service de VIROLOGIE
CHRU de Lille

Centre Hospitalier Régional Universitaire de Lille

VHB: nouvelles perspectives thérapeutiques

Journée Régionale de Pathologie Infectieuse
Laurence Bocket -- Virologie CHRU Lille
11/10/2016

liens d’intérêt

honoraires et participation aux frais de formation continue / congrès

Bristol-Myers Squibb Gilead Sciences Janssen-Cilag MSD

contexte

pandémie VHB

cycle VHB

traitement actuel VHB

recherche thérapeutique

nouvelles cibles virales

immunité

« cure »

Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013

Aparna Schweitzer, Johannes Horn, Rafael T Mikolajczyk, Gérard Krause, Jördis J Ott

www.thelancet.com Published online July 28, 2015 http://dx.doi.org/10.1016/S0140-6736(15)61412-X

analyse données épidémiologiques « HBs prevalence » (1965 à 2013)

- 1862 publications
- 161 pays
- 109 415 627 personnes

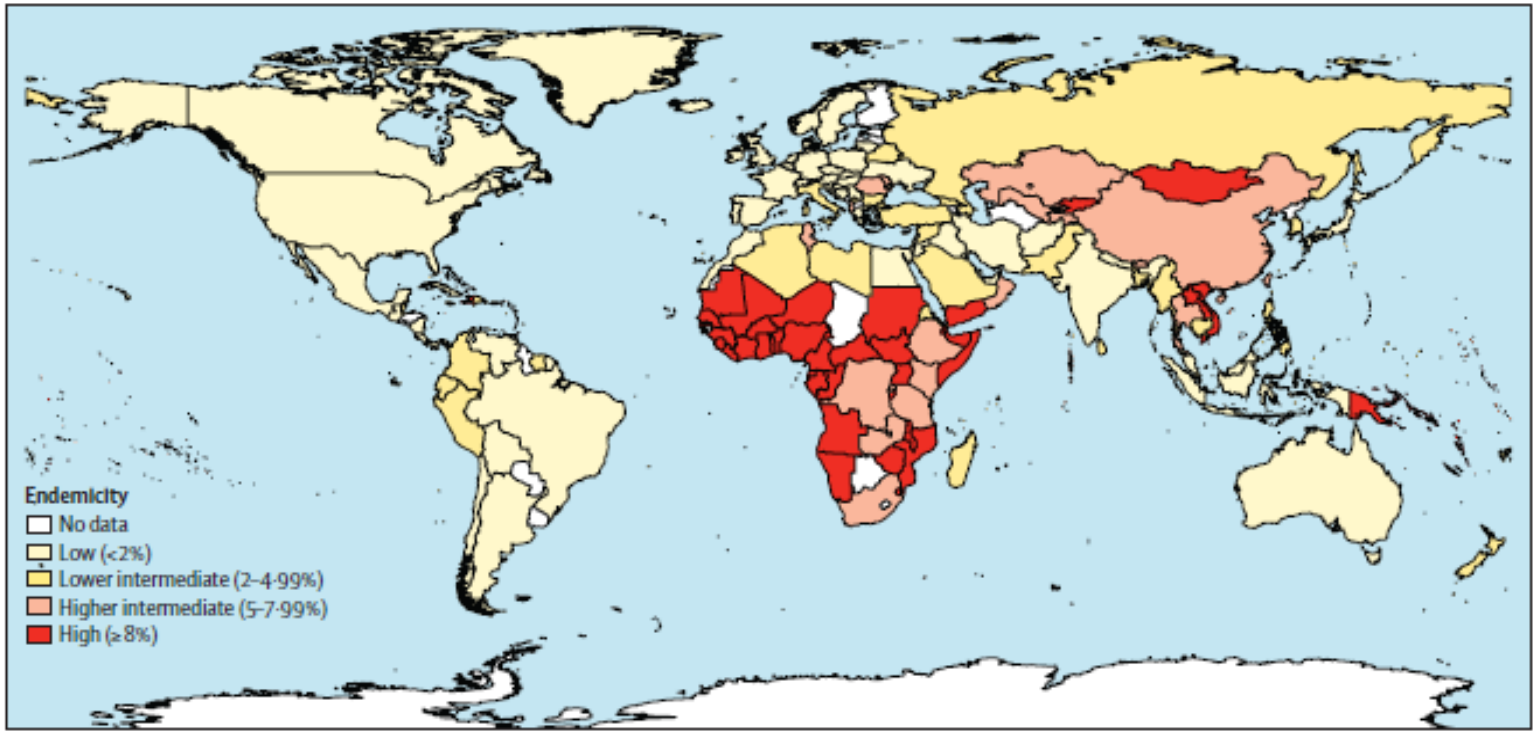
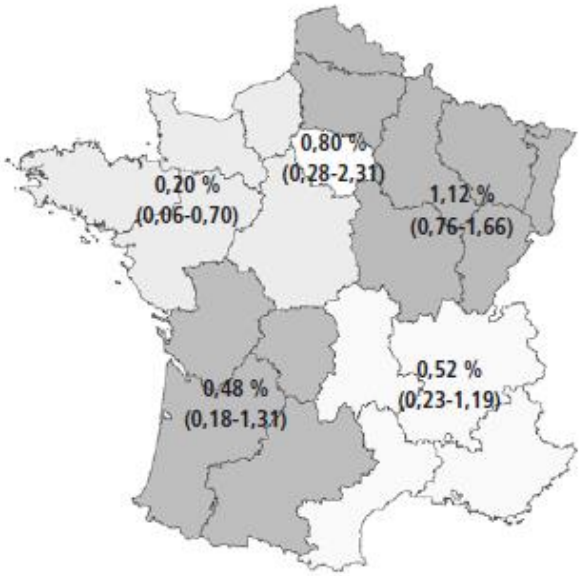


Figure 2: Global HBsAg endemicity (1957–2013)

prévalence globale: 3,61%
 # 248 millions porteurs Ag HBs
 # 700 000 morts / an

ESTIMATION DE LA PRÉVALENCE DE L'AGHBS PAR INTERRÉGION DE RÉSIDENCE POUR LA POPULATION DE FRANCE MÉTROPOLITAINE ÂGÉE DE 18 À 80 ANS, 2003-2004



Prévalence des hépatites B et C en France en 2004 — INSTITUT DE VEILLE SANITAIRE

prévalence globale: 0,65% (1,10 ♂ - 0,21 ♀)
= 280821 personnes

Estimation du nombre annuel de nouvelles infections par le virus de l'hépatite B en France, 2004-2007

Denise Antona (d.antona@invs.sante.fr), **Marie-José Letort, Daniel Lévy-Bruhl**
Institut de veille sanitaire, Saint-Maurice, France

BEH thématique 20-21 / 19 mai 2009

Prévalence de l'infection chronique en 2004 (nombre de personnes atteintes)	Estimation de l'incidence (nombre de nouvelles infections annuelles)	Nombre de décès annuels associés à une infection chronique	Nombre de décès annuels imputables
280 821	2 578	1 507	1 327

incidence annuelle 2578 infections VHB (4,1/100000 hab)
→209 passage chronicité
→1327 décès directement imputables

…pas de données très récentes…

HBV « the stealth virus »

90%

hépatite aiguë

10% (périnatal 90%)

guérison

hépatite chronique

4-20%

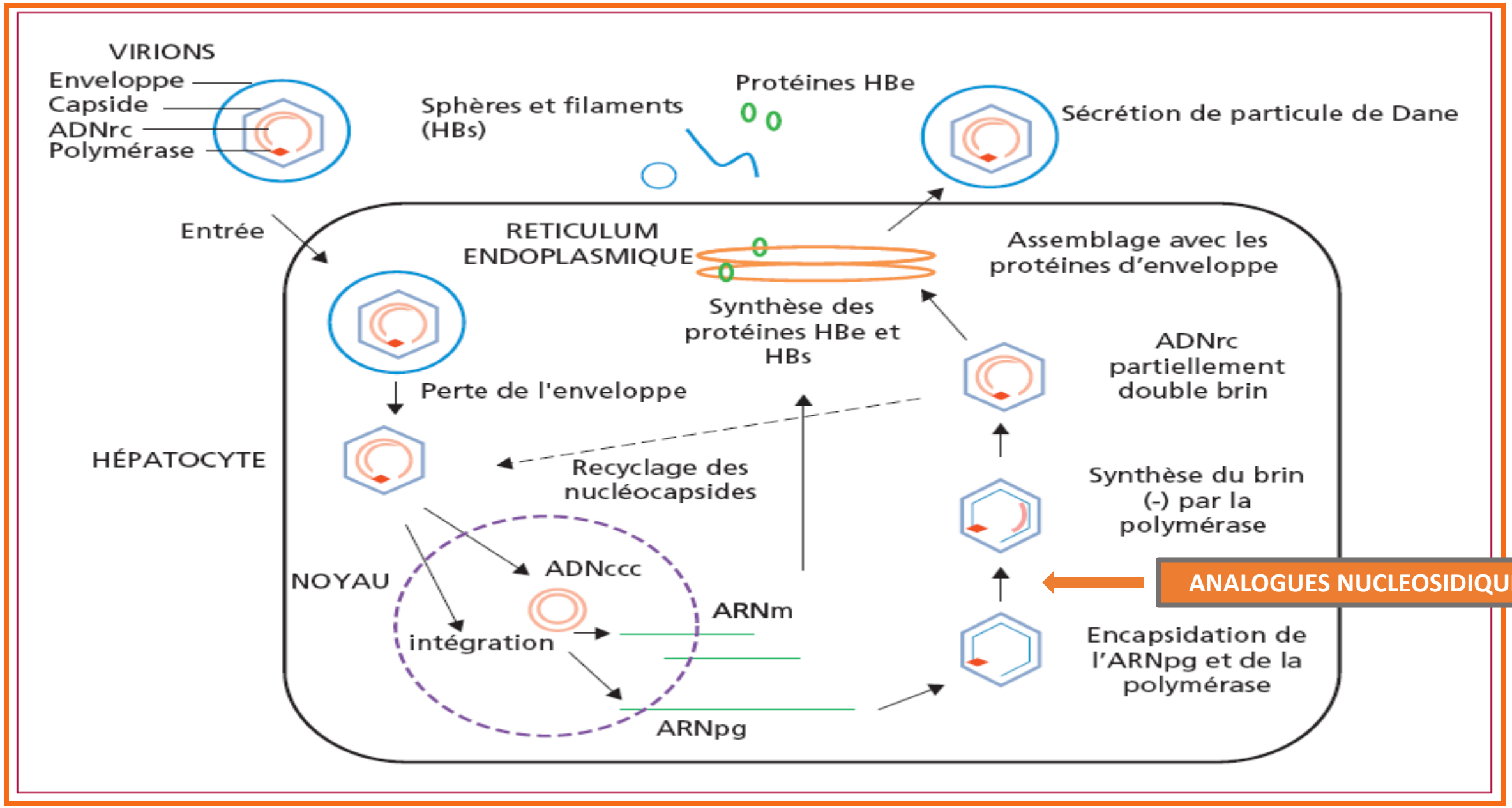
1 -4% /an

réplication virale

intégration virale

inflammation

10 à 50 ans


VIRIONS
Enveloppe
Capside
ADNrc
Polymérase
Sphères et filaments (HBs)
Protéines HBe
Sécrétion de particule de Dane
Entrée
RETICULUM ENDOPLASMIQUE
Assemblage avec les protéines d'enveloppe
Synthèse des protéines HBe et HBs
ADNrc partiellement double brin
Perte de l'enveloppe
HÉPATOCYTE
Recyclage des nucléocapsides
Synthèse du brin (-) par la polymérase
NOYAU
ADNccc
ARNm
intégration
ANALOGUES NUCLEOSIDIQUES
Encapsidation de l'ARNpg et de la polymérase
ARNpg

traitements actuels: efficacité virologique et clinique

	Entecavir[1,2]	Tenofovir[3]	PEG-IFN α-2a[4,5]
HBeAg positive	n = 354	n = 176	n = 271
HBV DNA undetectable	**67%**	**76%**	**25%[a]**
HBeAg seroconversion	21%	21%	27%
ALT normalisation	68%	68%	39%
HBsAg loss	**2%**	**3.2%**	**2.9%[b]**
HBeAg negative	n = 325	n = 250	n = 177
HBV DNA undetectable	**90%**	**93%**	**63%[a]**
ALT normalisation	78%	76%	38%
HBsAg loss	**0.3%**	**0%**	**0.6%[b]**

Results at 48 weeks [a] HBV DNA < 400 copies/mL; [b] At 72 weeks

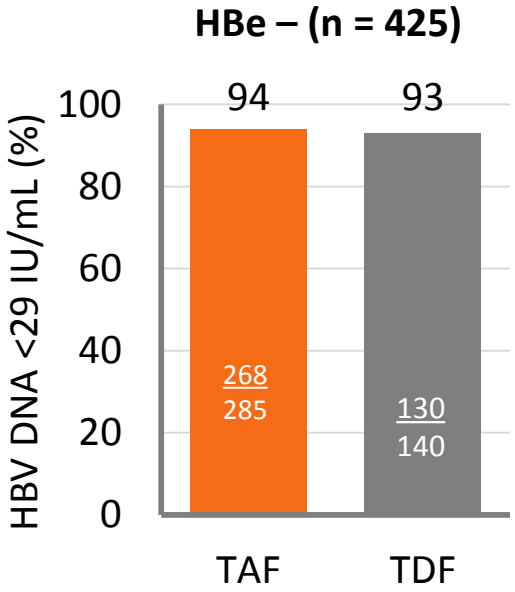
1. Chang T-T, et al. N Engl J Med 2006;354:1001–10.
2. Lai C-L, et al. N Engl J Med 2006;354:1011–20.
3. Marcellin P, et al. N Engl J Med 2008;359:2442–55.
4. Lau GKK, et al. N Engl J Med 2005;352:2682–95.
5. Marcellin P, et al. N Engl J Med 2004;351:1206–17.

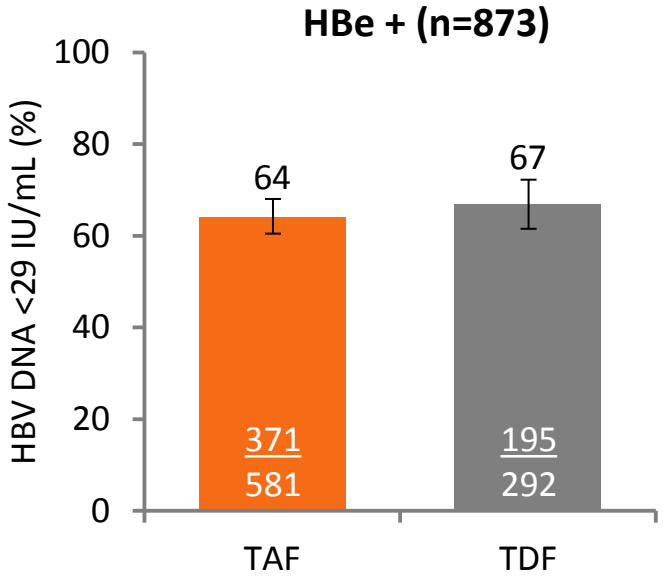
« nouveaux » analogues:
1/ TAF: ténofovir alafénamide

pro-drogue du ténofovir

études de phase 3 HBe + et HBe- TAF 25mg QD vs TDF 300mg QD, sem. 48

→ non inférieur et mieux pour rein et os





Buti Met al EASL 2016 Chan HLY et al EASL 2016

« nouveaux » analogues:

2/ Besifovir (LB80380 – guanosine monophosphonate, acyclique)

Two-year treatment outcome of chronic hepatitis B infection treated with besifovir *vs.* entecavir: Results from a multicentre study

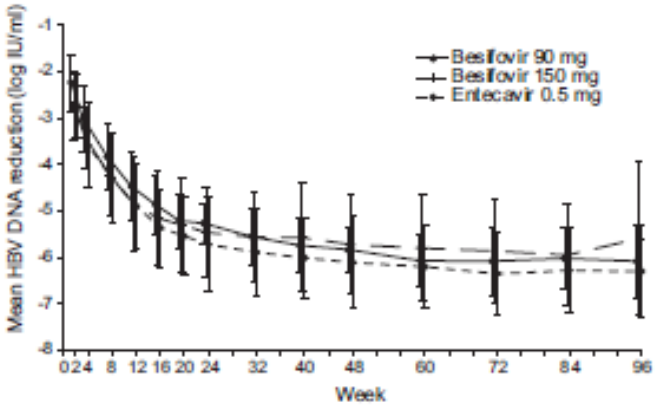
Man-Fung Yuen[1,†], Sang Hoon Ahn[2,†], Kwan Sik Lee[2], Soon Ho Um[3], Mong Cho[4], Seung Kew Yoon[5], Jin-Woo Lee[6], Neung Hwa Park[7], Young-Oh Kweon[8], Joo Hyun Sohn[9], Jiyoon Lee[10], Jeong-Ae Kim[10], Ching-Lung Lai[1,*], Kwang-Hyub Han[2,*]

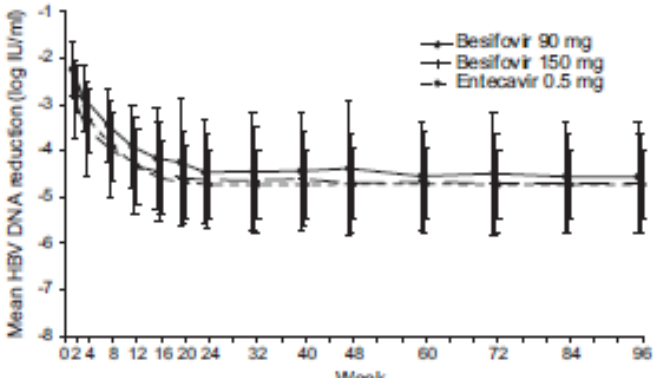
Journal of Hepatology **2015** vol. 62 | 526–532

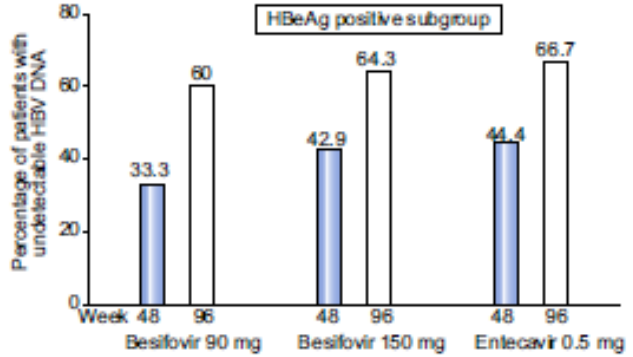
Patients naïfs VHB chroniques

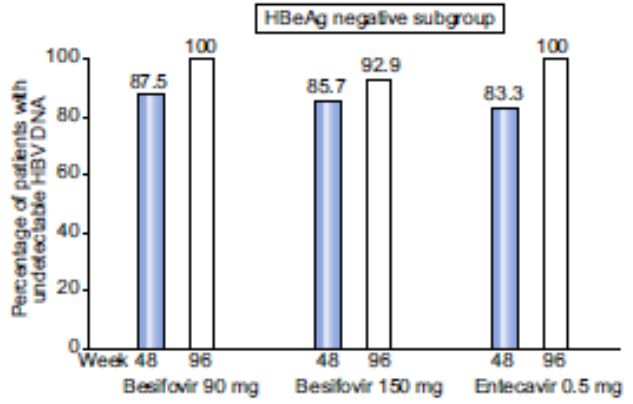
Besifovir 90mg (n=31) vs 150 mg (n=28) vs ETV 0,5mg (n=30)

⇒ non –infériorité /ETV
pas de résistance
bonne tolérance (déplétion en L-carnitine)









« nouveaux » analogues

	Targets	Compounds	Developer	Stage of development	ClinicalTrials.gov identifier
DAA	HBpol	GS-7340; Tenofovir Alafenamide (prodrug of tenofovir)	Gilead	Phase 3	NCT01940471 and NCT01940341
	HBpol	AGX-1009 (prodrug)	Agenix	Phase 3 (?)	No identifier found
	HBpol	Besifovir	IlDong Pharmaceutical	Phase 3	NCT01937806
	HBpol	CMX-157 (lipid acyclic nucleoside phosphonate)	Contravir	Phase 1	NCT02585440

Durantel et Zoulim. Journal of Hepatology 2016

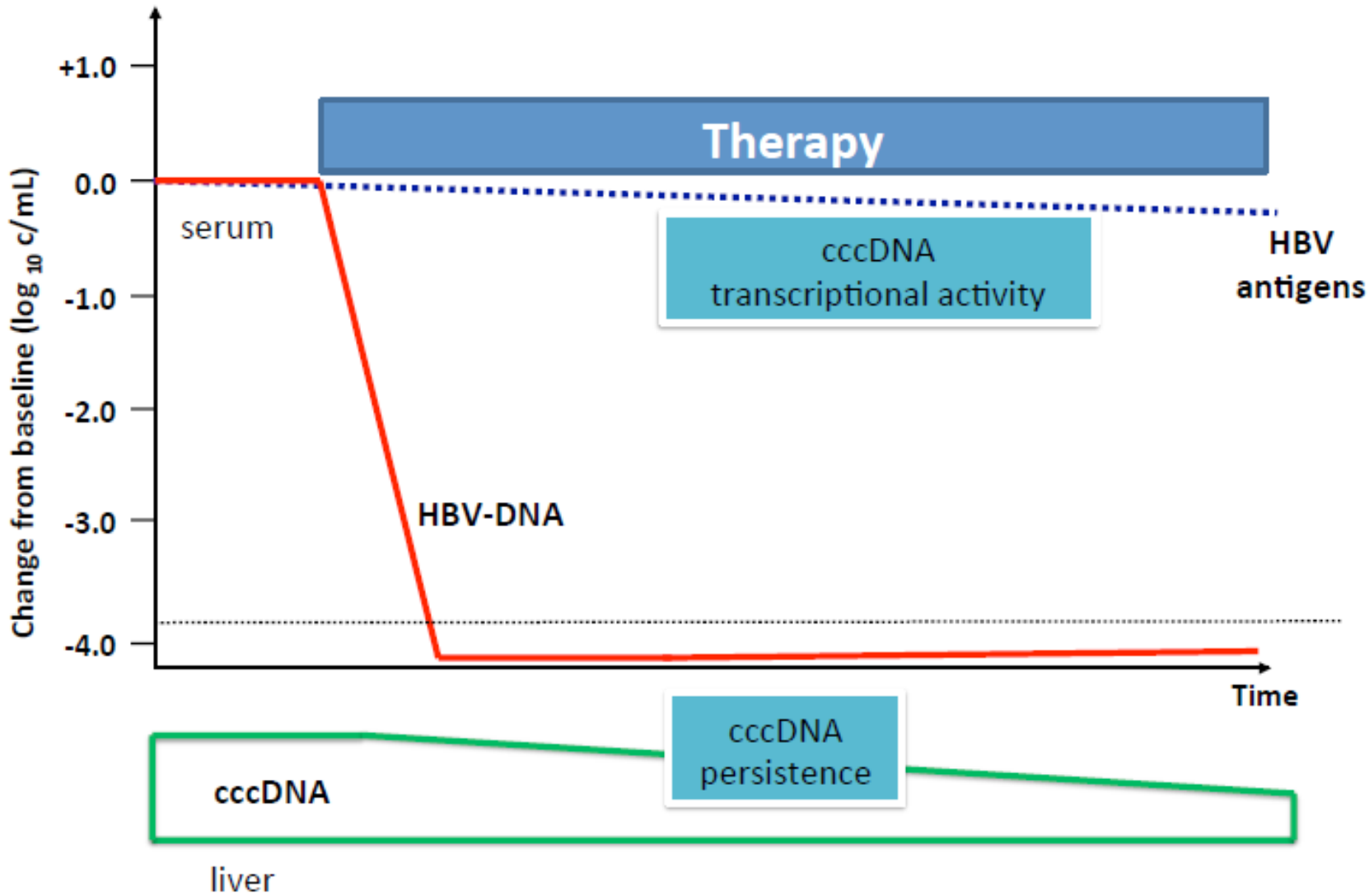
analogues + peg-IFN

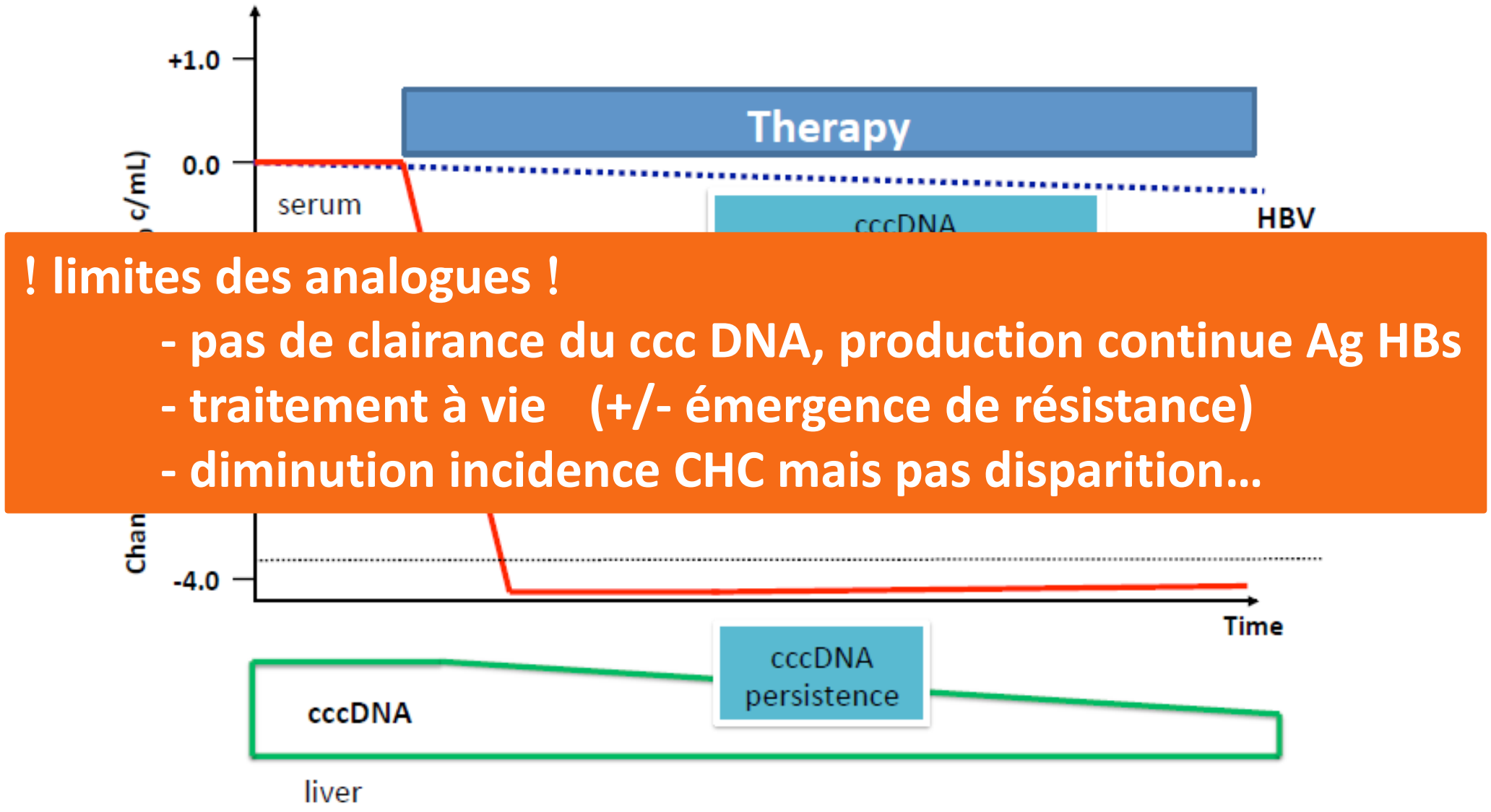
HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD
HEPATOLOGY, Vol. 61, No. 5, 2015

The Royal Wedding in Chronic Hepatitis B: The Haves and the Have-Nots for the Combination of Pegylated Interferon and Nucleos(t)ide Therapy

The "royal" wedding must be postponed once more. After so many years of loyal and faithful engagement, the two betrothed are thinking about other partners. To remain single might be a good option too.

Pietro Lampertico, M.D., Ph.D.
A.M.e.A. Migliavacca Center for the Study of Liver Disease
Division of Gastroenterology and Hepatology


+1.0
0.0
-1.0
-2.0
-3.0
-4.0
Change from baseline (log 10 c/mL)
Therapy
serum
cccDNA
transcriptional activity
HBV
antigens
HBV-DNA
Time
cccDNA
persistence
cccDNA
liver



! limites des analogues !

- pas de clairance du ccc DNA, production continue Ag HBs
- traitement à vie (+/- émergence de résistance)
- diminution incidence CHC mais pas disparition…

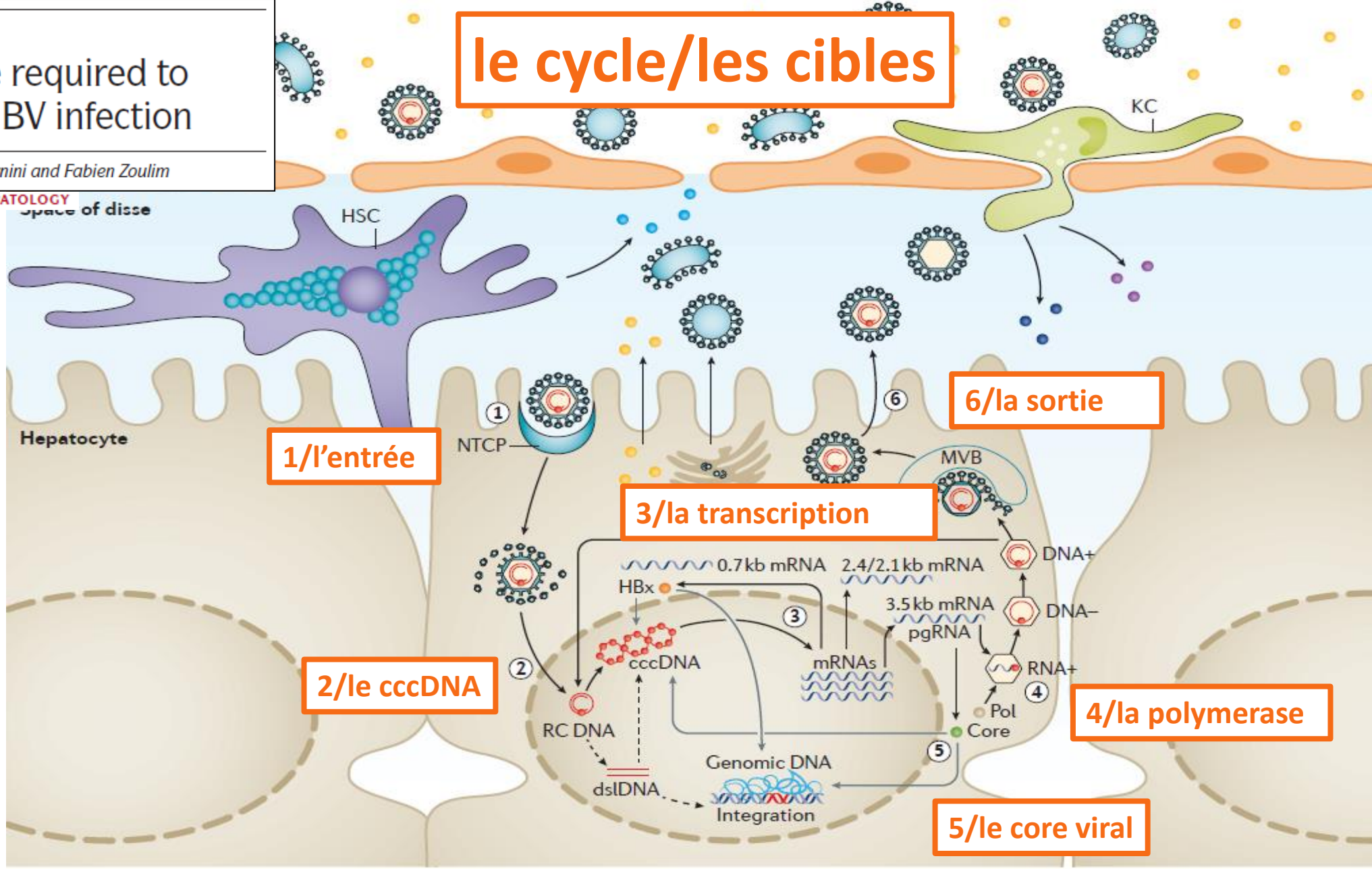
OPINION

Global strategies are required to cure and eliminate HBV infection

Peter Revill, Barbara Testoni, Stephen Locarnini and Fabien Zoulim

NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY

le cycle/les cibles



doi:10.1038/nrgastro.2016.7
Published online 24 Feb 2016;
corrected online 17 March 2016

HBV

Subviral particles composed of HBV genome-free enveloped capsids

Subviral particles (SVP) composed of HBV envelope proteins (spheres)

Subviral particles (SVP) composed of HBV envelope proteins (filaments)

HBe
TGFβ
IL6
IFNβ
HBs

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Present and Future Therapies of Hepatitis B: From Discovery to Cure

T. Jake Liang,[1] Timothy M. Block,[2] Brian J. McMahon,[3] Marc G. Ghany,[1] Stephan Urban,[4] Ju-Tao Guo,[2] Stephen Locarnini,[5] Fabien Zoulim,[6] Kyong-Mi Chang,[7] and Anna S. Lok[8]

HEPATOLOGY, Vol. 62, No. 6, 2015

Compound	Mechanism/ Target†	Stage of Development	Sponsor	Reference
Direct-acting antivirals:				
GS-7340 (tenofovir alafenamide fumarate	Polymerase (prodrug of tenofovir)	Phase 2/3	Gilead Sciences	47; NCT0194047, NCT01940341‡
CMX157	Polymerase (prodrug of tenofovir)	Phase 1/2§	Contravir (Chimerix)	146; NCT01080820‡
NVR1221/3778	Capsid	Phase 1/2	Novira	84; NCT02112799‡
Sulfamoylbenzamides	Capsid	Animal	Oncore	147
GLS4	Capsid	Phase 1	HEC Pharm Group, China	148
Bay41-4109	Capsid	Phase 1	AiCuris	83
REP 2139-Ca	Assembly/HBsAg	Phase 1/2	Replicor	NCT02233075‡
ARC-520	RNAi	Phase 1/2	Arrowhead	94; sponsor's website; NCT02065336‡
TKM-HBV	RNAi	Phase 1	Tekmira	Sponsor's website; NCT02041715‡
ALN-HBV	RNAi	Animal	Alnylam	Sponsor's website
DNA-directed RNAi	RNAi	Animal	Benitec	Sponsor's website
ISIS HBV	Antisense	Phase 1	Isis	Sponsor's website
Host targeting agents:				
Myrcludex B	Entry/NTCP	Phase 1/2	Myr-GmbH/Hepatera	75
Birinapant	Apoptosis/second mitochondrial activator of caspases	Phase 1	Tetralogic	Sponsor's website; NCT02288208‡
Flavonoids	STING agonist (pattern recognition receptor)	Animal	Oncore	149
NVP018	Cyclophilins, IRF-9	Animal	Oncore (NeuroVive)	Sponsor's website
Epitope HBV	Glucosidase/therapeutic vaccine	Animal	Blumberg Institute	150
Immune modulatory agents:				
GS-9620	TLR-7 agonist	Phase 2	Gilead Sciences	122; NCT02166047‡
Nivolumab	PD-1 blockade	Phase 1‖	BMS	151; Sponsor's website, NCT01658878‡
SB 9200HBV	RIG-I and NOD2 activation	Phase 1/2	INC/Springbank	152; NCT01803308‡
GS-4774	Therapeutic vaccine	Phase 2/3	Gilead Sciences/GlobeImmune	144; NCT02174276‡
ANRS HB02	Therapeutic vaccine	Phase 1/2	French National Agency for Research on AIDS and Viral Hepatitis	141; NCT02166047‡
Heplisav B Dynavax 601	Therapeutic vaccine	Phase 1	Dynavax	153; NCT01023230‡
Nasvac	Therapeutic vaccine	Phase 2/3	CGEB, Cuba	154
TG1050	Therapeutic vaccine	Phase 1/1b	Transgene	NCT02428400
HBIG + GM-CSF + HBV vaccine	Therapeutic vaccine	Phase 1/2	Beijing 302 Hospital	NCT01878565
HBV vaccine + IFN-α2b + IL-2	Therapeutic vaccine	Phase 2/3	Tongji Hospital	NCT02360592 (labeled as Phase 4)
HBV vaccine-activated dendritic cells	Therapeutic vaccine	Phase 1/2	Third Affiliated Hospital, Sun Yat-Sen University	NCT01935635
Euvax + PEG-IFN-α	Therapeutic vaccine	Phase 2/3	Seoul National University	NCT02097004 (labeled as Phase 4)
PD-1 monoclonal antibody	PD1 blockade	Animal	AcadSin	155
Altravax HBV	Therapeutic vaccine	Animal	Altravax	Sponsor's website
INO-1800	Therapeutic vaccine	Animal	Innovio	Sponsor's website

JOURNAL OF HEPATOLOGY

New antiviral targets for innovative treatment concepts for hepatitis B virus and hepatitis delta virus

David Durantel[1,2,3,†], Fabien Zoulim[1,2,3,4,5,*,†]

Journal of Hepatology **2016** vol. 64 | S117–S131

Table 1. A summary of clinical trials and their strategies for HBV treatment.

	Targets	Compounds	Developer	Stage of development	ClinicalTrials.gov identifier
DAA	HBpol	GS-7340; Tenofovir Alafenamide (prodrug of tenofovir)	Gilead	Phase 3	NCT01940471 and NCT01940341
	HBpol	AGX-1009 (prodrug)	Agenix	Phase 3 (?)	No identifier found
	HBpol	Besifovir	IlDong Pharmaceutical	Phase 3	NCT01937806
	HBpol	CMX-157 (lipid acyclic nucleoside phosphonate)	Contravir	Phase 1	NCT02585440
	HBc	GLS-4 (Morphothiadine mesilate)	HEC Pharm/SUnshine	Phase 2	China-CFDA
	HBc	NVR 3-778	Novira Pharmaceuticals	Phase 1	NCT02112799 & NCT02401737
	HBs	REP-2139 (nucleic acid polymers)	Replicor	Phase 2 for both HBV and HDV	NCT02565719 and NCT02233075
	Viral RNAs	siRNA: ARC-520/ARC-521	Arrowhead	Phase 2	NCT02604212 and NCT02604199
	Viral RNAs	siRNA: ISIS-HBVRx	Ionis pharmaceuticals	Phase 1 or 2 (?)	No identifier found
HTA	NTCP	Myrcludex	Hepatera and MYR GmbH	Phase 2 for both HBV and HDV	Development in Russian Federation
	Promotion of apoptosis in infected cells	Birinapant	Tetralogic	Phase 1	NCT02288208
	Prenylation/farnesylation	Lonafarnib	Eiger BioPharmaceuticals	Phase 2 for HDV	NCT02430181, NCT02430194, NCT02511431
	Immune stimulation	Thymosin alpha	Seoul National University Hospital	Phase 4	NCT00291616
	pDC stimulation	GS-9620 (TLR7 agonist)	Gilead	Phase 2	NCT02166047 & NCT02579382
	Immune stimulation	INO-1800	Inovio Pharmaceuticals	Phase 1	NCT02431312
	Immune stimulation	Cyt-107 (IL-7)	Cythesis	Phase 1/2 (discontinued)	NCT01027065
	Immune stimulation	IFN-lambda	BMS	Phase 2 (discontinued)	NCT01204762
	Adaptive responses	ABX-203	Abivax	Phase 2/3	NCT02249988
	Adaptive responses	GS-4774 (therapeutic vaccine)	Gilead	Phase 2	NCT01943799 & NCT02174276
	Adaptive responses	TG-1050 (therapeutic vaccine)	Transgene	Phase 1	NCT02428400
	Adaptive responses	DV-601 (therapeutic vaccine)	Dynavax	Phase 1	NCT01023230
	Adaptive response	HB-110	Genexine	Phase 1	NCT01641536
	Adaptive responses	Nivolumab (Anti-PD1 mAb)	Ono Pharmaceuticals/ BMS	Phase 1/2 for HCC	NCT01658878

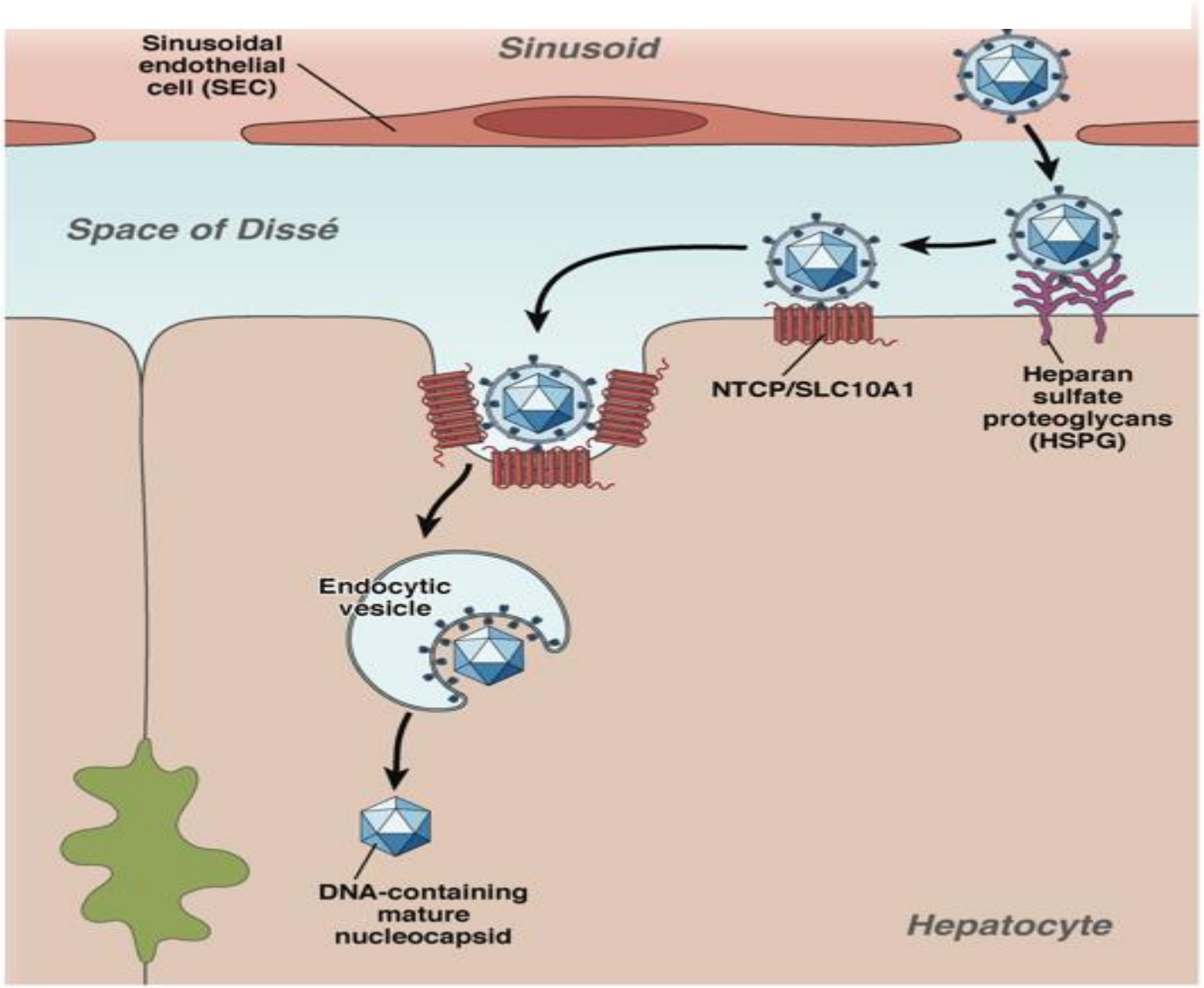
1/ l'entrée

1/ fixation faible affinité **AgHBs ↔ HSPG** (= heparan sulfate proteoglycan)

2/ interaction haute affinité **domaine préS1 myristoylé AgHBs ↔ NTCP** récepteur spécifique = sodium taurocholate co-transporteur polypeptide

NTCP ↔ membrane basale des H¢ rôle = transport des sels biliaires conjugués dans les hépatocytes

= élément clé du tropisme viral et de la spécificité d'espèce du VHB



Li et al, elife 2012; Urban et al, Gastroenterology 2014

inhibiteurs d'entrée

myrcludex

- « host targeting agent » fixation sur NTCP
- peptide synthétisé chimiquement (47AA, N-acylated préS1)
- injectable
- antiVHB et VHD (phase 2)

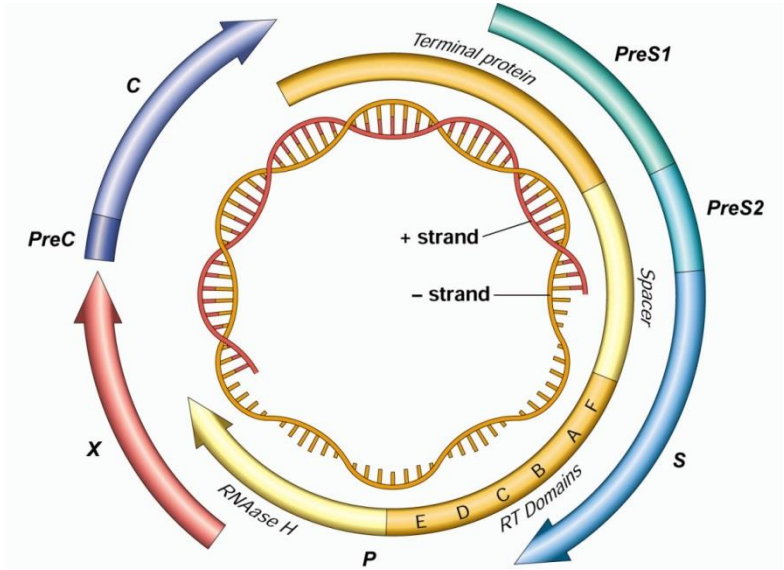
autres

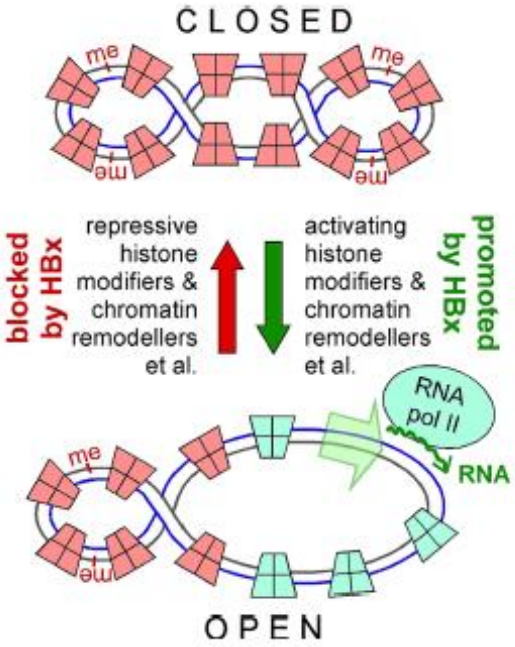
- ezitimib
- cyclosporine

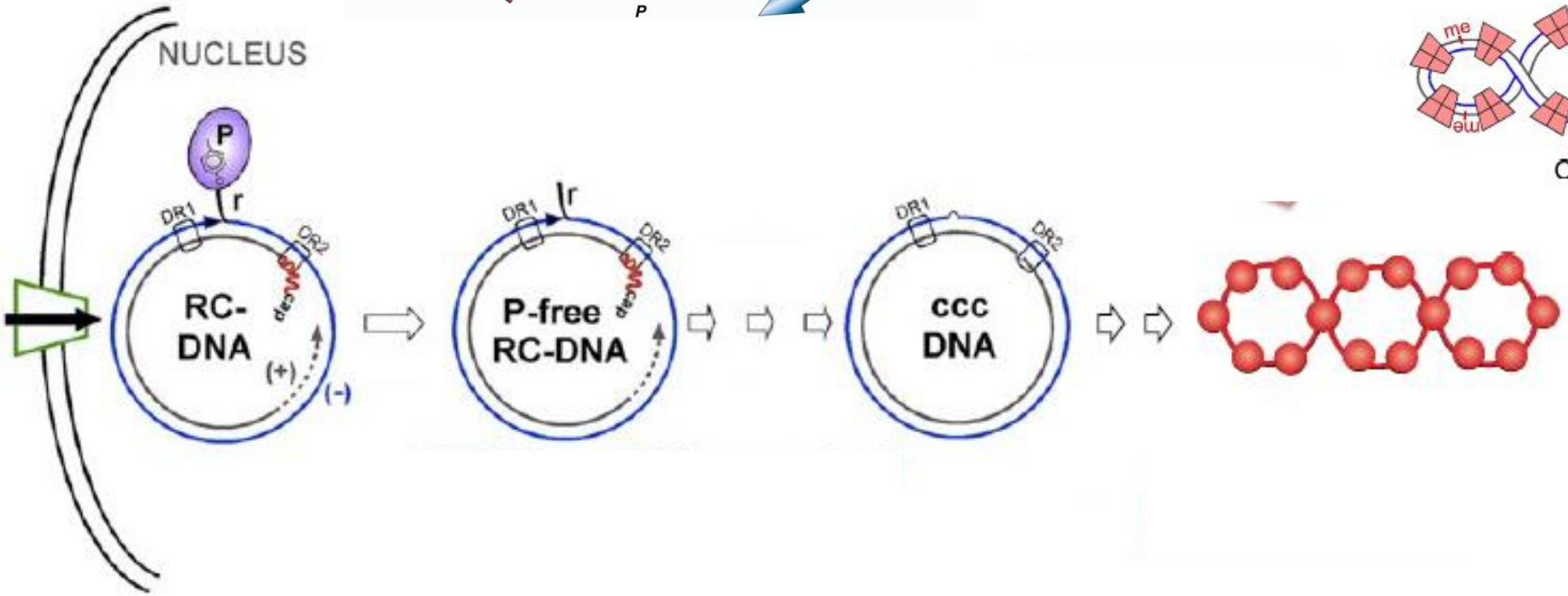
→ limites des inhibiteurs d'entrée

- activité surtout en préventif et pour les infections aiguës
- en curatif et phase chronique ??

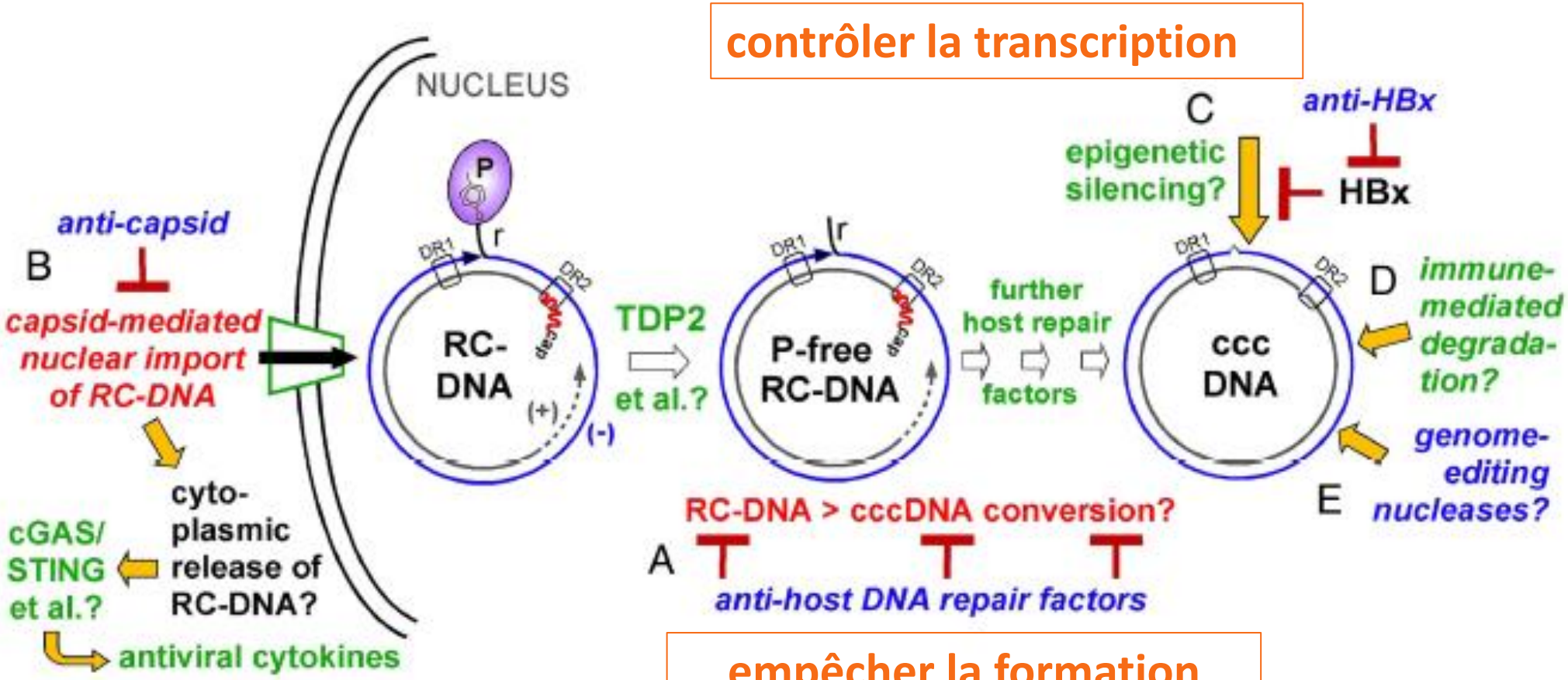
2/le ccc DNA


Terminal protein
PreS1
PreS2
C
PreC
+ strand
– strand
Spacer
X
RNAase H
P
E D C B A F
RT Domains
S


CLOSED
me
blocked by HBx
repressive histone modifiers & chromatin remodellers et al.
activating histone modifiers & chromatin remodellers et al.
promoted by HBx
RNA pol II
RNA
OPEN


NUCLEUS
P
r
DR1
DR2
RC-DNA
(+)
(-)
P-free RC-DNA
ccc DNA

contrôler la transcription



détruire le cccDNA

empêcher la formation

Nassal M. *Gut* 2015

cccDNA

- **formation du cccDNA: RC DNA → ccc DNA = « boite noire »**
  - host DNA repair, enzymes cellulaires (TDP tyrosyl DNA phosphodiesterase)
  - inhibiteurs de conversion : disubstituted sulfonamides DSS
  - efficacité uniquement en phase d'établissement de l'infection (ou phase de turn-over important des H¢)
- **« dilution » du ccc DNA/augmentation du turn-over des H¢ infectés**
  - difficile à contrôler, pourrait favoriser émergence clonale (oncogénicité)
- **destruction cccDNA par stimulation voie APOBEC3A ou 3B/cytokines**
- **destruction cccDNA par des nucléases spécifiques (*endonucleases cleavage*)**
  - ZFN, TALENs CRISPR/Cas9 (→ délétions dans le cccDNA)
  - actuellement # aucun contrôle in vivo et spécificité d'action ?
- **contrôle épigénétique / cytokines, histones**
  - proof of concept préclinique,
  - complexité des réponses, durée?, effets hors-cible??

3/ la transcription

- **HBx** requis pour la transcription (et la réplication), pas d'activité enzymatique, recherche ciblant les interactions HBx-H¢
- **RNA silencing (siRNA) RNA interference (RNAi)**
  - différentes cibles mais overlapping génome
  - Ag HBs

Table 1. Experimental HBV Therapeutics in Late Preclinical or Clinical Stage*

Compound	Mechanism/ Target†	Stage of Development	Sponsor	Reference
ARC-520	RNAi	Phase 1/2	Arrowhead	94; sponsor's website; NCT02065336‡
TKM-HBV	RNAi	Phase 1	Tekmira	Sponsor's website; NCT02041715‡
ALN-HBV	RNAi	Animal	Alnylam	Sponsor's website
DNA-directed RNAi	RNAi	Animal	Benitec	Sponsor's website
ISIS HBV	Antisense	Phase 1	Isis	Sponsor's website

4/ la polymerase

- inh. polymerase
- inh. RNAse H: en développement…

Lu G, Lomonosova E, Cheng X, Moran EA, Meyers MJ, Le Grice SFJ, et al. Hydroxylated tropolones inhibit hepatitis B virus replication by blocking viral ribonuclease H activity. Antimicrob Agents Chemother 2015;59:1070–1079.

5/ le core viral

- **HBc protéine multifonctionnelle / cytoplasme et noyau des H¢ infectés**
  - encapsidation (cytoplasme)
  - fixation au cccDNA et régulation expression gènes viraux (noyau)
  - régulation expression certains gènes cellulaires de l'immunité innée
- 3 familles **«core protein allosteric modulators CpAMs»** identifiées
  - dérivés phenylpropenamide
  - heteroarydihydropyrimidines HAP
  - sulfamoyl benzamides , sulfamoyl carboxamides **NVR** 3-778
- 1ère «classe» d'agents antiviraux spécifiques potentiellement anti-cccDNA

  (+ autres mécanismes d'action, spectre variable selon les produits)

Table 1. Experimental HBV Therapeutics in Late Preclinical or Clinical Stage*

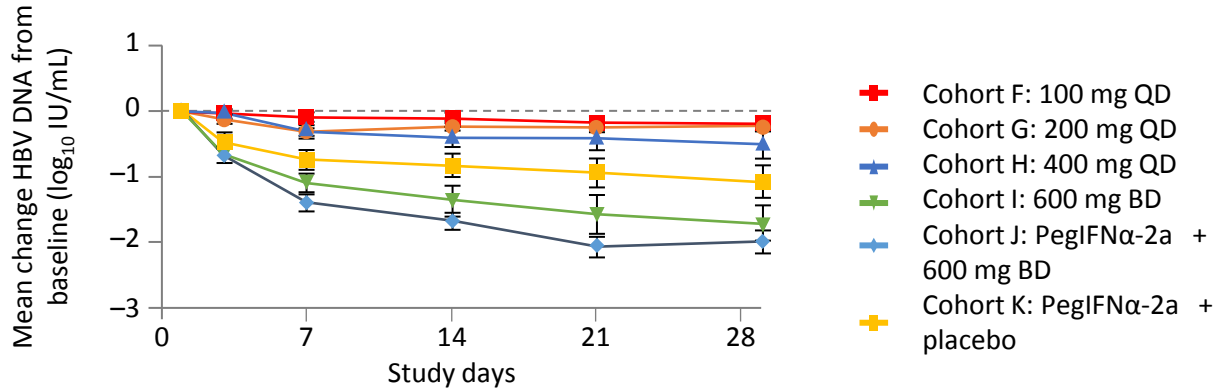
Compound	Mechanism/ Target†	Stage of Development	Sponsor	Reference
NVR1221/3778	Capsid	Phase 1/2	Novira	84; NCT02112799‡
Sulfamoylbenzamides	Capsid	Animal	Oncore	147
GLS4	Capsid	Phase 1	HEC Pharm Group, China	148
Bay41-4109	Capsid	Phase 1	AiCuris	83

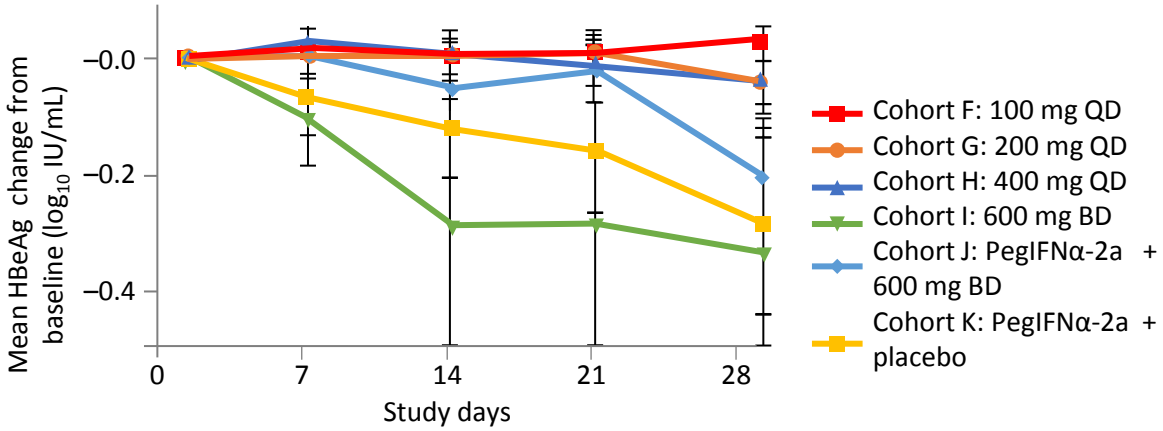
Table 1. A summary of clinical trials and their strategies for HBV treatment.

Targets	Compounds	Developer	Stage of development	ClinicalTrials.gov identifier
HBc	GLS-4 (Morphothiadine mesilate)	HEC Pharm/SUnshine	Phase 2	China-CFDA
HBc	NVR 3-778	Novira Pharmaceuticals	Phase 1	NCT02112799 & NCT02401737

NVR 3-778, seul ou combiné au PegIFN chez des patients naïfs, Hbe + résultats à 4 semaines

- phase 1b, 64 patients, 6 bras (petits effectifs..)
- réponse dose-dépendante: effet optimal pour la dose 600-mg BD (1.72 log IU/mL)





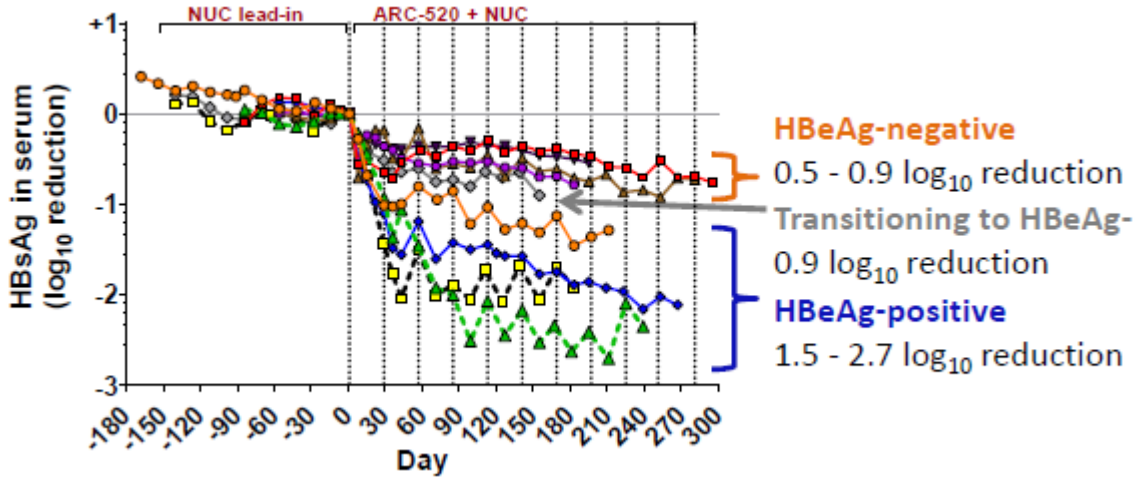
→ effet additif NVR 3-778 – PegIFN (-1,97log)

Yuen M-F, et al. EASL 2016, Barcelona. LBO6

6/ la sortie: AgHBs

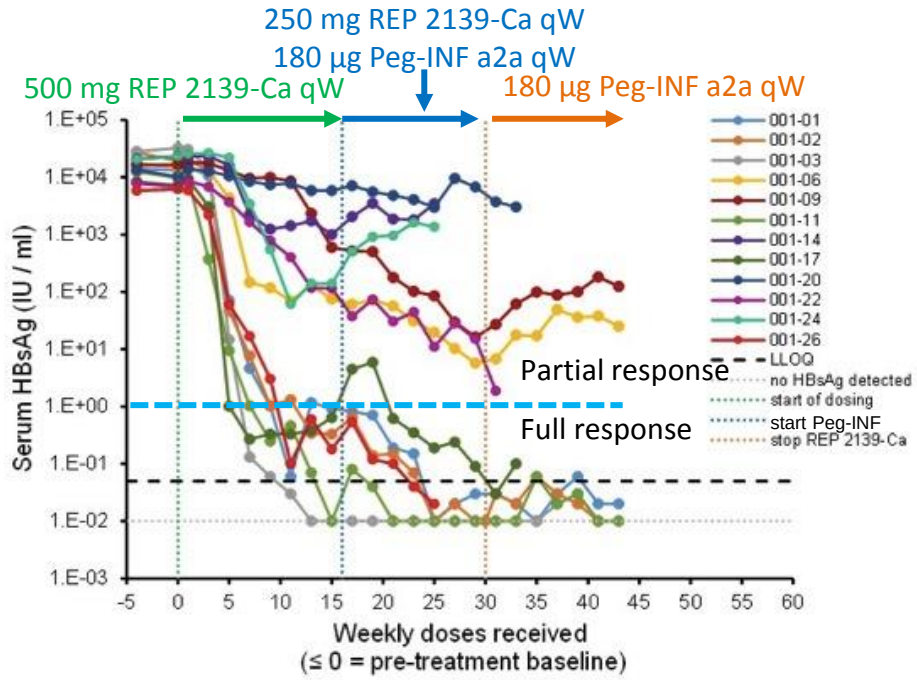
- excès d'Ag HBs ⇒ épuisement du système immunitaire
- plusieurs stratégies en évaluation:
  - si mRNA (ARC-520)
  - nucleic acid polymer (NAP) Rep 2139 (voie IV)
  - anticorps antiHBs

ARC 520 / 9 chimpanzés



Xu Z, et al. EASL 2016, Barcelona. THU-213

Rep 2139 /12 patients



Bazinet M, et al. AASLD 2015, San Francisco. #31.

A summary of clinical trials and their strategies for HBV treatment.

Targets	Compounds	Developer	Stage of development	ClinicalTrials.gov identifier
HBs	REP-2139 (nucleic acid polymers)	Replicor	Phase 2 for both HBV and HDV	NCT02565719 and NCT02233075
Viral RNAs	siRNA: ARC-520/ARC-521	Arrowhead	Phase 2	NCT02604212 and NCT02604199
Viral RNAs	siRNA: ISIS-HBVRx	Ionis pharmaceuticals	Phase 1 or 2 (?)	No identifier found

booster/restaurer l'immunité
1 - immunité innée

- 2 rôles déterminants dans l'évolution clinique
  - 1er contrôle de l'infection
  - activation et maturation de l'immunité spécifique
- récepteurs de l'immunité innée **pattern recognition receptors PRRs**
  - reconnaissance de motifs antigéniques moléculaires (PAMPs)
  - production cytokines inflammatoires (IFNα et β, TNFα, IL…)
  - TLRs, RLRs, Nod, NLRs, CLRs, STING
- TLR7
  - ¢ dendritiques plasmocytoïdes, ligand = ARN simple brin (virus) → secrétion IFNα et IL-12
  - agoniste de TLR7 (GS 9620)… décevant (Gane et al, J.Hepatol 2015)

booster/ restaurer l'immunité
2- immunité spécifique

- réplication importante VHB ↔ épuisement et dysfonctionnement des ¢ T par induction de molécules telles que PD-1 ou CTLA-4 (= co-récepteurs inhibiteurs immunologiques »)

  → **Acs monoclonaux anti-PD-1 (Nivolumab) ou anti CTLA-4 (Ipilimumab)** en stratégie d'association (+ antiviraux et/ou vaccination thérapeutique)

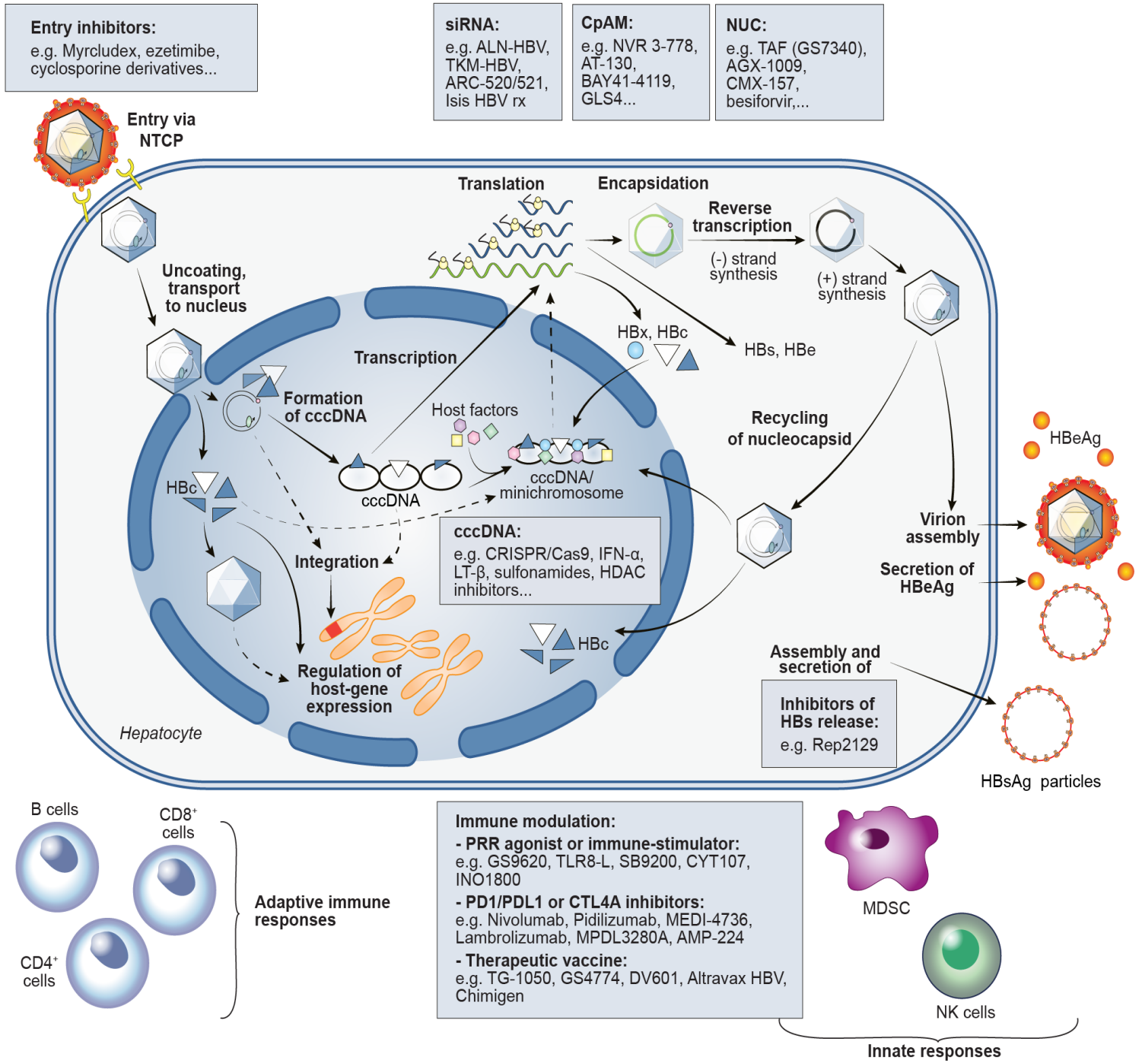
- **vaccination thérapeutique**

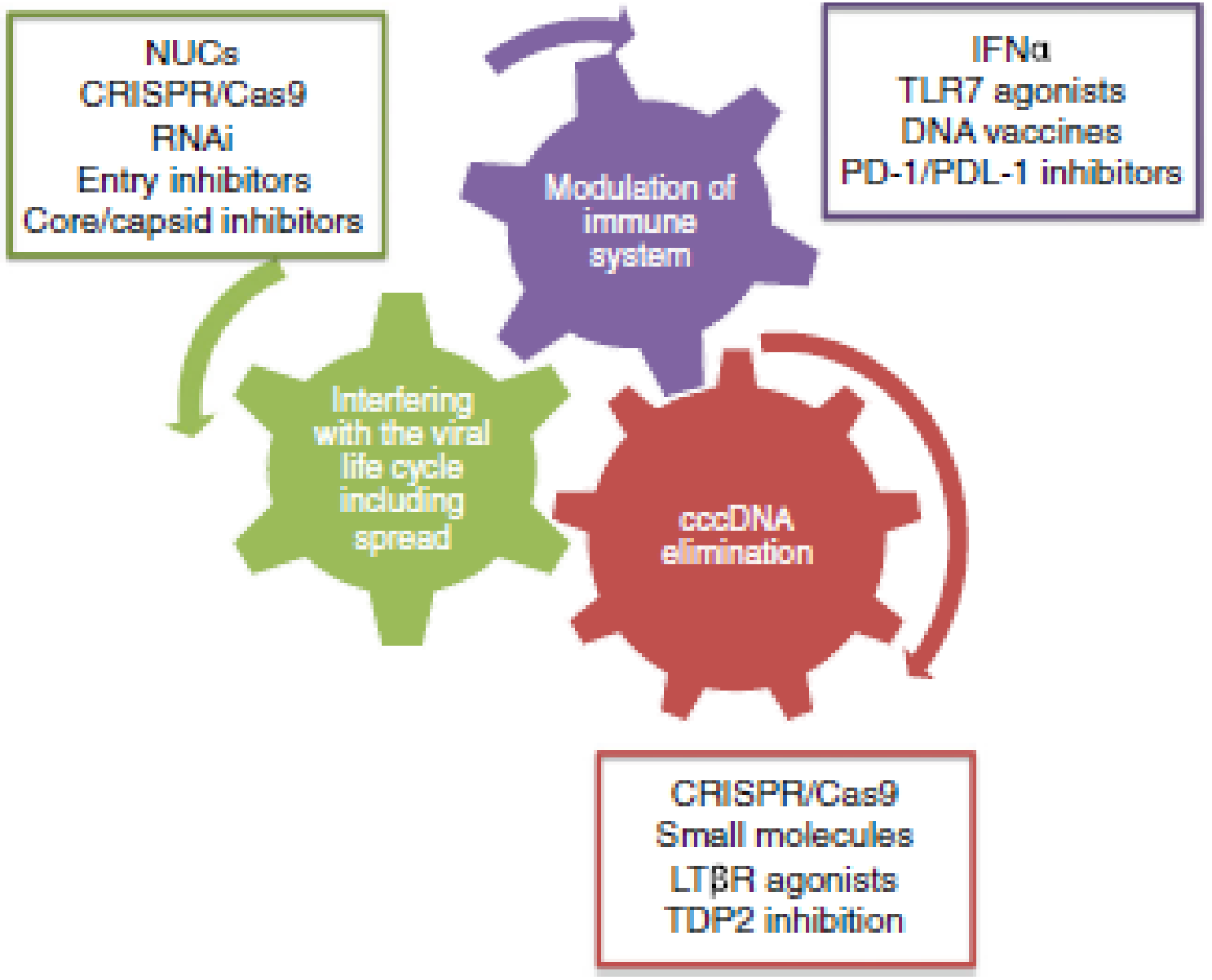
HBV cure – le pipeline

Testoni & Zoulim, Hepatology 2015
Durantel & Zoulim, J Hepatol 2016

- **ANRS HBV cure**
- **ICE-HBV** International Coalition to Eliminate Hepatitis B Virus

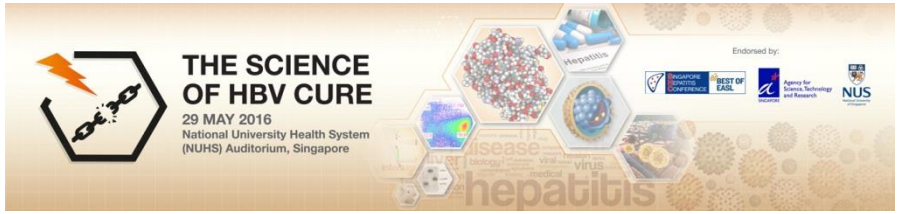
- cure fonctionnelle = contrôle sans traitement
- cure absolue = éradication cccDNA

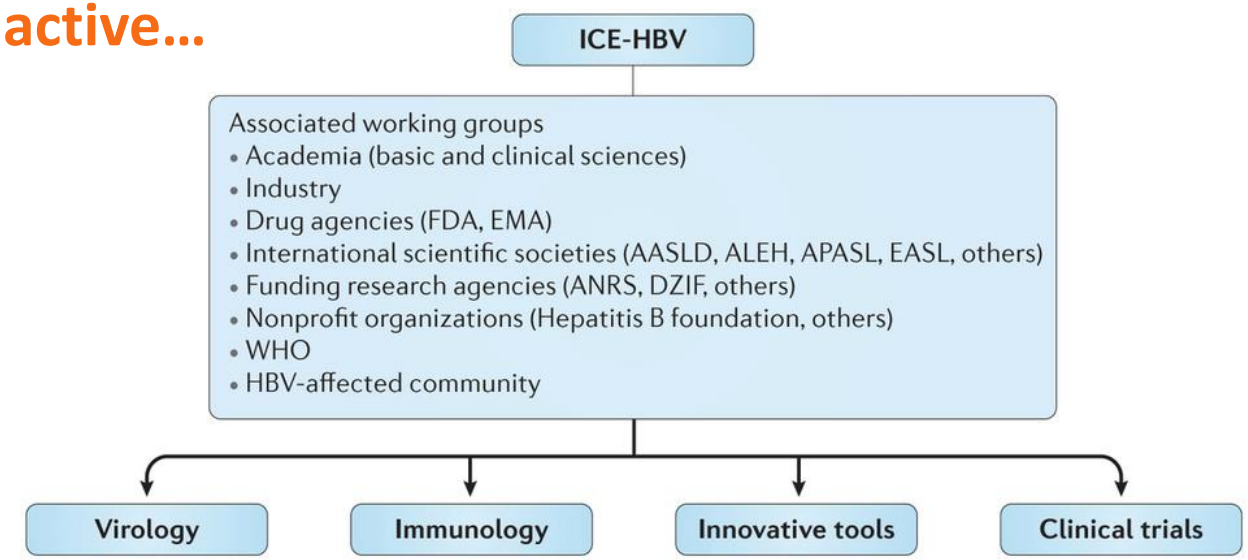


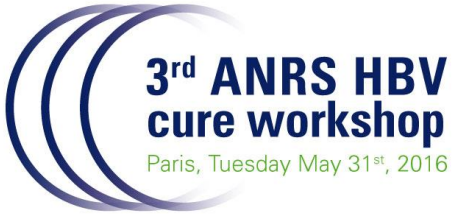


Bitton Alaluf and Shlomai, Liver Int 2016

Recherche très active…







Et sinon…