INSTITUTE OF HUMAN VIROLOGY

Strategies to Eradicate HBV

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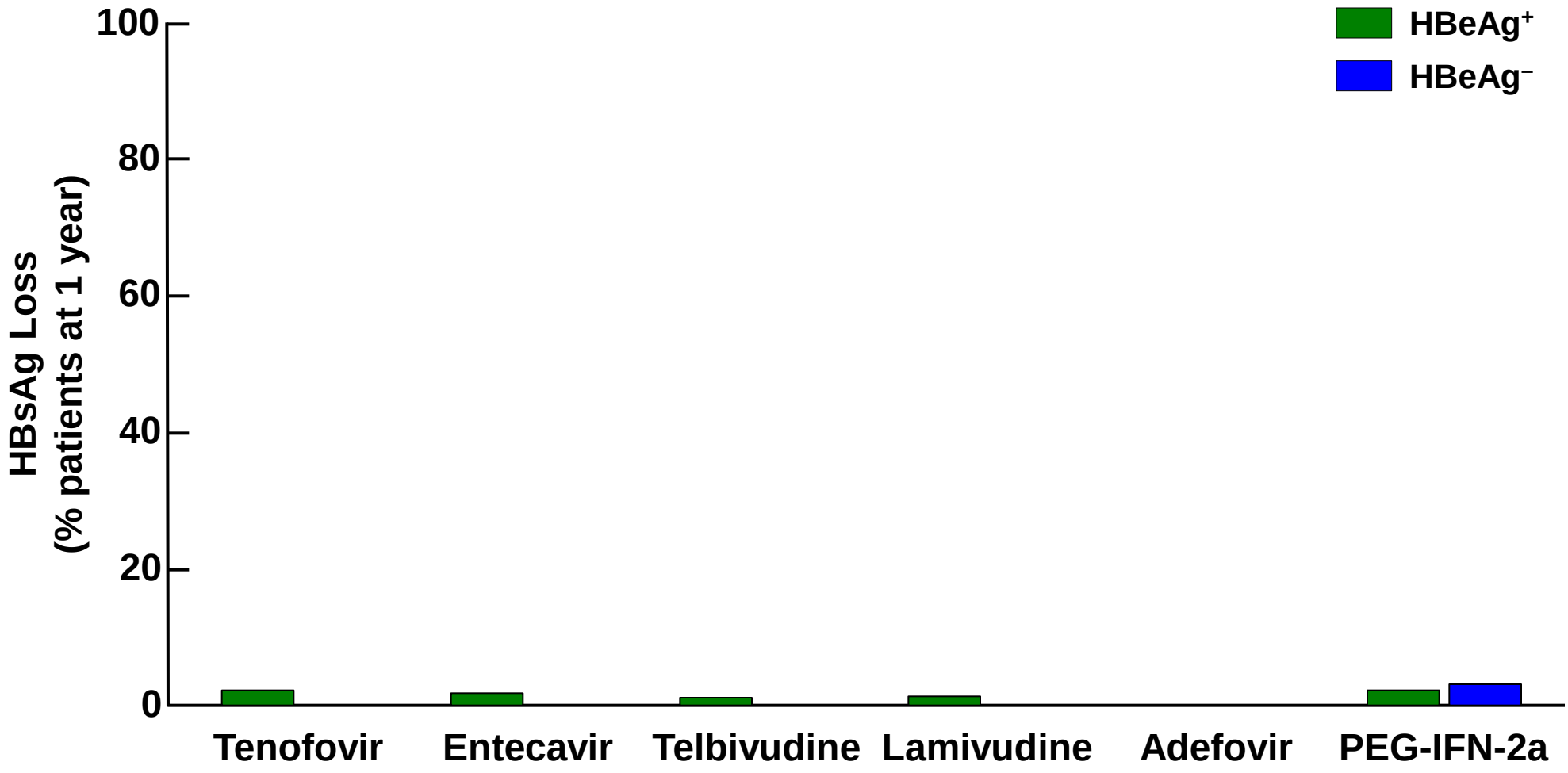
Research Matters

June 07, 2018

Efficacy of HBV Agents After One Year of Therapy: HBsAg Loss



Data from 2012 EASL HBV Management Guidelines

Pitfalls of Current Therapy

- **Nucleoside analog therapy has little effect on HBsAg levels, HBsAg loss and depletion of cccDNA**
- **Emergence of resistance is a potential problem with long term nucleoside analog therapy**
- **Long term adverse events may occur with continued use of nucleoside analogs**

Goals for Eradication

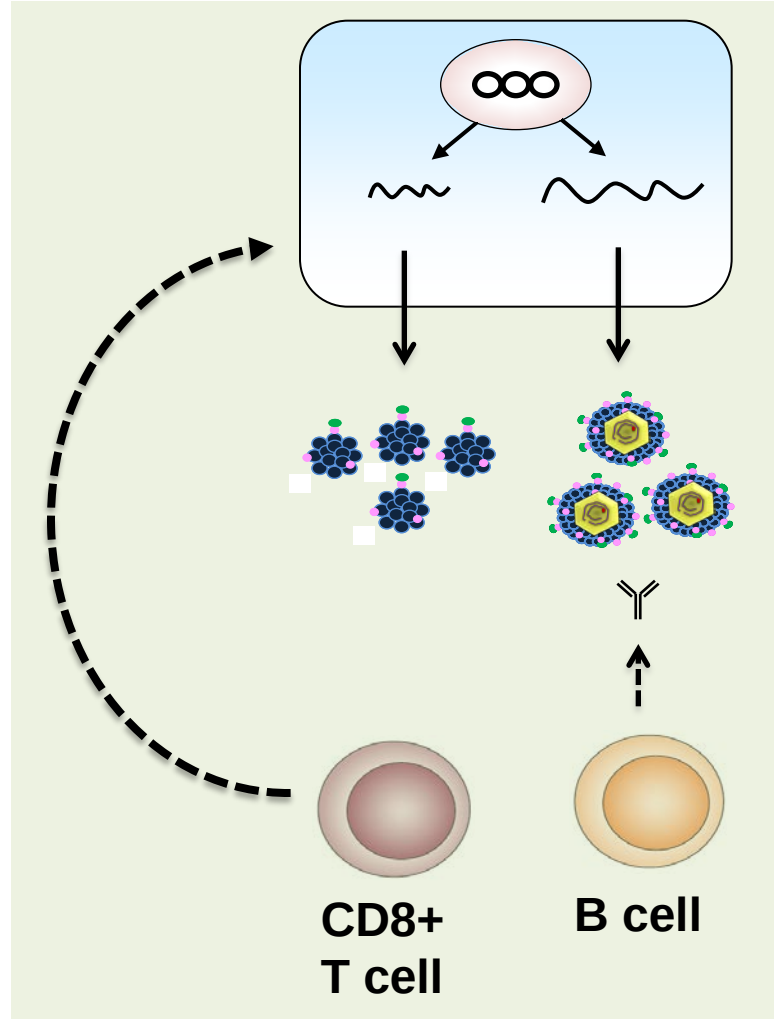
- **Absence of plasma HBV DNA after stopping antiviral therapy**
- **Loss of HBsAg with or without HBsAg seroconversion**

Barriers to Resolution of Chronic HBV Infection

cccDNA reservoir

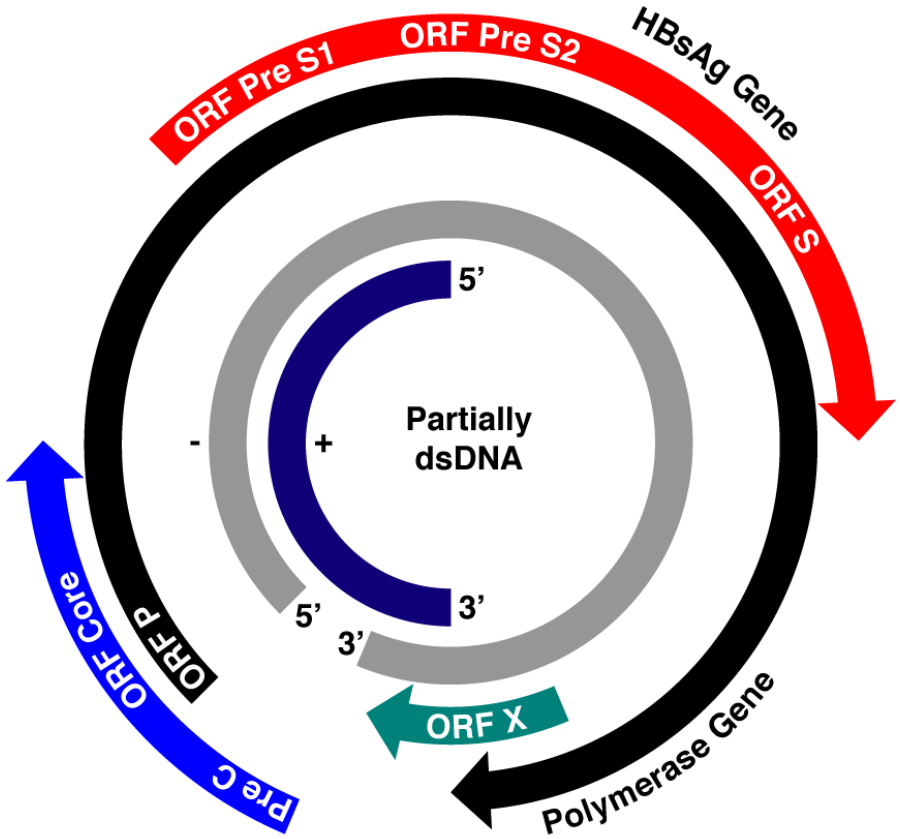
Dysfunctional T-cell response

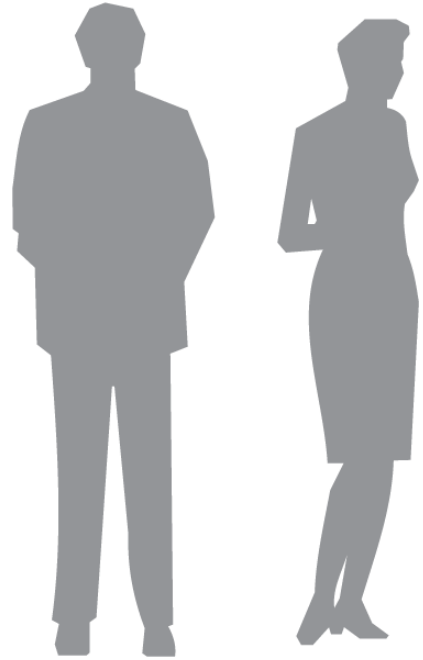
Insufficient B-cell response



Novel Strategies to Eradicate HBV

Target the Virus and/or Target the Host

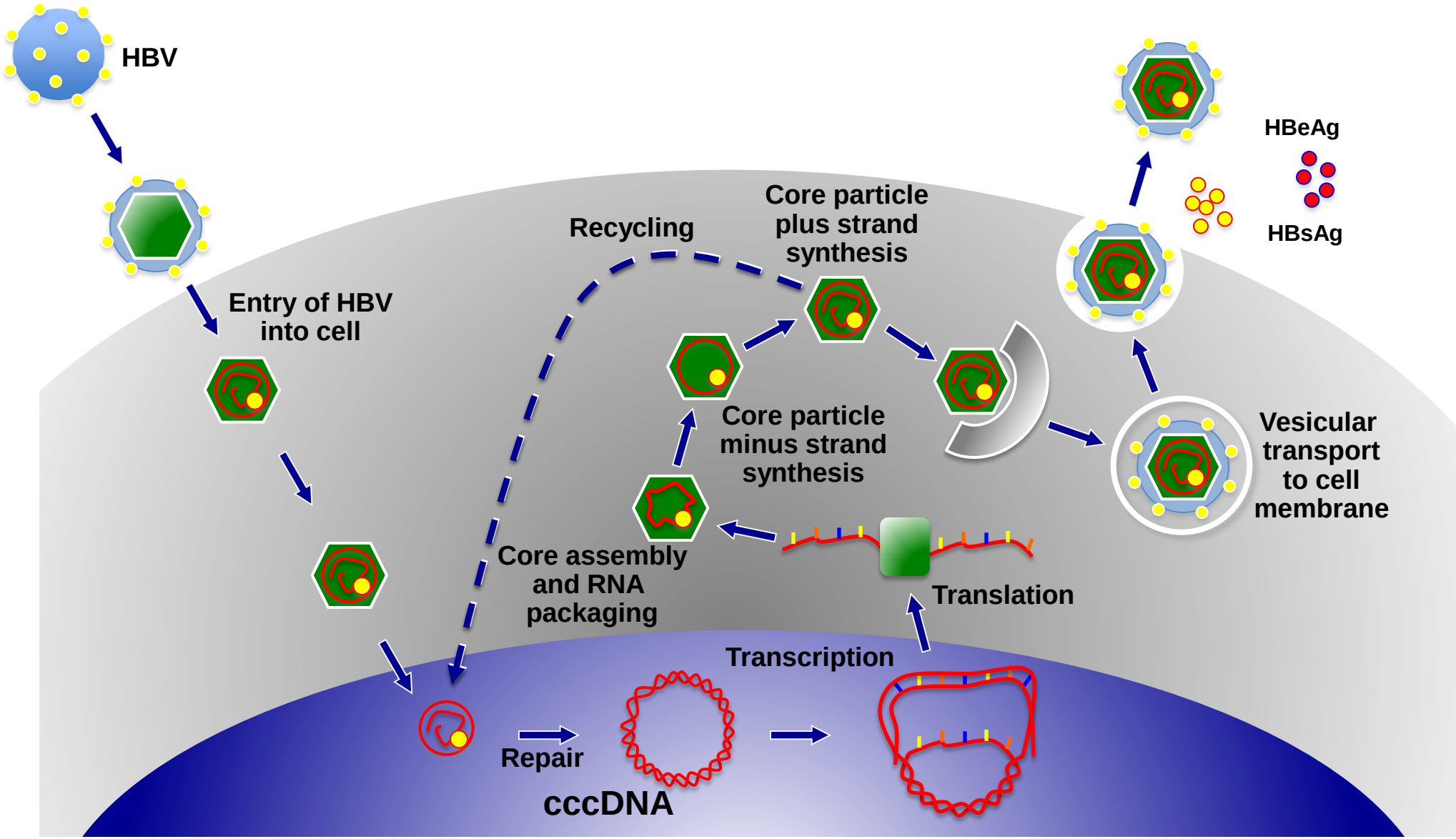




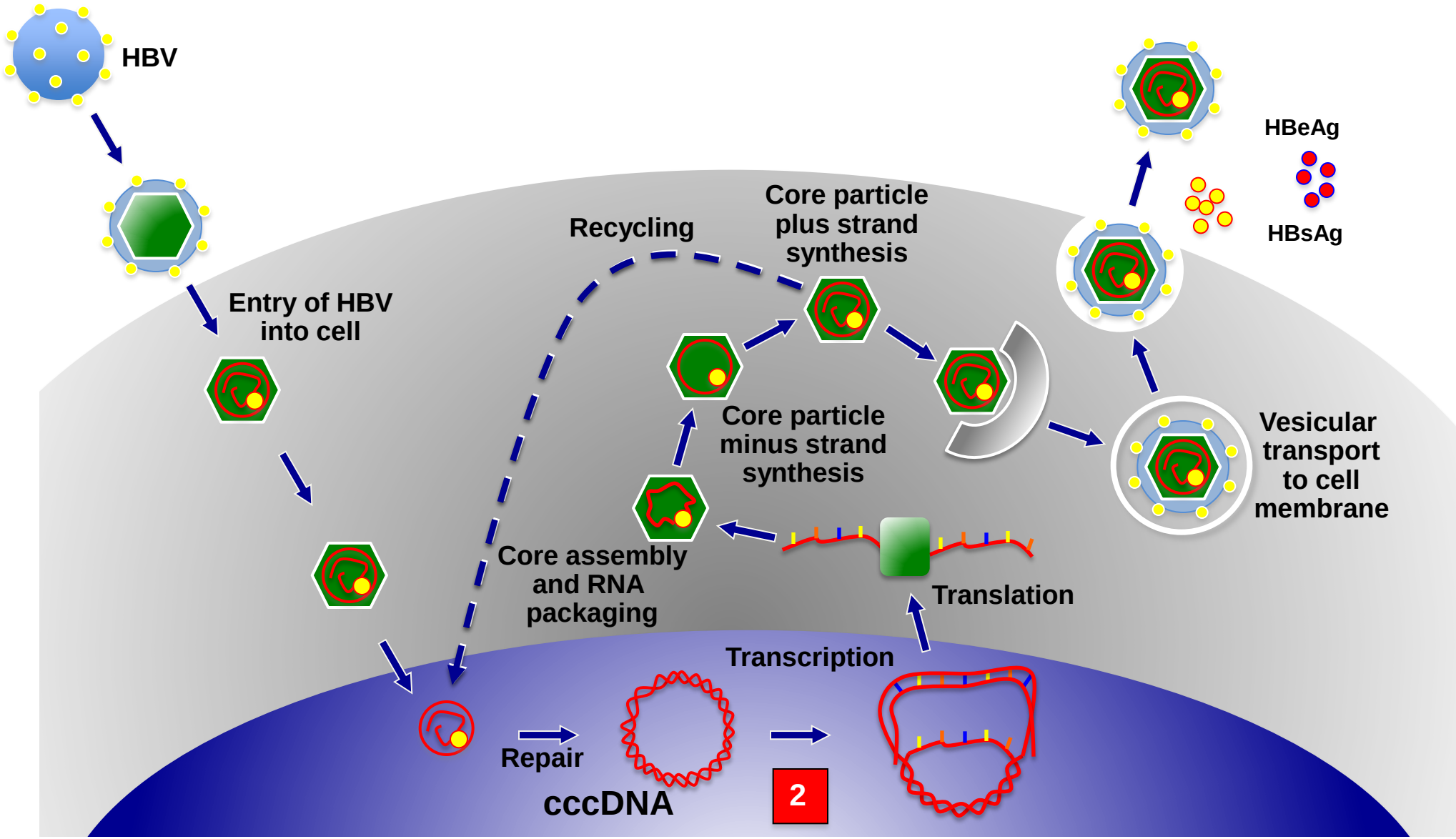
- **Viral proteins or nucleic acids**

- **Host proteins necessary for viral replication**
- **Innate or adaptive immune system**

HBV Life Cycle, Potential Targets



Targeting cccDNA



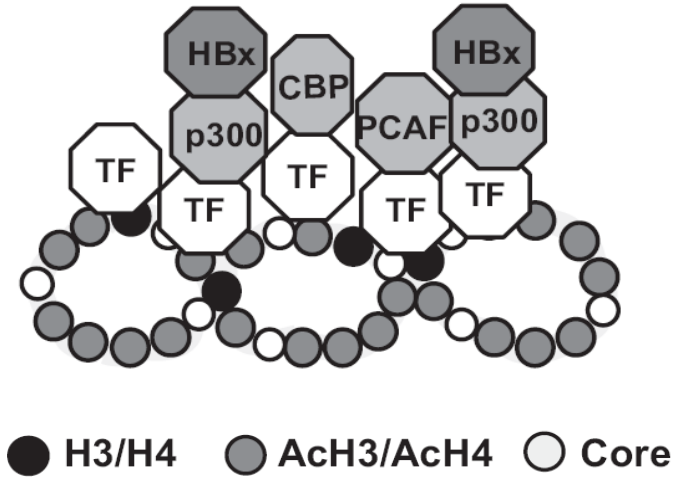
Depleting or Inactivating cccDNA

Key issues:

- **cccDNA = reservoir of infection**

- **Formation of *new* cccDNA can be blocked by inhibiting replication**

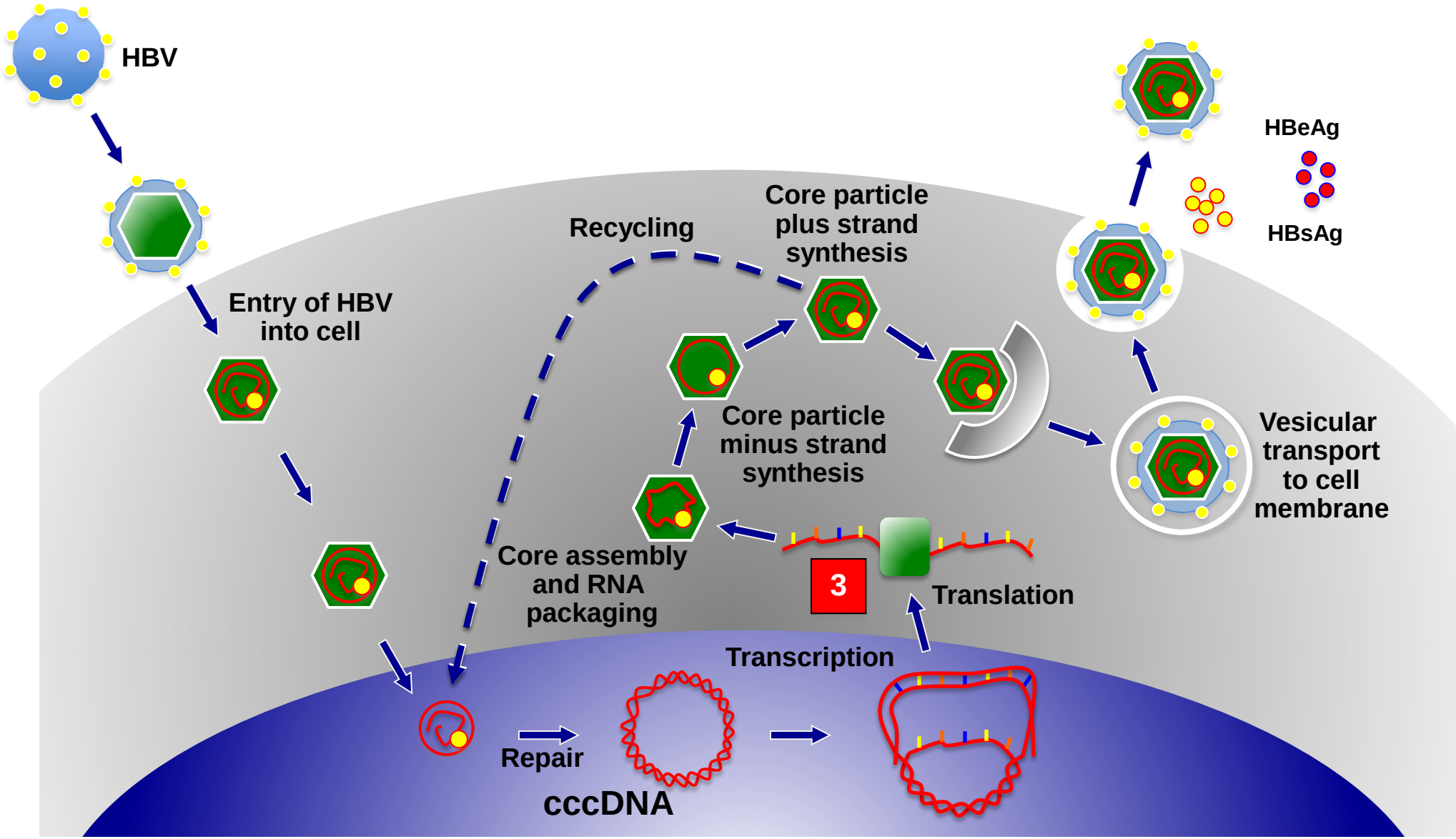
- **Existing cccDNA is not affected directly by current therapies and has a long half-life**



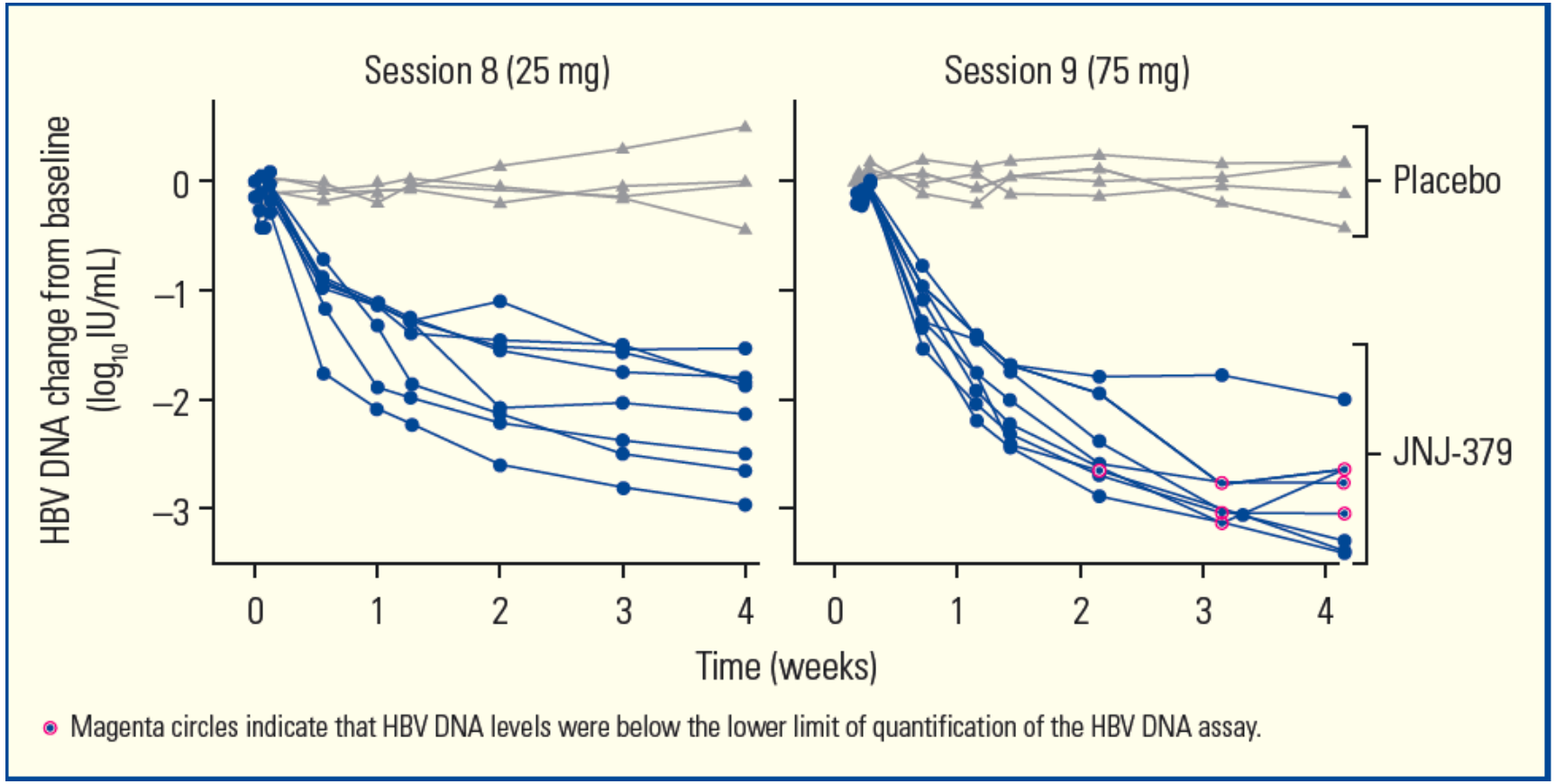
- **Is it possible to silence cccDNA epigenetically?**

- **Is it possible to destabilize cccDNA?**

Targeting Encapsidation



Antiviral Activity of JNJ-56136379, a novel HBV Nucleocapsid Inhibitor



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Antiviral Activity of JNJ-56136379, a novel HBV Nucleocapsid Inhibitor

Table 3. Summary Statistics of HBV RNA and DNA at Baseline and Day 29 by Treatment Arm

	HBV DNA				HBV RNA			
	Baseline		Day 29		Baseline*		Day 29	
Treatment Arm	N	Mean (SD) Log_{10} IU/mL	Mean (SD) Change from Baseline Log_{10} IU/mL	<LLOQ	N	Mean (SD) Log_{10} cp/mL	Mean (SD) Change from Baseline Log_{10} cp/mL	Not detected
25 mg QD	8	6.90 (1.91)	–2.16 (0.49)	0	8	5.60 (2.37)	–2.30 (0.59)	3
75 mg QD	8	5.26 (1.50)	–2.89 (0.48)	3	8	3.39 (2.21)	–1.85 (1.42)	6
Pooled placebo	8	5.49 (1.77)	–0.01 (0.31)	0	8	4.03 (2.64)	–0.18 (0.72)	2

*Two patients in the 75 mg JNJ-379 group, and one patient in the placebo group had undetectable HBV RNA at baseline.
LLOQ: Lower limit of quantification

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Targeting Host immunity

- **Innate immune responses**
- **Immunoregulation/ adpative immune responses**
- **Therapeutic immunization**

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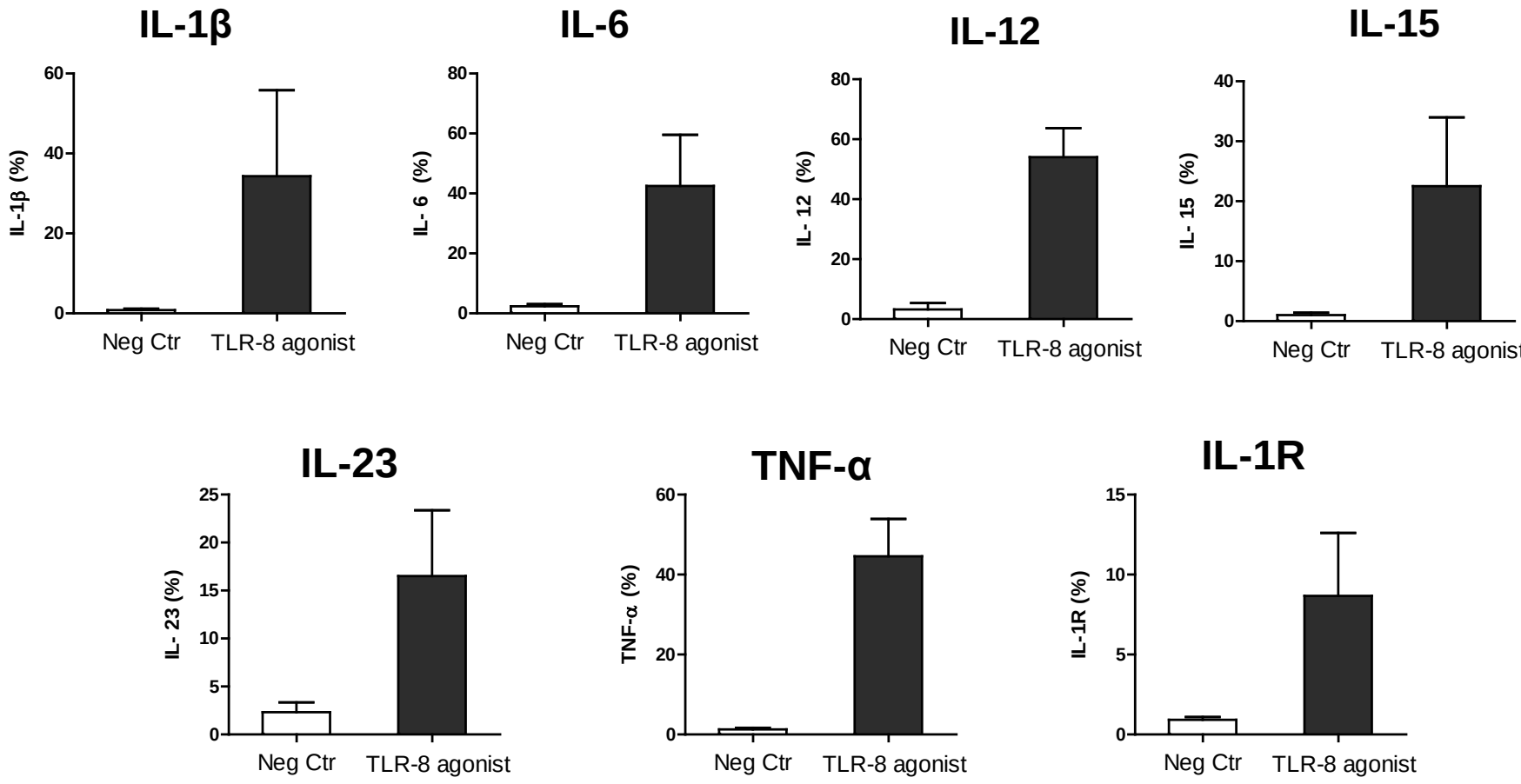
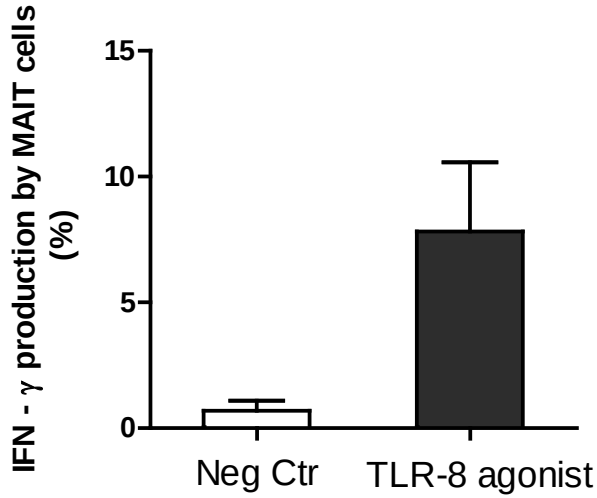
Increase in Dendritic Cell-related Cytokine Production Post TLR-8 Agonist (Truculture)

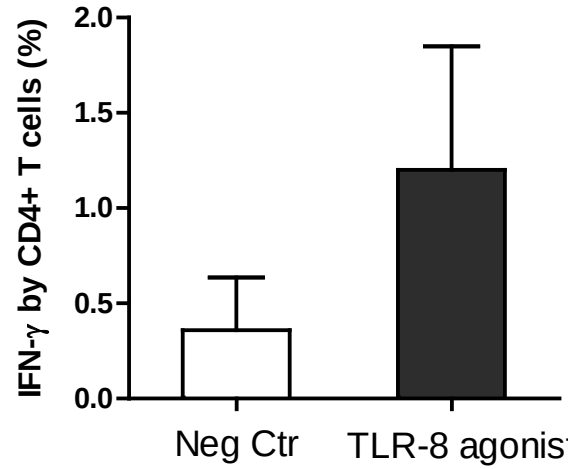


Increase IFN-γ Production Post TLR-8 Agonist Treatment (Truculture)

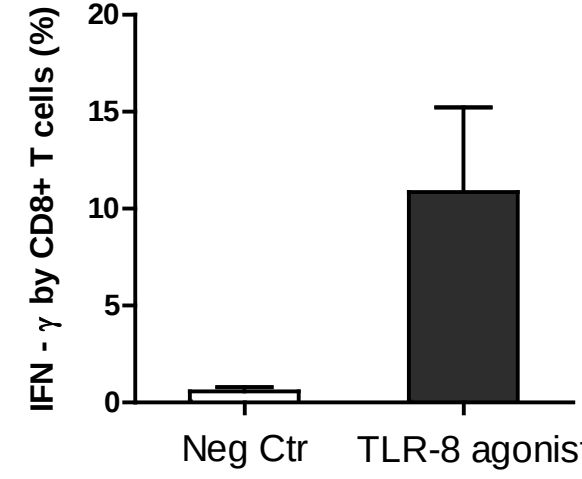
A. MAIT cells



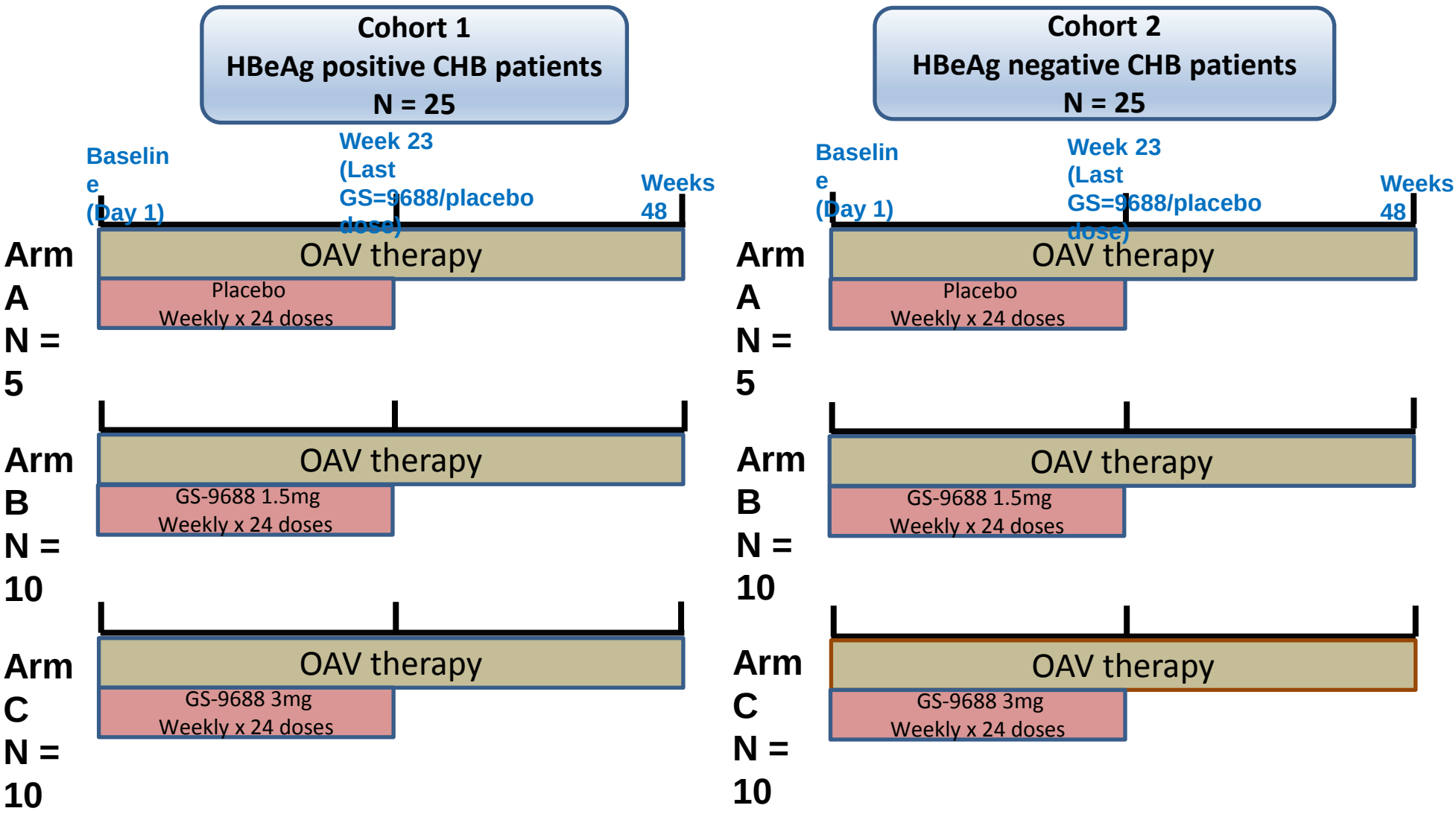
B. CD4+ T cells



C. CD8+ T cells



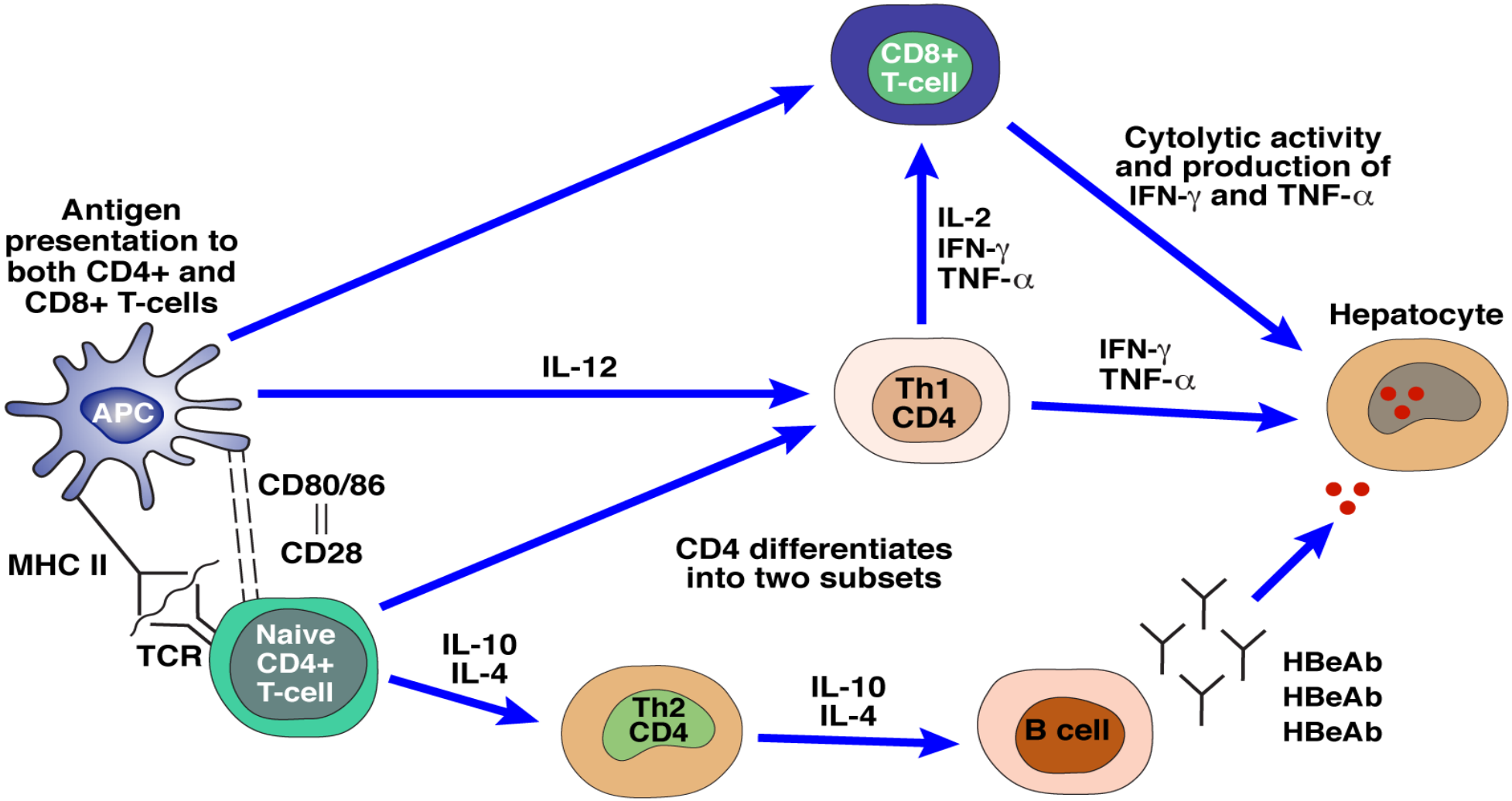
TLR8 Single Site Study Design



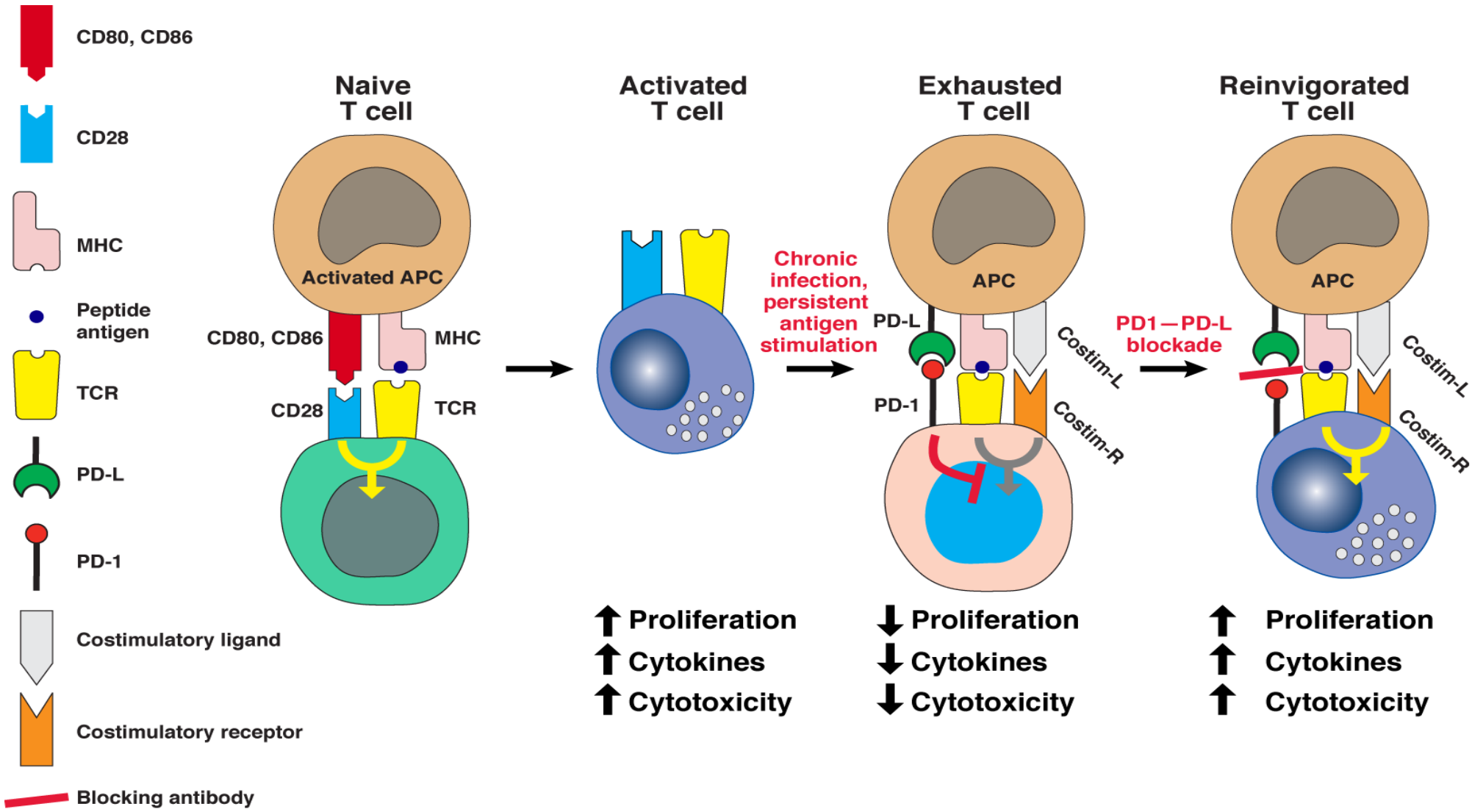
Targeting Host immunity

- Innate immune responses
- **Immunoregulation/ adpative immune responses**
- Therapeutic immunization

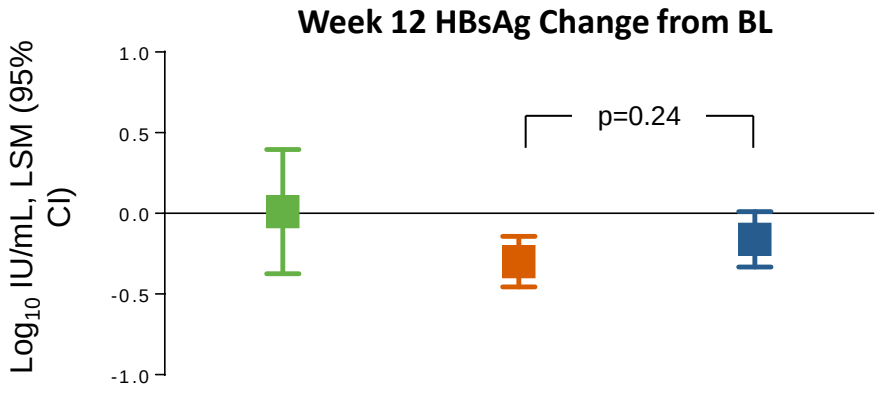
Adaptive Immunity in Chronic Hepatitis B Infection



Effect of PD-1/L1 on Antiviral Immunity



Results: HBsAg Change From Baseline

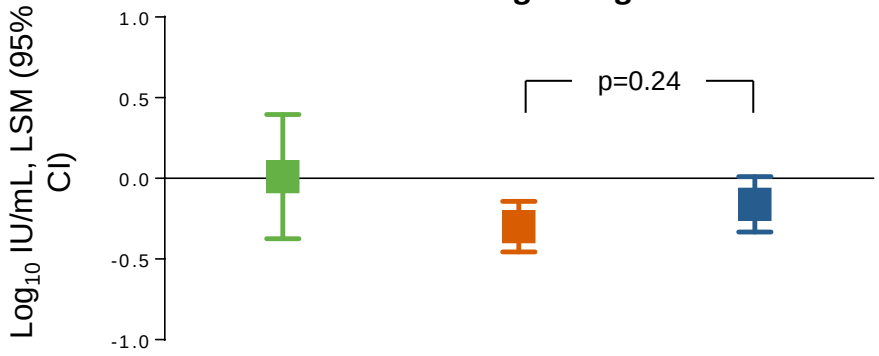


	Nivolumab 0.1 mg/kg n=2	Nivolumab 0.3 mg/kg n=12	Nivolumab 0.3 mg/kg + GS-4774 n=10
Mean (SD)	**0.016** (0.011)	**-0.30** (0.61)	**-0.16** (.20)
Median (IQR)	**0.016** (0.008, 0.024)	**-0.13** (-0.20, 0.06)	**-0.08** (-0.21, -0.02)

BL, baseline; IQR, interquartile range; LMS, least-squares mean.

Results: HBsAg Change From Baseline

Week 12 HBsAg Change from BL



	Nivolumab 0.1 mg/kg n=2	Nivolumab 0.3 mg/kg n=12	Nivolumab 0.3 mg/kg + GS-4774 n=10
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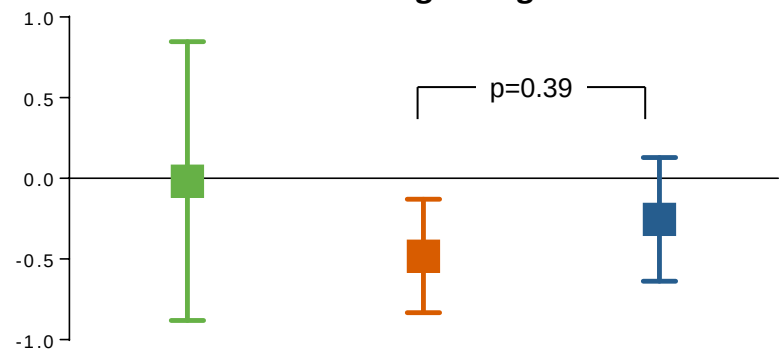
Week 24 HBsAg Change from BL



	Nivolumab 0.1 mg/kg n=2	Nivolumab 0.3 mg/kg n=12	Nivolumab 0.3 mg/kg + GS-4774 n=10
Mean (SD)	**-0.049** (0.035)	**-0.47** (1.26)	**-0.26** (0.24)
Median (IQR)	**-0.049** (0.074, 0.024)	**-0.14** (-0.19, 0.05)	**-0.20** (-0.39, -0.05)

BL, baseline; IQR, interquartile range; LMS, least-squares mean.

Targeting Host immunity

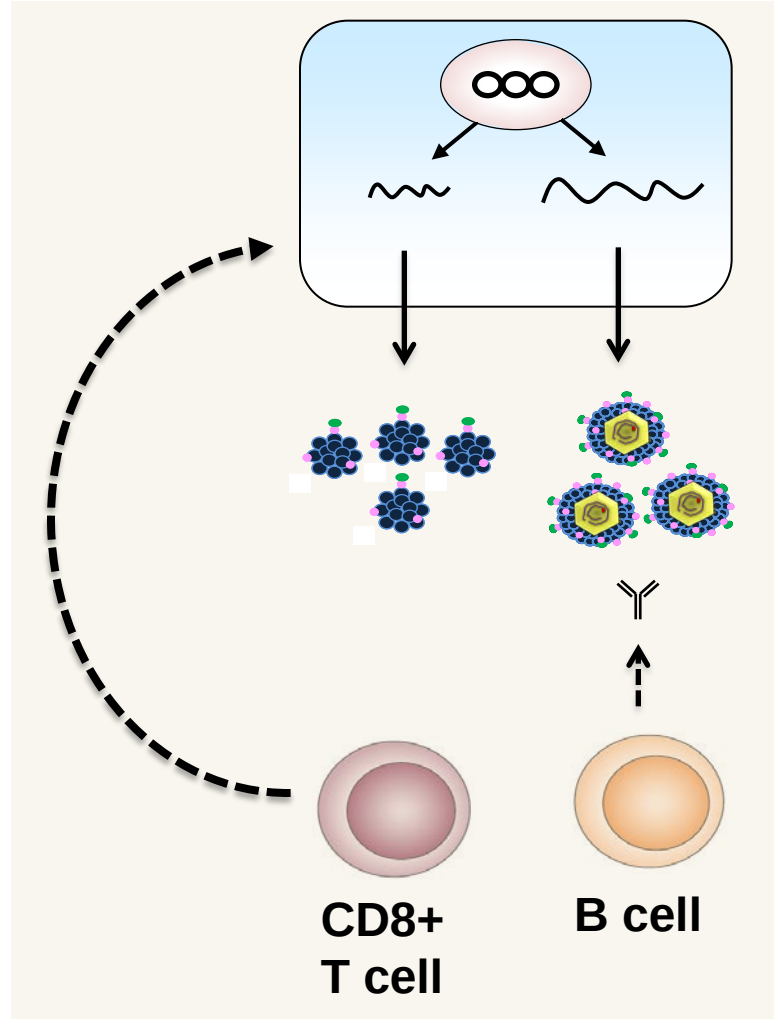
- Innate immune responses
- Immunoregulation/ adpative immune responses
- **Therapeutic immunization**

Barriers to Resolution of Chronic HBV Infection

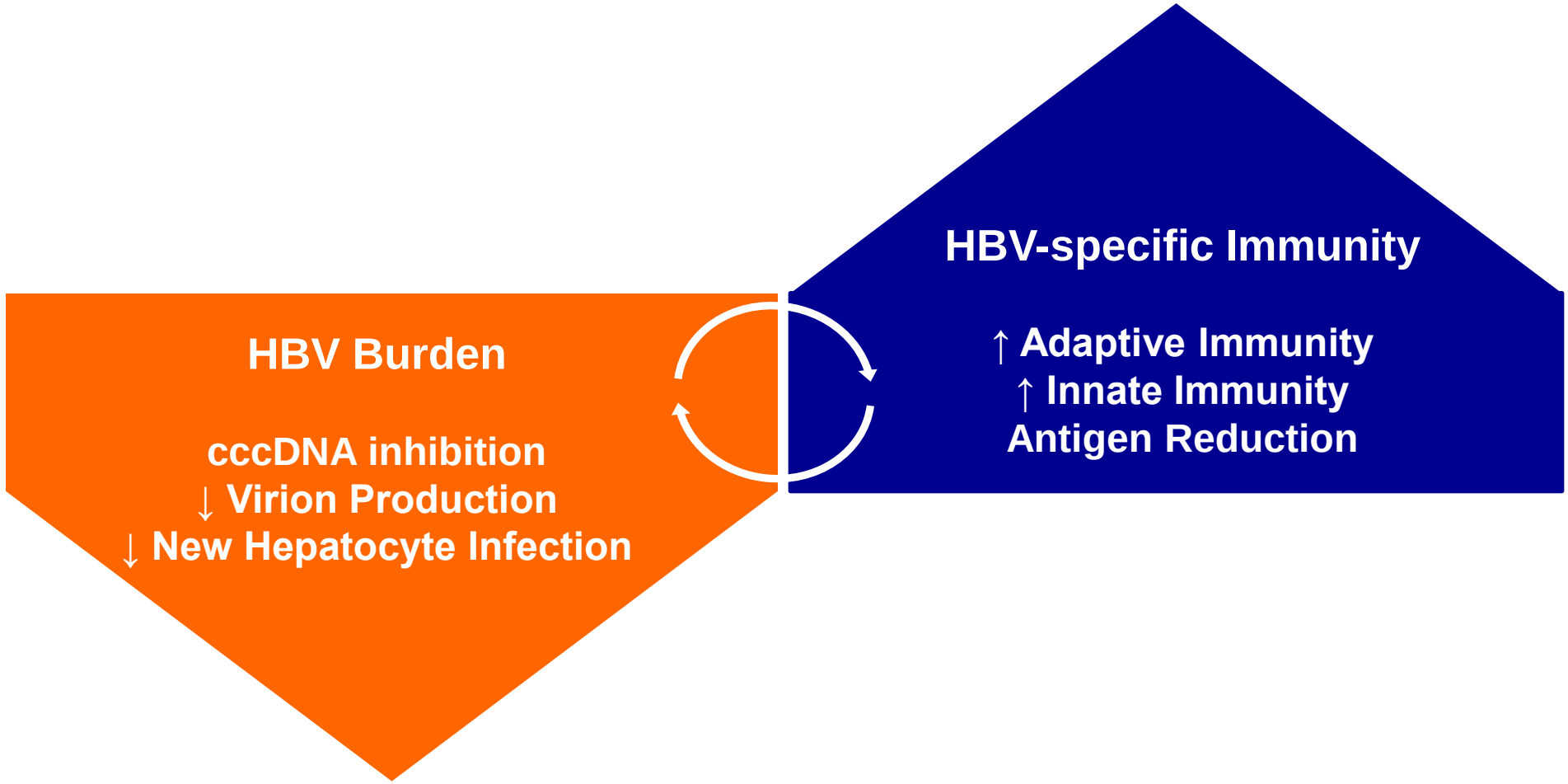
cccDNA reservoir

Dysfunctional T-cell response

Insufficient B-cell response



Research Approach



Conclusions

- **Our goal is to achieve sustained suppression of HBV *and* HBsAg loss after cessation of therapy**
- **Approaches to target virus include inhibition of viral entry, HBV antigen production, and elimination or silencing of cccDNA**
- **Approaches to target host include non specific inhibition of immunoregulatory pathways and boosting of HBV specific immunity**
- **Realistically, a combination approach may be necessary to achieve sustained virologic remission**

Acknowledgments

Institute of Human Virology
- **Benjamin Emmanuel BS**
- **Mallika Govindan BS**
- **Jennifer Hoffmann CRNP**
- **Lee Ki Seok Ph.D**
- **Amy Nelson RN**
- **Bhawna Poonia Ph.D**
- **Shikha Shrivastava Ph.D.**
- **Lydia Tang MD**
- **Haley Ward BS**
- **Eleanor Wilson MD**

- **Robert Redfield MD**
- **Robert Gallo MD**

University of Maryland
School of Meicine
- **Stephen Davis MBBS**

St. Joseph's Hospital, Phoenix
Anita Kohli MD

CCMD, CC, NIH
- **Henry Masur MD**

Dalhousie University, Canada
Lisa Barrett MD Ph.D

Greenebaum Cancer Center
-Kevin Cullen MD

Medical University of South Carolina
Eric Meissner MD. Ph.D.

Gilead Sciences Inc
Anu Osinusi MD

NIH DC-Program for AIDS Progress
- **Charisse Ahmed BA**
- **Elizabeth Akoth RN**
- **Chloe Gross RN**
- **Michelle Espinosa**
- **Angie Price CRNP**
- **Elana Rosenthal MD**
- **Rachel Silk RN**
- **Sarah Kattakuzhy MD**
- **Aurielle Thomas BA**

Patients