New Anti-HBV Strategies Towards HBV CURE?

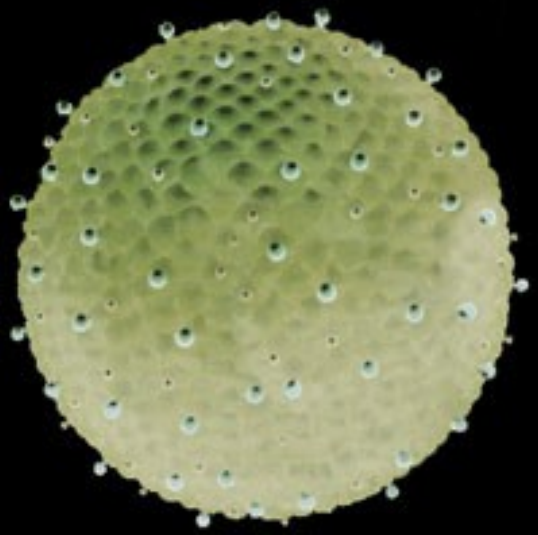
10TH ANNIVERSARY

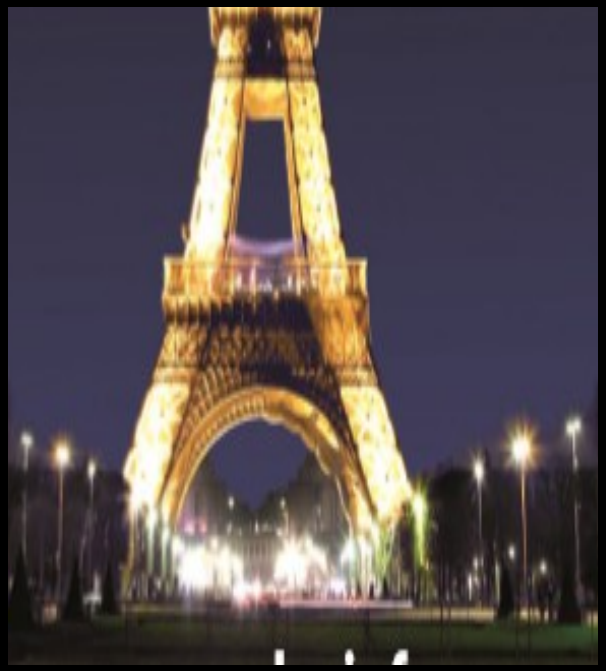
2017

10th PARIS HEPATOLOGY CONFERENCE

30 & 31 January 2017

PARIS - Palais des Congrès





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Disclosures

- Ed Gane is Investigator/Advisor for:
  - Alios, Alnylam, Arbutus, Arrowhead, Assembly, BMS, Eiger, Gilead, Janssen, GSK, Novartis and Roche

The New Goal: Complete Cure

Finite treatment duration

Cessation of all treatment

Absence of HBV DNA and HBsAg

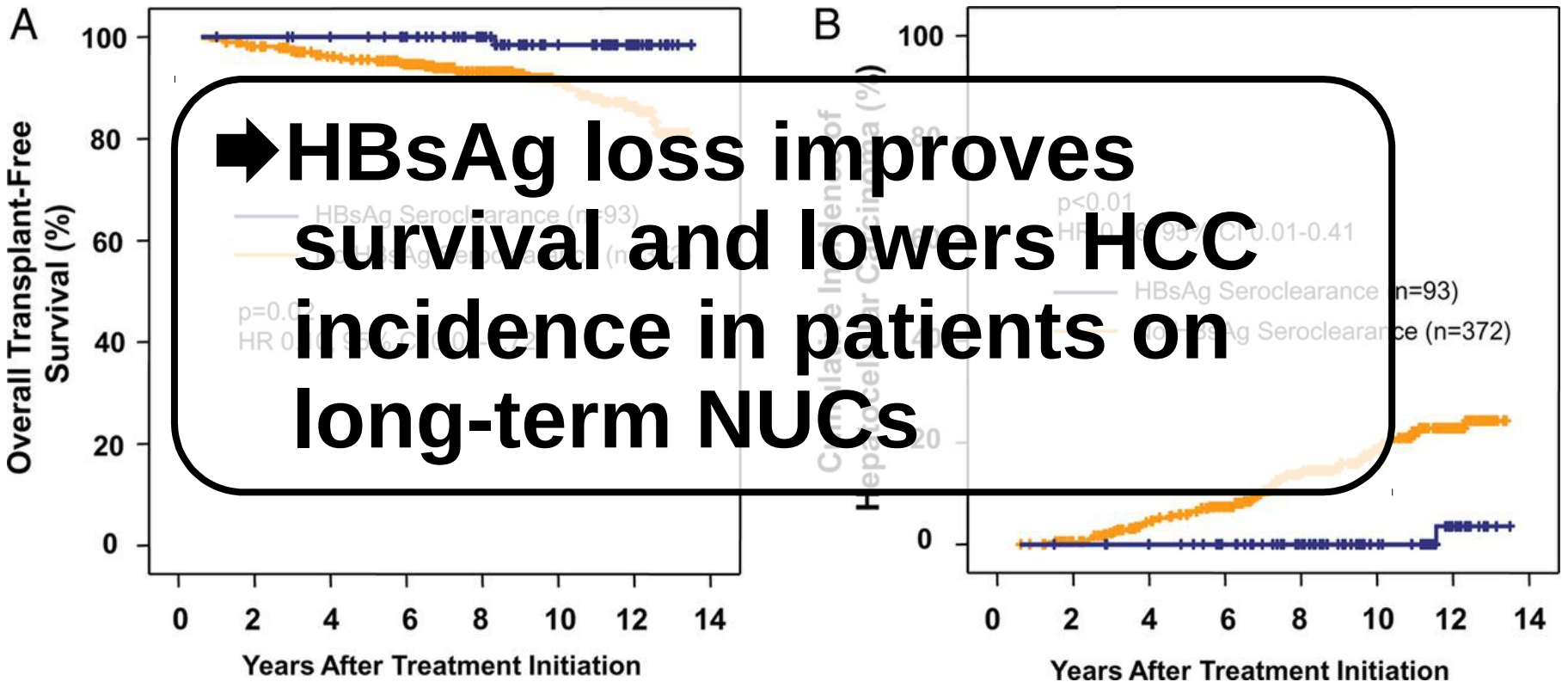
"Naturally Resolved"

Clearance of cccDNA

"Never Infected"

Why is HBV CURE important?

- 5409 CHB patients on long-term LAM or Entecavir
- After 6 years, 110 (2%) lost HBsAg (0.3% per annum)



➡**HBsAg loss improves survival and lowers HCC incidence in patients on long-term NUCs**

Kim GA et al. *Gut* 2014;63:1325-1332

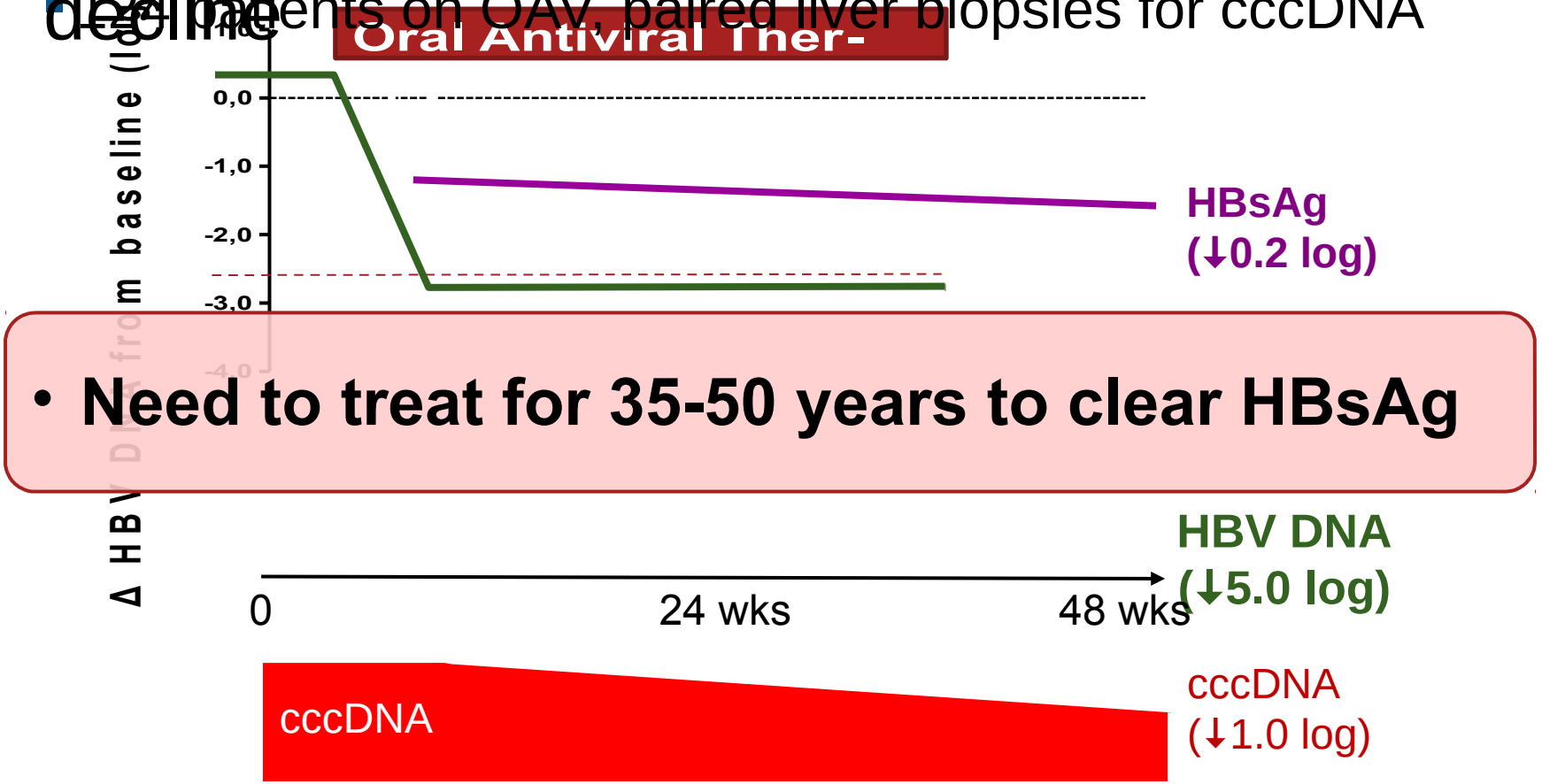
Disadvantages of long-term oral antiviral therapy

1. Treatment limited to only patients in immune active phase (high ALT, HBV DNA, fibrosis)
2. High cost limits access in low-income countries, ⇨LAM, ADV use ⇨high rate of treatment failure
3. No clear stopping criteria, especially in eAg neg
4. Viral breakthrough from non-adherence or resistance ⇨ flares ⇨ liver failure
5. Cumulative toxicity from long-term use

Hildt E, et al Recent Results Cancer Res 1998;154:315-29; Hino 2002, Warner & Locarnini 2009

Disadvantages of long-term oral antiviral therapy

6. Slow rate of HBsAg loss and cccDNA decline
   - 124 patients on OAV, paired liver biopsies for cccDNA



Wong D, et al. CGH 2013;11:1004–10
Zoutendijk R,. Et al. J Infect Dis. 2011;204:415–418
. Chevaliez S, et al.J Hepatol. 2013;58:676–683

Can we do better with current therapies?

1. **Combine different NUCs**
   - No synergistic viral suppression or HBsAg loss

Lok et al, Gastroenterology 2012; Zoulim et al, J Hepatol 2015

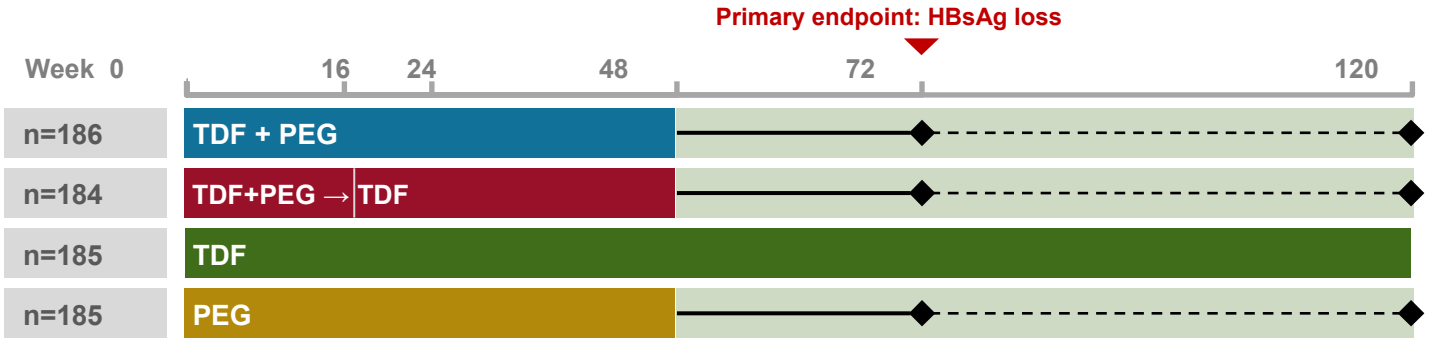
2. **Stop NUCs after long-term suppression**
   - HBsAg loss is rare
   - HBeAg loss ⇨ off-treatment rebound and flares
     - HBsAg levels may be best predictor of durability

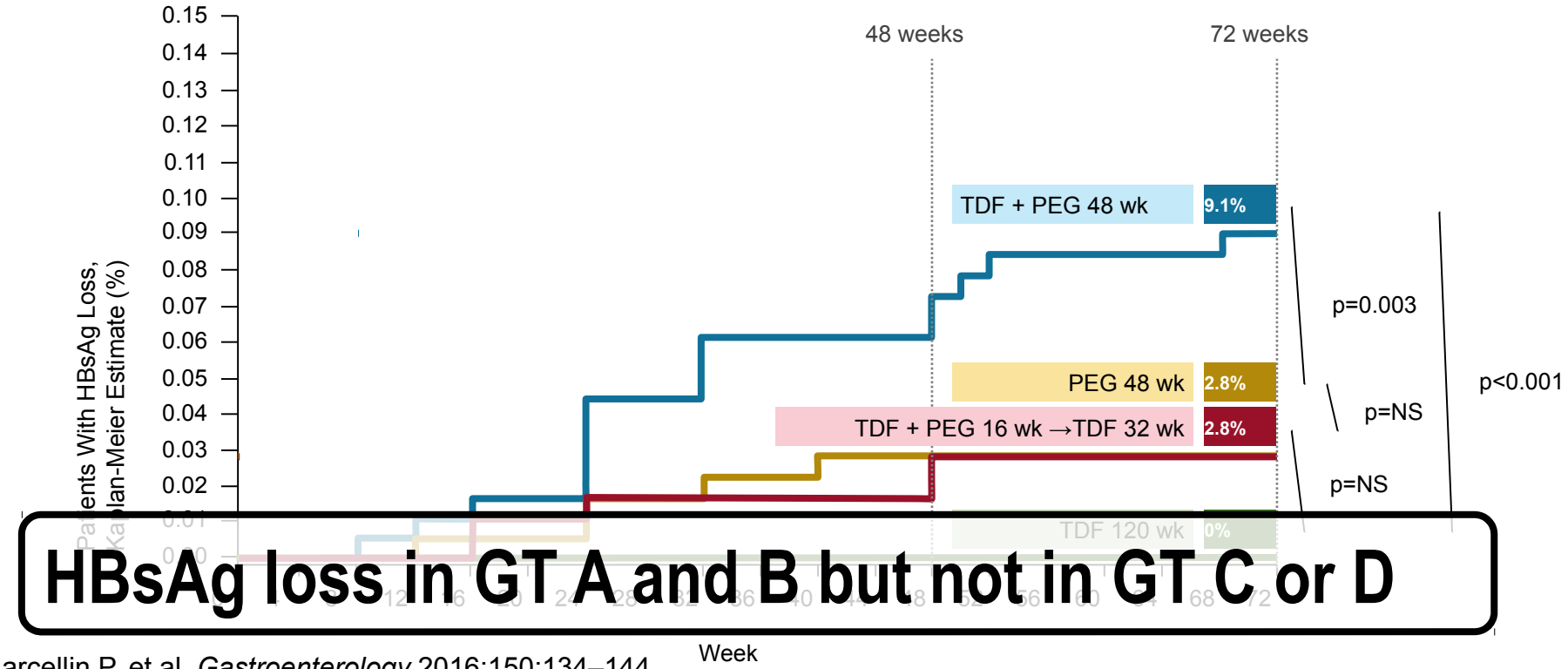
Berg et al, EASL 2015; Buti et al, AASLD 2015; Hadziyannis et al, Gastroenterology 2012; Gill et al, AASLD 2015; Boni et al, Hepatology 2015

3. **Add Pegylated-IFN to long-term NUCs**

Add Pegylated-IFN to Nucleotide Analogue Study GS-US-174-0149

740 CHB patients
No cirrhosis
Randomised 1:1:1:1
Stratified by GT



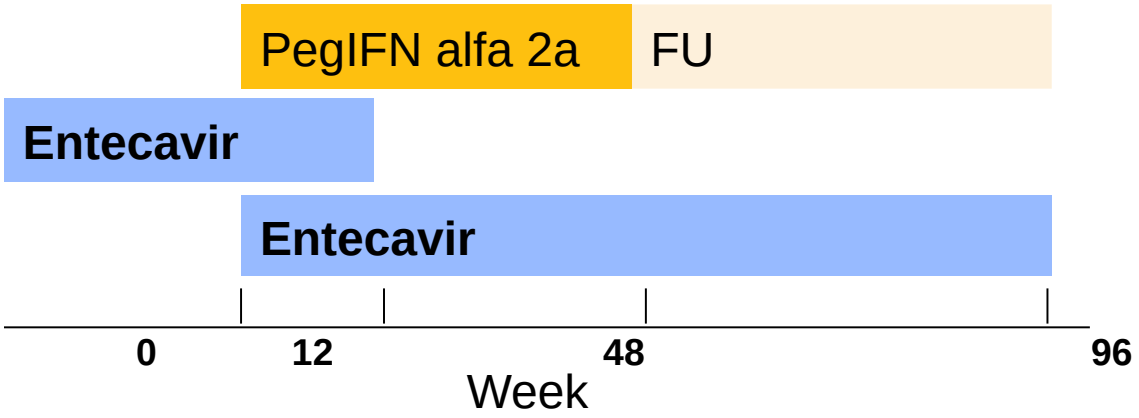


HBsAg loss in GT A and B but not in GT C or D

Marcellin P, et al. *Gastroenterology* 2016;150:134–144

Switch from Long-term NUC to Peg-IFN in Genotype C CHB

144 CHB patients
Long-term ETV
Randomised 1:1

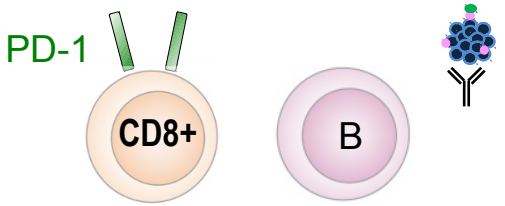


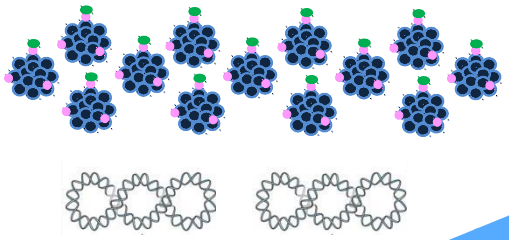
	PegIFN	NA	P-value
HBsAg decline (log)	0.3	0.014	<0.001
HBeAg seroconversion (%)	24.5	0	<0.005
HBsAg loss (%)	1.9	0	NS
HBV DNA <2000 IU/ml (%)	66.7	100	<0.001
HBV DNA <20 IU/ml (%)	35.2	90.3	<0.001
ALT flare (%)	4	1.9	NS

Woo HY, et al. AASLD 2016, Boston. #71

Why can’t antiviral therapy cure HBV?

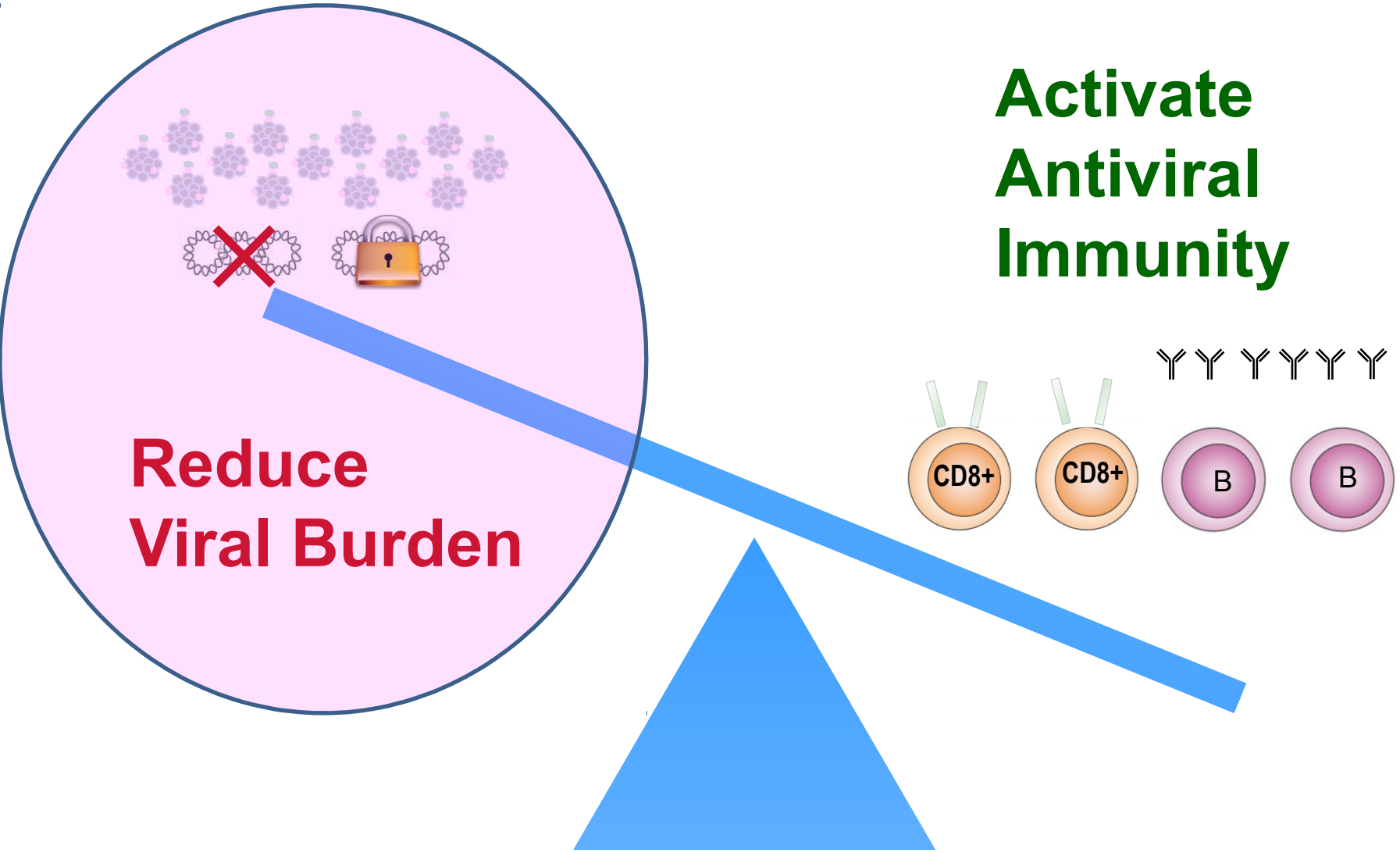
High Viral Burden



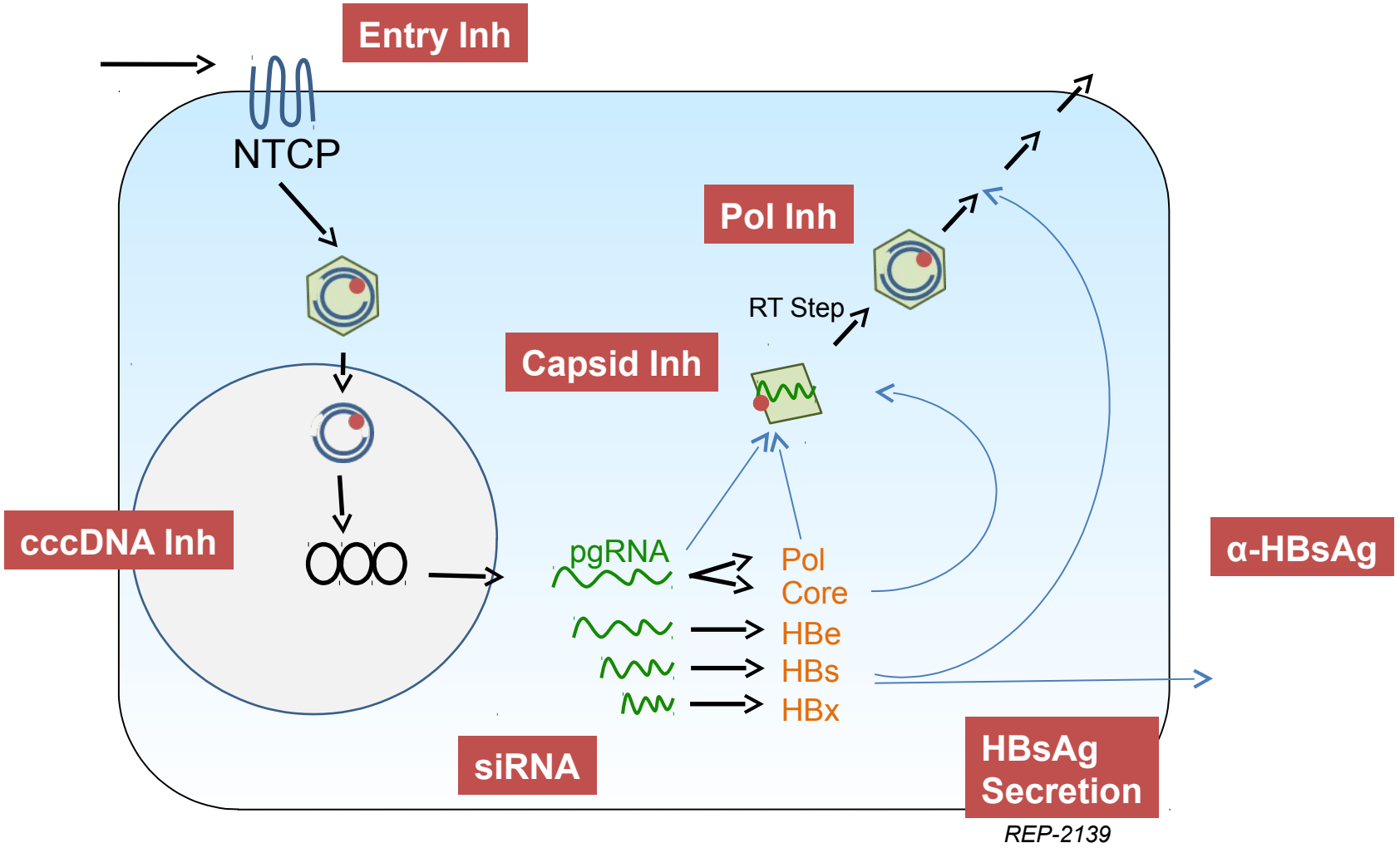


Weak Immune Response

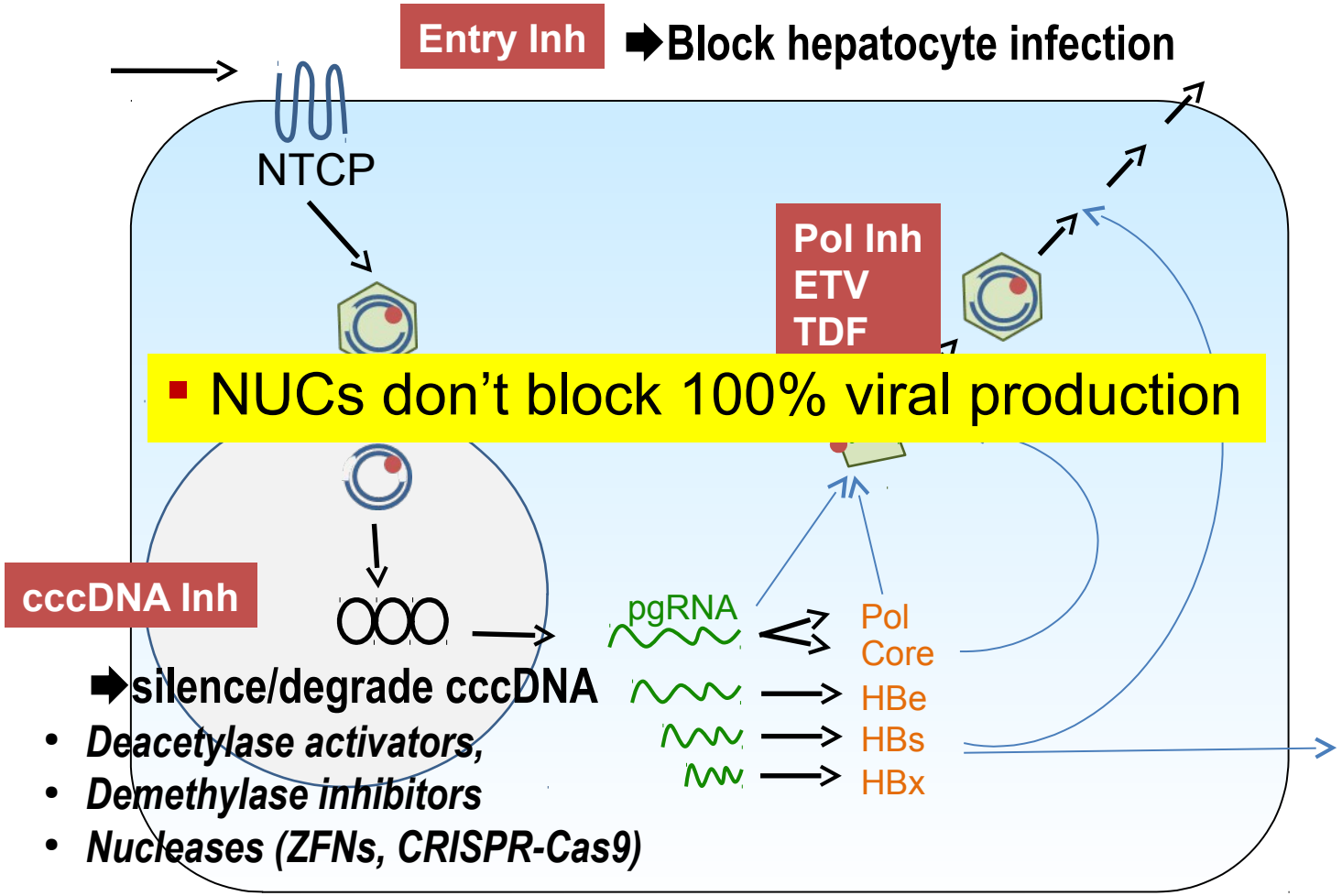
Therapeutic Strategies for HBV Cure



HBV Life Cycle offers many targets for Antivirals



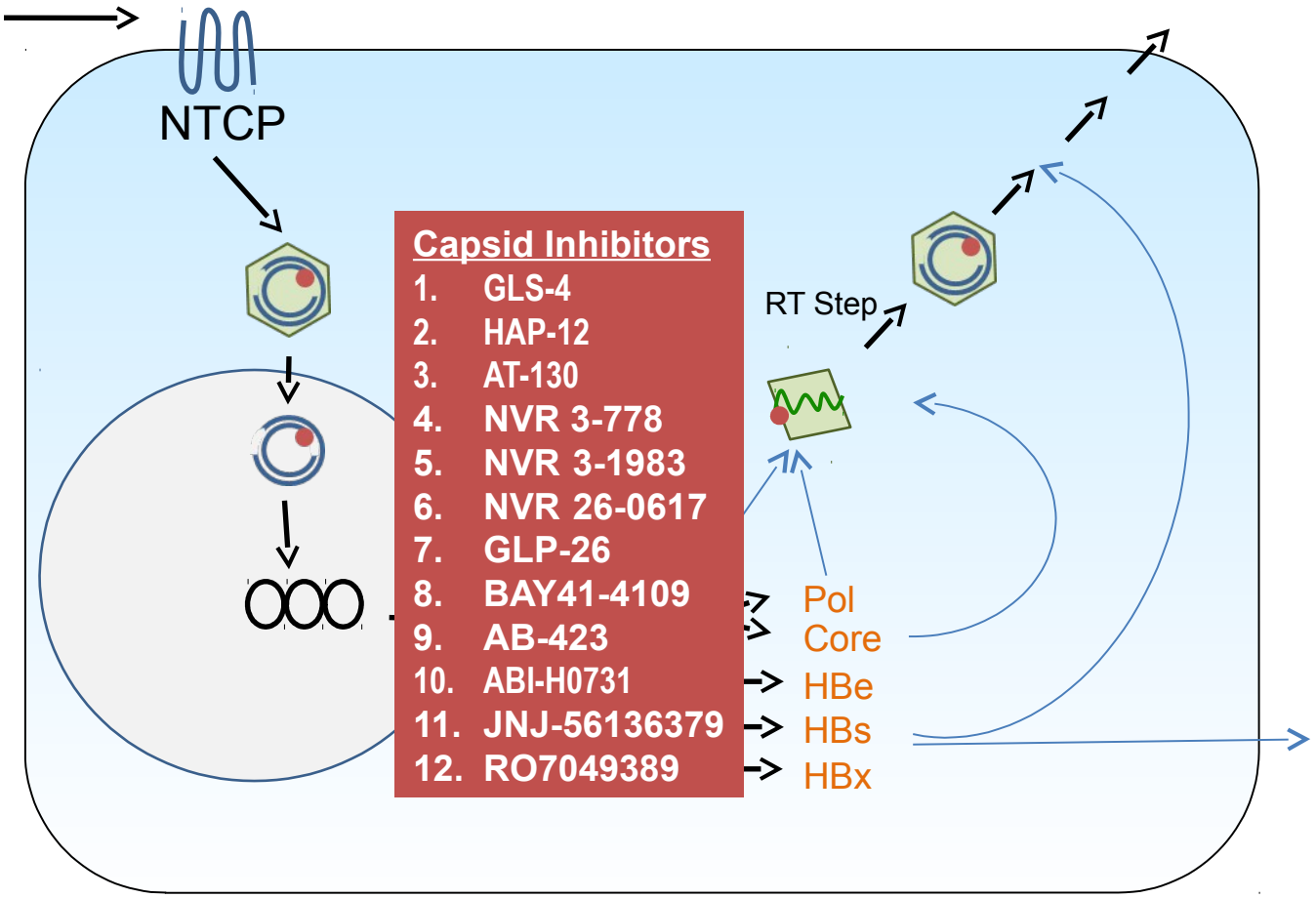
New Targets: Block HBV DNA production



New Targets: cccDNA- challenges and risks

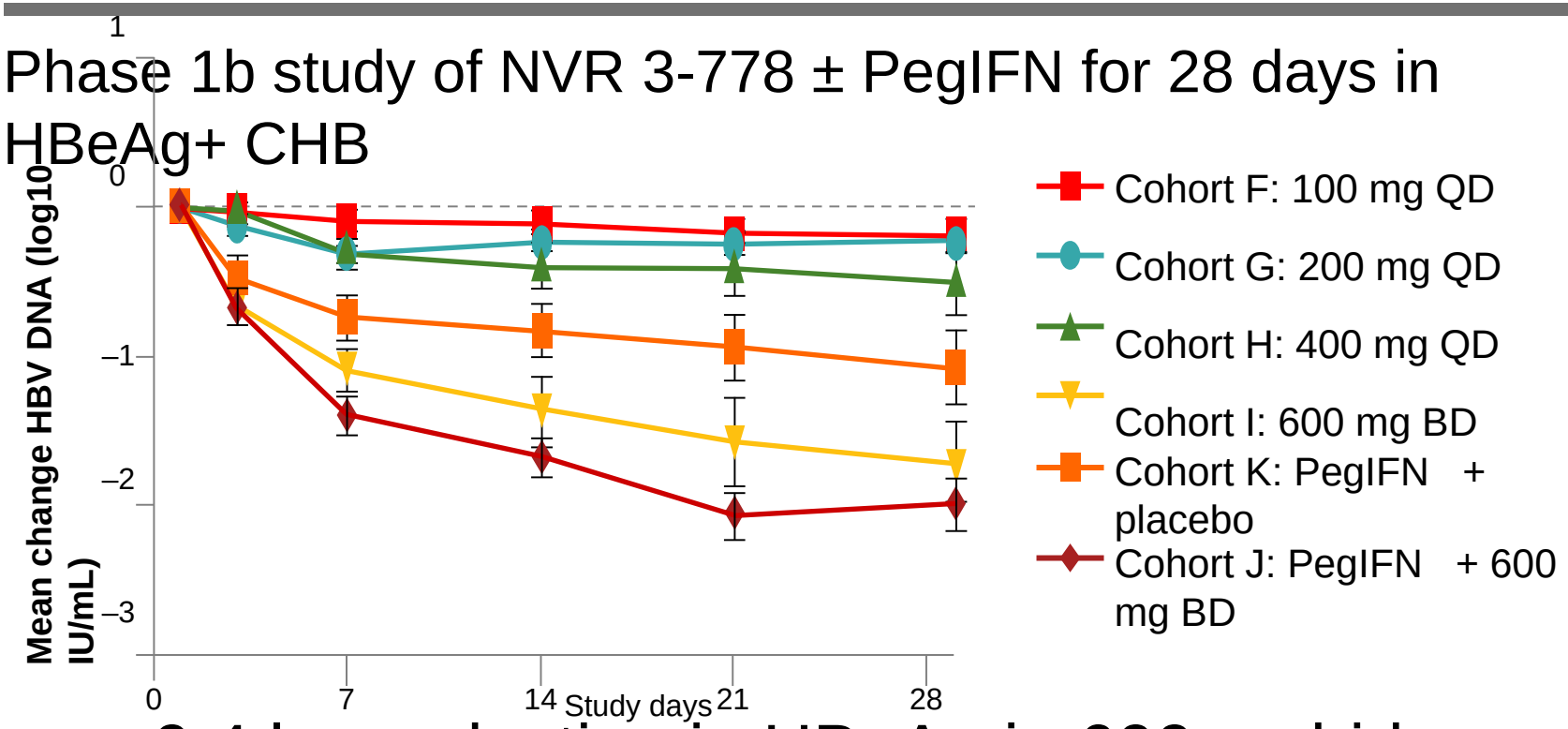
- **No standardised assays to assess cccDNA**
  - **Delivering the drug to the target**
    - into hepatocyte nucleus
    - Into **every** infected hepatocyte
- **Host epigenetic modulators have risks**
  - Direct toxicities
  - Off-target effects of drug on host DNA
  - Long-term risks in young patients
- **Viral epigenetic modulators should be safer**
  - **X-protein**
  - **Capsid protein**

New Targets: Block HBV Capsid Assembly



Oral HBV capsid assembly inhibitor NVR 3-778 Clinical Profile: synergism with Peg-IFN

- Phase 1b study of NVR 3-778 ± PegIFN for 28 days in HBeAg+ CHB



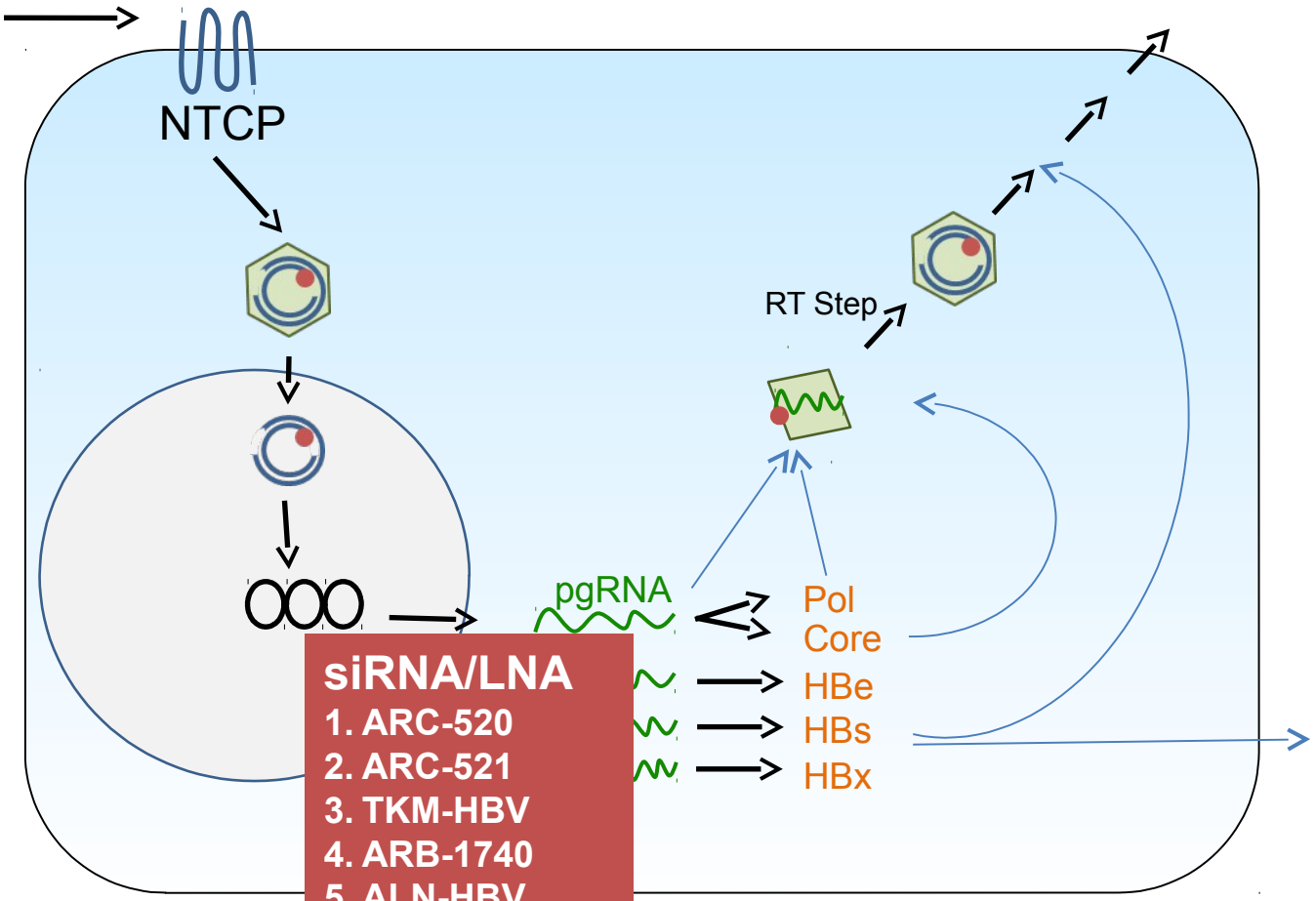
  - 0.4 log reduction in HBeAg in 600mg bid
  - No effect on HbsAg levels after 28 days

➡ **Phase II: Combine with NUC ± Peg-IFN for 52 wks**

➡ **More potent capsid inhibitors in development**

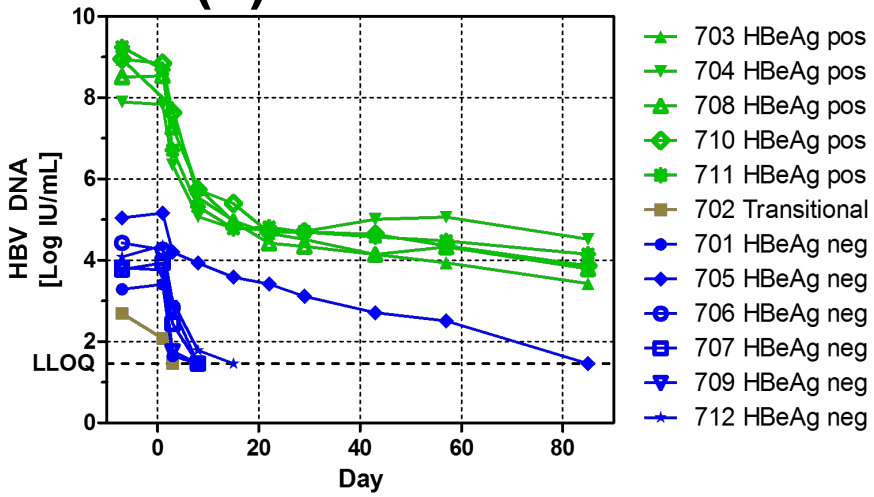
Gane E, et al. AASLD 2015; Yuen M-F, et al. EASL 2016

New Targets: Block HBV antigen production

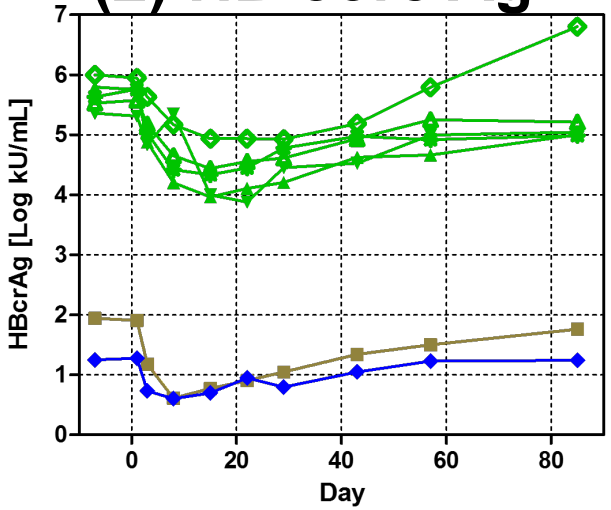


Single IV dose ARC-520 in patients reduces all HBV proteins and HBV DNA (HEPARC-1)

(1) HBV DNA

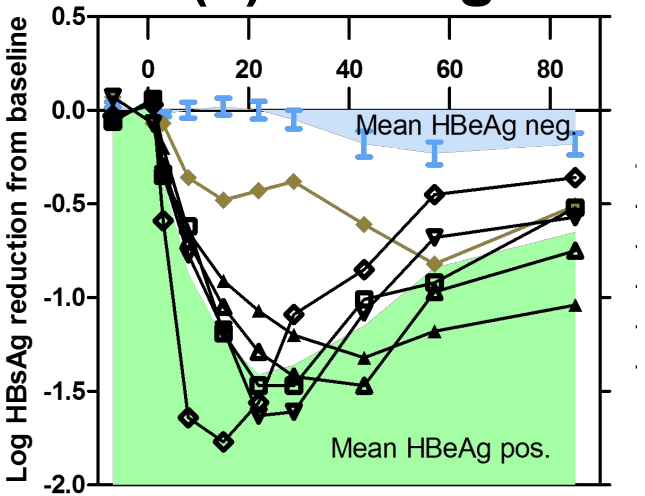


(2) HB core Ag



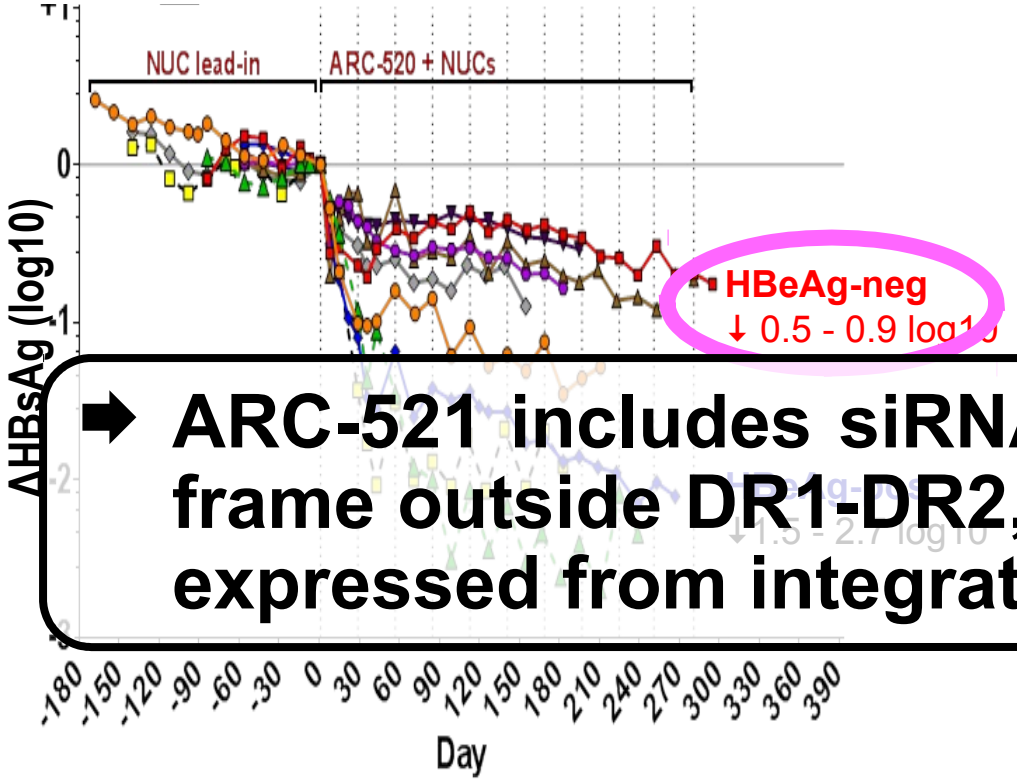
(3) HBeAg

(4) HBsAg

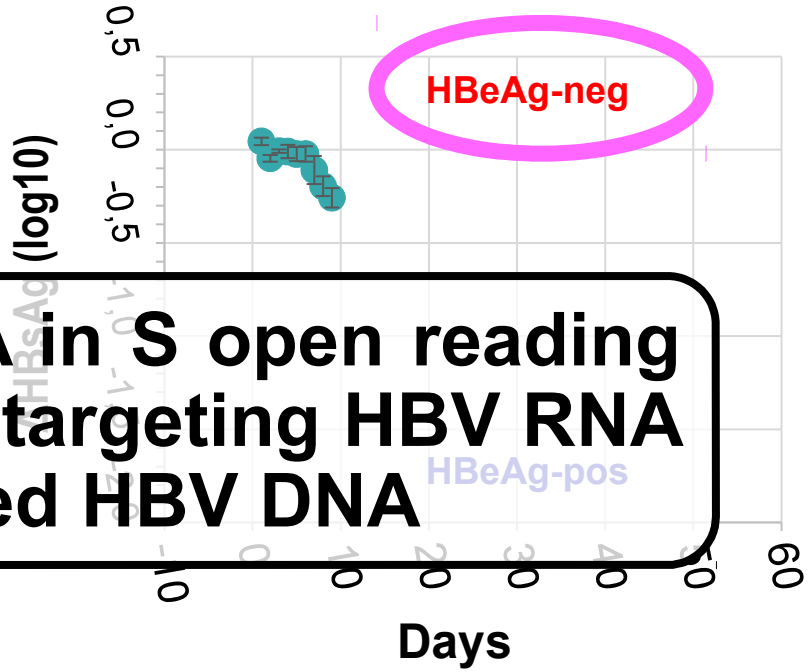


Multiple dosing of ARC-520
Effect on HBsAg reduced in HBeAg neg CHB

(i) Chimps



(ii) Patients



➡ **ARC-521 includes siRNA in S open reading frame outside DR1-DR2, targeting HBV RNA expressed from integrated HBV DNA**

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

Yuen M, et al. AASLD 2014; Poster #LB-21
Yuen M, et al. AASLD 2015; Poster #LB-9

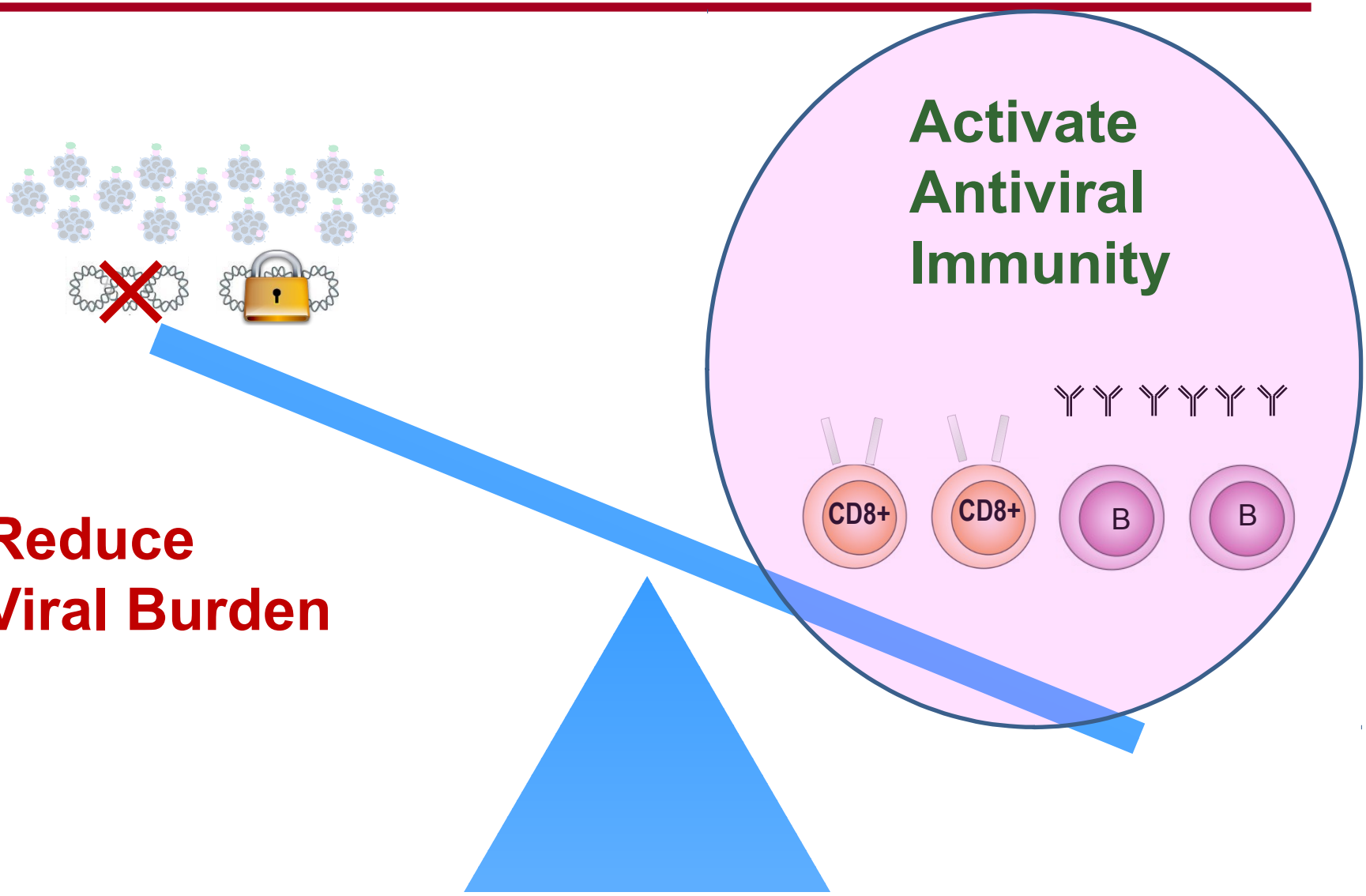
ARC-521 reduces HBsAg in HBeAg- chimps

- 3 monthly IV doses ARC-521 administered to 2 HBeAg neg chimps after 6 monthly doses of ARC-520

- **ARC-520/521 on FDA hold due to toxicity in preclinical studies and infusion reactions in clinical studies**

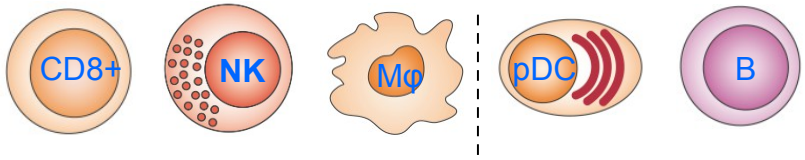
HBsAg reduction with ARC 521 same as ARC-520 in HBeAg+.

Therapeutic Strategies for HBV Cure



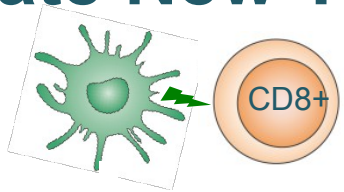
Ways to activate Antiviral Immunity against HBV

1. Stimulate Antiviral Effector Cells



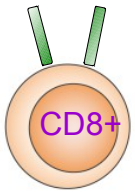
- TLR-7, TLR-8, RLRs, CLRs, NLRs
- DNA sensors

2. Generate New T cells



- Therapeutic vaccines

3. "Rescue" Exhausted T cells



- Reduce viral antigens
- Modulate immune receptors (PD-1)
- Relieve suppression of T cells
- Inhibit T regs

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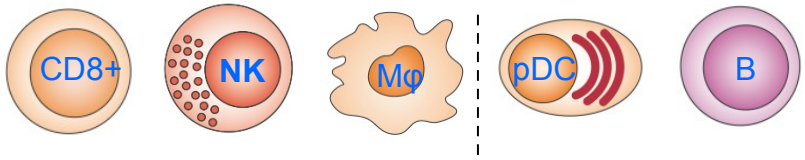

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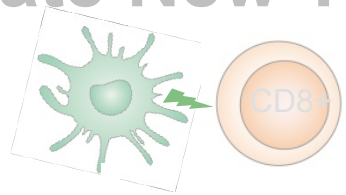

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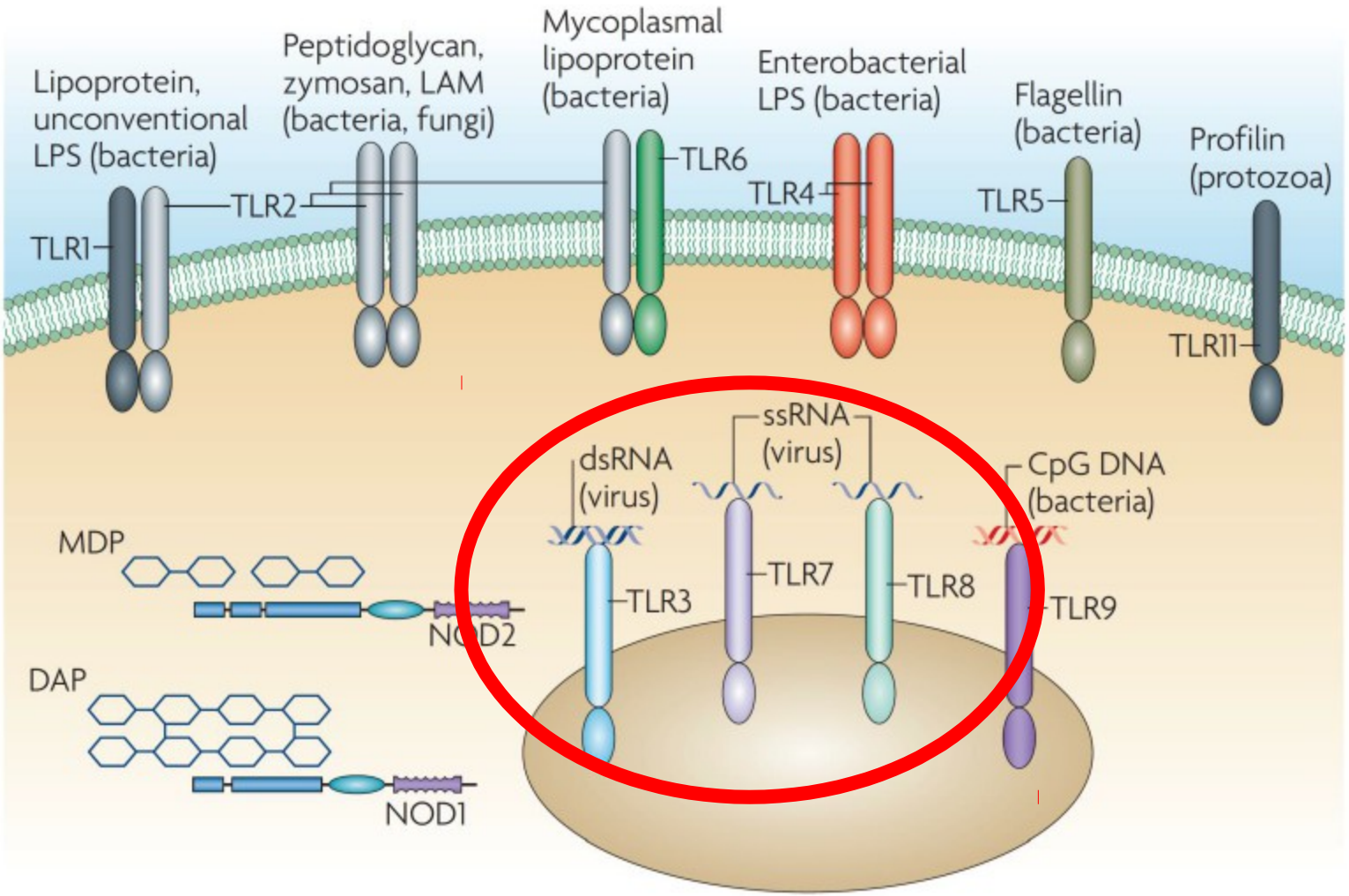
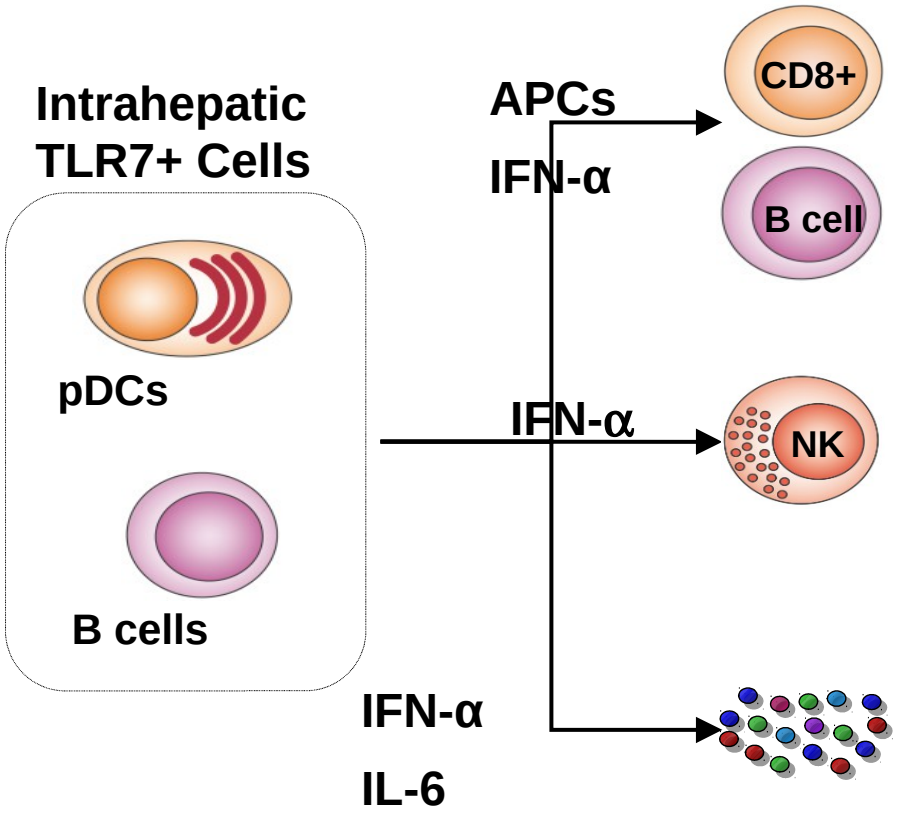
TLRs: Pattern Recognition Receptors that Recognize Pathogen-Associated Molecular Patterns



GS-9620 Toll-like Receptor 7 (TLR7)



pDC, Plasmacytoid dendritic cell
APC, Antigen presenting cell.
IFN, interferon

❶ Adaptive immunity

- Kill infected cells
- Antiviral cytokines (e.g. IFN-γ)
- Neutralizing antibodies

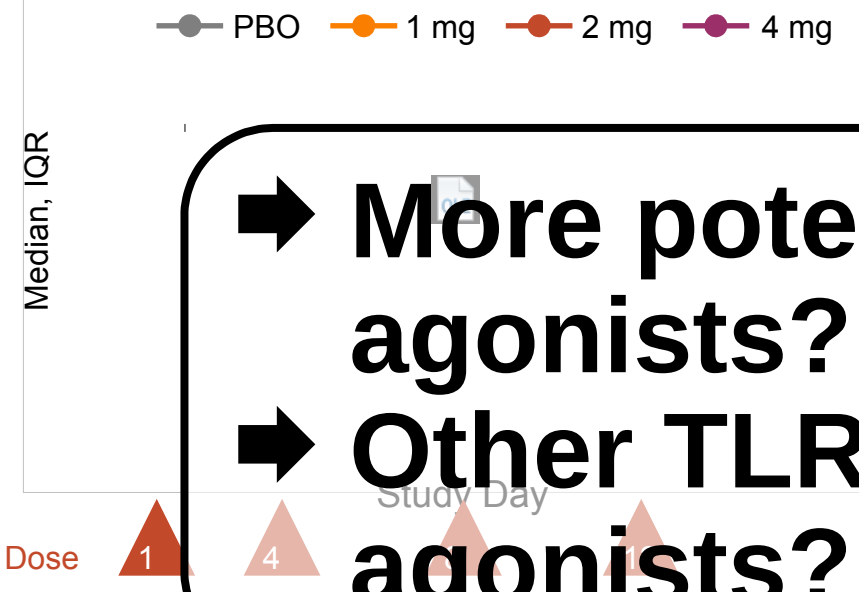
❷ Innate Immunity

- Kill infected cells
- Antiviral cytokines (e.g. IFN-γ)

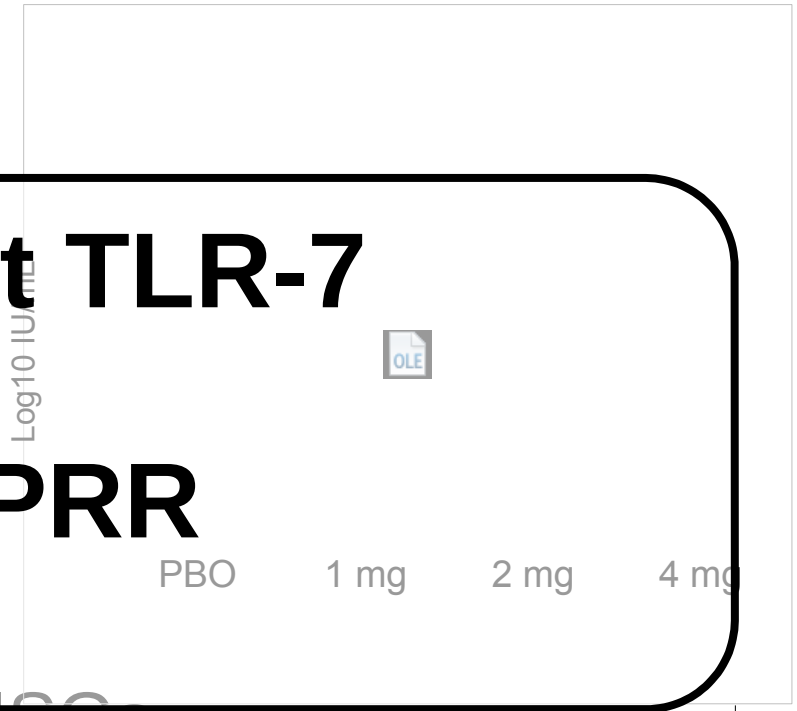
❸ Antiviral cytokines

GS-9620 Phase 2 study in suppressed CHB

ISG15 Expression



Change in HBsAg level



➡ **More potent TLR-7 agonists?**

➡ **Other TLR/PRR agonists?**

- ~~Dose-related increase ISGs~~
- Peripheral T-cell/NK cell activation by 8 weeks
- No systemic IFN, no flares, no cytopenias
- **BUT Minimal change in HBsAg levels**

Janssen HL, et al. AASLD 2016, Boston. #1851

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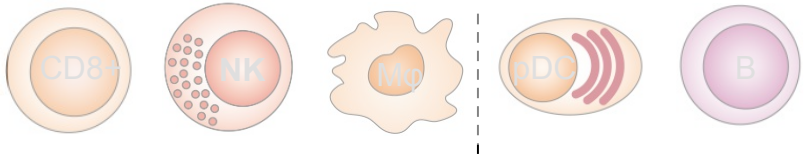

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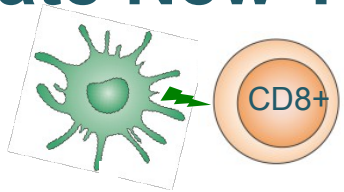

- Therapeutic vaccines

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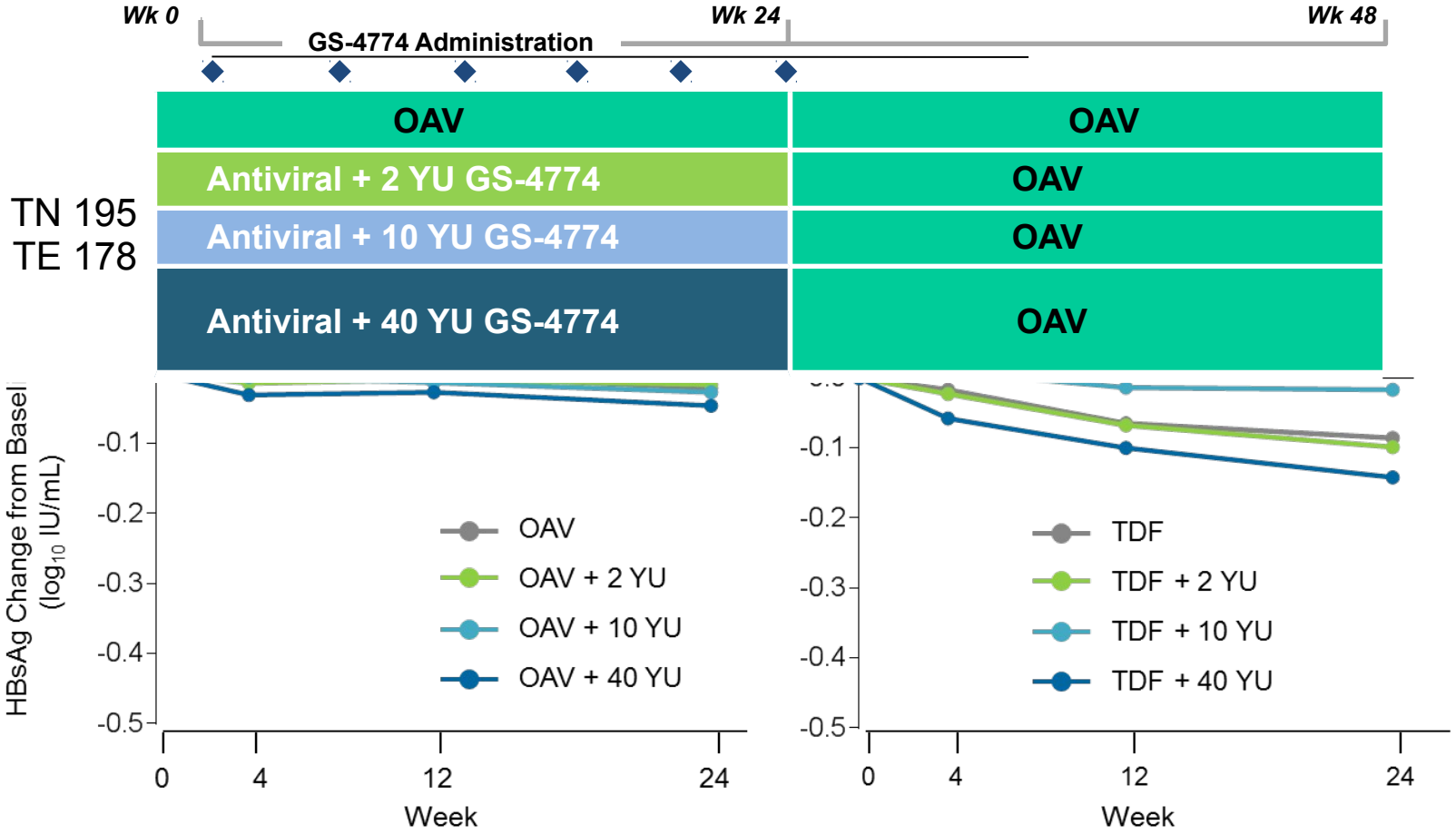
T-cell Vaccine (GS-4774)



- No change in HBsAg levels
- No change in HBV-specific T-cell responses

➡ **Need to overcome T-cell exhaustion?**

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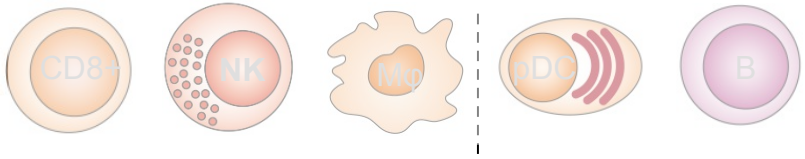

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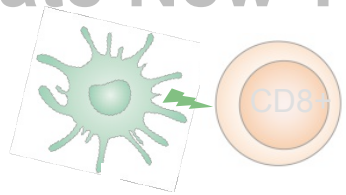

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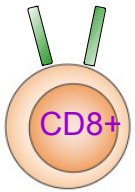

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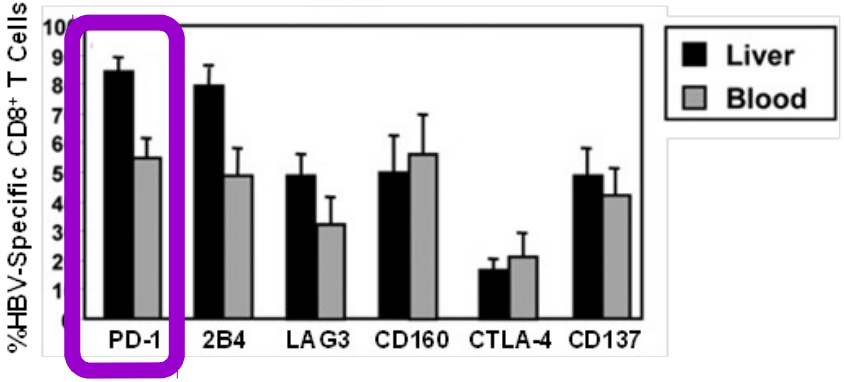
Role of PD-1:PD-L1 Interactions for HBV

- Persistent HBV infection has exhausted CD8 T-cell phenotype
  - PD-1 most strongly expressed among inhibitory markers1

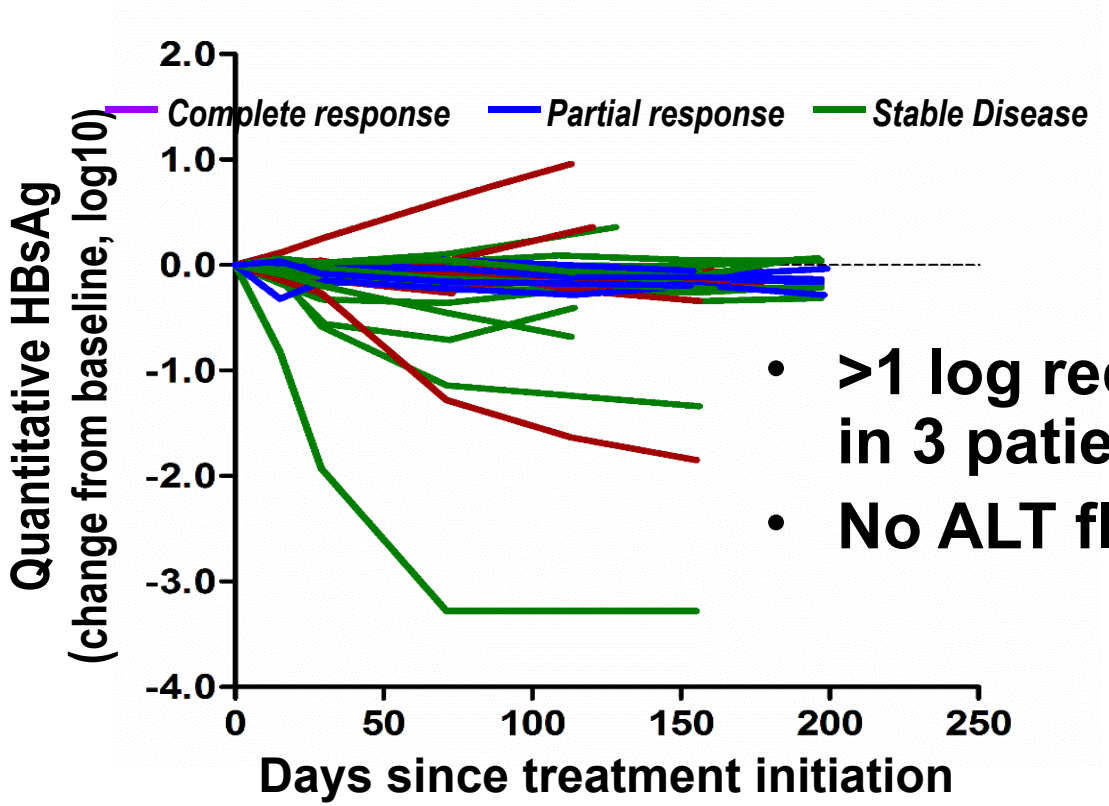


- PD-L1 ligand is up-regulated in HBV-infected liver2
- PD-1:PD-L1 blockade reverses immune dysfunction in murine and woodchuck HBV models3-5
- PD-1 inhibitors suppress HBV in patients with HBV-HCC6

1Fisicario P. et al. Gastroenterology. 143, 2012; 2Chen J. et al. Inflamm Res. 60 2011;
3Maier H. et al. J Immunol. 178, 2007; 4Zeng H. et al. PLoS One. 7, 2012.
5Liu, J. et al. PLoS Pathogens. 10. 2014
6Sangro B, et al. AASLD 2016

Are PD-1 Inhibitors safe in Chronic Hepatitis B?

- CheckMate 040 Study: Nivolumab in Advanced HCC
  - Included 51 patients with chronic hepatitis B

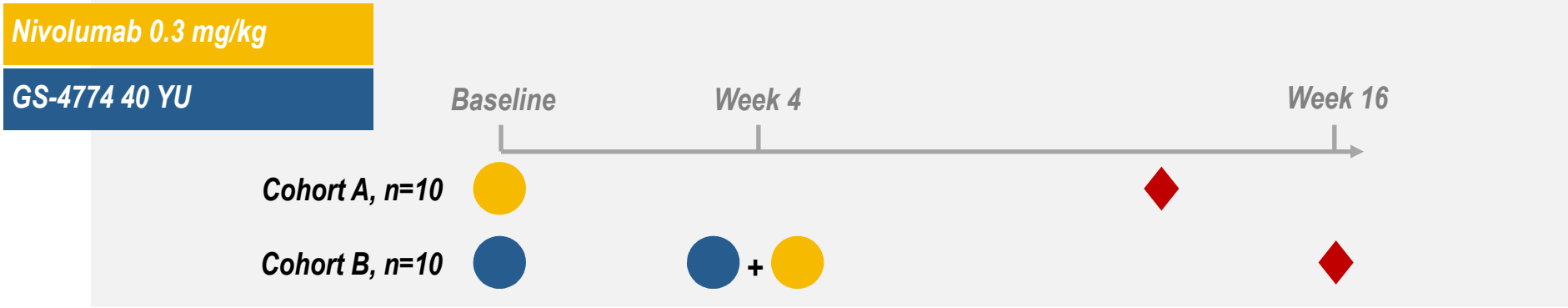


- **>1 log reduction in HBsAg in 3 patients over 6 months**
- **No ALT flares**

Sangro B, et al. AASLD 2016[31]

Are PD-1 Inhibitors safe in Chronic Hepatitis B?

- GS-US-330-1938 Study: PD-1 inhibition with or without therapeutic vaccine in suppressed CHB patients



- Primary Endpoints
  - log10 HBsAg decline at 12 weeks post-dose
  - Safety and tolerability
- Exploratory Endpoints
  - Changes in HBV-specific immune responses, T-cell subsets and cytokine level after treatment

Gane E, et al. EASL 2017

Combination strategy to achieve Functional Cure

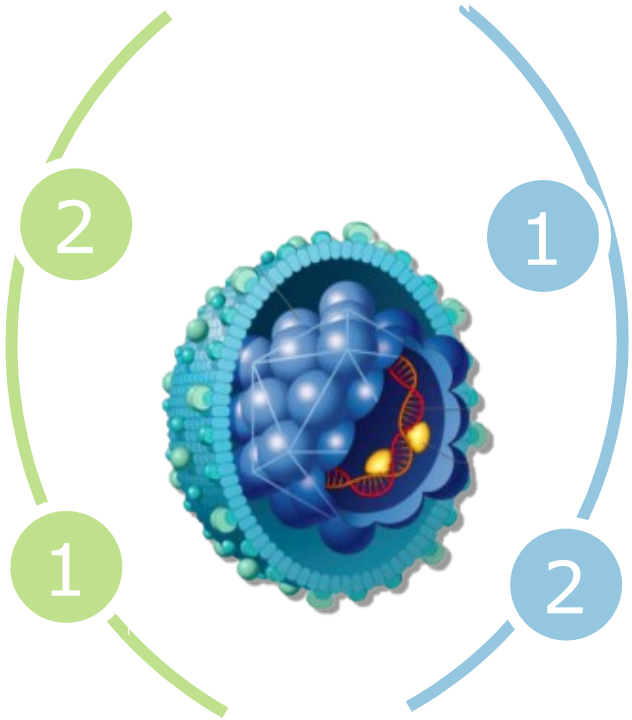
Boost Immune response

Boost specific T-cell responses

- Therapeutic vaccines
- TLR agonists
- Checkpoint modulation

Boost Innate Immunity

- TLR agonists



Reduce Viral Burden

Block cccDNA production

- Capsid assembly modulators

Reduce antigen load (sAg, capsid)

- siRNA
- Antisense

cccDNA silencing & degradation

- TALENs
- CRISPR / CAS9

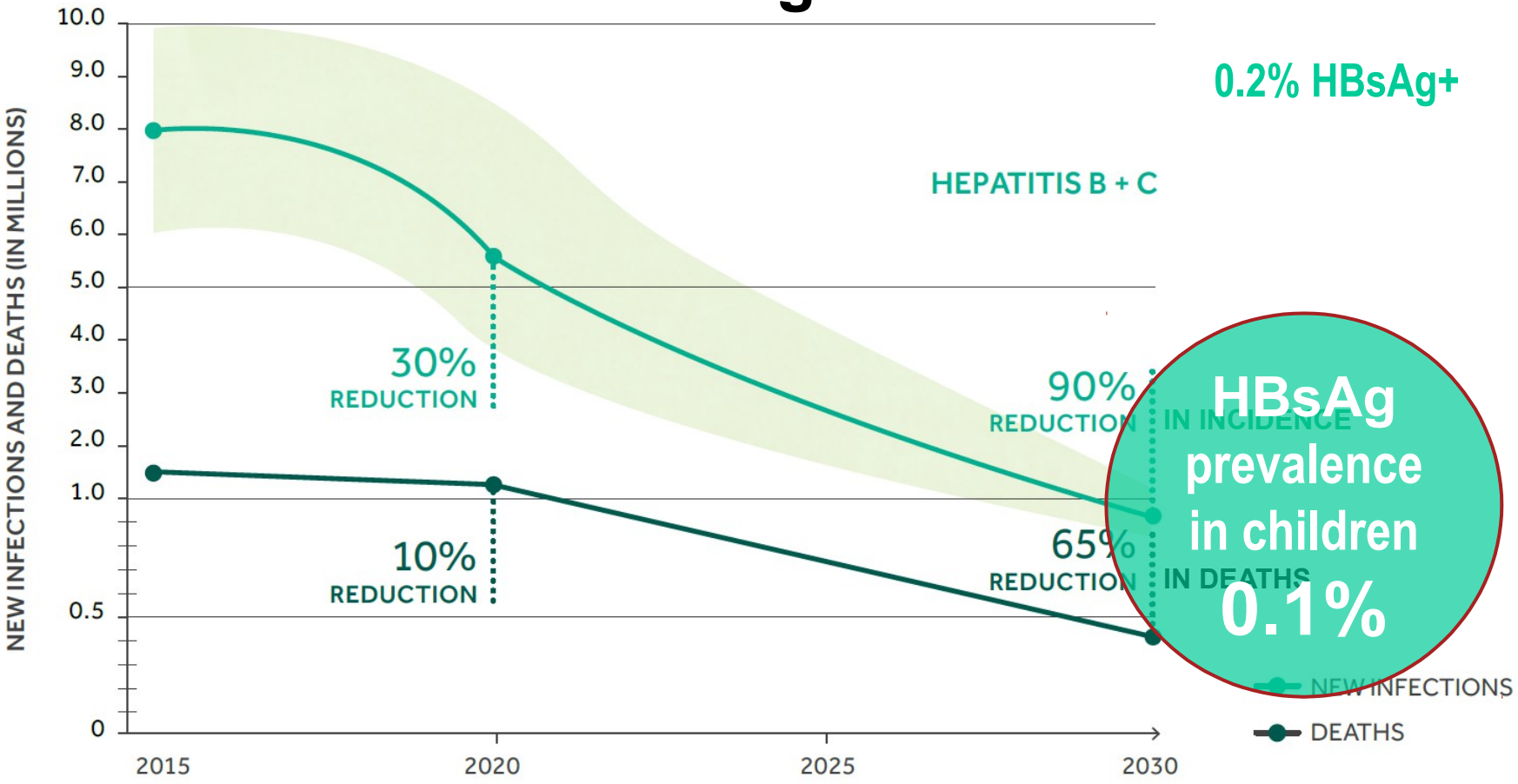
Conclusions
HBV CURE

- HBV CURE will require combination therapies which inactivate cccDNA and overcome T-cell exhaustion
- HBV CURE could provide treatment for ALL HBsAg+
- HBV CURE could prevent most HCC
- **SAFETY** will be the priority in order to avoid hepatitis flares and off-target toxicities
- Short duration, convenience (sc/oral), affordability, will be crucial for uptake in low-

Will HBV CURE expedite global eradication?

Global Health Sector Strategy on Viral Hepatitis (2016-2021)

WHO Global Targets for 2030

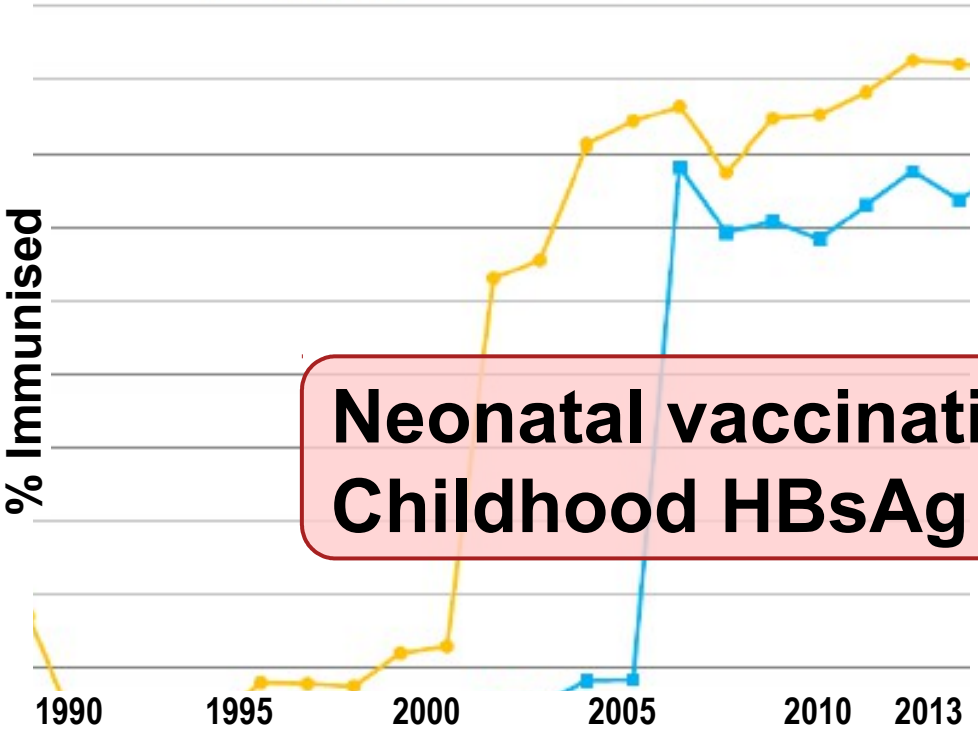


WHO Global Health Sector Strategy on viral hepatitis, 2016–2021. Available at http://www.who.int/hiv/draft-hep-strategy-2016-2021_en.pdf (accessed June 2015)

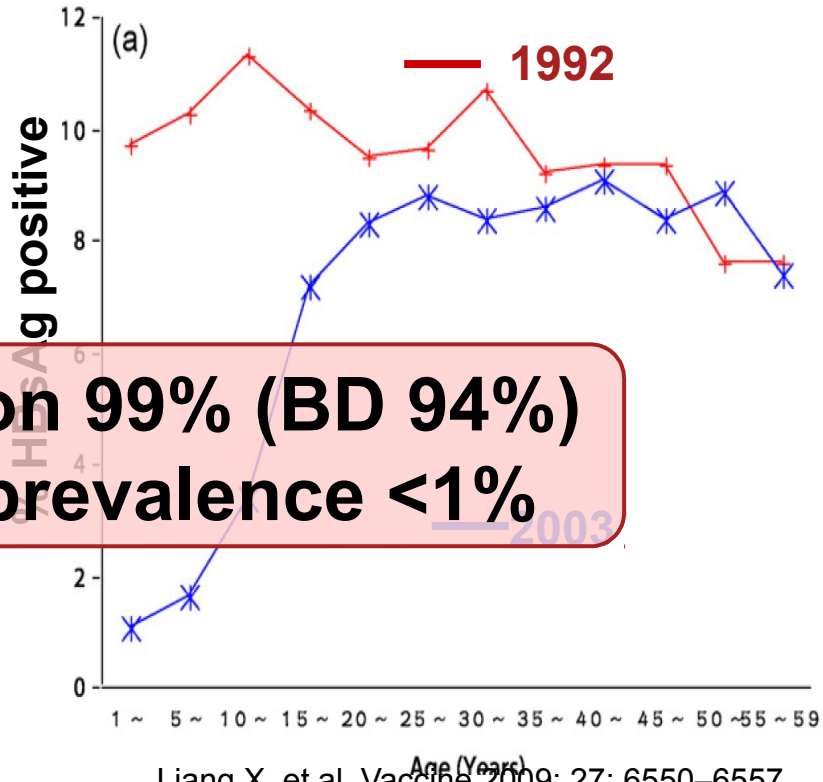
Do we need an HBV CURE?

- In 1990, HBsAg prevalence in Chinese children was 9.8%
- Neonatal vaccination rolled out since 1992

HBV Vaccine coverage 1990-2013[1]



HBsAg Prevalence 1992 and 2003

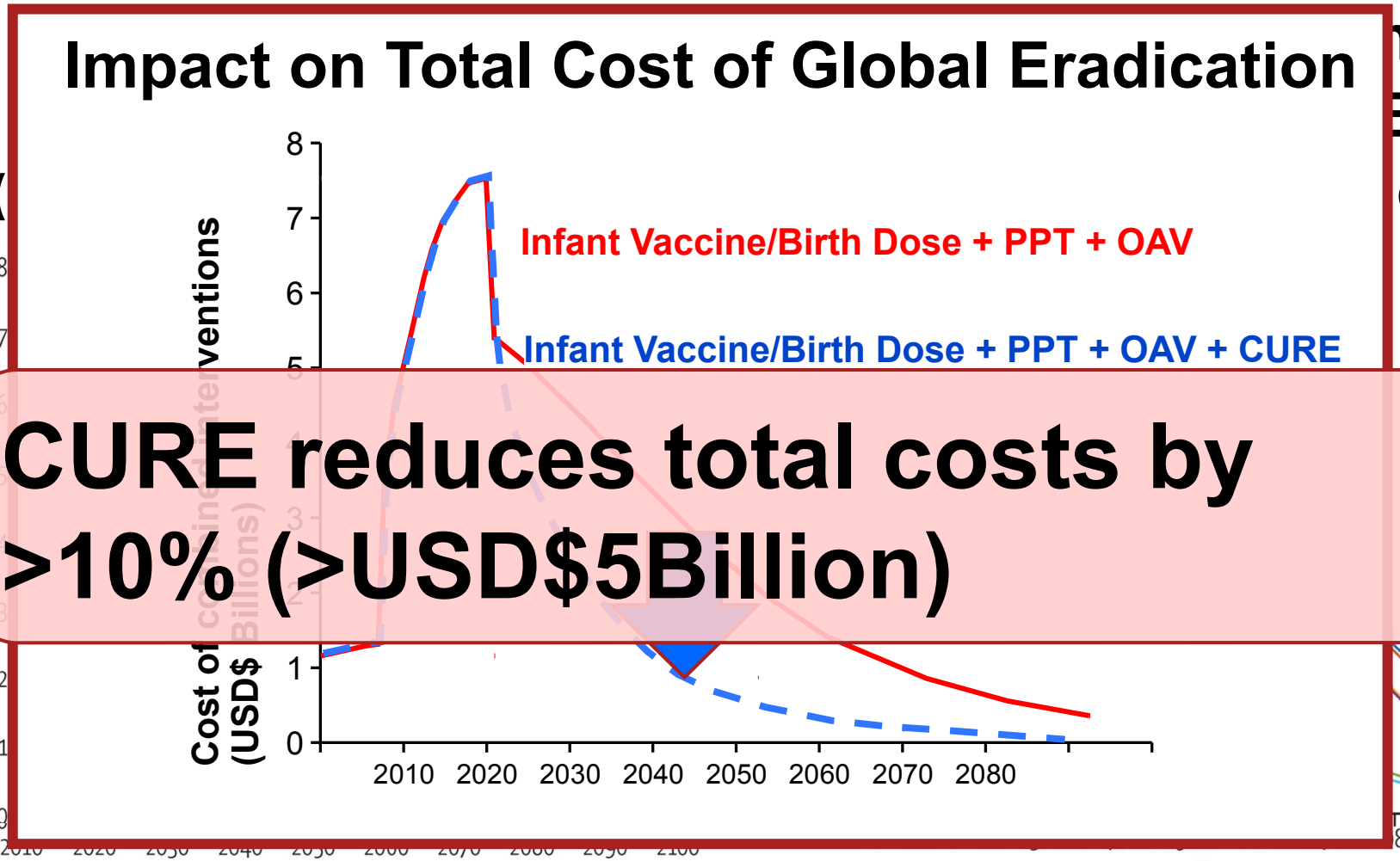


Neonatal vaccination 99% (BD 94%)
Childhood HBsAg prevalence <1%

1WHO/UNICEF Joint Reporting Form for Immunization

Liang X, et al. Vaccine 2009; 27: 6550–6557

Do we need an HBV CURE?



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Thank you!

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