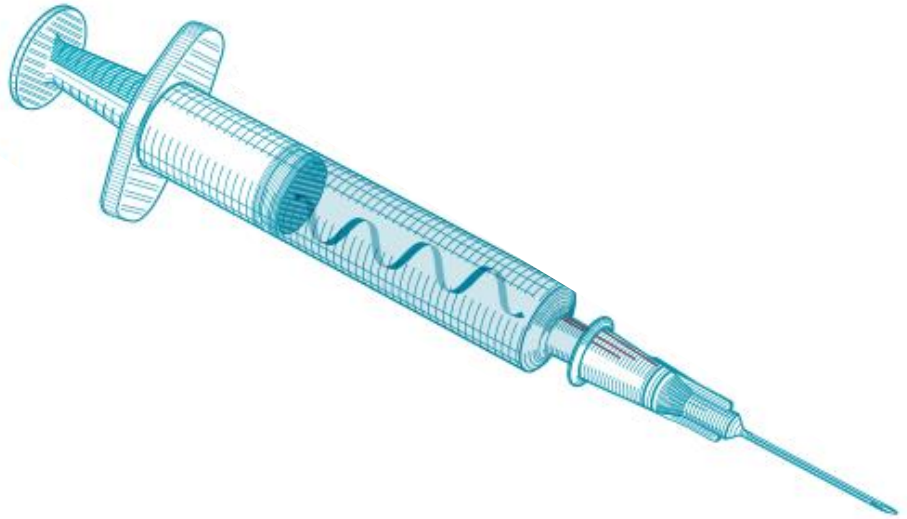
In the name of Allah



mRNA Cancer Vaccine

By

Elham Babaeinia

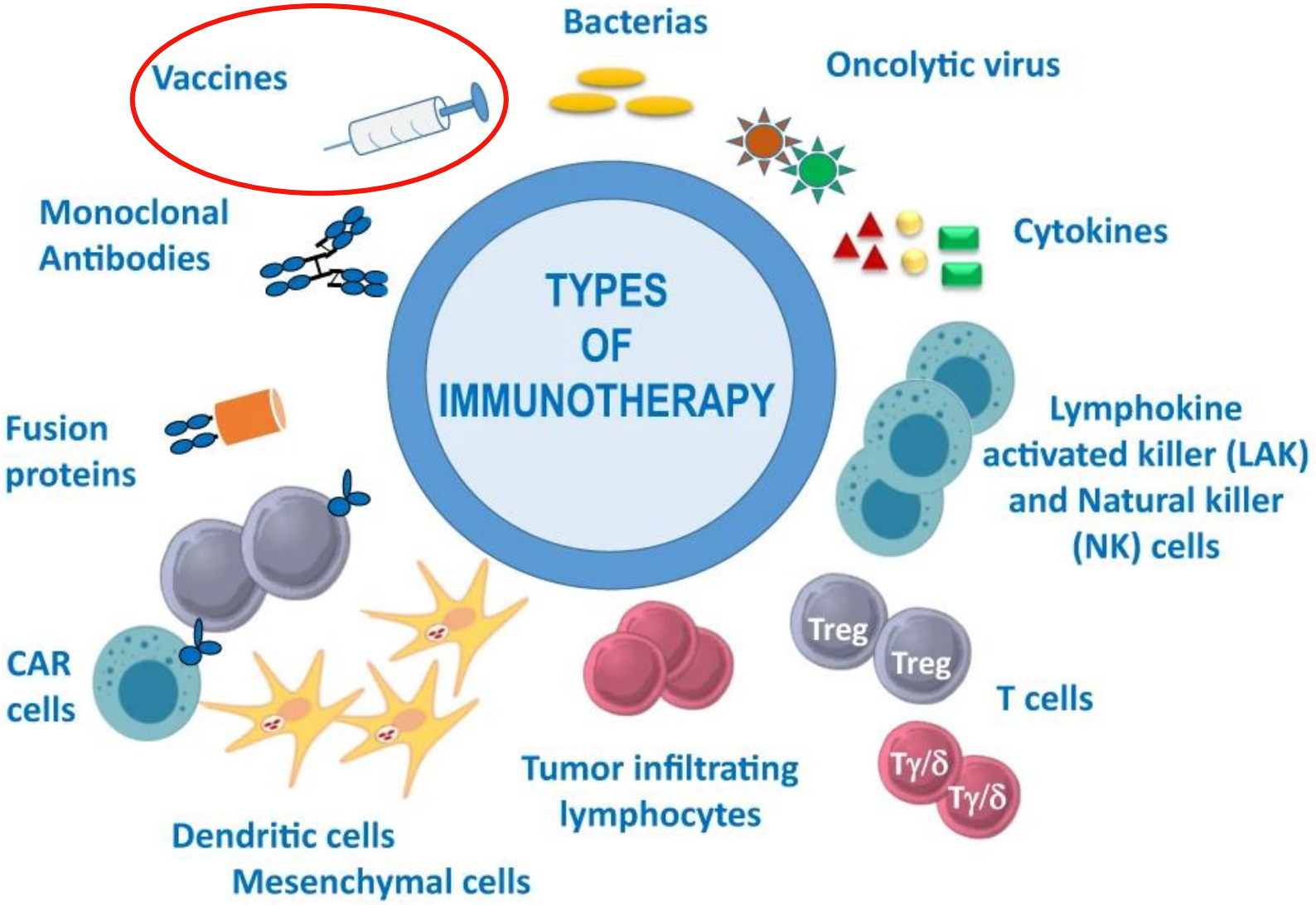
PhD Student of Medical Immunology

November 2023

Introduction

- Cancer is a leading cause of death worldwide.
- The **lack of effective cancer treatments** is the main reason for high mortality among cancer patients.
- Cancer treatment has progressed from surgical resection, radiation therapy and chemotherapy to **immunotherapy**.

Introduction



Varadé et al. Cellular & Molecular Immunology **2020**

Cancer Vaccine

- Cancer vaccines are an attractive alternative immunotherapeutic option with both prophylactic and therapeutic potentials.

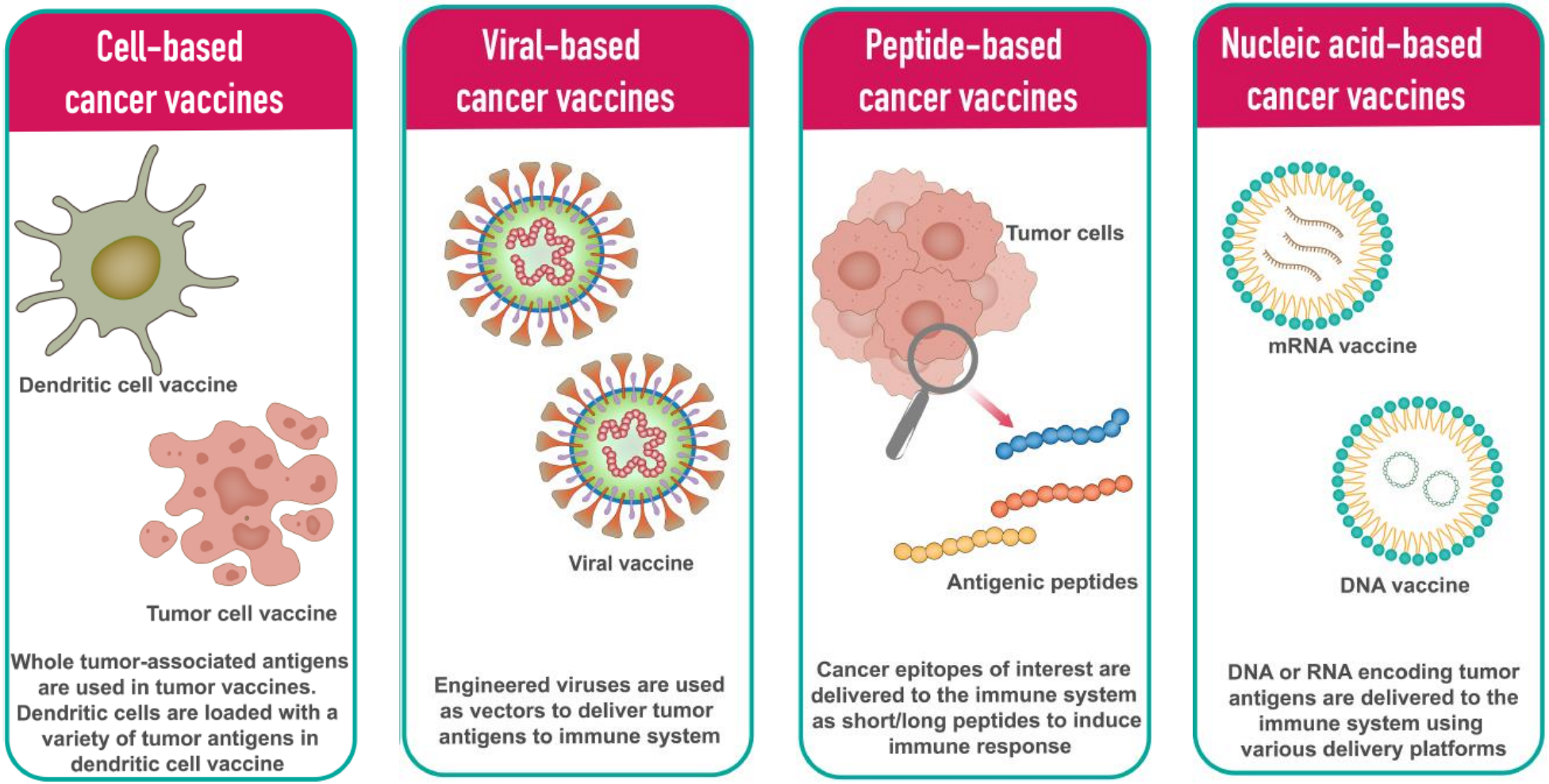
Despite considerable efforts to develop cancer vaccines, clinical translations of cancer vaccines into efficacious therapies have remained challenging for decades mostly due to highly variate tumor antigens and relevantly low immune response.

compared to other immunotherapies.

Cancer Vaccines

- FDA approved Cancer vaccin:
  - ✓Preventive or prophylactic strategy
    - ❖HPV preventive vaccine ….. Hepatocellular Carcinoma
    - ❖HBV preventive vaccine …… Cervical Cancer
  - ✓ Therapeutic strategy
    - ❖Bacillus Calmette-Guérin (BCG) ….. Early-stage bladder cancer
    - ❖Sipuleucel-T (Provenge) …… Prostate cancer

Cancer vaccine platform types



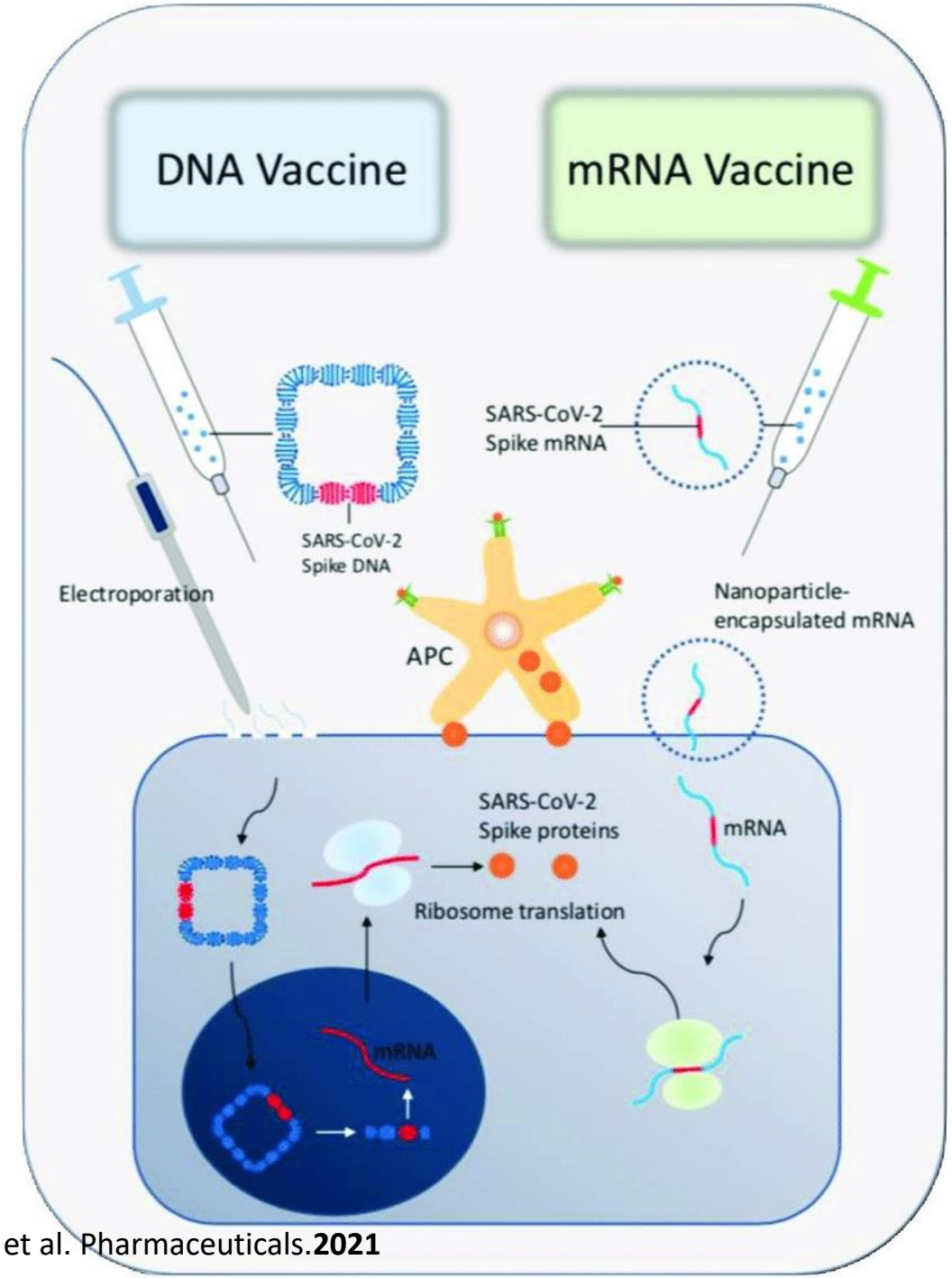
Vishweshwaraiah et al. fimmu **2022**

Advantages Of Nucleic Acid Based Cancer Vaccine

- 1- Nucleic acid vaccines allow **simultaneous** delivery of **multiple antigens** covering various TAAs or TSAs.

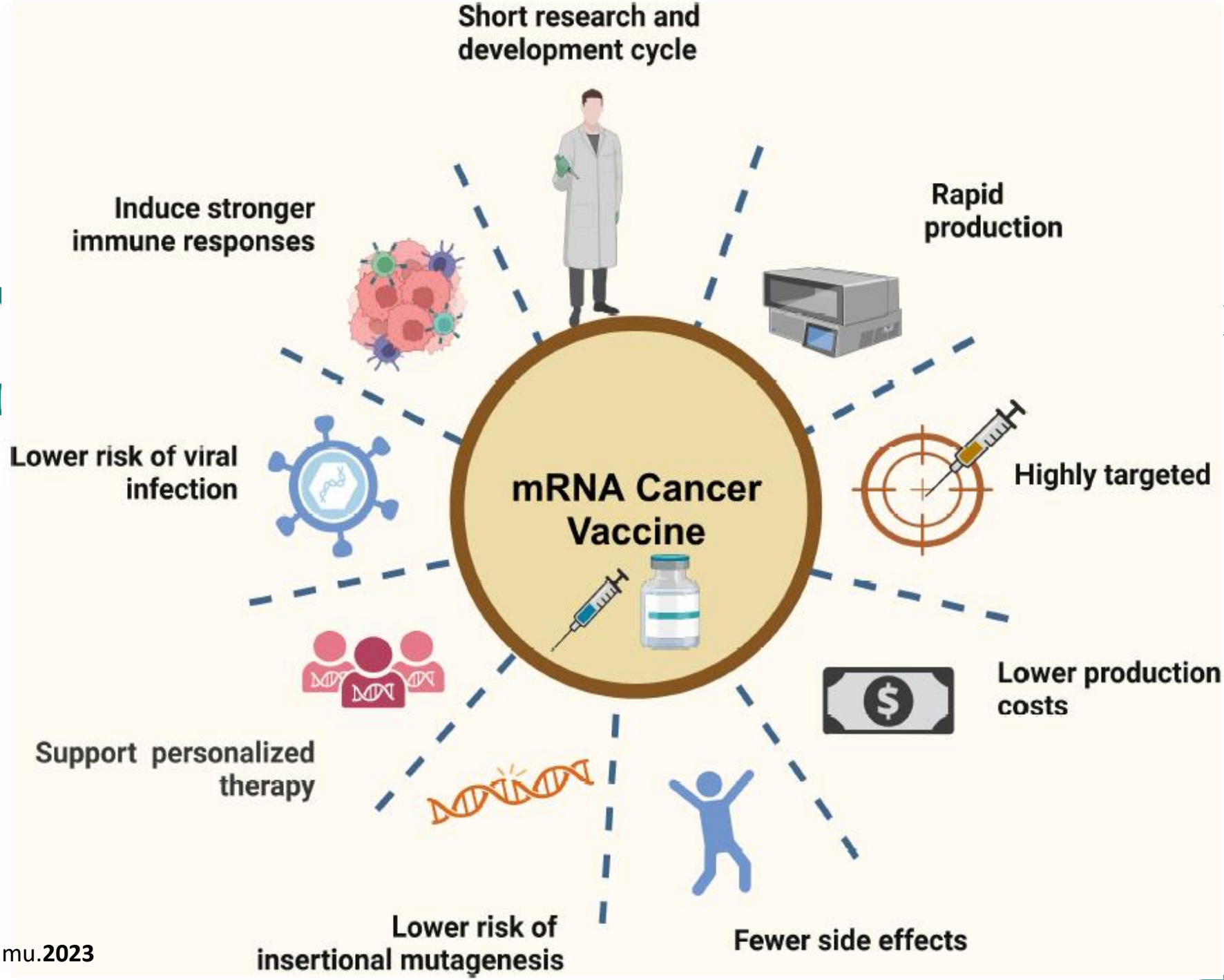
- 2- Unlike peptide vaccines, nucleic acid vaccines can encode **full length** tumor antigens.

- 3- It proposed that nucleic acid vaccines are **non-infectious**, **free of protein or virus-derived contaminations** during production.



Yan et al. Pharmaceuticals.**2021**

It seems that mRNA vaccine is an appealing alternative to DNA vaccine for infectious disease preventions and anti-cancer treatments.

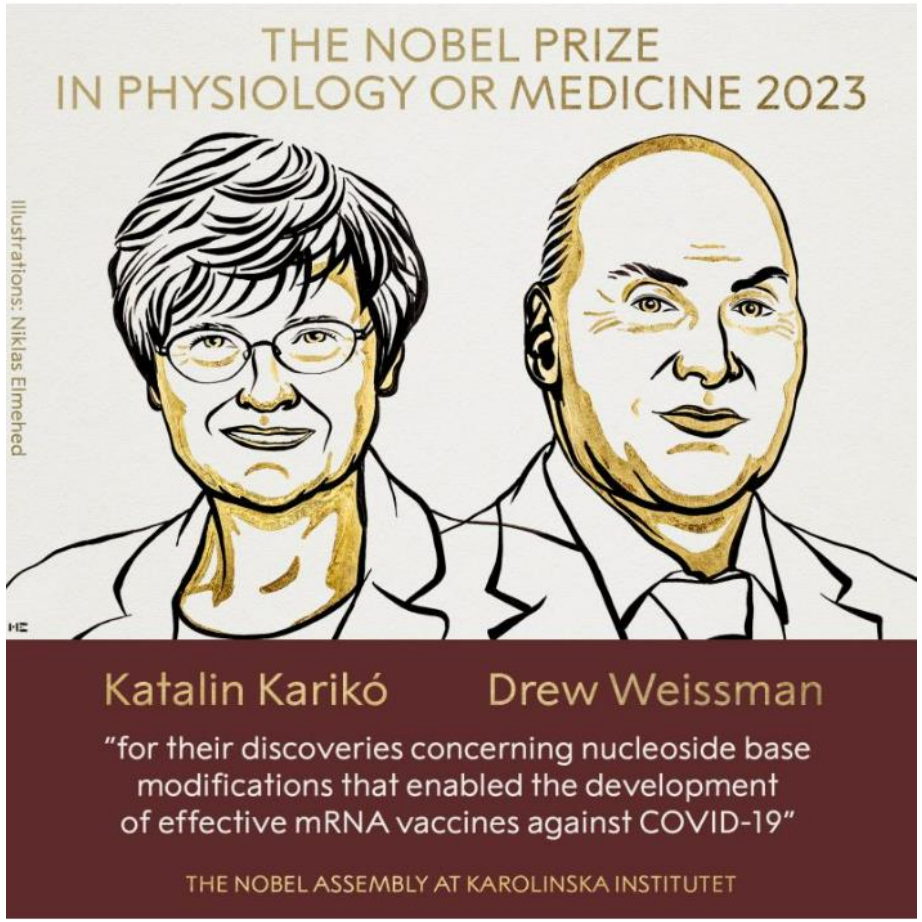


Wang et al. fimmu.**2023**

mRNA Vaccine disadvantages

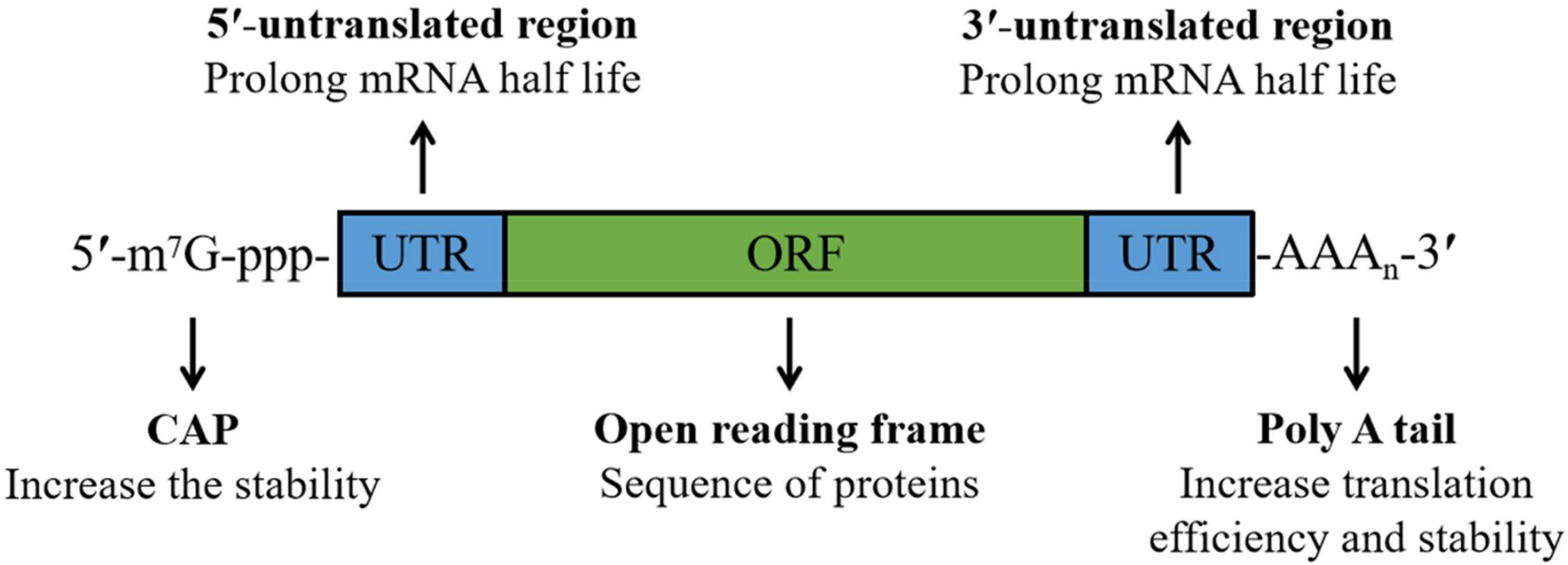
- Despite these promising advantages, the development of mRNA vaccines initially faced **several limitations**:
  - **Instability**
  - **Possible innate immunogenicity**
  - **Inefficient in vivo transportation**

- With the U.S. FDA's approval of two mRNA-based vaccines from Pfizer-BioNTech and Moderna for use in COVID-19 prevention, the mRNA vaccine field will attract widespread interest in both cancer and infectious disease applications.

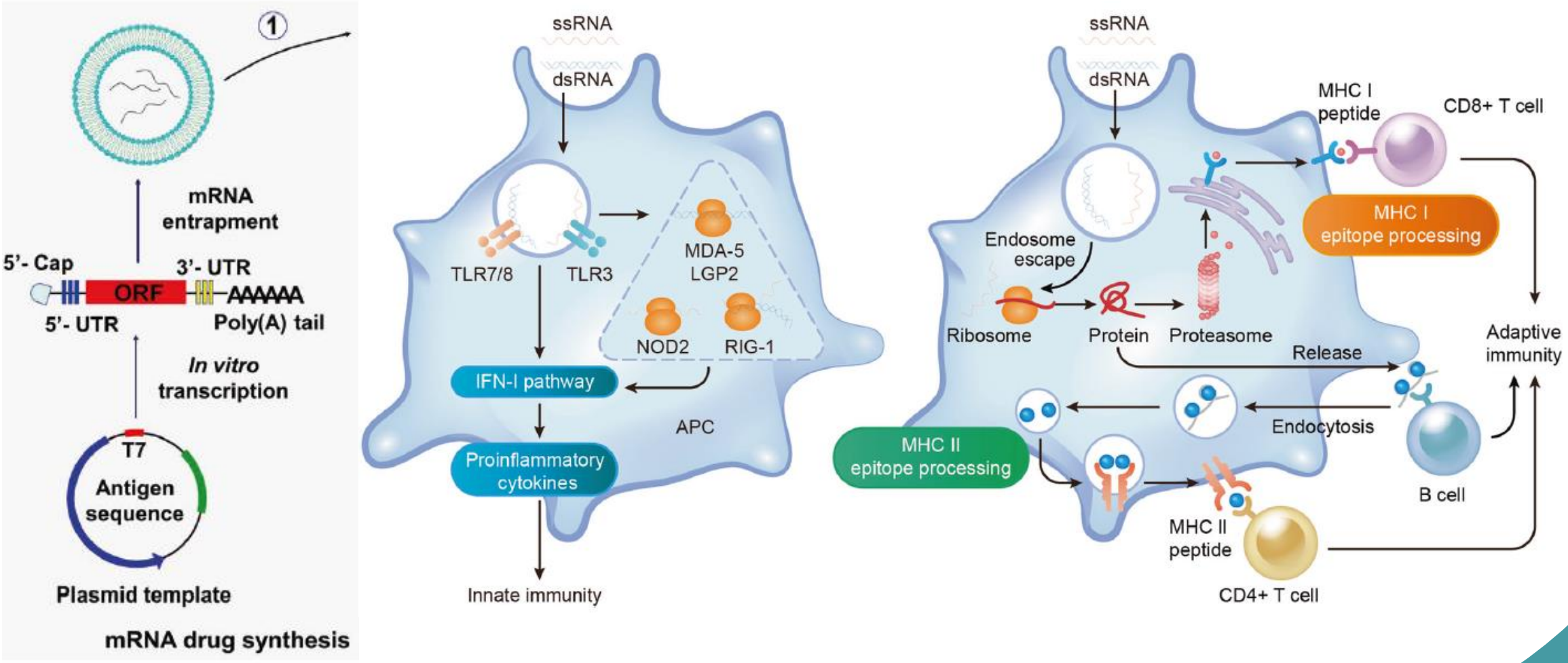


mRNA Structure

- The typical mRNA consists of:

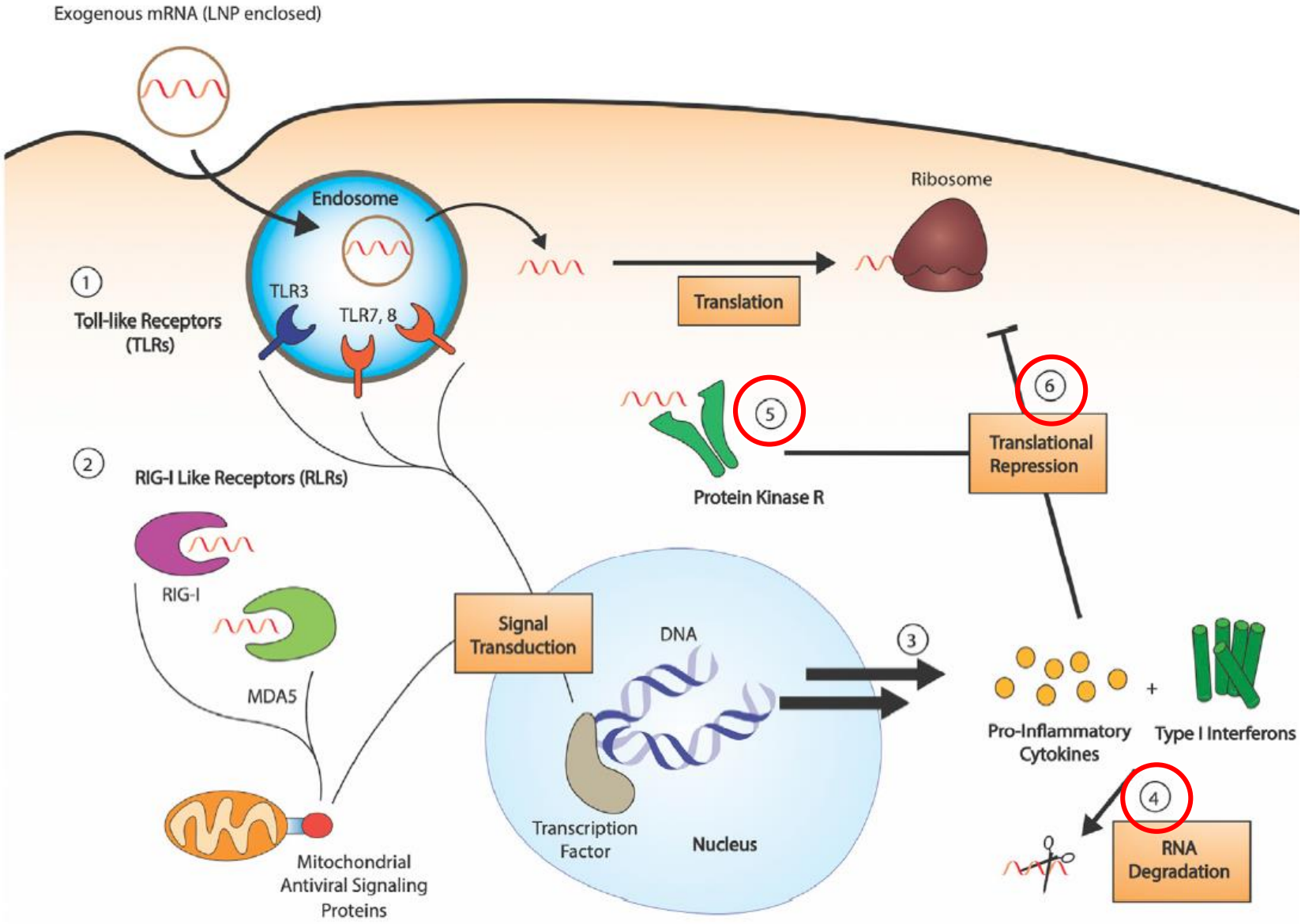


Principle of mRNA Vaccine Synthesis and immunity



Qin et al, Zhang et al. Signal Transduction and Targeted Therapy. **2022, 2023**

RNA sensing by the innate immune system



Frontiers in Cell and Developmental Biology. **2022**

Modulating immunogenicity of mRNA

- Effective methods to reduce the immunogenicity of mRNAs:
  - Incorporation of Modified nucleotides
  - Adding poly (A) tails
  - Improving mRNA purification

1- Modifying nucleotides chemically

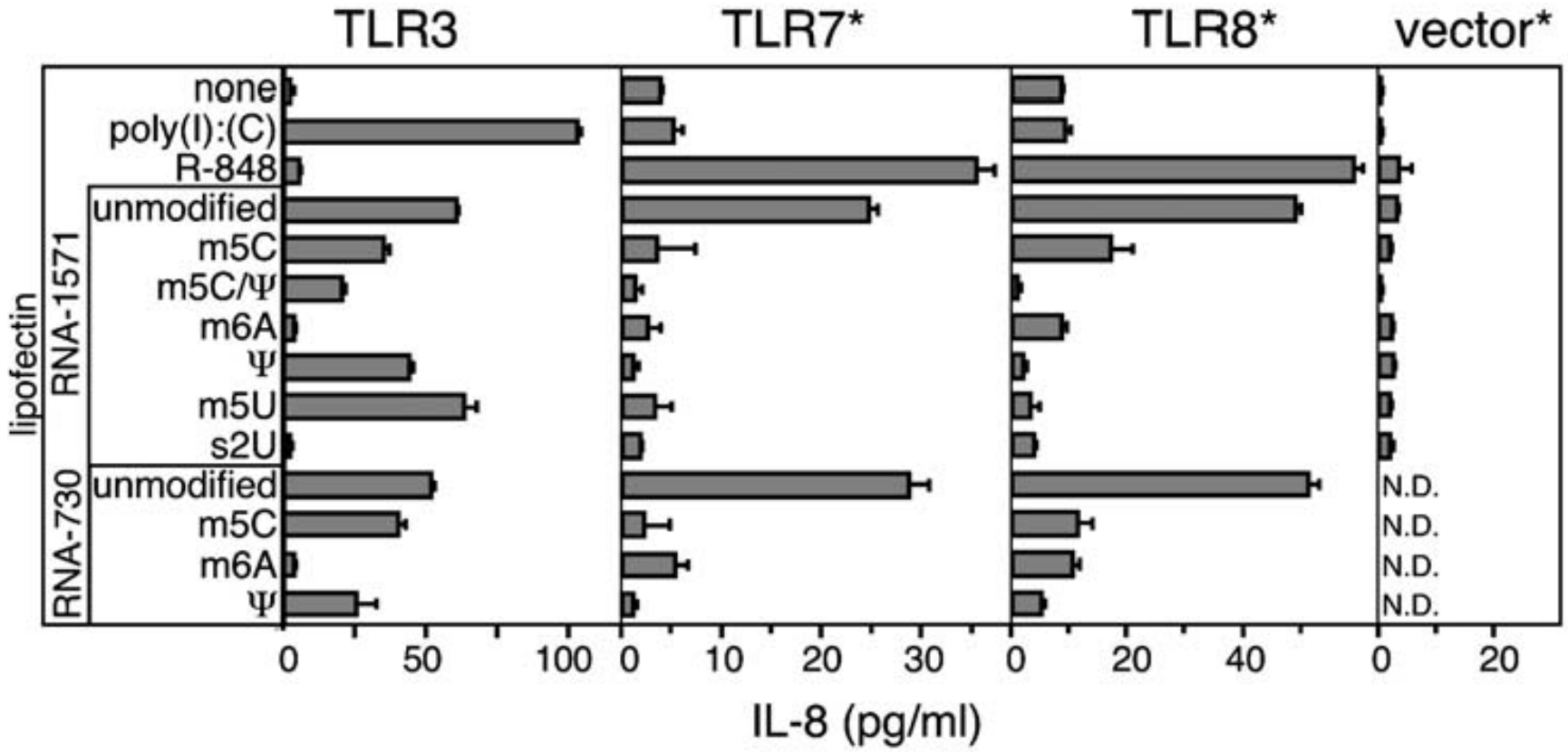
Cytidine	5-methylcytidine (m5C)
Uridine	5-methyluridine (m5U)
	pseudouridine (ψ)
	N1-methylpseudouridine (m1ψ)
	2-thiouridine (s2U)
	5-methoxyuridine (5moU)
Adenosine	N1-methyladenosine (m1A)
	N6-methyladenosine (m6A)

Immunity

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

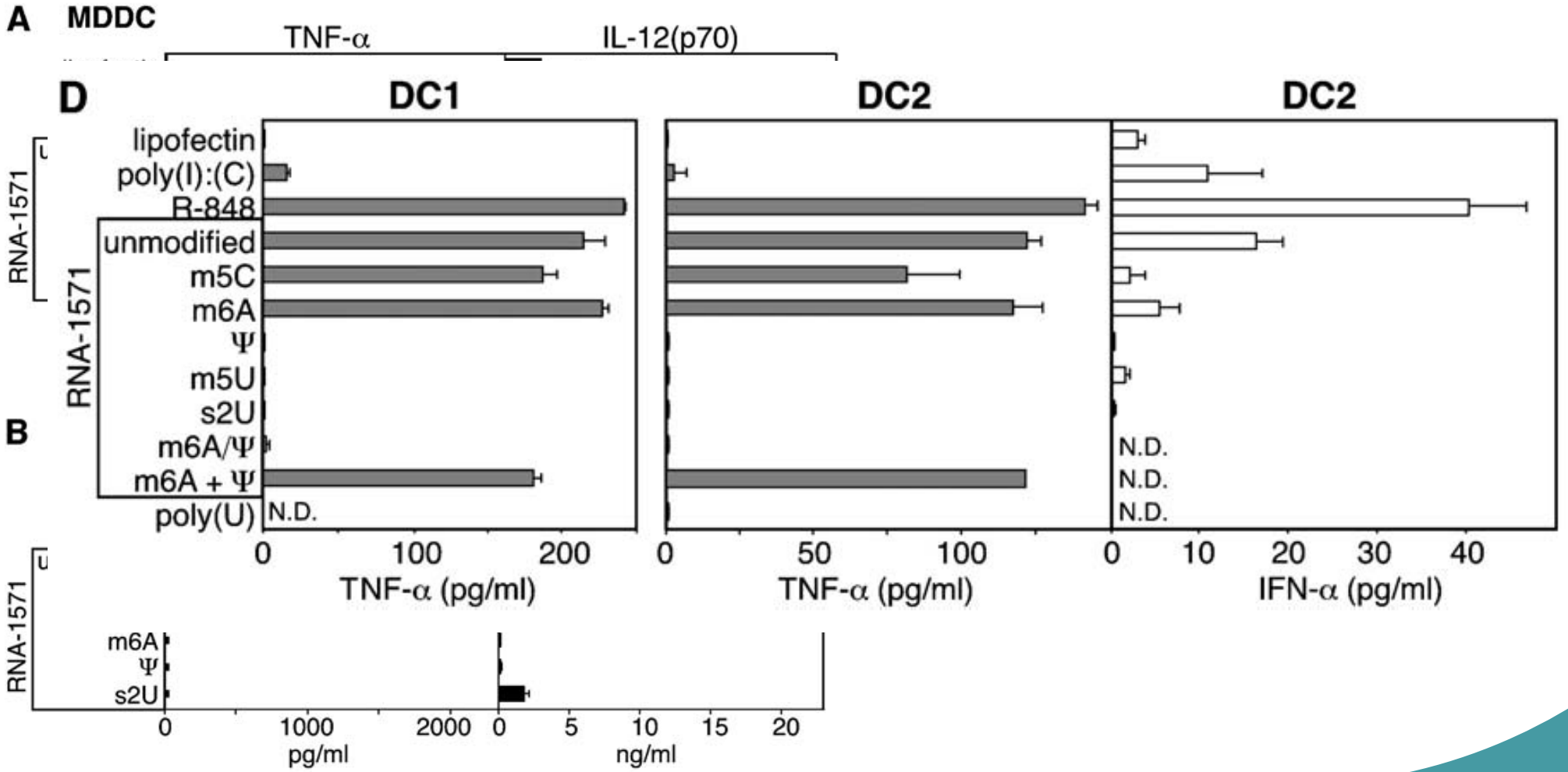
Katalin Karikó,[1,*] Michael Buckstein,[2] Houping Ni,[2] and Drew Weissman[2]

- In Vitro-Transcribed RNA Stimulates Human TLR3, TLR7, and TLR8, but Most of the Nucleoside to stimulate MDDCs



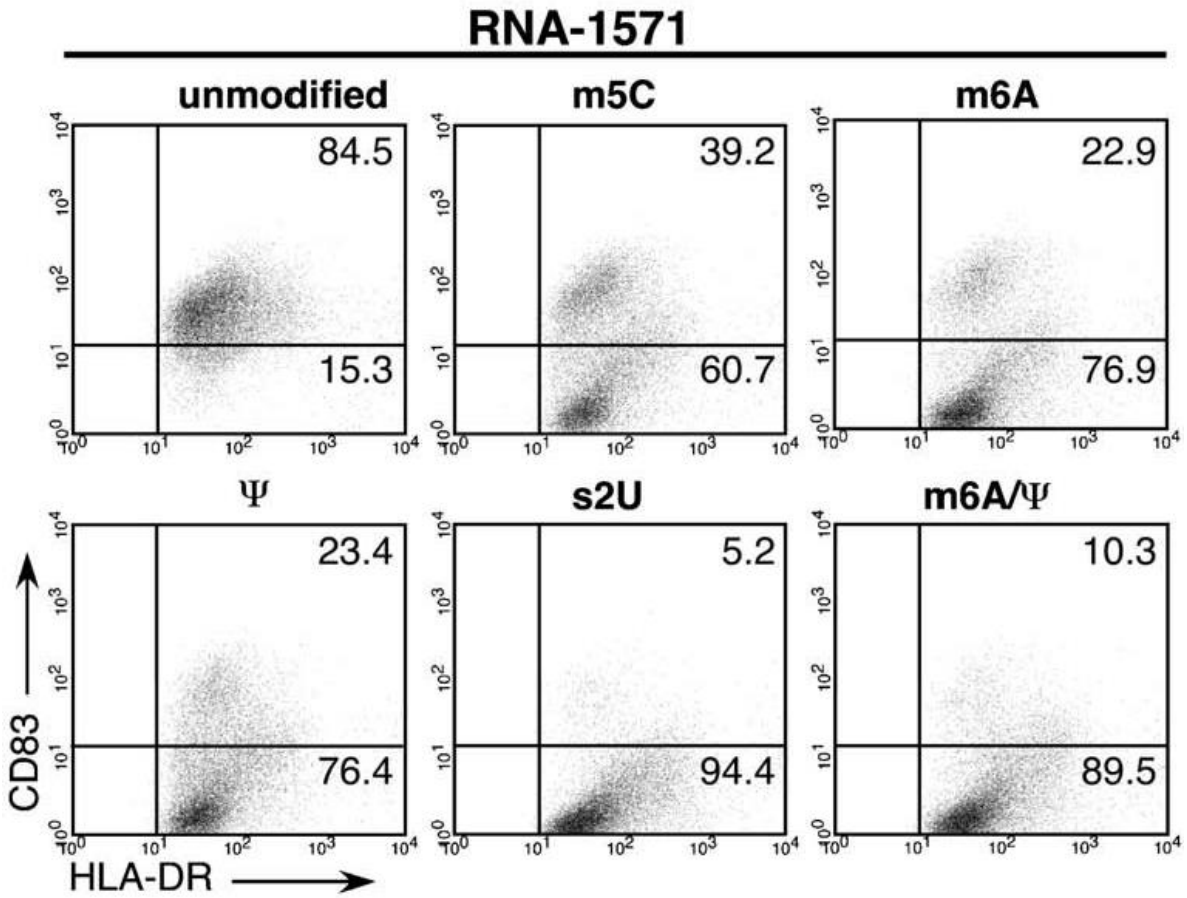
Cont….

- **Modified Nucleosides Reduce the Capacity of RNA to Induce Cytokine Secretion and Activation Marker Expression by DCs**



Cont....

- **Activation of DCs by RNA MDDCs were treated for 20 h with lipofectin alone or complexed with Modified nucleosides RNA.**

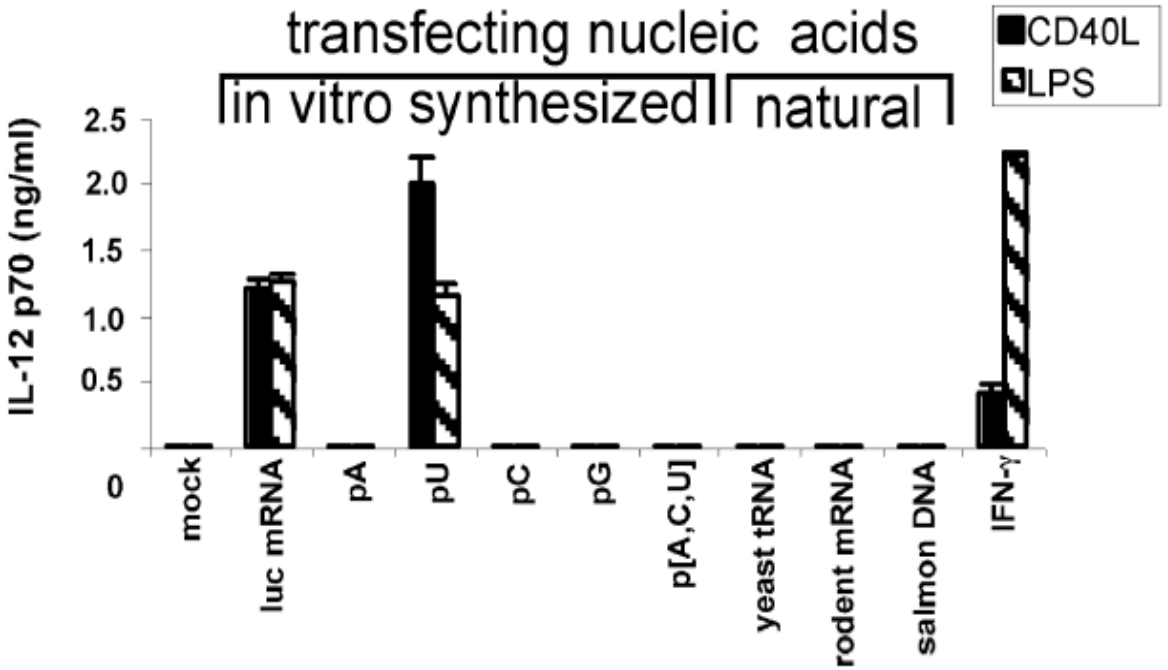


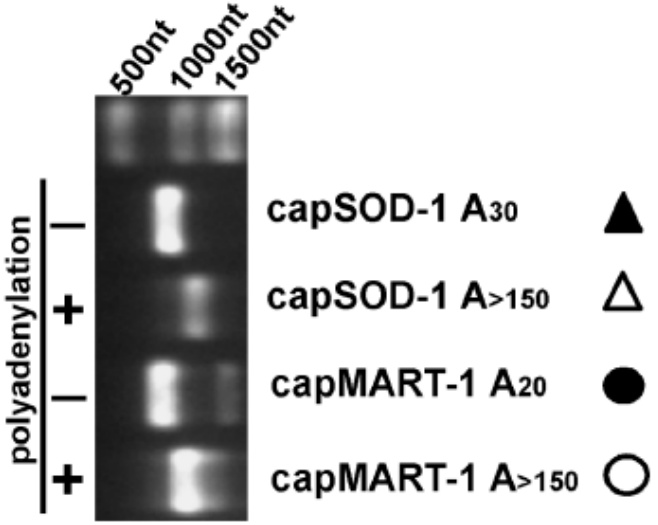
	TNF-α*	CD80	CD86
	pg/ml	mean fluorescence	
lipofectin	0	7.6	55.3
poly(I):(C)	45.6	59.4	257.4
R848	48.3	55.2	235.4
RNA-1866			
unmodified	26.7	52.7	246.4
m5C	0	16.4	108.6
m6A	0	12.4	78.4
Ψ	0	12.0	87.5
s2U	0	8.0	62.7
m6A/Ψ	0	8.6	68.4

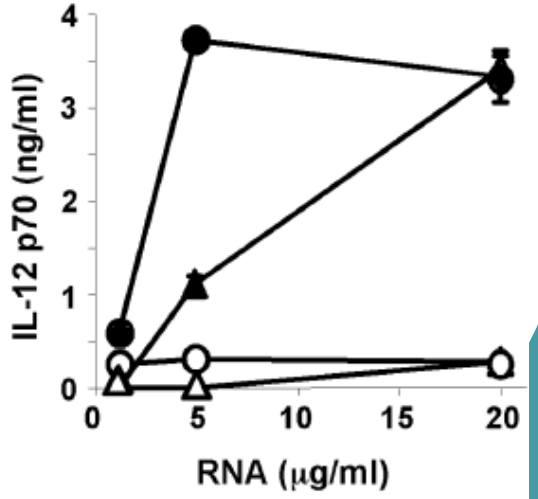
2- Adding poly (A) tails

The Journal of Immunology
BRIEF REPORT | APRIL 01 2004

Cutting Edge: Innate Immune System Discriminates between RNA Containing Bacterial versus Eukaryotic Structural Features That Prime for High-Level IL-12 Secretion by Dendritic Cells[1]

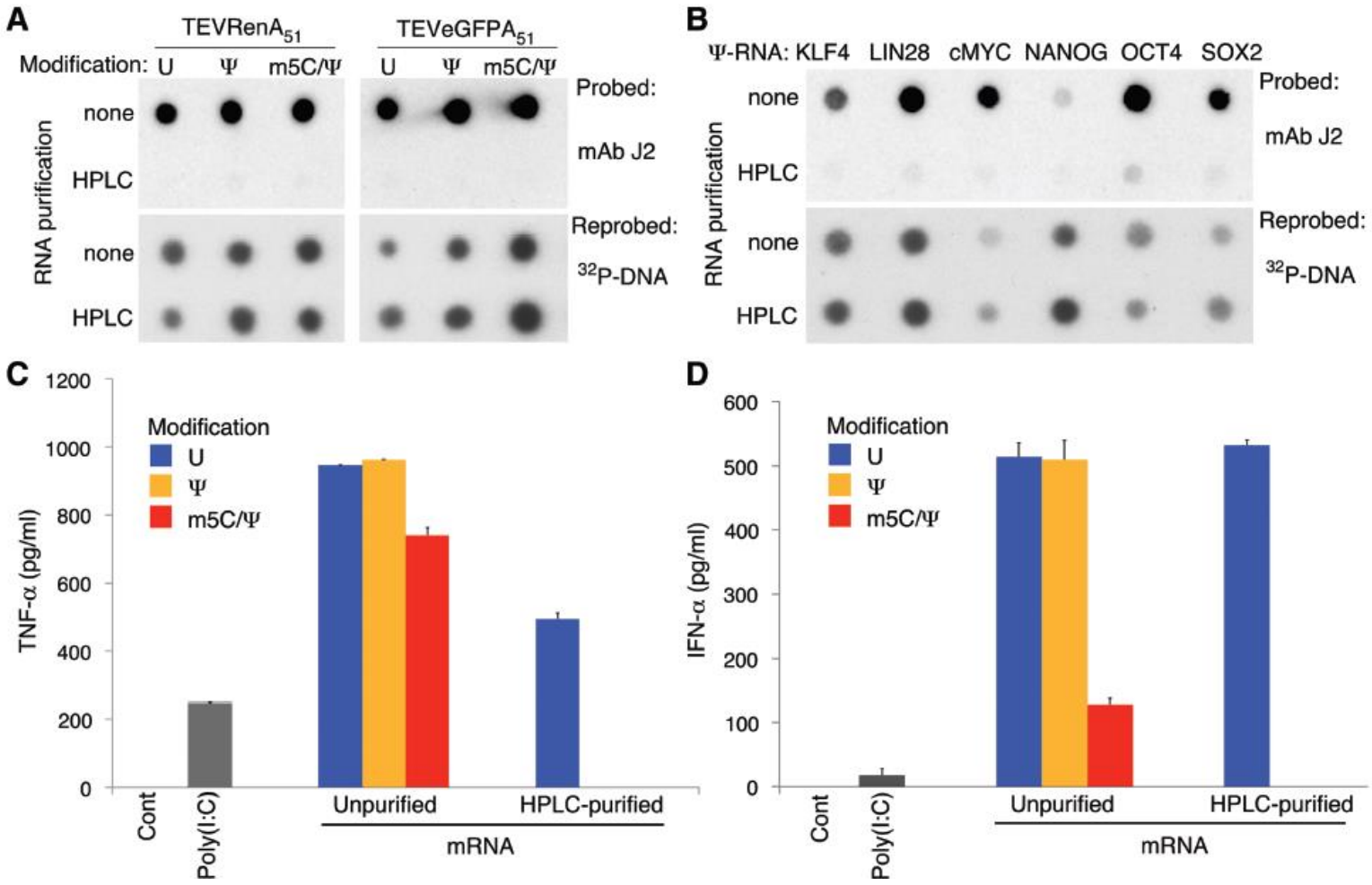






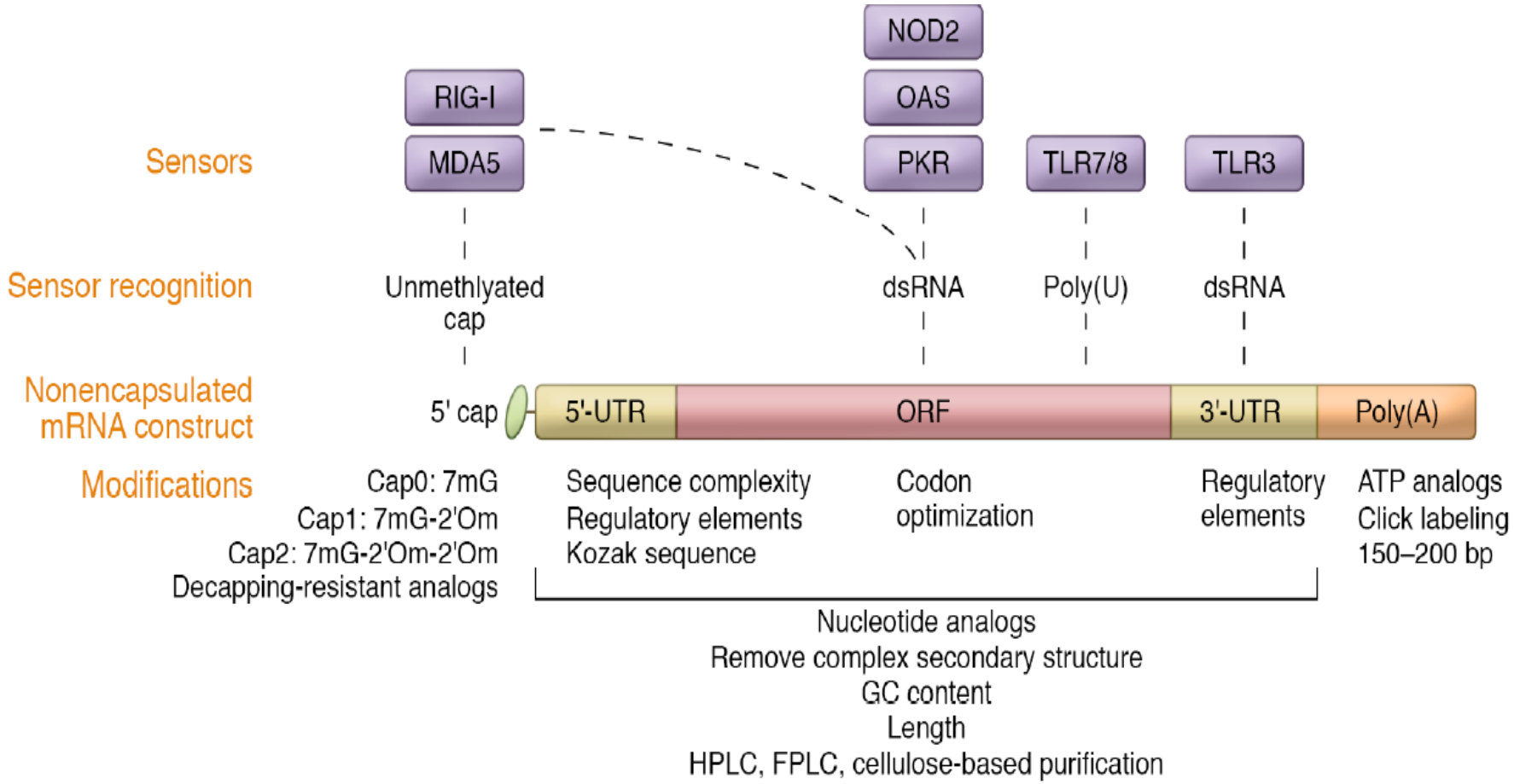
Nucleic Acids Research, 2011, Vol. 39, No. 21 ***e142***
doi:10.1093/nar/gkr695

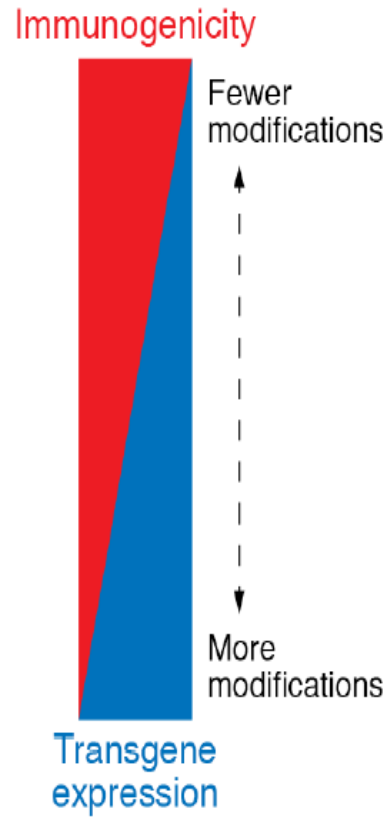
Generating the optimal mRNA for therapy: HPLC purification eliminates immune activation and improves translation of nucleoside-modified, protein-encoding mRNA



More mRNA Vaccine Modifications

- To improve mRNA stability and translation efficacy



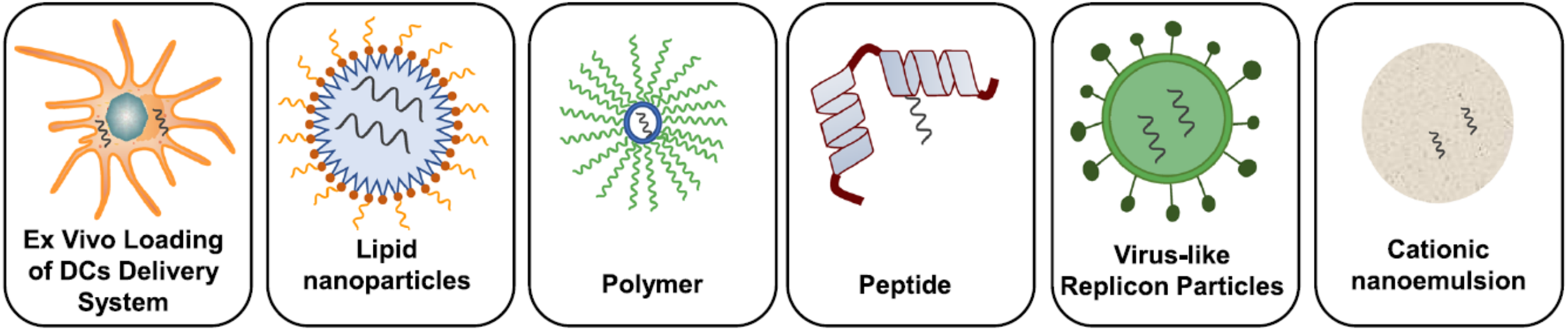


J Clin Invest **2022**

mRNA Vaccine Delivery

- Because of the **negatively charged** structure of naked RNA and the **large molecular size**, mRNA is prone to degradation by nucleases and cannot cross the cell membrane.
- To overcome this obstacle, several mRNA vaccine delivery strategies have been developed:
  - Ex vivo loading of mRNA into DCs,
  - Direct injection of mRNA with or without a carrier.

Major delivery methods for mRNA vaccines



Yuan et al. Biomarker Research. **2023**

mRNA cancer vaccine platforms

- mRNA-based cancer immunotherapies can be divided to:
  - Tumor-associated antigen (TAA) mRNA vaccine
  - Neoantigen or tumor-specific antigens (TSAs) mRNA vaccine
  - Immunomodulatory molecules and tumor suppressor genes mRNA vaccine

Overview of representative mRNA-based cancer vaccine clinical trials

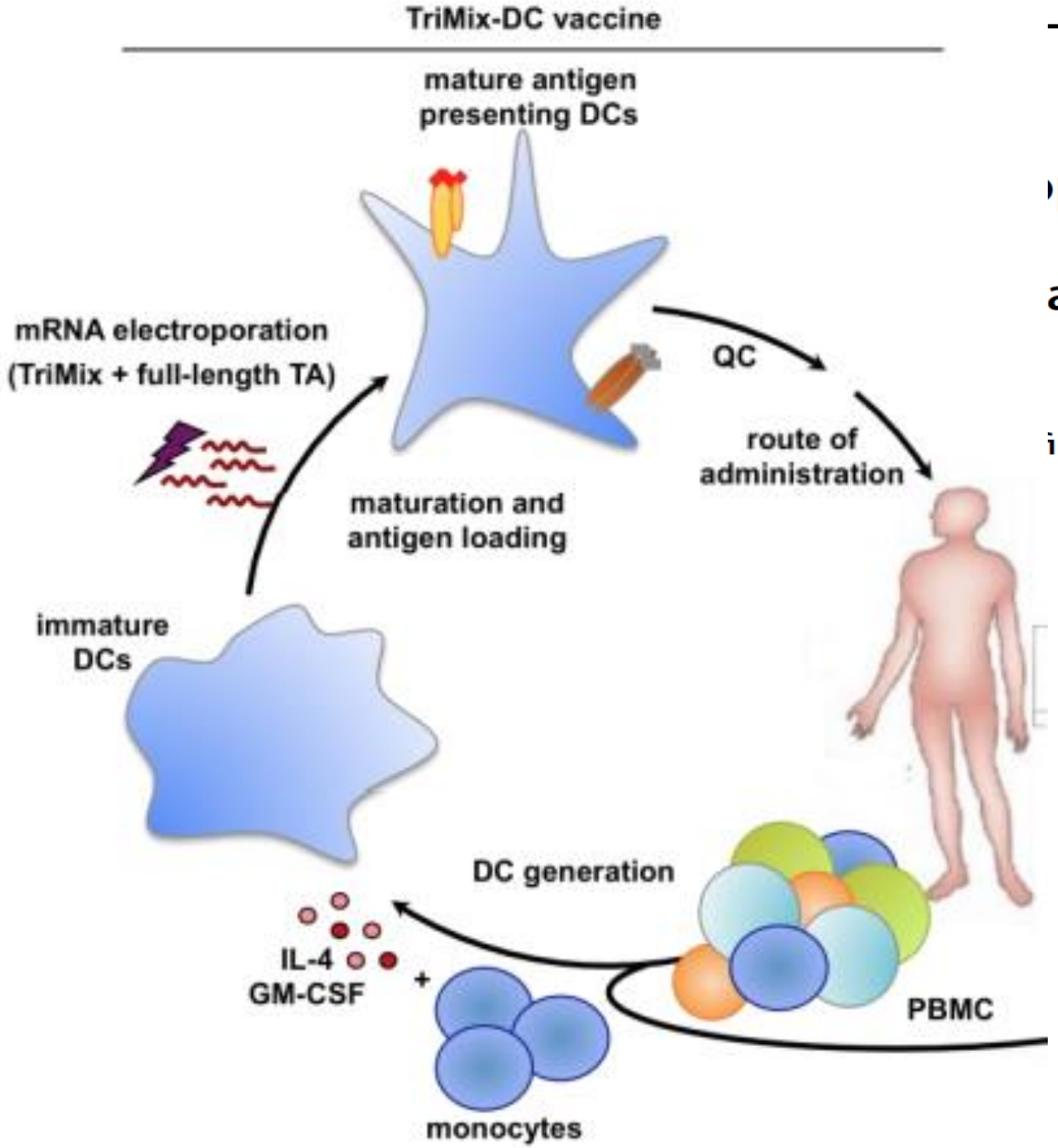
Vaccine type	Antigens and costimulatory molecules	Outcomes	Challenges
Autologous dendritic cell	• TriMixDC-MEL: mRNAs encoding CD70, CD40L, constitutively active TLR4 and tumor antigens (134, 180) • WT-1 dendritic cell: mRNA encoding WT-1 (181) AGS-003: whole-tumor mRNA and synthetic CD40L mRNA (182) • RNA/dendritic cell vaccine: whole-tumor RNA (183)	• Safe toxicity profile • Antigen-specific T cell responses in some patients • Proinflammatory changes in TME observed in some patients	• Costly • Laborious to produce • Variation in patient-specific dendritic cell preparations limiting • Variation in dendritic cell trafficking after injection
Lipid-complexed mRNAs	• mRNA-2416 (Moderna): mRNA encoding OX40L (188) • mRNA-2752: mRNA encoding OX40L, IL-23, IL-36Y (189) • mRNA-4157 (Moderna): mRNA encoding patient-specific neoantigens (190, 191) • FixVac, BNT111 (BioNTech): mRNA encoding NY-ESO-1, tyrosinase, MAGE-A3, TPTE (5, 152)	• Safe toxicity profile, mild adverse events • Activation of antigen-specific $CD4^+$ or $CD8^+$ T cells in large subset of patients • Proinflammatory changes in TME • Durable disease control for some patients • Promising clinical responses in combination with ICB	• Variable tumor-associated antigen–specific responses in subsets of patients
Protamine-coated mRNAs	• RNActive, CV9201: mRNA encoding NY-ESO-1, MAGE-C1, MAGE-C2, survivin, 5T4 (186) • RNActive, CV9103: mRNA encoding PSA, PSCA, PSMA, and STEAP1 (187)	• Safe toxicity profile, mild to moderate adverse events • Activation of T cell responses in small proportion of patients • Significant increase in B cell responses	• Modest immunogenicity
Naked mRNA	• TriMix: mRNA encoding CD70, CD40L, and constitutively active TLR4 (184) • IVAC MUTANOME (BioNTech): mRNA encoding personalized neoantigens (4) • mRNA-Mix: mRNA encoding MAGE-A1, MUC1, CEA, and survivin (185)	• Safe toxicity profile, mild adverse events • Antigen-specific T cell responses detected after vaccination in subset of patients • Promising clinical responses in combination with ICB	• Short half-life • Limited uptake in cells • Requires ultrasound-guided injection into lymph nodes

Cancer Immunology, Immunotherapy
https://doi.org/10.1007/s00262-0

ORIGINAL ARTICLE

A randomized co…porated autologous mon… are as adjuvant treat… disease-free follo…

Yanina Jansen[1] · Vibeke… · …ila Seremet[1] · Carlo Heirman[3] · Lieve Br…



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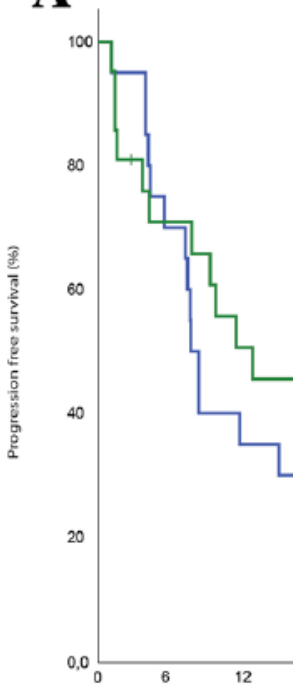

O.	N.	Number of patients	a
21	12	14	10
20	14	14	7

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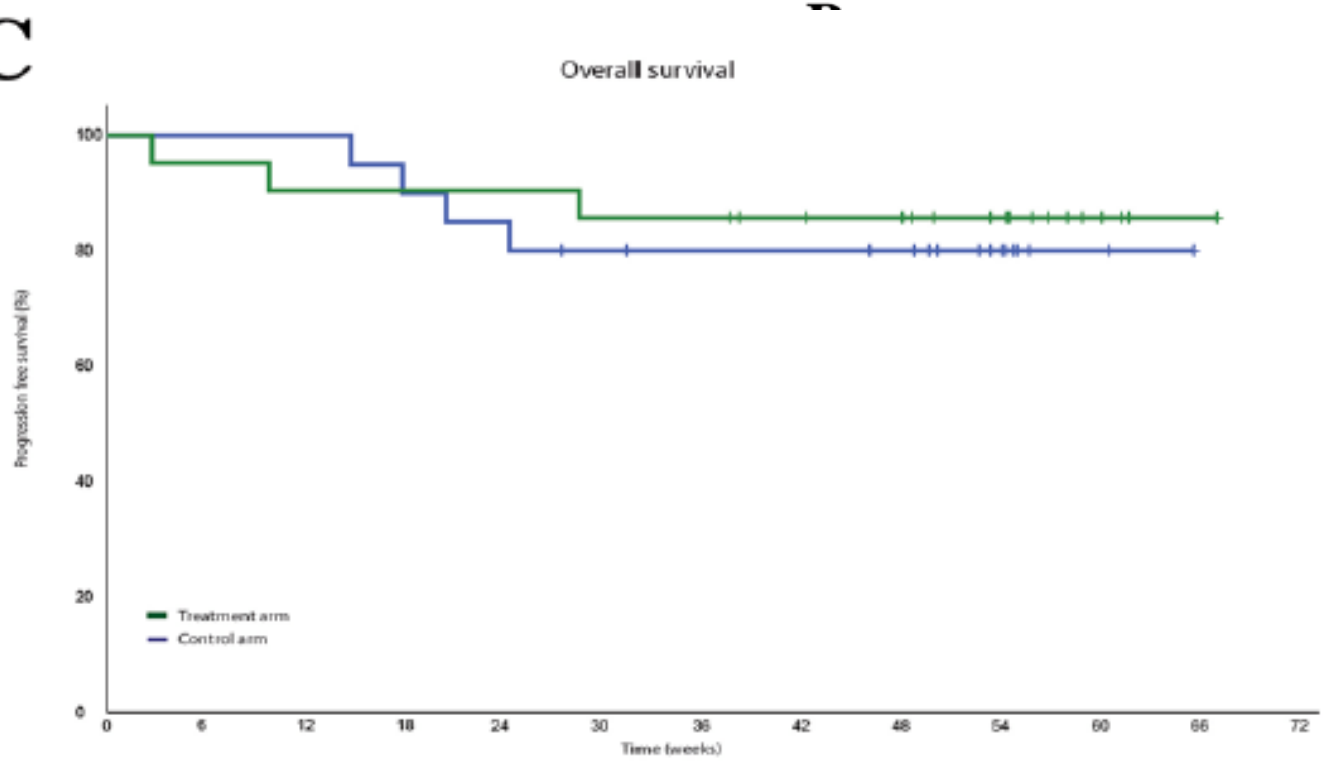
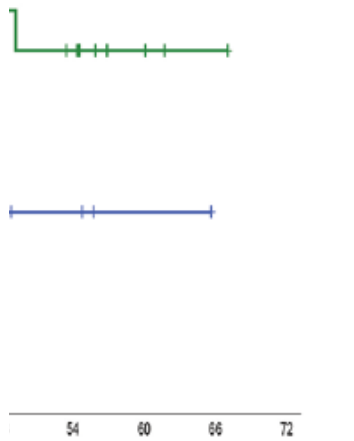


O.	N.	Number of patients at risk										
21	3	20	19	19	19	18	16	12	9	4	1	Treatment arm
20	4	20	20	18	17	14	13	11	5	1		Control arm



3	1	Treatment arm
1		Control arm

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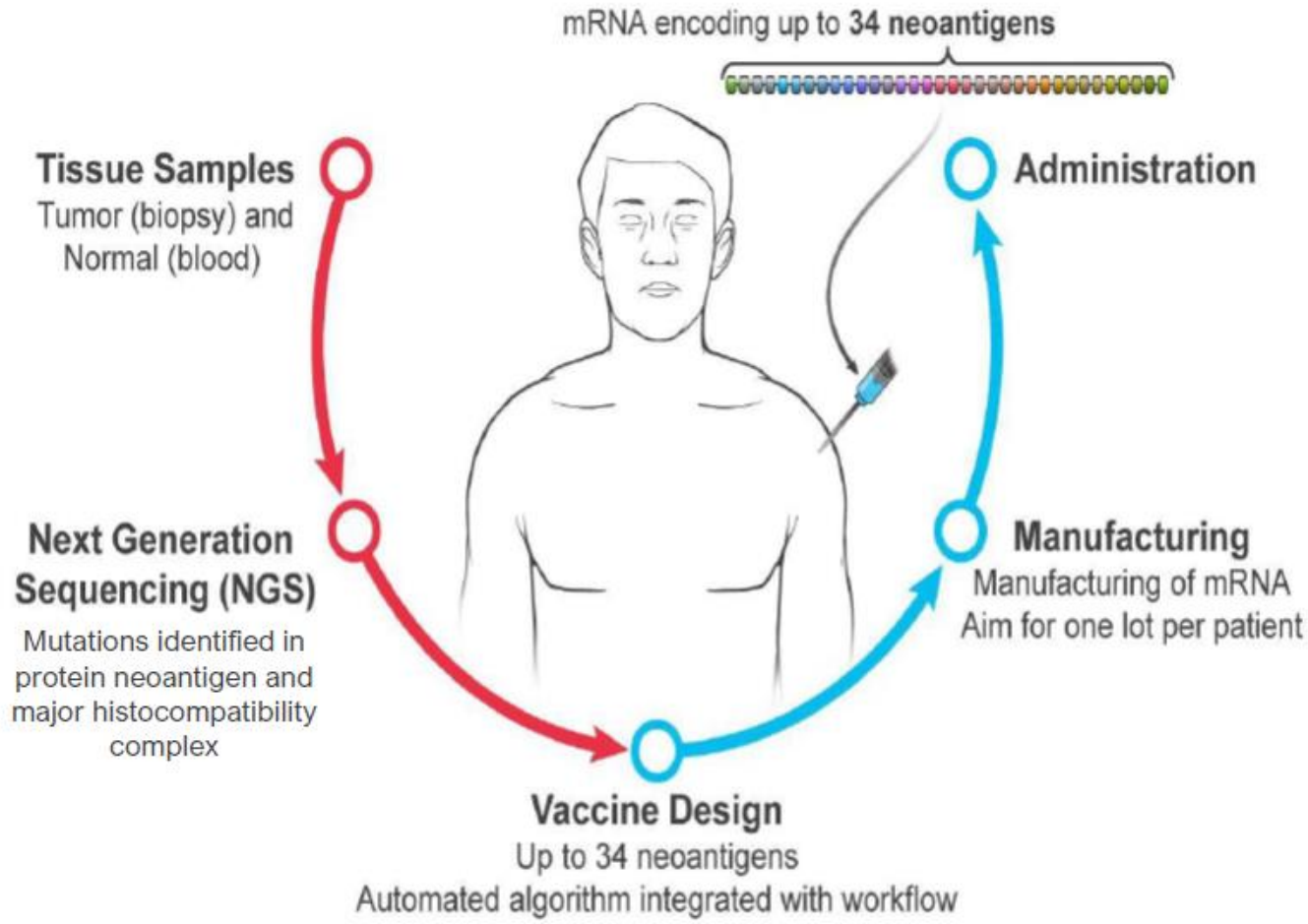
Personalized cancer vaccine (mRNA-4157)



Current challenges and future perspectives

- 1- Tumor heterogeneity
- 2- Immunosuppressive tumor microenvironment
- 3- Vaccine administration routes
- 4- Biomarkers for monitoring the treatment response

Conclusion

- ✓It seems mRNA cancer vaccines present a promising new approach to anticancer therapies with both opportunities and challenges.
- ✓The highly personalized and specific nature of this technology offers tremendous potential for precision medicine in the fight against cancer.
- ✓Further clinical trials are necessary to fully establish the safety and efficacy of mRNA cancer vaccines and additional preclinical studies are warranted to explore the combined use of mRNA cancer vaccine and other anticancer therapies.

Cont....

- ✓Addressing issues such as tumoral heterogeneity, routes of administration and development of methods to assess the efficacy processes will be critical for advancing this technology toward meaningful clinical outcomes.
- ✓With continued research and investment, mRNA cancer vaccines hold great promise as a transformative therapy for cancer patients.

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Thank you