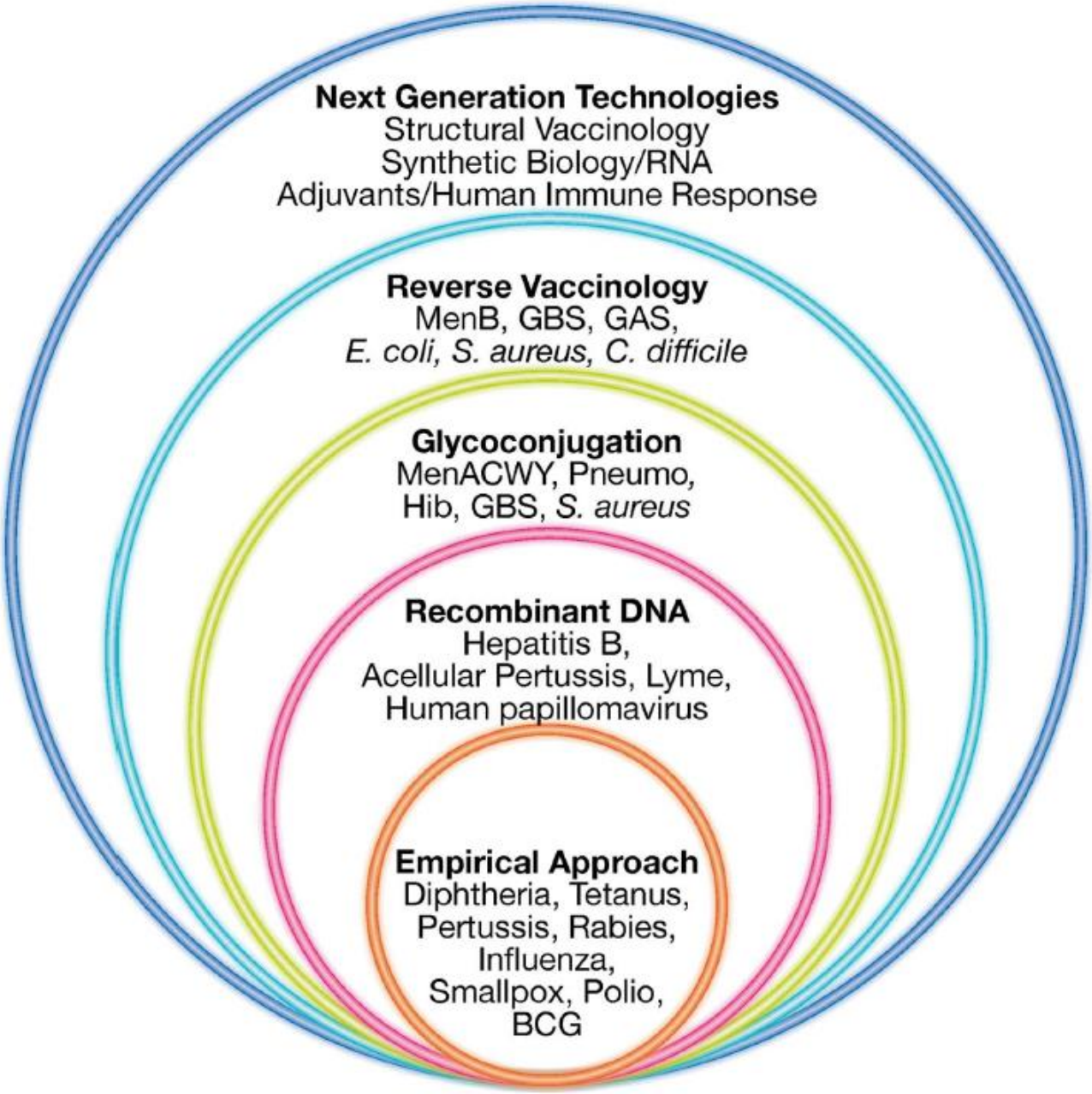
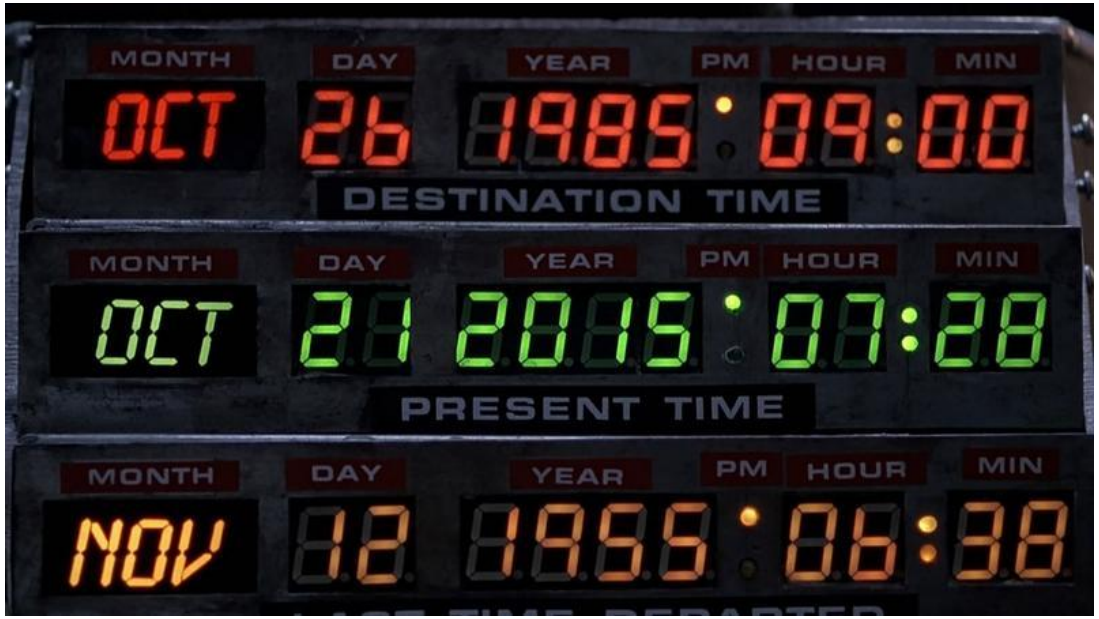
KLİMİK
TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ
Bilimle Sağlıkla 30 Yıl

Geleceğin Aşıları

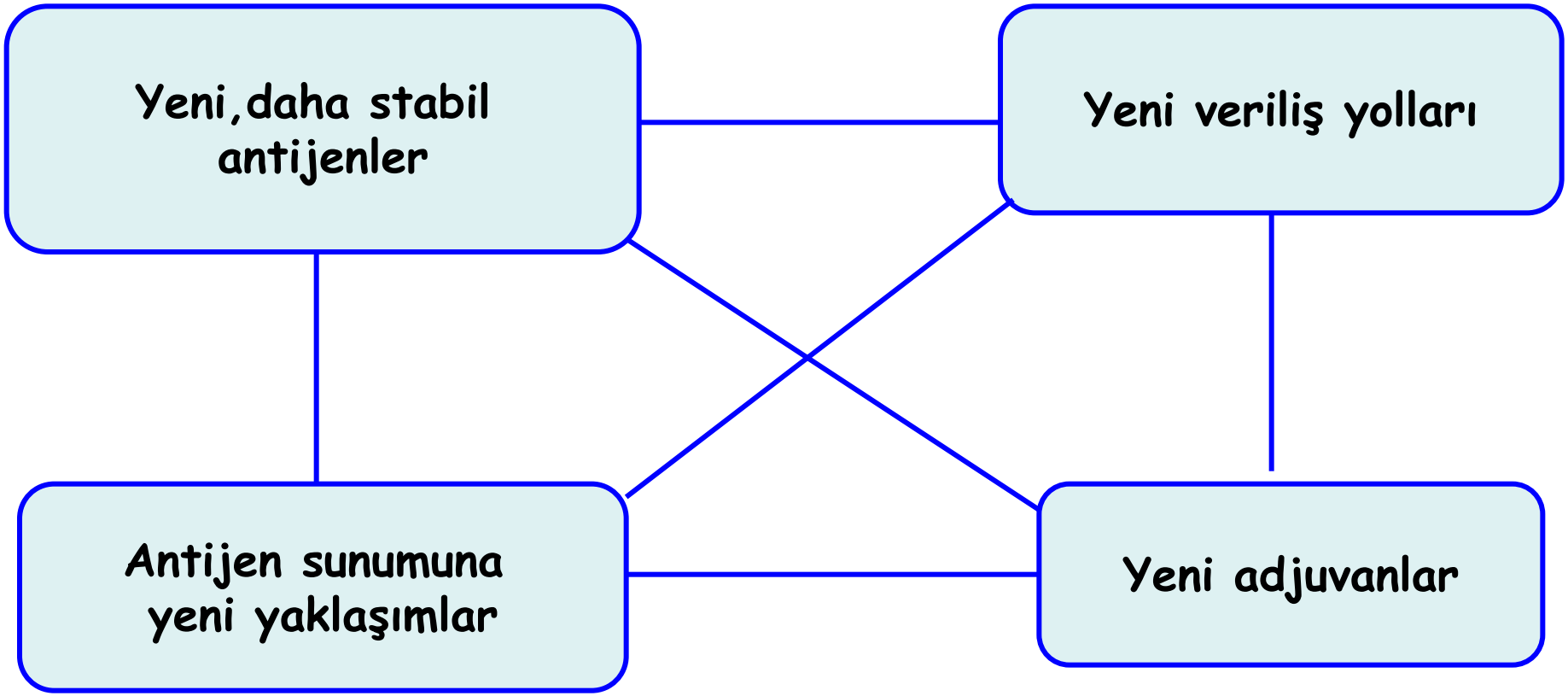
Dr.Funda Timurkaynak
Başkent Üniversitesi
Klinik Mikrobiyoloji ve İnfeksiyon Hastalıkları Anabilim Dalı
İstanbul Hastanesi


ROBERT THOM


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

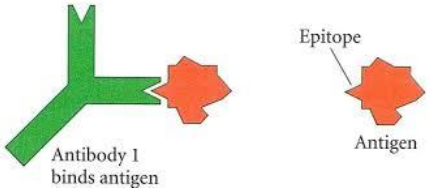

MONTH DAY YEAR PM HOUR MIN
OCT 26 1985 09:00
DESTINATION TIME
MONTH DAY YEAR PM HOUR MIN
OCT 21 2015 07:28
PRESENT TIME
MONTH DAY YEAR PM HOUR MIN
NOV 12 1955 06:38


STEVEN SPIELBERG PRESENTS
BACK TO THE FUTURE PART II
A ROBERT ZEMECKIS FILM
haberport


Yeni,daha stabil antijenler
Yeni veriliş yolları
Antijen sunumuna yeni yaklaşımlar
Yeni adjuvanlar

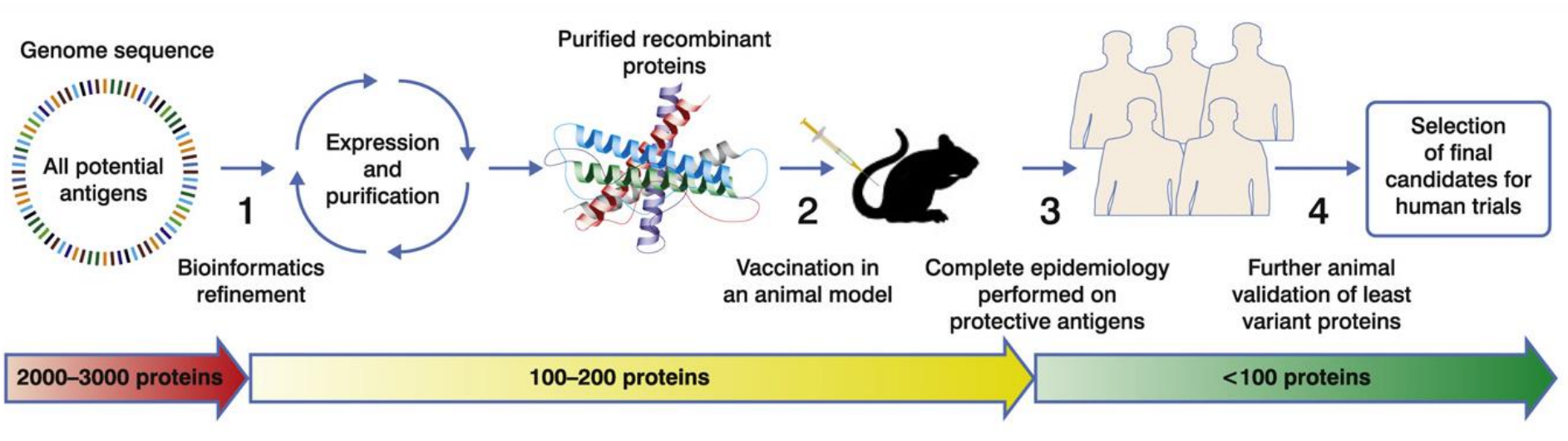
Yeni antijenler saptanması

- Amaç T ve B hücreleri tarafından tanınan özgül antijenleri belirlemek
  - Ters aşı teknolojisi "*Revers Vaccinology*"
    - Epitop belirleme



Stanberry LR, Strugnell R.. Perspectives in Vaccinology. 2011;1(1):151

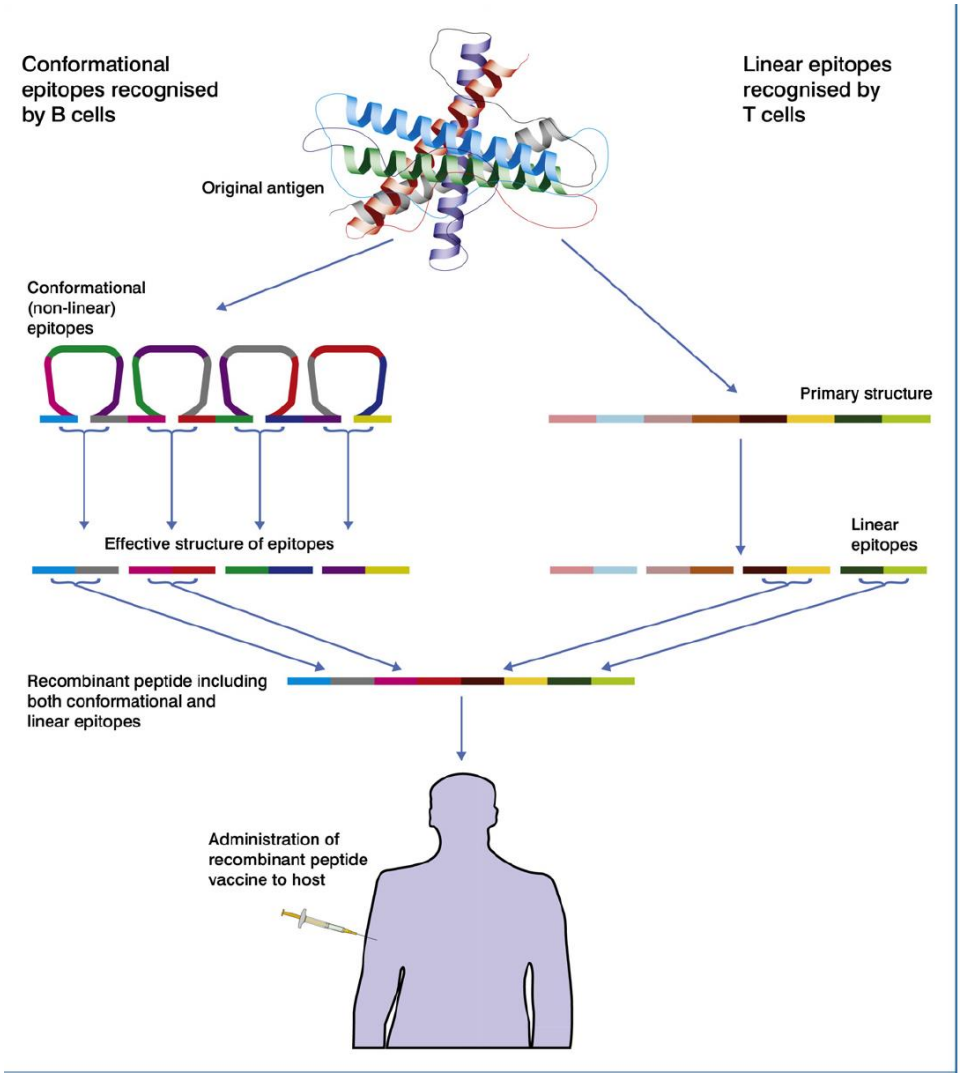
Ters aşı teknolojisi



Stanberry LR, Strugnell R.. Perspectives in Vaccinology. 2011;1(1):151

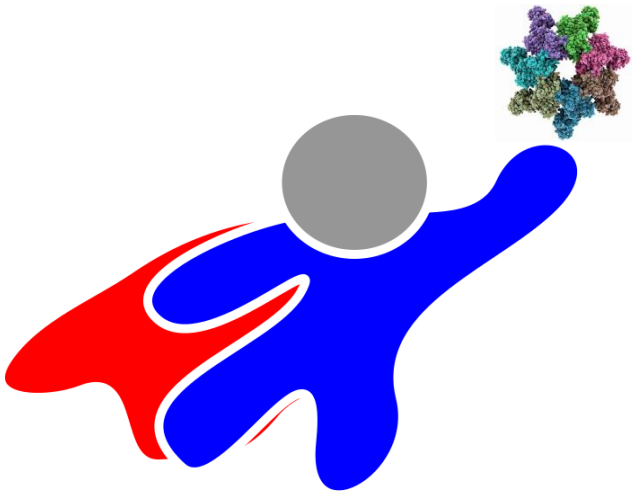
Epitop teknolojisi

- Etkin immün yanıt için antijenin tümü gerekli değil
- Patojen proteinlerinden çoklu epitop içeren antijeni oluşturmak üzere peptid parçaları birleştiriliyor
- Saflaştırılıyor



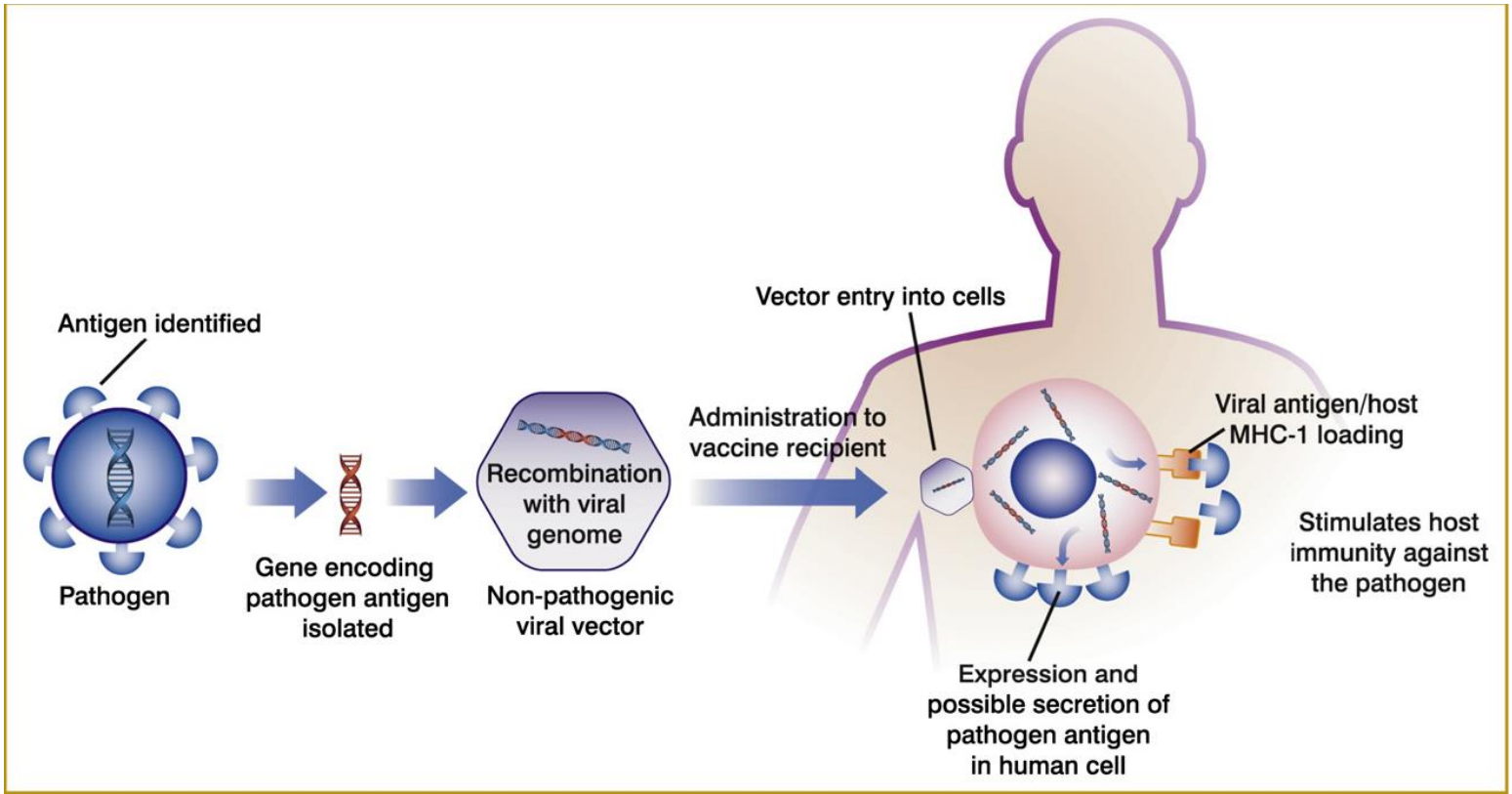
Yeni antijen sunum teknikleri

- Amaç antijeni humoral ve hücresel immüniteyi daha etkin uyaracak ve mukozal immünite sağlayacak bir yapı kullanarak taşımak
  - Viral vektör aşıları
  - Bakteriyel vektör aşıları
    - *Vibrio cholerae, Salmonella typhi, Listeria monocytogenes*
  - DNA aşıları
  - RNA aşıları
    - Melanom, renal cell ca,CMV
  - Dendritik hücre aşıları
    - Prostat Ca



Viral vektör aşılar

- Antijeni kodlayan genler patojenite genleri uzaklaştırılmış virüse yerleştirilir
  - En sık Modifiye Vaccinia Virus Ankara (MVA), Canarypoxvirus, Adenovirus



Viral vektör aşılar

- **Faz I**
  - Adenovirus ; HIV,Ebola, HCV,pandemik influenza
  - Atenüe influenza virus; TBC,HIV, influenza virus
  - Vaccinia virus; HCV
  - Replikasyon incomplet adenovektör; HSV,HCV
- **Faz II**
  - Adenovirus; Sıtma, TBC,HIV
  - MVA;TBC, HIV, HPV,kanser, çiçek
  - Replikasyon incomplet adenovektör; HIV,sıtma
- **Faz III**
  - MVA; kanser
  - Canarypox virus; HIV

Viral vektör aşılar

Avantajları

- Hücresel ve humoral immüniteyi güçlü ve uzun ömürlü uyaran yolakları kullanır
- Mukozaya uygulanabilir
- Kolay geliştirilir

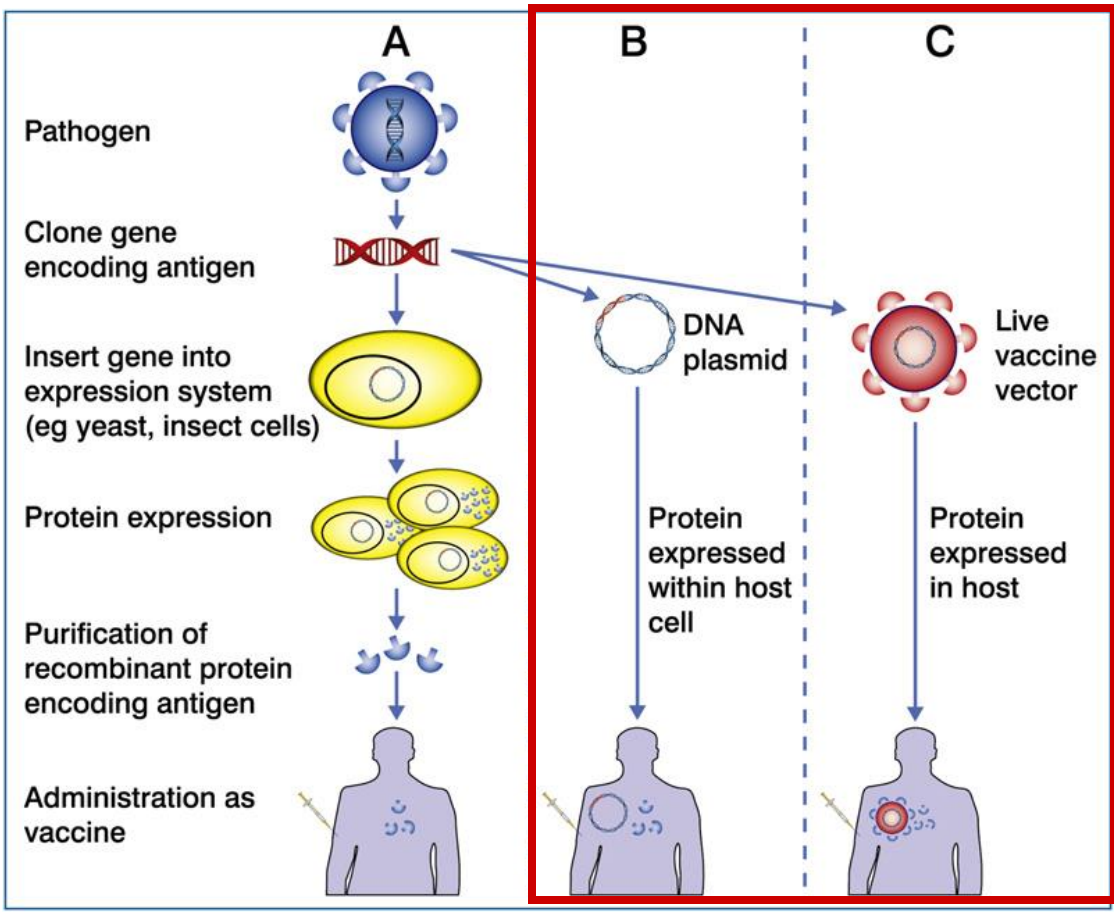
Dezavantajları

- Vektörün atenüe olmama olasılığı
- Fazla atenüasyonla immünojenite kaybı
- Virulansa neden olacak rekombinasyon riski
- Vektöre spesifik antikorlar sonraki dozları etkileyebilir
- Vektöre bağlı persistan veya latent inf riski

DNA vektör aşılar

DNA/RNA ile taşınan antijen konakta üretilir

- **Faz I**
  - HIV, HPV,
  - influenza, Ebola, Batı Nil virusu, SARS, şarbon, kanser
- **Faz II**
  - HIV,HBV,HCV, kanser
- **Faz III**
  - Melanom



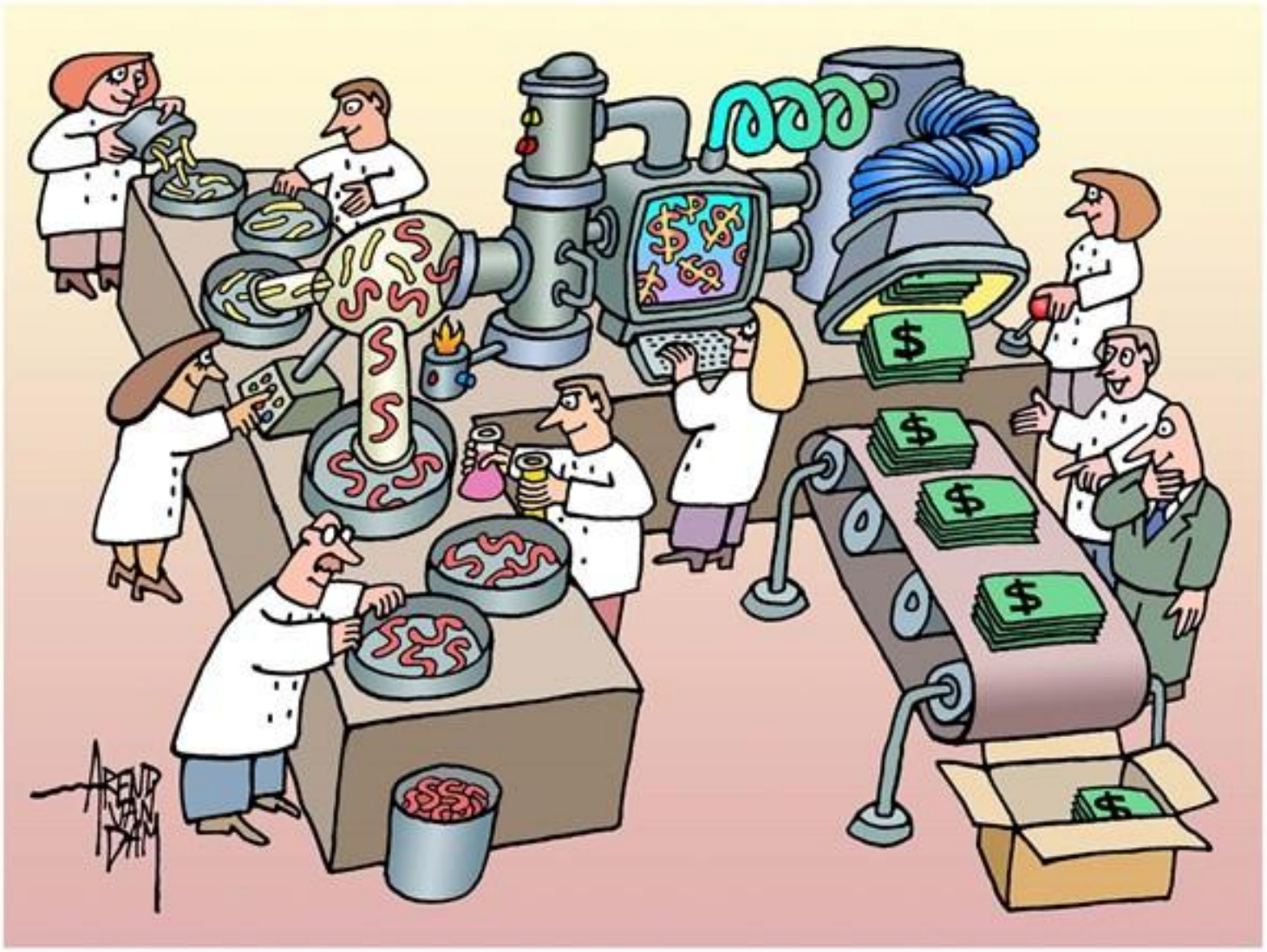
DNA vektör aşılar

Avantajları

- T hücre yanıtını indükleyen, replike olmayan bir platform sağlar
- Terapatik aşılarda kullanım olasılığı
- Çok sayıda epitop kodlama olasılığı
- Doğal bağışıklığı indükler

Dezavantajları

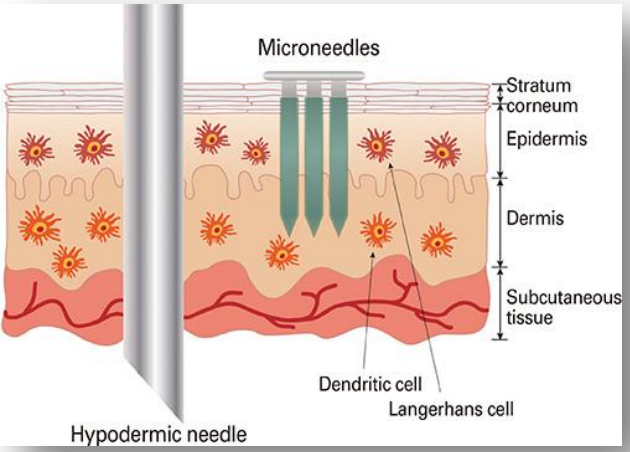
- İnsanda zayıf immünite
- Konak genomuna entegrasyon riski

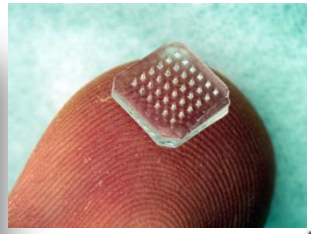


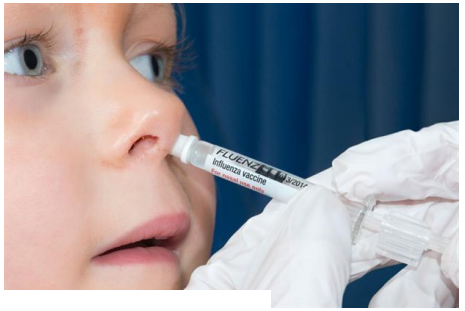
BIOTECH

Aşı veriliş yolunda yenilikler

- Amaç
  - İmmüniteyi arttırmak
  - Uygulama kolaylığı sağlamak
    - İnfeksiyonun giriş kapısı (mukoza, solunum yolu)
    - İntradermal
    - Transdermal mikro enjeksiyon"Patch"







Yeni adjuvanlar

İmmünojenite artışı

Güçlü immün yanıt

Daha az antijen kullanımı

Tedavi edici aşılar

Adjuvant name	Description	Route of delivery	Current vaccine targets	Manufacturer
Early-stage development (Phase I)				
NanoStat™	Nanoemulsion	Intranasal	Influenza Hepatitis B*	NanoBio Corporation
CpG	TLR9 agonist	Intramuscular	Malaria	Coley
LT	*Escherichia coli* heat-labile toxin	Intranasal	TB	Novartis
Montanide™ ISA720	Water-in-oil emulsion	Intramuscular	Malaria Cancer	Seppic
Resiquimod	TLR7/8 agonist	Intramuscular	Melanoma	3M
ISCOM™ (with antigen included) *ISCOMATRIX*™ (without antigen)	Lipids, cholesterol, saponin in a cage-like structure	Intramuscular	Alzheimer's disease	CSL Behring
IC31™	TLR9 agonist and targets antigen to APC	Intramuscular	Influenza	Intercell
Mid-stage development (Phase II)				
ISCOM™ (with antigen included) *ISCOMATRIX*™ (without antigen)	Lipids, cholesterol, saponin in a cage-like structure	Intramuscular	Influenza Melanoma HCV	CSL Behring
Flagellin (conjugated with antigen)	TLR5 agonist	Intramuscular	Influenza	VaxInnate
IC31™	TLR9 agonist and targets antigen to APC	Intramuscular	TB	Intercell
MF59™	Squalene-based oil-in-water emulsion	Intramuscular	CMV	Novartis
AS01	Liposome, lipopolysaccharide derivative (*MPL*) and saponin (QS21)	Intramuscular	TB HIV	GSK Biologicals

Late-stage development (Phase III)				
ISS	TLR9 agonist	Intramuscular	HBV	Dynavax
AS01	Liposome, lipopolysaccharide derivative (MPL) and saponin (QS21)	Intramuscular	Malaria	GSK Biologicals
AS03	α-tocopherol and squalene in an oil-in-water emulsion	Intramuscular	Influenza	GSK Biologicals
AS04	Lipopolysaccharide derivative (MPL) and aluminium salt	Intramuscular	HSV	GSK Biologicals
AS15	Liposome, lipopolysaccharide derivative (MPL), saponin (QS21) and TLR9 agonist (CpG)	Intramuscular	Lung cancer Melanoma	GSK Biologicals
Montanide™ ISA51	Water-in-oil emulsion	Intramuscular	Cancer	Seppic
MF59™**	Squalene-based oil-in-water emulsion	Intramuscular	Influenza	Novartis
MPL	Lipopolysaccharide derivative	Subcutaneous	Non-small-cell lung cancer	Merck

Yakın geleceğin aşıları

Universal flu vaccine comes closer, scientists say

By Michelle Roberts
Health editor, BBC News online

24 August 2015 | Health

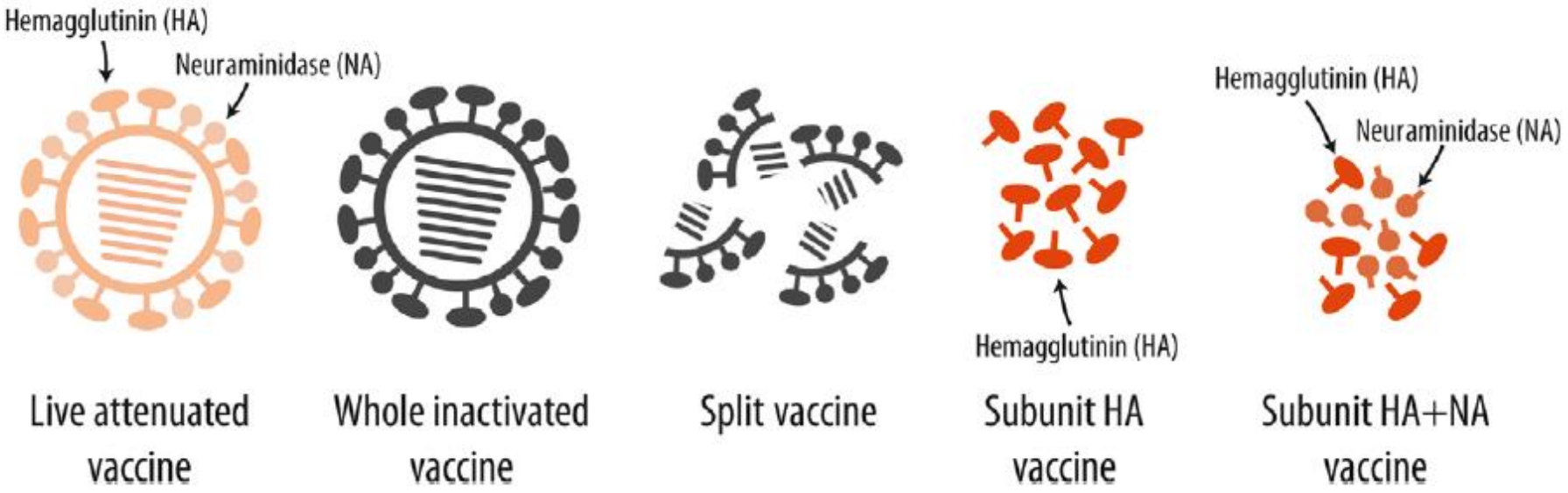
Viruses mutate, making them harder to combat

Researchers say they are closer to developing a vaccine to give life-long protection against any type of flu, after promising trials in animals.

Two separate US teams have found success with an approach that homes in on a

Geniş spekturumlu

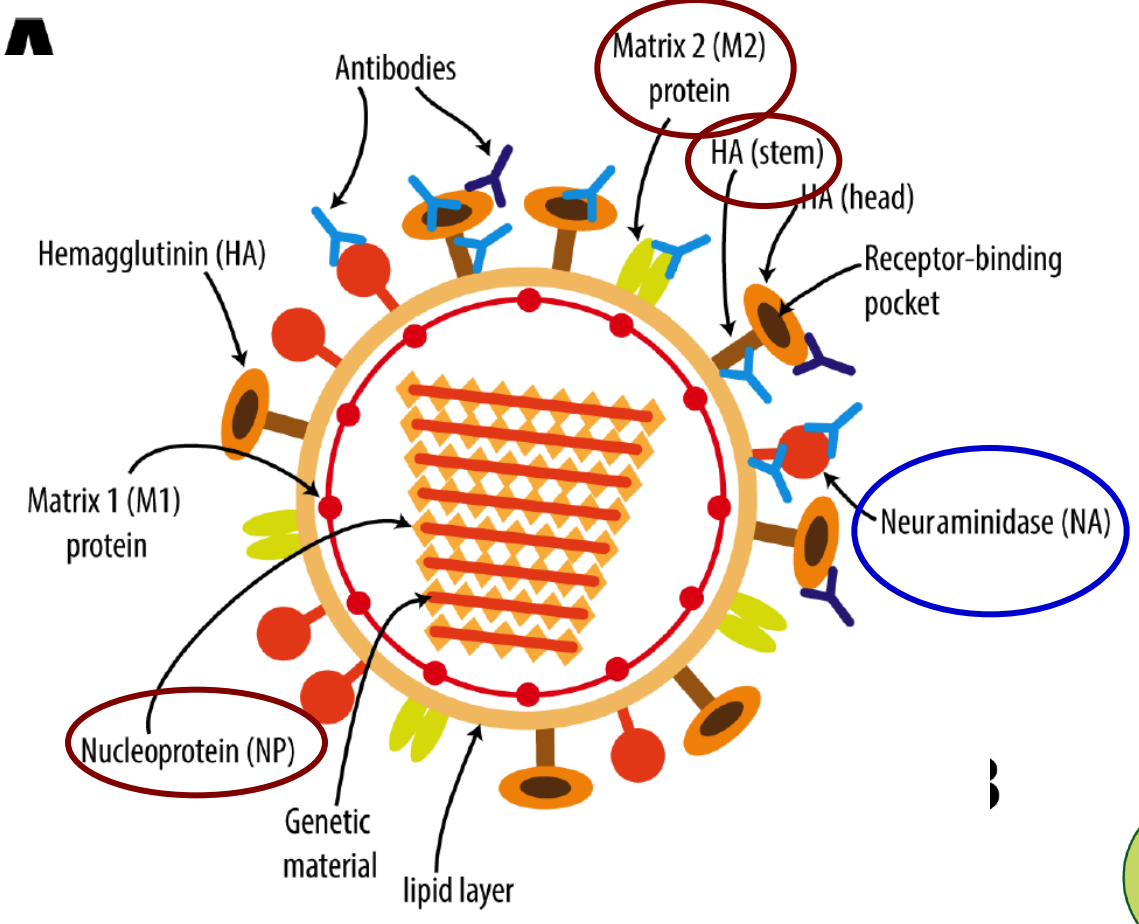
Klinik kullanımda olan aşılar

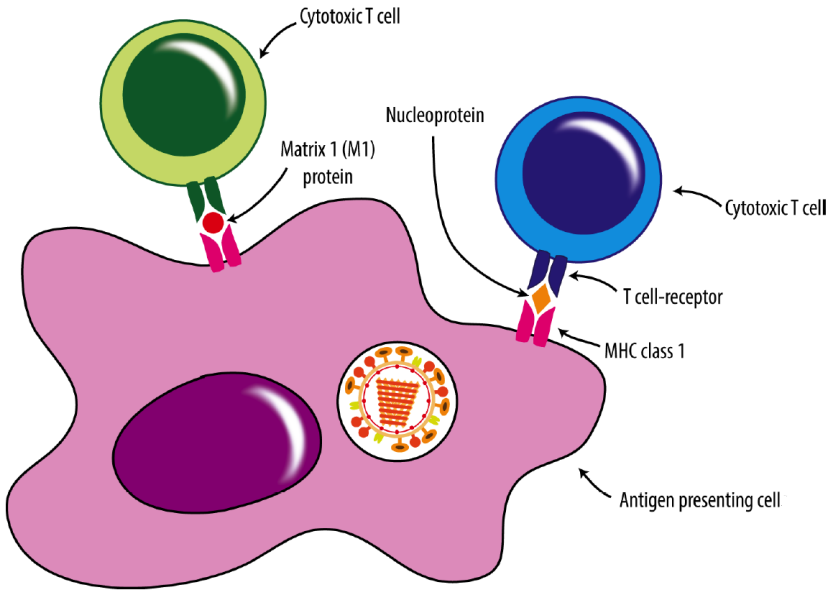


- HA ve NA'a karşı nötralizan antikor yanıtı

- Çapraz koruma yok
  - Antijenik shift/drift

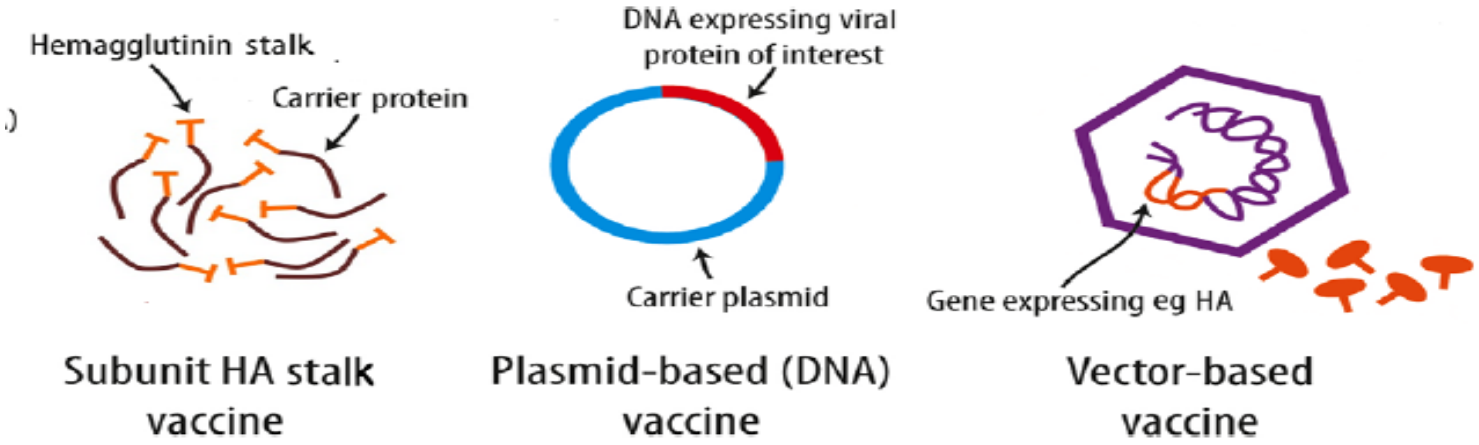
Aday antijenler





- Nötralizan antikor; HA kök, NA
- Hücresel immünite; NP, T hücre epitopları
- Antikor bağımlı hücresel sitototoksisite; M2e

Aday yöntemler



- Taşıyıcı protein (örn flagellin, HBsAg) + HA subunit
- Vektör aşılar
  - DNA
  - RNA
  - Viral vektör
    - MVA, Adenovirus
- Prime-boost stratejisi
  - Adenovirus+NP+M1 ⇒ MVA+NP+M1
  - MVA+NP+M1 ⇒ mevsimsel influenza aşısı

Aday aşılar

Universal influenza vaccine concepts currently in the clinical phase of development.

Targeted response	Concept	Status
M2e antibodies	VAX102 (recombinant M2e fused to flagellin)	Phase I/II completed
	VAX102 + seasonal vaccine (coadministered)	Phase I completed
	ACAM FLU-A (recombinant M2e fused to hepatitis B core protein)	Phase I completed
	VGX-3400X (DNA plasmid encoding for HA, NA and M2e-NP of H5N1 delivered by electroporation)	Phase I completed
Influenza-specific T cells	FP-01.1 (long peptides containing multiple T cell epitopes)	Phase I completed, phase II ongoing
	FP-01.1 + undisclosed adjuvant	Phase I completed
	FP-01.1 combined with seasonal vaccine (prime) + FP-01.1 (boost)	Phase I completed
	Flu-v (long peptides containing multiple T cell epitopes)	Phase I completed
	Multimeric-001 (recombinant protein containing multiple T cell epitopes)	Phase I/II completed
	Multimeric-001 (prime) + seasonal vaccine (boost)	Phase I/II completed
	MVA-NP + M1 (modified vaccinia virus Ankara vectored vaccine containing multiple T cell epitopes)	Phase I/II completed
	MVA-NP + M1 + seasonal vaccine (coadministered)	Phase I completed
	ChAdOx1 NP + M1 (simian adenovirus vectored vaccine containing multiple T cell epitopes) + MVA-NP + M1 (mixed prime/boost)	Phase I ongoing

Child malaria vaccine: Final trials bring hope

24 April 2015 | Health

There is no licensed vaccine against malaria anywhere in the world at present

Final clinical trials of a malaria vaccine - the first to reach this stage - suggest it could help protect millions of children against malaria.

But tests on 16,000 children from seven African countries found that booster doses were of limited use and vaccines in young babies were not effective.

After children aged 5-17 months were given three doses of the vaccine, the immunisation was only 46% effective.

But experts say getting the vaccine this far is a scientific milestone.

Data from the trial published in **The Lancet** showed that the success rate fell to even lower levels in younger infants.

Sporozoid motilitesini inhb., karaciğer invazyonunu önler

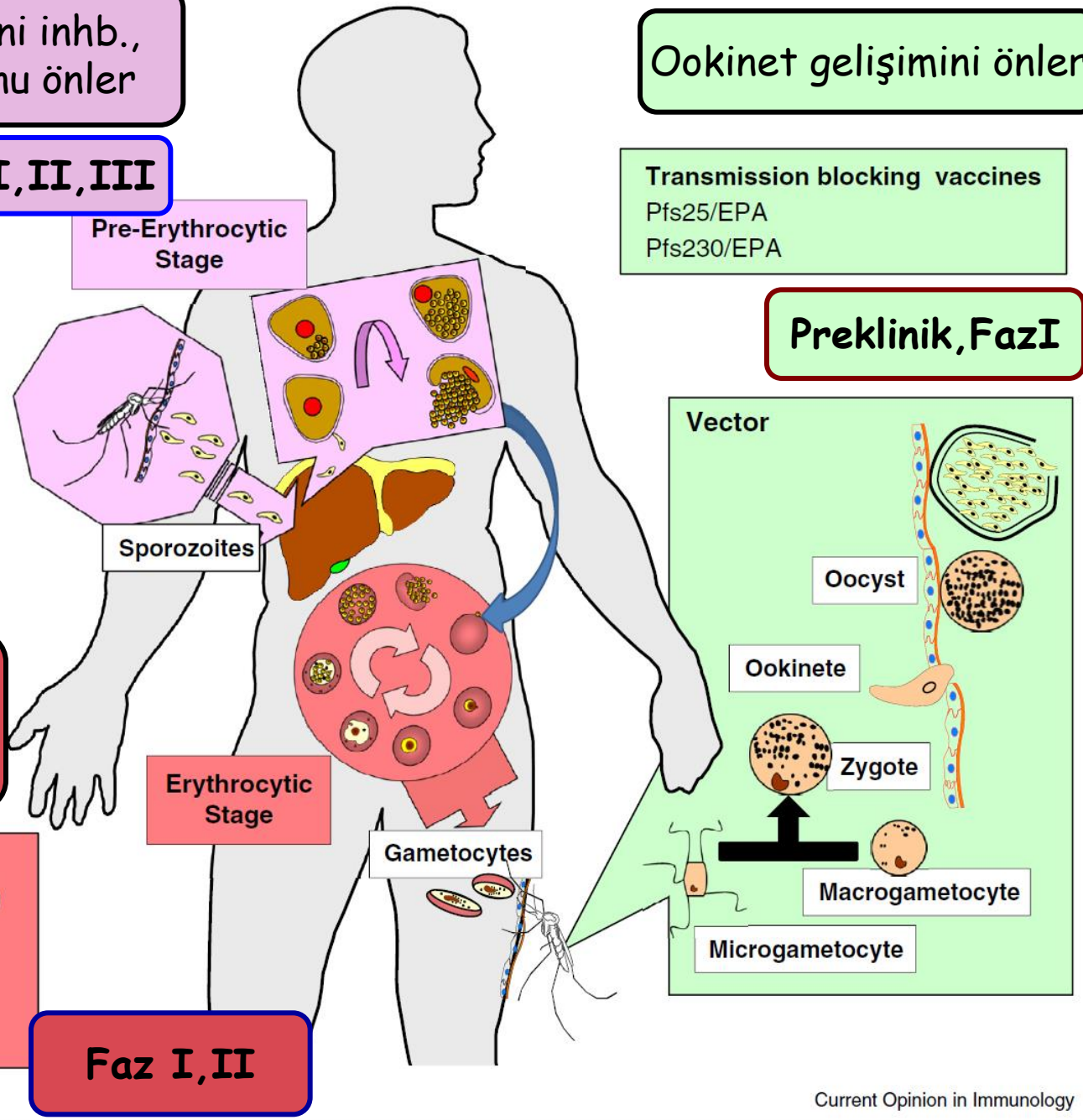
Ookinet gelişimini önler

FazI,II,III

Pre-erythrocytic vaccines
RTS,S/AS01A
PfME-TRAP (ChAd63/MVA)
PfCSP (ChAd63/MVA)
PfSPZ (iSPZ, GAS, CPS)
PfCSP (DNA/Ad5)
PfCSP + PfAMA-1 (Ad5)
PfCelTOS
PfCSP (Ad35)
PvCSP (VMP001/AS01B)

Transmission blocking vaccines
Pfs25/EPA
Pfs230/EPA

Preklinik,FazI



Merozoid yüzey/ ligand inh, eritrosit invazyonunu önler

Erythrocytic vaccines
PfMSP1 – PfAMA-1 (ChAd63/MVA)
PfAMA-1/AS02A (FMP2.1)
PfAMA-1 (DiCo)
PfGLURP/PfMSP3 (GMZ2)
PvDBP (ChAd63/MVA)

Faz I,II

Current Opinion in Immunology

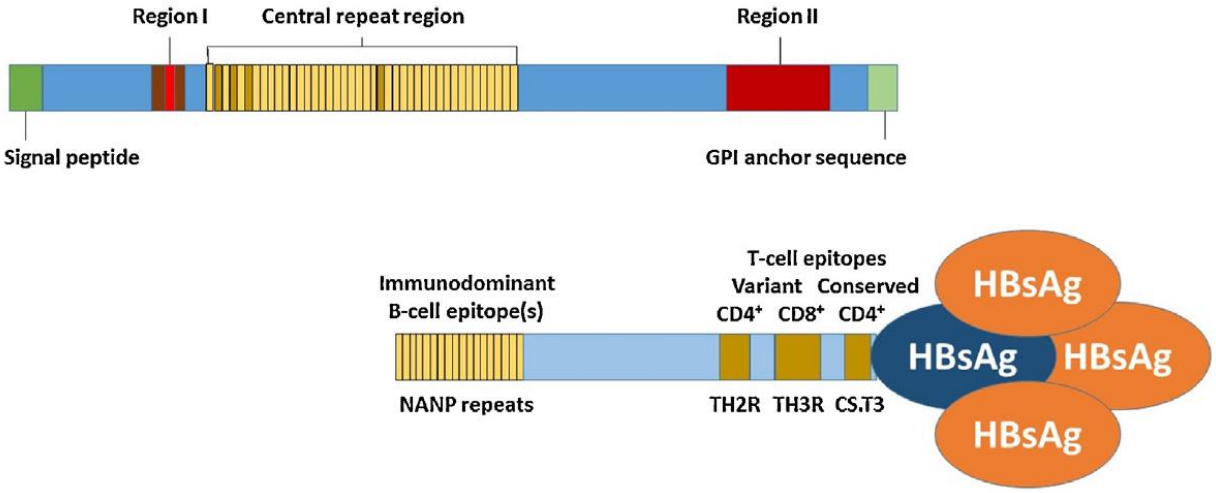
Target	Antigen	Antigen Description	Most Advanced Status
Plasmodium falciparum pre-erythrocytic	RTS,S	Circumsporozoite protein fused to hepatitis B surface antigen	Phase 3 clinical testing
	ChAd63/MVA, ME-TRAP	Chimpanzee adenovirus 63/modified vaccinia Ankara, multiple epitope string with thrombospondin-related adhesion protein	Phase 2 clinical testing
	PfSPZ	Radiation-attenuated whole organism *P. falciparum* sporozoites	Phase 1 clinical testing
	PfCelTOS	*P. falciparum* cell-traversal protein for ookinetes and sporozoites	Phase 1 clinical testing
	Recombinant CSP	Recombinant circumsporozoite protein	Preclinical testing
	Genetically attenuated sporozoites	Genetically attenuated whole organism *P. falciparum* sporozoites	Preclinical testing

- Hepatosit invazyonunu önlemek için hücresel ve humoral immünite gerekli
- Aşı hedefi sporozoid yüzey proteini (CSP)
  - CSP'ye oluşan antikorların in-vitro ve hayvan çalışmalarında invazyonu önlediği gösterilmiş

Ouattara A, Laurens MB.Clin Infect Dis. 2015;60(6):930

RTS, S

- **R**epeat:CSP'in tekrarlayan tetrapeptid sekansları (N-asetilnöraminik asit fosfotaz-NANP)
- **T**: $CD4^+$,$CD8^+$ T hücre epitopları (Th2R ve Th3R)
- **S**urface: Bağlanmış HBsAg
- **S**urface: Bağlanmamış HBsAg

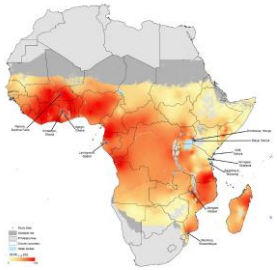


OPEN ACCESS Freely available online

PLOS | MEDICINE

Efficacy and Safety of the RTS,S/AS01 Malaria Vaccine during 18 Months after Vaccination: A Phase 3 Randomized, Controlled Trial in Children and Young Infants at 11 African Sites

The RTS,S Clinical Trials Partnership¶*



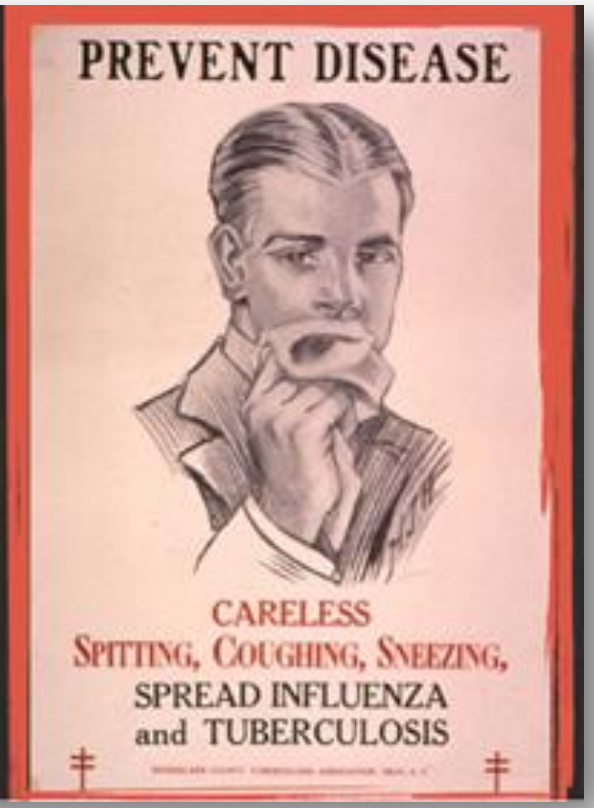
- Çift kör, Faz III çalışma
- 7 Afrika ülkesi, 11 merkez
- 6537 infant (6-12 hf) (İ), 8923 çocuk (5-17 ay) (Ç)
- Aşı etkinliği Ç'da %46, İ'da %27
  - Ciddi sıtmayı önleme Ç'da %34, İ'da %0
- Yan etki: ateş en sık
  - Ciddi yan etki: menenjit?

Agnandji ST,et al. PLoS Med 2014;11:e1001685

This Day in Science 1924:

The first tuberculosis vaccine was released

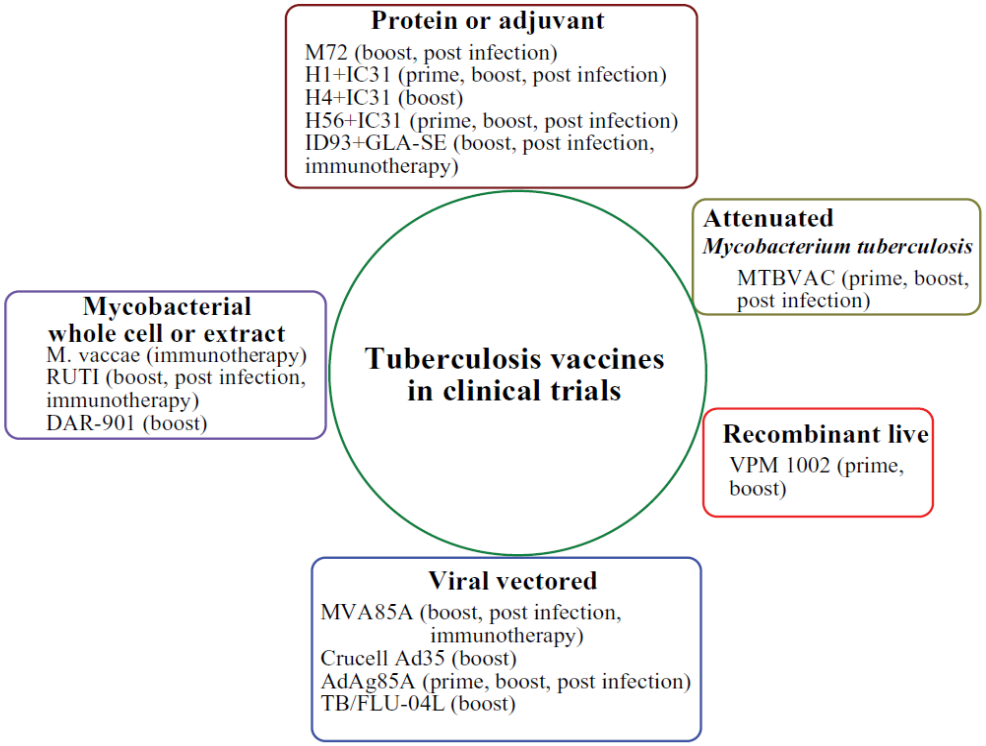
www.stressmarq.com/blog



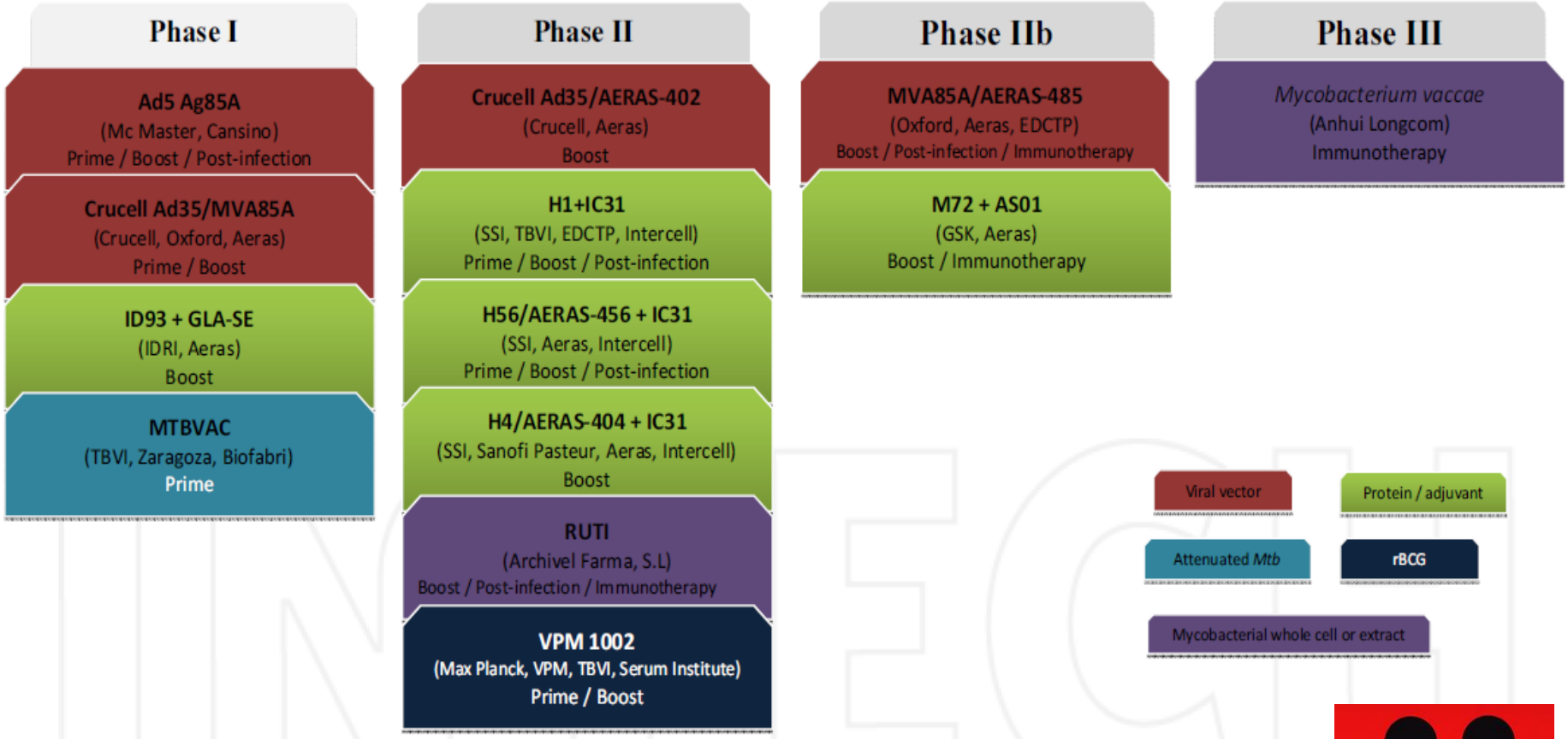
Daha gelişmiş BCG

İmmunoterapi

Prime- boost stratejisi

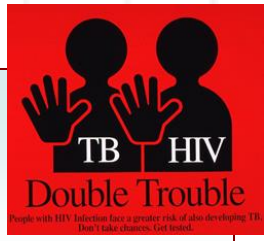


Ahsan MJ. Ther Adv Vaccines. 2015 ;3(3):66



M.vaccae

- HIV+ hastalarda güvenli, immunojen
- Tbc tedavisi + MV; hızlı balgam negatifliği ve X-ray düzelme



Getting dirty may lift your mood

Press release issued: 2 April 2007

Treatment of mice with a 'friendly' bacteria, normally found in the soil, altered their behavior in a way similar to that produced by antidepressant drugs, reports research published in the latest issue of *Neuroscience.*
These findings, identified by researchers at the University of Bristol and colleagues at University College London, aid the understanding of why an imbalance in the immune system leaves some individuals vulnerable to mood disorders like depression.

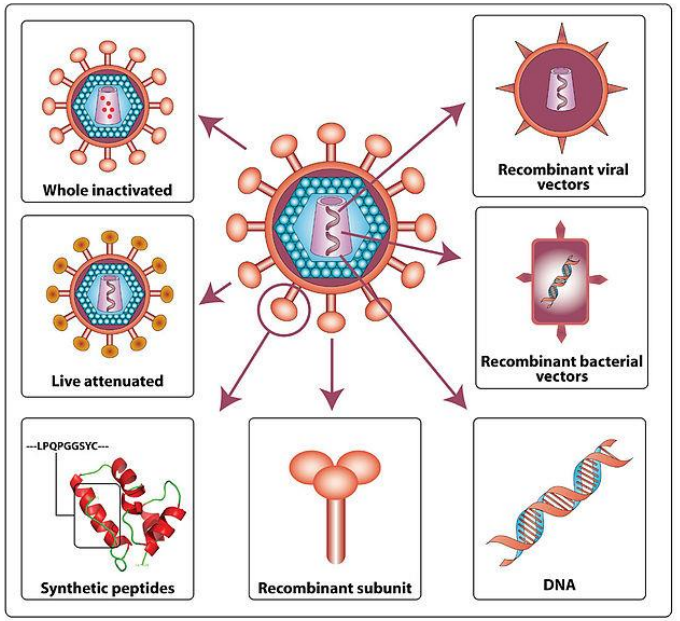
Dr Chris Lowry, lead author on the paper from Bristol University, said: "These studies help us understand how the body communicates with the brain and why a healthy immune system is important for maintaining mental health. They also leave us wondering if we shouldn't all be spending more time playing in the dirt."

Interest in the project arose after human cancer patients being treated with the bacteria Mycobacterium vaccae unexpectedly reported increases in their quality of life. Lowry and his colleagues reasoned that this effect could be caused by activation of neurons in the brain that contained serotonin.

Mycobacterium vaccae
Image credit: Laura Rosa Brunet

HIV

- Aşı zor
  - Antijenik varyantlar
  - Virüsün hedefi kilit immün sistem hücreleri
- Faz III çalışma
  - >16.000 yetişkin
  - ALVAC (Canarypox virus+CRF-AE gp120) –AIDSVAX (gp120 subunit)
  - Etkinlik :%31.2



Rerks-Ngarm S,et al.N Engl J Med. 2009 ;361(23):2209-20.