



12 & 13 January 2015

PARIS - Palais des Congrès

**International Conference on the Management
of Patients with Viral Hepatitis**

HBV and the immune response



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Laboratory of Viral Immunopathology
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Italy***

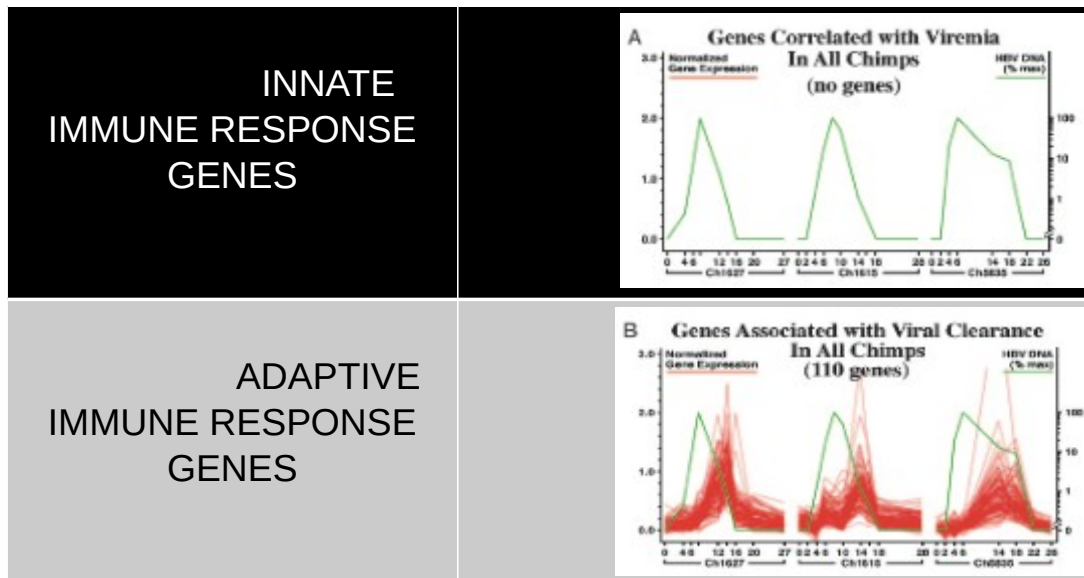
List of topics

- Kinetics of immune responses: from the early stages of infection to HBV control or persistence
- Features of T cell and NK responses in chronic infection
- Mechanisms of T cell dysfunction in chronic HBV infection
- Effect of virus control on T and NK cell responses in chronic patients
- Potential strategies to reconstitute the anti-viral T cell function

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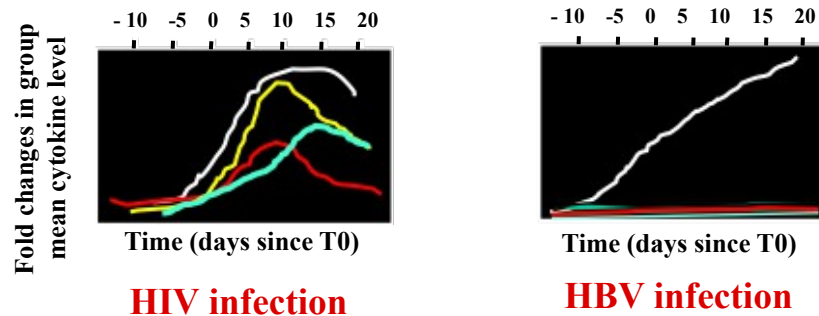
HBV is a '*stealth virus*' poorly sensed by the innate immune system



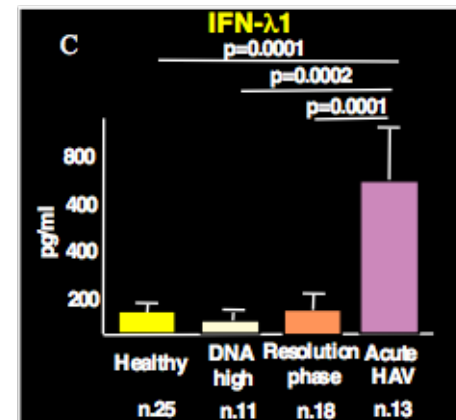
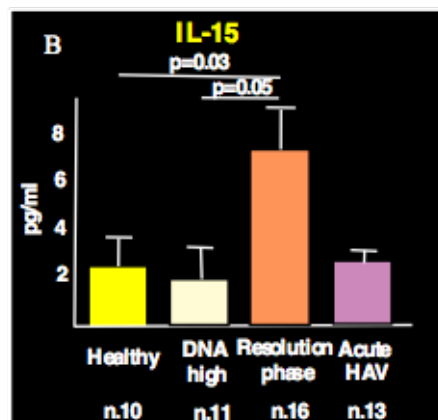
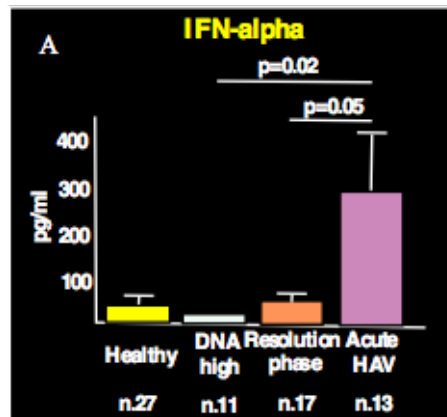
Wieland S et al. PNAS 2004

HBV is a poor inducer of innate responses

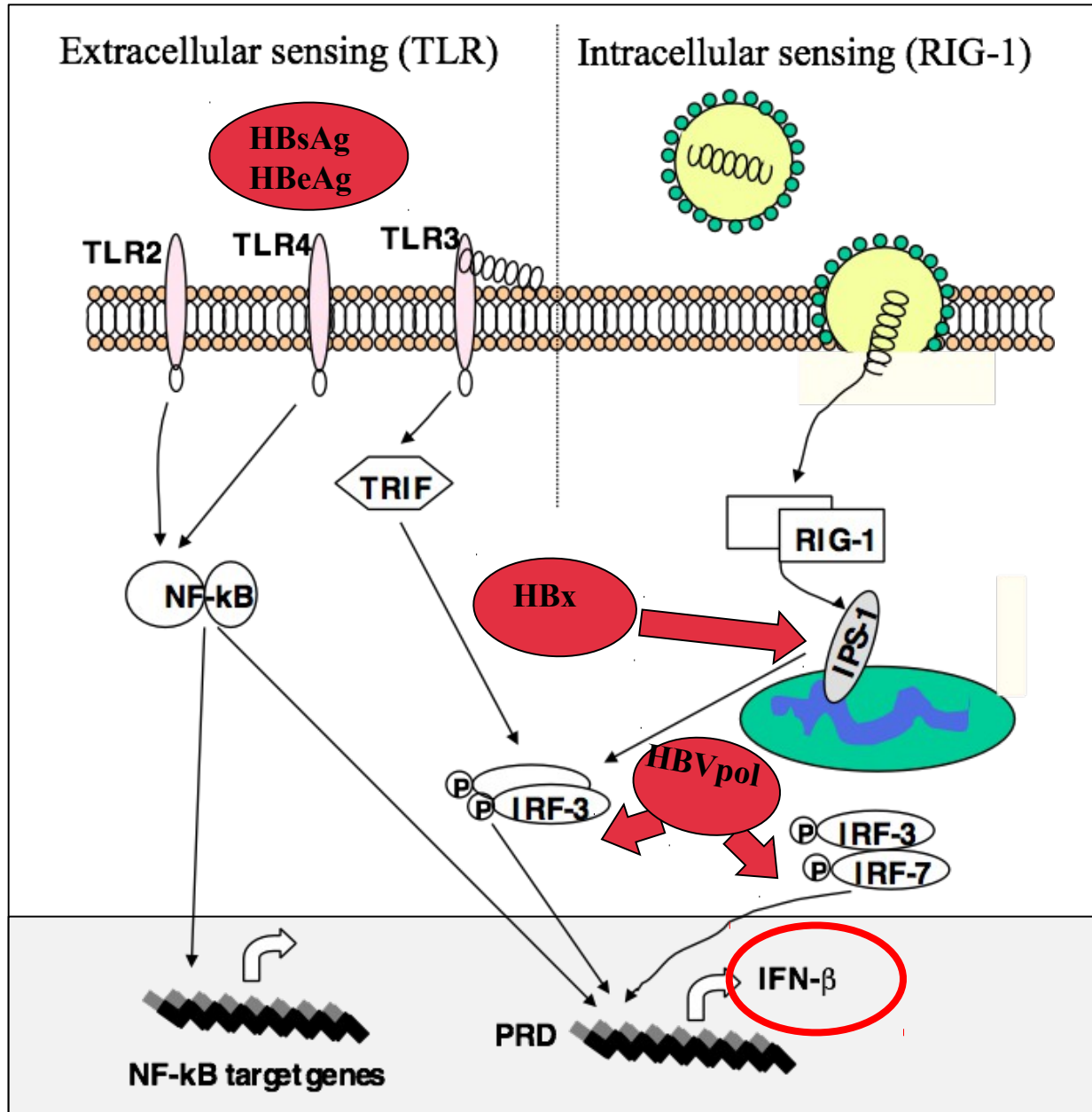
- Cytokine and chemokine production in acute HBV infection is significantly more modest and delayed compared with acute HIV infection (*Stacey AR J. Virol. 2009*)



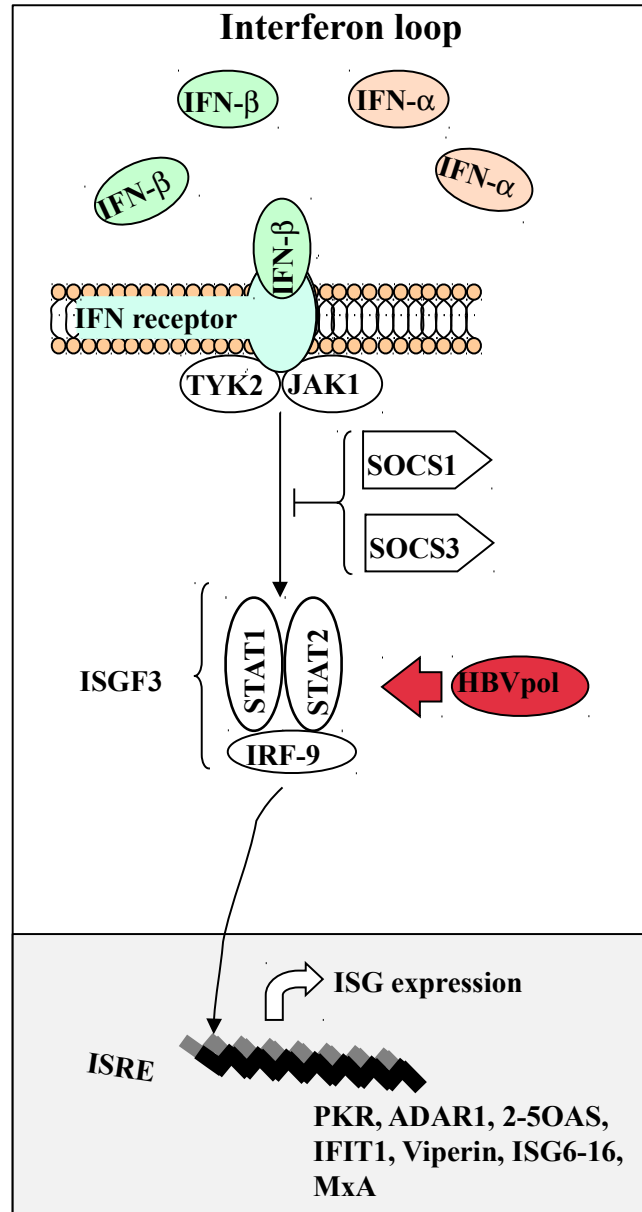
- Low production of type I IFN, IL-15 and IFN- λ 1, associated with high serum IL-10 levels, at the early stages of HBV infection (*Dunn C. et al Gastroenterology 2009*)



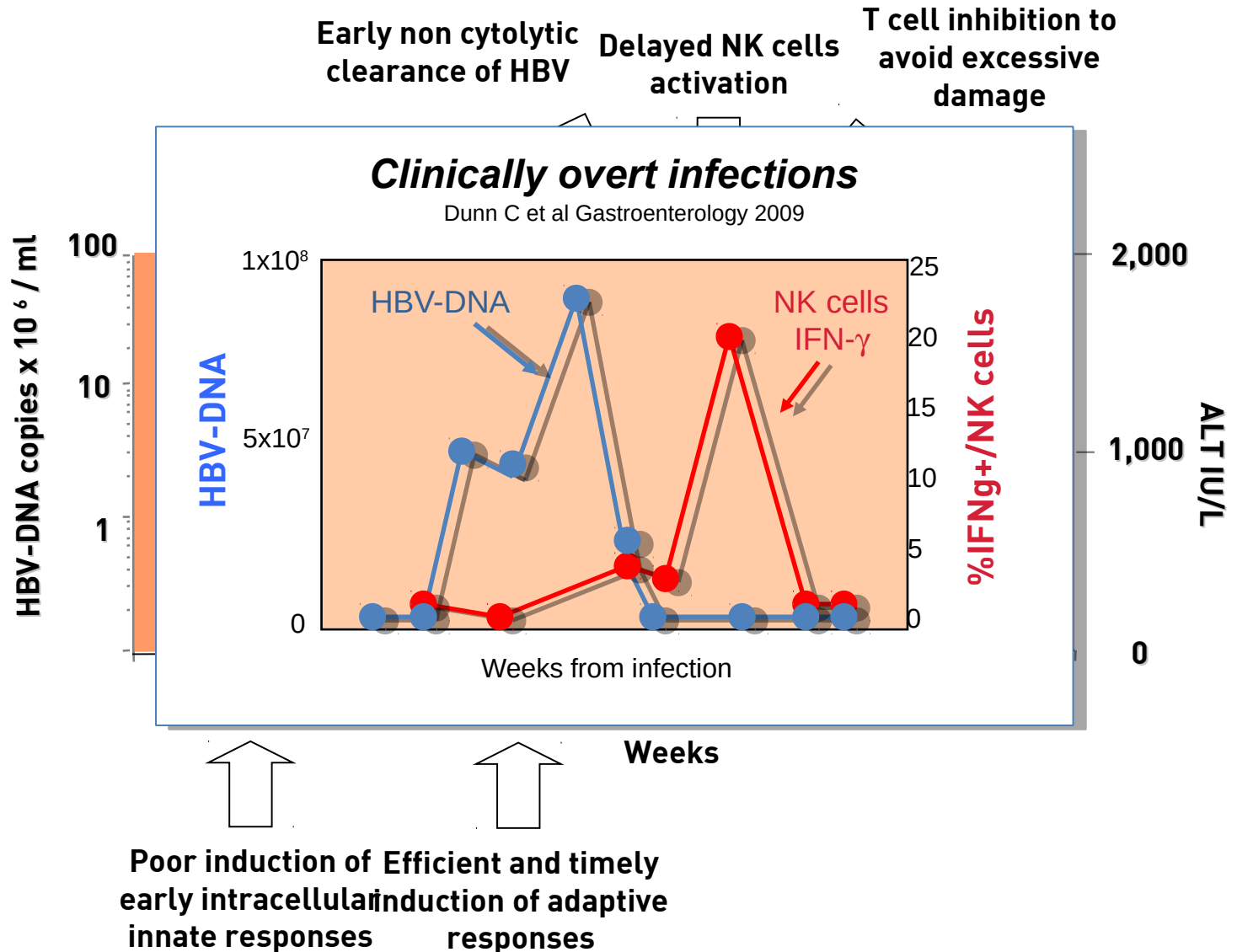
Is HBV able to inhibit innate responses?



Is HBV able to inhibit innate responses?



Summary of the early events in HBV infection



Maturation of long-lasting memory T cell responses in self-limited HBV infections

HBV INFECTION



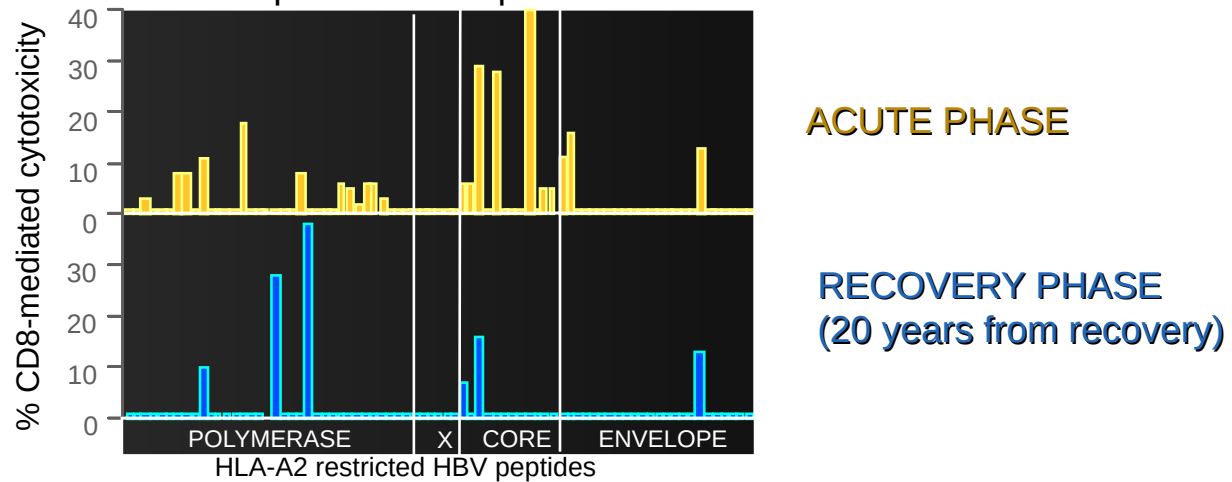
Strong, multi-specific, T1 oriented
T cell responses



Self-limited



Long-lasting
protective responses



Virus control / occult infection

Progressive T cell functional impairment in chronically evolving acute HBV infections

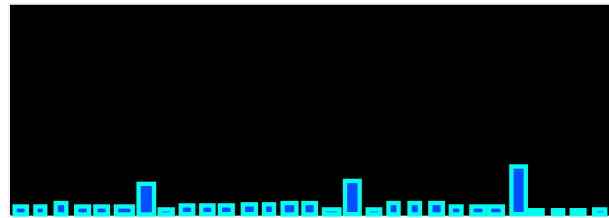
HBV INFECTION

↓
Weak and narrowly focused T cell responses

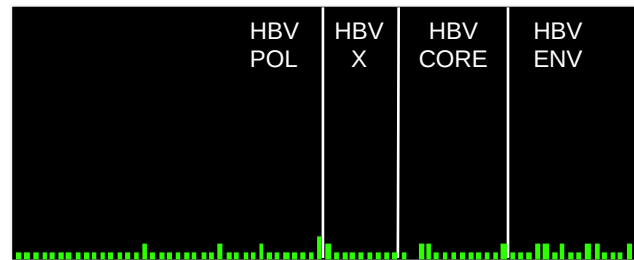
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Chronic evolution

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Persistent and progressive impairment of protective responses

CD4 RESPONSES
(to core peptides)



CD8 RESPONSES
(to HBV peptides)



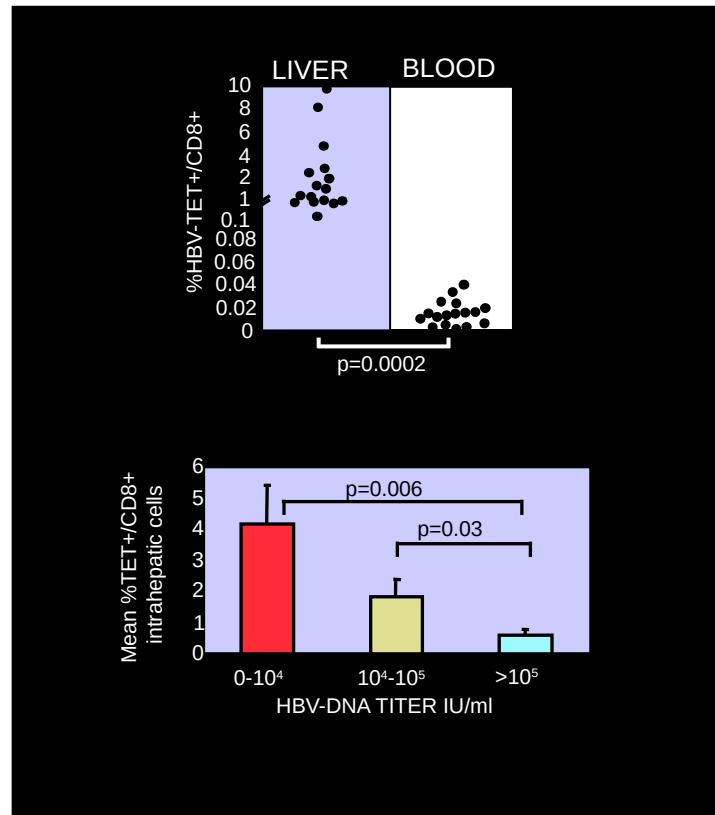
HBV peptides

↓
Virus persistence

HBV-specific T cells in chronic infection

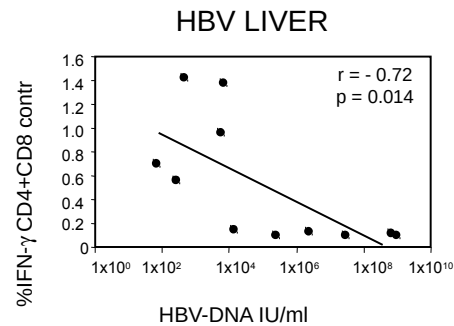
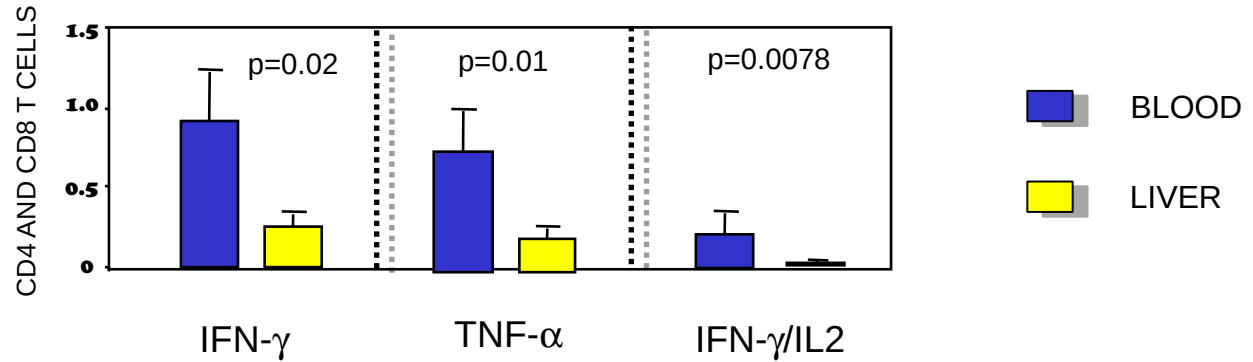
HBV-SPECIFIC CD8 CELLS ARE PREFERENTIALLY CONCENTRATED WITHIN THE LIVER IN PATIENTS WITH CHRONIC HBV INFECTION

(Fisicaro P. et al. Gastroenterology 2010)



INTRAHEPATIC HBV-SPECIFIC T CELLS ARE MORE DEEPLY EXHAUSTED THAN THEIR PERIPHERAL BLOOD COUNTERPARTS IN CHRONIC HBV INFECTION

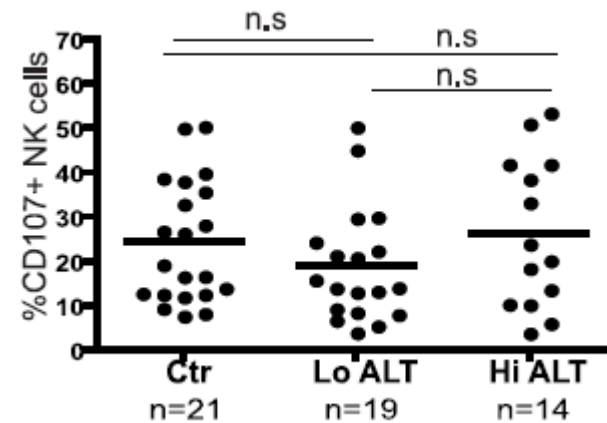
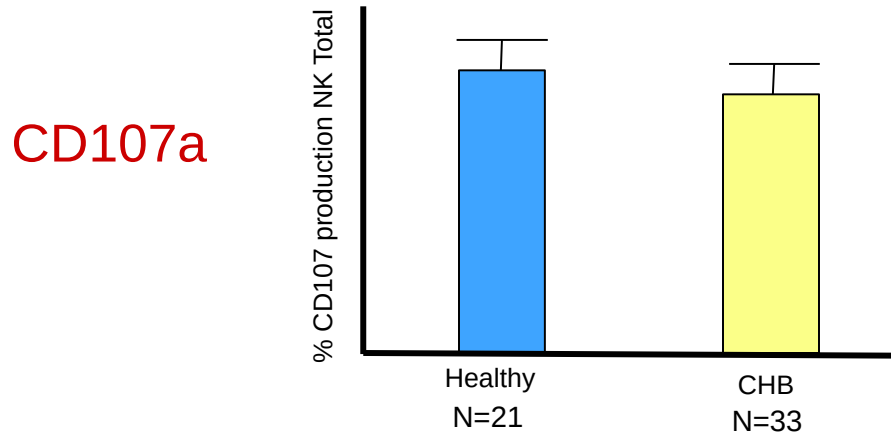
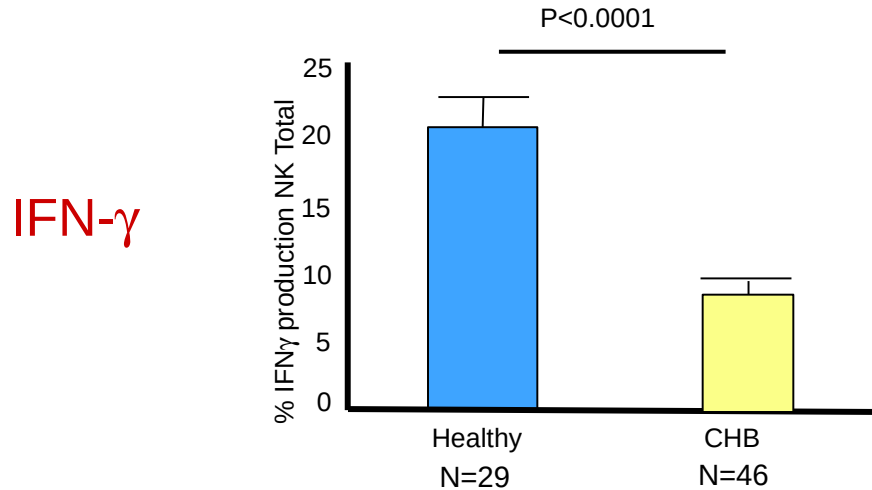
(Fiscaro P. et al. Gastroenterology 2012 and personal communication)



NK cells in chronic infection

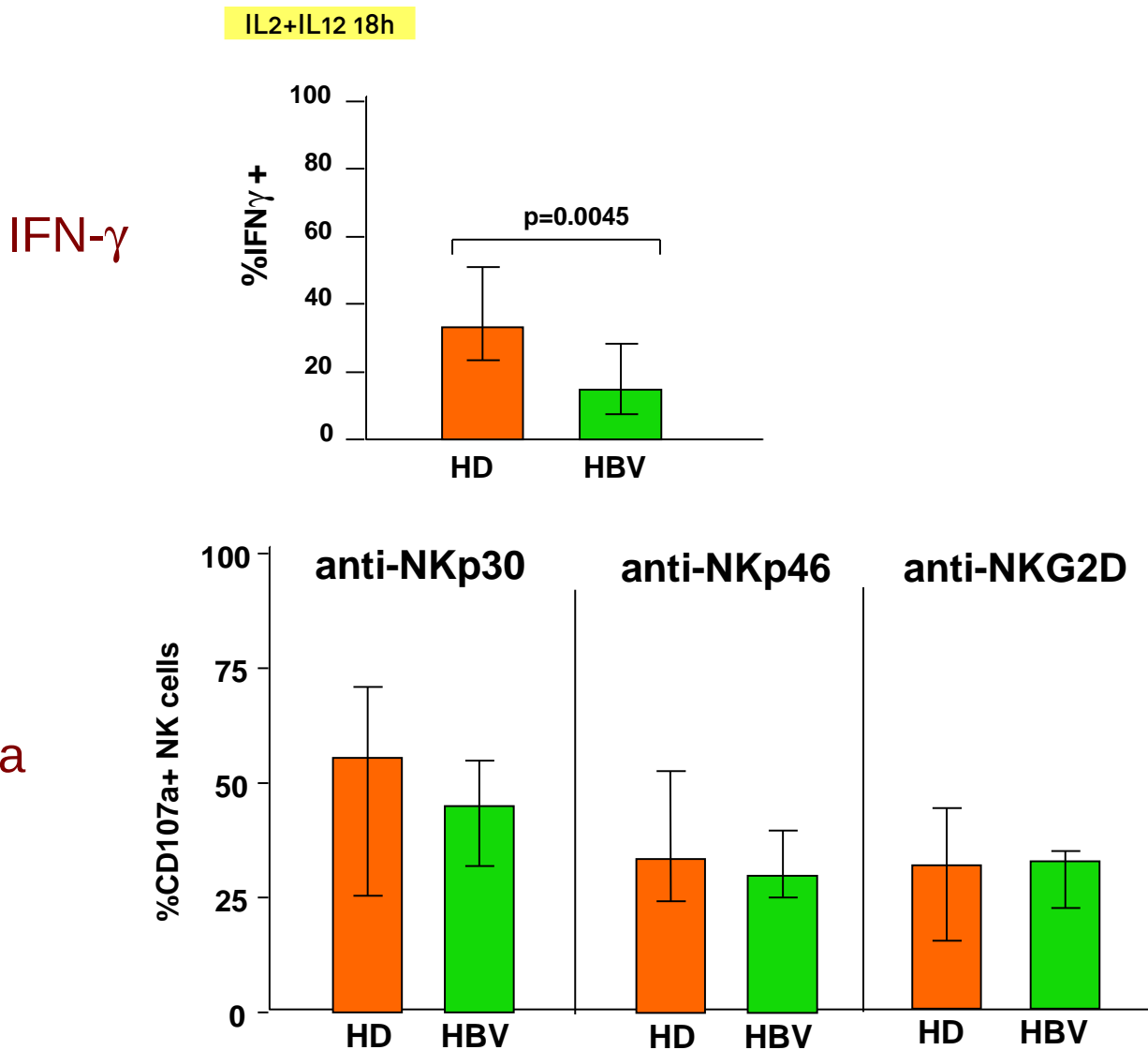
NK cell functional dichotomy in chronic HBV infection

Impaired IFN- γ production with normal cytotoxicity (I)



NK cell functional dichotomy in chronic HBV infection

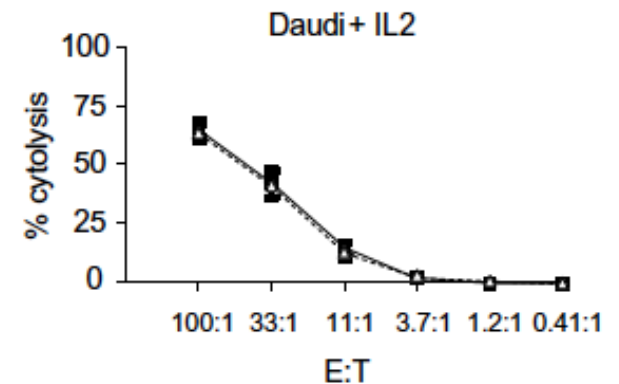
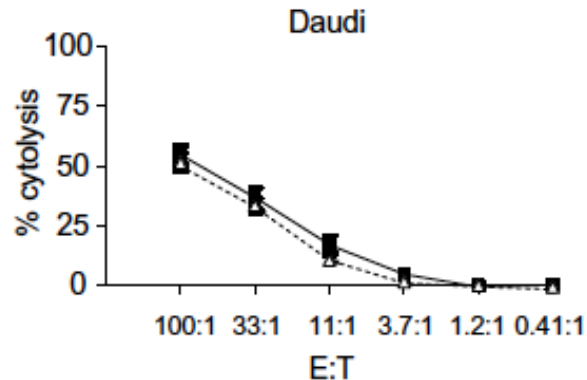
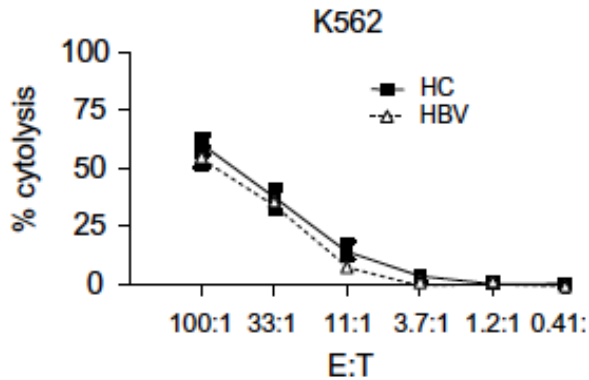
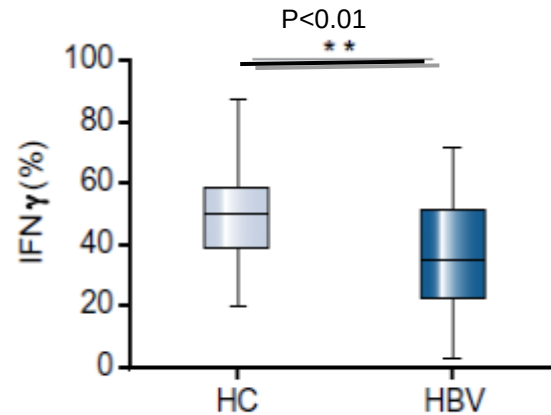
Impaired IFN- γ production with normal cytotoxicity (II)



NK cell functional dichotomy in chronic HBV infection

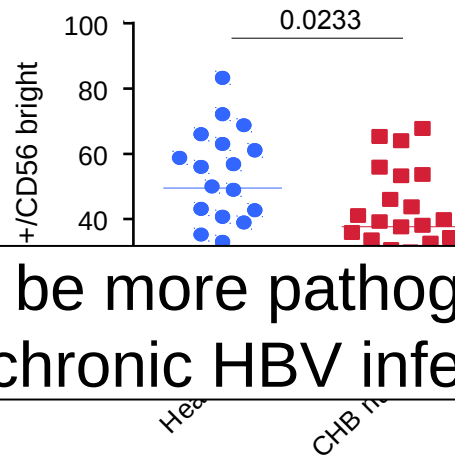
Impaired IFN- γ production with normal cytotoxicity (III)

IL12+IL18 24h

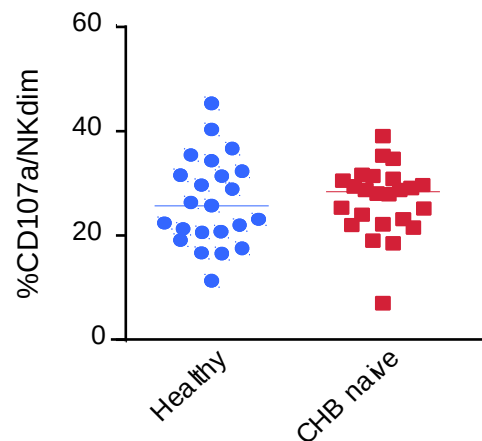


NK cell functional dichotomy in chronic HBV infection

Impaired IFN- γ production with normal cytotoxicity (IV)



NK cells seem to be more pathogenic than protective in chronic HBV infection



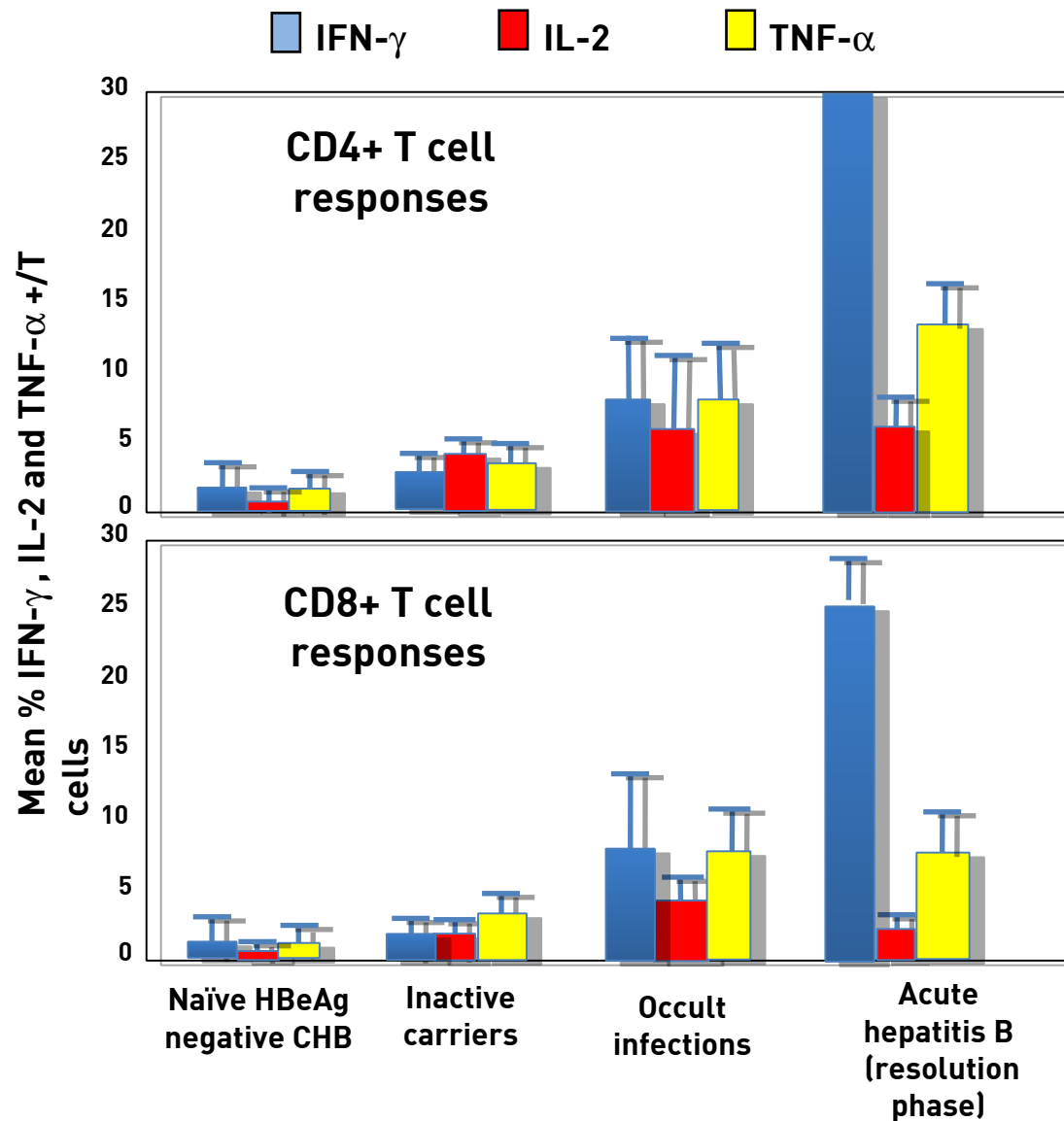
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- Kinetics of immune responses: from the early stages of infection to HBV control or persistence
- Feature of T cell and NK responses in chronic infection

Mechanisms of T cell dysfunction in chronic HBV infection

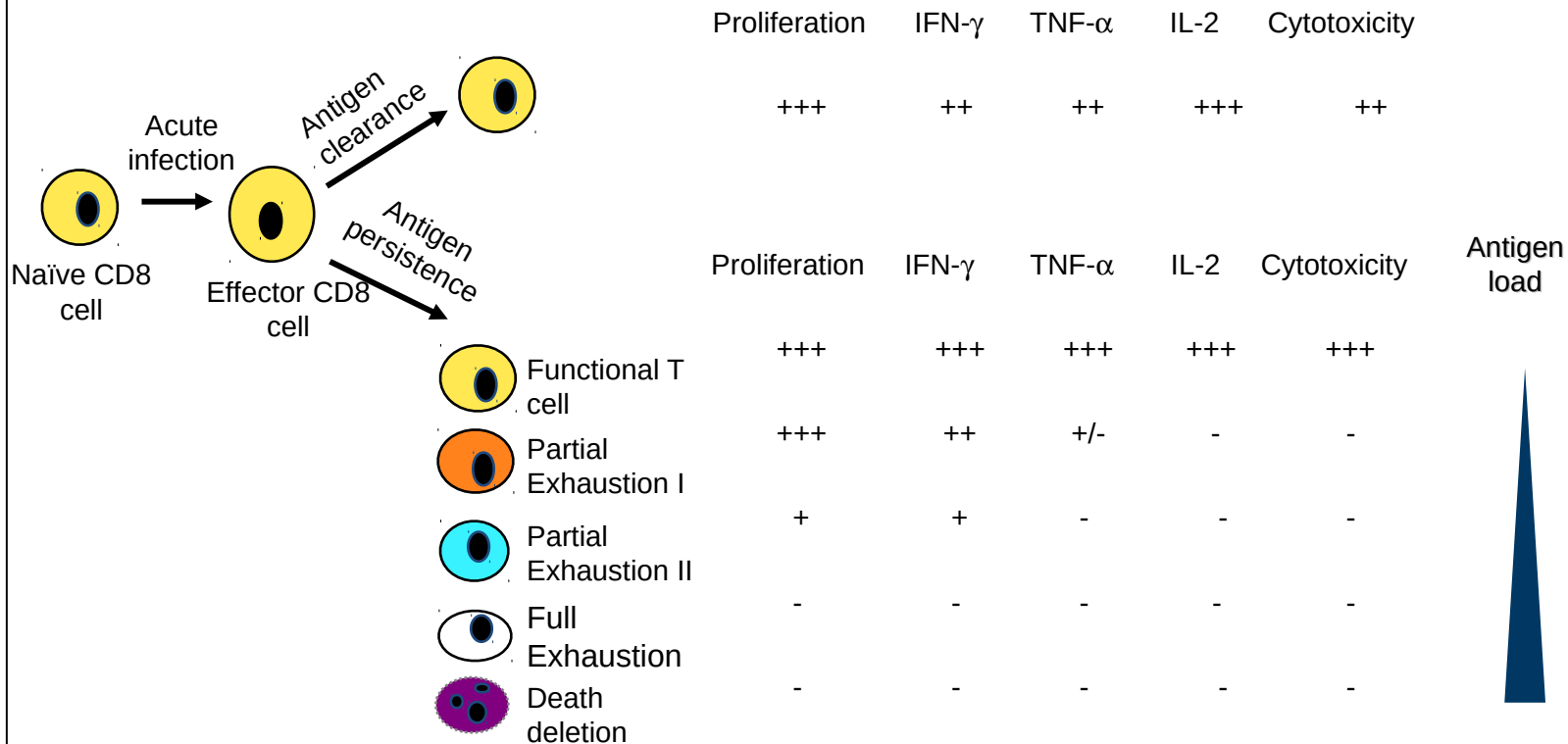
- Effect of virus control on T and NK cell responses in chronic patients
- Potential strategies to reconstitute the anti-viral T cell function

Different levels of T cell functional efficiency in different conditions of HBV control



PUTATIVE MECHANISMS OF T CELL EXHAUSTION IN HBV INFECTION

MODEL FOR HIERARCHICAL LOSS OF CD8 FUNCTIONS DURING CHRONIC VIRAL INFECTIONS

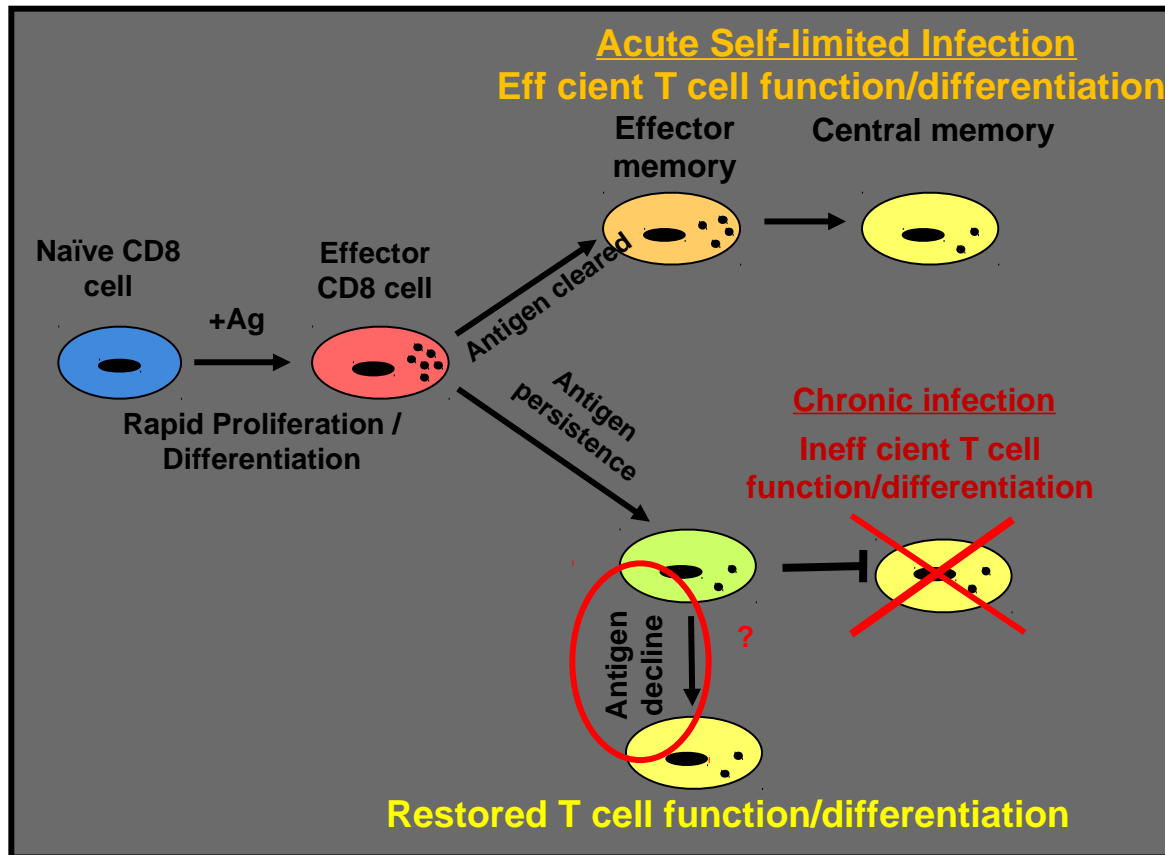


Wherry EJ et al J.Virol. 77:4911-27;2003



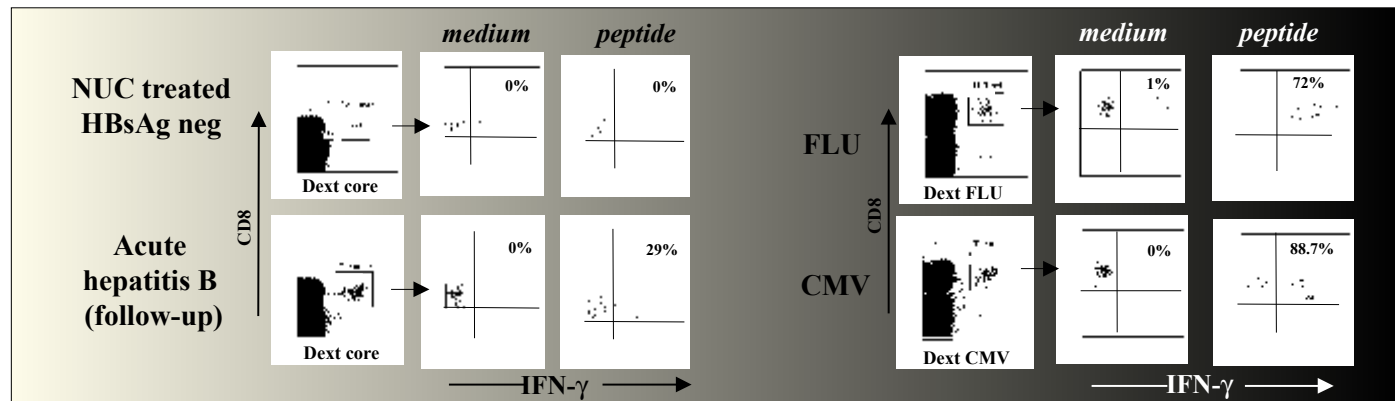
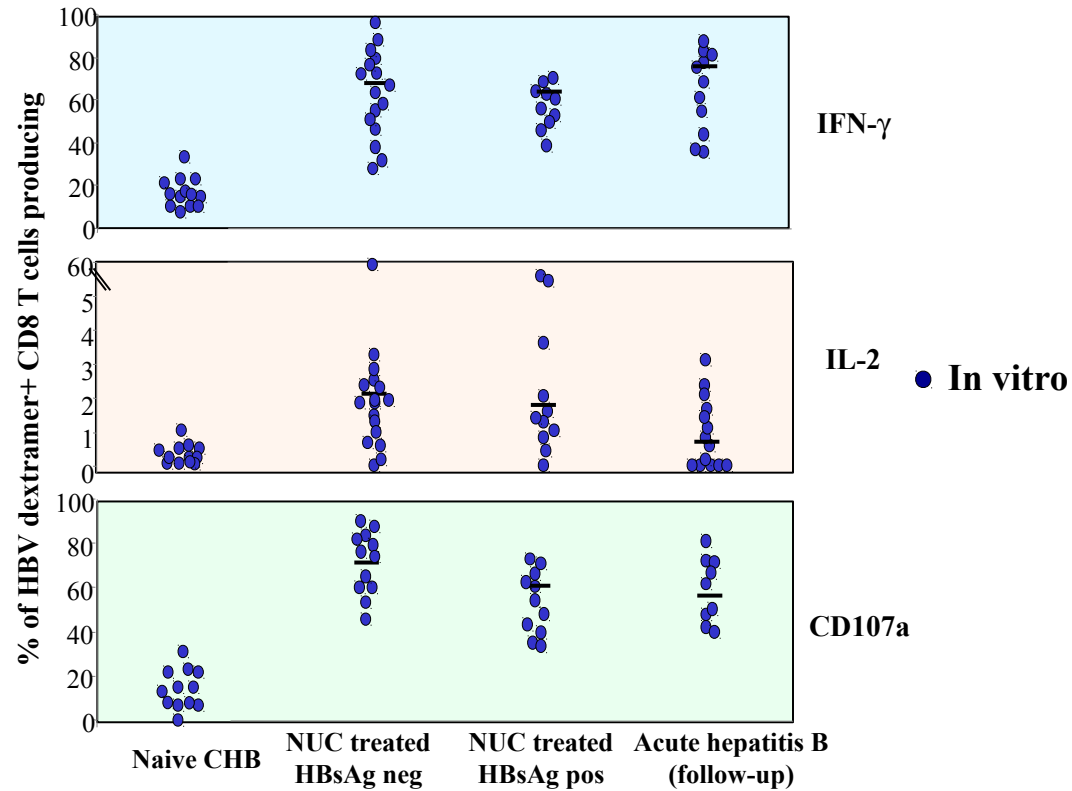
Are the virus-specific T cell defects of chronic HBV infection reversible?

Effect of antigen decline

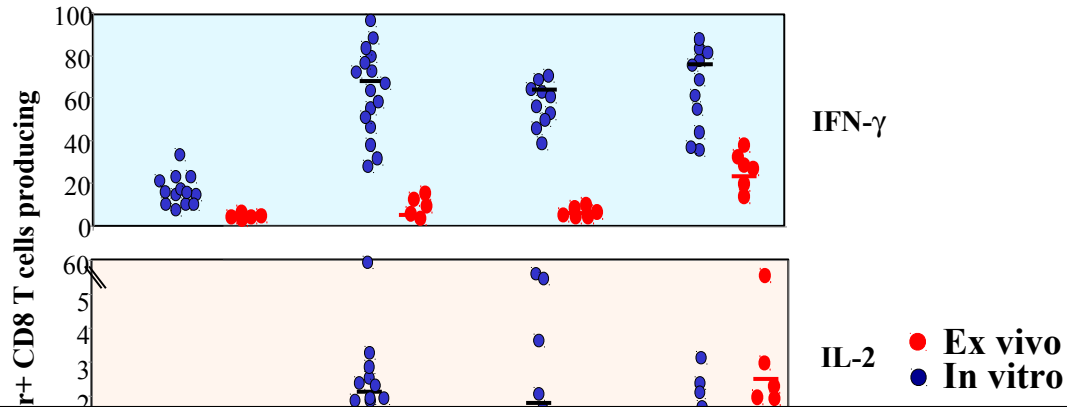


Effect of long-term NUC therapy on T cell responses

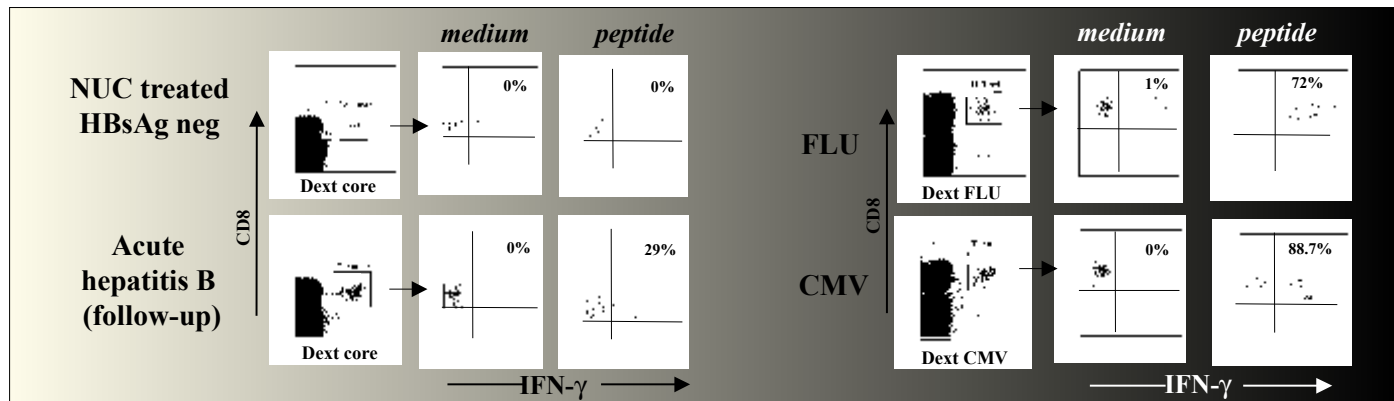
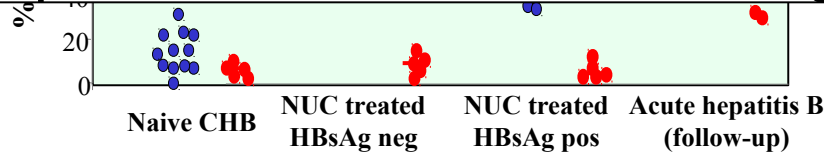
T cell restoration following long-term NUC treatment is efficient in vitro



T cell restoration following long-term NUC treatment is partial ex vivo



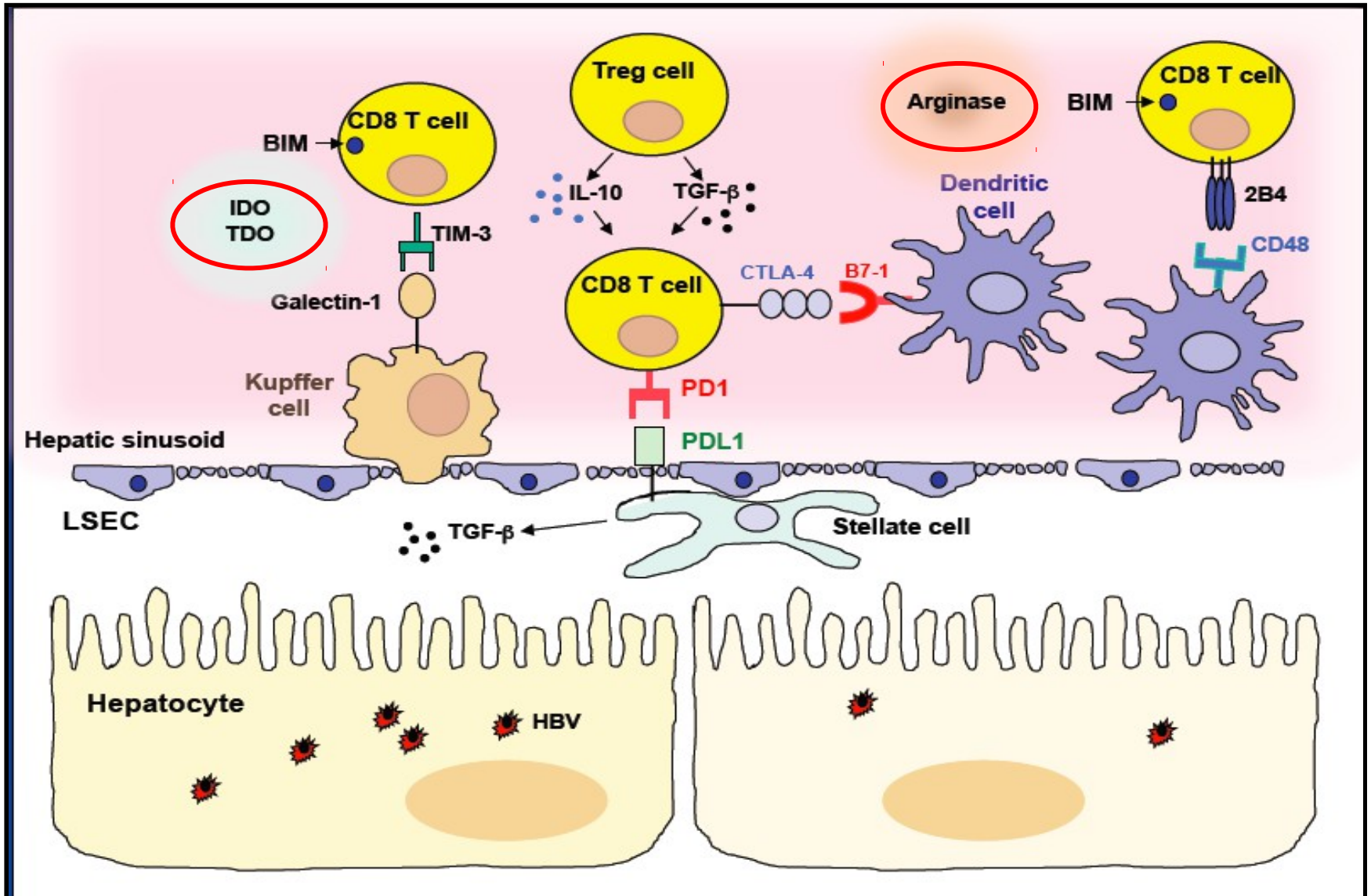
Restoration of the T cell function is efficient in vitro but only partial ex vivo even following complete control of virus replication and decline of antigen



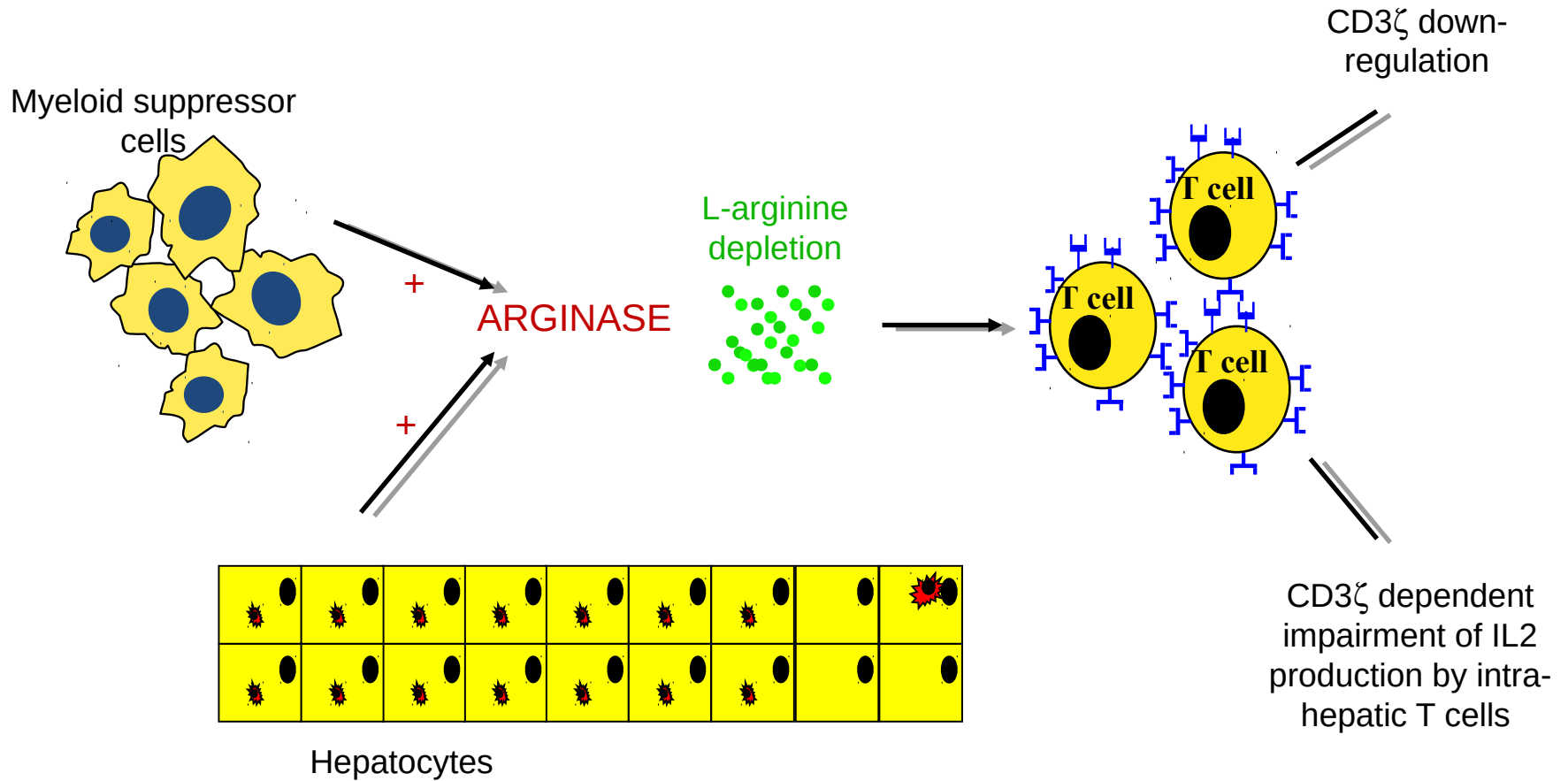
List of topics

- Kinetics of T cell responses: from the early stages of infection to HBV control or persistence
- **Additional mechanisms of T cell dysfunction in chronic HBV infection**
- Effect of virus control on T cell responses in chronic patients
- Potential strategies to reconstitute the anti-viral T cell function
- Implications for future therapies

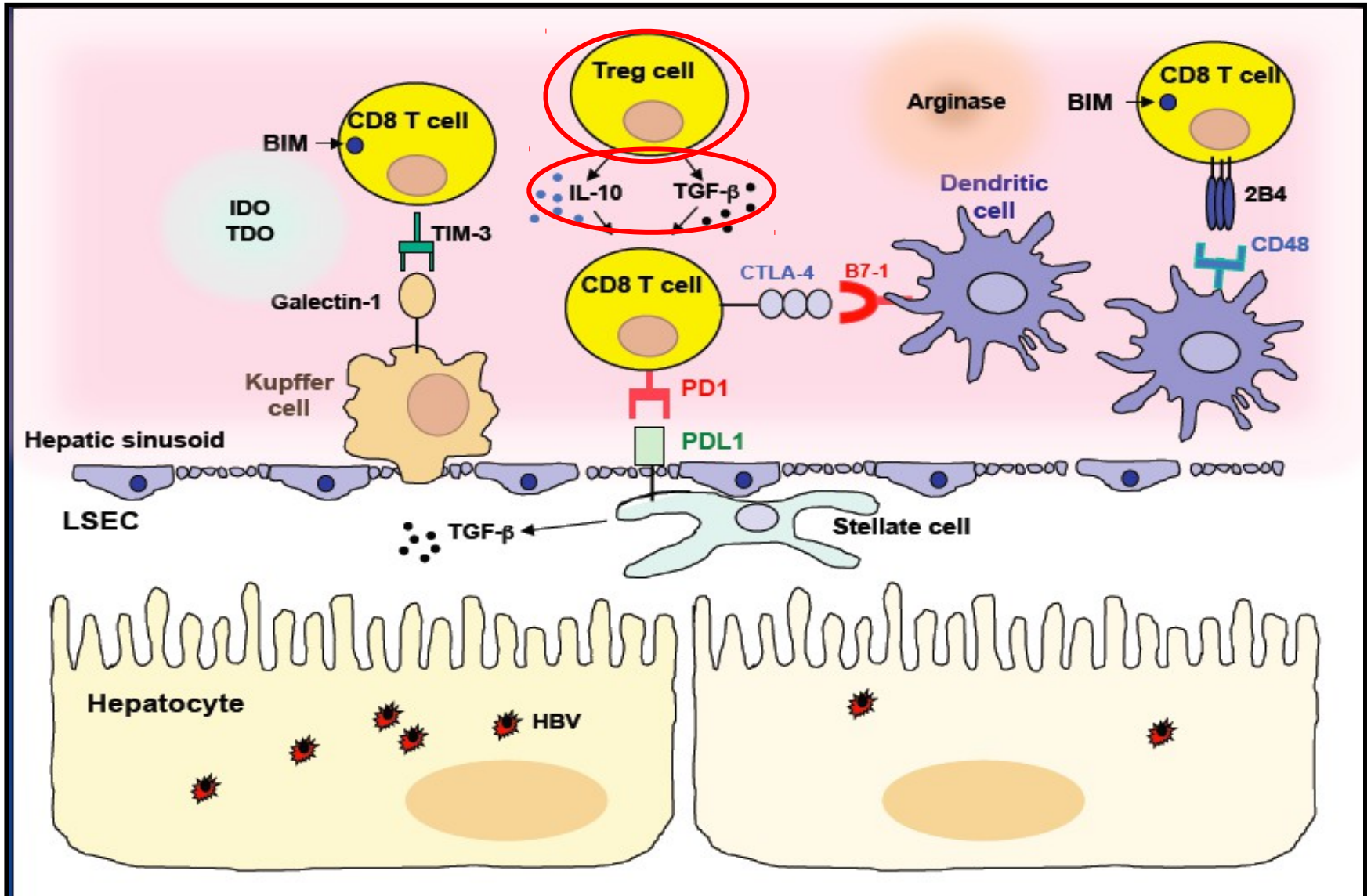
INTRAHEPATIC INHIBITORY MECHANISMS



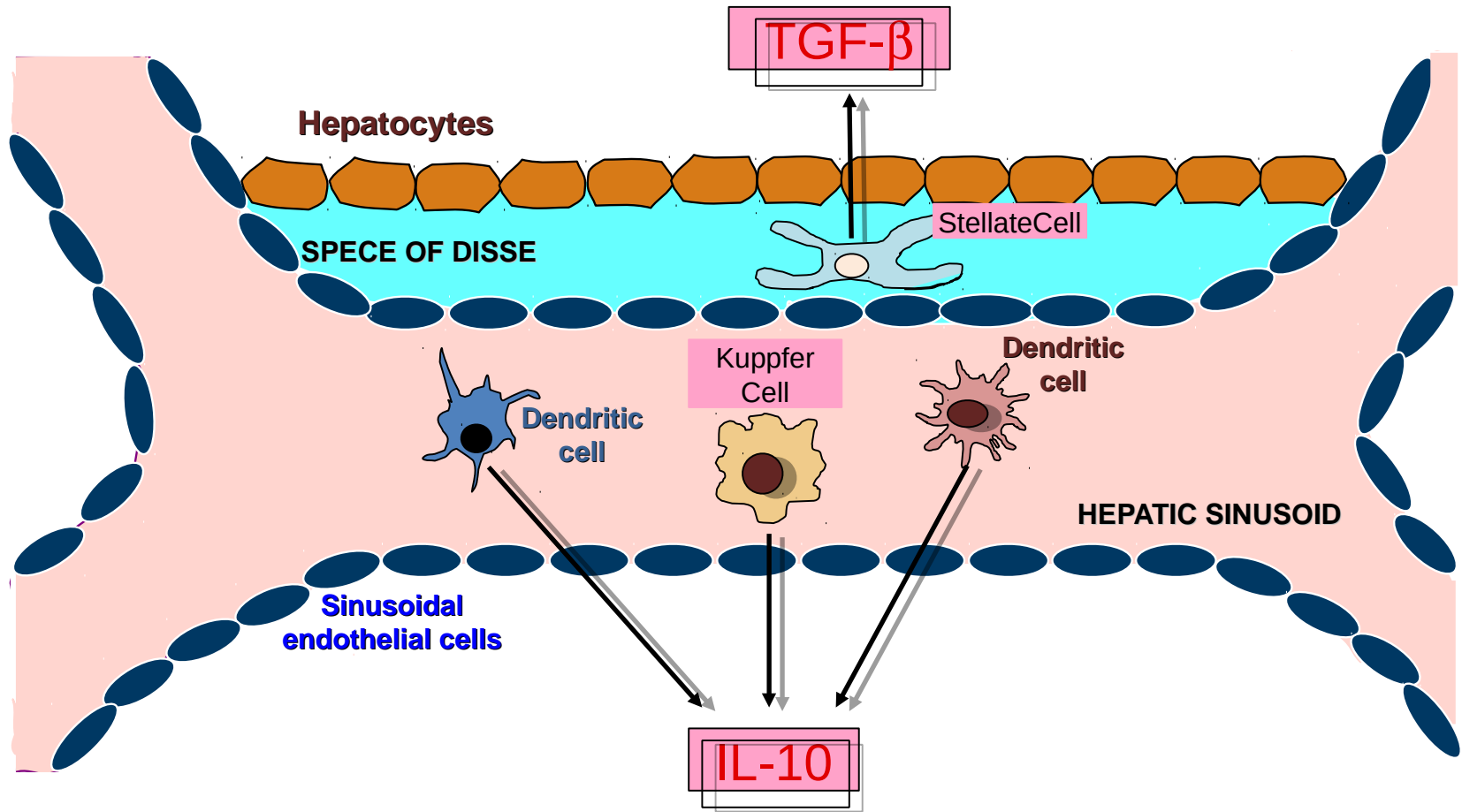
THE INTRAHEPATIC MILIEU IMPAIRS IL-2 PRODUCTION BY T CELLS



INTRAHEPATIC INHIBITORY MECHANISMS

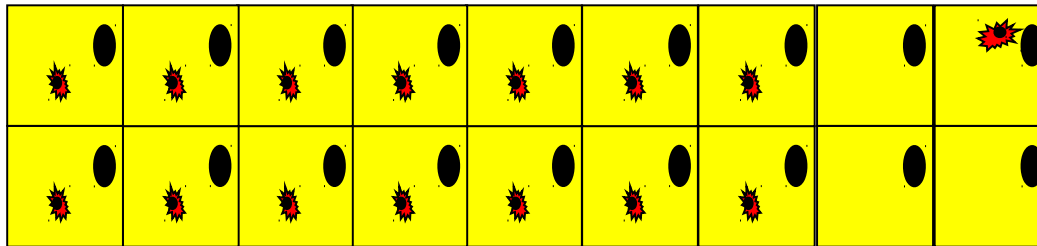


MECHANISMS OF HEPATIC TOLERANCE: IMMUNOSUPPRESSIVE CYTOKINE MILIEU



THE IMMUNOSUPPRESSIVE CYTOKINE MILIEU CAN IMPAIR IFN- γ PRODUCTION BY NK CELLS LIMITING THEIR ANTI-VIRAL ACTIVITY

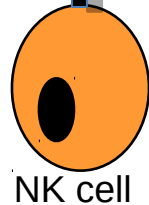
HBV infected hepatocytes



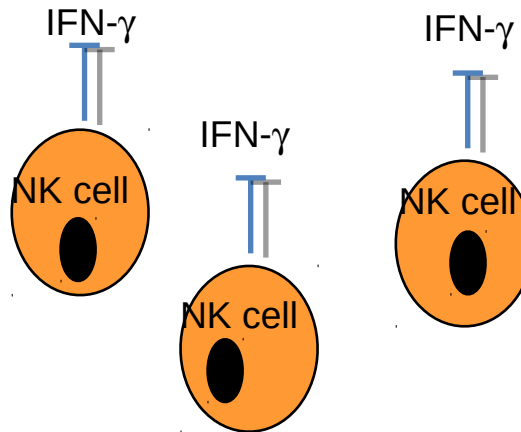
VIRAL PERSISTENCE AND LIVER DAMAGE

TRAIL-R2

TRAIL



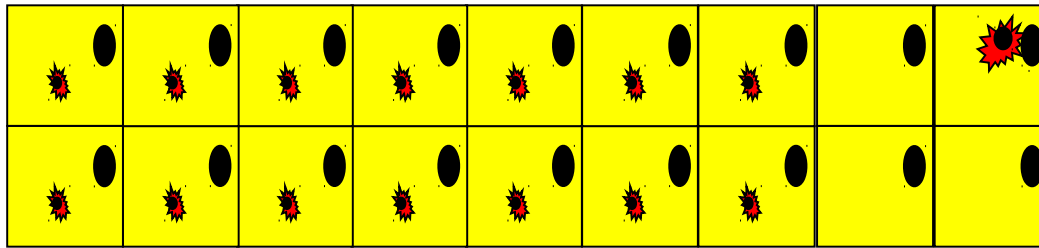
Preserved cytolytic activity



IL-10 and TGF β -mediated suppression of IFN- γ production by NK cells

NK CELL MEDIATED DELETION OF HBV-SPECIFIC T CELLS

HBV infected hepatocytes



VIRAL PERSISTENCE AND LIVER DAMAGE

TRAIL-R2

TRAIL

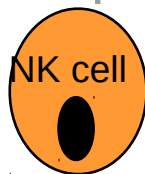
NK cell

TRAIL-mediated T cell deletion

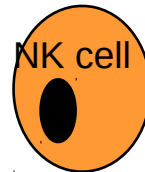
TRAIL-R2

T cell

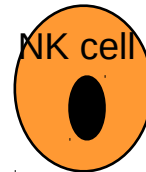
IFN- γ



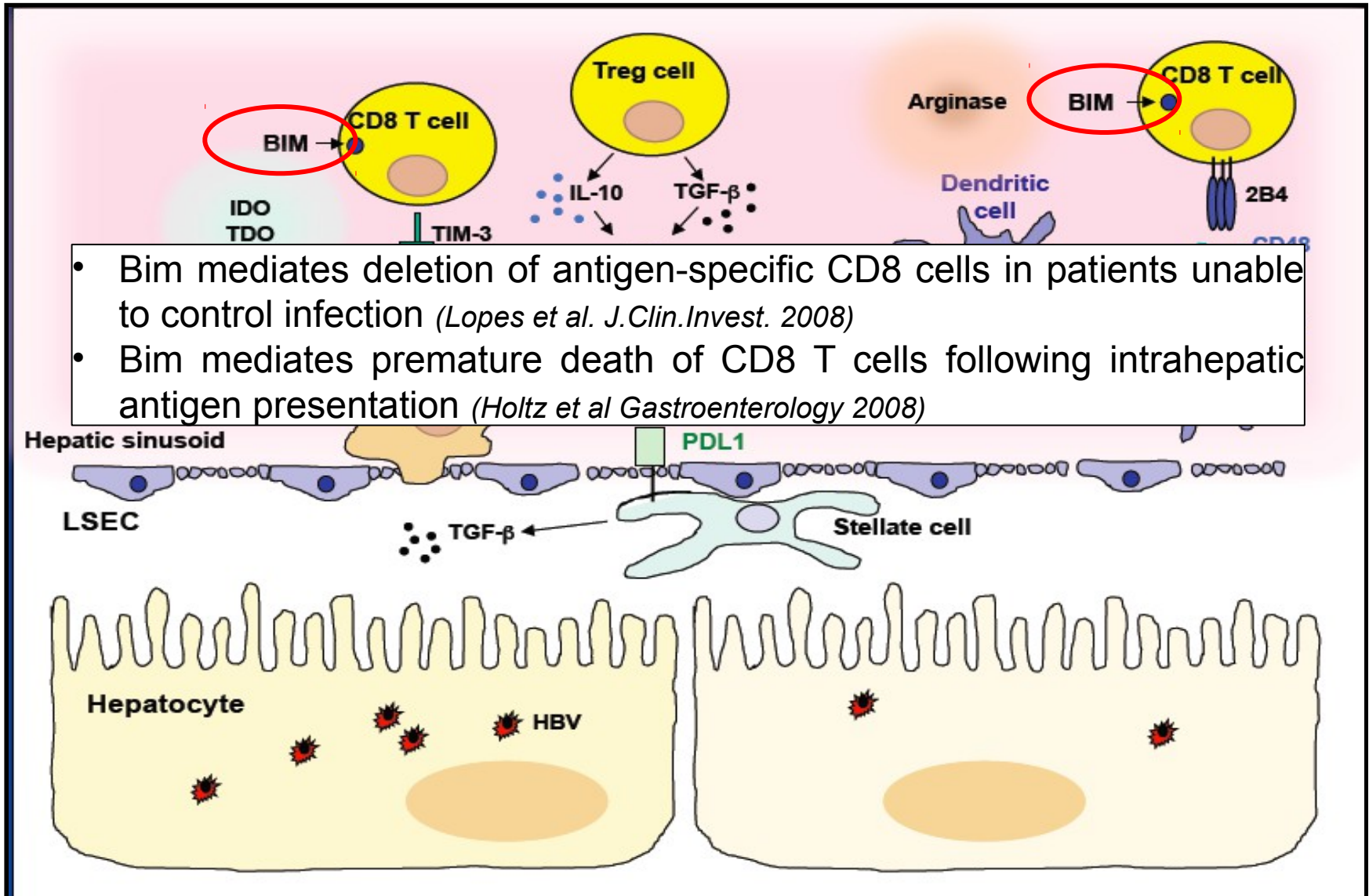
IFN- γ



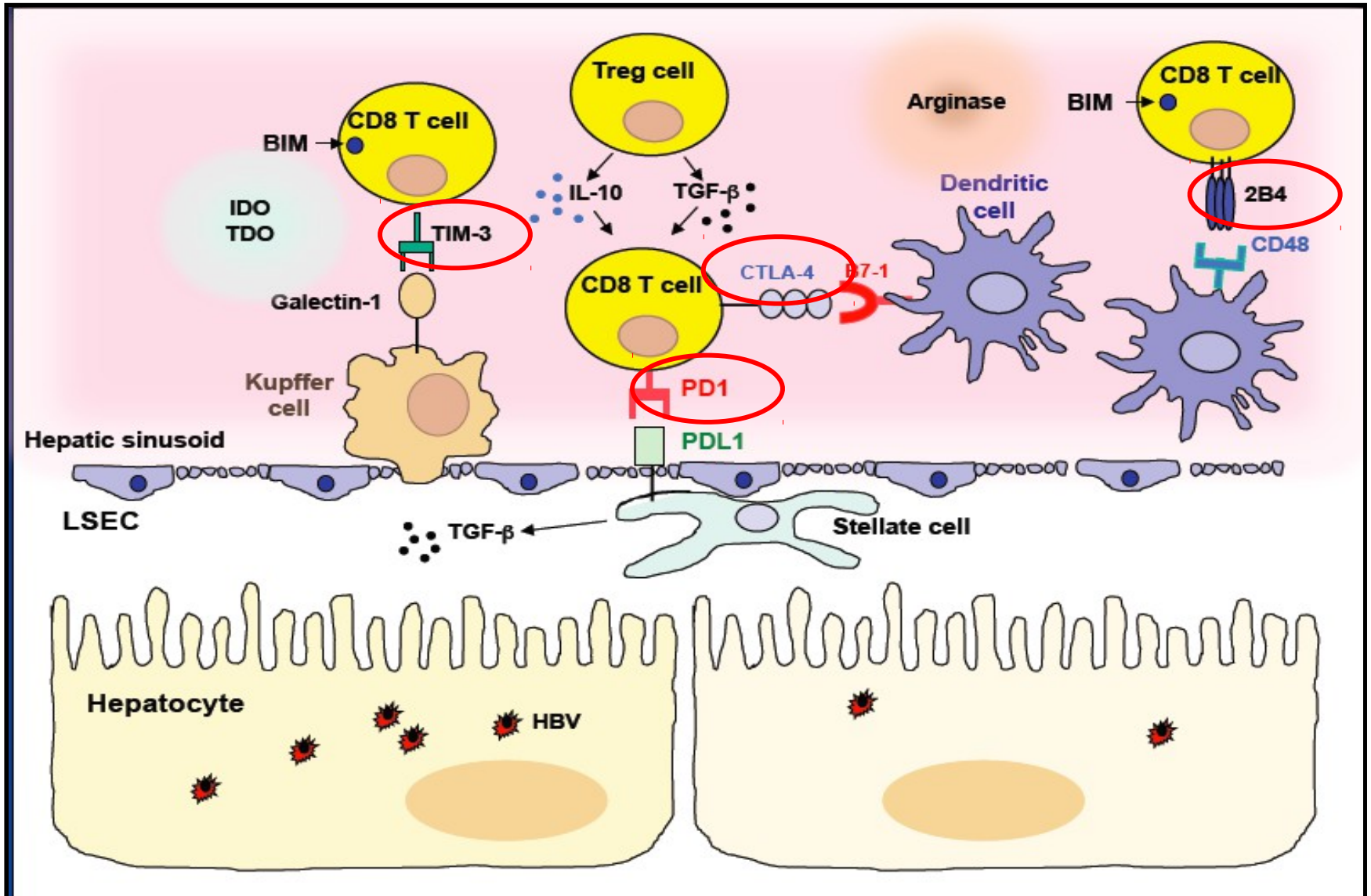
IFN- γ



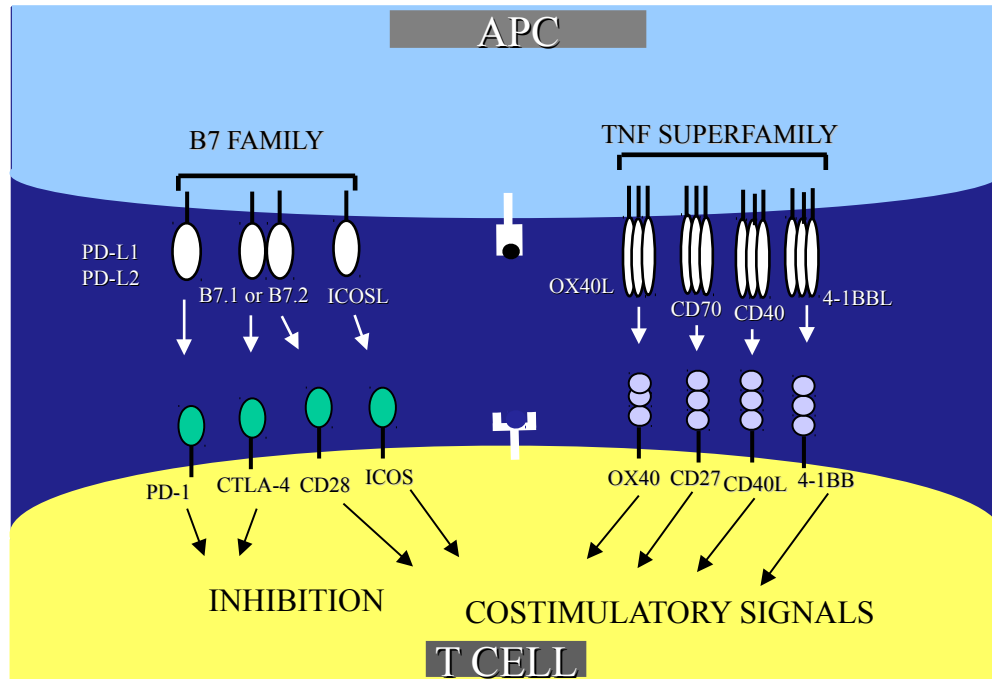
INTRAHEPATIC INHIBITORY MECHANISMS



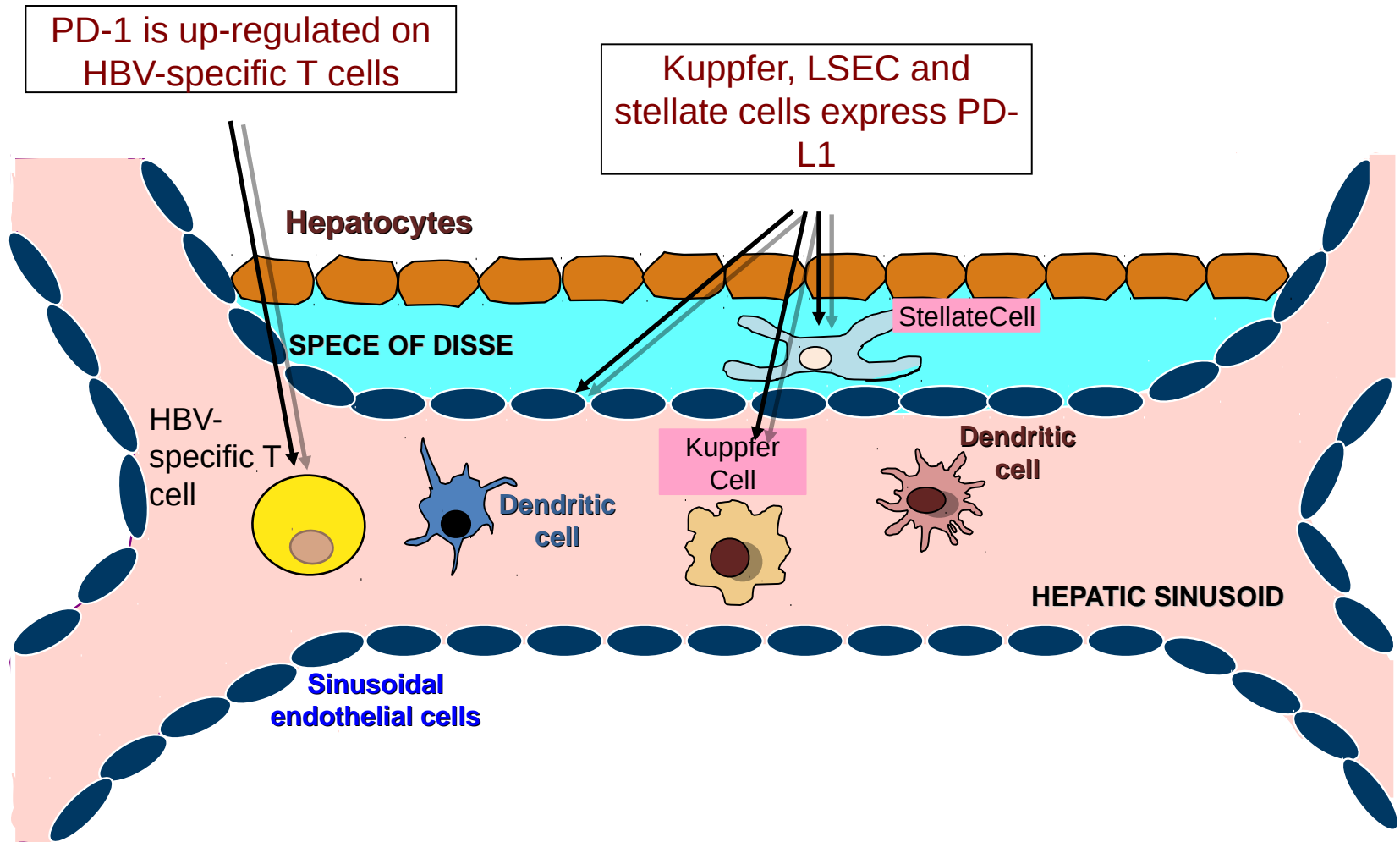
INTRAHEPATIC INHIBITORY MECHANISMS



Expression of various inhibitory receptors on circulating and intrahepatic virus-specific CD8 cells of patients with chronic HBV infection



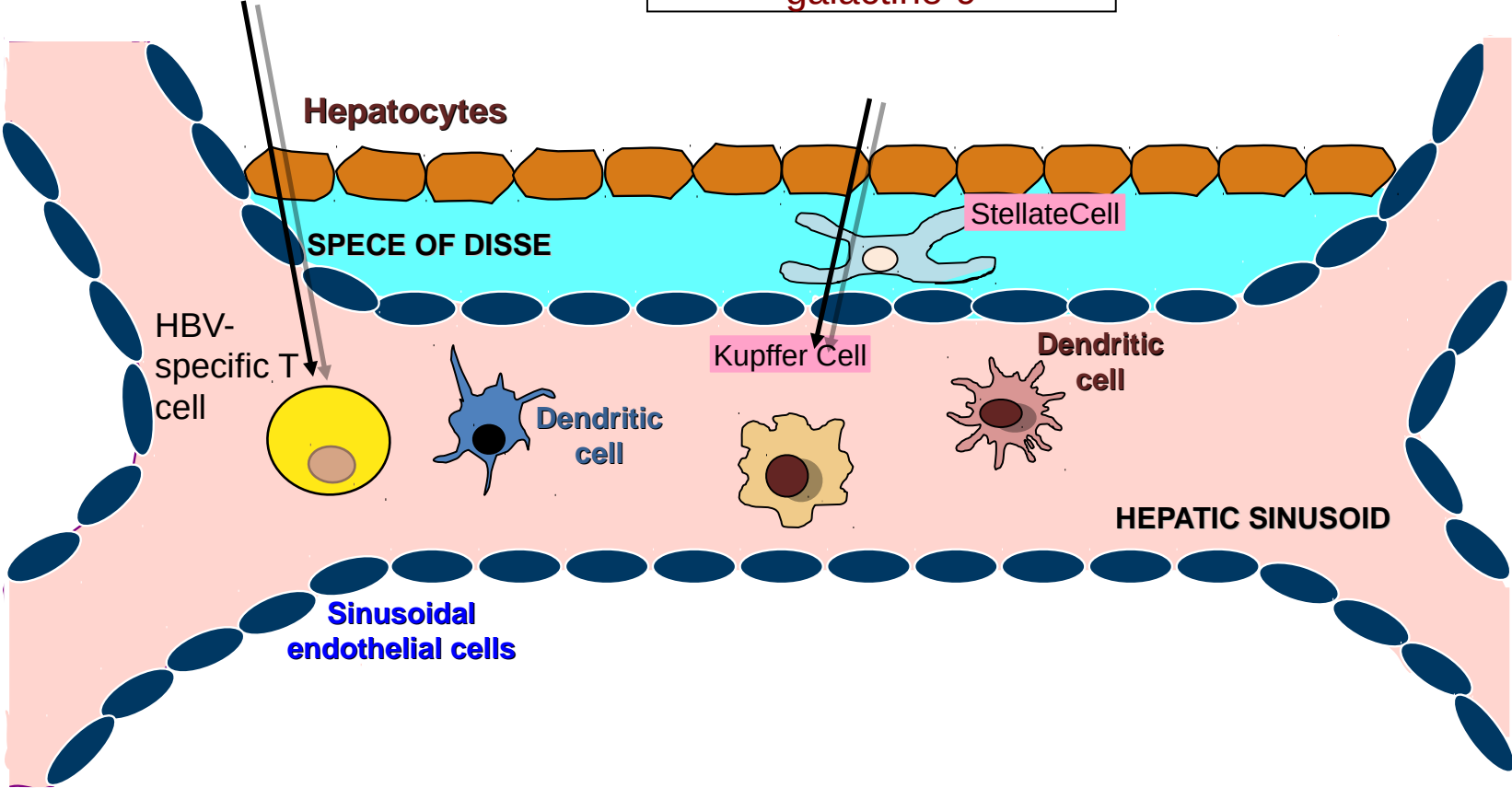
T CELL CO-INHIBITORY MOLECULES IN THE LIVER



T CELL CO-INHIBITORY MOLECULES IN THE LIVER

TIM-3 is up-regulated on HBV-specific T cells

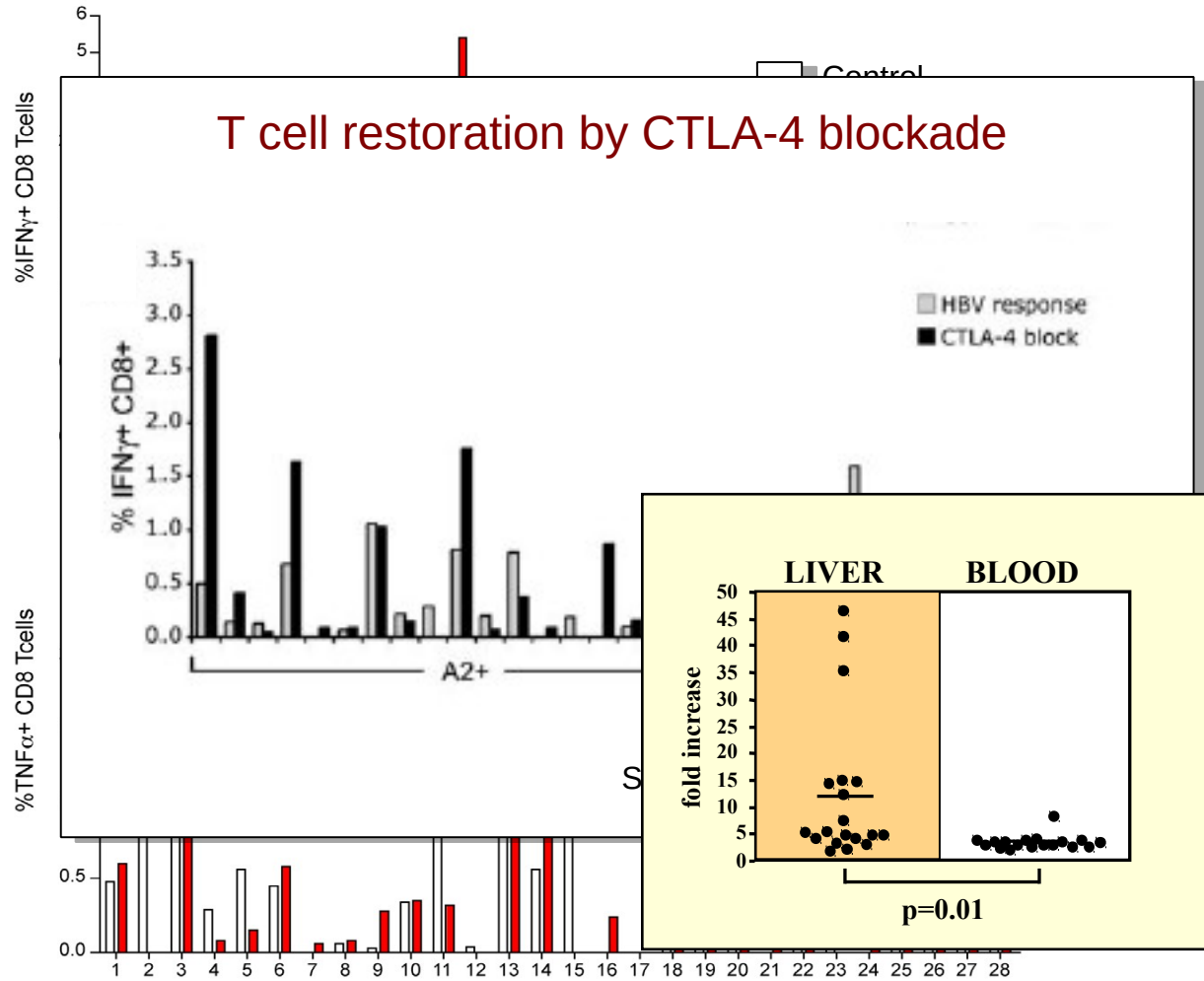
Kupffer cells express galactine-9




Exp
intra

g and
chronic

T cell restoration by Tim-3 blockade




HBV-specific T cells



Genome-wide
expression profiling



Mysregulated genes and
pathways associated with T cell
exhaustion



Correction strategies to
restore anti-viral T cell
functions

TRANSCRIPTOME STUDY IN ACUTE AND CHRONIC HBV INFECTION

Patient	Infection	Infection	LT
1	E	ACUT	785
2	E	ACUT	98
3	E	ACUT	59
4	E	ACUT	118
5	E	ACUT	11
1	LVED HEP B	RESO	6
2	LVED HEP B	RESO	7
3	LVED HEP B	RESO	0
CONTROLS			
CELL SPECIFICITY			
1	THY	HEAL	LU
2	THY	HEAL	LU
3	THY	HEAL	LU

A

1

9

→ 6

1

2

1

1

2

1

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Isolation of
HBV/FLU-specific
CD8+ T cells
by cell sorting



RNA extraction and
amplification

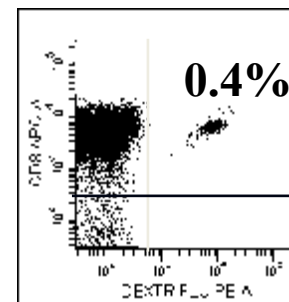


Gene expression
by microarray analysis
(4x44K Agilent)

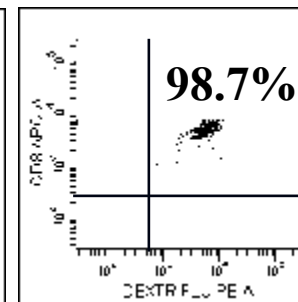


⌘ VALIDATION AND DISCOVERY
OF NEW TARGETS

Pre-sorting



Post-sorting

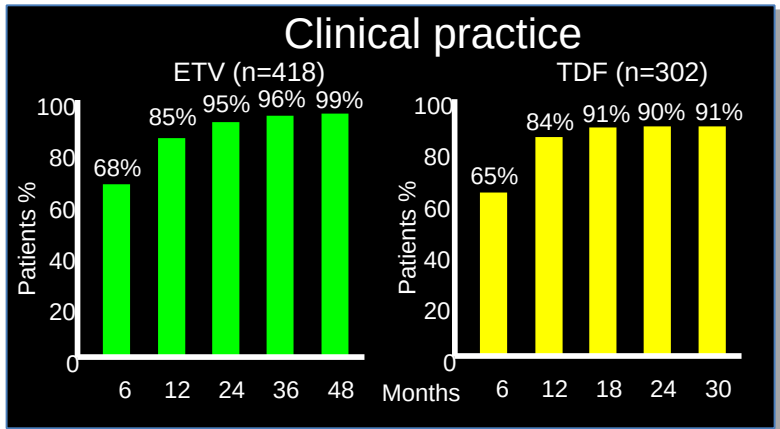


Main message
Question

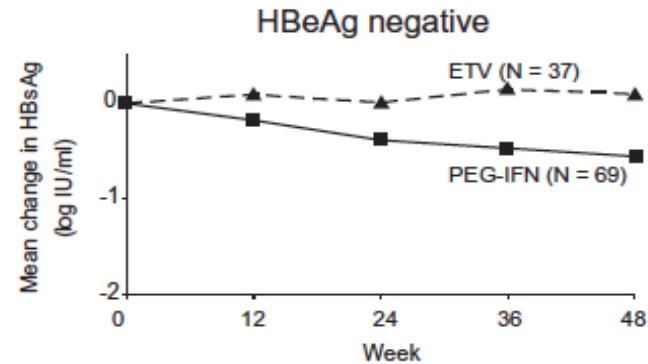
A deep metabolic and energetic impairment is typical of exhausted T cells
Multiple levels of correction will certainly be needed to restore an efficient anti-tumor T cell function
Is restoration an achievable objective?

Potential strategies to reconstitute the anti-viral T cell function and implications for future therapies

Efficient control of HBV replication by NUC therapy



Slow HBsAg decline during NUC therapy: need of life-long NUC administration



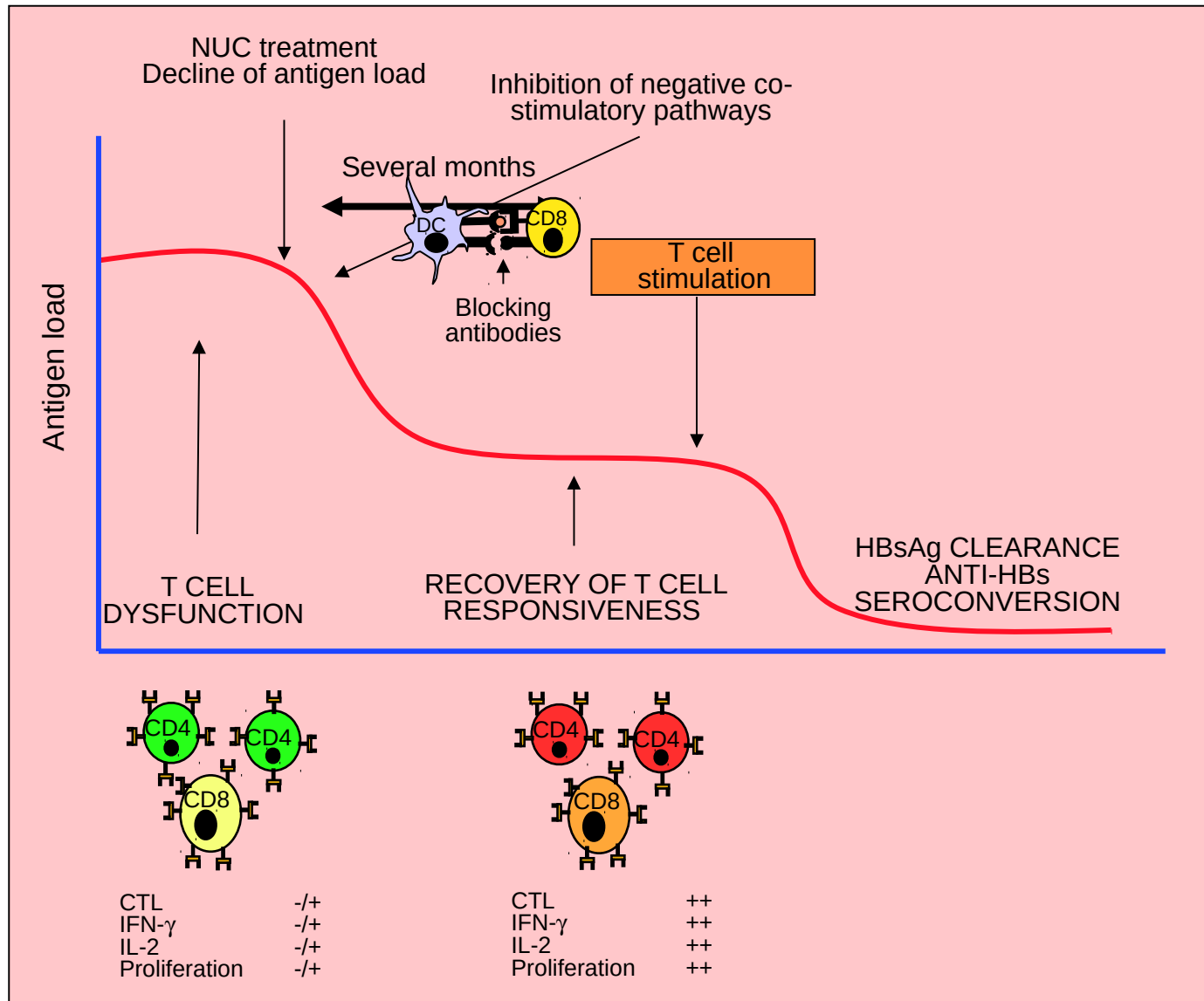
Reijnders JGP et al J-Hepatol. 2011

Clinical needs in HBV therapy for CH-B:

to shorten NUC therapy by accelerating
HBsAg clearance

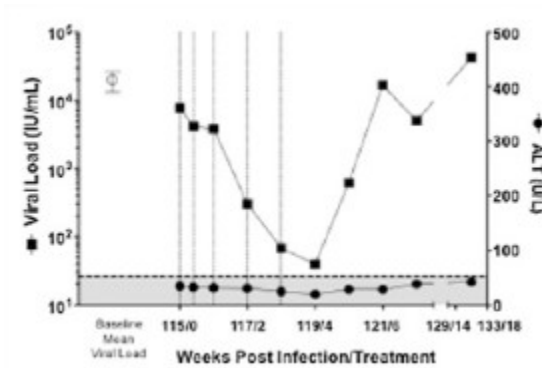
SEQUENTIAL NUC/IFN- α THERAPY

Potential strategy to shorten NUC therapies

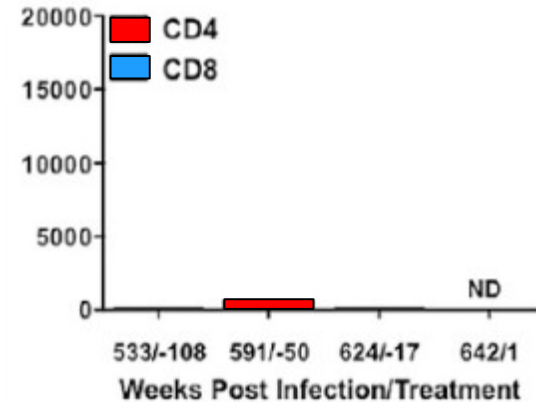
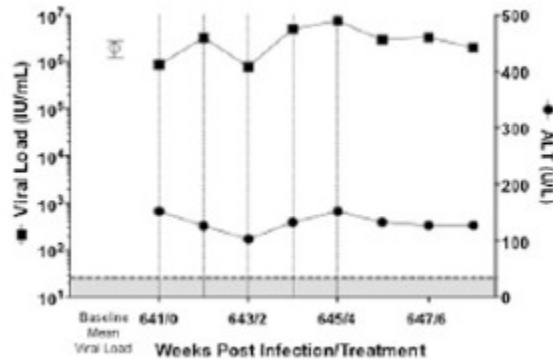
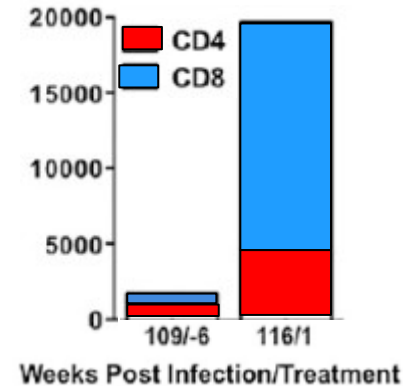


EFFECT OF ANTI-PD-1 THERAPY ON HCV INFECTED CHIMPANZEES

Effect on viral load

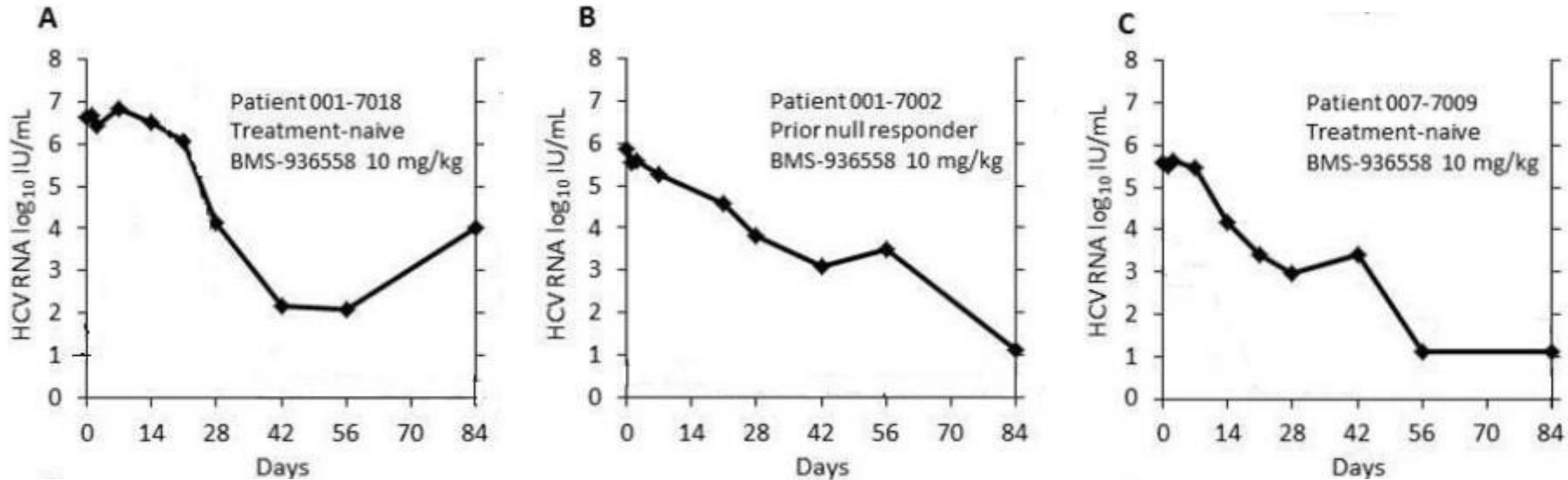


Effect on magnitude of T cell responses



PD-1 PATHWAY BLOCKADE

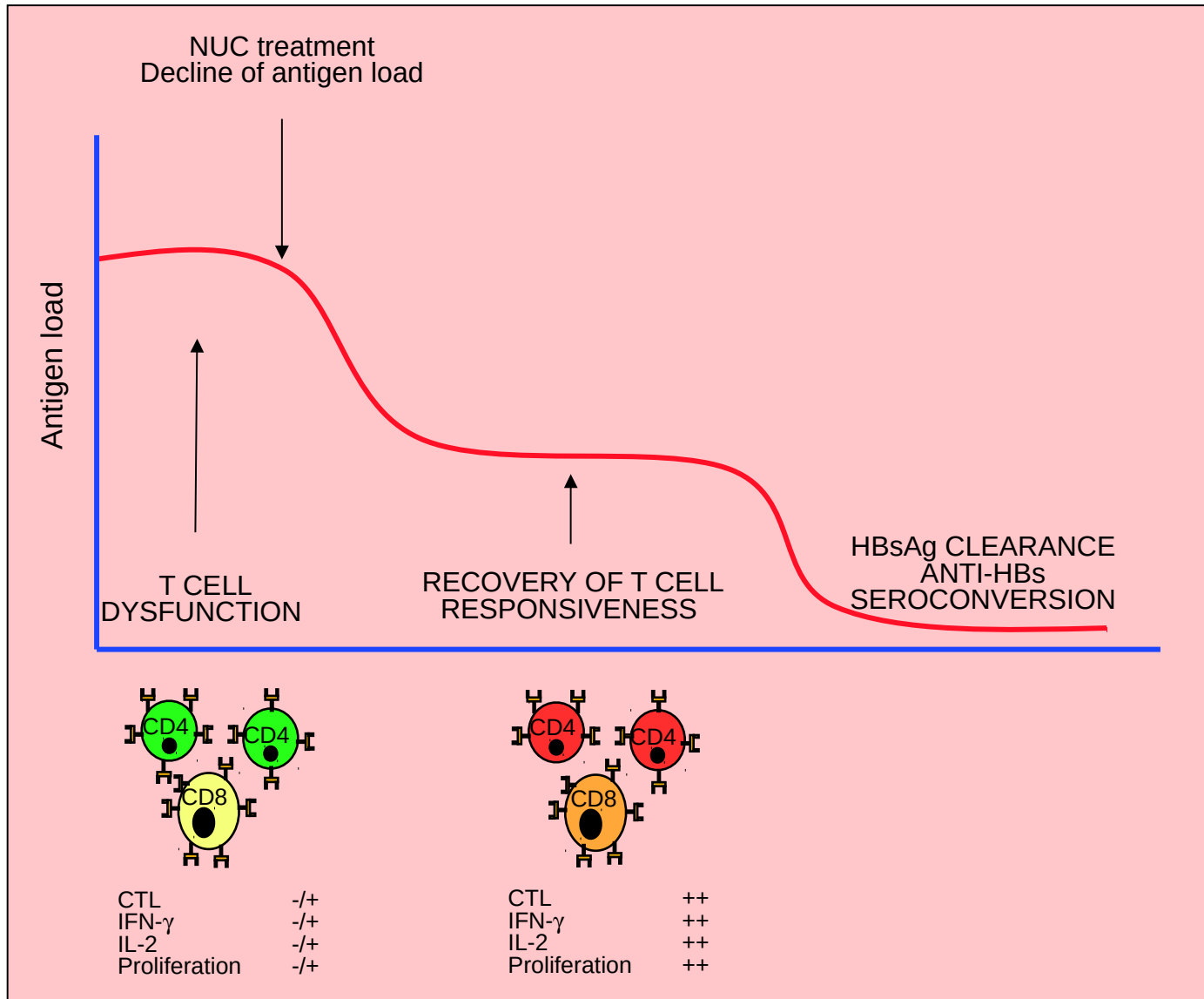
Proof of concept of α -PD-1 in Chronic HCV



- Blinded, PBO controlled, SAD study
- α -PD-1 in 54 HCV infected patients, IFN failures and treatment naive
- 0.03mg/kg -10mg/kg
- 3 subjects w/ > 4 log HCV RNA decline: All 3 received 10mg/kg dose
 - 1 subject (A) had isolated, transient Grade 4 ALT increase to ~17x ULN
- 1 subject (B) undetectable > 1 year post treatment

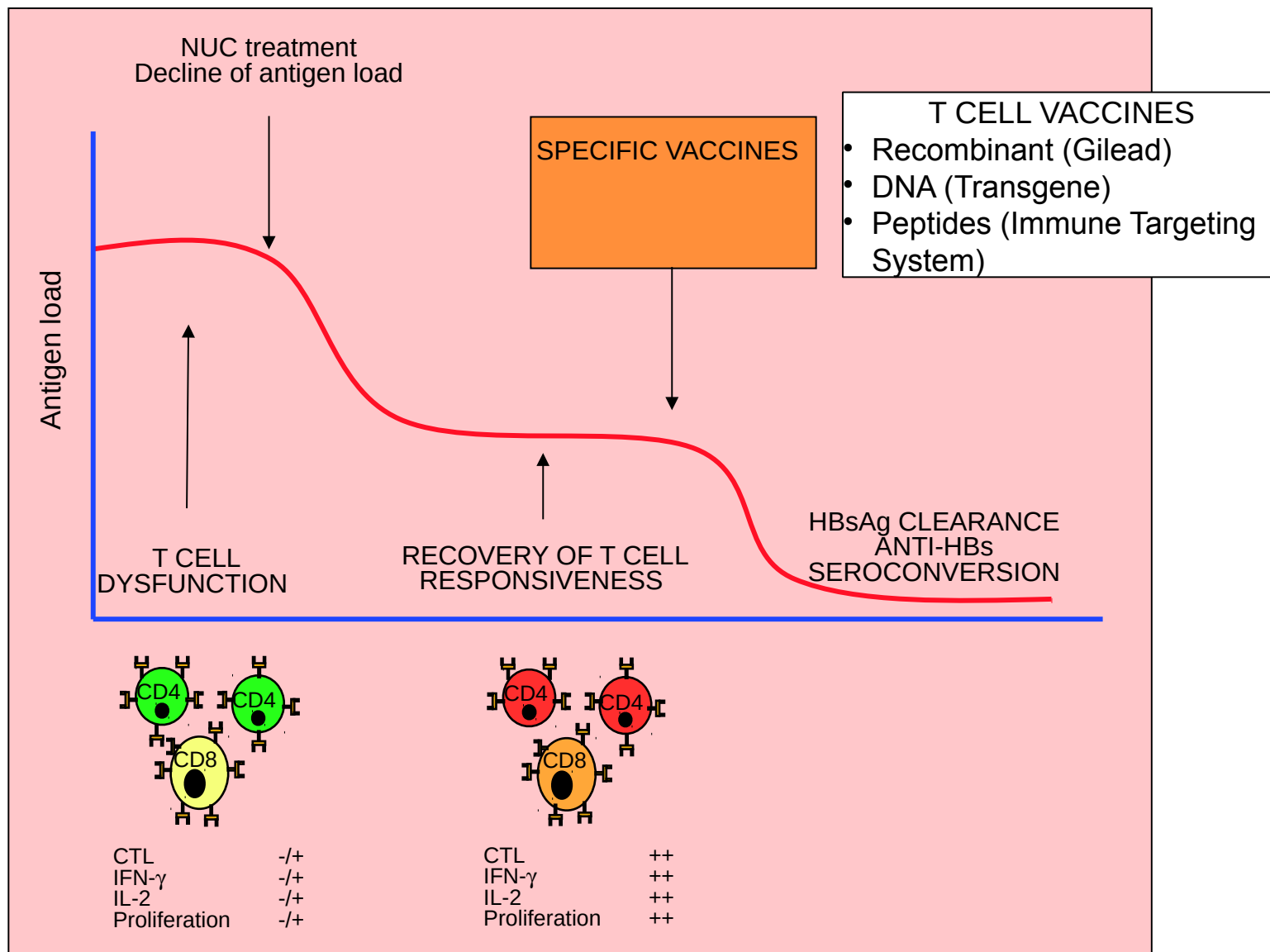
SEQUENTIAL NUC/IFN- α THERAPY

Potential strategy to optimize IFN- α efficacy and to shorten NUC therapies



SEQUENTIAL NUC/IFN- α THERAPY

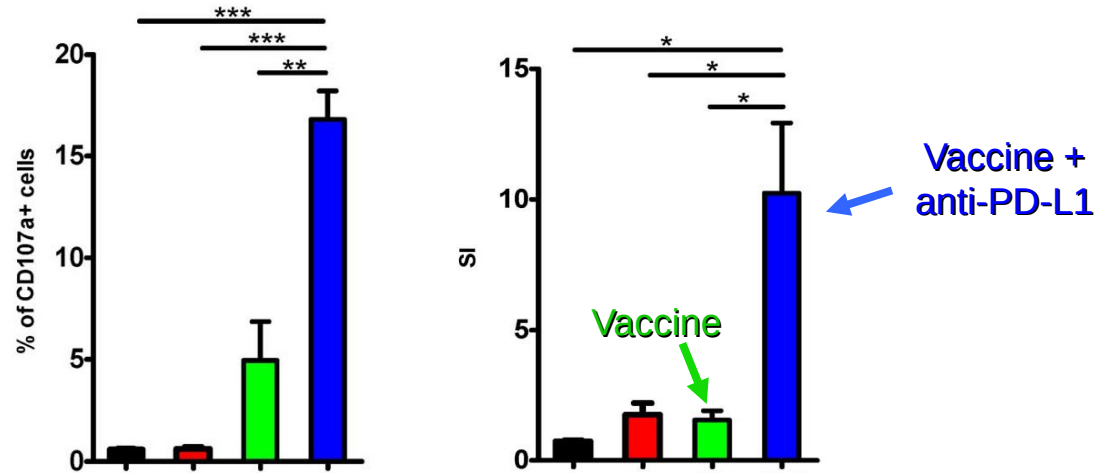
Potential strategy to optimize IFN- α efficacy and to shorten NUC therapies



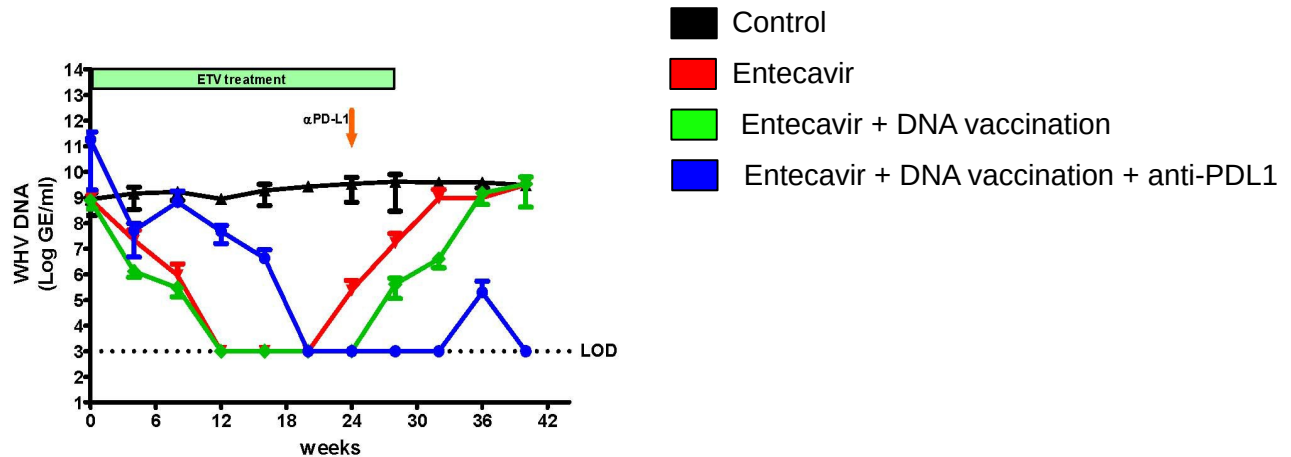
Synergistic effect of PD-L1 blockade and therapeutic vaccination on T cell responses and viral control

(Liu J. et al. PLOS Pathogens 2014)

T cell immunity

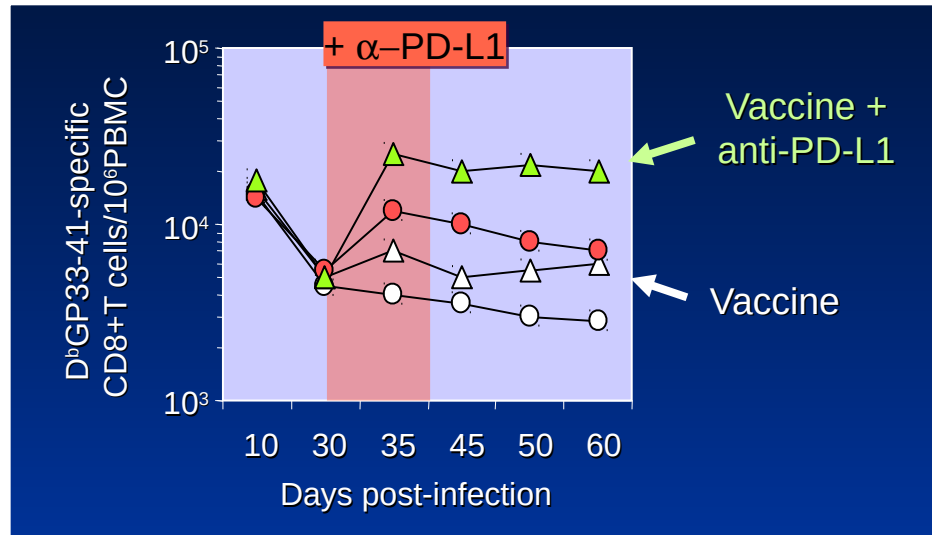


WHA replication

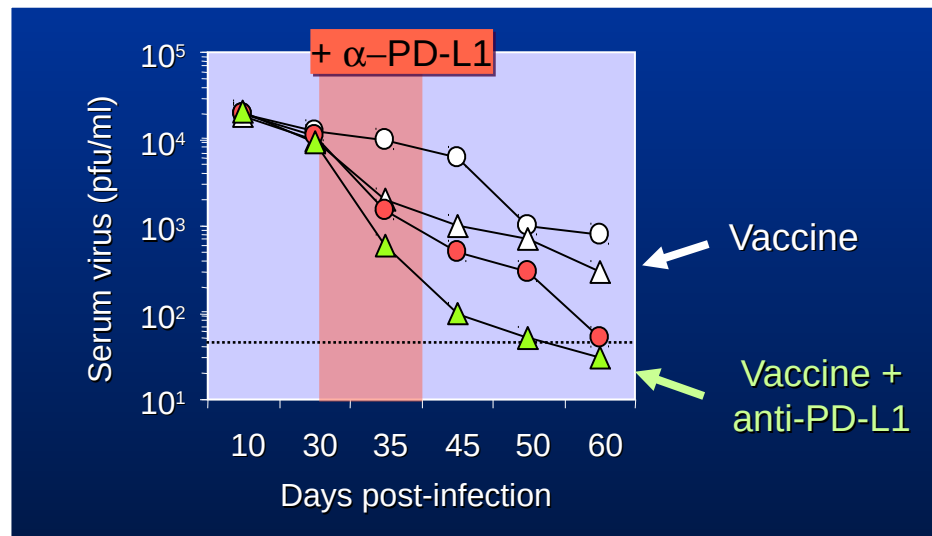


Synergistic effect of PD-L1 blockade and therapeutic vaccination on T cell responses and viral control

(Ha S-J. et al. *J. Exp. Med.* 2008)

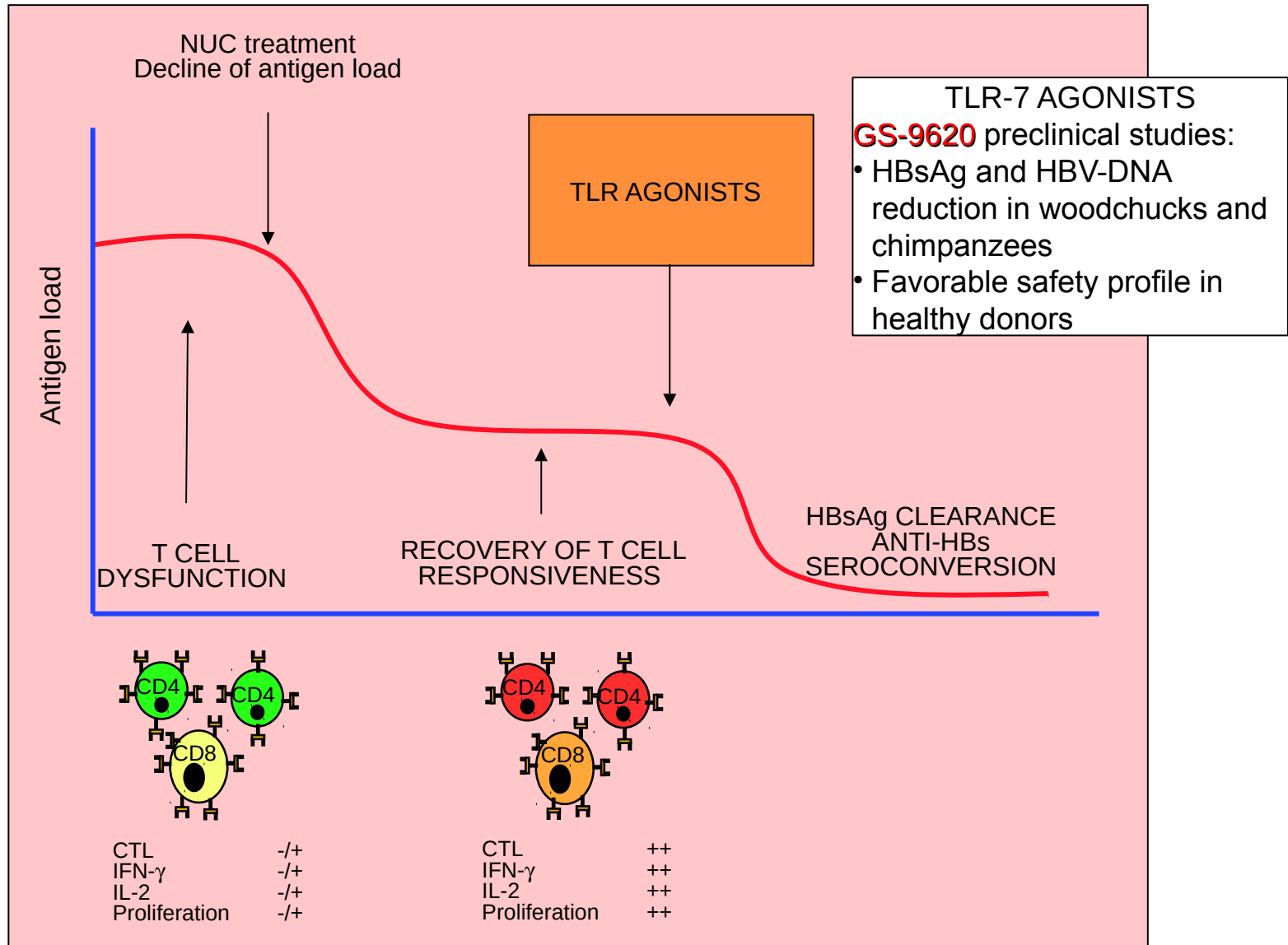


- VV/WT
- △ VV/GP33
- VV/WT + αPD-L1
- ▲ VV/GP33 + αPD-L1

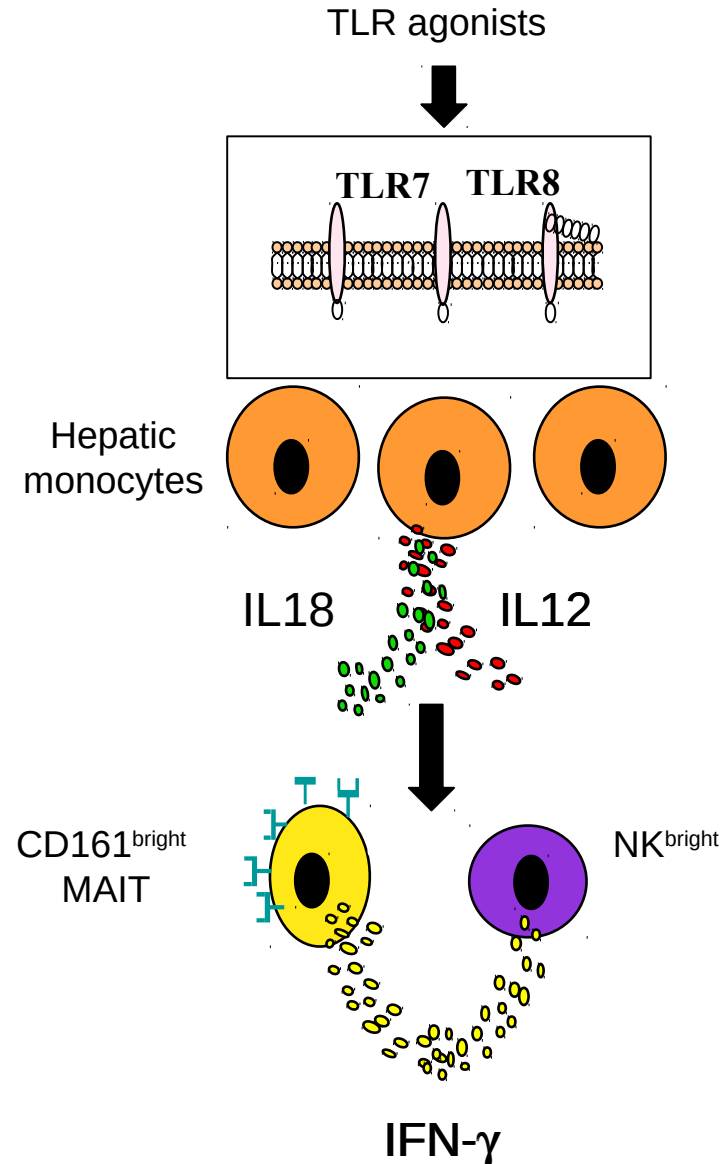


SEQUENTIAL NUC/IFN- α THERAPY

Potential strategy to optimize IFN- α efficacy and to shorten NUC therapies

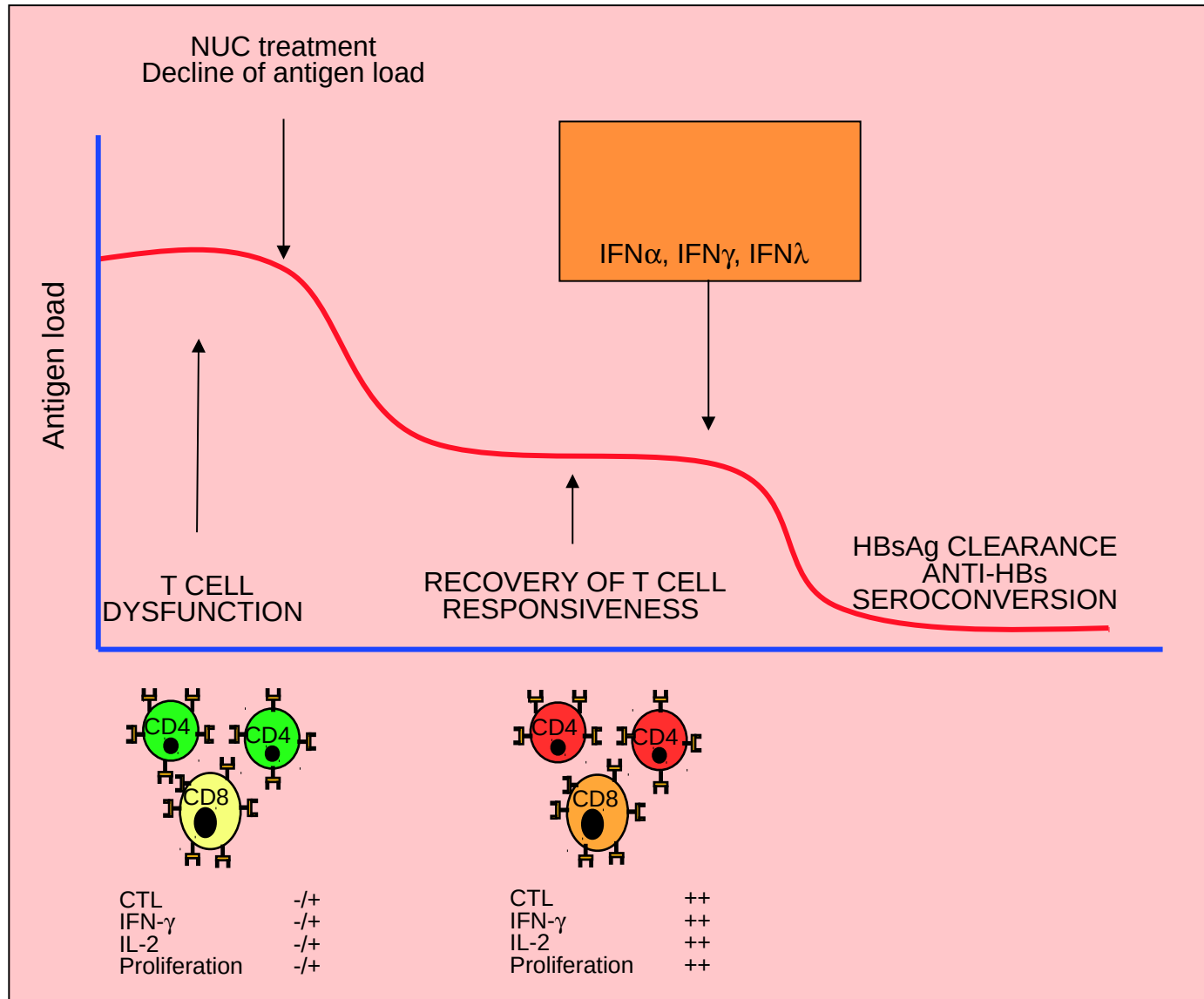


TLR8 agonists can trigger potent activation of innate immune cells in human liver

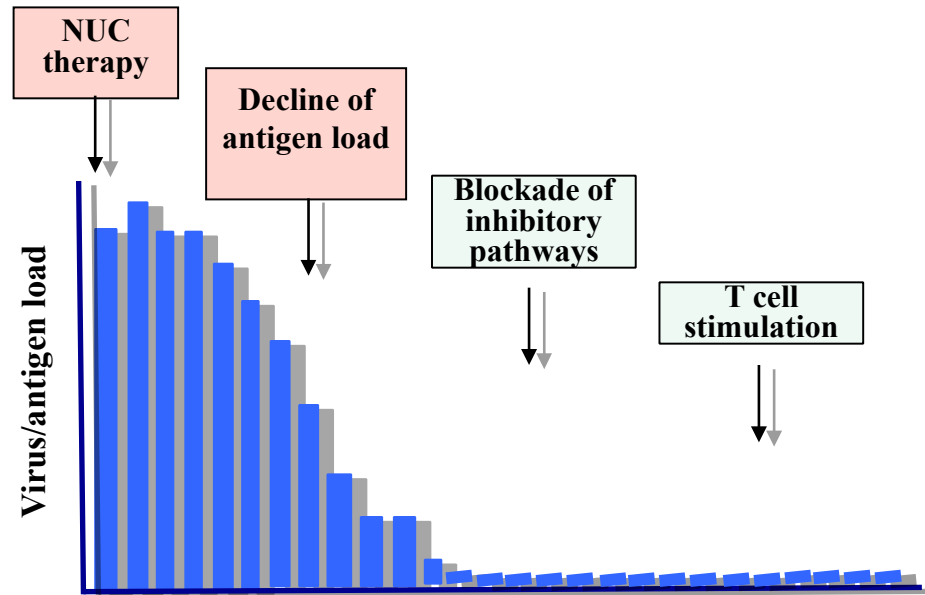


SEQUENTIAL NUC/IFN- α THERAPY

Potential strategy to optimize IFN- α efficacy and to shorten NUC therapies



FUTURE POTENTIAL IMMUNE MODOLATORY STRATEGIES TO TREAT HBV INFECTION



Full T cell exhaustion



Partial T cell exhaustion



Partial T cell restoration

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