RCB300 - Tópicos em Biotecnologia III
08 de maio de 2024

mRNA Vaccines in Disease Prevention and Treatment

Vacinas de mRNA na prevenção e no tratamento de doenças

Bruno Correia de Oliveira (12540930)
Helena de Andrade Barbosa Guilherme (13658015)
Lorena de Oliveira Agati (13715641)

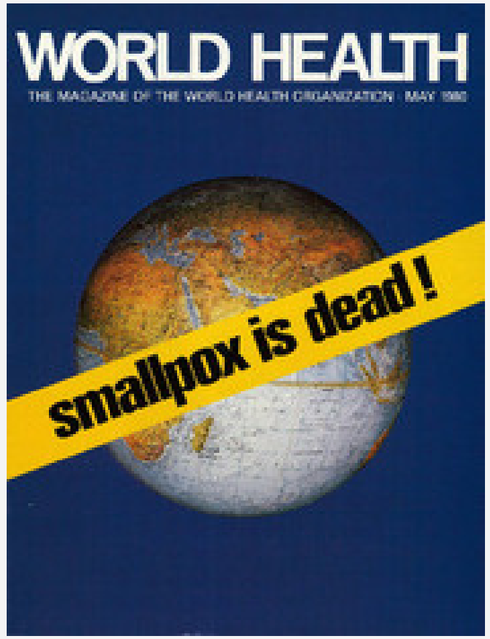
Tópicos

Helena de Andrade Barbosa Guilherme

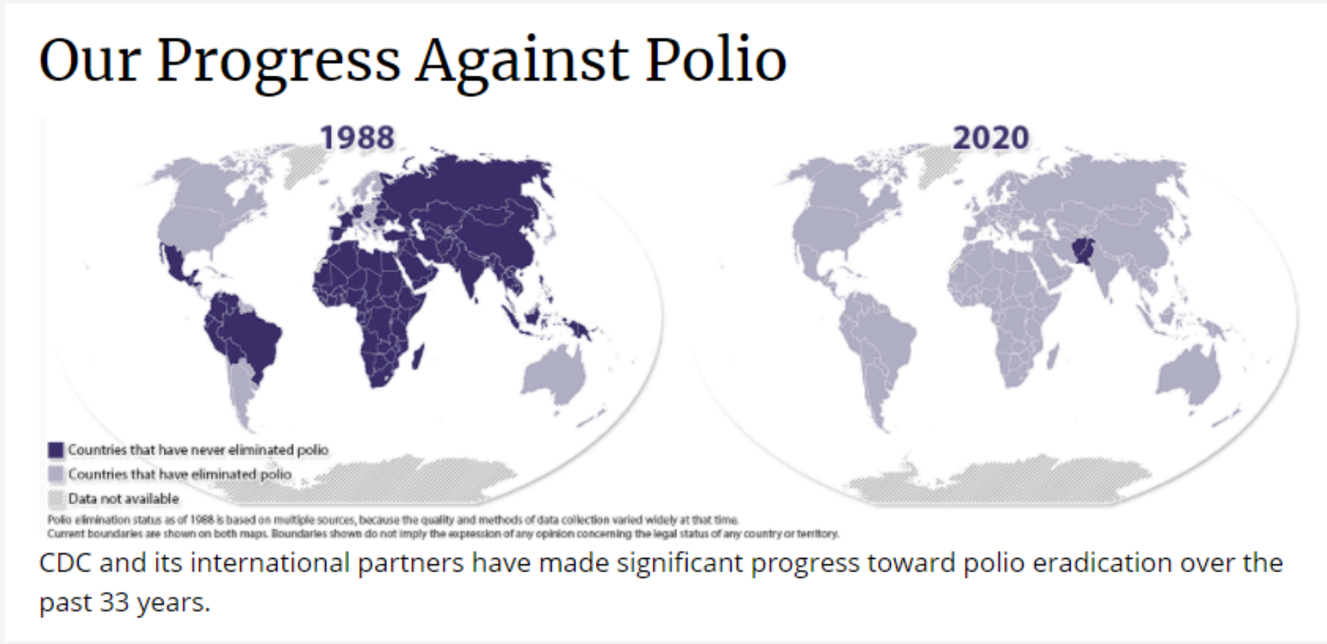
01. Introduction

Vaccines

Prevent the spread of infectious diseases ⟶ Preserve lives (2M/year)



WHO, 1980.



NIH History and Stetten Museum, 2020.

Helena

Types of vaccines

Vaccine platform	Advantages	Disadvantages
Whole inactivated virus vaccine	Stronger immune response; Safer than live attenuated virus CoronaVac	Potential epitope alteration by inactivation process
Live attenuated virus vaccine	Stronger immune response; Preservation of native antigen; Mimicking natural infection	Risk of residual virulence, especially for immunocompromised people
Viral vector vaccine	Stronger immune response; Preservation of native antigen; Mimicking natural infection Astrazeneca e Janssen	More complicated manufacturing process; Risk of genomic integration; Response dampened by pre-existing immunity against vector
Subunit vaccine	Safe and well-tolerated Novavax	Lower immunogenicity; Requirement of adjuvant or conjugate to increase immunogenicity
Viral-like particle vaccine	Safe and well-tolerated; mimicking native virus conformation	Lower immunogenicity; More complicated manufacturing process
DNA vaccine	Safe and well-tolerated; Stable under room temperature; Highly adaptable to new pathogen; Native antigen expression	Lower immunogenicity; Difficult administration route; Risk of genomic integration
RNA vaccine	Safe and well-tolerated; Highly adaptable to new pathogen; Native antigen expression Pfizer e Moderna	Lower immunogenicity; Requirement of low temperature storage and transportation; Potential risk of RNA-induced interferon response

Modified from Coronavirus vaccine development,
Yen-der Li et al, 2020.

Relevance of mRNA vaccines

Extraordinary performance in recent years against COVID-19.
Before COVID-19 erupted, a mRNA influenza vaccine was already in clinical trials.

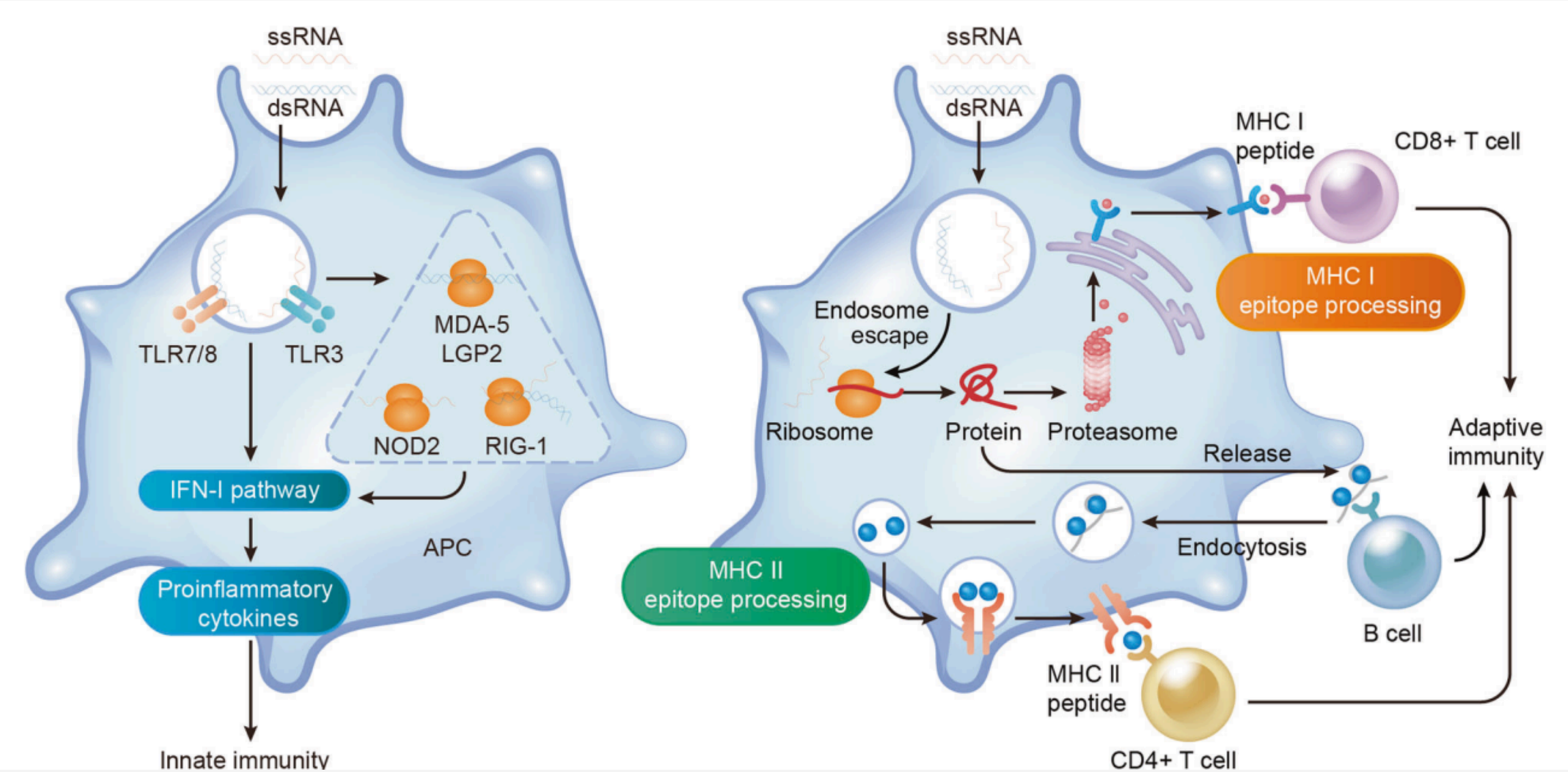
Pros

- Efficacy;
- Safety;
- Large-scale manufacture.

Cons

- Storage and transportation;
- Protective immunity is short-lasting;
- mRNA is unstable.

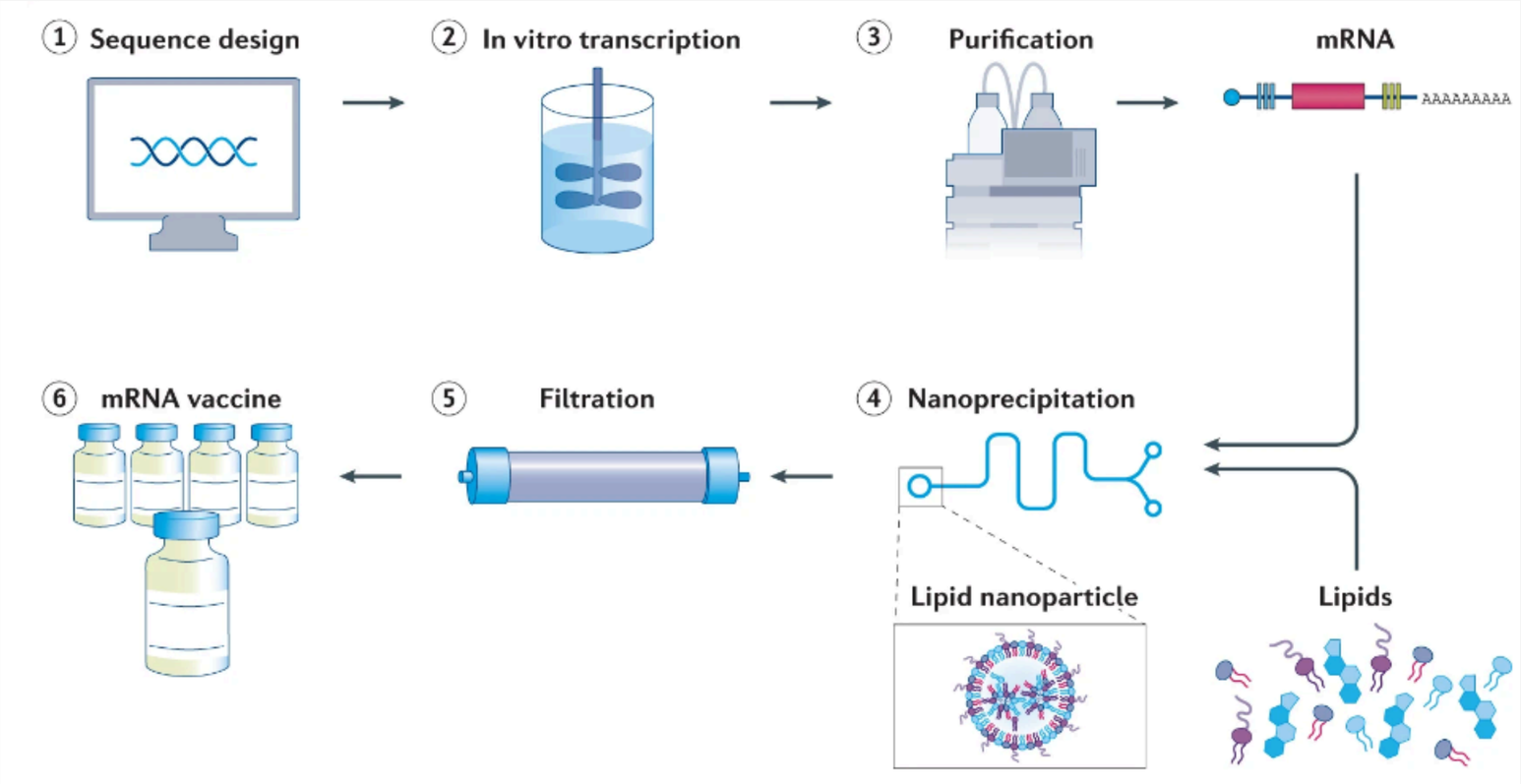
How do mRNA vaccines work?



Zhang et al, 2023.

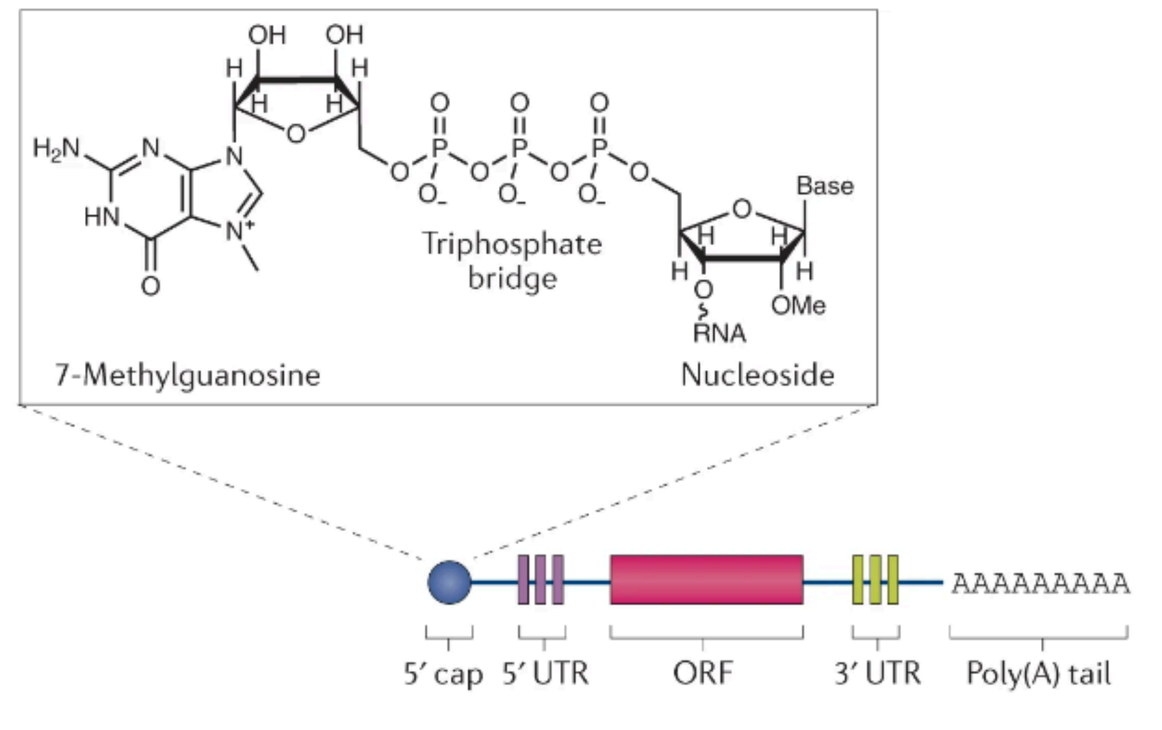
02. mRNA Vaccine Development

Pipeline



Chaudhary et al, 2021

mRNA Design

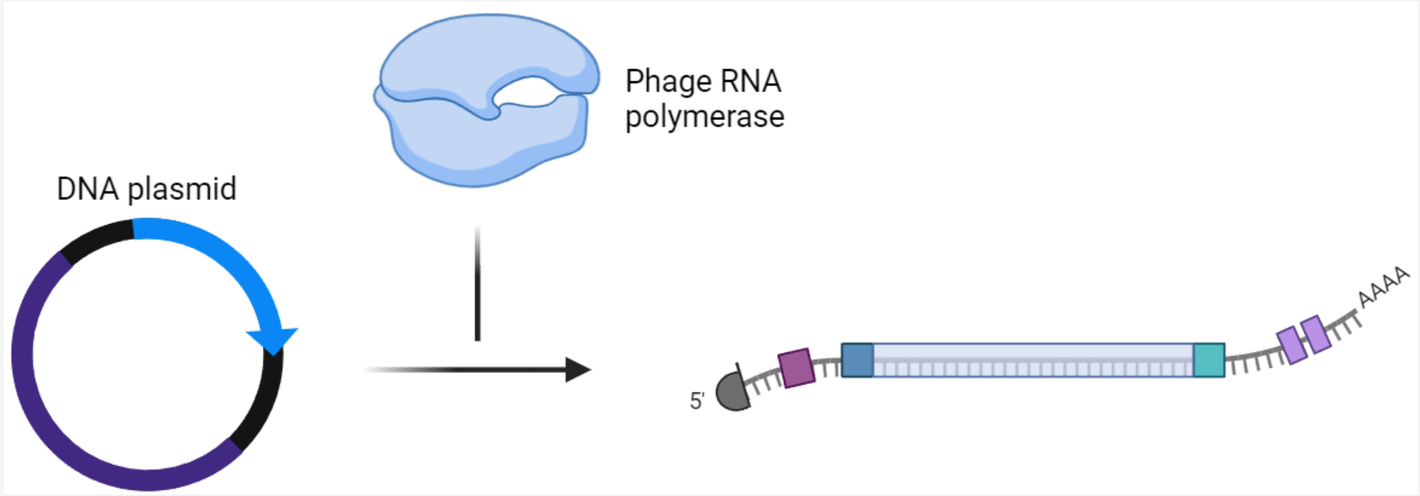


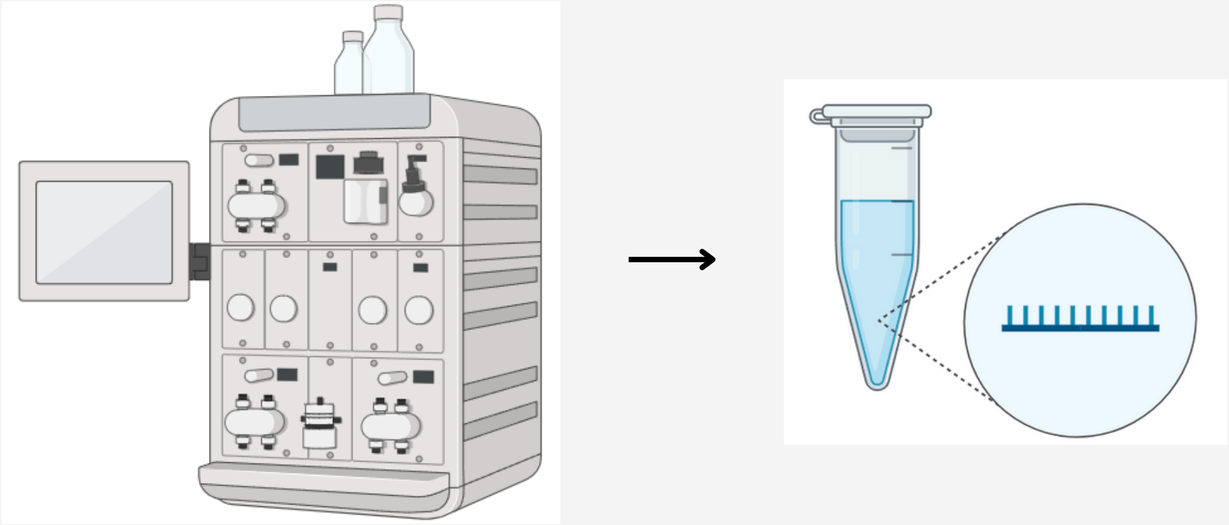
Chaudhary et al, 2021

Modifications to enhance mRNA stability and translation efficiency, such as:

- Codon Optimization
- Modified Nucleosides

Transcription and Purification

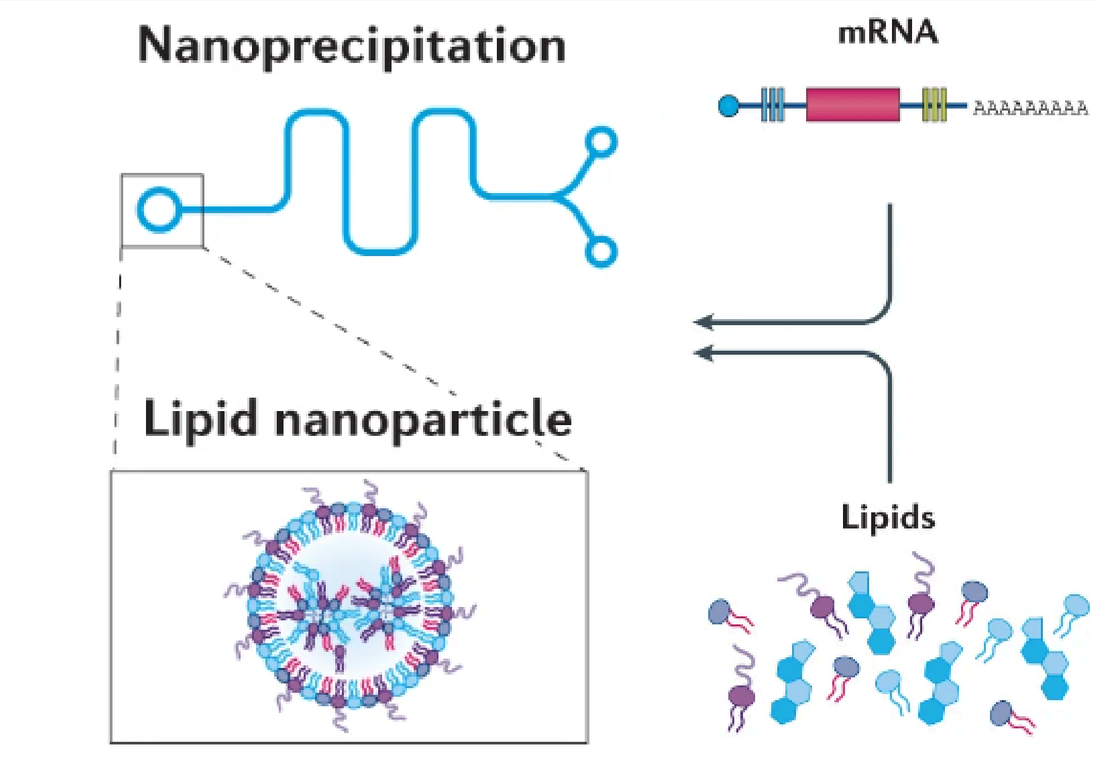




Created with BioRender, 2024.

Delivery system

To overcome destabilization and degradation



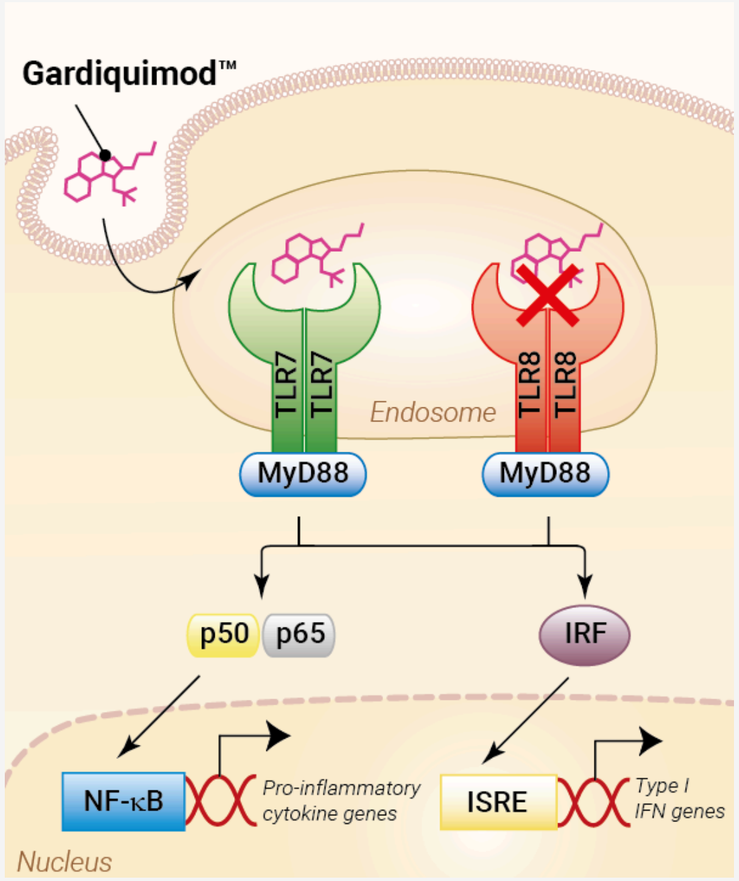
Chaudhary et al, 2021

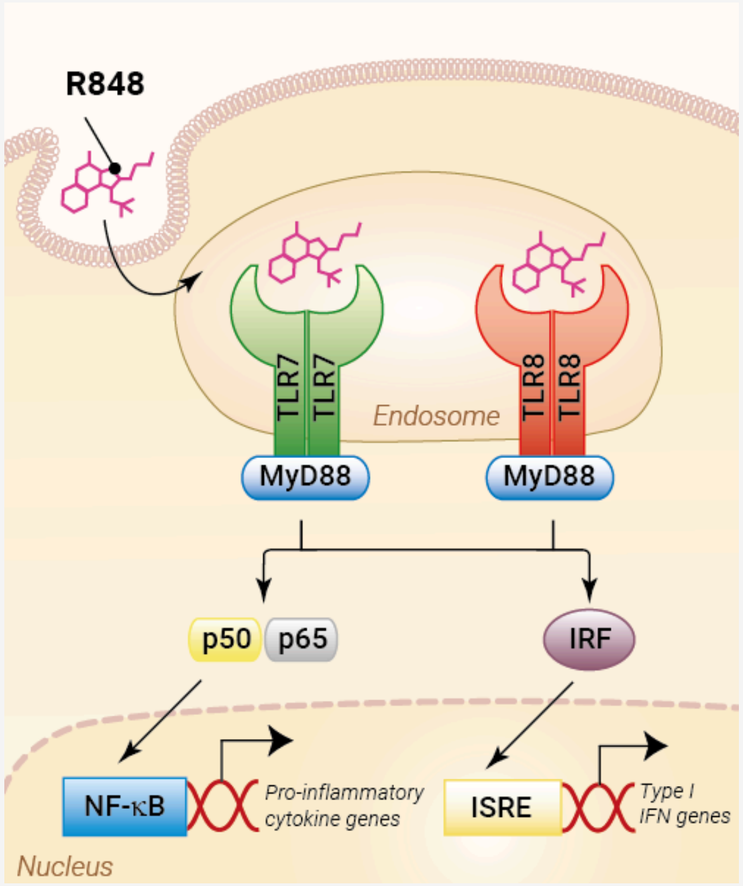
Can be modified to:

- Reduce toxicity;
- Facilitate delivery and endossomal release.

Adjuvants

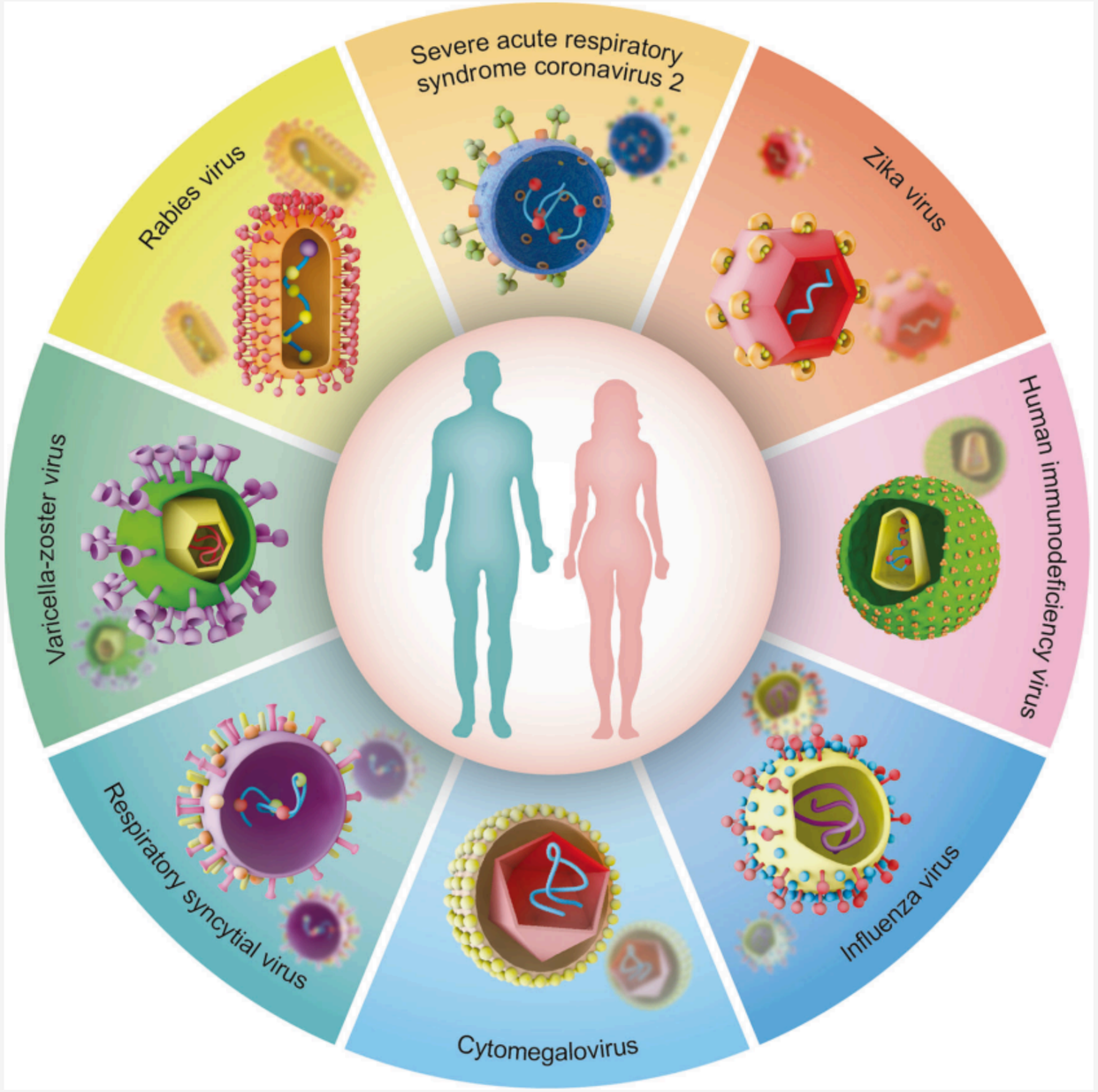
To help boost the body’s response to the vaccine





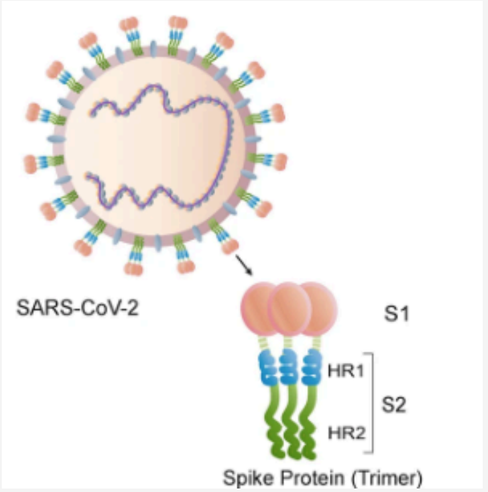
InVivoGen

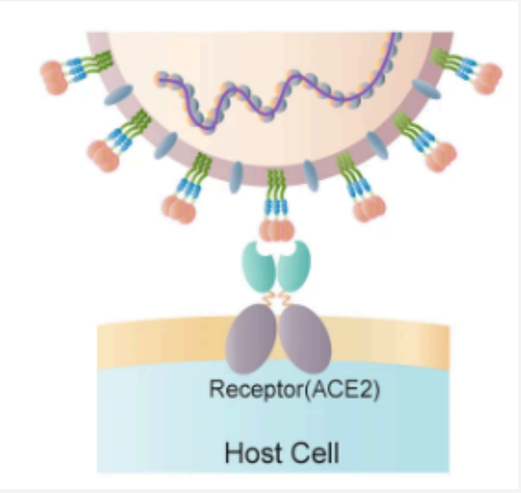
03. mRNA Vaccines in Infectious Diseases



Zhang et al, 2023.

mRNA vaccines against COVID-19





Huang et al, 2020.

BNT162b2 (Pfizer)

- Spike S-2P;
- Ionizable lipid (ALC-0315);
- Efficacy: 95%.

mRNA-1273 (Moderna)

- Spike S-2P;
- Ionizable lipid (SM-102);
- Efficacy: 94,1%.

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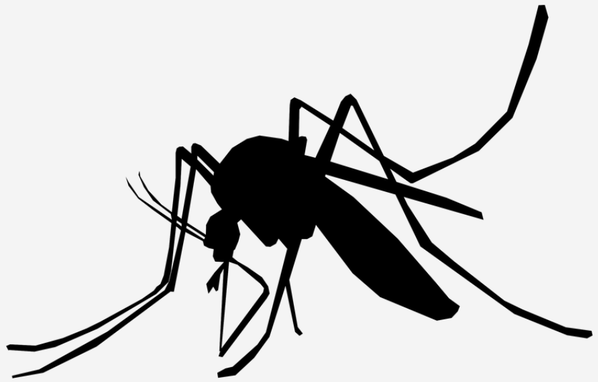
mRNA vaccines against Zika virus



- Membrane and envelope proteins are common antigens for mRNA vaccines against ZIKV.

2017

LNP-enclosed mRNA vaccine

LNP-enclosed mRNA vaccine
original type + variant glycoproteins

IgG + T CD4+

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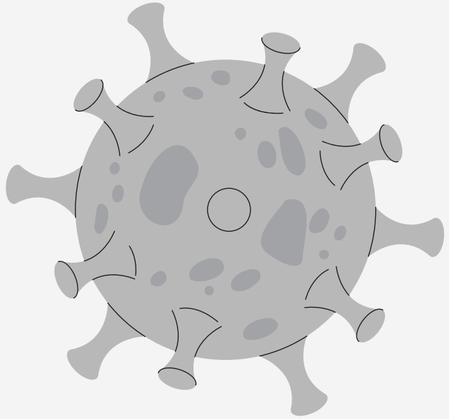
mRNA vaccines against HIV



- There is no effective preventive vaccine, due to the antigenic diversity of the protein found in the HIV viral envelope.

2016
mRNA-transfected autologous DCs

T CD4+ **IFN-γ** **T CD8+**

2017
conserved targets of antiviral T-cell responses

✗

2020
HIV Env proteins + SIV Gag proteins

Neutralizing antibodies **T CD4+**

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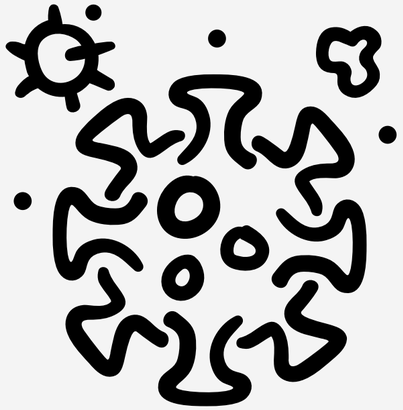
mRNA vaccines against influenza virus



- The typical target of the mRNA vaccine is the glycoprotein haemagglutinin (HA).

2012

mRNA vaccine against influenza (PR8HA)

T CD8+
Neutralizing antibodies
Immunological memory

2021

LNP-encapsulated mRNA encoding HA or NA

Antibody and cellular immune responses

2022

Multivalent nucleoside-modified mRNA vaccine

Reactivity against 20 encoded antigens

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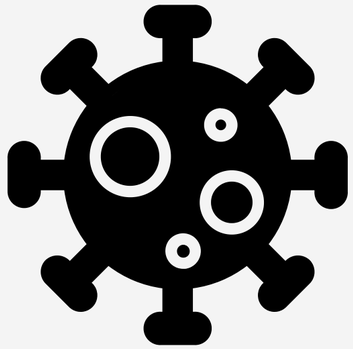
mRNA vaccines against RSV



- The typical target of the mRNA vaccine is the fusion protein (F protein).

2020

mRNA vaccines encoding RSV F proteins with different conformations (mRNA-1345)

Neutralizing antibody
T-cell response

2023

Moderna - mRNA vaccine that encodes F protein stabilized in the prefusion conformation (mRNA-1777)

Neutralizing antibodies
T CD4+

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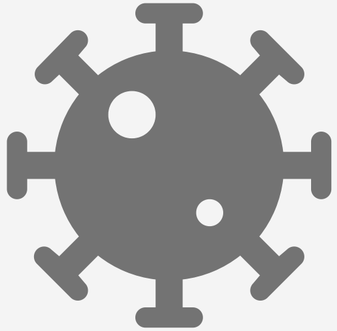
mRNA vaccines against VZV



2020

LNP-enclosed mRNA vaccine encoding the VZV gE antigen

Potent humoral and cellular immunity

×

Vaccines approved on the market: live attenuated virus + subunit protein.

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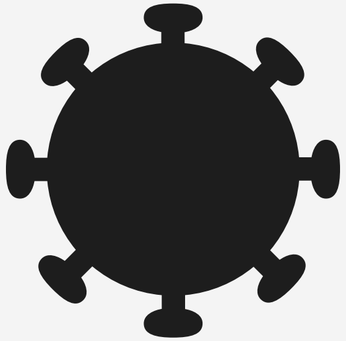
mRNA vaccines against rabies virus



- The typical target of the mRNA vaccine is the surface glycoprotein RABV-G

2016

vaccine composed of mRNA encoding RABV-G

Neutralizing antibodies
T CD4+

2017

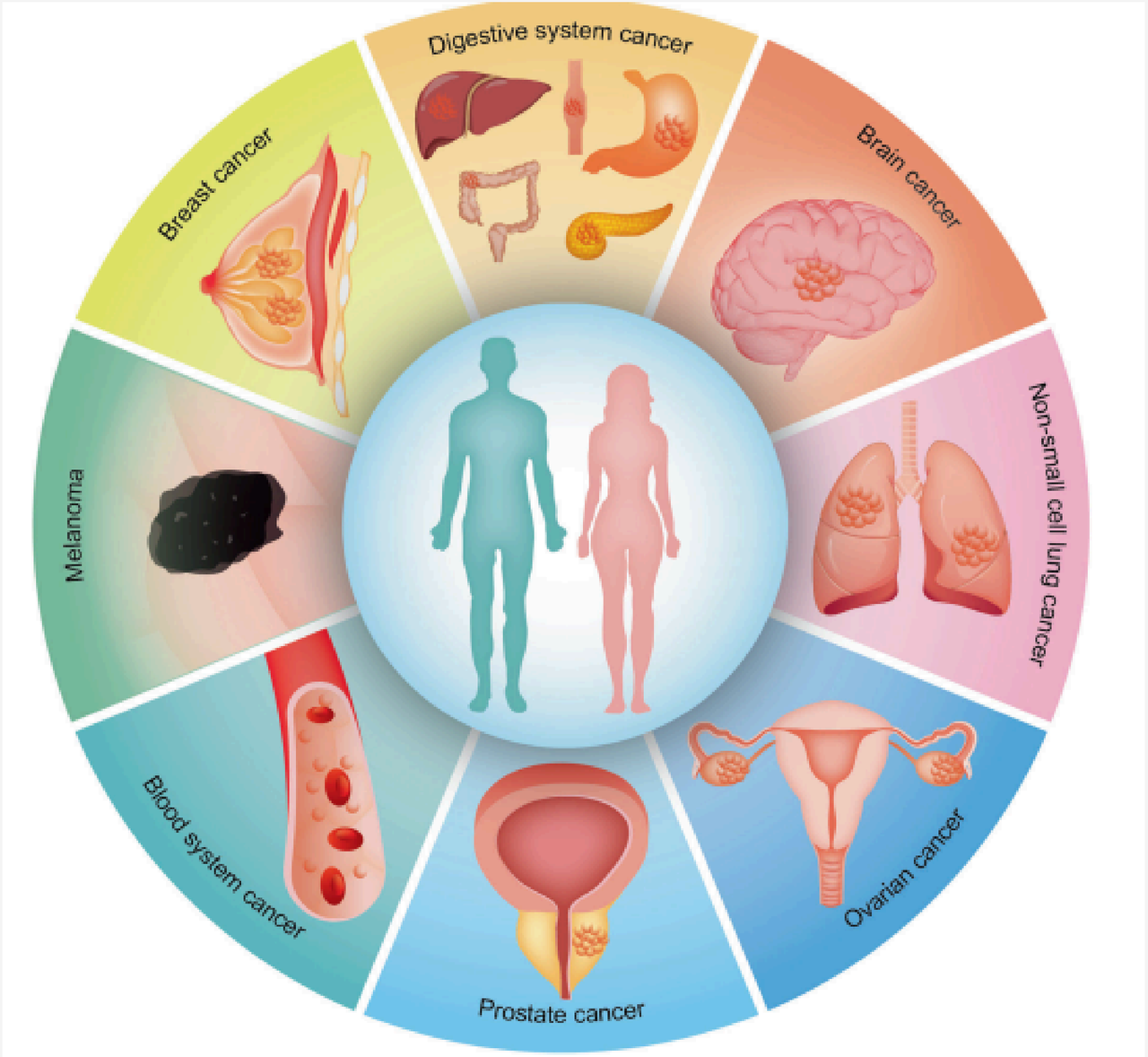
first phase I clinical study using the mRNA rabies vaccine (CV7201.140)

IgM e IgG
T CD4+

04. mRNA Vaccines in Cancers

mRNA Vaccines in Cancers

- Usually applied in a therapeutic setting;
- Designed to encode tumor associated antigens (TAAs) or neoantigens to activate antitumour immune responses



Zhang et al, 2023.

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mRNA vaccines against melanoma

- Diverse DC-based mRNA vaccines have been tested in melanoma patients;
- Antigens targets for mRNA vaccine: MAGE-A3, MAGE-A2, gp100, and tyrosinase;
- Immunological adjuvants are used to stimulate and amplify the immune responses;
  - TriMix
- 2015 ➔ BNT111 is a liposomal RNA vaccine encoding four TAAs;
- GenenTech and BioNTech ➔ personalized lipid-encapsulated mRNA vaccines;
- mRNA vaccines + other therapeutic strategies may further enhance their effectiveness and promote their potential for approval.

mRNA vaccines against brain cancer

DC-pulsed tumor mRNA

- Autologous tumor mRNA-loaded DCs
- Specific CD8+ cytotoxic T-cell response
- pp65 encoding -> increased pp65-specific interferon-γ levels were correlated with overall survival.

mRNA vaccines against non-small cell lung cancer

CV9201 - MAGE-C1, MAGE-C2, NY-ESO-1, 5T4 and survivin

- moderate reaction
- twofold activated IgD+CD38hi B cells

CV9202 - MAGE-C1, MAGE-C2, NY-ESO-1, 5T4, survivin and mucin-1

- Moderate reaction
- Twofold increase in functional CD8+/CD4+ T cells

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mRNA vaccines against ovarian cancer

DC-pulsed mRNA vaccine encoding folate-receptor-α (FR-α)

- The vaccination was well tolerated
- Regression of over 50% of the lymph-node metastases, and consistently, the vaccinations induced an FR-α-specific immune response

DC-pulsed mRNA vaccine encoding WT1

- Induced increased CD137+ antigen-specific T cells, IL-2, and IFN-γ in ovarian carcinoma and CD137+ antigen-specific T cells, IL-2, and TNF-α in ovarian carcinosarcoma

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mRNA vaccines against prostate cancer

"Islam et al. developed an **adjuvant-pulsed mRNA vaccine nanoparticle** containing an **ovalbumin-coded mRNA** and a palmitic acid-modified **TLR7/8 agonist** R848 (C16-R848) **encapsulated with a lipid-polyethylene glycol shell**"

CV9103 encodes four TAAs in prostate cancer: PSA, PSMA, PSCA, and STEAP, and it is the first-in-human tested mRNA vaccine

- notable improvement in mRNA transfection efficacy, with a rate exceeding 95%
- 60% reduction of tumor vs. control
- The most frequent adverse events were a reaction at the injection site or flu-like symptoms

CV9104 -> two additional antugens, PAP and mucin-1

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mRNA vaccines against blood system cancer

“Hematological malignancies encompass a range of diseases involving the abnormal proliferation of hematopoietic stem cells, including **leukemia, myeloma, and lymphoma**”

Acute myeloid leukemia (AML)

- autologous DC-pulsed mRNA vaccine encoding WT1
- Well tolerated by all patients
- Khoury et al. also investigated a DC-pulsed mRNA vaccine encoding hTERT

mRNA vaccines in other human blood system cancers
are principally in the preclinical phase

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mRNA vaccines against digestive system cancer

DC-pulsed tumor mRNA

- MAGE-A4, NY-ESO1 e LAGE1

“Altogether, although clinical trials using mRNA vaccines to combat digestive system cancer are limited, some effectiveness was shown in a fraction of patients”

mRNA vaccines against breast cancer

BioNTech AG launched The Mutanome Engineered RNA Immuno-Therapy project

mRNA WAREHOUSE vaccine

- personalized 20 unique neoepitopes identified by next-generation sequencing
- more trials are needed to promote them in clinical practice.

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05. Other uses

mRNA vaccines in immunological diseases

Autoimmune diseases -> chronic inflammation due to a dysregulated immune response to self-antigens

- mouse models
- Krienke et al. introduced a liposomal formulation that systemically delivers antigens encoded by the mRNA vaccine into lymphoid tissue
- **anti-inflammatory responses were enhanced**

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mRNA vaccines in immunological diseases

Allergy -> hypersensitivity reaction of the immune system to a foreign substance that is typically harmless to most individuals

mRNA vaccines

- mouse models
- anti-inflammatory responses were enhanced
- long-term memory responses

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mRNA vaccines in tissue damage

Tissue damage refers to any physical injury or harm that occurs to the body's tissues.

mRNA vaccines have shown effectiveness in multiple soft tissue damages

- Treatment of irreversible cardiovascular diseases -> AZD860

Liver regeneration, growth of lymphatic vessels, bone regeneration, calvarian defects -> mRNA vaccines show promising potential in the promotion of tissue generation

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mRNA vaccines in rare diseases

Rare diseases -> medical conditions that impact a small proportion of the population, characterized by their low prevalence and often limited understanding due to their rarity

Cystic fibrosis, Inherited metabolic disorders -> lack of therapeutic agents that can cure these rare diseases

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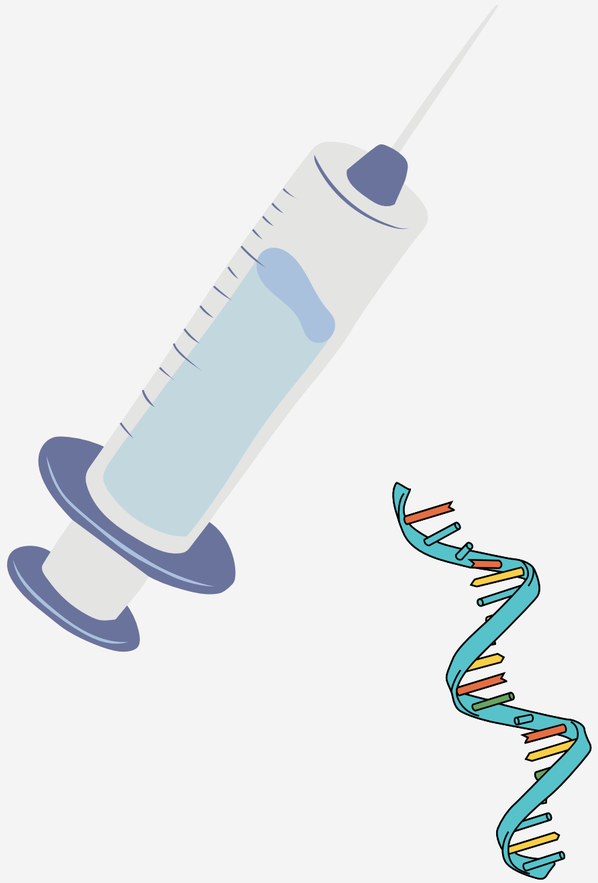
06. Conclusion and perspectives

Conclusions and perspectives

- Importance of the vaccine for the world
- Importance of the discovery of the mRNA vaccine
- mRNA vaccines have become a hotspot in disease prevention and treatment, becoming predominant in preclinical and clinical trials, especially in infectious diseases and cancers



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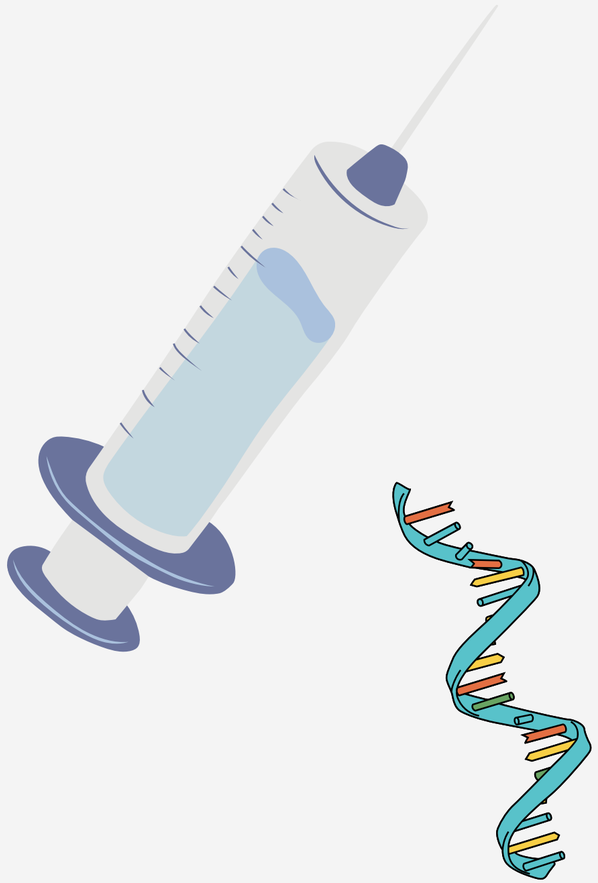
Conclusions and perspectives

- Difficulty in clinical approval

- The adjuvant effect of mRNA vaccines promotes innate and adaptive immunity, but excessive innate immunity inhibits mRNA translation.

- Security and production



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THANK YOU!

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