

*First International Course on Translational Hepatology
Focus on HCV Disease*

Florence, March 9-11, 2011

HCV AND ADAPTIVE IMMUNITY

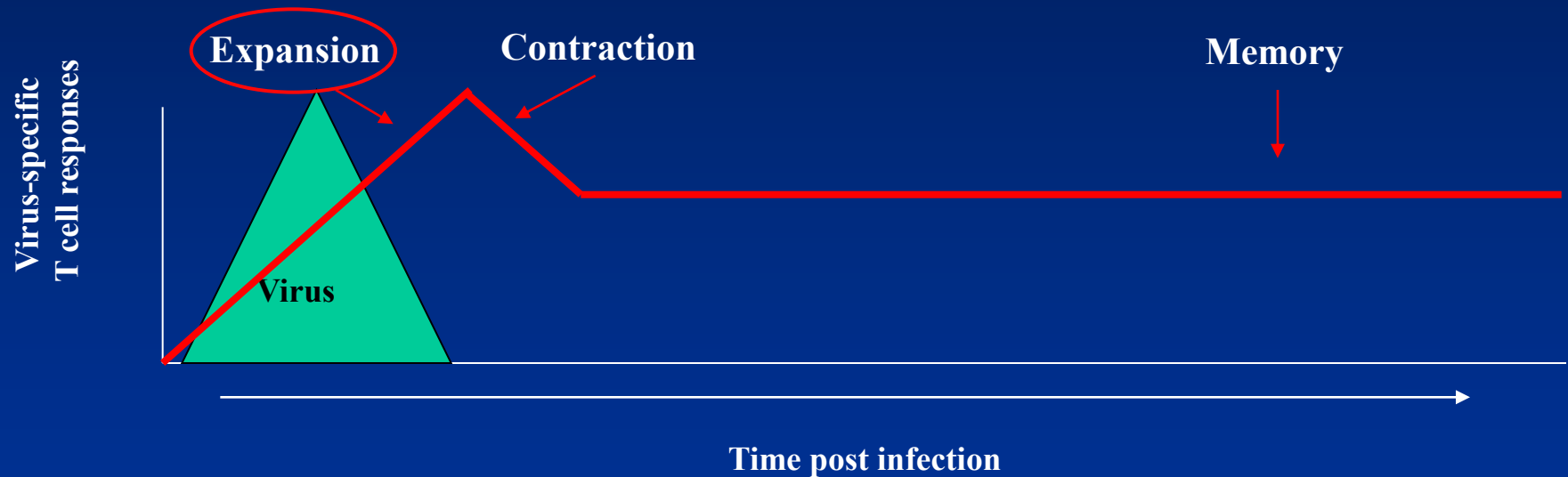
C. Ferrari

U.O. Malattie Infettive ed Epatologia
Laboratorio di Immunopatologia Virale
Azienda Ospedaliero-Universitaria di Parma, Italy

SUMMARY

- **Early kinetics of HCV-specific responses**
- **HCV-specific responses**
 - in acute HCV infection**
 - in chronic HCV infection**
- **Effect of therapy on T cell responses**
- **Strategies of functional T cell restoration**

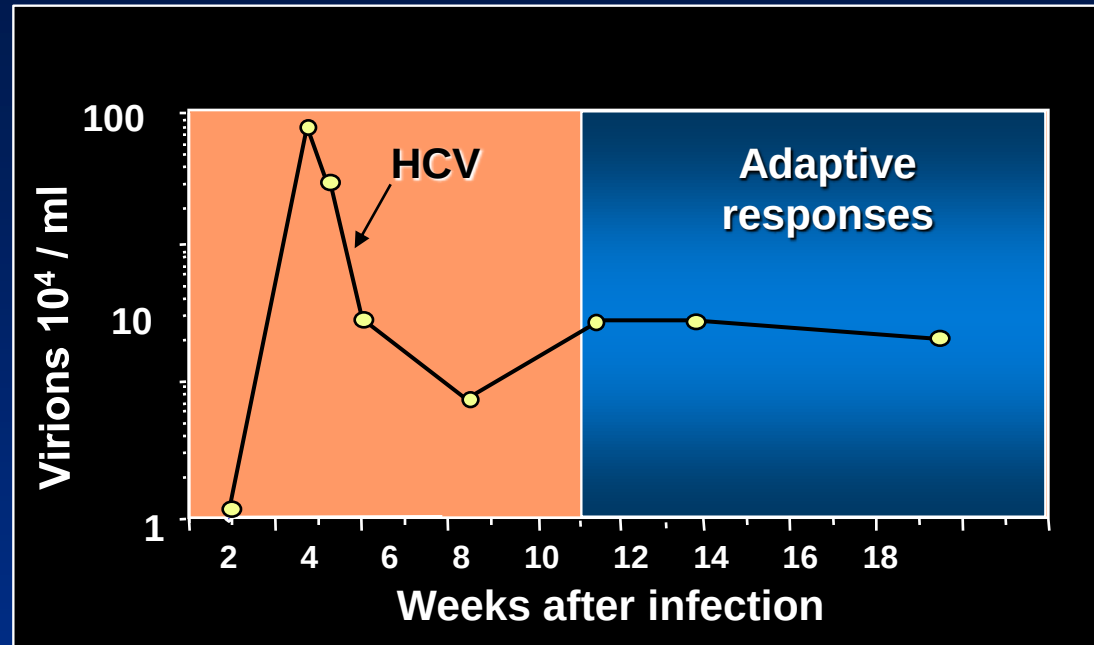
KINETICS OF THE DEVELOPMENT OF VIRUS-SPECIFIC T CELL RESPONSES AFTER INFECTION



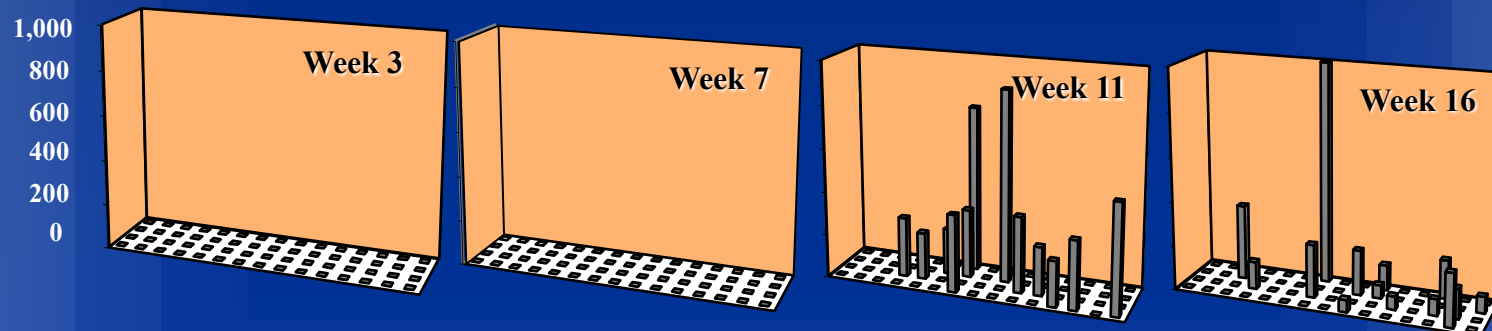
EVOLUTION OF HCV INFECTION



Kinetics of virus replication and HCV-specific T cell responses early after HCV infection (I)

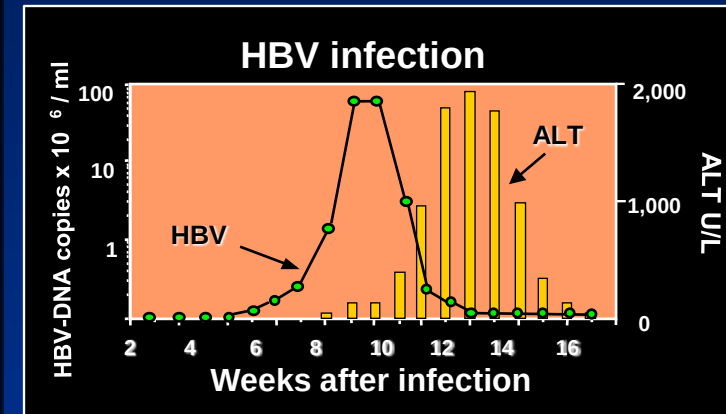
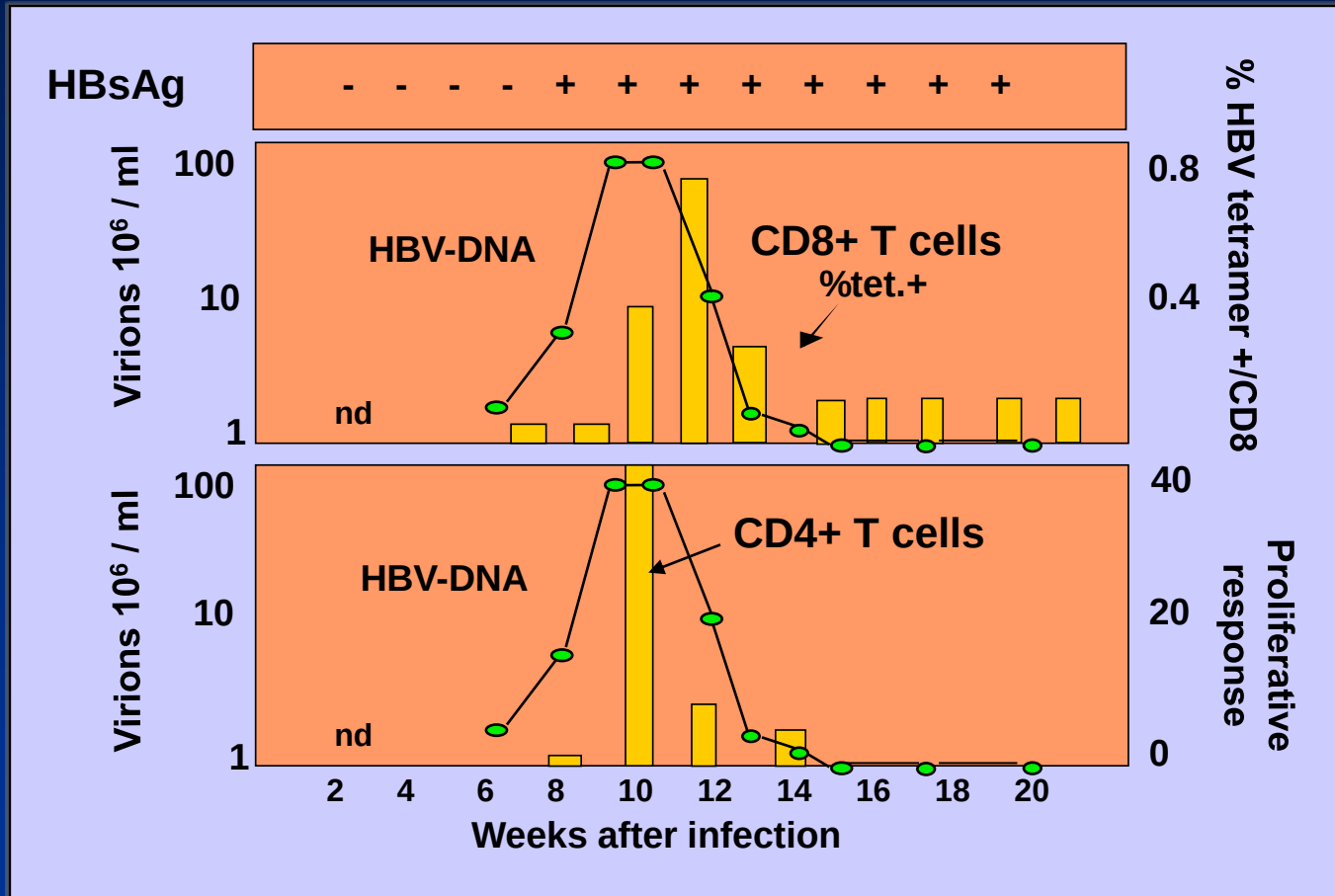


Longitudinal analysis from *the time of exposure*



Urbani S. et al. J.Exp.Med. 2005

HBV-specific T cell responses are timely induced during acute infection



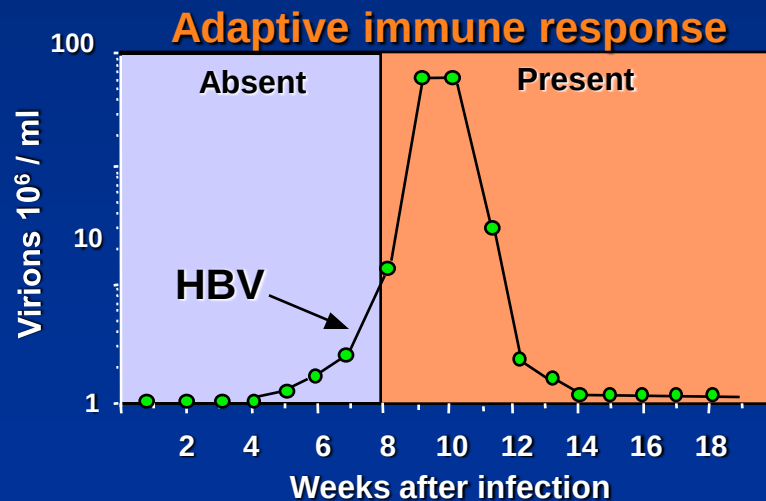
Adapted from Webster GR, et al, *Hepatology* 2000;32:1117-1124. Unpublished data/ speaker's personal communication.

Different kinetics of viral replication but similar kinetics of T cell induction in HCV and HBV infections

HBV



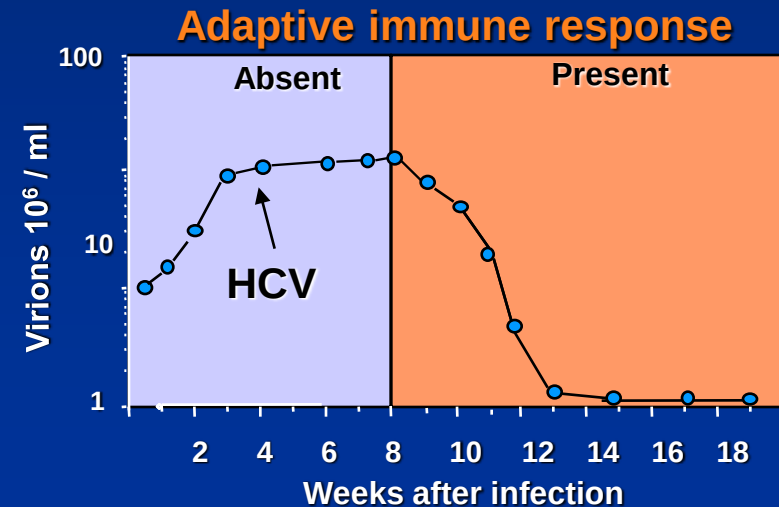
Limited quantity of HBV antigens present in the early phases of infection



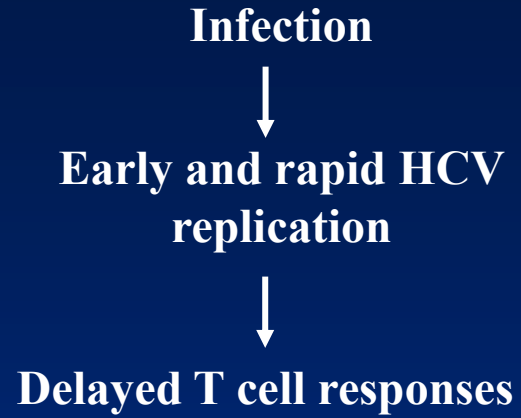
HCV



Adaptive immunity ignores for at least 7-8 weeks substantial quantities of antigen



EVOLUTION OF HCV INFECTION

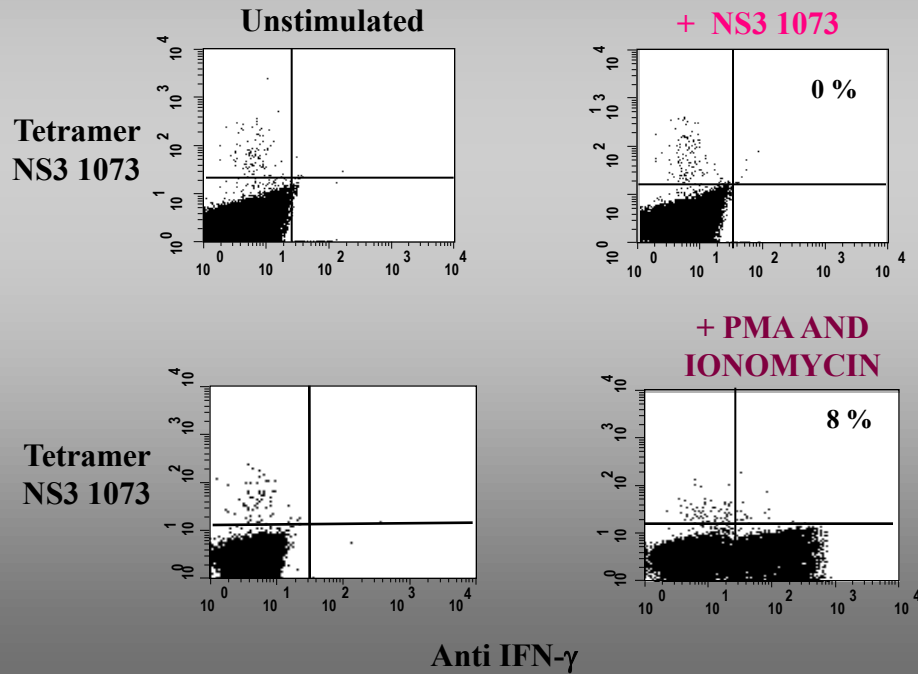
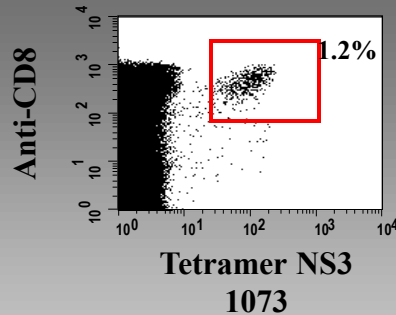


IMPAIRED IFN- γ PRODUCTION BY HCV-SPECIFIC CD8 CELLS

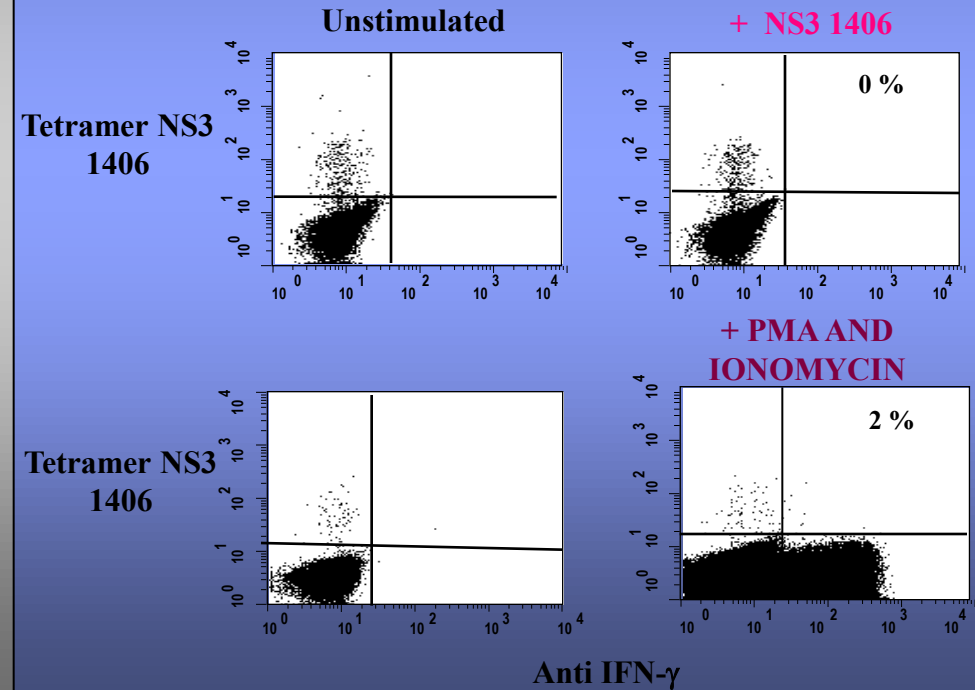
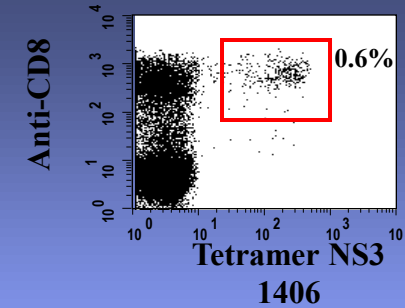
ACUTE STAGE OF HCV INFECTION

Ex-vivo Intracellular Cytokine Staining

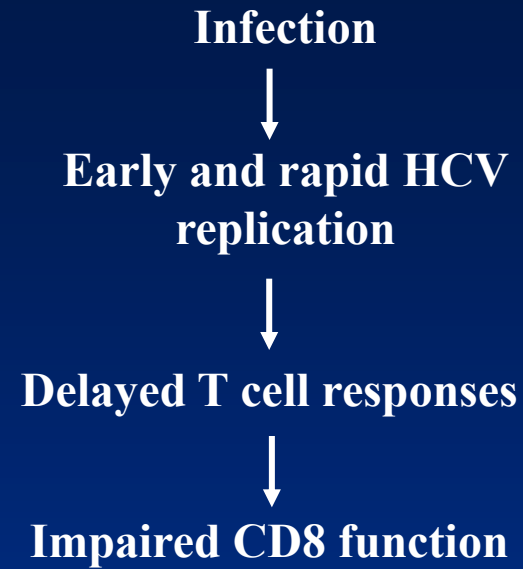
Self-limited evolution



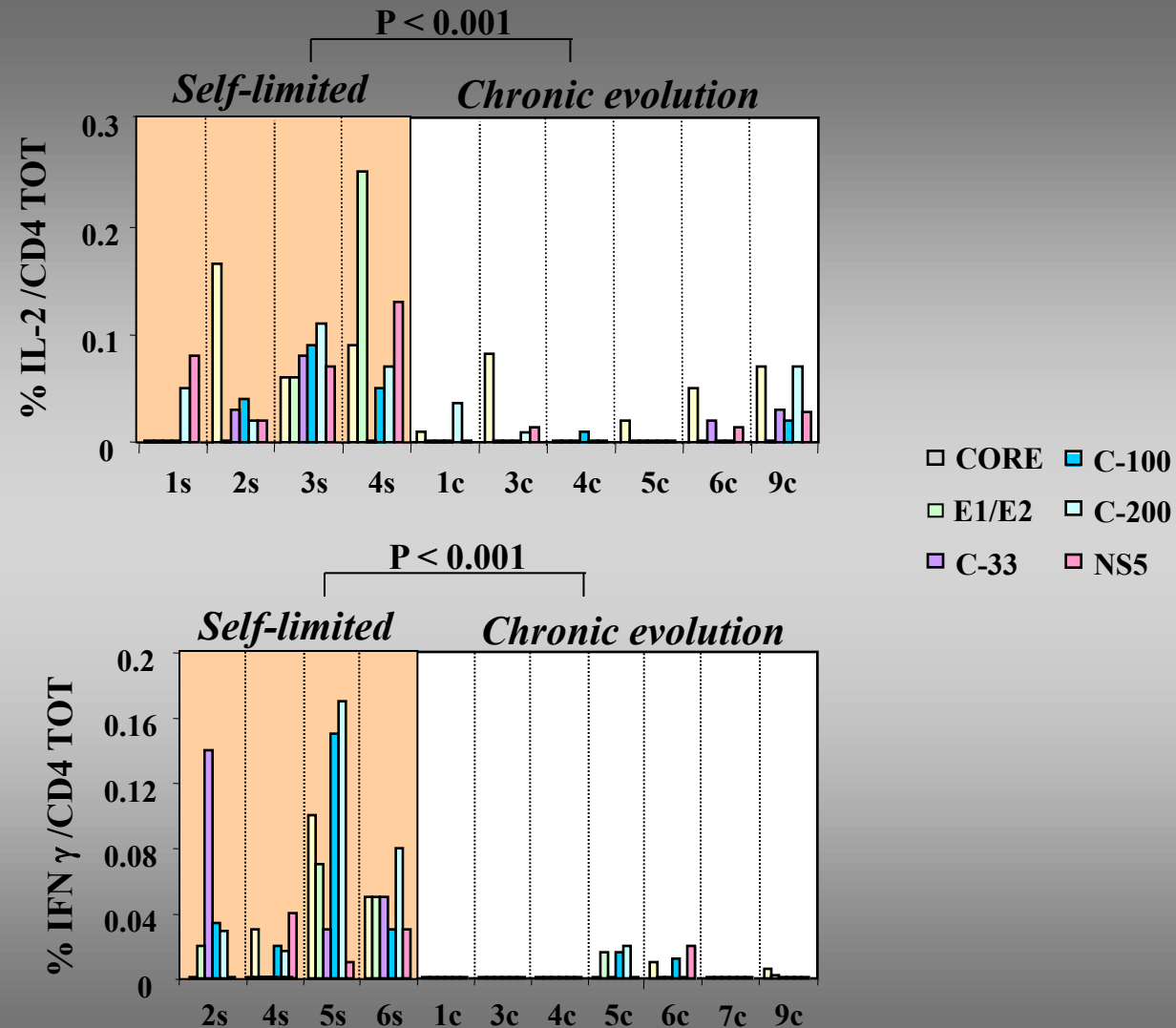
Chronic evolution



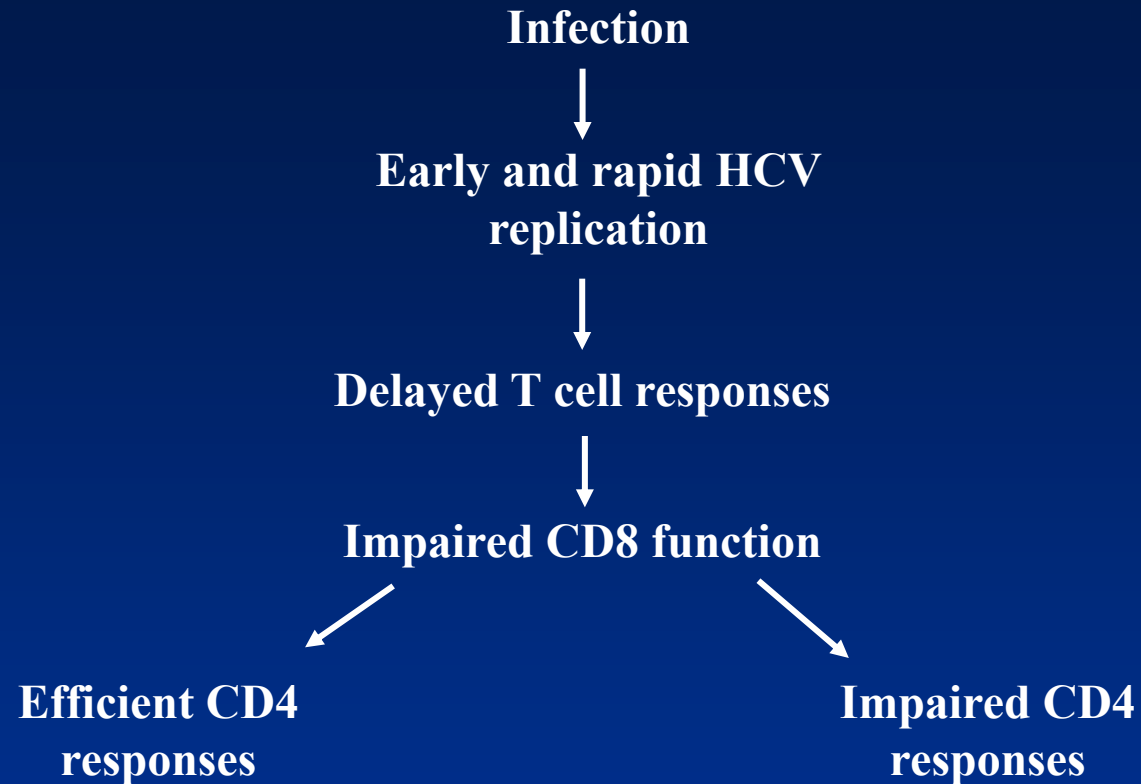
EVOLUTION OF HCV INFECTION



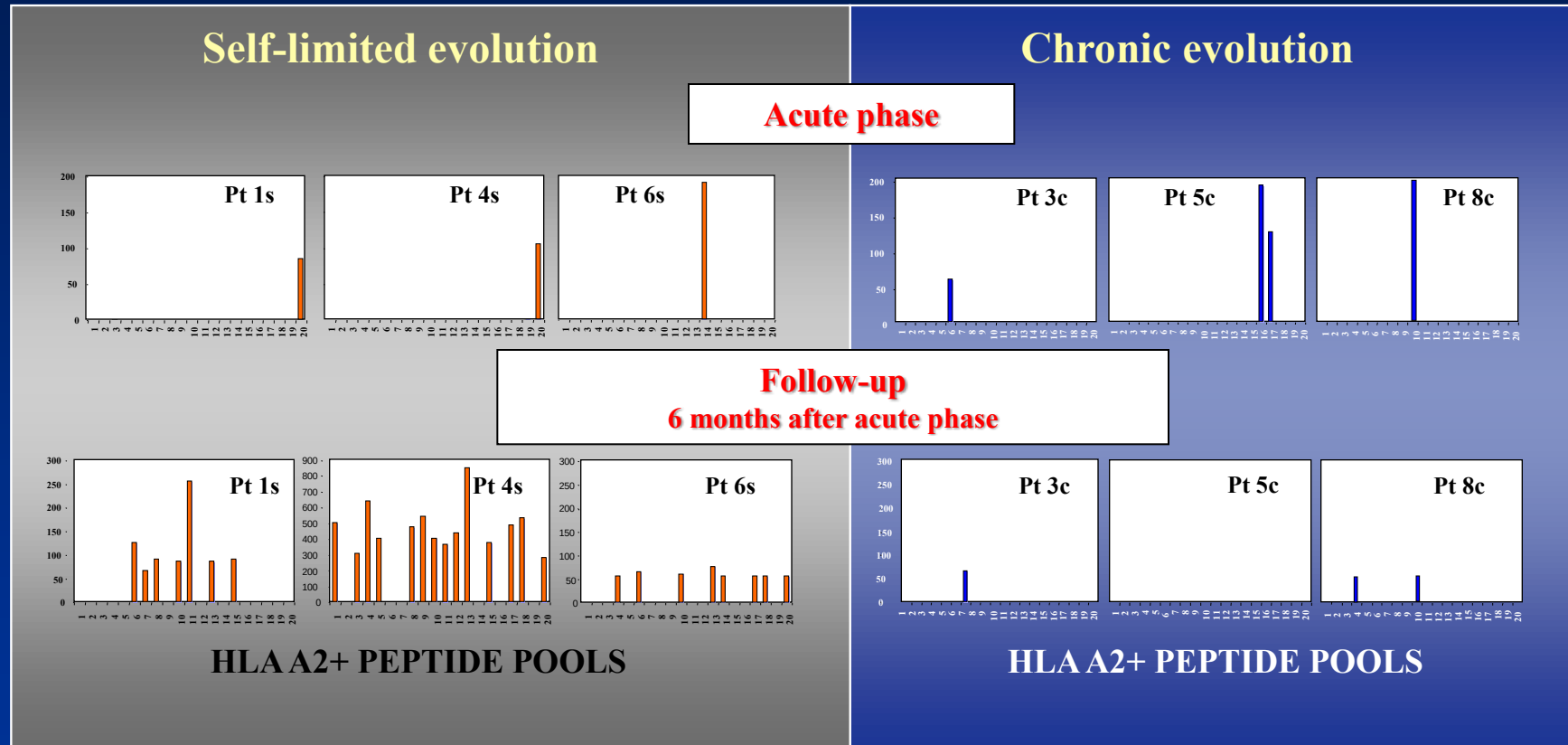
Cytokine profile of HCV-specific CD4 responses



EVOLUTION OF HCV INFECTION

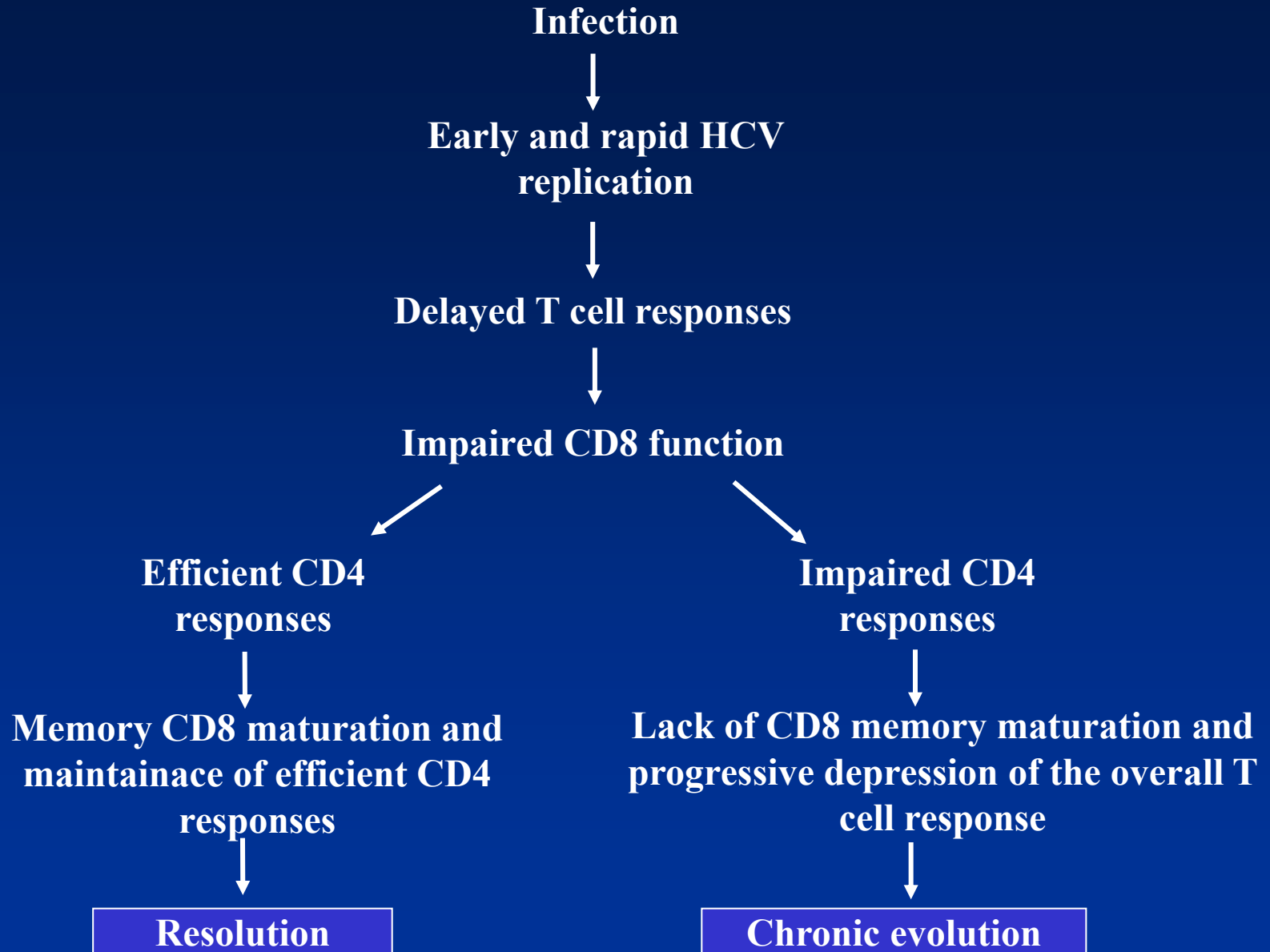


HCV-specific CD8 responses associated with virus control or virus persistence



Urbani S. et al. Hepatology 2006

EVOLUTION OF HCV INFECTION



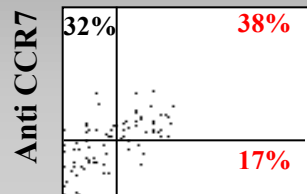
PHENOTYPE OF HCV-SPECIFIC CD8 CELLS

Urbani S. et al. Hepatology 2006

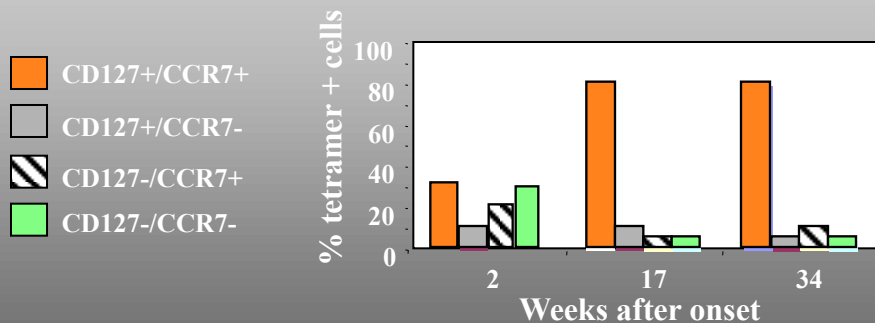
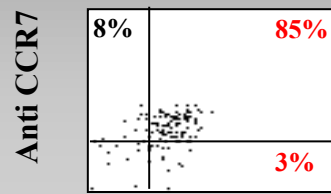
Self-limited infection

HCV 1073 tetramer-specific
CD8 cells

Acute phase



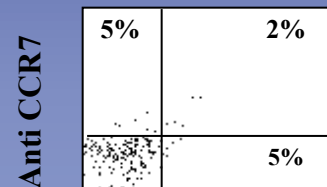
Follow up



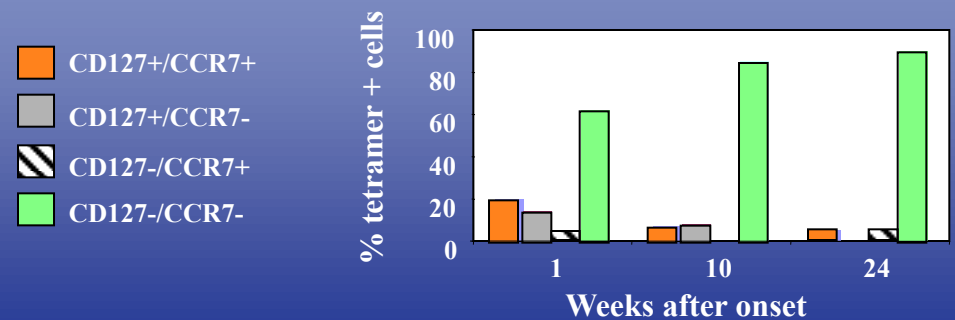
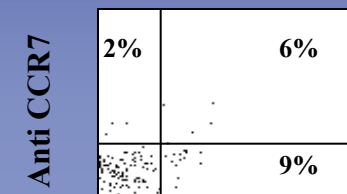
Chronically evolving infection

HCV 1073 tetramer-specific
CD8 cells

Acute phase



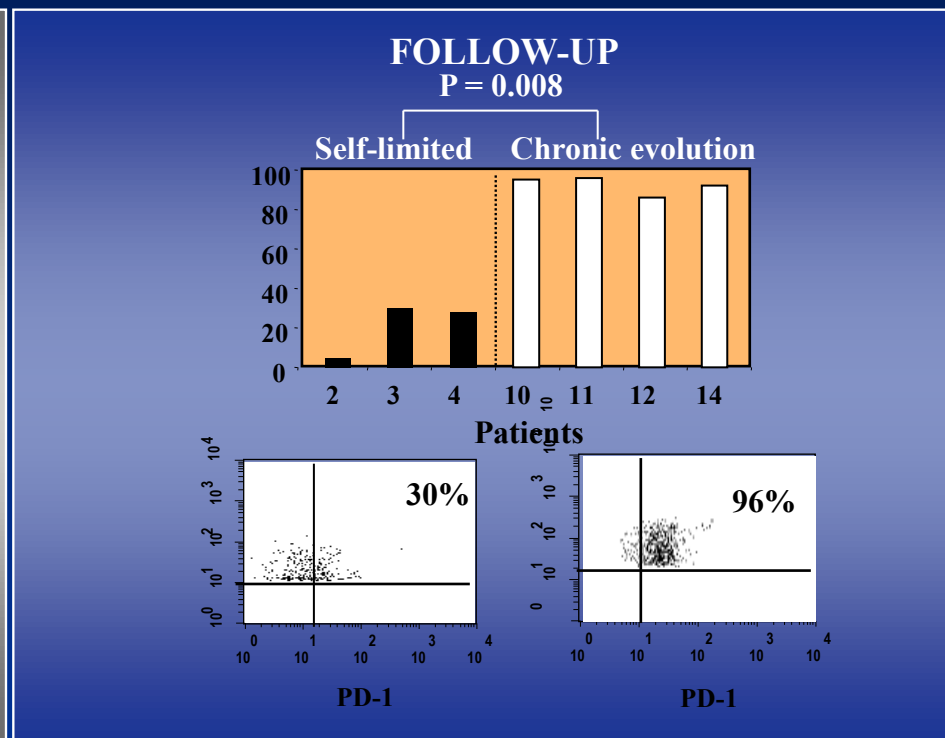
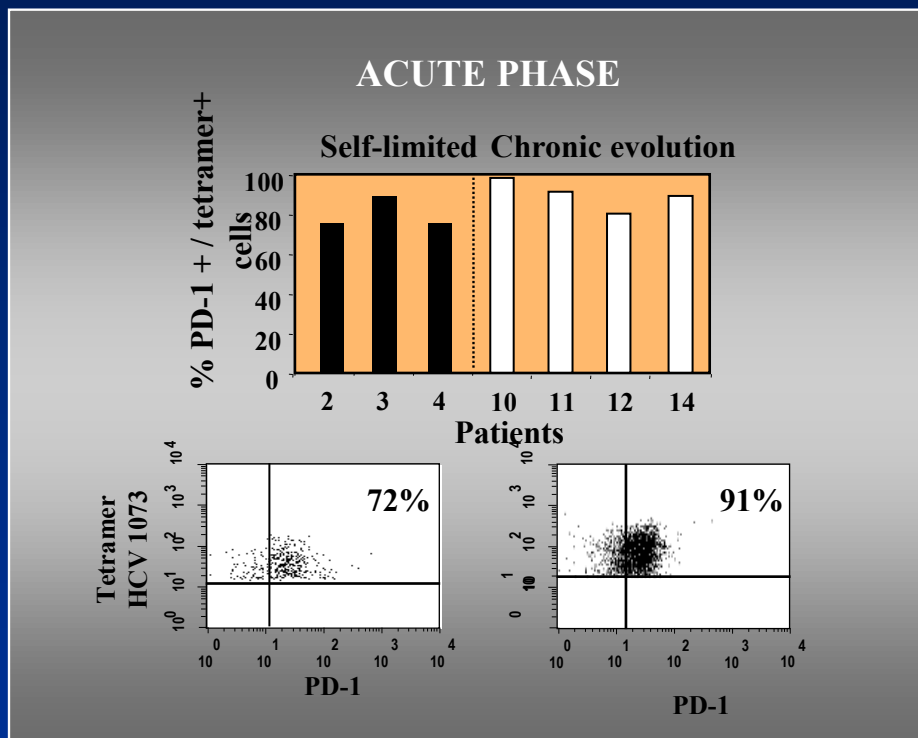
Follow up



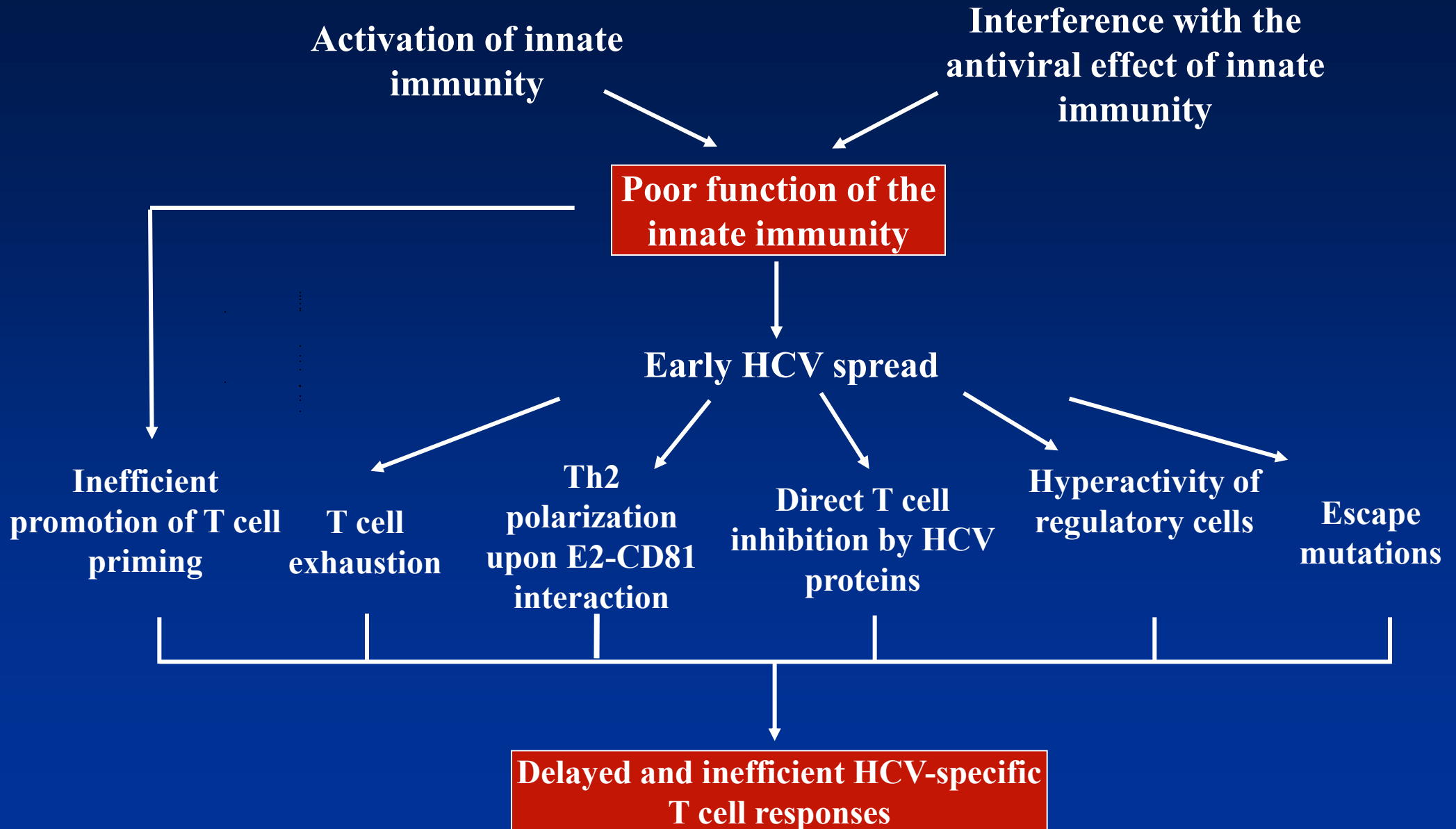
Urbani S. et al. J. Virol. 2006; Hepatology 2006

PD-1 expression on HCV-specific peripheral blood CD8 cells

Urbani S. et al. J. Virol. 2006



HCV INFECTION



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

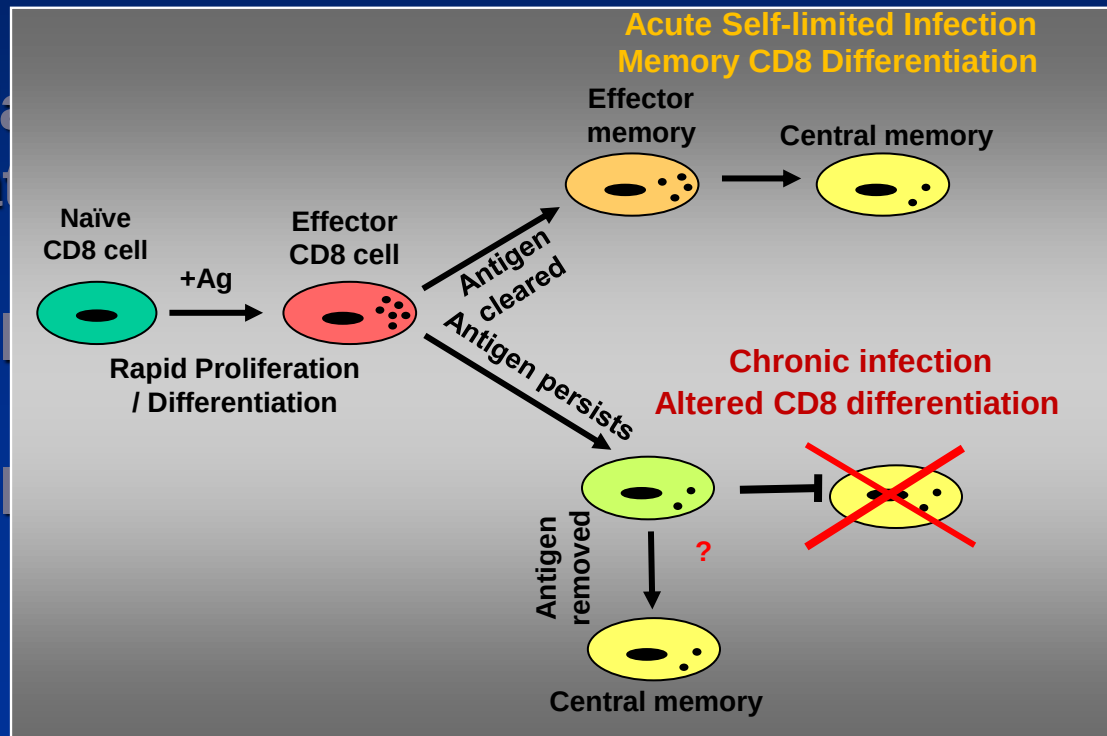
Potential strategies to restore the T cell function

- Decline of antigen load
- Modulation of the suppressive effect of CD4+FoxP3+ regulatory T cells
- Modulation of regulatory cytokines (IL-10, TGF- β)
- Modulation of T cell costimulatory pathways

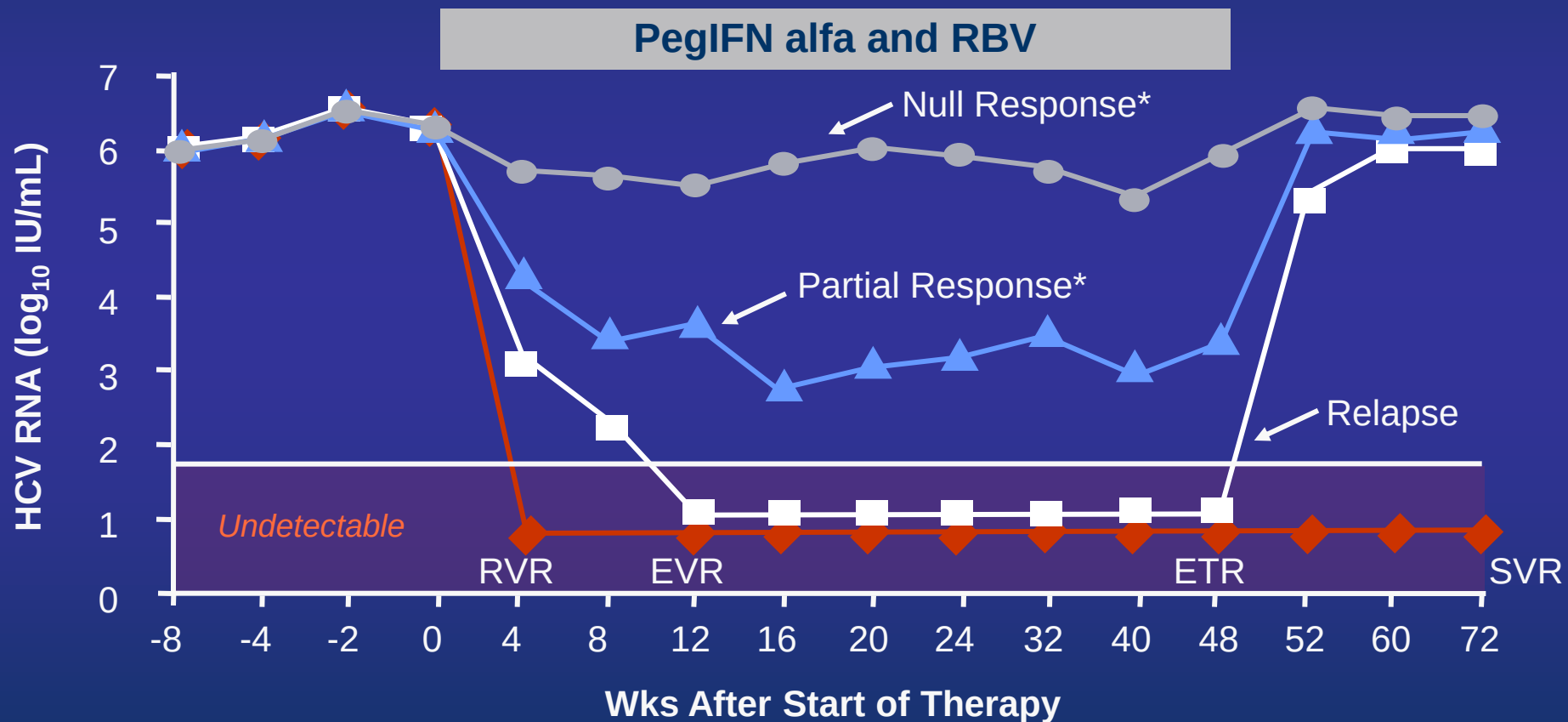
Are the HCV-specific T cell defects of chronic HCV infection reversible?

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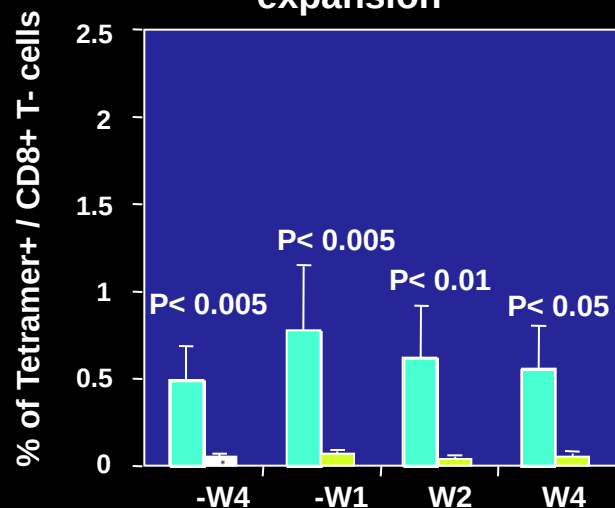
Patterns of Virologic Response to PegIFN alfa and Ribavirin Therapy



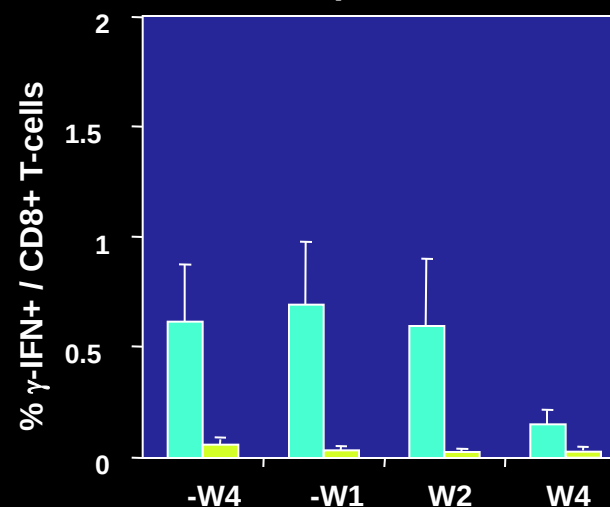
*Subset of Nonresponse

LACK OF IMPROVEMENT OF HCV-SPECIFIC CD8 RESPONSES IN THE FIRST 4 WEEKS OF THERAPY

Tetramer pos CD8 cells after in-vitro expansion



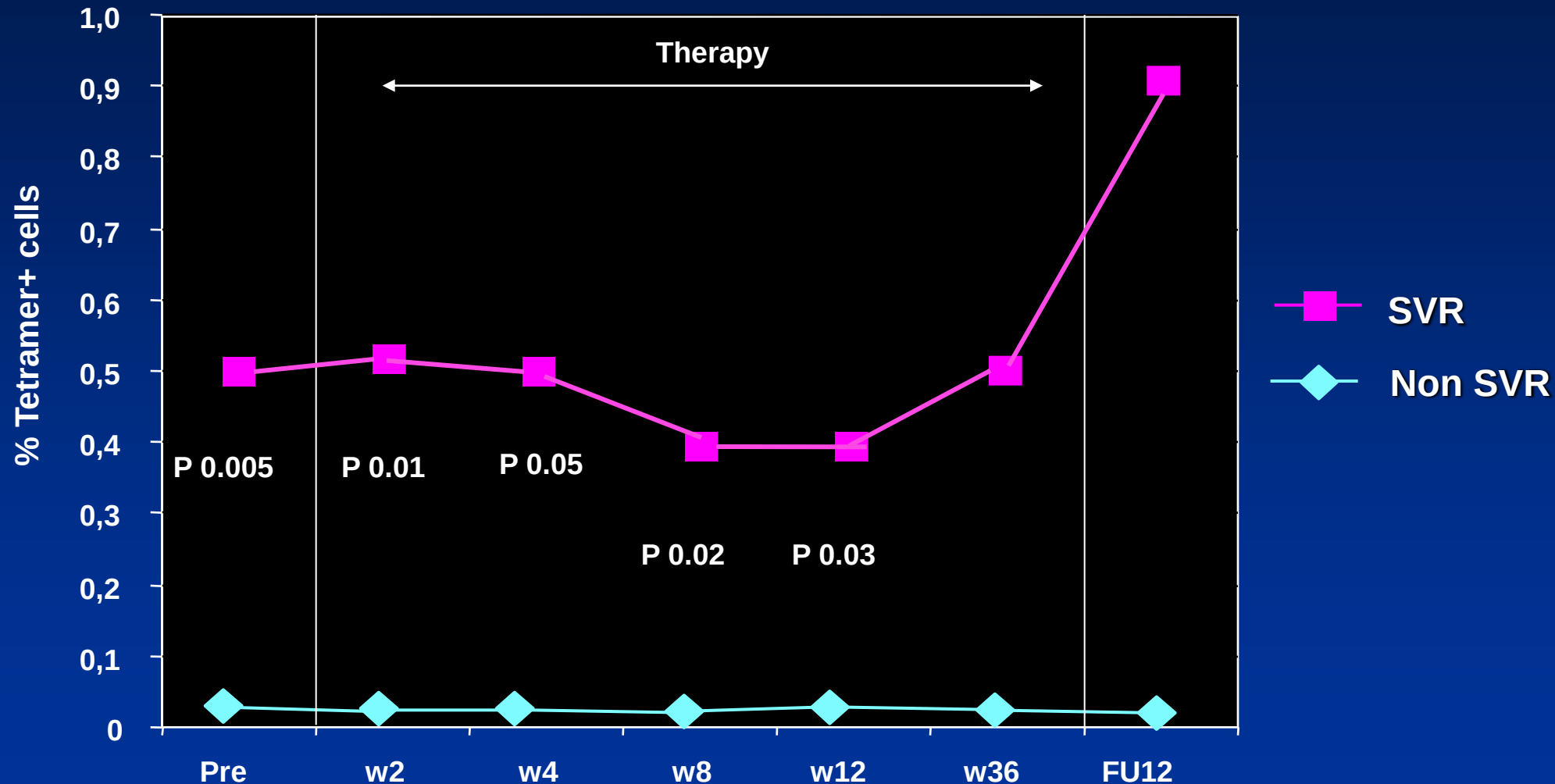
IFN- γ pos CD8 cells after in-vitro expansion



■ Sustained viral responders
Genotype 1
■ Non sustained viral responders
Genotype 1

Pilli M. et al. Gastroenterology 2007

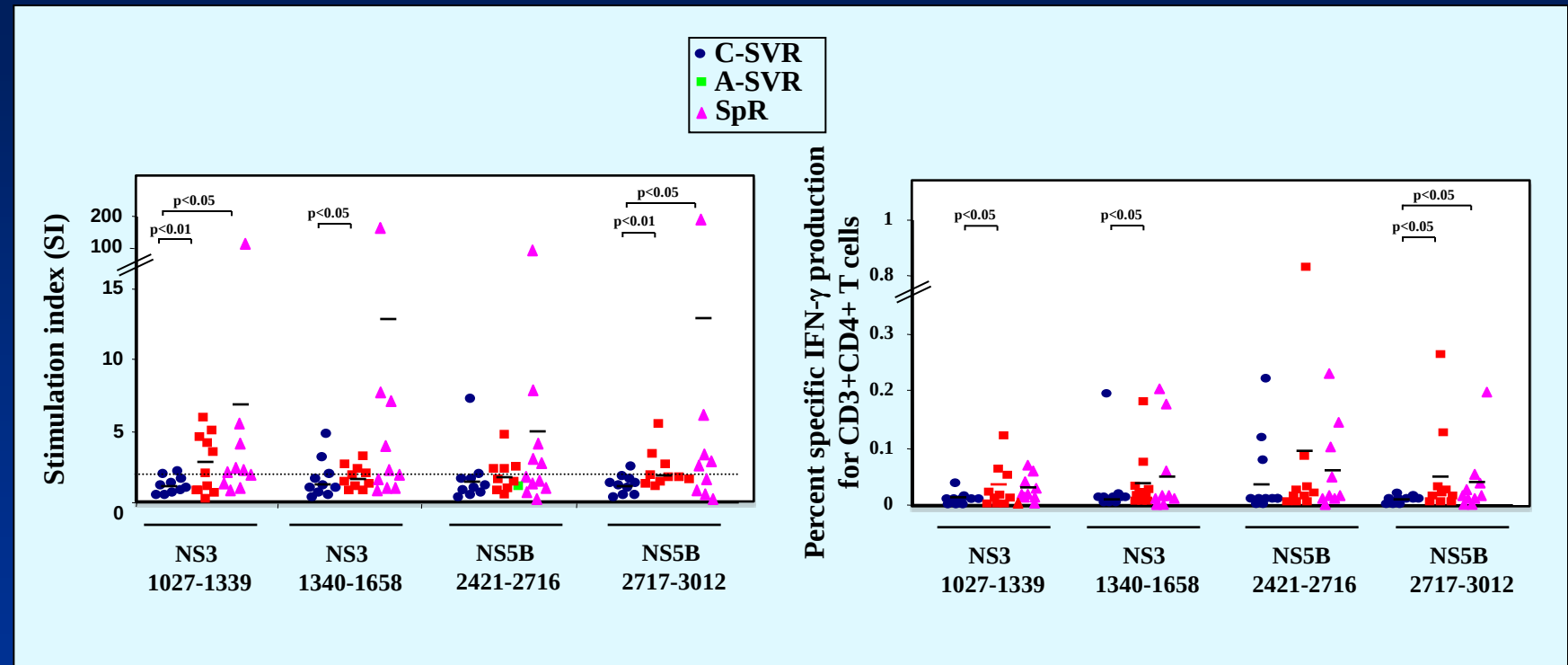
THE CAPACITY OF CD8 EXPANSION BEFORE TREATMENT CAN PREDICT THE RESPONSE TO THERAPY?



Pilli M. et al. Gastroenterology 2007

INEFFICIENT RESTORATION OF HCV-SPECIFIC CD4 AND CD8 FUNCTION AFTER ANTI-VIRAL THERAPY

(Abdel-Hakeem MS et al J.Virol. 2010;84:10429-10435)



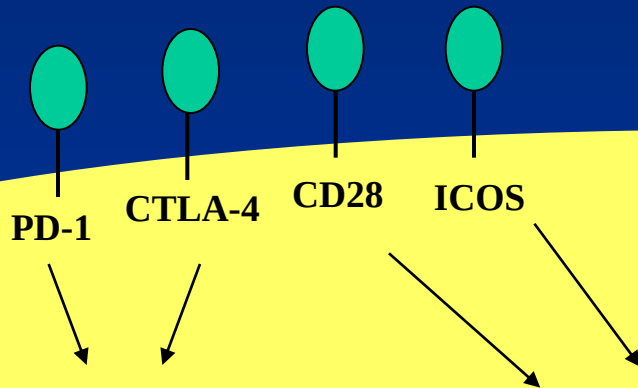
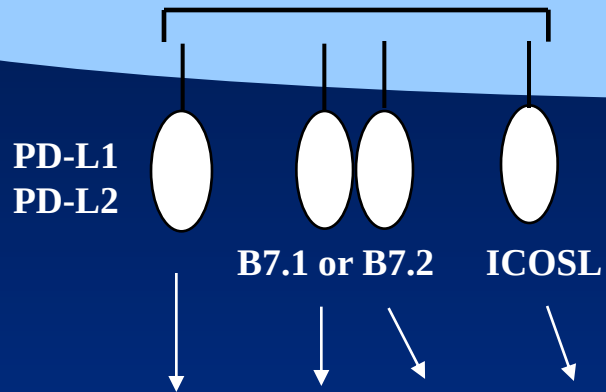
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APC

B7 FAMILY

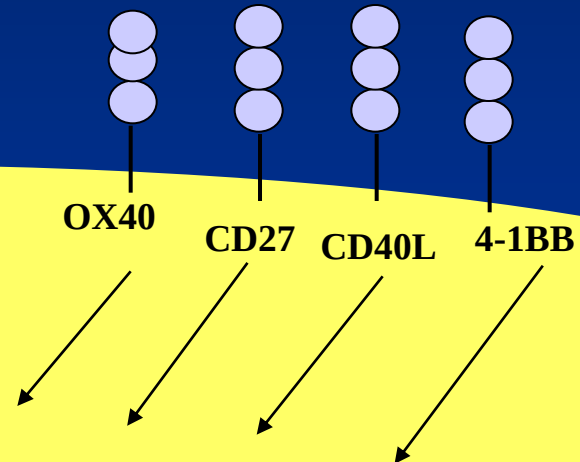
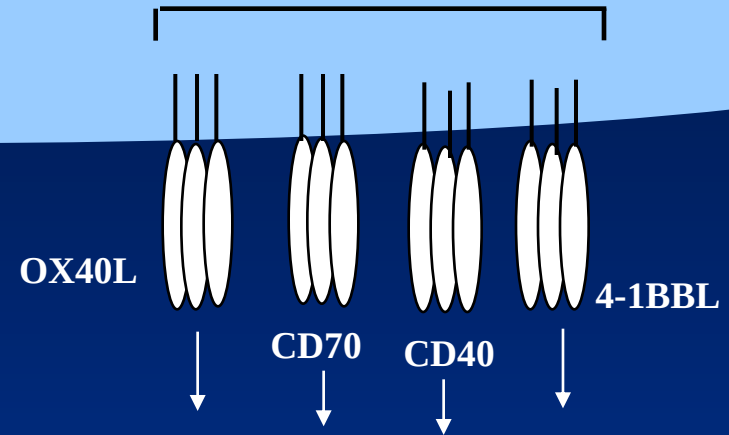


INHIBITION

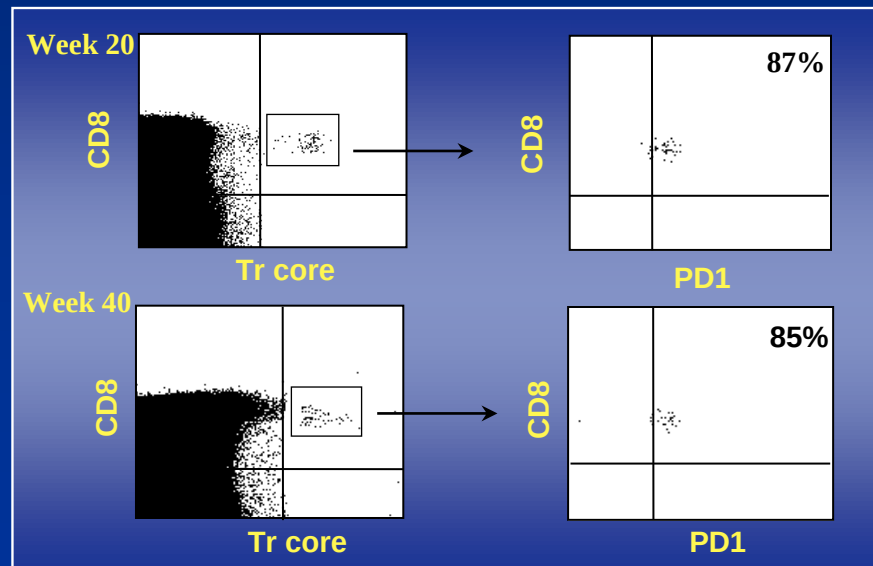
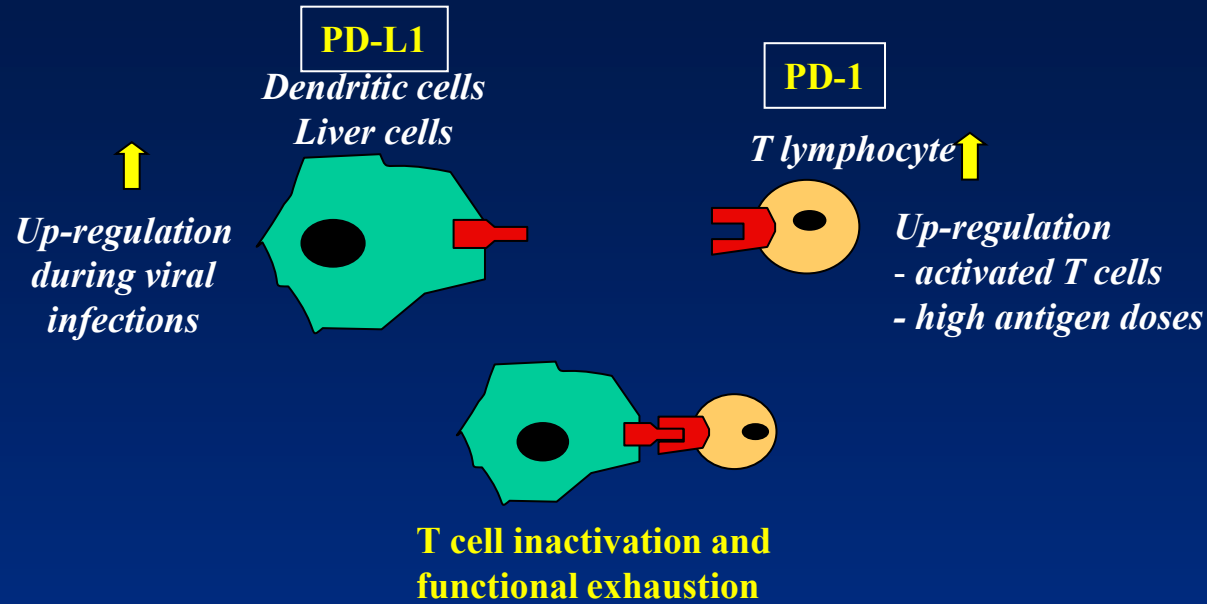
COSTIMULATORY SIGNALS

T CELL

TNF SUPERFAMILY



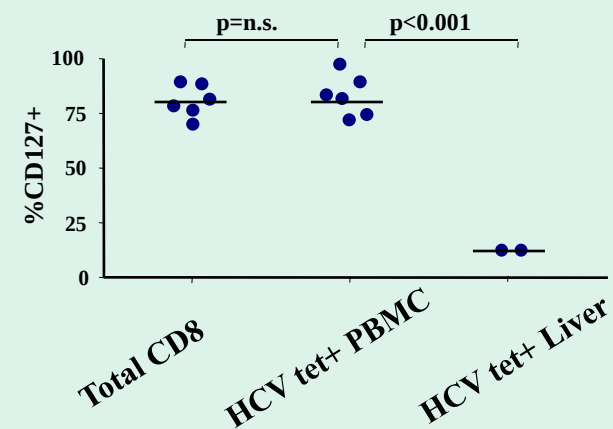
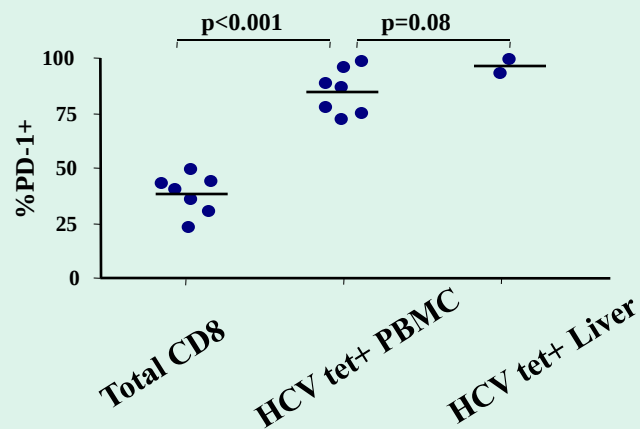
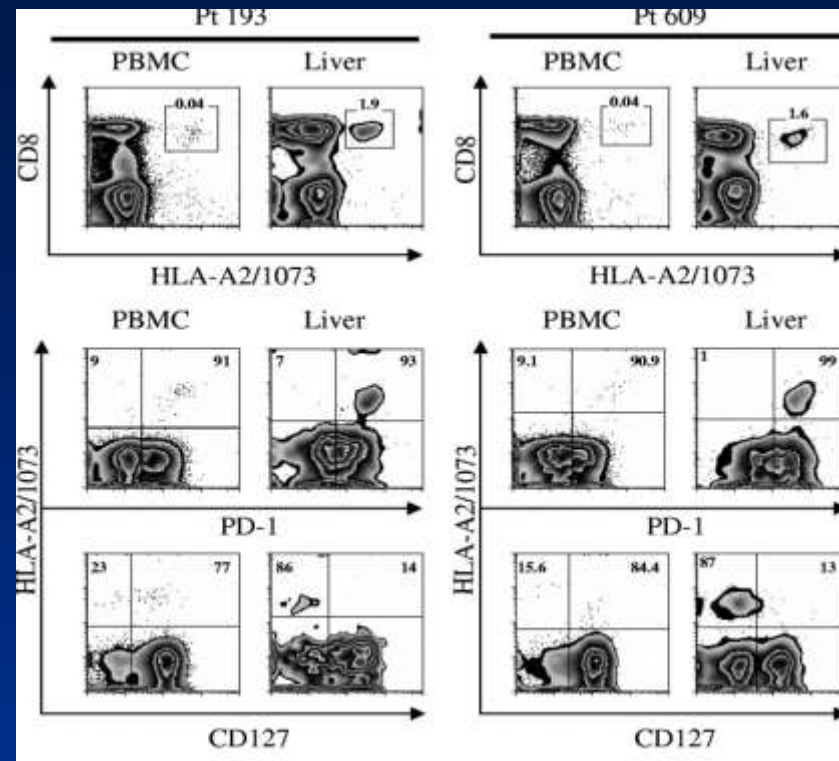
PD-1 EXPRESSION ON HCV-SPECIFIC CD8 CELLS OF PATIENTS WITH CHRONIC HCV INFECTION



Penna A. et al. Hepatology 2007

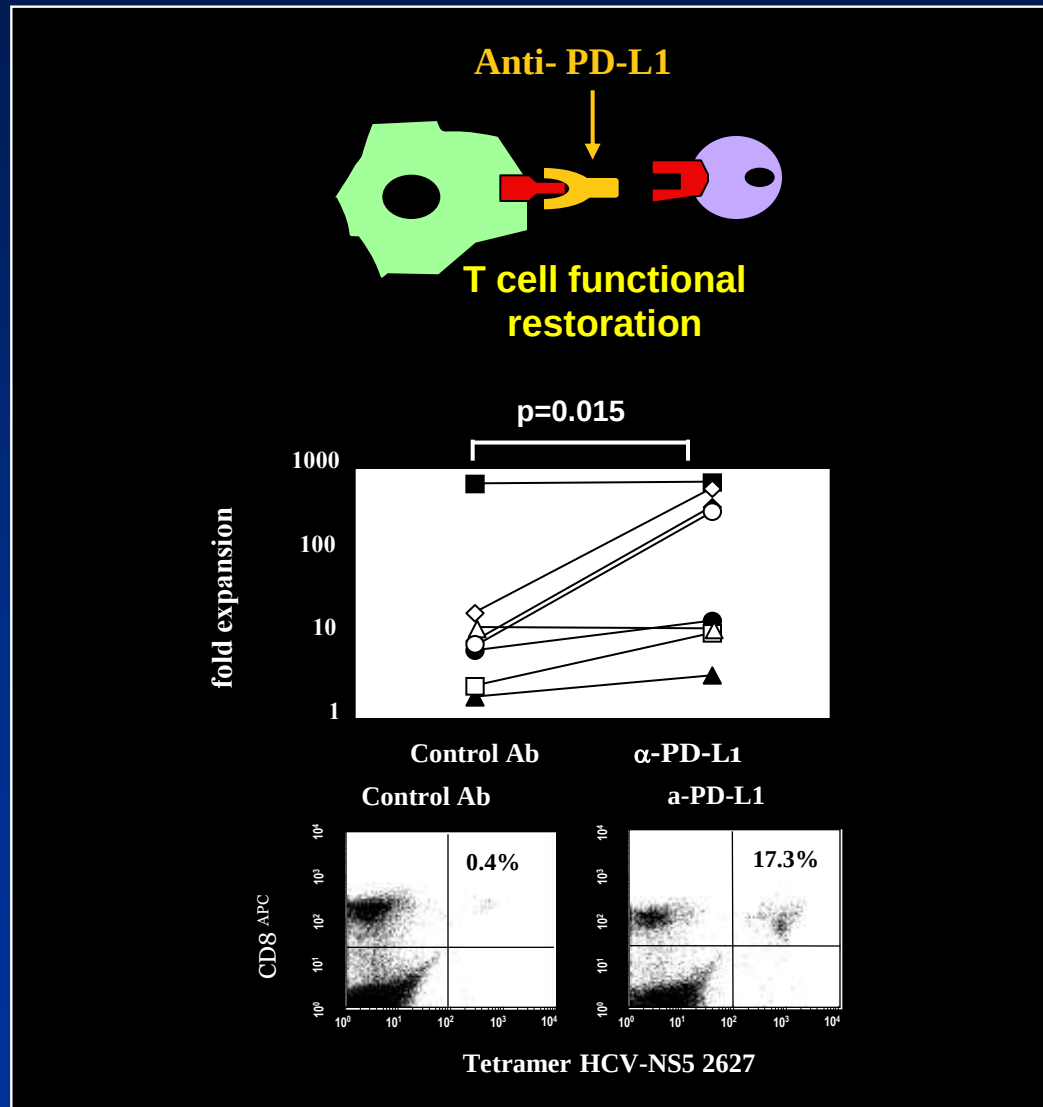
PD-1 AND CD127 EXPRESSION ON PERIPHERAL AND INTRAHEPATIC HCV-SPECIFIC CD8 CELLS OF PATIENTS WITH CHRONIC HCV INFECTION

(Radziewicz H. et al. J Virol 2007)



PD-1/PD-L1 blockade can improve peripheral blood HCV-specific T cell responses in patients with chronic HCV infection

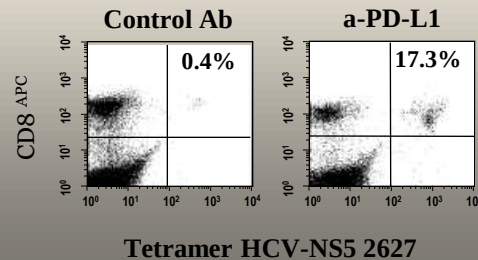
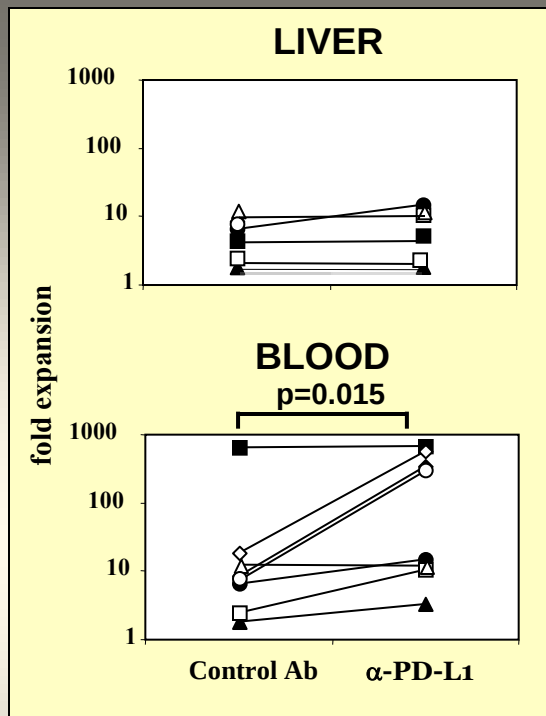
(Penna et al. Hepatology 2007)



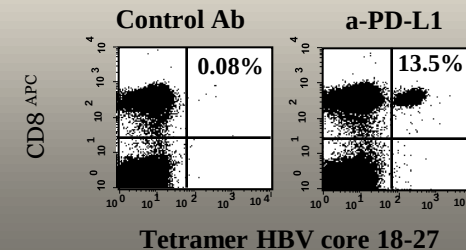
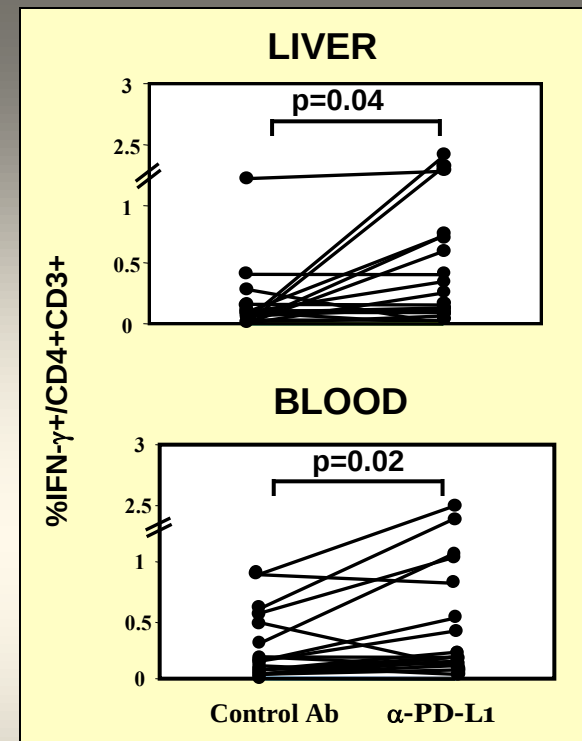
Different effect of PD-1/PD-L1 blockade on intrahepatic HBV- and HCV-specific T cell responses

(Penna A et al. Hepatology 2007; Fisticaro P. et al 2010 Gastroenterology)

HCV

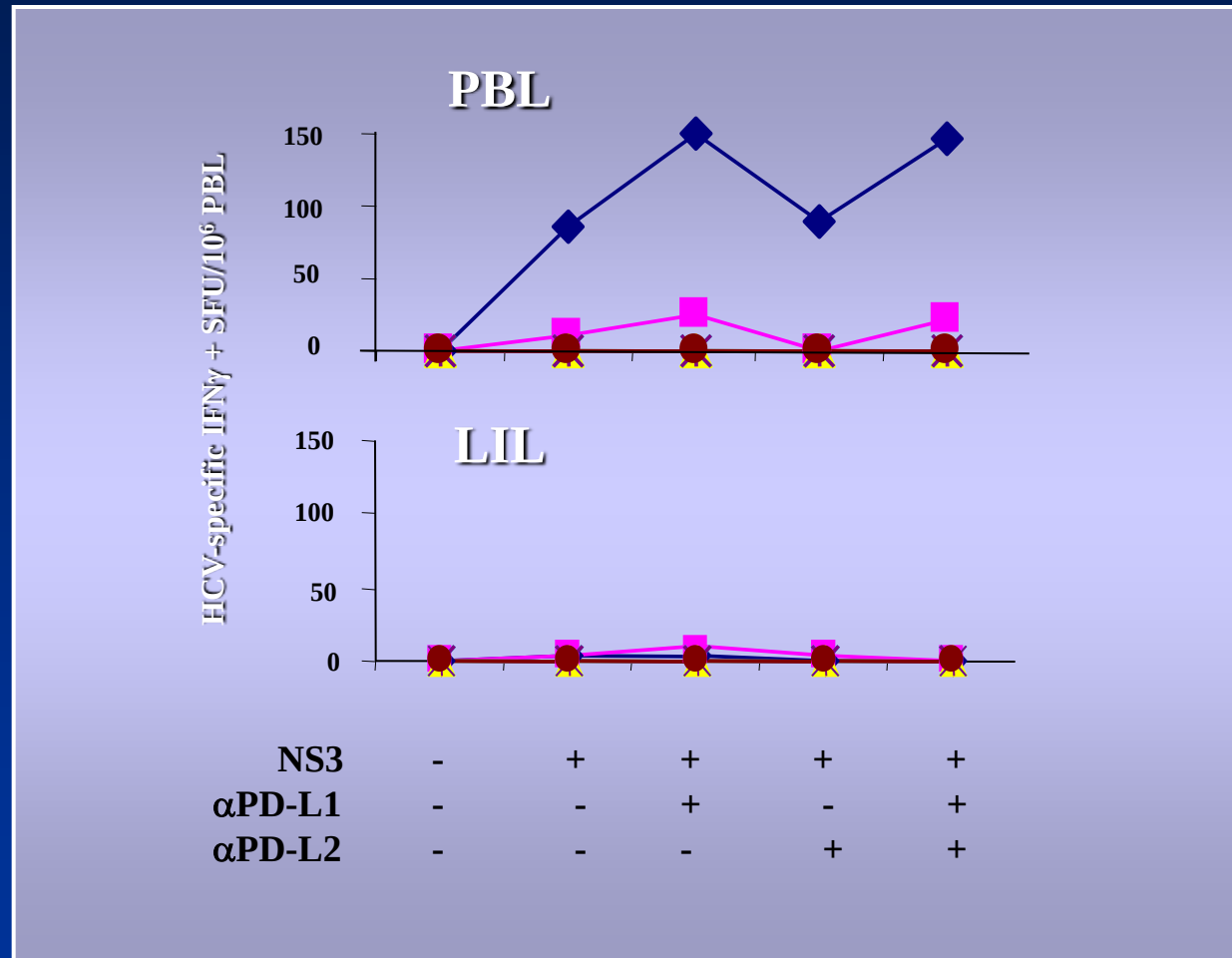


HBV



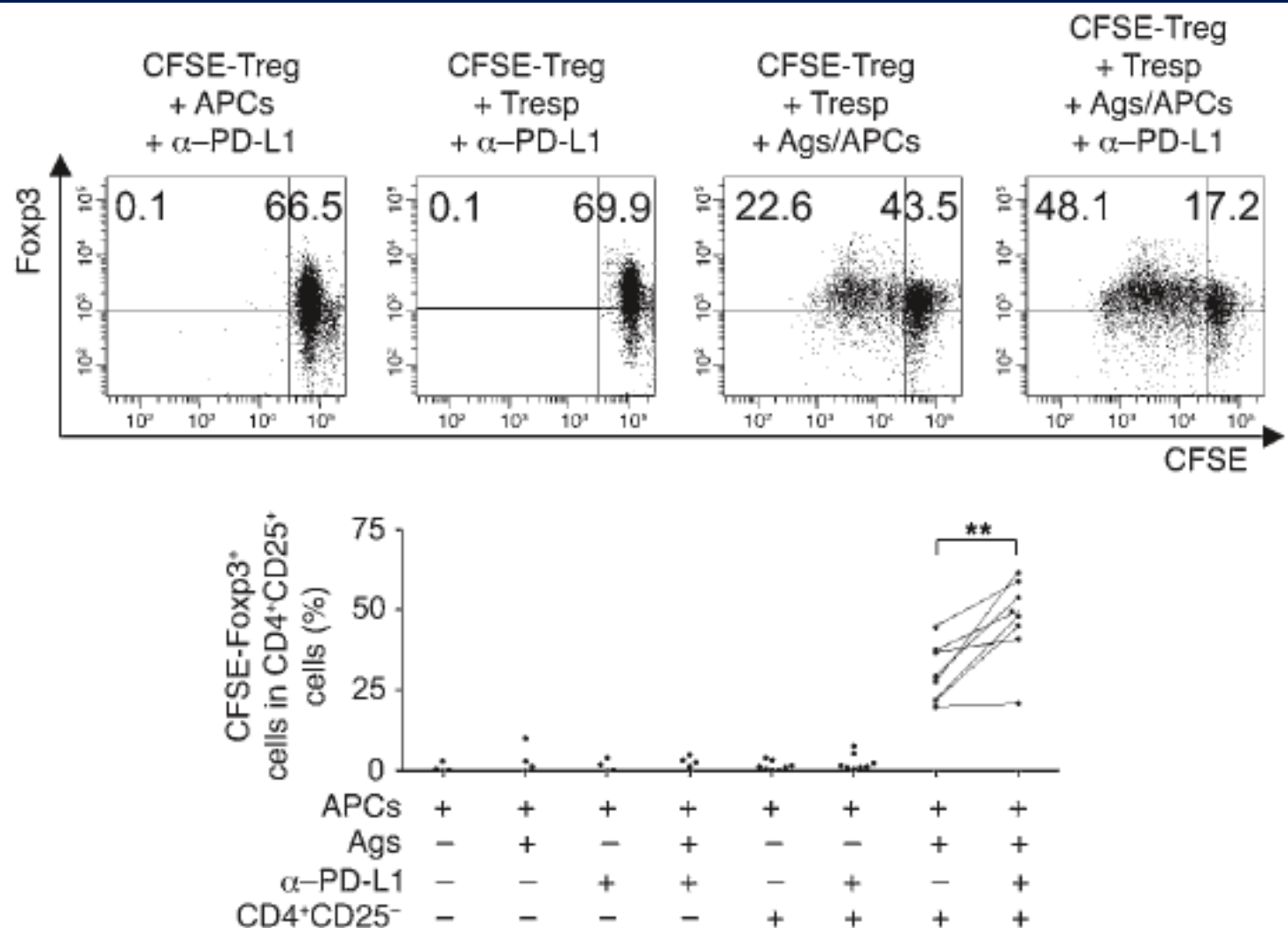
Effect of anti PD-L1 treatment on intrahepatic and circulating HCV-specific T cells in chronic HCV infection

Nakamoto N, et al. Gastroenterology 2008;134(7):1927-37.

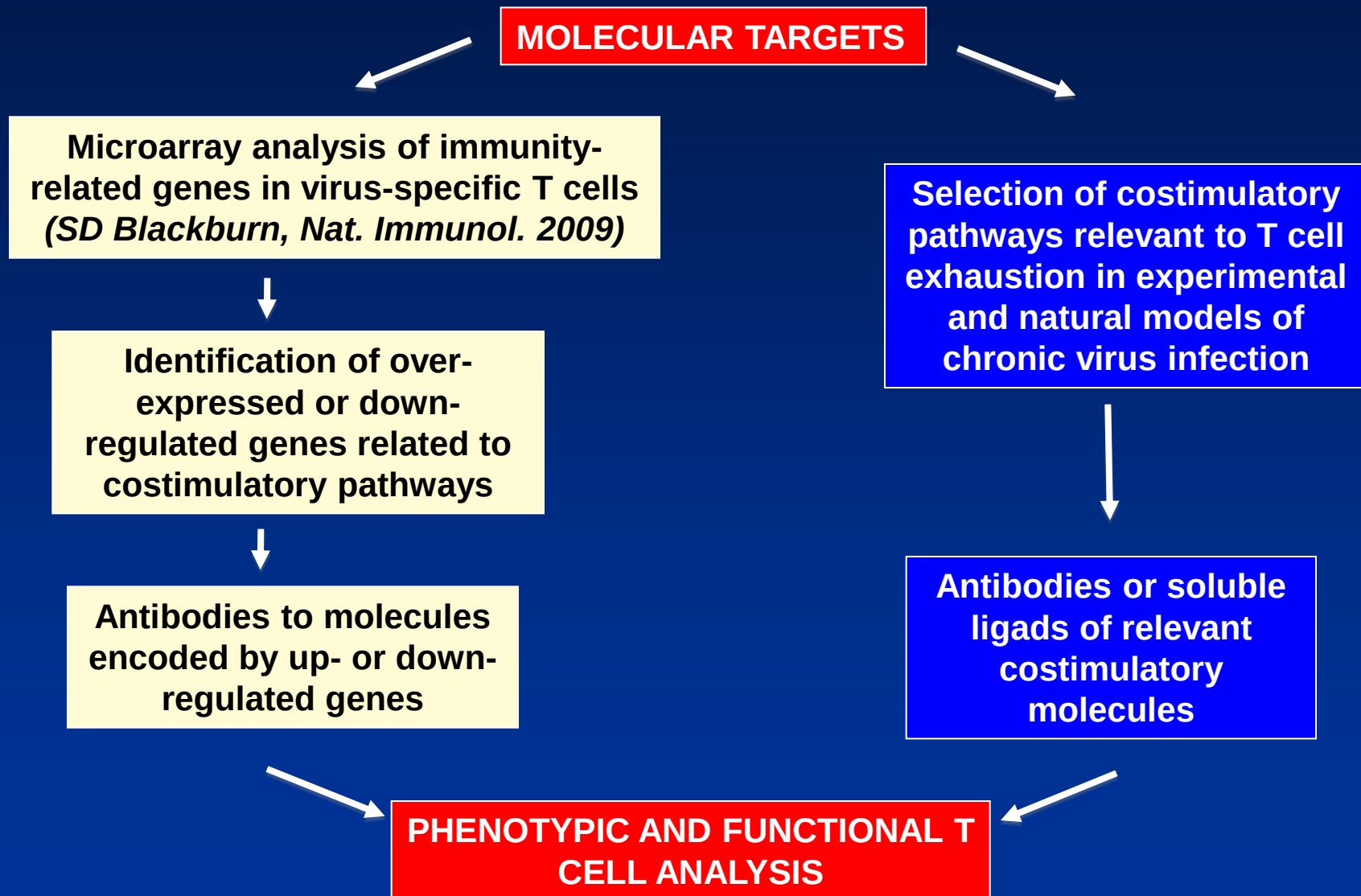


Effect of anti PD-L1 blockade on T reg proliferation

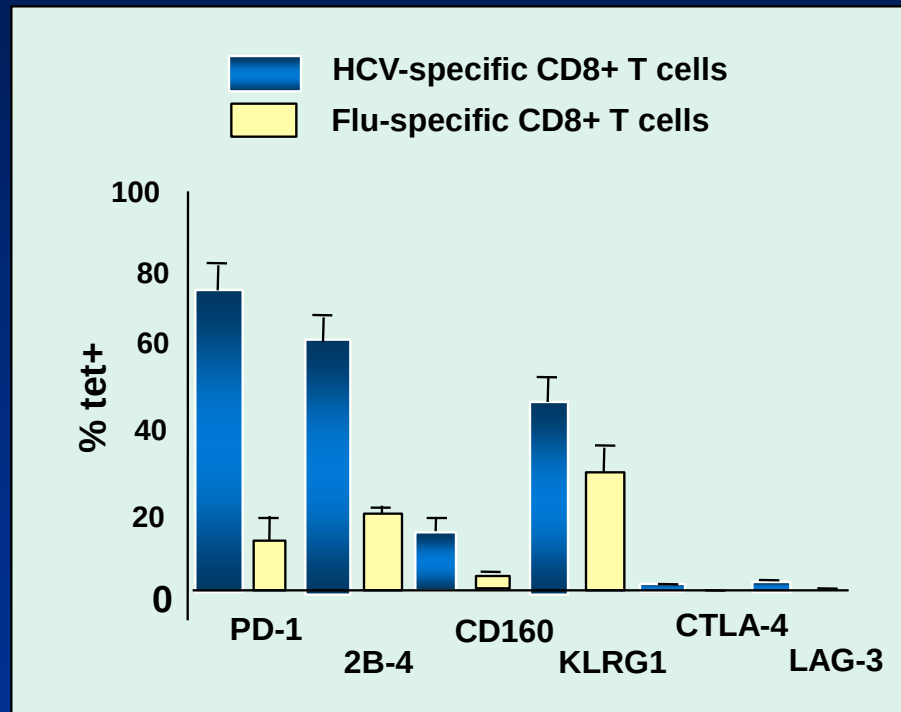
(Franceschini D et al. J.Clin. Invest. 2009)



IDENTIFICATION OF MOLECULAR TARGETS FOR RESTORATION OF EXHAUSTED HCV-SPECIFIC T CELL RESPONSES



EXPRESSION OF VARIOUS INHIBITORY RECEPTORS ON CIRCULATING HCV-SPECIFIC CD8 CELLS OF PATIENTS WITH CHRONIC HCV INFECTION

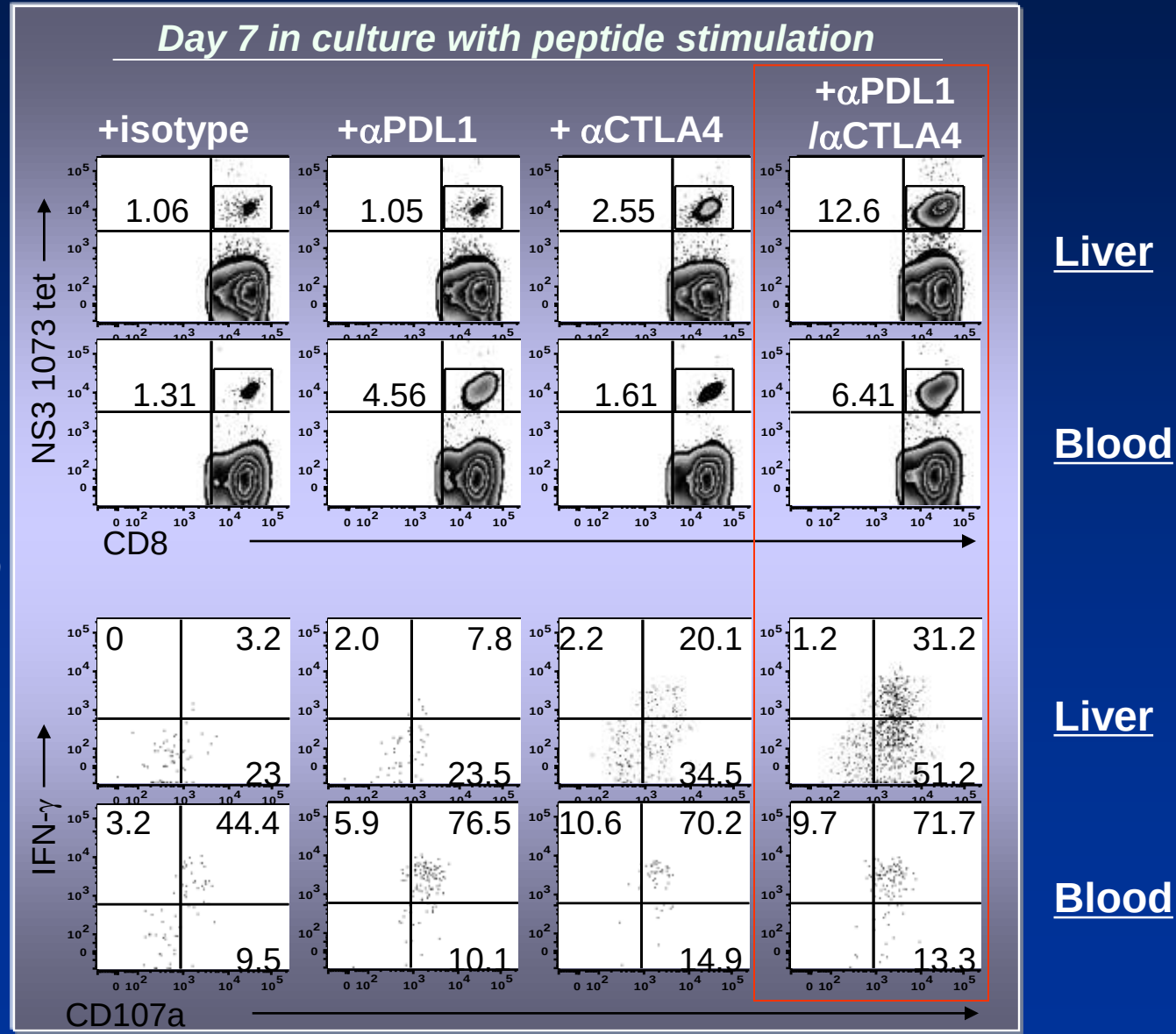


(Bensch B. et al. PLoS Pathogens 2010)

Synergistic enhancement of intrahepatic HCV-specific CD8 T cell expansion and effector function in vitro by combined PD-1/CTLA-4 blockade

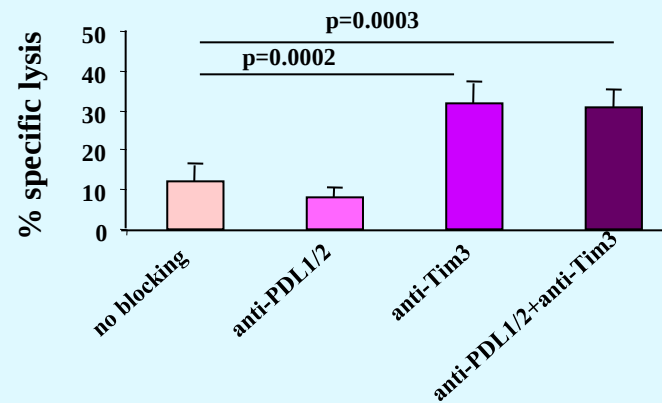
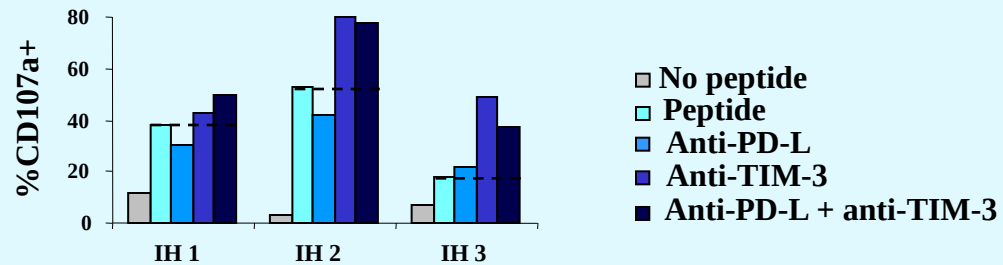
Chronic HCV Patient

*Nakamoto N et al. 2009
PLoS Pathogens*

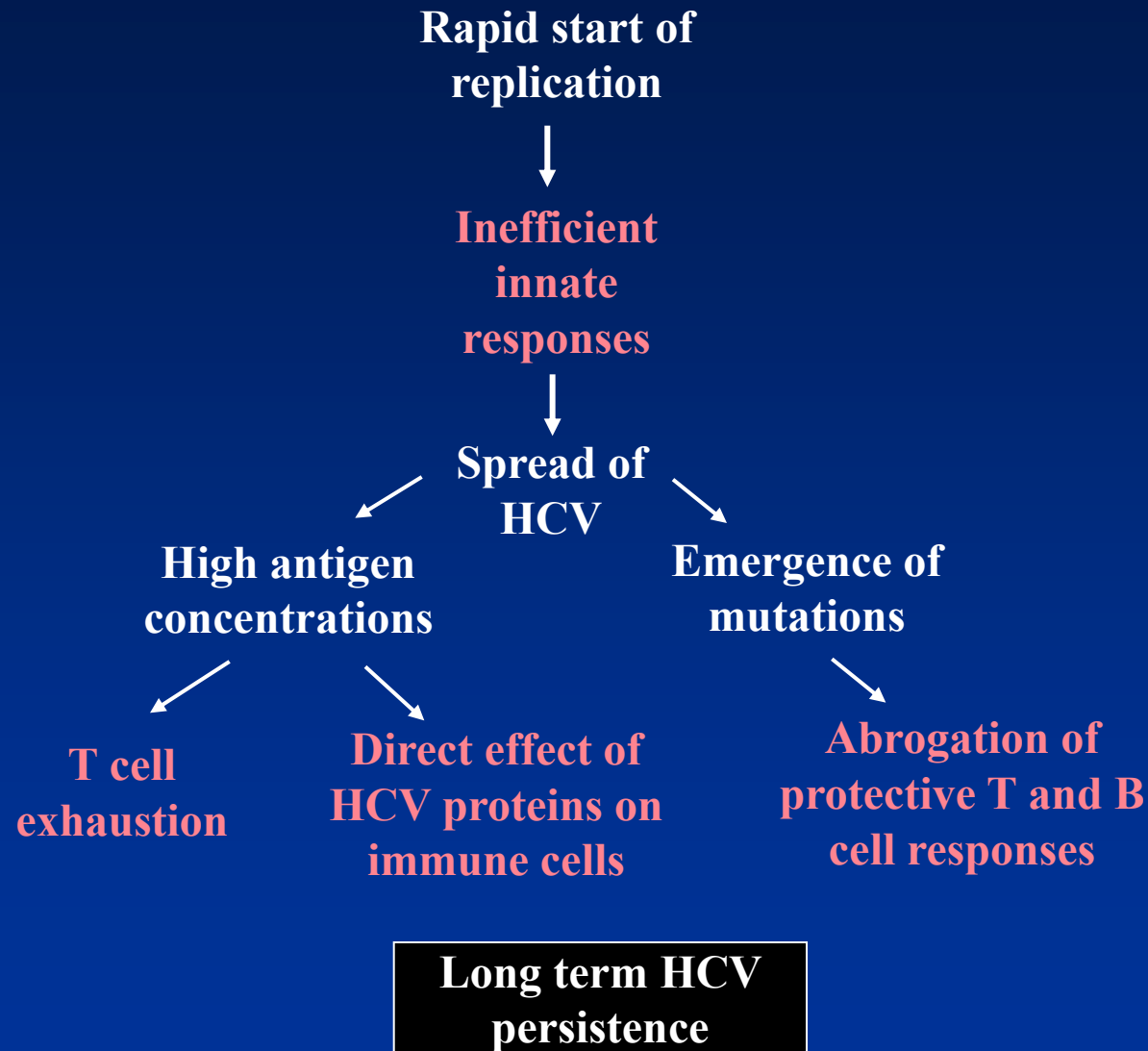


RESTORATION OF HCV-SPECIFIC CD8 T CELL CYTOTOXICITY BY TIM-3 BLOCKADE

(McMahan R et al. J.Clin.Invest. 2010)



VIRUS/HOST INTERPLAY: THE PROTECTIVE IMMUNE RESPONSE IS OUTPACED BY HCV





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R. Bertoni, L. Sacchelli, A. Orlandini,
A. G. Missale**