

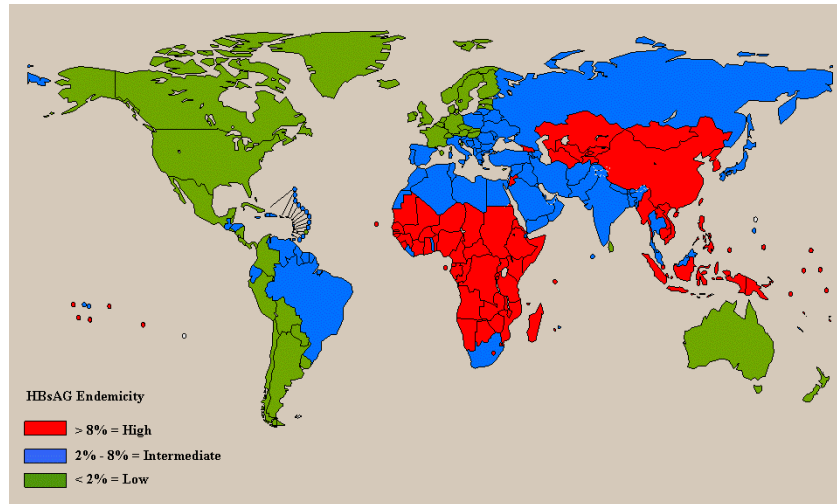
# Perspectives for immunotherapy in HBV and HCV



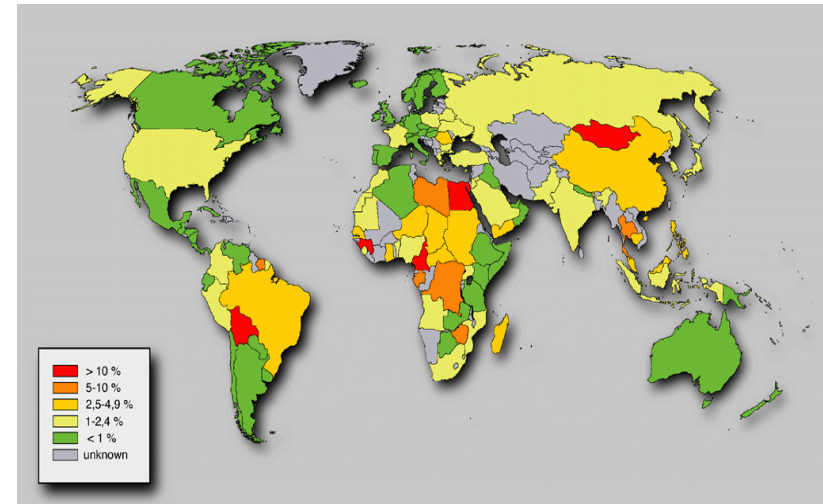
Robert Thimme

Department of Medicine II (Gastroenterology,  
Hepatology, Endocrinology and Infectious Diseases)

# Epidemiology and course of HBV and HCV



Chron. HBV-Infektion: ~ 240.000.000



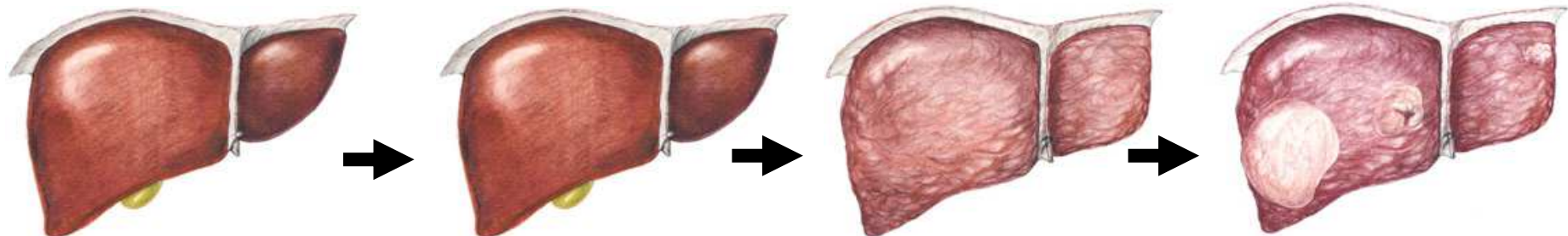
Chron. HCV-Infektion: ~ 160.000.000

Acute Hepatitis

Chronic Hepatitis

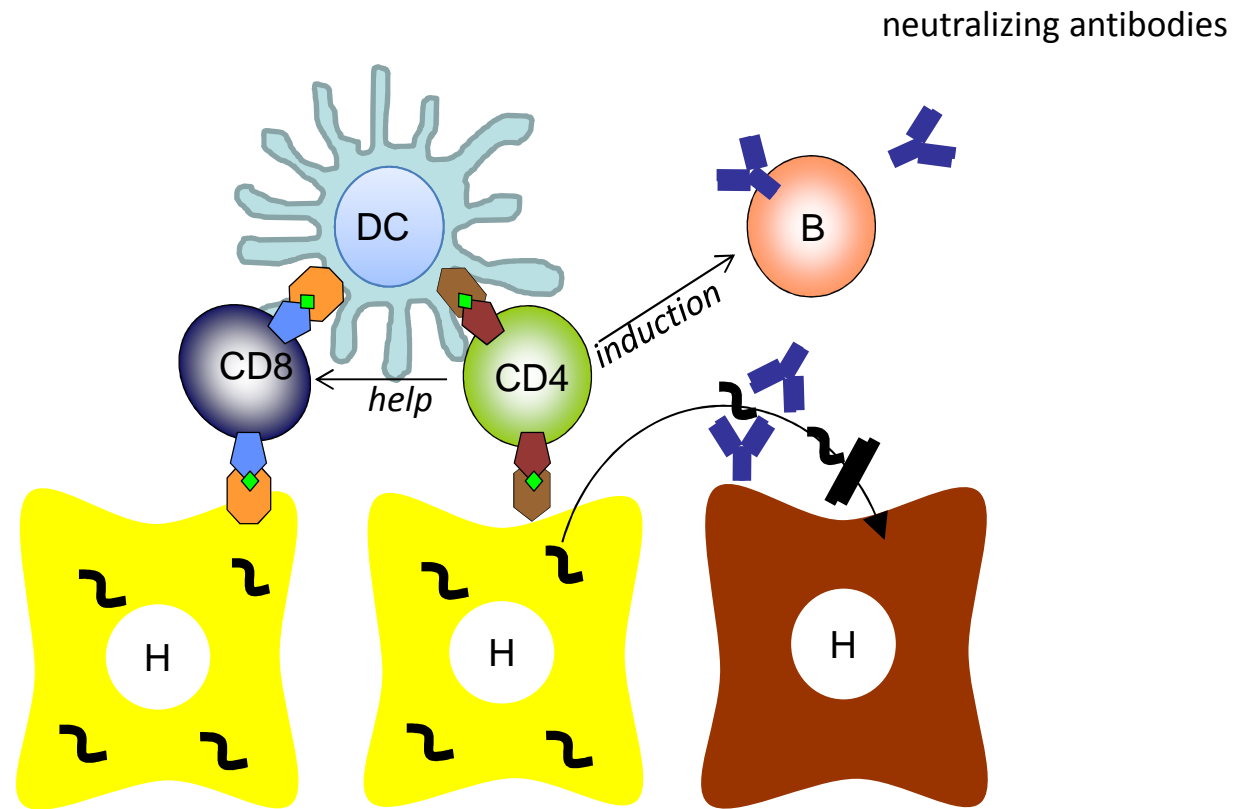
Cirrhosis

HCC



# Question

- What immune cells should be induced?



# Role of CD4<sup>+</sup> T cells in HBV and HCV infection

**HBV**

**HCV**

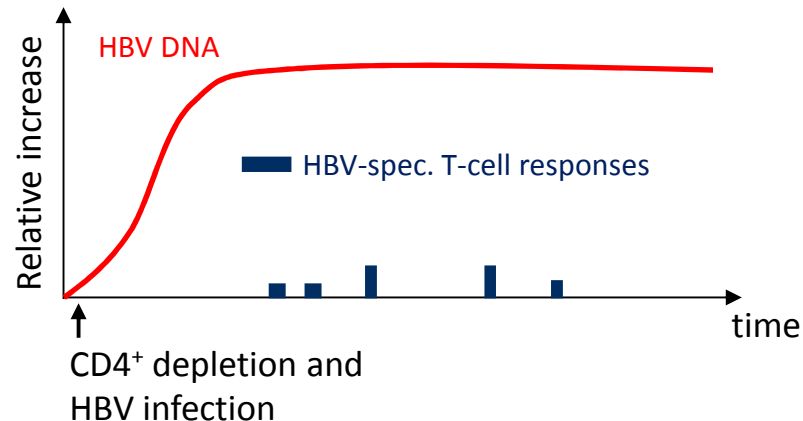
**Strong CD4<sup>+</sup> T cell responses are associated with virus clearance**

*Ferrari et al., J Immunol 1990*

*Diepolder et al., Lancet 1995*

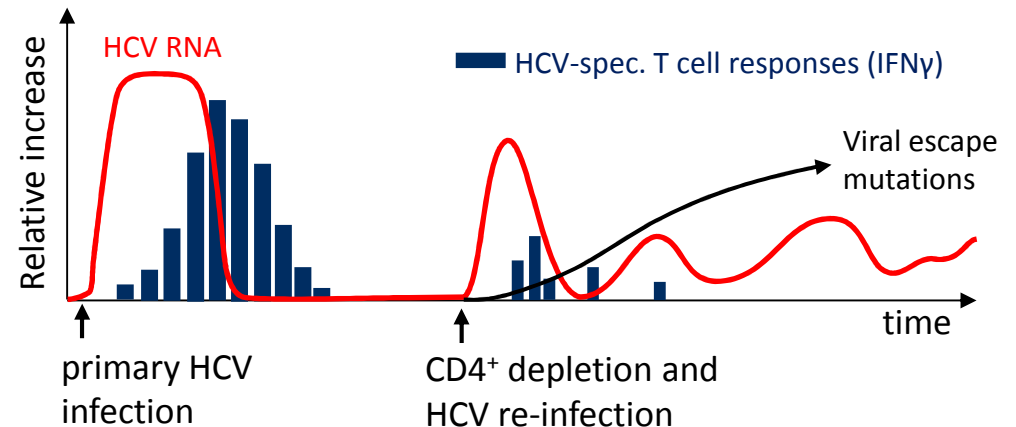
**Early CD4<sup>+</sup> T-cell responses contribute indirectly to viral control by facilitating induction and maintenance of HBV-specific CD8<sup>+</sup> T cells**

*Asabe et al., J Virol 2009.*



**Depletion of CD4<sup>+</sup> T cells leads to HCV persistence and CD8<sup>+</sup> escape variants**

*Grakoui et al., Science 2003*



# Role of CD8<sup>+</sup> T cells in HBV and HCV infection

**HBV**

**HCV**

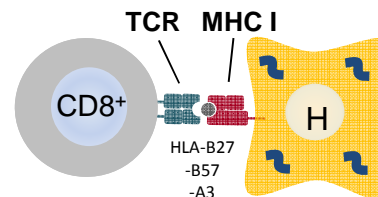
## Temporal association of CD8<sup>+</sup> T-cell response and viral load

Maini, Bertolotti Gastro 2001  
Boettler, Thimme, J Virol 2005

Lechner, Walker, J Exp Med 2000  
Grüner, Pape, J Infect Disease 2000  
Thimme, Chisari, J Exp Med 2001  
Lauer, Walker, J Virol 2005  
Kaplan, Chang, Gastro 2007  
Urbani, Ferrai, Hepatol 2006

## Association of class I alleles and outcome

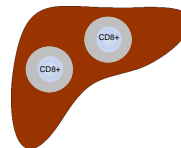
?



McKiernan, Kelleher, Hepatol 2004  
Neumann-Haefelin, Thimme, Hepatol 2006  
Kim, Lauer, Gastro 2011  
Fitzmaurice, Klenerman, Gut 2011

## Intrahepatic accumulation of CD8<sup>+</sup> T-cell responses during viral clearance

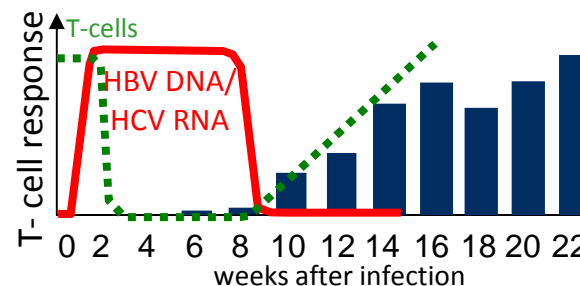
Guidotti, Chisari, Science 1999  
Thimme, Chisari, J Virol 2003



Erickson, Walker, Immunity 1999  
Thimme, Chisari, PNAS 2002  
Shin, Rehermann, J Virol 2008  
Watanabe, Major, J Viral Hepat 2010

## Depletion of CD8<sup>+</sup> T cells prolongs viremia

Thimme, Chisari, J Virol 2003

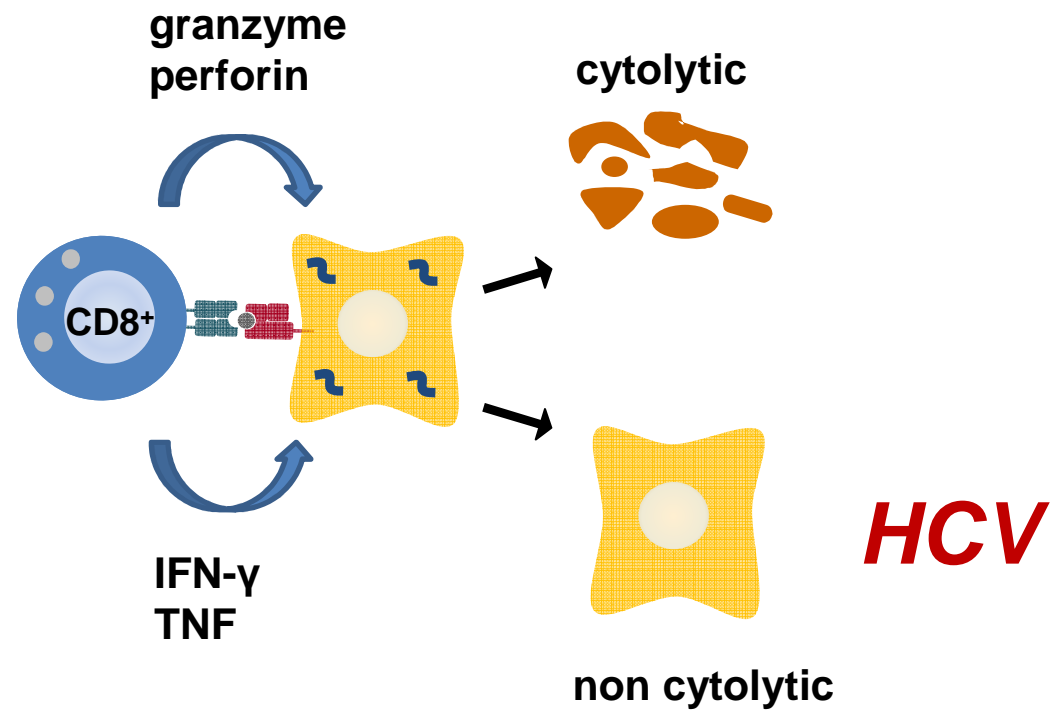


Shoukry, Walker, J Exp Med 2003

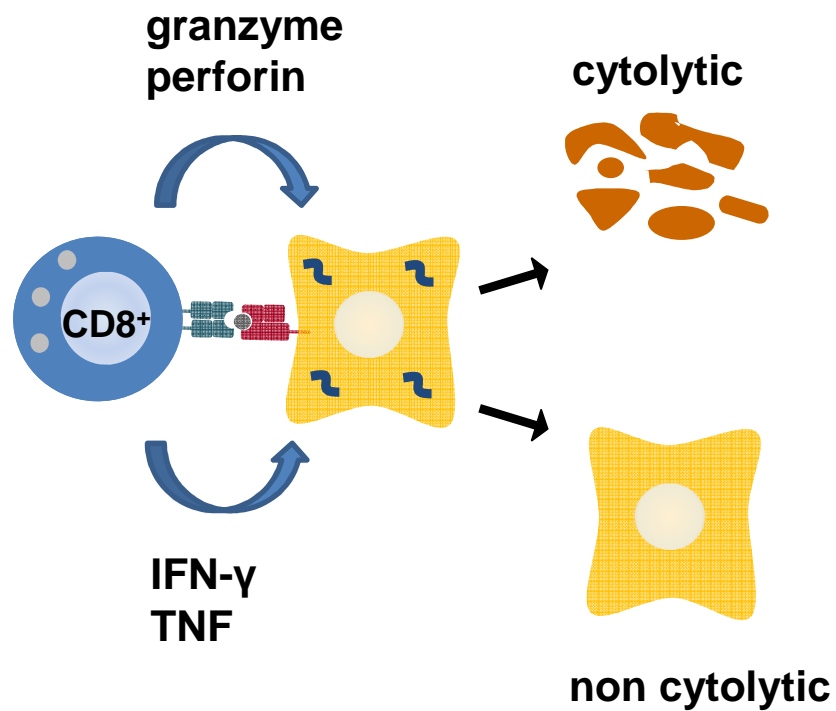
# Questions

- What immune cells should be induced?
- What effector functions are used by CD8+ T cells?
- Mechanisms of virus-specific CD8+ T cell failure?
- Restoration of virus-specific CD8+ T cell dysfunction?

# Effector functions of CD8<sup>+</sup> T cells in HBV and HCV infection



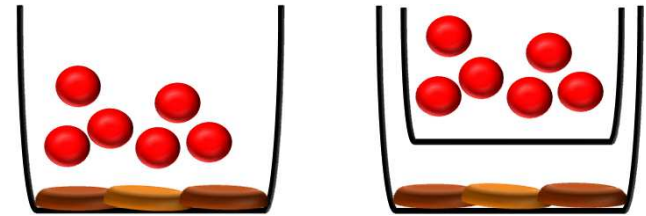
# Effector functions of CD8<sup>+</sup> T cells in HBV and HCV infection



**HBV**

## Assay for co-cultures:

- HBV infected HepG2<sup>hNTCP</sup> cells
- HLA-matched core<sub>18-27</sub>-specific CD8<sup>+</sup> T cells<sup>§</sup>
- duration: 4 d
- direct and indirect conditions

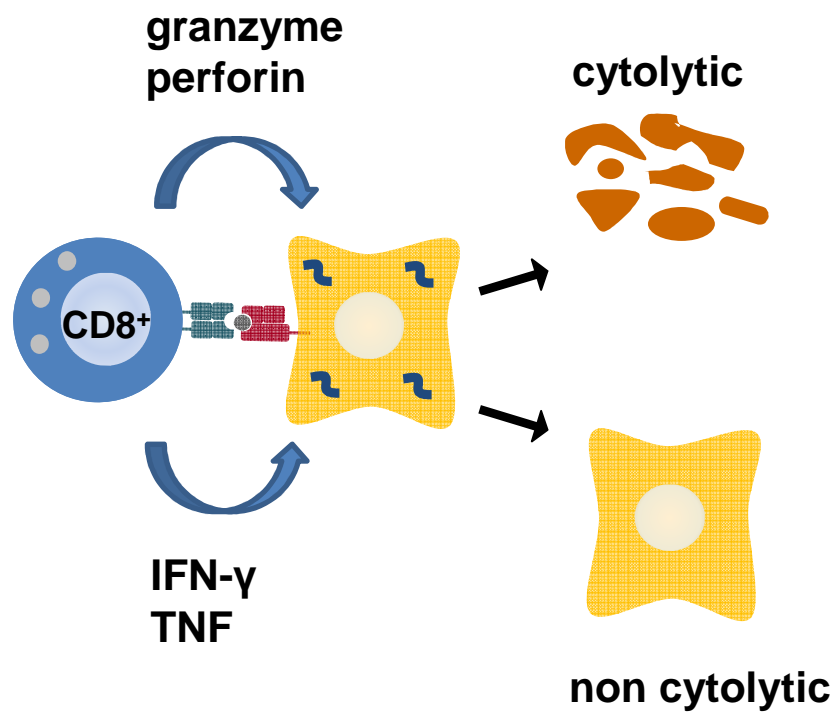


## Read-out:

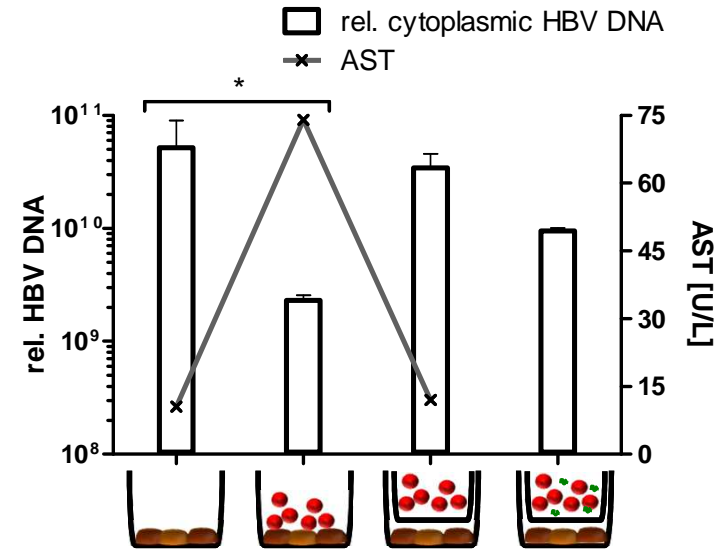
- cytoplasmic viral load (qPCR)
- transaminase level (AST)



# Effector functions of CD8<sup>+</sup> T cells in HBV and HCV infection

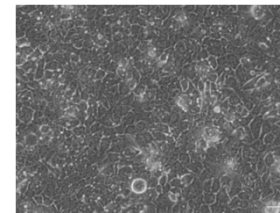


**HBV**

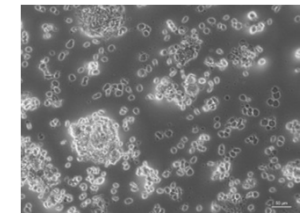


Hoh, Thimme, J Virology 2015

untreated



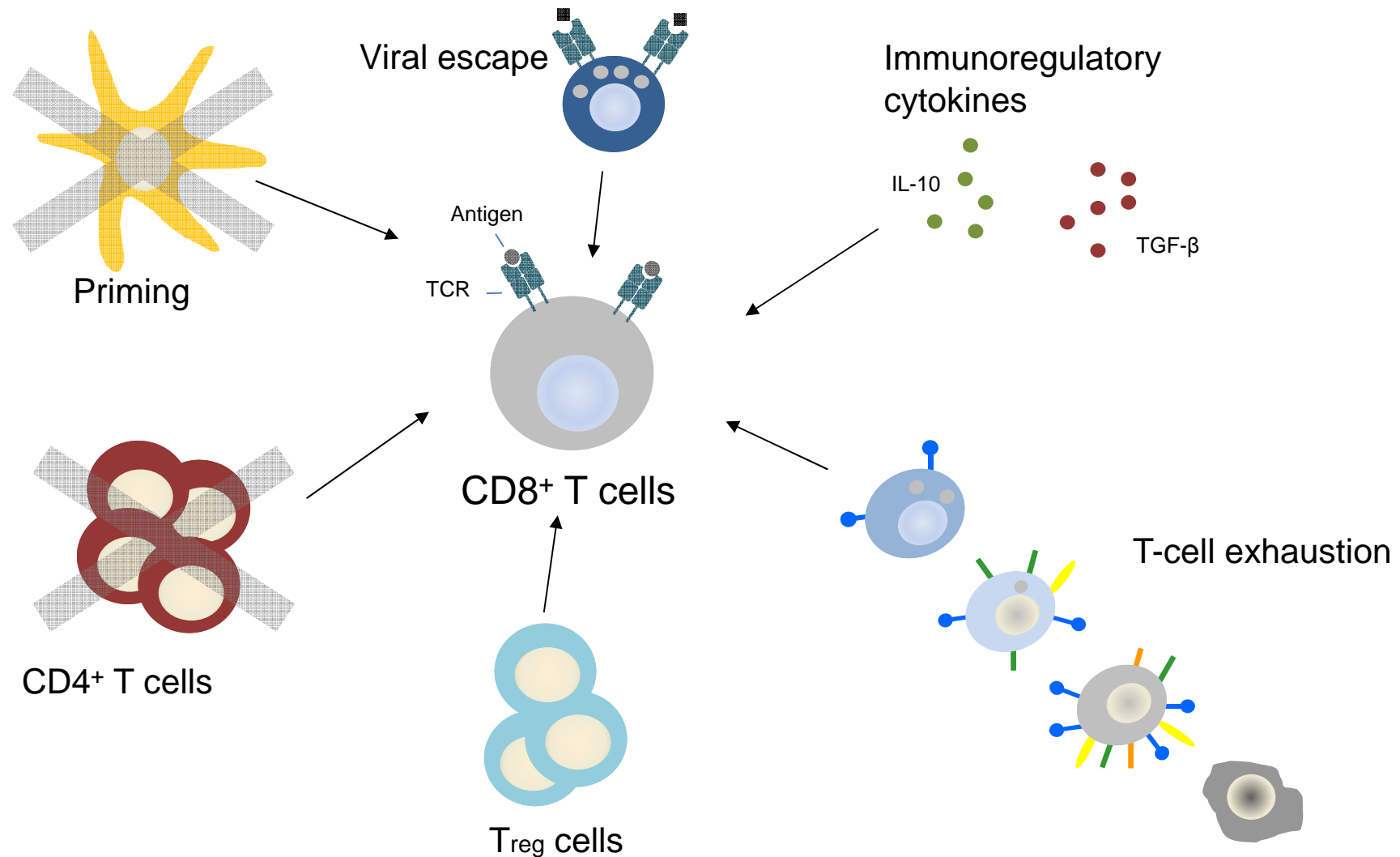
direct



# Questions

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# Mechanisms of CD8<sup>+</sup> T cell failure in HBV and HCV infection

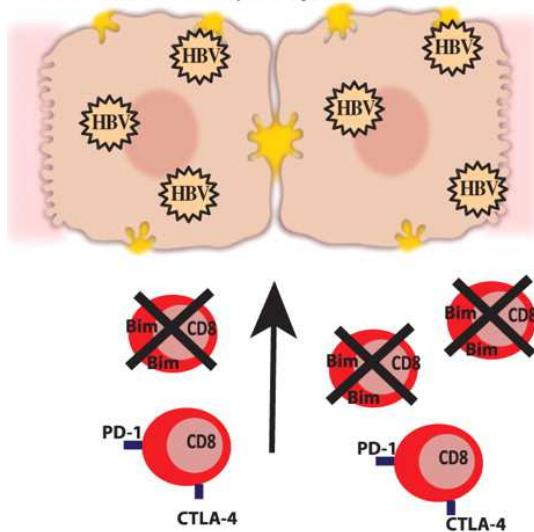


Knolle, Thimme, Gastroenterology 2014  
Heim, Thimme, J Hepatology 2014

# CD8+ T cell failure in chronic HBV infection

## Viral persistence in chronic HBV infection

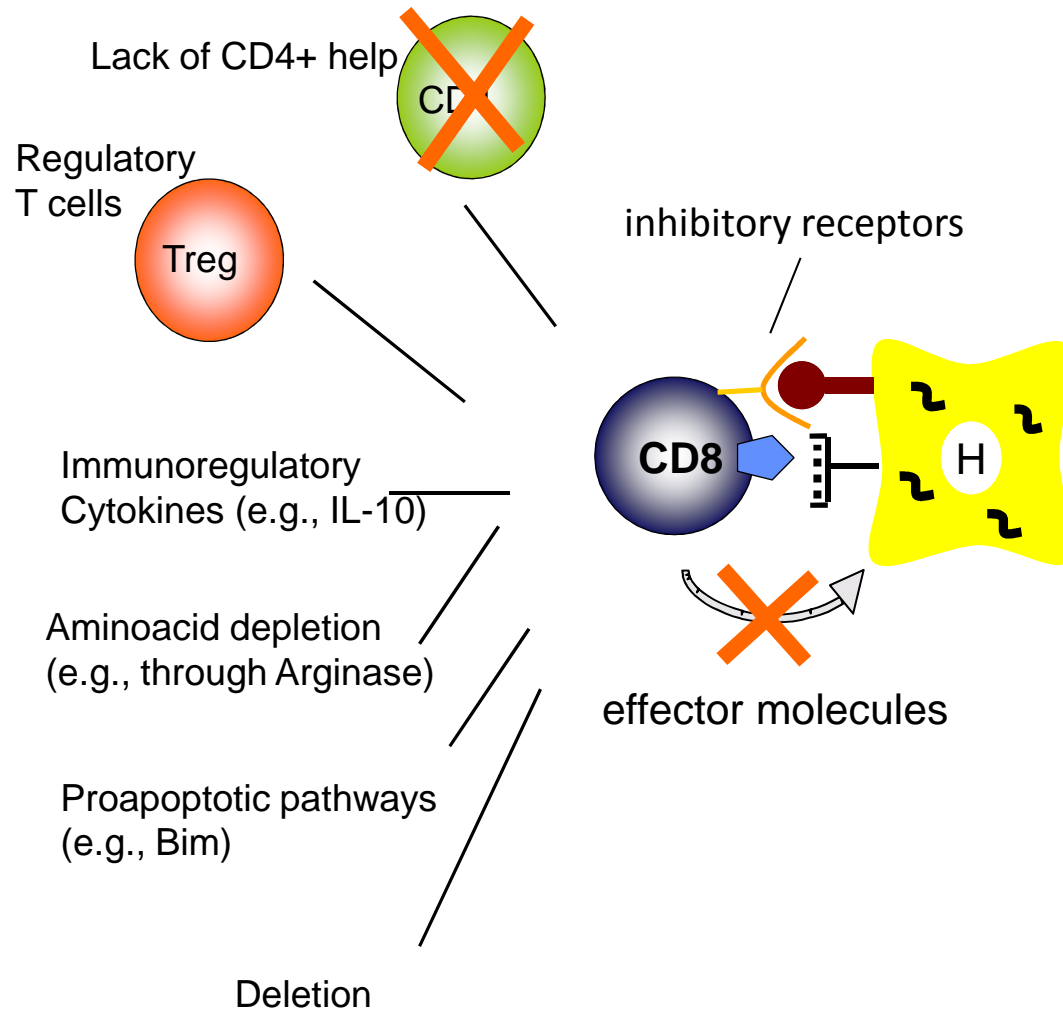
HBV Infected Hepatocytes



### T cell defects and attenuated viral control:

- Hierarchical loss of T cell function
- Excessive Co-inhibition
- Liver micronutrient depletion
- Elevated IL-10, TGF- $\beta$
- Extrinsic regulation
- Bim mediated apoptosis

# T cell failure in chronic HBV



PD-1	Maier / Chisari	<i>J Immunology</i> 2007
	Boni / Ferrari	<i>J Virology</i> 2007
	Zhang / Wang	<i>Gastroenterology</i> 2008
	Peng / Chen	<i>Mol. Immunol</i> 2008
	Fisicaro / Ferrari	<i>Gastroenterology</i> 2010
	Fisicaro / Ferrari	<i>Gastroenterology</i> 2012
2B4	Raziorrouh / Jung	<i>Hepatology</i> 2010
CTLA4	Schurich / Maini	<i>Hepatology</i> 2011
Tim-3	Wu / Chen	<i>Eur. J. Immunol</i> 2012
	Nebbia / Maini	<i>PLOS One</i> 2012

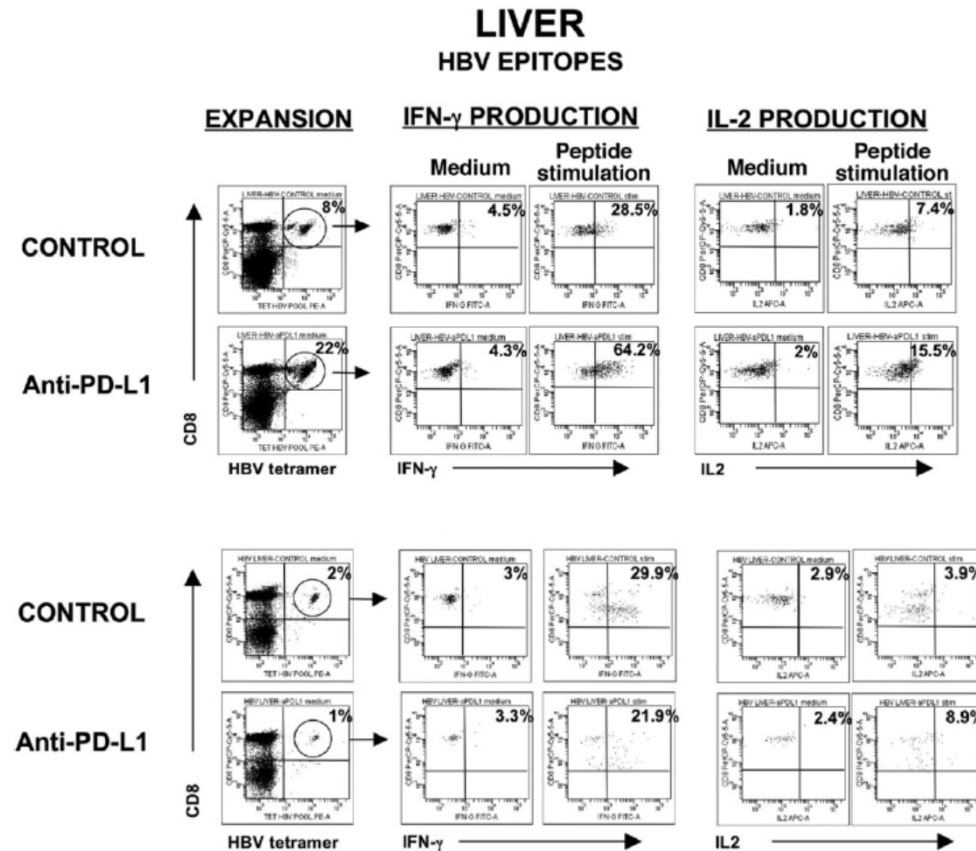
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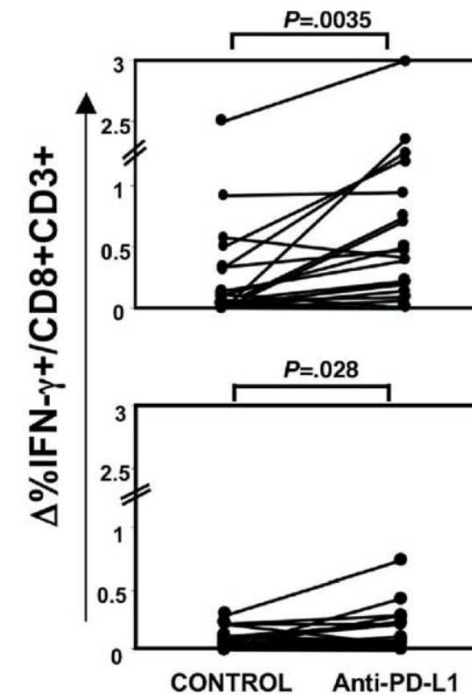
# Blockade of PD-1

## Antiviral Intrahepatic T-Cell Responses Can Be Restored by Blocking Programmed Death-1 Pathway in Chronic Hepatitis B

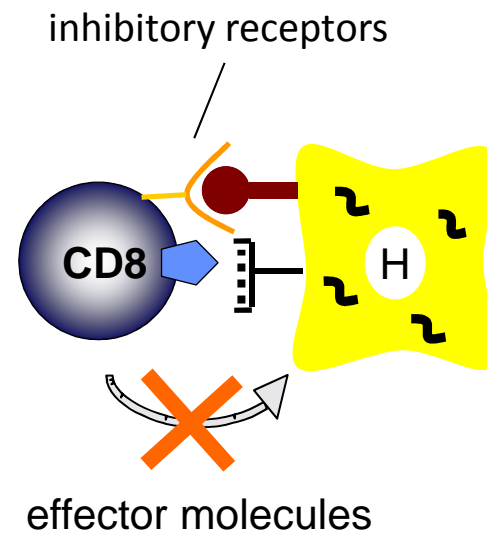
PAOLA FISICARO,\* CATERINA VALDATTA,\* MARCO MASSARI,<sup>†</sup> ELISABETTA LOGGI,<sup>§</sup> ELISABETTA BIASINI,\*  
LUCA SACCHELLI,\* MARIA CRISTINA CAVALLO,\* ENRICO M. SILINI,<sup>||</sup> PIETRO ANDREONE,<sup>§</sup> GABRIELE MISSALE,\* and  
CARLO FERRARI\*



GASTROENTEROLOGY 2010;138:682-693



# Restoration of T cell function



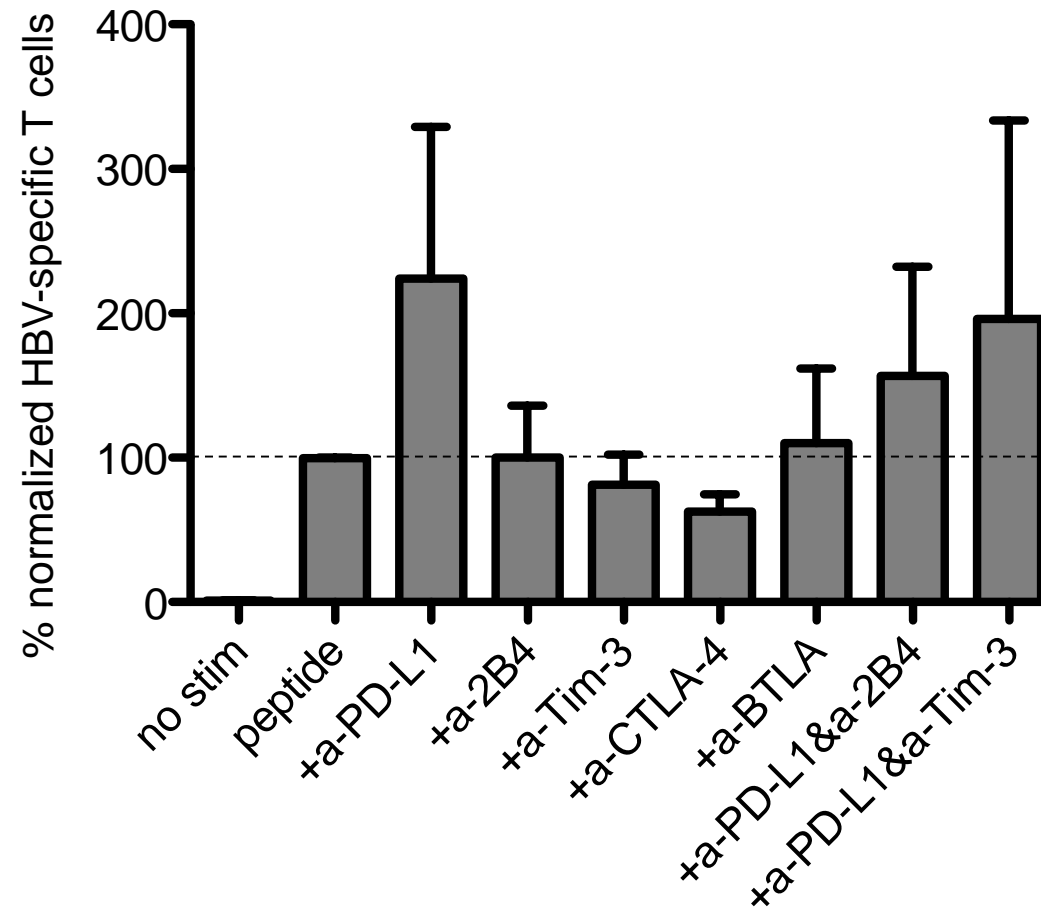
PD-1	Maier / Chisari	<i>J Immunology</i> 2007
	Boni / Ferrari	<i>J Virology</i> 2007
	Zhang / Wang	<i>Gastroenterology</i> 2008
	Peng / Chen	<i>Mol. Immunol</i> 2008
	Fisicaro / Ferrari	<i>Gastroenterology</i> 2010
2B4	Fisicaro / Ferrari	<i>Gastroenterology</i> 2012
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	Nebbia / Maini	<i>PLOS One</i> 2012

→ Inhibitory receptor blockade possible for each receptor, but variable response rates

→ Comprehensive analysis of inhibitory receptor blockade



## Summary: Response to inh. receptor blockade

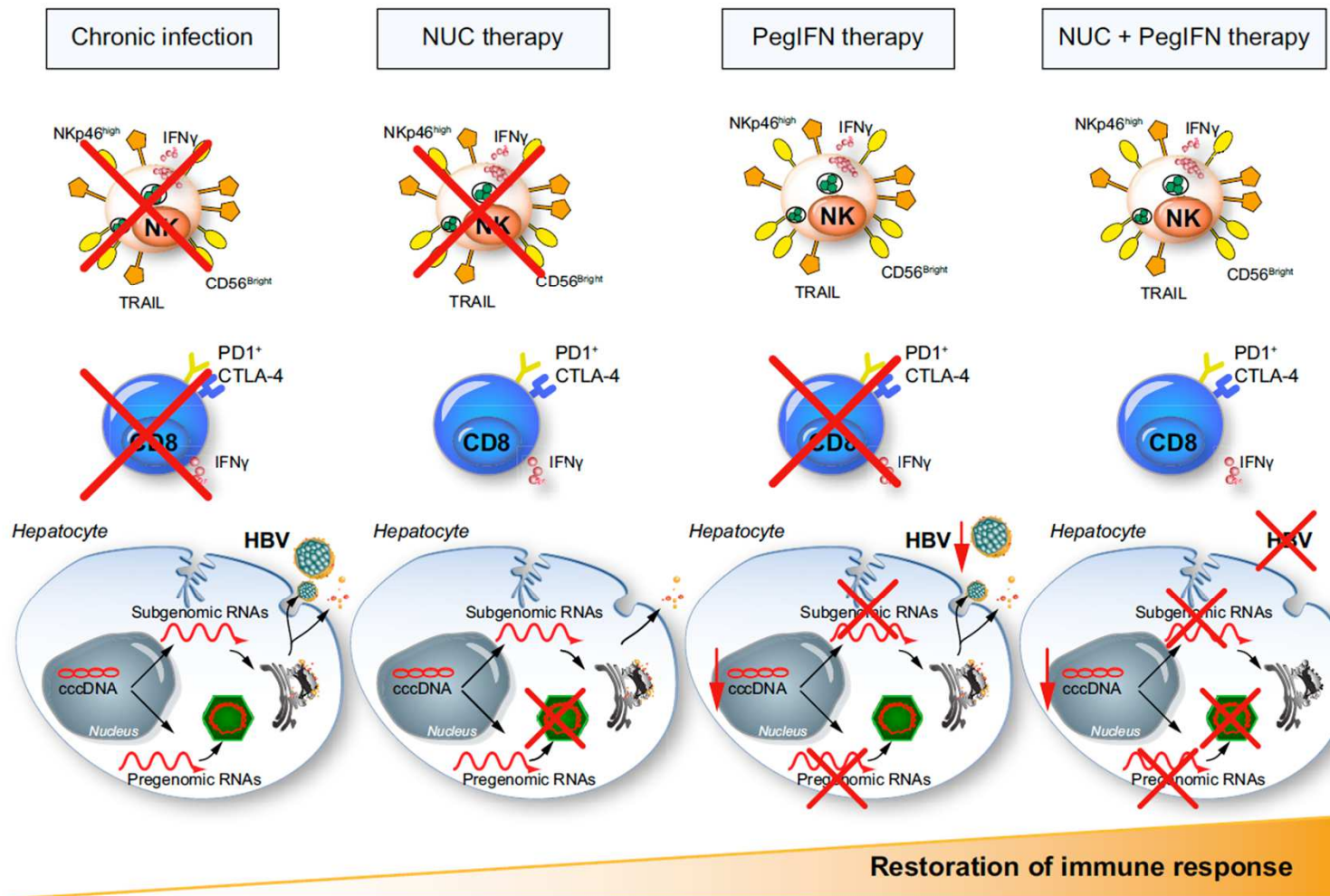


- High variability of response among patients and epitopes
- PD-L1 mono-blockade has the strongest effect

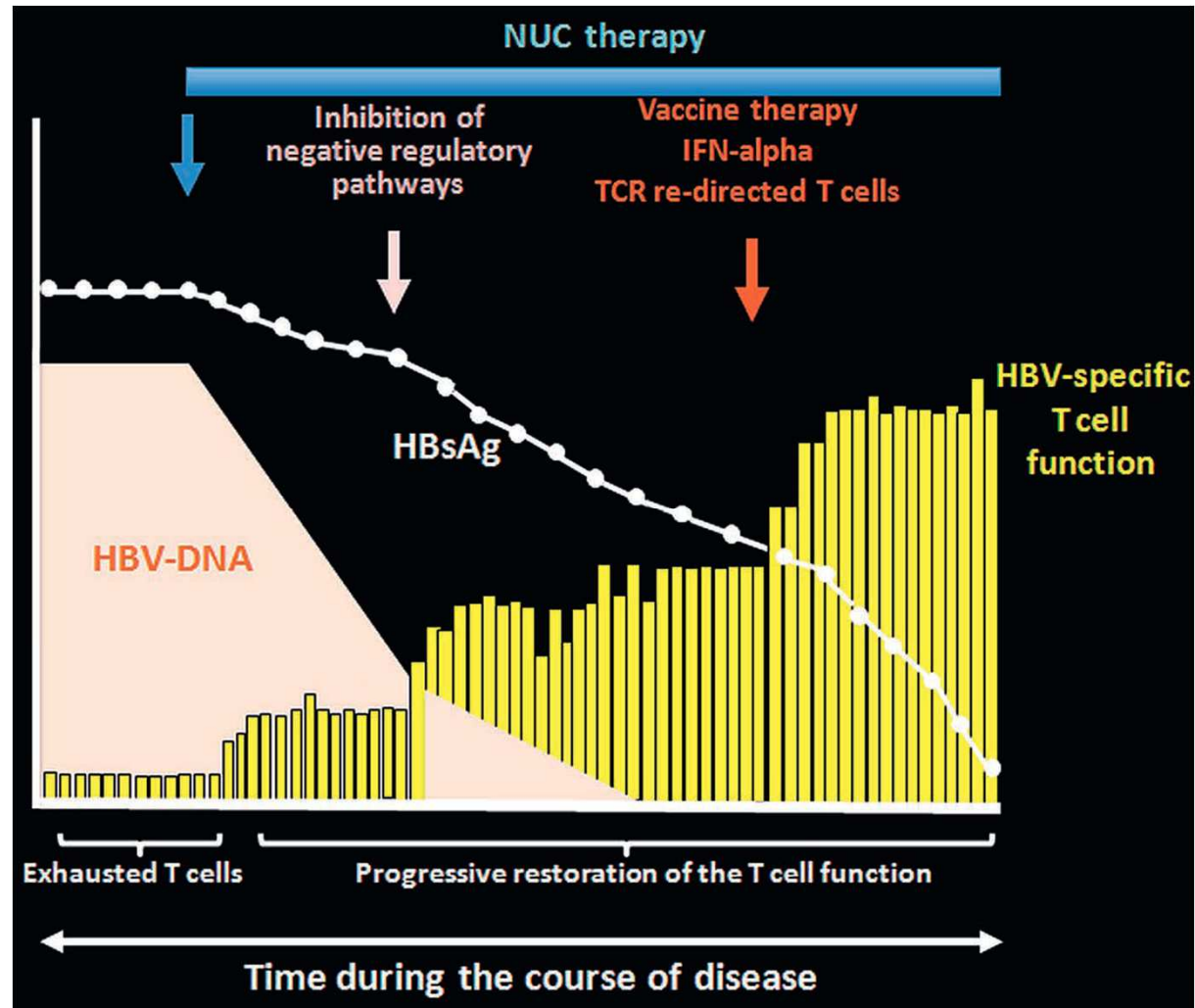
# Questions

- What immune cells should be induced?
- What effector functions are used by CD8+ T cells?
- Mechanisms of HBV-specific CD8+ T cell failure?
- Restoration of HBV-specific CD8+ T cell dysfunction?
- Combination with antiviral therapy?

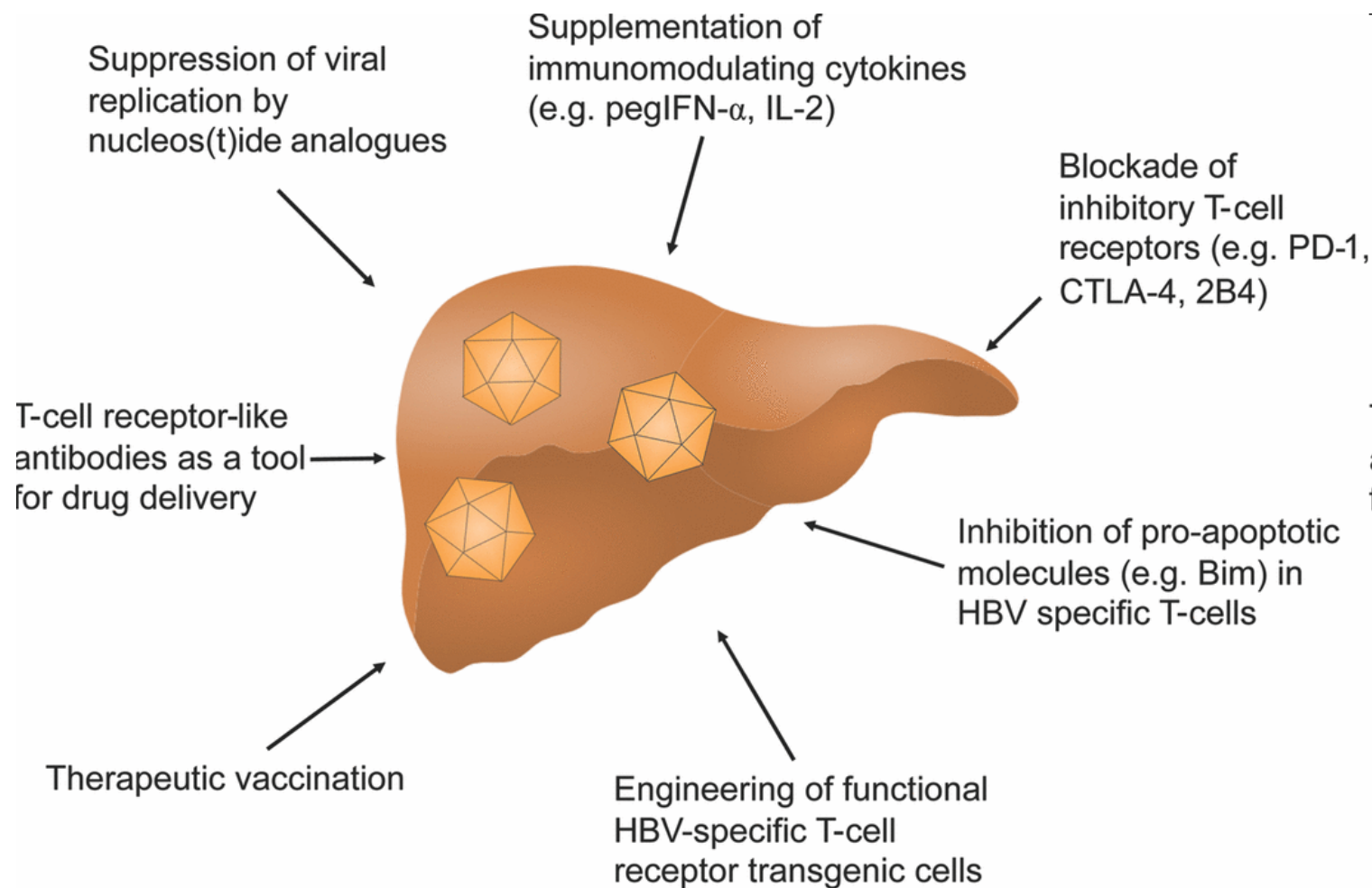
# Effect of antiviral therapy on immune response



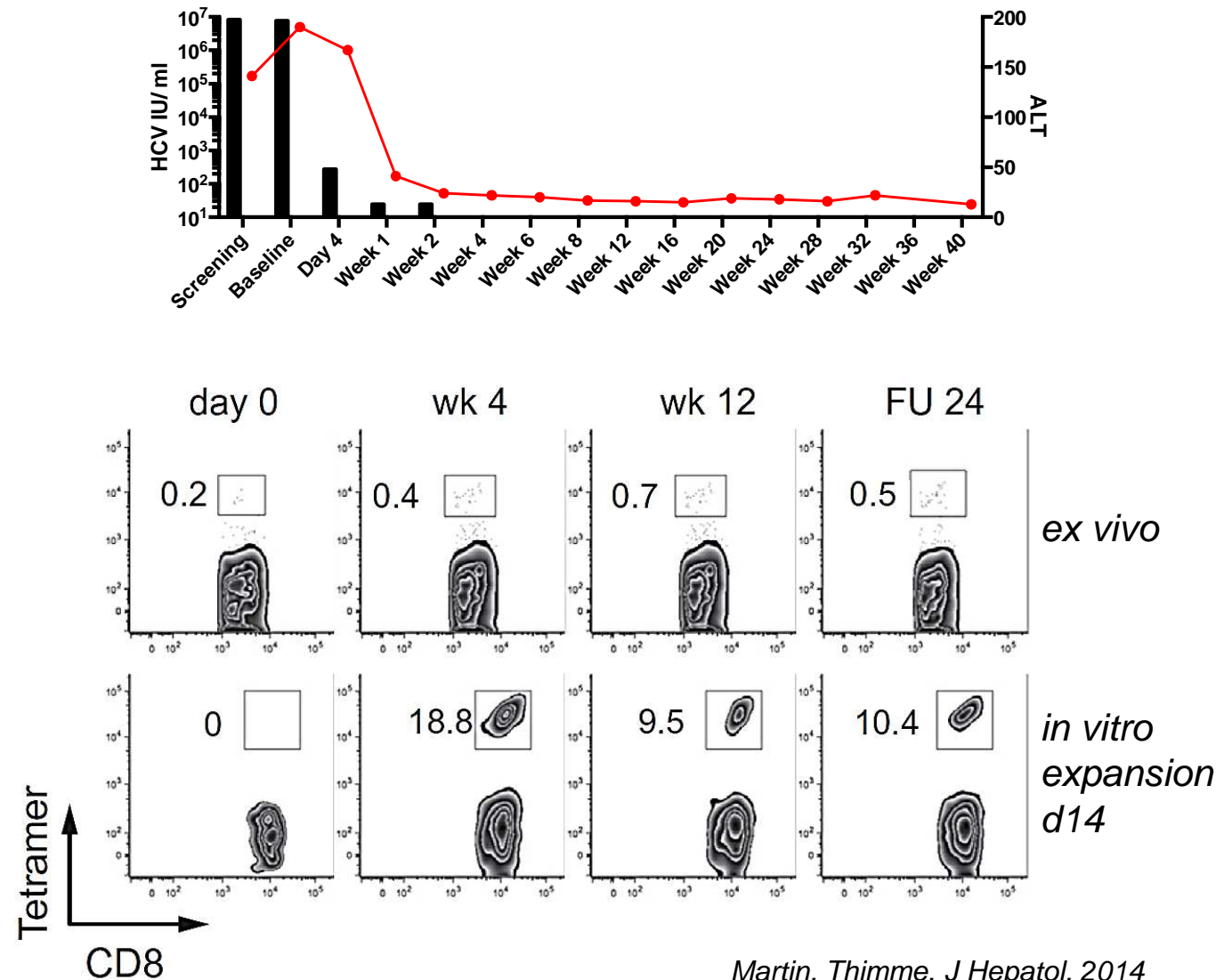
# Combination of antiviral and immuno-therapy



# Perspectives of immunotherapy in HBV



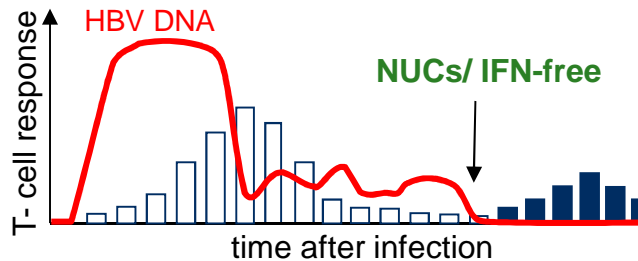
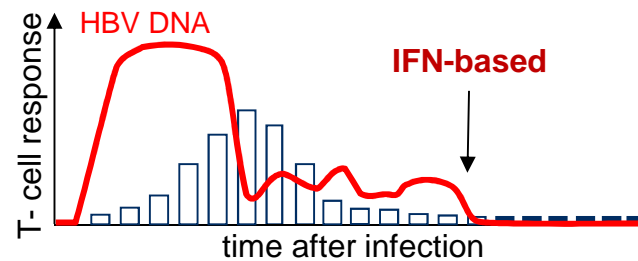
# Restoration of phenotype and function of HCV-specific T cells by IFN-free therapy



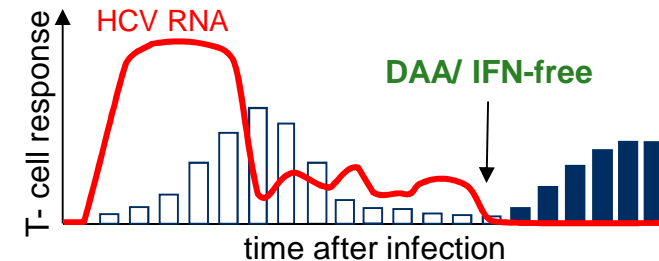
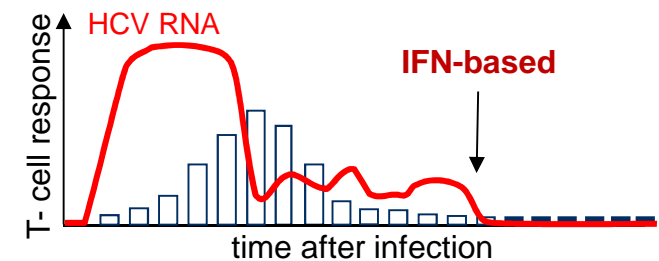
# Restoration of virus-specific CD8<sup>+</sup> T-cell failure by antiviral therapy

chronic  
infection

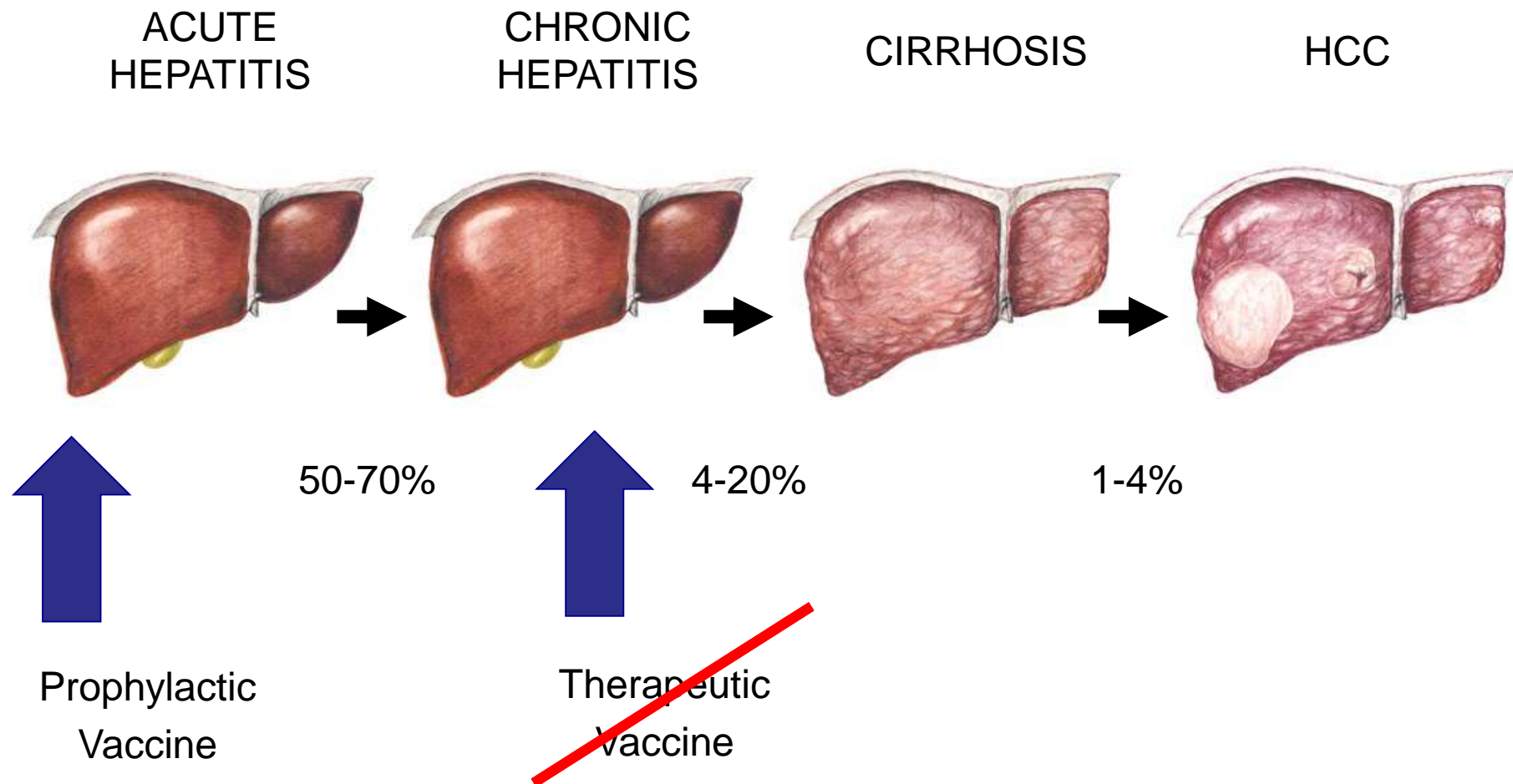
**HBV**



**HCV**



# Hepatitis C- Vaccine





# Summary

- Insights into virus-specific CD8+ T cell function by using novel models:
  - HCV: primarily non-cytolytic
  - HBV: primarily cytolytic
- Virus-specific CD8+ T cell failure is difficult to overcome by checkpoint inhibitors
- Virus-specific CD8+ T cell exhaustion partially reversible by antigen removal
- There is a role for immunotherapy, but additional studies needed to overcome T cell exhaustion by vaccination etc



### Organizers

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# Acknowledgements

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