



UNIVERZITET U NOVOM SADU
MEDICINSKI FAKULTET

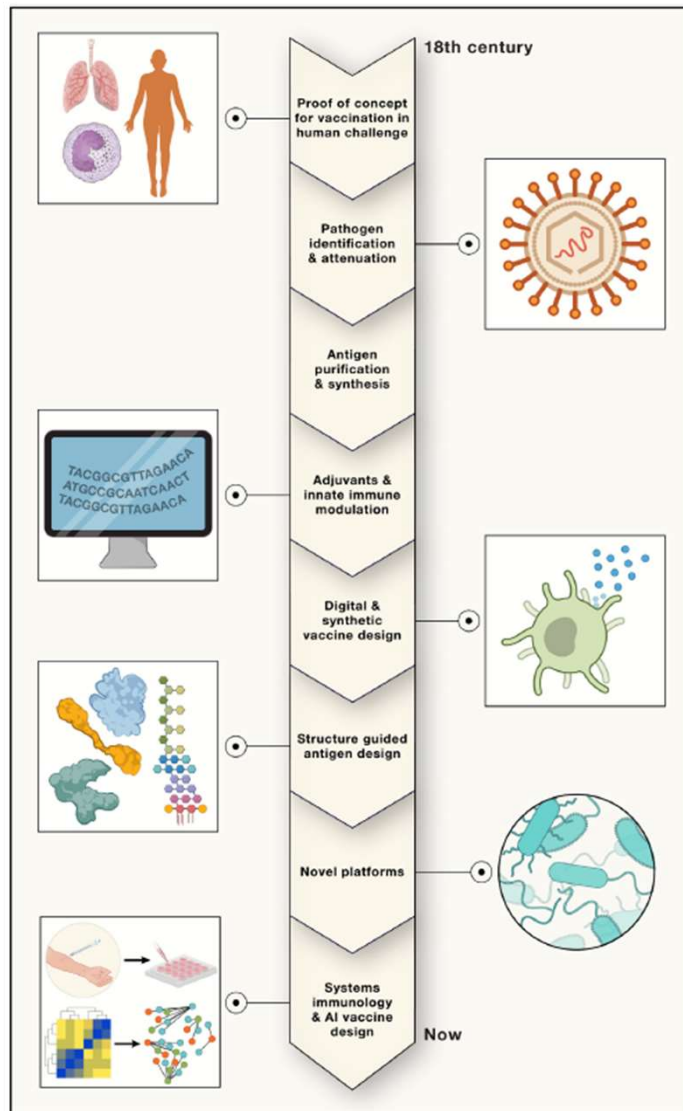


Nacionalni simpozijum sa međunarodnim učešćem
„4. DAN VAKCINACIJE“
6-7. novembar 2024. godine
Hotel Sheraton, Novi Sad

Nove tehnologije u razvoju vakcina

Miloš Marković

Institut za mikrobiologiju i imunologiju
Medicinski fakultet Univerziteta u Beogradu



Napredak tehnologije kroz istoriju vakcina

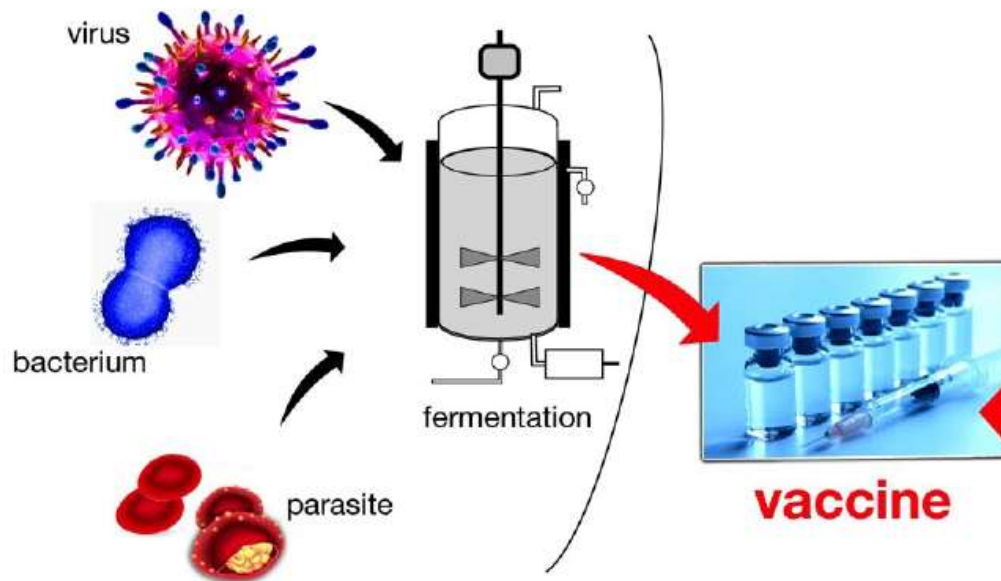
- Napredak u imunologiji i bolje razumevanju protektivnog imunskog odgovora
- Sekvenciranje genoma patogena i reverzna vakcinologija
- Dizajn antigena u vakcinama zasnovan na njegovoj strukturi
- Sistemska imunologija zasnovana na “high-throughput” tehnikama i veštačkoj inteligenciji
- Inovativne platforme za pravljenje vakcina

Racionalni dizajn vakcina
i razvoj novih i
unapređenih vakcina

Reverzna vakcinologija

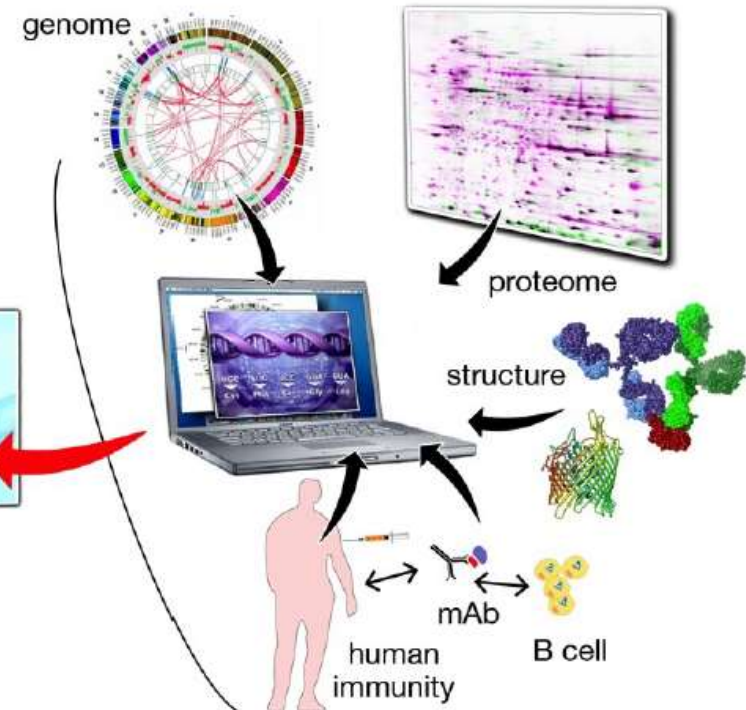
CLASSICAL VACCINOLOGY

growing pathogens



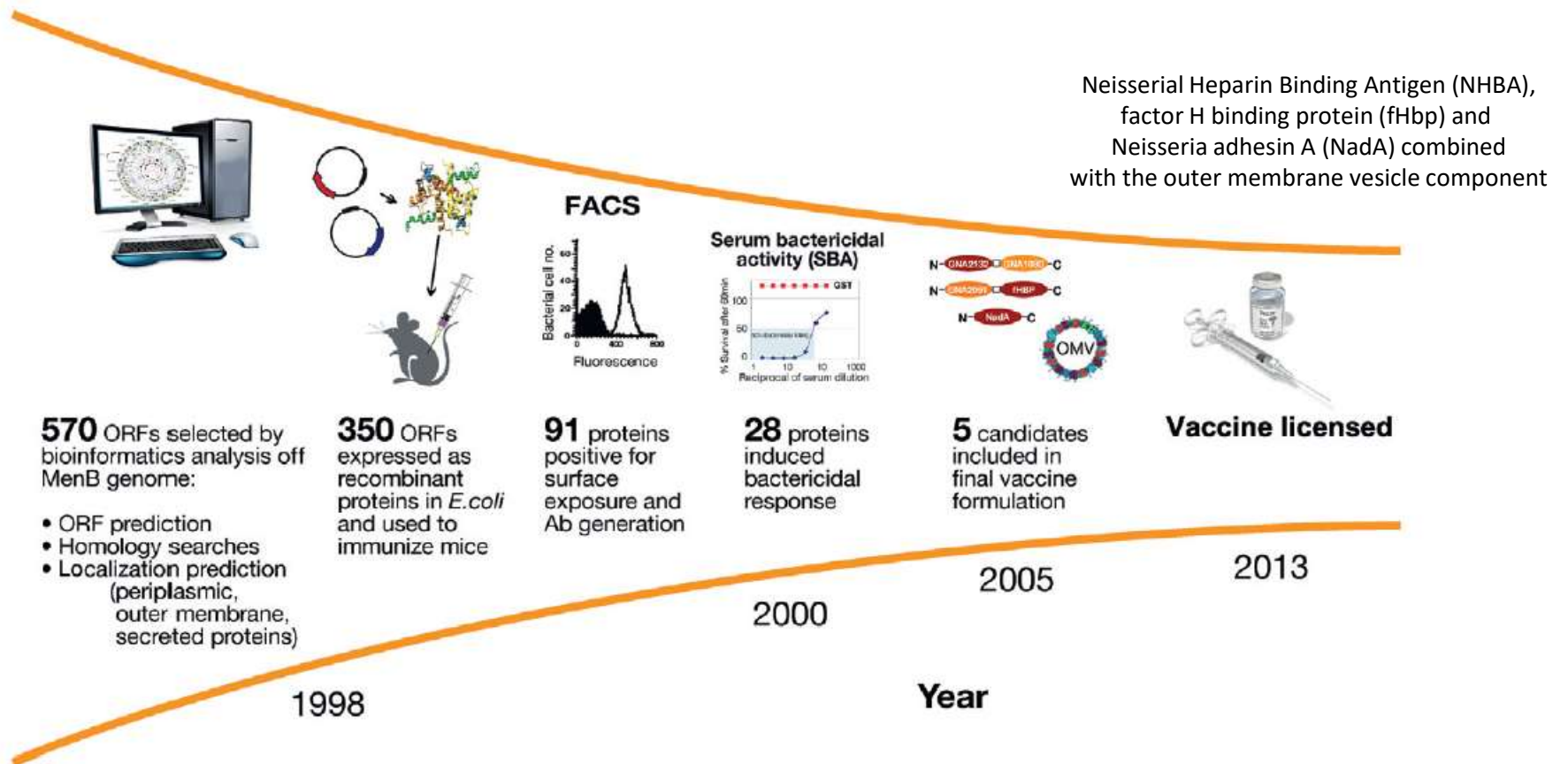
REVERSE VACCINOLOGY

design from information

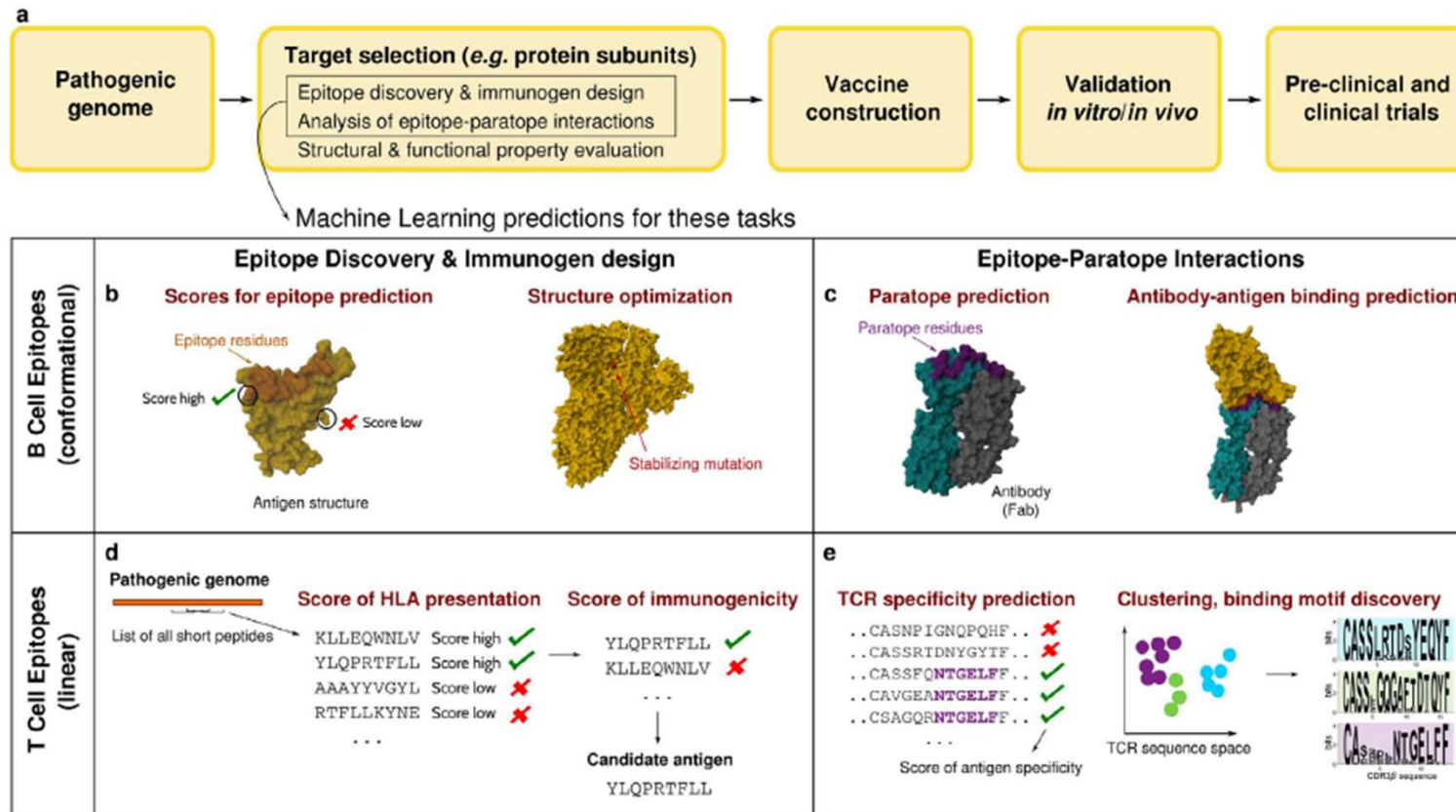


Reverzna vakcinologija

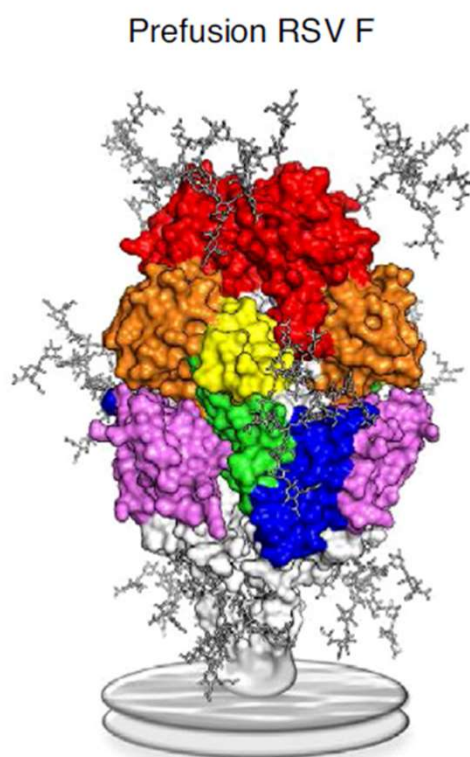
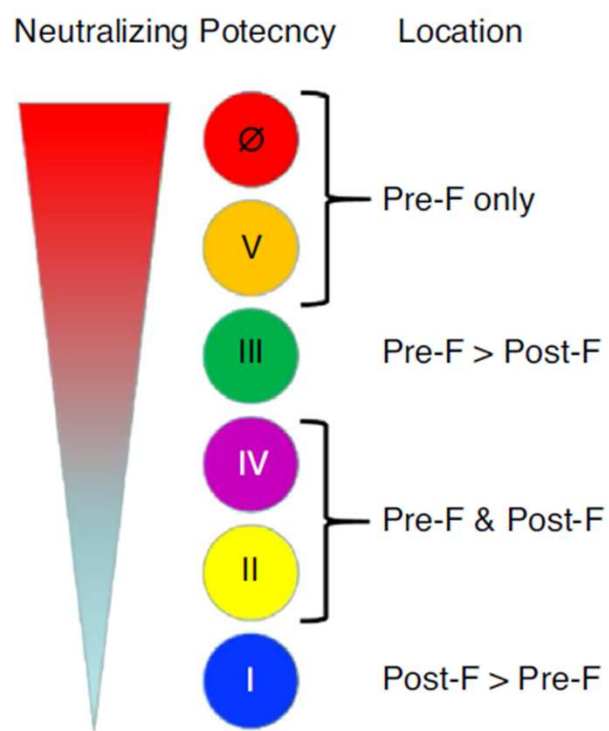
- Vakcina za grupu B meningokoka (4CMenB) dobijena reverznom vakcinologijom



Uloga veštačke inteligencije u racionalnom dizajnu vakcina

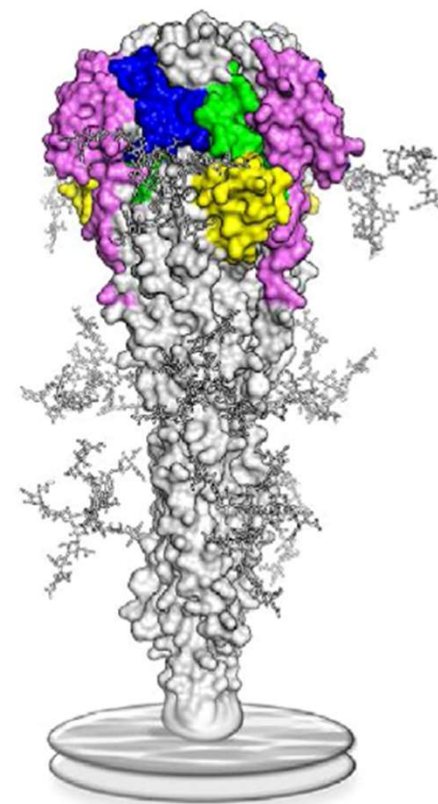


Antigenske determinante na F proteinu RSV



Site Ø
 Site I
 Site II
 Site III
 Site IV
 Site V

Postfusion RSV F



Current Opinion in Virology

Rešavanje “prefusion” strukture F proteina RSV

10 Å Projection



Ulrich Baxa

Negative stain EM

RSV F+D25



Tim Beaumont
Hergen Spits

RSV F+AM22

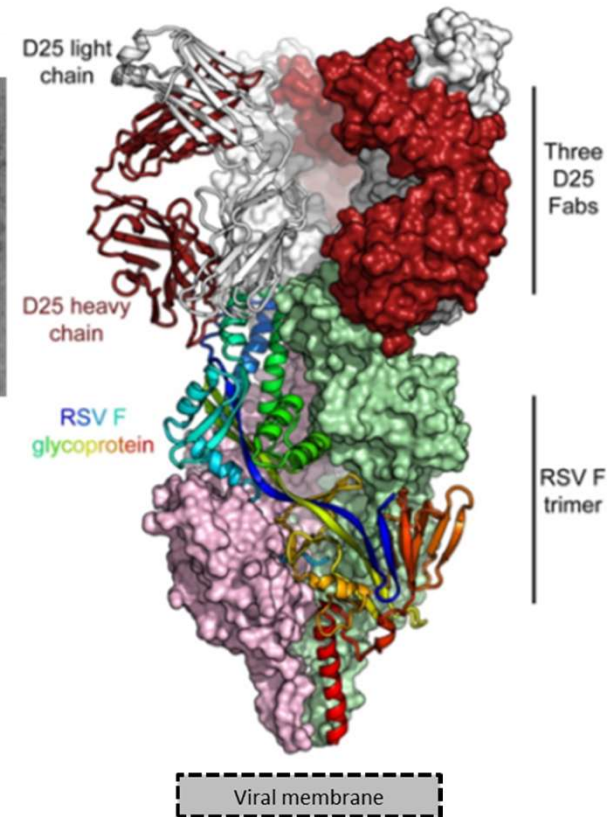
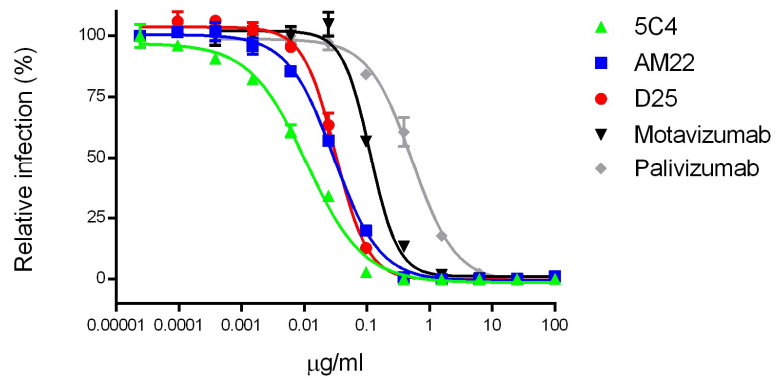


RSV F+5C4



Ningshao Xia, ZZ
Zheng, Min Zhao

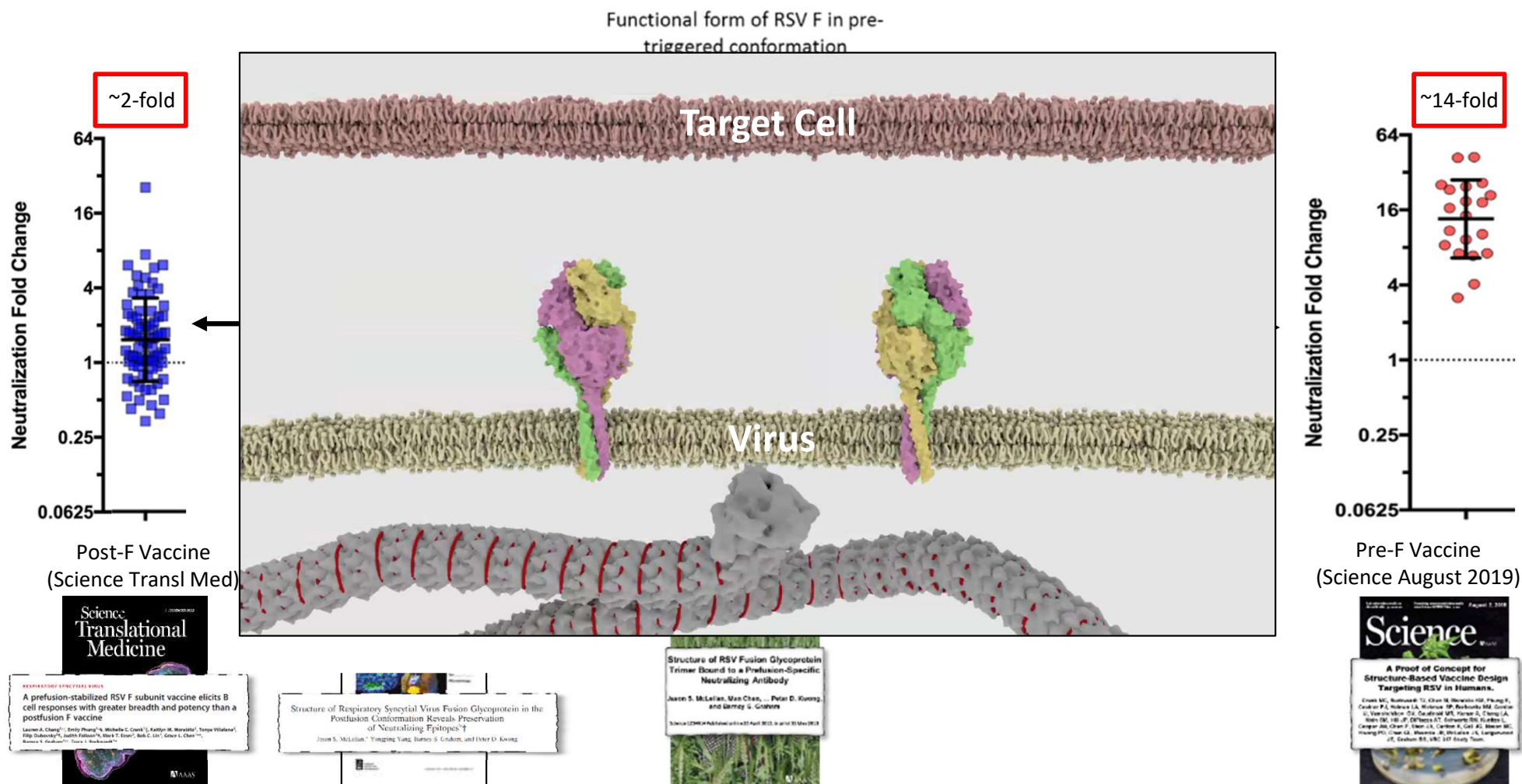
RSV neutralization



McLellan et al. Science 2013 #1

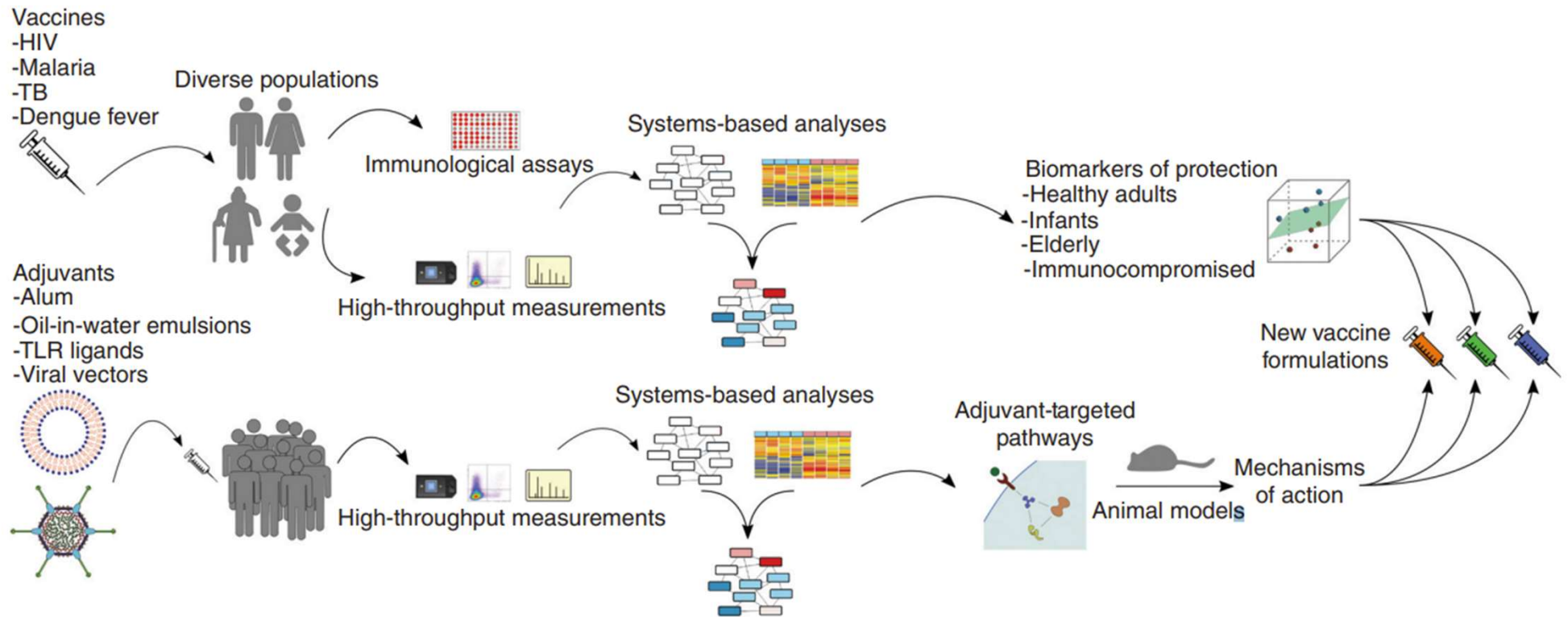
Ljubaznošću: Barney Graham, MD, PhD, Morehouse School of Medicine, Atlanta, GA, USA

Imunogenost antigenских determinanti na F proteinu RSV

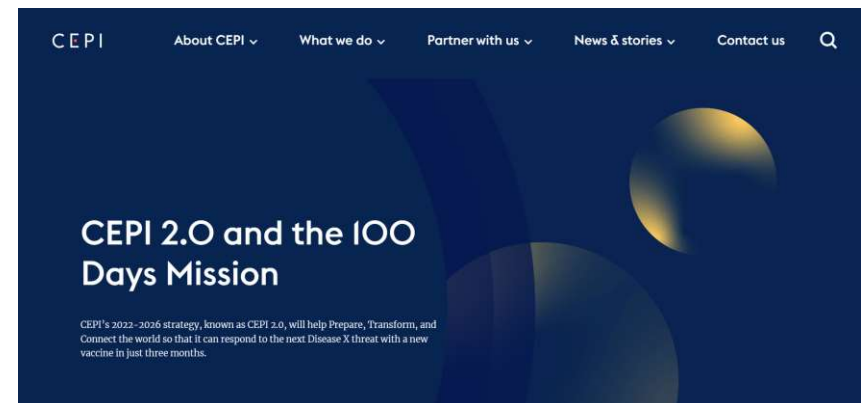
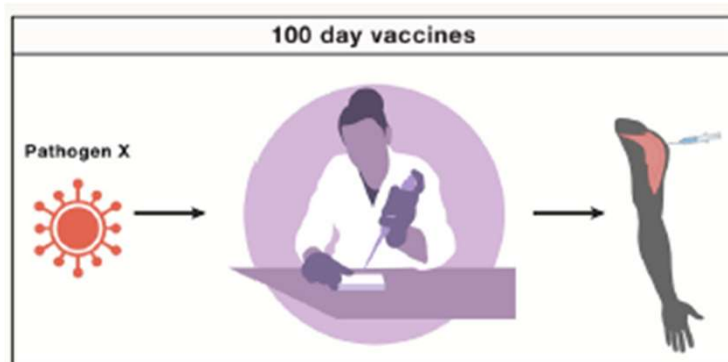
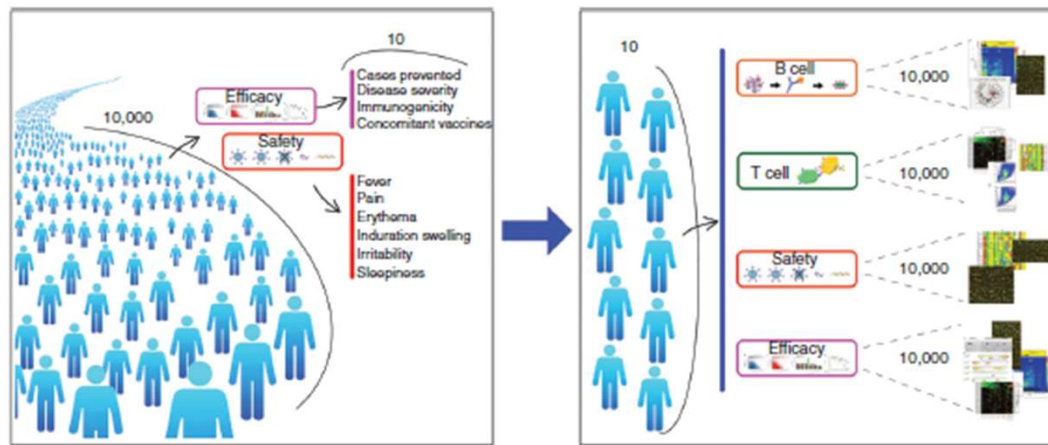


Ljubaznošću: Barney Graham, MD, PhD, Morehouse School of Medicine, Atlanta, GA, USA

Uloga sistemske imunologije u racionalnom dizajnu vakcina



Sistemska imunologija i veštačka inteligencija i dobijanje novih i unapređenih vakcina

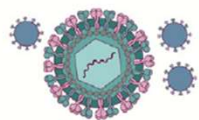


Rappuoli et al. *Cell*. 2024 Sep 19;187(19):5171-5194.
Rappouli et al. *Cold Spring Harb Perspect Biol*. 2018;10(8):a029256.

Coalition for Epidemic Preparedness Innovations. Dostupno na: <https://cepi.net/> (Pristupljeno 4.11.2024.)

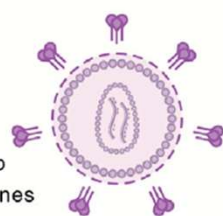
Najvažnije plaforme vakcina protiv infektivnih bolesti kod ljudi

Live attenuated



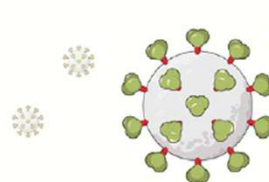
- BCG
- Mumps
- Rubella
- Measles
- Varicella
- Smallpox
- Oral polio
- Yellow fever
- Influenza

Inactivated viruses



- Rabies
- Hepatitis A
- Inactivated polio
- COVID-19 vaccines
- Influenza

mRNA



- RSV (developed by Moderna)
- COVID-19 vaccines (e.g. developed by Pfizer/BioNTech and Moderna)

DNA



- COVID-19 (Cadila Healthcare)

Inactivated toxoids



- Diphtheria
- Pertussis
- Tetanus vaccines (DTP)

Recombinant protein



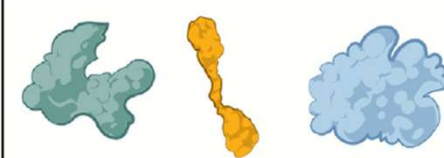
- Hepatitis B
- Meningococcal B
- Acellular pertussis
- Human Papilloma Virus
- Shingles (developed by GSK)
- Malaria vaccines (developed by GSK and Oxford/Serum Institute of India)

Recombinant vector



- Ebola
- COVID-19 vaccines (e.g. AstraZeneca, Jansen)

Polysaccharide or conjugate

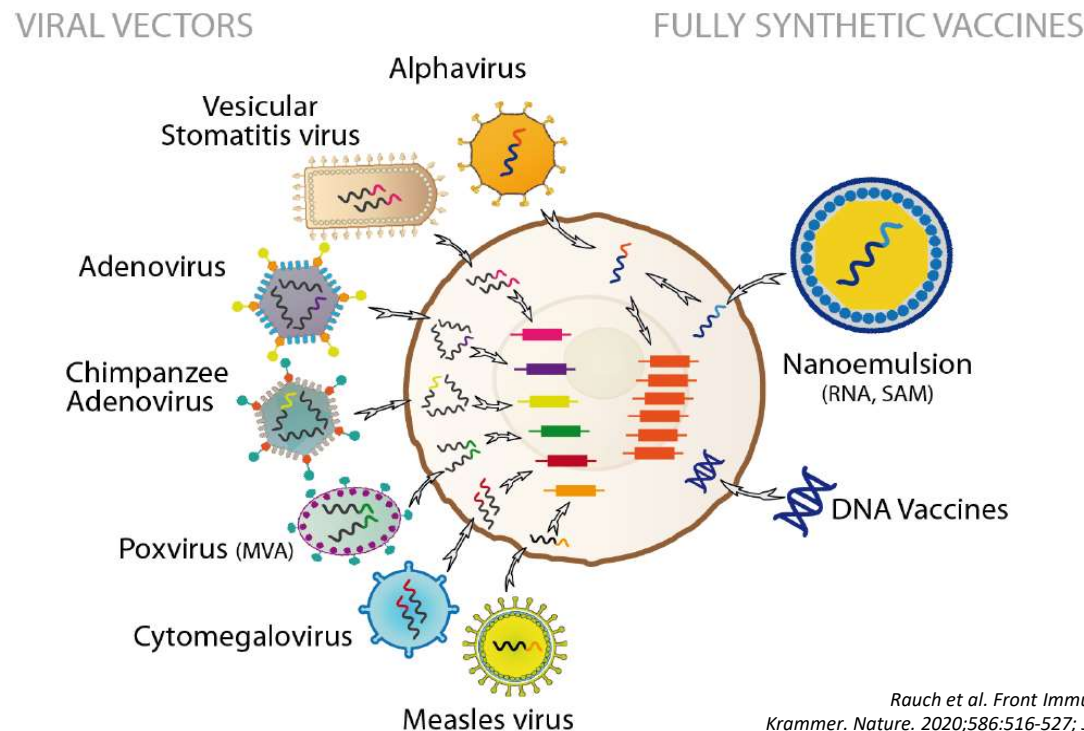


- Typhoid polysaccharide and conjugate
- Haemophilus influenzae type B conjugate
- Pneumococcus polysaccharide and conjugate
- Meningococcus conjugate

Konvencionalne vs. inovativne platforme

Konvencionalne vakcine (**žive, inaktivisane, subjedinične...**) → davanje čitavog patogena (**atenuisanog ili inaktivisanog**) ili njegovog **dela** (ili delova) ili **produkta** (npr. modifikovanog toksina - toksoida)

Inovativne vakcine (**vektorske, DNK i RNK vakcine**) → davanje **nukleinske kiseline (DNK ili RNK)** koja nosi informaciju za imunodominantni/e antigen(e)/epitop(e) patogena od interesa



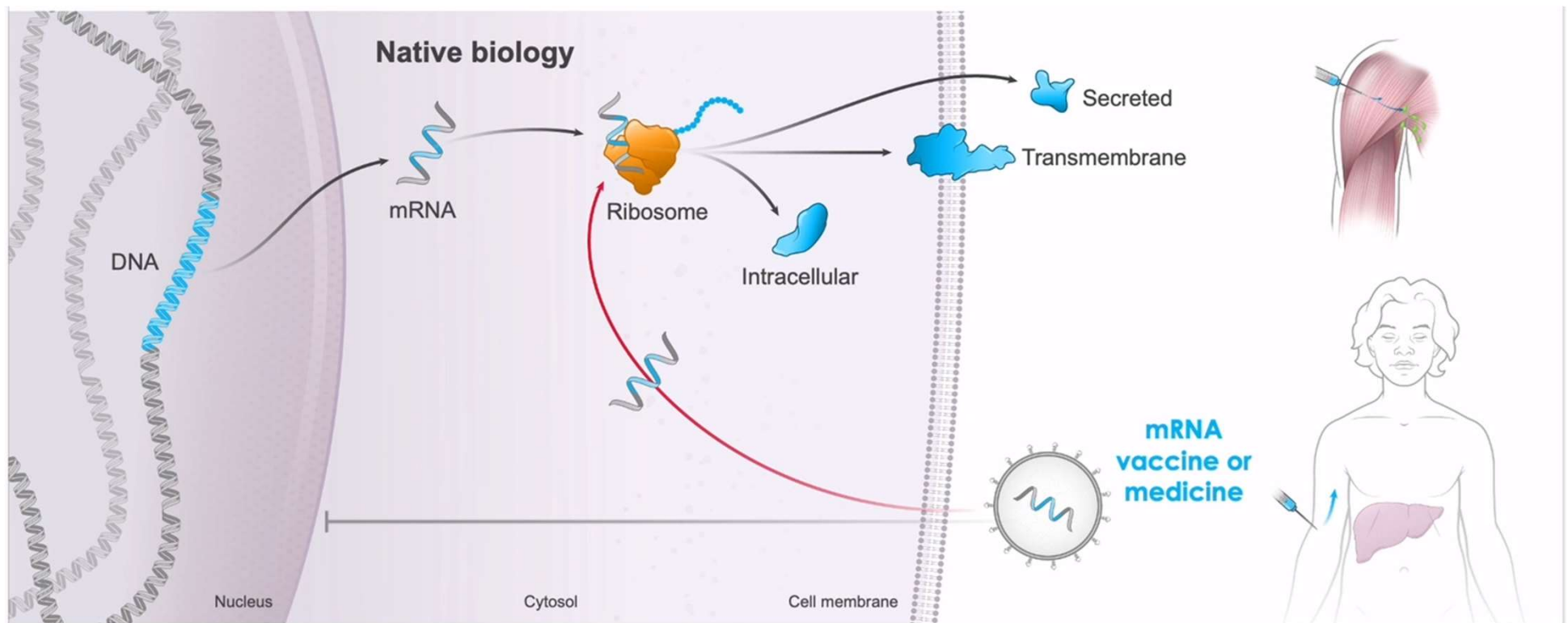
Rauch et al. Front Immunol. 2018;9:1963; Rego et al. Vaccines 2020;8:474; Krammer. Nature. 2020;586:516-527; Jeyanathan et al. Nat Rev Immunol. 2020;20:615-63

Konvencionalne vs. inovativne platforme

- **Konvencionalne vakcine** (žive, inaktivisane, subjedinične...)
 - **Imunogene i efikasne** (neke vakcine se daju u više doza i sa adjuvansima)
 - **Dobar bezbednosni profil**, ali ograničenja kod nekih vakcina (npr. žive vakcine kod imunokompromitovanih)
 - Potrebe za kultivacijom i propagacijom patogena (visok nivo biosigurnosti potreban)
 - **Ograničen kapacitet za proizvodnju** velikog broja vakcina
 - **Dugo vreme** za razvoj (u proseku 10 godina) i **visoki troškovi** (0,5-1 milijarde \$/vakcini)
- **Inovativne platforme** (vektorske, DNK i RNK vakcine)
 - **Visoka imunogenost i efikasnost** → indukcija i humoralnog (visokoafinitetnih antitela) i ćelijskog odgovora
 - **Dobar bezbednosni profil** (bez perzistencije u ćeliji i/ili integracije u genom)
 - Bez potrebe za kultivacijom i propagacijom patogena (lakši i brži razvoj i proizvodnja vakcina)
 - Mogućnost **velikog kapaciteta za proizvodnju** (povećanje produkcije vakcina **u kratkom periodu - meseci**)
 - **Svestranost platforme** (potrebna je samo promena gena) – nekada se koriste isti kapaciteti za proizvodnju
 - **Niska cena** razvoja i proizvodnje

RNK vakcine

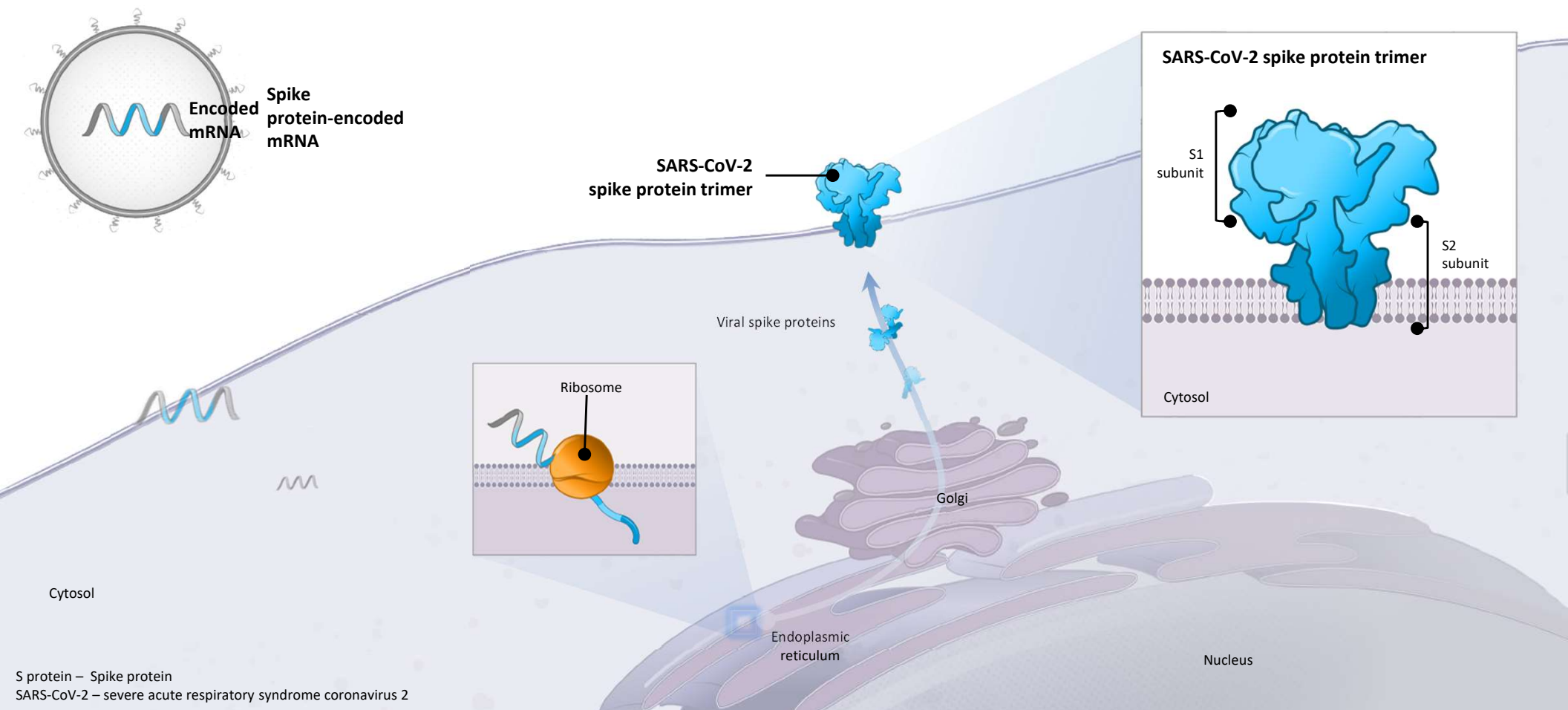
- Imunizacija sa **iRNK** koja nosi informaciju za imunodominanti/e epitop(e)/antigen(e) patogena od interesa



- RNK vakcine “hakuju” biosintetsku mašineriju ćelije

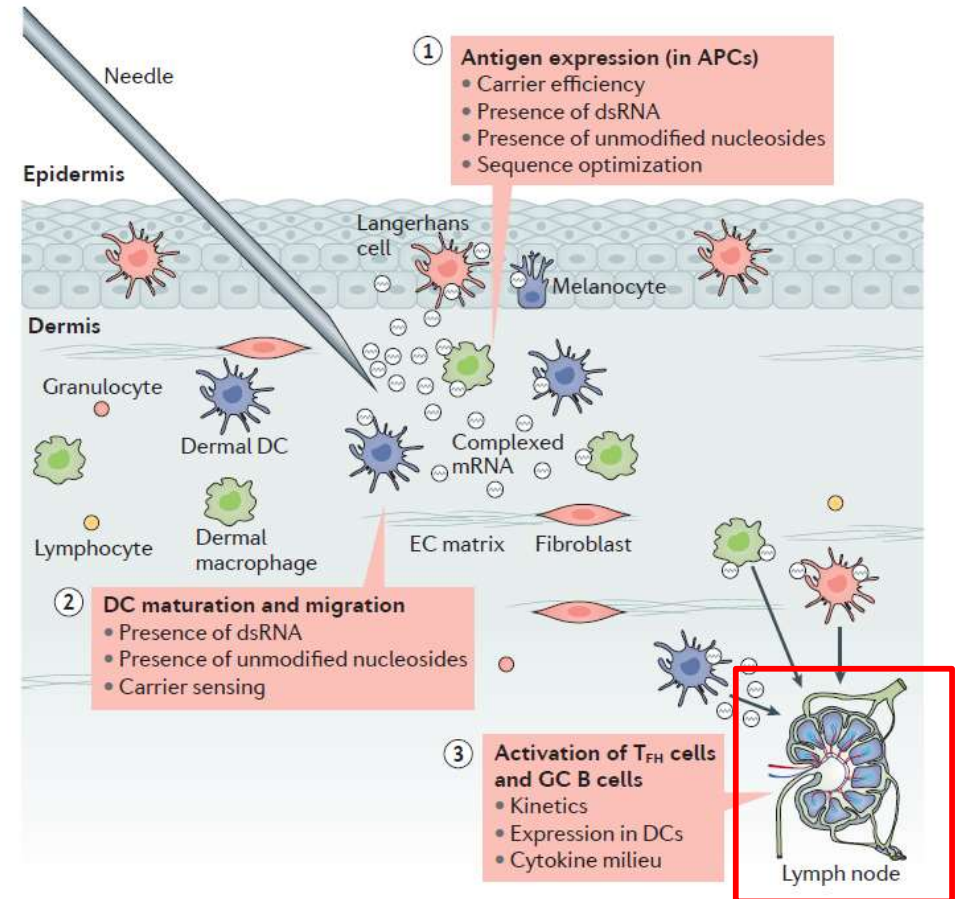
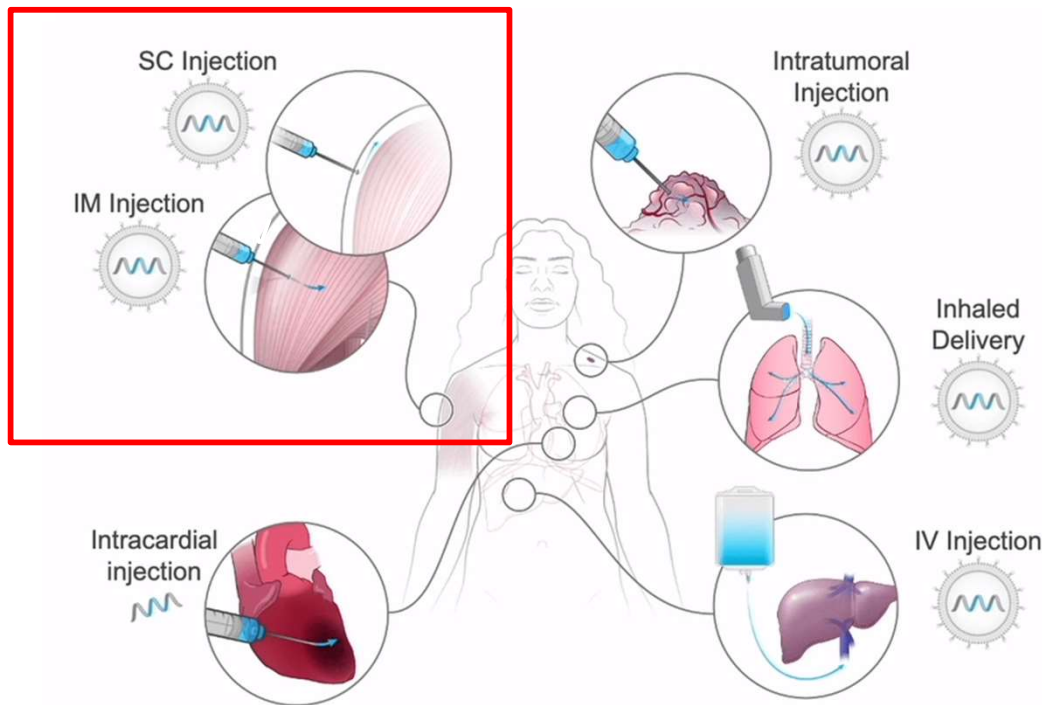
Mehanizam dejstva RNK vakcina

(primer: mRNA-1273 vakcina koja kodira S protein SARS-CoV-2)



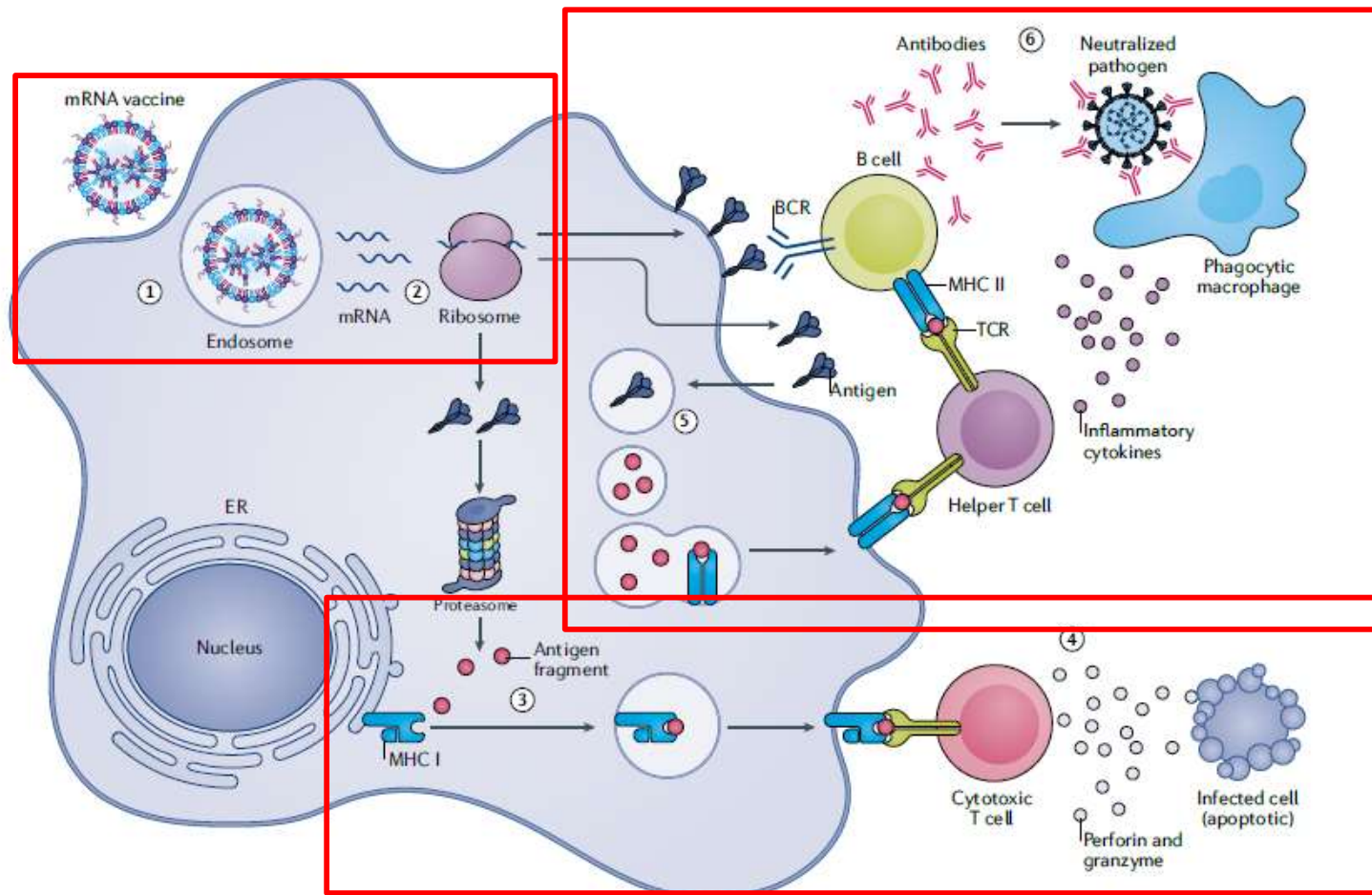
RNK vaccine

(Način davanja i indukovanja imunskog odgovora)



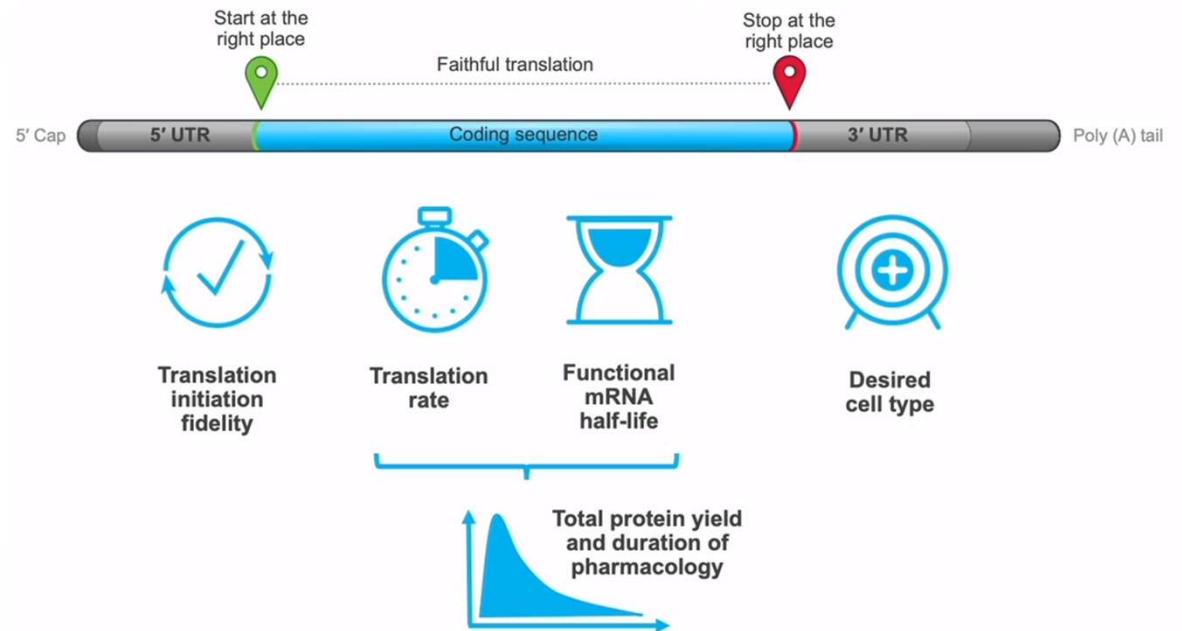
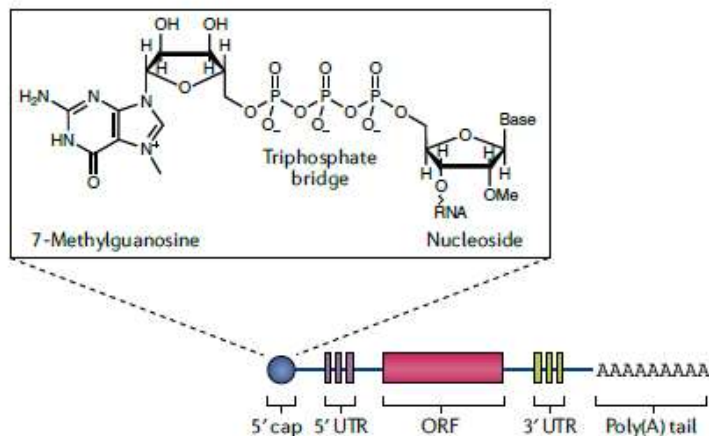
RNK vaccine

(Način davanja i indukovanja imunskog odgovora)



Principi dizajniranja RNK vakcina

- iRNK struktura **identična sisarskim iRNK** → dizajnirana da maksimalno dovede do produkcije proteina



Principi dizajniranja RNK vakcina

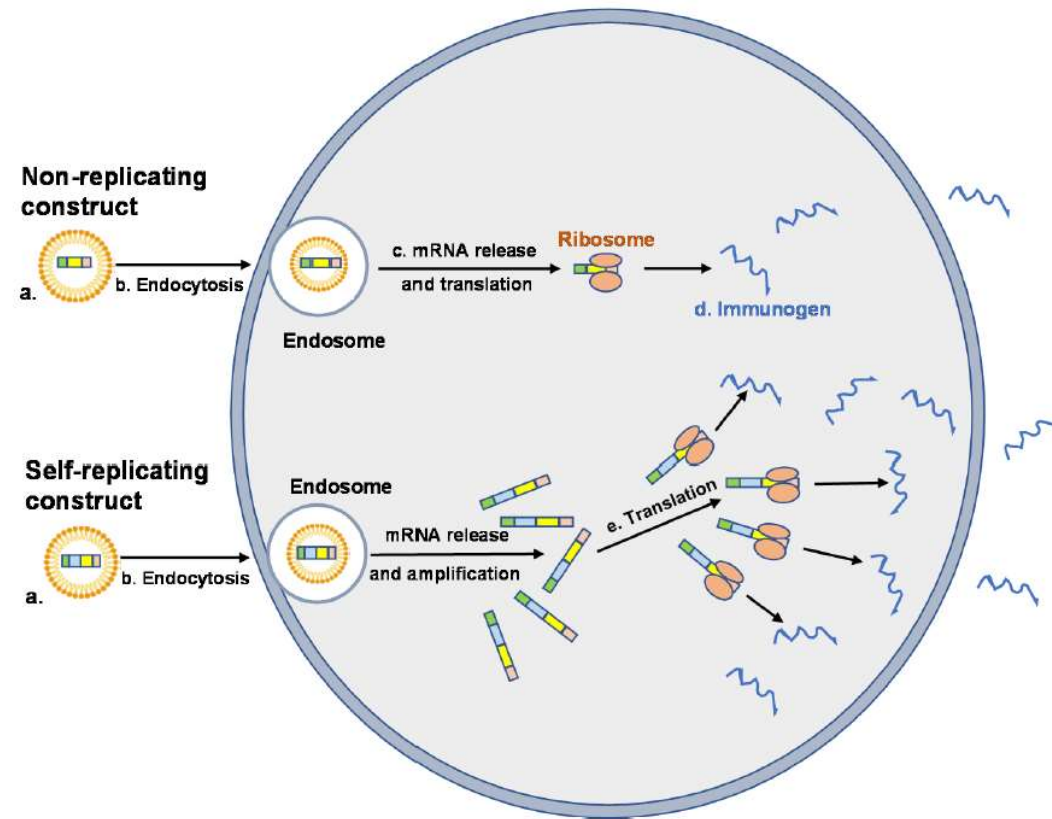
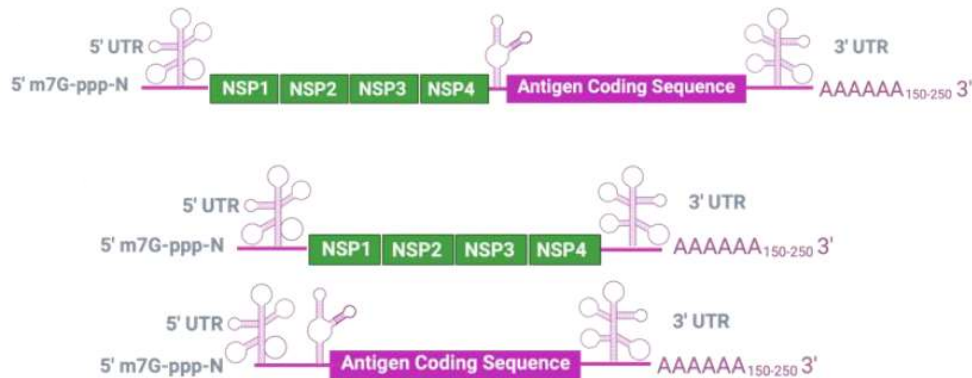
- iRNK struktura **identična sisarskim iRNK** → dizajnirana da maksimalno dovede do produkcije proteina
 - **Nereplikujuća RNK** → jednostavna konstrukcija, ali niži stepen ekspresije antigena
 - **“Samoamplifikujuća” RNK** (Self-amplifying RNA) bazirana na genomu alfavirusa → komplikovanija konstrukcija, ali veća ekspresija antigena

Dva glavna tipa iRNK korišćenih u vakcinama (Nereplikujuće i samoamplifikujuće iRNK vakcine)

Nereplikujuća iRNK

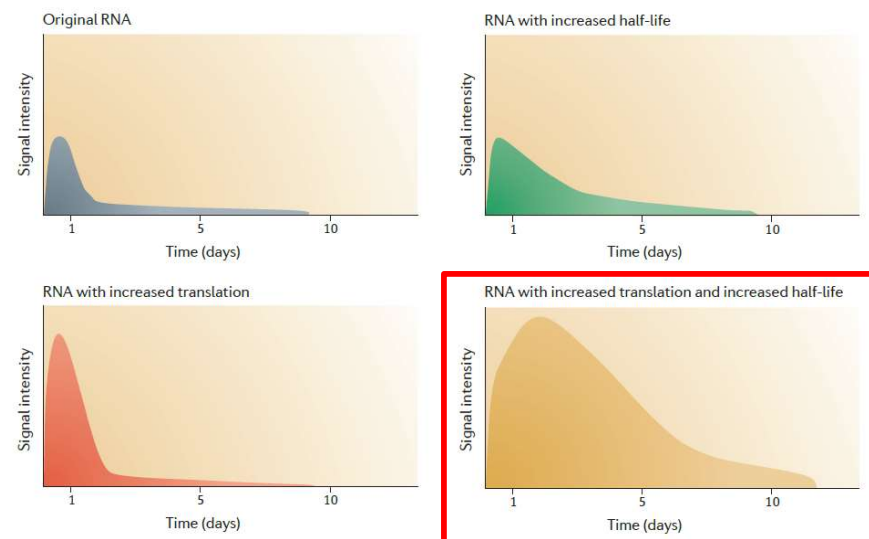


Samoamplifikujuća iRNK (sadrži replikazu iz alfa virusa)



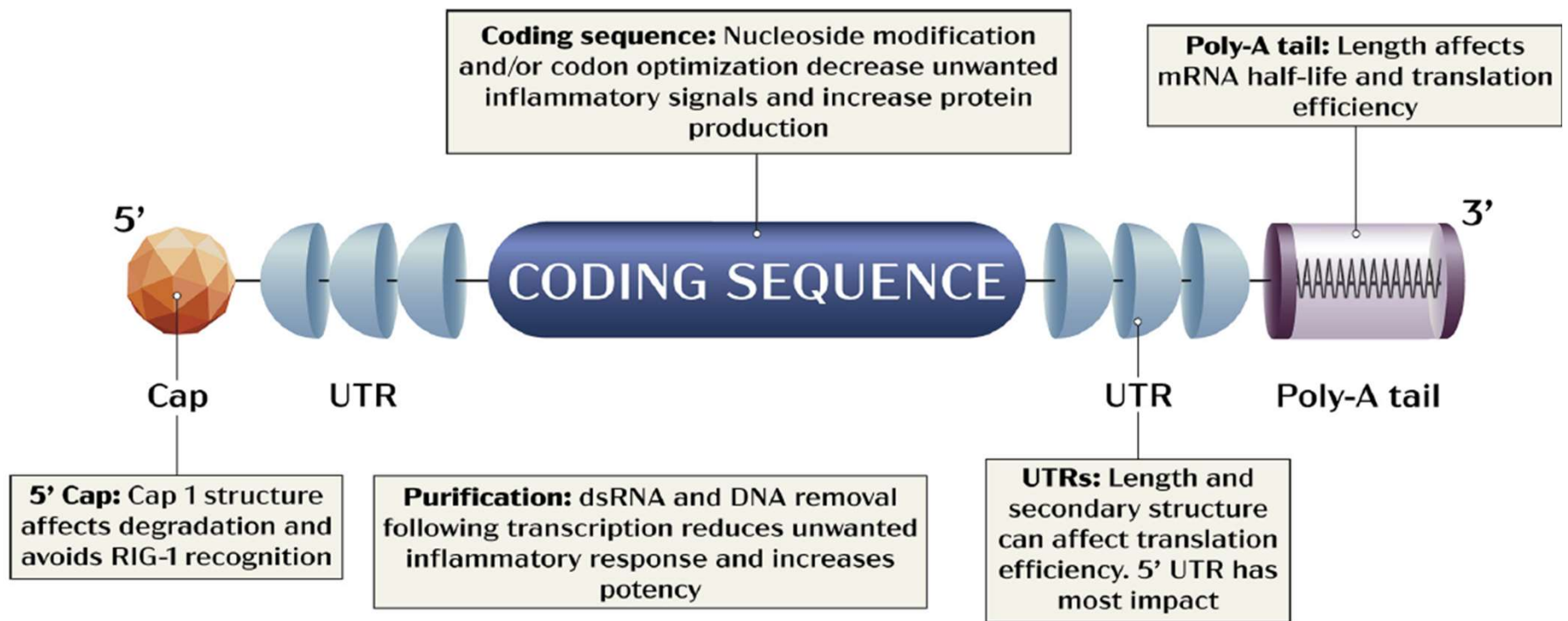
Principi dizajniranja RNK vakcina

- iRNK struktura **identična sisarskim iRNK** → dizajnirana da maksimalno dovede do produkcije proteina
 - **Nereplikujuća RNK** → jednostavna konstrukcija, ali niži stepen ekspresije antigena
 - **“Samoamplifikujuća” RNK** (Self-amplifying RNA) bazirana na genomu alfavirusa → komplikovanija konstrukcija, ali veća ekspresija antigena
- Strategije za **optimizaciju farmakoloških osobina iRNK**
 - Optimizacija translacije i stabilnosti iRNK



Sahin et al. Nat Rev Drug Discov. 2014;13:759-80

Optimizacija translacije i stabilnosti iRNK



Principi dizajniranja RNK vakcina

- iRNK struktura **identična sisarskim iRNK** → dizajnirana da maksimalno dovede do produkcije proteina
 - **Nereplikujuća RNK** → jednostavna konstrukcija, ali niži stepen ekspresije antigena
 - **“Samoamplifikujuća” RNK** (Self-amplifying RNA) bazirana na genomu alfavirusa → komplikovanija konstrukcija, ali veća ekspresija antigena
- Strategije za **optimizaciju farmakoloških osobina iRNK**
 - Optimizacija translacije i stabilnosti iRNK
 - Modulacija imunogenosti

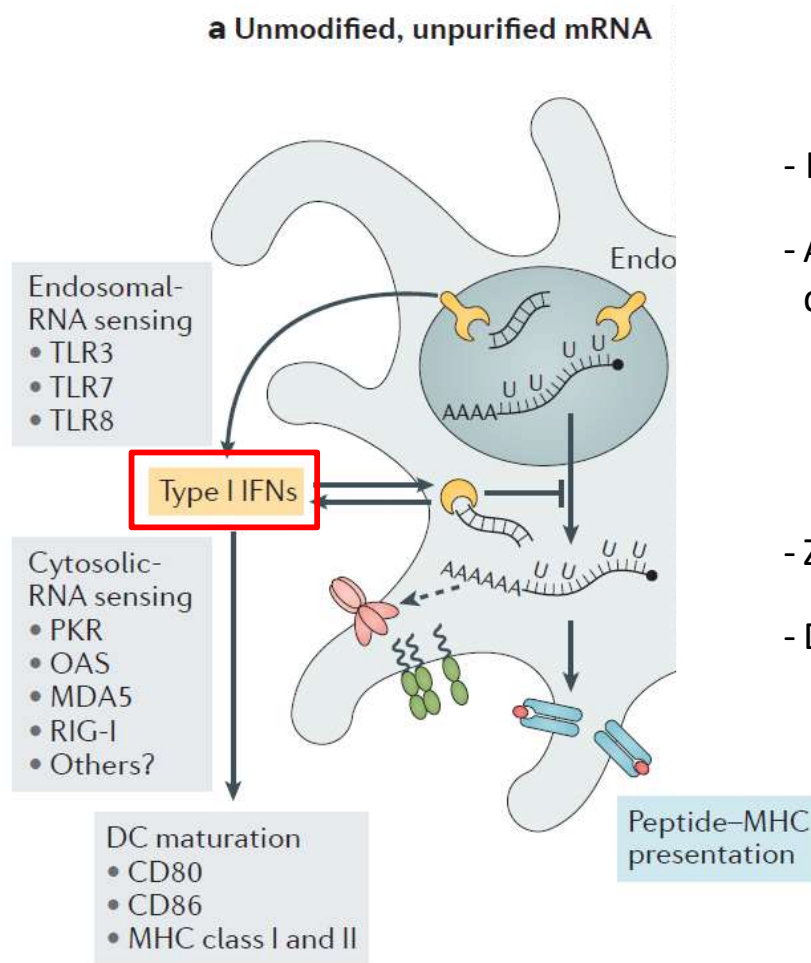
Modulacija imunogenosti

- Egzogena iRNK je izrazito imunostimulativna, jer je prepoznaje veliki broj različitih receptora urođene imunosti koji se nalaze na površini ćelije, u endozomima i u citosolu

↑ imunski odgovor

ILI

↓ imunski odgovor



↑ imunski odgovor

- Indukcija inflamacije
- Aktivacija i sazrevanje dendritskih ćelija

↓ imunski odgovor

- Zaustavljanje translacije
- Degradacija RNK

Modulacija imunogenosti

- Egzogena iRNK je izrazito imunostimulativna, jer je prepoznaje veliki broj različitih receptora urođene imunosti koji se nalaze na površini ćelije, u endozomima i u citosolu

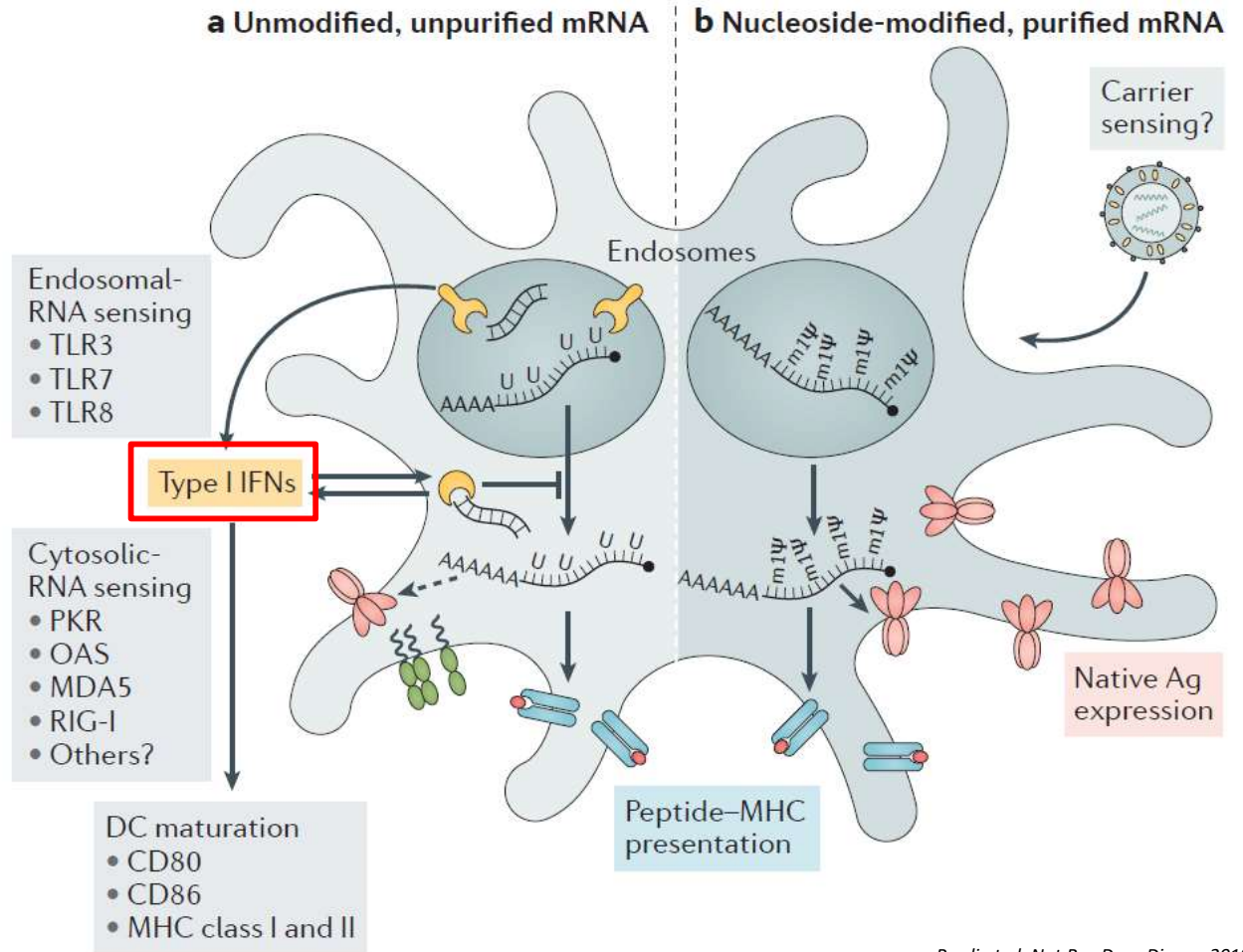
↑ imunski odgovor

ILI

↓ imunski odgovor

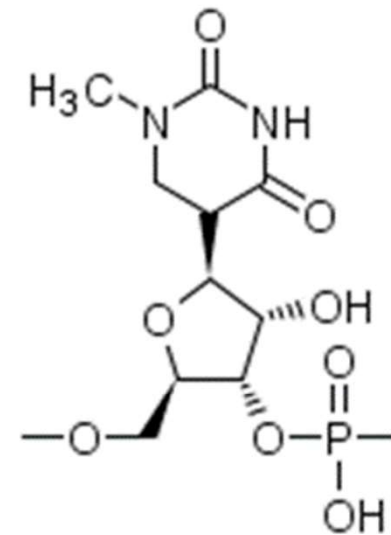
Modulacija imunogenosti

- Prečišćavanje iRNK
- Udruživanje sa molekulima nosačima
- Modifikacija nukleozida



Modifikacija nukleozida

- Zamena **uridina** sa **modifikovanim nukleozidima**
 - Pseudouridin
 - 1-Metilpseudouridin
 - ...
- Ovakvi nukleozidi se normalno nalaze u našoj sopstvenoj RNK
- Pomažu našim ćelijama da prerano ne razgrade RNK pre nego što se prevede u dovoljno proteina
- U transkripciji se čita kao uracil



$m^1\Psi$ = 1-methyl-3'-pseudouridylyl

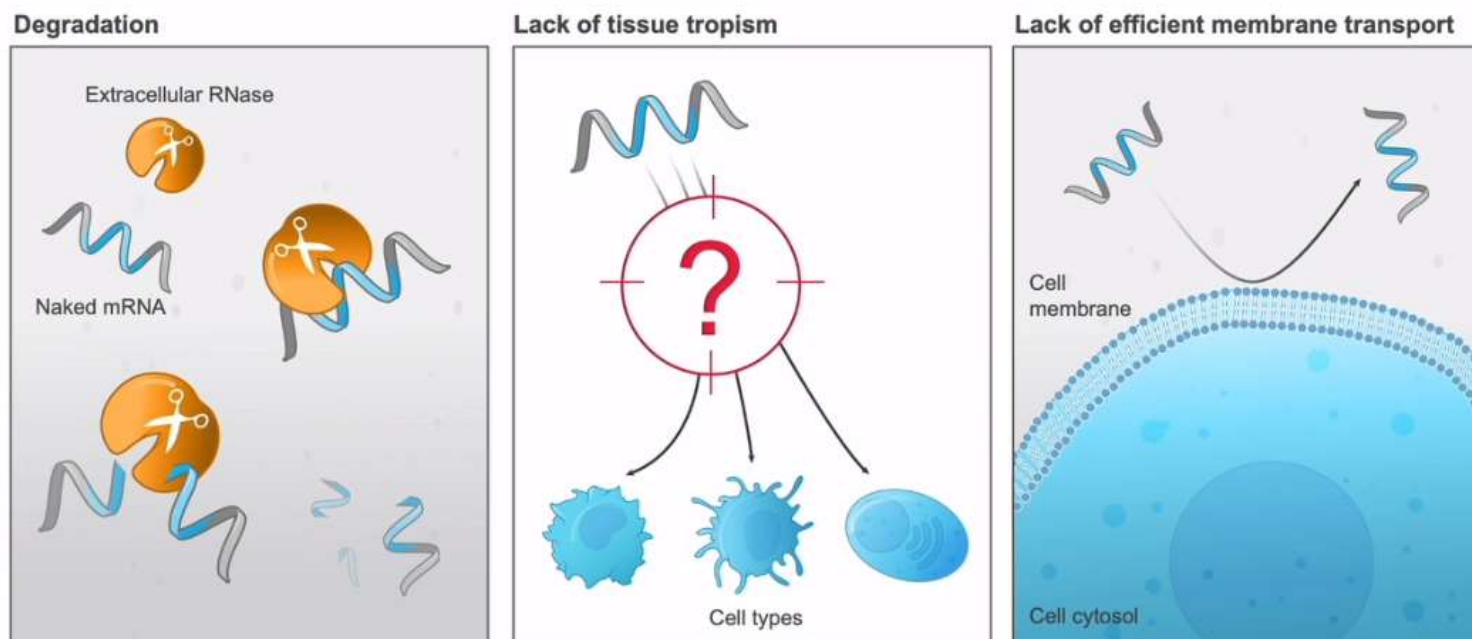
Principi dizajniranja RNK vakcina

- iRNK struktura **identična sisarskim iRNK** → dizajnirana da maksimalno dovede do produkcije proteina
 - **Nereplikujuća RNK** → jednostavna konstrukcija, ali niži stepen ekspresije antigena
 - **“Samoamplifikujuća” RNK** (Self-amplifying RNA) bazirana na genomu alfavirusa → komplikovanija konstrukcija, ali veća ekspresija antigena
- Strategije za **optimizaciju farmakoloških osobina iRNK**
 - Optimizacija translacije i stabilnosti iRNK
 - Modulacija imunogenosti
 - Povećanje efikasnosti unošenja iRNK

RNK vakcine

(Glavni načini davanja)

- iRNK treba da dospe u cioplazmu ćelije (za iRNK vakcine → antigen-presentujuće ćelije)
- Ogoljenja iRNK nije pogodna da se koristi kao lek

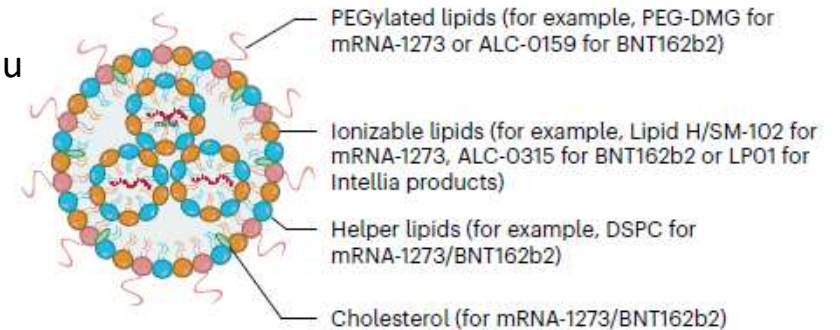


RNK vakcine

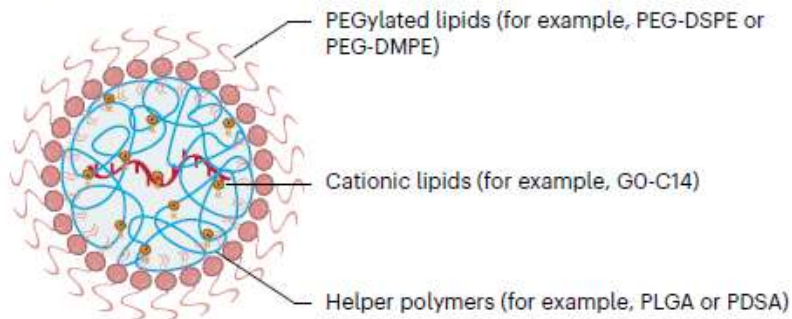
(Glavni načini davanja)

- Dva načina davanja
 - Unošenje u dendritske ćelije *ex vivo* i reinfuzija tih ćelija
 - Direktno parenteralno davanje iRNK (obično inkapsulirano u molekule nosača)
- Različiti pristupi – nisu svi podjednako efikasni *in vivo*
- Različite nanočestice – najbolji rezultati

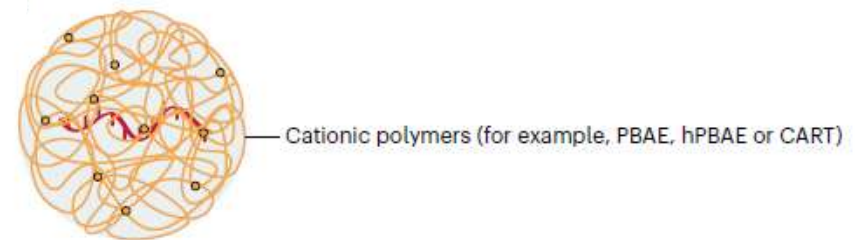
Lipid nanoparticles



Lipid-polymer hybrid nanoparticles



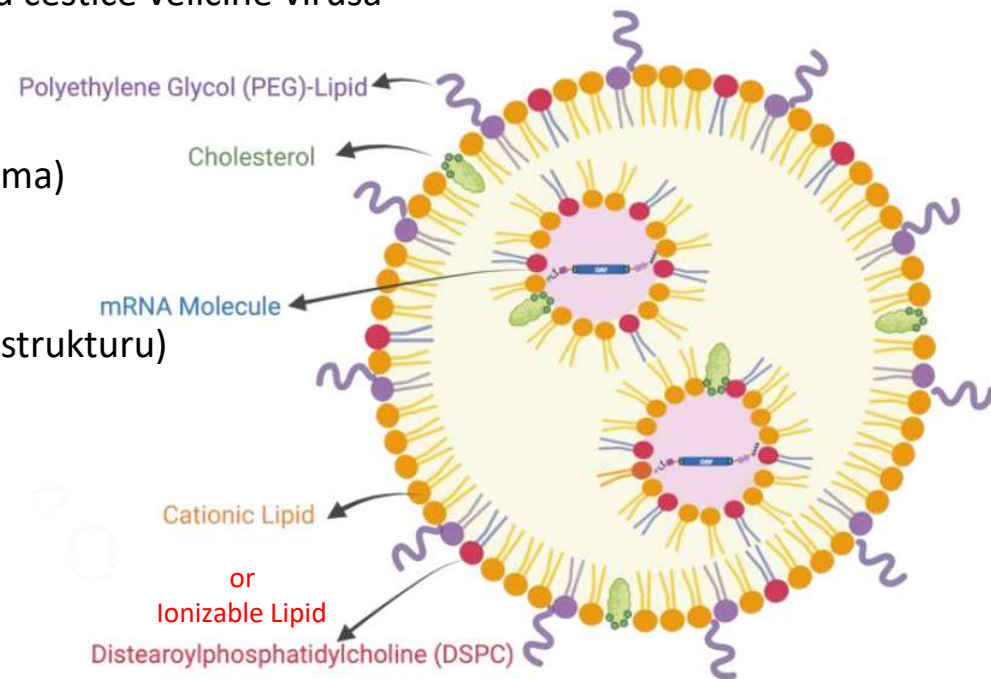
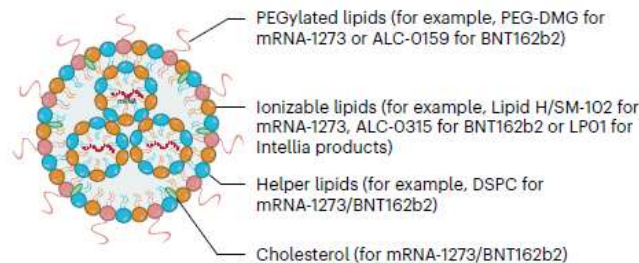
Polymeric nanoparticles



RNK vakcine

(Glavni načini davanja)

- **Lipidne nanočestice (Lipid nanoparticles, LNP)** – najefikasniji način unošenja RNK u ćelije
 - **Jonizujući ili katjonski lipidi** (promovišu samosklapanje u čestice veličine virusa i omogućavaju njihovo oslobađanje u endozomima)
 - **Polietilen glikol (PEG) povezan sa lipidima** (produžava polужivot i sprečava fuziju sa ostalim česticama)
 - **Holesterol** (stabilizujući agens)
 - **Pomoćni lipid/Fosfolipidi** (podržavaju lipidnu dvoslojnu strukturu)
 - Koriste se u svim do sada registrovanim RNK vakcinama (BNT162b2, mRNA-1273 i mRNA-1345)



Sastav RNK vakcina

(primer: mRNA-1273 vakcina koja kodira S protein SARS-CoV-2)

- Sve su komponente biorazgradive



mRNA

- Contains all naturally occurring nucleotides, including modified Uridine
- Eliminated by endogenous mRNA decay machinery



Ionizable lipid (RNA binding lipid)

- Readily breaks down to saturated fatty acids ready for elimination



Cholesterol

- Widely present in the human body



Distearoyl phosphatidylcholine (DSPC)

- Core phospholipid component of cell membranes



Polyethylene glycol (PEG) lipid

- Rapidly digested into two fatty acids and a 2k PEG polymer, which is found in numerous consumer products from toothpaste to Tylenol®



Water



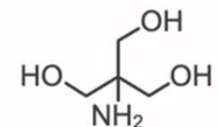
Sucrose



Sodium Chloride

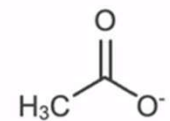


The only other components are water, sugar, salt, & GRAS pharmaceutical buffers



Tris buffer

Approved IV drug
Approved as excipient



Acetate

GRAS

RNK vakcine (Indukcija imunskog odgovora)

Article

COVID-19 vaccine BNT162b1 elicits human antibody and T_H1 T cell responses

<https://doi.org/10.1038/s41586-020-2814-7>

Received: 16 July 2020

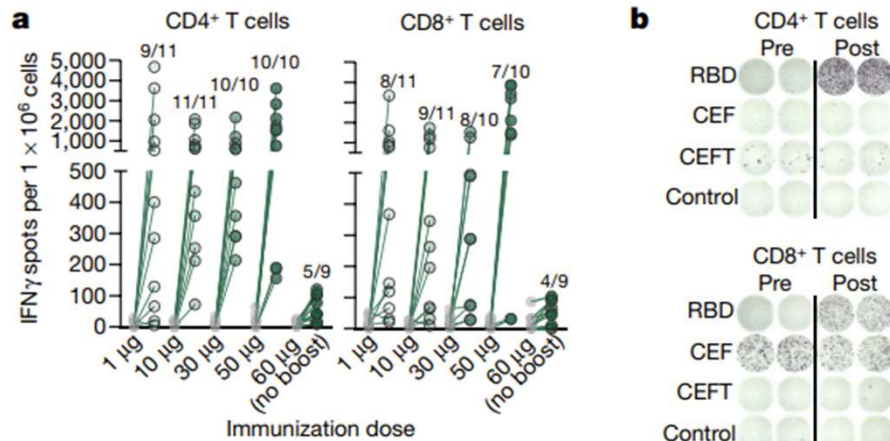
Accepted: 22 September 2020

Published online: 30 September 2020

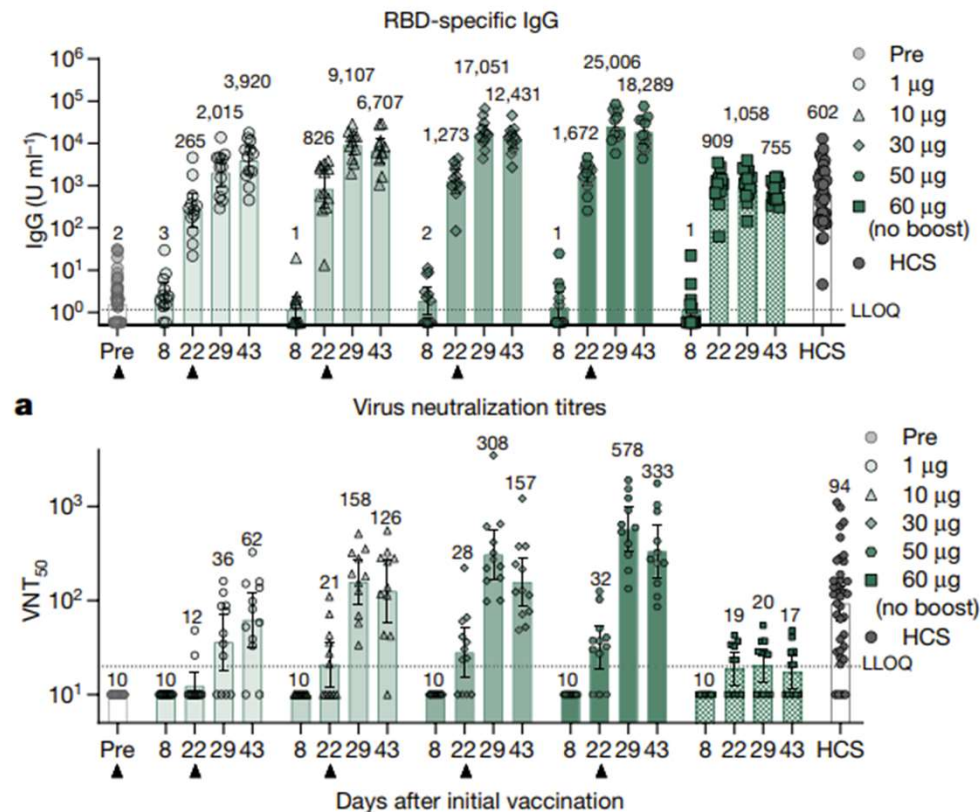
Check for updates

Ugur Sahin^{1,2}, Alexander Muik¹, Evelyn Derhovanessian¹, Isabel Vogler¹, Lena M. Kranz¹, Mathias Vormehr¹, Alina Baum³, Kristen Pascal³, Jasmin Quandt¹, Daniel Maurus¹, Sebastian Brachtendorf¹, Verena Lörks¹, Julian Sikorski¹, Rolf Hilker¹, Dirk Becker¹, Ann-Kathrin Eller¹, Jan Grützner¹, Carsten Boesler¹, Corinna Rosenbaum¹, Marie-Cristine Kühnle¹, Ulrich Luxemburger¹, Alexandra Kemmer-Brück¹, David Langer¹, Martin Bexon⁴, Stefanie Bolte¹, Katalin Karikó⁵, Tania Palanche⁶, Boris Fischer¹, Armin Schultz¹, Pei-Yong Shi⁶, Camila Fontes-Garfias⁶, John L. Perez⁷, Kena A. Swanson⁷, Jakob Loschko⁷, Ingrid L. Scully⁷, Mark Cutler⁷, Warren Kalina⁷, Christos A. Kyriatsos⁷, David Cooper⁷, Philip R. Dormitzer⁷, Kathrin U. Jansen⁷ & Özlem Türeci¹

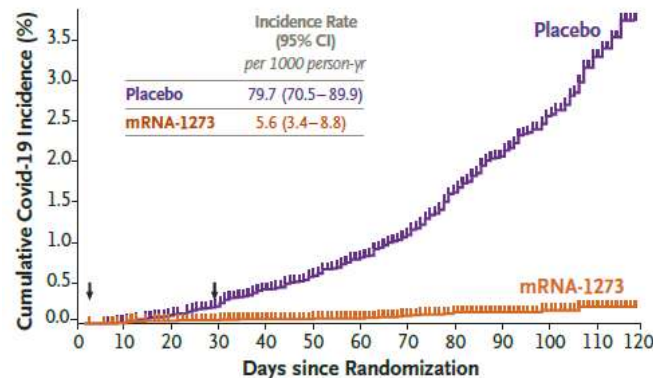
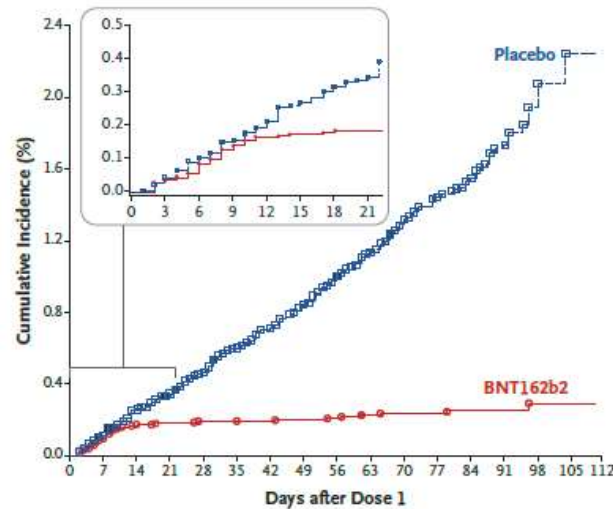
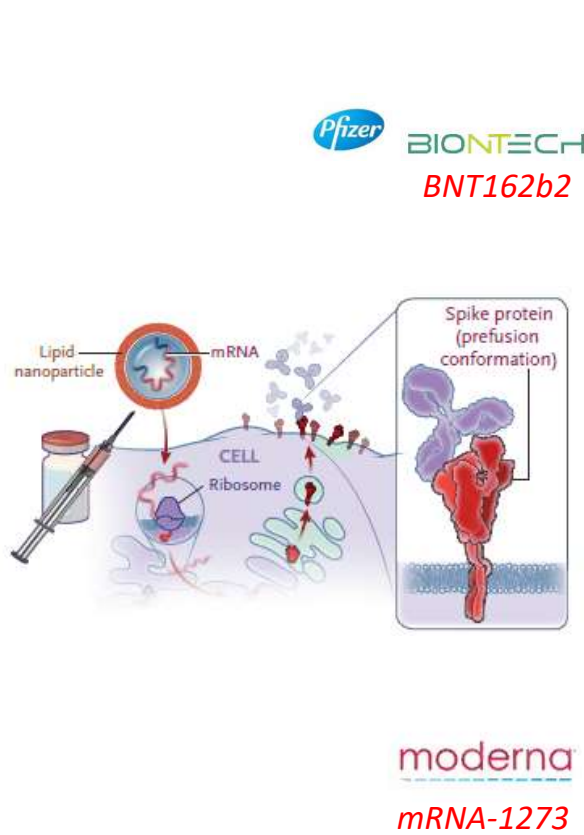
T cell response



Antibody response



Vakcine protiv COVID-19 bazirane na iRNK



	BNT162b2 Vaccine	Placebo
Symptomatic Covid-19	8	162
	N=18198	N=18325
Severe Covid-19	1	9
	N=21669	N=21686

Vaccine efficacy of **95%** (95% credible interval, 90.3–97.6%)

CONCLUSIONS

Two doses of an mRNA-based vaccine were safe over a median of two months and provided 95% protection against symptomatic Covid-19 in persons 16 years of age or older.

Polack et al. *N Engl J Med.* 2020;383:2603-15

	mRNA-1273 Vaccine	Placebo
	N=14,550	N=14,598
Symptomatic Covid-19	11	185
Severe Covid-19	0	30

Vaccine efficacy of **94.1%** (95% CI, 89.3–96.8%; $P < 0.001$)

CONCLUSIONS

Two doses of a SARS-CoV-2 mRNA-based vaccine were safe and provided 94% efficacy against symptomatic Covid-19 in persons 18 or older.

Baden et al. *N Engl J Med.* 2021;384:403-16.

RNK vakcine protiv COVID-19

(Bezbednost)

- Povoljan bezbednosni profil (milioni datih doza) – ↑ reaktogenost
- Najčešće neželjene reakcije blage i prolazne (bol , umor, bol u glavi i mišićima, jeza, groznica...)
- Teške alergijske reakcije (**anafilaksa**) veoma retke
 - 4.7/milion datih doza nakon BTN162b2 i 2.5/milion nakon mRNA-1273 (dva do četiri puta češće u odnosu na konvencionalne vakcine)
- Retki slučajevi **miokarditisa** i perikarditisa prijavljeni

- Obično 3-5 dana posle 2. doze
- Ređe nakon 3. ili 4. doze
- Češće kod mlađih muškaraca (12-29 godina)
- Miokarditis znatno češći nakon SARS-CoV-2 infekcije

Cases of Myocarditis Following mRNA COVID-19 Vaccine

- **UK:** overall rates after both doses of Pfizer/BioNTech mRNA vaccine were **4.3 myocarditis cases per million doses**^{[a]*}
- **United States:** cases of myocarditis per million second doses of mRNA vaccines^[b]:
 - **Females 12 to 29 years: 4.2 cases**
 - **Males 12 to 29 years: 40.6 cases**
 - **Females ≥ 30 years: 1 case**
 - **Males ≥ 30 years: 2.4 cases**

Cases of Myocarditis Following COVID-19 Infection

- In the United States, cases of myocarditis were estimated to be **450 myocarditis cases per million cases of COVID-19 infection**
- Cases of myocarditis per million cases of COVID-19 infection
 - **Females 12 to 17 years: 213 cases**^[c]

RNK vakcine

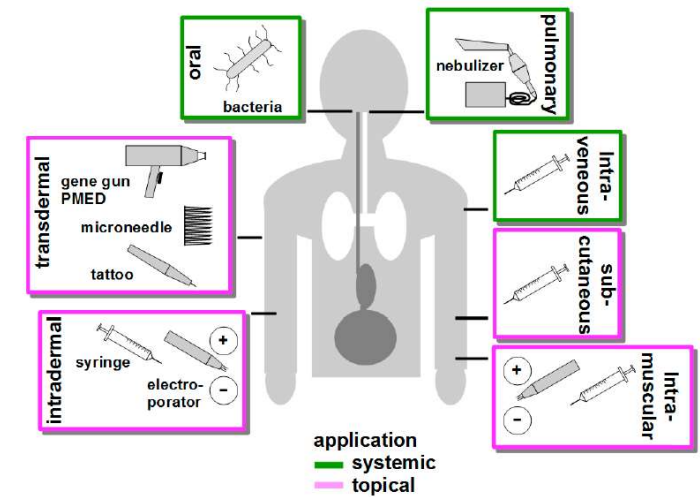
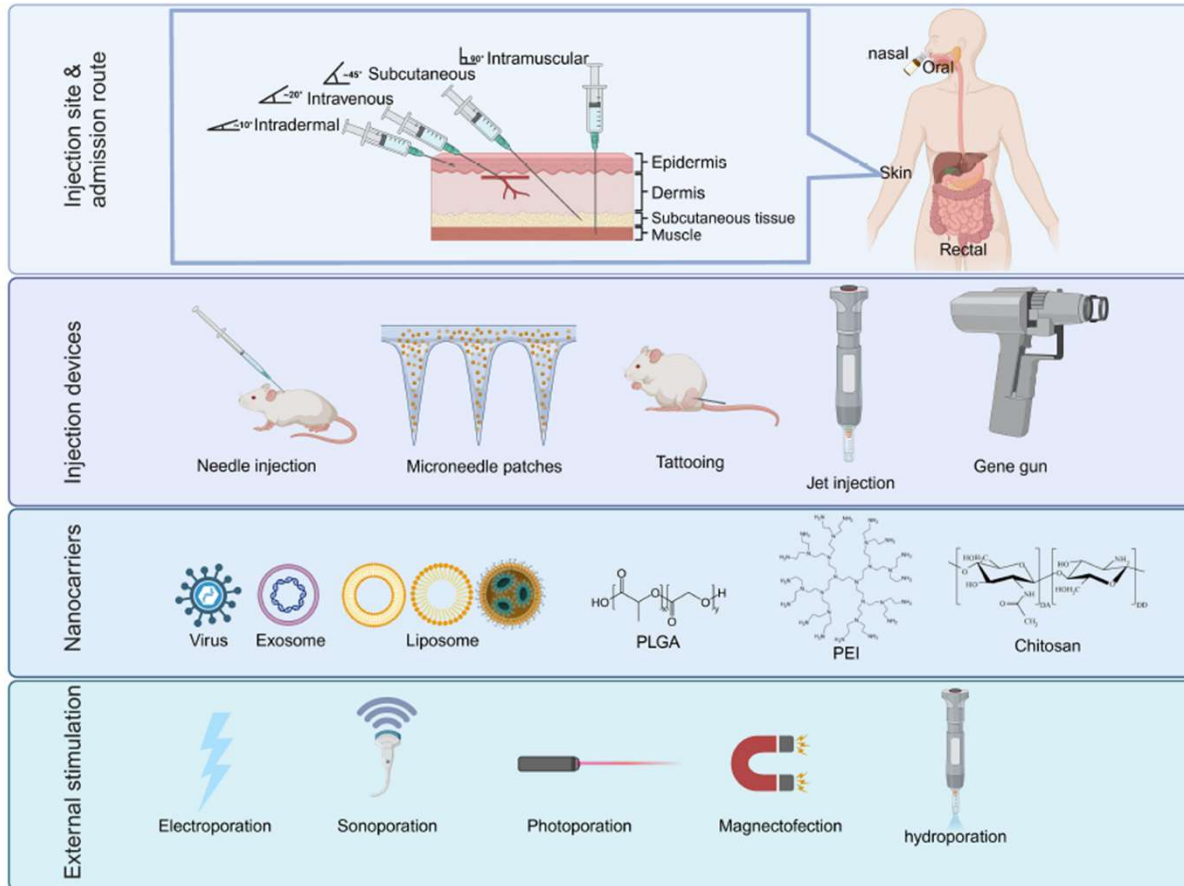
- **Prednosti (RNK vakcine ispunjavaju mnoge aspekte idealnih vakcina)**
 - Dobar bezbedonosni profil (ne perzistira u ćelijama i ne integriše se u genom)
 - Visoka imunogenost → indukcija i humoralnog (visokoafinitetna antitela) i celularnog imunskog odgovora
 - “Self-adjuvanting” efekat RNK (bez potrebe za adjuvansima)
 - Mogućnost ponovljenog davanja (nema imuniteta na RNK kao kod vektora)
 - Platforma se raznim mogućnostima (“multiplexing” i korišćenje istih kapaciteta za različite patogene)
 - Poptuno sintetička vakcina (“amenable to scale-up at low costs”) → brz razvoj novih vakcina
- **Ograničenja**
 - Nestabilnost RNK molekula (termolabilnost) i potreba da čuvanjem/transportom na niskim temperaturama
 - Problemi sa relativno kraćim trajanjem imunskog odgovora (kratka perzistencija iRNK u ćelijama)
 - Mogućnost indukcije snažnog imunskog odgovora – ↑ reaktogenost
 - Retke teže neželjene reakcije (miokarditis i anafilaktički šok)

DNK vakcine

- Imunizacija sa **bakterijskim plazmidom** koji sadrži gen(e) za imunodominantne antigene određenog/ih patogena
 - Gen patogena zajedno sa elementima neophodnim za ekspresiju u eukariotskim ćelijama (“eukaryotic expression cassette”) se ubacuje u bakterijski plazmid koji se potom umnožava u *E. coli* i prečišćava
 - Vakcina se daje na različite načine sa ciljem da plazmid ubaci u ćeliju (neophodno je da dospe u jedro)
 - Transfektovane ćelije domaćina (dendritske ćelije, miociti, keratinociti...) eksprimiraju antigen(e) patogena
 - Dendritske ćelje prezentuju antigen(e) patogena naivnim T-limfocitima u sklopu MHC molekula I i II klase → aktivacija CD4⁺ i CD8⁺ T-ćelija
 - Indukcija i celularnog i humoralnog imunskog odgovora

DNK vaccine

(Načini davanja vakcine)



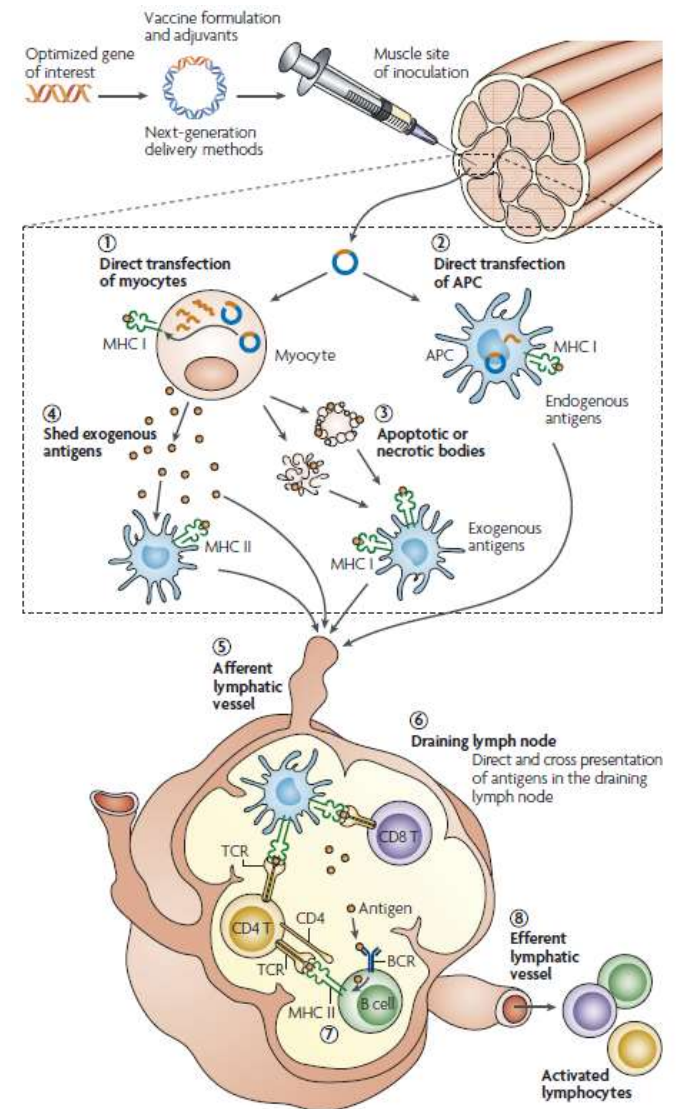
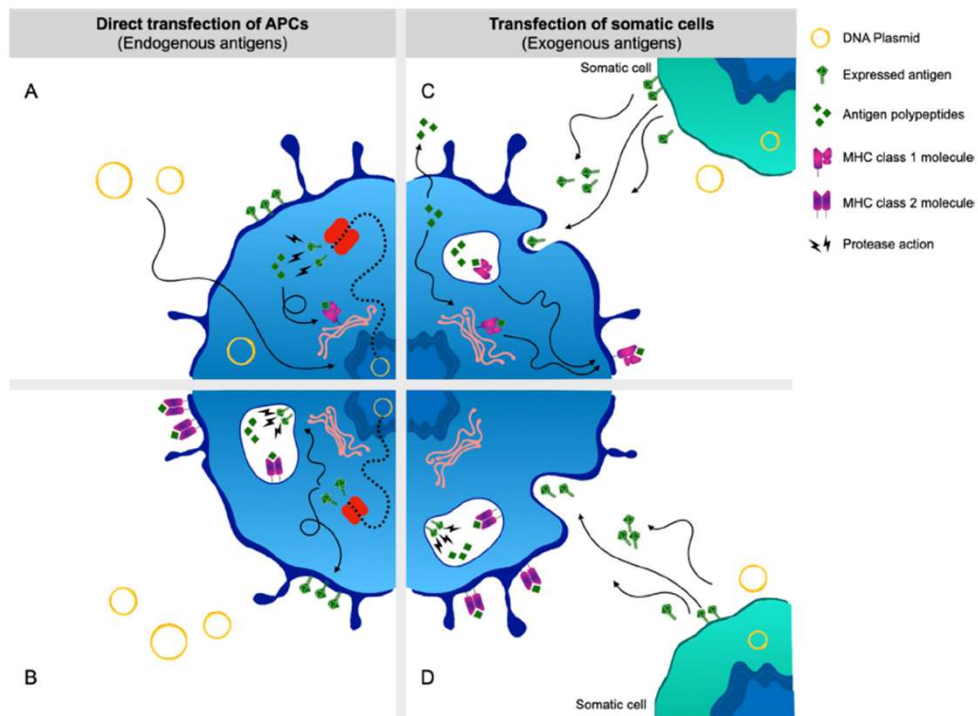
PLGA – Poly D,L-lactic-co-glycolic acid
 PEI – Polyethylenimine

Lu et al. Front Immunol. 2024;15:1332939.

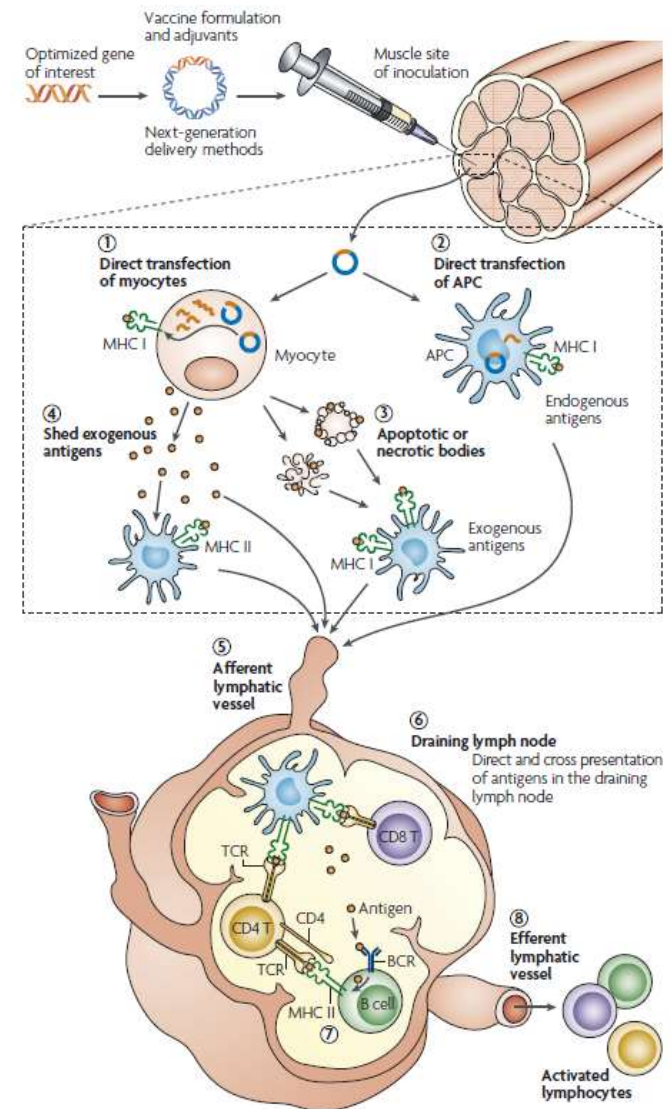
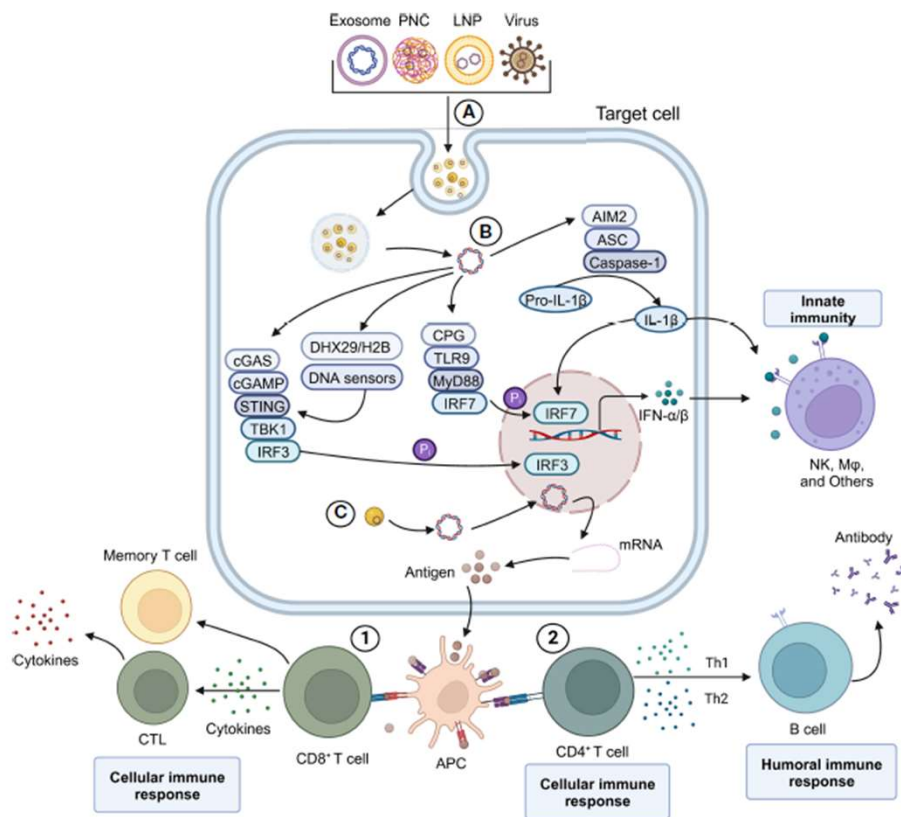
Hobernik et al. Int J Mol Sci. 2018;19:3605

DNK vakcine

(Indukcija imunskog odgovora)



DNK vakcine (Indukcija imunskog odgovora)



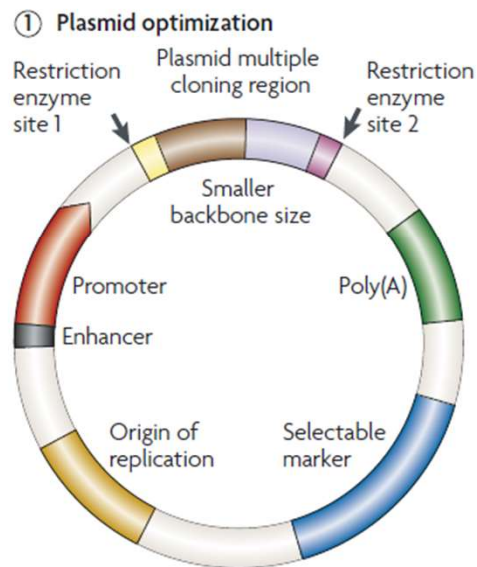
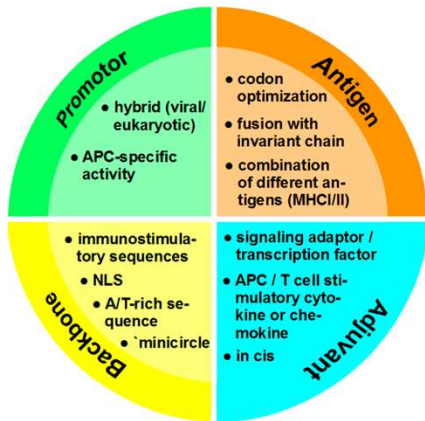
DNK vakcine

- Imunizacija sa **bakterijskim plazmidom** koji sadrži gen(e) za imunodominantne antigene određenog/ih patogena
 - Gen patogena zajedno sa elementima neophodnim za ekspresiju u eukariotskim ćelijama (“eukaryotic expression cassette”) se ubacuje u bakterijski plazmid koji se potom umnožava u *E. coli* i prečišćava
 - Vakcina se daje na različite načine sa ciljem da plazmid ubaci u ćeliju (neophodno je da dospe u jedro)
 - Transfektovane ćelije domaćina (dendritske ćelije, miociti, keratinociti...) eksprimiraju antigen(e) patogena
 - Dendritske ćelje prezentuju antigen(e) patogena naivnim T-limfocitima u sklopu MHC molekula I i II klase → aktivacija CD4⁺ i CD8⁺ T-ćelija
 - Indukcija i celularnog i humoralnog imunskog odgovora
- Ograničenje DNK vakcina
 - Problemi sa preuzimanjem plazmida i dospevanjem DNK u jedro → smanjena produkcija antigena →
→ **smanjena imunogenost i efikasnost DNK vakcina**
 - Otpimalan dizajn DNK vakcina i način davanja vakcina su ključni za efikasnost ovih vakcina

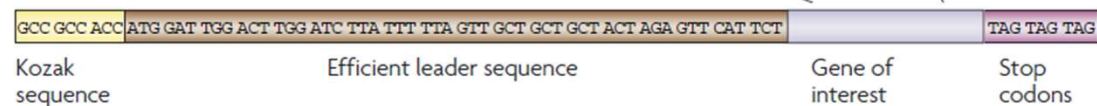
Kutzler et al. Nat Rev Genet. 2008;9:776-88
Hobernik et al. Int J Mol Sci. 2018;19:3605
Rauch et al. Front Immunol. 2018 Sep 19;9:1963.
Pagliari et al. J Mol Biol. 2023;435(23):168297

DNK vakcine

(Optimizacija DNK vakcina)



② Gene optimization



Select

- High GC content
- Species-specific codon utilization
- Consensus immunogens
- Targeting sequences
- Nuclear localization sequences
- Ubiquitin
- Chemokine fusions
- Glycosylation changes
- Helper epitopes

Avoid

- Internal TATA-boxes
- Chi-sites
- Ribosomal entry sites
- AT-rich sequence stretches
- Repeat sequences
- RNA secondary structures
- Cryptic splice donor or acceptor sites
- Branch points

③ Formulation adjuvants

- Alum
- Saponins
- Anesthetics
- Microsphere/nanoparticle
- Liposomes
- Polymers
- Microemulsion

④ Immune plasmid adjuvants

- Cytokine
- Chemokine
- Toll-receptor ligands
- Costimulatory molecules
- Heat shock proteins

⑤ Delivery

- Intramuscular
- Electroporation
- Transcutaneous microneedle
- Skin abrasion
- Gene gun
- Ultrasound
- Tattoo perforating needle
- Jet-injector
- Topical patch



APC – Antigen-presenting cell
NLS – Nuclear localization signal

Kutzler et al. *Nat Rev Genet.* 2008;9:776-88
Hobernik et al. *Int J Mol Sci.* 2018;19:3605

DNK vakcine

- Prednosti DNK vakcina
 - Lakoća manipulacije i višestruka mogućnost primene (mogu antigeni većina patogena)
 - Jednostavna proizvodnja (različite vakcine mogu da se prave sa istom opremom)
 - Mogućnost brze produkcije velikih količina (uz male troškove)
 - Indukuju dugotrajan celularni i humoralni odgovor
 - Velika stabilnost DNK molekula → termostabilnost DNK vakcina (bez potrebe za hladnim lancem)
 - Ne indukuju odgovor na plazmid → mogu da se daju više puta
 - Nisu žive vakcine → potencijalno mogu da se daju i imunokompromitovanim osobama

DNK vakcine

- Prednosti DNK vakcina
 - Lakoća manipulacije i višestruka mogućnost primene (mogu antigeni većina patogena)
 - Jednostavna proizvodnja (različite vakcine mogu da se prave sa istom opremom)
 - Mogućnost brze produkcije velikih količina (uz male troškove)
 - Indukuju dugotrajan celularni i humoralni odgovor
 - Velika stabilnost DNK molekula → termostabilnost DNK vakcina (bez potrebe za hladnim lancem)
 - Ne indukuju odgovor na plazmid → mogu da se daju više puta
 - Nisu žive vakcine → potencijalno mogu da se daju i imunokompromitovanim osobama
- DNK vakcine u razvoju još od 1990-tih godina
 - Veliki broj vakcina u razvoju u različitim kliničkim fazama (HIV, Ebola, grip, malarija, Zika, RSV, ...)
 - Nekoliko vakcina odobrene za upotrebu u veterinarskoj medicini (npr. protiv West-Nile virusa kod konja)
 - Nijedna vakcina se za sada redovno ne koristi u humanoj medicini (jedna DNK vakcina protiv SARS-CoV-2 virusa bila je odobrena u Indiji tokom pandemije)

DNK vakcine

(Vakcine u razvoju i registrovane vakcine)

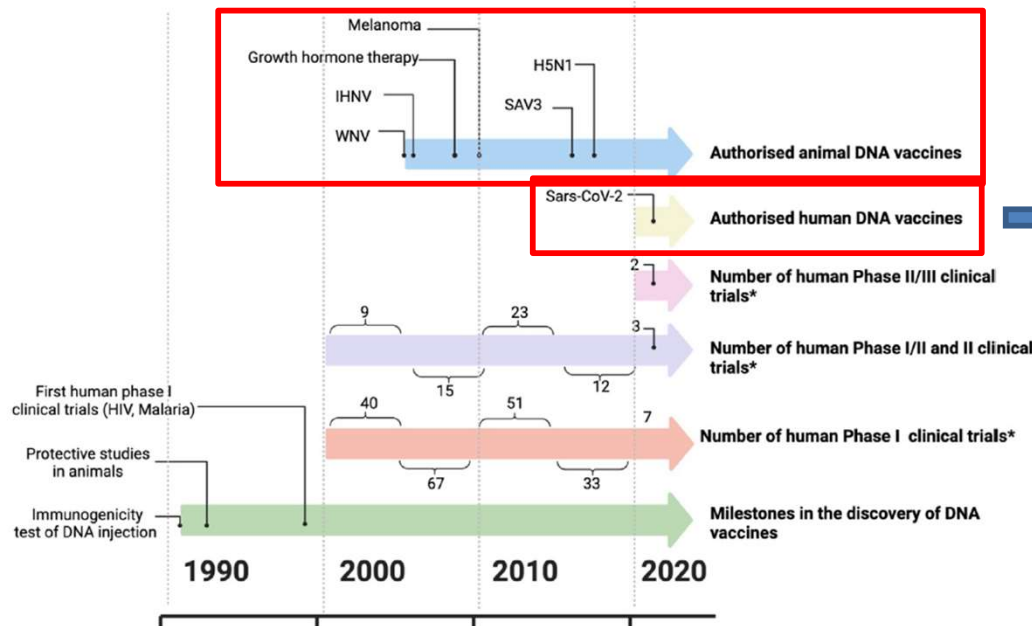


Table 1 DNA vaccines licensed for veterinary use.

Type	Species	Target	Product/Company	Licensed date/Country	Route of administration
Prophylactic vaccine	Horses	West Nile Virus (WNV)	West Nile-Innovator/ CDC and Fort Dodge Animal Health	2005/USA	IM
	Salmon	Infectious haematopoietic necrosis virus (IHN)	Apex-IHN/Novartis Animal Health	2005/Canada	IM
	Salmon	Salmon alphavirus subtype 3 (SAV3)	Cynav/Elanco Animal Health	2016/EU	IM
Cancer Immunotherapy	Poultry	Avian Influenza A (H5N1)	ExactVac/AgriLabs	2017/USA	IM
	Dogs	Melanoma	Oncept/Merial	2010/USA	ID needle-free
	Swine	Growth hormone	LifeTide/SWS/VGX Animal Health	2008/Australia	IM followed by electroporation

IM: Intramuscular; ID: Intradermal.

Developer	Vaccine	Description	Status
Zydus Cadila; Department of Biotechnology, Government of India	ZyCoV-D	Three-dose DNA plasmid vaccine encoding SARS-CoV-2 S protein and IgE signal peptide delivered intradermally by the needle-free PharmaJet Tropis device	Received Emergency Use Authorization in India, 20 August 2021

First COVID-19 DNA vaccine approved, others in hot pursuit

India's approval of a nucleic acid vaccine hints at a solution for low-income nations—if the limitations of current delivery technology can be overcome.

The Emergency Use Authorization of a DNA-based COVID-19 vaccine by India's regulator is a milestone for a nucleic acid technology that has been largely overlooked during the pandemic. Although the approval of ZyCoV-D from Indian pharma Zydus Cadila represents a historic first for DNA-based vaccines, peer-reviewed data describing the safety and efficacy of the spike-protein-encoding vaccine have yet to be published. If DNA vaccines can overcome historic inefficiencies of delivery to antigen-presenting cells (APCs) and concerns can be allayed as to potential genotoxicity risks that could arise from chromosomal integration, their high stability, durability of response (including enhanced T-cell immunity) and ease of manufacture could make them a valuable alternative to mRNA, adenoviral vector and recombinant protein vaccine technologies.



India's ZyCoV-D vaccine uses circular DNA to protect against SARS-CoV-2 infection. Credit: Zydus Cadila

Sheridan. *Nat Biotechnol.* 202139(12):1479-1482.
Pagliari et al. *J Mol Biol.* 2023;435(23):168297.

DNK vakcine

(Vakcine u razvoju i registrovane vakcine)

Efficacy, safety, and immunogenicity of the DNA SARS-CoV-2 vaccine (ZyCoV-D): the interim efficacy results of a phase 3, randomised, double-blind, placebo-controlled study in India

Akash Khobragade, Suresh Bhat, Vijendra Ramaiah, Shrikant Deshpande, Krishna Giri, Himanshu Phophle, Pravin Supe, Inderjeet Godara, Ramesh Revanna, Rajnish Nagarkar, Jayesh Sanmukhani, Ayan Dey, T M Chozhavel Rajanathan, Kevinkumar Kansagra, Parshottam Koradia, on behalf of the ZyCoV-D phase 3 Study Investigator Group*

Summary

Background ZyCoV-D, a DNA-based vaccine, showed promising safety and immunogenicity in a phase 1/2 trial. We now report the interim efficacy results of phase 3 clinical trial with ZyCoV-D vaccine in India.

Methods We conducted an interim analysis of a multicentre, double-blind, randomised, placebo-controlled phase 3 trial at 49 centres in India. Healthy participants aged at least 12 years were enrolled and randomly assigned (1:1) to receive either ZyCoV-D vaccine (Cadila Healthcare; 2 mg per dose) or placebo. An interactive web response system was used for randomisation (blocks of four) of participants as well as to enrol those aged 60 years and older with or without comorbid conditions, and those aged 12–17 years. It was also used to identify 600 participants for immunogenicity (blocks of six). Participants, investigators, and outcome assessors were masked to treatment assignment. Three doses of vaccine or placebo were administered intradermally via a needle-free injection system 28 days apart. The primary outcome was the number of participants with first occurrence of symptomatic RT-PCR-positive COVID-19 28 days after the third dose, until the targeted number of cases (interim analysis n=79, full analysis n=158) have been achieved. The analysis was done in the per-protocol population, which consisted of all participants with negative baseline SARS-CoV-2 status who received three doses of vaccine or placebo. Assessment of safety and tolerability was based on the safety population, which consisted of all enrolled participants who were known to have received at least one dose of study vaccine or placebo. This trial is registered with Clinical Trial Registry India, CTRI/2021/01/030416, and is ongoing.

Findings Between Jan 16, and June 23, 2021 (data cutoff), 33194 individuals were screened, of whom 5241 did not meet screening criteria and 27703 were enrolled and randomly assigned to receive ZyCoV-D (n=13851) or placebo (n=13852). Per-protocol, 81 cases were eligible and included in efficacy analysis (20 of 12320 in the ZyCoV-D group and 61 of 12320 in placebo group). The ZyCoV-D vaccine efficacy was found to be 66.6% (95% CI 47.6–80.7). The occurrence of solicited adverse events was similar between the treatment groups (623 [4.49%] in the ZyCoV-D group vs 620 [4.47%] in the placebo group). There were two deaths (one in each group) reported at the data cutoff, neither of which was considered related to the study treatments.

Interpretation In this interim analysis, ZyCoV-D vaccine was found to be efficacious, safe, and immunogenic in a phase 3 trial.



Lancet 2022; 399: 1313–21
See Comment page 1281

*Group members are listed at end of the Article

Grant Government Medical College and Sir JJ Group of Hospital, Byculla, Mumbai, India (A Khobragade MD); Jeevan Rekha Hospital, Belagavi, Karnataka, India (S Bhat MD); Kempegowda Institute of Medical Sciences Hospital and Research Center, Bengaluru, Karnataka, India (V Ramaiah MD); Ashirwad Hospital, Ulhasnagar, Maharashtra, India (S Deshpande MD); Dhadiwal Hospital Research Department, Nashik, Maharashtra, India (K Giri MD); Ace Hospital, Pune, Maharashtra, India (H Phophle MD); Supe Hospital, Nashik, Maharashtra, India (P Supe MD); Manudhar Hospital, Jalpur, Rajasthan, India (I Godara MD); N R R Hospital, Bengaluru, Karnataka, India (R Revanna MD); HCG Manavata Cancer Centre, Nashik, Maharashtra, India (R Nagarkar MD); Zydus Corporate Park

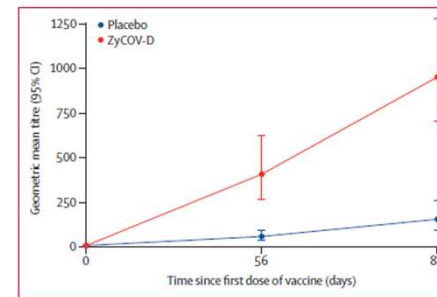


Figure 2: IgG comparison of geometric mean titre of ZyCoV-D and placebo at days 0, 56, and 84

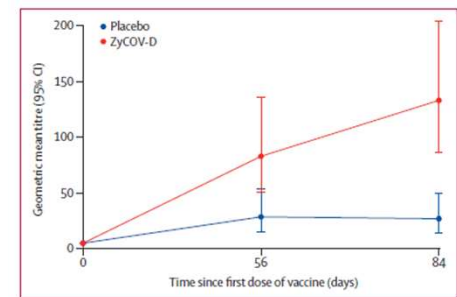


Figure 3: NAB (PRNT₅₀) comparison of geometric mean titre of ZyCoV-D and placebo at days 0, 56, and 84

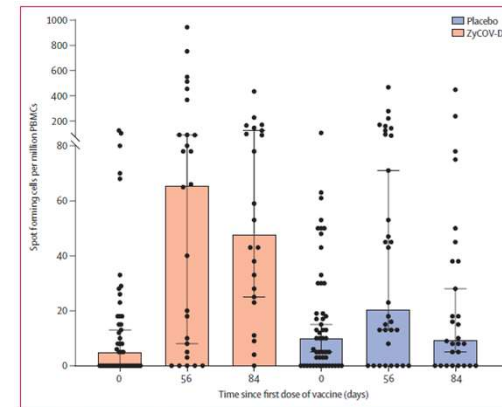


Figure 4: Cellular response (IFN-γ) to ZyCoV-D and placebo at days 0, 56, and 84
PBMC=peripheral blood mononuclear cells.

DNK vakcine

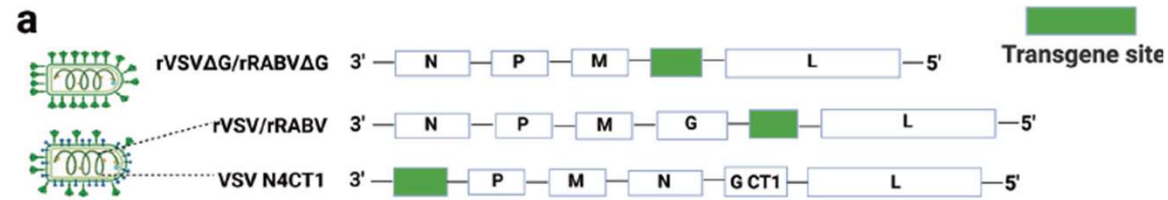
- Bezbednosni apsekti i potencijalni rizici
 - Generalno se DNK vakcine **smatraju bezbednim**
 - Mogućnost **duže perzistencije plazmida i integracije u genom domaćina** (?)
 - Mogućnost indukcije zapaljenja i auto-antitela (npr. anti-DNK antitela) → **autoimunost i/ili honična inflamacija** (?)
 - Duža perzistencije plazmida (naročito na mestu davanja) evidentna u nekim animalnim modelima
 - Integracija detektovana u nekim animalnim modelima nakon elektroporacije (tri reda veličine ređa u odnosu na spontane mutacije)
 - Kliničke studije kod ljudi → **nema dokaza** da plazmidska DNK može da se integriše u genom ćelije vakcinisane osobe i/ili indukuje autoimunost (WHO, 2020)
 - WHO – preporuke da se rade prekliničke studije koji ispituju integraciju DNK
 - FDA – preporuke da se rade studije koji ispituju integraciju DNK, ako broj kopija plazmidske DNK prelazi 30.000 kopija na 1 µg DNK domaćina

Vektorske vakcine

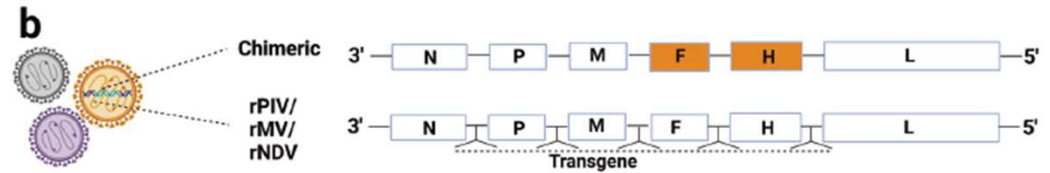
- Imunizacija sa „vektorima“ (najčešće modifikovanim virusima) koji sadrže gen(e) za imunodominantne antigene patogena
 - Gen od interesa poreklom od patogena (nesrodan sa virusom) se ubacuje u genom virusnog vektora
 - Nereplikujući virusi – najčešće adenovirusi (humani Ad5 i Ad26, i primata ChAdOx1)...
 - Replikujući (atenuisani) virusi – virus vezikularnog stomatitisa (VSV), morbili, CMV...
 - Nakon ulaska vektora u ćelije domaćina (transdukcije), one počinju da eksprimiraju antigen(e) patogena (obično dugotrajno) i indukuju imunski odgovor
 - Dendritske ćelje prezentuju antigen(e) patogena naivnim T-limfocitima u sklopu MHC molekula I i II klase → aktivacija CD4⁺ i CD8⁺ T-ćelija
 - Indukcija i celularnog i humoralnog imunskog odgovora

Različiti virusni vektori koji se koriste u vakcinama

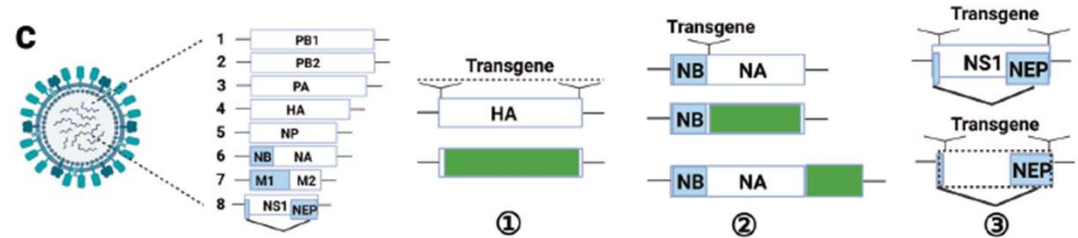
Rhabdovirus vector



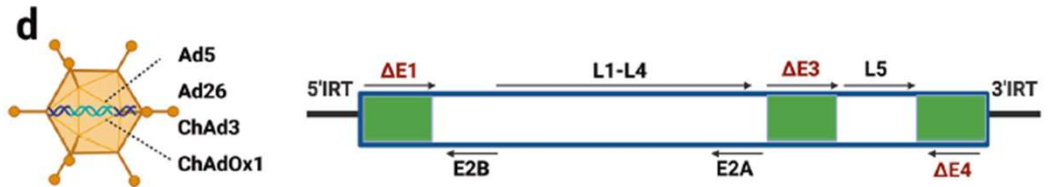
Chimeric paramyxovirus vector



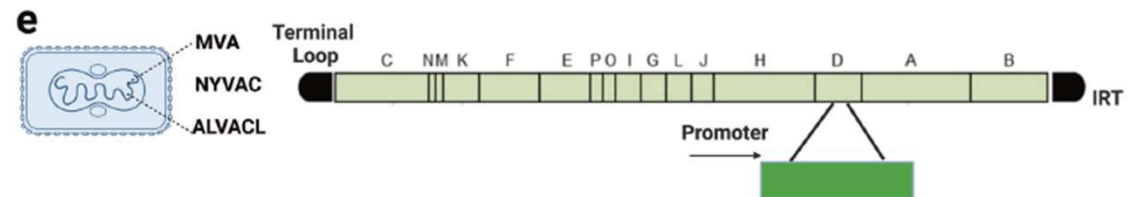
Influenza virus vector



Adenovirus vector



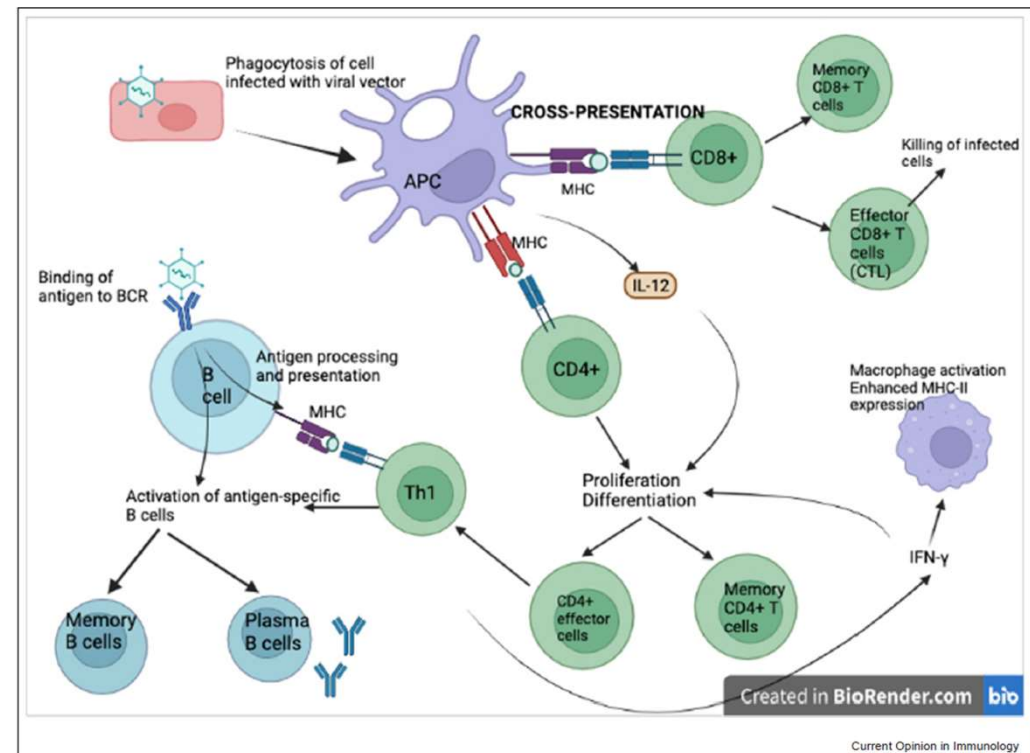
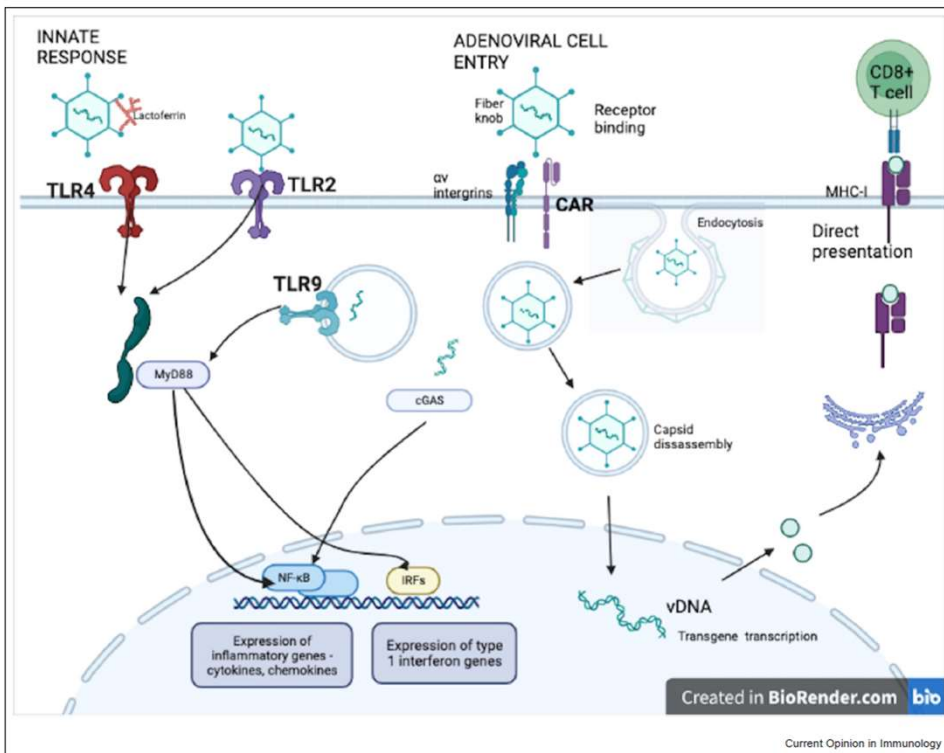
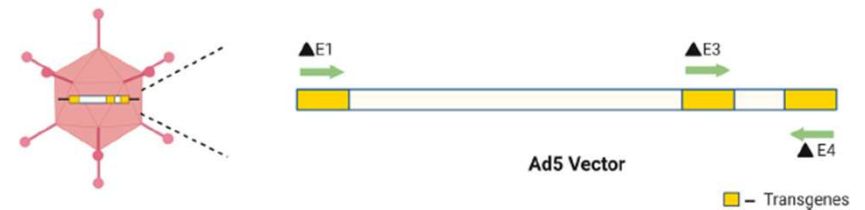
Poxvirus vector



Wang et al. Signal Transduct Target Ther. 2023;8(1):149.

VSV – Vesicular stomatitis virus
RABV – Rabies virus
PIV – Parainfluenza virus
MV – Measles virus
NDV– Newcastle disease virus
IFV – Influenza virus
Ad – Adenovirus
ChAd – Chimpanzee adenovirus
MVA – Modified vaccinia virus Ankara
ALVACL – Canarypox virus
NYVAC – New York attenuated vaccinia virus

Vektorske vakcine (Indukcija imunskog odgovora)



Vektorske vakcine (Indukcija imunskog odgovora)

- ChAdOx1 nCoV-19 vakcina

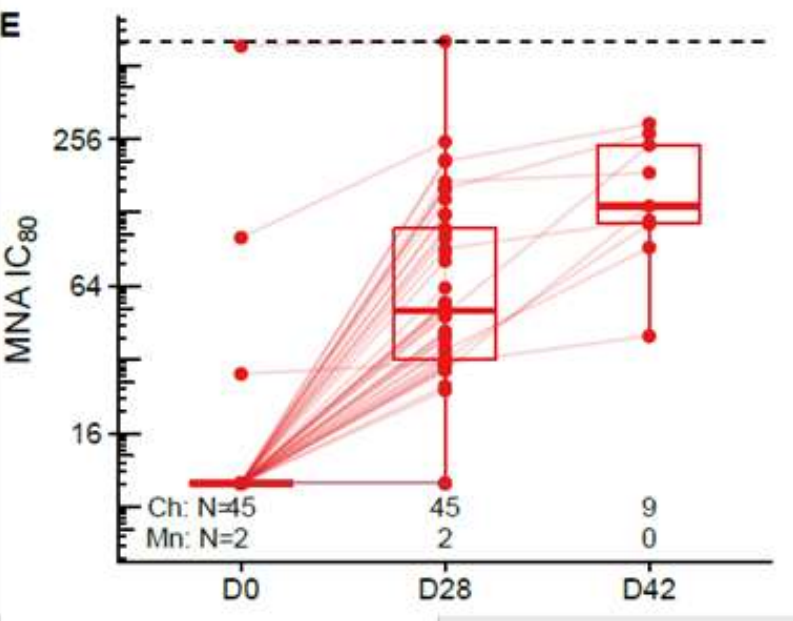
Articles

Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial

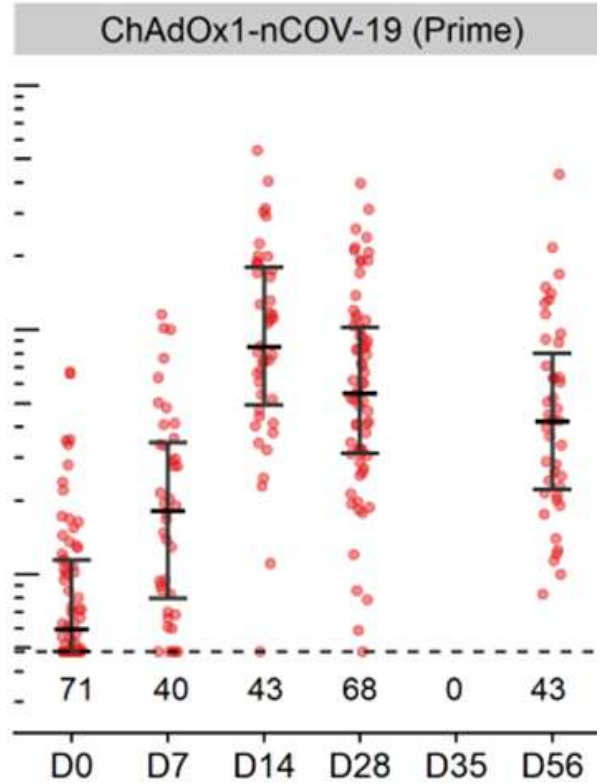
Pietro M Folegatti¹*, Katie J Ewer², Parvinder K Aley, Brian Angus, Stephan Becker, Sandra Belij-Rammensdorff, Duncan Bellamy, Sagida Bibi, Mustapha Bittaye, Elizabeth A Clutterbuck, Christina Dold, Saul N Faust, Adam Finn, Amy L Flaxman, Bassam Hallis, Paul Heath, Daniel Jenkins, Rajeka Lazarus, Rebecca Makinson, Angela M Minassian, Katrina M Pollack, Maheshi Ramassamy, Hannah Robinson, Matthew Snape, Richard Tarrant, Meryn Voysey, Catharine Green³, Alexander D Douglas⁴, Adrian V S Hill⁵, Teresa Lamb⁶, Sarah C Gilbert⁴, Andrew J Pollard⁴, on behalf of the Oxford COVID Vaccine Trial Group†

Summary
Background The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might be curtailed vaccination. We assessed the safety, reactogenicity, and immunogenicity of a viral vectored coronavirus vaccine that expresses the spike protein of SARS-CoV-2.

Methods We did a phase 1/2, single-blind, randomised controlled trial in five trial sites in the UK of a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein compared with a meningococcal conjugate vaccine (MenACWY) as control. Healthy adults aged 18–55 years with no history of laboratory confirmed SARS-CoV-2 infection were recruited. The primary endpoint was the proportion of participants with a serological response to the vaccine at day 28.



T cells response



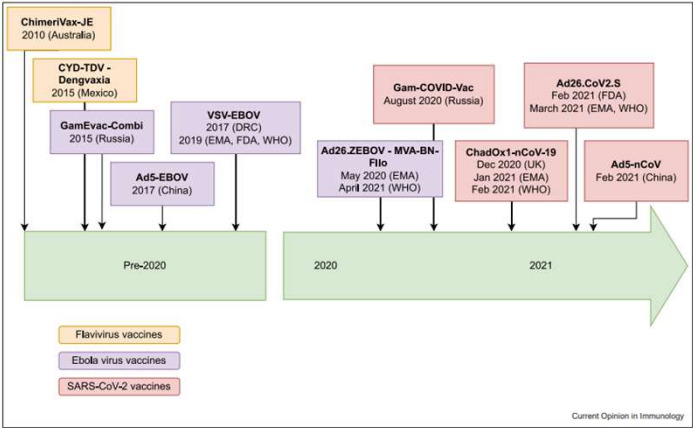
Folegatti et al. Lancet. 2020;396(10249):466.

Vektorske vakcine

- Prednosti vektorskih vakcina
 - Dobar bezbedosni profil (smanjena reaktogenost naročito kod nereplikujućih vektora) i potencijal za multivalentne vakcine (prezentacija više antigena istovremeno)
 - Indukcija snažnog i dugotrajnog celularnog i humoralnog imunskog odgovora
 - Mogu da budu dizajnirani da indukuju ekspresiju antigena u određenoj/om ćeliji/tkivu
 - Različita mogućnost davanja (tipično intramuskularno, ali moguće i intradermalno, oralno, nazalno, preko aerosola...)
 - ↑ stabilnost liofilizacijom, mogućnost produkcije velikih količina (uz male troškove)
- Ograničenje vektorskih vakcina
 - Postojanje imuniteta na vektor kod vakcinisanog ili razvoj imuniteta na prethodnu dozu – ↓ efektivnost vakcina i problem za revakcinaciju istim vektorom
 - Smanjena imunogenost kod nereplikujućih vektora (potreba za višom dozom i davanjem bustera)
 - Kompleksna proizvodnja (mnoge kontrole) i ne mogu da se kombinuju različiti vektori korišćenjem iste opreme
 - Mogućnost perzistentne replikacije virusa kod imunodeficientnih osoba (za replikujuće vektore)

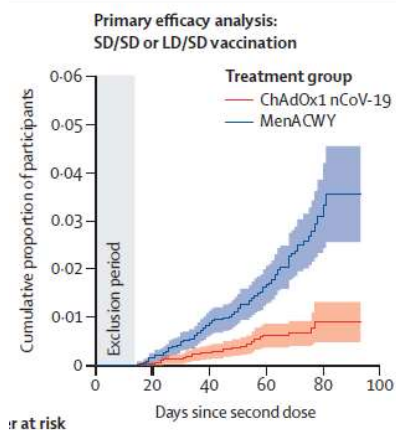
Vektorske vakcine

- Dugo traju istraživanja (još od 1980-tih) i urađeno je puno pretkliničkih i kliničkih studija
 - Veliki broj eksperimentalnih vakcina (HIV, Zika, MERS, malarija, influenza ...)
 - Registrovane vakcine – protiv Ebole (npr. Ervebo sa VSV) i denge (npr. Dengvaxia sa virusom žute groznice) i nekoliko vakcina protiv COVID-19 („AstraZeneca“, „Sputnik V“, „Janssen/Johnson&Johnson“)



Currently licensed viral vector vaccines for use in humans.					
Vector class	Vector	Vaccine	Target pathogen	Encoded antigen	Developer
Adenoviruses	Ad5	Ad5-nCoV (Convidecia)	SARS-CoV-2	Spike protein	CanSino Biologics (China)
		Ad5-EBOV	Ebola virus	Zaire strain (Makona) of glycoprotein	CanSino Biologics Inc
	Ad26	Ad26, CoV	SARS-CoV-2	Pre-fusion- stabilised spike protein	Janssen Pharmaceutical Companies
		Sputnik light	SARS-CoV-2	Spike protein	Gamaleya Research Institute of Epidemiology and Microbiology (Russia)
	ChAdOx1	ChAdOx1- nCoV-19 (Covishield, Vaxzevria)	SARS-CoV-2	Spike protein with tissue plasminogen leader sequence	University of Oxford/AstraZeneca
Rhabdoviruses	VSV	VSV-EBOV (rVSV-ZEBOV, Ervebo)	Ebola virus	Zaire strain (Kikwit 1995) of glycoprotein	Merck
Flaviviruses	YF 17D	ChimeriVax-JE (Imojev)	Japanese encephalitis	Viral envelope (prM and E) of JE strain SA14-14-2	Sanofi Pasteur
Heterologous regimens	Ad5/Ad26	CYD-TDV (Dengvaxia)	Dengue	prM and E genes of DENV 1-4	Sanofi Pasteur
		Gam-COVID-Vac (Sputnik V)	SARS-CoV-2	Both spike proteins	Gamaleya Research Institute of Epidemiology and Microbiology (Russia)
	VSV/Ad5	GamEvac-Combi	Ebola virus	Both glycoproteins	Gamaleya Research Institute of Epidemiology and Microbiology (Russia)
	Ad26/MVA	Ad26, ZEBOV (Zabdeno) MVA-BN-Filo (Mvabea)	Ebola virus	Ad26 — Zaire strain MVA — glycoproteins from the Zaire Ebola virus (Mayinga strain), Sudan virus (Gulu strain) and Marburg virus (Musoke strain), and the nucleoprotein from the Tai Forest virus	Janssen Pharmaceutical Companies

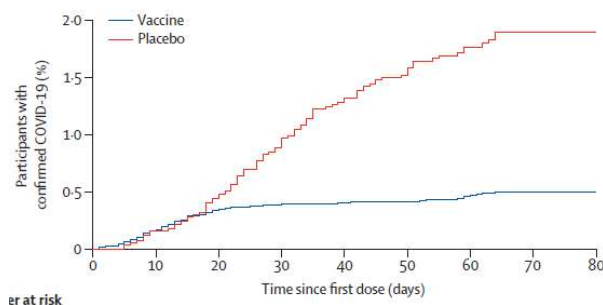
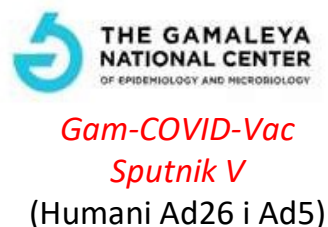
Vakcine protiv COVID-19 bazirane na vektorskoj tehnologiji



	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)	
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	76%	
All LD/SD and SD/SD recipients	131	30/5807 (0.5%)	44.1 (248 299)	101/5829 (1.7%)	149.2 (247 228)	70.4%	54.8 to 80.6)†
COV002 (UK)	86	18/3744 (0.5%)	38.6 (170 369)	68/3804 (1.8%)	145.7 (170 448)	73.5%	(55.5 to 84.2)
LD/SD recipients	33	3/1367 (0.2%)	14.9 (73 313)	30/1374 (2.2%)	150.2 (72 949)	90.0%	67.4 to 97.0)‡§
SD/SD recipients	53	15/2377 (0.6%)	56.4 (97 056)	38/2430 (1.6%)	142.4 (97 499)	60.3%	(28.0 to 78.2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0.6%)	56.2 (77 930)	33/2025 (1.6%)	157.0 (76 780)	64.2%	(30.7 to 81.5)‡
All SD/SD recipients	98	27/4440 (0.6%)	56.4 (174 986)	71/4455 (1.6%)	148.8 (174 279)	62.1%	(41.0 to 75.7)

10 hospitalizovanih (svi u placebo grupi)

Voysey et al. Lancet. 2021;397:99-111.



	Total cases	Vaccine group	Placebo group	Vaccine efficacy (95% CI)	p value
First COVID-19 occurrence from 21 days after dose 1 (day of dose 2)*					
Overall	78	16/14 964 (0.1%)	62/4902 (1.3%)	91.6% (85.6–95.2)	<0.0001
Age group (years)					
18–30	5	1/1596 (0.1%)	4/521 (0.8%)	91.9% (51.2–99.3)	0.0146
31–40	17	4/3848 (0.1%)	13/1259 (1.0%)	90.0% (71.1–96.5)	<0.0001
41–50	19	4/4399 (0.1%)	15/1443 (1.0%)	91.3% (73.7–96.9)	<0.0001
51–60	27	5/3510 (0.1%)	22/1146 (1.9%)	92.7% (81.1–97.0)	<0.0001
>60	10	2/1611 (0.1%)	8/533 (1.5%)	91.8% (67.1–98.3)	0.0004
Sex					
Female	32	9/5821 (0.2%)	23/1887 (1.2%)	87.5% (73.4–94.2)	<0.0001
Male	46	7/9143 (0.1%)	39/3015 (1.3%)	94.2% (87.2–97.4)	<0.0001
Moderate or severe cases	20	0/14 964	20/4902 (0.4%)	100% (94.4–100.0)	<0.0001

Logunov et al. Lancet. 2021;397:671-81.

Vektorske vakcine protiv COVID-19

(Bezbednost)

- Sindrom tromboze sa trombocitopenijom – „thrombosis with thrombocytopenia syndrome“ (TTS)
- Tromboza sa trombocitopenijom indukovana vakcinama – „Vaccine-induced immune thrombotic thrombocytopenia“ (VITT)
- Krajem februara 2021 određen broj slučajeva detektovan nakon davanja ChAdOx1 nCoV-19/AZD1222, a zatim i Ad26.COV2.S vakcine (obe vakcine bazirane na adenovirusnom vektoru)
- Javlja se posle 5-30 dana nakon davanja vakcine (mnogo češće nakon prve doze)
- Manifestuje se tipično kao tromboza dubokih vena udružena sa trombocitopenijom
 - Najčešće tromboza u cerebralnom venskom sinusu, ali i u drugim krvnim sudovima
- Smrtnost veoma visoka u početku (oko 50%), kasnije oko 15-20%
- Faktori rizika i patogenetski mehanizmi ?
 - Prisustvo antitela na PF4 (Platelet factor 4 ili CXCL4) → aktiviraju trombocite (važna uloga u patogenezi)
- Veoma retko se javlja (učestalost varira u zavisnosti od vakcine i zemlje, odnosno kvaliteta nadzora)

Vektorske vakcine protiv COVID-19

(Bezbednost)

Manufacturer	Vaccine name	Vaccine type	Vaccine efficacy	VITT Incidence, as of Q1 2022	VITT mortality rate, as of Q1 2022	Total # of vaccines administered in the USA or EU (in millions) (5)
Moderna	mRNA-1273	mRNA (Lipid nanoparticle)	94% (6)	Low	n/a	398
BioNTech-Pfizer	BNT162b2	mRNA (Lipid nanoparticle)	95% (6)	Low	n/a	1,044
Oxford/AstraZeneca	ChAdOx1 nCoV-19	Adenoviral vector (Y25)	63% (6)	1/64,000 (7), 1/125,000 (8)	18% (7)	67
Johnson & Johnson/Janssen	Ad26.COV2.S	Adenoviral vector (Ad26)	67% (9)	1/310,000 (7), 1/200,000 (8)	15% (7, 10)	37
Gamaleya Research Institute of Epidemiology and Microbiology	Sputnik V	Adenoviral vector (Ad26 and Ad5)	91% (6)	Low (11)	n/a	1.8
CanSino Biologics	Ad5-nCoV-S	Adenoviral vector (Ad5)	58% (12)	n/a	n/a	n/a
Sinovac Biotech	CoronaVac	Inactivated virus	50% (6)	n/a	n/a	0.007
Sinopharm	BBIBP-CorV	Inactivated virus	78% (6)	Low (13)	n/a	2.3
Bharat Biotech	BBV152	Inactivated virus	78% (14)	n/a	n/a	0.0001
NovaVax	NVX-CoV2373	Adjuvanted protein	90% (15)	n/a	n/a	0.29

Vektorske vakcine protiv COVID-19

(Bezbednost)

- Sistematski pregledni rad – 66 studija sa 28.173 pacijenata hospitalizovanih zbog COVID-19

TABLE 3 Prevalence of venous thromboembolism, pulmonary embolism and deep vein thrombosis in ICU and non-ICU hospitalized patients with COVID-19

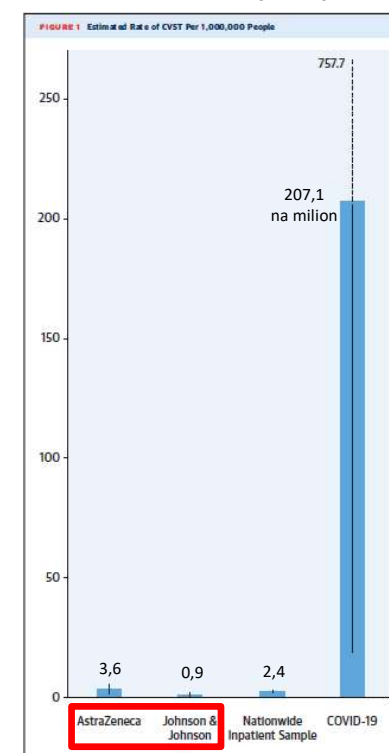
Outcome	Studies	Number of patients	Number of outcomes	Estimate of prevalence, % (95%CI)	Heterogeneity (I ²)
ICU patients only					
VTE (studies reporting both outcomes)	25	2966	617	22.7 (16.1-27.6)	87.3
No Screening	20	2791	535	18.7 (14.9-22.9)	83.1
Screening*	5	175	82	45.6 (30.6-61.1)	73.4
PE (±DVT) ^b	27	3085	410	13.7 (10.0-17.9)	87.6
DVT (±PE)	28	3001	423	18.7 (12.6-25.6)	94.6
No Screening	19	2642	251	8.9 (5.8-12.4)	86.2
Screening*	9	359	172	48.5 (31.0-66.2)	91.0
Non-ICU hospitalized patients^c					
VTE (studies reporting both outcomes)	23	7390	411	7.9 (5.1-11.2)	94.6
No Screening	19	7053	321	5.5 (3.6-7.9)	91.0
Screening*	4	337	90	23.0 (3.2-52.5)	96.5
PE (±DVT) ^b	23	8698	263	3.5 (2.2-5.1)	88.9
DVT (±PE)	22	10 519	256	4.1 (2.3-6.4)	94.6
No Screening	14	9835	144	1.4 (0.7-2.3)	85.0
Screening*	8	684	112	12.7 (3.7-25.5)	94.1

Učestalost CVST nakon vakcinacije sa ChAdOx1 nCoV-19/AZD1222 (V. Britanija) i Ad26.COV2.S (SAD) i nakon SARS-CoV-2 infekcije (SAD)

Skoro 23% pacijenata na intenzivnoj nezi razvije venske tromboembolijske komplikacije

Skoro 8% pacijenata koji nisu na intenzivnoj nezi razvije venske tromboembolijske komplikacije

CVST – tromboza cerebralnog venskog sinusa



Vakcinacija protiv COVID-19 u svetu

- Preko **13 milijardi doza** vakcina u prve dve godine
- Preko 5 milijardi ljudi vakcinisano (**oko 70% cele svetske populacije**)

Global impact of the first year of COVID-19 vaccination: a mathematical modelling study

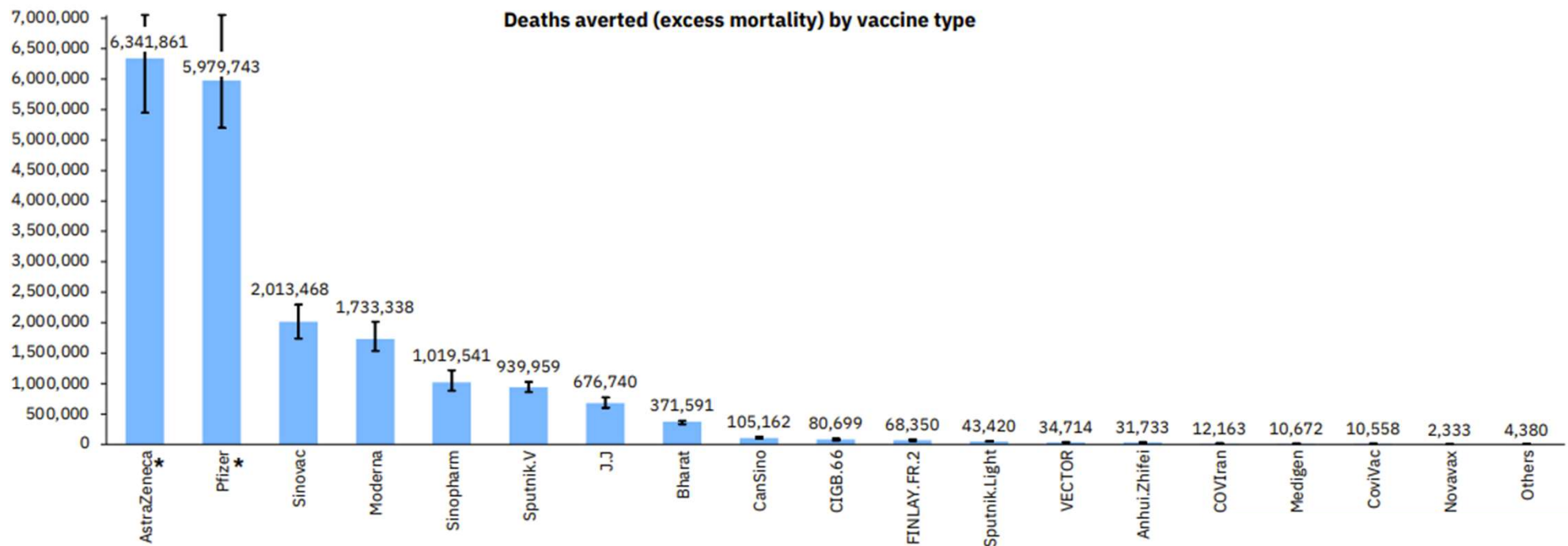
Oliver J Watson*, Gregory Bamsley*, Jaspreet Toor, Alexandra B Hogan, Peter Winskill, Azra C Ghani

Findings Based on official reported COVID-19 deaths, we estimated that vaccinations prevented 14.4 million (95% credible interval [CrI] 13.7–15.9) deaths from COVID-19 in 185 countries and territories between Dec 8, 2020, and Dec 8, 2021. This estimate rose to 19.8 million (95% CrI 19.1–20.4) deaths from COVID-19 averted when we used excess deaths as an estimate of the true extent of the pandemic, representing a global reduction of 63% in total deaths (19.8 million of 31.4 million) during the first year of COVID-19 vaccination. In COVAX Advance Market Commitment countries, we estimated that 41% of excess mortality (7.4 million [95% CrI 6.8–7.7] of 17.9 million deaths) was averted. In low-income countries, we estimated that an additional 45% (95% CrI 42–49) of deaths could have been averted had the 20% vaccination coverage target set by COVAX been met by each country, and that an additional 111% (105–118) of deaths could have been averted had the 40% target set by WHO been met by each country by the end of 2021.

Oko 20 miliona života
spašeno vakcinacijom
samo u 2021. godini

Vakcinacija protiv COVID-19 u svetu

- Preko **12 miliona života spašeno** vakcinacijom sa ChAdOx1 nCoV-19 (vektorska, AstraZeneca) i BNT162b2 (RNK, Pfizer)
- Preko **16 miliona života spašeno** vakcinama baziranim na novim tehnologijama



Airfinity. Dostupno na: <https://www.airfinity.com/articles/astrazeneca-and-pfizer-biotech-saved-over-12-million-lives-in-the-first> (Pristupljeno 1.11.2024.)

Inovativne vakcine (Perspektive za budućnost)

RNK, DNK i vektorske vakcine predstavljaju
moćne platforme sa velikim mogućnostima

ali...

**Vaccines Don't Save Lives.
Vaccinations Save Lives.**

Prof. Walter Orenstein
Emory University, Atlanta, USA



UNIVERZITET U NOVOM SADU
MEDICINSKI FAKULTET



Nacionalni simpozijum sa međunarodnim učešćem
„4. DANI VAKCINACIJE“
6-7. novembar 2024. godine
Hotel Sheraton, Novi Sad

Hvala na pažnji!
Pitanja?



Miloš Marković
milos.markovic@med.bg.ac.rs