HCV and Host Innate Immunity

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Host Immunity Against Pathogens

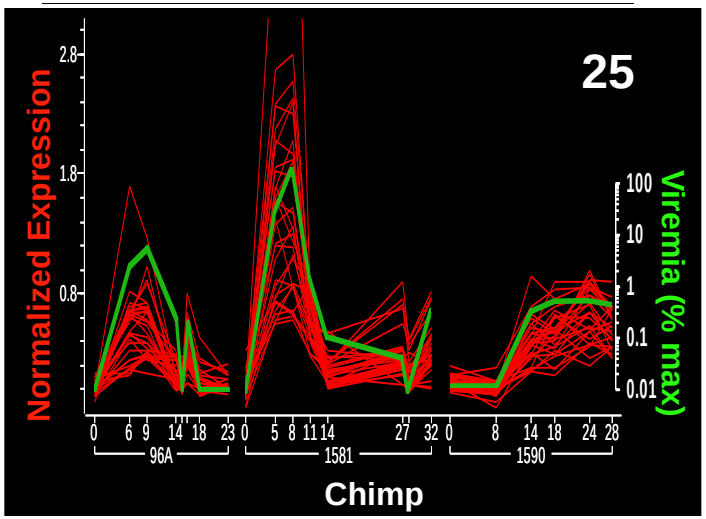
- Innate immunity:
  - Evolutionarily ancient
  - Universal, all multicellular organisms
  - Constitutive, germ line configuration
  - No memory (?)
  - Rapid response, pattern recognition central
  - Effector cells: NK, NKT, $\gamma\delta$ T, Mϕ, DC, B-1
- Adaptive immunity:
  - Delayed responses
  - Rearranged TCR or IgR
  - Memory
  - Highly specific, responsible for pathogen clearance

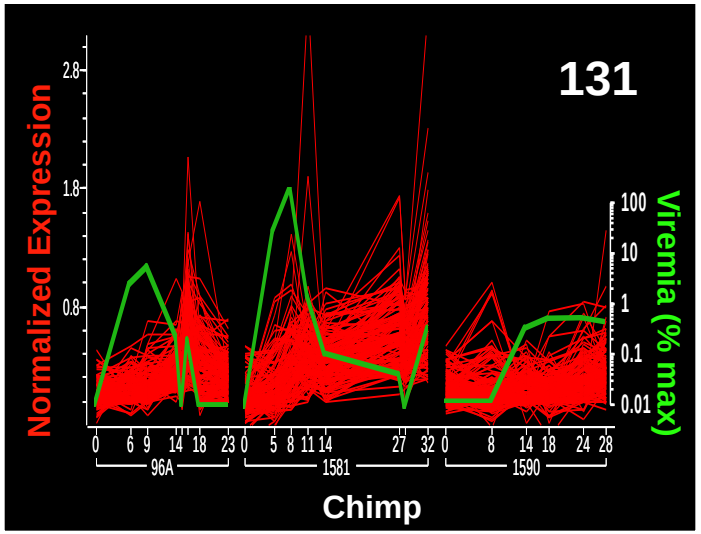
Liver Gene Expression Profiles

Virus-induced

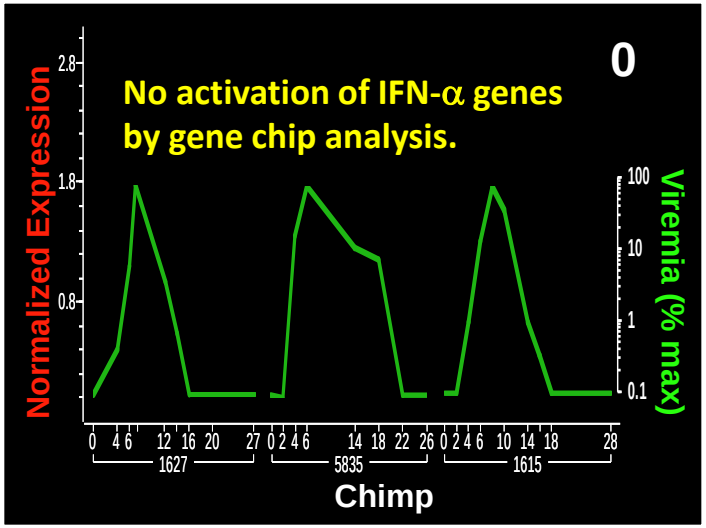
Clearance-related

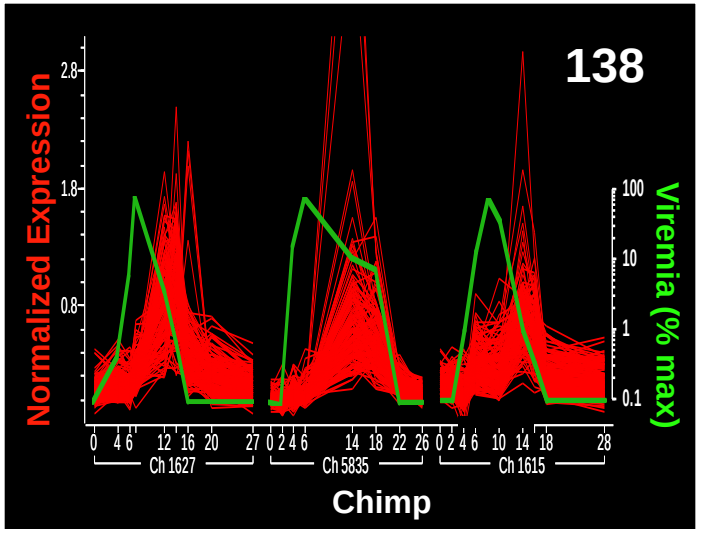
HCV





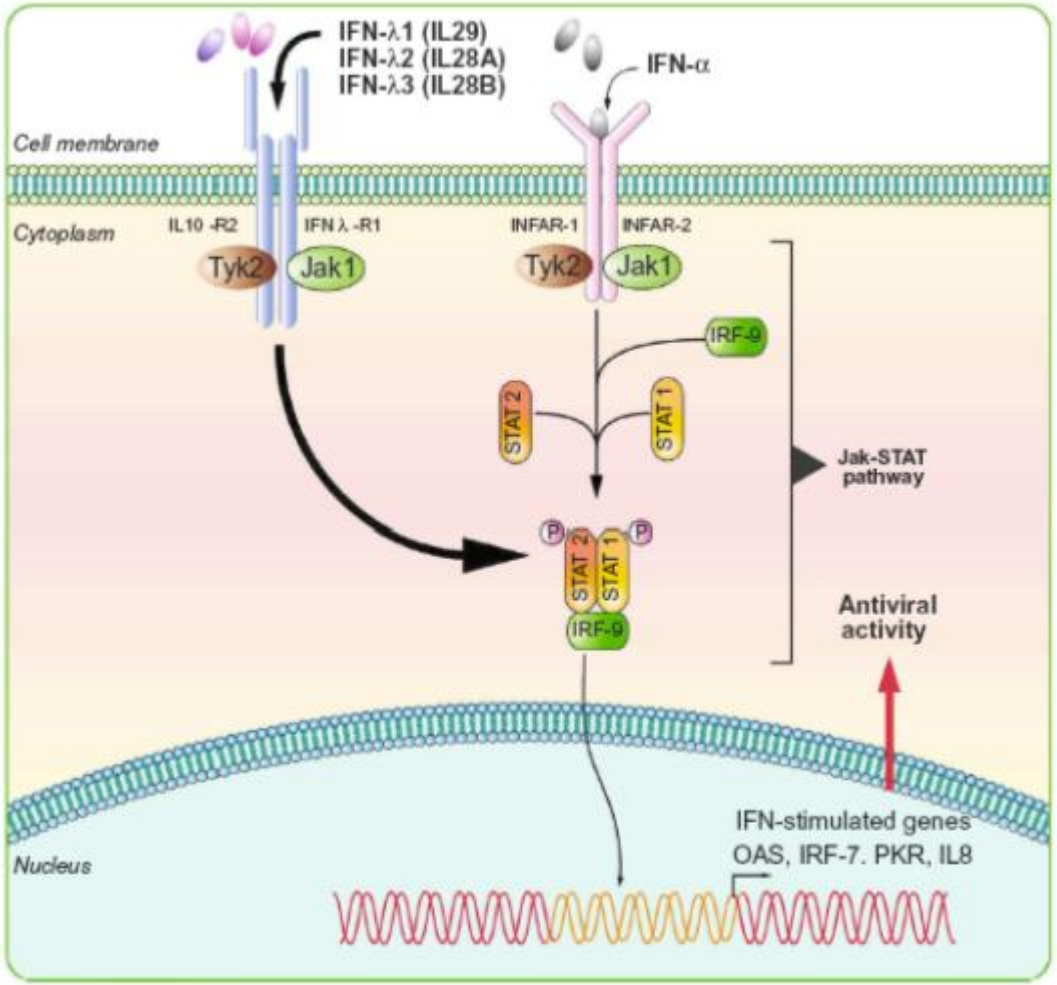
HBV

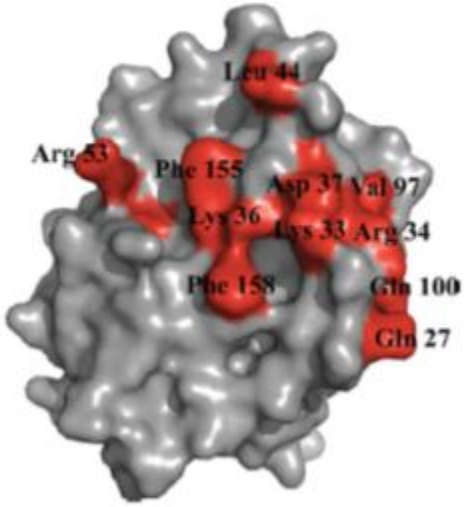




Wieland S, et al. *Proc Natl Acad Sci USA*. 2004;101:6669-74.

IFN-λ3 (*IL28B*): Mechanism of Action

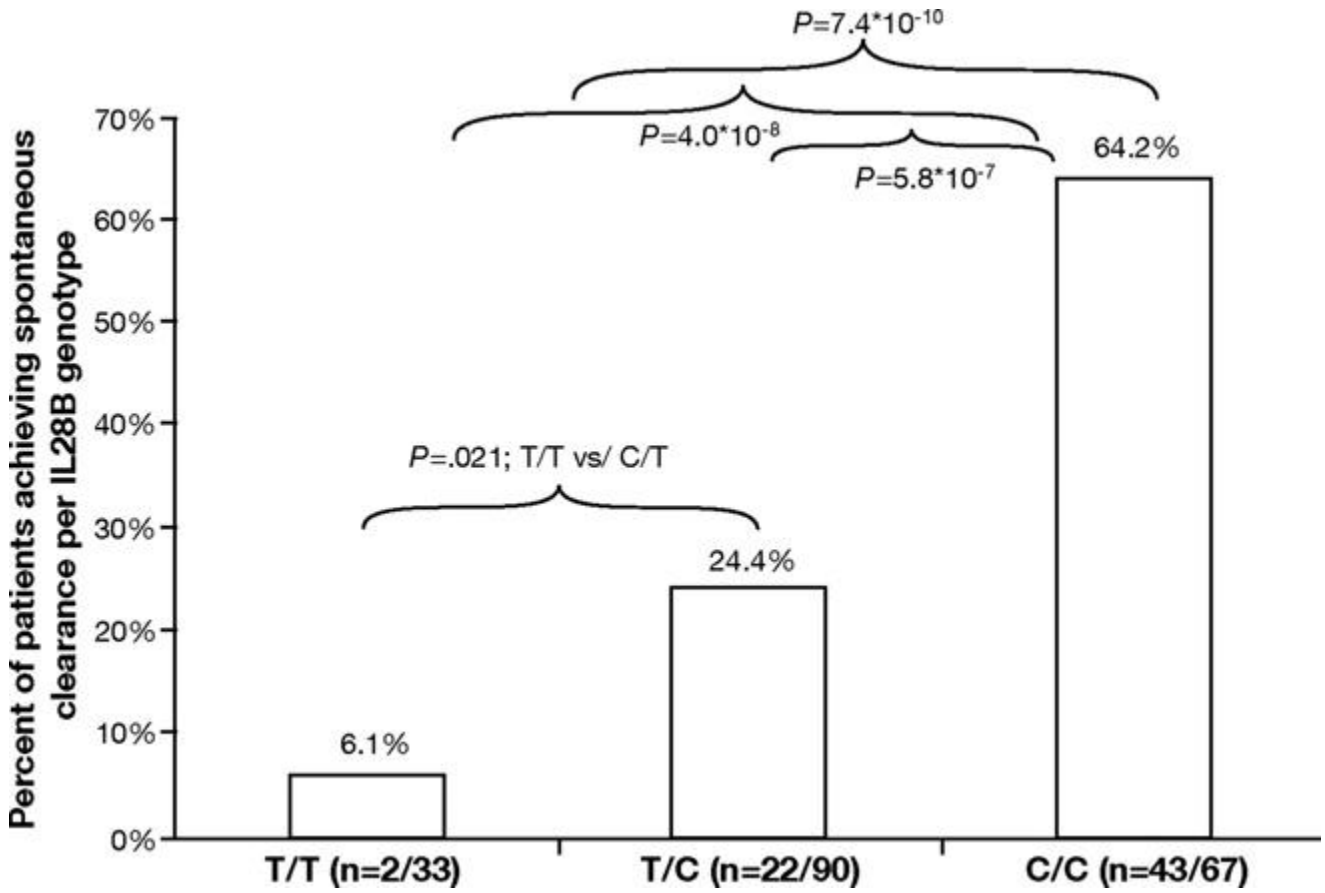




Antiviral activity of

	-Fold increase
WT	
Gln-27 → Ala	10
Gln-30 → Ala	2
Lys-33 → Ala	38
Arg-34 → Ala	33
Lys-36 → Ala	51
Asp-37 → Ala	43
Leu-44 → Ala	12
Cys-48 → Ala	1
Arg-51 → Ala	1
Arg-53 → Ala	7
Leu-54 → Ala	6
Asp-96 → Ala	4
Val-97 → Ala	68
Gln-100 → Ala	46
Phe-155 → Ala	40
Phe-158 → Ala	>650

IL28B Genotype and Spontaneous Clearance rs12979860 SNP



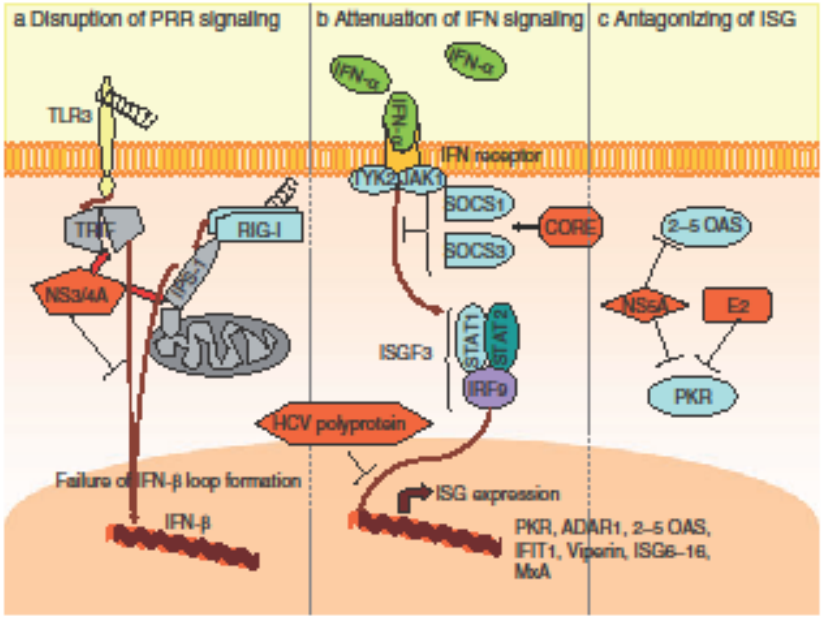
Tillmann HL et al., *Gastroenterology* 2010;139:1586–1592

Innate Immunity in Chronic HCV

Viral protein interference with host response: first host response blocked

Immune evasion by hepatitis C virus NS3/4A protease-mediated cleavage of the Toll-like receptor 3 adaptor protein TRIF. Li, K. *et al. Proc. Natl Acad. Sci. USA* 102, 2992–2997 (2005).

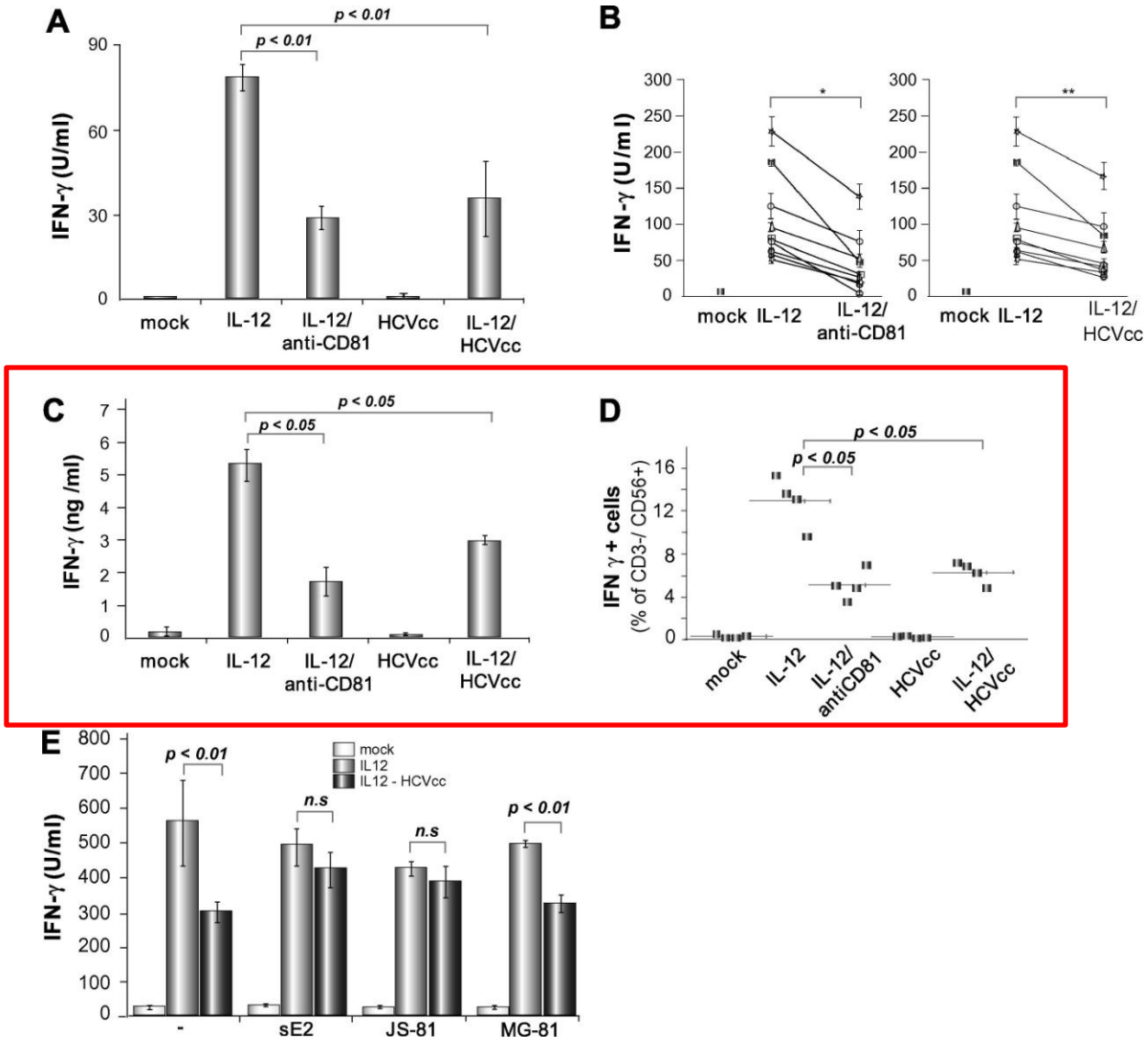
IFN- antagonistic activity of HCV core protein involves induction of suppressor of cytokine signaling-3. Bode, J. G. *et al. FASEB J.* 17, 488–490 (2003).



Control of antiviral defenses through hepatitis C virus disruption of retinoic acid-inducible gene-I signaling. Foy, E. *et al. Proc. Natl Acad. Sci. USA* 102, 2986–2991 (2005).

Inhibition of the interferon inducible protein kinase PKR by HCV E2 protein. Taylor, D. R., *et al*. *Science* 285, 107–110 (1999).

Cell-Associated HCV Inhibits IFNγ Production by NK Cells through Engagement of CD81 in Chronic HCV Infection

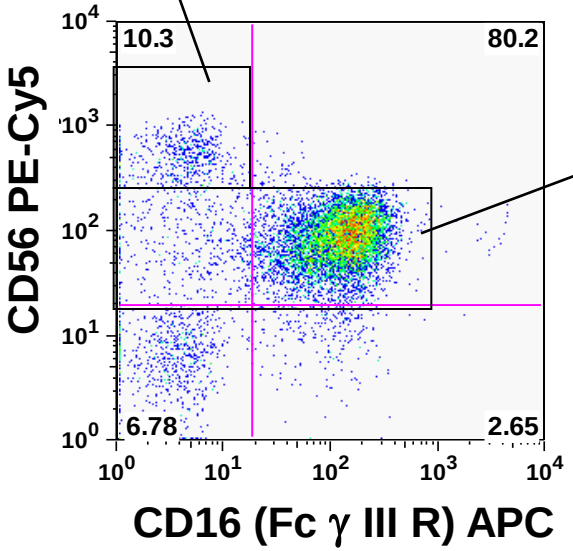


Crotta et al., *J Hepatol* 2010;52:183-90.

NK CELL FUNCTIONS

CD56^{bright}/CD16^{-}

Cytokine secretion
(TNF-α, IFN-γ, TGF-β, GM-CSF)



CD56^{dim}/CD16$^{+/-}$

Cytotoxicity vs virus infected or tumour targets

Activating Receptors

Induced by cell stress

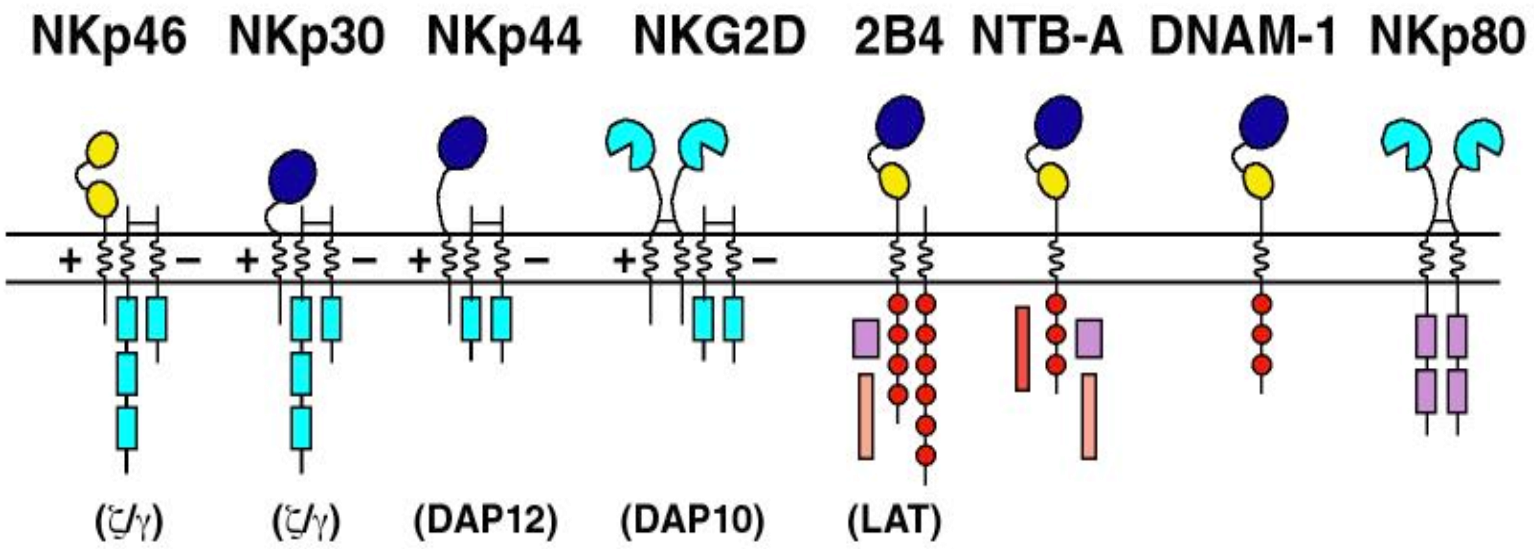
Natural Cytotoxicity Receptors (NCRs)

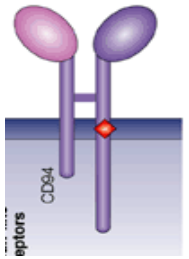
MICA/MICB
ULBP

Co-receptors

HLA-E

CD94/ NKG2C



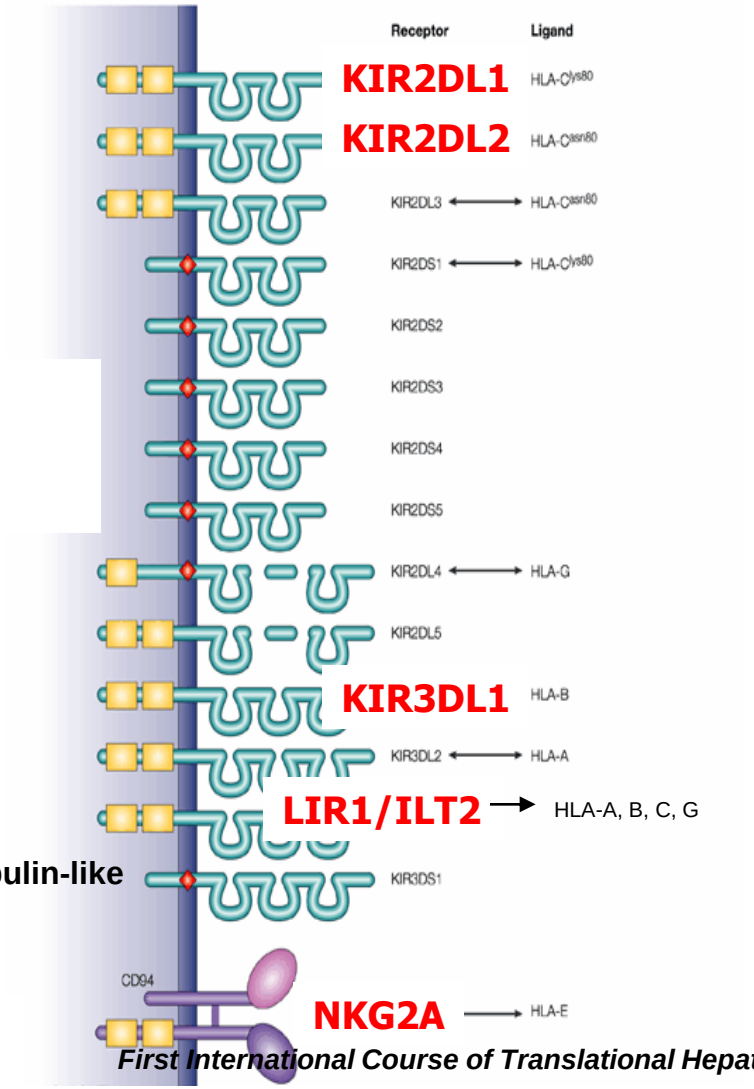


Lectin-like Receptors

Inhibitory Receptors

HLA-specific Receptors

Killer Ig-like Receptors (KIRs)



Leukocyte Immunoglobulin-like Receptor

Lectin-like Receptors

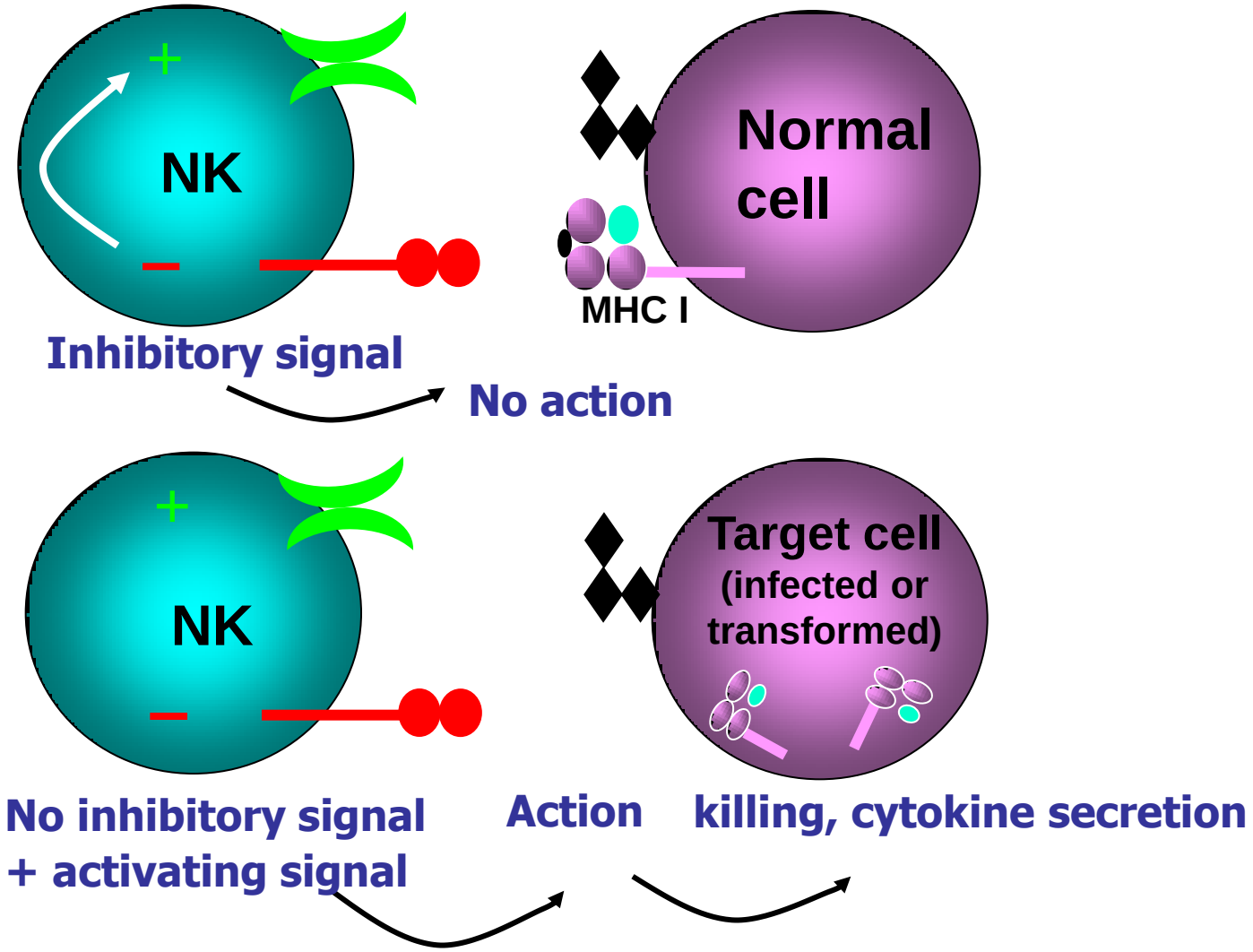
Non-HLA-specific Receptors

IRp60
(NK, Mø, Granulocytes, T-cell subsets)

p75/AIRM1
High degree of amino acid sequence identity with CD33. Binds Sialic Acid.

NK CELL-TARGET INTERACTION: THE ”MISSING-SELF” CONCEPT

NK cells test qualitative/quantitative expression of MHC I on target cell

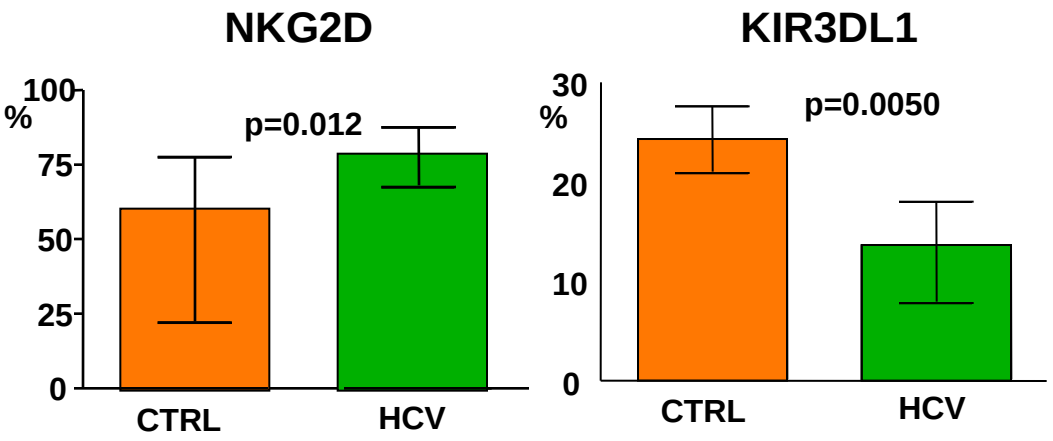


NK Cell Function in Chronic HCV Infection

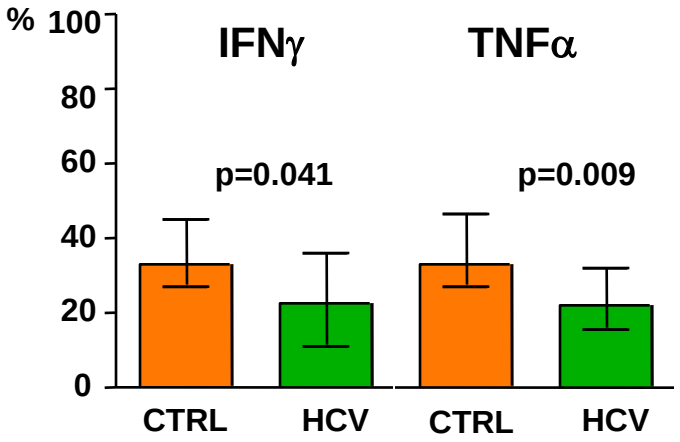
- Controversial findings:
  - Phenotype:
    - Activating receptors: NKG2D, NKp30, NKp46, NKp44, NKG2C, DNAM-1.
    - Inhibitory receptors: KIRs, NKG2A.
    - Activation: CD69, …
  - Cytolytic activity: CD107a, TRAIL, Perforin
  - Cytokine production: IFN-γ, TNF-α.

NK Cell Functional Dichotomy in Patients with Chronic HCV Infection

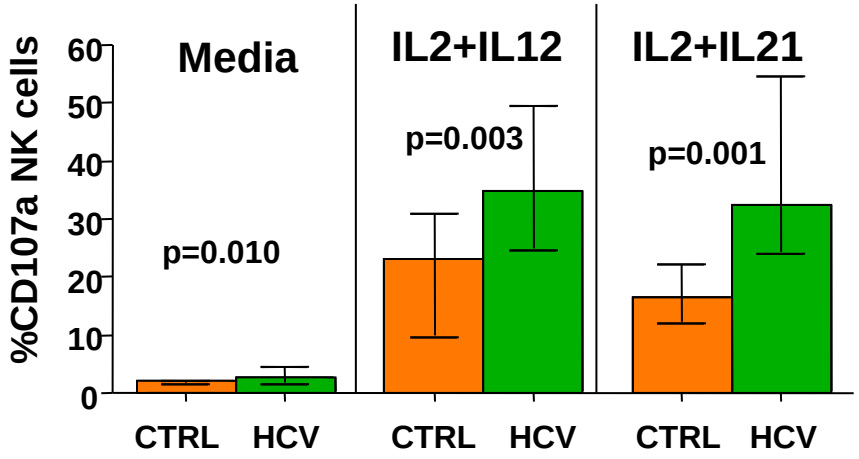
Phenotype skewed towards activation



Dysfunctional cytokine production

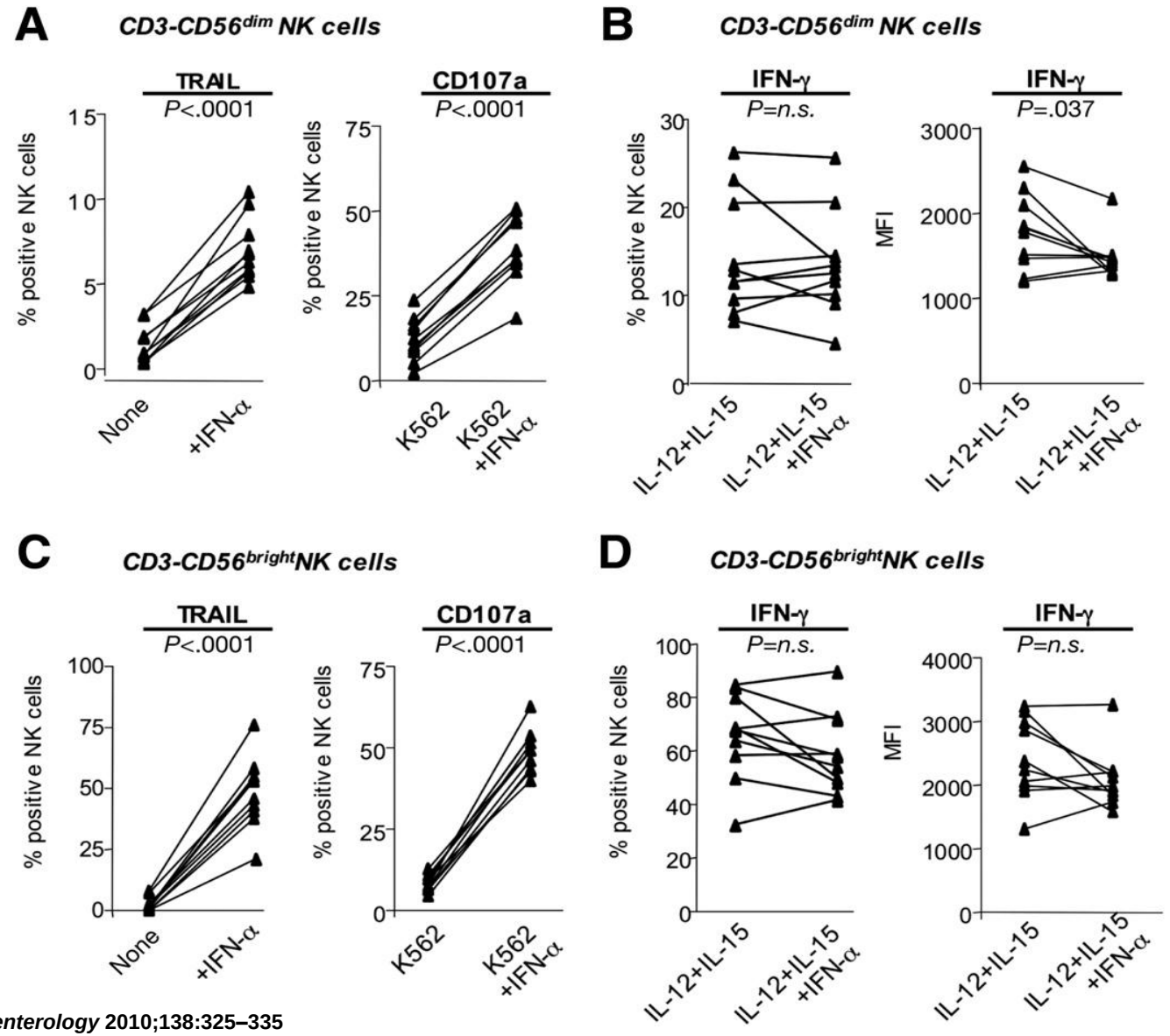


Increased cytotoxic activity



Oliviero B, et al. *Gastroenterology* 2009;137:1151-60.

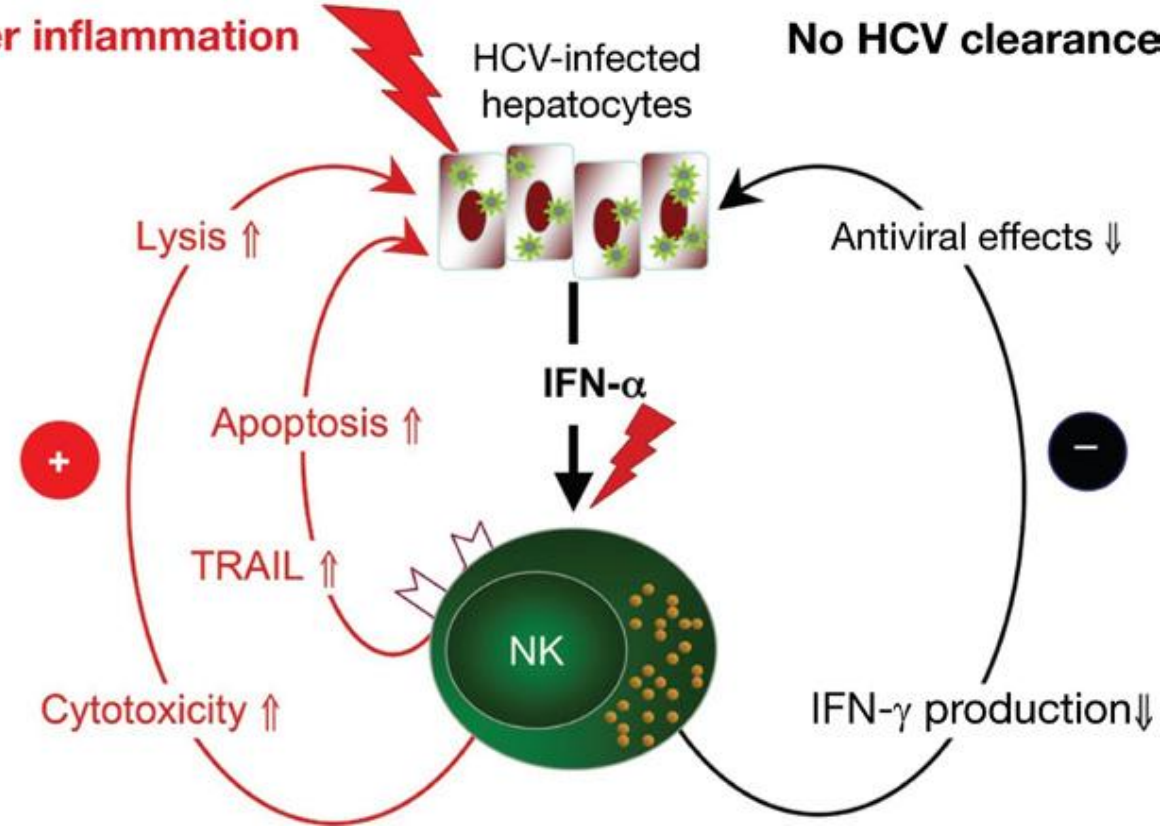
In Vitro Exposure to IFN-α Up-Regulates Markers of Cytotoxicity on NK Cells



Ahlenstiel, et al. *Gastroenterology* 2010;138:325–335

NK Cells Are Polarized Towards Cytotoxicity in Chronic HCV Infection:

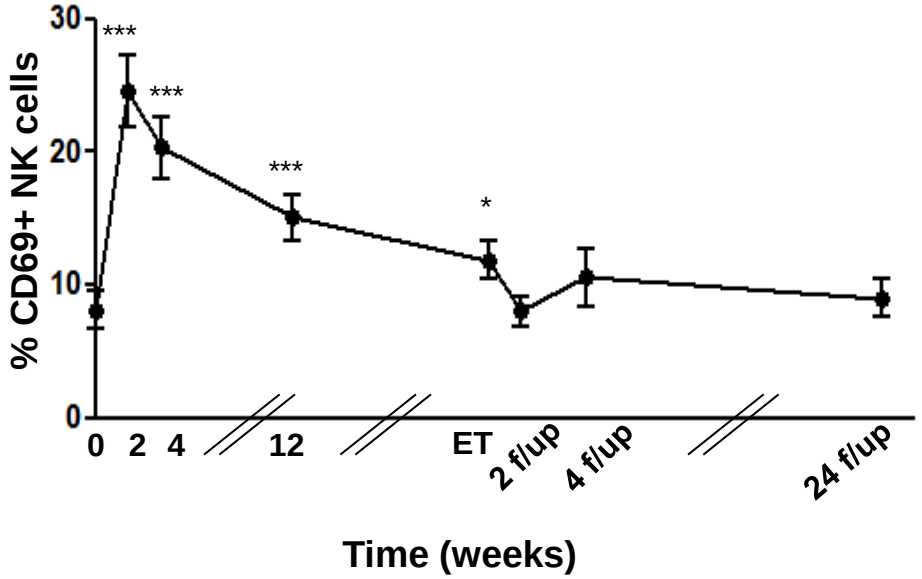
A Model for Virus-Induced Inflammation and Immune Escape

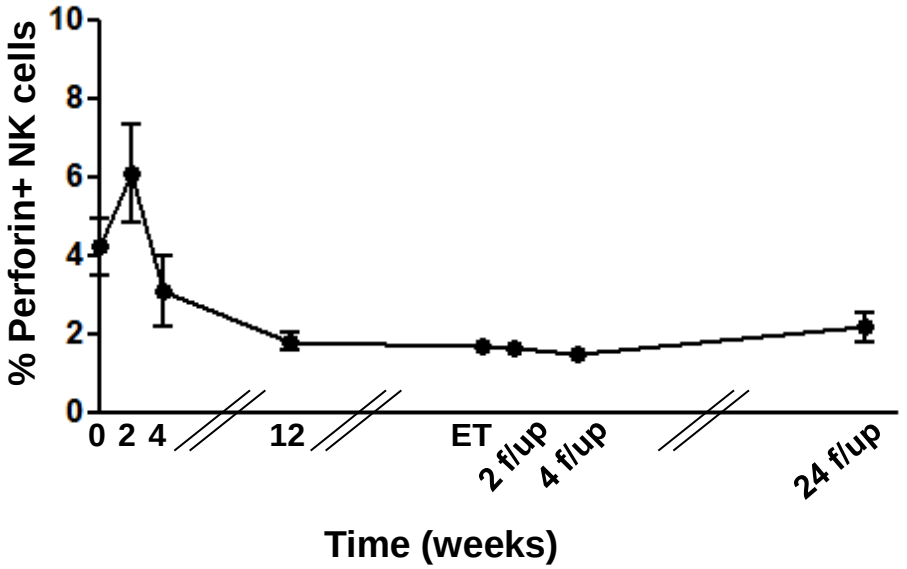


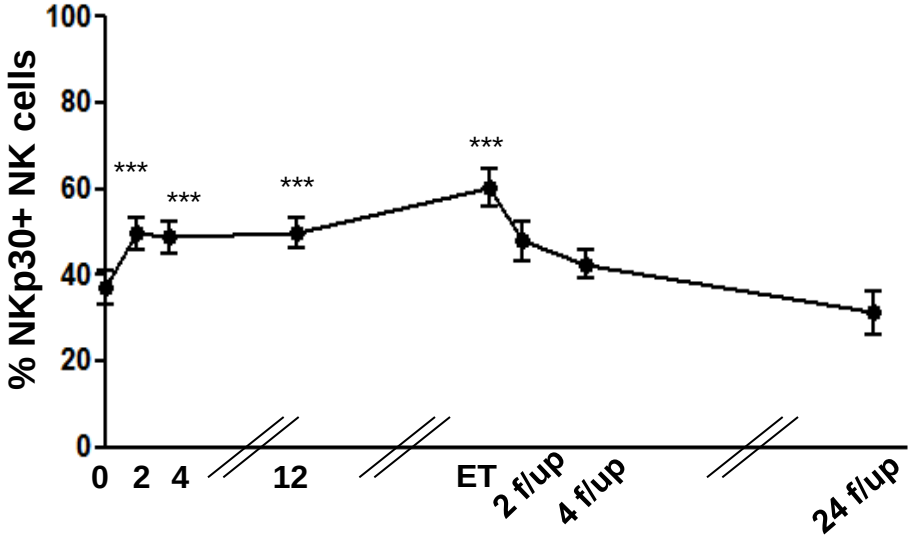
Chronic Exposure to HCV-Induced IFNα Contributes to Liver Inflammation via Cytotoxic Mechanisms but not to Viral Clearance Because of Insufficient IFNγ production.

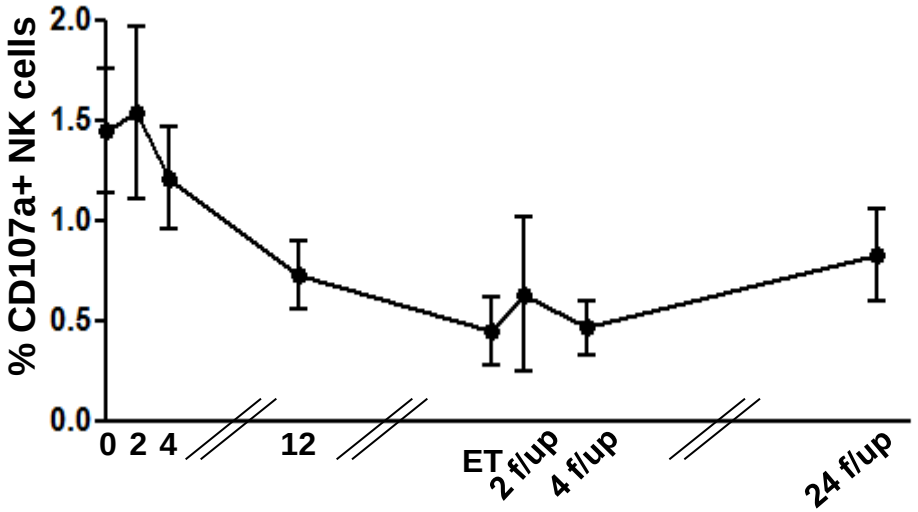
Ahlenstiel, et al. *Gastroenterology* 2010;138:325–335

Peg-IFNα/RBV Treatment Induces Early NK Cell Activation



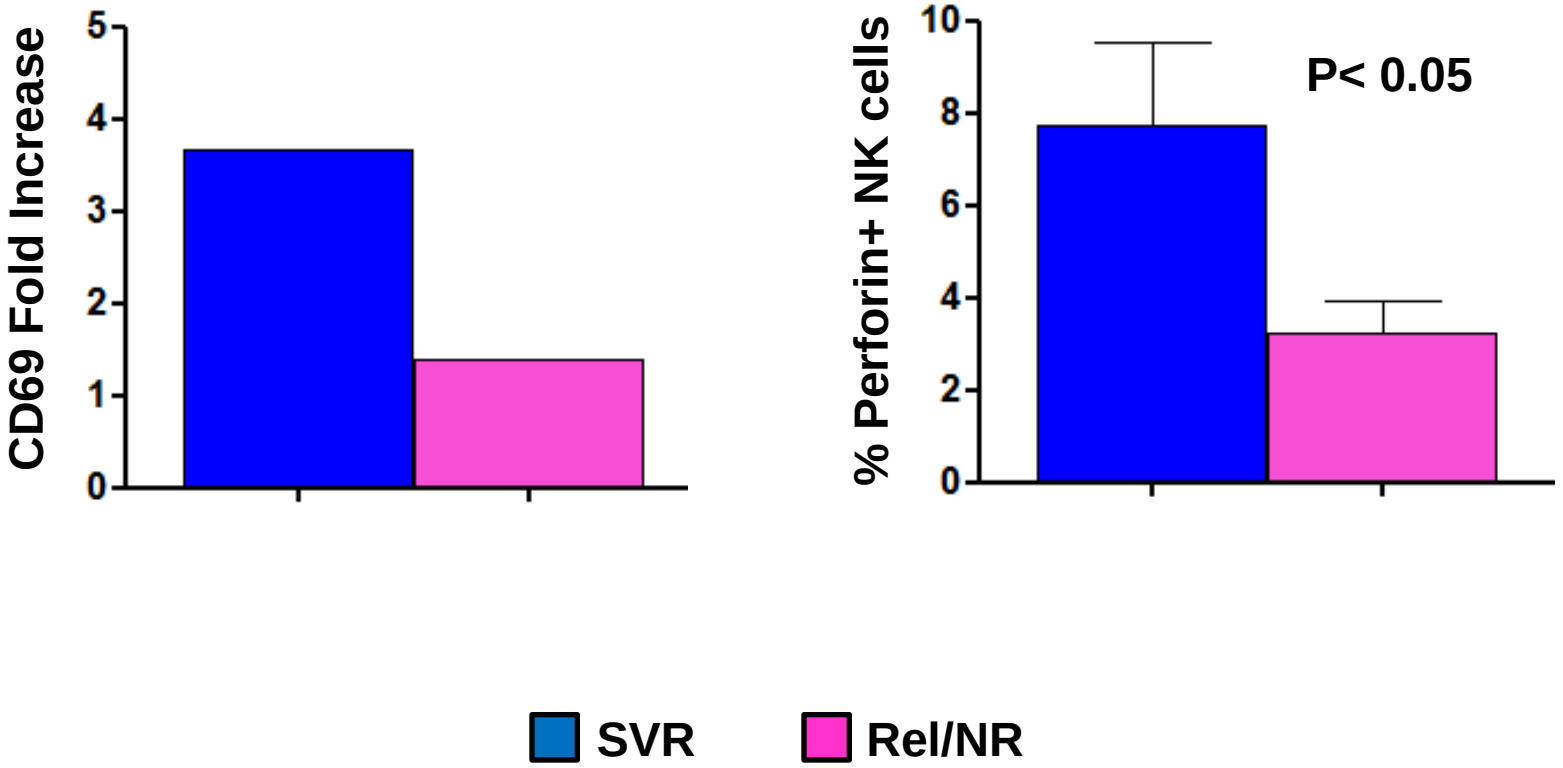






Early NK Cell Activated Phenotype Predicts Treatment Outcome in Chronic HCV Infection

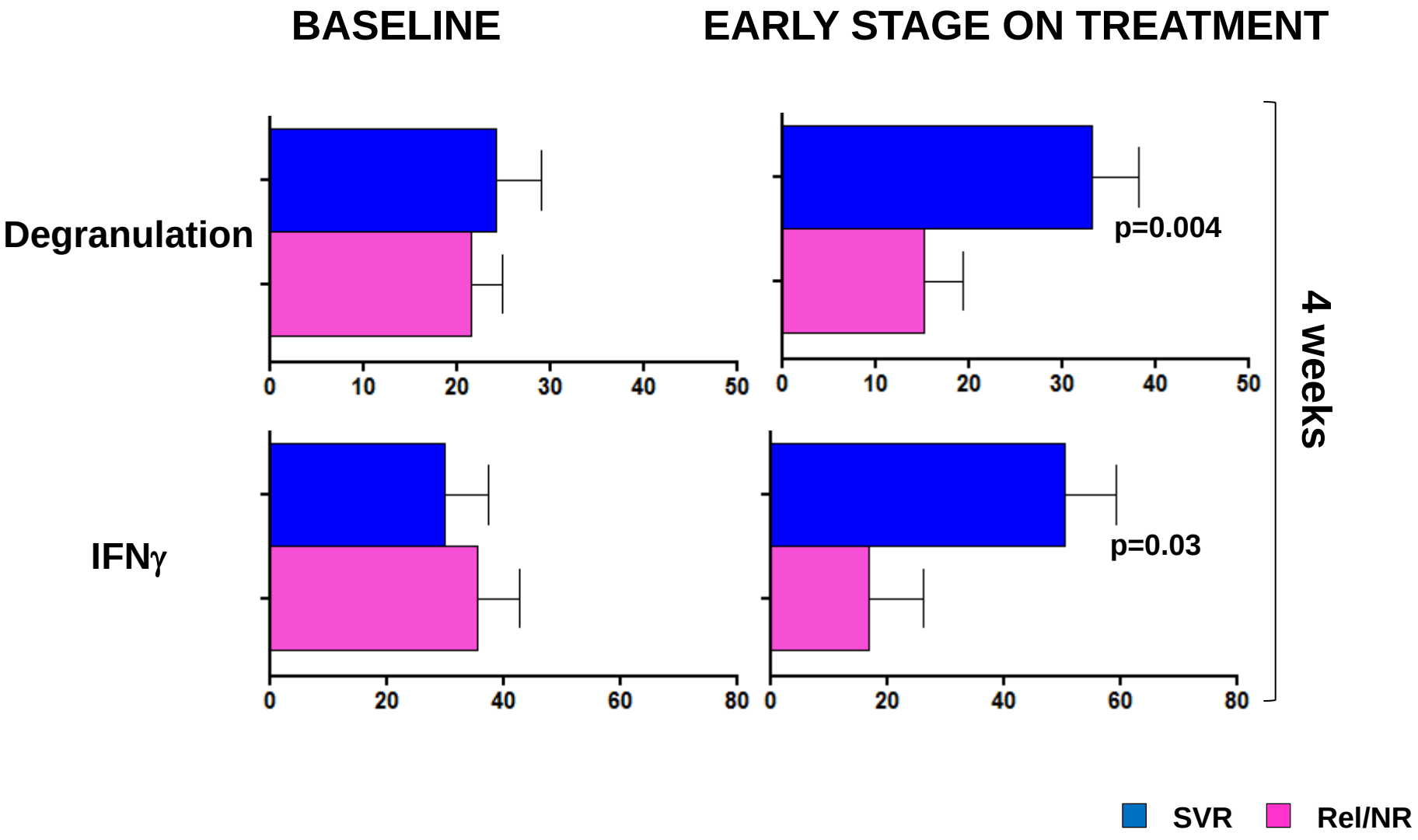
2 weeks on treatment



Oliviero, EASL 2011

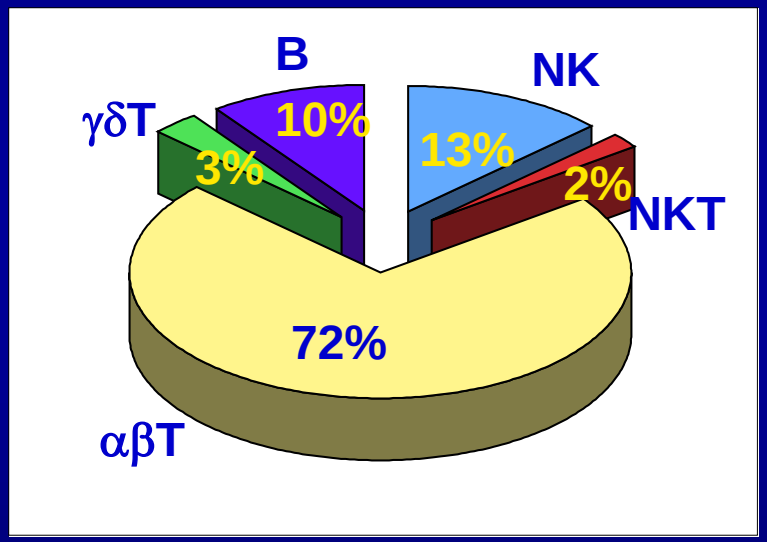
First International Course of Translational Hepatology, Florence, 2011

Early Effector NK Cell Functional Activation Predicts Treatment Outcome in Chronic HCV Infection

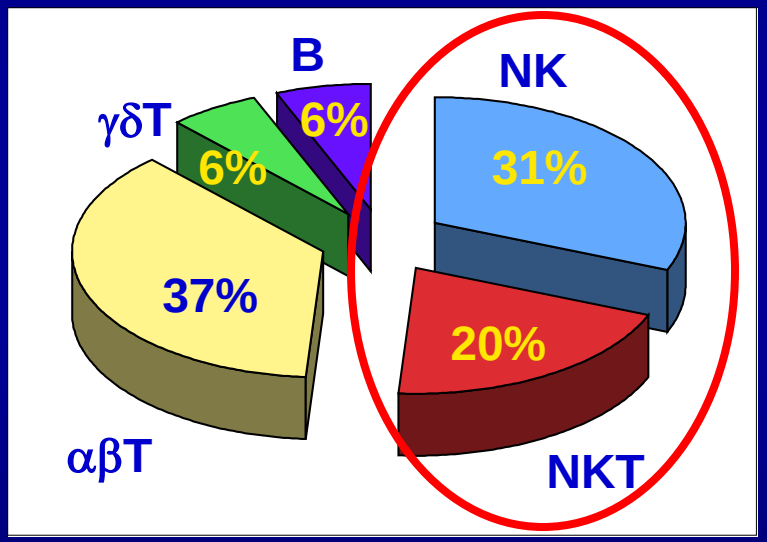


Relative Distribution of Lymphocyte Subsets in PB and Liver

BLOOD

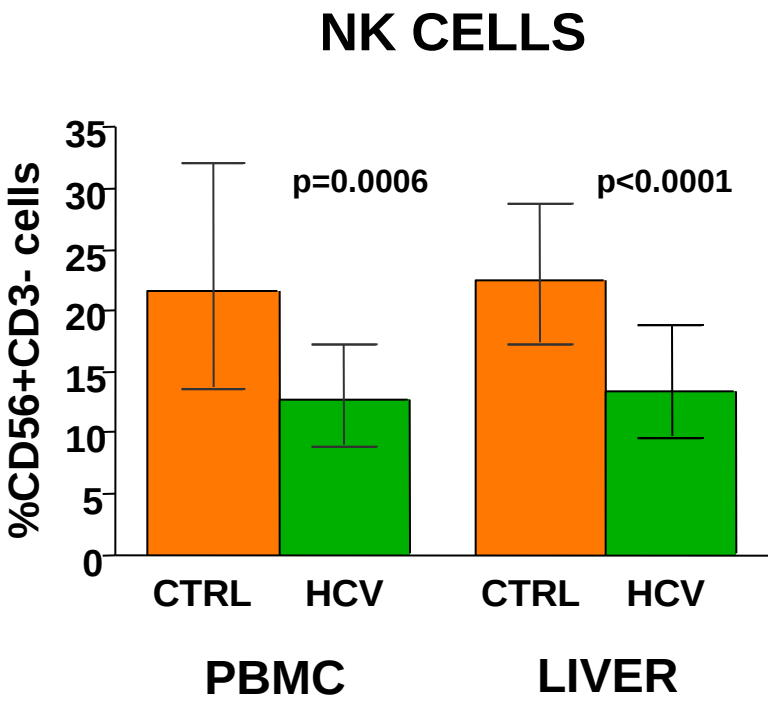


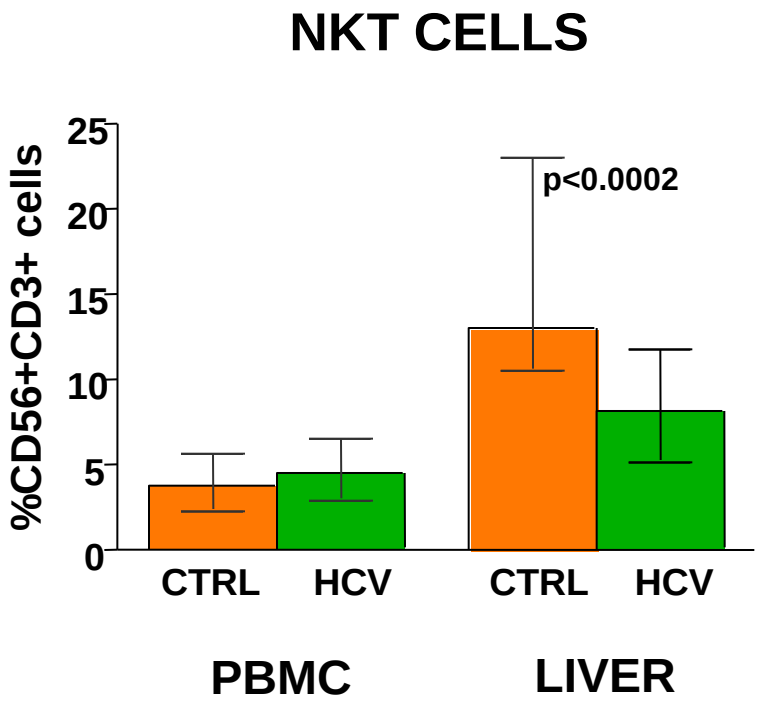
LIVER



Modified from O'Farrelly *Immunol Rev* 2000.

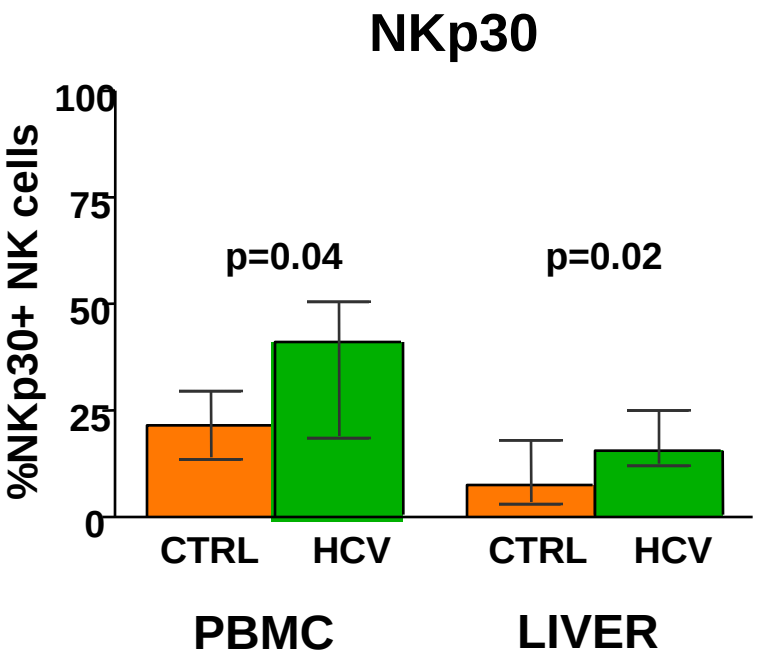
The Proportions of Intrahepatic Innate Immune Cells Are Reduced in Chronic HCV Infection

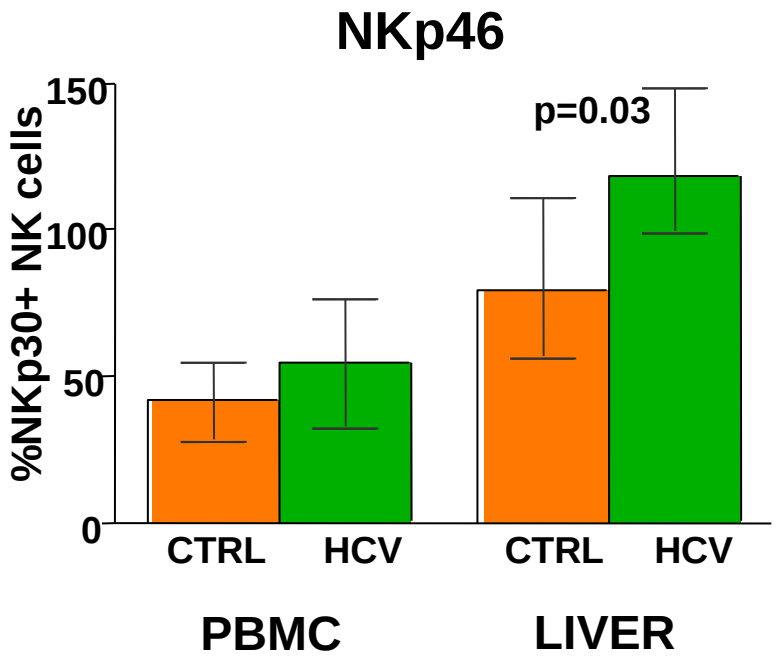




Varchetta et al., AASLD 2009. Abstract 175

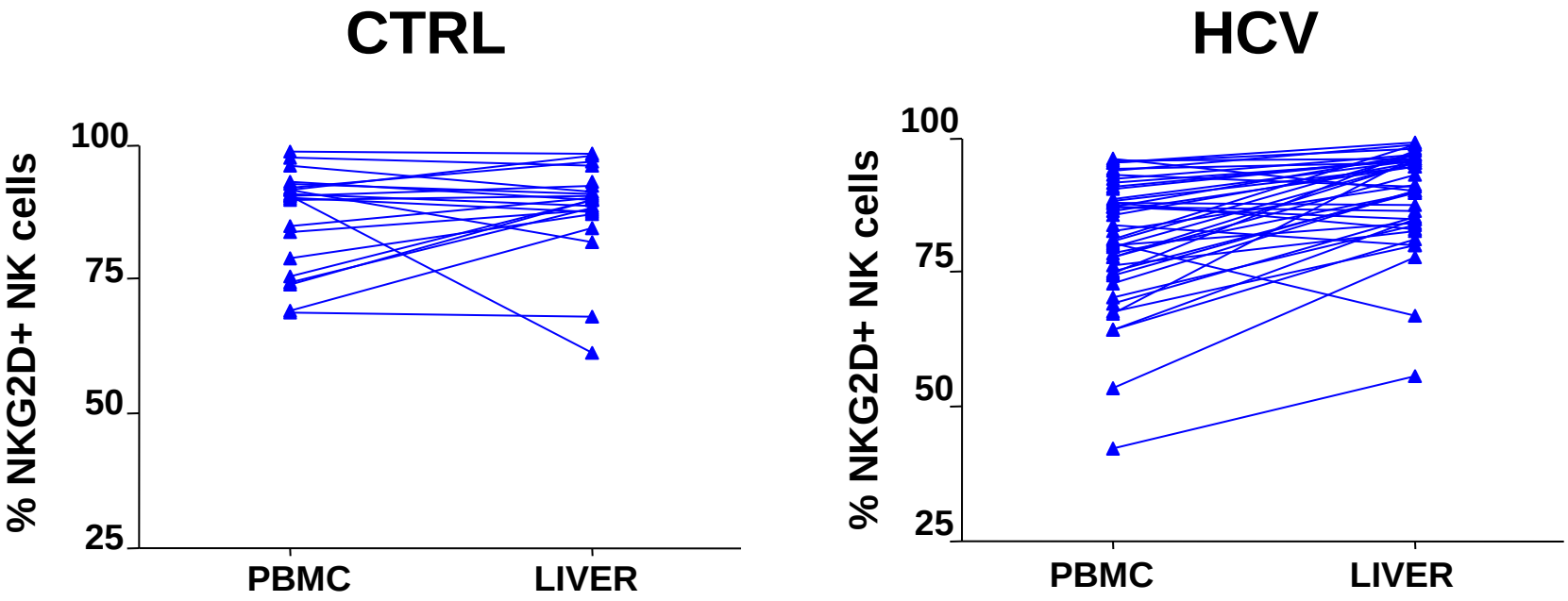
IH NK Cells Expressing NCRs Are Enriched in the HCV-Infected Liver





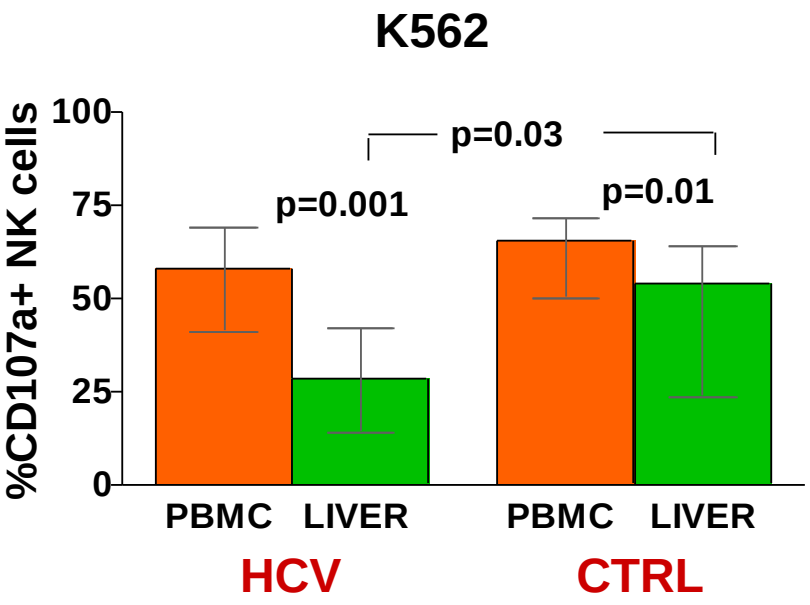
Varchetta et al., AASLD 2009. Abstract 175

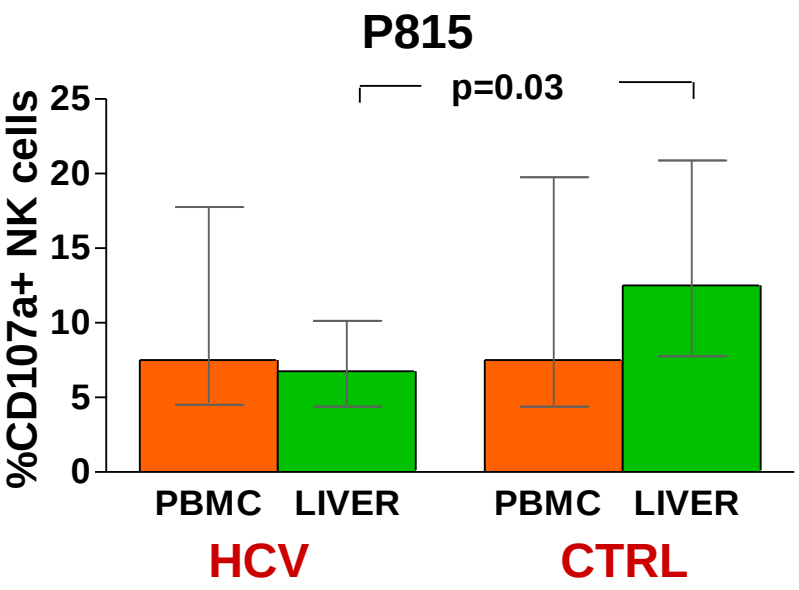
NKG2D+ NK Cells Are Enriched in the HCV-Infected Liver

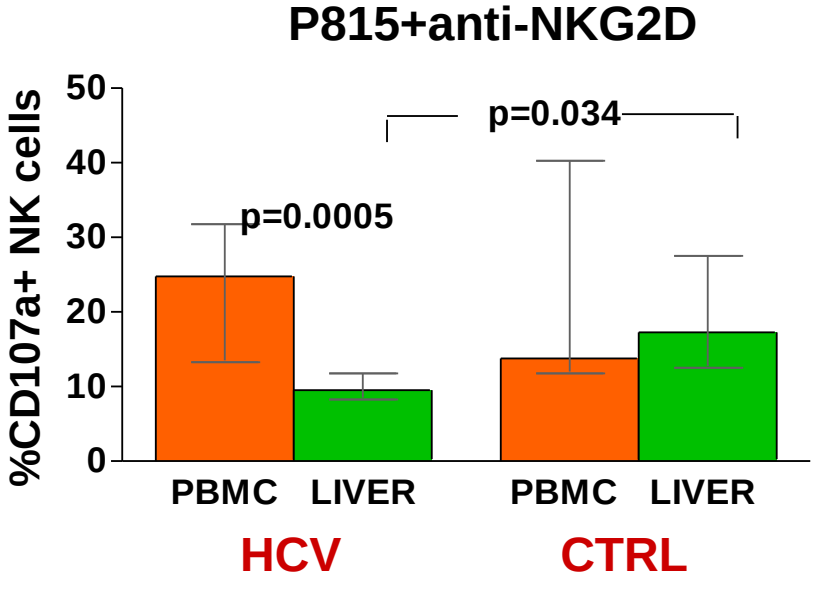


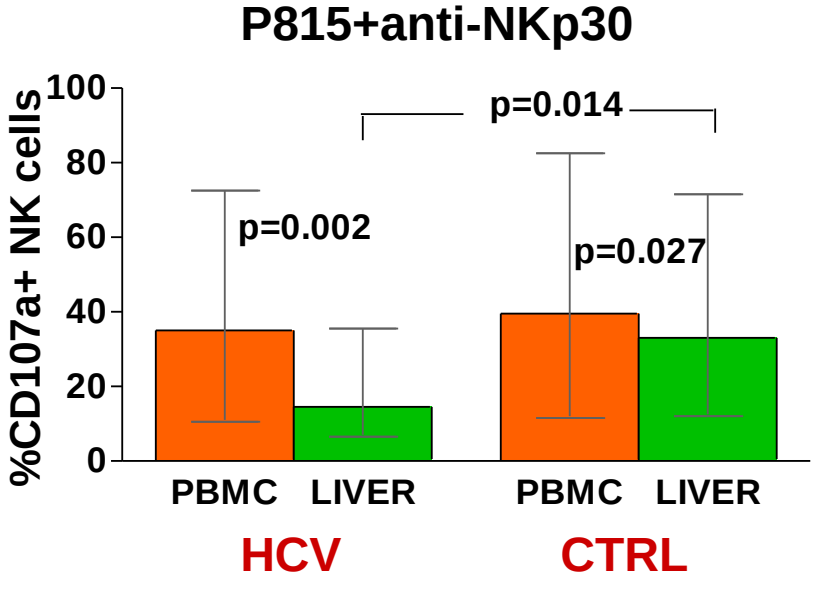
Varchetta et al., AASLD 2009. Abstract 175

IH NK Cells from HCV+ Patients Show Lower Cytotoxic Potential than Control IHNK Cells

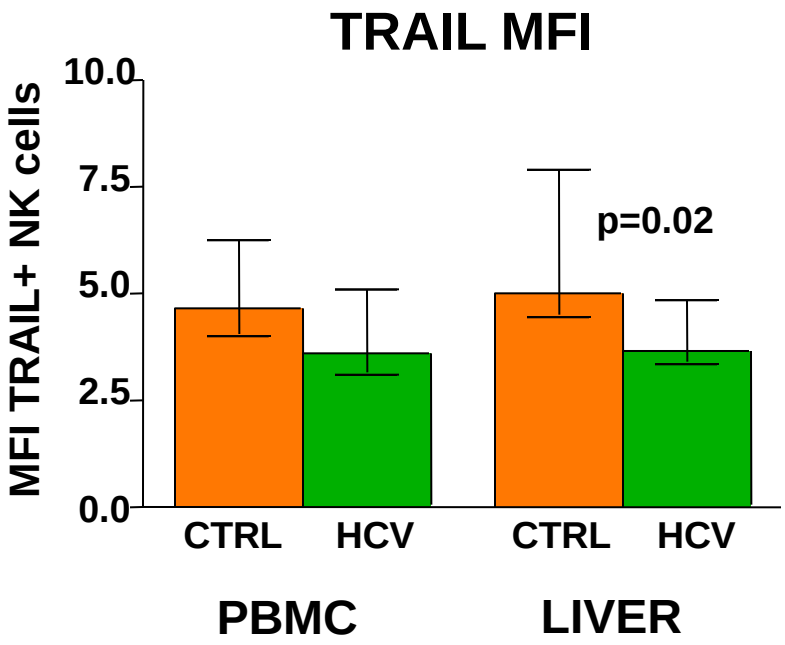








Expression of TRAIL on IH NK Cells Is Lower in HCV-Infected Patients



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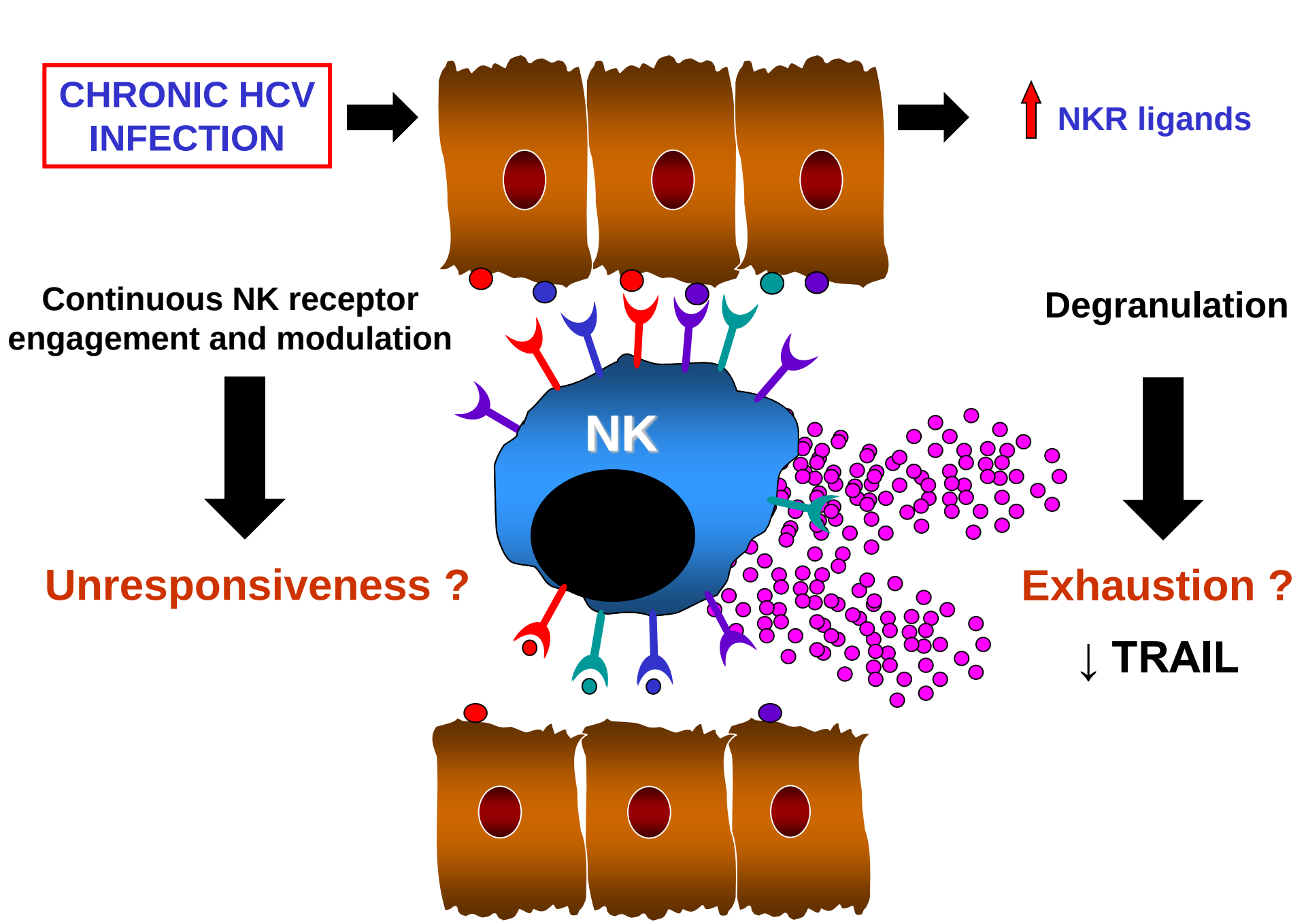
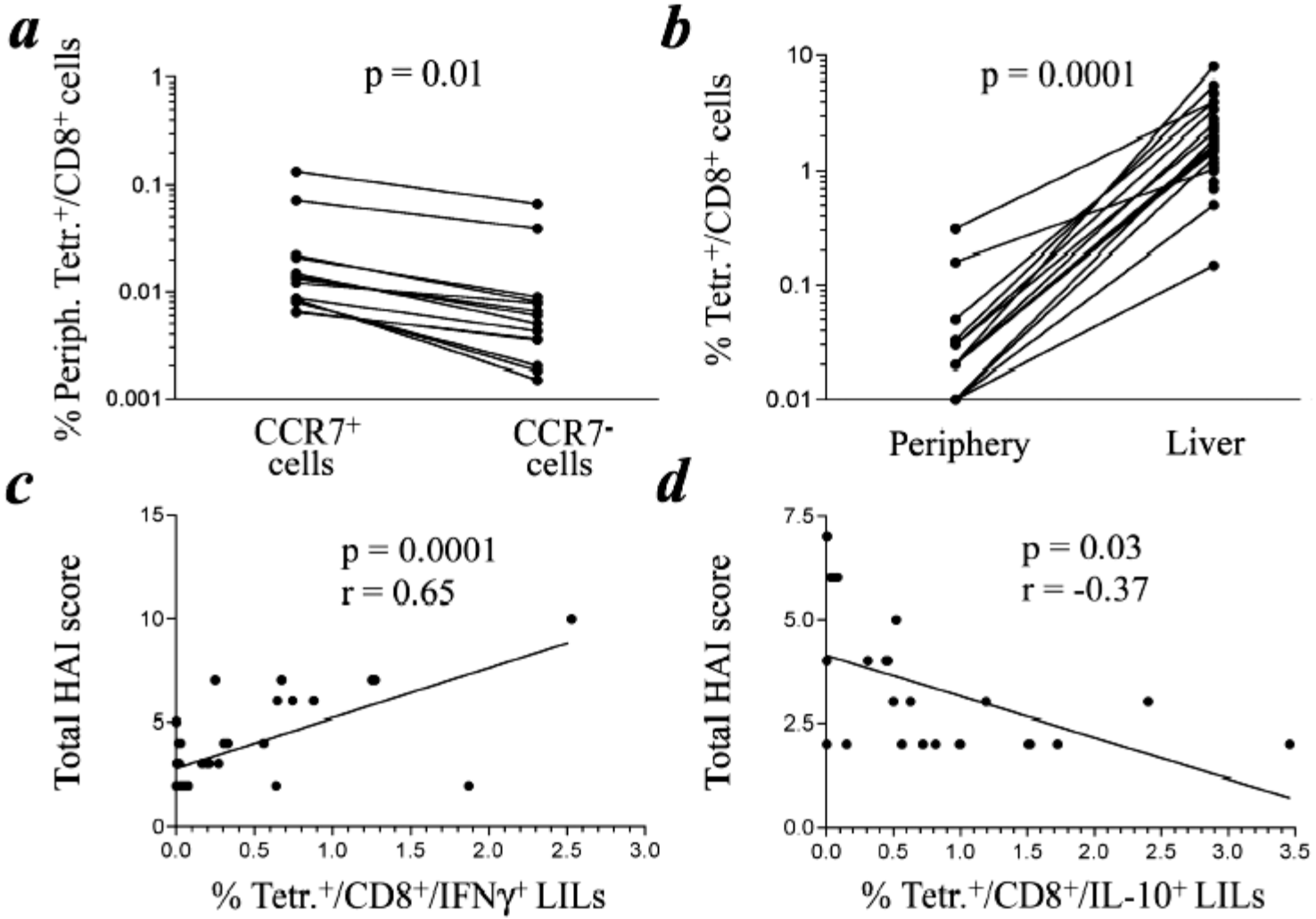
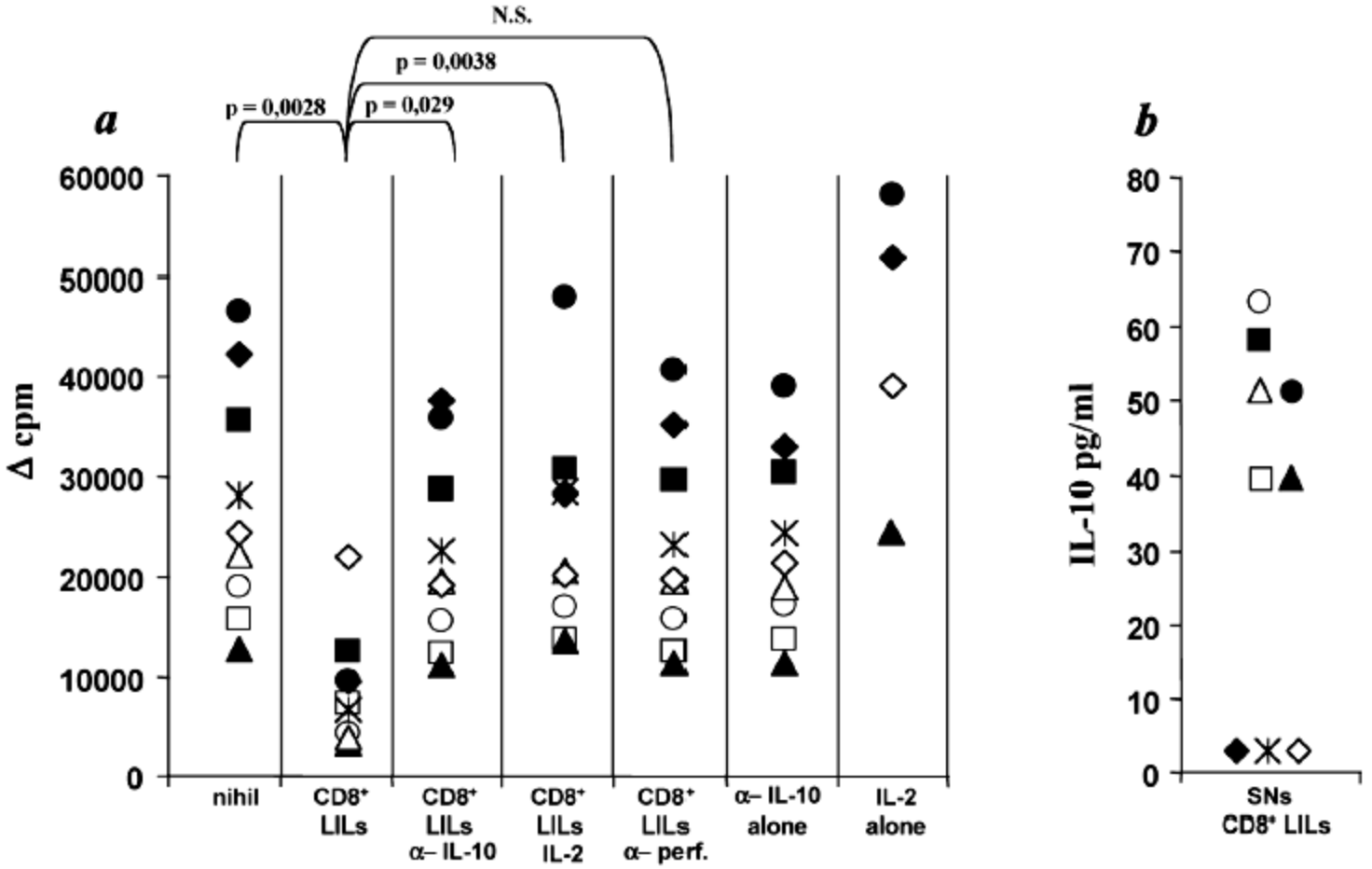

CHRONIC HCV INFECTION
NKR ligands
Continuous NK receptor engagement and modulation
Degranulation
NK
Unresponsiveness ?
Exhaustion ?
↓ TRAIL

CD8+ IL-10 Producing Treg Cells Are Enriched in the Liver of Patients with Chronic HCV Infection

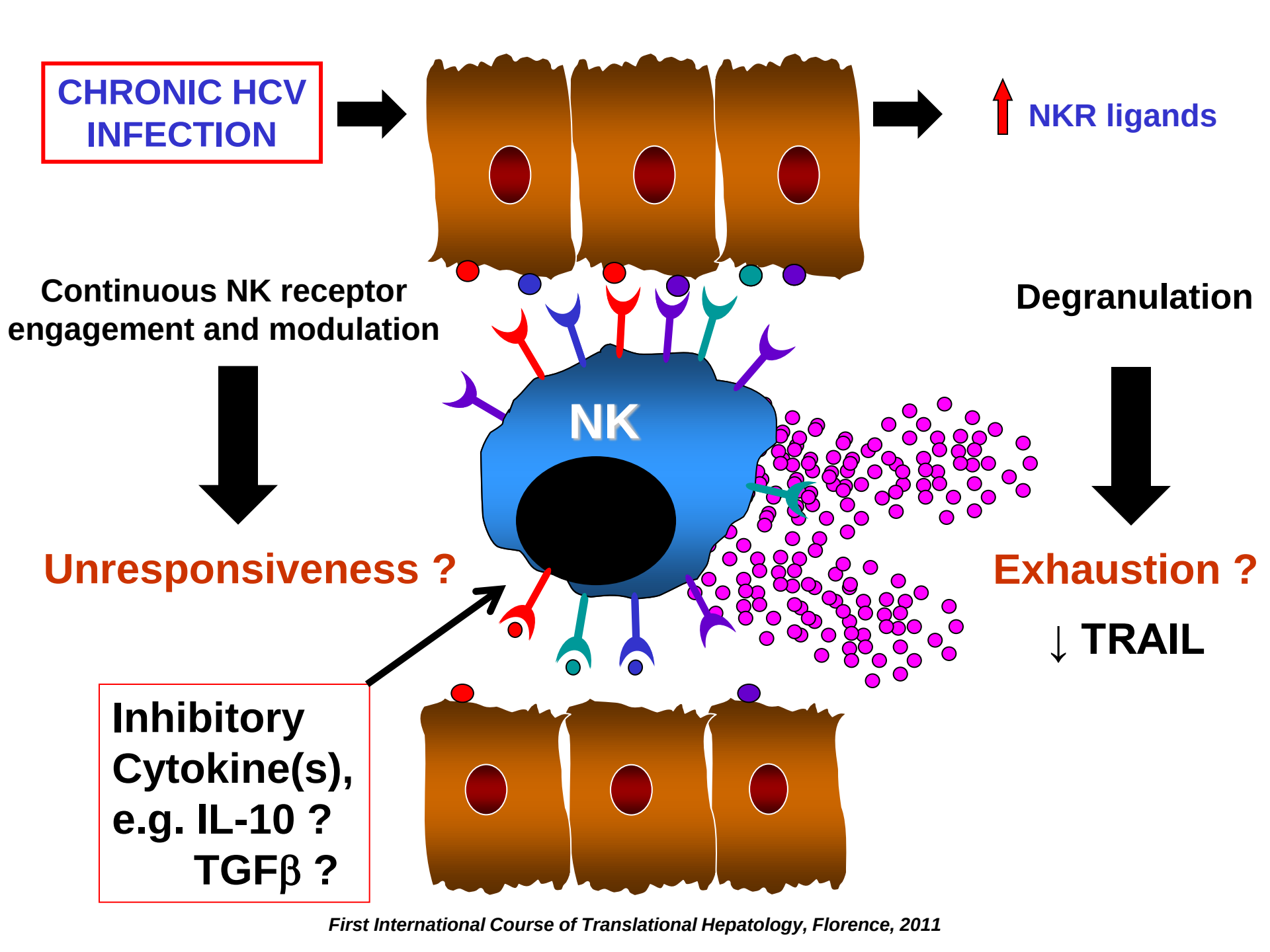


Accapezzato *et al*., *J Clin Invest* 2004;113:963-72

Intrahepatic, IL-10-Producing CD8+ T cells Perform Regulatory Function



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


CHRONIC HCV INFECTION
NKR ligands
Continuous NK receptor engagement and modulation
Degranulation
NK
Unresponsiveness ?
Exhaustion ?
↓ TRAIL
Inhibitory Cytokine(s), e.g. IL-10 ? TGFβ ?

Conclusions

- Impaired intrahepatic NK cytolytic function in HCV infection may represent an additional mechanism contributing to viral escape and persistence.

Acknowledgements

S.C. Laboratori di Infettivologia, Dipartimento di Malattie Infettive,
Fondazione IRCCS Policlinico San Matteo e Università di Pavia

Lab Team:
- Stefania Varchetta
- Barbara Oliviero
- Stefania Mantovani
- Eleonora Cremonesi
- Dalila Mele

Clinical Team:
- Giuseppe Michelone
- Marco Zaramella
- Serena Ludovisi

Collaborators:
- Savino Bruno, Liver Unit, Dept. of Medicine, Ospedale Fatebenefratelli, Milan
- Paolo Dionigi, Andrea Pietrabissa, 1st and 2nd Divisions of Surgery, San Matteo
- Marco Montorsi, Riccardo Rosati, Division of Surgery, ICH, Rozzano.
- Elisabetta Degasperi, Massimo Colombo, IRCCS Ospedale Maggiore…, Milano