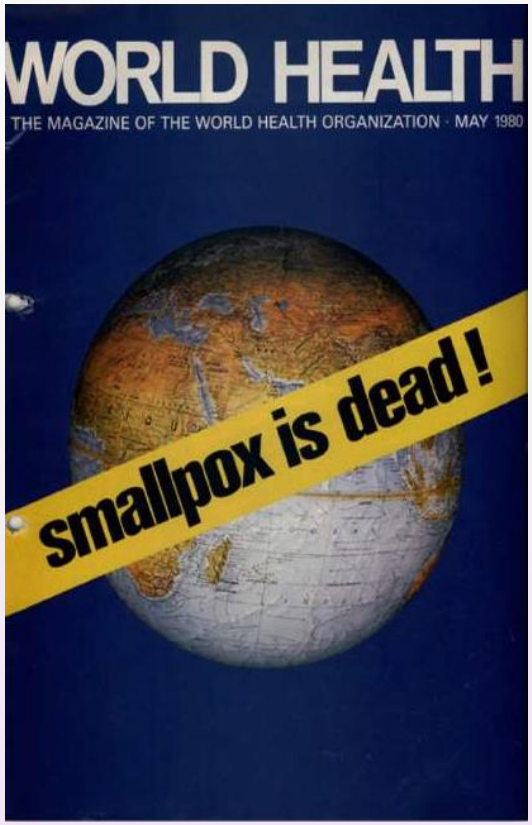
Gelecek Aşıları ve Beklentilerimiz (HIV, Yeni Teknoloji, Yeni Adjuvan) vs.)

Prof. Dr. Necla TÜLEK

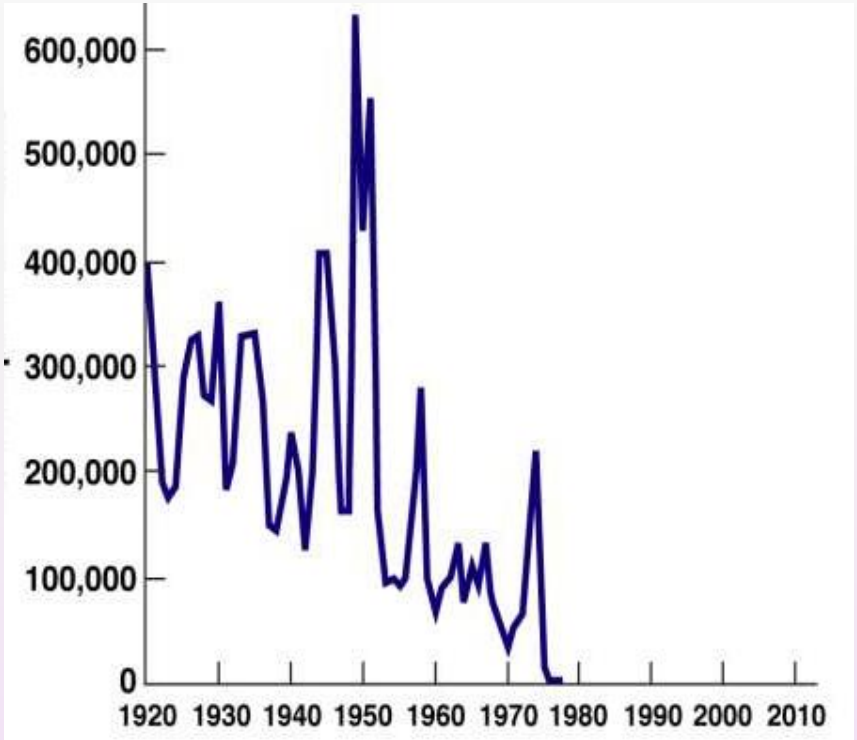
Ankara Eğitim ve Araştırma Hastanesi

İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

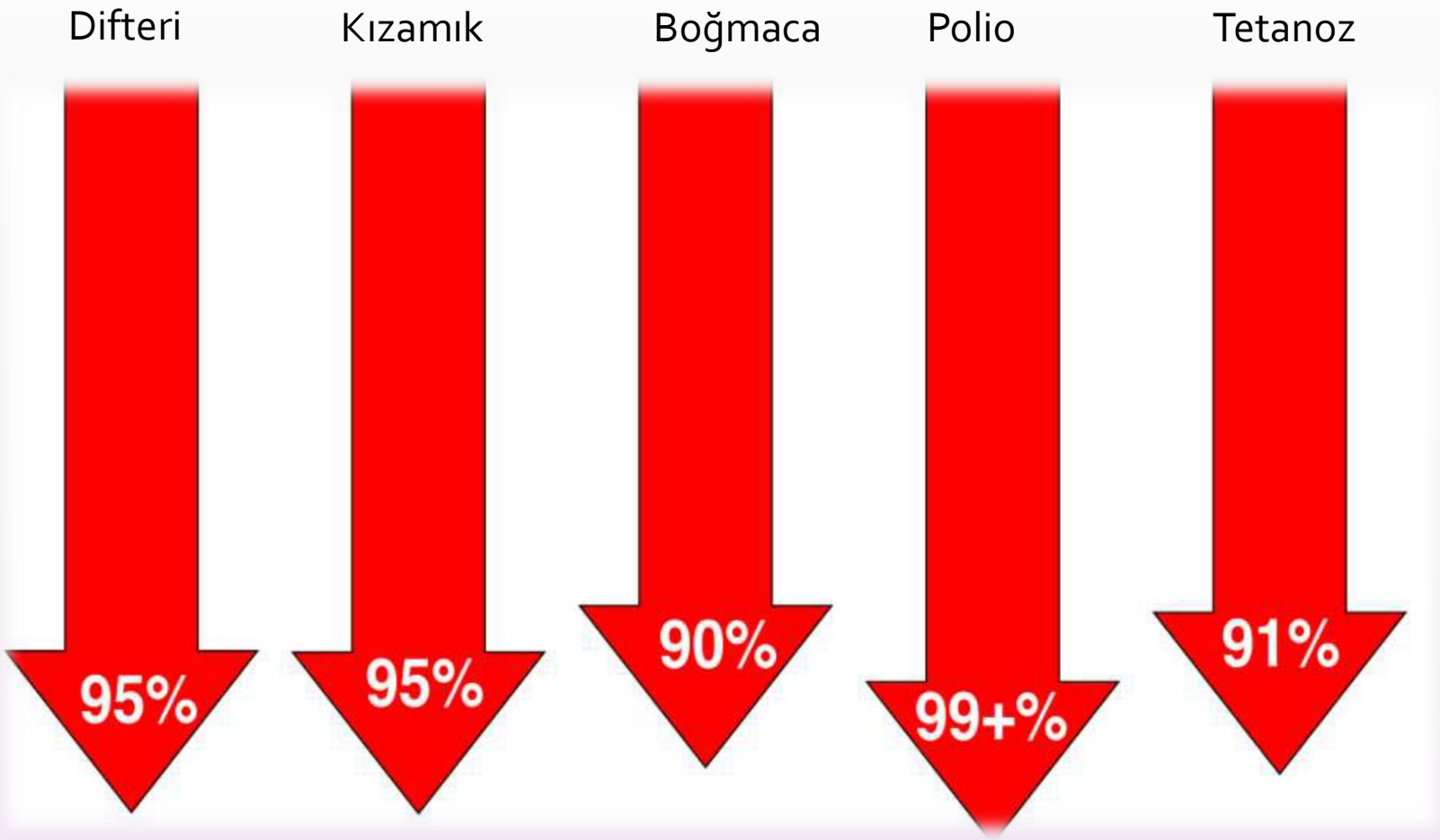
- Aşılar tıbbın en büyük başarılarından
- Kısa sürede dünya tarihi değişmiştir.



Tüm dünyada çiçek olguları



Aşılamanın Etkisi (1980-2012)



R Lozano, CJL Murray et al, *Lancet*, 380(9859), 2012.

Yeni Aşı Gereksinimleri

1. Birçok hastalık için henüz aşı yok
2. Yetersiz doğal immünite (HIV, sıtma)
3. Yeni ve yeniden sorun oluşturan infeksiyonlar
4. Antijenik varyasyon
5. Daha etkin aşı gereksinimi
6. Güvenlik ve riskler
7. Aşı üretim sorunları
8. Dağıtım ve kullanımda sorunlar
9. Özel koşullarda uygulayabilme
10. Maliyet

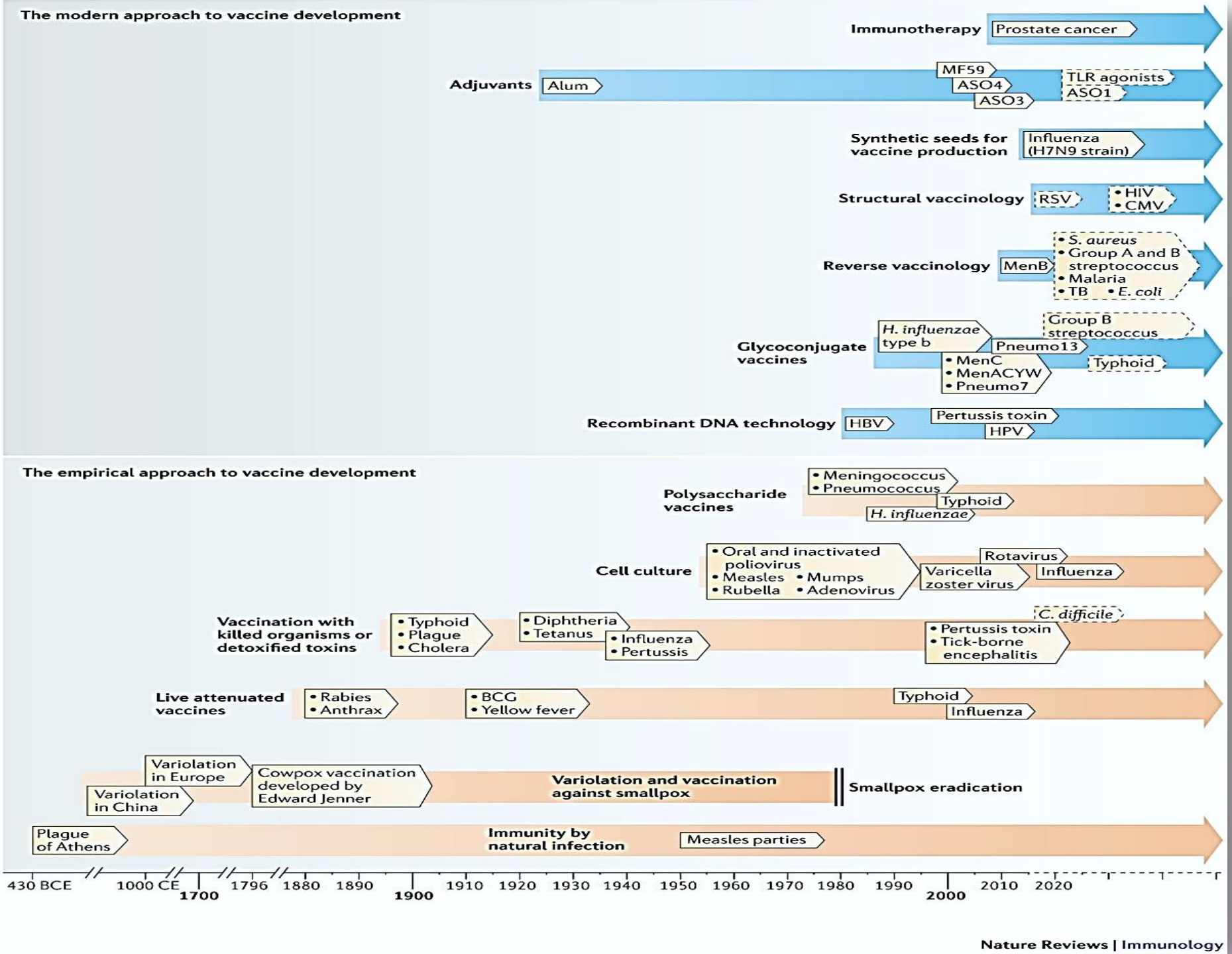
Klasik Aşılar- I. Kuşak Aşılar

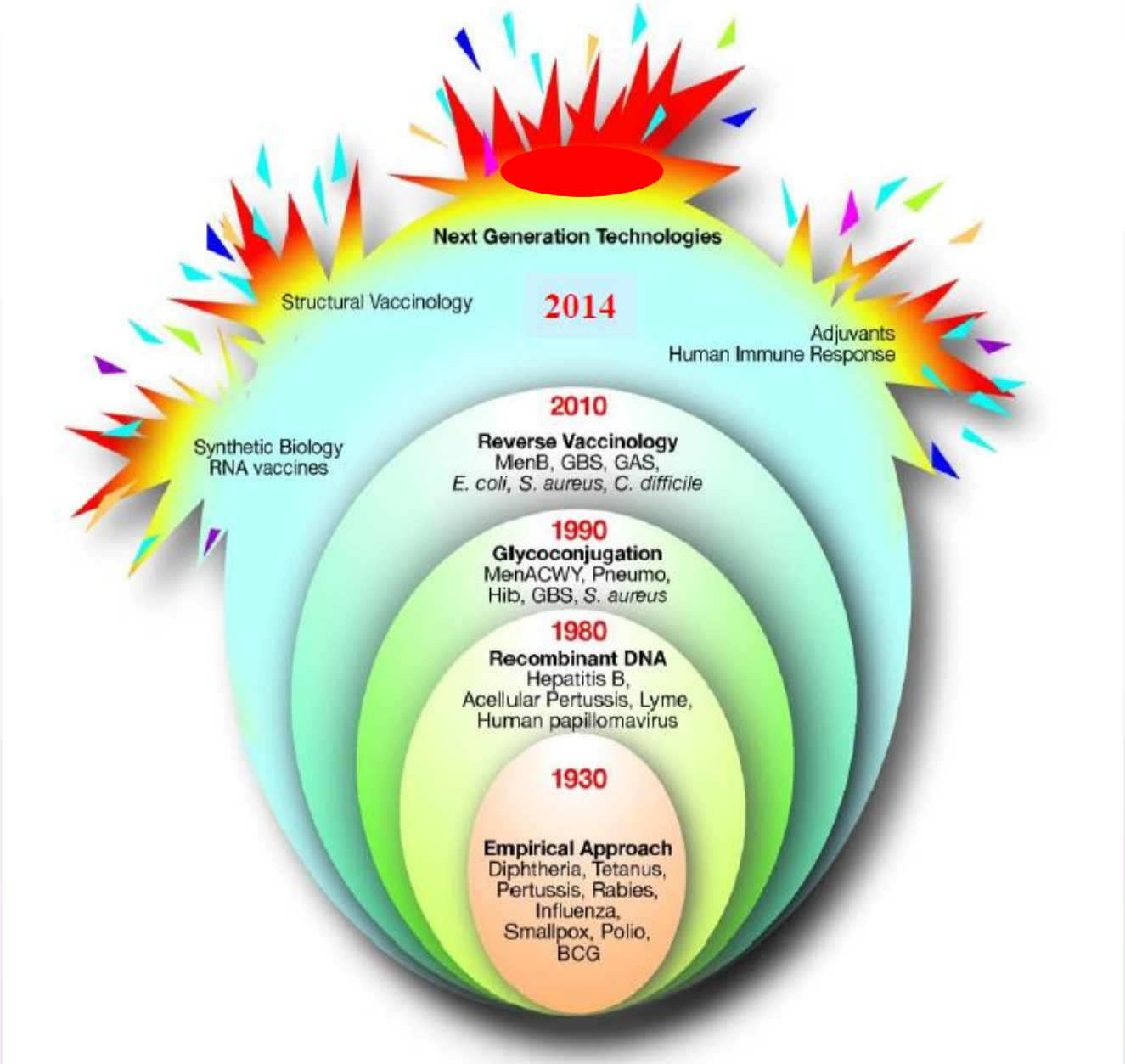
Tüm hücre aşıları
- Canlı
- Attenue

Toksoid aşılar

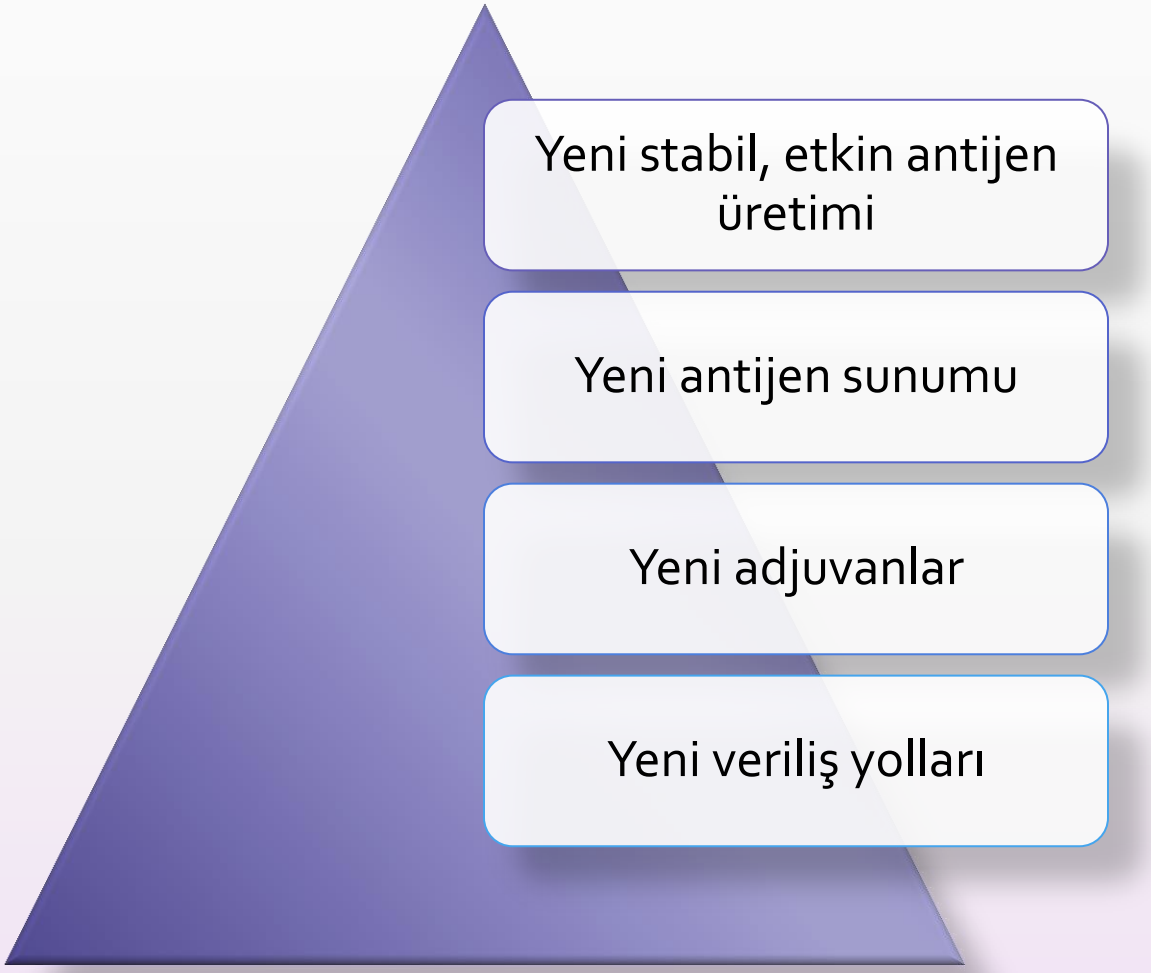
İzole et, inaktive et, enjekte et

Doğal infeksiyonu taklit → Doğal immünite benzeri yanıt


The modern approach to vaccine development
Immunotherapy
Prostate cancer
Adjuvants
Alum
MF59
ASO4
ASO3
TLR agonists
ASO1
Synthetic seeds for vaccine production
Influenza (H7N9 strain)
Structural vaccinology
RSV
• HIV
• CMV
Reverse vaccinology
MenB
• S. aureus
• Group A and B streptococcus
• Malaria
• TB • E. coli
Glycoconjugate vaccines
H. influenzae type b
Group B streptococcus
Pneumo13
• MenC
• MenACYW
• Pneumo7
Typhoid
Recombinant DNA technology
HBV
Pertussis toxin
HPV
The empirical approach to vaccine development
Polysaccharide vaccines
• Meningococcus
• Pneumococcus
Typhoid
H. influenzae
Cell culture
• Oral and inactivated poliovirus
• Measles • Mumps
• Rubella • Adenovirus
Rotavirus
Varicella zoster virus
Influenza
Vaccination with killed organisms or detoxified toxins
• Typhoid
• Plague
• Cholera
• Diphtheria
• Tetanus
• Influenza
• Pertussis
C. difficile
• Pertussis toxin
• Tick-borne encephalitis
Live attenuated vaccines
• Rabies
• Anthrax
• BCG
• Yellow fever
Typhoid
Influenza
Variolation in Europe
Variolation in China
Cowpox vaccination developed by Edward Jenner
Variolation and vaccination against smallpox
Smallpox eradication
Plague of Athens
Immunity by natural infection
Measles parties
430 BCE
1000 CE
1700
1796
1880
1890
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
2020


Next Generation Technologies
Structural Vaccinology
2014
Adjuvants
Human Immune Response
Synthetic Biology
RNA vaccines
2010
Reverse Vaccinology
MenB, GBS, GAS,
E. coli, S. aureus, C. difficile
1990
Glycoconjugation
MenACWY, Pneumo,
Hib, GBS, S. aureus
1980
Recombinant DNA
Hepatitis B,
Acellular Pertussis, Lyme,
Human papillomavirus
1930
Empirical Approach
Diphtheria, Tetanus,
Pertussis, Rabies,
Influenza,
Smallpox, Polio,
BCG

Aşılamada Yeni Teknolojiler



Subunit –Rekombinan Aşılar

Protein/peptit
Karbohidrat antijenler

Avantajları

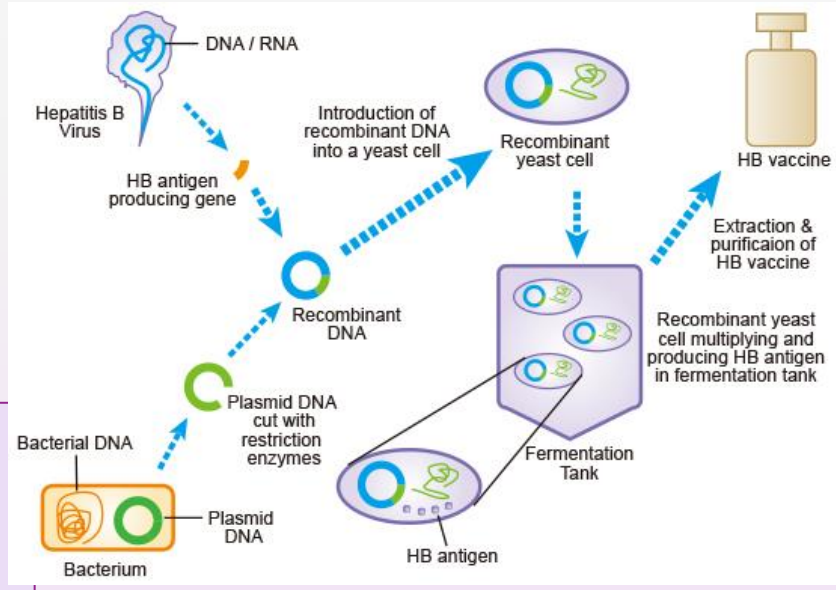
- Patojenite riski yok
- Çok miktarda üretilebilir
- Yan etki az

Dezavantajları

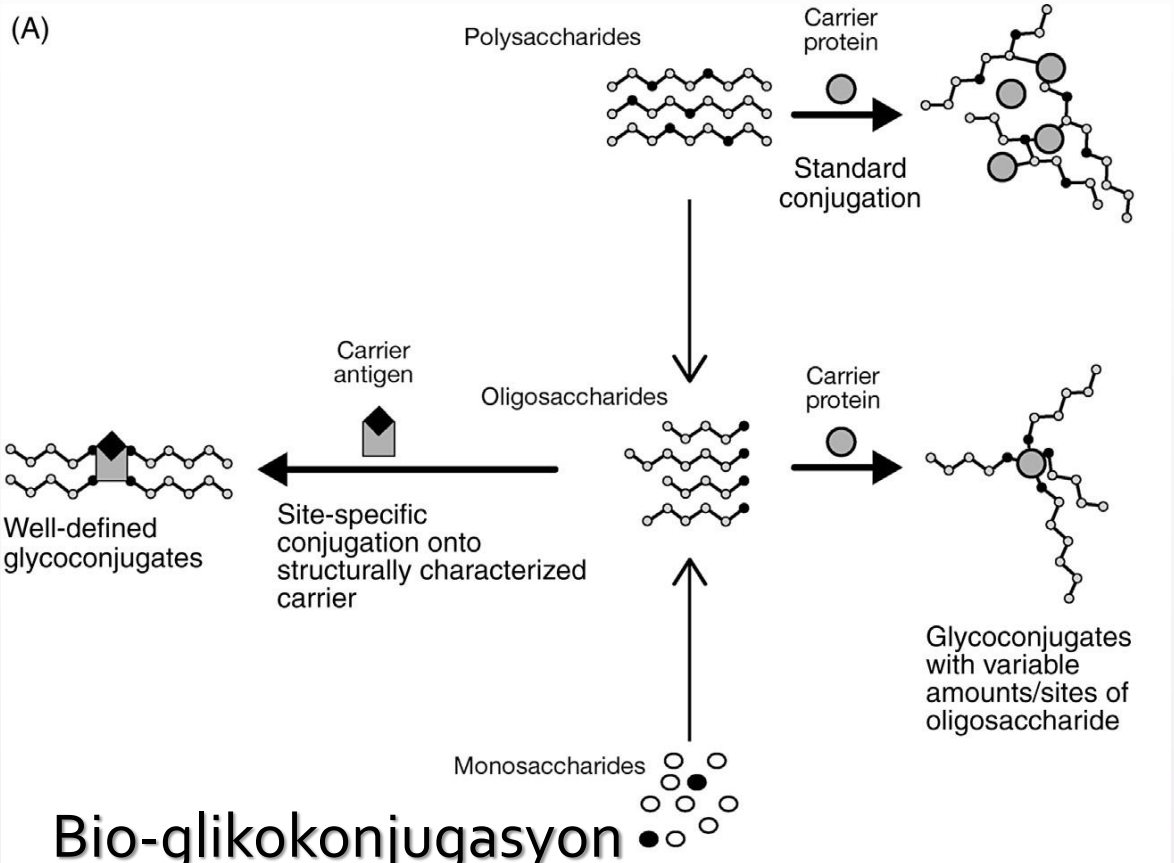
- Çoklu doz gerekli
- Adjuvan gerekli

- Aselüler boğmaca aşısı
- HBV aşısı
- HPV aşıları

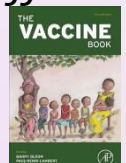
İnfluenza, RSV, norovirus, parvovirus aşılarında erken faz çalışmaları



Glikokonjuge Aşılar



S. aureus
Shigella dysenteriae
Clostridium difficile



Gliko-konjuge Aşılar

- *Haemophilus influenzae tip b*
- *Streptococcus pneumoniae*
- *Neisseria meningitides*

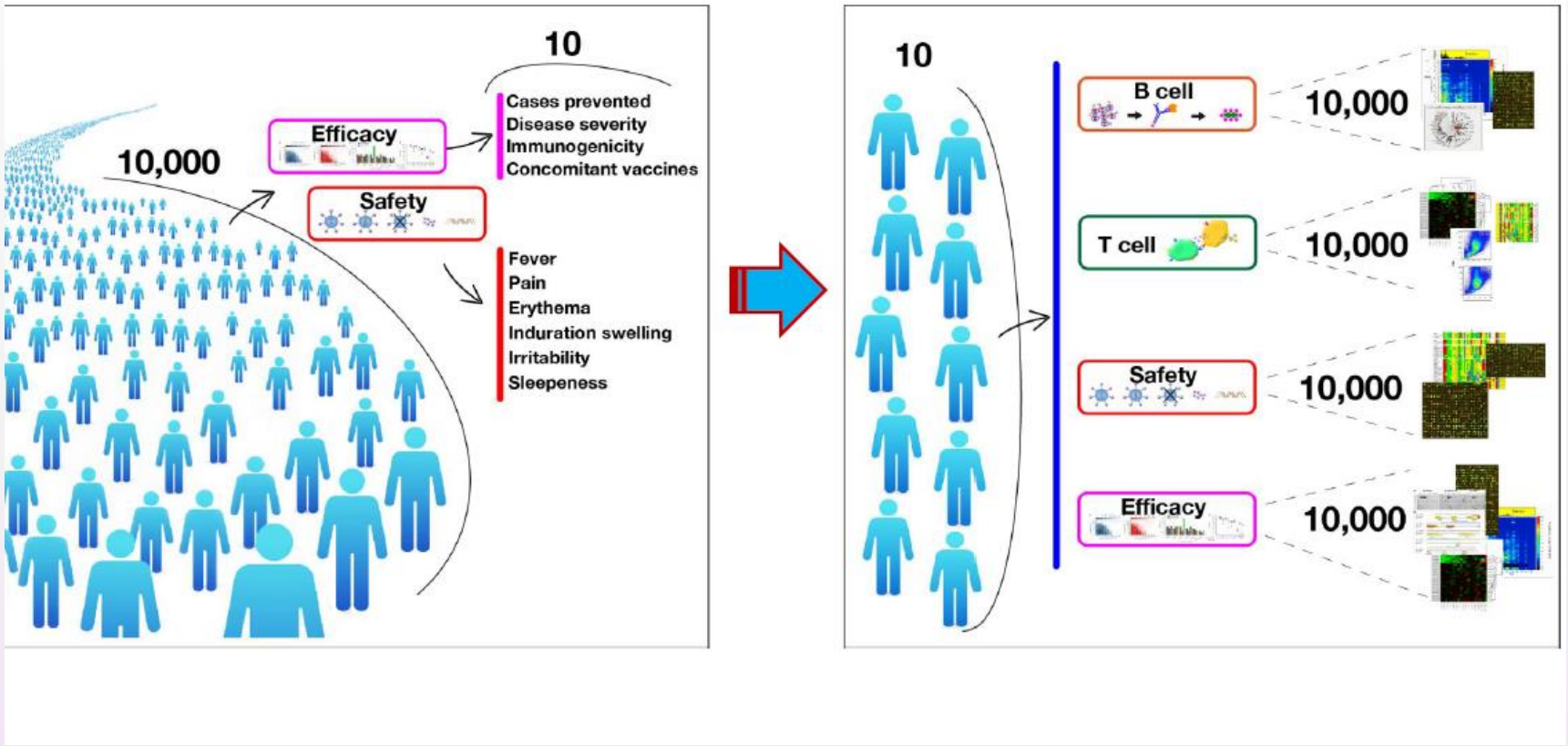
- MenACWYX
- MenX
- Grup B streptokok
- *Salmonella* Typhi

} Preklinik aşama

Aşılamada Yeni Kavramlar

- Ampirik değil rasyonel yaklaşım
- Multidisipliner yaklaşım
- Sistem biyolojisi
- Doğal oluşan immün yanıtın ötesine geçiş
  - Doğal olmayan immüniteyi indükleyebilmek

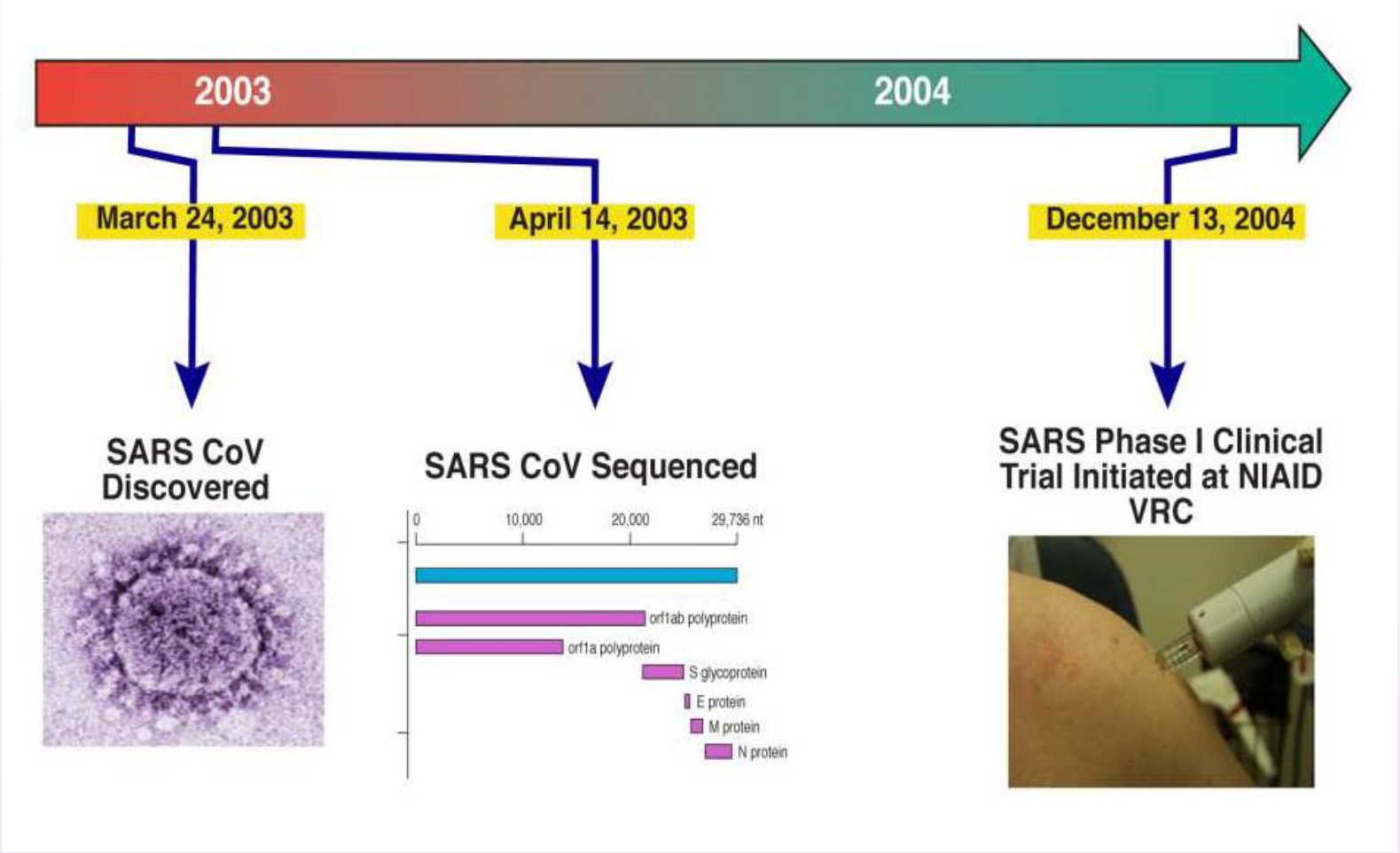
Sistem Biyolojisi ile 10000 kişiden 10 veri yerine 10 kişiden 10000 veri



Yeni Antijen Üretim Teknolojileri

- Hızlı genom sekanslama
- Ters aşı teknolojisi
- Yapı temelli aşı tasarımı

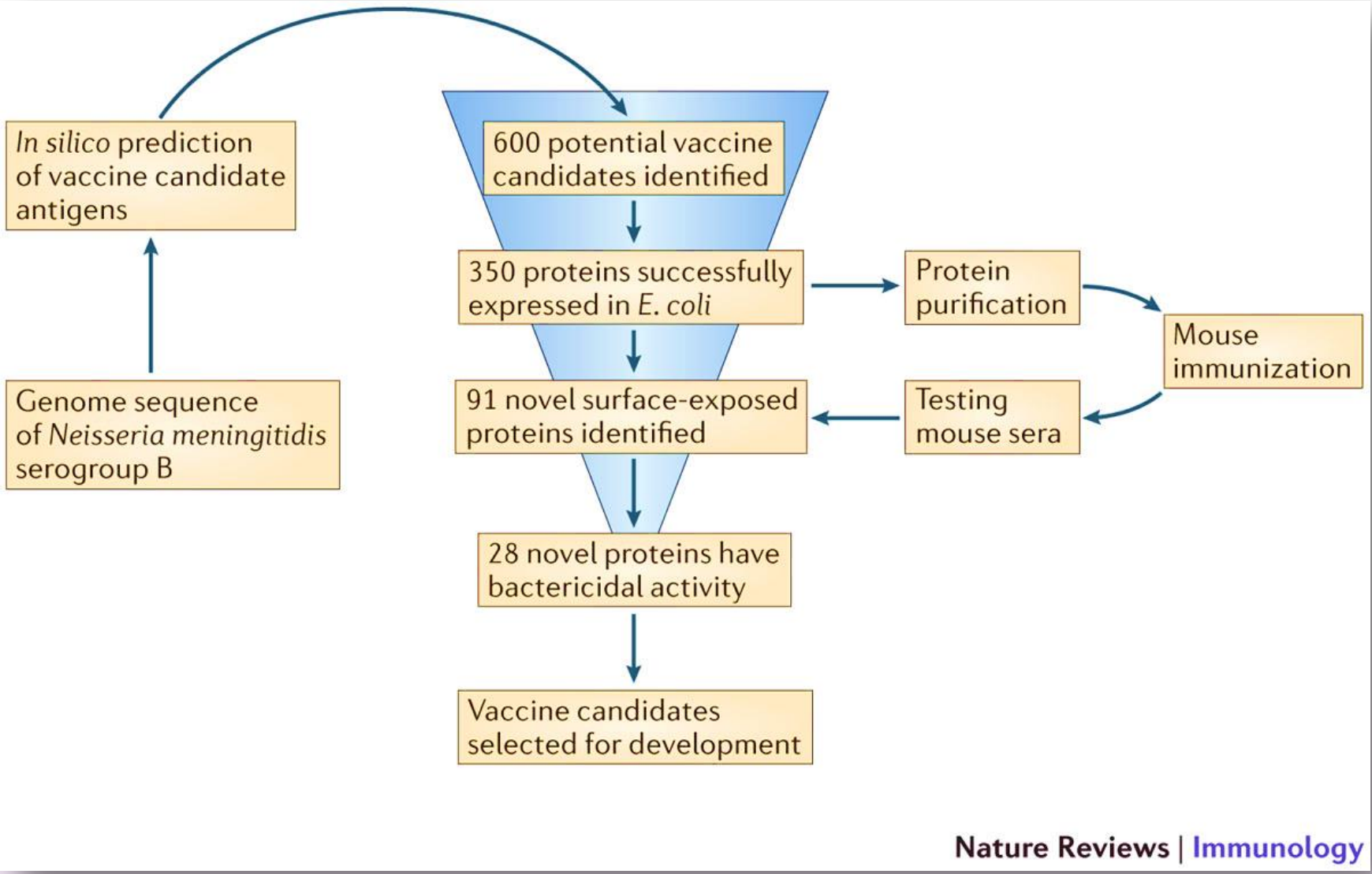
Hızlı Genom Sekanslama: SARS



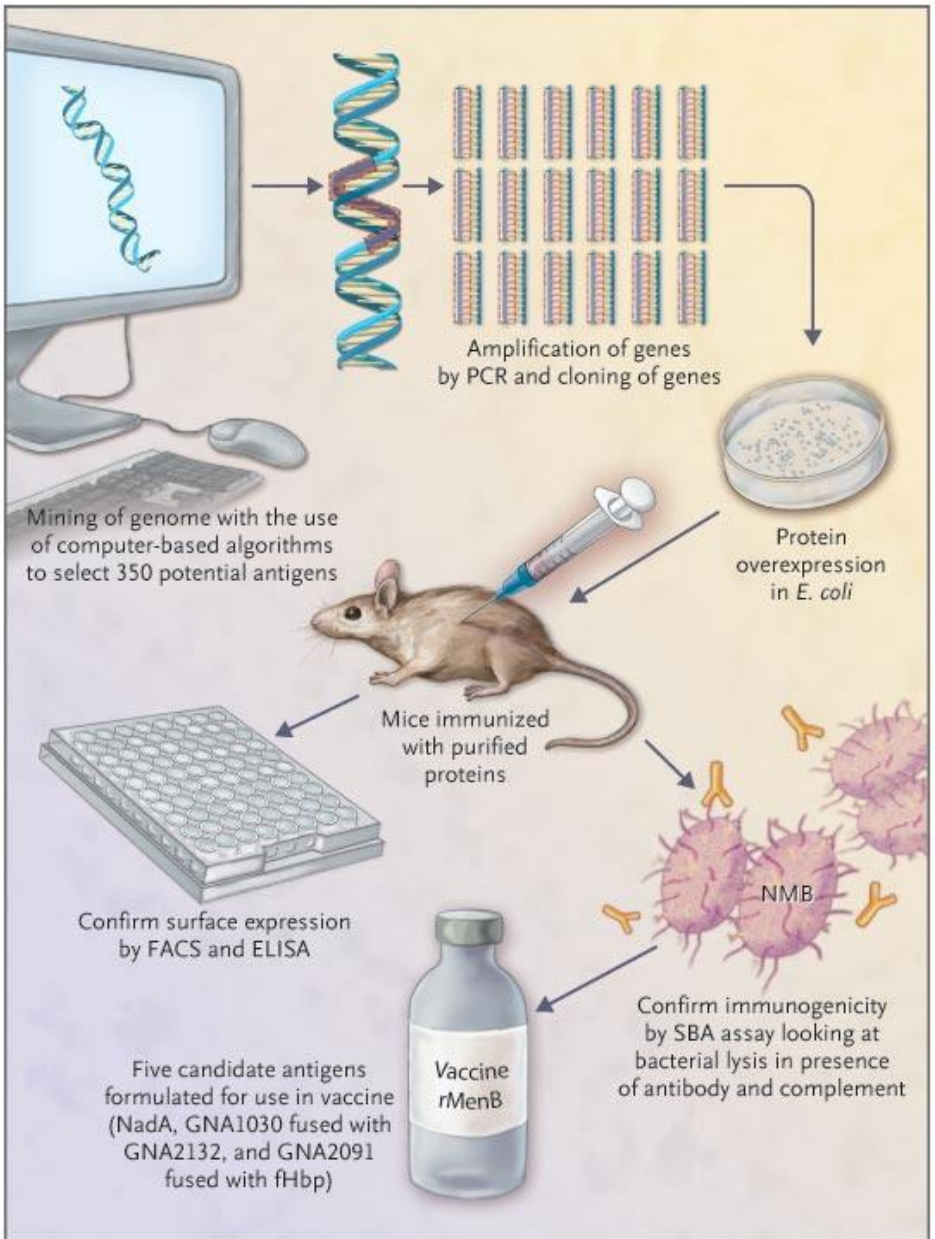
Fauci AS, 2014

Ters Aşı Teknolojisi

Genom bazlı antijen keşfi



Ters Aşı Teknolojisi



Yeni çalışmalar

Grup B streptokok

Ekstraintestinal patojenik *E. coli,*

S. aureus

Chlamydia pneumoniae

Mycobacterium tuberculosis

Polisakkarit antijenler

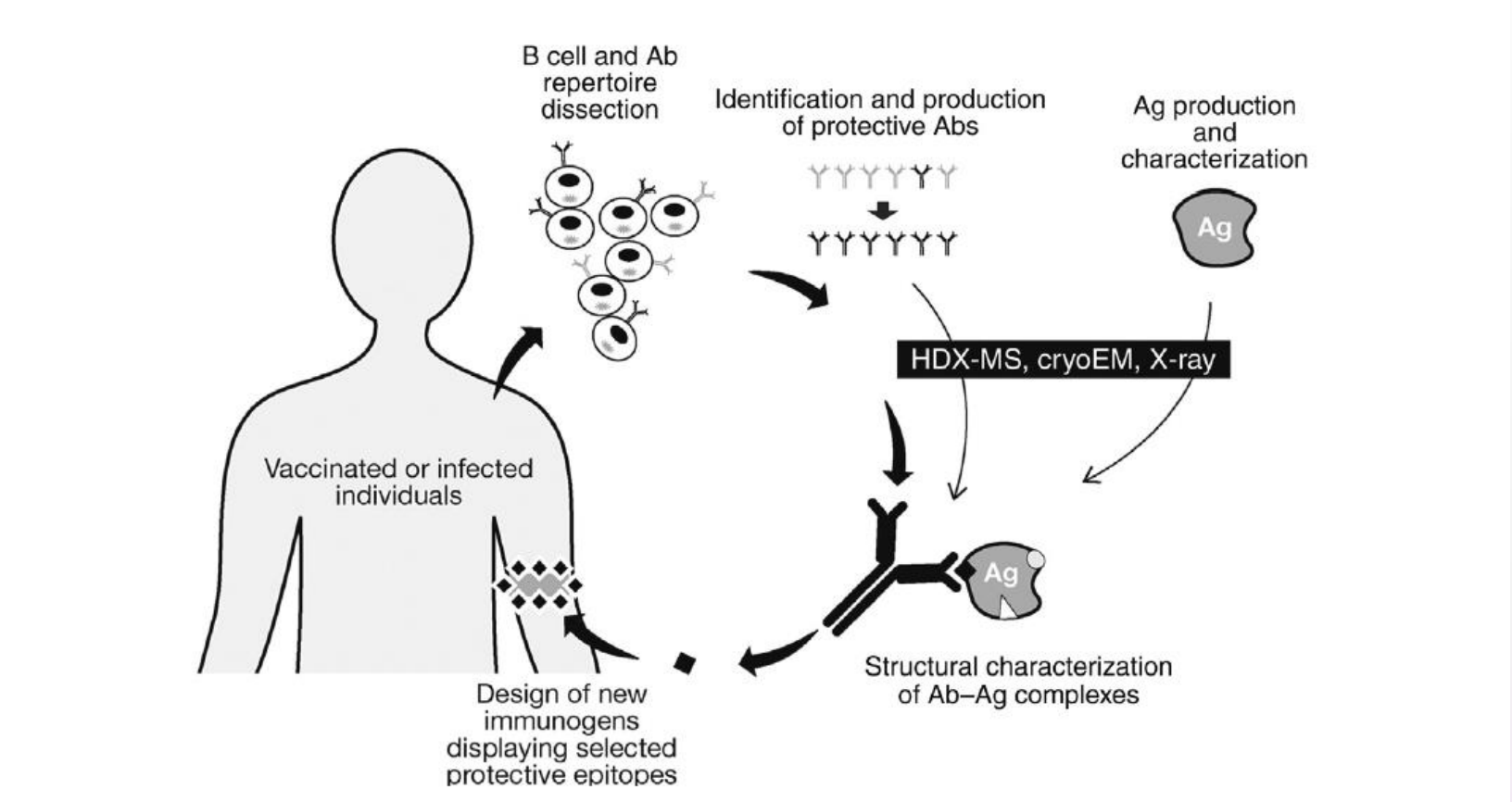
HIV, RSV için uygun değil

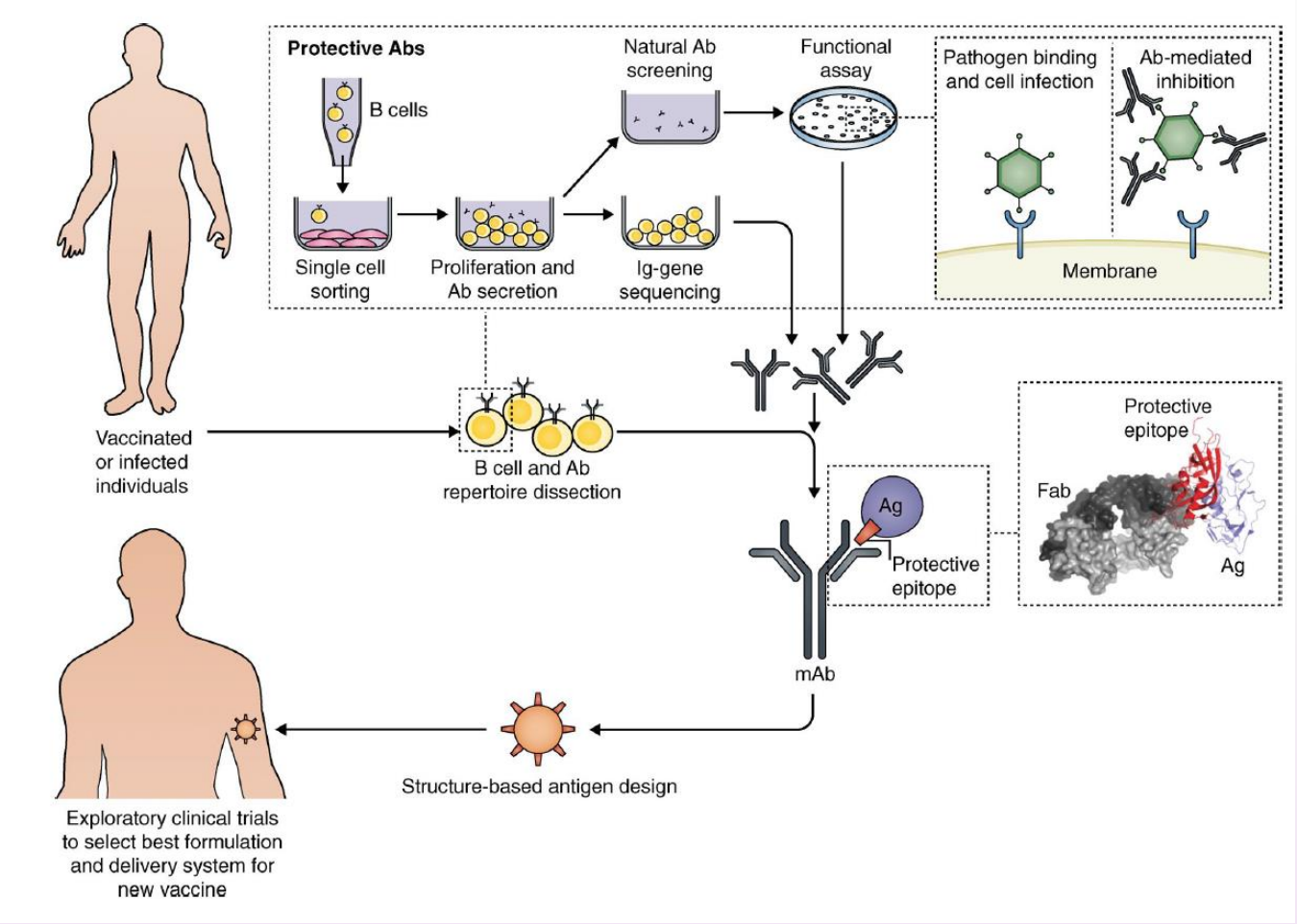
Yapı-Temelli Aşı Teknolojisi

Yapılandırılmış Aşı Teknolojisi

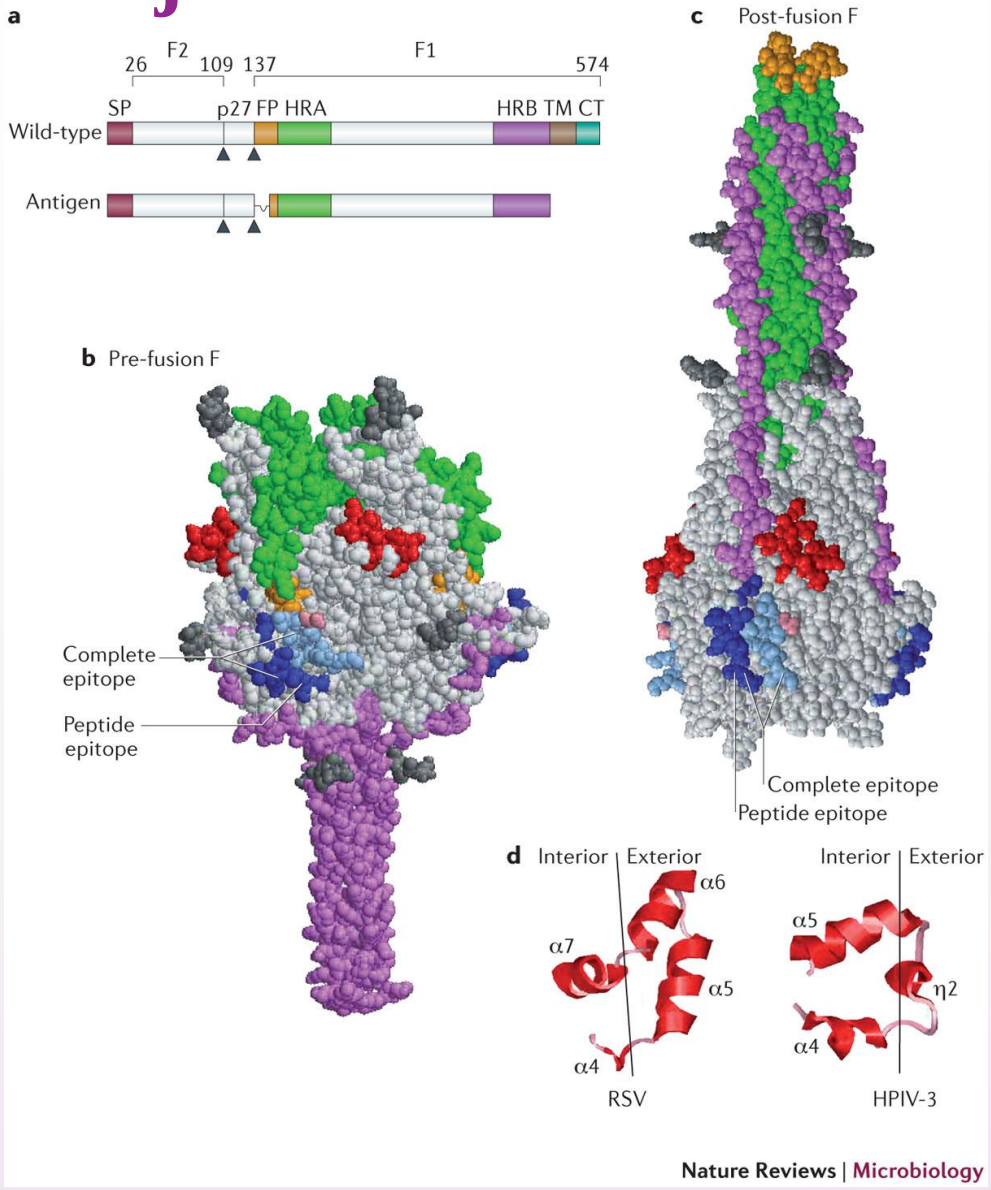
- Yapısal stabilizasyon
- Spesifik epitopların hedeflenmesi

- Yeni aşı adaylarının şekillendirilmesi

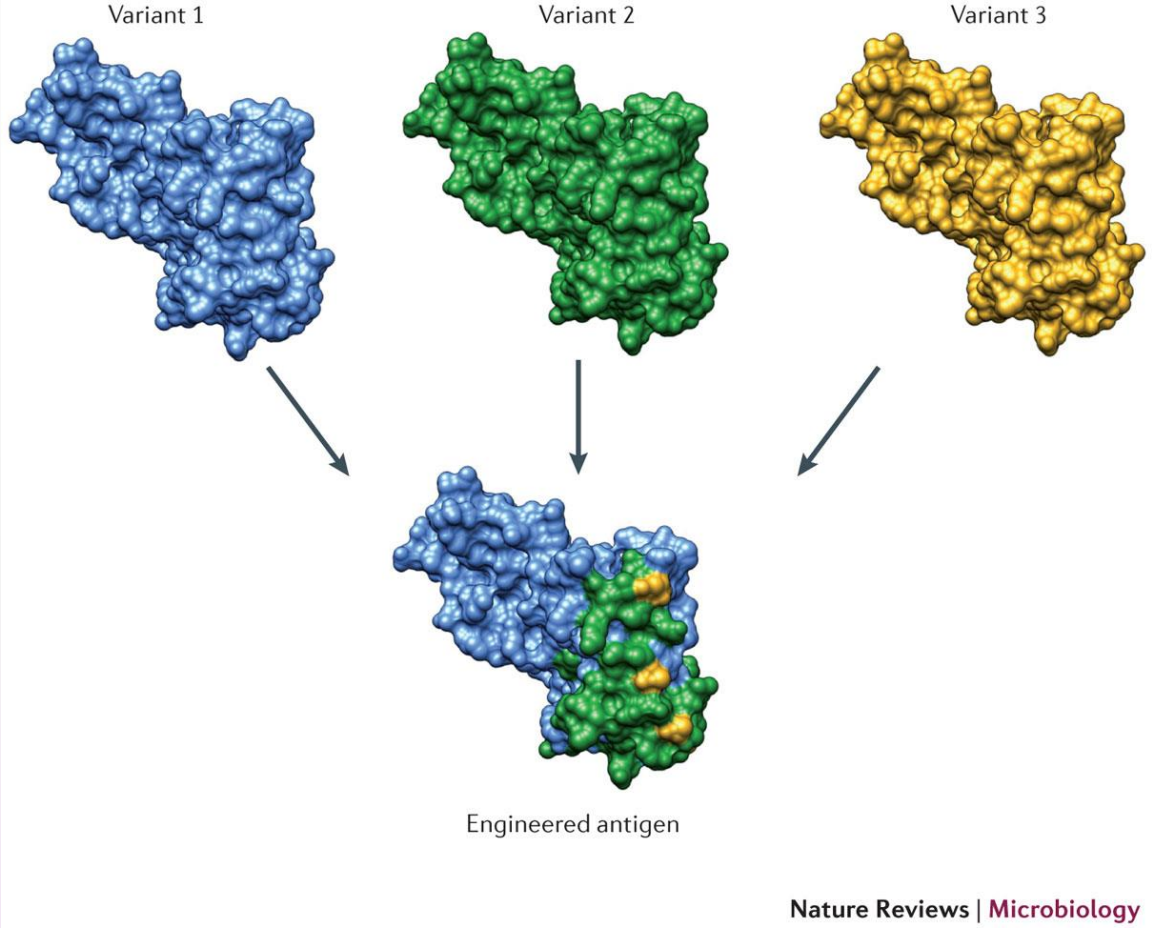

B cell and Ab repertoire dissection
Identification and production of protective Abs
Ag production and characterization
Ag
HDX-MS, cryoEM, X-ray
Vaccinated or infected individuals
Ag
Structural characterization of Ab–Ag complexes
Design of new immunogens displaying selected protective epitopes

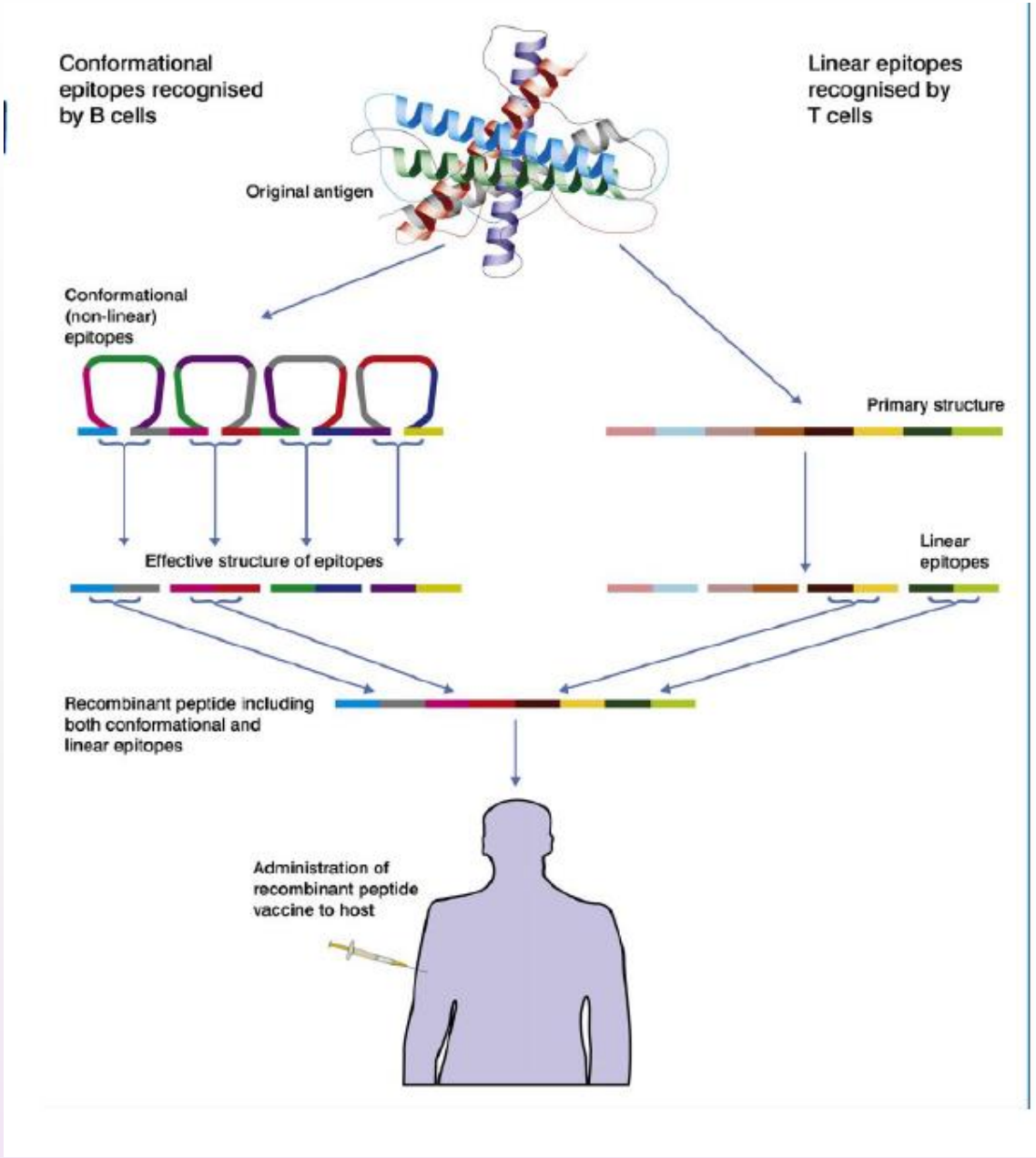

Protective Abs
B cells
Natural Ab screening
Functional assay
Pathogen binding and cell infection
Ab-mediated inhibition
Membrane
Single cell sorting
Proliferation and Ab secretion
Ig-gene sequencing
Vaccinated or infected individuals
B cell and Ab repertoire dissection
Protective epitope
Fab
Ag
Protective epitope
Ag
mAb
Structure-based antigen design
Exploratory clinical trials to select best formulation and delivery system for new vaccine

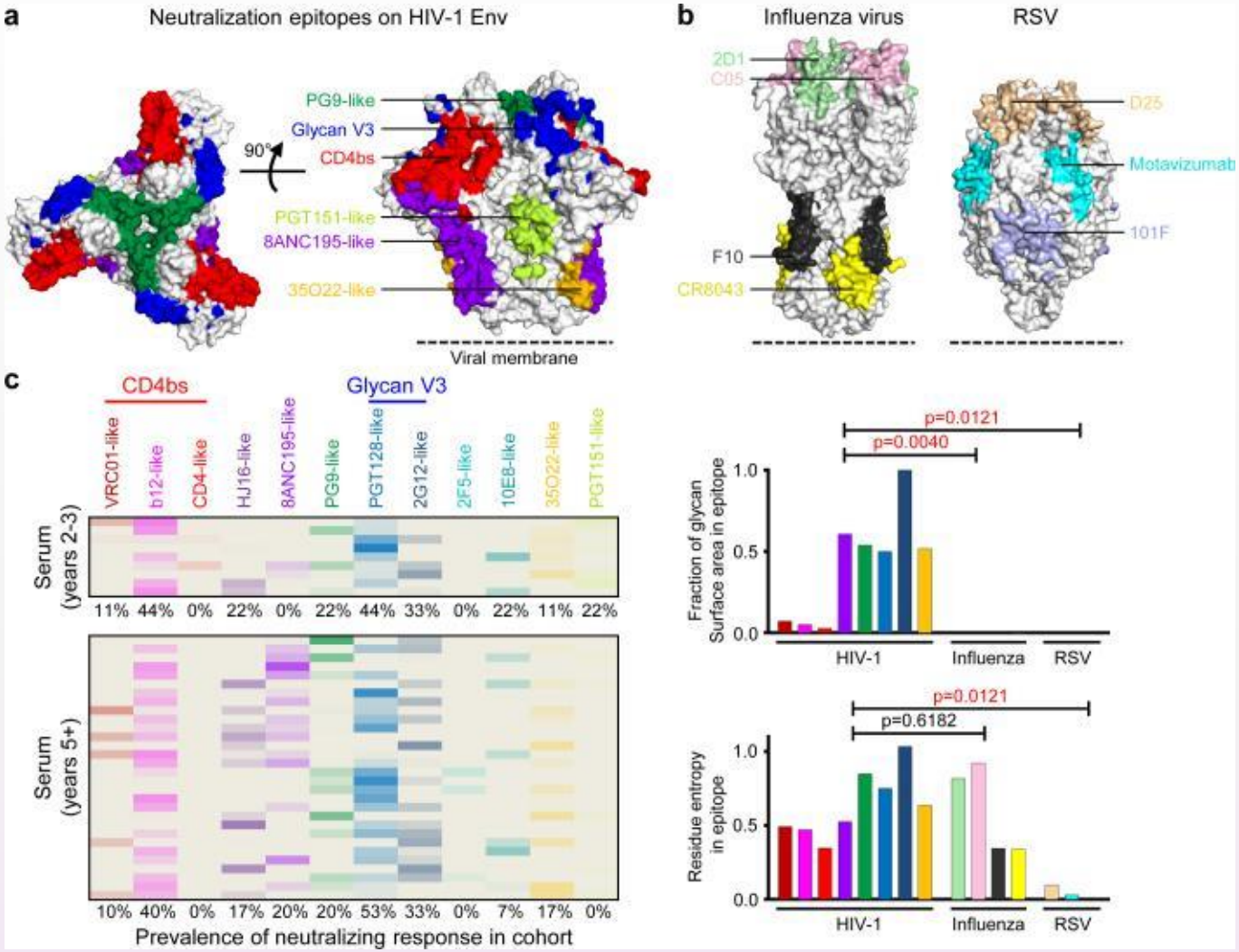
Antijenin Stabil Hale Getirilmesi



Varyantlardaki farklı epitopların tek bir antijende toplanılması




Conformational epitopes recognised by B cells
Linear epitopes recognised by T cells
Original antigen
Conformational (non-linear) epitopes
Primary structure
Effective structure of epitopes
Linear epitopes
Recombinant peptide including both conformational and linear epitopes
Administration of recombinant peptide vaccine to host



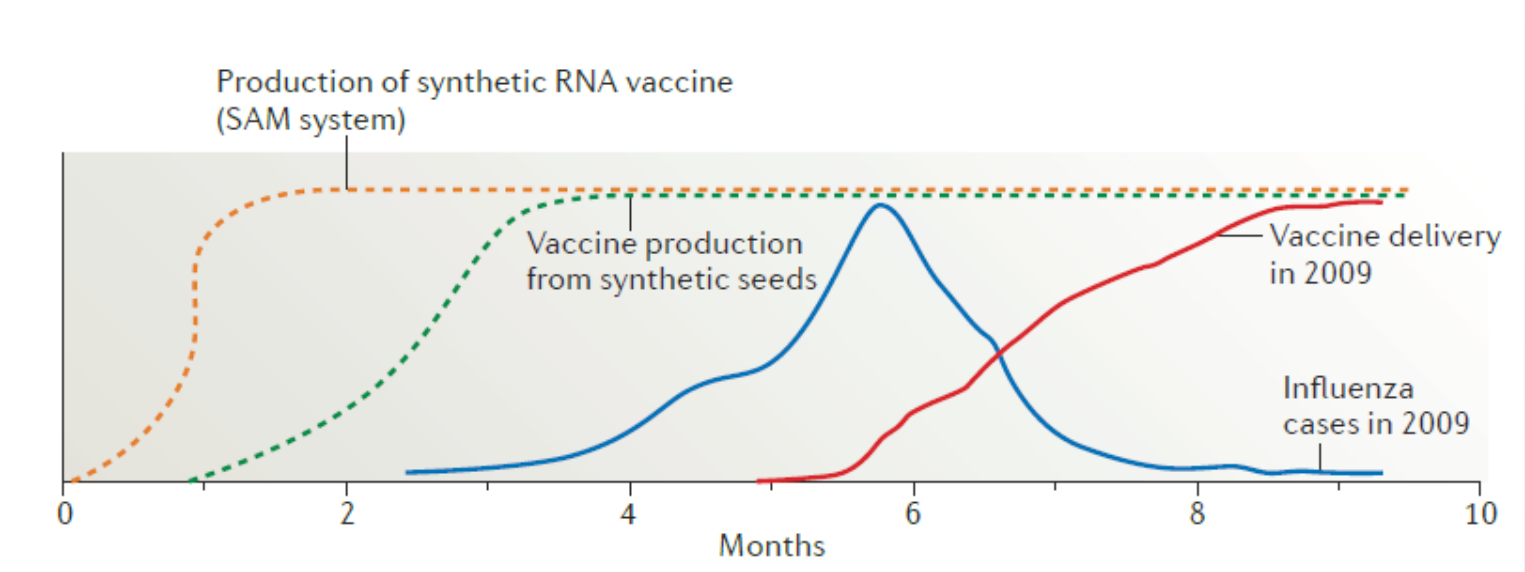
Pancera et al. Nature. 2014 Oct 23; 514(7523): 4

Sentetik Viral Tanecikler

- Sentetik genom oluşturma
- Hücre olmayan gen montaj teknikleri
- İnfluenza virüsünde hemagglutinin (HA) ve nöraminidaz gen sentezi ve viral diğer genleri sentezleyen plazmid DNA'lar
- Madin–Darby köpek böbrek hücrelerinde transfeksiyon, çoğaltma
- Hızlı aşı üretimi

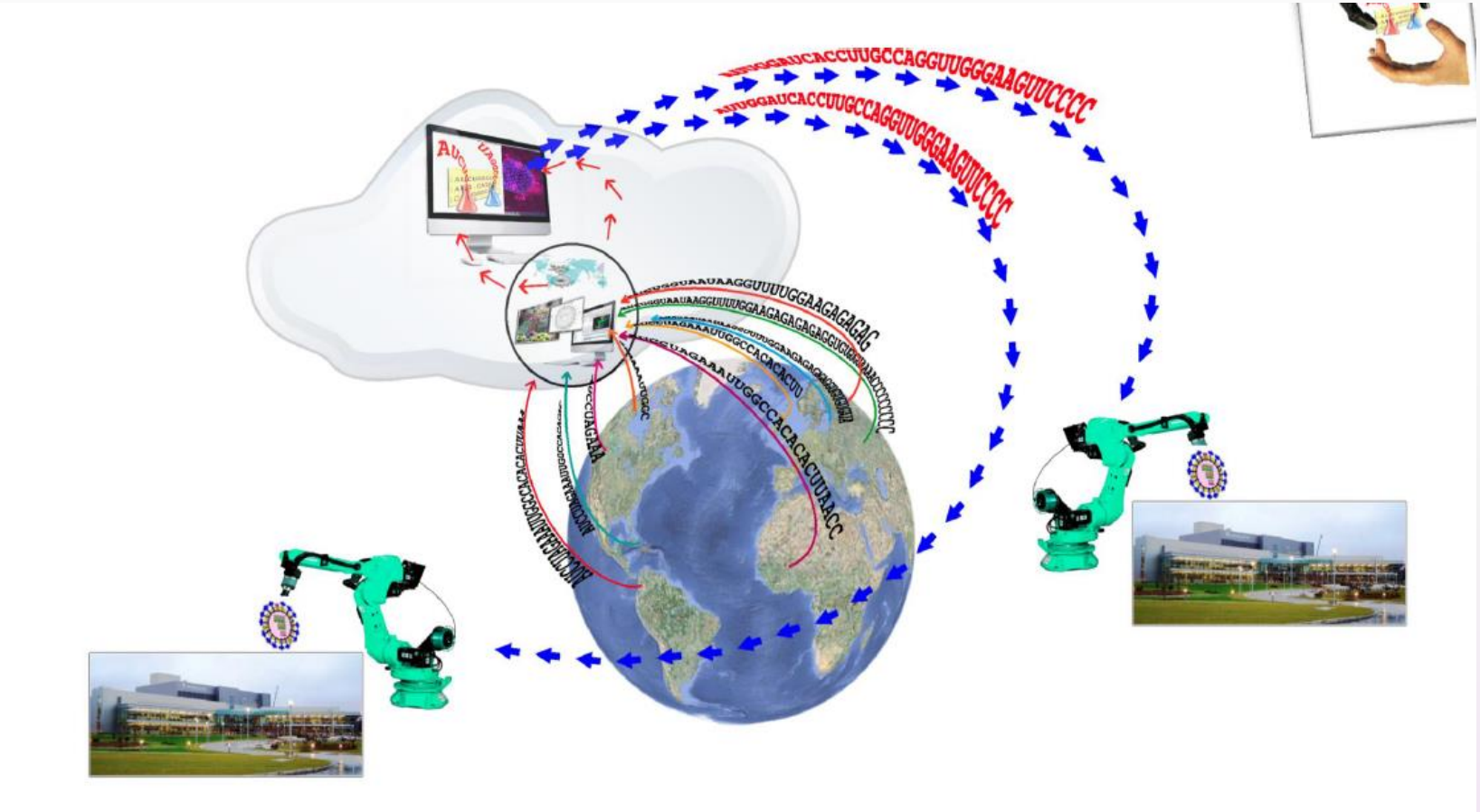
- Kendi çoğalan mRNA tekniği de var.

Sentetik Biyoloji-İnfluenza Aşıları



Rappuoli, R. & Dormitzer, P. R. Influenza: options to improve pandemic preparation. *Science* 336, 1531–1533 (2012).

Sentetik Biyoloji-İnfluenza Aşıları (5 günde ulaşım)



Aşılarda Antijen Sunumu

- Kullanımda olan aşıların çoğunda beklenen yanıt koruyucu-nötralizan antikor oluşturmak
- Gerçekte hücresel immün mekanizmalar korunmada majör rol oynar
- Amaç: Humoral ve hücresel immüniteyi daha etkin uyaracak bir sunum

Viral vektör aşıları
Bakteriyel vektör aşıları
DNA aşıları
RNA aşıları
Dendritik hücre aşıları

Viral Vektör Aşıları

Alphavirus, poxvirus, lentivirus,modifiye Vaccinia Virus Ankara (MVA), Canarypoxvirus, Adenovirus

Hücresel ve humoral, mukozal immün yanıtı uyarma,kolay üretim

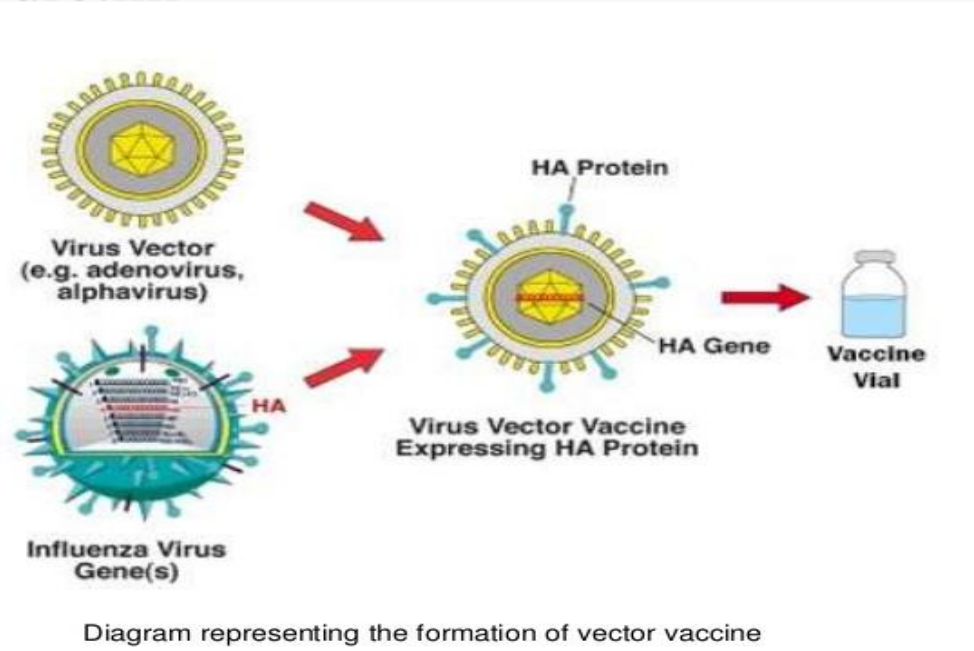


Diagram representing the formation of vector vaccine

Sorunlar

Vektörün atenüe olmama riski

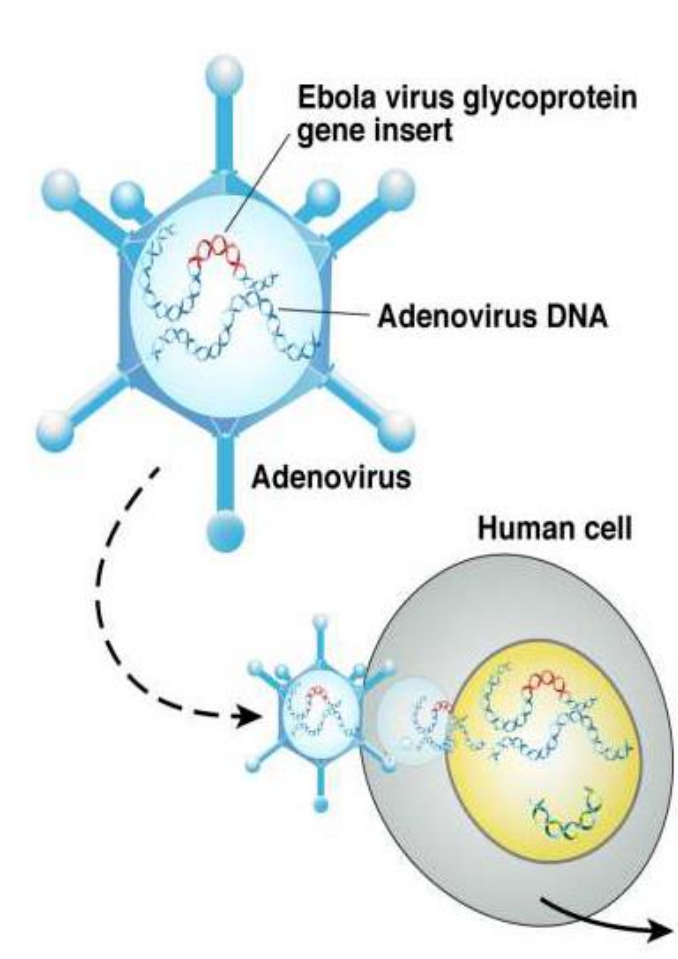
Fazla atenüasyonla immünojenite kaybı

Virulansa neden olacak rekombinasyon riski

Vektöre spesifik antikorlar

Vektöre bağlı persistan veya latent inf riski

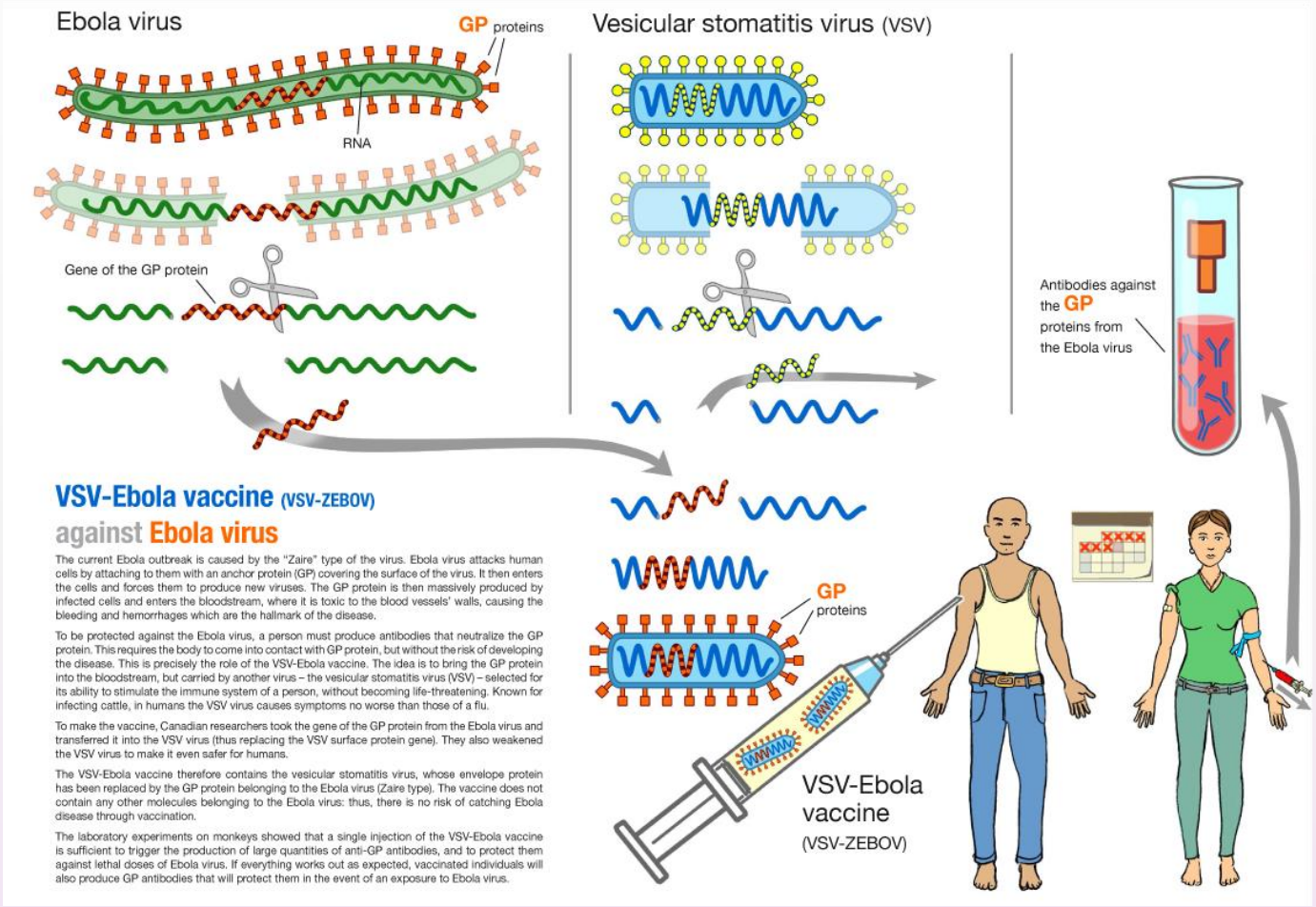
Ebola Virüs Aşısı-Adenovirus



Ebola glikoproteinleri

Richardson JS, et al. PlosOne, 2009

VZV-Ebola Aşısı



Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!)

www.thelancet.com Published online December 22, 2016 http://dx.doi.org/10.1016/S0140-6736(16)32621-6

Ana Maria Henao-Restrepo, Anton Camacho, Ira M Longini, Conall H Watson, W John Edmunds, Matthias Egger, Miles W Carroll, Natalie E Dean, Ibrahima Diatta, Moussa Doumbia, Bertrand Draguez, Sophie Duraffour, Godwin Enwere, Rebecca Grais, Stephan Gunther, Pierre-Stéphane Gsell, Stefanie Hossmann, Sara Viksmoen Watle, Mandy Kader Kondé, Sakoba Kéïta, Soulevmane Kone, Fewa Kuisma, Myron M Levine, Sema Mandal

Summary

Background rVSV-ZEBOV is a recombinant, replication competent vesicular stomatitis virus-based candidate vaccine expressing a surface glycoprotein of Zaire Ebolavirus. We tested the effect of rVSV-ZEBOV in preventing Ebola virus disease in contacts and contacts of contacts of recently confirmed cases in Guinea, west Africa

Interpretation The results add weight to the interim assessment that rVSV-ZEBOV offers substantial protection against Ebola virus disease, with no cases among vaccinated individuals from day 10 after vaccination in both randomised and non-randomised clusters.

	All clusters*				Randomised clusters†			
	1	2	3	4	5	6	7	8
	All vaccinated in immediate (group A) *vs* all contacts and contacts of	All vaccinated in immediate (group A) *vs* all eligible in	All contacts and contacts of contacts in	All vaccinated in immediate (group A) *vs* all	All vaccinated in immediate (group A) *vs* all eligible	All vaccinated in immediate (group A) *vs*	All eligible in immediate (group A) *vs* all	All contacts and contacts of contacts in
Group A								
Number of individuals (clusters)	377[illegible]							4513 (51)
Cases of Ebola virus disease (clusters affected)	[illegible]							10 (5)
Attack rate	[illegible]							0·22%
Group B								
Number of individuals (clusters)	7995 (116)	4507 (104)	4529 (47)	1432 (57)	1429 (46)	3075 (47)	3075 (47)	4529 (47)
Cases of Ebola virus disease (clusters affected)	34 (15)	23 (11)	22 (8)	7 (4)	10 (4)	16 (7)	16 (7)	22 (8)
Attack rate	0·43%	0·51%	0·49%	0·49%	0·7%	0·52%	0·52%	0·49%
Vaccine effect								
Vaccine efficacy/ effectiveness‡ (%, 95% CI)	100% (77·0 to 100·0)	100% (79·3 to 100·0)	70·1% (−4·9 to 91·5)	100% (−51·5 to 100·0)	100% (63·5 to 100·0)	100% (68·9 to 100·0)	64·6% (−46·5 to 91·4)	64·6% (−44·2 to 91·3)
p value§	0·0012	0·0033	0·2759	0·125	0·0471	0·0045	0·344	0·3761

rVSV-ZEBOV uygulama sonrası 10 gün içinde hiç olgu tespiti yok

nature International weekly journal of science

NATURE | NEWS

Ebola vaccine approved for use in ongoing outbreak

Officials have signed off on an experimental vaccine in the Democratic Republic of the Congo, but the decision on whether to deploy it remains up in the air.

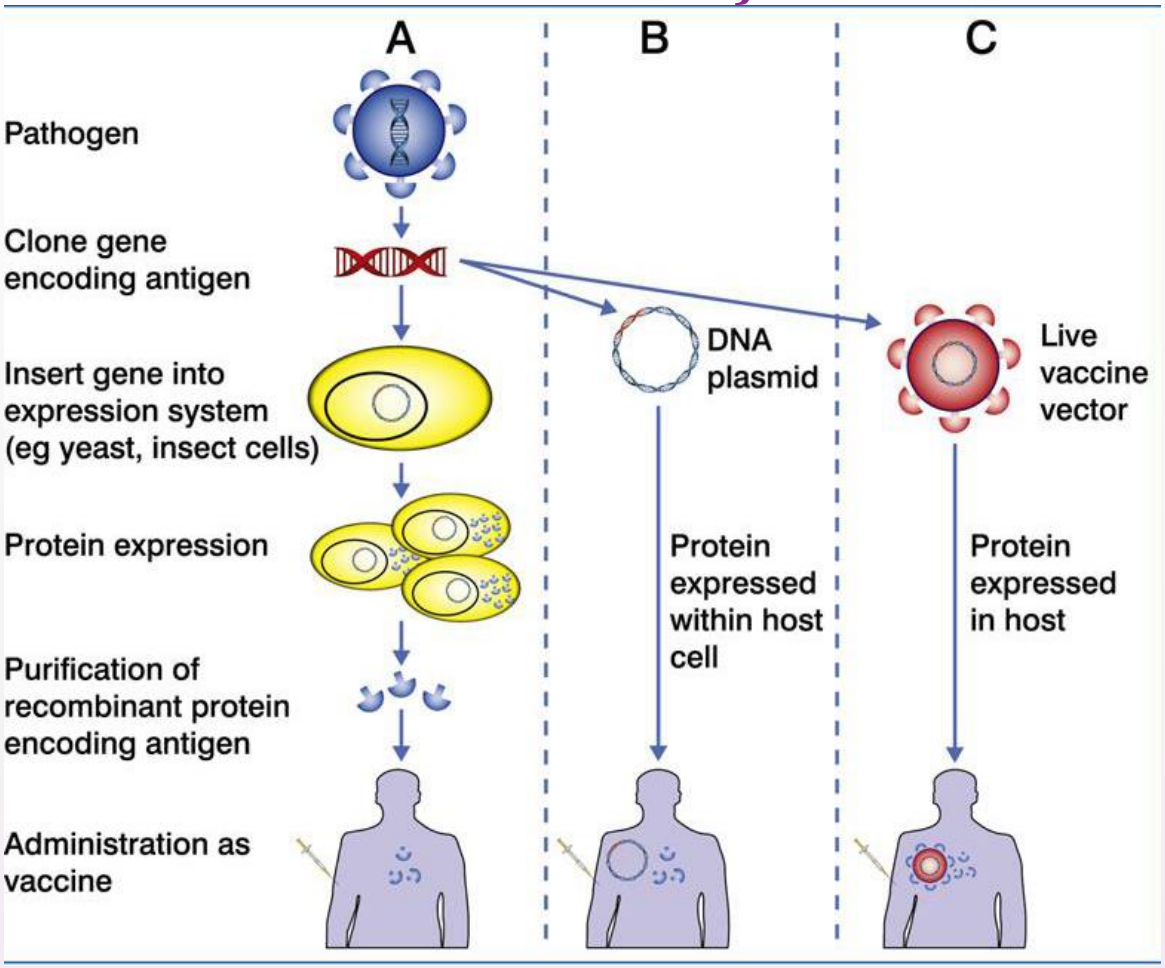
Amy Maxmen

30 May 2017

Nukleik Asid Vektör Aşı Sunum Sistemleri

- DNA-temelli sistemler
- RNA- temelli sistemler

DNA Aşıları



Dezavantajları

- İnsanda zayıf immünite
- Konak genomuna entegrasyon riski

RNA Temelli-Sistemler

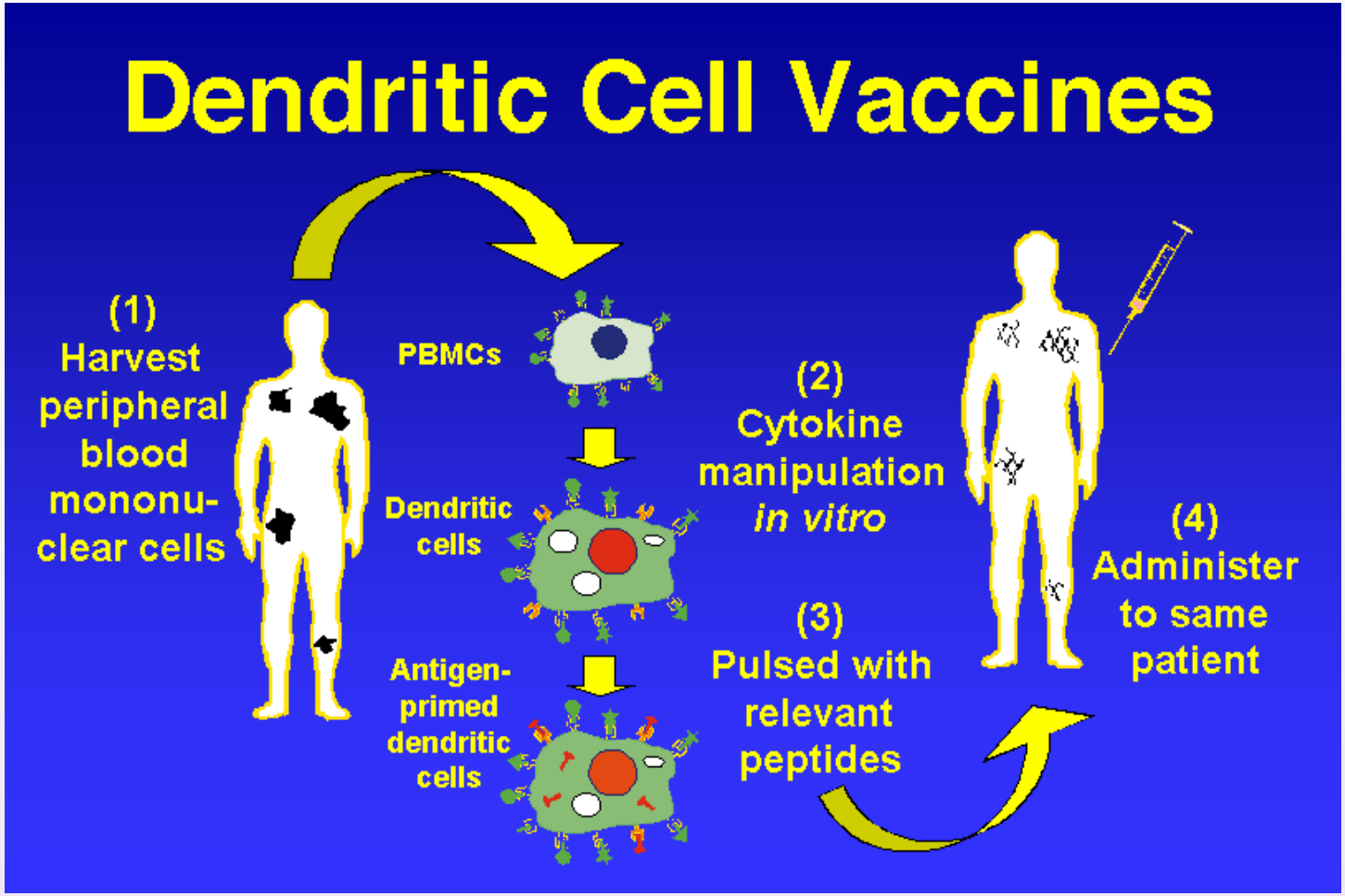
Avantaj

- RNA genoma integre olmaz
- Antijen ekspresyonu hızlı
- Antijen yıkımı hızlı
- Daha iyi antijen ekspresyonu
- Daha güçlü immün yanıt-doğal immün yanıt

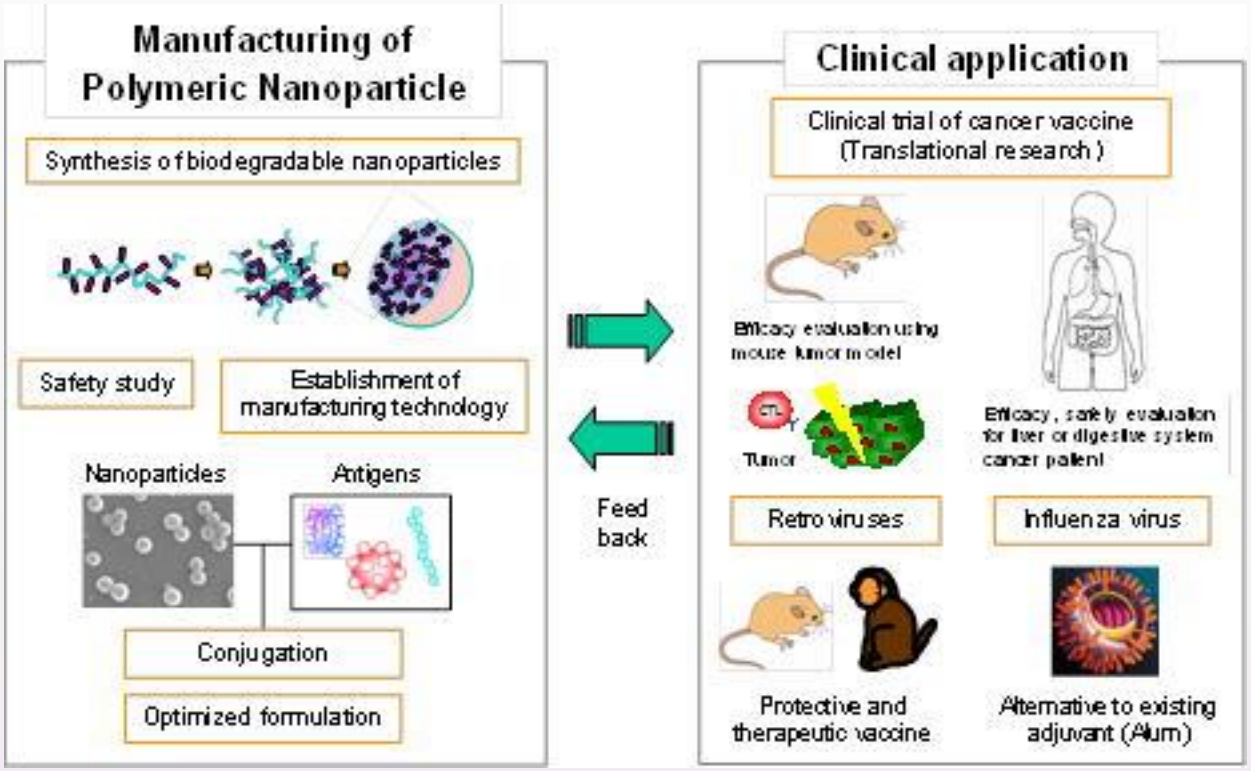
- RNA stabilitesi düşük

self-amplifying mRNA (SAM®) aşı teknolojisi (lipid nanopartiküllerle kaplanarak) Prostat kanseri ve melanom
CMV, kuduz, klinik çalışma aşamasında
İnfluenza, HIV, tüberküloz için araştırma aşamasında

Dendritik Hücre Aşıları



Nanopartikül Aşılar



Nanopartikül Aşılar

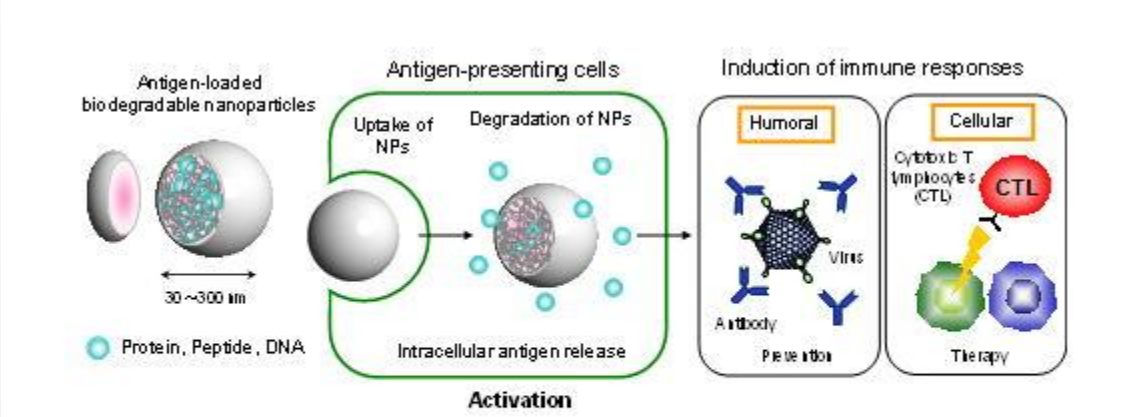
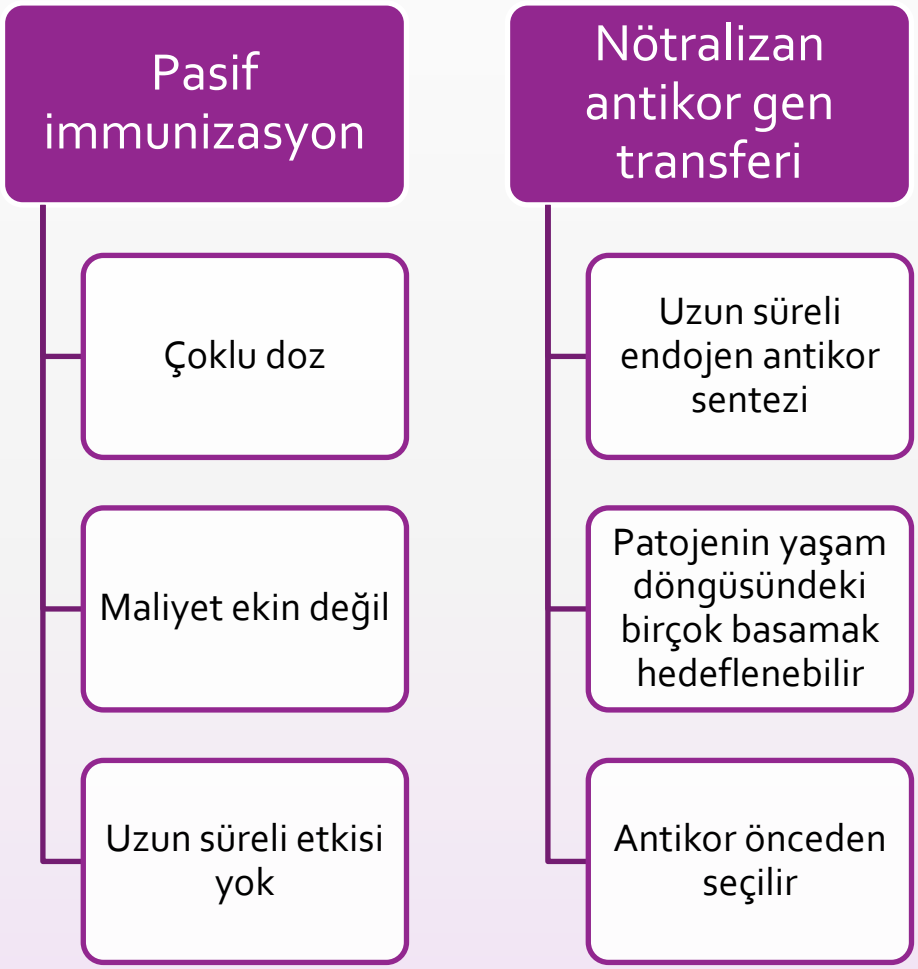
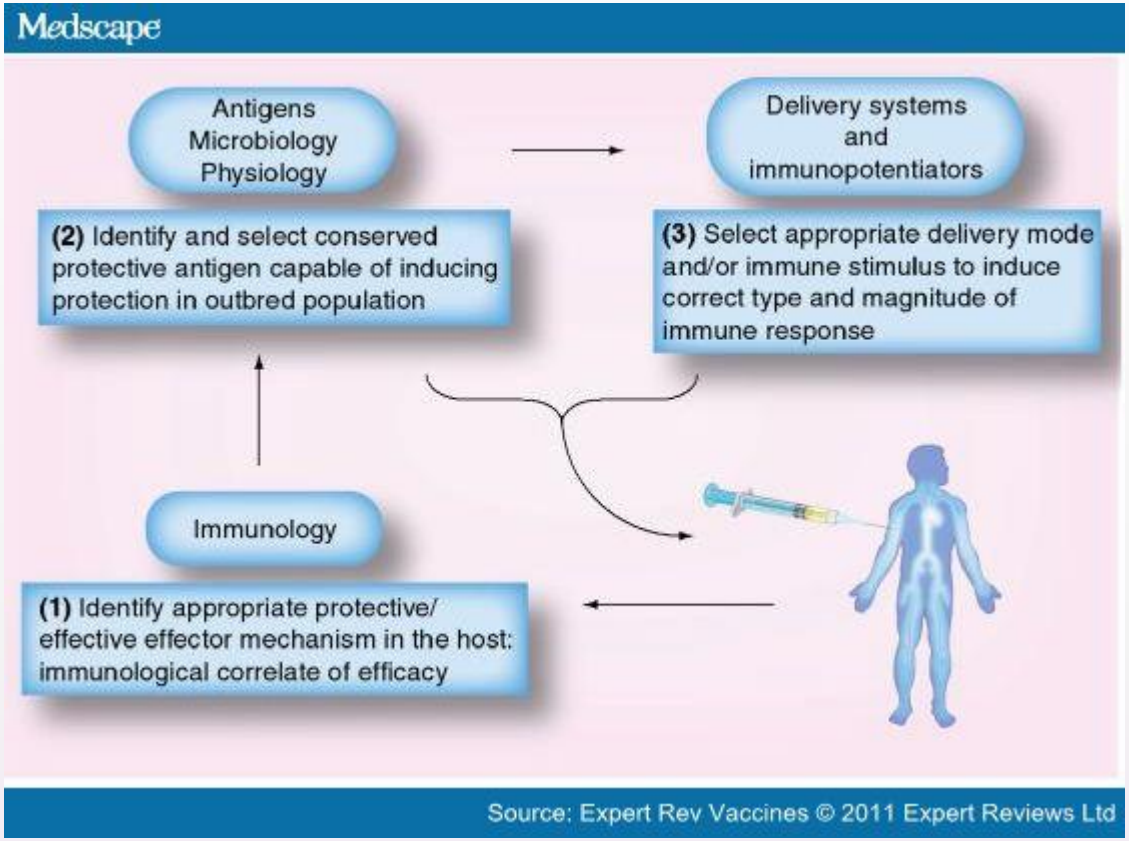


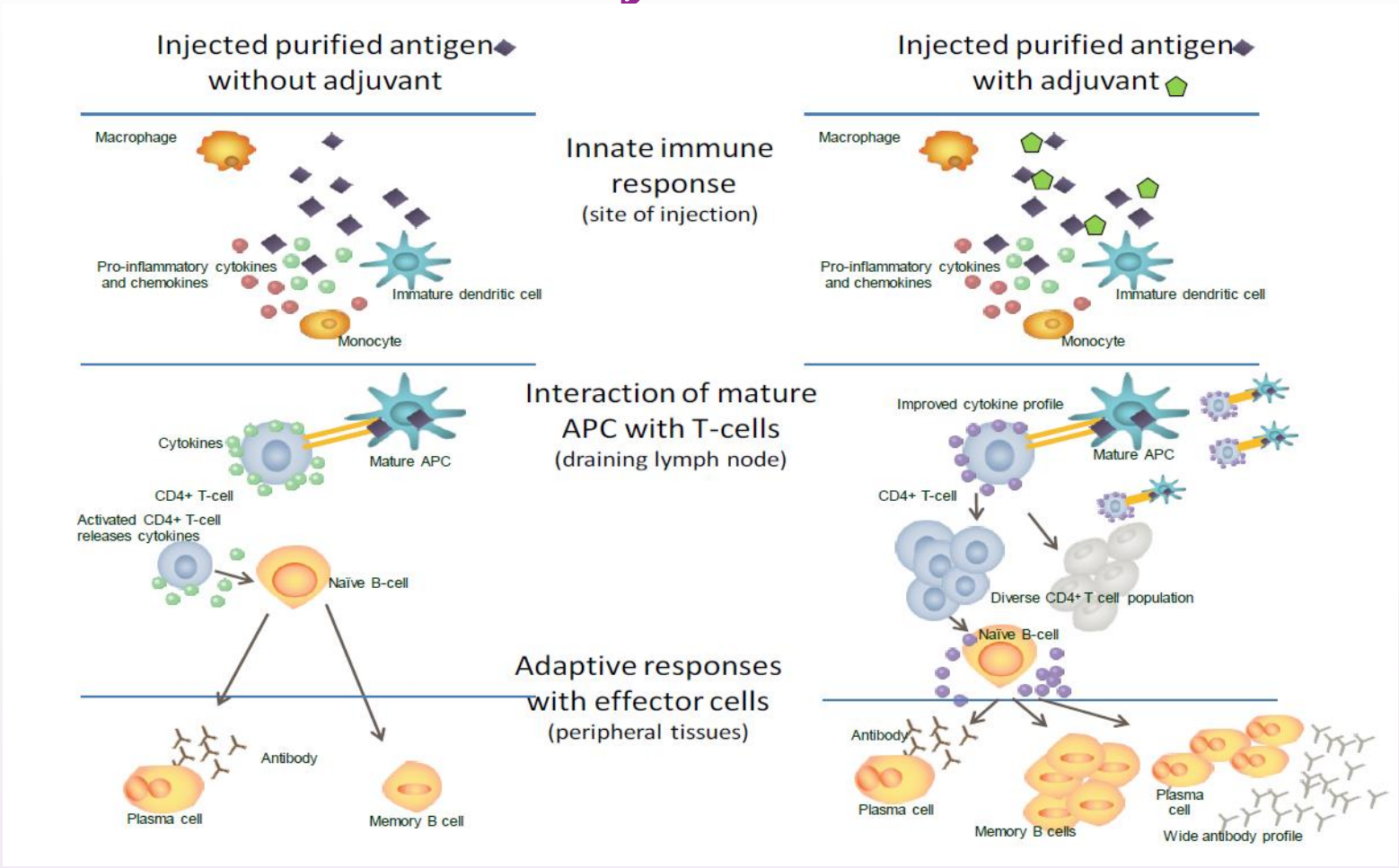
Fig.1 Development of nanoparticle-based vaccine adjuvants and delivery systems for immunotherapy.

Gen Transferi İle İmmunoprofilaksi




Medscape
Antigens
Microbiology
Physiology
Delivery systems
and
immunopotentiators
(2) Identify and select conserved protective antigen capable of inducing protection in outbred population
(3) Select appropriate delivery mode and/or immune stimulus to induce correct type and magnitude of immune response
Immunology
(1) Identify appropriate protective/ effective effector mechanism in the host: immunological correlate of efficacy
Source: Expert Rev Vaccines © 2011 Expert Reviews Ltd

Adjuvanlar

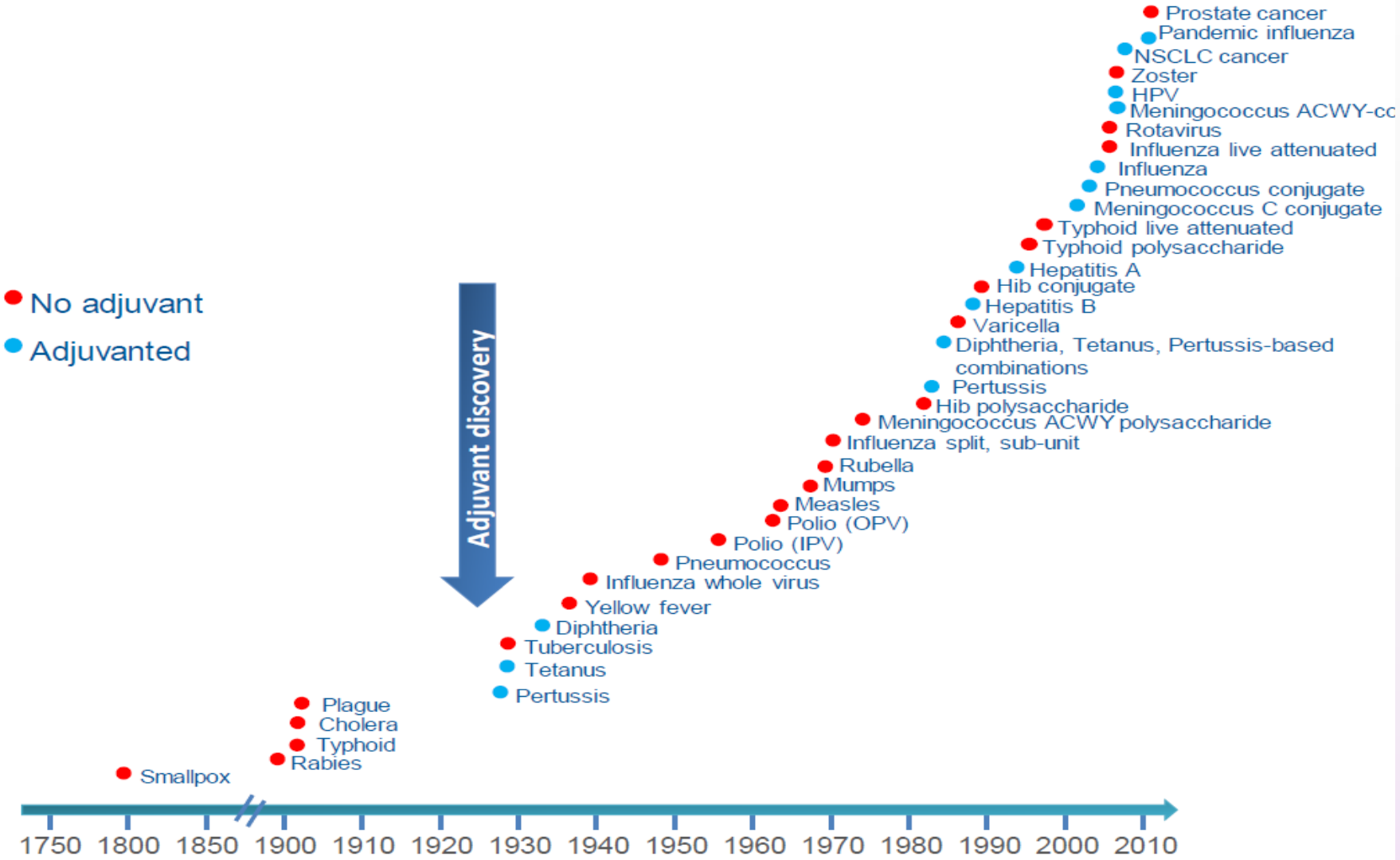

Injected purified antigen without adjuvant
Injected purified antigen with adjuvant
Macrophage
Pro-inflammatory cytokines and chemokines
Immature dendritic cell
Monocyte
Innate immune response (site of injection)
Cytokines
Mature APC
CD4+ T-cell
Activated CD4+ T-cell releases cytokines
Naïve B-cell
Interaction of mature APC with T-cells (draining lymph node)
Improved cytokine profile
Diverse CD4+ T cell population
Antibody
Plasma cell
Memory B cell
Adaptive responses with effector cells (peripheral tissues)
Memory B cells
Wide antibody profile

Adjuvanların Katkıları

- Antijen dozunu azaltır
- Aşı dozunu azaltır
- Bebek, yaşlı ve immunokompromizelerde aşı etkinliği artar
- Fonksiyonel antikor titresi artar
- Hızlı ve uzun süreli immün yanıt indükler
- Güçlü hücresel immün yanıt
- Geniş korunma (çapraz reaktivite)
- Mukozal immüniteyi kolaylaştırır
- Kombine aşılarda antijen kompetisyonunu önler

Immune network . 52(15(2): 2: 51-57, 2015

Adjuvanlı ve Adjuvansız Aşılar



Adjuvanlar

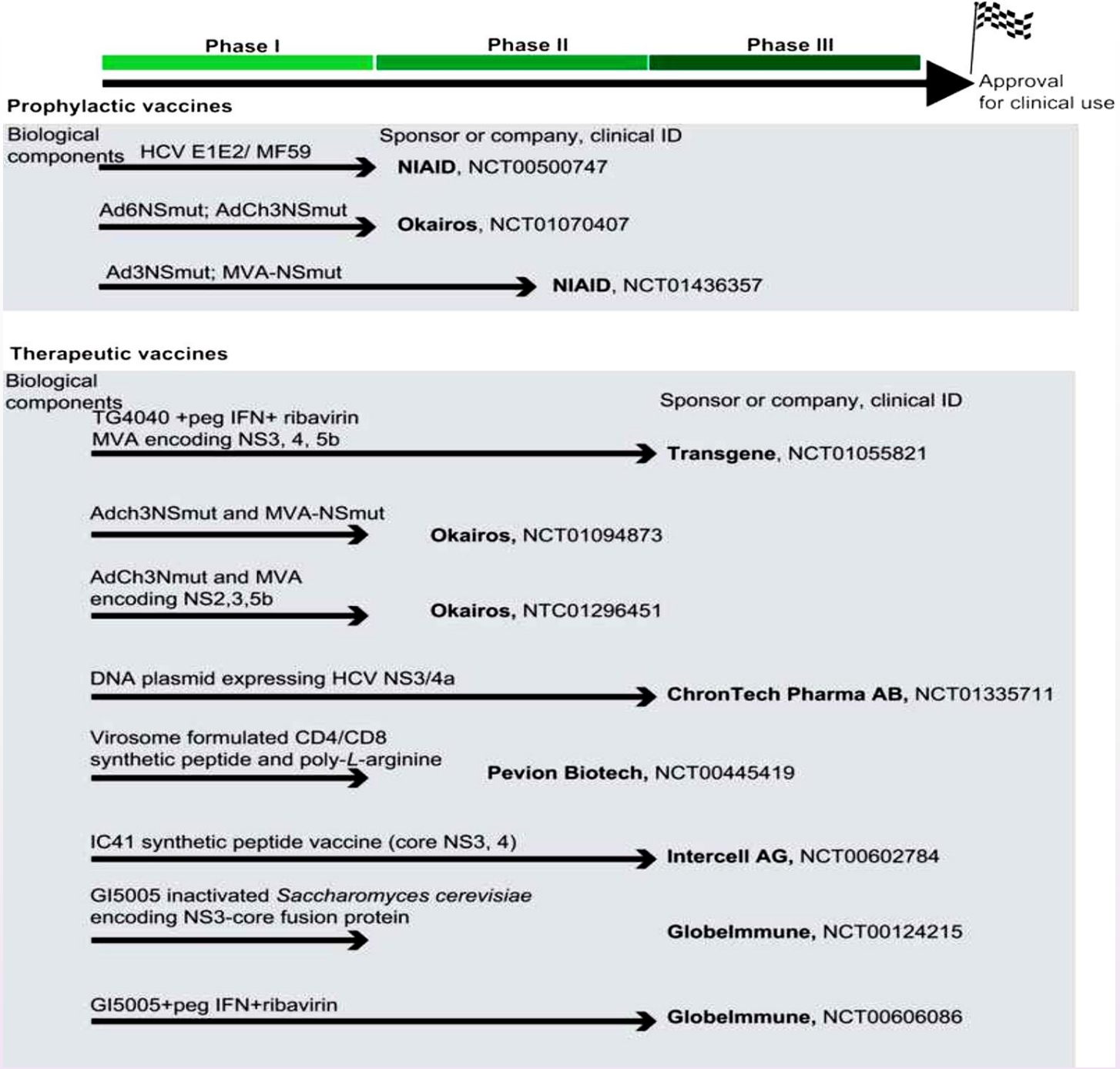
Depo Adjuvanlar

- **Mineral bazlı adjuvanlar**
  - **Aluminyum tuzları**
  - Kalsiyum tuzları
- Tensio-aktif adjuvanlar
  - Saponin
- Emülsiyonlar
  - Suda yağ emülsiyonları
  - **MF59**
  - **Stabil emülsiyon**
  - Adjuvan sistem 03(AS03
- Polimerik mikrosfer
- Lipozomlar

İmmunostimülan(potensiatör) adjuvanlar

- Mikrobiyal adjuvanlar
- Sitokinler (IFN-g, GM-CSF_
- **TLR agonistleri**
  - (TLR 4 agonisti) monophosphoryl lipid A (MPL),
  - ASO4 (HPV,HBV aşısında kullanılıyor)
  - CpG oligonucleotides (TLR9 agonists),
- Karbohidrat adjuvanlar(çitosan)
- Polyriboinosinic acid-polyribocytidylic acid (poly I:C)
- **Virozomlar** (HAV, IV)
- Lazer aşı adjuvanları
- Immune stimulating complexes (ISCOM)
- Virüs benzeri partiküller
- Sentetik adjuvanlar……

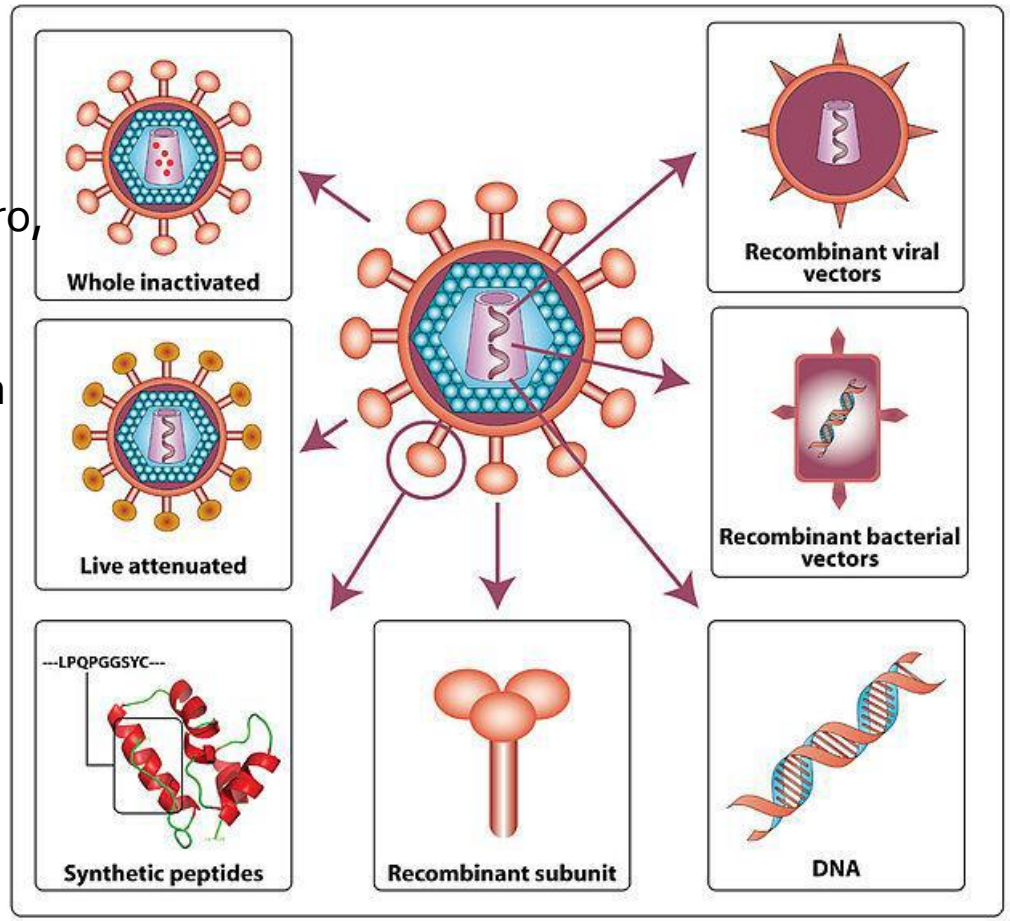
Mohanty NN, et al. MA (2016) J Infect Dis Ther 4:260.



Int J Mol Cell Med. 2014 Autumn; 3(4): 207–215.

HIV Aşı Çalışmaları

Canarypox vektorvirus+ BHIV gag,pro,
E gp120
(ALVAC-HIV)
bivalan (AIDSVAX) B/E gp120 protein
kombinasyon aşısı %31 koruma
Aşının iyileştirilmesi ile %50



HIV Aşı Çalışmaları

Trial	Trial number	Sponsor	Phase	Status
DNA-based vaccine				
GTU-MultiHIV B Clade Vaccine	NCT02457689	Imperial College London	I/II	Active
DermaVir (topically applied DNA)	NCT00711230	Genetic Immunity	II	Unknown
DermaVir	NCT00918840	Genetic Immunity	II	Completed
DermaVir	NCT00270205	AIDS Clinical Trials Group	I/II	Completed [48]
DermaVir	NCT00712530	Genetic Immunity	I	Completed [49]
PENNVAX-B (Gag, Pol, Env)	NCT01082692	Inovio Pharmaceuticals	I	Completed [50]
PENNVAX-B ± IL-12 or IL-15	NCT00775424	University of Pennsylvania	I	Completed
MAG pDNA vaccine ± IL-12	NCT01266616	NIAID	I	Completed
DNA + lipopeptide vaccines				
GTU-Multi-HIV B Clade Vaccine + LIPO-5	NCT01492985	French National Institute for Health and Medical Research/French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	II	Active/closed to enrollment
DNA + viral vector vaccines				
MAG-pDNA + rVSVIN HIV-1 Gag	NCT01859325	NIAID/Profectus Biosciences, Inc.	I	Active/closed to enrollment
D-GPE DNA + M-GPE MVA	NCT01881581	Centers for Disease Control and Prevention, China	I	Unknown
JS7 DNA + MVA62B	NCT01378156	GeoVax, Inc.	I	Completed [HIV R4P 2014, Abstract OA05.03 (webcast)]
RNA-based vaccine				
iHIVARNA-01 (TriMix and HIV antigen naked messenger RNA)	NCT02413645	Biomedical Research Institute August Pi i Sunyer (IDIBAPS)	I	Active
Peptide-based vaccine				
VAC-3S	NCT02041247	InnaVirVax	II	Active/closed to enrollment
VAC-3S	NCT02390466	InnaVirVax	I/IIa	Active/closed to enrollment
Vacc-4x	NCT00659789	Bionor Immuno AS	II	Completed [51]
VAC-3S	NCT01549119	InnaVirVax	I/IIa	Completed (30 years of HIV Science, 2013, poster abstract 145; IAS 2015 toward an HIV Cure Symposium, Poster Abstract PE67 LB)
TUTI-16 (synthetic HIV-1 Tat epitope)	NCT01335191	Thymon, LLC	I/II	Completed [52]
Vacc-C5	NCT01627678	Bionor Immuno AS	I/II	Completed
AFO-18	NCT01141205	Statens Serum Institut (SSI)/ Ministry of the Interior and Health, Denmark/European and Developing Countries Clinical Trials Partnership	I	Completed [53]

Trial	Trial number	Sponsor	Phase	Status
Ad5-Gag	NCT02762045	Centers for Disease Control and Prevention, China	I	Active
HIVAX	NCT01428596	GeneCure Biotechnologies	I	Active
ChAdV63.HIVcons + MVA.HIVconsv	NCT01712425	IrsiCaixa/Fundació Lluita contra la SIDA (AIDS)/ Hospital Clinic of Barcelona/HIVACAT/ University of Oxford	I	Completed (IAS 2015, Poster abstract MOPEA036)
MVA.HIVconsv	NCT01024842	University of Oxford/Medical Research Council	I	Terminated
Protein-based vaccine				
Tat Oyi	NCT01793818	Biosantech	I/II	Active/closed to enrollment
GSK Biologicals HIV Vaccine 732462 (p24-RT-Nef-p17 fusion protein)	NCT01218113	GlaxoSmithKline	II	Completed
Tat protein vaccine	NCT01513135	Barbara Ensoli, MD, Istituto Superiore di Sanità/Italian Ministry of Foreign Affairs – General Direction for Cooperation and Development	II	Completed [56,57]
AT20-KLH (Synthetic HIV-1 matrix protein p17-based AT20-KLH)	MED-AT20-001	Medestea Research & Production SpA, Turin	I	Completed [58]
DC-based vaccine				
AGS-004 (DC-based vaccine with HIV antigens)	NCT02042248	University of North Carolina at Chapel Hill/Argos Therapeutics/US National Institutes of Health (NIH)	I/II	Active
AGS-004	NCT00672191	Argos Therapeutics	IIb	Completed [59]
AGS-004	NCT01069809	Argos Therapeutics	IIb	Completed (IAS 2015 toward an HIV Cure Symposium, Combination Therapy Trials Roundtable)
Dendritic cells pulsed with chemically inactivated HIV	NCT02766049	University of Sao Paulo General Hospital	I/II	Completed [60,61]
Dendritic cell vaccine	NCT00833781	Massachusetts General Hospital	I/II	Completed [62]
Autologous HIV-1 ApB DC Vaccine	NCT00510497	Sharon Riddler, University of Pittsburgh/NIAID	I/II	Completed [63]
Dendritic cell vaccine (DCV-2)	NCT00402142	Hospital Clinic of Barcelona	I/II	Completed [64]
Dendritic cells loaded with HIV-1 lipopeptides	NCT00796770	Baylor Research Institute/ ANRS	I	Completed [65,66]

Curr Opin HIV AIDS 2016, 11:576–584

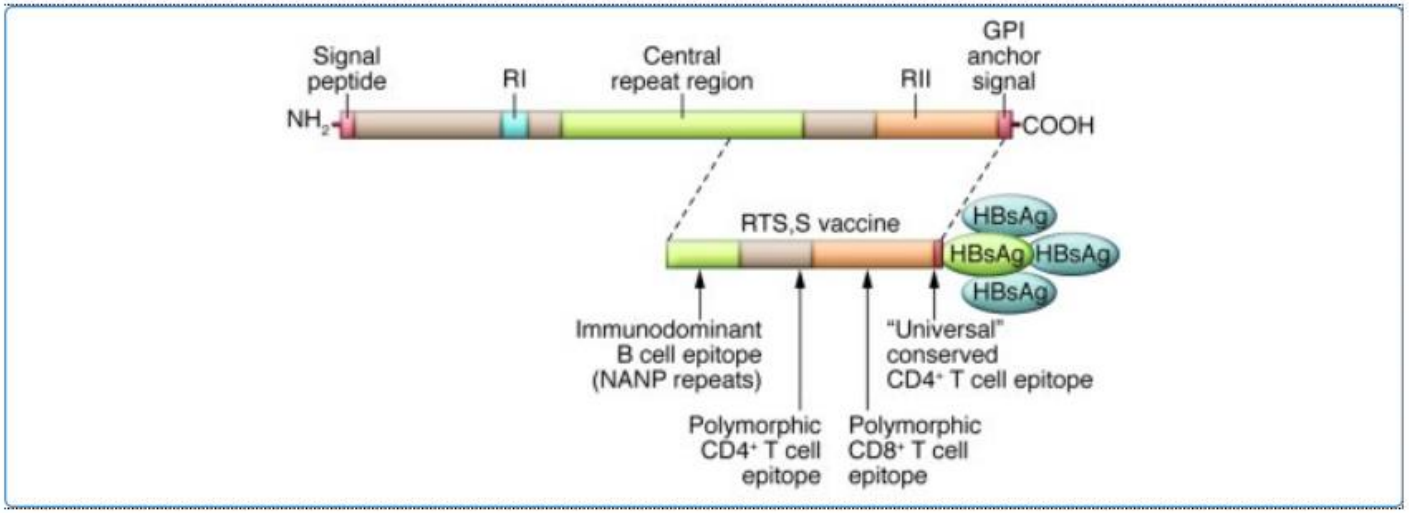
- Profilaktik aşılar
- Terapötik aşılar

WHO Vaccine Pipeline Tracker

HIV | Malaria | TB | Enterics | RSV | Ebola | Zika | Dengue | Priority emerging pathogens | Drop downs

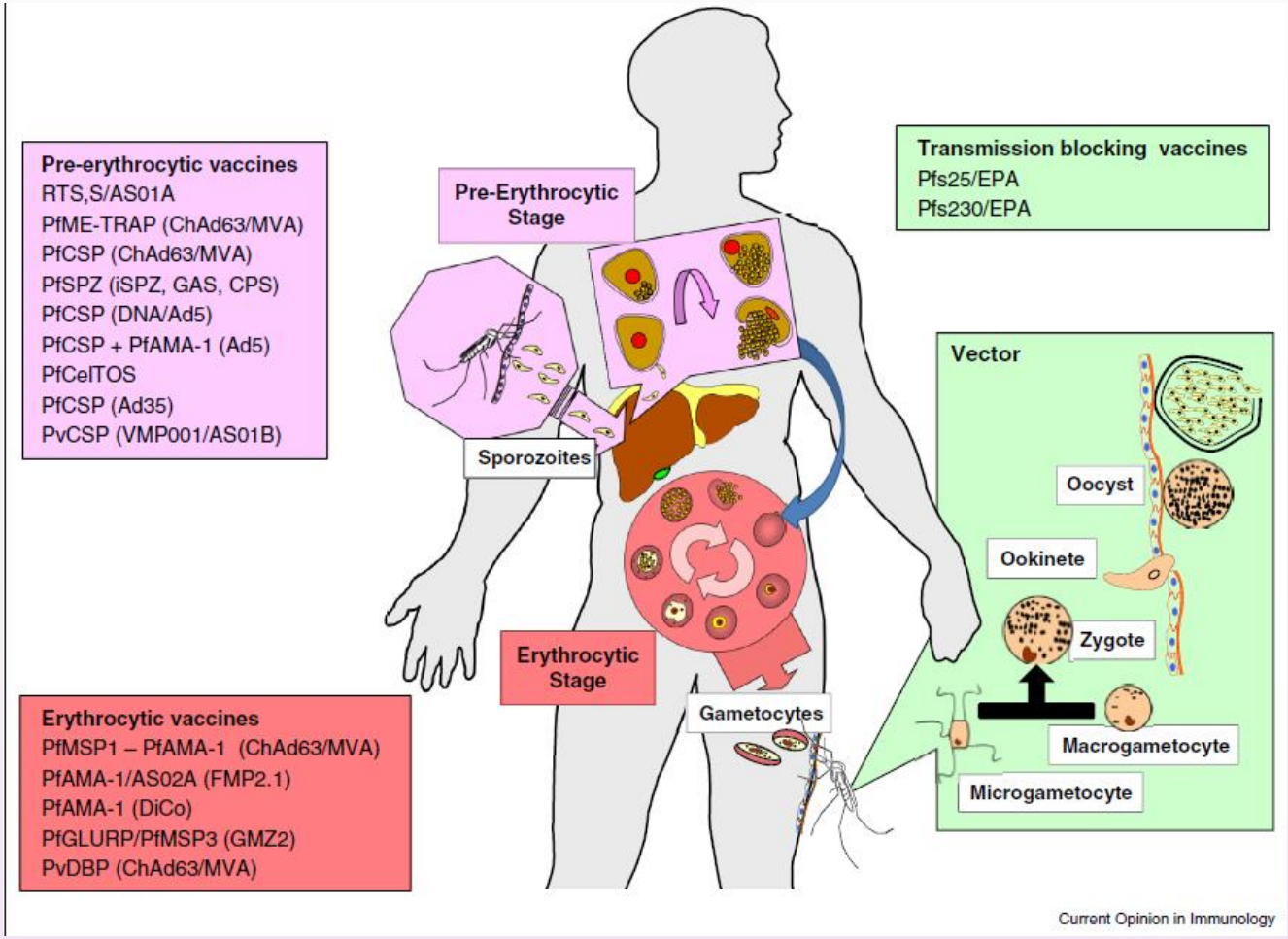
Candidate vaccine name	Disease / Pathogen	Indication goal (select from drop down menu)	Platform (select from drop down menu)	Immunogen (select type from drop down menu and then enter specific target)	Adjuvant (select from drop down menu)	Most advanced trial phase (select from drop down menu)	Trial Registration No (provide link, click to go to site)	Trial Sponsor	Start Date	Study Completion Date (estimated / actual LSLV
DNA multiclade rAd5 multiclade	HIV-1	Prevention (active) infection/transmission	Recombinant viral vector DNA	Protein: gag-pol, nef, env gag-pol, env	None	Phase 2b	NCT00955006 NCT00865566	DAIDS/NIAID/NIH	12-Sep-11 11-Jun-09	21-Nov-17 08-Apr-18
ALVAC-HIV (vCP2438) Bivalent Subtype C gp120/MF59	HIV-1	Prevention (active) infection/transmission	Subunit (e.g., toxoid, carbohydrate) from target organism Recombinant viral vector	Protein: gag-pro, env Env	Novel other: specify MF59	Other: specify Phase 1	NCT02404311	DAIDS/NIAID/NIH	9-Feb.-15	26-Dez.-16
VRC01 mAb	HIV-1	Prevention (passive) infection/transmission	Other: monoclonal	n/a	None	Other: specify Phase 1	NCT02165267	DAIDS/NIAID/NIH	9-Sep.-14	5-März-16
DNA MVA CRF01_AE	HIV-1	Prevention (active) infection/transmission	Recombinant viral vector DNA	Protein: Env Env, gag-pol	None	Other: specify Phase 1	NCT02296541	DAIDS/NIAID/NIH	20-Jan.-15	8-Sep.-20
Ad4 AIDSVAX® B/E Substypes B, E, gp120	HIV-1	Prevention (active) infection/transmission	Other: live attenuated viral vector Subunit (e.g., toxoid, carbohydrate) from target organism	Protein: gag, env Env	Aluminum salts (alum)	Other: specify Phase 1	n/a	PaxVax, Inc.	24-März-15	25-Feb.-17
DNA clade B rVSVIN clade B	HIV-1	Prevention (active) infection/transmission	Recombinant viral vector DNA	Protein: gag, pol, nef, tat, vif, env	None	Other: specify Phase 1	NCT01578889	DAIDS/NIAID/NIH	21-Mai-12	5-Sep.-16
PENNVAX-G DNA MVA CRF01_AE	HIV-1	Prevention (active) infection/transmission	Recombinant viral vector DNA	Protein: Env, gag	Novel other: IL-15 DNA Plasmid for PENNVAX; None for MVA Boost	Other: specify Phase 1	NCT01260727	DAIDS/NIAID/NIH	1st vax-27 Oct 2010	Juni-2015
ALVAC-HIV (vCP1521) AIDSVAX® B/E	HIV-1	Prevention (active) infection/transmission	Recombinant viral vector; Recombinant subunit (non VLP)	Protein: Gag, protease, env	AlVAC: None; AIDSVAX B/E: Alhydrogel	Phase 2	NCT01435135	USAMRMC	Apr.-2012	Dez.-2017

Sıtma Aşısı



RTS,S/AS01 — trade name Mosquirix — is a recombinant protein-based malaria vaccine. Approved for use by European regulators in July 2015, it is not only the world's first licensed malaria vaccine, but the first vaccine licensed for use against a parasitic disease of any kind. The RTS,S vaccine was conceived of and created in the late 1980s by scientists working at SmithKline Beecham Biologicals (now GlaxoSmithKline Vaccines) laboratories in Belgium. The vaccine was further developed through a collaboration between GSK and the Walter Reed Army Institute of Research and has been funded in part by the PATH Malaria Vaccine Initiative and the Bill and Melinda Gates Foundation. Its efficacy ranges from 26 to 50% in infants and young children.

Sıtma Aşıları



Malaria vaccine clinical trials pipeline.

Antigen	Vaccine platform	References
P. falciparum CSP (RTS,S)	VLP-in-adjuvant	[5,6•]
P. falciparum CSP + *P. falciparum* AMA-1	DNA/Ad5 prime-boost regimen	[8,9]
P. falciparum CSP	Ad35 vectored	[12,13]
P. falciparum CSP + RTS,S	Ad35 vectored/VLP-in-adjuvant prime-boost regimen	NCT01366534
P. falciparum ME-TRAP	ChAd63/MVA prime-boost regimen	[14–17]
P. falciparum ME-TRAP + RTS,S	ChAd63/MVA vectored + VLP-in-adjuvant coadministration	NCT02252640 *
P. falciparum CelTOS	Protein-in-adjuvant	NCT02174978 *
P. falciparum radiation-attenuated sporozoites	Whole organism	[19,20]
P. falciparum genetically-attenuated sporozoites	Whole organism	[21]
P. falciparum sporozoite inoculation under prophylaxis	Whole organism	[22,23•]
P. falciparum MSP-1/*P. falciparum* AMA-1	ChAd63/MVA prime-boost regimens	[25•,26]
P. falciparum AMA-1 (FMP2.1)	Protein-in-adjuvant	[27,28]
P. falciparum AMA-1 (DiCo)	Protein-in-adjuvant	NCT02014727 *
P. falciparum hybrid GLURP + MSP-3 (GMZ2)	Protein-in-adjuvant	[34]
P. falciparum Pfs25-EPA	Conjugated vaccine	NCT02334462 *
P. falciparum Pfs230-EPA	Conjugated vaccine	NCT02334462 *
P. vivax CSP (VMP001)	Protein-in-adjuvant	NCT01157897 *
P. vivax DBP	ChAd63/MVA prime-boost regimen	NCT01816113 *

* Clinical Trial Registration Number.

First malaria vaccine to be widely tested in Africa next year

By Jen Christensen, CNN
Updated 1349 GMT (2149 HKT) April 26, 2017

News & buzz

Tuberküloz Aşıları

- Tüm hücre aşıları
- Viral vektör aşıları
- Adjuvanlı protein subunit aşılar
- Rekombinan BCG,,

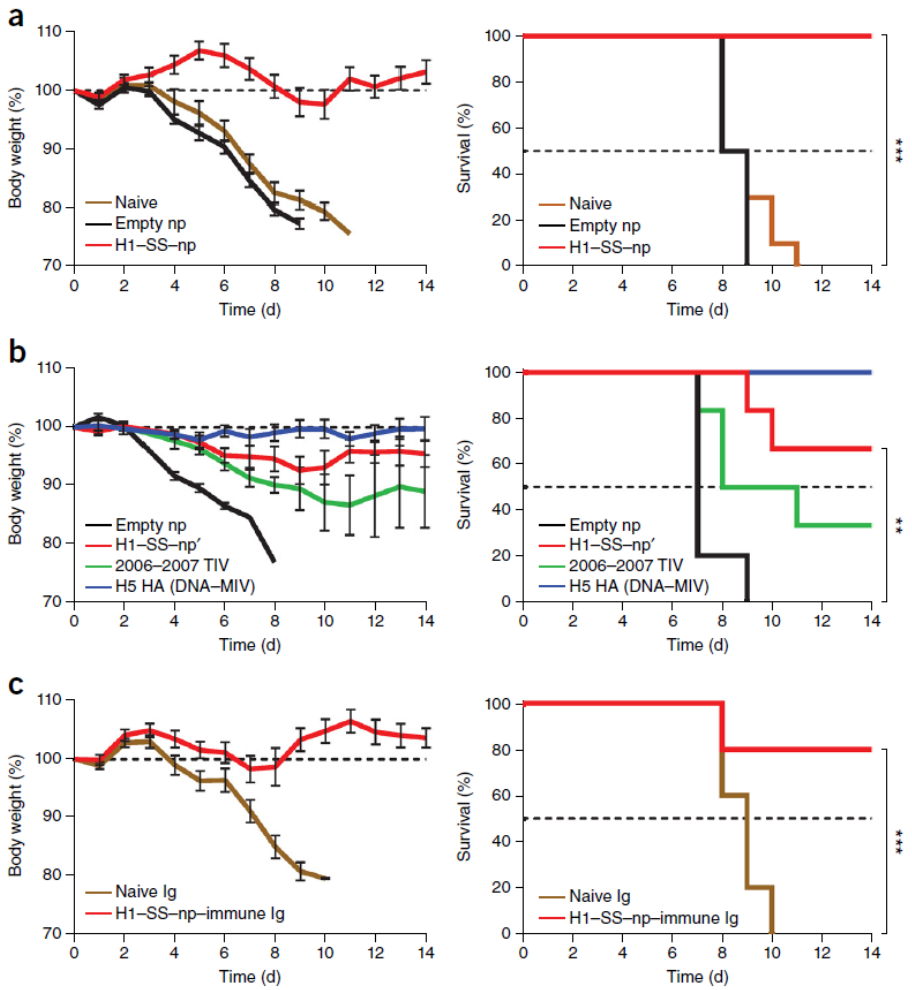
12 aşı çalışmada

rekombinan antijenlere örnek
; Mtb72F fusion protein , Ag85B-ESAT-6 fusion protein +adjuvan AS02,
Ag85-TB10.4 fusion protein + adjuvant IC31

Hemagglutinin-stem nanoparticles generate heterosubtypic influenza protection

Hadi M Yassine[1,6], Jeffrey C Boyington[1,6], Patrick M McTamney[1,5,6], Chih-Jen Wei[1,5,6], Masaru Kanekiyo[1], Wing-Pui Kong[1], John R Gallagher[2], Lingshu Wang[1], Yi Zhang[1], M Gordon Joyce[1], Daniel Lingwood[1,5], Syed M Moin[1], Hanne Andersen[3], Yoshinobu Okuno[4], Srinivas S Rao[1,5], Audray K Harris[2], Peter D Kwong[1], John R Mascola[1], Gary J Nabel[1,5] & Barney S Graham[1]

The antibody response to influenza is primarily focused on the head region of the hemagglutinin (HA) glycoprotein, which in turn undergoes antigenic drift, thus necessitating annual updates of influenza vaccines. In contrast, the immunogenically subdominant stem region of HA is highly conserved and recognized by antibodies capable of binding multiple HA subtypes[1–6]. Here we report the structure-based development of an H1 HA stem–only immunogen that confers heterosubtypic protection in mice and ferrets. Six iterative cycles of structure-based design (Gen1–Gen6) yielded successive H1 HA stabilized-stem (HA–SS) immunogens that lack the immunodominant head domain. Antigenic characterization, determination of two HA–SS crystal structures in complex with stem-specific monoclonal antibodies and cryo-electron microscopy analysis of HA–SS on ferritin nanoparticles (H1–SS–np) confirmed the preservation of key structural elements. Vaccination of mice and ferrets with H1–SS–np elicited broadly cross-reactive antibodies that completely protected mice and partially protected ferrets against lethal heterosubtypic H5N1 influenza virus challenge despite the absence of detectable H5N1 neutralizing activity *in vitro*. Passive transfer of immunoglobulin from H1–SS–np–immunized mice to naive mice conferred protection against H5N1 challenge, indicating that vaccine-elicited HA stem–specific antibodies can protect against diverse group 1 influenza strains.



nature medicine

Aşı Klinik Çalışmaları

Table 1 Number of vaccine clinical trials currently registered on clinicaltrials.gov for specified diseases. (Current as of 6 May 2016)

Disease	N Trials		Phase III & IV		Completed with results		Completed with results phase III & IV		Vaccine currently available
	All	Peds	All	Peds	All	Peds	All	Peds	
All vaccine clinical trials	6061	2159	1815	1042	976	490	524	326	–
CMV	36	4	5	0	1	0	0	0	No
Dengue virus	83	27	8	7	2	1	0	0	Yes
Ebola virus	45	5	6	2	0	0	0	0	No
GAS	18	2	0	0	4	0	0	0	No
GBS	15	0	0	0	4	0	0	0	No
HIV†	576	113	72	20	43	14	5	3	No
HPV	233	134	99	68	74	46	48	31	Yes
Influenza	1366	491	589	274	318	135	187	94	Yes
Malaria	172	53	12	12	7	7	0	0	No
Meningococcus	91	80	53	48	32	30	15	13	Yes
Rotavirus	127	120	58	58	32	31	22	22	Yes
RSV	38	15	3	1	3	3	0	0	No*
Staphylococcus aureus	24	0	8	0	5	0	0	0	No
Tuberculosis	96	22	8	2	5	2	0	0	Yes (BCG)
Zika virus	0	0	0	0	0	0	0	0	No

* Passive immunisation via monoclonal antibody infusion (Palivizumab)

† Includes clinical trials of HIV vaccines and other vaccines in HIV-infected population

CMV Cytomegalovirus, *GAS* Group A Streptococcus, *GBS* Group B Streptococcus, *HIV* Human immunodeficiency virus, *HPV* Human papillomavirus, *RSV* Respiratory syncytial virus, *BCG* Bacillus Calmette-Guérin

Curr Pediatr Rep (2016) 4:74–83

Günümüzde Aşılamada Hedefler

Poverty

Cholera
Dengue
ETEC
HAV
HBV
HEV
Flu
JEV
Malaria
Men B
Parasitic infections
Paratyphoid
Rabies
Rotavirus
Salmonella
S. enterica
S. typhimurium
Shigella
TB
Typhoid fever

Emerging infections

AIDS
Anthrax
Avian influenza
Cholera
Diphtheria
Dengue
Ebola
EV71
Malaria
SARS
TB
Smallpox
West Nile
Yersinia

Travelers

Cholera
Dengue
ETEC
Flu
HAV
HBV
JEV
Malaria
Men
Paratyphoid
Rabies
Shigella
TB
Typhoid fever
Yellow Fever

Patients with Chronic diseases

CMV
Flu
Fungal infections
P. aeruginosa
Parainfluenza
RSV
Staph
TB

Immunotherapy/therapeutic vaccines?

Cancer
Antoimmune diseases
Alzheimer
Chronic infections
(HCV, HBV, HPV, HIV, ...)
Metabolic diseases
Allergy
Drug addiction

- TEŞEKKÜRLER.