New Targets for HBV Therapy

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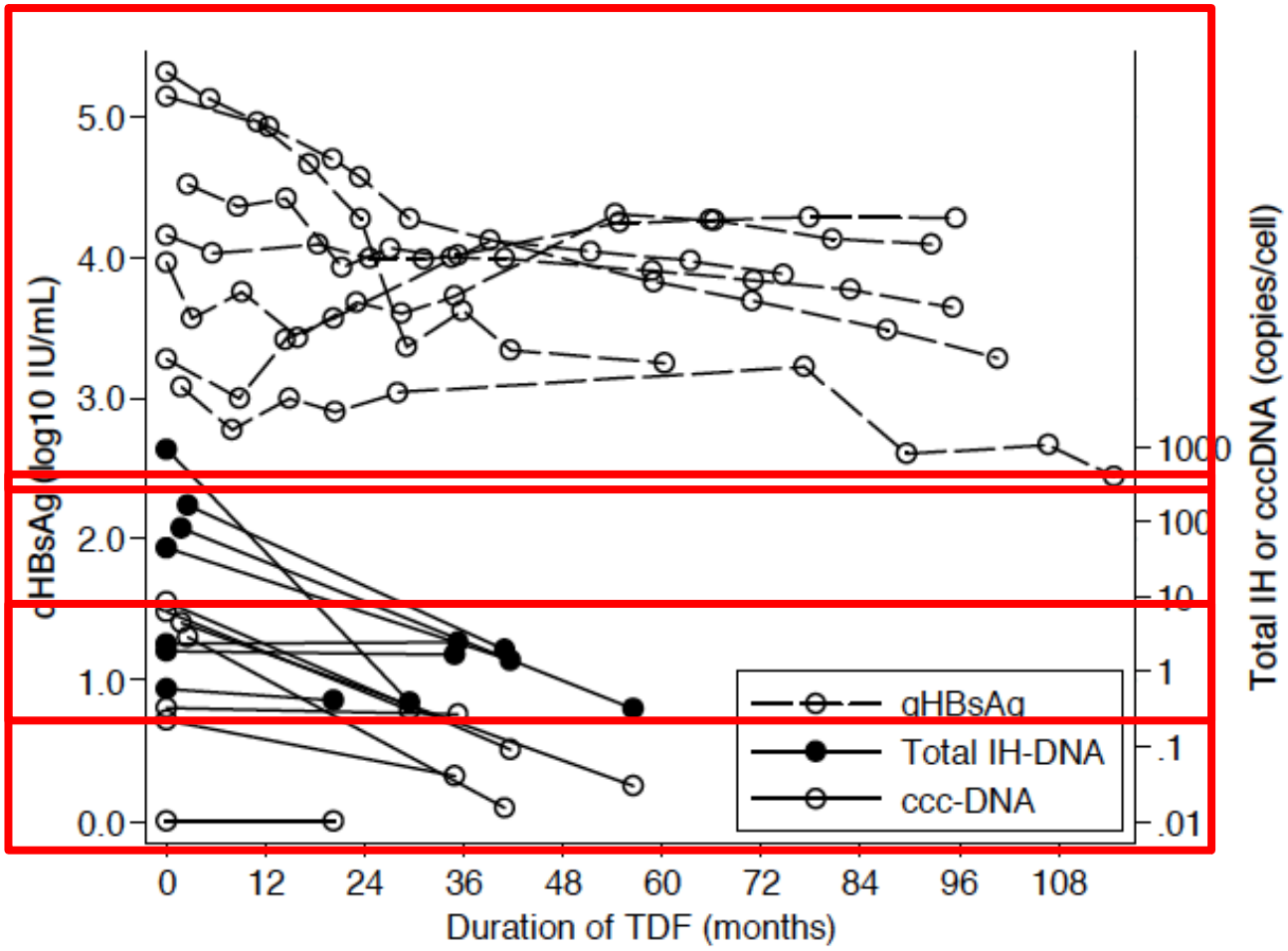
Virus suppression but persistence of intrahepatic viral DNA synthesis during



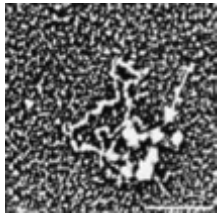
New round of infection and/or replenishment of the cccDNA pool occur despite « viral suppression »

Boyd et al, J Hepatol 2016

Major virologic discoveries for HBV cure research programs

- **Better knowledge of the viral life cycle**

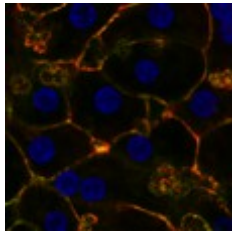
  Receptor – cccDNA - HBx



- **Improvement of cell culture for target identification and drug screening**

  Hepatoma cell lines – receptor and cccDNA formation

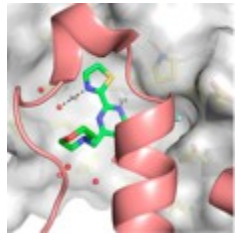
  Primary Human Hepatocytes and other culture systems



- **Improvement of animal models for target identification and drug screening**

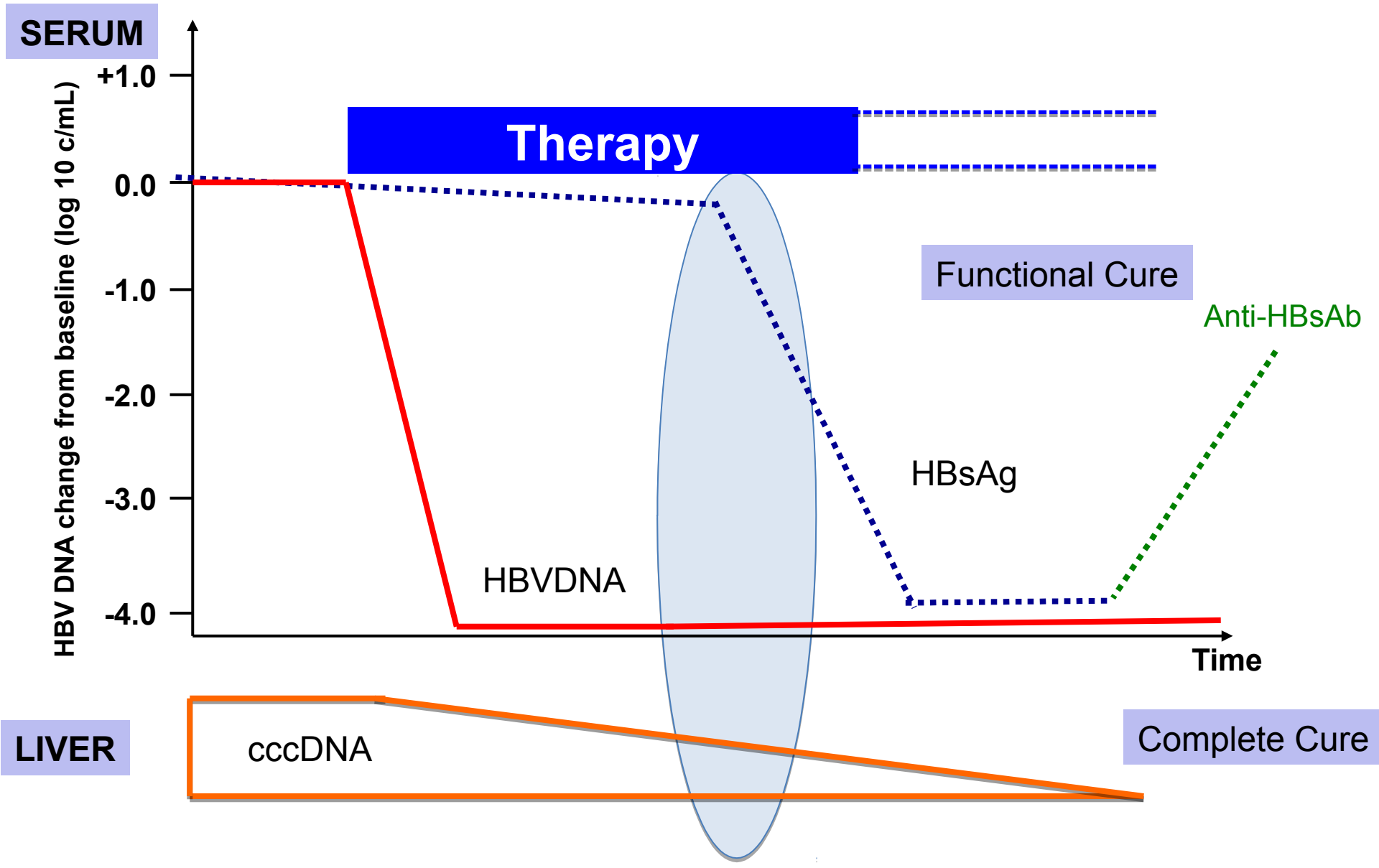
  Liver humanized mouse models

- **Identification & characterization of novel targets**

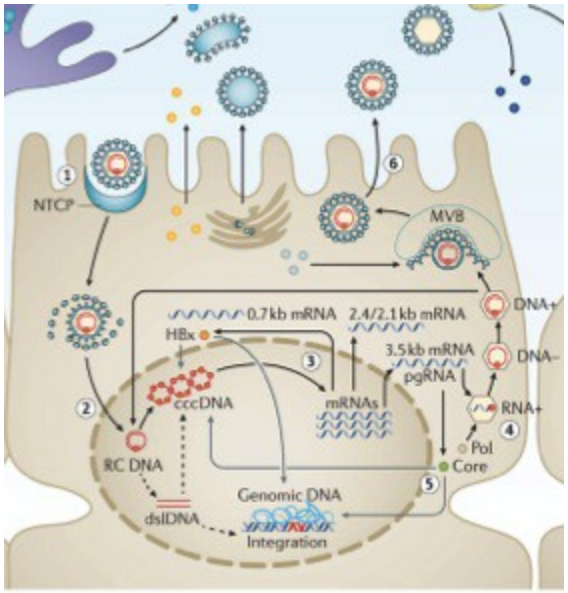


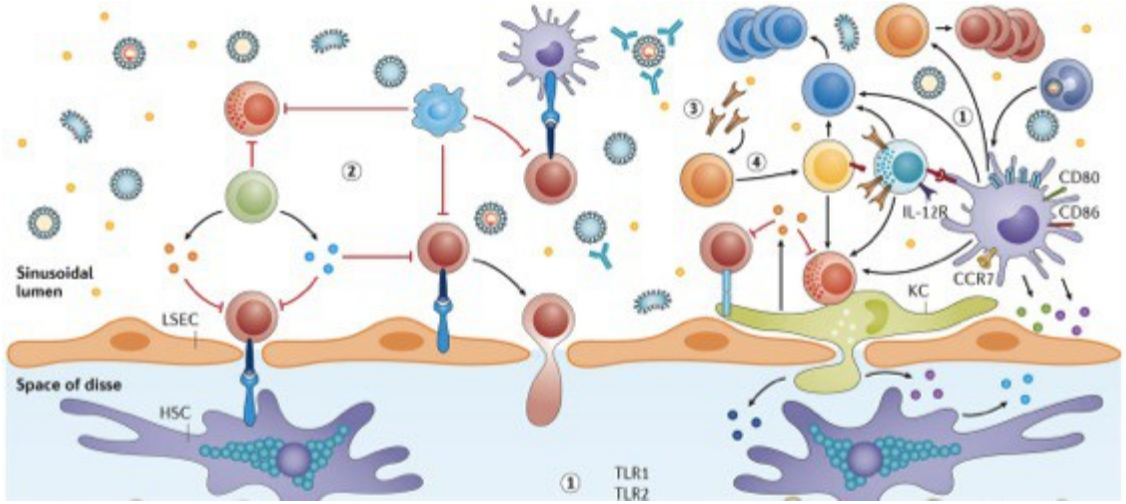
Zeisel et al, Gut 2015; Li et al, elife 2012; Königer et al, PNAS 2014; Shlomai et al, PNAS 2014; March et al, Nat Protoc 2015; Dandri et al J Hepatol 2016; Decorsière et al Nature 2016

New treatment concepts for HBV cure



Mechanisms of viral persistence





cccDNA reservoir

Antigenic load

Liver tolerance

HBV persistence

Defective CD8+ response

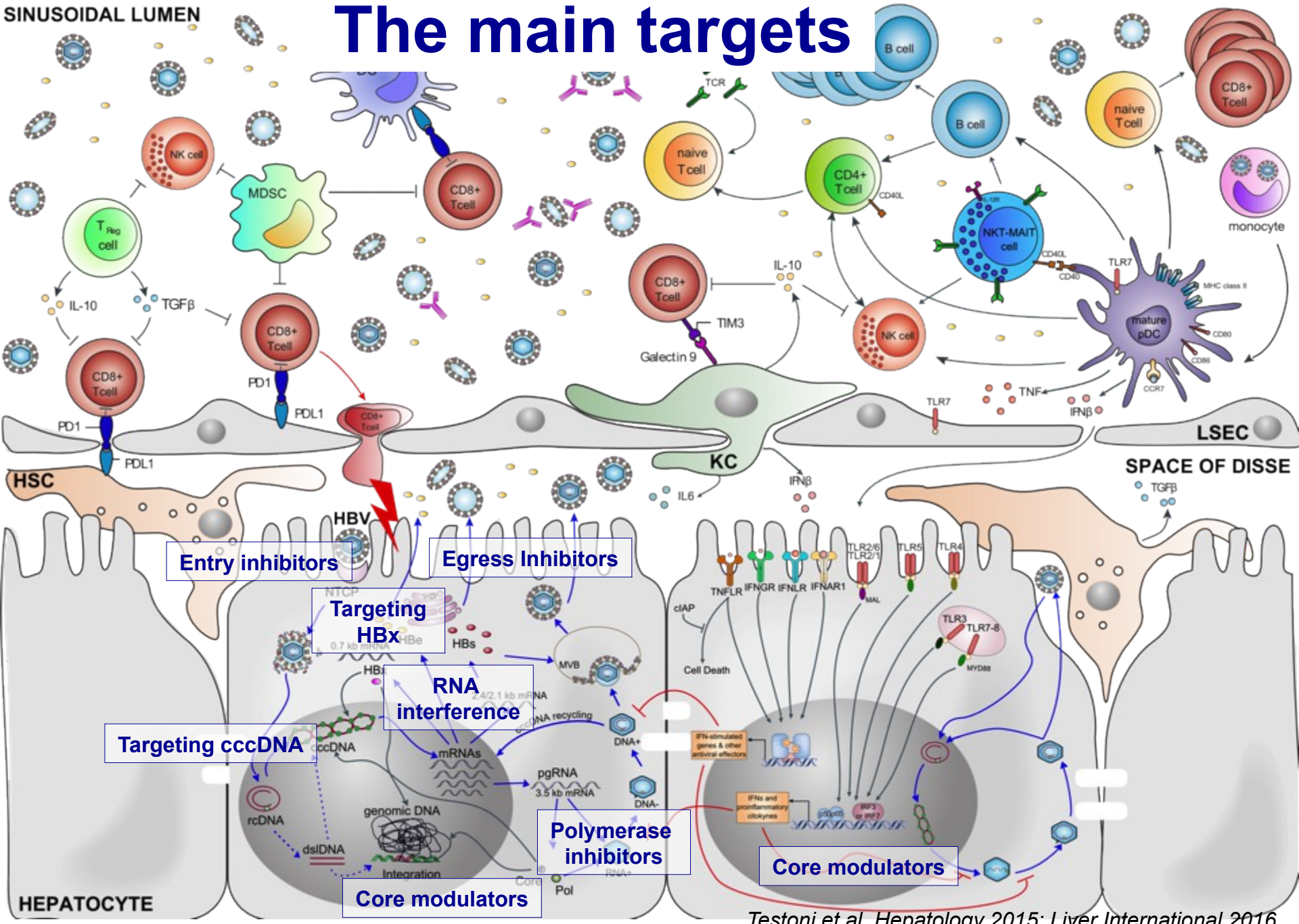
Defective B cell response

Inefficient innate response

Defective immune responses

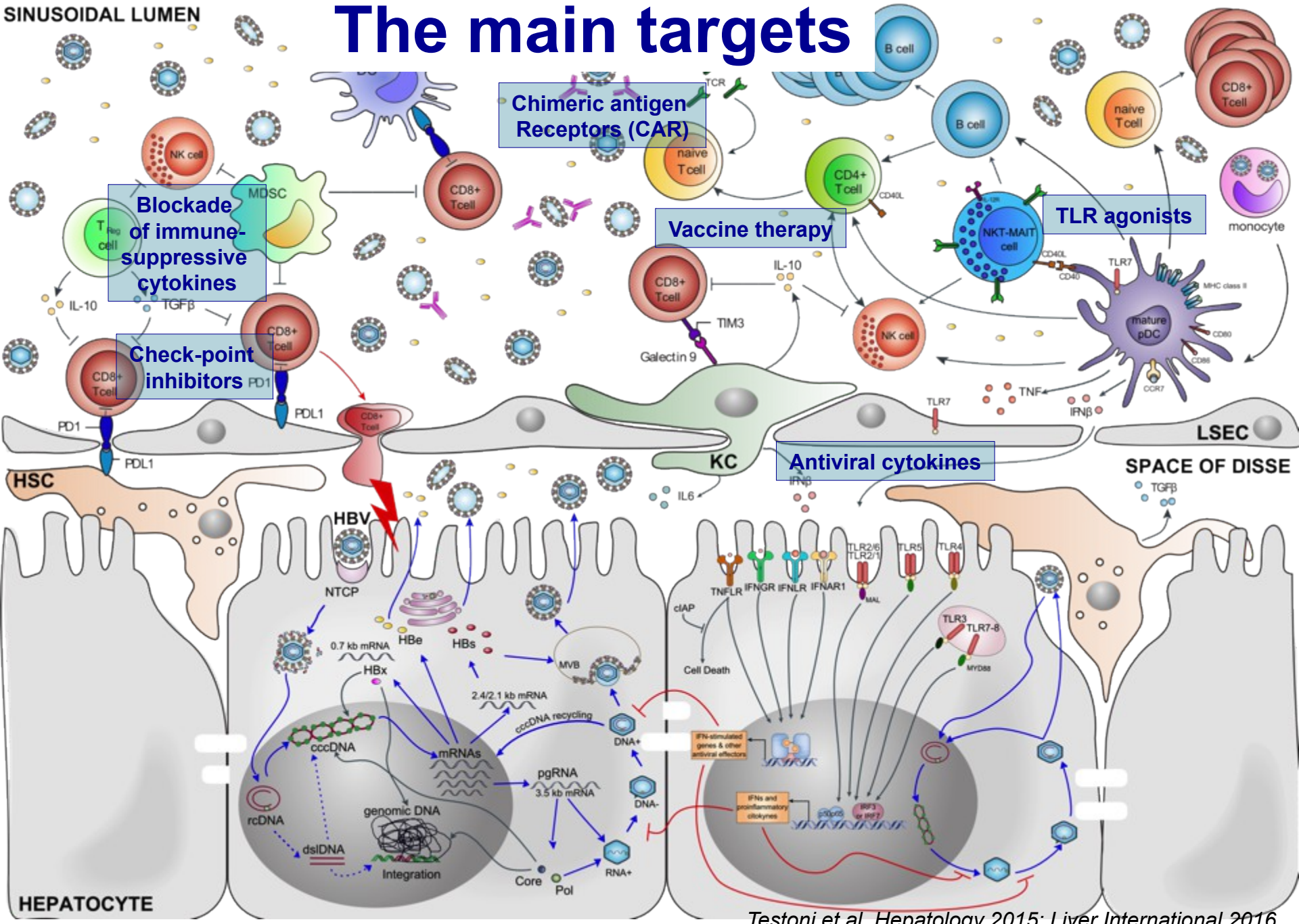
Locarnini, S. & Zoulim, F. et al. (2016) Global strategies are required to cure and eliminate HBV infectionNat. Rev. Gastroenterol. Hepatol.

The main targets



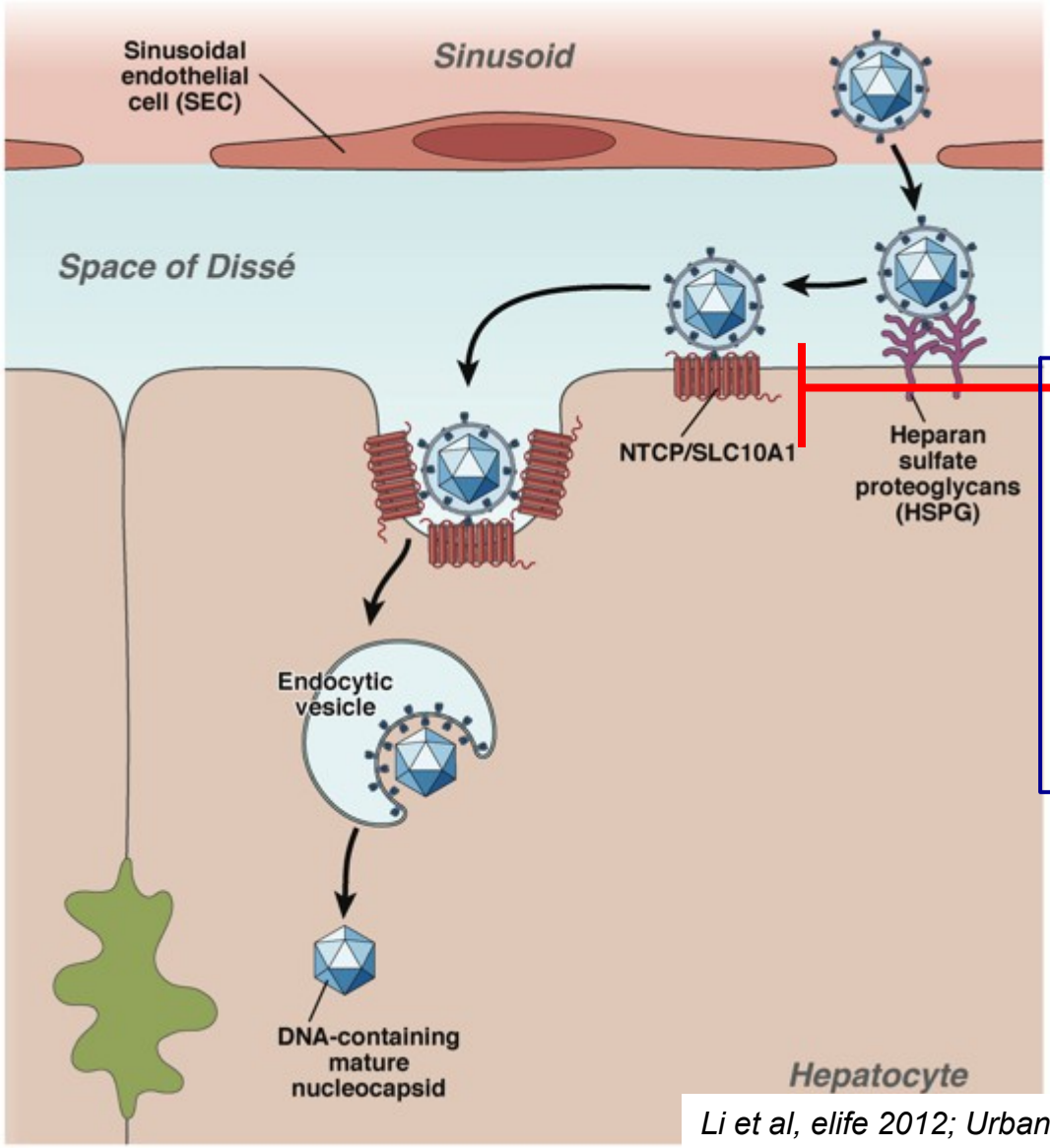
Testoni et al, Hepatology 2015; Liver International 2016

The main targets



Testoni et al, Hepatology 2015; Liver International 2016

Model for HBV entry in hepatocytes and development of entry inhibitors



Entry inhibitors

Myrcludex (pre-S1 peptide)

Blank et al, J Hepatol 2016

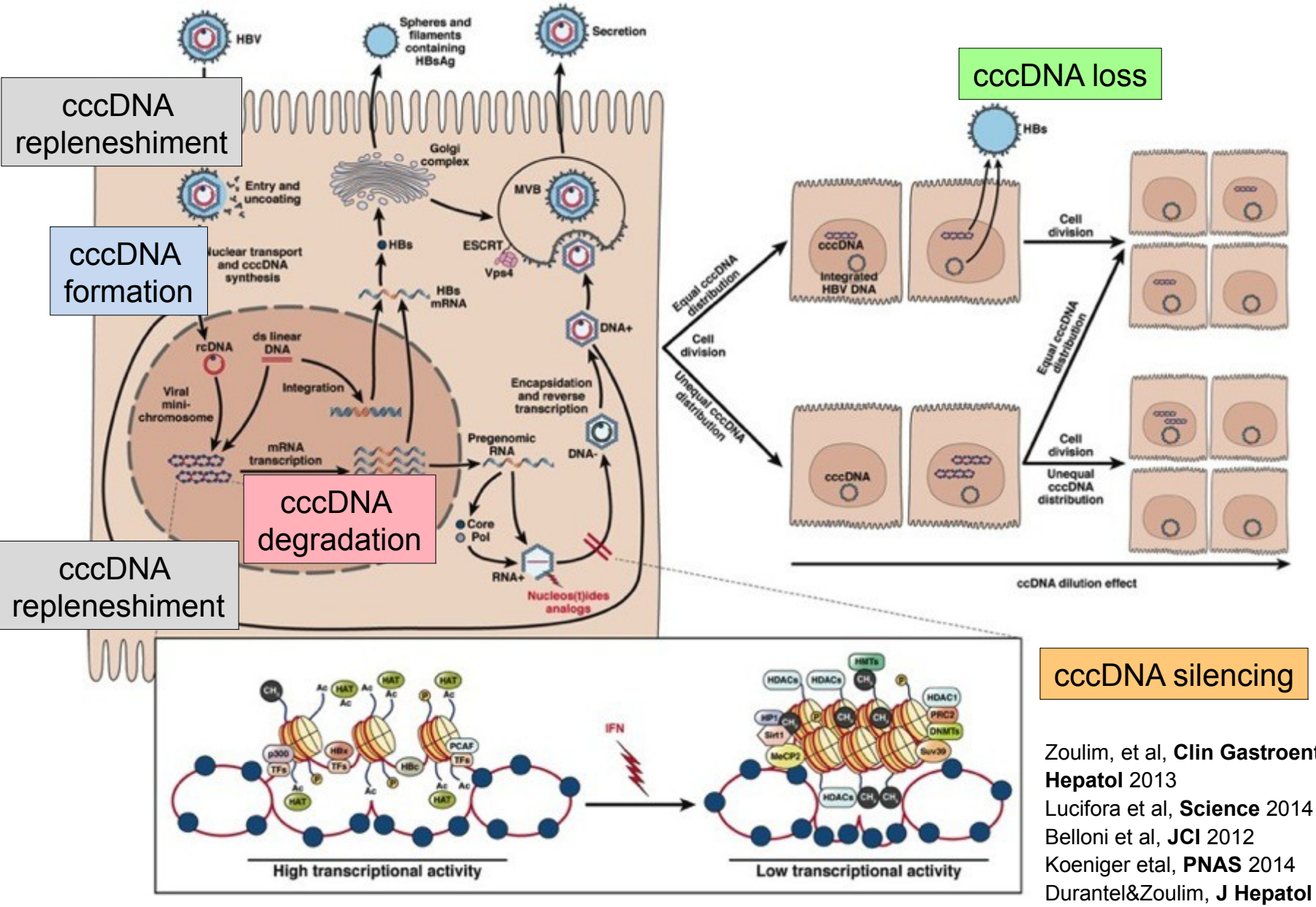
Bogomolov et al, J Hepatol 2016

Ezetimib

Cyclosporin

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

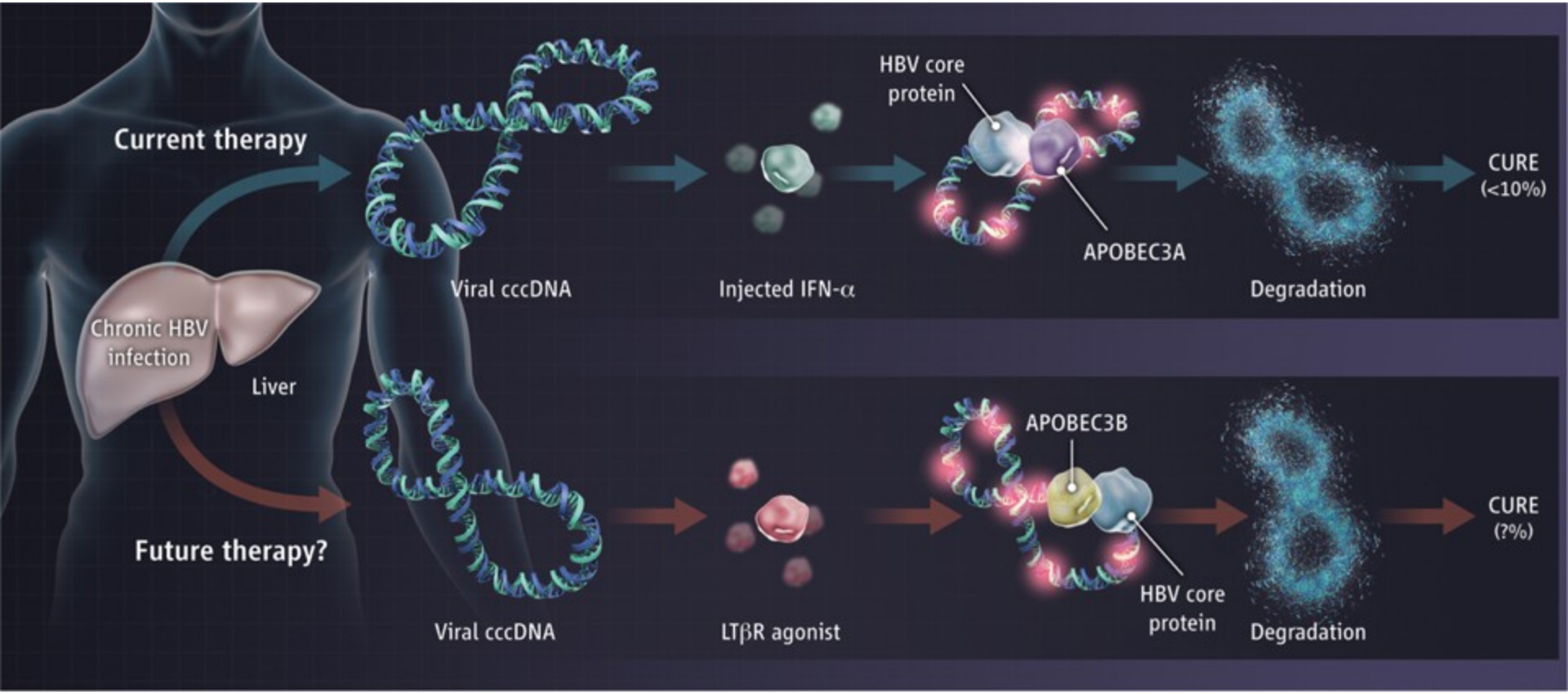
Targeting cccDNA, the viral minichromosome



Zoulim, et al, **Clin Gastroenterol Hepatol** 2013
Lucifora et al, **Science** 2014
Belloni et al, **JCI** 2012
Koeniger etal, **PNAS** 2014
Durantel&Zoulim, **J Hepatol 2016**

Model for cccDNA degradation

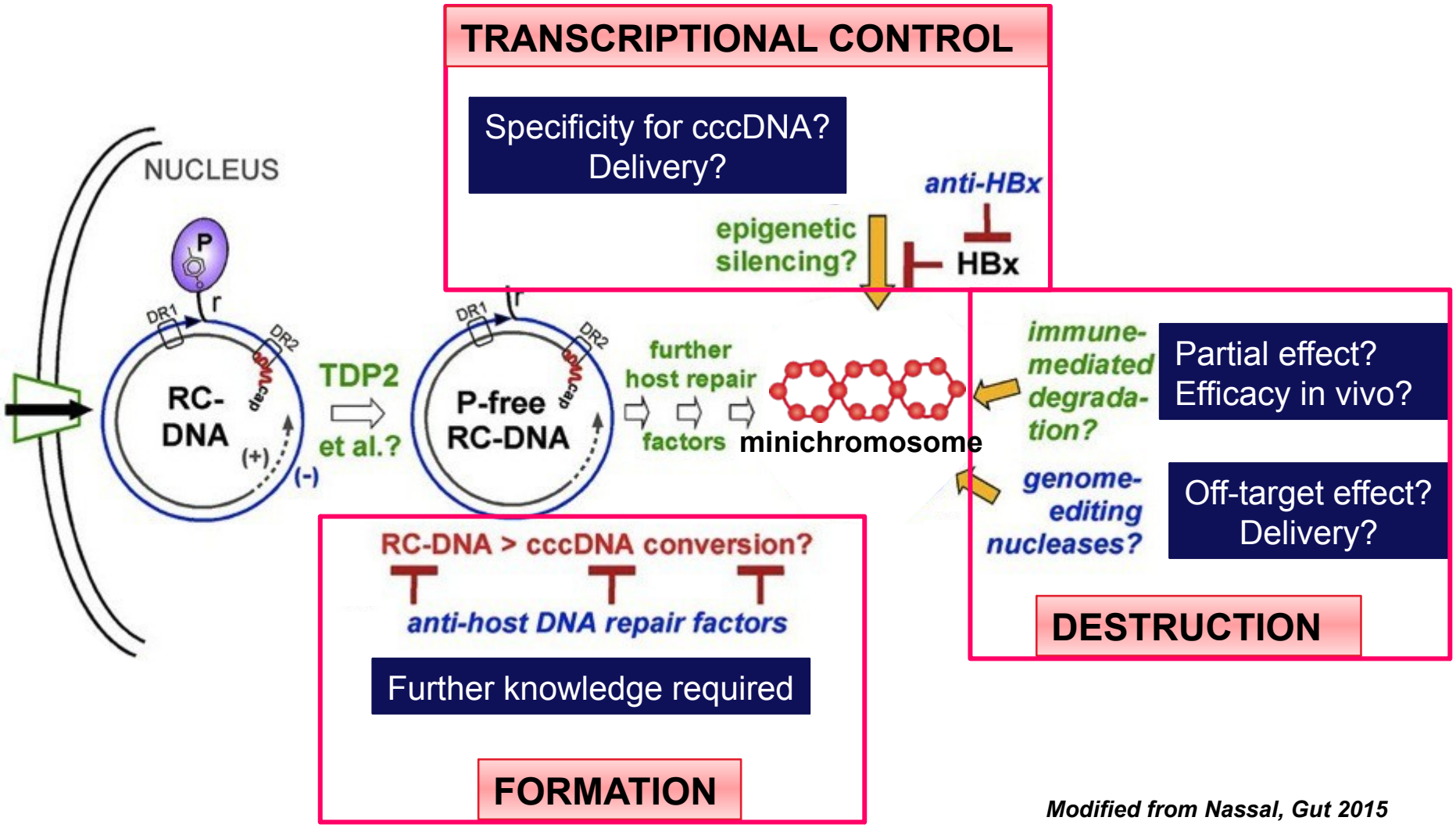
IFNalpha /Lymphotoxin beta can induce **APOBEC3A/B dependent degradation** of HBV cccDNA



Lucifora et al, Science 2014; Shlomai & Rice, Science 2014

Similar observation with IFNγ and TNFα – *Xia et al, Gastroenterology 2015*

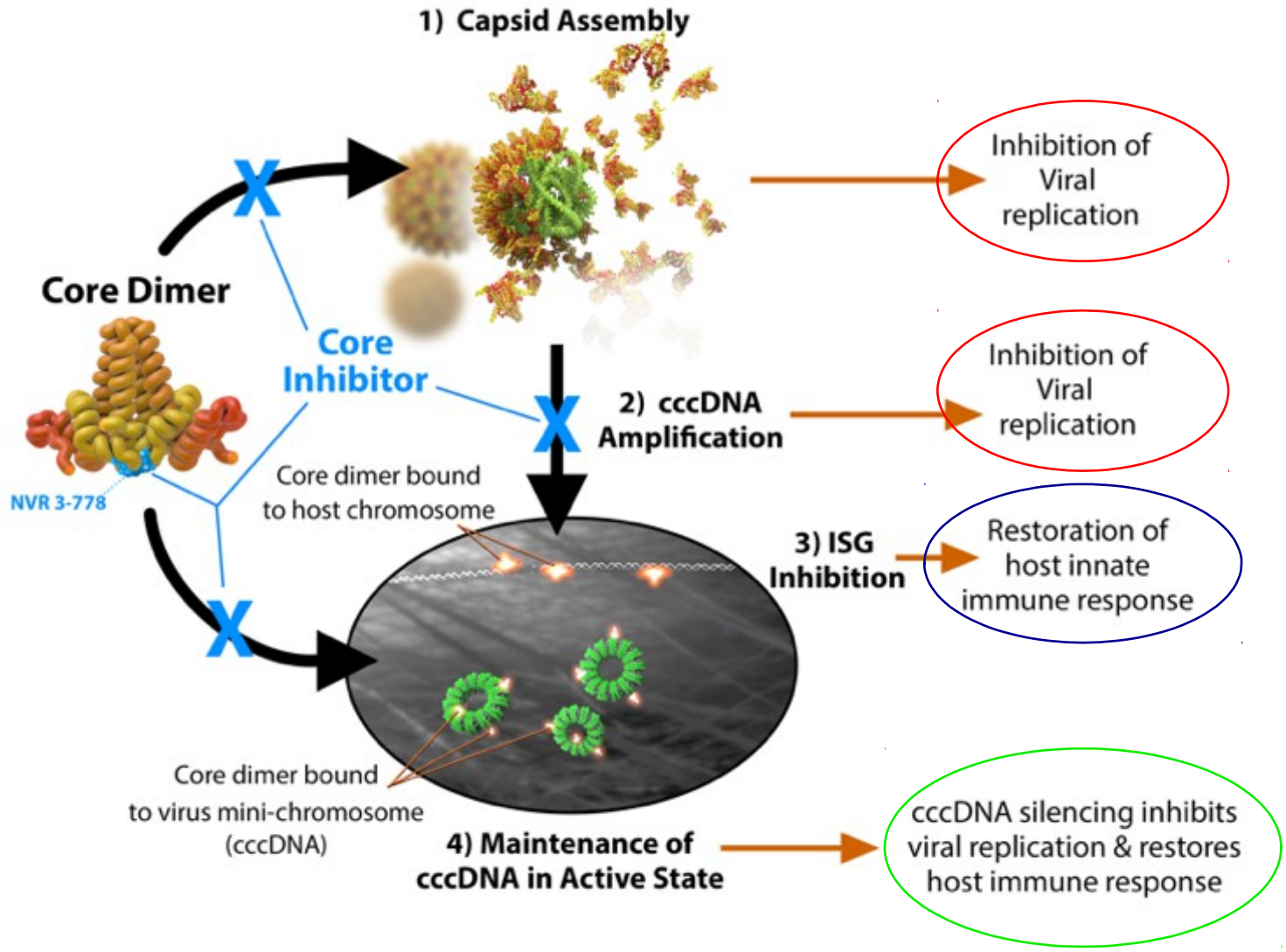
Challenges in targeting cccDNA



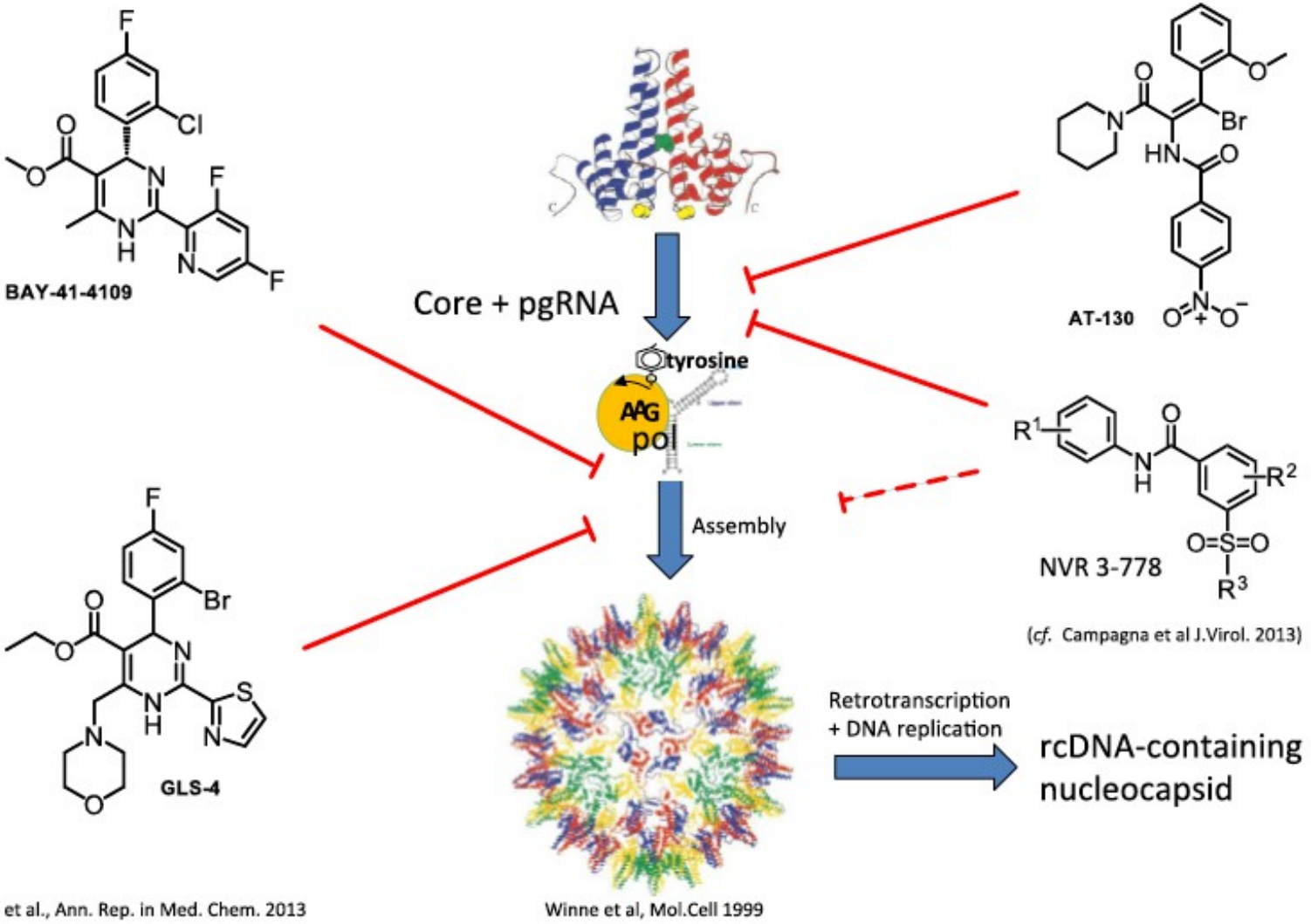
Modified from Nassal, Gut 2015

Lucifora et al, Science 2014; Shlomai & Rice, Science 2014; Xia et al, Gastroenterology 2015; Seeger et al, Mol Ther Nucleic Acids. 2014&2016; Tropberger et al, PNAS 2015; Decorsiere et al, Nature 2016

Targeting the HBV capsid with capsid assembly modulators



Billioud et al, Antiviral Res 2011; Klumpp K et al, PNAS 2015; Venkatakrishnan B et al, J Virol 2016

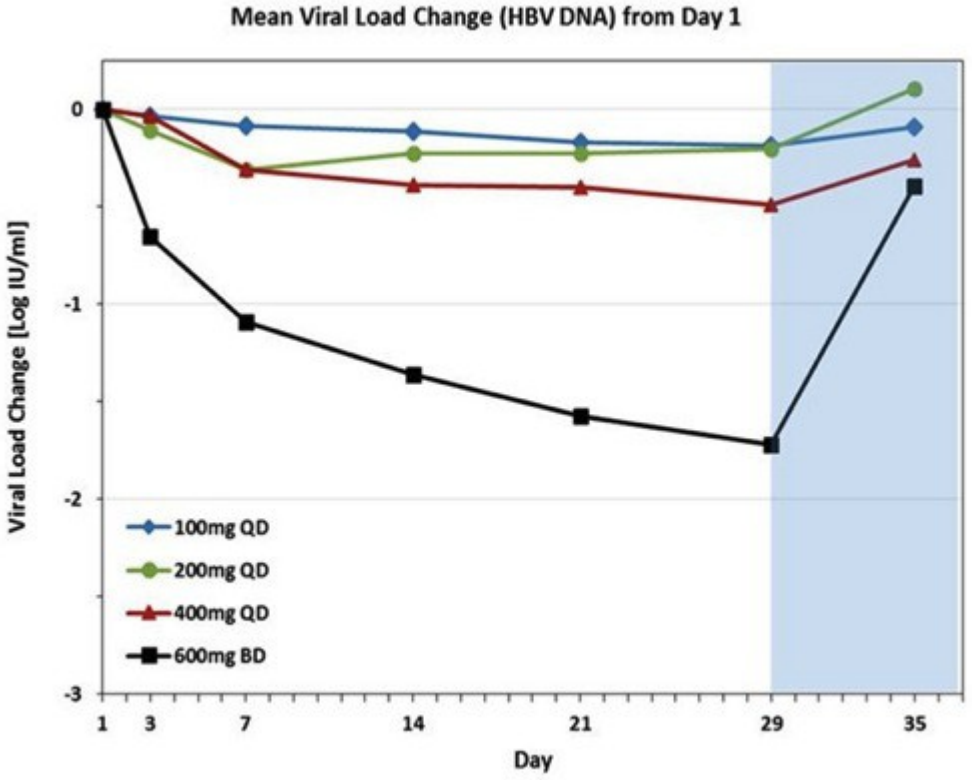

BAY-41-4109
Core + pgRNA
tyrosine
AAG
pol
Assembly
AT-130
NVR 3-778
(cf. Campagna et al J.Virol. 2013)
GLS-4
Retrotranscription
+ DNA replication
rcDNA-containing
nucleocapsid
Hu et al., Ann. Rep. in Med. Chem. 2013
Winne et al, Mol.Cell 1999

Phase 1b clinical trial: CpAM NVR 3-778 reduces serum HBV DNA and RNA

Pre-clinical evaluation in hepatocyte culture and chimeric mouse models

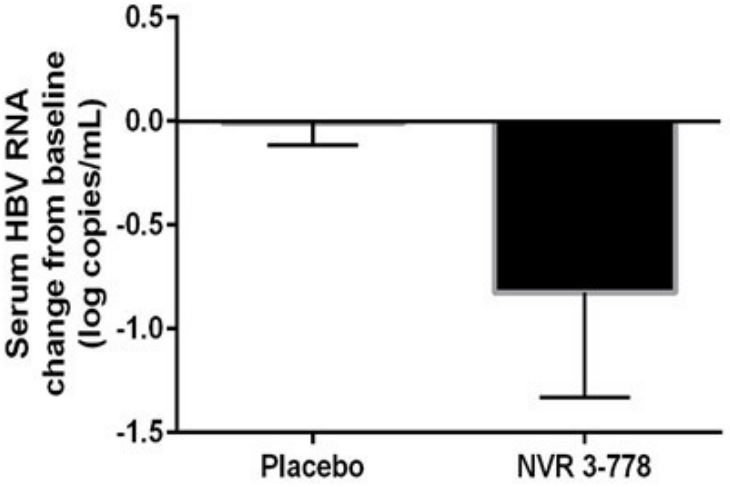
Serum HBV DNA: mean 1.7 log reduction (600 mg BID)

Serum HBV RNA: mean 0.86 log reduction (600 mg BID)



Cohort I: 600 mg BID

Decrease of circulating HBV RNA



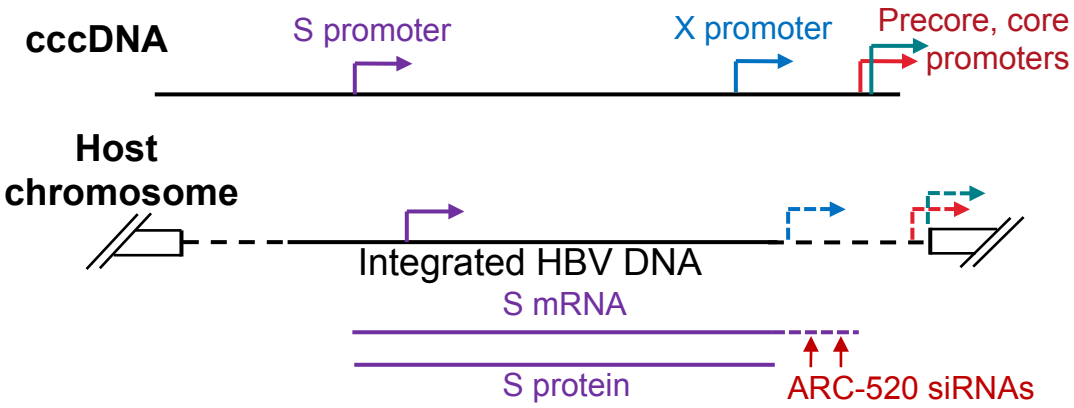
Yuen M-F, et al. AASLD 2015, San Francisco. #LB-10

HBsAg targeting strategies

- HBsAg clearance an **endpoint of therapy**
- Decline in HBsAg levels may **restore the antiviral activity of exhausted T cells**
- **Several strategies** in evaluation
  - RNA interference (SiRNA): « gene silencing »
  - Nucleic acid polymers (NAPs): HBsAg release
  - HBs antibodies

SiRNA ARC-520 produces deep and durable knockdown of viral antigens and DNA in a phase II study

HBsAg reduction in ETV naive patients with a single 4 mg dose (cohort 7)



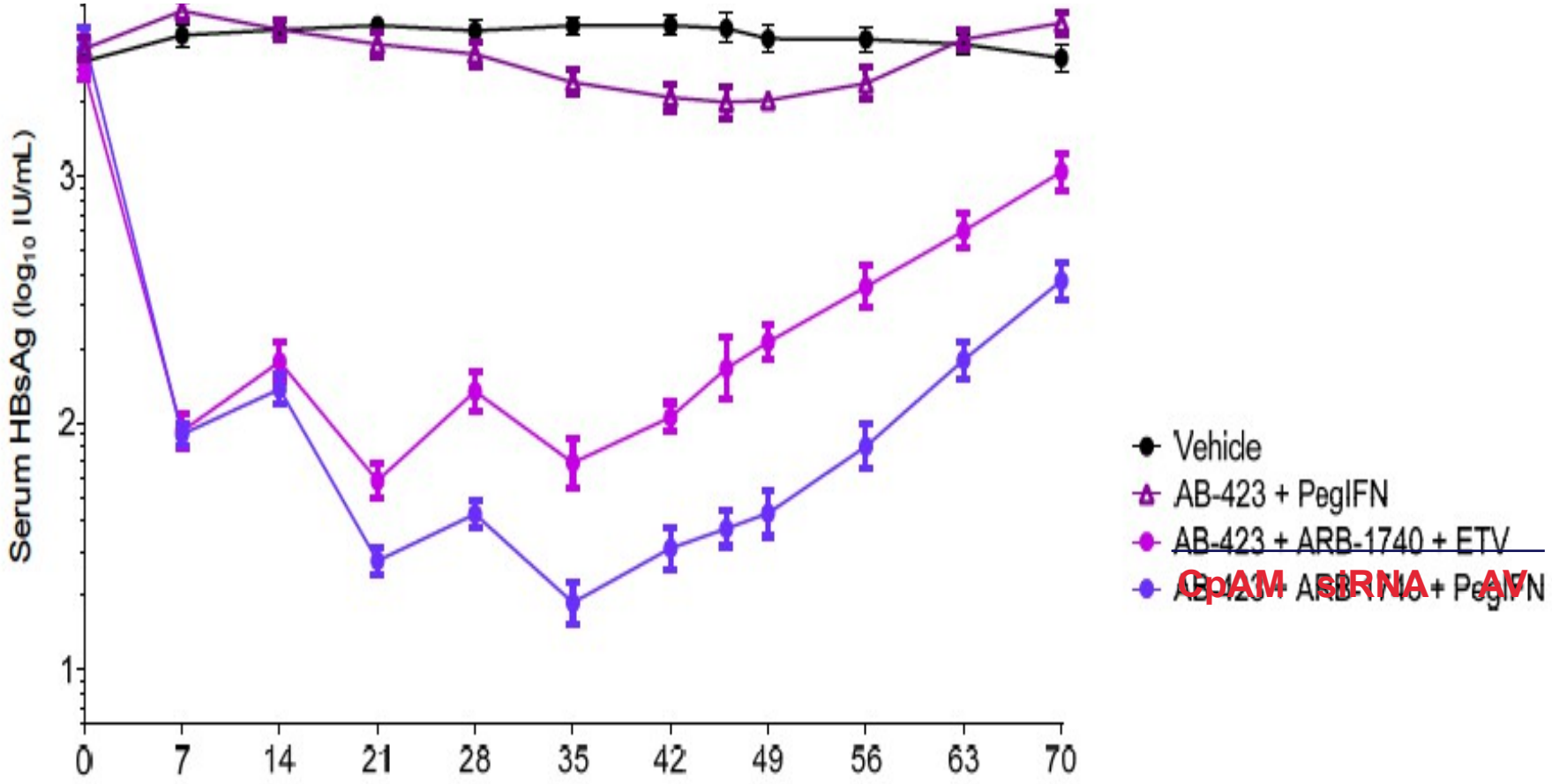
Impact of integrated sequences on siRNA efficacy

Will this result in restoration of immune responses ?

Yuen M-F, et al. AASLD 2015, San Francisco. #LB-9

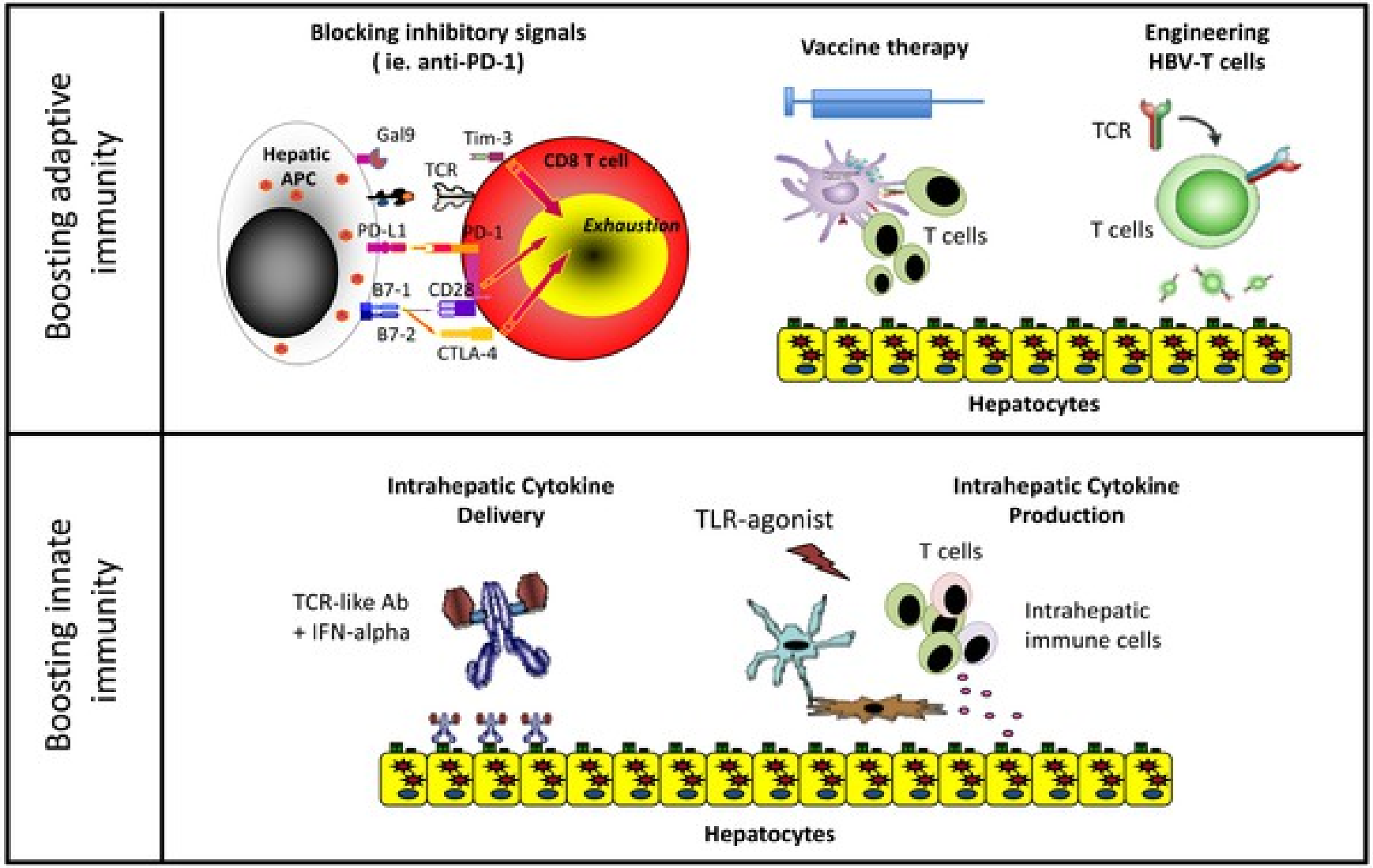
Towards combination therapy

Effect of a triple combination therapy on viral antigen load in a humanized mouse model



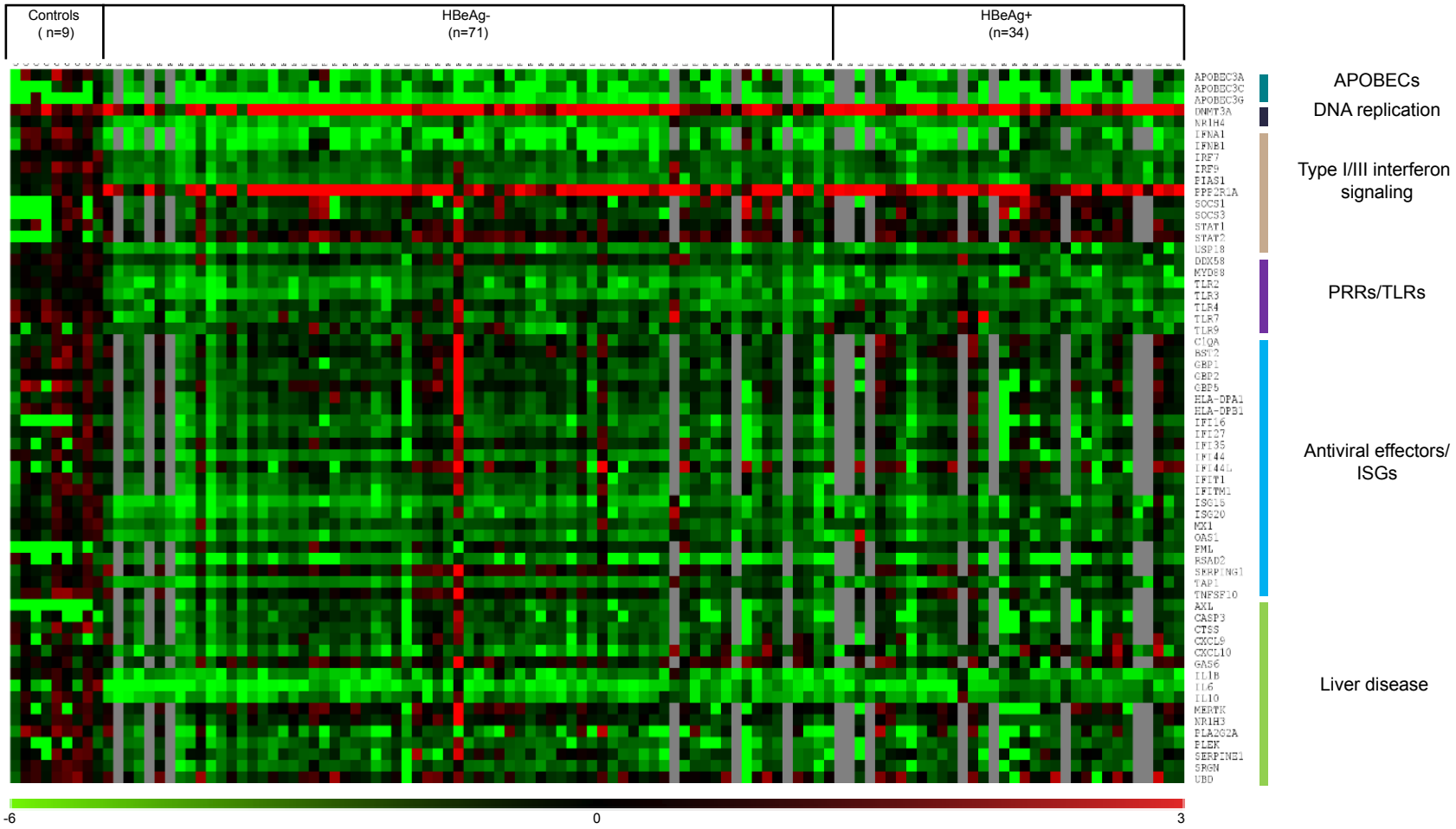
Lee et al, AASLD 2016

Restoration of antiviral immunity



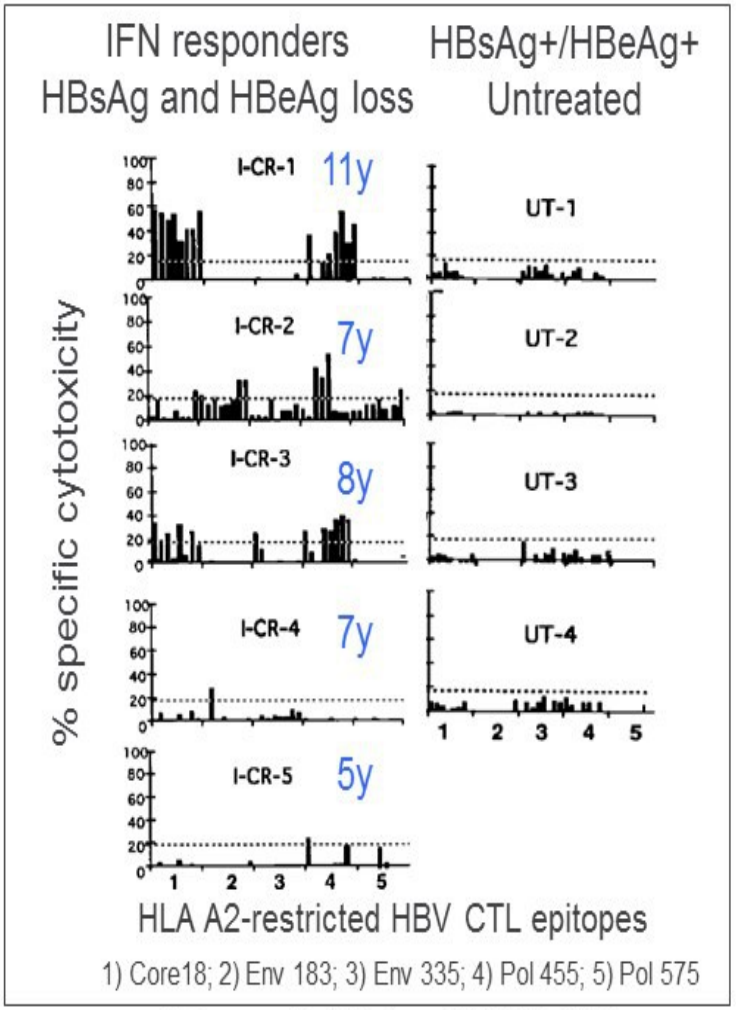
Bertoletti A, Gehring AJ (2013) Immune Therapeutic Strategies in Chronic Hepatitis B Virus Infection: Virus or Inflammation Control?. PLoS Pathog

Repression of intrahepatic expression of innate immunity genes in CHB patients

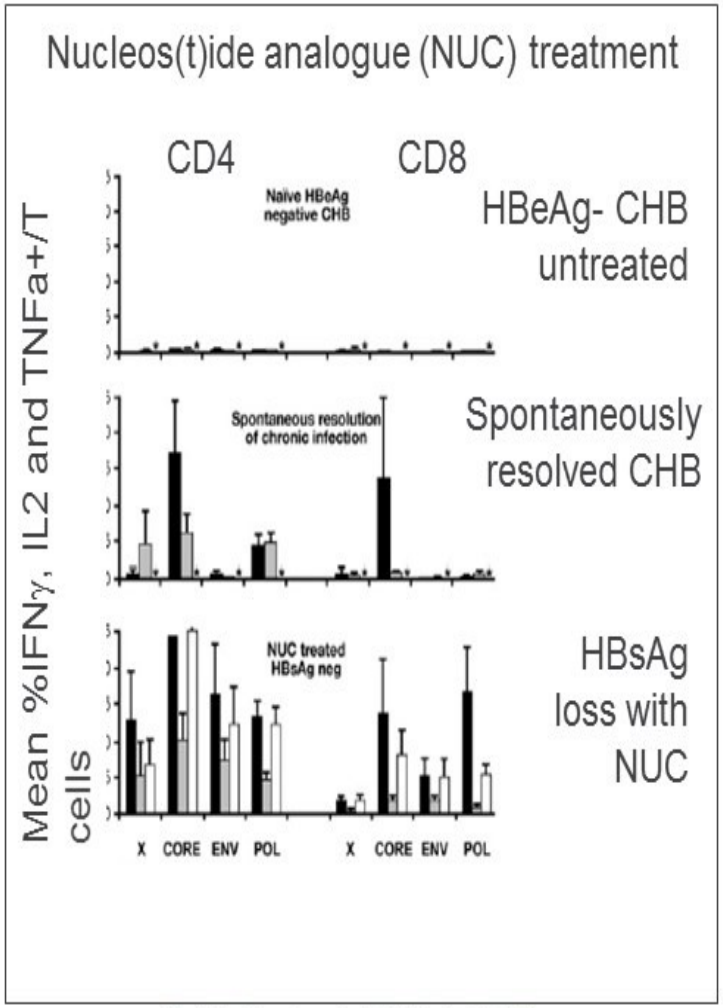


Lebossé, Testoni et al, J Hepatol 2017

Recovery of T cell response is possible after resolution of chronic HBV



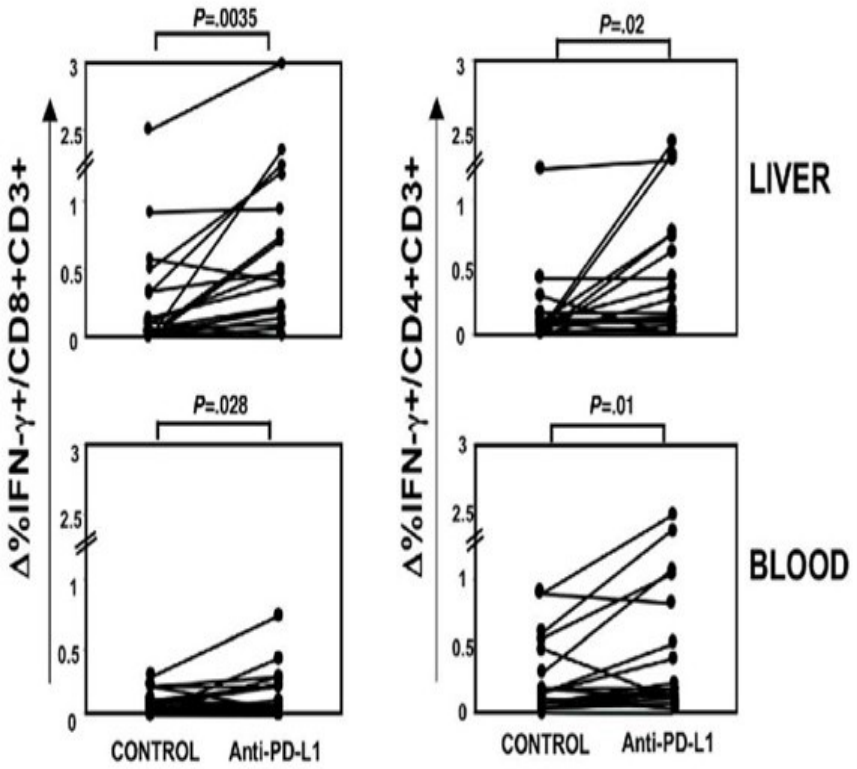
Rehermann B, J Clin Invest 1996; 97: 1655



Boni C, Gastroentrol 2012; 143: 963

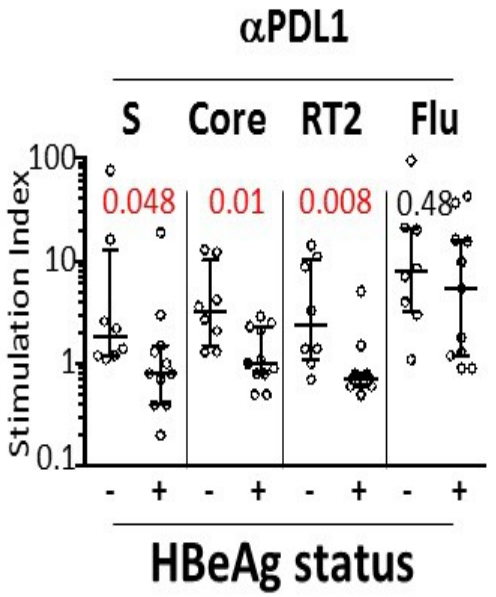
PD-1 blockade enhances HBV-specific T cell function

In liver and blood



Fisicaro P, Gastroenterol 2010; 138: 682

With differential impact based on HBeAg status



Park J, Gastroenterol 2016; 150: 684

Clinical Evaluation of Immunotherapeutics

- **Innate Immunity**

- TLR-7 agonists (other TLR agonists ?): inducing endogenous type I IFN responses

- Targeting RIG-I: Restoration of endogenous IFN profuction & interference on Polymerase/pgRNA interaction

- Restoring innate responses: blocking virus specific functions

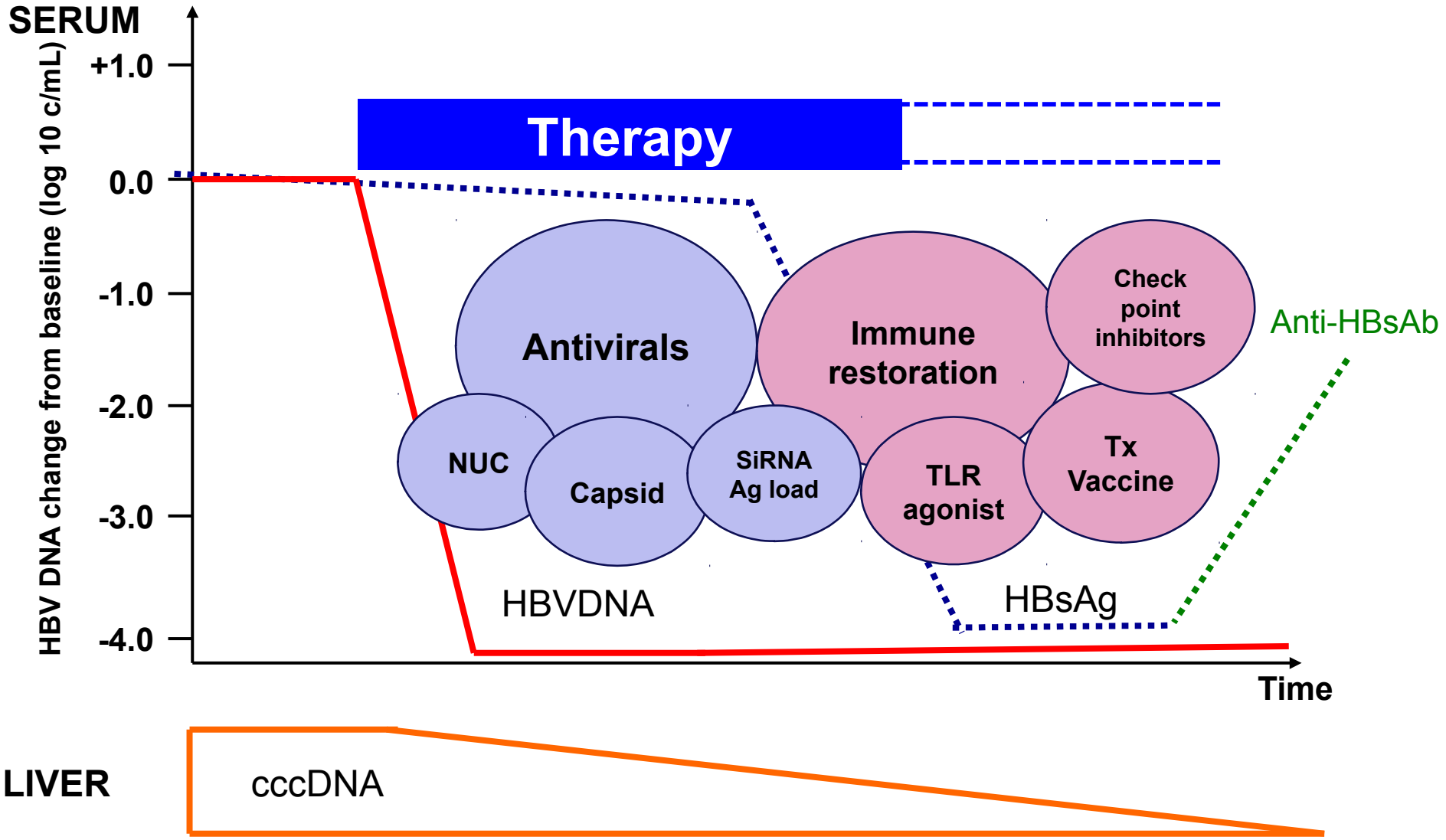
- **Adaptive immunity**

- Therapeutic vaccines: stimulating HBV specific CD4 and CD8 T cells

- Check-point inhibitors: restoration of specific CD4 and CD8 T cells

- T Cell engineering: redirecting T cells to infected hepatocytes

HBV cure - New treatment concepts – Will we need combination of DAA and immune therapy ?



HBV cure - Where are we going ?

- **Towards improved therapies & cure within the next decade !**

Acknowledgements

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P Revill, Melbourne

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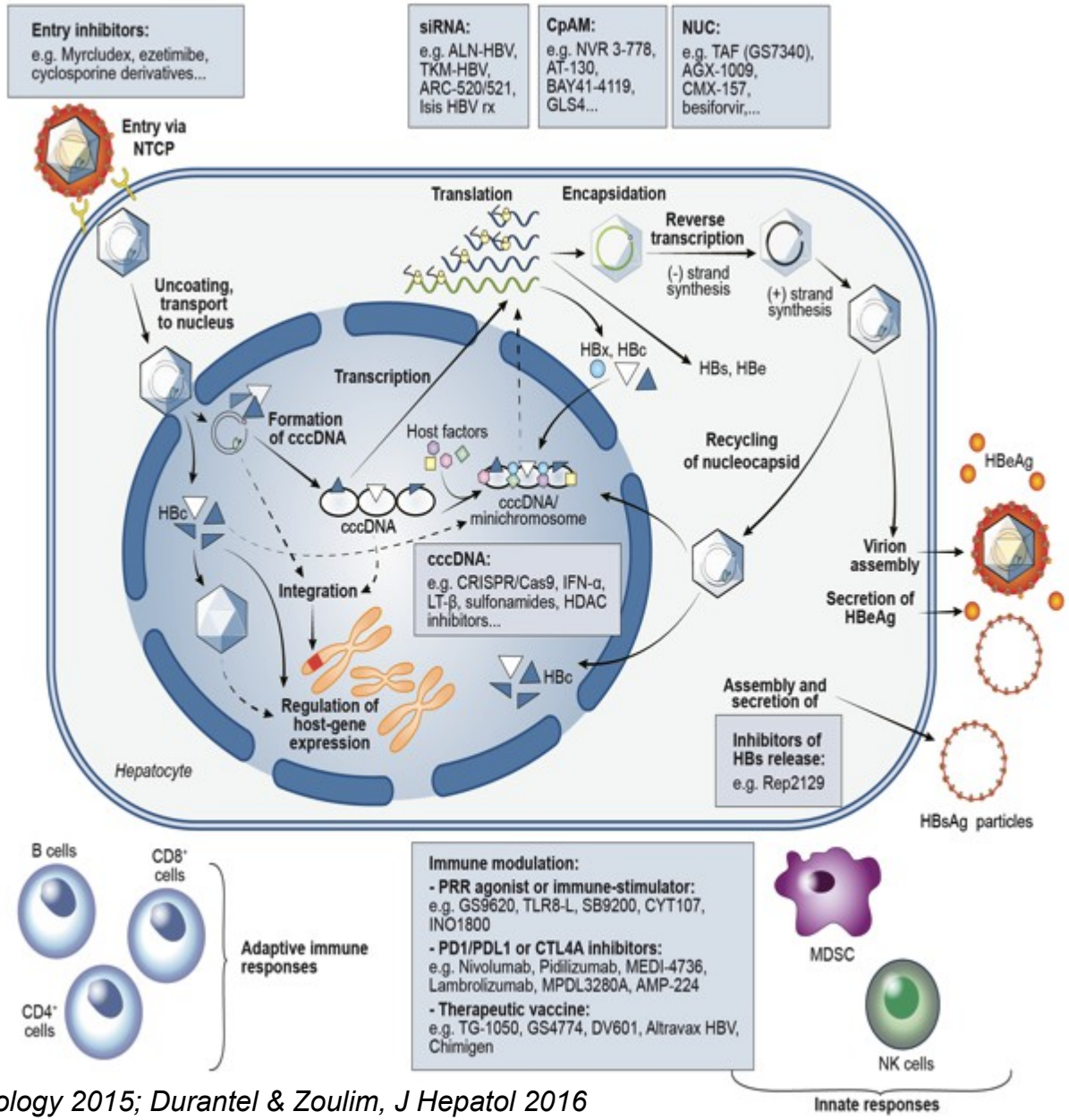
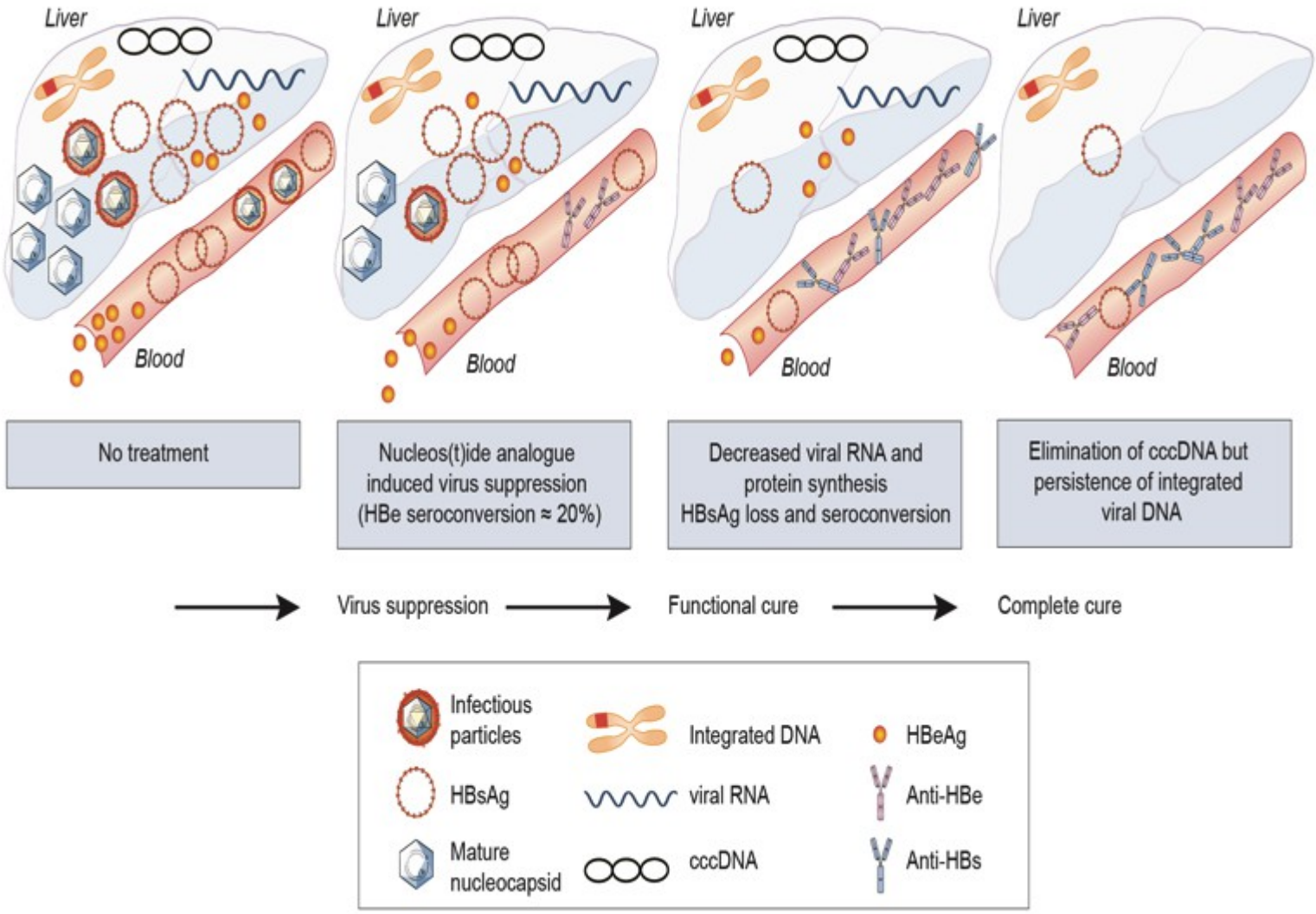
HBV cure - A highly dynamic drug discovery effort



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

Definition of Cure



Durantel & Zoulim, J Hepatol 2016;
Zeisel, Lucifora et al, Gut 2015; Revill et al, Nature Reviews Gastroenterol Hepatol 2016

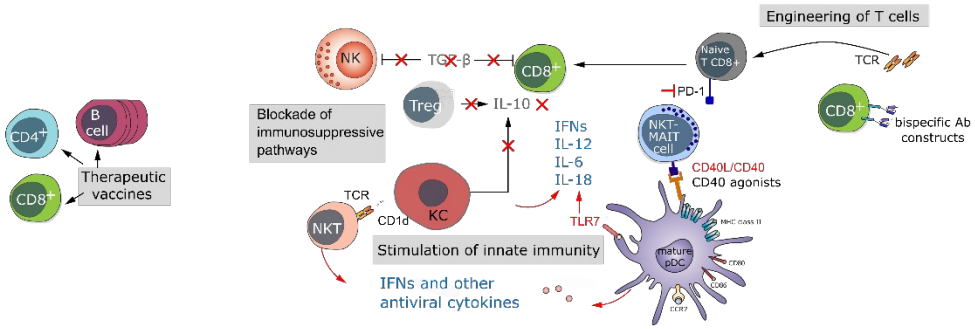
Realistic definition of HBV cure

	Complete cure	Idealistic functional cure	Realistic functional cure	Partial "cure"
Clinical scenario	**Never infected**	**Recovery after acute HBV**	**Chronic HBV with HBsAg loss**	**Inactive carrier off treatment**
HBsAg	Negative	Negative	Negative	Positive
Anti-HBs	Positive/negative	Positive	Positive/negative	Negative
Serum HBV DNA	Not detected	Not detected	Not detected	Low level or not detected
Hepatic cccDNA, transcription	Not detected Not active	Detected Not active	Detected Not active	Detected Low level
Integrated HBV DNA	Not detected	Detected?	Detected	Detected
Liver disease	None	None	Inactive, fibrosis regression over time	Inactive
Risk of HCC	Not increased	Not increased	Declines with time	Risk lower vs. immune active phases

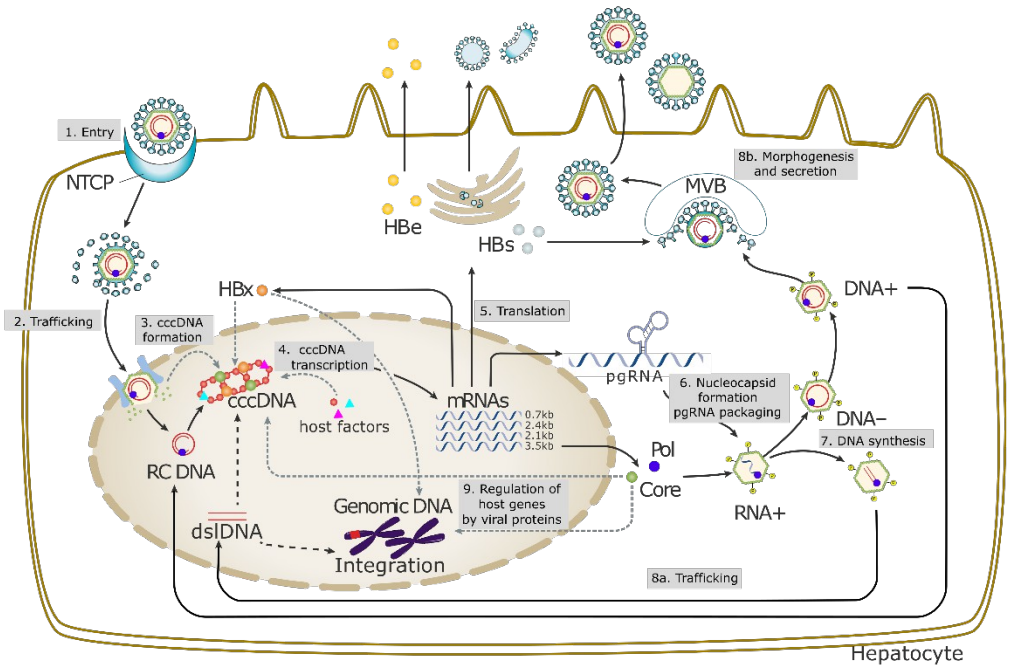
AASLD/EASL endpoint workshop, 2016

The main targets

Immune system



Viral lifecycle



Testoni et al, Liver International 2017