

Immunopathogenesis of Liver Injury in HIV

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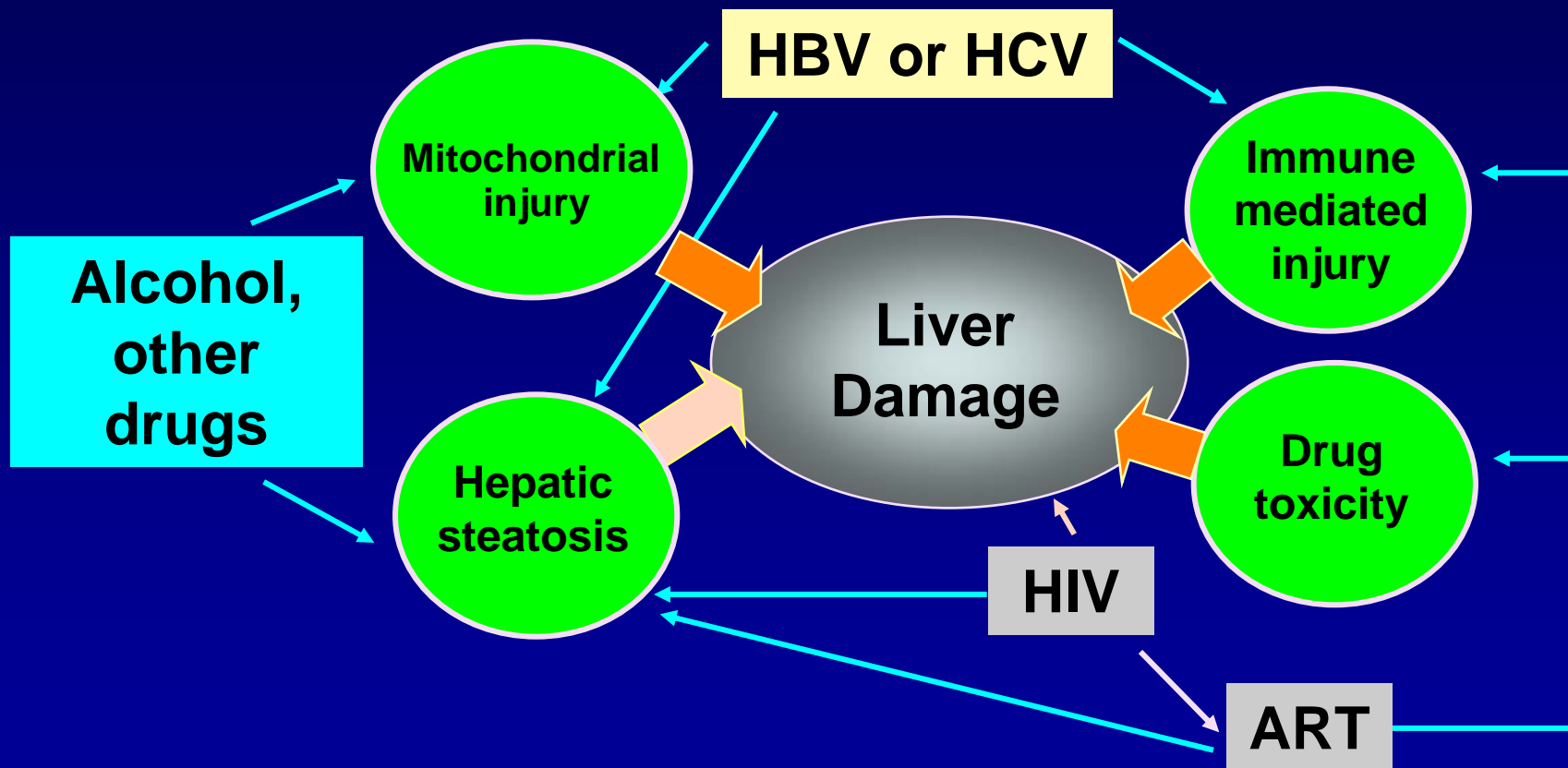
Beth Israel Deaconess Medical Center

and

Novartis Institutes of Biomedical Research

Boston, MA

Liver Damage in Co-infection is Multifactorial



CD4 and CD8 Responses in Acute HCV

- CD4 responses
 - Are essential to recovery
 - Must be directed against multiple epitopes
 - Must be maintained to maintain protection
- CD8 responses
 - Correlate with recovery
 - Must be directed against multiple epitopes
- CD4 responses are critical to overall response
 - CD8 without CD4 promotes immune escape

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Missale G, et al. *JCI*. 1996;98:706-14.

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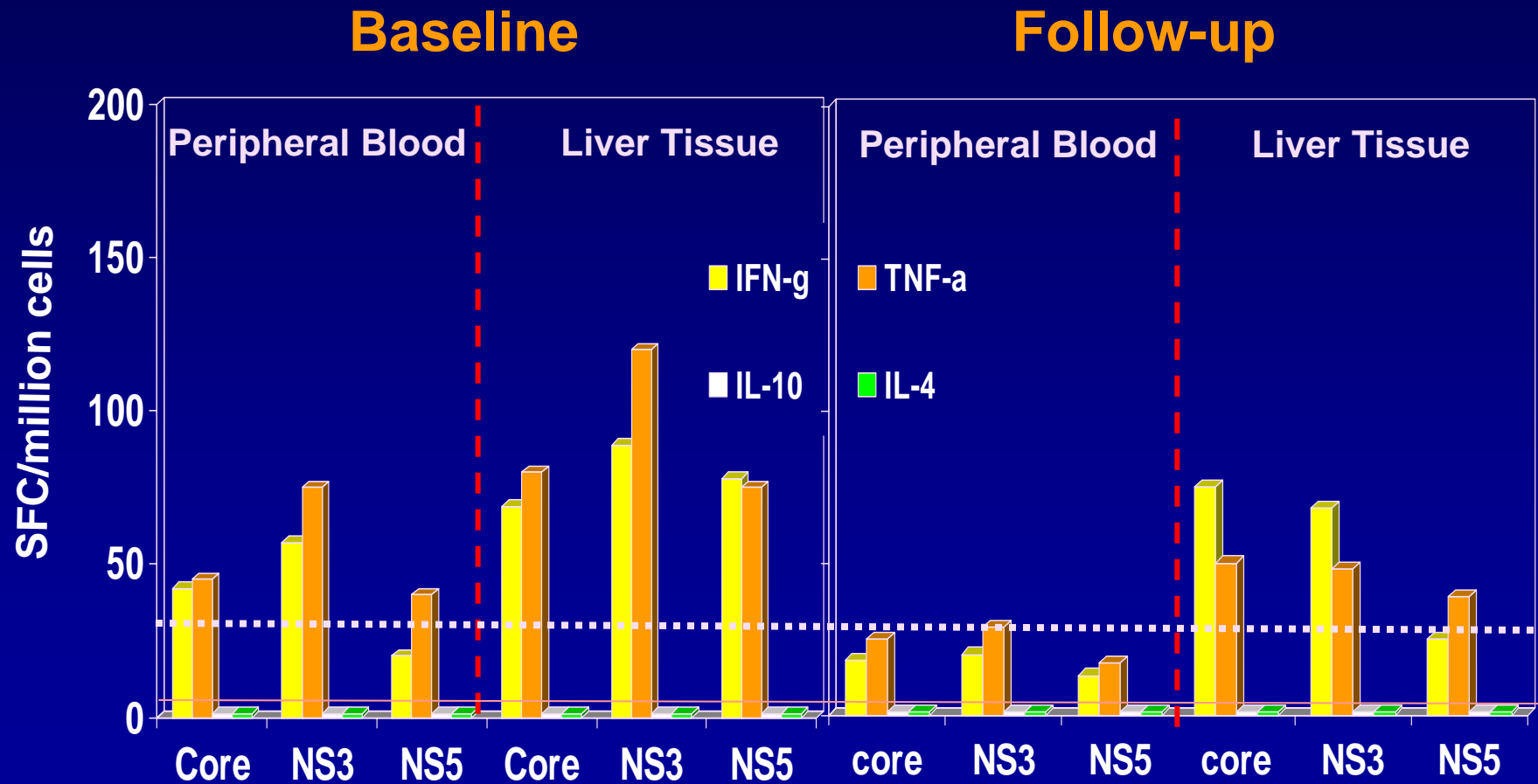
Grakoui G, et al. *Science*. 2003;302:659-60.

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Why Do Immune Responses Fail in HCV?

- Immune escape
 - High error rate of RNA polymerase: sequence diversity greater than HIV-1
 - Demonstrated for Ab, CD4 and CD8
- HCV interference with endogenous IFN response
- Dysfunction of innate immunity (NK, dendritic cells)
- Functional “stunning”: failure to produce IFN γ
- Exhaustion (e.g. PD-1)

HCV Specificity is Lost in the Periphery but Maintained in the Liver During Chronic HCV



The Immune Response is Not Absent in Chronic HCV: It Hides

- Early in chronic infection, CD4+ responses wane in the PBMC but are maintained in the liver
- Multiple CD4+ ,CD8+ T and NKT cells can be found in most with chronic disease in the liver, even in HIV
 - Example: 10 fold higher frequency using tetramer
- The phenotypes differ between PBMC and liver
 - Unique maturation markers (eg CD161)
 - Absence of canonical NKT marker ($V\alpha 24$)
- However, no differences in epitope specificity seen

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Koziel MJ, et al. *J Clin Invest.* 1995;96:2311-21.

Alatrakchi N, et al. *J Infect Dis.* 2005;191:702-9.

Graham CS, et al. *Hepatology.* 2004;40:125-32.

Kamal SM, et al. *J Infect Dis.* 2004;189:1140-50.

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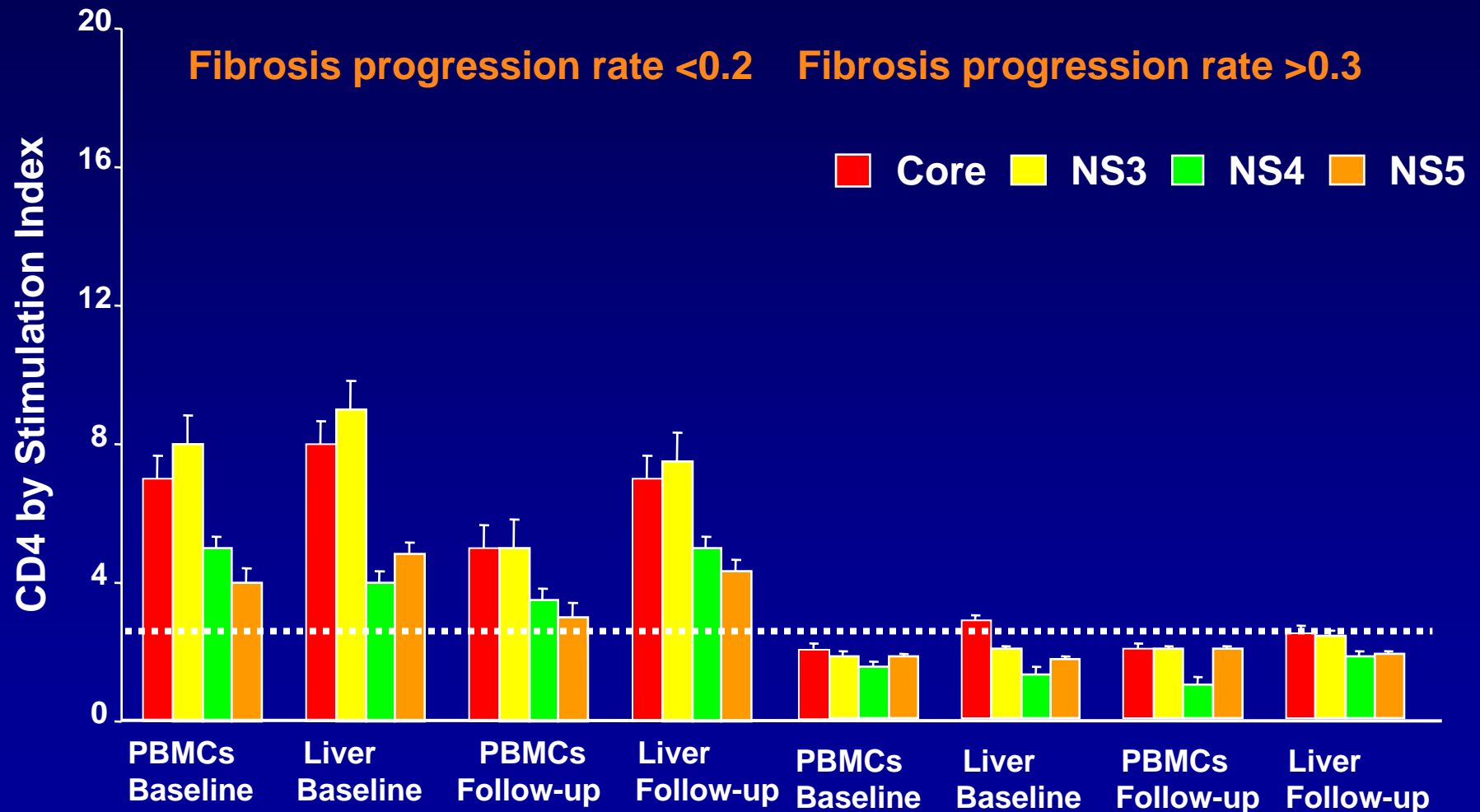
Durante-Mangoni E, et al. *J Immun.* 2004;173:2159-66.

Intrahepatic Lymphocytes are Enriched for HCV-specific T Cells in Chronic HIV/HCV

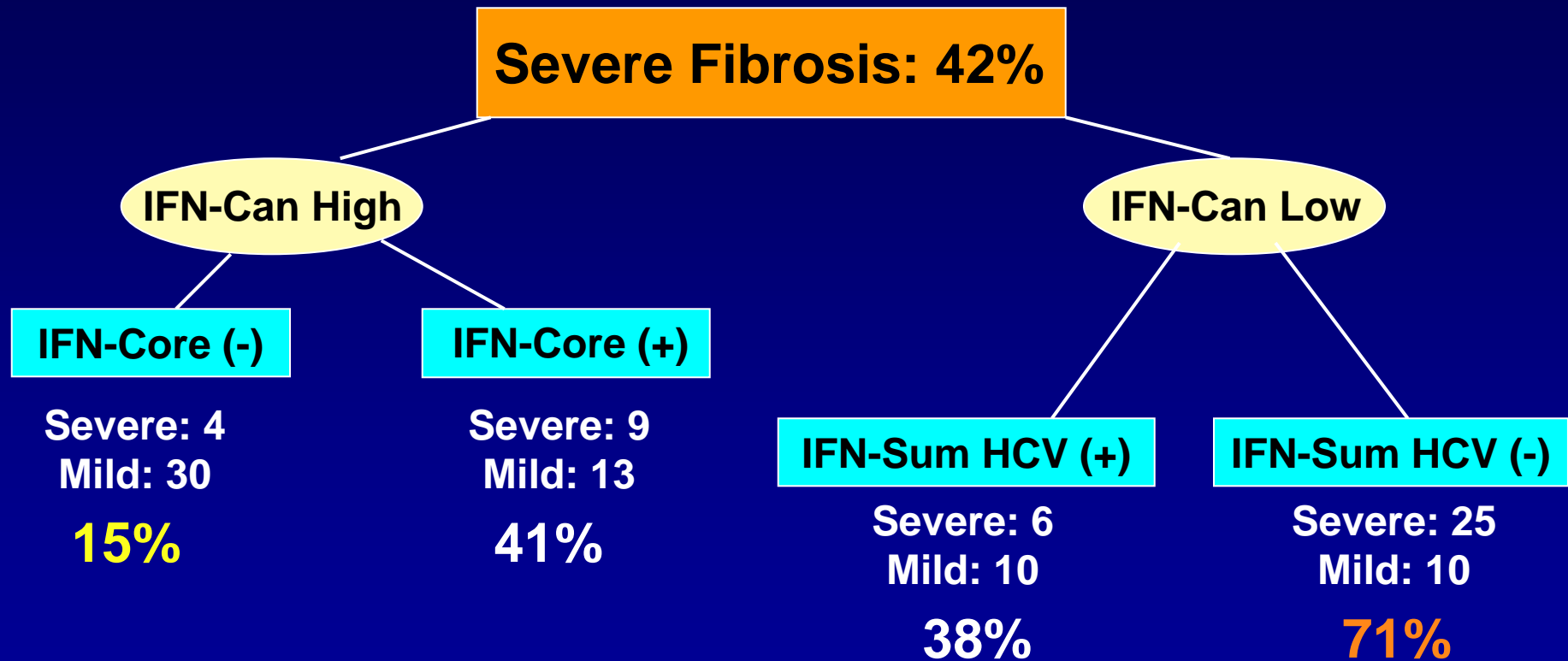
% of Patients with a Positive

Antigen	IFN γ ELIspot		IL-10 ELIspot	
	PBMC	IHL	PBMC	IHL
Core	4.7	28	0	57
NS3	0	43	4.7	57
NS5	4.7	28	4.7	86
Candida	82	57	19	57

Accelerated Progression of Fibrosis is Associated With Weak HCV-specific CD4+ T Cells During Early Chronic Infection



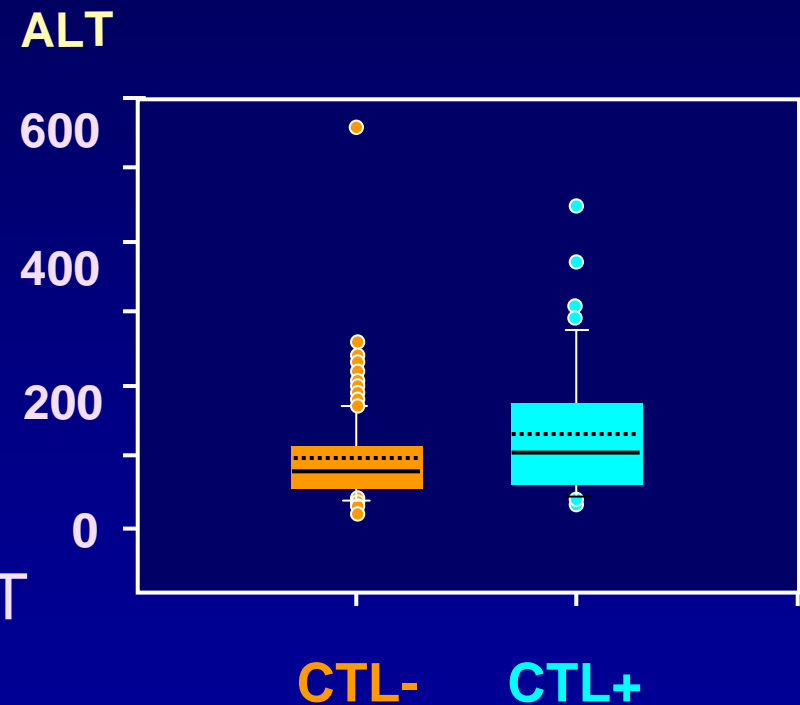
Multivariate Modeling to Predict Severe Fibrosis in a Cohort With HIV/HCV



Variables: IFN γ and IL-10 responses to HCV and recall antigens, age, sex, race, CD4, HIV and HCV VL, HCV genotype

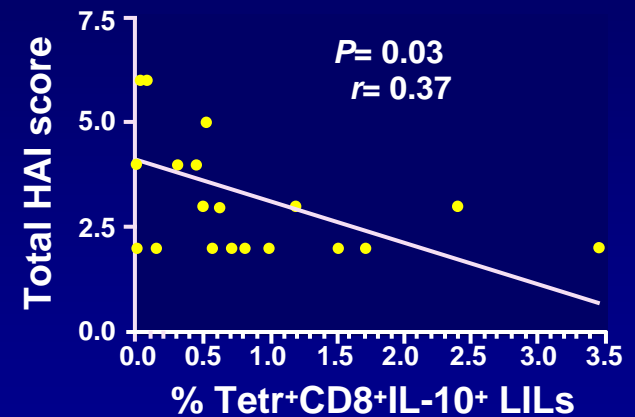
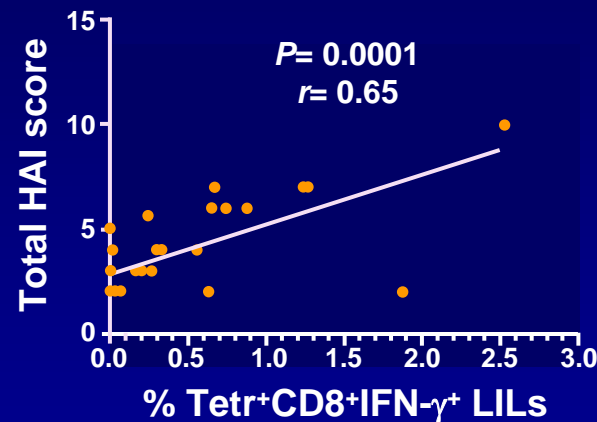
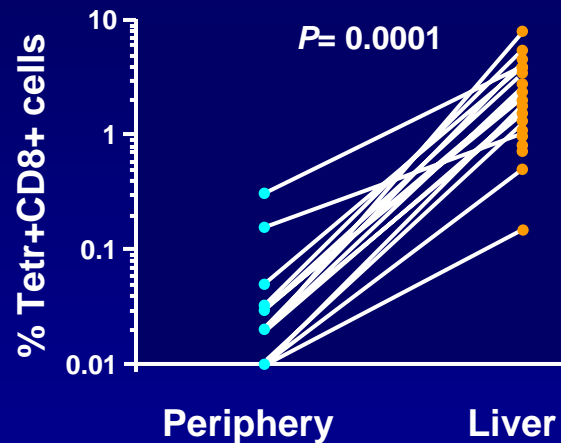
Evidence that CTL Promote Tissue Damage in HCV

- Transgenic mice:
 - Constitutive expression \neq inflammation
 - Inducible immunity \rightarrow inflammation
- Anti CD8 monoclonal Ab improve transaminases in humans and mice
- Cytotoxic function \rightarrow increased ALT



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Rothman AL, et al. *Hepatology.* 2005;41(3):617-25.
Hiroishi K, et al. *Hepatology.* 1997;25(3):705-12.
Kawamura T, et al. *Hepatology.* 1997;25(4):1014-21.
Kiefersauer S, et al. *J Immunol.* 1997;159(8):4064-71.
Wakita T, et al. *J Med Virol.* 2000;62(3):308-17.

IL-10+ CD8+: Inverse Association with Inflammation



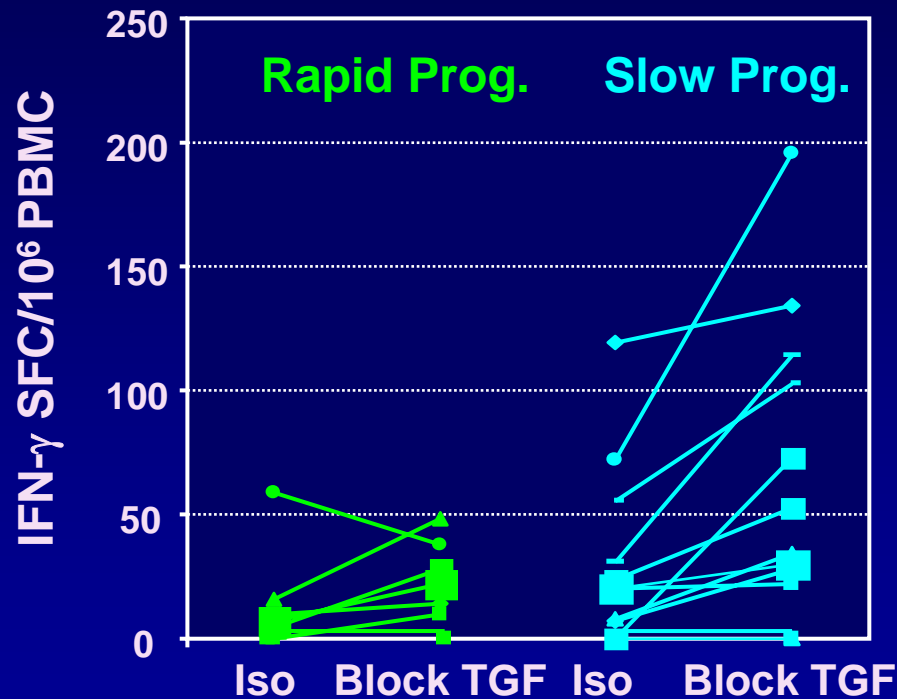
Accapezzato D, et al. *J Clin Invest.* 2004;113:963-72.

Abel M, et al. *Hepatology.* 2006;44:1604-16.

Slow Progression of Disease Associated with Suppression of IFN γ Responses

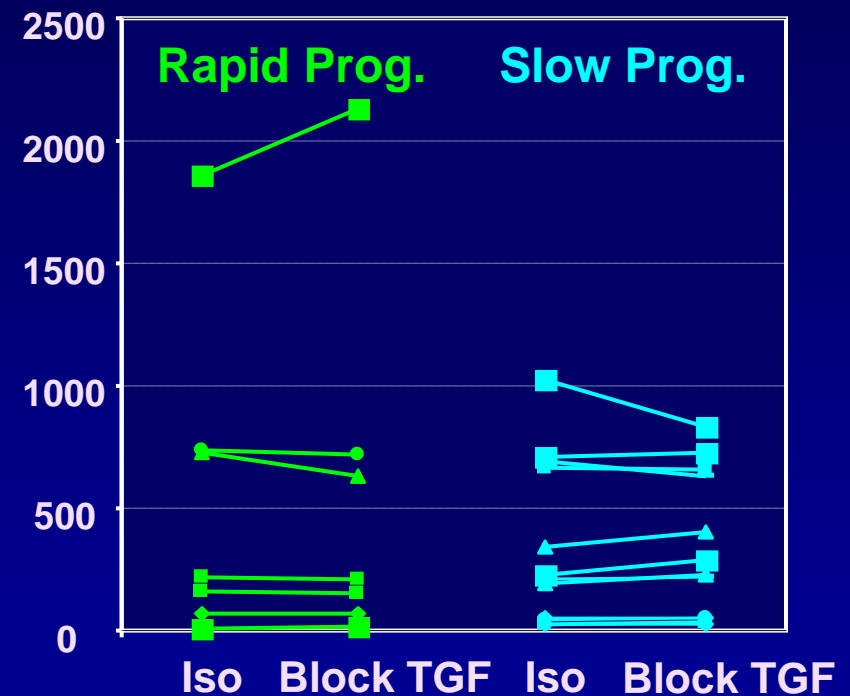
HCV core

Control (CEF)



$P = 0.34$

$P = 0.005$



$P = 0.75$

$P = 0.21$

Group:

Iso vs Block: $P = 0.002$

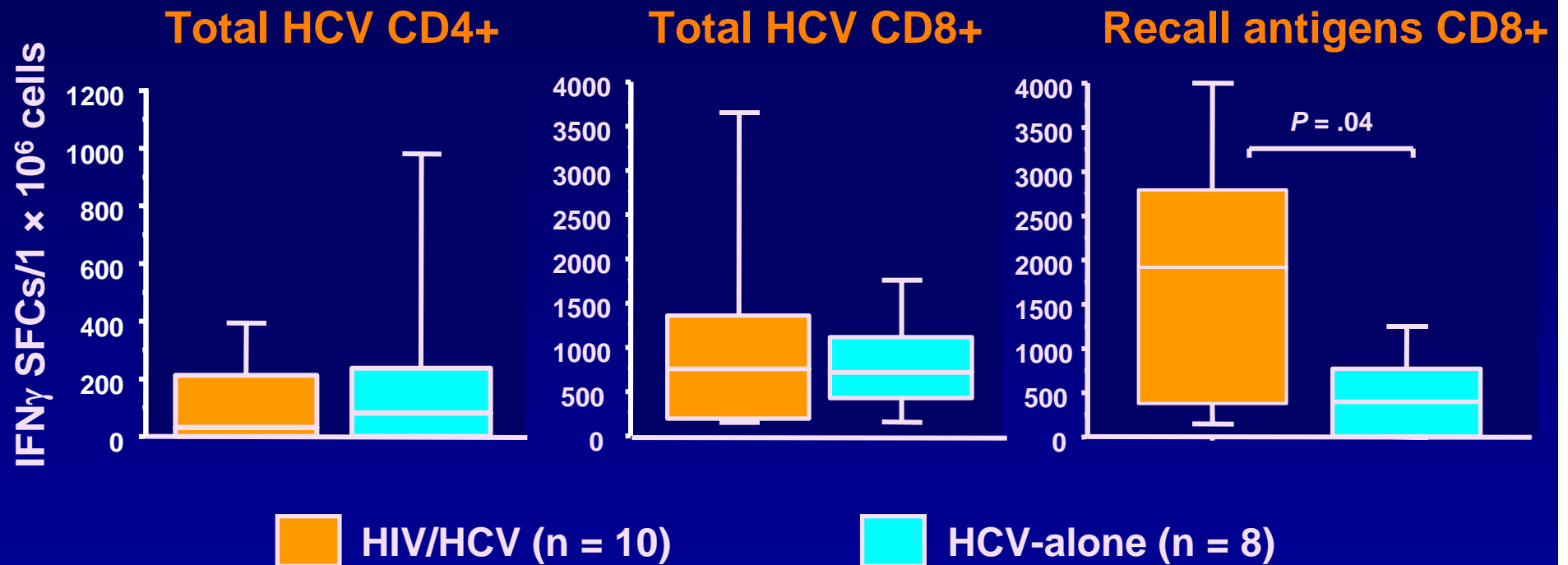
No Ab vs Iso: $P = 0.53$

No Ab vs Block: $P = 0.003$

How Could HIV Alter Immune Responses in the Liver?

- Alter number of virus-specific T cells and other cells
- Alter function of virus-specific T cells and other cells
- Induce apoptosis of liver cells (thereby increasing inflammation)
- Increase inflammation within the liver
 - Microbial translocation

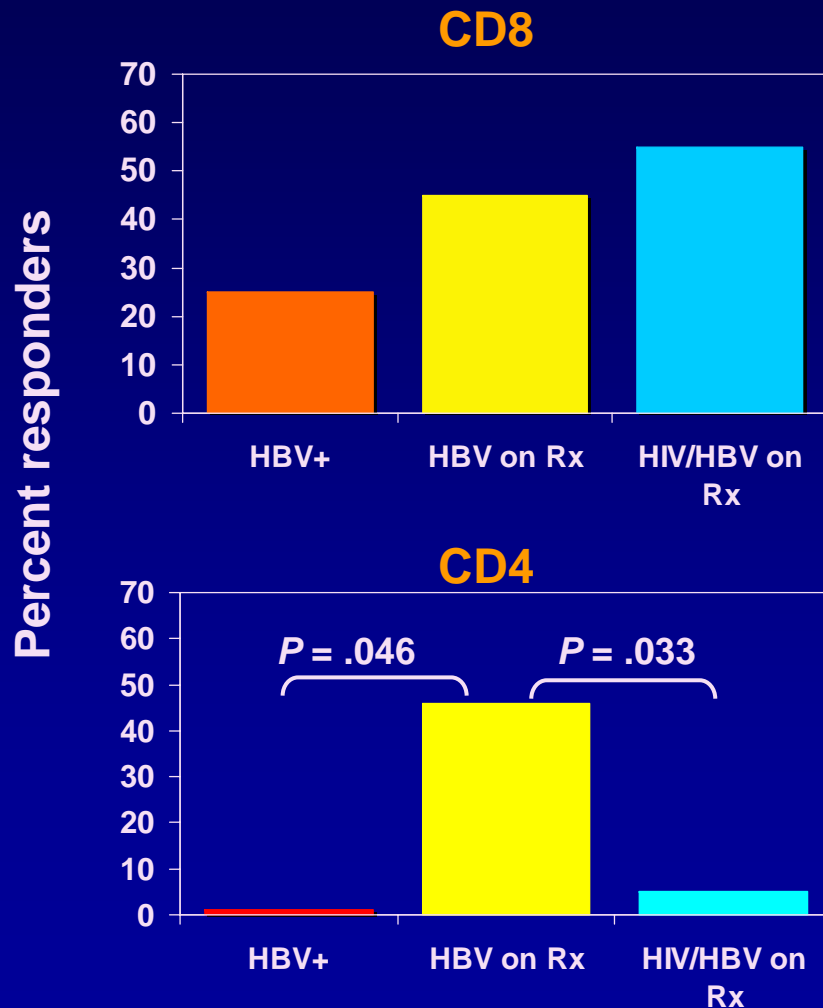
Total Intra-hepatic HCV-specific IFN γ Responses are Not Different in HIV/HCV vs HCV Alone



Alatrakchi N, et al. *J Infect Dis.* 2005;191:702-9.

Morishima C, et al. *J Infect Dis.* 2007;196:577-86.

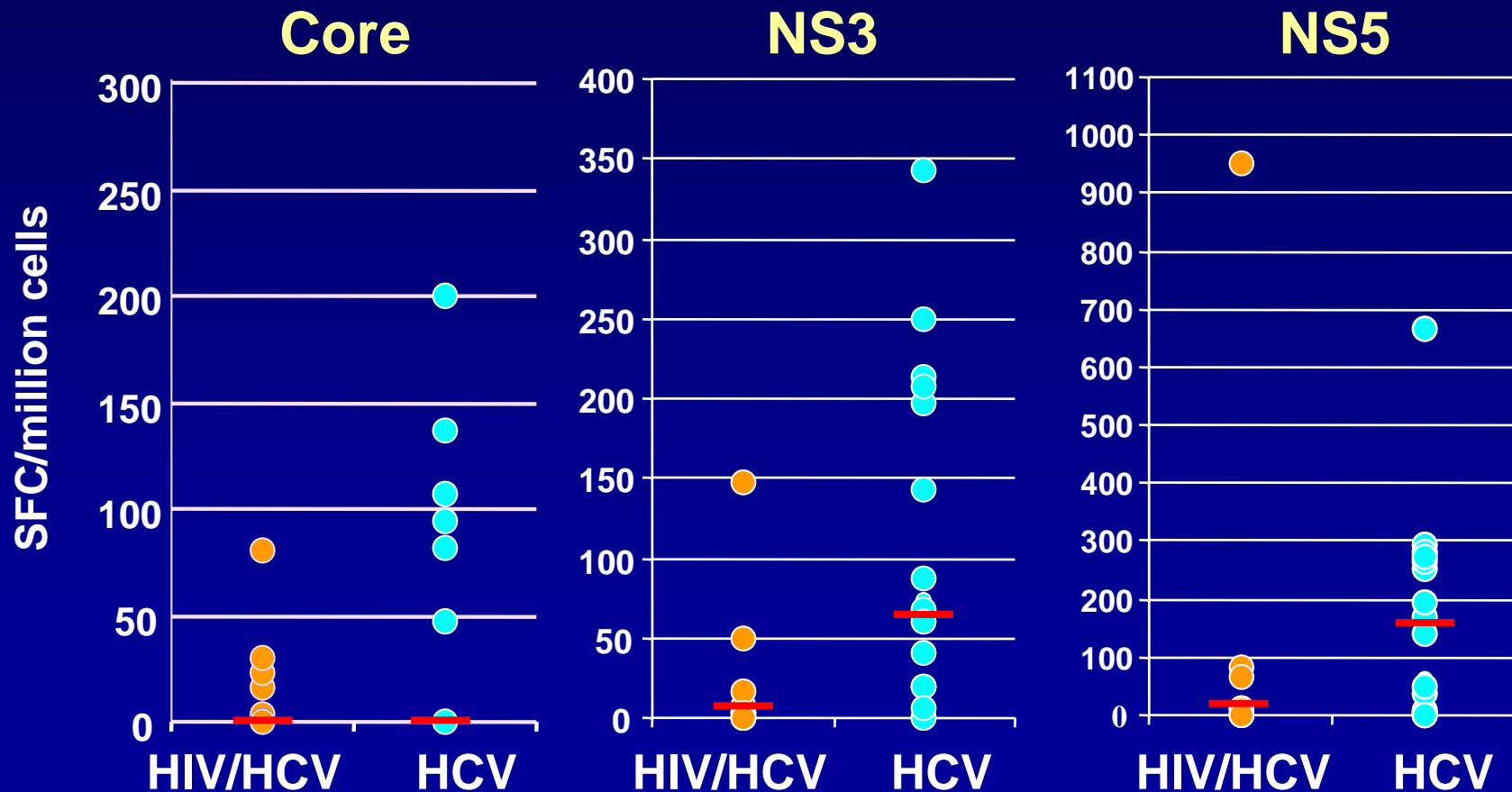
Discordant Effect of HIV on HBV-specific T Cells



- Frequency and breadth of CD8 responses preserved in HIV/HBV
- Reduced CD4 responses
- No correlation with HBV DNA or CD4+

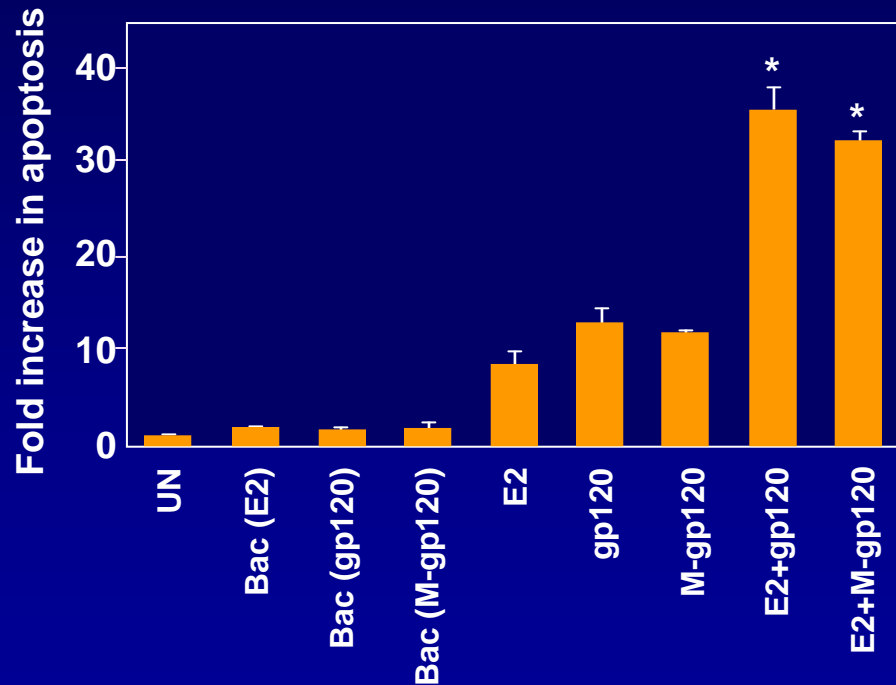
Qualitative but Not Quantitative Differences in the Intrahepatic Immune Response in HIV/HCV

IL-10 responses are higher in HCV alone

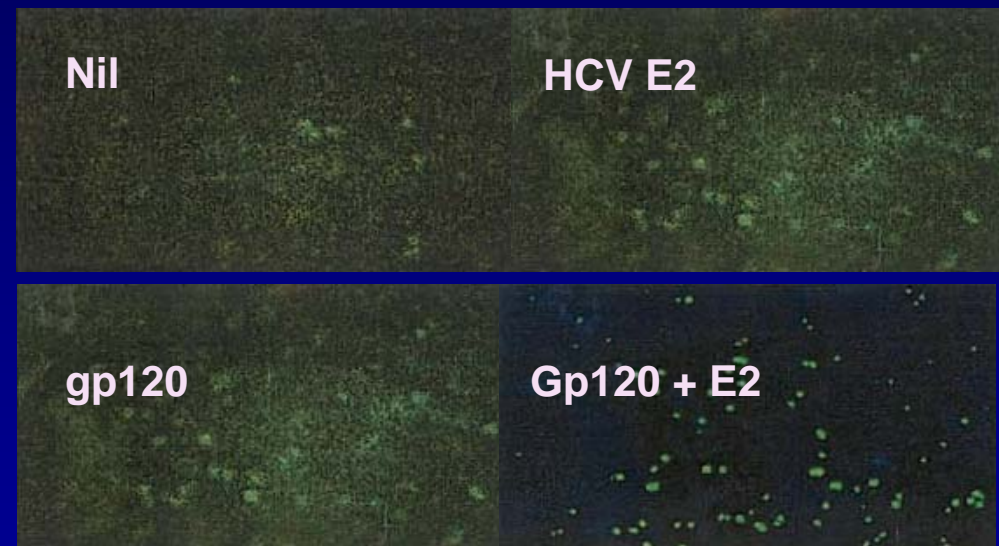


HIV and HCV Protein Binding Can Cause Apoptosis of Hepatocytes

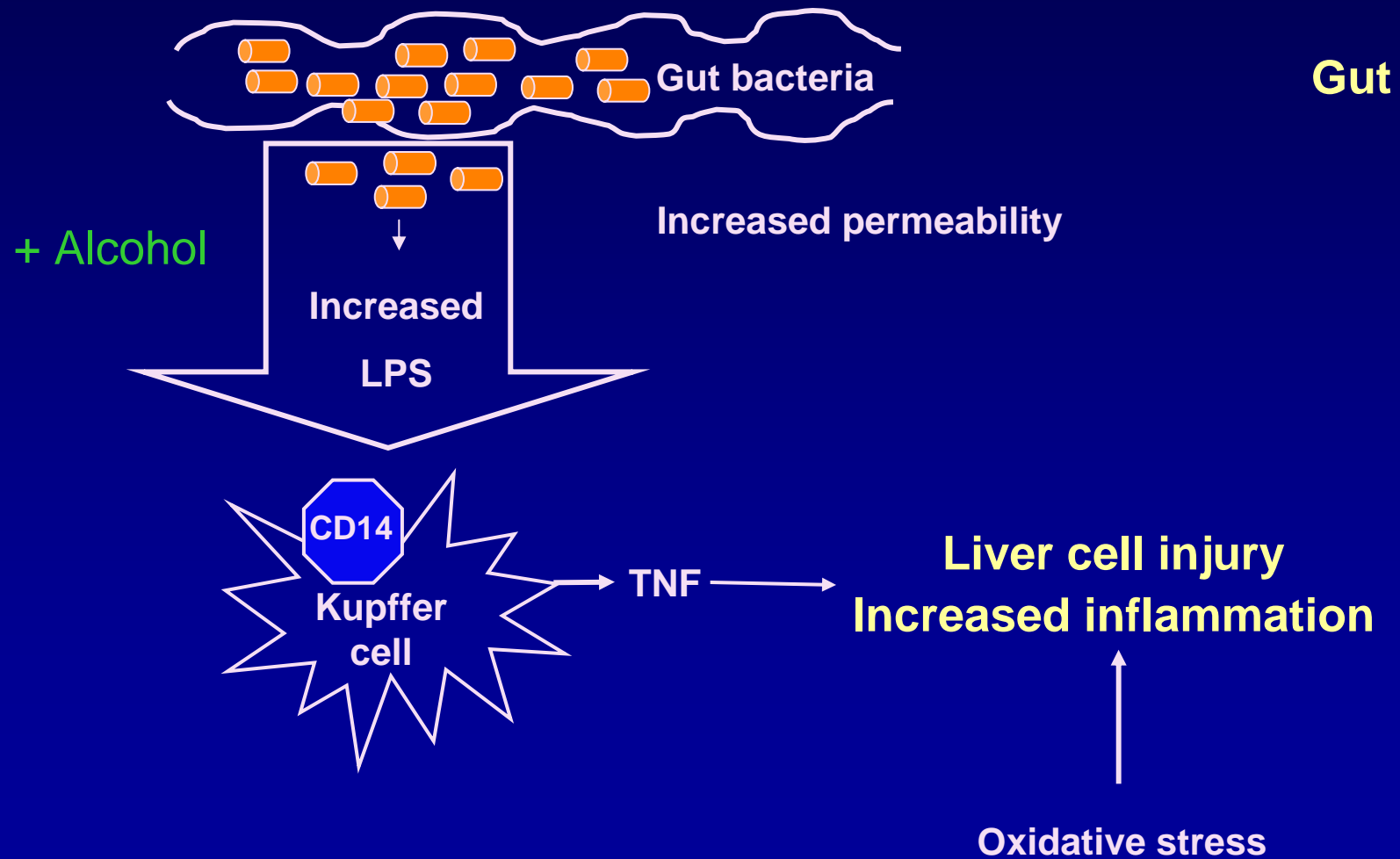
HepG2 cells



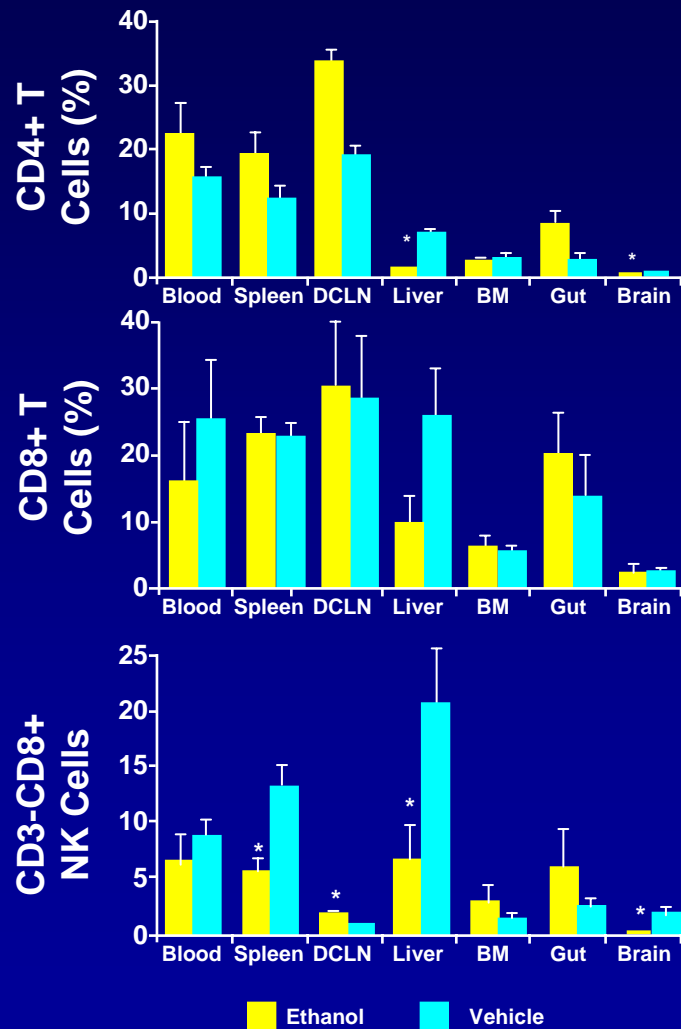
Primary hepatocytes



Microbial Translocation and the Liver: Role of Alcohol

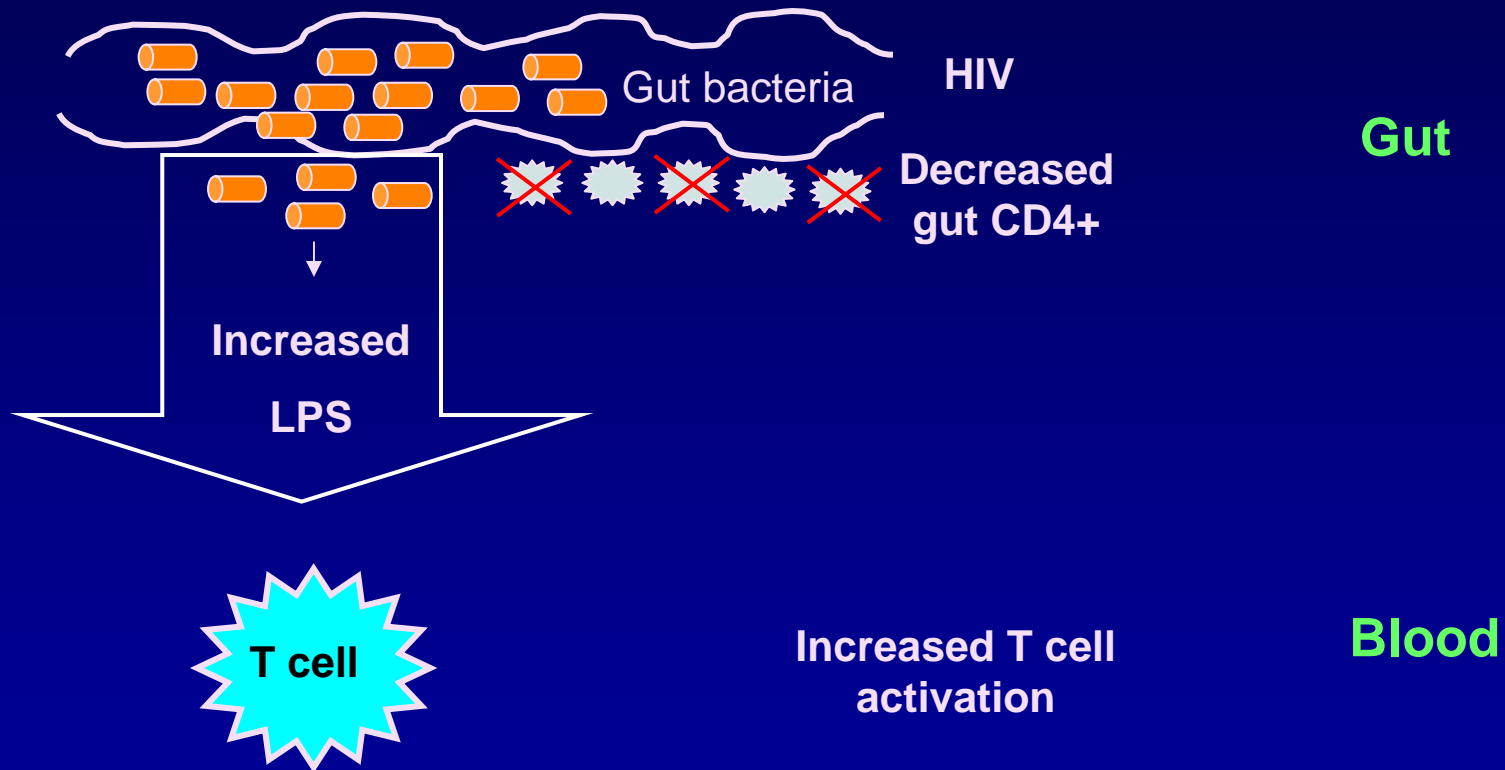


Alcohol Alters the Liver Immune Environment in Acute SIV



- Acute SIVmac251 of macaques with chronic alcohol ingestion
- Decrease in intrahepatic CD4, CD8, NK cells
- Decrease of “effector memory” T cells in the liver

Microbial Translocation and HIV



Association of Microbial Translocation and Cirrhosis

	OR	95% CI	P value
Univariate			
LPS >42 pg/ml	19.0	2.98-120.79	.0018
LBP	4.39	0.99-19.36	.05
sCD14	8.65	1.98-37.72	.0041
CD4 <350/mm ³	7.02	1.36-36.31	.02
Multivariate (adjusted for CD4 depletion)			
LPS >42 pg/ml	18.71	2.62-133.8	.0035
CD4 <350/mm ³	6.29	0.97-40.7	.054

Summary

- What role do immune responses play in spontaneous recovery ?
 - CD4 and CD8
 - Innate immunity: further research on NK, DC

Summary

- What role do immune responses play in spontaneous recovery ?
- What role do immune responses have in disease once chronic infection is established?
 - CD4: protect against disease progression
 - NKT, CD8: role currently unknown
 - Subpopulations of CD8 protective

Summary

- What role do immune responses play in spontaneous recovery ?
- What role do immune responses have in disease once chronic infection is established?
- Intersection of alcohol, viruses and HIV deserves further study