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Journée nationale de lutte contre les hépatites virales, 25 Septembre 2019

Etat de la recherche pour guérir l'hépatite B (HBV CURE)

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Circulation, metabolism, nutrition

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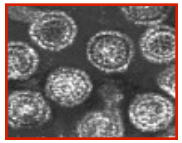
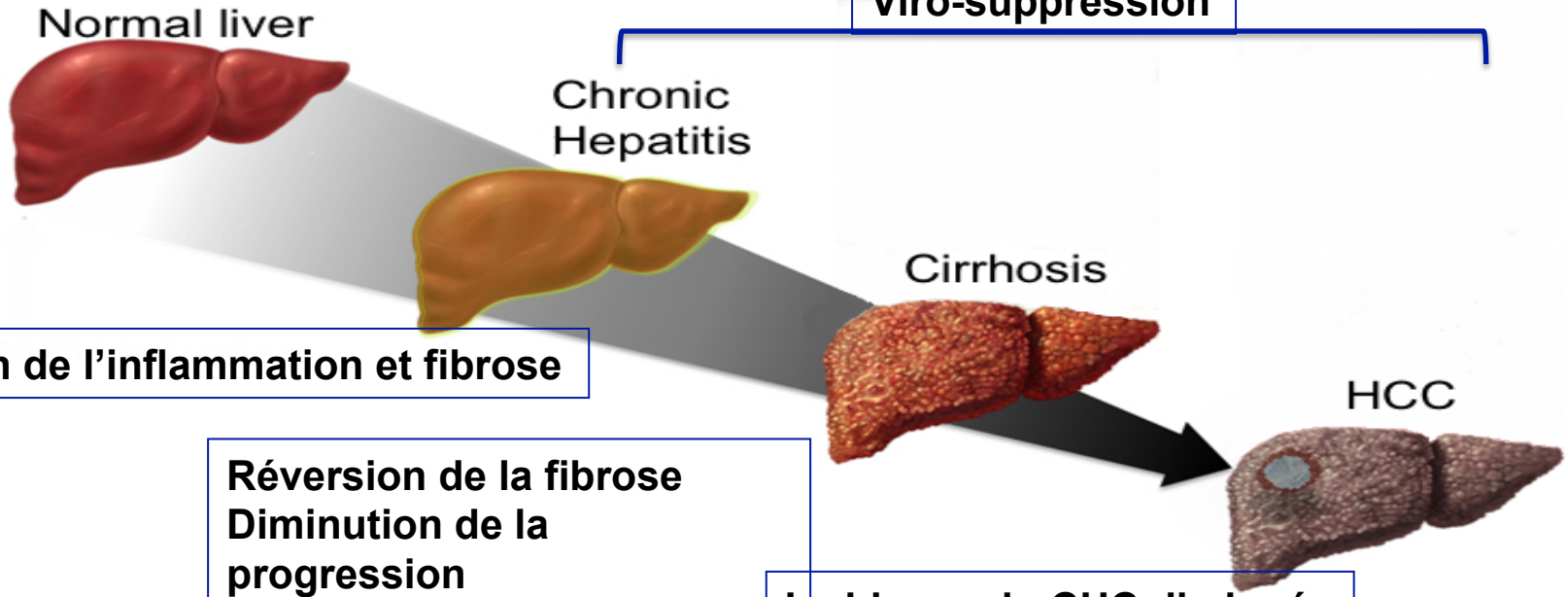
Liens d’intérêt

- BMS
- Gilead
- Janssen
- MSD

Traitements actuels: viro-suppression et rémission de la maladie hépatique





Viro-suppression

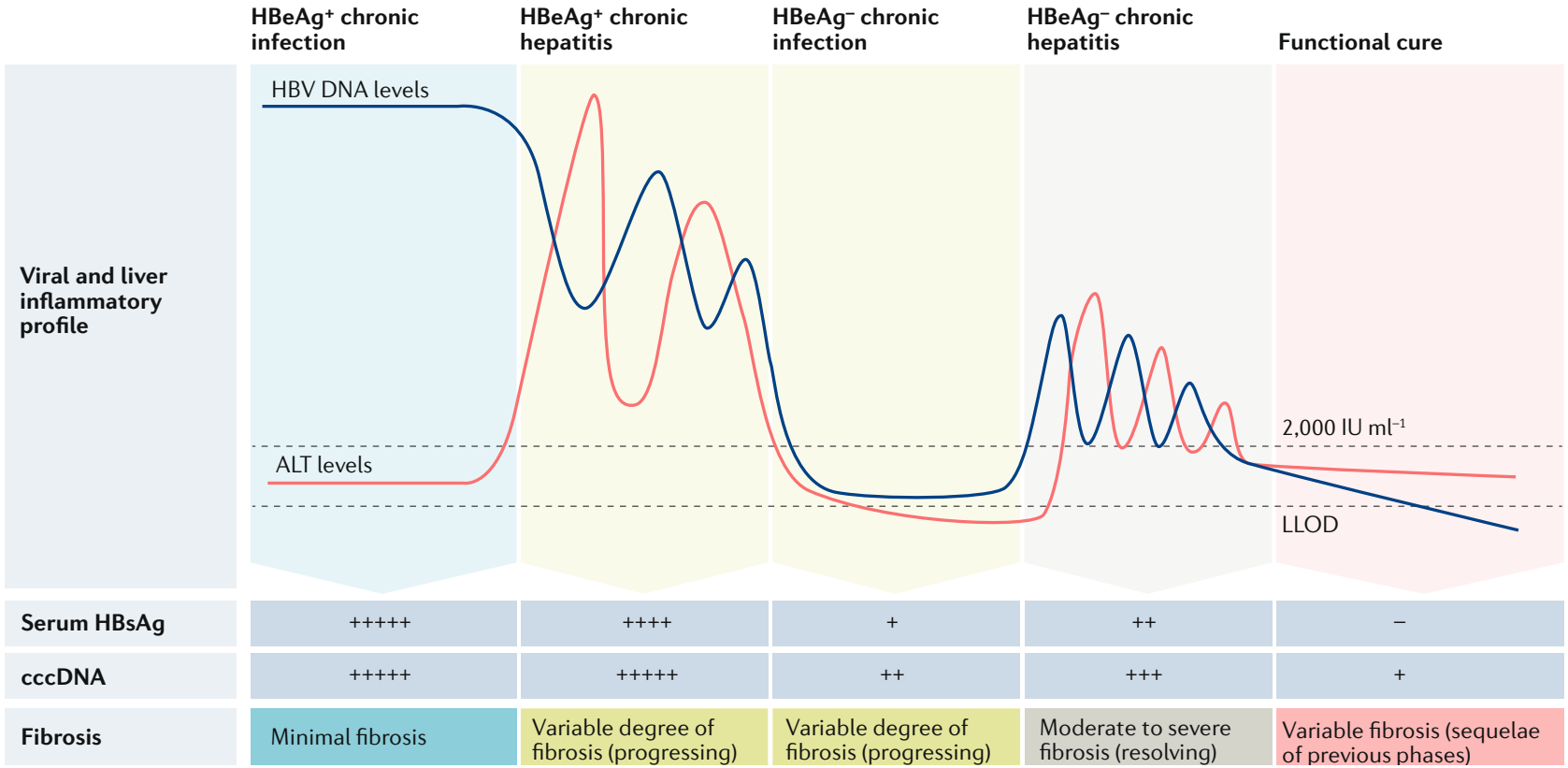
Amélioration de l'inflammation et fibrose

Réversion de la fibrose
Diminution de la progression

Incidence du CHC diminuée mais pas éliminée

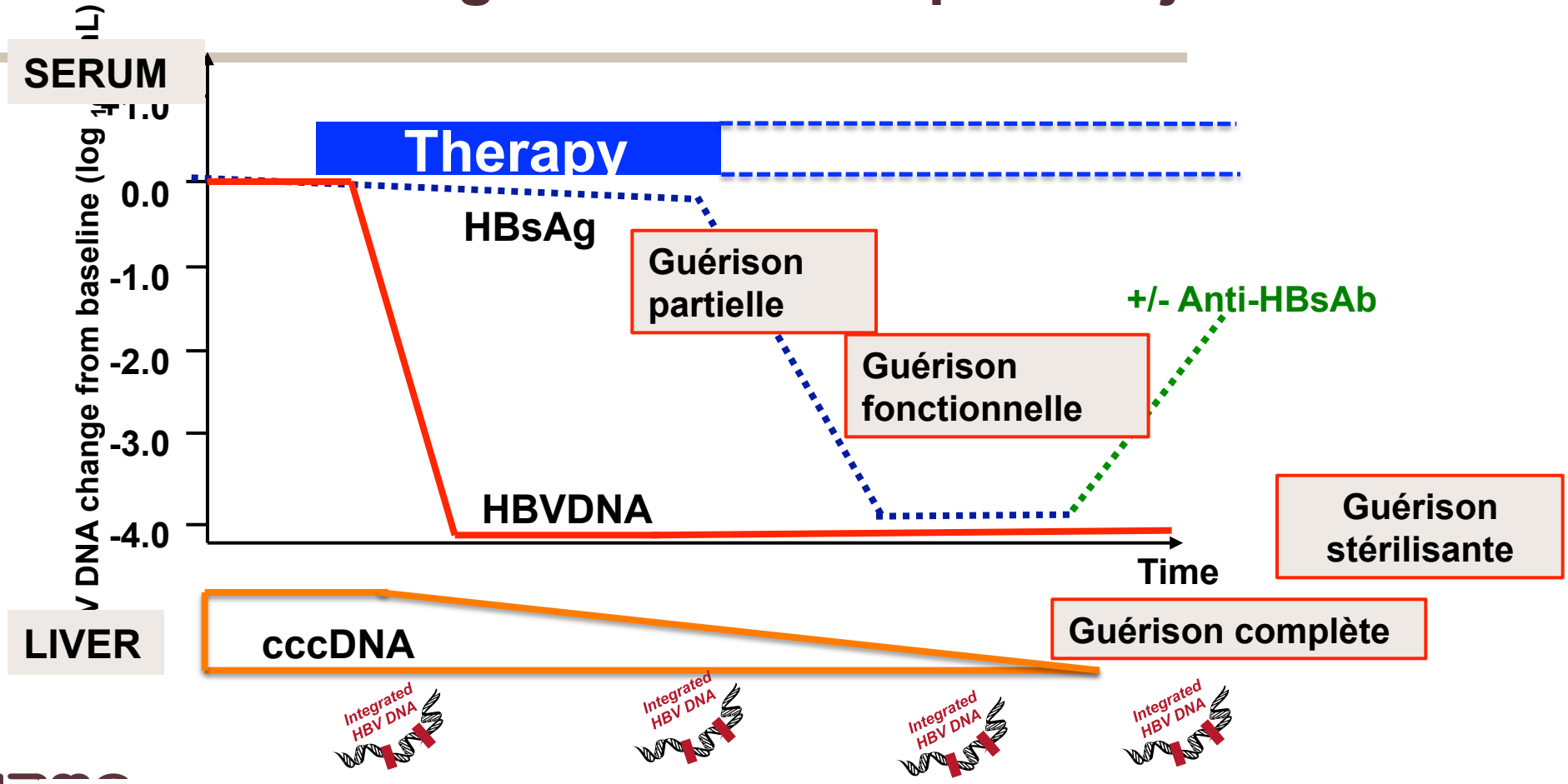
Liaw YF et al, N Engl J Med. 2004; Chang et al, Hepatology 2010; Marcellin et al, Lancet 2013; Hosaka et al, Hepatology 2013; Kim et al, Cancer 2015; Papatheodoridis et al, J Hepatol 2015 ; Zoulim EASL ILC 2016

Histoire naturelle de l'infection VHB



Fanning GC, et al. Nature Review 2019

Définition de la guérison HBV: quels objectifs ? 1



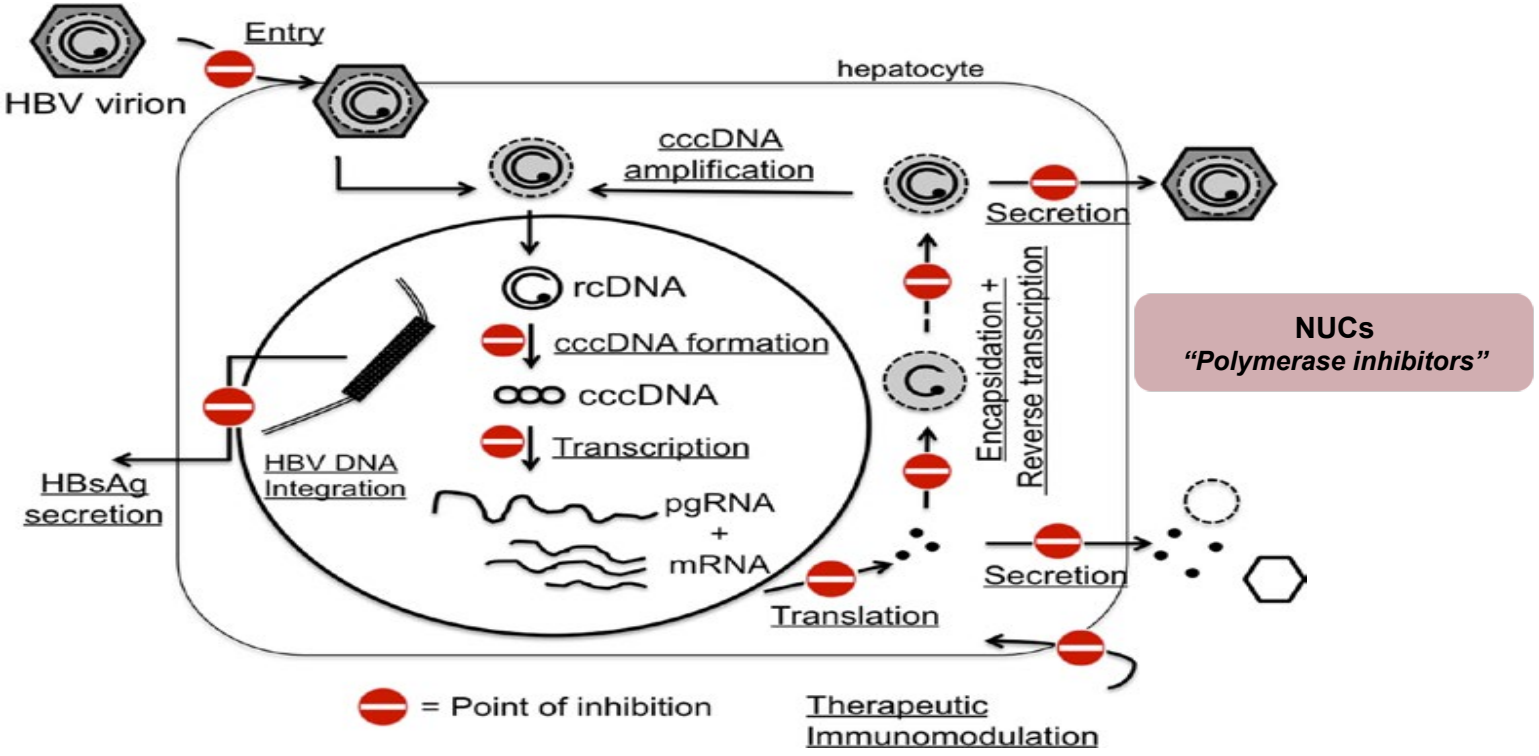
Lok et al, J Hepatol

Definition de la guérison HBV

- **« Guérison fonctionnelle »**
  - Arrêt du traitement avec risque minime de rechute.
  - Perte de l'AgHBs avec ou sans séroconversion HBs.
  - Persistance du cccDNA.
- **« Guérison complète »**
  - Elimination de l'AgHBs et du cccDNA.
  - La guérison complète devrait être associée avec une diminution du risque de progression de la maladie et de CHC.
  - L'impact de la persistance de séquences virales intégrées dans le génome doit être évalué.

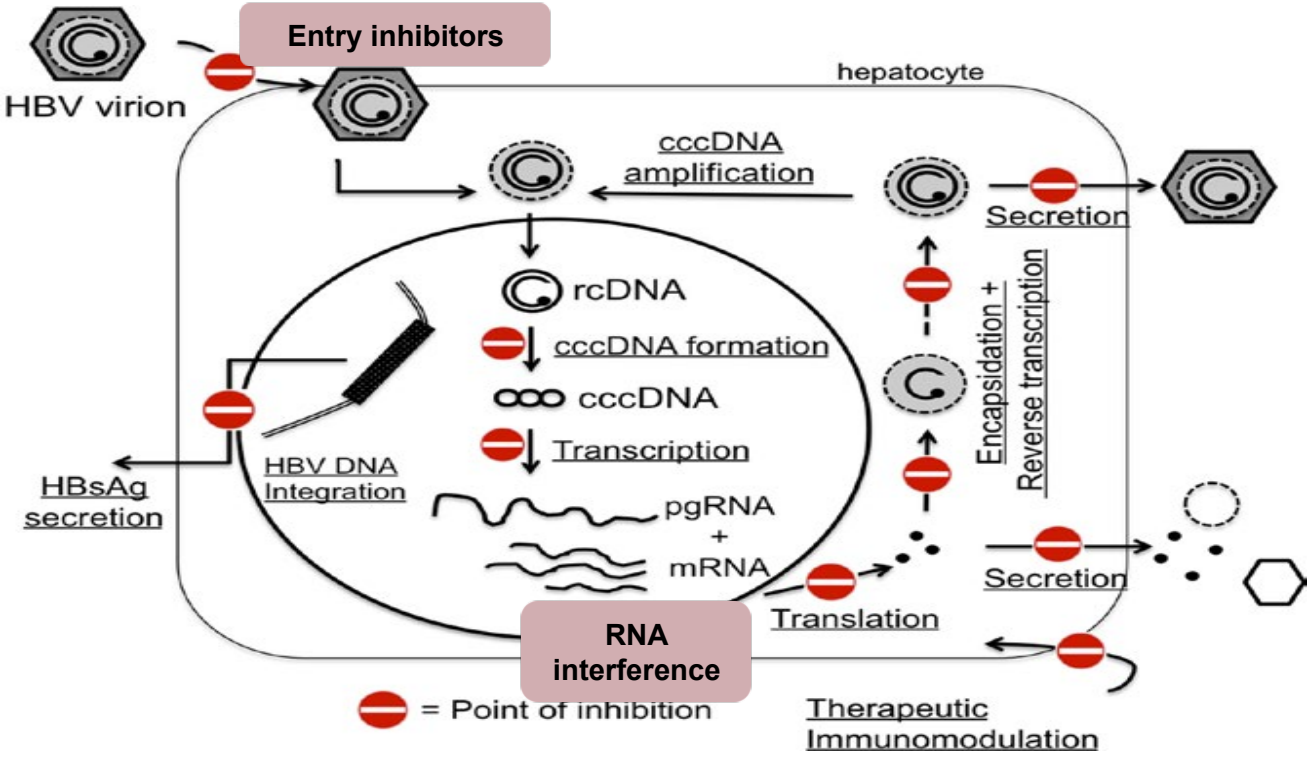
Zeisel, Lucifora et al, Gut 2015; Revill et al, Nature Reviews Gastroenterol Hepatol 2016

Les principales cibles antivirales et immunologiques



Schinazi R, et al. Liver Int 2018

Les principales cibles antivirales et immunologiques



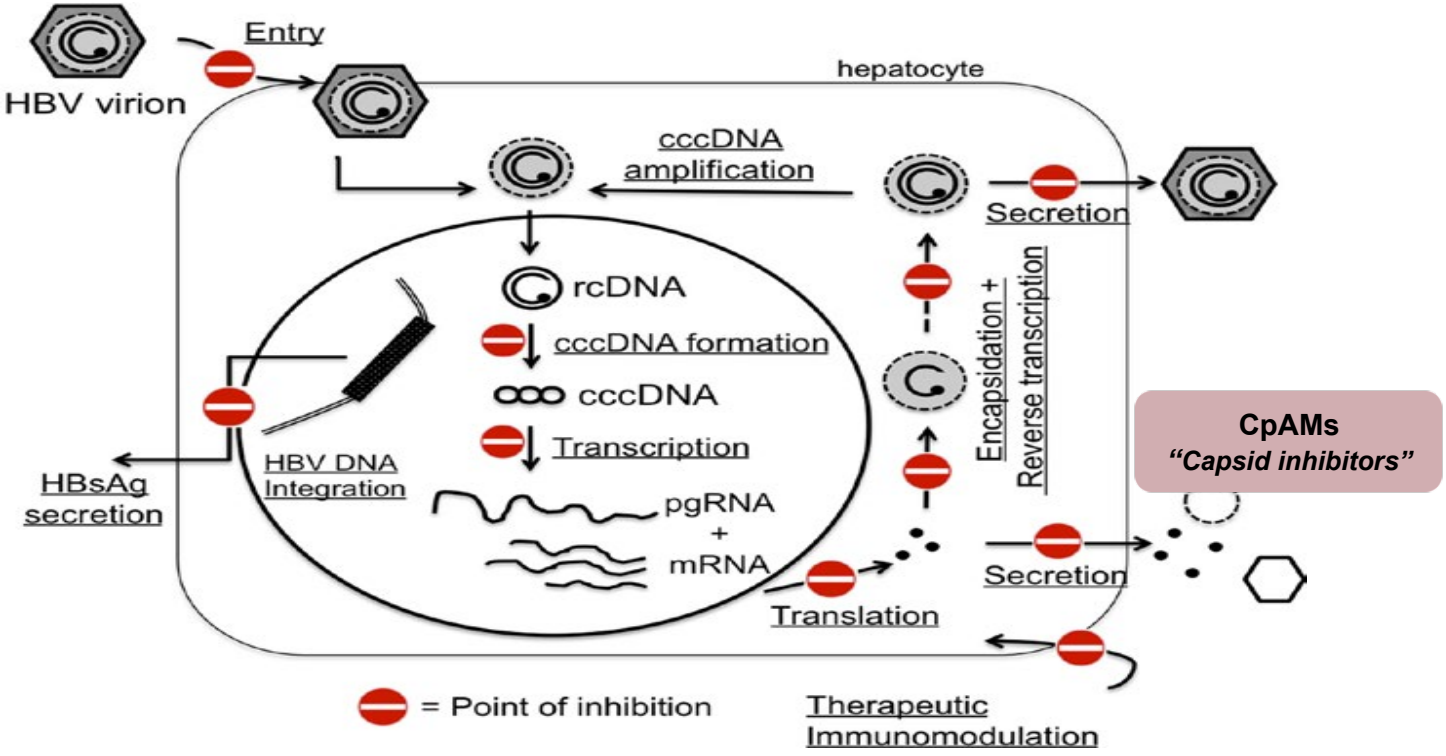
Schinazi R, et al. Liver Intern 2018

Inhibiteurs d'entrée et siRNA : les essais

Drug name	Sponsor	Mechanism of action	Class	Clinical stage	Notes
Entry inhibitors					
Myrcludex B (bulevirtide)	MYR Pharmaceuticals	Blocks NTCP	Peptide	II	2 mg Myrcludex B + IFNα treatment resulted in 40% responders with HBsAg loss observed in 26.7% of the cohort
CRV431	Contravir	Blocks NTCP and protein folding	Small molecule	I	Single-ascending-dose study performed up to a dose of 525 mg
Translation inhibitors					
JNJ3989	Janssen	mRNA degradation	siRNA	II	Most patients had HBsAg levels <100 IU mL^{-1} after 3 doses. Range of 1.3–3.8 (at nadir) log decrease in HBsAg levels
ARB-1467	Arbutus	mRNA degradation	siRNA	II	7 of 11 patients had >1 log decrease in HBsAg levels after 10 weeks of dosing (responders). Biweekly dosing better than monthly dosing
GSK3389404	GlaxoSmithKline	mRNA degradation	ASO	II	Safe and well tolerated in healthy volunteers

Fanning GC, et al. Nature Review 2019

Les principales cibles antivirales et immunologiques



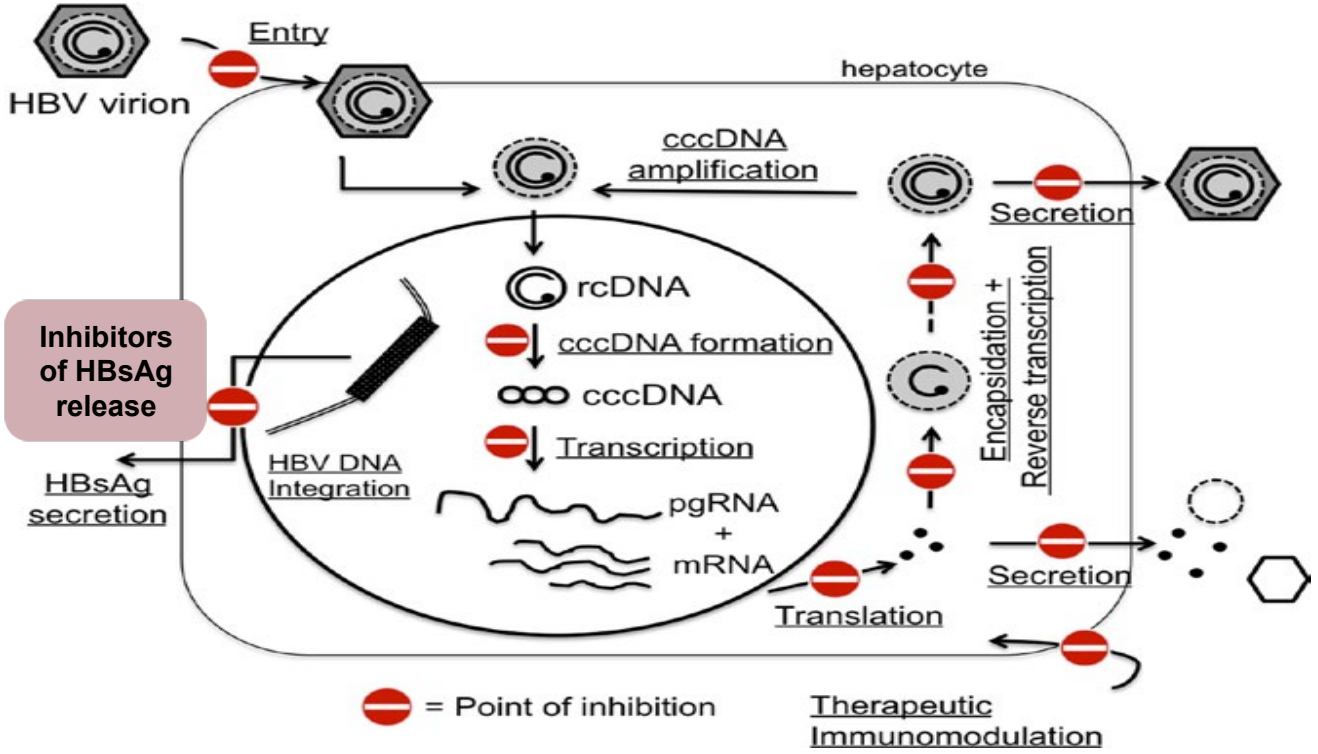
Schinazi R, et al. Liver Intern 2018

Inhibiteurs de capside : les essais

Drug name	Sponsor	Mechanism of action	Class	Clinical stage	Notes
Capsid assembly inhibitors					
ABI-H0731	Assembly	Core binding	Small molecule	II	Combined with entecavir, ABI-H0731 caused a 4.54 log decrease in HBV DNA levels at 12 weeks and a 5.94 log decrease at 24 weeks
JNJ6379	Janssen	Core binding	Small molecule	II	Mean DNA level log decrease of 2.16–2.89 and a dose correlation for a number of patients who had a DNA level less than the LOQ at the end of the trial (28 days)
JNJ0440	Janssen	Core binding	Small molecule	I	Single and multiple-ascending-dose studies in healthy volunteers. Doses up to 2,000 mg QD well tolerated in the 7-day multiple-ascending-dose study
GLS4	HEC Pharma	Core binding	Small molecule	II	Interim (20 week) data showed DNA level log reduction of 1.48–5.58 for BID administration and 1.51–6.09 log reduction for TID administration
RO7049389	Roche	Core binding	Small molecule	II	Median DNA level declines of 2.7 (200 mg BID), 3.2 (400 mg BID) and 2.9 (600 mg QD) observed at the end of the trial (28 days)
AB-506	Arbutus	Core binding	Small molecule	I	10-day study in healthy volunteers completed

Fanning GC, et al. Nature Review 2019

Les principales cibles antivirales et immunologiques



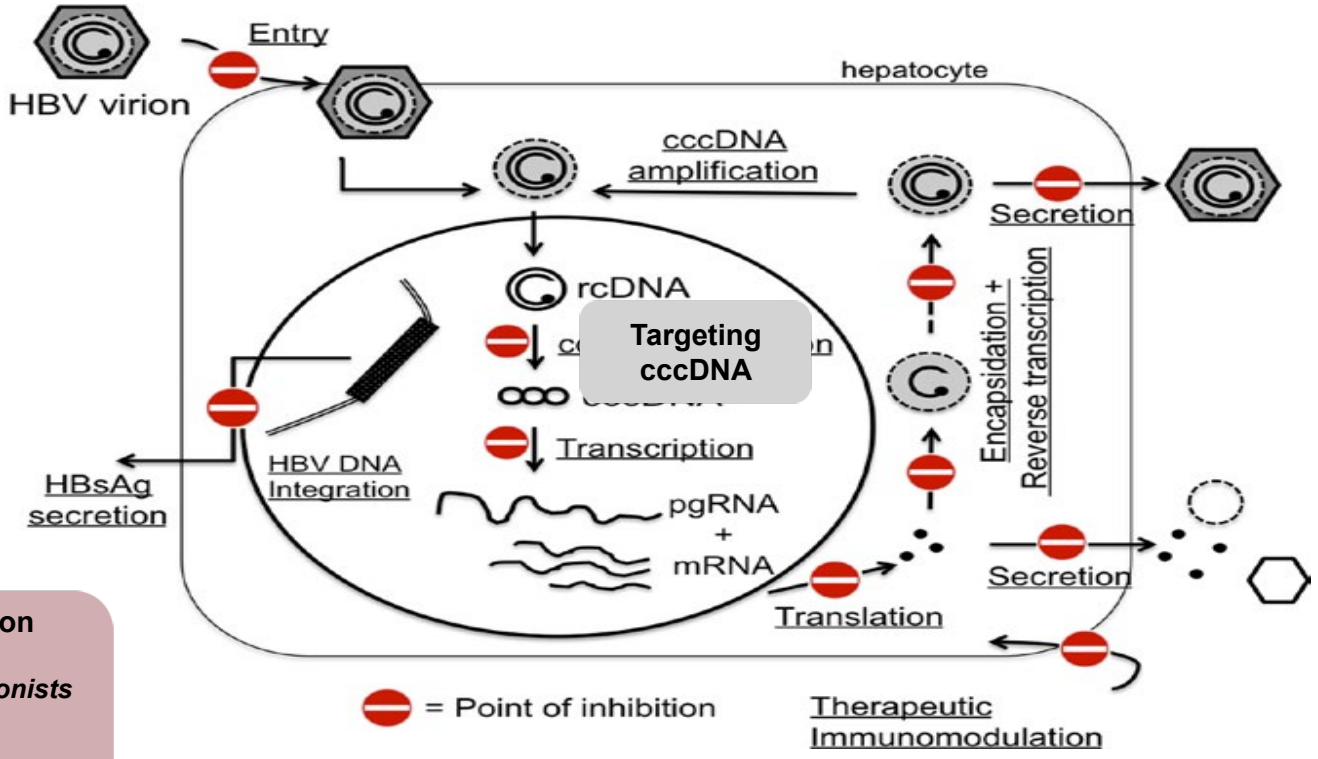
Schinazi R, et al. Liver Intern 2018

Inhibiteurs de secretion de l'AgHBs: les essais

Drug name	Sponsor	Mechanism of action	Class	Clinical stage	Notes
HBsAg secretion inhibitors					
REP 2139 and REP 2165	Replicor	HBsAg binding	Nucleic acid-based polymer	II	At the end of the trial, 60% of patients had HBsAg loss (53% had HBsAg loss at 24 weeks and 50% had HBsAg loss at 48 weeks). Anti-HBs antibodies were detectable in 56% of patients at 48 weeks

Fanning GC, et al. Nature Review 2019

Les principales cibles antivirales et immunologiques

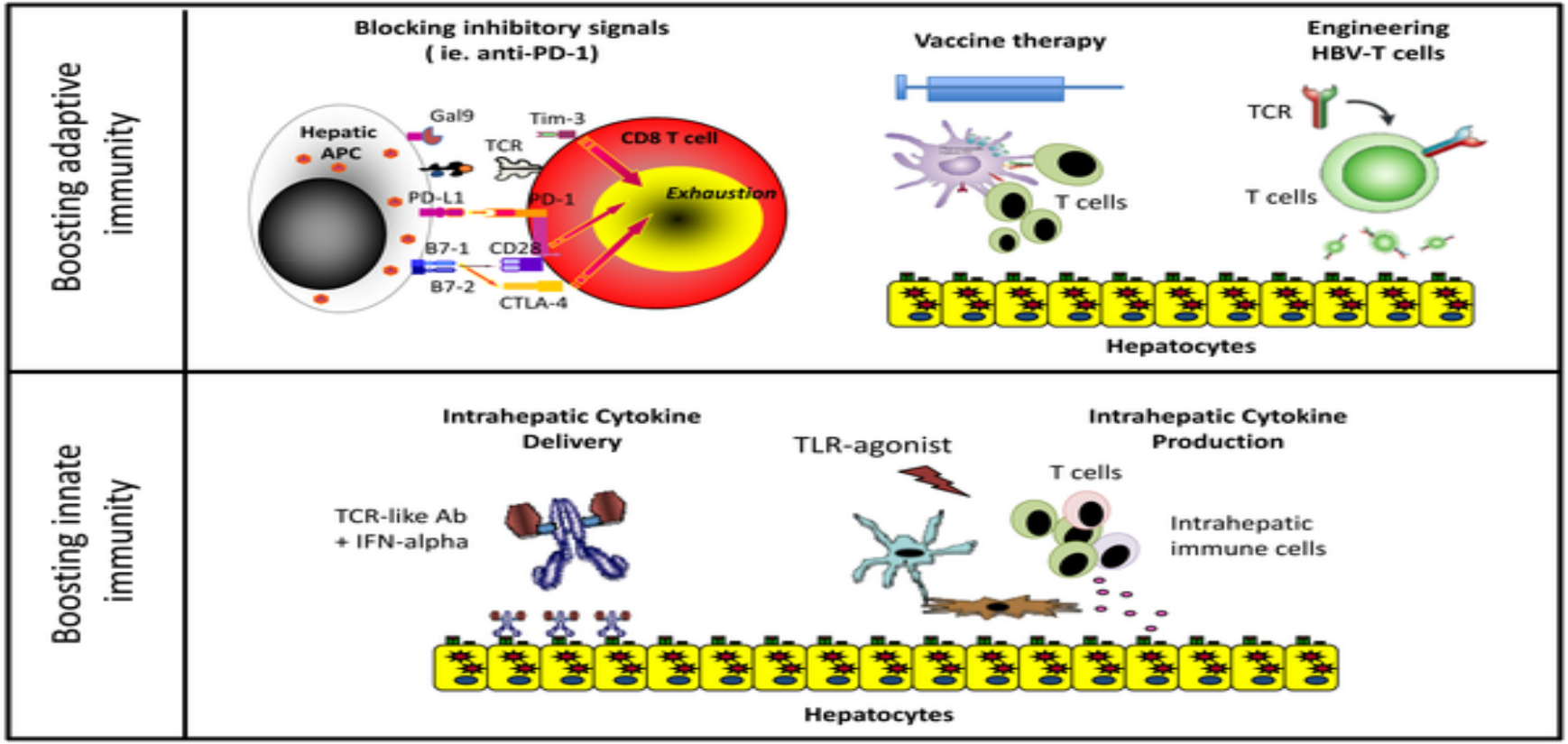


Immune modulation

- ***Toll-like receptors agonists***
- ***Anti-PD-1 mAb***
- ***Vaccine therapy***
- ***Redirection of T cells***

Schinazi R, et al. Liver Intern 2018

Comment restaurer l'immunité antivirale ?



Bertoletti A (2013); PLoS Pathog

Immunomodulateurs: les essais

Drug name	Sponsor	Mechanism of action	Class	Clinical stage	Notes
Innate immunity activators					
Inarigivir	Springbank	RIG-I agonist and polymerase inhibitor	Small molecule	II	Dose-dependent decrease in HBV DNA levels (1.54 log decrease with 200 mg). After switch to TDF, 88% of participants had DNA levels below the LOQ
RO7020531	Roche	TLR7 agonist	Small molecule	I	Immune activation observed in all patients. No viral data reported
GS-9620	Gilead	TLR7	Small molecule	II	No change in HBsAg levels. Transient dose-dependent induction of ISG15 and change in NK cell and T cell phenotype observed
GS-9688	Gilead	TLR8	Small molecule	I	Dose-dependent IL-12 and IL-1β production noted in healthy volunteers
Adaptive immunity activators					
TG-1050 (T101)	Transgene/Talsy	Vaccine	Ad5 delivery	I	HBV T cell responses induced by vaccine. Anti-Ad5 antibodies seen with higher dose. Mean 0.45 log decrease in HBsAg levels observed at day 197
HepTcell	Altimmune	Vaccine	Peptide plus IC31 (adjuvant)	I	T cell responses strongest for vaccine plus adjuvant. Safe, but no decline in HBsAg levels was observed after three administrations of vaccine

Nouveaux endpoints, nouveaux biomarqueurs

- **Quantification de l'AgHBs**
  - perte de l'AgHBs: critère de jugement des nouveaux traitements
  - corrélé au cccDNA et HBVDNA intégré
- **RNA circulant**
  - inhibiteurs de capside
  - corrélé à l'activité transcriptionnelle du cccDNA
- **AgHBcr**
  - corrélé à l'HBV DNA et le cccDNA
  - prédit la rechute à l'arrêt des NUC
- **Le retour de la biopsie hépatique ?**
  - Evaluation du cccDNA: quantification, epigenetics
  - Immunité intrahepatique : ISGs, Immune cells

L’hépatite Delta: essais thérapeutiques

Compound	Phase of development	Comments / Data
Entry (NTCP) inhibitor **Myrcludex (Bulevirtide) (Myr Pharma-ceuticals)**	Phase 3 (in progress)	• s.c. application • well tolerated in phase 1/2 clinical studies • increase in bile acids (no itching) • monotherapy: decrease in HDV RNA, no effect on HBsAg (135) • combination with PEG-IFN alfa: stronger effect on HDV RNA and HBsAg decline (136)
Farnesyltransferase inhibitor Lonafarnib (Eiger)	Phase 3 (in progress)	• oral application • higher doses associated with GI side effects (137) • boosting with ritonavir allows lower doses and reduced side effects • monotherapy: HDV RNA decline, no effect on HBsAg • combination with PEG-IFN alfa: stronger effect on HDV RNA • post-treatment viral and biochemical flares, which were associated with subsequent HDV RNA and ALT response (138)
Interferon Pegylated Interferon lambda (Eiger)	Phase 2	• s.c. application • fewer adverse events compared with PEG-IFN alfa • on treatment ALT flares • > 2log decrease of HDV RNA in 50% (139)
Nucleic acid polymers (REP compound series) (Replicor)	Phase 2	• i.v. application • in combination with TDF and PEG-IFN alfa: ALT flares • strong effect on HDV RNA and HBsAg (44)

Hépatite Delta : ATU Myrcludex

- ATU nominative, puis de cohorte
  - Fibrose F3/F4, F2 avec cytolyse
  - Monothérapie ou association avec PEGIFN
  - Possibilité d'augmenter la posologie
- Observatoire ANRS en collaboration avec ANSM (BlueDelta)

L’ANRS : un acteur majeur

- Actions Coordonnées
- Cohorte HEPATHER
- Observatoires ATU
- Workshop HBV Cure : meeting international annuel
- Relations internationales ICE-HBV

Vaccination chez le nouveau-né: diminution de l'incidence du CHC à Taiwan en 20 ans

Variable	Group	Person-years	No. of HCCs	RR (95% CI)	*P*
Birth cohort	Nonvaccinated	78 496 404	444	1.00 (referent)	
	Vaccinated	37 709 340	64	0.31 (0.24 to 0.41)	<.001
Age, y	6–9	32 051 011	100	1.00 (referent)	
	10–14	41 404 604	180	1.18 (0.92 to 1.51)	.183
	15–19	42 750 129	228	1.26 (0.99 to 1.60)	.065
Sex	Female	56 129 109	140	1.00 (referent)	
	Male	60 076 635	368	2.50 (2.04 to 3.01)	<.001

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[I]*Chang MH et al. Natl Cancer Inst 2009*