

BVHG & BASL SIG HBV Meeting
Chronic Hepatitis B – What is possible & why is it needed?

**Immunological approaches to achieving
functional cure for Chronic Hepatitis B**

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Declaration

- Conflicts of interest
None
- Honoraria and sponsorship
JNJ – educational funding

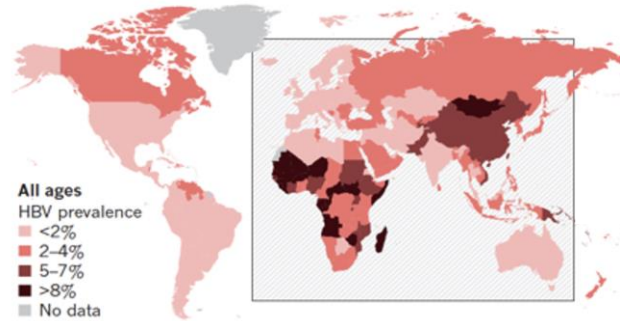
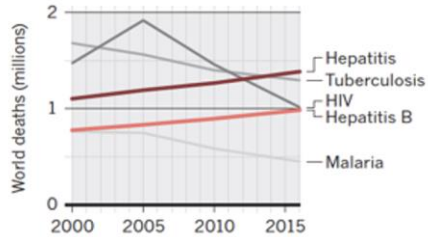
Chronic Hepatitis B – unmet needs

THE BURDEN OF HEPATITIS B

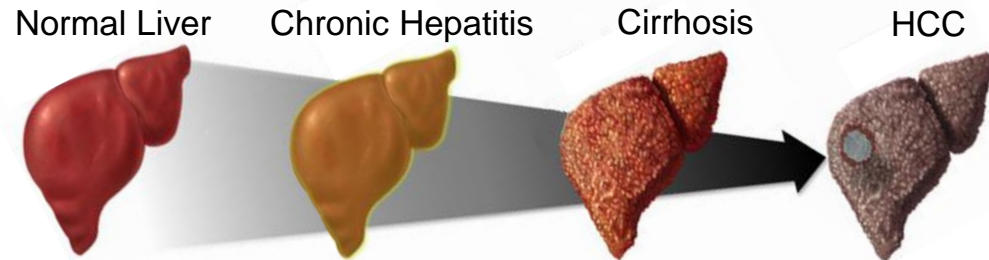
More than 250 million people live with the virus; few of them are diagnosed and not enough children are vaccinated against it.

Rising death toll

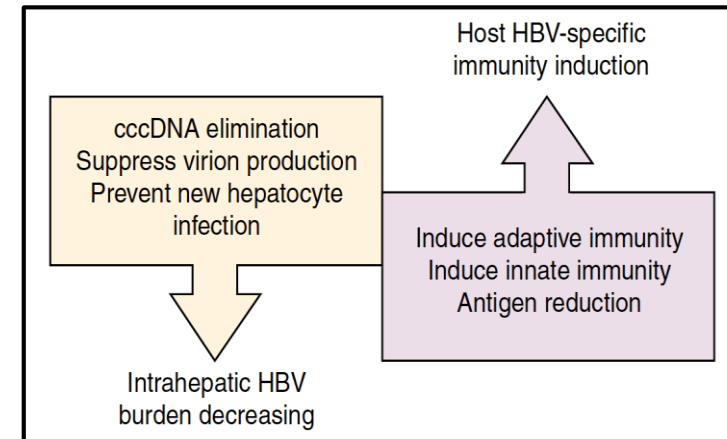
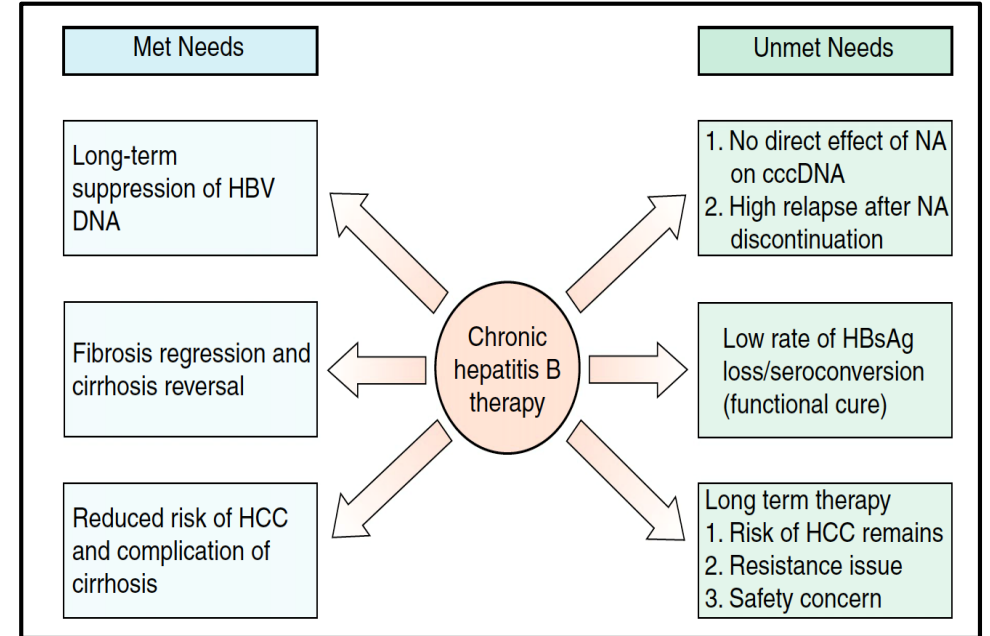
Hepatitis infections are now associated with more deaths globally than are tuberculosis, HIV or malaria.



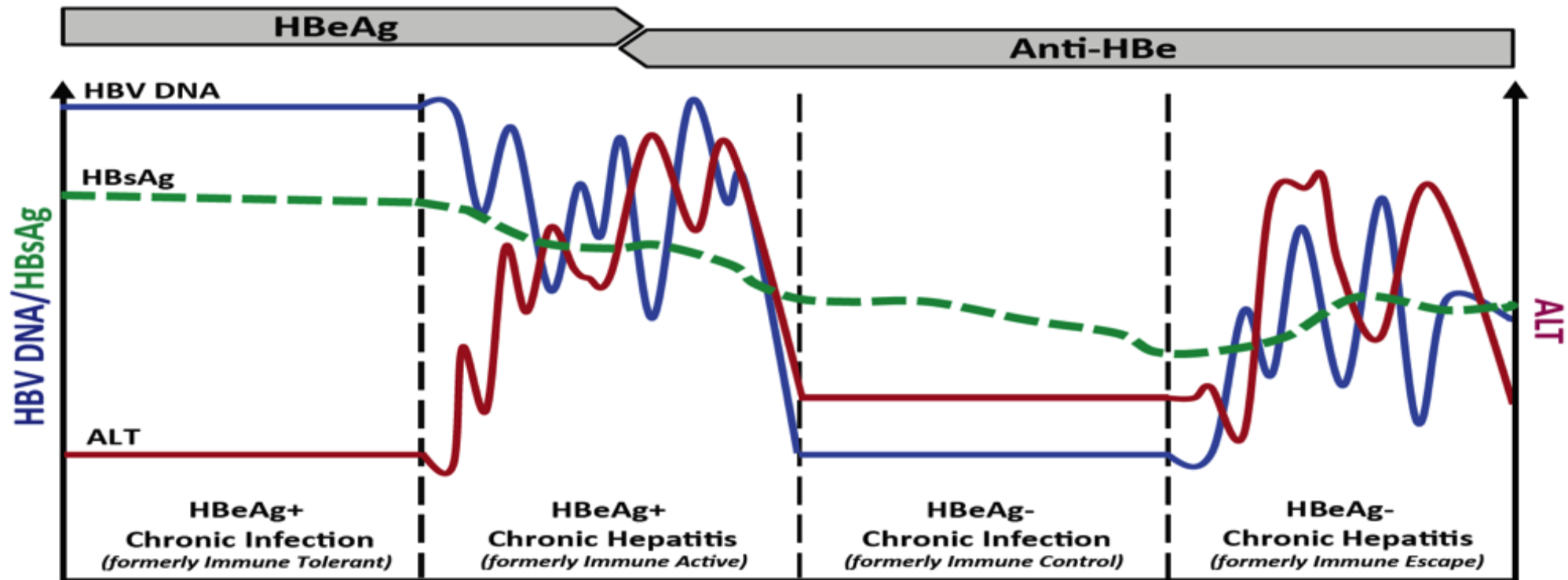
Graber-Stiehl, Nature News 2018



- High prevalence of Hepatitis B in East London
- Leading cause of LIVER CANCER globally
- Liver damage is immune mediated
- Current antivirals lower viral load, but not 'curative'



Natural history & disease phase of CHB



Adapted from Gill & Kennedy, Clin Med 2015

Clinical Practice Guidelines

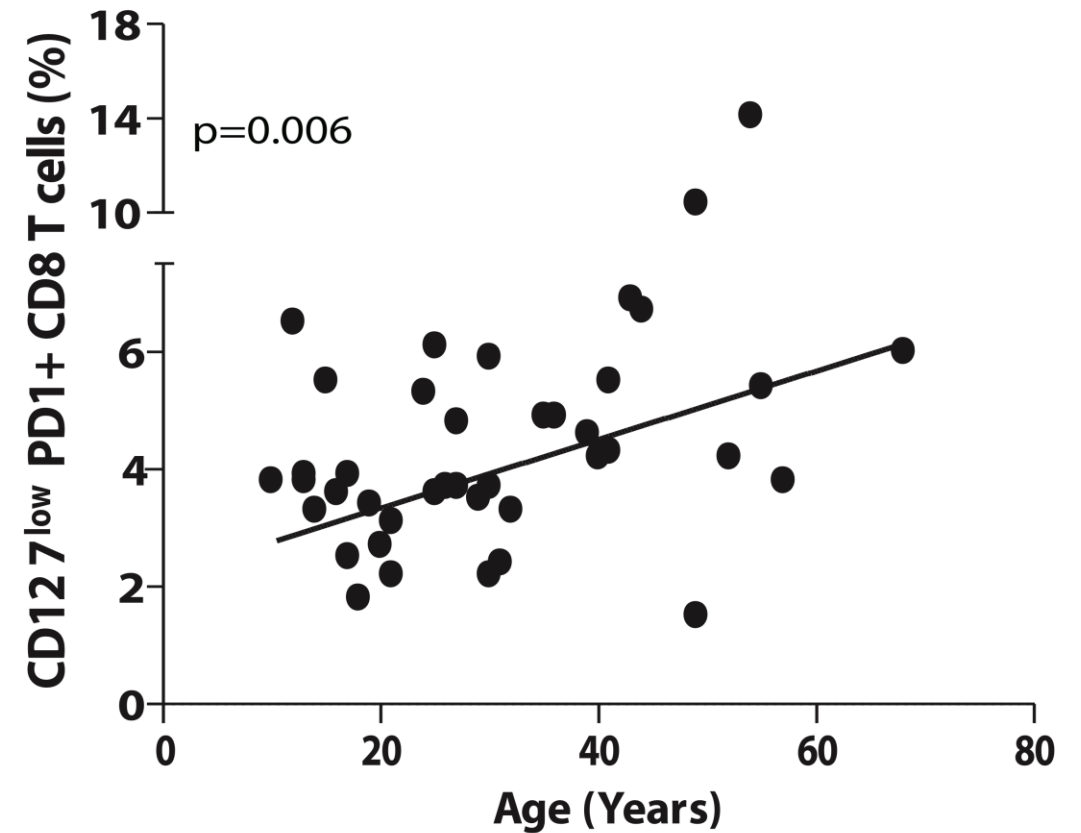
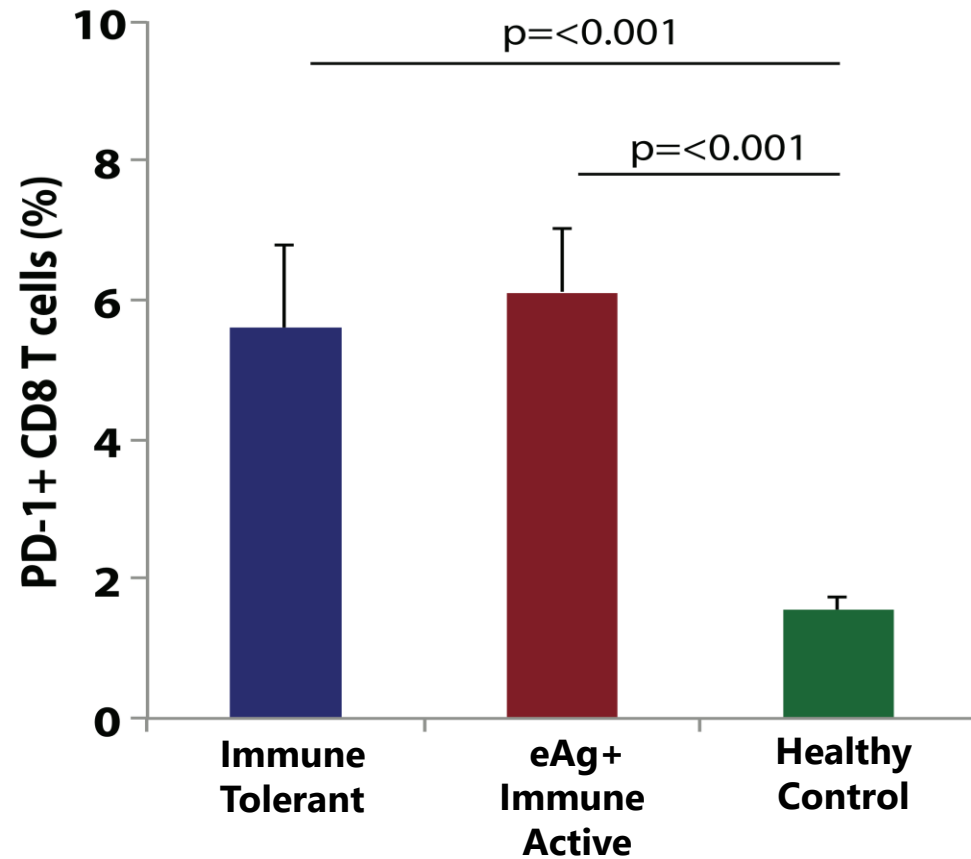
 **EASL** | JOURNAL OF HEPATOLOGY

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection ☆

European Association for the Study of the Liver*

T cell responses in HBeAg positive chronic infection

Evidence of immune activity in the 'immune tolerant' disease phase

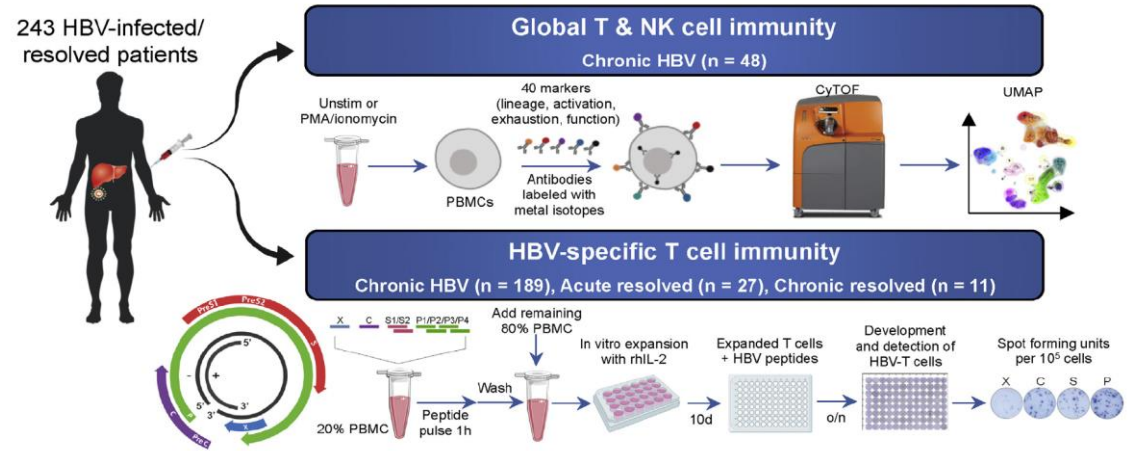


Age related immune changes in chronic hepatitis B

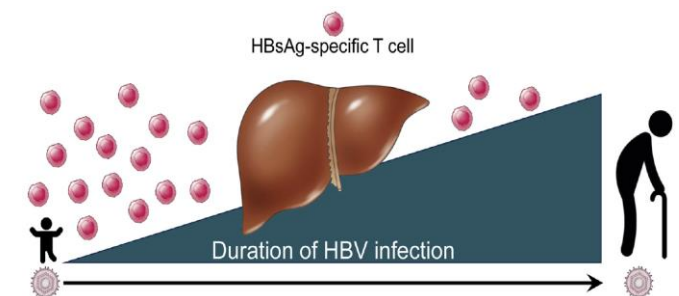
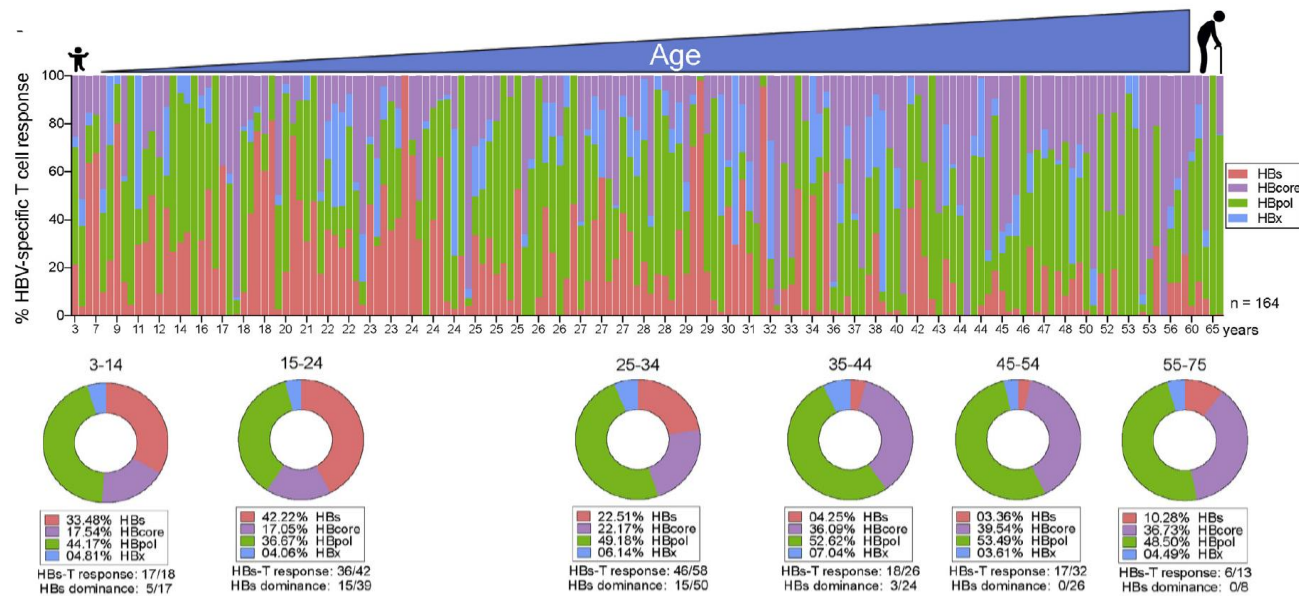
Gastroenterology 2020;159:652–664

Effects of Hepatitis B Surface Antigen on Virus-Specific and Global T Cells in Patients With Chronic Hepatitis B Virus Infection

Nina Le Bert,^{1,*} Upkar S. Gill,^{2,*} Michelle Hong,^{1,*} Kamini Kunasegaran,¹ Damien Z. M. Tan,¹ Raidah Ahmad,¹ Yang Cheng,³ Charles-A. Dutertre,^{1,3} Andreas Heinecke,⁴ Laura Rivino,^{1,5} Anthony Tan,¹ Navjyot K. Hansi,² Min Zhang,⁶ Sujuan Xi,⁶ Yutian Chong,⁶ Stefan Pflanz,⁷ Evan W. Newell,³ Patrick T. F. Kennedy,^{2,§} and Antonio Bertoletti^{1,3,§}

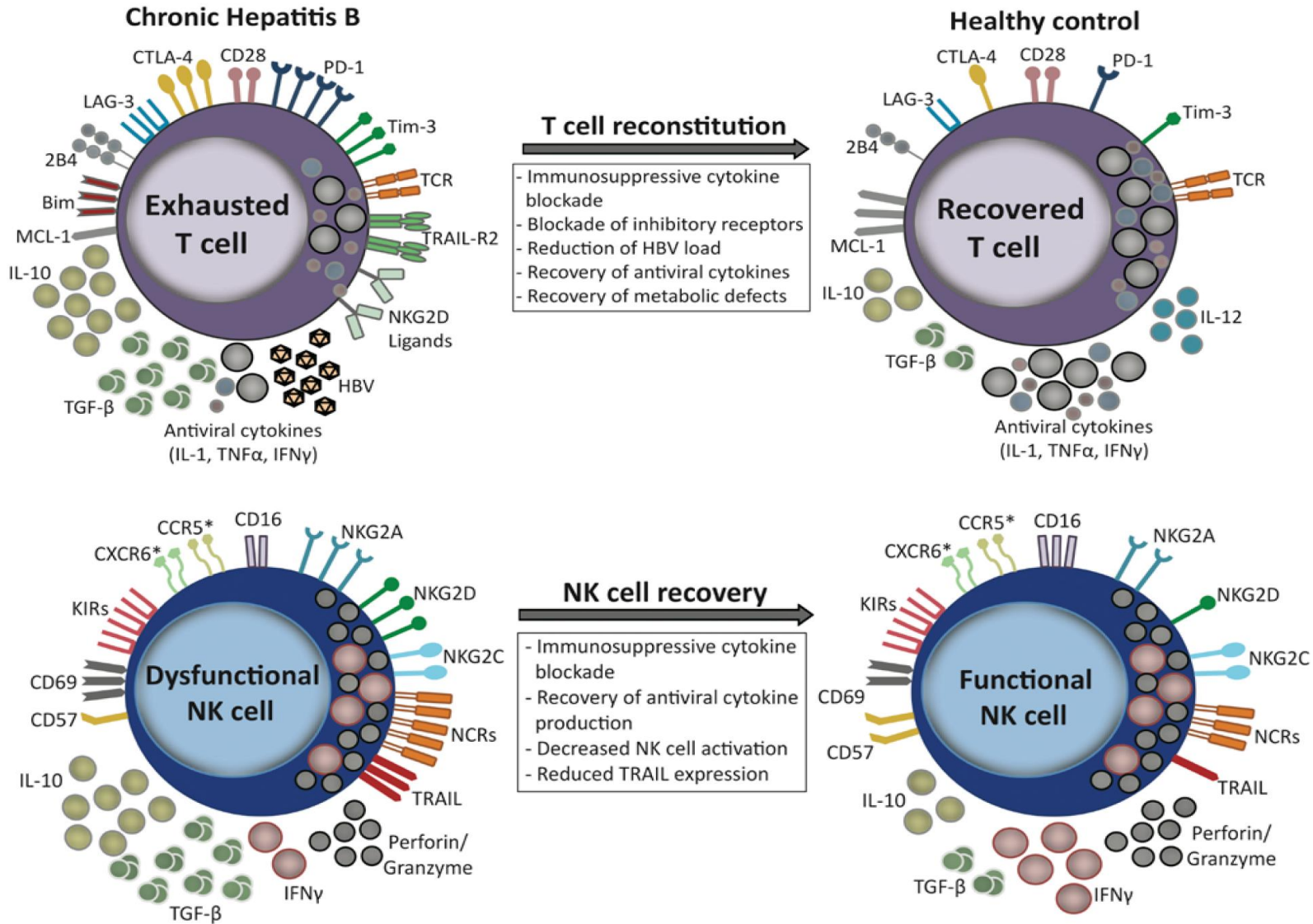


HBs-specific T cells reduce based on duration of infection, rather than HBsAg quantity



- HBV-specific T cells ↓ with age
- Earlier treatment may be beneficial for HBsAg loss

Dysfunctional immune responses in CHB



Boni, Fiscaro et al., *J Virol* 2007

Lopes, Kellam et al., *JCI* 2008

Schurich, Khanna et al., *Hepatology* 2011

Nebbia, Peppia et al., *PLoS One* 2012

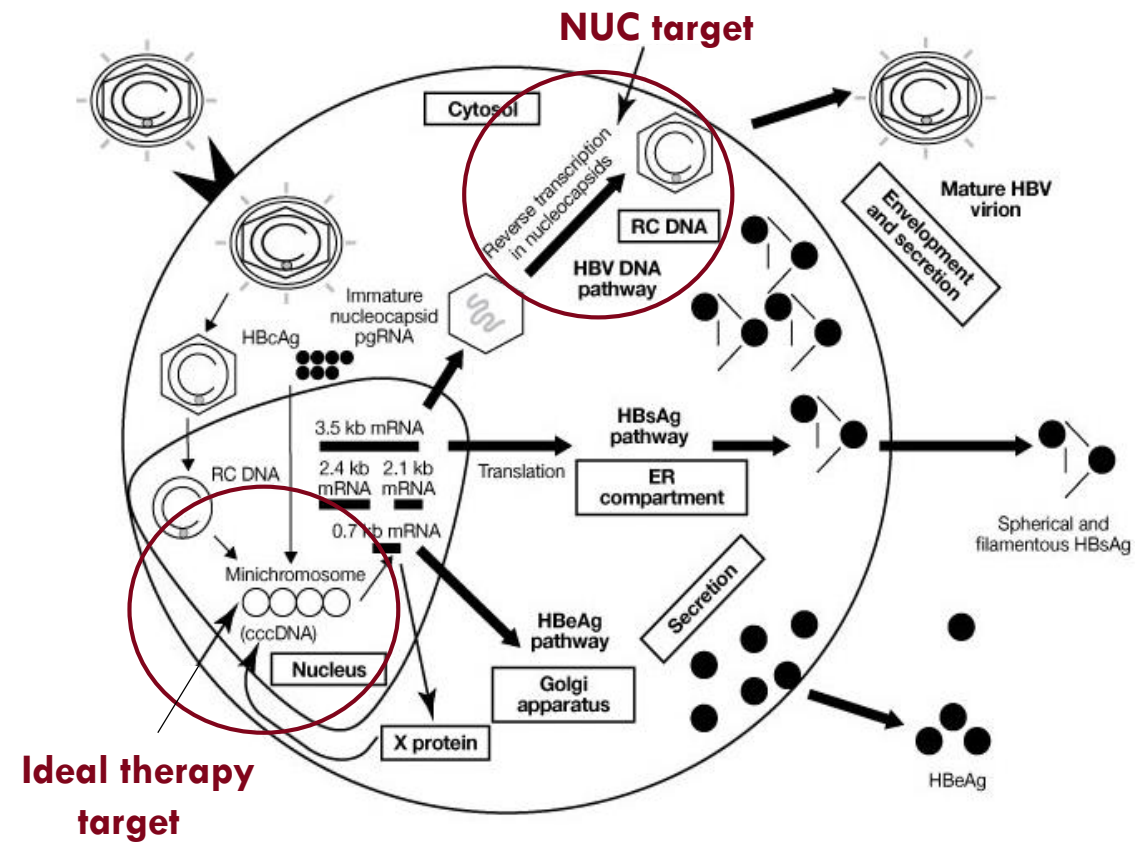
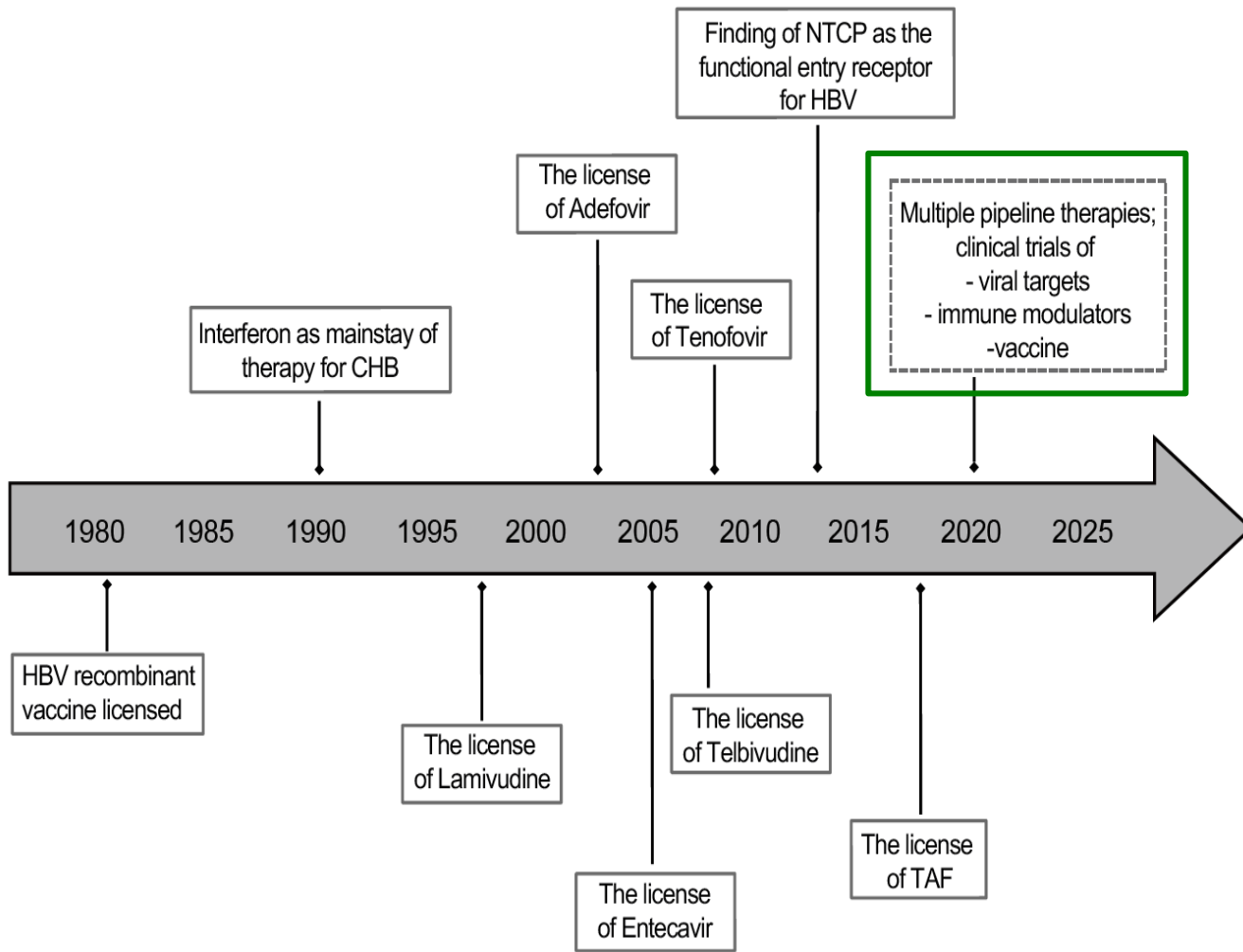
Bonorino, Ramzan et al., *J Hepatol* 2009

Oliviera, Varchetta et al., *Gastroenterology* 2009

Peppia, Micco et al., *PLoS Pathog.* 2010

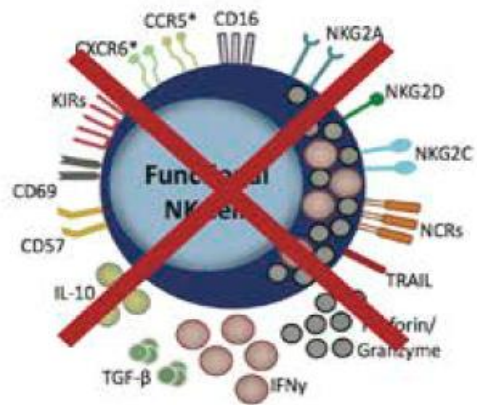
Lunemann, Malone et al., *JID* 2014

Current therapies for chronic hepatitis B

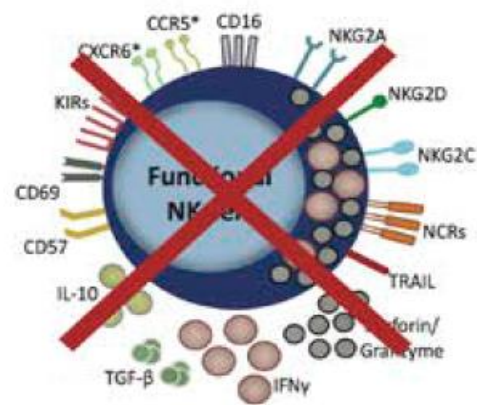


Differential immune responses with HBV therapies

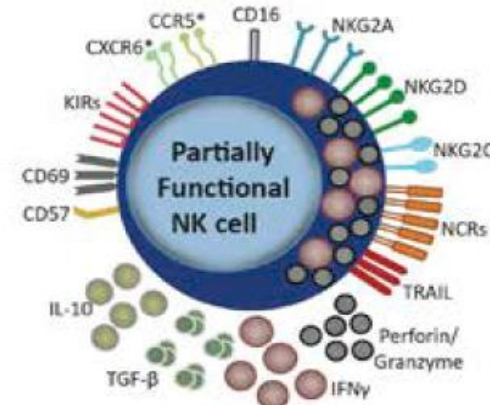
Chronic Hepatitis B



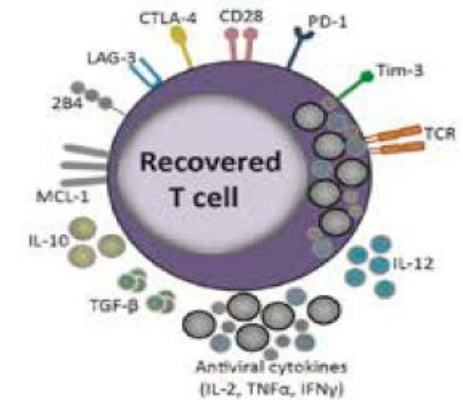
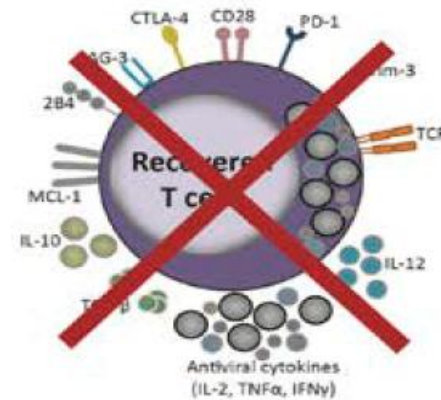
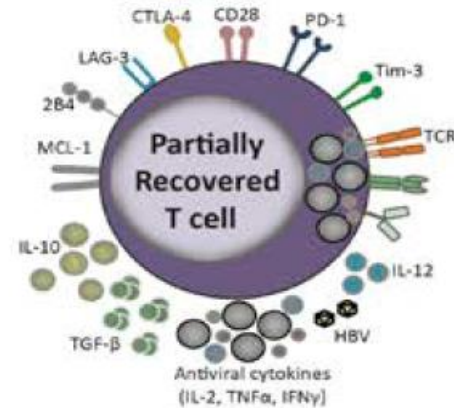
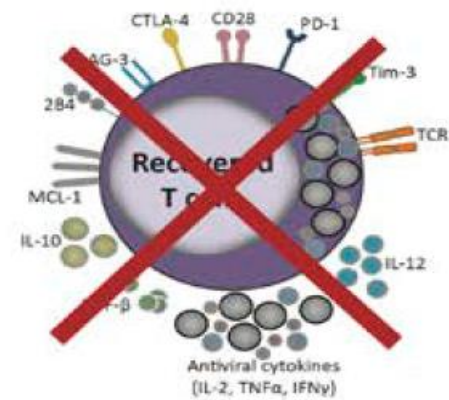
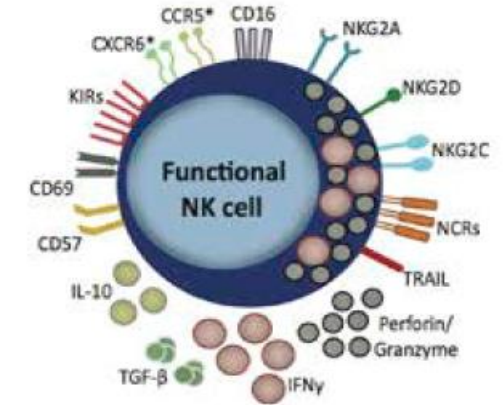
NUC therapy



PegIFNα therapy



**Sequential/combo
PegIFNα/NUC therapy**



Immune Restoration

Improved immune cell function following Interferon priming

Research Article

EASL | JOURNAL OF HEPATOLOGY

Restoration of T cell function in chronic hepatitis B patients upon treatment with interferon based combination therapy

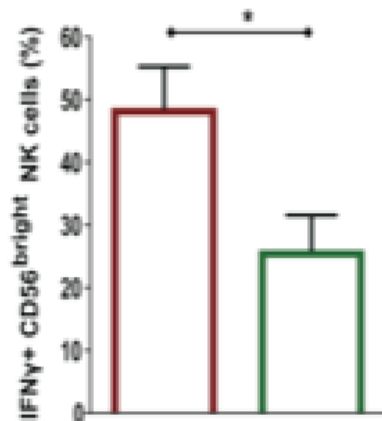
Annikki de Niet^{1,2,†}, Femke Stelma^{1,2,†}, Louis Jansen^{1,2}, Marjan J. Sinnige², Ester B.M. Remmerswaal², R. Bart Takkenberg¹, Neeltje A. Kootstra², Hendrik W. Reesink^{1,2,*}, Rene A.W. van Lier^{2,3}, Ester M.M. van Leeuwen²

PLOS | PATHOGENS

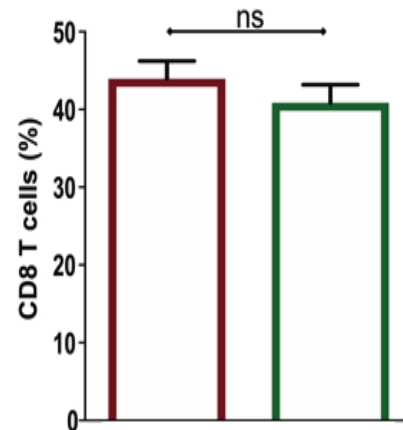
Interferon Alpha Induces Sustained Changes in NK Cell Responsiveness to Hepatitis B Viral Load Suppression In Vivo

Upkar S. Gill^{1,2}, Dimitra Peppas³, Lorenzo Micco³, Harsimran D. Singh³, Ivana Carey⁴, Graham R. Foster^{1,2}, Mala K. Maini^{3†*}, Patrick T. F. Kennedy^{1,2†*}

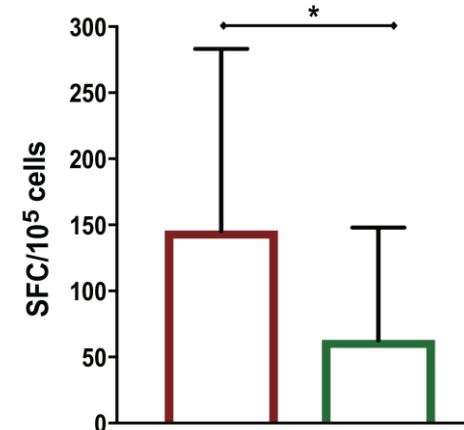
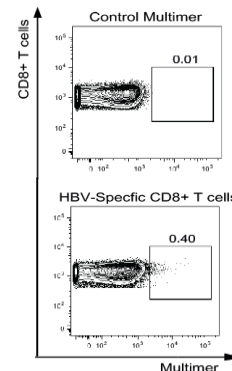
NK cell cytokine production



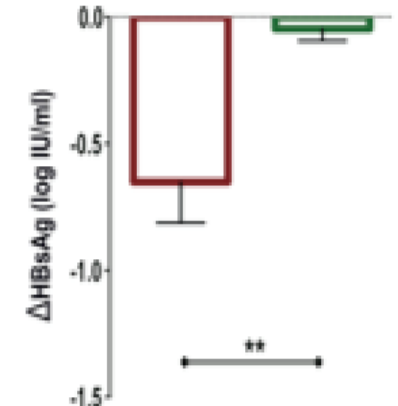
Global CD8 T cells



HBV-specific T cells



Clinical Response



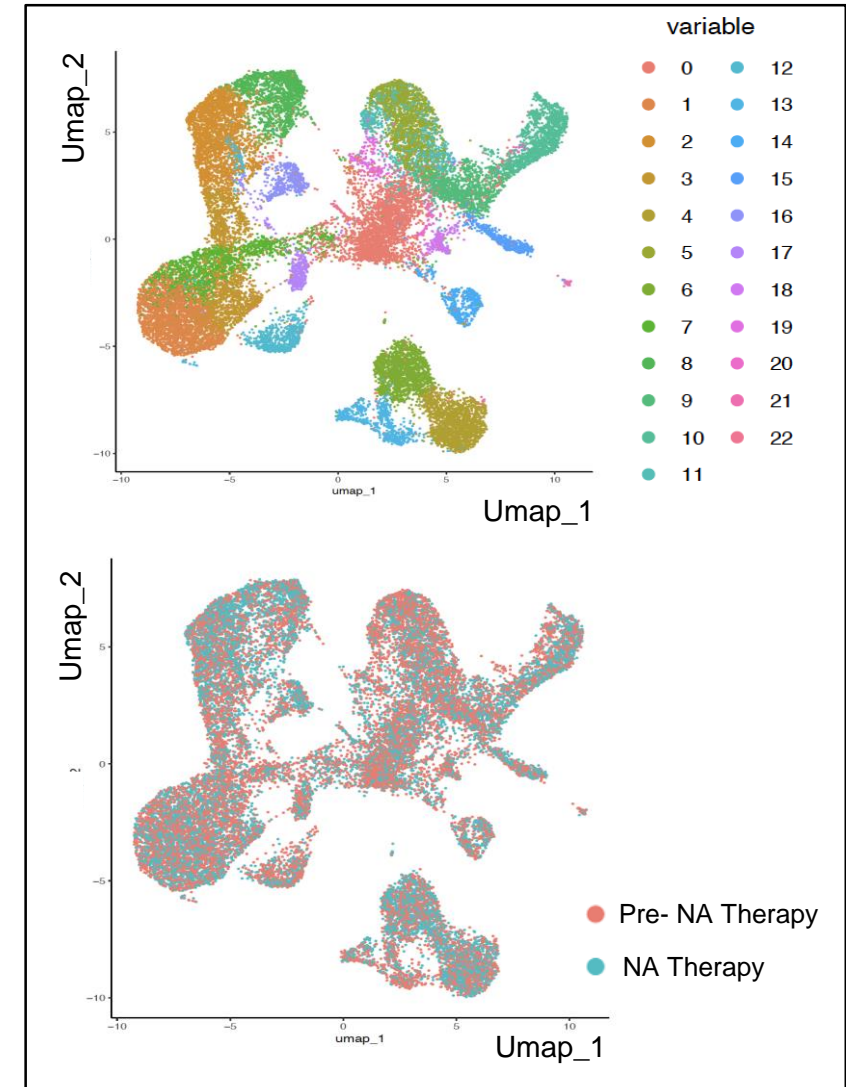
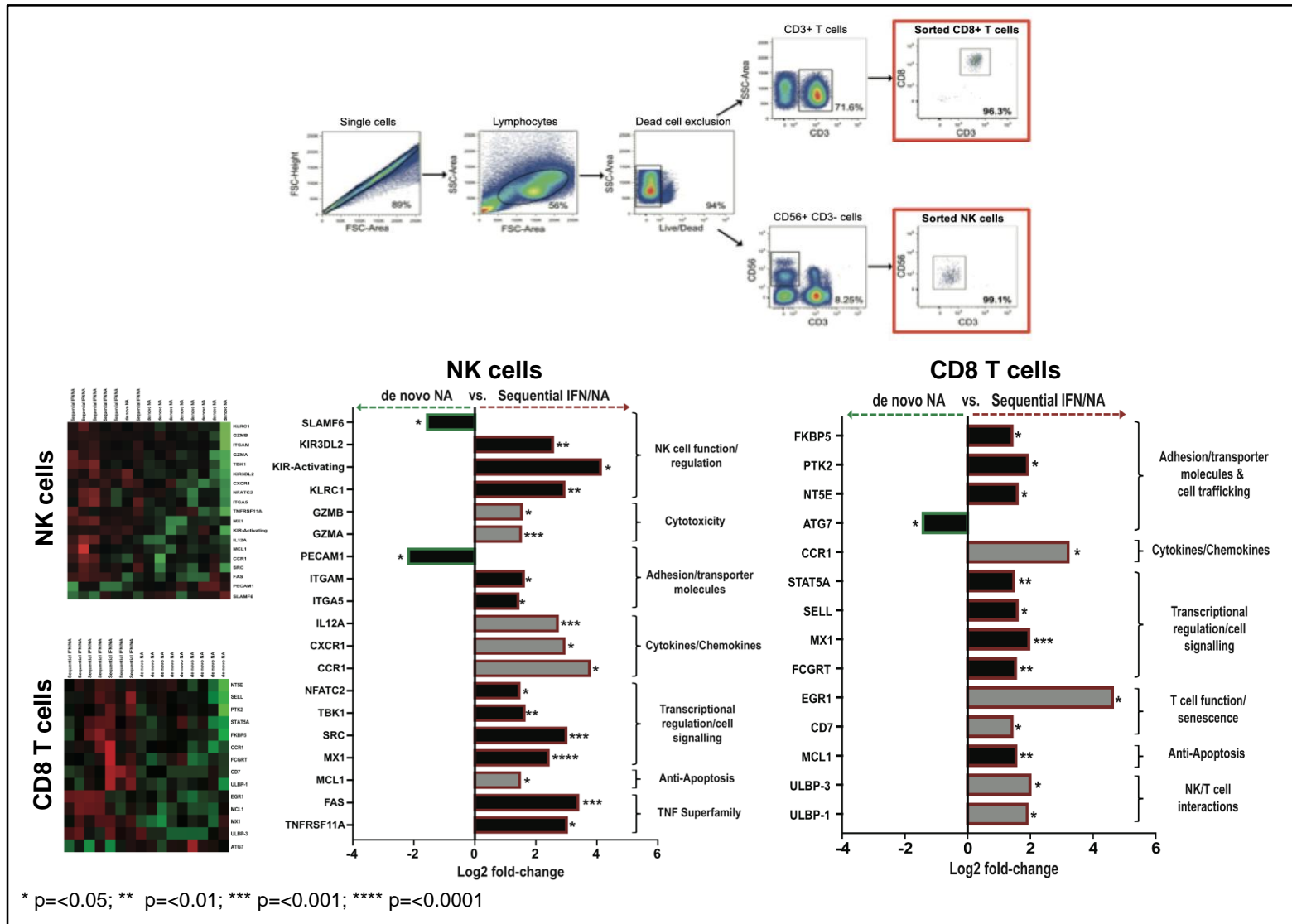
Sequential IFN/NA (red box)
de novo NA (green box)

* p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001; ns=not significant

Comparative analysis of the transcriptome in treated CHB patients

Analysis of mRNA transcripts of sorted immune cells using NanoString Technology

Single cell RNA sequencing analysis of treated CHB patients



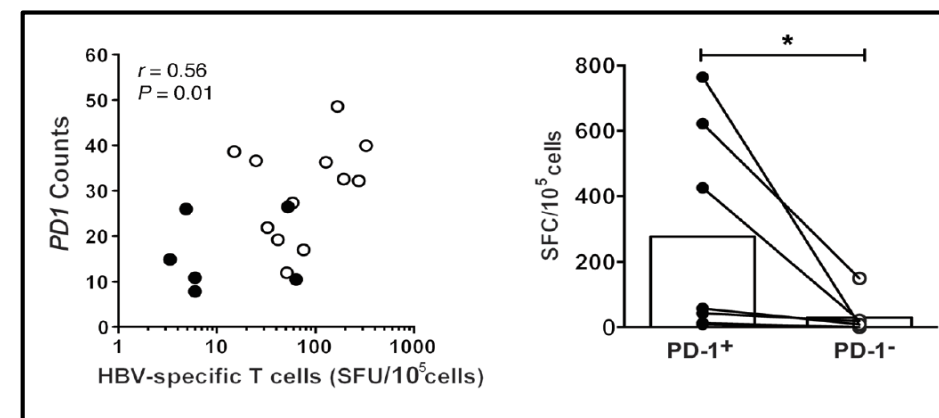
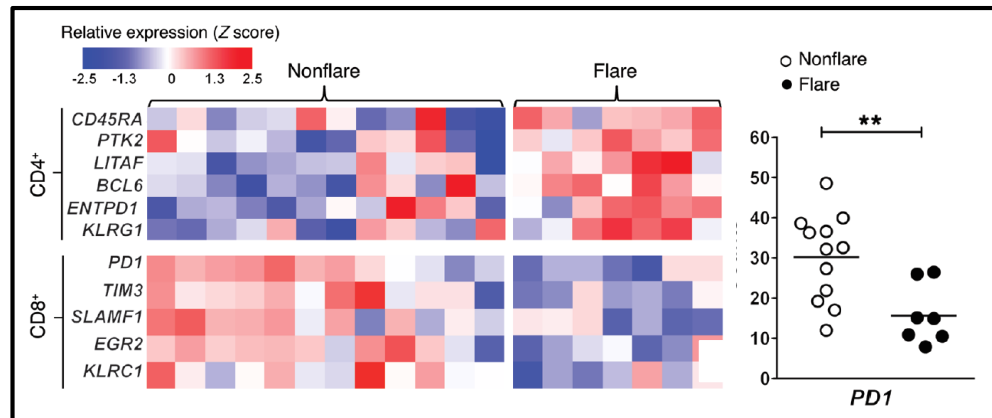
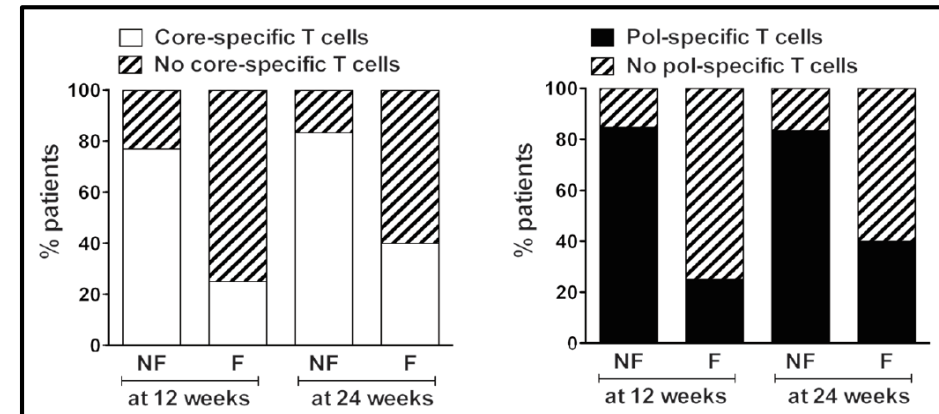
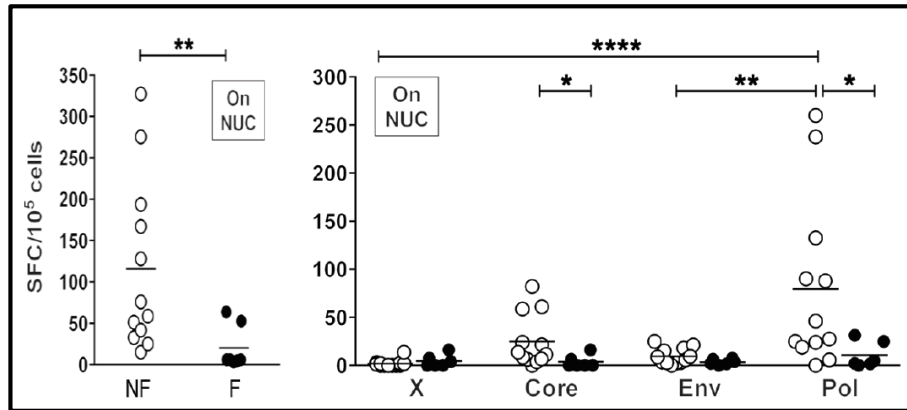
Differential HBV-specific T cell responses in patients controlling virus following treatment discontinuation

CLINICAL MEDICINE

The Journal of Clinical Investigation

Hepatitis B virus-specific T cells associate with viral control upon nucleos(t)ide-analogue therapy discontinuation

Laura Rivino,¹ Nina Le Bert,^{1,2} Upkar S. Gill,^{1,3} Kamini Kunasegaran,¹ Yang Cheng,⁴ Damien Z.M. Tan,² Etienne Becht,⁴ Navjyot K. Hansi,³ Graham R. Foster,³ Tung-Hung Su,⁵ Tai-Chung Tseng,⁵ Seng Gee Lim,⁶ Jia-Horng Kao,⁵ Evan W. Newell,⁴ Patrick T.F. Kennedy,³ and Antonio Bertolotti^{1,2,4}

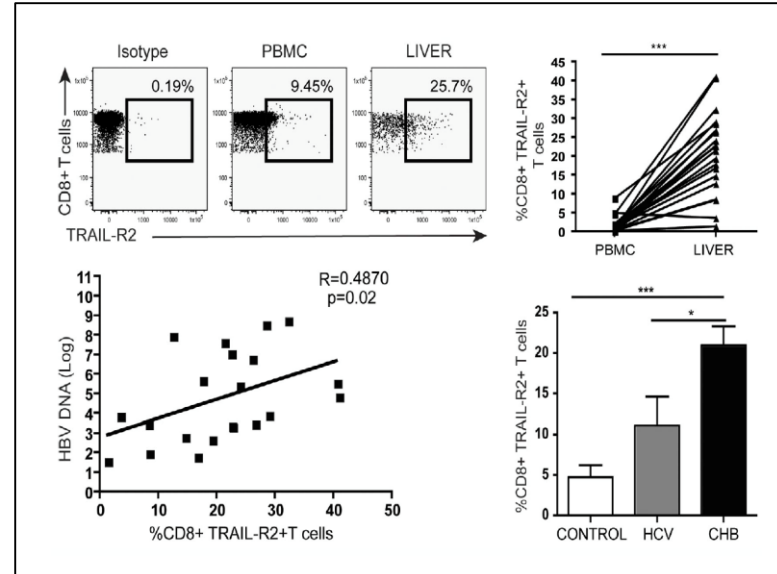
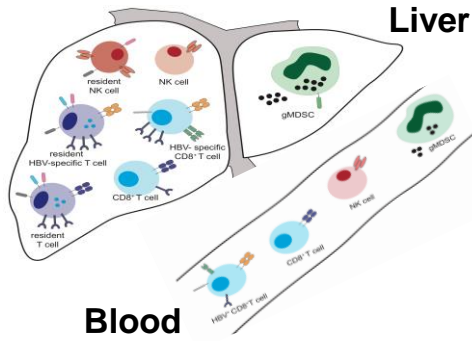


Do we need to sample the intrahepatic compartment?

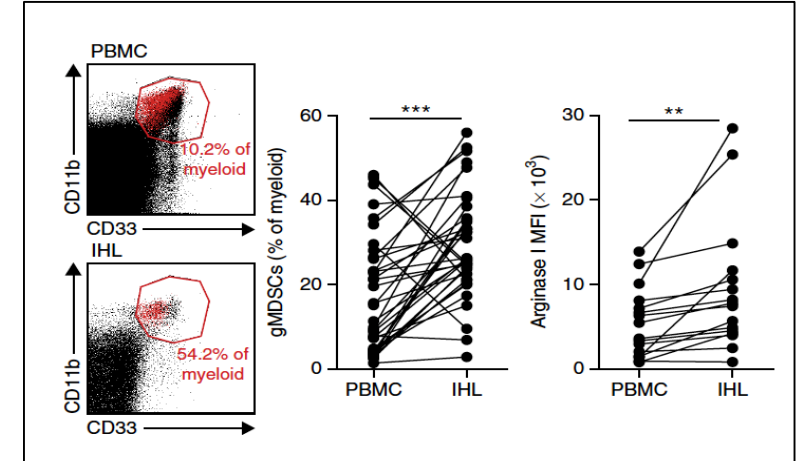
Recent advances in basic science

Liver sampling: a vital window into HBV pathogenesis on the path to functional cure

Upkar S Gill,¹ Laura J Pallett,² Patrick T F Kennedy,¹ Mala K Maini²

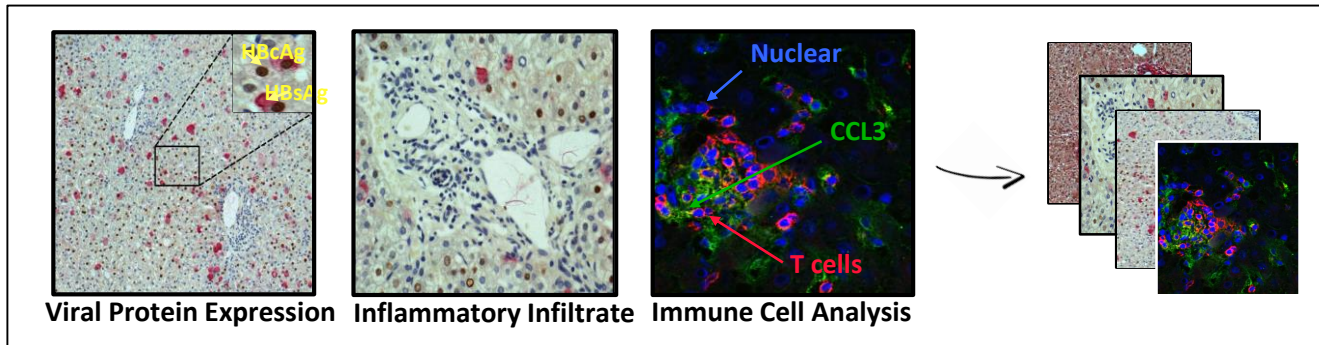


Peppas, Gill et al., JEM 2013

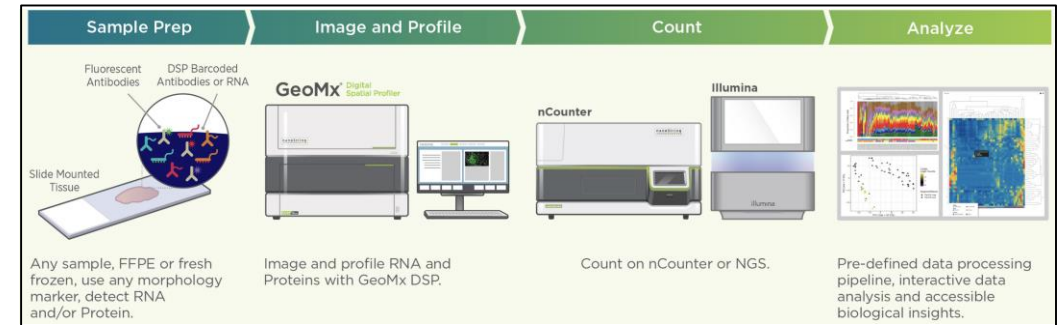


Pallett, Gill et al., Nat Med 2015

- Comparisons with blood & tissue; immune populations 'exaggerated' in liver



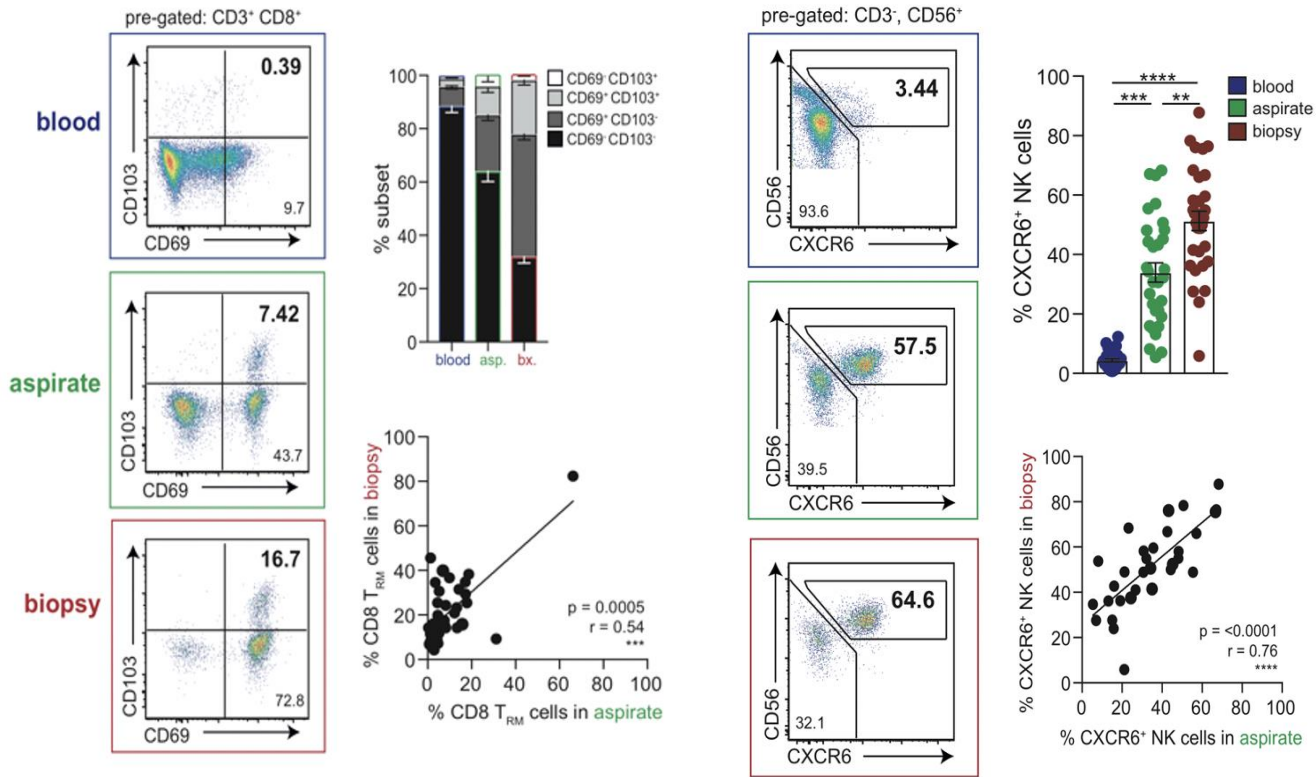
Mason, Gill et al., Gastroenterology 2016 & Courtesy Shishir Shetty



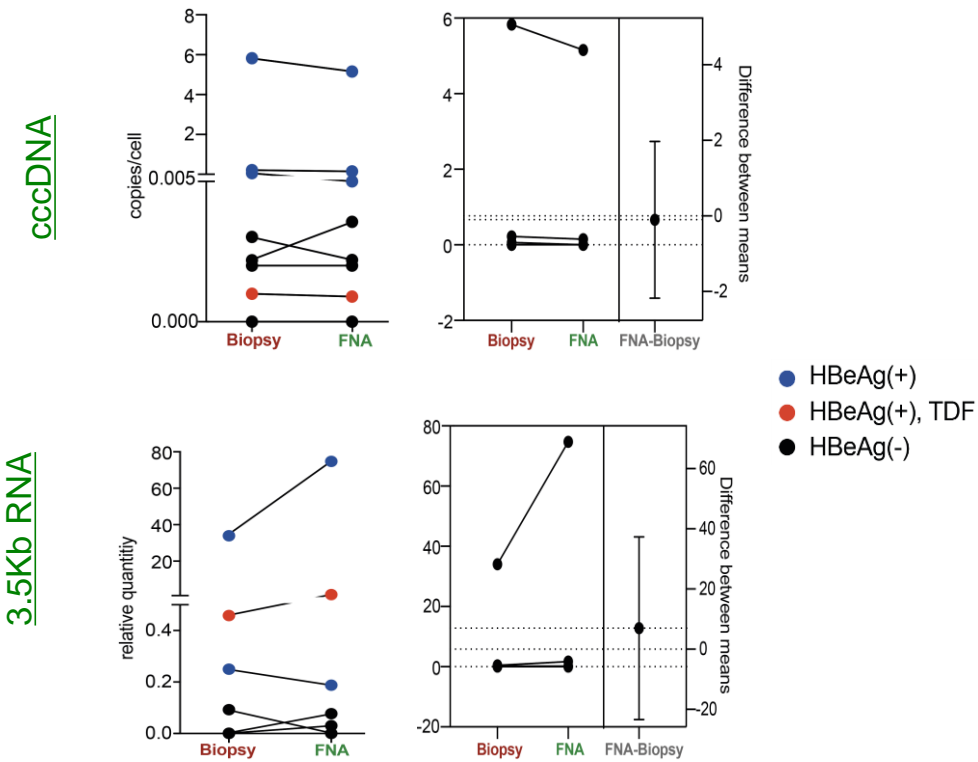
- Sampling of the intrahepatic compartment provides important scientific information
- Critical for the analysis of tissue resident immunity
- Tissue sequencing; GeoMx Human Whole Transcriptome Atlas Assay
- On-treatment sampling is valuable to aid the HBV-cure program
- FNA sampling may be modality for this....

Intrahepatic sampling

Tissue Resident CD8 T cells & NK cells detected by FNA sampling



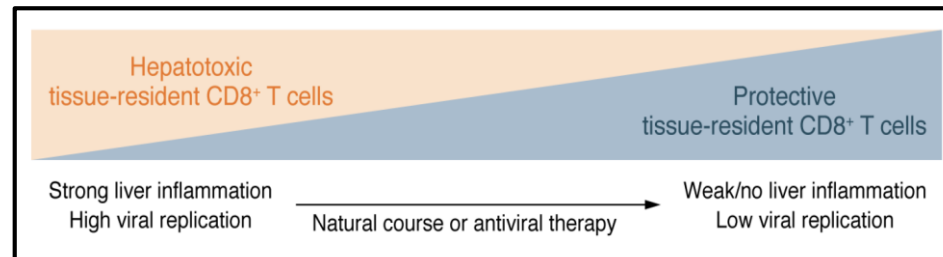
cccDNA & HBV RNA quantification by ddPCR with FNA sampling



Gill*, Pallett* et al., Gut 2018

Specific & sensitive quantification of cccDNA & 3.5Kb RNA
Consistent results between FNA & biopsy

The Journal of Clinical Investigation
Longitudinal liver sampling in patients with chronic hepatitis B starting antiviral therapy reveals hepatotoxic CD8⁺ T cells
Shirin Nkongolo,¹ Deeqa Mahamed,¹ Adrian Kuiper,^{1,2} Juan D. Sanchez Vasquez,^{1,2} Samuel C. Kim,² Aman Mehrotra,¹ Anjali Patel,¹ Christine Hu,¹ Ian McGilvray,³ Jordan J. Feld,¹ Scott Fung,¹ Diana Chen,² Jeffrey J. Wallin,³ Anuj Gaggar,³ Harry L.A. Janssen,¹ and Adam J. Gehring^{1,2}



Unpublished Data
Collaboration with
Dr Testoni & Prof. Zoulim (INSERM, Lyon)

Therapeutic immune modulation

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

New Approaches to Chronic Hepatitis B

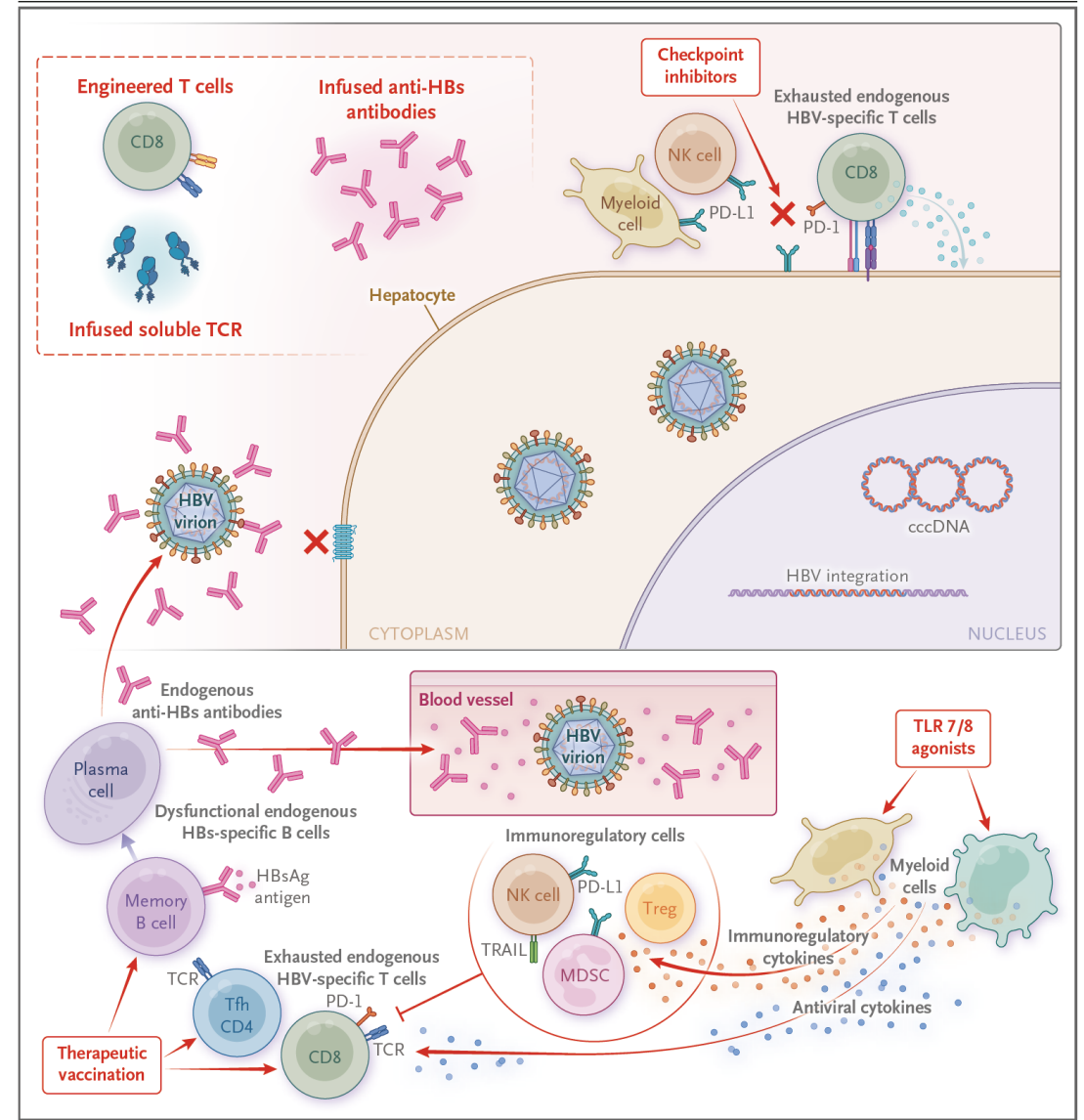
Geoffrey Dusheiko, M.D., Kosh Agarwal, M.D., and Mala K. Maini, M.D., Ph.D.

nature reviews gastroenterology & hepatology

Review article

The scientific basis of combination therapy for chronic hepatitis B functional cure

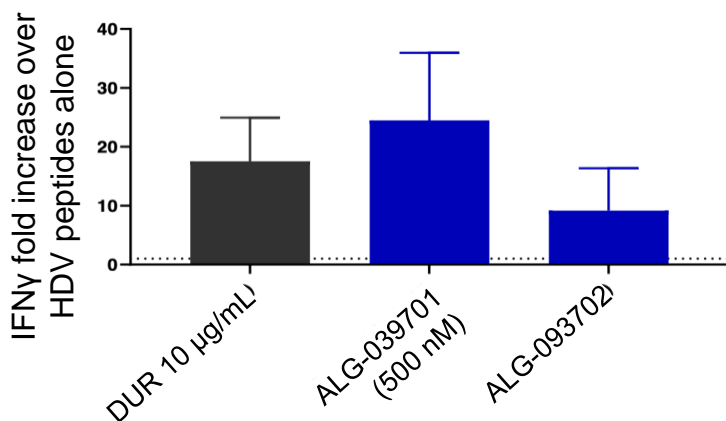
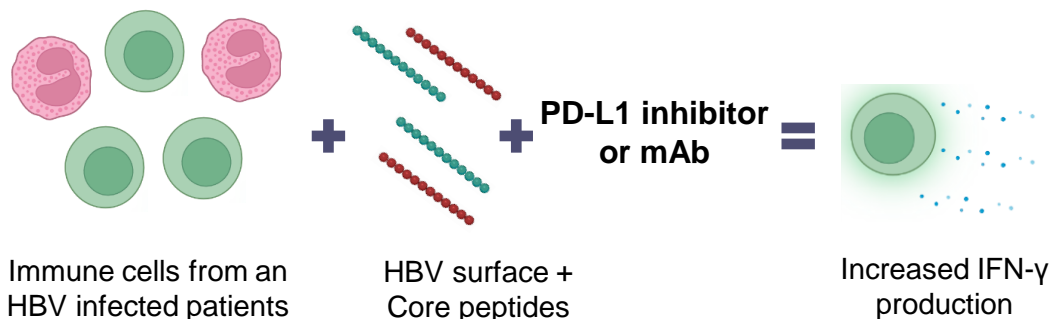
Seng Gee Lim¹, Thomas F. Baumert², Carolina Boni³, Ed Gane⁴, Massimo Levrero⁵, Anna S. Lok⁶, Mala K. Maini⁷, Norah A. Terrault⁸ & Fabien Zoulim⁹



Dusheiko et al., NEJM 2023

Discovery of liver-targeted oral PD-L1 small molecule inhibitors for the treatment of CHB and HCC

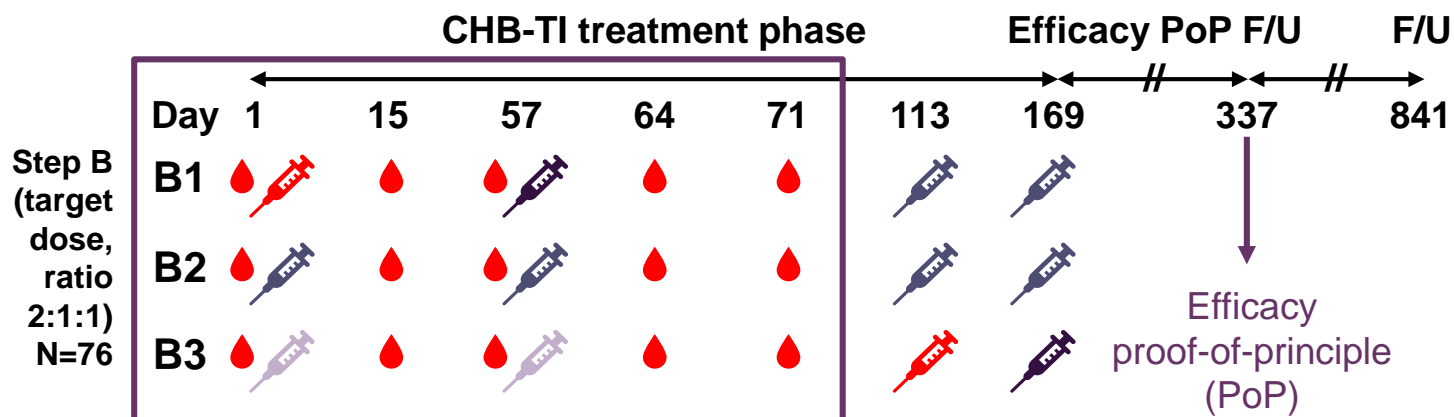
PD-L1 inhibition reactivates the HBV-specific T cell response



- ALG-093702 blocks PD-1/PD-L1 interaction reducing cell surface PD-L1
- ALG-093702 demonstrates higher liver exposure vs other tested tissues
- ALG-093702 reactivates HBV-specific T cells from an HBV-infected patient to a similar extent as durvalumab
- Promising liver-specific novel approach
- Concern about liver specific toxicity and duration of effect?

Targeted immunotherapy of viral vectors and adjuvanted HBc/HBs proteins: Step B cohort of Phase 1/2 trial

- **CHB targeted immunotherapy (CHB-TI):** Heterologous prime-boost administration of chimpanzee-derived adenovirus encoding a fusion of the human invariant chain (hli, CD74) and HBV protein (ChAd155-hli-HBV) and MVA encoding HBV proteins (MVA-HBV), and adjuvanted recombination proteins (HBc-HBs/AS01_B)
- Ongoing, Phase 1/2, randomized, single-blind trial
- Interim cell-mediated immunity results up to 14 days post-dose 2 of the Step B cohort receiving a sequential regimen CHB-TI



Current CMI analysis (performed on exposed set with available data, N=58)

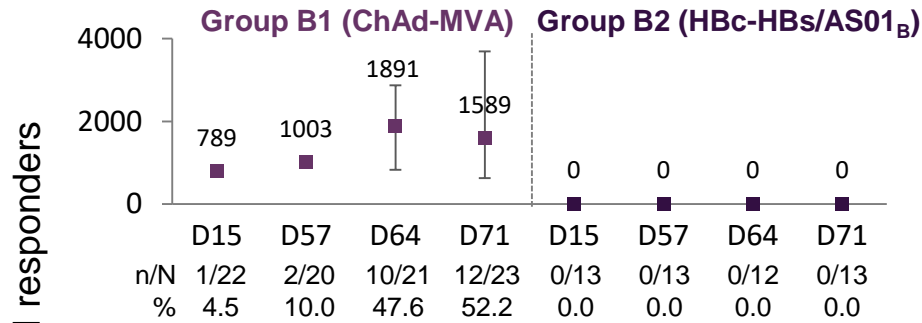


Activation marker	CD40	TNFα	IFN-γ	IL-2	IL-13	IL-17	CD137 (4-1BB)
Costimulatory markers	✓						✓
Cytokines		✓	✓	✓	✓	✓	

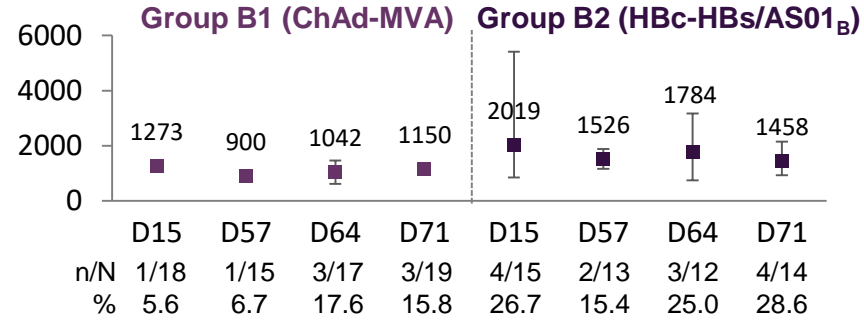
- Positive response by 2+ activation markers, including 1 cytokine
- 58 patients for analysis (exposed set with available CMI samples)

Targeted immunotherapy of viral vectors and adjuvanted HBc/HBs proteins: Step B cohort of Phase 1/2 trial

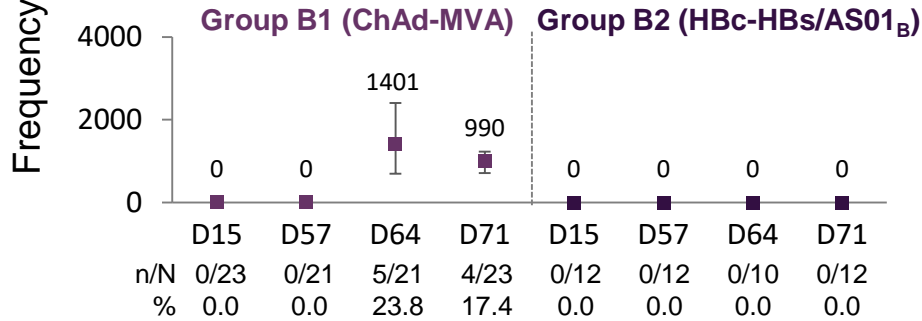
HBc-specific CD8⁺ T cells*



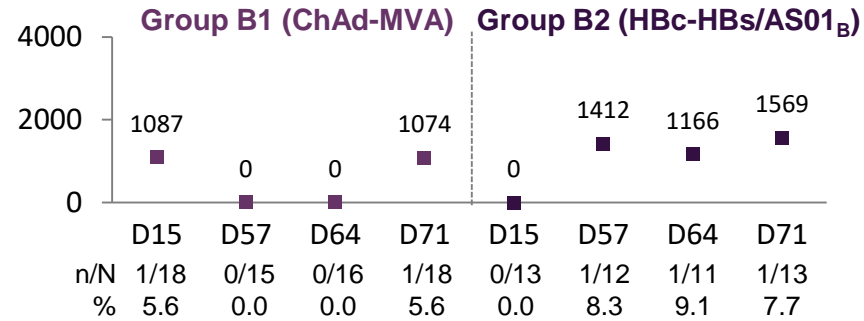
HBc-specific CD4⁺ T cells*



HBs-specific CD8⁺ T cells*



HBs-specific CD4⁺ T cells*



- Polyfunctional CMI responses observed in ChAd-MVA recipients (group B1) in terms of HBc- and HBs-specific CD8⁺ T cells
- In HBc-HBs/AS01B recipients (Group B2) in terms of HBc- and HBs-specific CD4⁺ T cells

- Measurable CD8 T cell responses ex vivo with ChAd-MVA
- CD8/4 T cell response was weak with recombinant antigen
- Finding T cell responses ex vivo with ICS is encouraging
 - More sensitive assays should be used to measure T cell immunity
- Combining HBs/HBc-ASO1 with ChAd-MVA may enhance CD4 response in last 2 doses
- Anti-HBs yet to be reported

Summary points & moving forward.....



Natural history of HBV (& HDV)

1. Further studies on natural history of disease phase are still required
2. Who should be treated? Should the treatment candidacy pool be widened



Potential promise of new therapies

1. Combination therapies (viral & immune targets) required, but which are best?
2. Evaluating the immune/viral repertoire on therapy



Evaluating novel agents

1. Will be important to determine why certain agents not efficacious
2. In vivo studies of novel agents using blood & liver FNA samples

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Fox Chase

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University of Birmingham

Shishir Shetty
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Duke-NUS

Nina Le Bert
Kamini Kunasegaran
Damien Tan
Laura Rivino

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Tom Pembroke
Andy Godkin



**Patrick
Kennedy**



**Mala
Maini**



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