productos en investigación

La próxima generación de vacunas

- Esto solo acaba de empezar



OMS, investigación en vacunas en curso

Candidatos en estudio: 272

- 86 en fase clínica
- 186 en fase preclínica

86 candidatos a vacunas en investigación clínica

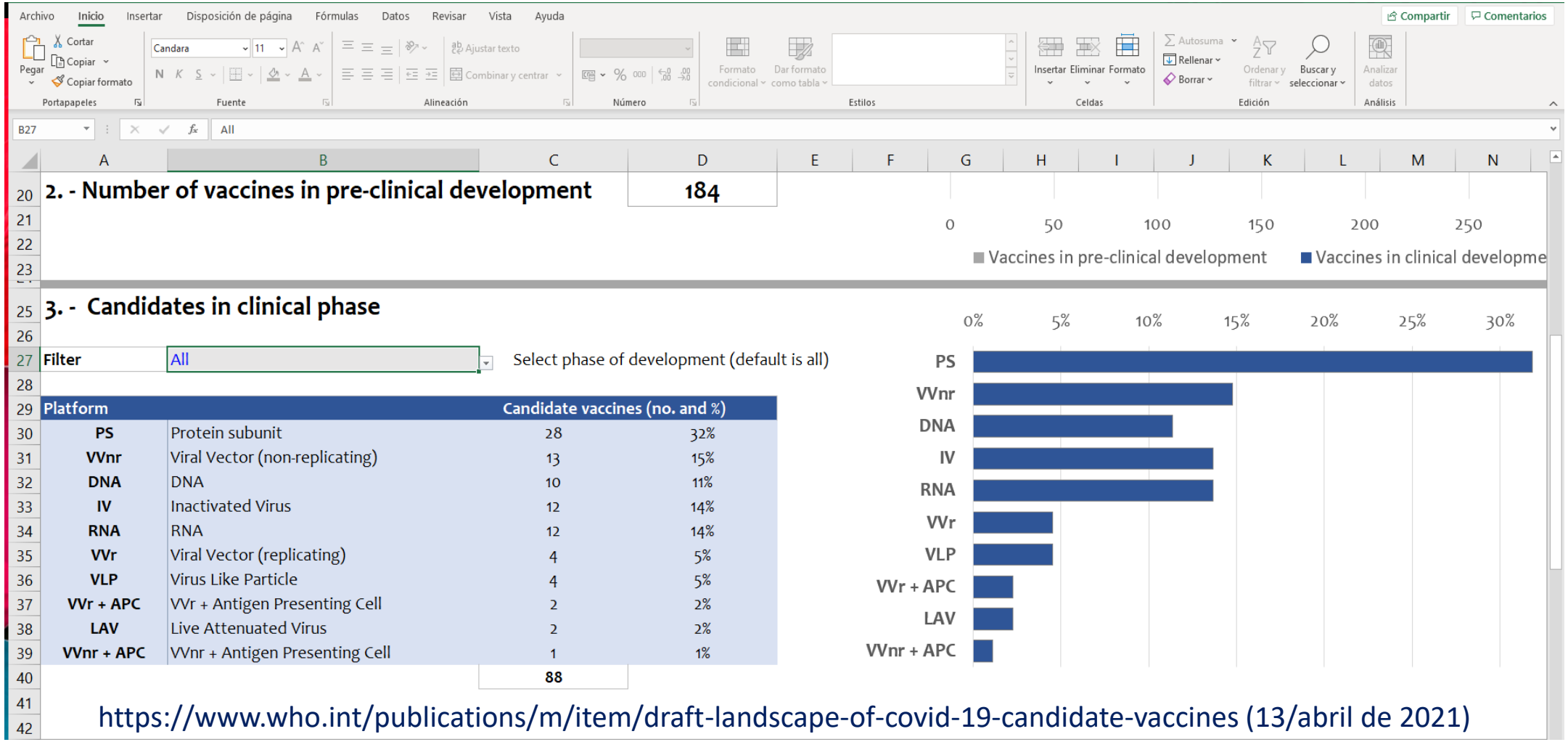
- 262 estudios registrados
- 50 publicaciones originales revisadas

7/abril de 2021
Draft landscape and tracker of COVID-19 candidate vaccines

Vacunas del covid
Nuevos productos en investigación

La próxima generación de vacunas

- Esto solo acaba de empezar



2. - Number of vaccines in pre-clinical development: 184

3. - Candidates in clinical phase

Filter: All — Select phase of development (default is all)

Platform		Candidate vaccines (no. and %)	
PS	Protein subunit	28	32%
VVnr	Viral Vector (non-replicating)	13	15%
DNA	DNA	10	11%
IV	Inactivated Virus	12	14%
RNA	RNA	12	14%
VVr	Viral Vector (replicating)	4	5%
VLP	Virus Like Particle	4	5%
VVr + APC	VVr + Antigen Presenting Cell	2	2%
LAV	Live Attenuated Virus	2	2%
VVnr + APC	VVnr + Antigen Presenting Cell	1	1%
		88	

https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (13/abril de 2021)

Vacunas del covid futuras
Vacunas de ARNm

La próxima generación de vacunas

- Esto solo acaba de empezar

Campos de investigación

- Cáncer
- Terapia génica
- Terapia celular
- Vacunas terapéuticas
- Vacunas preventivas

Vacunas preventivas

- Zika
- Gripe
- VIH
- Rabia
- Coronavirus

Profilaxis pasiva

- ARNm que codifica anticuerpos específicos (chikunguña)

Ventajas

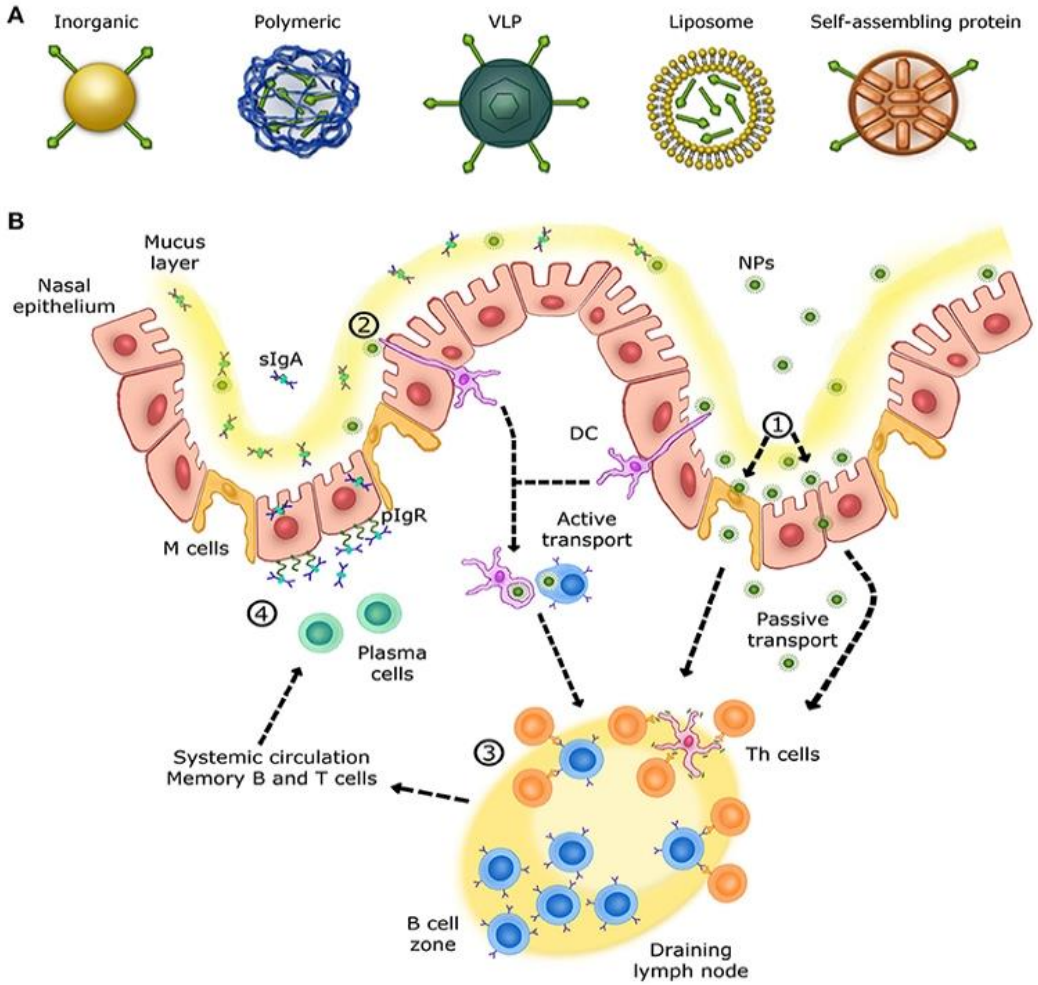
- Abre vías de avance en patologías sin alternativas farmacológicas
- Diseño relativamente sencillo, al alcance de pequeños grupos
- Flexibilidad: adaptación a nuevos objetivos
- Medicina personalizada

Vacunas de ARNm futuras

Retos: estabilidad

La próxima generación de vacunas

- Esto solo acaba de empezar

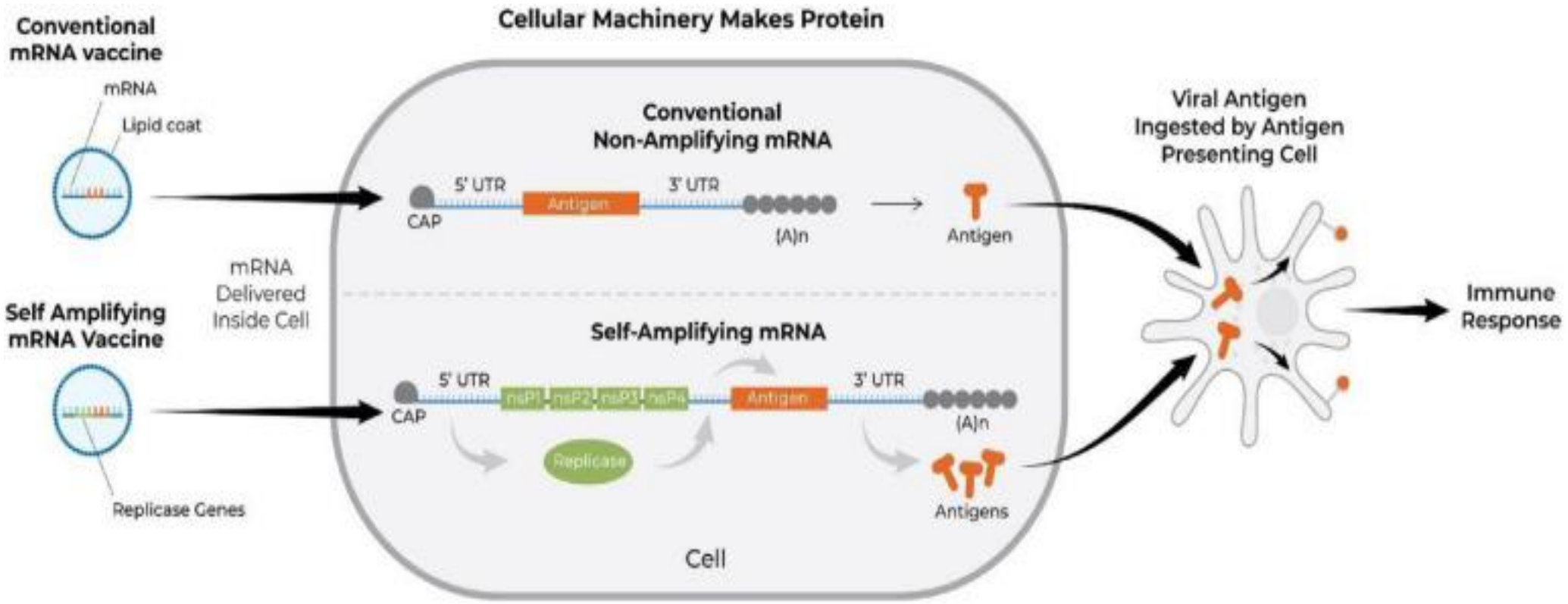


Nanopartículas ● S. Al-Halifa. Front Immunol. 2019, 24/ene

Vacunas de ARNm futuras
Retos: rendimiento

La próxima generación de vacunas

- Esto solo acaba de empezar



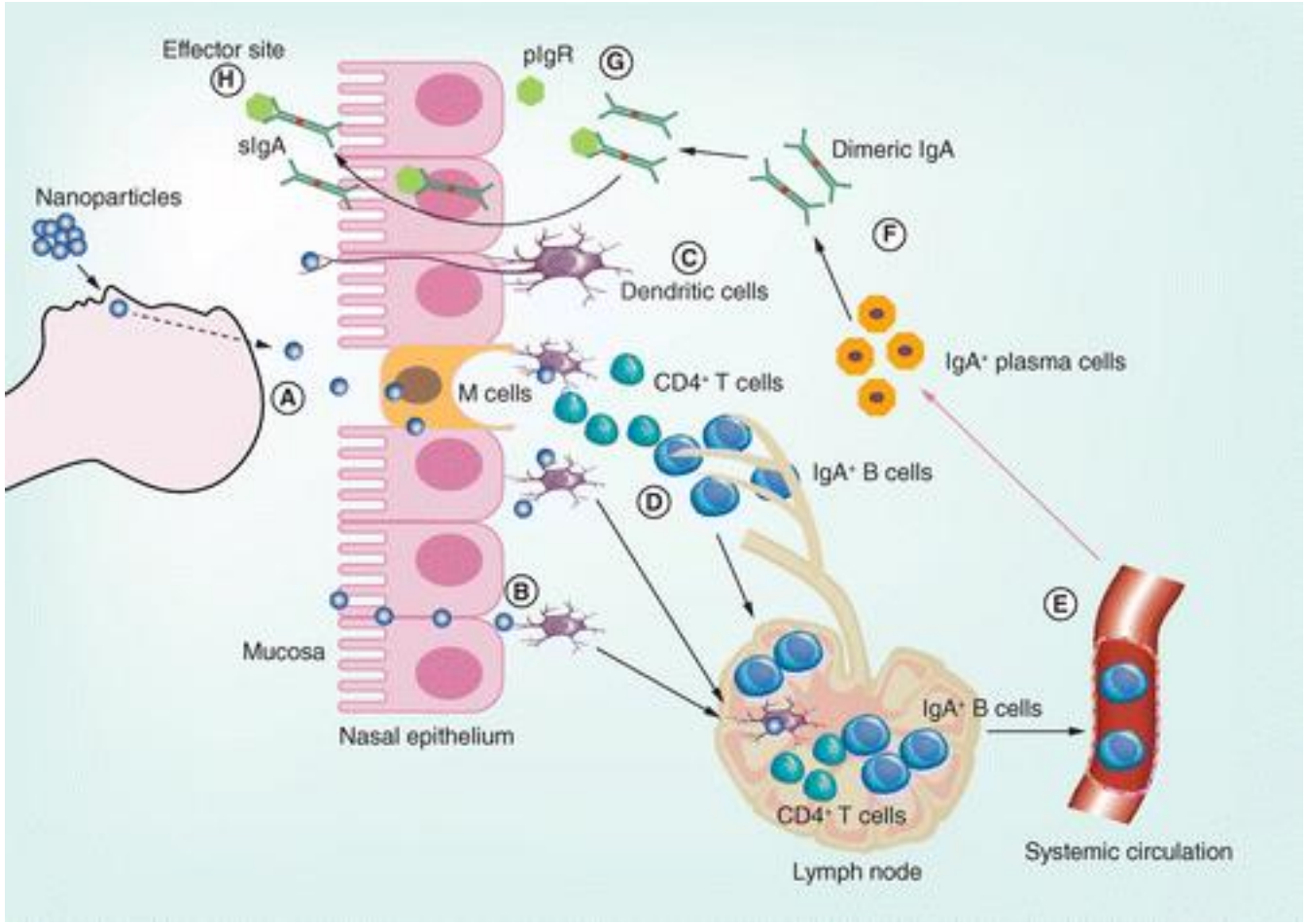
ARNm autorreplicante ● TR. Damase. Front Bioeng Biotechnol. 2021;9:628137

Vacunas de ARNm futuras

Retos: inmunidad mucosal

La próxima generación de vacunas

- Esto solo acaba de empezar



Las vacunas de ARNm no son flor de un día

Las vacunas de ARNm no son flor de un día

- Las vacunas del covid, un antes y un después

nature reviews drug discovery

Published: 12 January 2018

mRNA vaccines – a new era in vaccinology

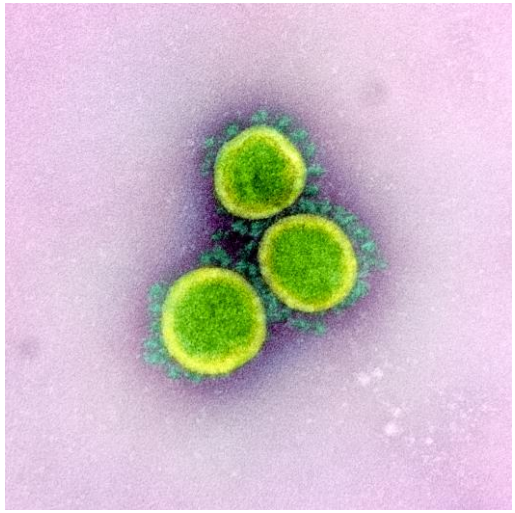
Norbert Pardi, Michael J. Hogan, Frederick W. Porter & Drew Weissman

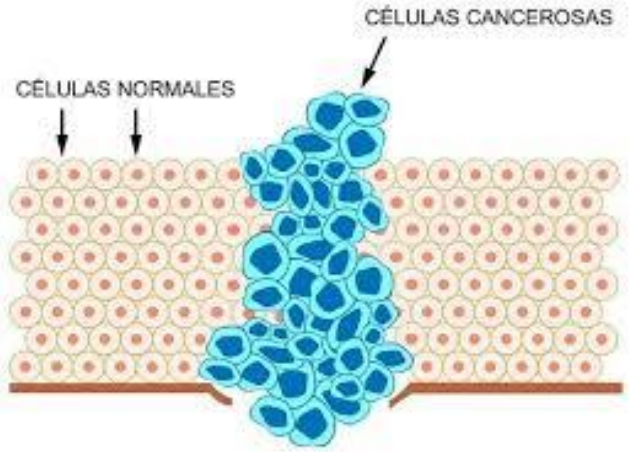
Nature Reviews Drug Discovery **17**, 261–279(2018) | Cite this article

1.50m Accesses | **523** Citations | **4476** Altmetric | Metrics

Key Points

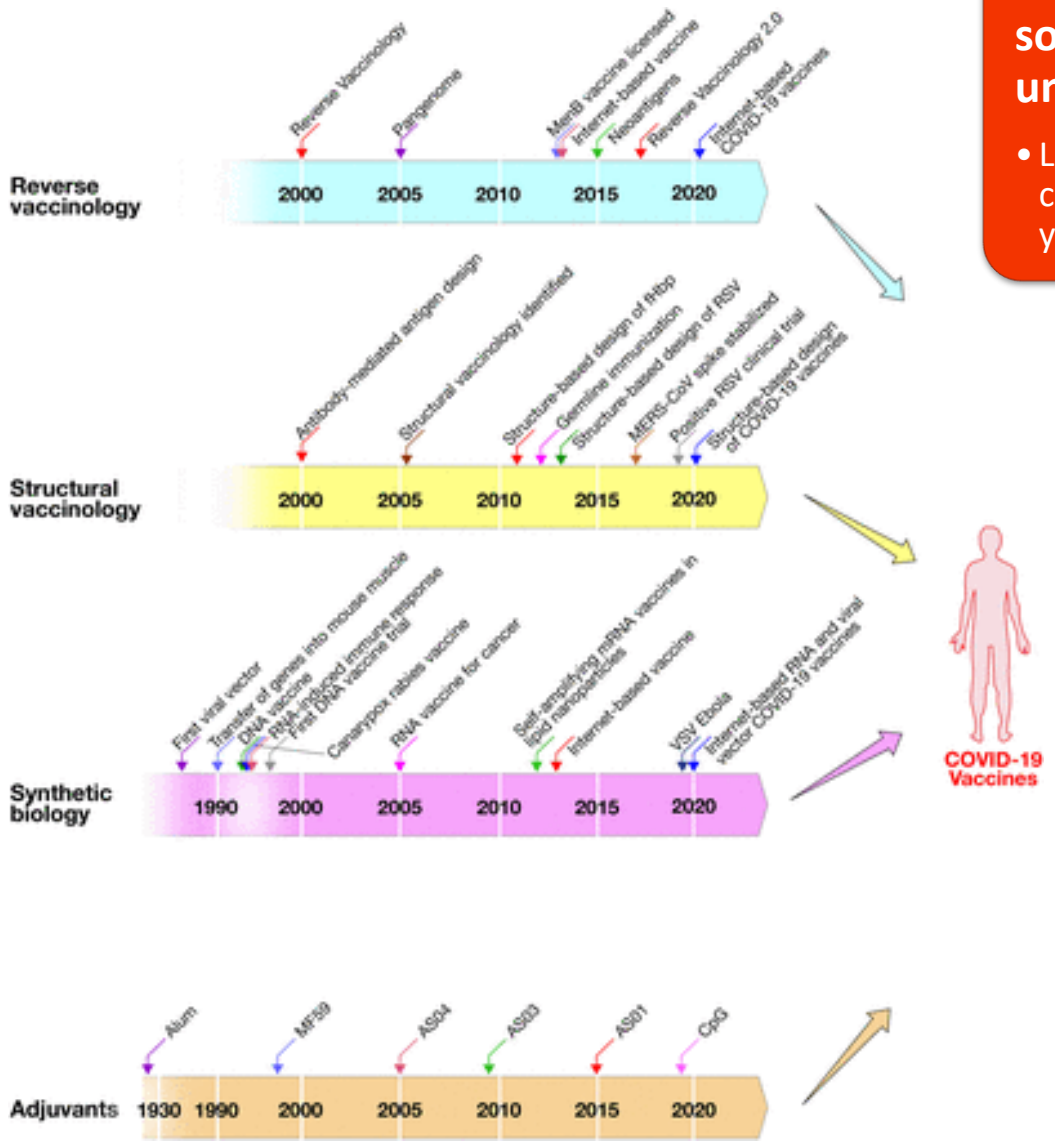
- Recent improvements in mRNA vaccines act to increase protein translation, modulate innate and adaptive immunogenicity and improve delivery.
- mRNA vaccines have elicited potent immunity against infectious disease targets in animal models of influenza virus, Zika virus, rabies virus and others, especially in recent years, using lipid-encapsulated or naked forms of sequence-optimized mRNA.
- Diverse approaches to mRNA cancer vaccines, including dendritic cell vaccines and various types of directly injectable mRNA, have been employed in numerous cancer





Las vacunas del covid son producto de una combinación de tecnologías usadas por separado antes

R. Rappuoli. PNAS. 2021;118(3):e2020368118



Las vacunas de ARNm no son flor de un día

- Las vacunas del covid, un antes y un después

Vacunas del covid: regreso al futuro
Ideas clave

Pasado, presente y futuro

- ¿Cómo hemos llegado hasta aquí?
- "A hombros de gigantes"
- Grandes hitos y personajes en el desarrollo de las vacunas

Las vacunas del covid no son producto de la suerte

- Valor de la investigación básica
- Las vacunas del covid son producto de más de una década de investigación
- Papel de Katalin Kariko y Drew Weissman (entre otros)

El futuro de la pandemia

- Retos pendientes
- Producción y logística
- Condiciones de conservación
- Duración, efectividad, seguridad
- Variantes virales y vacunación

La próxima generación de vacunas

- Esto solo acaba de empezar
- Cientos de productos en investigación
- Ventajas de las plataformas de ARN
- Estabilidad: nanopartículas y otros vehículos
- Rendimiento: ARN audtoamplificante
- Inmunida mucosal

Las vacunas de ARNm no son flor de un día

- Las vacunas del covid, un antes y un después
- La tecnología del ARN abre la puerta a nuevas opciones en patologías sin alternativas válidas hasta ahora

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