University of São Paulo - USP
Ribeirão Preto Medical School
RCB0300 - Biotechnology

Race with virus evolution: The development and application of mRNA vaccines against SARS-CoV-2

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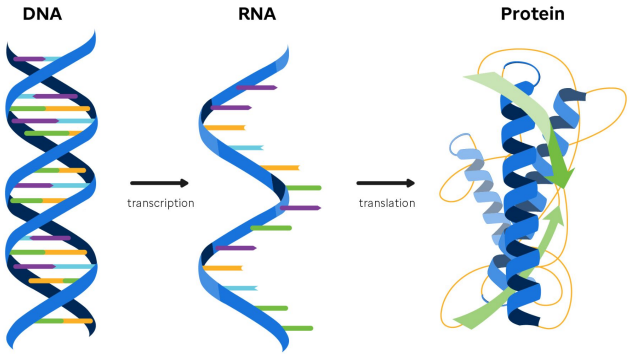
Introduction

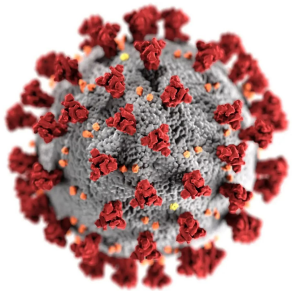
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

The application of nucleic acids in vaccine development is considered a new-generation technology.

1990: directly delivering mRNA for protein expression in vivo was demonstrated in mouse and rat models.

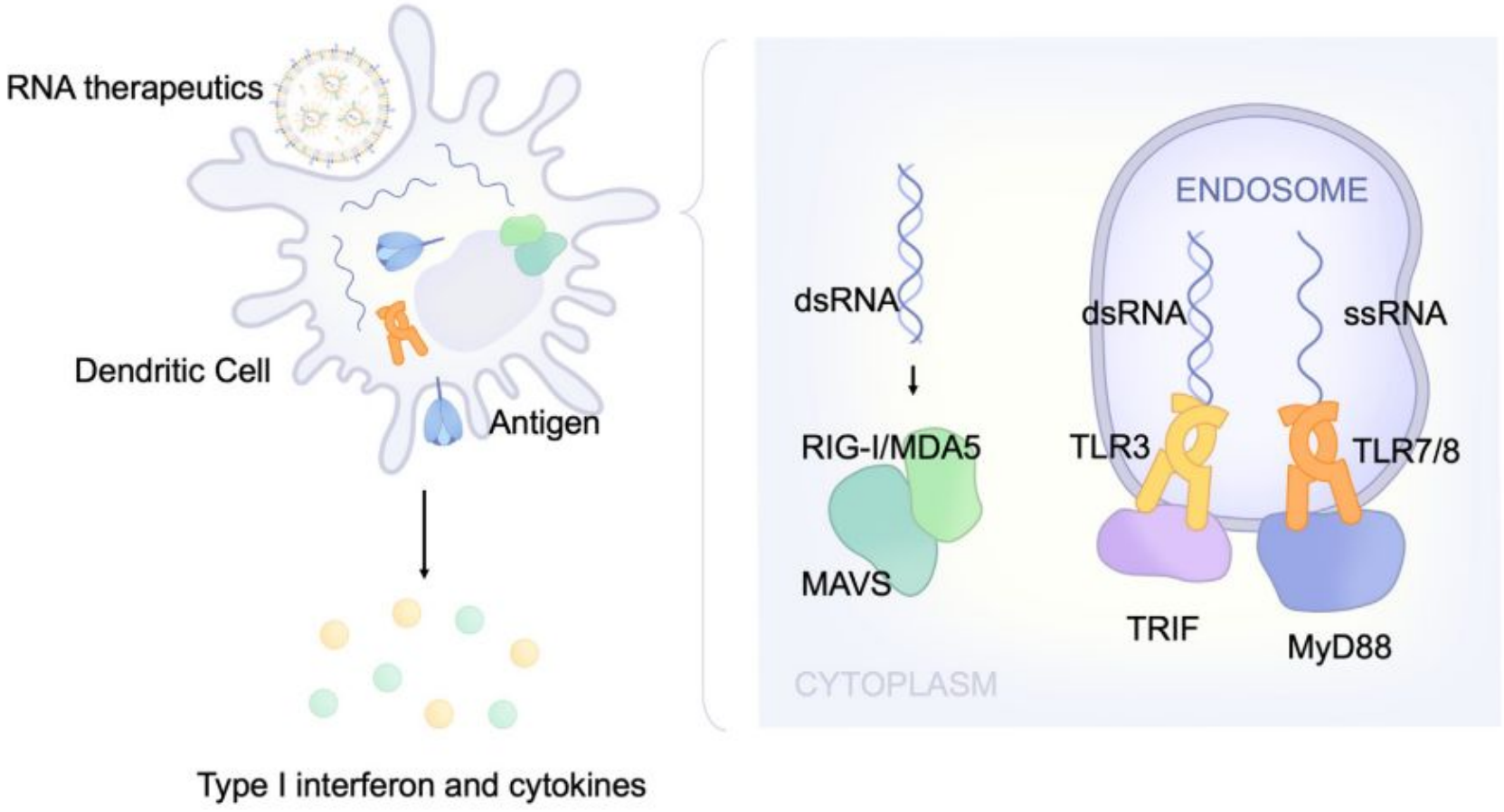


Recent advances in improving RNA stability and delivery systems have made the application of mRNA therapeutic purposes possible

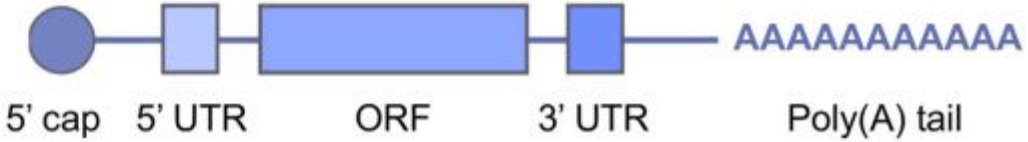


Principles and technology of mRNA vaccines

Balanced immune stimulation



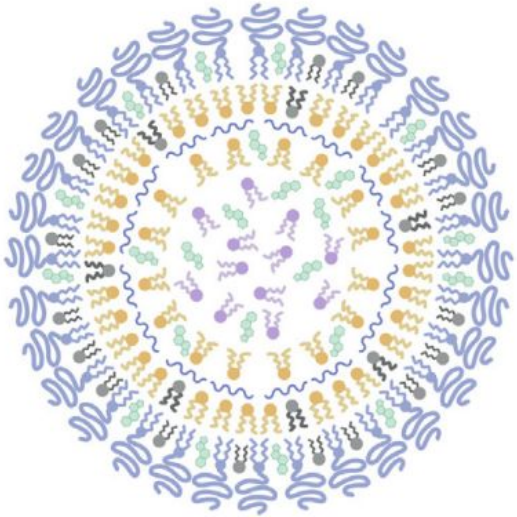
Optimized translation yield



- Protect mRNA from nuclease attack
- Increase the translation yield
- Contribute to protein expression
- Increase the stability of the RNA

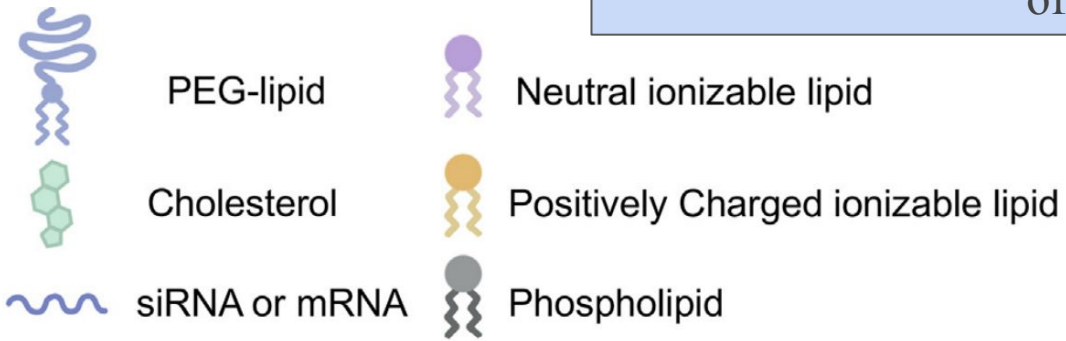
The pseudouridine-incorporated ribonucleic acids can be modified by the 5' cap and 3' polyadenylation whereas other regulatory cis-elements contributing to the translation efficiency and mRNA stability can be engineered in the 5' and 3' untranslated regions (UTRs).

Suitable delivery system



Even when an immunocompromised mRNA with a high translation yield is synthesized, its intrinsic instability in the environment impedes its clinical application unless an appropriate delivery system for nucleic acids is available.

It improves the solubility and stability of the nanoparticle, and also allows for more effective delivery of the mRNA.



Safety and efficacy of COVID-19 mRNA vaccines

Safety and efficacy

Pfizer-Biontech BNT162b2 → 95% efficacy

Moderna mRNA-1273 vaccines → 94.1% efficacy

Immune escape contributes for a reduced neutralizing activity against new strains
Omicron → two doses of mRNA vaccine had reduced neutralizing activity

A booster dose of mRNA vaccine → neutralizing antibody response

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Bivalent mRNA vaccine mRNA-1273.214 → mRNA expressing WT and omicron BA.1 spike protein

Immunogenicity as a booster dose against omicron BA.1

Safety and efficacy: Immune response activated by the mRNA vaccine

Trigger immune responses:

- **Proteasomal degradation**
- **Transmembrane deposition**

Humoral response:

- **CD8 and CD4 activation**
- **Antibodies**

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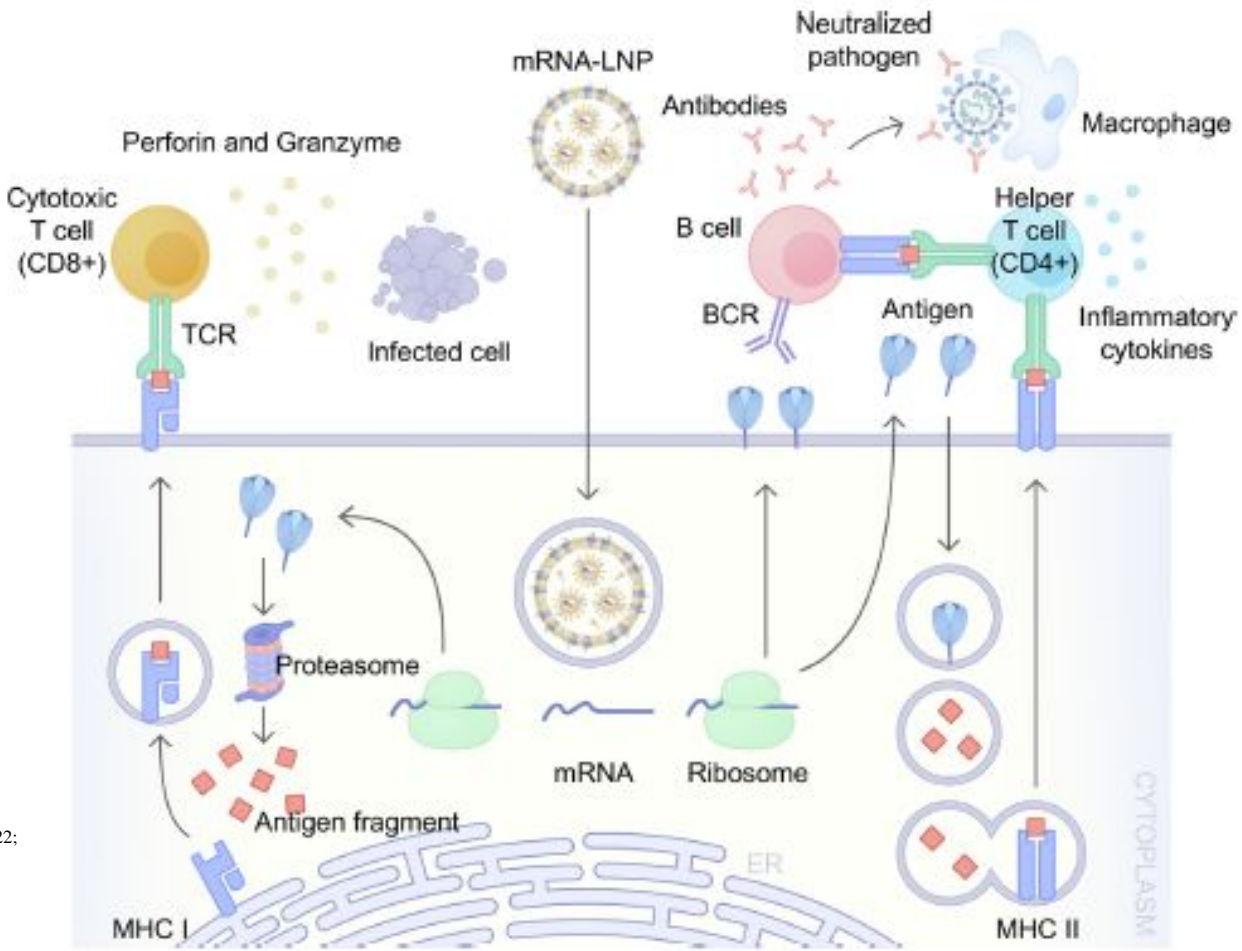

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Safety and efficacy: Immune response activated by the mRNA vaccine

mRNA vaccines vs. viral vector-based vaccines

mRNA vaccines:

- Antibodies + INF
- BNT162b2 mRNA vaccine → TCD8 activation
- phosphorylated STAT3 and STAT1, IFN-g, antiviral and IFN response genes → upregulated

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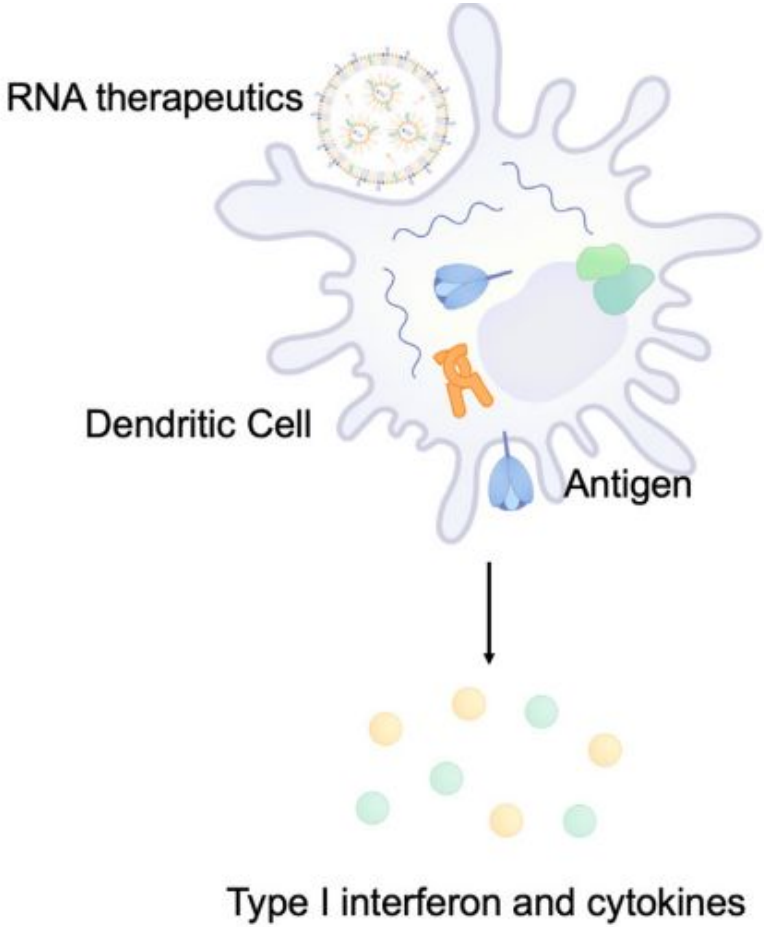
Adaptive and **innate response**



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Safety and efficacy: mRNA vaccines against viral infectious diseases

mRNA vaccines in development:

- Seasonal influenza, Zika, Rabies and Chikungunya virus

- **self-amplifying mRNA (saRNA)**

- increase the level of translation-competent mRNA

- low doses are sufficient to boost the immune response

Safety and efficacy: mRNA vaccines against viral infectious diseases

B. Self-amplifying

Target	Name	Sponsor/Collaborators	Clinical trial phase	NCT number	
SARS-CoV-2	AAHI -SC2, AAHI -SC3	ImmunityBio, Inc.	Phase 1|Phase 2	NCT05370040	
	ARCT-021-01, ARCT-165-01	Arcturus Therapeutics, Inc.	Phase 1|Phase 2	NCT05037097	
	ARCT-154-01	Arcturus Therapeutics, Inc.	Phase 2|Phase 3	NCT05012943	
	CoV2 SAM (LNP)	GlaxoSmithKline	Phase 1	NCT04758962	
	COVID-4.015	ImmunityBio, Inc.	Phase 1|Phase 2	NCT05370040	
	EXG-5003	Elixirgen Therapeutics, Inc.	Phase 1|Phase 2	NCT04863131	
	GRT-R912, GRT-R914, and GRT-R918	Gritstone bio, Inc.	Phase 1	NCT05435027	Beta and omicron variants
	LNP-nCOV saRNA-02	MRC/UVRI and LSHTM Uganda Research Unit	Phase 1	NCT04934111	
Influenza virus	C4861001	Pfizer	Phase 1	NCT05227001	
Rabies	RG SAM (CNE) vaccine	GlaxoSmithKline	Phase 1	NCT04062669	

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Conclusions

Maria Laura

Conclusions

- The development of vaccines during the SARS-CoV-2 pandemic as the virus evolves and spreads.
- The administration of vaccines during the pandemic was crucial for reducing hospitalizations and deaths.
- The mRNA vaccines are widely applied. They are also advantageous for an efficient production process and low contamination of host DNA and viral components.
- The mRNA-1273 and BNT162b2 vaccines were potent during the pandemic.
- There are still concerns about the safety of mRNA vaccines, such as: systemic inflammation and induction of autoreactive antibodies.
- Risks x benefits assessment encourage the continued development of vaccines.

Take home message…

Technology of mRNA vaccines

Dependent on:

- ➔ compromised immune stimulation
- ➔ optimized expression
- ➔ suitable delivery system

Yield

Codon optimization through structural modifications

Take home message…

Delivery system

lipid-based vehicle

LNP:
lipid nanoparticle

Safety and efficacy

Initially mRNA Pfizer-BioNTech and Moderna showed efficacy, but new strategies such as booster doses and bivalent vaccines are needed

Take home message…

Immune response

mRNA vaccines trigger both adaptive and innate immune responses

Vaccines under development

saRNA vaccines: low doses with better immune response

saRNA:
self-amplifying mRNA

Thank you for your attention!