Hepatit B Tedavisinde Yeni Ne Var?

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E.Ü.T.F Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

İZMİR

Tedavi stratejileri

- ETV, TDF, TAF ön planda, PEG-IFN tedavi seçenekleri arasında

- LAM, ADV, LTD kalkmış durumda

- NA+PegIFN tartışılmış ama yeni veriler gerekmekte

Kronik hepatit B tedavisinde yeni ilaçlar

Target	Mode of action	Compound	Clinical trial
DAA			
NTCP			Phase IIa
HBV Polyme			Phase III
			Phase III
cccDNA			Pre-clinical
			Pre-clinical
			Pre-clinical
			Phase Ia
HBV RNA	Knock down HBV RNA, viral proteins and HBV DNA	ARC-520	Phase IIa
HBsAg	Blocks HBsAg secretion	REP 9 AC	Phase II
HTA			
Innate immunity	Induce APOBEC3A and APOBEC3B	Lymphotoxin-β receptor agonist	Pre-clinical
	Exogenous interferon stimulation	Toll-like receptor (TLR) agonist (GS-9620)	Phase II
Adaptive immunity	Therapeutic vaccine	GS-4774	Phase II
		DV601	Phase Ib
		TG1050	Phase I
	Immune checkpoint inhibitor to activate $CD8^+$ T cells	Programmed death-1 (PD-1) inhibitor	Pre-clinical

APOBEC, apolipoprotein B mRNA editing enzyme, catalytic polypeptide 3A and 3B; cccDNA, covalently closed circular DNA; CRISPR/Cas, clustered regulatory interspaced short palindromic repeats (CRISPR) and CRISPR associated (Cas) systems; DAA, direct acting anti-virals; HBV, hepatitis B virus; HTA, host targeting agents; NTCP, sodium taurocholate co-transporting polypeptide; TALENs, transcription activator-like effector nucleases; ZFNs, zinc-finger nucleases.

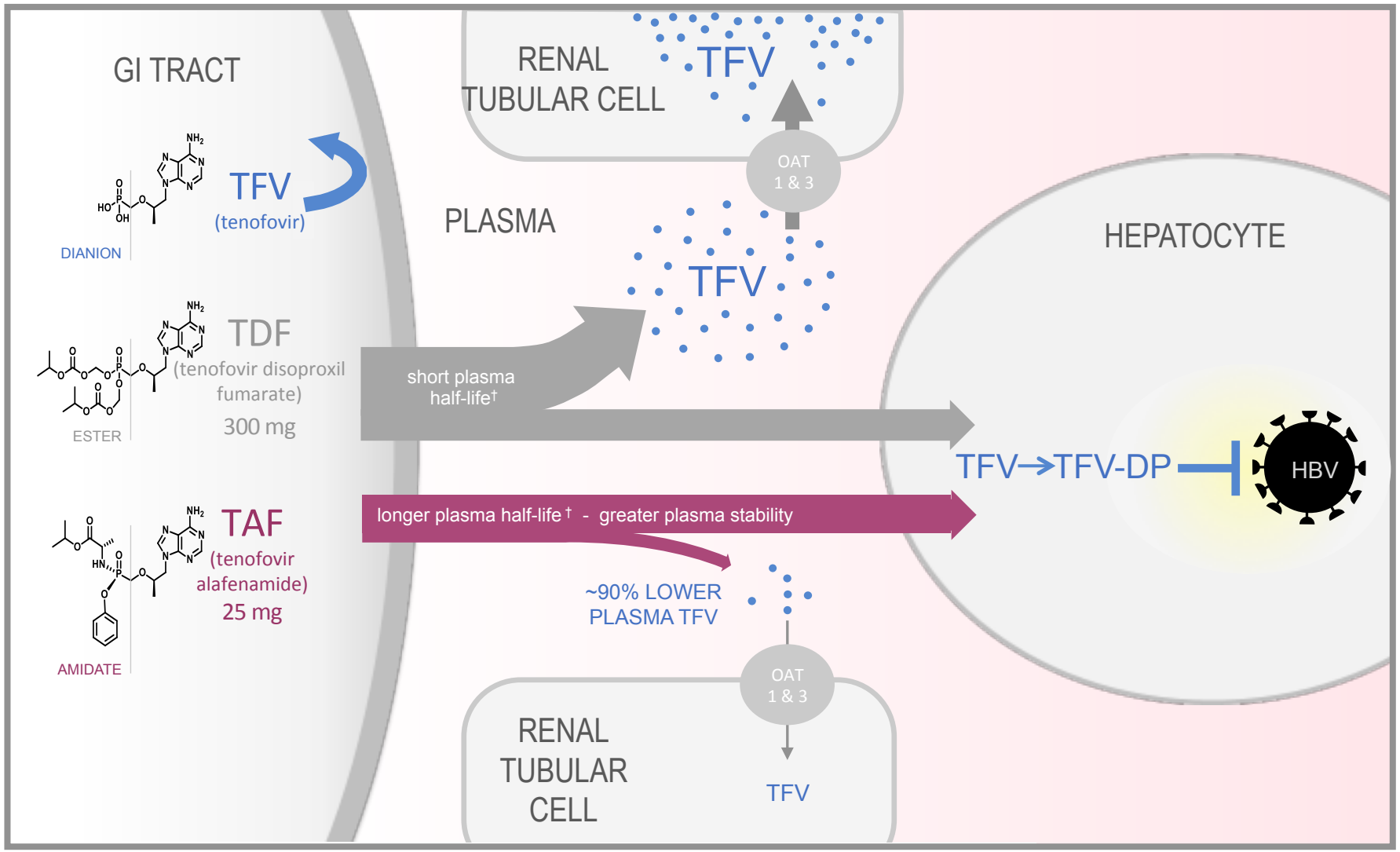
Karnitin eksikliği

Besivo
Besifovir Dipivoxil 150mg

vs

Vemlidy
tenofovir alafenamide 25mg tablets

Tenofovir alafenamide (TAF) – Tenofovir'in yeni ön ilacı



† $T_{1/2}$ based on *in vitro* plasma data - TDF = 0.4 minutes, TAF = 30-90 minutes.

Lee W et. *Antimicr Agents Chemo* 2005;49(5):1898-1906. Birkus G et al. *Antimicr Agents Chemo* 2007;51(2):543-550. Babusis D, et al. *Mol Pharm* 2013;10(2):459-66. Ruane P, et al. *J Acquir Immune Defic Syndr* 2013; 63:449-5. Sax P, et al. *JAIDS* 2014. 2014 Sep 1;67(1):52-8. Sax P, et al. *Lancet* 2015. Jun 27;385(9987):2606-15. Agarwal K et al. *J Hepatology* 2015; 62: 533-540; Buti M et al. Lancet G&H 2016; doi: 10.1016/S2468-1253(16)30107-8; Chan HLY et al. Lancet G&H 2016; doi: /10.1016/S2468-1253(16)30024-3

Güvenlik uyarıları daha çok vurgulanmakta

- All patients treated with NA should be followed with periodical assessments including ALT and serum HBV DNA (Evidence level I, grade of recommendation 1).
- Patients at risk of renal disease treated with any NA and all patients regardless of renal risk treated with TDF should undergo periodical renal monitoring including at least estimated glomerular filtration rate (eGFR) and serum phosphate levels (Evidence level II-2, grade of recommendation 1).
- Patients on TDF at risk of development and/or with underlying renal or bone disease should be considered for a switch to ETV or TAF, depending on previous LAM exposure (Evidence level II-2/I, grade of recommendation 1).

Table 5. Indications for selecting ETV or TAF over TDF.*

1. Age >60 years
2. Bone disease
Chronic steroid use or use of other medications that worsen bone density
History of fragility fracture
Osteoporosis
3. Renal alteration**
eGFR <60 ml/min/1.73 m^2
Albuminuria >30 mg/24 h or moderate dipstick proteinuria
Low phosphate (<2.5 mg/dl)
Hemodialysis

* TAF should be preferred to ETV in patients with previous exposure to nucleoside analogues.

** ETV dose needs to be adjusted if eGFR <50 ml/min; no dose adjustment of TAF is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) ⩾15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis.

TAF (Tenofovir alafenamide) (Vemlidy)

HBe serokonversiyon ve HBsAg kaybı yine düşük

Study	Regimen (mg once daily)	HBV DNA <29 IU/mL (% pts)[a] [FAS]	Normalization ALT (% pts) [no. of pts]		HBeAg loss[b] (% pts) [no. of pts]	HBeAg seroconversion[b] (% pts) [no. of pts]	HBsAg loss[c] (% pts) [no. of pts]
			By central laboratory[d]	By AASLD[e]			
In HBeAg-positive pts							
Chan et al. [20]	TAF 25 + PL	64 NI [581]	72 [537]	45* [572]	14 [565]	10 [565]	1 [576]
	TDF 300 + PL	67 [292]	67 [268]	36 [290]	12 [285]	8 [285]	<1 [288]
In HBeAg-negative pts							
Buti et al. [19]	TAF 25 + PL	94 NI [285]	83 [236][f]	50** [276][f]	NA	NA	0 [281]
	TDF 300 + PL	93 [140]	75 [121][f]	32 [138][f]	NA	NA	0 [138]

NA not applicable, *NI* noninferior vs. TDF, *PL* placebo, *pts* patients, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil fumarate

Tenofovire göre farmakokinetik özellikleri daha iyi
Sistemik etkileri daha az
Kemikler ve renal yönden güvenli

Drugs (2017) 77:1017–1028

Tüm antiviraller ve kombinasyon tedavileri ile HBs Ag kaybı çok düşük oranlarda görülüyor

	Monotherapies							Combination therapies		
Treatment response	3TC	ADV	ETV	LdT	TDF	PEG-IFN α	TDF+PEG-IFN α	ETV+PEG-IFN α	ADV+PEG-IFN α	ETV+TDF
HBeAg-positive patients										
At week 48 or 52										
HBsAg loss, %	<1	0	2	0	3	3	6	1	3	1
Cumulative percentage during extended treatment										
HBsAg loss, % (in years)	0-3 (2-3)	2 (5)	5 (2)	1.3 (2)	10 (5)	11 (3.5)	9 (1.5)	1 (2.5)	3 (0.5)	5 (2)
HBeAg-negative patients										
At week 48 or 52										
HBsAg loss, %	<1	0	<1	<1	0	4	5			0
Cumulative percentage during extended treatment										
HBsAg loss, % (in years)	<1 (4)	5 (5)	NA	<1 (2)	0.3 (5)	8 (3)	5 (1.5)			0 (2)

3TC, lamivudine; ADV, adefovir; CHB, chronic hepatitis B; ETV, entecavir; LdT, telbivudine; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; PEG-IFN, pegylated interferon; TDF, tenofovir disoproxil fumarate.

Liver International 2017; 37 (Suppl. 1): 59–66

Mevcut tedaviler ccc DNA'yı ne kadar etkiliyor?

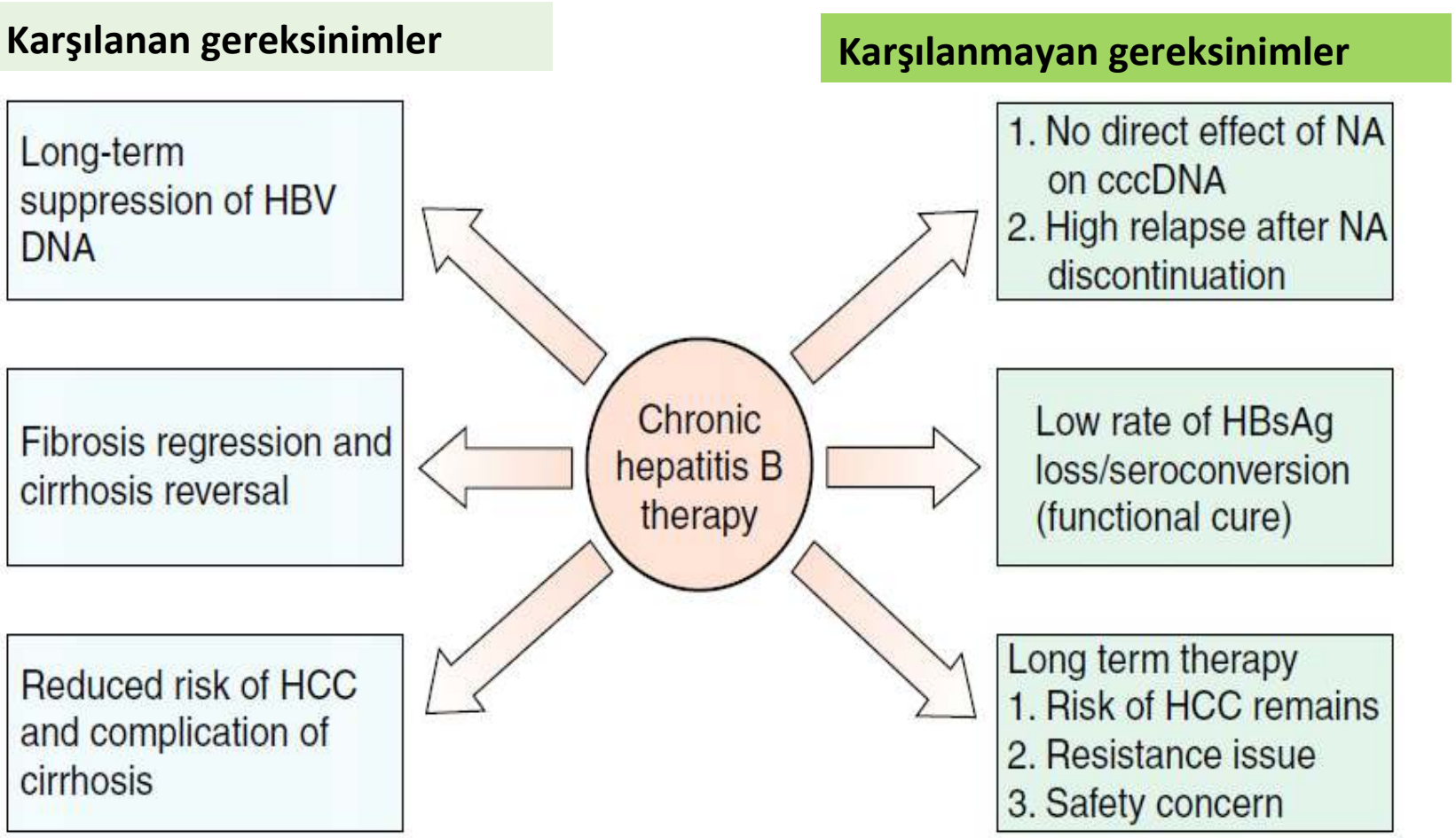
- Wong ve ark;
  - 117 hastada NA öncesi ve NA'dan bir yıl sonra KC biyopsisi yapıyor.
  - Karaciğer içi HBV DNA'da 4–7 log düşme görüyor.
- Fakat
  - qHBsAg ve cccDNA'da minimal düşüş görüyor
  - 117 hastanın ancak **5'inde** 1 yıl NA sonrası cccDNA saptanamıyor

British Medical Bulletin, 2015, 116:79–91

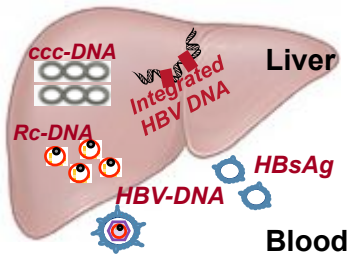
Neden yeni tedavilere ihtiyaç var?

- Klasik tedavilerle kür şansı çok düşük, ancak virüsu baskılayabiliyoruz
- Çoğunlukla yaşam boyu tedavi gerekiyor
- Tedaviyi kesmede ciddi sorunlar var, ciddi alevlenmeler olabiliyor
- Bazı ilaçlarda direnç sorunu var
- Tedavi altında bile HCC için rezidüel risk devam ediyor

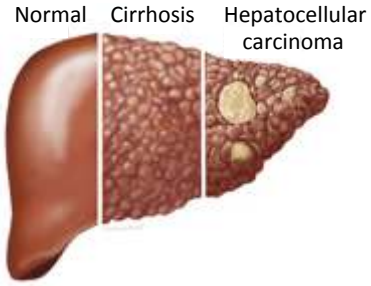
Kronik hepatit B tedavisiyle karşılanan ve karşılanmayan gereksinimler

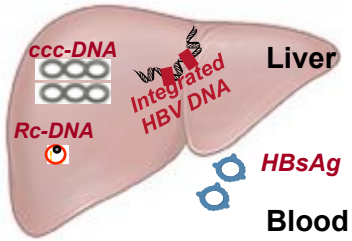


Viral baskılamadan küre doğru

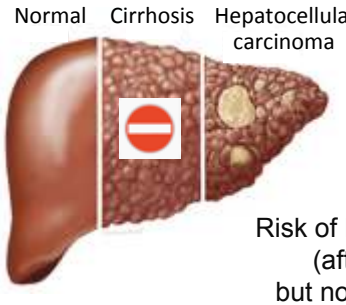


UNTREATED

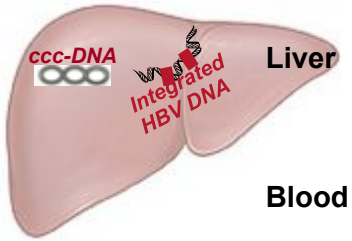


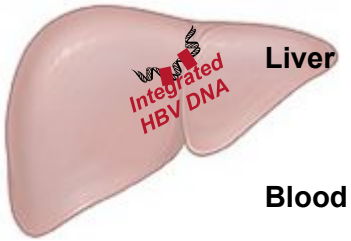


NUCs



Risk of HCC reduced
(after 5 yrs)
but not eliminated

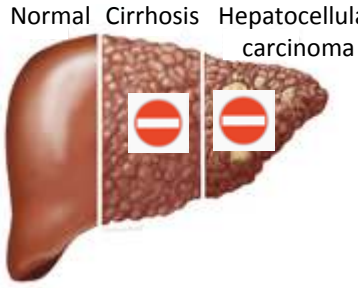




"cure"

Direct Antiviral Agents

Immunomodulatory strategies



Fonksiyonel kür ve komplet (virolojik kür) kavramı nedir?

Cure Definition	Blood				Liver
	ALT	Hepatitis B virus DNA	Hepatitis B surface antigen	Anti-HBs	Covalently closed circular DNA[a]
Functional cure	Normal	Undetectable (quantitative PCR)	Undetectable	Detected	Present
Virological (complete) cure	Normal	Undetectable (qualitative PCR)	Undetectable	Detected	Undetectable

Abbreviation: ALT, alanine aminotransferase; Anti-HBs, antibody to Hepatitis B surface antigen; PCR, polymerase chain reaction.

[a]As detected in the liver. These assays are not currently commercially available or standardized.

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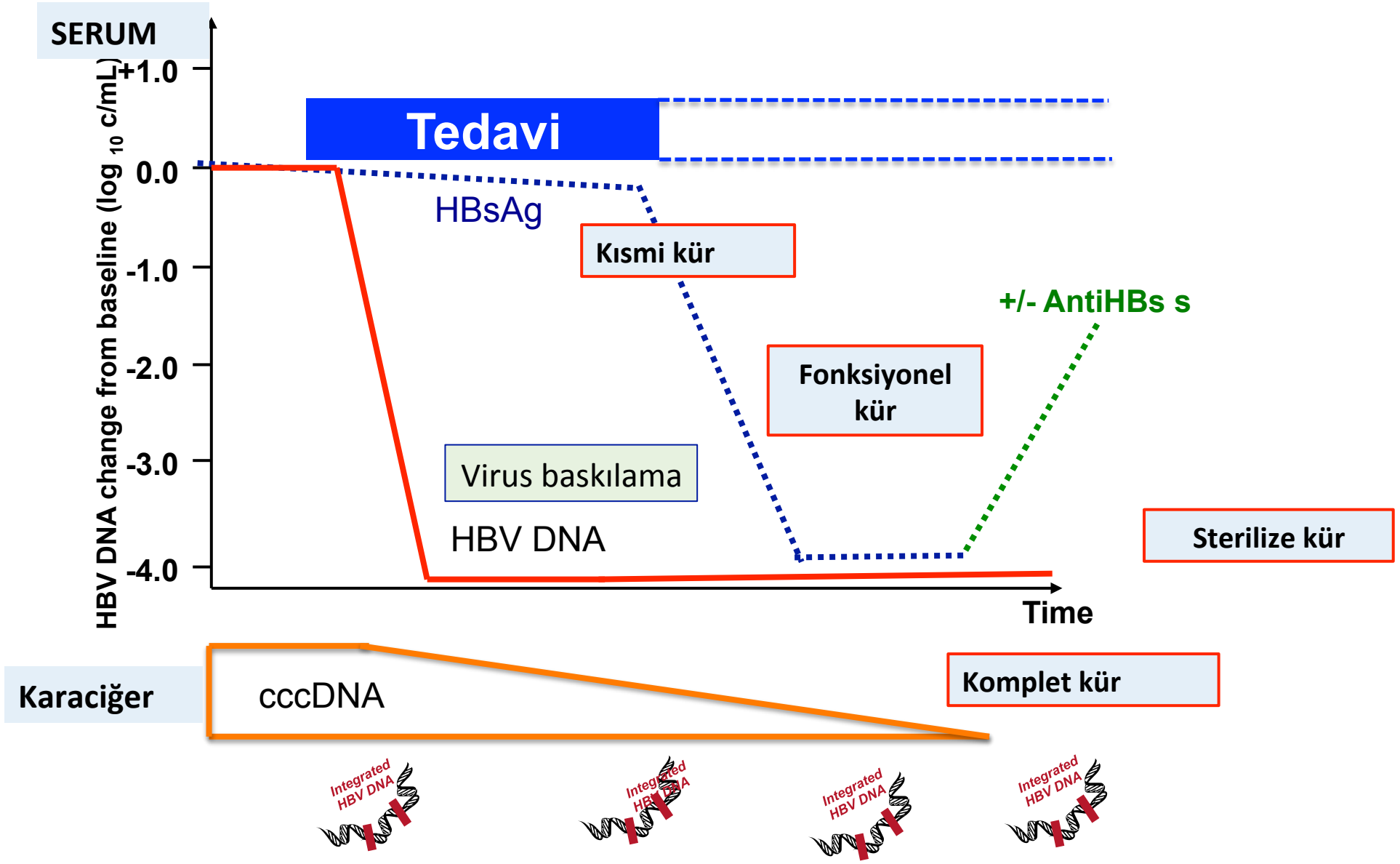
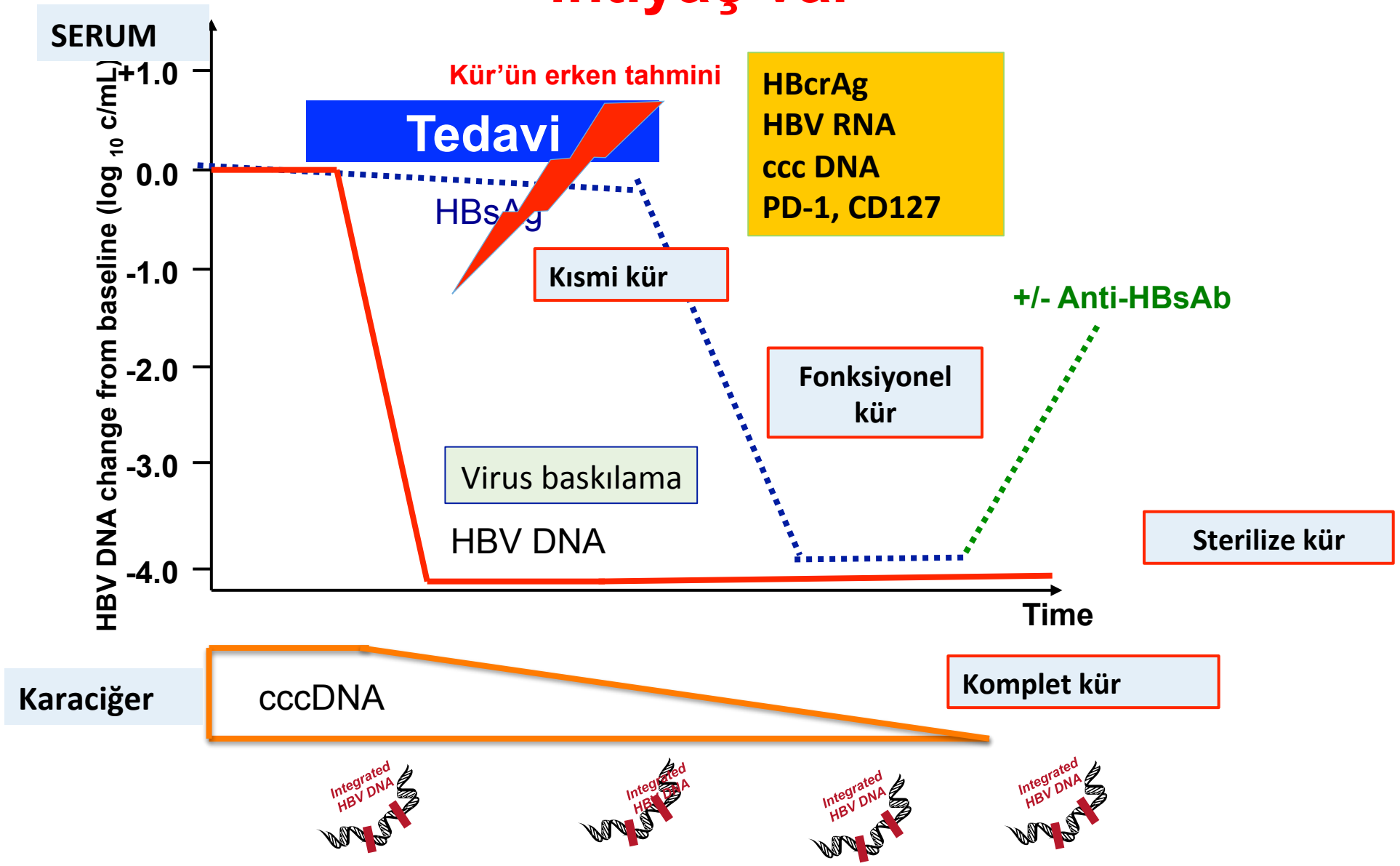
HBV'de kürün tanımı: Ne elde etmek istiyoruz?



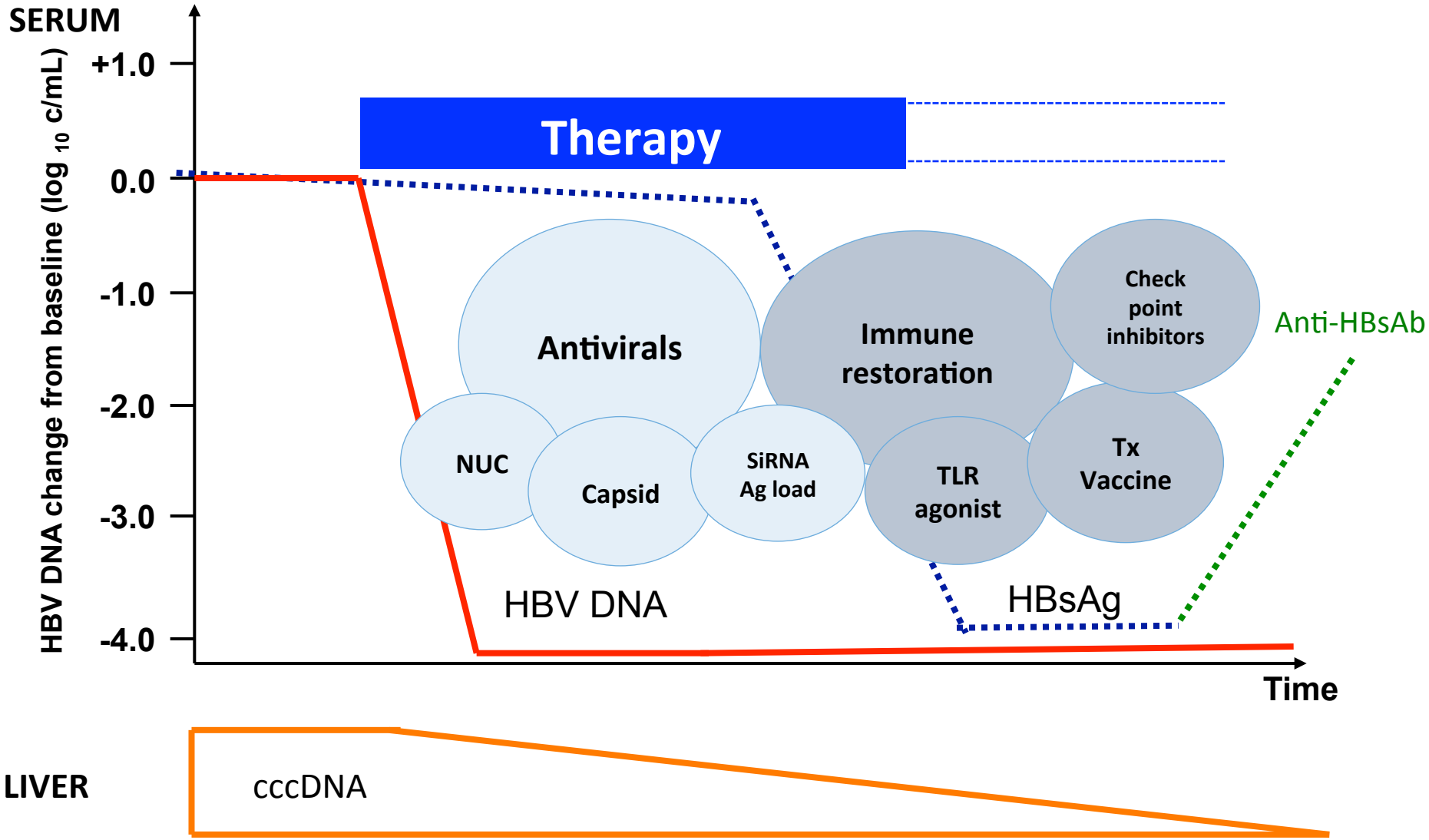
Lok et al, Hepatology / J Hepatol ; Testoni et al, Sem Liver Dis

Kürün erken tahmini için yeni göstergelere ihtiyaç var



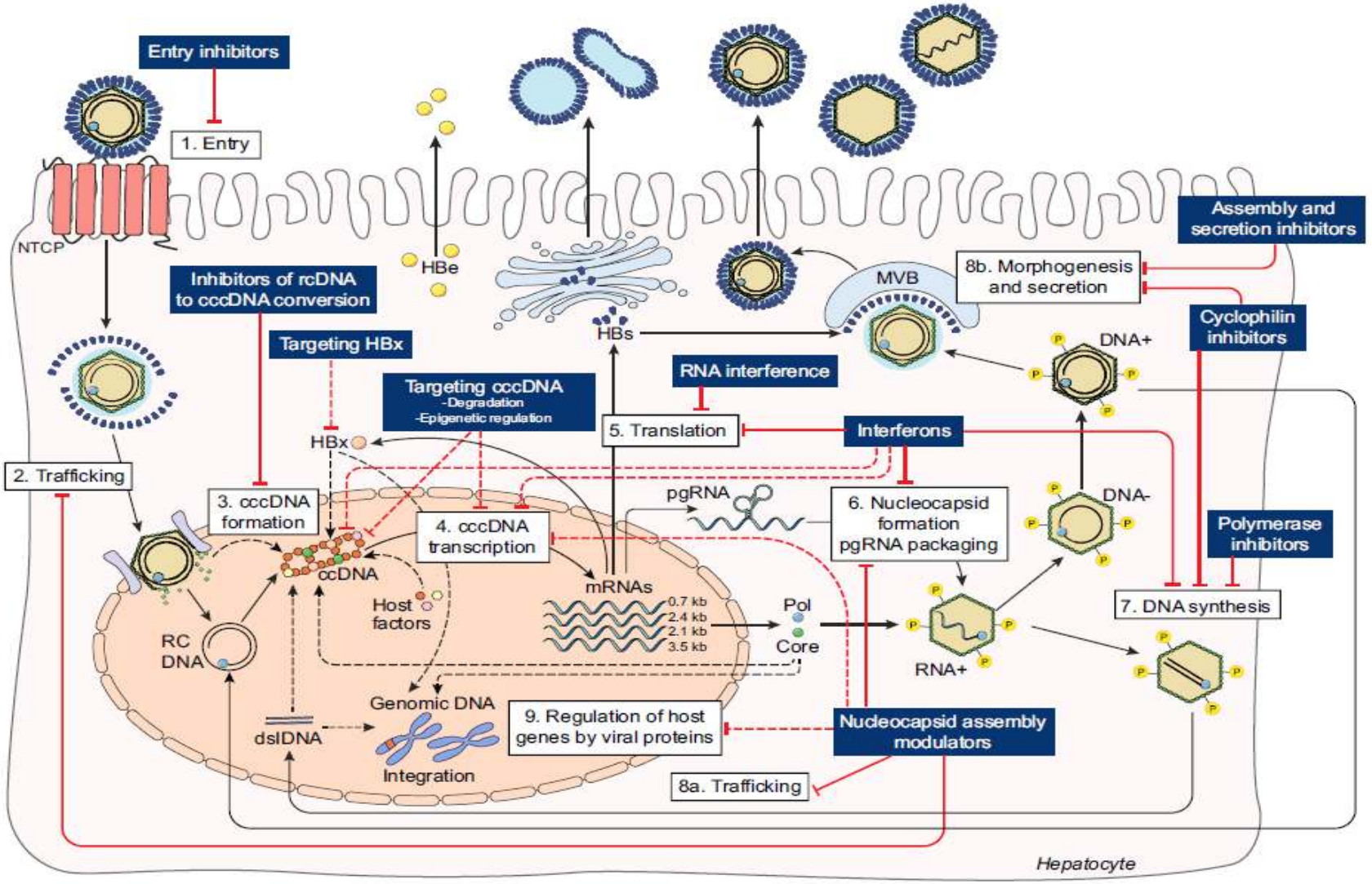
Lok et al, Hepatology / J Hepatol ; Testoni et al, Sem Liver Dis

HBV için kür- Yeni tedavi konseptleri– DAA ve immünmodülatör kombinasyonları?



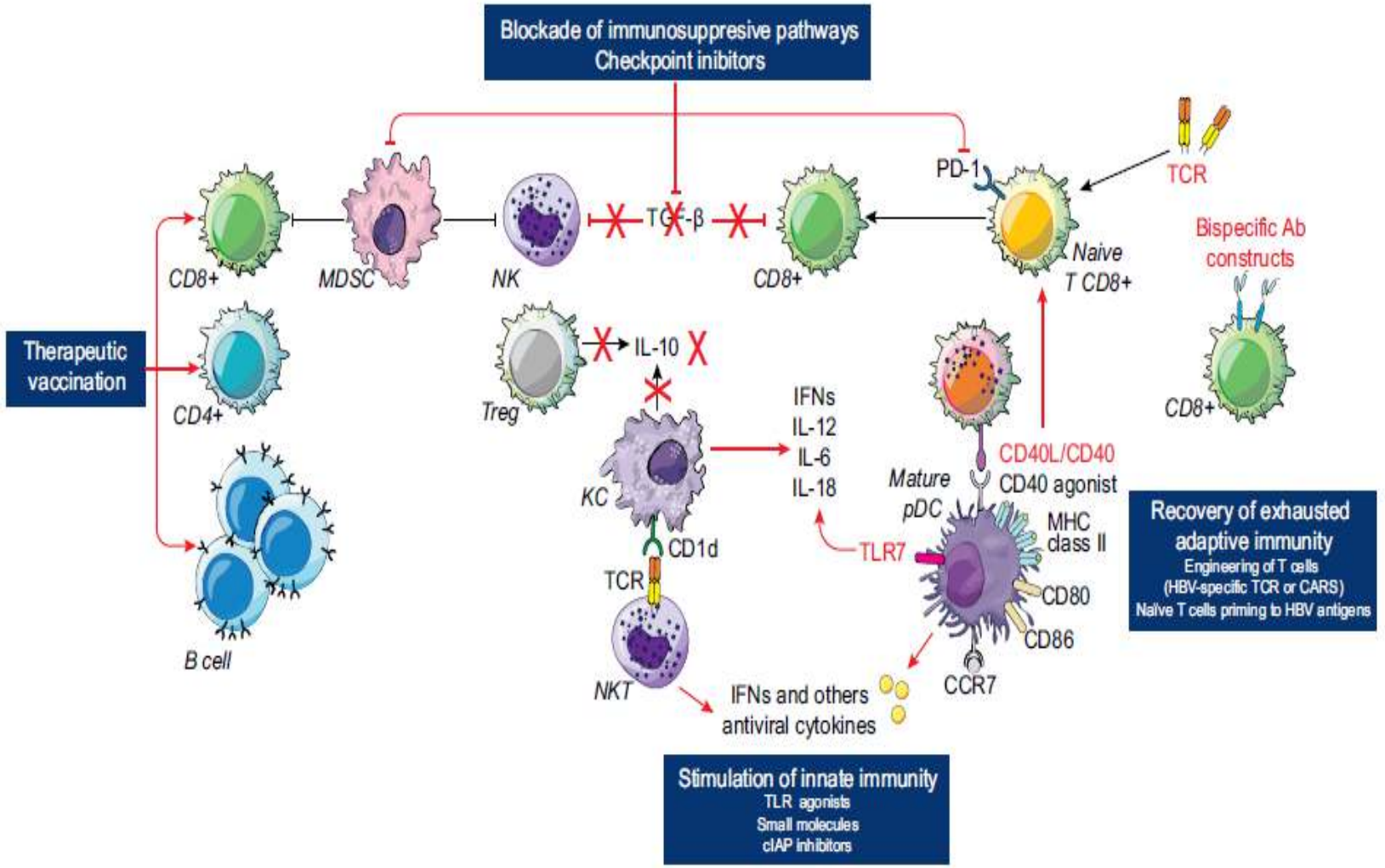
Testoni et al, Liver International 2017

HBV yaşam döngüsü ve antiviral hedefler



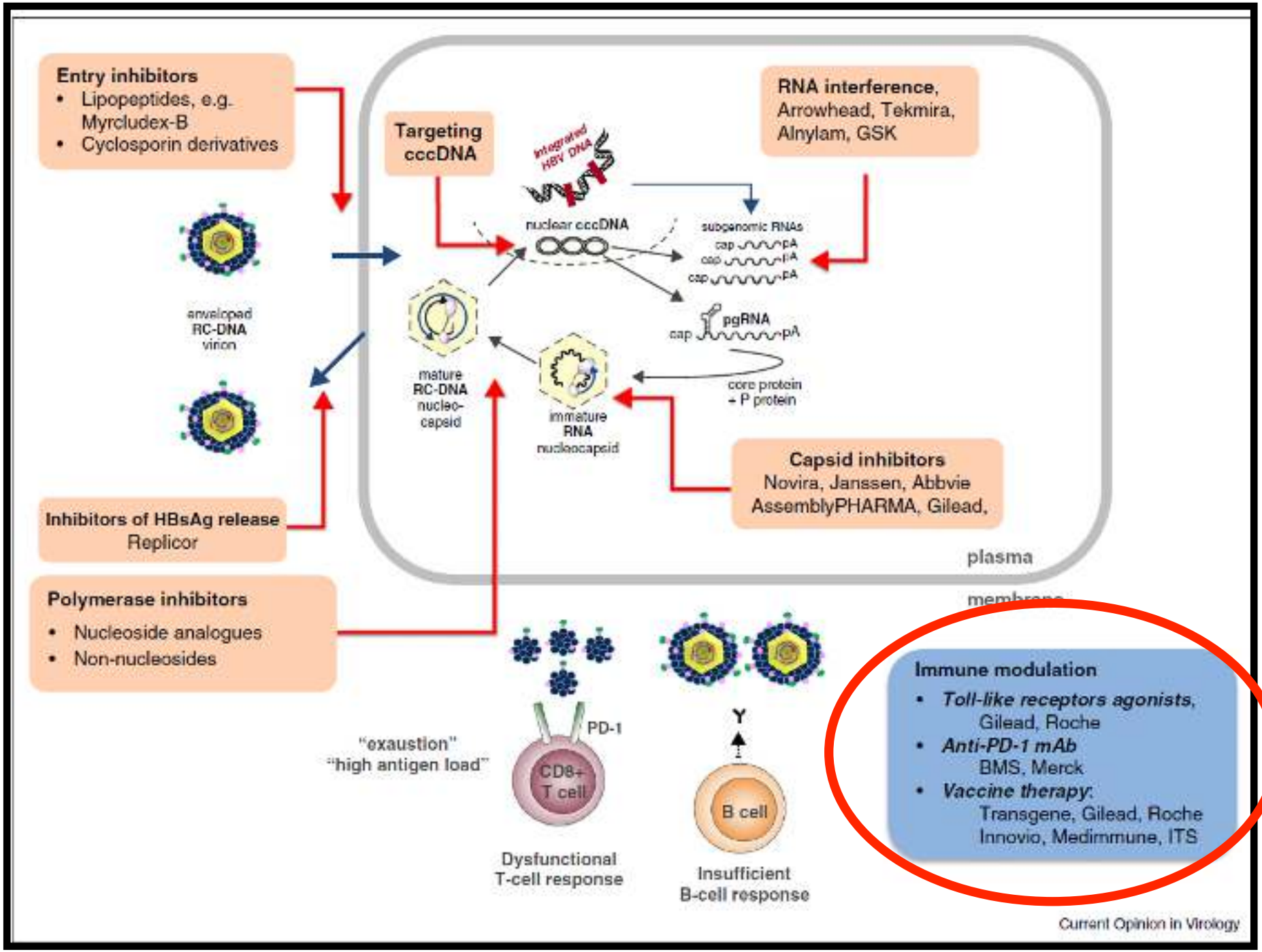
Journal of Hepatology 2017 vol. 67 j 847–861

Karaciğerin immün sistemi ve immünmodülatör hedefler



Journal of Hepatology 2017 vol. 67 j 847–861

TERAPÖTİK AŞI ADAYLARI


Entry inhibitors
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Targeting cccDNA
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integrated HBV DNA
nuclear cccDNA
subgenomic RNAs
cap pA
pgRNA
enveloped RC-DNA virion
mature RC-DNA nucleo-capsid
immature RNA nucleocapsid
core protein + P protein
Capsid inhibitors
Novira, Janssen, Abbvie AssemblyPHARMA, Gilead,
plasma membrane
Inhibitors of HBsAg release
Replicor
Polymerase inhibitors
• Nucleoside analogues
• Non-nucleosides
"exaustion"
"high antigen load"
PD-1
CD8+ T cell
B cell
Dysfunctional T-cell response
Insufficient B-cell response
Immune modulation
• Toll-like receptors agonists, Gilead, Roche
• Anti-PD-1 mAb BMS, Merck
• Vaccine therapy: Transgene, Gilead, Roche Innovio, Medimmune, ITS
Current Opinion in Virology

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Current Opinion in Virology

Therapeutic vaccination for chronic hepatitis B

Anna D Kosinska[1,2], Tanja Bauer[1,2] and Ulrike Protzer[1,2]

Current Opinion in Virology 2017, **23**:75–81

This review comes from a themed issue on **Preventive and therapeutic vaccines**

Edited by **Rino Rappuoli** and **Gerd Sutter**

For a complete overview see the Issue and the Editorial

Available online 25th April 2017

http://dx.doi.org/10.1016/j.coviro.2017.03.011

ELSEVIER

Therapeu

Anna D Ko

Ulrike Prot

Preclinical development of therapeutic hepatitis B vaccines

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gy

To overcome immune tolerance in chronic hepatitis B different approaches have been investigated using pre-clinical models. Hereby, a focus was on inducing effector T cell responses using DNA or peptide vaccines, vector- or cell-based vaccines. Multi-epitope therapeutic vaccine candidates that cover sufficient different HBV genotypes and most frequent HLA types have been developed.

ossMark

DNA veya POLİPEPTİD AŞILAR, VEKTÖR BAZLI AŞILAR İLE T HÜCRE YANITLARINI ARTIRMAK

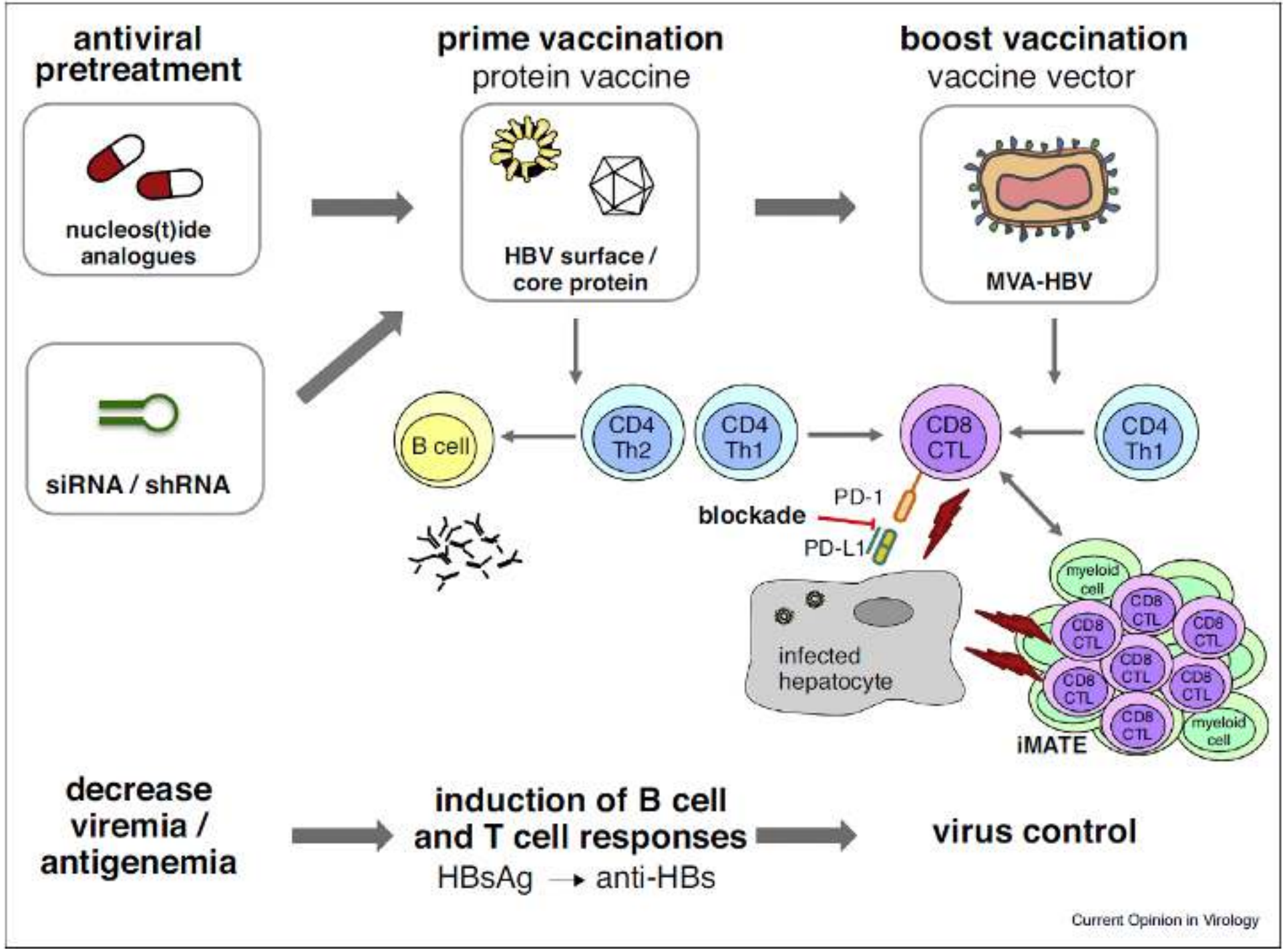

antiviral pretreatment
prime vaccination
protein vaccine
boost vaccination
vaccine vector
nucleos(t)ide analogues
siRNA / shRNA
HBV surface / core protein
MVA-HBV
B cell
CD4 Th2
CD4 Th1
CD8 CTL
CD4 Th1
PD-1
blockade
PD-L1
infected hepatocyte
myeloid cell
CD8 CTL
iMATE
decrease viremia / antigenemia
induction of B cell and T cell responses
HBsAg → anti-HBs
virus control
Current Opinion in Virology

Table 1

Therapeutic hepatitis B candidate vaccines currently in clinical trials

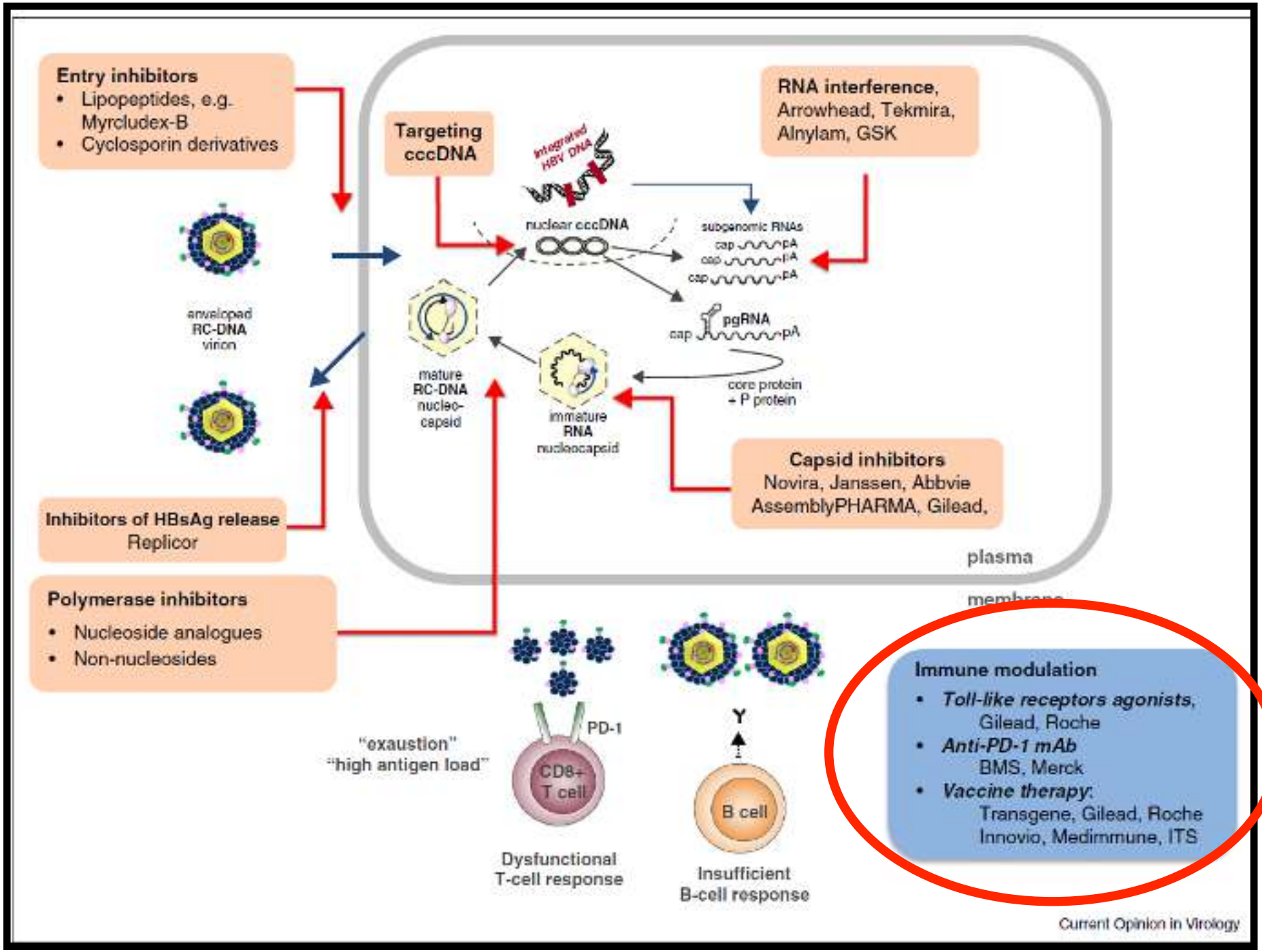
Vaccine name	Vaccine type/composition	Results available[a]	Sponsor	Clinical stage	Reference
HB-110	DNA vaccine	Completed; results not reported	Genexine	Phase I	NCT01813487 NCT01641536 NCT00513968
HepTcell™	FP-02.2 vaccine; IC31® adjuvant	Recruiting	Altimmune, Inc.	Phase I	NCT02496897
pDPSC18	DNA vaccine administered by particle mediated epidermal delivery	Completed; results not reported	PowderMed	Phase I	NCT00277576
INO-1800	Multi antigen (S, core) DNA vaccine:	Recruiting	Inovio		pharmaceuticals
Phase I	NCT02431312				
TG1050	Non-replicative adenoviral vector encoding HBV core, polymerase, surface fusion protein	Recruiting	Transgene	Phase I	NCT02428400
Theravax (DV-601)	Protein (s, core) vaccine, Iscomatrix	Well tolerated; anti-viral response observed in all patients	Dynvax Technologies Corporation	Phase Ib	NCT01023230
pSG2.HBs/MVA.HBs	Protein prime/viral vector boost; HBs	Well tolerated but did not control HBV infection	Oxxon Therapeutics	Phase IIa	ISRCTN67270384
HB02 VAC-ADN	pCMV-S2.S DNA (pre-S/S) vaccine	Well tolerated; no change in relapse rate in HBV-treated patients or decrease of virological breakthrough	ANRS	Phase I/II	NCT00536627
CVI-HBV-002	DNA (S) vaccine	Recruiting	CHA Vaccine Institute Co., Ltd.	Phase I/II	NCT02693652
HPDCs-T immune therapy	HBsAg activated dendritic cells	Recruiting	Sun Yat-Sen University	Phase I/II	NCT01935635
GS-4774	Fusion protein (S, core, X) vaccine; Tarmogen T cell immunity stimulator	Phase 2 of naïve group ongoing; no significant viral decrease in treatment-experienced patients	Gilead	Phase II	NCT01943799 NCT01779505 NCT02174276
εPA-44	Multi-peptide vaccine	Recruitment status unknown	Chongqing Jiachen Biotechnology Ltd.	Phase II	NCT01326546
ABX 203	Protein (S, core) vaccine	Ongoing	ABIVAX S.A.	Multicenter Phase II/III Trials	NCT02249988

Terapötik hepatit B aşıları, henüz faz çalışmalarının başlangıcında klinik başarıları henüz düşük olsa da yakın gelecekte ilgi odağı olmaya devam edecek gibi görünüyor kombinasyonlar ile kür sağlanabilir.

Conclusion/outlook

Therapeutic hepatitis B vaccination currently receives a lot of attention although clinical success is still lacking. More efficient vaccination schemes, the combination with checkpoint inhibitors and emerging approaches to lower circulating antigen levels that contribute to immune tolerance in chronic HBV infection will yield very interesting results to finally improve clinical efficacy.

İMMÜN MODÜLASYON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• Vaccine therapy: Transgene, Gilead, Roche Innovio, Medimmune, ITS
Current Opinion in Virology

Gut Online First, published on February 10, 2015 as 10.1136/gutjnl-2014-308943

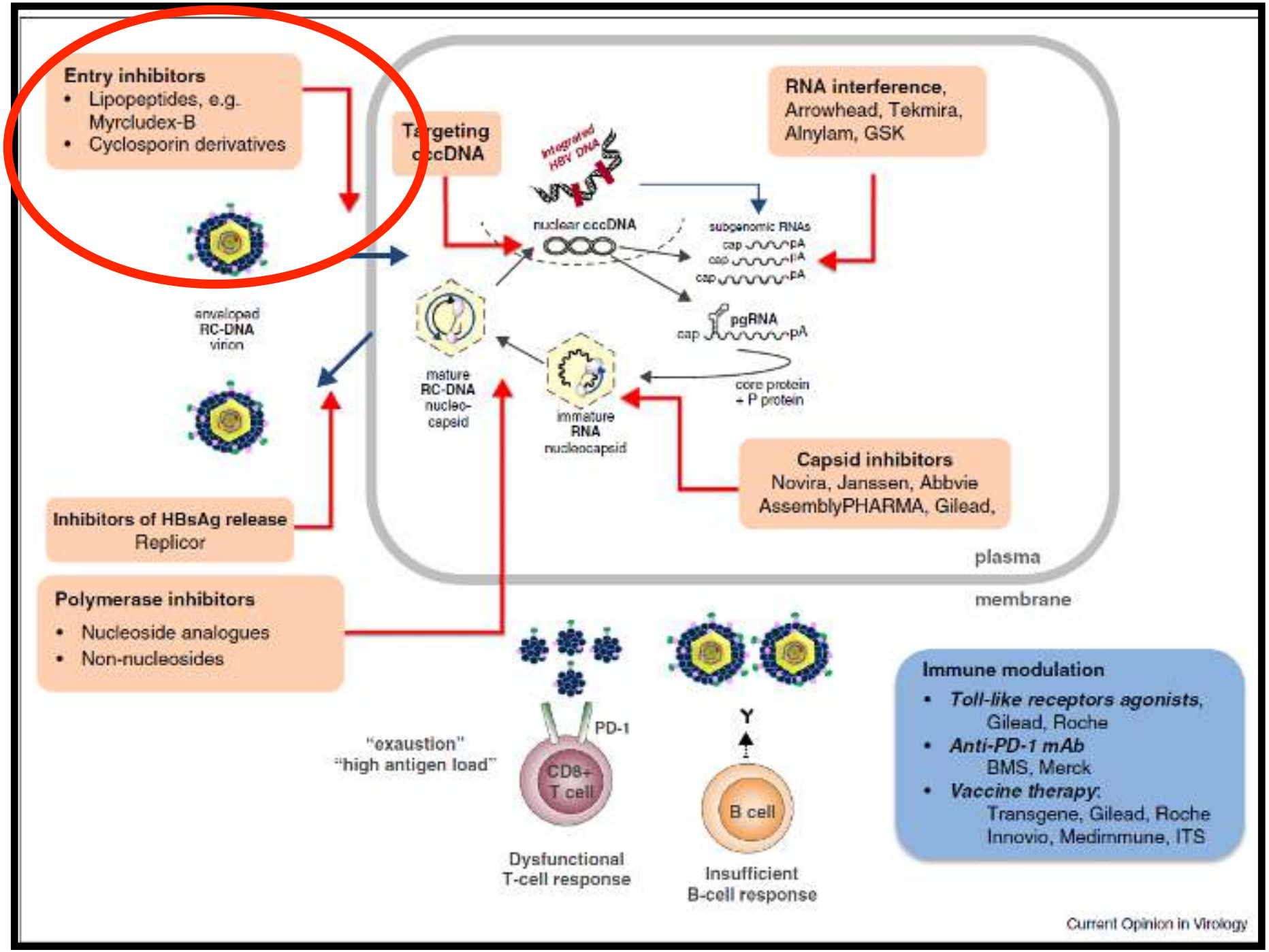
HBV-spesifik CD8 T hücresi yanıtını artırmak, IL-2 artırmak ve CD4 T hücresi artırmak karaciğerde Treg ve interlökin 10 sekrete eden T hücresini arttırmak

Fabien Zoulim

of non-HBV-specific T cells in the liver. Chronic HBV infection is characterised by (i) a low frequency of HBV-specific CD8+ T cell responses that have an exhausted phenotype characterised by overexpression of PD-1, CTLA-4, CD244, Tim3, and so on; (ii) an impaired production of interleukin (IL)-2 and impaired proliferation of CD4+ T cells and (iii) an increase in the number of Treg in the liver and in the number of IL-10-secreting T cells.[96]

	phosphorothioate oligonucleotides	HBV-Ag in phase II	
Innate immune responses	LTβR agonists	Preclinical	153
	TLR7 agonists	Phase II	NCT02166047
	thymosin α1	Phase IV	NCT00291616
	Nitazoxanide	Phase I	156, 157
	interleukin-7	Phase I/II	NCT01027065
	IFN-λ	Phase II	NCT01204762
Adaptive immune responses	PD1 blockade	Phase I/II for HCC	NCT01658878
			172, 173
	X-S-Core proteins (antigen-based vaccine)	GS-4774 in phase II,	159, 160
	HBV DNA (DNA-based vaccine)	DV-601 in phase I	
		DNA vaccine pCMVS2.S	NCT00536627
		in phase I/II	161, 162, 164

GİRİŞ İNHİBİTÖRLERİ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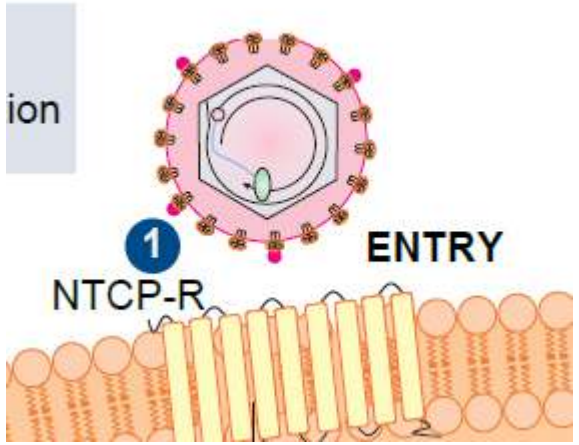
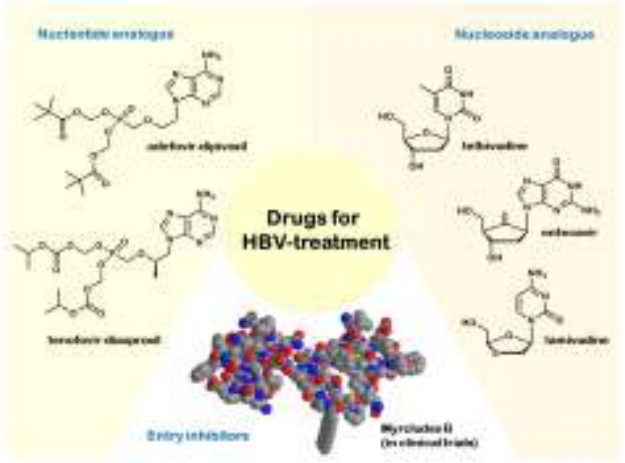


NTCP (Sodyum tauro kolat) inhibitörleri

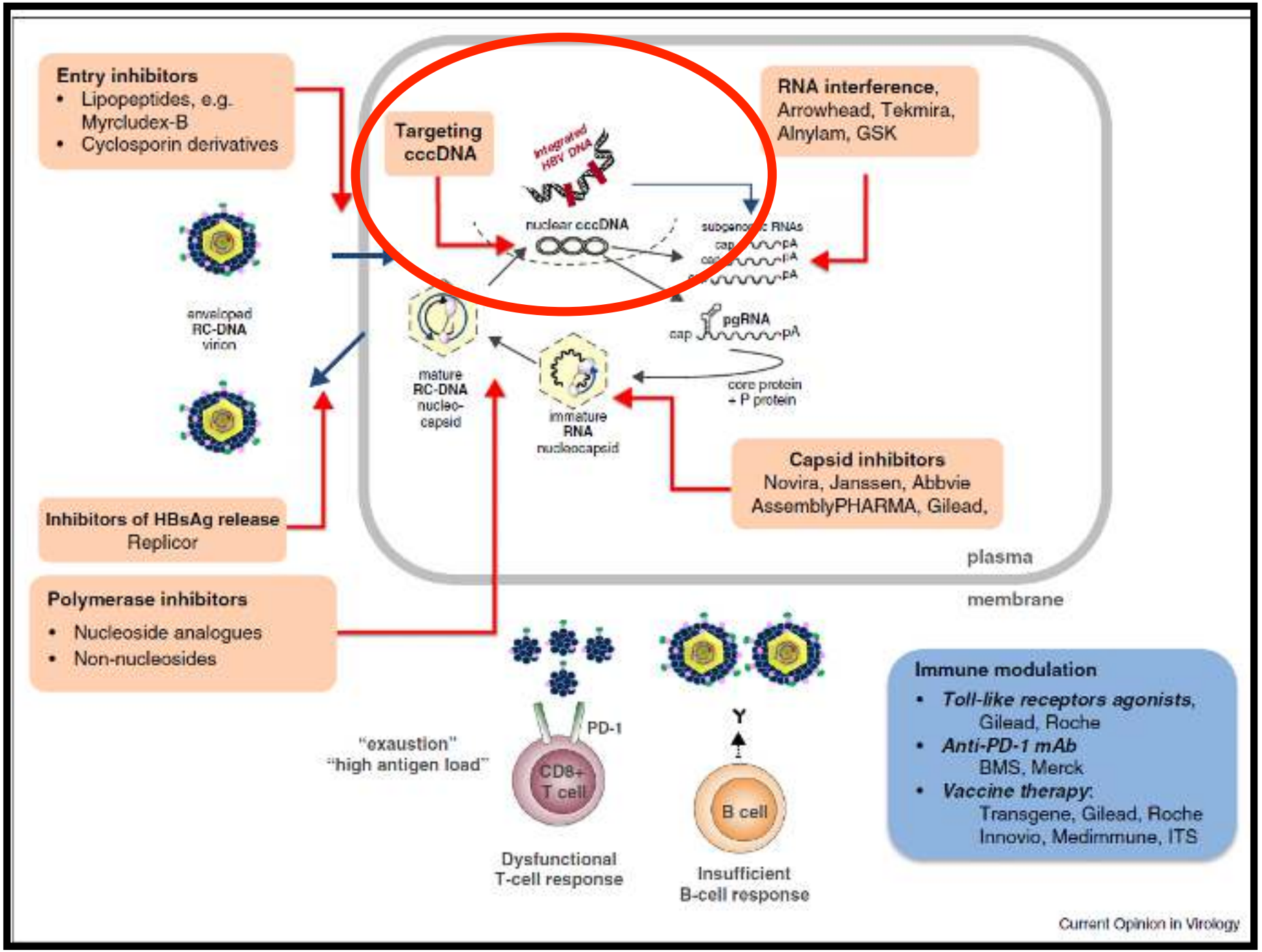
- Siklosporin A
- Myrcludex B
- Diğer: Ezetimibe, Konjuge safra tuzları



MYRCLUDEX: Miristile edilmiş Pre S1 peptid. NTCP'ye bağlanmada HBV ile yarışır

Study	Description	Results
MYR 101 Phase 1a Germany	Safety study in healthy volunteers (36 patients)	Excellent safety and tolerability
MYR 102 Phase 1 Germany	Drug interaction study in healthy volunteers (12 patients)	No interaction detected
MYR 201 Phase 1b/2a Russia NCT02881008	Study in Hepatitis B patients (40 patients)	HBV DNA decline ALT normalization
MYR 201 (HDV substudy) Phase 1b/2a Russia NCT02637999	Study in Hepatitis D patients (16 patients plus comparison arm)	HDV RNA decline or negativation ALT decrease
MYR 202 Phase 2 Germany, Russia	Study in Hepatitis D patients, on top of tenofovir (TDF) vs TDF (120 patients)	HDV RNA decline or negativation in all dose groups ALT decrease Liver stiffness improvement
MYR 203 Phase 2 Russia (ongoing)	Study in Hepatitis D patients, on top of peg-Interferon (INF) vs INF	Study in progress

CCC-DNA'YI HEDEF ALAN MOLEKÜLLER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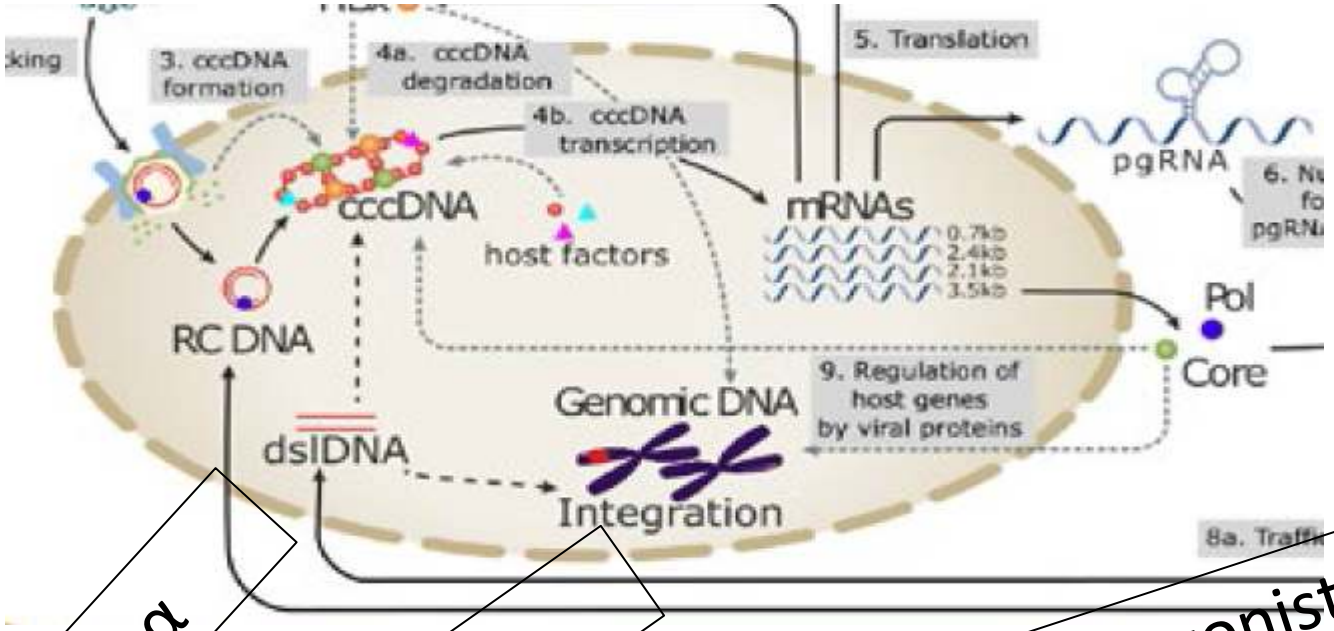
Current Opinion in Virology



İNTERFERON-α

IFN-γ ve TNF-α

lympotoxin-b reseptor agonistleri

ccc-DNA havuzunu kırmak çok zor
Ancak degradasyon ile ortadan kaldırılabilir

nükleer cytidine deaminazlar APOBEC3A ve APOBEC3B

Moleküler makaslar

Virus Research xxx (xxxx) xxx–xxx

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Virus Research

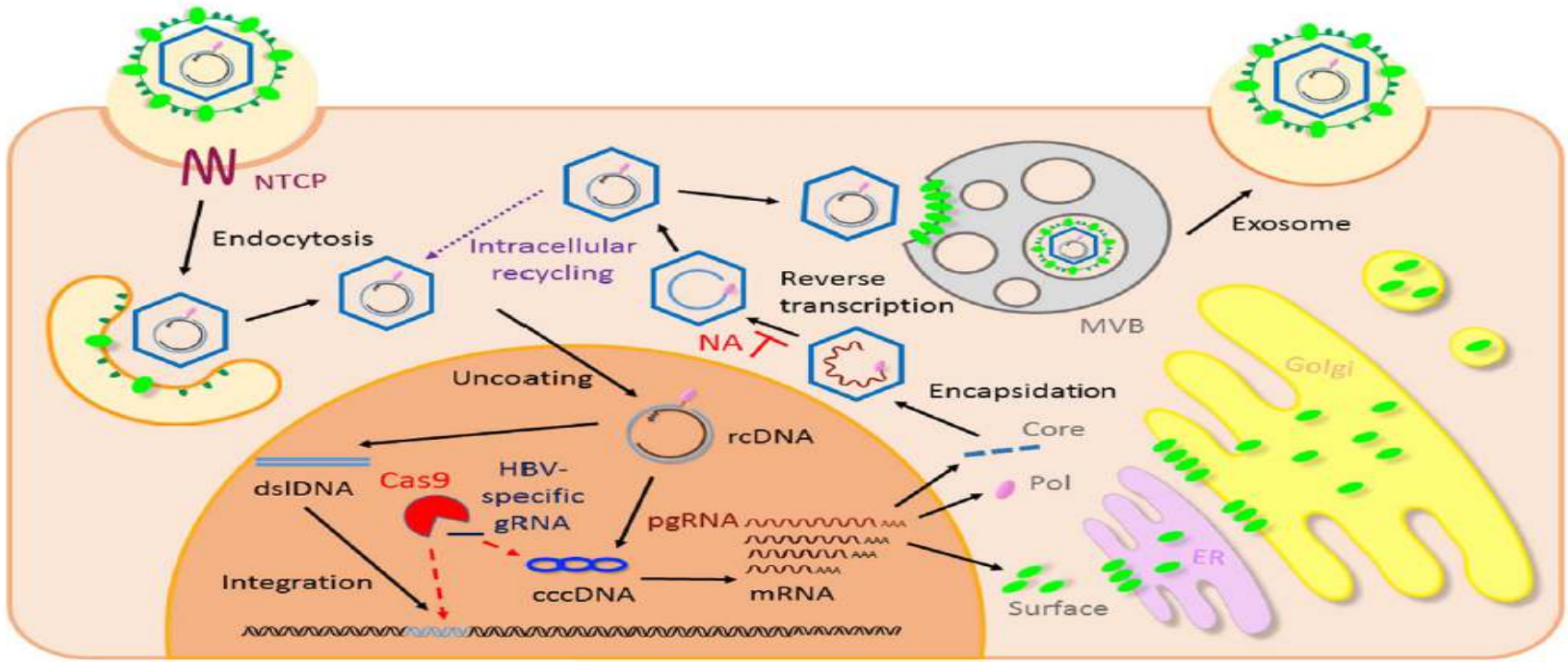
journal homepage: www.elsevier.com/locate/virusres

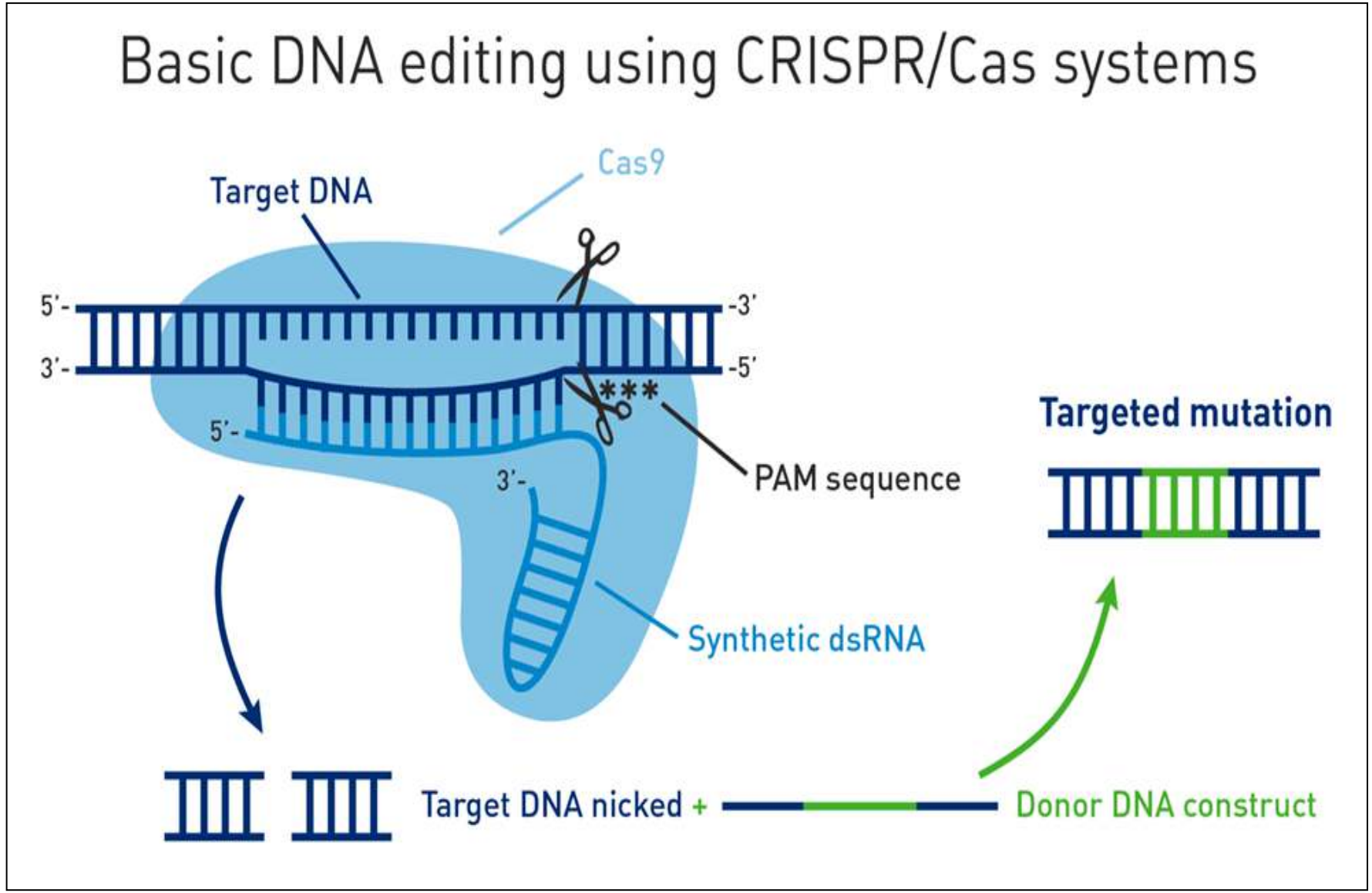
Review

The potential and challenges of CRISPR-Cas in eradication of hepatitis B virus covalently closed circular DNA

Hung-Chih Yang[a,b,c], Pei-Jer Chen[b,c,d,e,*]

[a] Department of Microbiology, National Taiwan University College of Medicine and National Taiwan University Hospital, Taipei, Taiwan
[b] Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine and National Taiwan University Hospital, Taipei, Taiwan



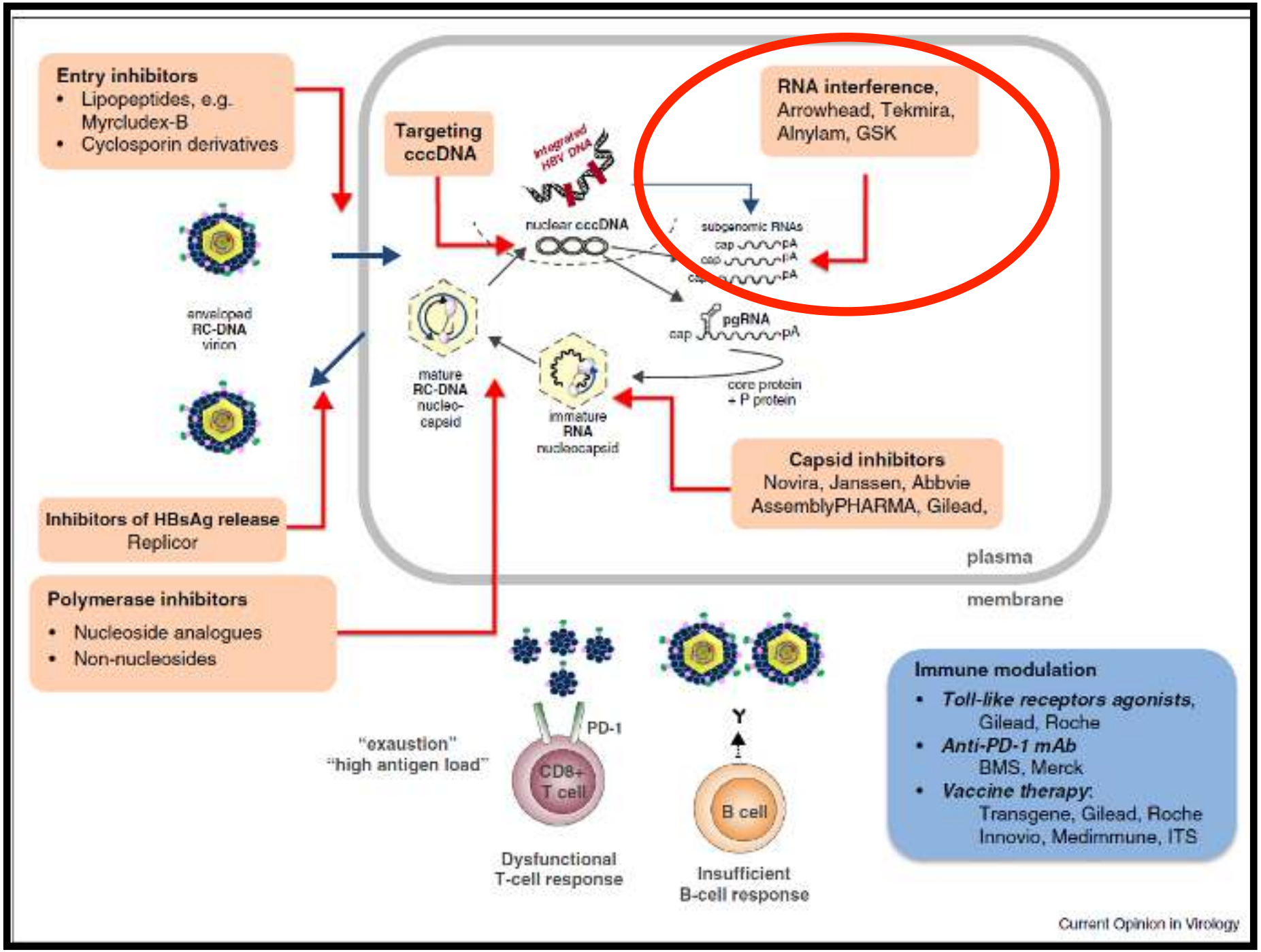

Basic DNA editing using CRISPR/Cas systems
Cas9
Target DNA
5'-
-3'
3'-
-5'
***
5'-
3'-
PAM sequence
Targeted mutation
Synthetic dsRNA
Target DNA nicked +
Donor DNA construct

Recent development of the CRISPR/Cas9 system has dramatically changed the landscape of the genome-editing technologies. The simplicity and flexibility of CRISPR/Cas systems have facilitated the progress of this novel technology and attracted wide interest. Specific cleavage of HBV genomes by CRISPR/Cas9 is considered a promising strategy to eliminate persistent HBV cccDNAs. Therefore, combined with NAs and CRISPR/Cas9 appears to be a potential strategy to cure chronic hepatitis B. However, a reliable and quantifiable *in vitro* culture system that can generate authentic HBV cccDNAs is currently lacking and required to explore the efficacy of CRISPR/Cas. Ideally, elimination of HBV cccDNA by CRISPR/Cas should be convincingly demonstrated in a clinically relevant *in vivo* models. Moreover, as discussed above, the CRISPR/Cas9 system encounters several challenges for its clinical application, namely off-target effects, *in vivo* delivery efficacy, and damage of host chromosomes by cleaving HBV integrants. Finding solu-

- **Persistan seyreden ccc-DNA yı elimine etmek**
- **Nükleozit analoglarıyla kombinasyonu kür sağlamada etkili olabilir**
- **In vivo modellere ihtiyaç var**
- **Tabi ki konak kromozomlarına da zarar verebilir**

5

RNA İNTERFERANSI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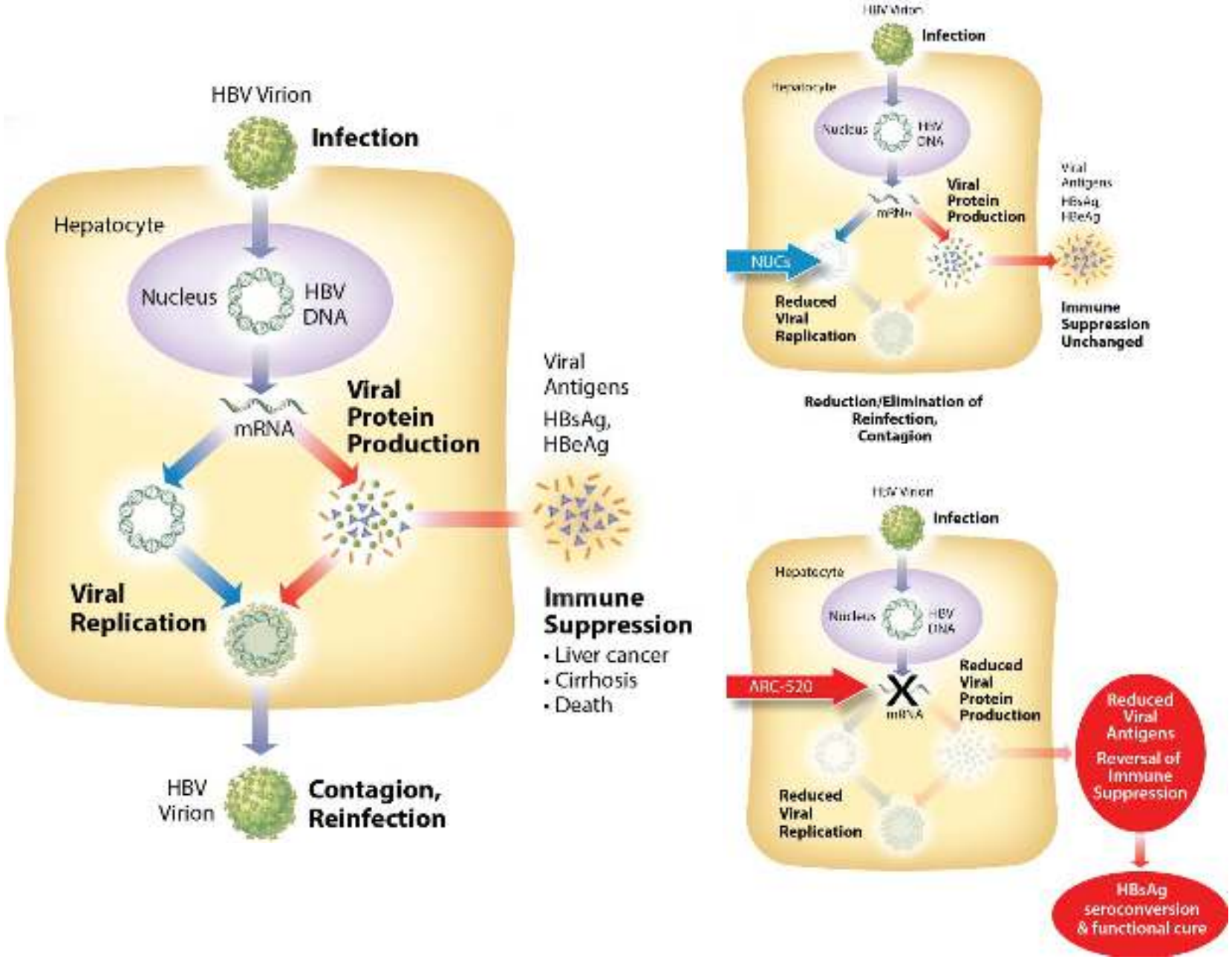
Current Opinion in Virology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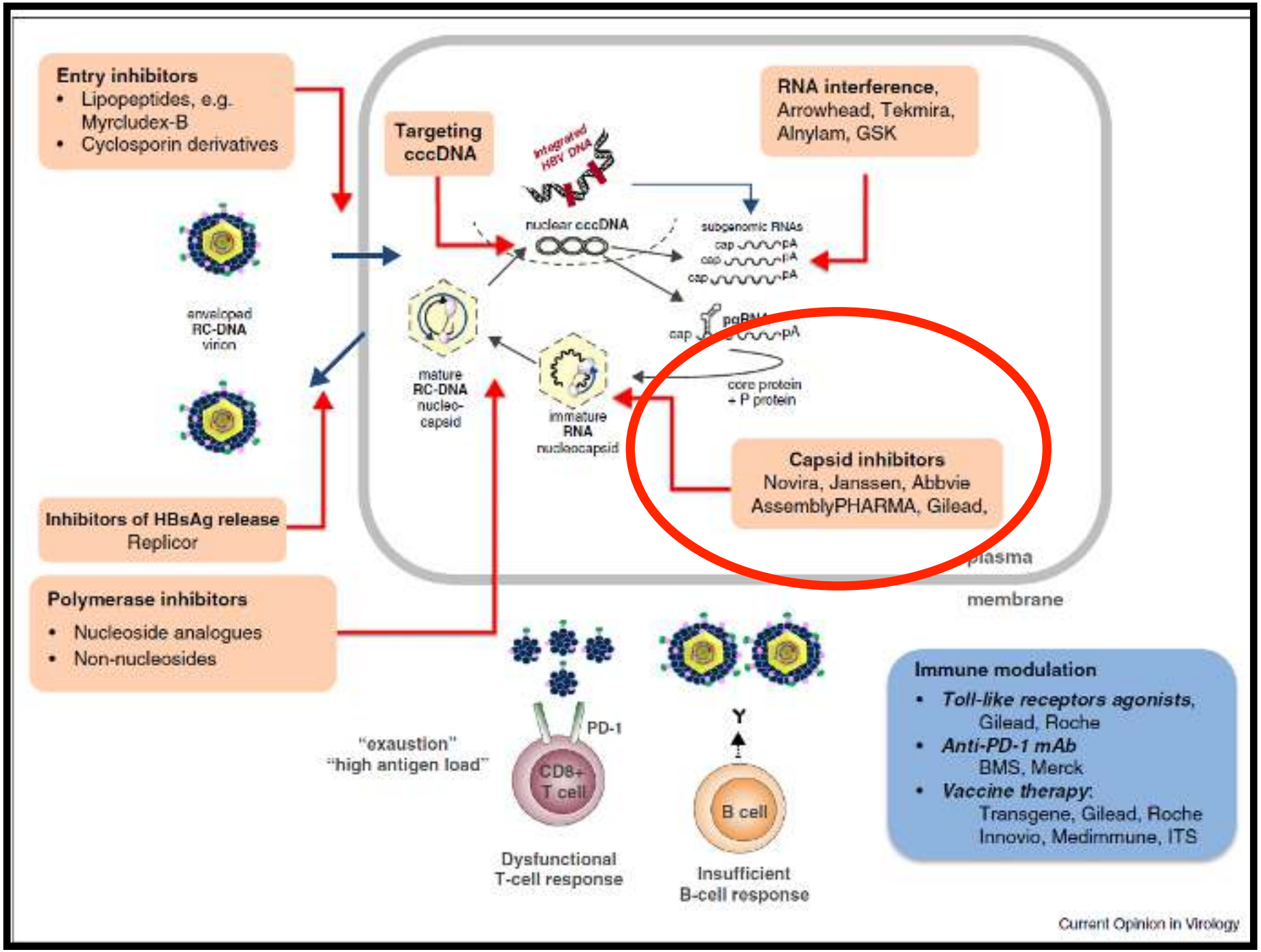
Reduced Viral Replication
Reduced Viral Antigens
Reversal of Immune Suppression
HBsAg seroconversion & functional cure

Viral RNAs	siRNA: ARC-520/ARC-521	Arrowhead	Phase 2
Viral RNAs	siRNA: ARB-1467	Arbutus Biopharma	Phase 2
Viral RNAs	siRNA: ALN-HBV	Alnylam	Phase 1/2
Viral RNAs	siRNA: ISIS-HBV_{Rx}	ISIS pharmaceuticals	Phase 1 or 2 (?)

Yaklaşık 20 molekülden 4 tanesi klinik çalışmaya aday olmuş

KAPSİT İNHİBİTÖRLERİ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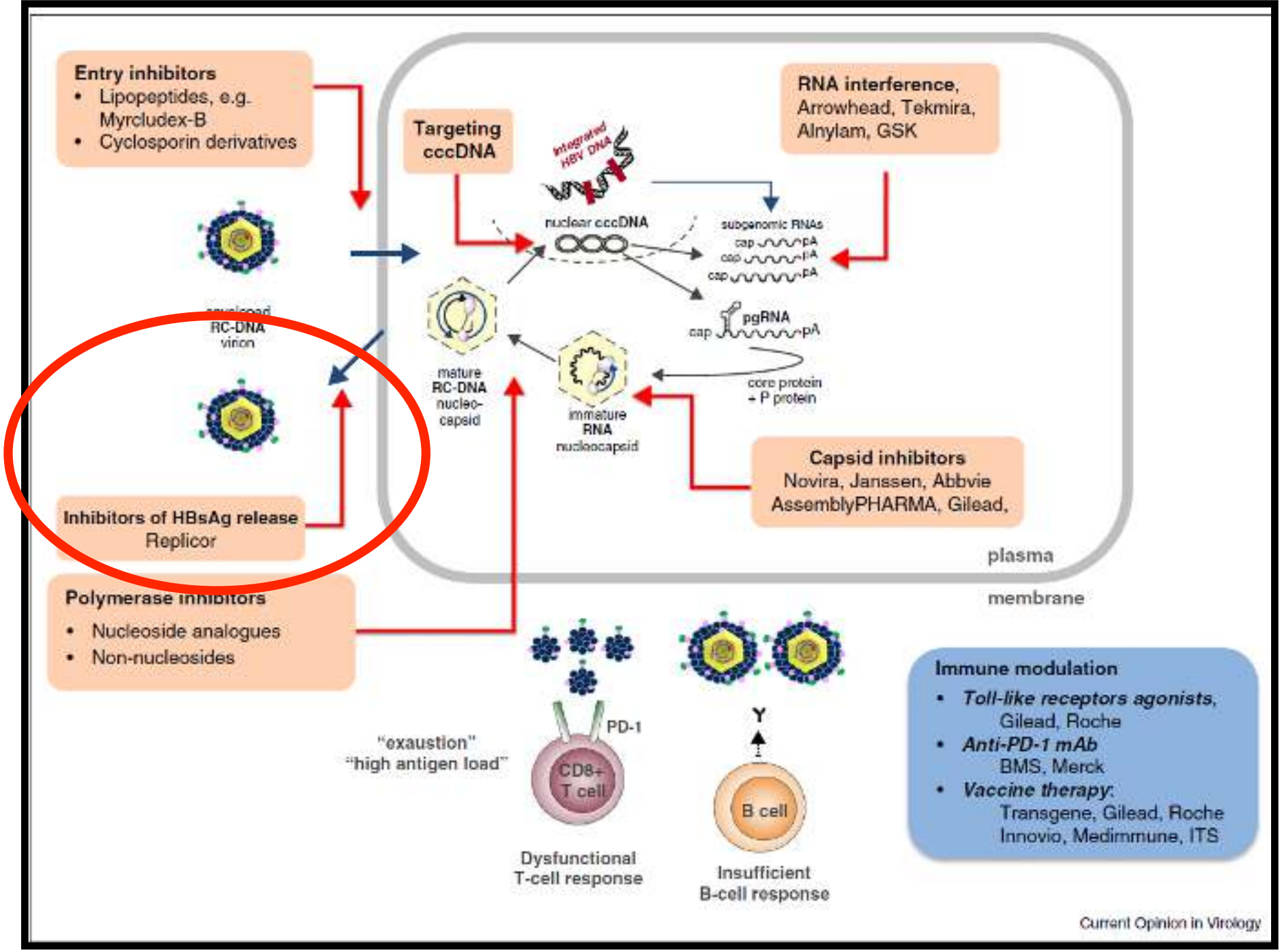
Capsid assembly modulators (CAMs)
Heteroaril dihidropirimidinler (HAPs) gibi nükleokapsit inhibitörleri çalışılmaktadır. Bunlardan ilk sınıf olan HBV CAM 73 HBeAg pozitif hastada çalışılmış

Core inhibitors have been described by multiple names, including capsid assembly modulators (CAMs),core protein allosteric modifiers (Assembly Biosciences), and nucleocapsid inhibitors such as heteroaryldihydropyrimidines (HAPs). AL-3778 (Alios/Johnson & Johnson) is an orally administered, first-in-class HBV CAM whose efficacy in 73 HBeAg-positive CHB patients was reported at the 2017 meeting of the Asian Pacific Association for the Study of the Liver.24 The investigators reported dose-related reductions in the levels of serum HBV DNA and serum HBV RNA, with additive reductions when combined with pegIFN, but without reduction in HBsAg levels. AL-3778 is a small molecule and direct-acting antiviral agent acting through aberrant core protein processing, thereby resulting in capsid misassembly and subsequent inhibition of HBV DNA replication. HAPs are nucleocapsid inhibitors that bind to core particles to reduce both HBV DNA and HBcAg levels, the latter via degradation by the proteasome pathway. Morphothiadine mesilate (GLS4, HEC) is another HAP nucleocapsid compound and triggers aberrant core particle assembly in vitro in Hep AD38 cells; phase 1/2 trials have been initiated in China

HBsAg SALINIM İNHİBİTÖRLERİ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Current Opinion in Virology

- Düşük olgu sayısına sahip faz 2 çalışmasında interferon ya da tenofovirle kombine edildiklerinde 3-4 kat daha fazla DNA düşmesini sağlıyorlar
- Tek başlarına kullanımları pek mümkün görünmüyor
- Çalışması devam eden 2 molekül mevcut

SON: ÖZET

Strategy		Candidate	Clinical development phase
Entry inhibitors			
1	Entry inhibitors	Myrcludex-B	Phase 2
Direct antiviral agents			
2	cccDNA inhibitors		
	Elimination	LT-βR agonist	Preclinical
		Zinc finger nucleases	Preclinical
		TALENs	Preclinical
		CRISPR-Cas9	Preclinical
3	Silencing	Epi-drugs	Preclinical
4	Capsid inhibitors	NVR 3-778	Phase 1/2
		HAPs	Phase 1
		Phenylpropenamide	Preclinical
5	HBV polymerase inhibitors	Tenofovir alafenamide	Phase 3
6	HBV RNA interference	ARC-520	Phase 2
		TKM-HBV	Phase 1
		ALN-HBV	Preclinical
7	HBsAg release inhibitors	REP-9AC'	Phase 2
		REP-2139-Ca	
Host targeting agents			
8	TLR agonist	GS-9620 (TLR7)	Phase 2
	Anti-PD-1	Nivolumab	Preclinical
		Pembrolizumab	Preclinical
	Therapeutic vaccine	ABX302	Phase 2b/3
		GS-4774 (tarmogen)	Phase 2
		INO-1800	Phase 1
		TS1050	Phase 1

- GELECEKTE YAPILACAK **KOMBİNASYONLARLA** KÜR ORANLARININ ARTACAĞI ÖNGÖRÜLMEKTE

- AŞI İLE ÖNLENEBİLEN BİR HASTALIK OLDUĞU İÇİN ŞANSLIYIZ

TEŞEKKÜRLER

Tutunma

Siklosporin A ve B

- HepaRG hücre sisteminde HBV girişini bloke ettiği,
- Siklosporin B>A

Myrcludex-B

- Sentetik lipopeptid L-HBsAg preS1 domain ligandı,

Oxysteroller

- Oksidize kolesterol türevleri,

Bu ilaçlar giriş yerinde HBV'yi bloke ederek yeni hepatositlerin infekte olmasını önlerler,

Ancak cccDNA içeren infekte hepatositler üzerinde etkinlikleri yoktur…

Giriş ve soyunma

Ezetimibe

- FDA onaylı kolesterol ilacı,
- Hepatik kolesterol alımı ve lipid transportuyla etkileşir

- HepaRG hücre modellerinde intrahepatik cccDNA oluşumunu inhibe ettiği ve viral protein ekspresyonunu azalttığı

Translasyon

- HBV mRNA’larını hedef alan komplementer **“siRNAs”**

- Bu yöntemle HBsAg sentezinin sonlandırılması immün toleransın aşılmasına da yardımcı olabilir.

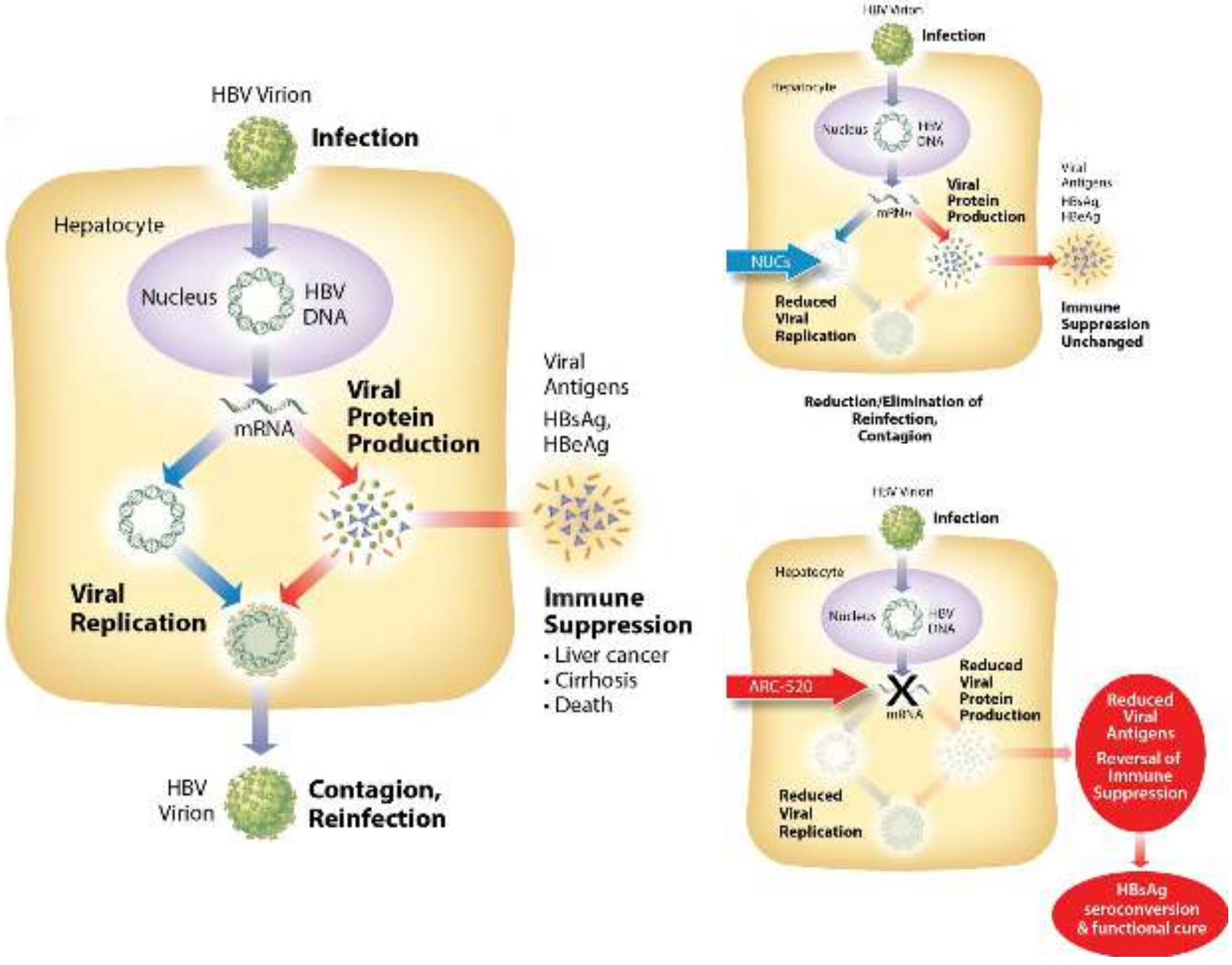
Translasyon

ARC-520

- HBV mRNA'larını hedef alan iki siRNA ve N asetil glukozaminle birleştirilmiş litik peptid molekülü

- Kronik HBV infeksiyonu olan şempanzelerde iki doz sonrası HBsAg, HBeAg ve DNA düzeylerinde %90-95 düşüş

- Faz 2a çalışmaları sürüyor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Reversal of Immune Suppression
HBsAg seroconversion & functional cure

Enkapsidasyon

Bay 41-4109

- Kapsid biraraya geliminin destabilizasyonu

GLS4

- Bay-41-4109 analogu
- İntraselüler cor Ag ve DNA düzeylerinde düşüş

NVR-1221

- Nükleokapsid formasyonu inhibisyonu

Replikasyon

NAs

RNase H inhibitörleri

Replikasyon

β thujapliclinol

- HIV RNase H inhibitörü
- Kimyasal türevleri çalışılıyor

Maturasyon ve salınım

Peptidomimetik bileşikler

- HBsAg-nükleokapsid biraraya geliminin bozulması

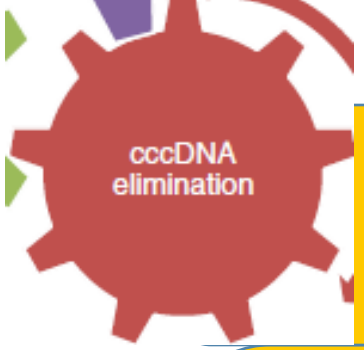
Glikosidaz inhibitörleri

- HBsAg glikozilasyonunun inhibisyonu

REP 9AC

- HBsAg salınımının inhibisyonu
- HBsAg düzeylerini düşürdüğü gösterilmiş

Viral yaşam döngüsü hedefleri

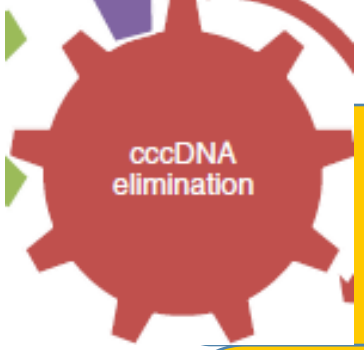


cccDNA

LTβR agonistleri / IHVR-25

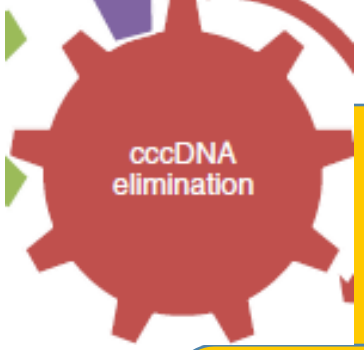
- İnterferon α aracılı APOBEC3A ve lenfotoksin β reseptör aracılı APOBEC3B adı verilen hücresel deaminazların aktivasyonu cccDNA deaminasyonu ve degredasyonunu sağlamakta…

- Genomik DNA bu süreçten etkilenmez.



cccDNA

- cccDNA histon asetilasyonunu sağlayan hücresel histon asetiltransferaz ve deasetilazların cccDNA transkripsiyonunda rolü gösterilmiştir…



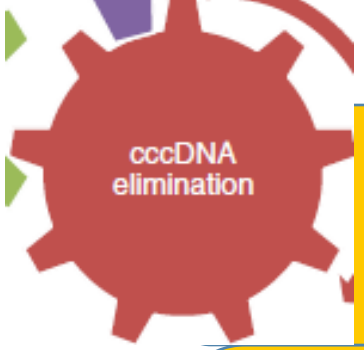
cccDNA

EML-264
- histon asetiltransferaz inhibitörü

MC-2791
- histon deasetilaz stimülasyonu

MC-3119
- histon demetilaz inhibitörü

- HepG2 hücre dizilerinde HBV replikasyonunu baskıladığı ve pgRNA düzeylerini düşürdükleri gösterilmiş…



cccDNA

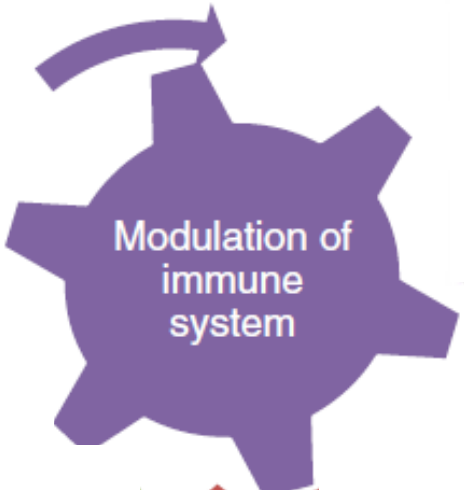
CRISPR/Cas9

- “Clustered regularly interspaced short palindromic repeats” ve “CRISPR associated protein” genleri

- Komplementer sekanslar yoluyla farklı DNA sekanslarını tanıyarak bağlanan ve degrade eden bir sistem

- Epizomal HBV DNA için CRISPR dizileri oluşturulmaya çalışılıyor…

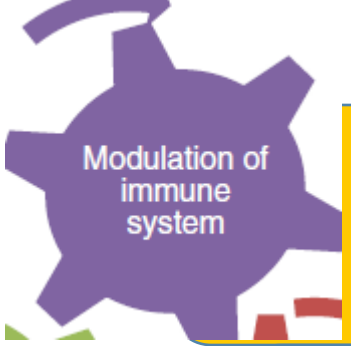
İmmünoteropatik yaklaşım



İmmünoteropatik yaklaşım

Doğal bağışık yanıt
- TLR7 agonistleri
- STING agonistleri

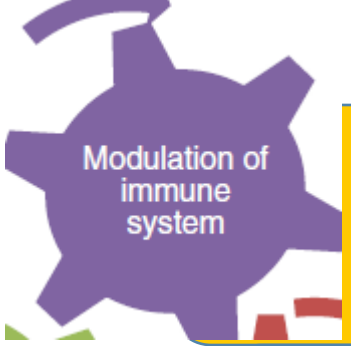
Adaptif bağışık yanıt
- Teropatik aşılarla stimülasyon
- T hücre tükenmesine yol açan immün inhibitör yolakların blokajı



TLR agonistleri

TLRs

- Doğal bağışık yanıt “PAMP” tanıyan reseptörlerle aktive olur,
- TLR-7, viral tek iplikçikli RNA moleküllerini tanır,
- IFN ve sitokin yanıtı üzerinden NK ve CTL hücre yanıtı

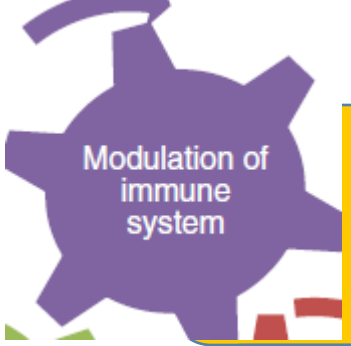


TLR agonistleri

GS-9620

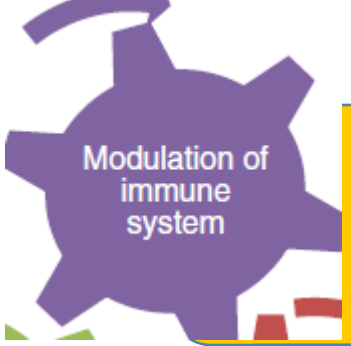
- WHV modelinde etkinliği gösterilmiş,
- İki faz 1b çalışmada HBsAg ve HBV DNA düzeylerinde değişiklik yok…

- Yüksek doz ve uzun süreli kullanıma dair çalışmalar bekleniyor…



STING agonistleri

STING
- “Stimulator of interferon genes”,
- Sitozolik DNA moleküllerini saptayan intraselüler DNA sensörü

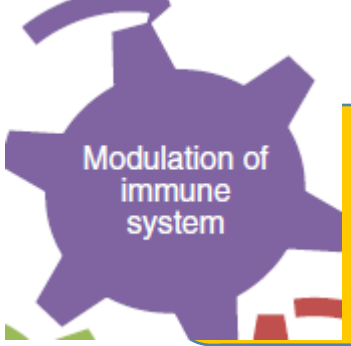


STING agonistleri

DMXAA / Vadimezan

- Tip I IFN benzeri sitokin yanıtı geliştiren STING agonisti
- Hücre sistemlerinde HBV replikasyonunu etkin biçimde baskılıyor,

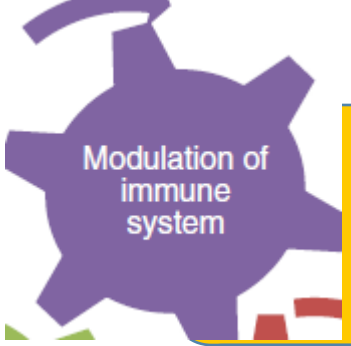
- TLR 7 agonistlerinden daha potent antiviral etkinlik…



Teropatik aşılar

- Günümüzdeki HBV aşıları Th2 immün yanıtı ile antikor üretimini sağlar,

- Hem humoral hem de sitotoksik T hücre yanıtlarını stimüle etmek ve toleransı kırmak hedeflenir.



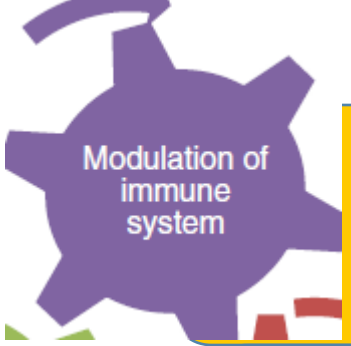
Teropatik aşılar

T helper ve CTL epitopları içeren aşılar,

HBsAg-HBcAg içeren aşılar,

GS-4774

- X protein, L-HBsAg ve cor proteini içerir



Teropatik aşılar

PD-1 reseptörü

- CD8 T hücrelerince eksprese edilen inhibitör bir reseptör
- CD8 T hücre yanıtsızlığıyla ilişkili

PD-L1 inhibitörleri

- HBV spesifik T hücre fonksiyonlarında düzelme ve WHV replikasyonunun baskılanmasını sağlamış…

Sonu

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HBV tedavisinde orta vadede yeni yaklaşımlarla karşılaşacağımız ve kombinasyon tedavileriyle eradikasyon sağlayacağımız günler geliyor…

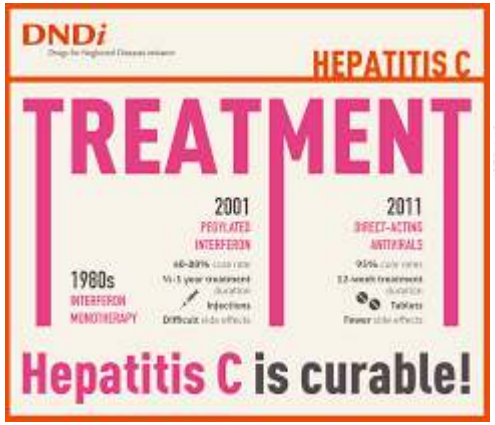
Science
AAAS

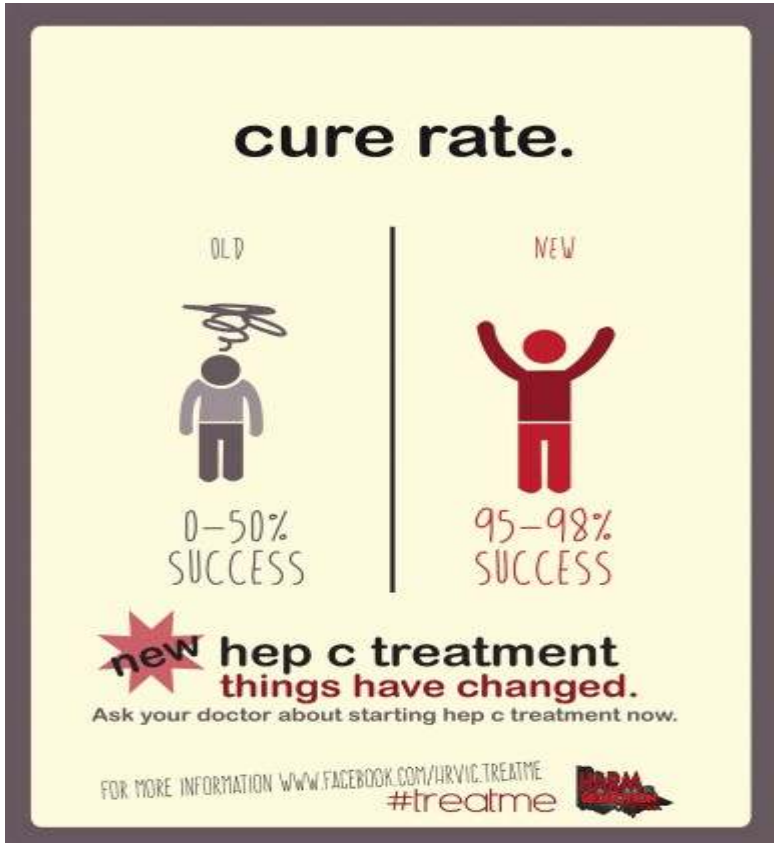
Specific and Nonhepatotoxic Degradation of Nuclear Hepatitis B Virus cccDNA

Julie Lucifora *et al.*

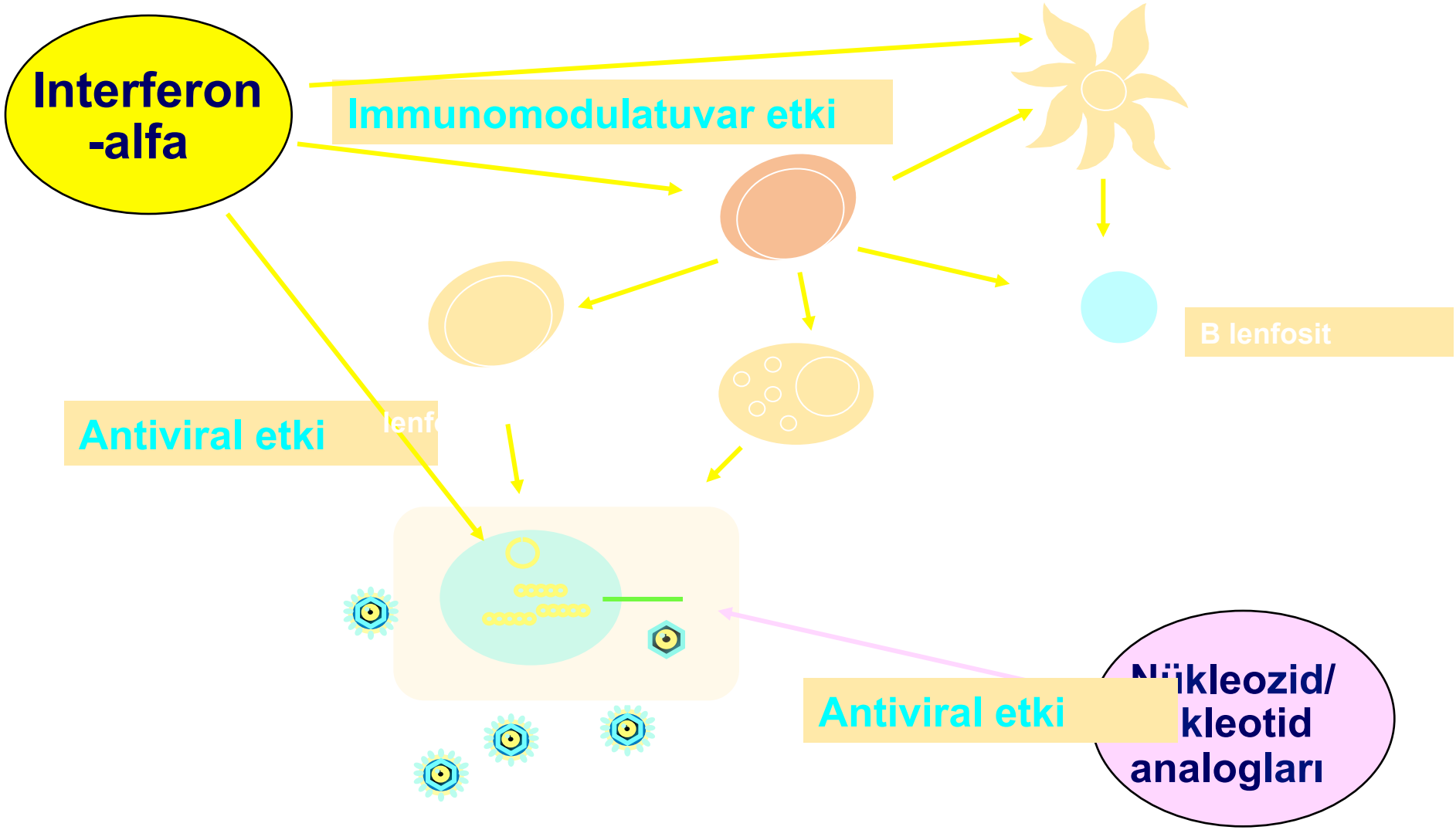
Science **343**, 1221 (2014);
DOI: 10.1126/science.1243462

Hepatit C’de kür görünce umutlandık AMA UMUTLAR BAŞKA BAHARA

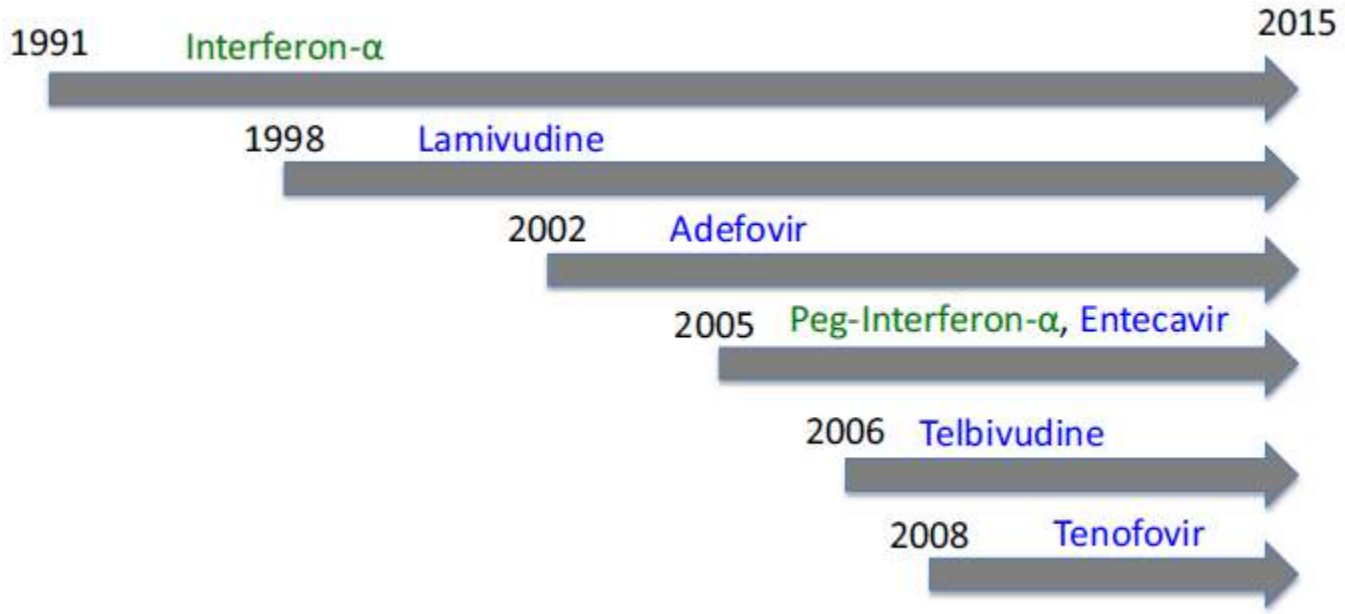




KHB'de mevcut tedavi seçenekleri

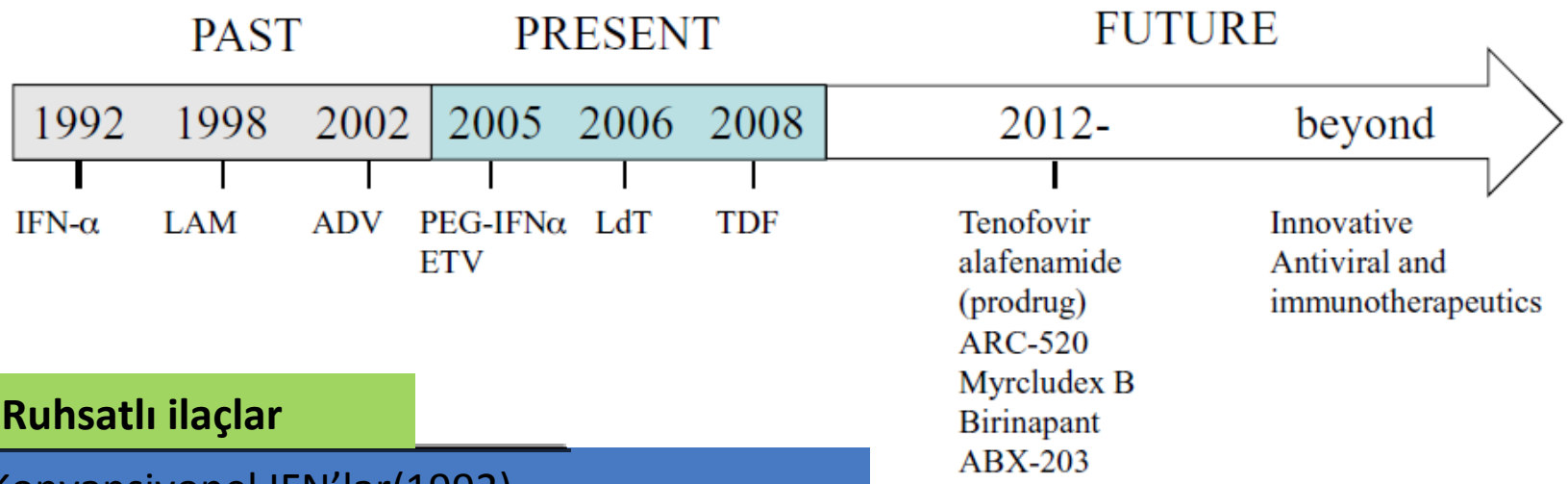


Hepatit b ilaçlarının yıllar içindeki gelişimi



Antiviral Research 121 (2015) 69–81

Hepatit B ilaçların gelecekteki gelişimi

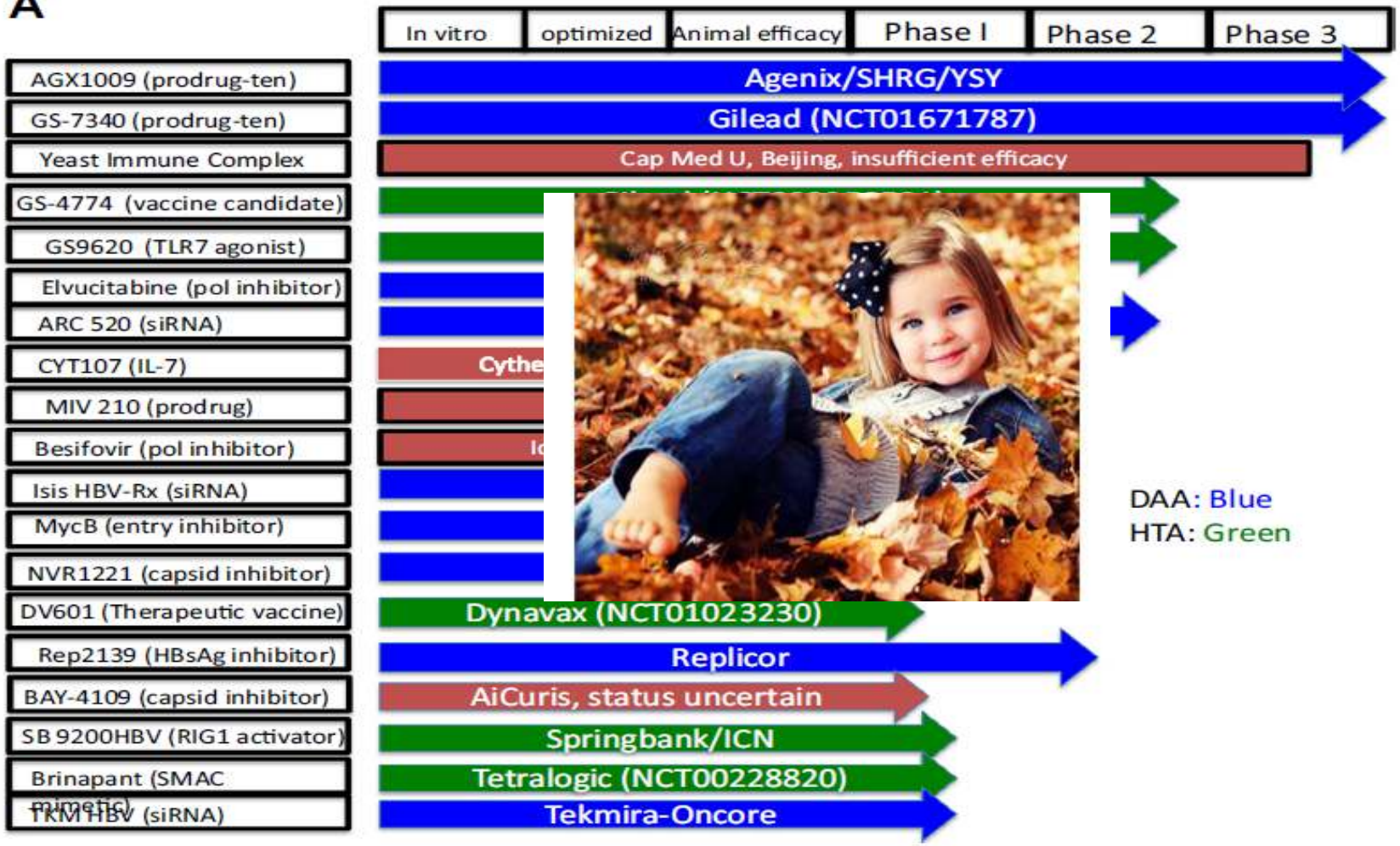


Ruhsatlı ilaçlar

- Konvansiyonel IFN'lar(1992)
- Lamivudin(1998)
- Adefovir(2002)
- Pegile IFN'lar(2006)
- Entekavir(Şubat 2007)
- Tenofovir disiproxil (Eylül 2008)
- Telbivudin(2009)
- Tenefovir alafenamide fumuroate(2016)

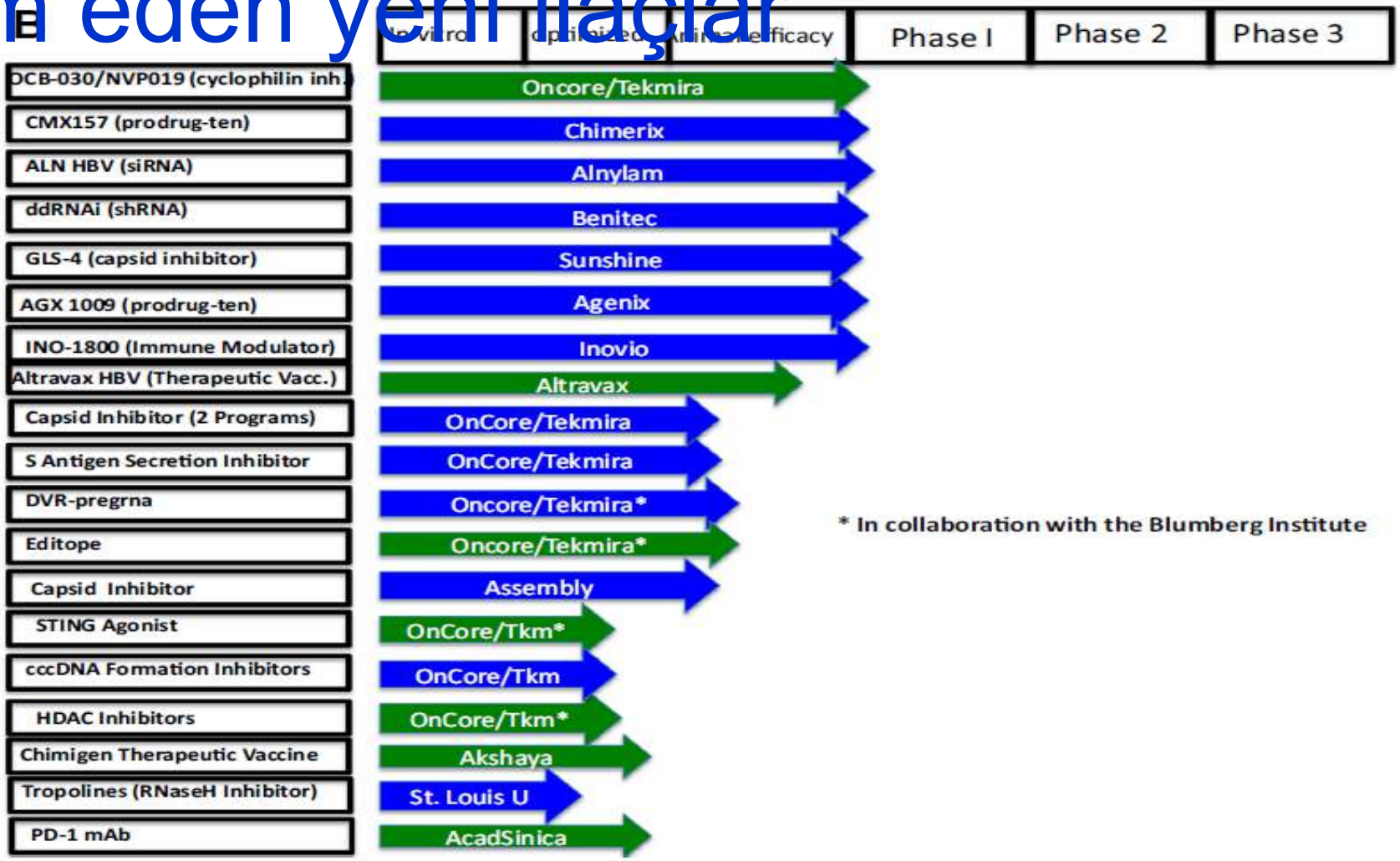
Digestive and Liver Disease 47 (2015) 836–841

Hepatit B tedavisinde klinik çalışmalar başlamış olan yeni ilaçlar



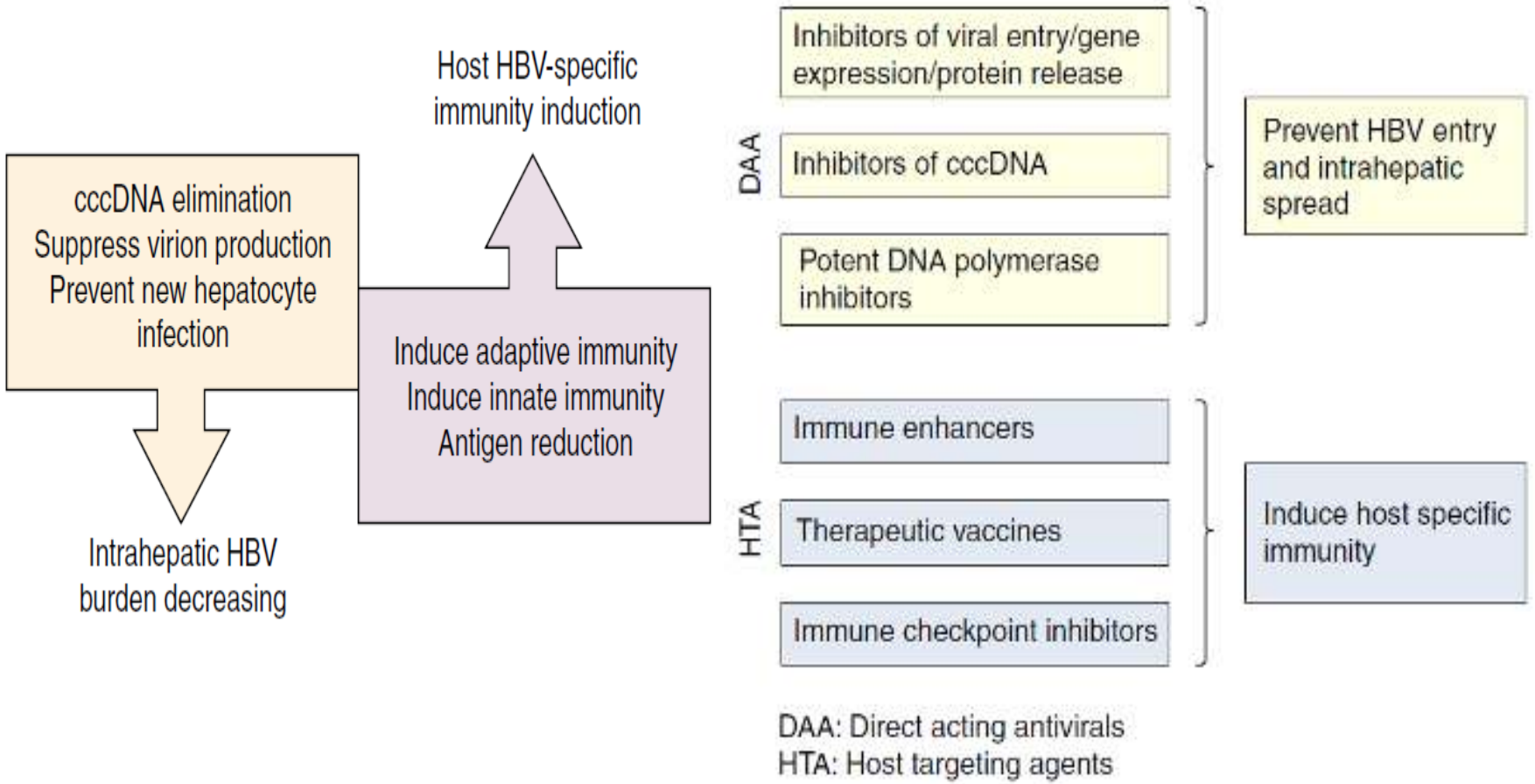
Antiviral Research 121 (2015) 69–81

Hepatit B tedavisinde hayvan çalışmaları devam eden yeni ilaçlar

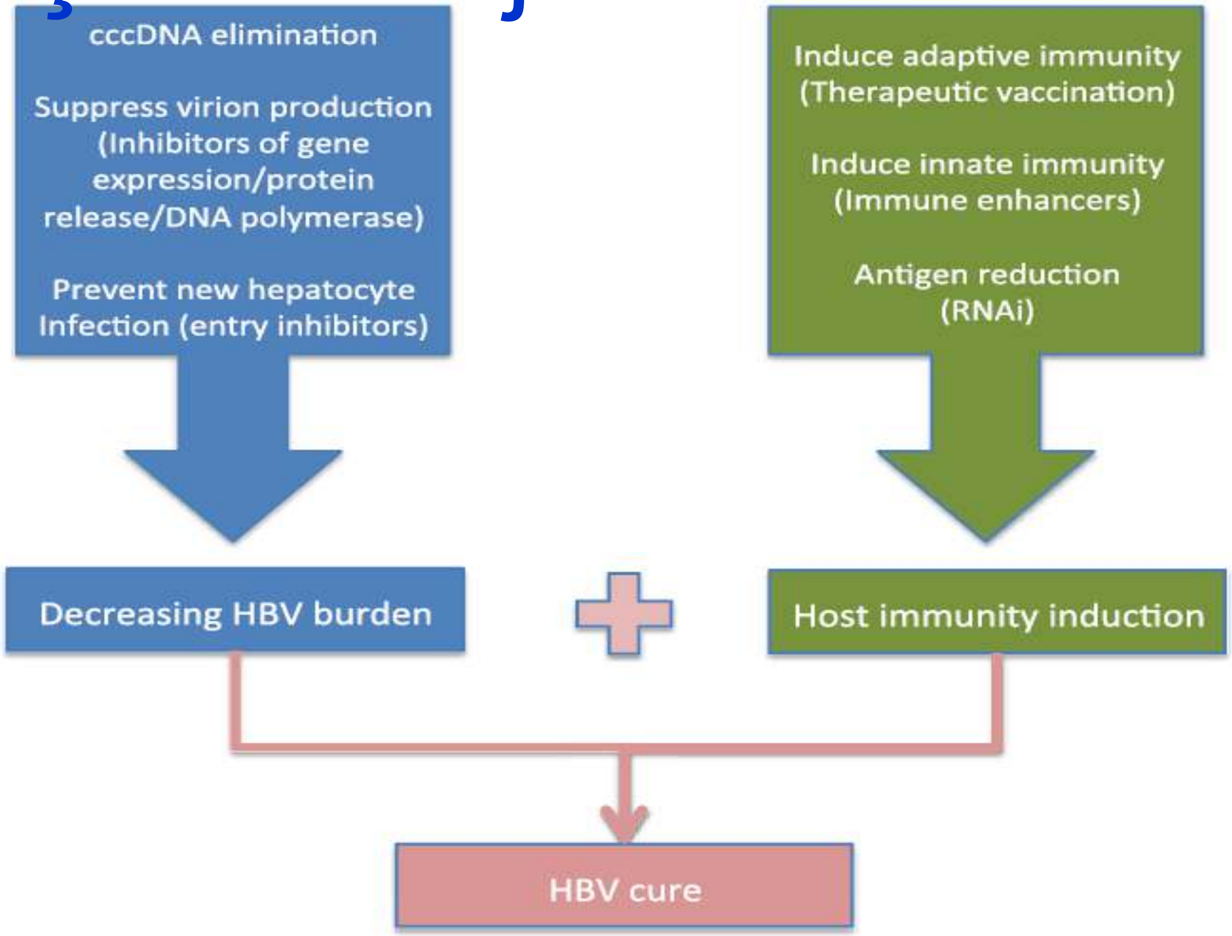


Antiviral Research 121 (2015) 69–81

HBV kürü için stratejimiz ne olmalıdır?



HBV kürü için stratejimiz ne olmalıdır?

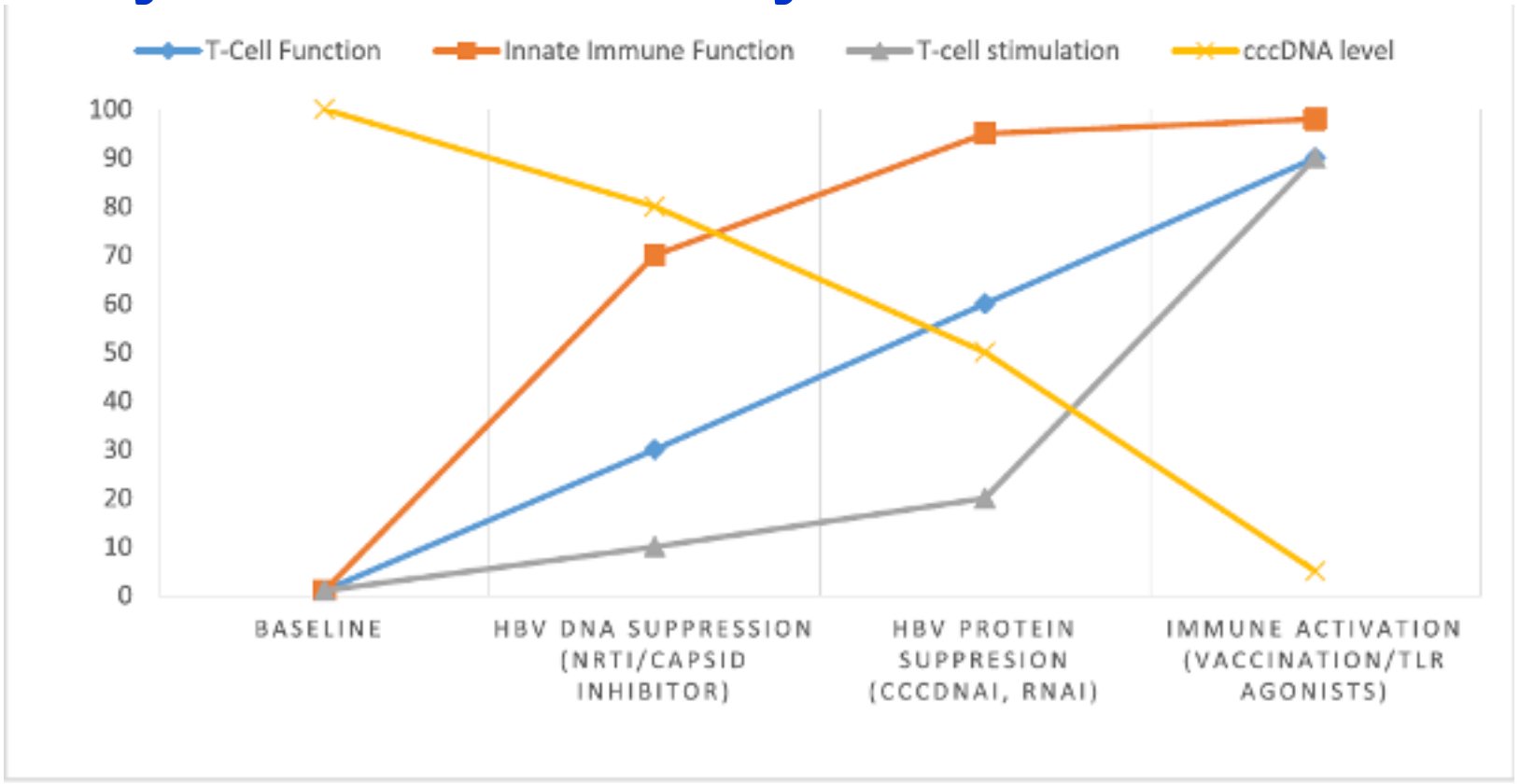


Upcoming pharmacological developments in chronic hepatitis B: can we glimpse a cure on the horizon?

Sonia Alonso, Adriana-René Guerra, Lourdes Carreira, Juan-Ángel Ferrer, María-Luisa Gutiérrez and Conrado M. Fernandez-Rodriguez*

Alonso *et al. BMC Gastroenterology* (2017) 17:168

Potansiyel kombinasyon tedavi önerisi

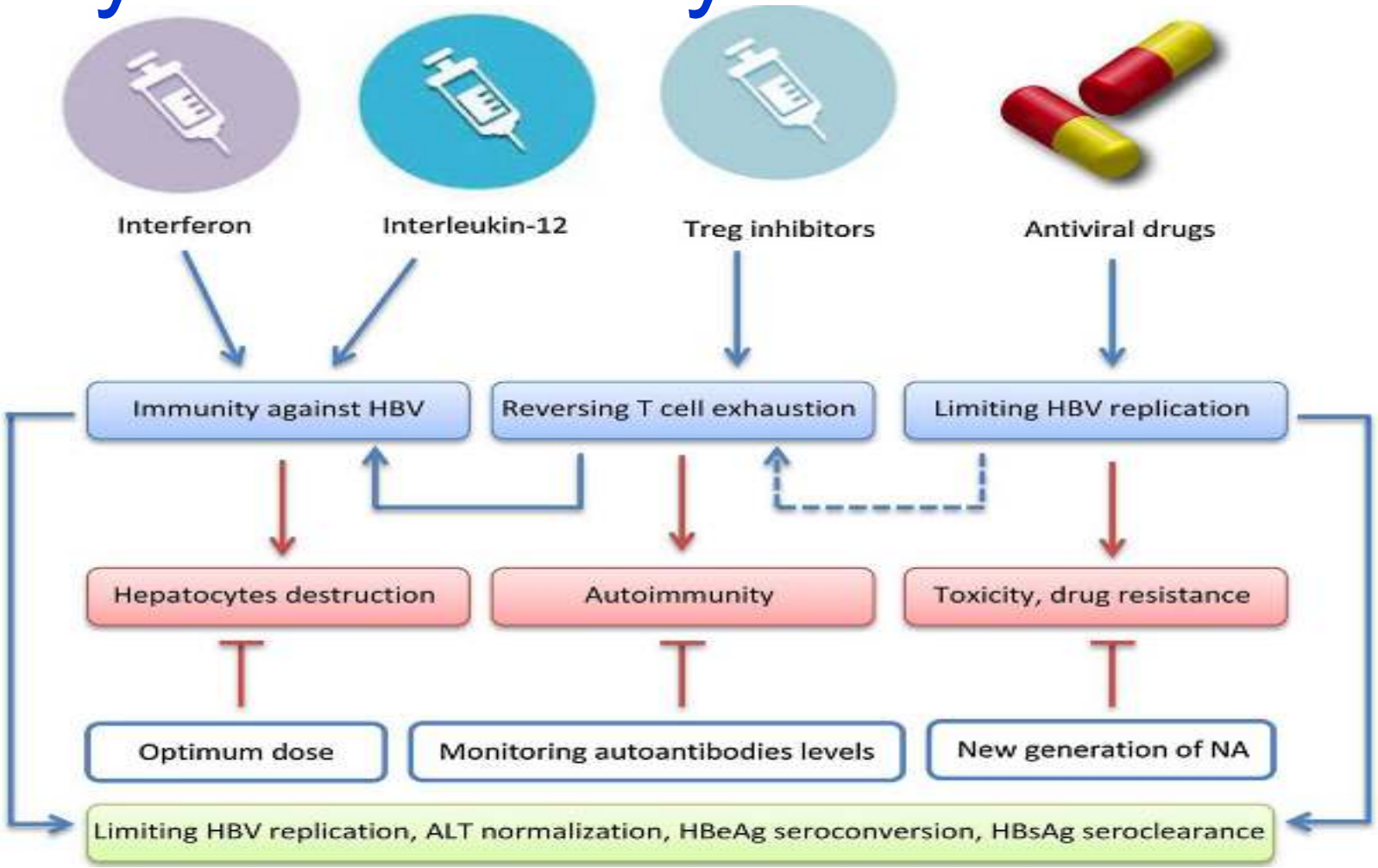


Potential combination strategy to achieve cure of hepatitis B.

- First, a DAA is used to lower viral replication and improve innate immune function
- A second DAA acts to decrease antigen load correcting immune tolerance.
- Finally, immunostimulatory agents could be added to upregulate T-cell mediated clearance of infected hepatocytes.

Best Practice & Research Clinical Gastroenterology 31 (2017)

Potansiyel kombinasyon tedavi önerisi



Immunology Letters 190 (2017) 206–212

HBV kürü için başka bir kombinasyon öneri

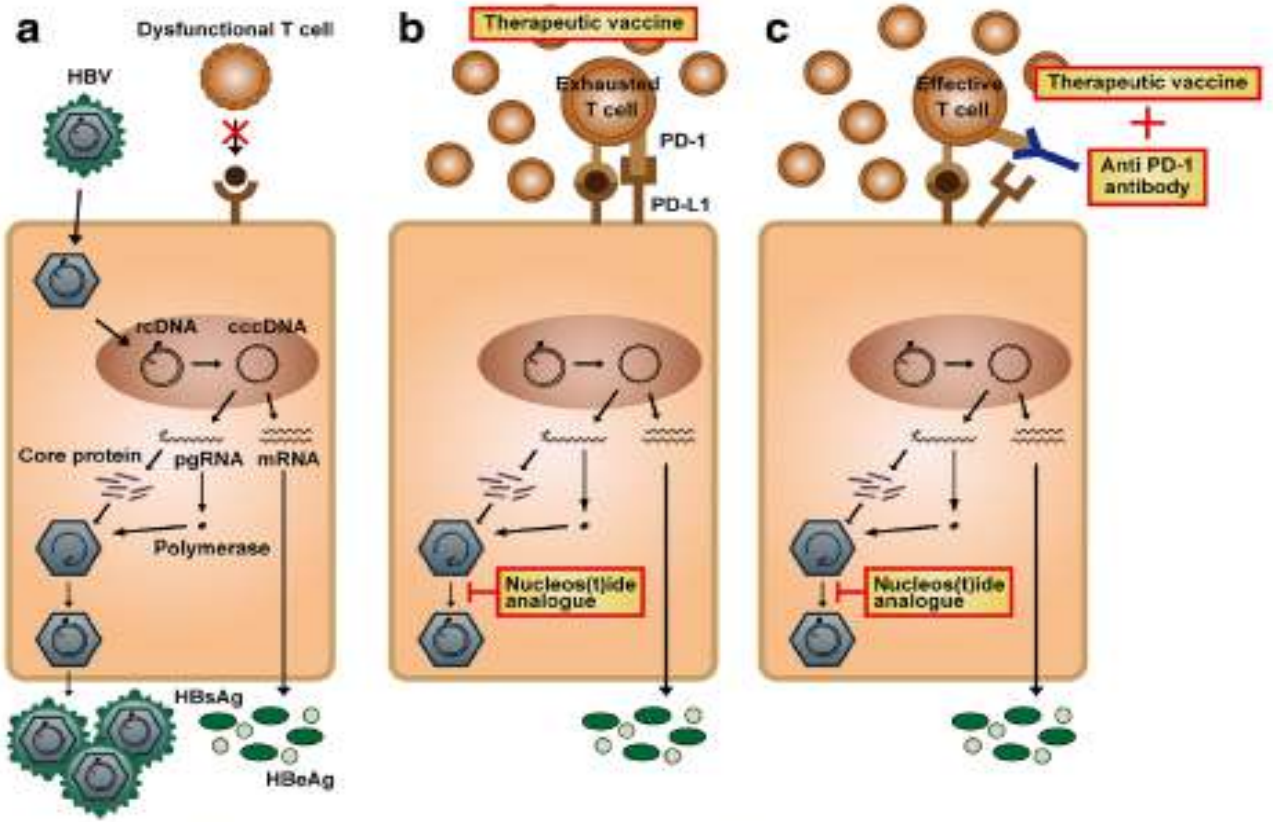


Fig. 1 a Patients with chronic hepatitis B are characterized by a high viral load and antigenaemia, as well as a small number of dysfunctional HBV-specific T-cells. **b** Failure of combining therapeutic vaccine and nucleos(t)ide analogue treatment could be attributed to T cell exhaustion induced by PD1 and PD-L1 engagement. **c** Combining anti-PD1, an immune checkpoint inhibitor, with strategy **b** may be a solution to cure chronic HBV infection

Elimination of Hepatitis B: Is It a Mission Possible?

Tai-Chung Tseng and Jia-Horng Kao

Tseng and Kao *BMC Medicine* (2017) 15:53

Direkt etkili ilaç ve imunmodülatör tedavi kombinasyon çalışmaları

Targets	Compounds	Phase	Results	Reference
Innate immune system + HBV protein replication				[76]
Innate immune system + cccDNA				[77]
Adaptive + NRTI				[57]
Adaptive + Innate				[78]
Adaptive + Innate + NRTI				NCT02431312
Innate + NRTI				[79]
Innate + Adaptive + NRTI				NCT01027065
Adaptive + NRTI				[80]
Adaptive + Innate + NRTI				NCT02249988
Adaptive + Innate + NRTI				NCT02360592
Adaptive + NRTI				[81]

Best Practice & Research Clinical Gastroenterology 31 (2017) 347e355

Sonuç olarak

- Mevcut tedaviler bize yeterli gelmiyor. Düşük oranda fonksiyonel kür olabiliyor.
- Hepatit C tedavisinde ulaşılan noktalar, hepatit B için de tam kür isteğimizi artırdı.
- Hepatit B, HCV'ye göre kür açısından daha zor bir virus
- İntegre DNA ve ccc DNA'yı yok etmek gerekiyor.
- HBV hücre içi ve dışı siklüsü ve immun sistemi etkileyen birçok ilaç çalışmaları var.
- Bu ilaçların bir kısmı klinik kullanıma ulaşamayacak
- Ancak klinik uygulamaya giren tek ilaçla kür zor görünüyor.
- Olasılıkla her basamağı etkileyen ilaç kombinasyonu ile ancak sterilize kür elde edilebilecek.

HBV kürü için hedefe ulaşmak:
1-2 dekatta mümkün olabilir

Teşekkürler