AŞI İMMUNOLOJİSİ VE AŞILARDA SON GELİŞMELER

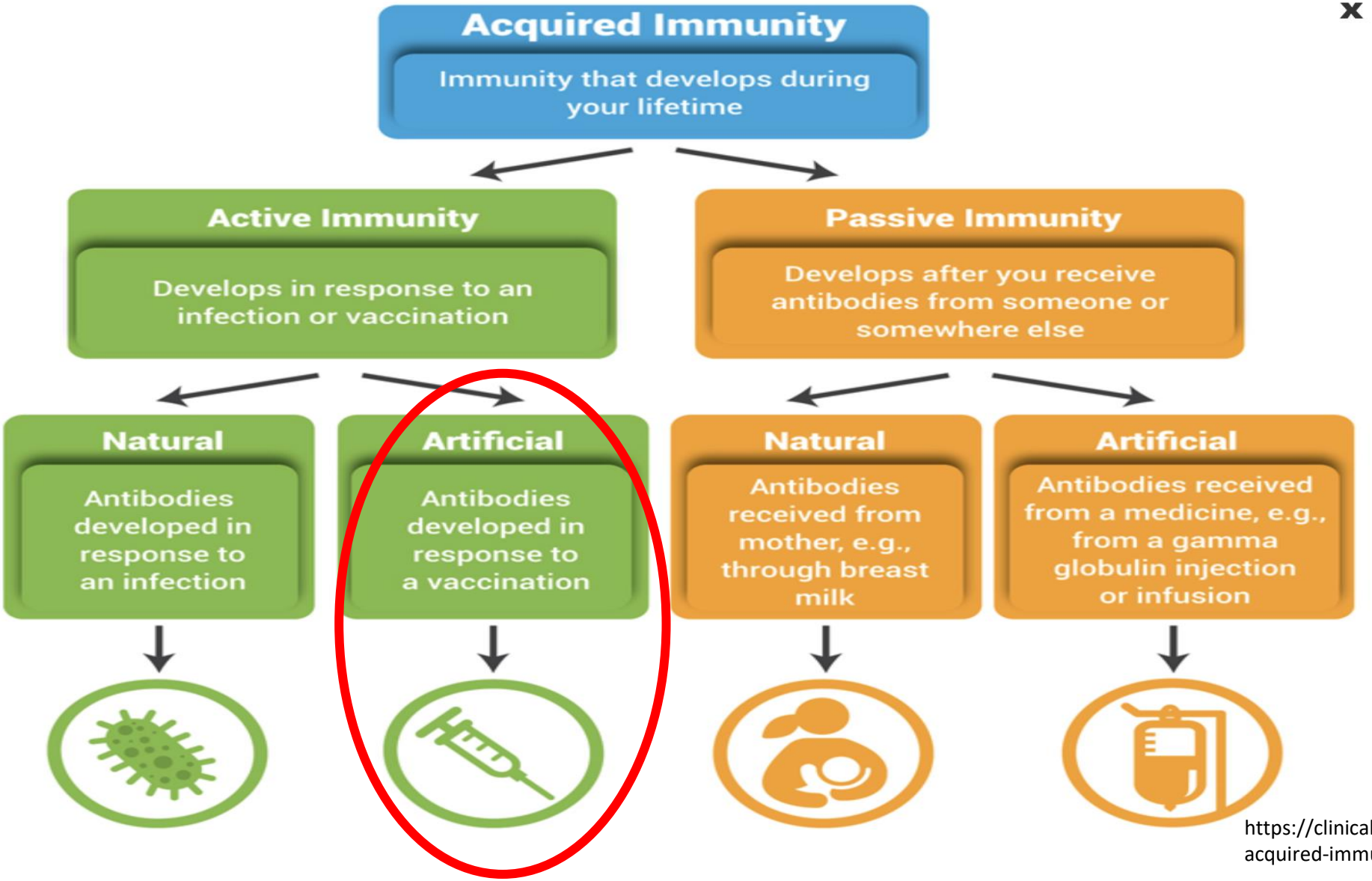
HÜSREV DİKTAŞ

İSTANBUL MEDİPOL ÜNİVERSİTESİ TIP FAKÜLTESİ

SUNU PLANI

- Aşı nedir?
- Aşıların tarihçesi
- Aşılar neden önemlidir?
- İmmunolojik yanıtın temelleri
- Aşılama sonrası ilk basamak: Doğal immunite ve Adjuvanlar
- Aşılama sonrası ikinci basamak: Humoral immunite
- Aşılama sonrası üçüncü basamak: Hücresel immunite
- mRNA aşıları ve getirdikleri/götürdükleri

Aşı nedir?

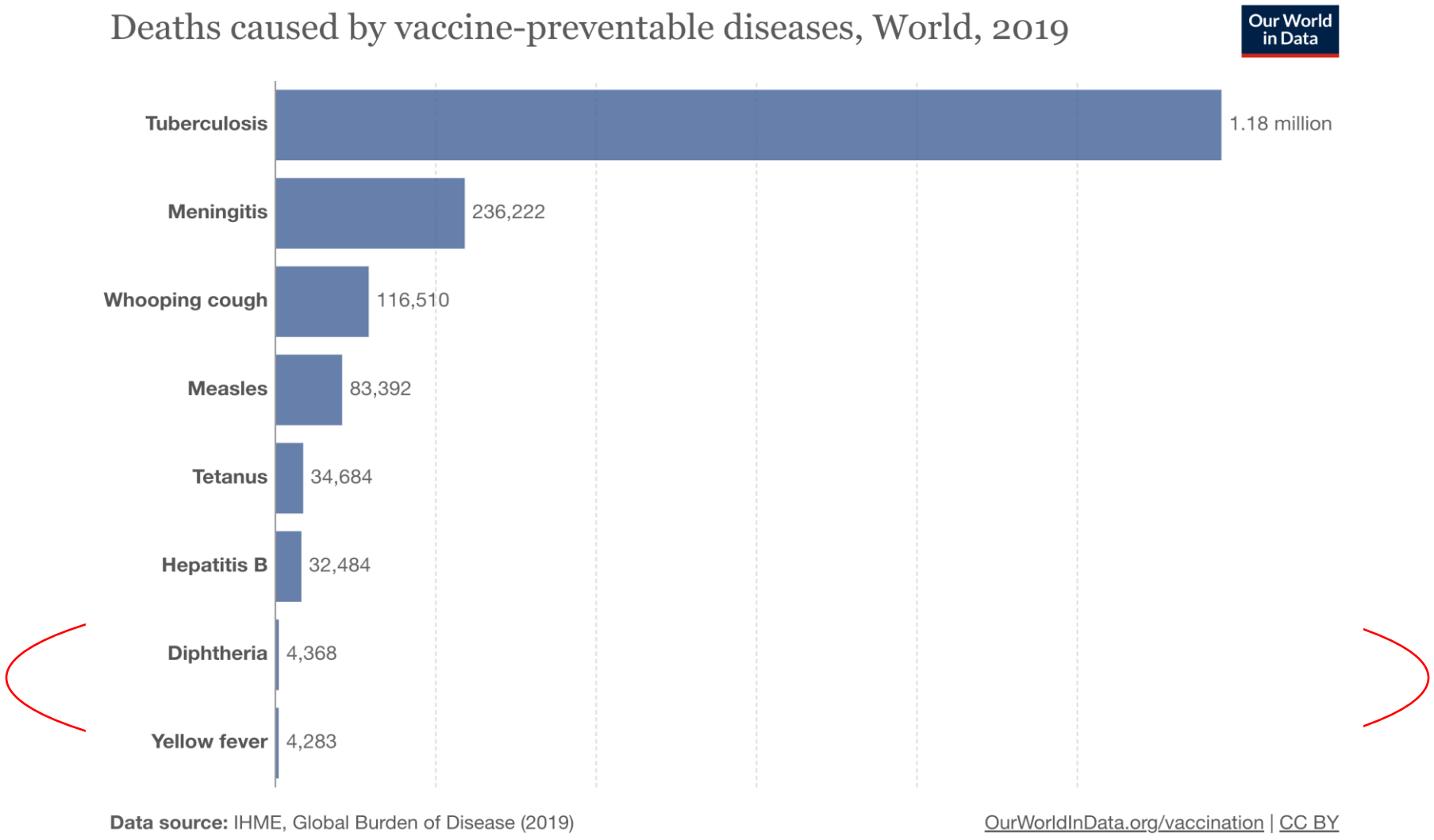


https://clinicalinfo.hiv.gov/en/glossary/acquired-immunity

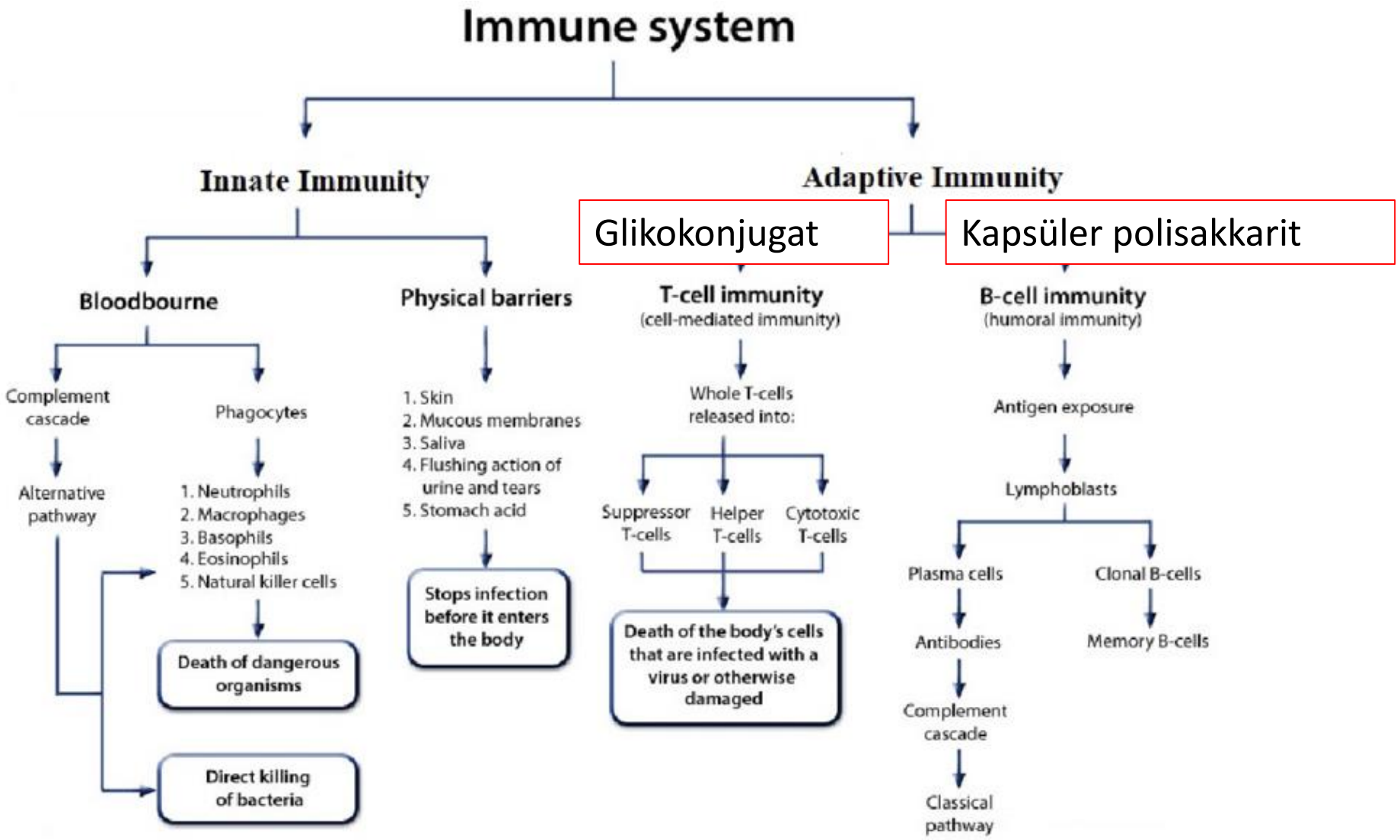
Aşıların tarihçesi

Edward Jenner-Smallpox

Aşılar neden önemlidir?



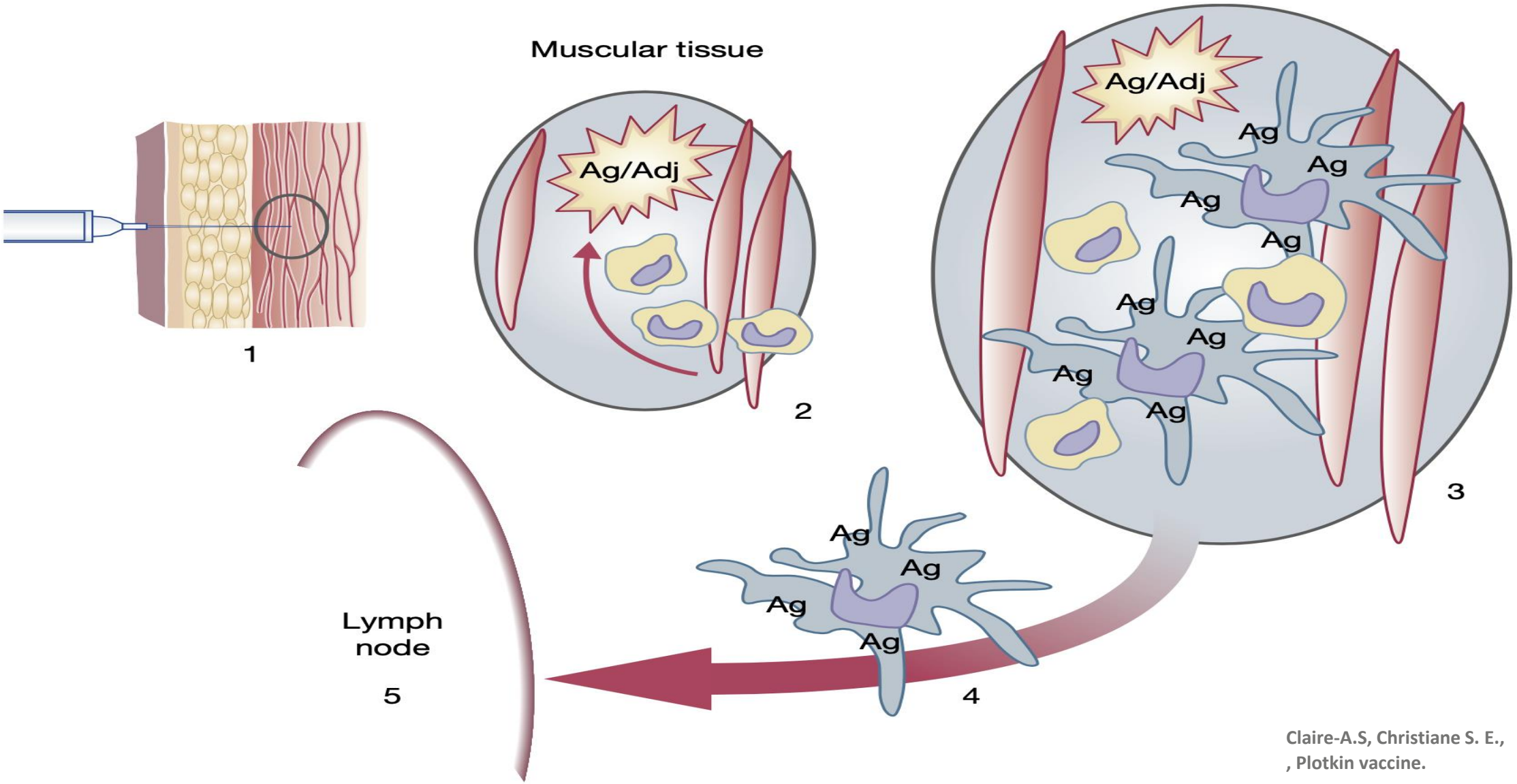
İmmunolojik yanıtın temelleri



Glikokonjugat

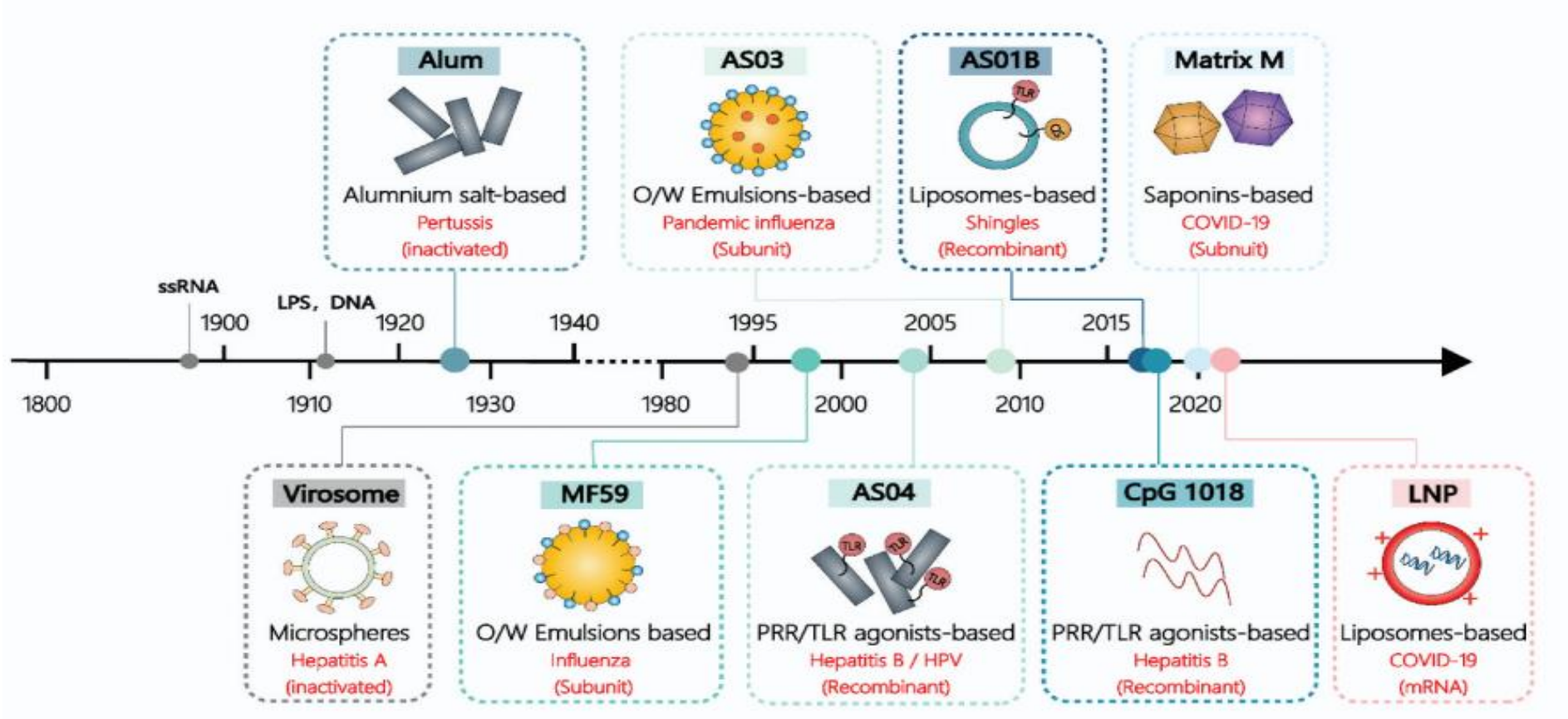
Kapsüler polisakkarit

Aşılama sonrası ilk basamak: Doğal immunite



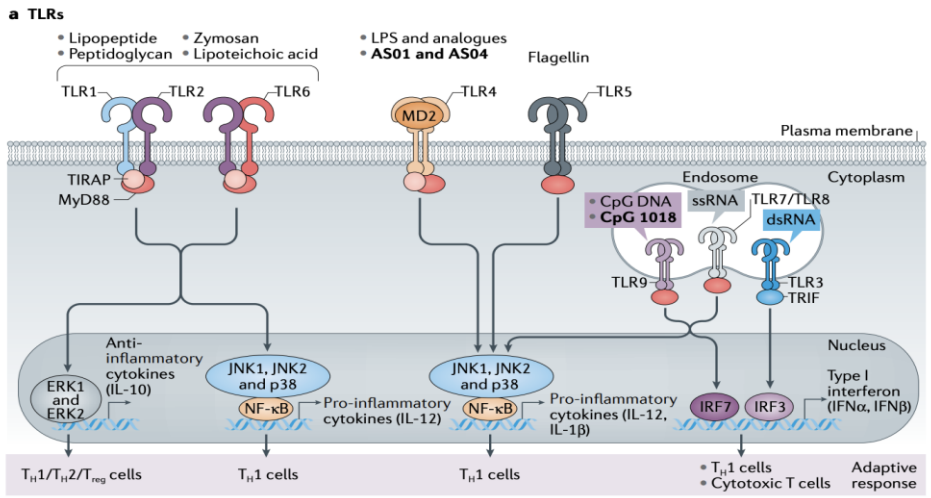
Claire-A.S, Christiane S. E.,
, Plotkin vaccine.

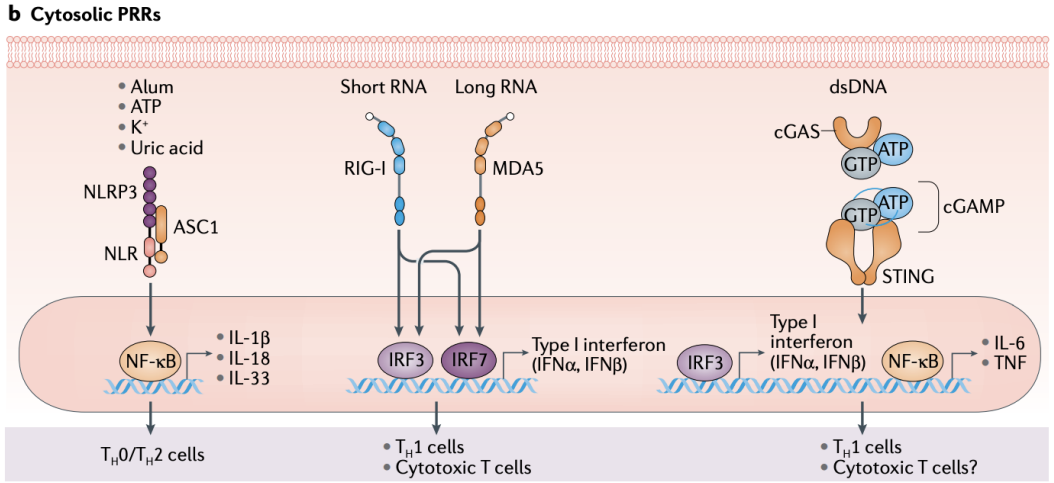
Aşılama sonrası ilk basamak: Adjuvanlar

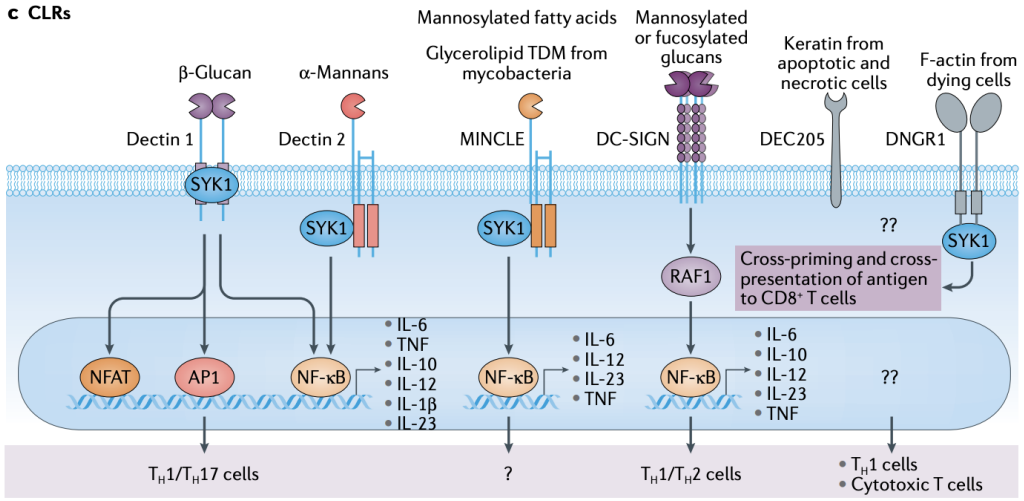


Expert Review of Vaccines,2023
https://doi.org/10.1080/14760584.2023.2238807

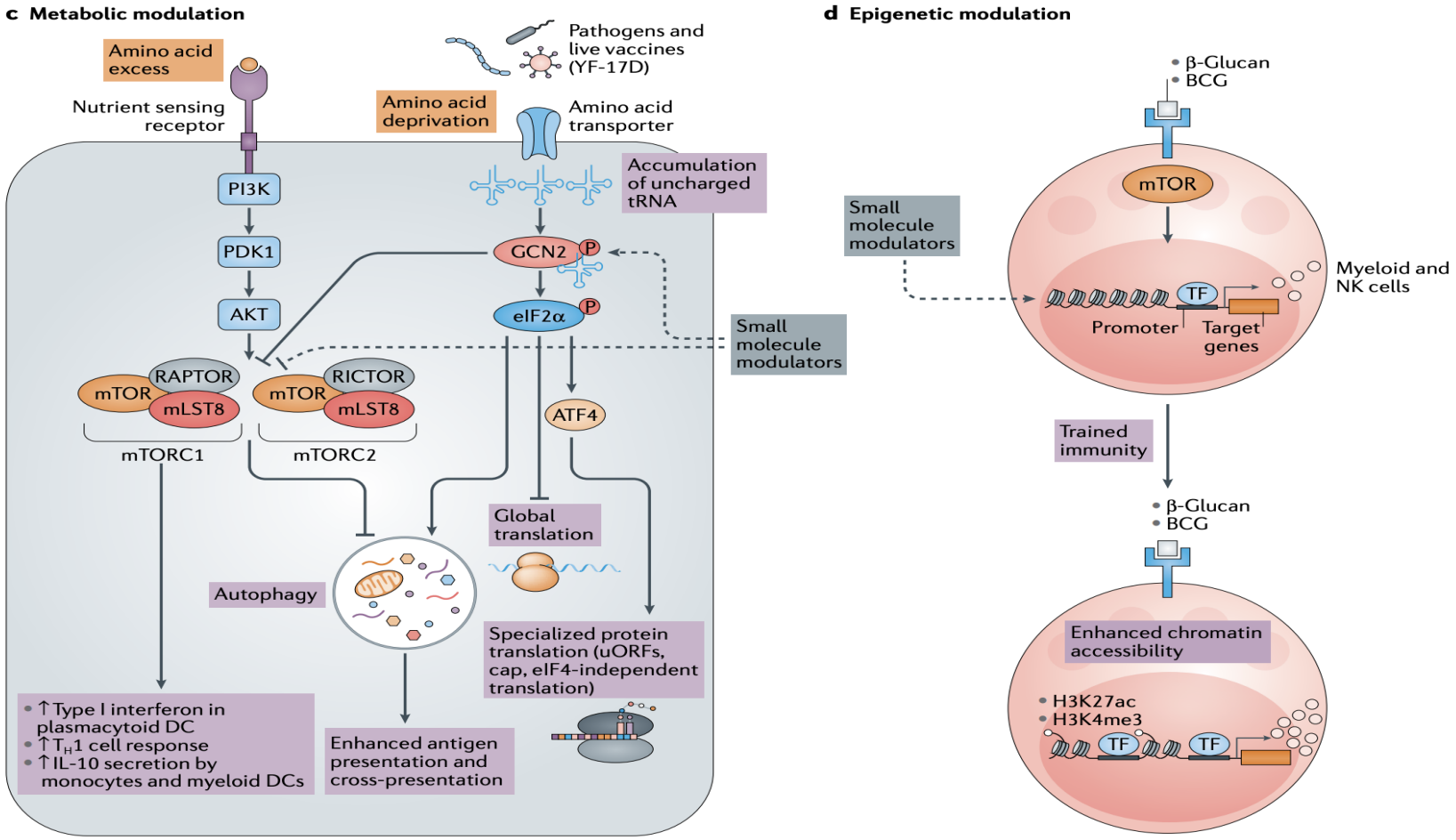
Aşılama sonrası ilk basamak-Adjuvanlar:







Aşılama sonrası ilk basamak-Adjuvanlar:



Pulendran B, Nat Rev Drug Discov. 2021 Jun;20(6):454-475.

Aşılama sonrası ilk basamak-Adjuvanlar:

Adjuvant	Vaccine	Manufacturers	Status	Refs
Alum	Inactivated SARS-CoV-2 virus vaccines	Sinopharm Sinovac	Approved for limited or emergency use in certain countries	65,66
Matrix-M	Recombinant SARS-CoV-2 spike (S) protein	Novavax	Phase III	230
AS03	Recombinant SARS-CoV-2 spike (S) protein as a soluble protein or on virus-like particles	GSK (AS03) Sanofi (antigen) Medicago (antigen)	Phase I/II Phase III	85,86
CpG 1018	Recombinant SARS-CoV-2 spike (S) protein on virus-like particles	Dynavax (CpG 1018) Medicago (antigen)	Phase I/II	86
TLR7/TLR8 ligand adsorbed in alum	Inactivated SARS-CoV-2 vaccines	Bharath Biotech	Phase III/emergency use in India	233

Aşılama sonrası ilk basamak: Adjuvanlar

Table 1. Types of adjuvant carrier in clinical development.

Carrier types	Compositions	Representatives	Vaccines registered
Inorganic salt	Aluminum-based	Aluminum hydroxide ($Al(OH)_3$)	Anthrax: Biothrax® (Emergent BioDefense, 1970)
		Aluminum phosphate ($AlPO_4$)	DTaP: DAPTACEL® (Sanofi Pasteur, 2002)
		Aluminum hydroxide& Aluminum phosphate	DTaP, hepatitis B, and inactivated polio: Pediarix® (GSK, 2002)
		Amorphous aluminum hydroxyphosphate sulfate (AAHS)	Hepatitis A: VAQTA® (Merck, 1996)
		AS04 (MPL)	HPV: Cervarix® (GSK, 2009)
		Alum+CpG 1018	COVID-19: SCB-2019* (Clover, 2022)
	Others	Calcium phosphates	DTaP, poliomyelitis (France)
		Mesoporous silica	-[b]
		Zinc compounds	-[b]
		Gold, Iron oxide	-[b]
Oil-Water Emulsion	Oil-in-water (O/W)	MF59 (Squalene)	Influenza: FLUAD® (Novartis, 1997)
		AS03 (Squalene, DL-a-tocopherol)	Influenza: Pandemrix® (GSK, 2013)
			COVID-19: COVIFENZ® (Medicago&GSK, 2022)
		AF03 (Squalene)	Influenza: Humenza™(Sanofi Pasteur, 2010)
		AS02 (MPL, QS21)	Malaria[a]/RSV [27]
		GLA-SE (Lipid A analogue)	Malaria/Influenza[a] [28]
	Water-in-oil (W/O)	Montanide ISA 51 (mineral oil)	Malaria/Influenza[a]
		Montanide ISA 720 (nonmineral vegetable oil) [29]	Malaria[a]
Microparticle antigen delivery system	Lipid-based	Virosomes	Hepatitis A: Epaxal® (Crucell, 1994)
		AS01 (MPL)	Malaria: Mosquirix® (GSK, 2015)
		AS01B (MPL, QS21)	Herpes zoster: SHINGRIX® (GSK, 2017)
		CAF01 (DDA, TDB) [30]	Tuberculosis[a]
		GLA-AF (Lipid A analogue) [31]	Influenza/HIV[a]
	ISCOMs	Matrix M (QS7, QS21)	COVID-19: NVX-CoV2373 (Novavax, 2020)
	Microspheres	PLGA	-[b]
		Chitosan	-[b]

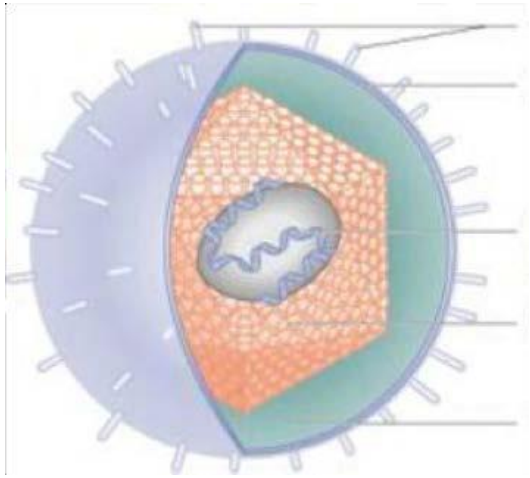
Expert Review of Vaccines,2023
https://doi.org/10.1080/14760584.2023.2238807

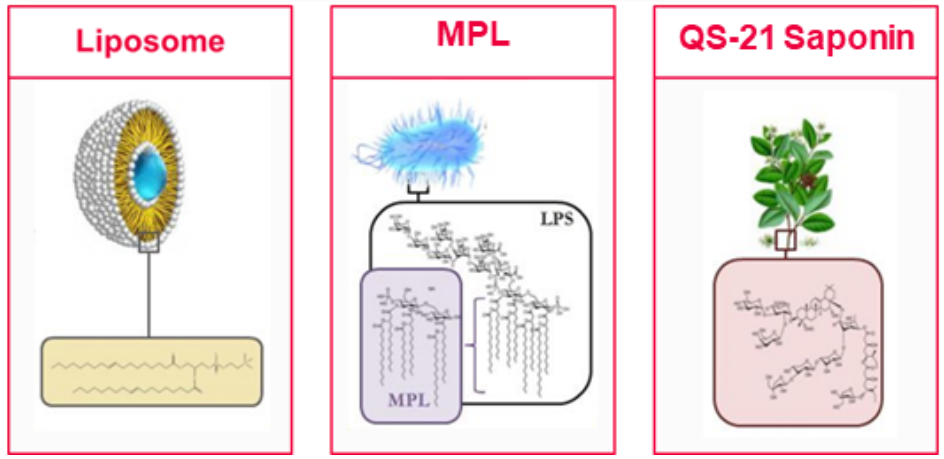
Aşılama sonrası ilk basamak: Adjuvanlar

RZV aşısı
Canlı olmayan

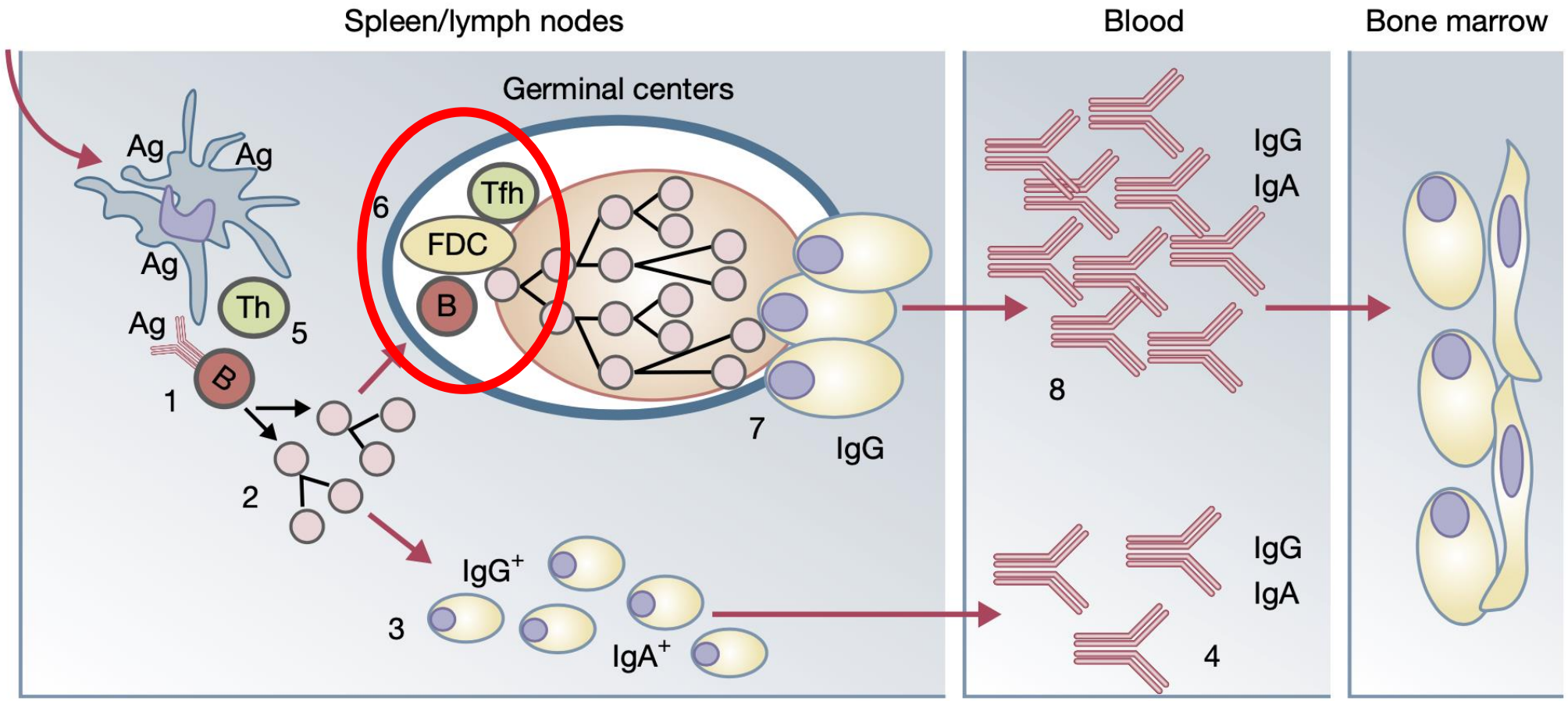
Antijen
Glikoprotein E (gE) - 50 µg

Adjuvan sistemi
$AS01_B$: QS-21* and MPL - 50 µg each



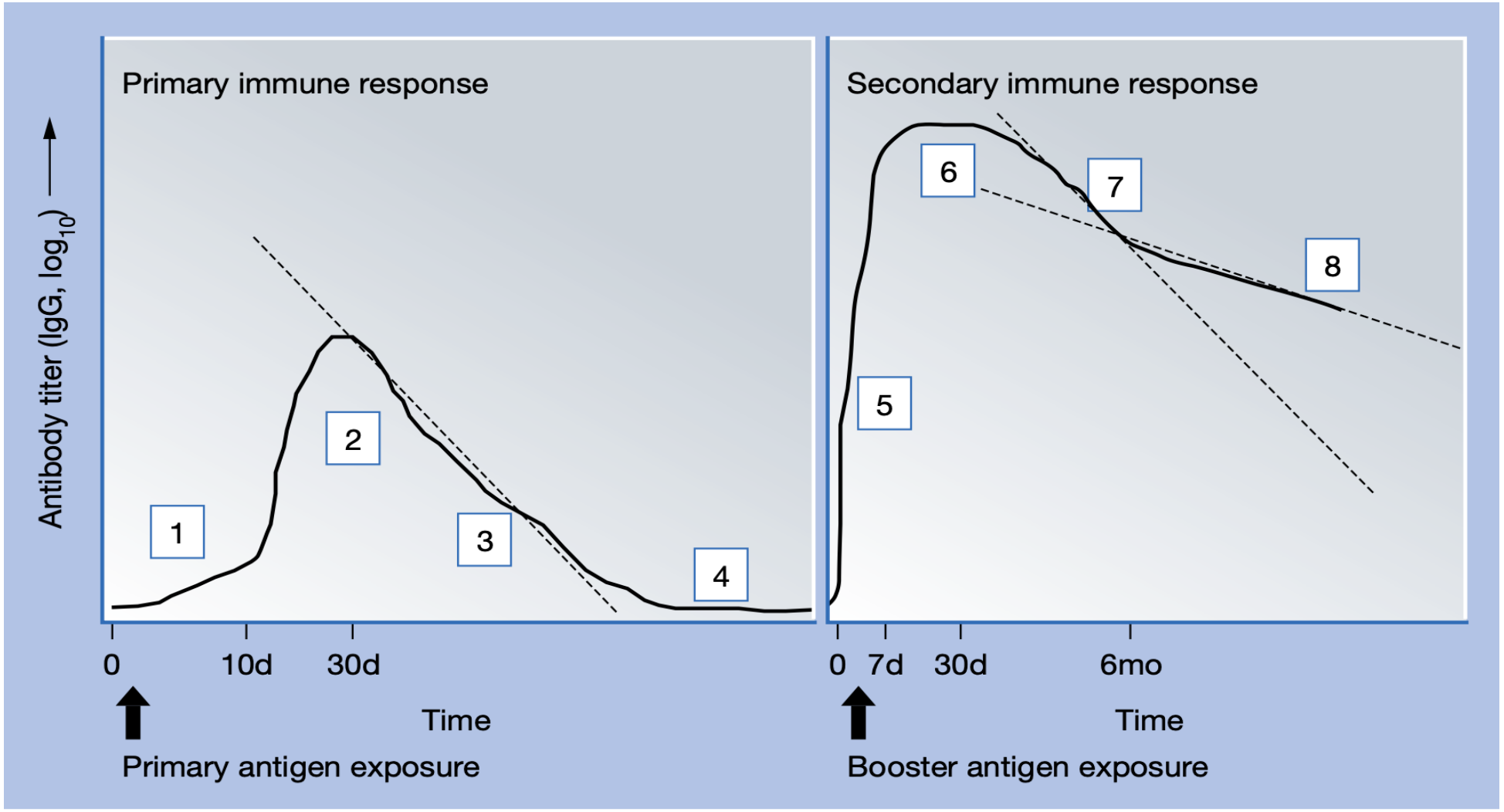


Aşılama sonrası 2. basamak: Humoral immunite



Claire-A.S, Christiane S. E.,
, Plotkin vaccine.

Aşılama sonrası 2. basamak: Humoral immunite



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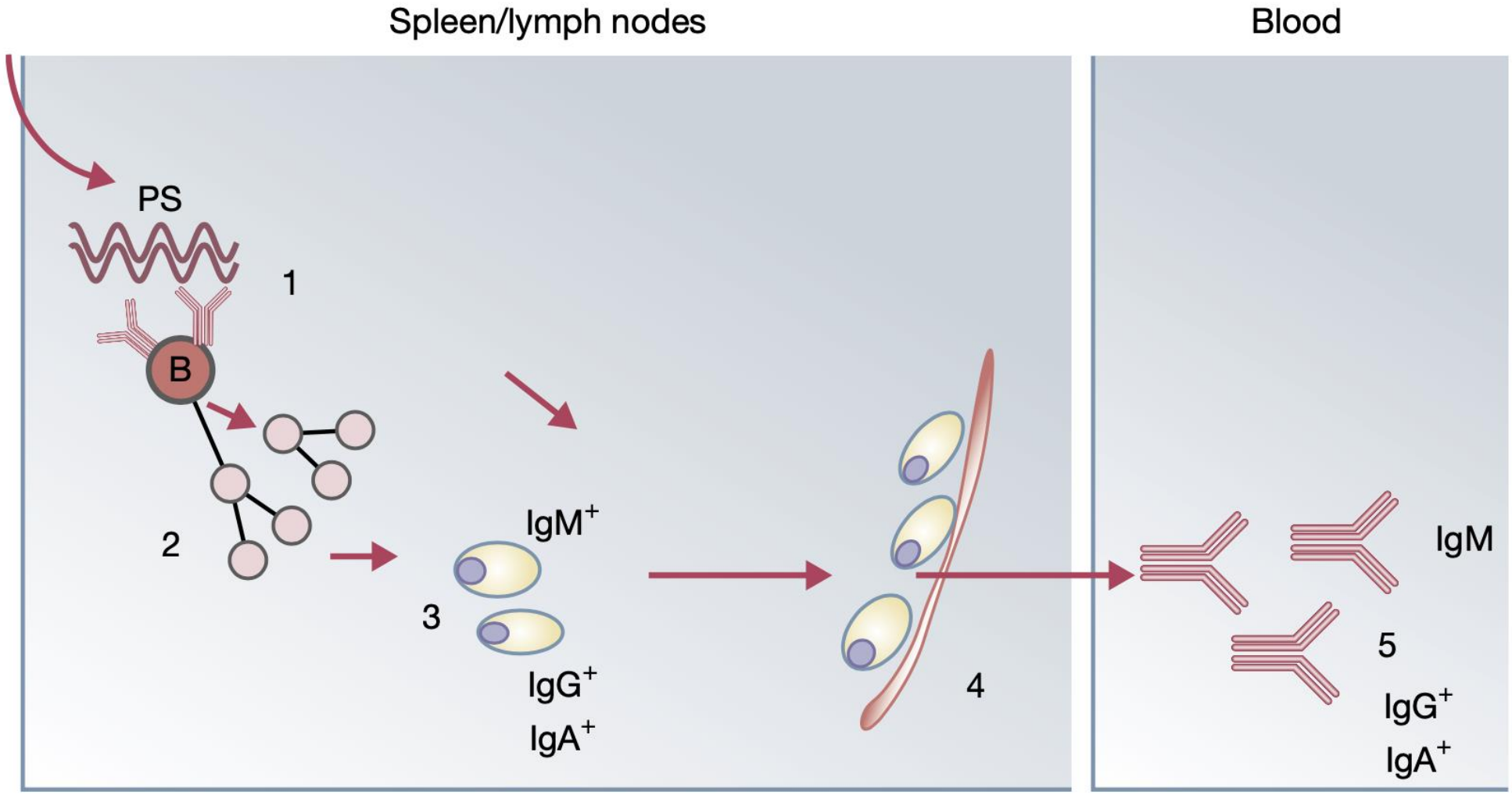
Aşılama sonrası 2. basamak: Humoral immunite



Claire-A.S, Christiane S. E.,
, Plotkin vaccine.

Aşılama sonrası 2. basamak: Humoral immunite

Review

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EXPERT REVIEWS

Hyporesponsiveness and its clinical implications after vaccination with polysaccharide or glycoconjugate vaccines

Expert Rev. Vaccines 10(3), 307–322 (2011)

Jan Poolman[†1] and Ray Borrow[2]

[1]*GlaxoSmithKline Biologicals, Rue de l'Institut 89, 1330 Rixensart, Belgium*
[2]*Clinical Sciences Building, PO Box 209, Manchester Royal Infirmary, Manchester, M13 9WZ, UK*
[†]*Author for correspondence:*
Tel.: +32 26 569 847
Fax: +32 26 568 436
jan.poolman@gskbio.com

Hyporesponsiveness (immune tolerance) follows vaccination with meningococcal polysaccharide and many pneumococcal polysaccharide serotypes. Hyporesponsiveness after *Haemophilus influenzae* type b polysaccharide vaccination has not been directly observed, but may follow exposure during disease in some individuals. Use of currently licensed conjugate vaccines has not been associated with hyporesponsiveness to date, with the possible exception of pneumococcal serotype 3. Introduction of polysaccharide vaccines anywhere into a conjugate vaccination schedule may result in reduced immune responses on subsequent exposure. This review of vaccine-induced hyporesponsiveness and its potential clinical implications considers recent evidence suggesting that hyporesponsiveness may occur for specific components of combined conjugate vaccines, such as pneumococcal serotype 3. These data have implications for the development of new multivalent vaccines.

Poolman J, Expert Rev Vaccines. 2011 Mar;10(3):307-22.

Aşılama sonrası 2. basamak: Humoral immunite

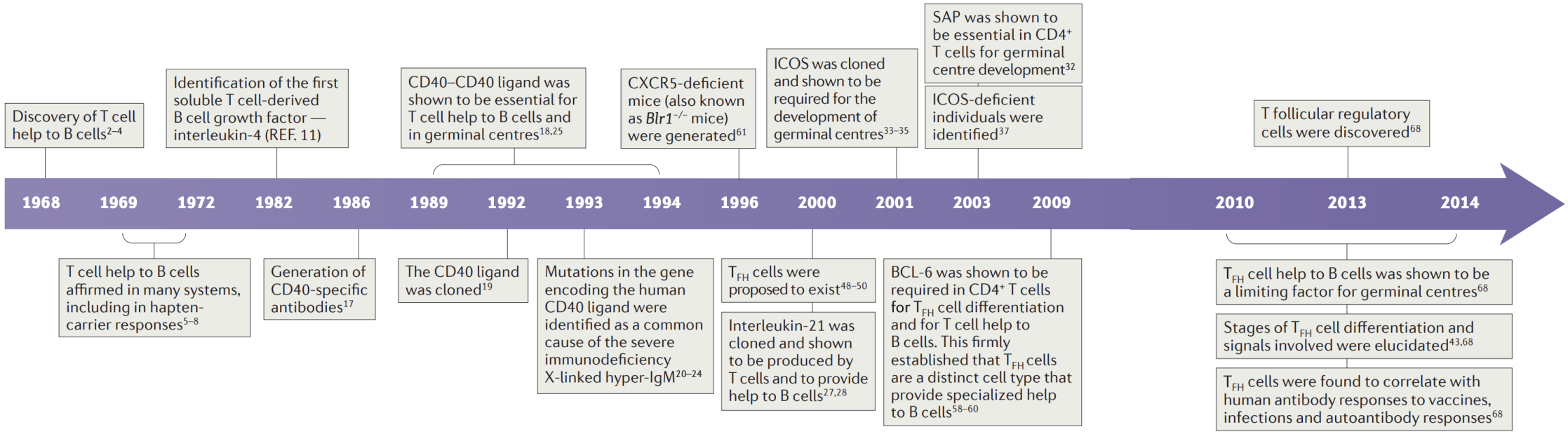
ANTİKOR YANITINI BELİRLEYEN FAKTÖRLER:
1. Antijenin yapısı
2. Antijenin dozu
3. İmmun yetersizlik durumu
4. Rapel arası süre

ANTİKOR YANITININ DEVAMLILIĞINI BELİRLEYEN FAKTÖRLER:
1. Aşı türü
2. Antijenin yapısı, Antijenin dozu
3. İmmun yetersizlik durumu
4. Rapel arası süre
5. Çevresel faktörler
6. Aşılanma yaşı

Aşılama sonrası 2. basamak: Humoral immunite

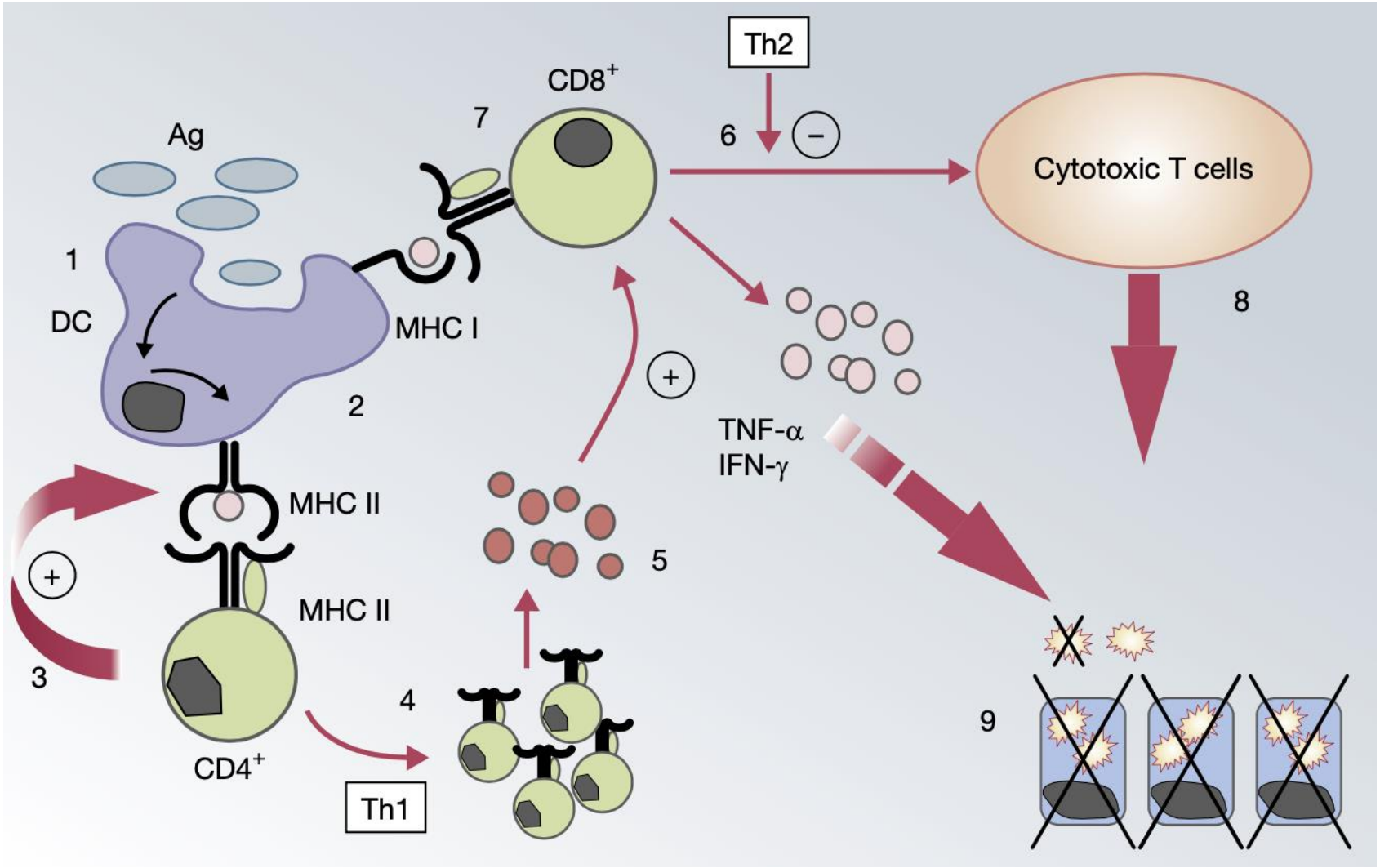
HAFIZA B HÜCRE OLUŞUMUNU ETKİLEYEN FAKTÖRLER
1. Tfh hücreleri ile germinal merkez yanıtı sonucu,
2. Dinlenme durumunda antikor üretmeyebilir,
3. 4-6 ay içerisinde affinite maturasyonuna giderler,
4. Antijen ile karşılaşma sonrası hızlıca antikor üretimi,

Aşılama sonrası 2. basamak: Hücresel immunite



Crotty S. Nat Rev Immunol. 2015 Mar;15(3):185-9.

Aşılama sonrası 2. basamak: Hücresel immunite



Claire-A.S, Christiane S. E.,
, Plotkin vaccine.

Aşılama sonrası 2. basamak: Hücresel immunite

Hafıza T hücre sayısını arttıran faktörler:

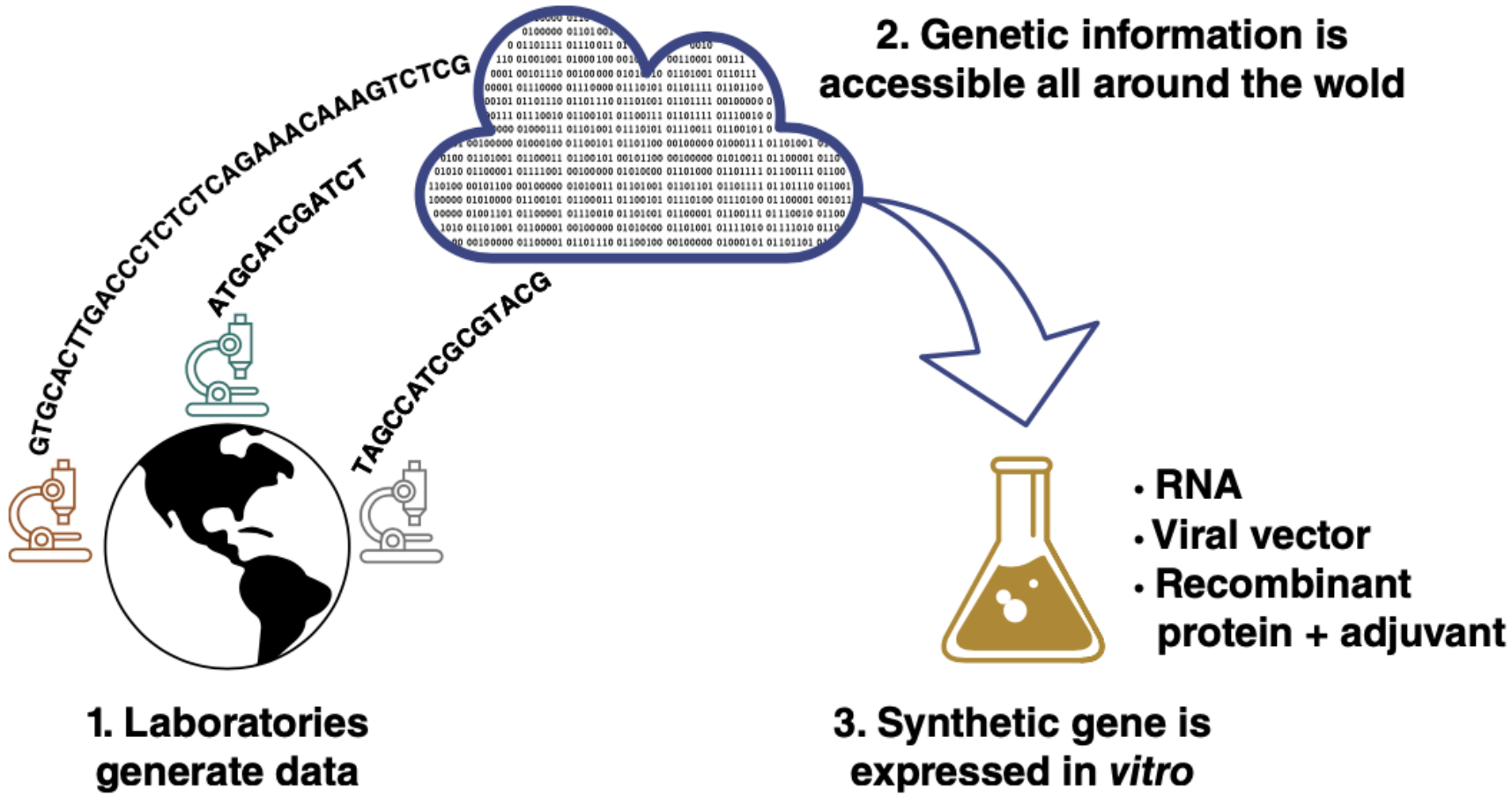
- Başlangıçtaki antijen miktarı
- Antijen devamlılık yüzdesi

Aşıların immunolojik etkilerinin karşılaştırılması

Vaccines	Vaccine Type	Serum IgG	Mucosal IgG	Mucosal IgA	T Cells
Pneumococcal PS	PS	++	(+)		
Pneumococcal conjugates	PS-protein	+++	++		
Polio Sabin	Live attenuated	++	++	++	
Polio Salk	Killed	++	+		
Rabies	Killed	++			
Rotavirus	VLPs	(+)	(+)	++	
Rubella	Live attenuated	+++			
SARS-CoV-2	Inactivated	++			
SARS-CoV-2	mRNA	+++			++ (CD4/CD8)
SARS-CoV-2	Viral vectors	++			+ (CD4/CD8)

Claire-A.S, Christiane S. E.,
, Plotkin vaccine.

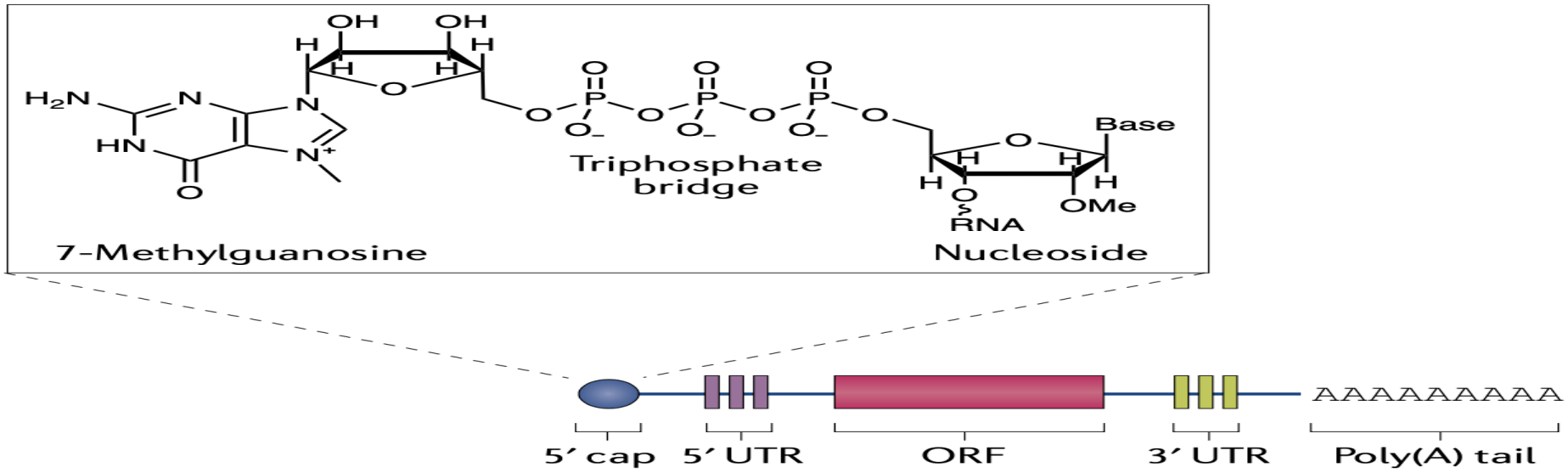
Nükleik asit temelli aşılar



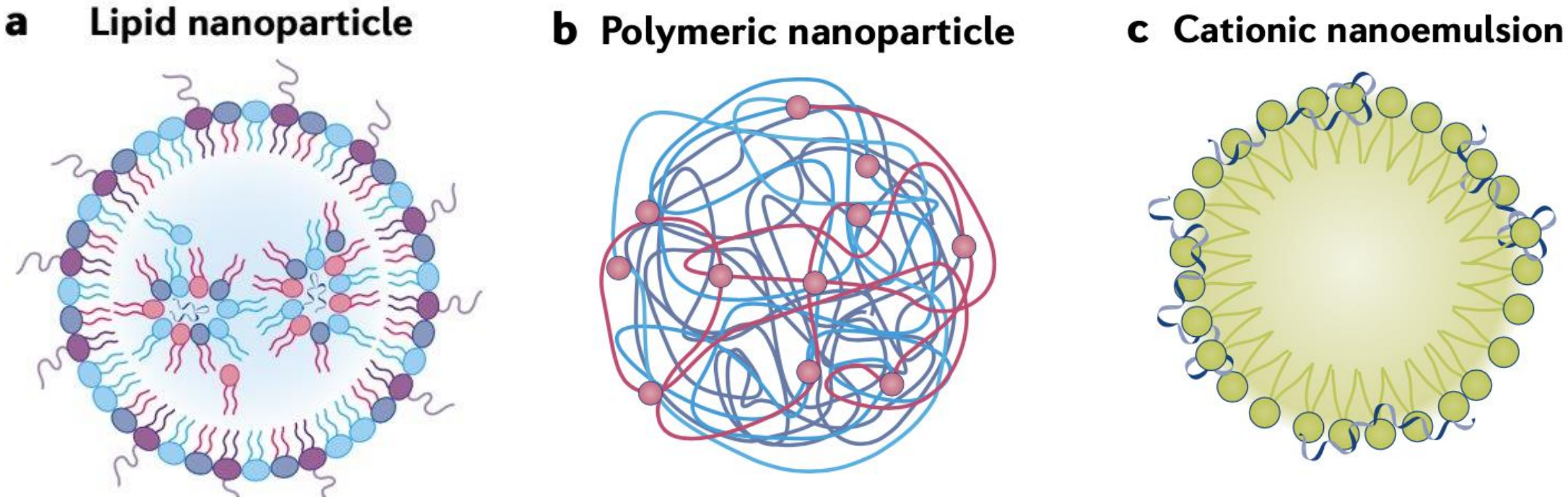
mRNA aşıları

mRNA vaccines for infectious diseases: principles, delivery and clinical translation

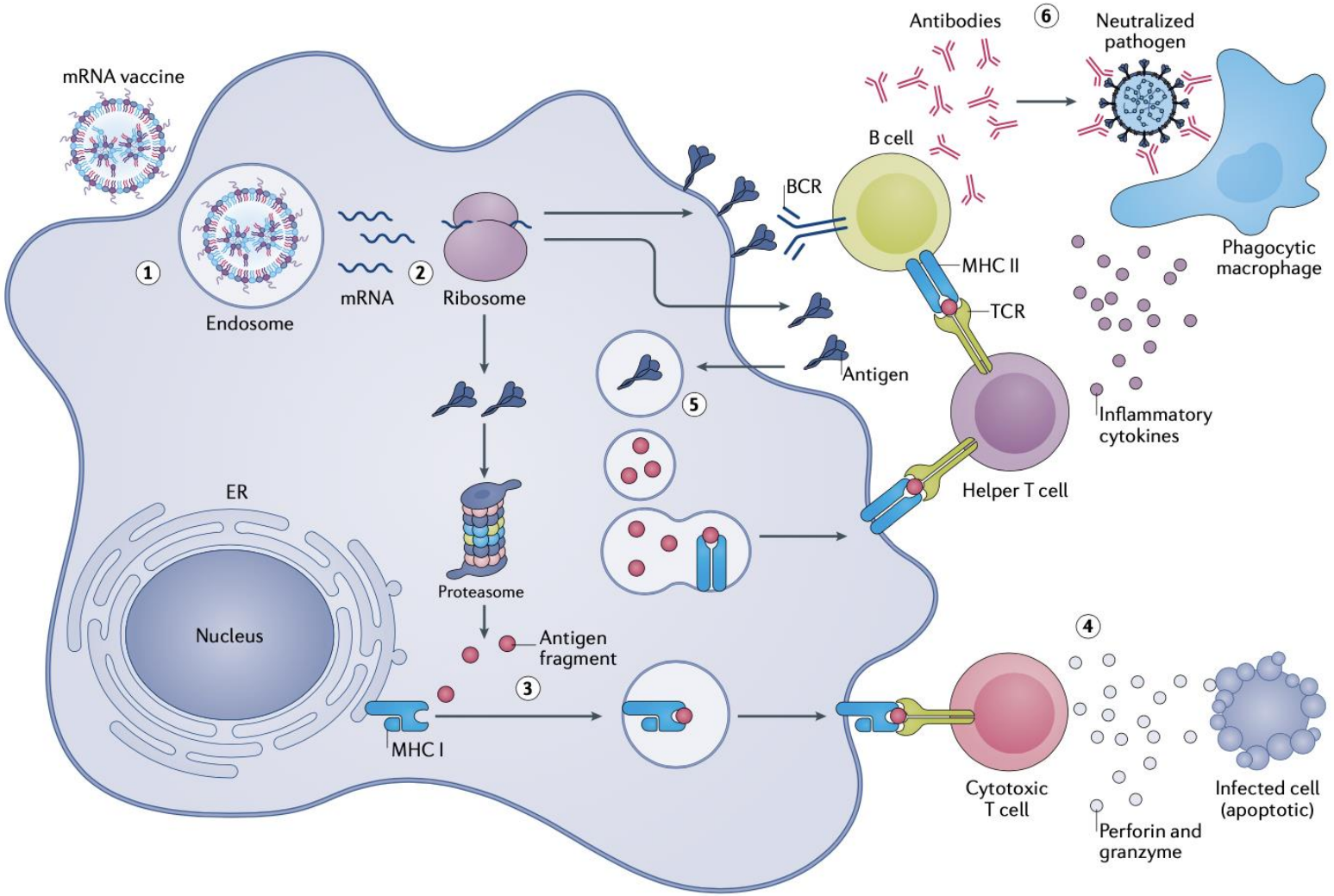
Namit Chaudhary[1], *Drew Weissman*[2] *and Kathryn A. Whitehead*[1,3]✉



mRNA aşıları



mRNA aşıları

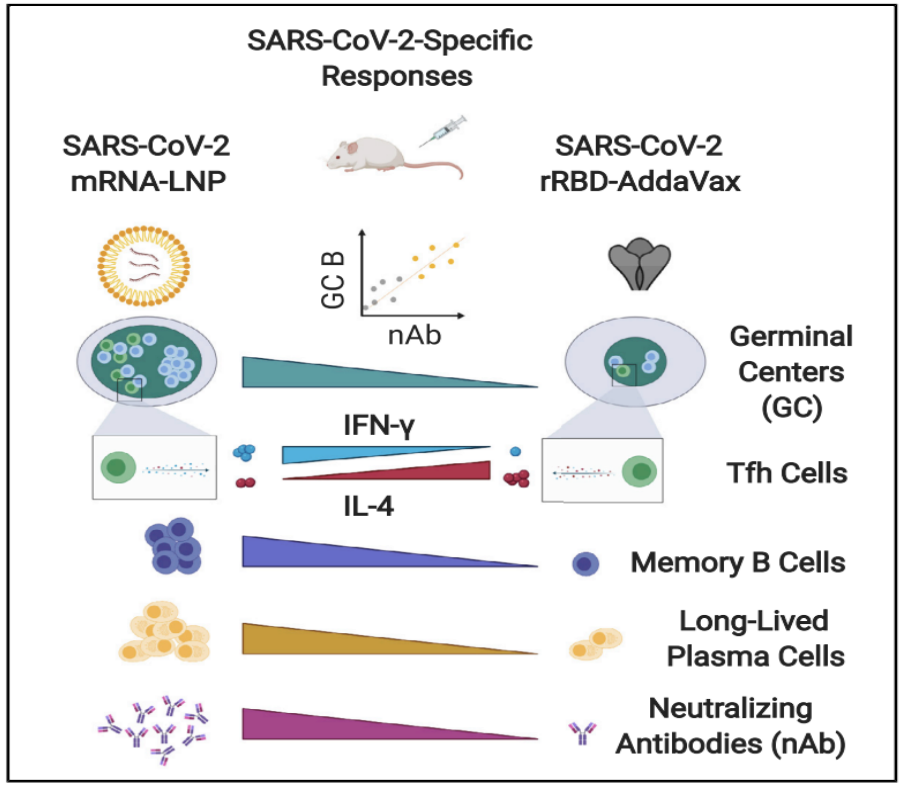


mRNA aşıları-İmmun yanıt

Immunity

SARS-CoV-2 mRNA Vaccines Foster Potent Antigen-Specific Germinal Center Responses Associated with Neutralizing Antibody Generation

Graphical Abstract



Authors

Katlyn Lederer, Diana Castaño, Daniela Gómez Atria, ..., Gregory D. Sempowski, Norbert Pardi, Michela Locci

Correspondence

michela.locci@pennmedicine.upenn.edu

In Brief

Herein, Lederer et al. show a nucleic-acid-based vaccine platform for SARS-CoV-2 that potently induces germinal center (GC) responses. GCs are microanatomical sites harboring the formation of high-quality, protective antibody responses. Such vaccine platforms can be promising candidates to mitigate the COVID-19 pandemic.

mRNA aşıları ve pangenotipik kullanımı

Article

Neutralizing antibody vaccine for pandemic and pre-emergent coronaviruses

https://doi.org/10.1038/s41586-021-03594-0

Received: 7 February 2021

Accepted: 29 April 2021

Published online: 10 May 2021

Check for updates

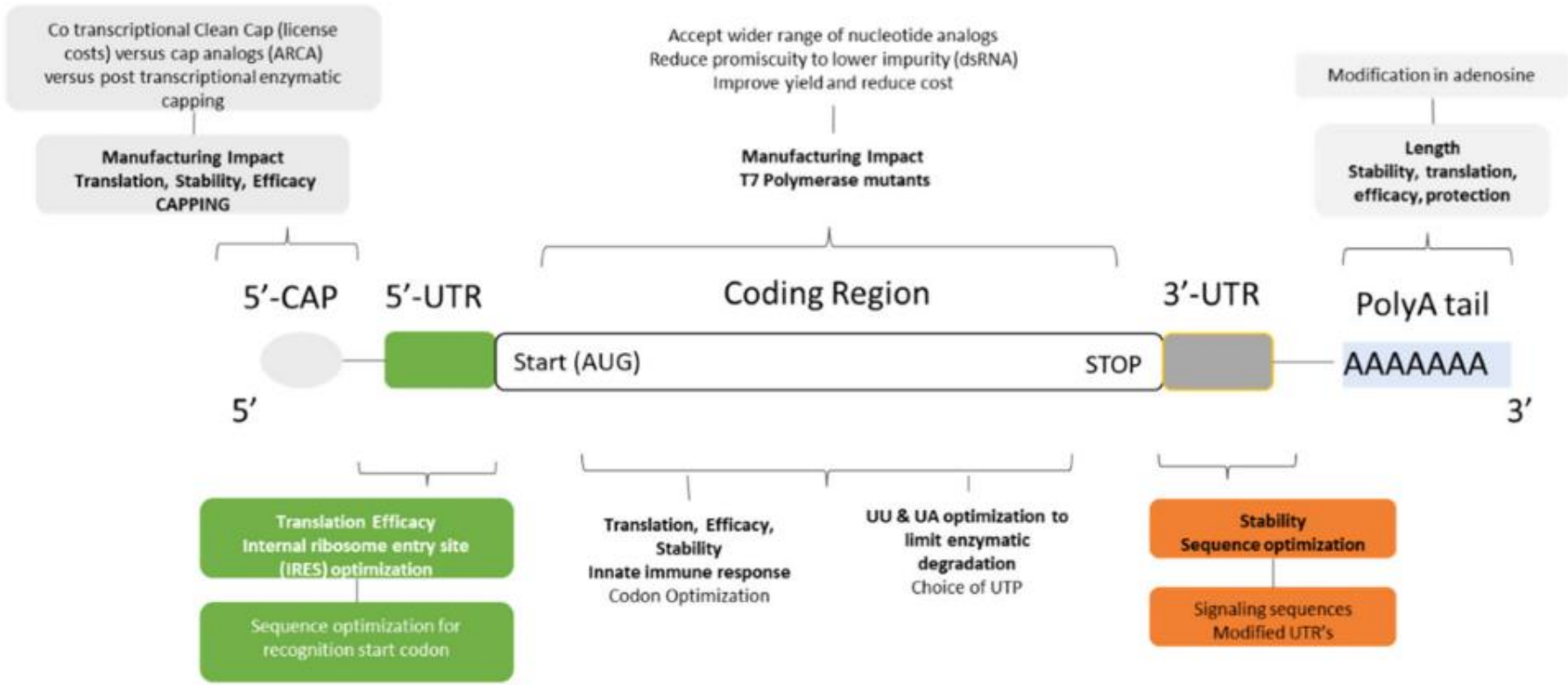
Kevin O. Saunders[1,2,3,4]✉, Esther Lee[1,5], Robert Parks[1,5], David R. Martinez[6], Dapeng Li[1,5], Haiyan Chen[1,5], Robert J. Edwards[1,5], Sophie Gobeil[1,5], Maggie Barr[1,5], Katayoun Mansouri[1,5], S. Munir Alam[1,5], Laura L. Sutherland[1,5], Fangping Cai[1,5], Aja M. Sanzone[1,5], Madison Berry[1,5], Kartik Manne[1,5], Kevin W. Bock[7], Mahnaz Minai[7], Bianca M. Nagata[7], Anyway B. Kapingidza[1,5], Mihai Azoitei[1,5], Longping V. Tse[6], Trevor D. Scobey[6], Rachel L. Spreng[1,5], R. Wes Rountree[1,5], C. Todd DeMarco[1,5], Thomas N. Denny[1,5], Christopher W. Woods[1,5,8], Elizabeth W. Petzold[8], Juanjie Tang[9], Thomas H. Oguin III[1,5], Gregory D. Sempowski[1,5], Matthew Gagne[10], Daniel C. Douek[10], Mark A. Tomai[11], Christopher B. Fox[12], Robert Seder[10], Kevin Wiehe[1,5], Drew Weissman[13], Norbert Pardi[13], Hana Golding[9], Surender Khurana[9], Priyamvada Acharya[1,2], Hanne Andersen[14], Mark G. Lewis[14], Ian N. Moore[7], David C. Montefiori[1,2], Ralph S. Baric[6] & Barton F. Haynes[1,3,5]✉

Saunders, K. O.Nature | Vol 594 | 24 June 2021

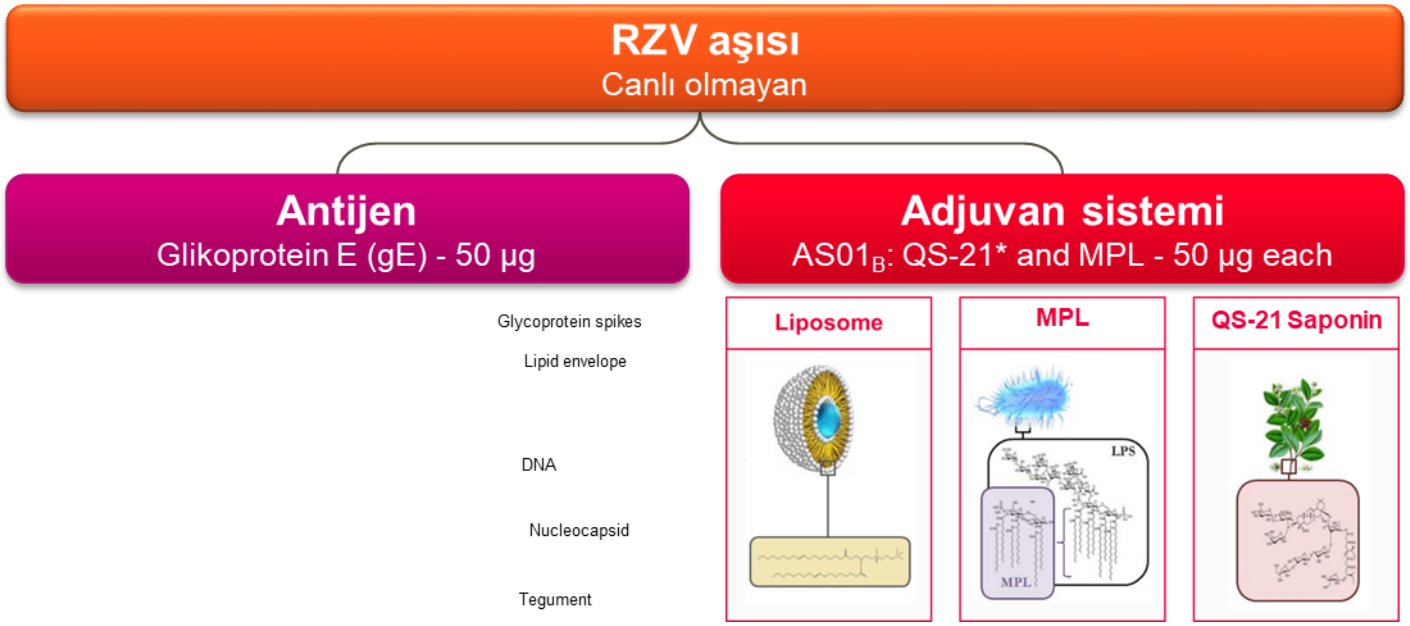
SONUÇ

İmmünobiyoloji, bir aşının etkili olabilmesi için uyarılması gereken bağışıklık sisteminin tanımlanmasını mümkün kılmalıdır.


THE FACE OF
VISION
EVERY 10th OF NOVEMBER AT 9:05 'TIME STOPS' IN TURKEY


Co transcriptional Clean Cap (license costs) versus cap analogs (ARCA) versus post transcriptional enzymatic capping
Manufacturing Impact
Translation, Stability, Efficacy
CAPPING
Accept wider range of nucleotide analogs
Reduce promiscuity to lower impurity (dsRNA)
Improve yield and reduce cost
Manufacturing Impact
T7 Polymerase mutants
Modification in adenosine
Length
Stability, translation, efficacy, protection
5'-CAP
5'-UTR
Coding Region
3'-UTR
PolyA tail
Start (AUG)
STOP
AAAAAAA
5'
3'
Translation Efficacy
Internal ribosome entry site (IRES) optimization
Sequence optimization for recognition start codon
Translation, Efficacy, Stability
Innate immune response
Codon Optimization
UU & UA optimization to limit enzymatic degradation
Choice of UTP
Stability
Sequence optimization
Signaling sequences
Modified UTR's

How Specific Are Vaccine Immune Responses?



mRNA aşıları

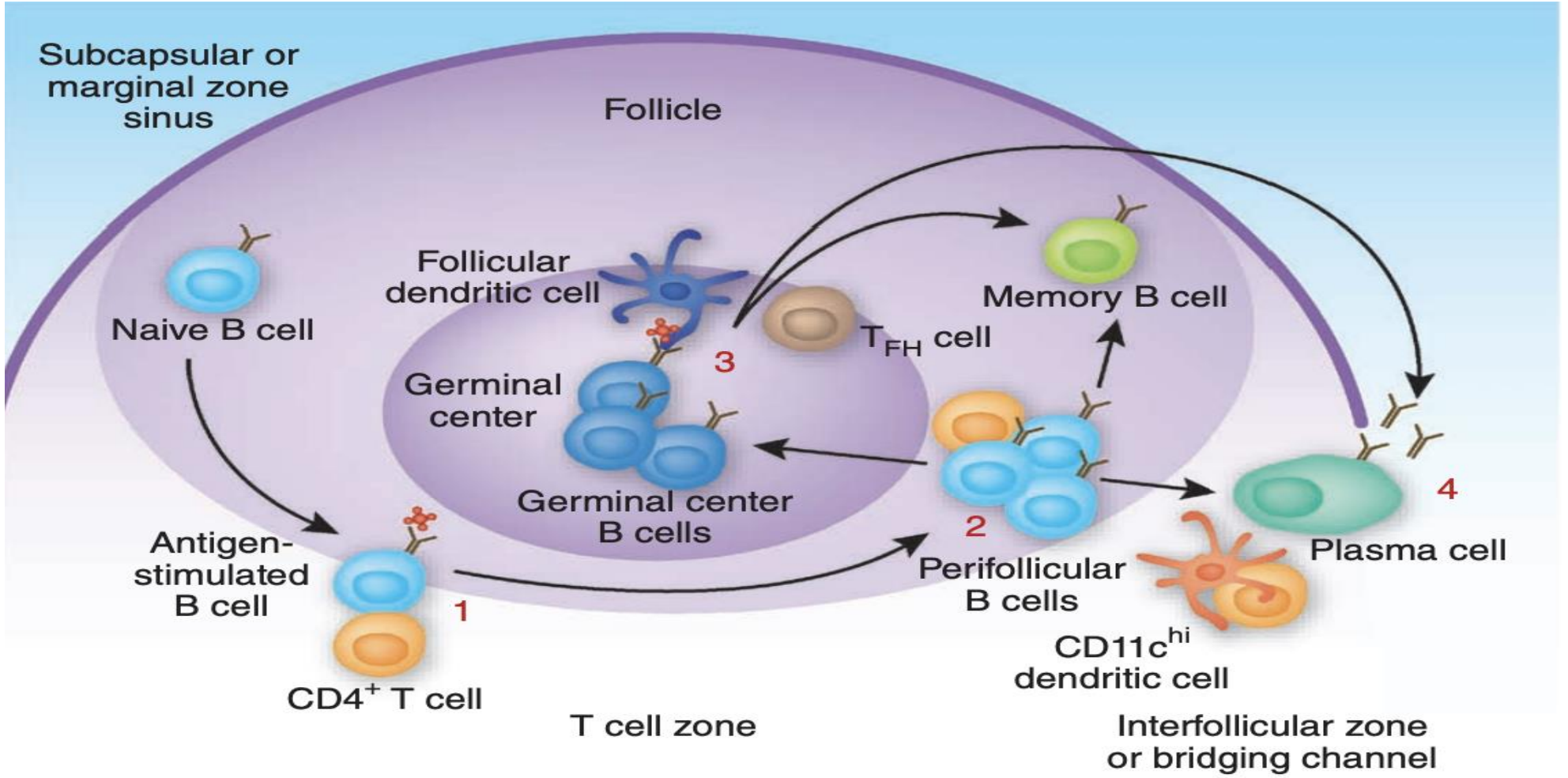
The NEW ENGLAND JOURNAL of MEDICINE

CONCLUSIONS

In this study in a nationwide mass vaccination setting, the BNT162b2 vaccine was not associated with an elevated risk of most of the adverse events examined. The vaccine was associated with an excess risk of myocarditis (1 to 5 events per 100,000 persons). The risk of this potentially serious adverse event and of many other serious adverse events was substantially increased after SARS-CoV-2 infection. (Funded by the Ivan and Francesca Berkowitz Family Living Laboratory Collaboration at Harvard Medical School and Clalit Research Institute.)

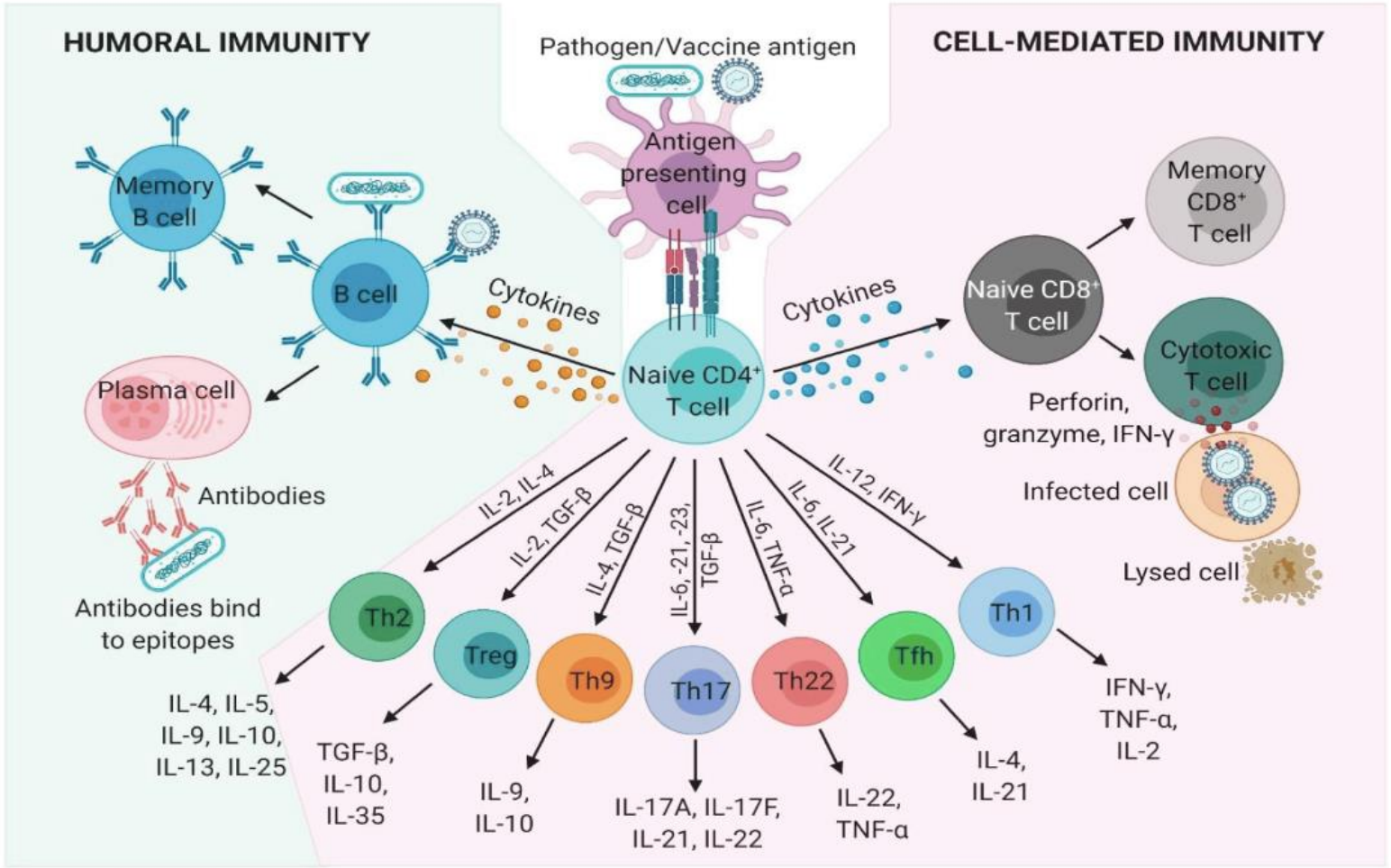
Barda N, N Engl J Med.
2021 Sep 16;385(12):1078-1090.

Aşılama sonrası 2. basamak: Humoral immunite



Goodnow CC. Nat Immunol. 2doi: 10.1038/ni.1900.

İmmunolojik yanıtın temelleri



HEALTH SCIENCES

Katalin Karikó and Drew Weissman, Penn's historic mRNA vaccine research team, win 2023 Nobel Prize in Medicine

The highest honor was bestowed for foundational discoveries that gave the world a vaccine to fight the COVID-19 pandemic.

Katalin Karikó and Drew Weissman are the recipients of the 2023 Nobel Prize in Medicine.

Vaccine 39 (2021) 7661–7668

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Tick immunity using mRNA, DNA and protein-based Salp14 delivery strategies

Jaqueline Matias [a,1], Cheyne Kurokawa [a,1], Andaleeb Sajid [a,1], Sukanya Narasimhan [a], Gunjan Arora [a], Husrev Diktas [a], Geoffrey E. Lynn [a], Kathleen DePonte [a], Norbert Pardi [b], Jesus G. Valenzuela [c], Drew Weissman [b], Erol Fikrig [a,1,*]

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[c] Vector Molecular Biology Section, Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Disease, National Institutes of Health, 12735 Twinbrook Parkway, Rockville, MD 20852, USA

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Nucleic acid vaccine

ABSTRACT

Guinea pigs exposed to multiple infestations with *Ixodes scapularis* ticks develop acquired resistance to ticks, which is also known as tick immunity. The *I. scapularis* salivary components that contribute to tick immunity are likely multifactorial. An anticoagulant that inhibits factor Xa, named Salp14, is present in tick saliva and is associated with partial tick immunity. A tick bite naturally releases tick saliva proteins into the vertebrate host for several days, which suggests that the mode of antigen delivery may influence the genesis of tick immunity. We therefore utilized Salp14 as a model antigen to examine tick immunity using mRNA lipid nanoparticles (LNPs), plasmid DNA, or recombinant protein platforms. *salp14* containing mRNA-LNPs vaccination elicited *erythema* at the tick bite site after tick challenge that occurred earlier, and that was more pronounced, compared with DNA or protein immunizations. Humoral and cellular responses associated with tick immunity were directed towards a 25 amino acid region of Salp14 at the carboxy terminus of the protein, as determined by antibody responses and skin-testing assays. This study demonstrates that the model of antigen delivery, also known as the vaccine platform, can influence the genesis of tick immunity in guinea pigs. mRNA-LNPs may be useful in helping to elicit *erythema* at the tick bite site, one of the most important early hallmarks of acquired tick resistance. mRNA-LNPs containing tick genes is a useful platform for the development of vaccines that can potentially prevent selected tick-borne diseases.