New Perspectives on HBV Immunology

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My “New” Perspective

Study mechanisms responsible for viral control and pathogenesis in chronic hepatitis B patients.

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Study mechanisms responsible for viral control and pathogenesis in chronic hepatitis B patients.

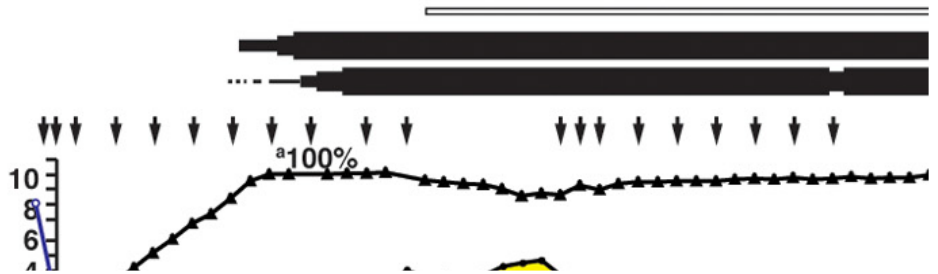
Vast majority of published patient-oriented research compares the immune response between resolved and chronic patients or features of exhaustion

Mechanisms of HBV pathogenesis and liver damage derived from acute models

T cell Responsible for Immune Control of HBV in Infected Chimpanzees

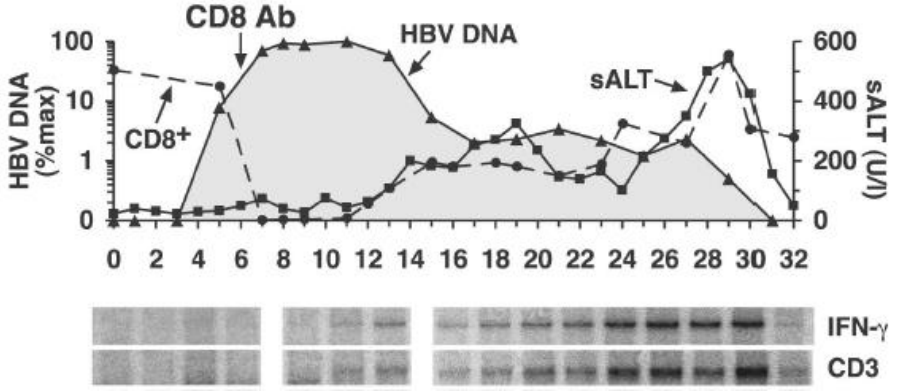
- **CD4 T cell response is required to prime functional CD8 T cells**
  - **Depletion prior to CD8 priming impaired HBV-specific CD8 Response**
  - **Led to persistent infection**

CD4 Depletion



- **CD8 T cell eliminate infected hepatocytes and drive non-specific hepatocyte damage**
  - **depletion prior to peak HBV DNA leads to persistent viremia & blunted inflammatory response**

CD8 Depletion



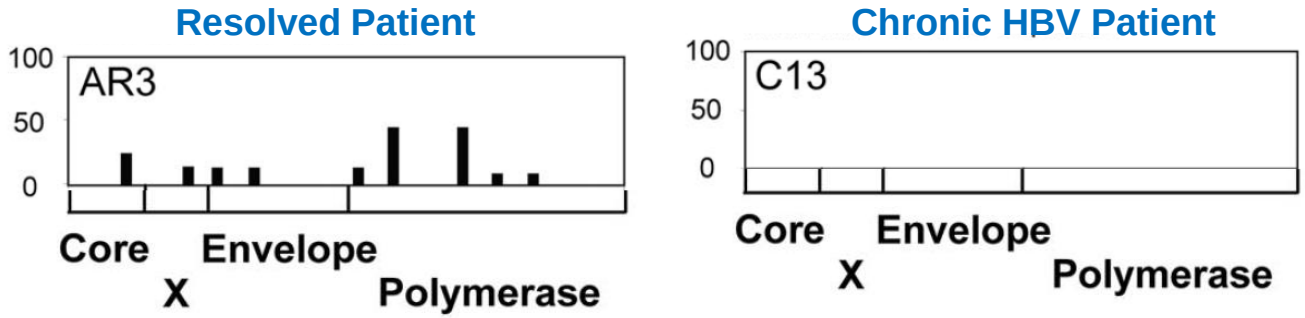
Asabe, S. *J Virol* **83**, 9652–9662 (2009).

Thimme et. al. J. Virol, 2003

Comparing Acute vs. Chronic Immune Response

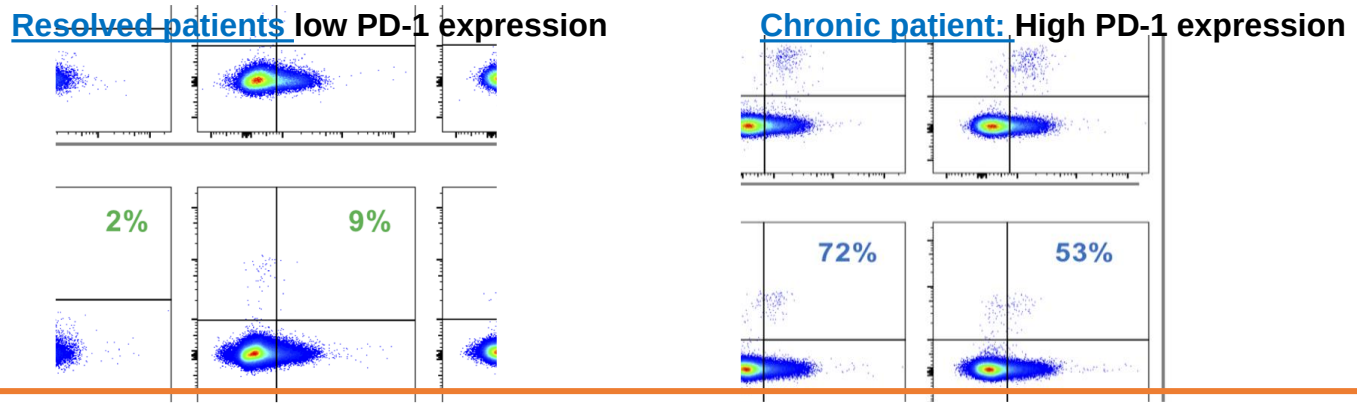
➢ HBV-specific T cell response

- **Comparing Magnitude:**



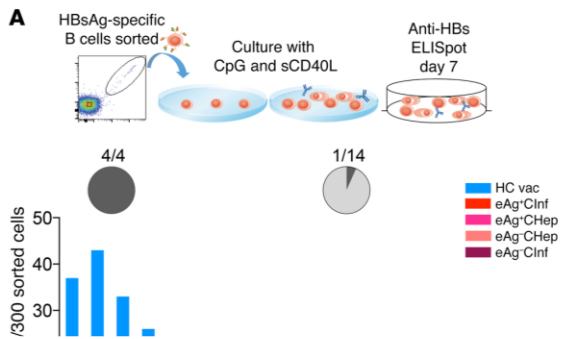
➢ HBV-specific T cell response

- **Comparing Phenotype**



➢ HBV-specific B cell response

- **Comparing function**



Healthy vaccinated: high anti-HBs
CHB patients: low anti-HBs

Tan, A. T. et al. J Virol 82, 10986–10997 (2008).

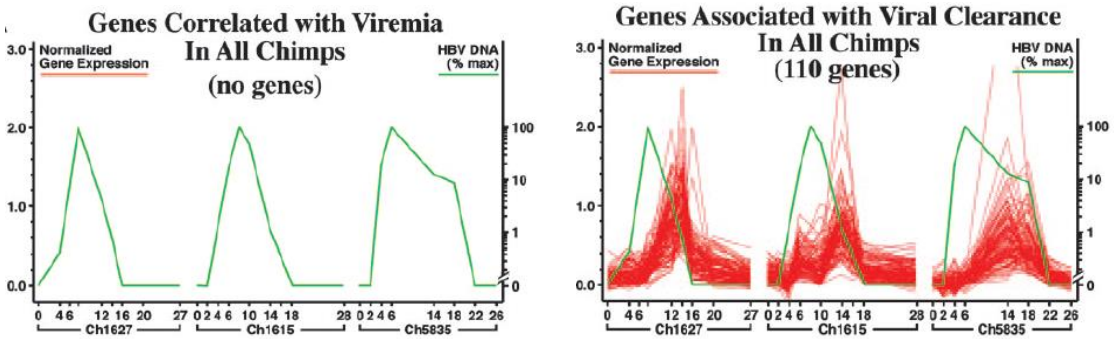
Hoogeveen, R. C. *et al. Gut* **68**, 893–904 (2018).

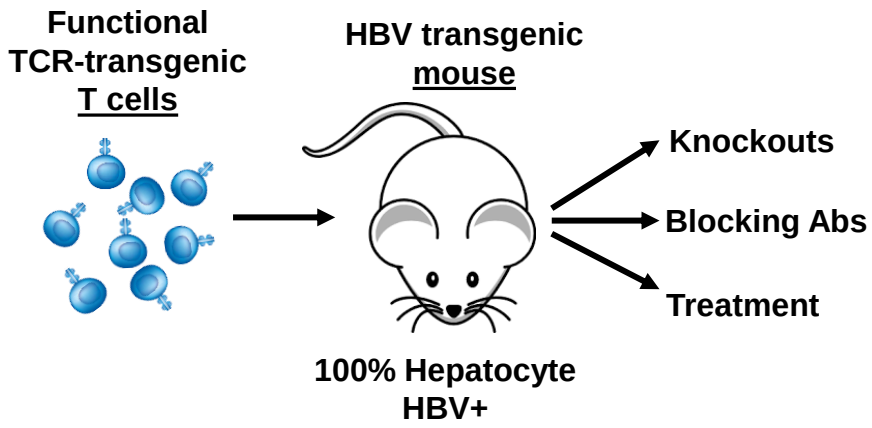
Salimzadeh, L. *et al. J Clin Investigation* **128**, 4573–4587 (2018).

Mechanisms of Liver Damage

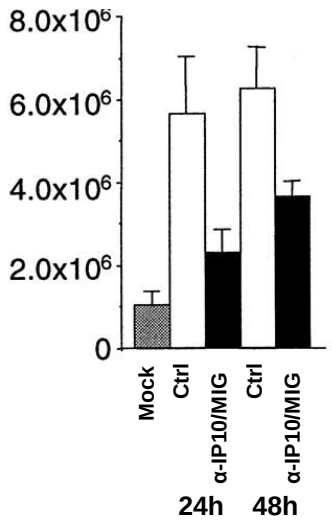
- Derived from acute models -

- **Transcriptional response to HBV infection in Chimps**
  (microarray: total RNA from biopsy)
  - **No genes associated with viral replication**
    - **100% of hepatocytes infected**
  - **Immune gene expression at the time of ALT increase**

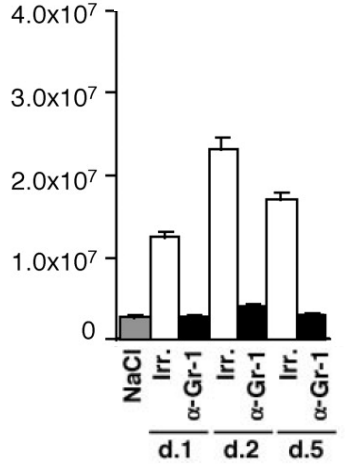




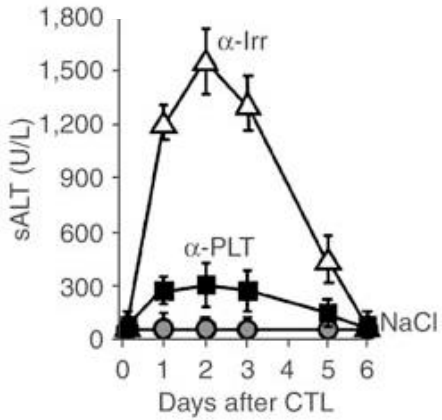
Chemokine Recruitment



Neutrophil facilitated



Platelet facilitated

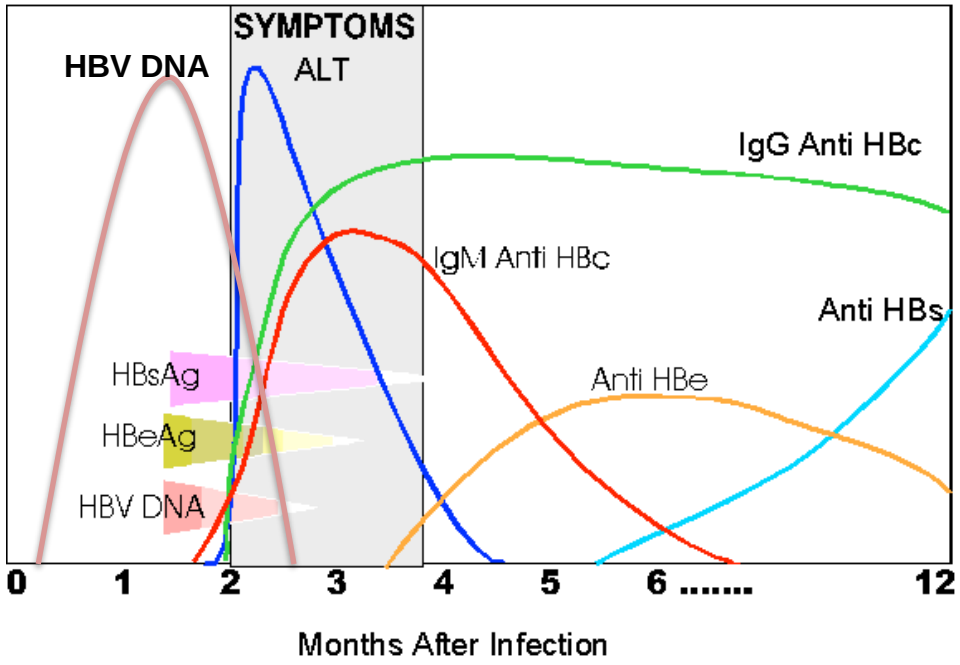


Wieland et. al. PNAS, 2004

Kakimi et al. J Exp Med 2001;194:1755-1766
Sitia et al. PNAS 2002;99:13717-13722
Iannacone et al., Nat Med. 2005 Oct 30;11(11):1167–9

Comparing Acute vs. Chronic Immune Response

Acute HepB = Months of infection



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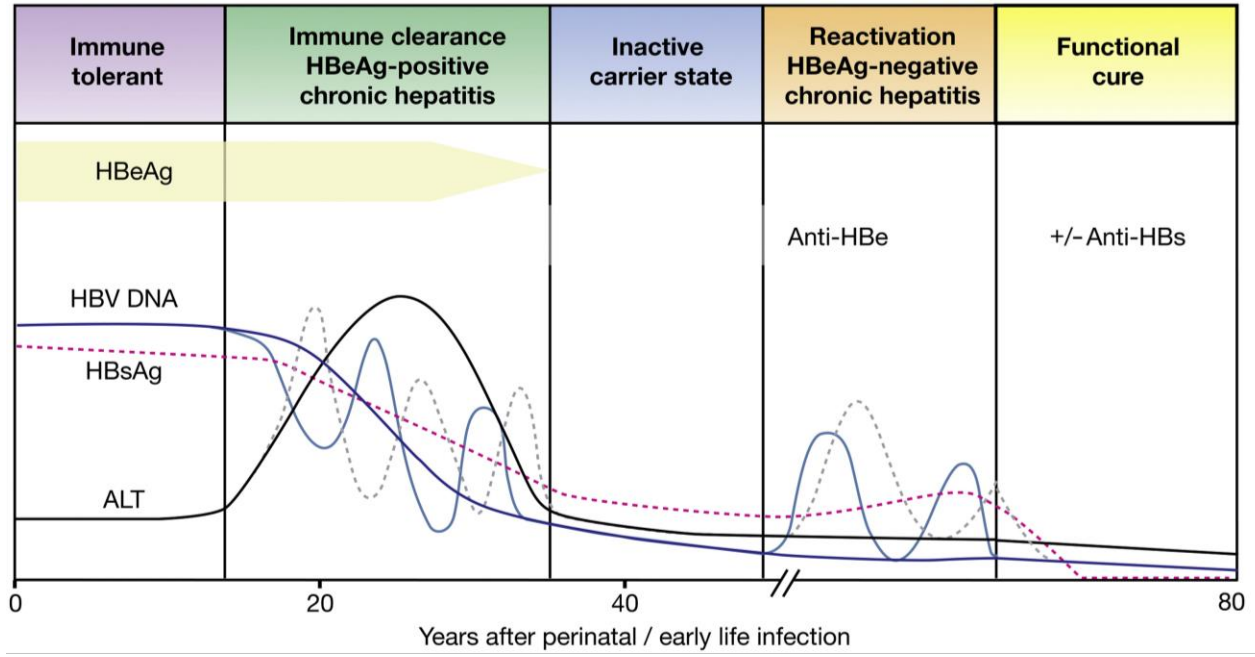
Chronic HepB = Decades of infection



Should we assume that the same mechanisms responsible for viral control and pathogenesis in acute infection will operate in chronic infection?

Should the goal of immunotherapy be to reach an immunological phenotype similar to a patient that resolved acute HepB? Is that even possible?

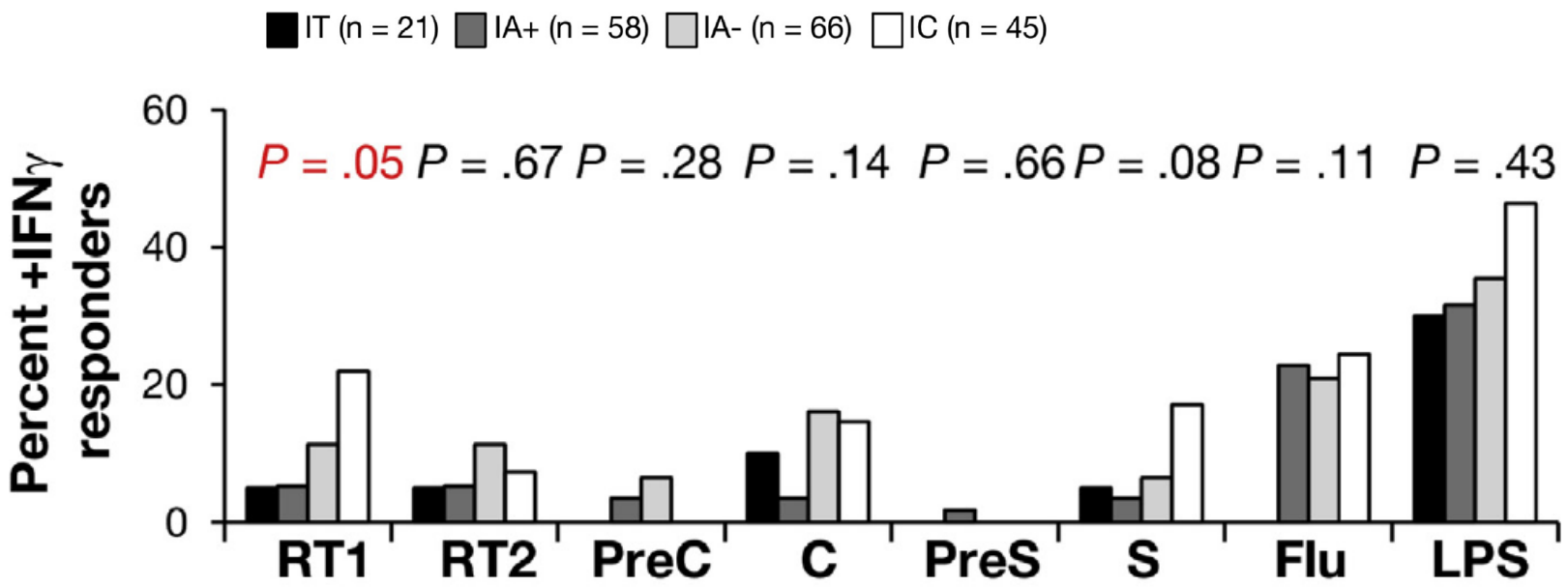
What do we need?

Immunological correlate of viral control in chronic hepatitis B patients.

How do we find it….is the challenge.

What CHB Patient Cohorts to Study?

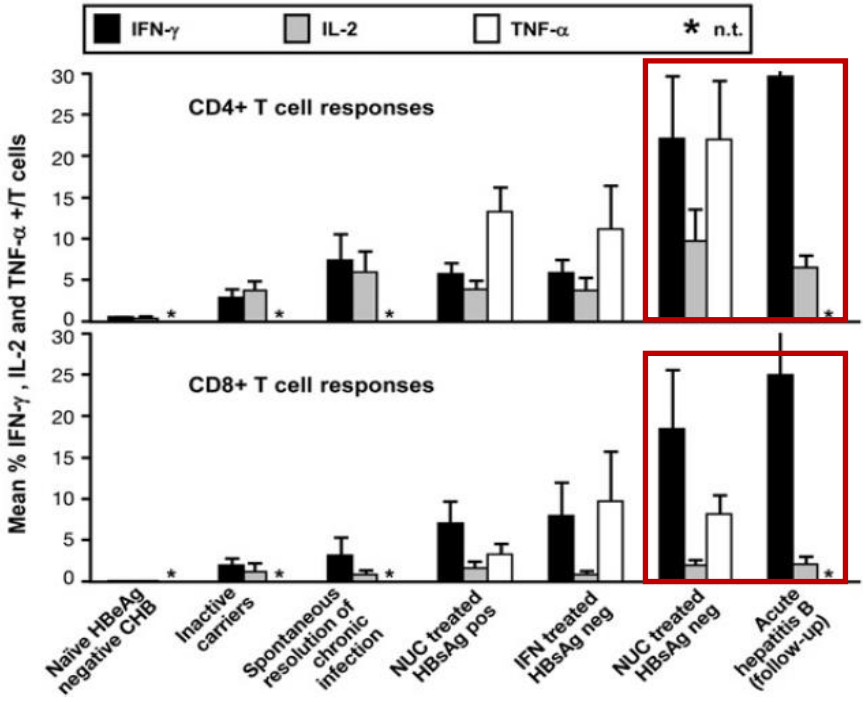
- **Across different stage of chronic hepatitis B that display different viral biomakers**
  - **Specifically high viral load vs. low viral load (+/- liver damage)**

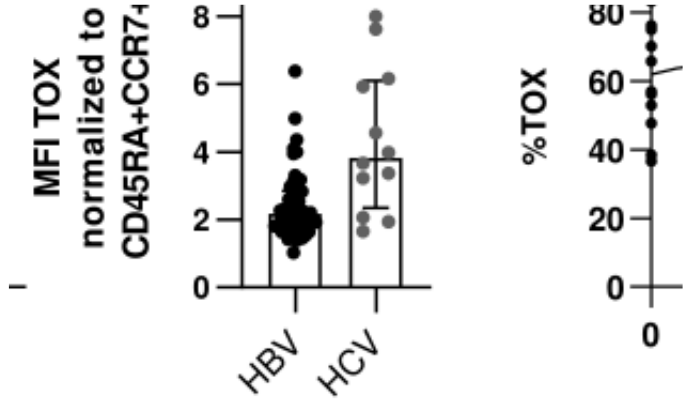


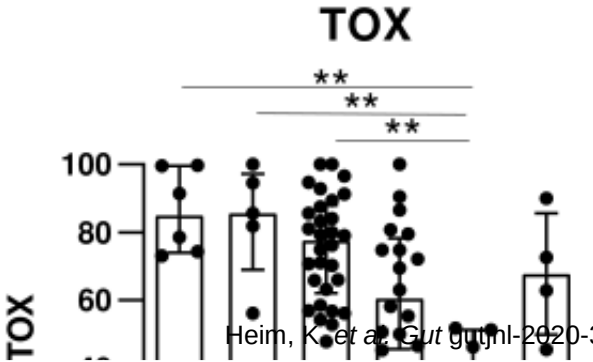
Park 2015 Dec;150(3):684–5.

What CHB Patient Cohorts to Study?

- **CHB patients that have achieved functional cure: HBsAg-, HBV DNA-, anti-HBs+/-**
  - **spontaneous or treatment induced**
  - **Hard to find but achieve the end goal of cure after decades of infection**







Boni, Gastroenterology. 2012 Oct;143(4):963–9.

Heim, K. *et al. Gut* gutjnl-2020-322404 (2020) doi:10.1136/gutjnl-2020-322404.

Incorporating Immunology in Phase 1/2 Clinical Trials

- **HBV Forum Immune Monitoring Working Group has just submitted a white paper on incorporating immunological studies into clinical trials.**

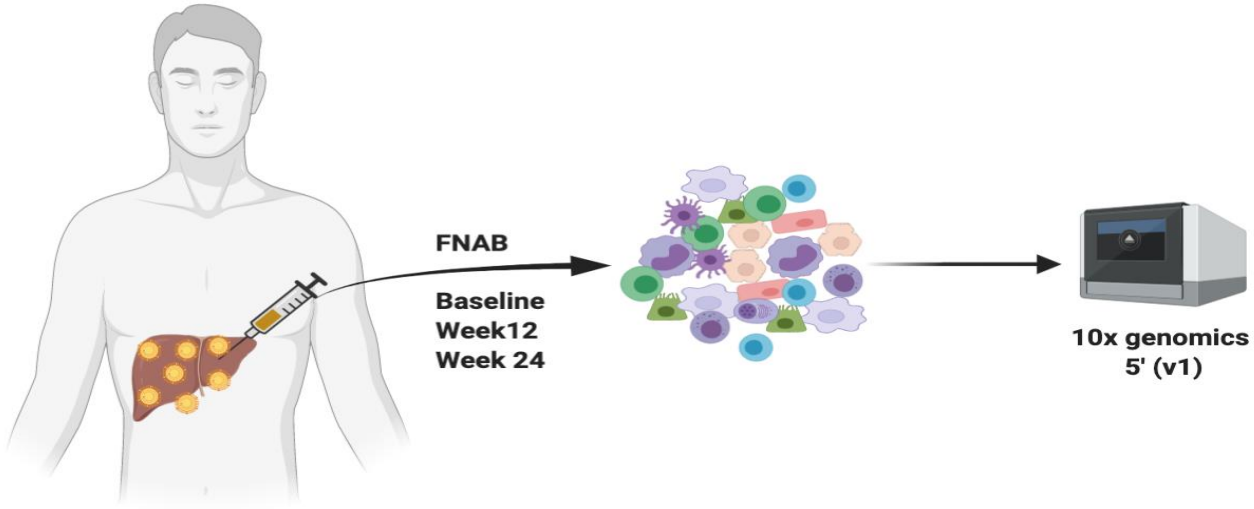
- **Novel drugs in development are**
  1. **Robust activators of immunity: vaccines, innate immunomodulators, checkpoint inhibitors**
  2. **Effectively alter virus and antigen distribution: siRNA, antisense oligos, CpAMs secretion inhibitors**

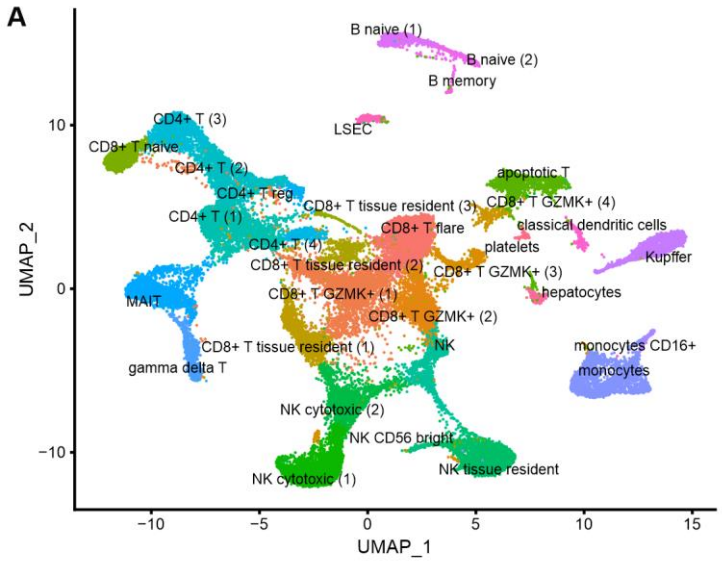
- **This likely represents the best opportunity to identify immunological mechanisms responsible for viral control in chronic hepatitis B patients**

Capitalize on the Growing Use of Liver Fine-needle Aspirates

- **Liver fine-needle aspirates (FNAs) allow for frequent, longitudinal sampling**
  - **Adaptable to different clinical trial designs**
  - **Deployed in focused ancillary studies to take a deep dive into mechanistic response to treatment intervention**

- **Single-cell technologies have revolutionized the amount of data obtained from few cells collected in liver FNAs**

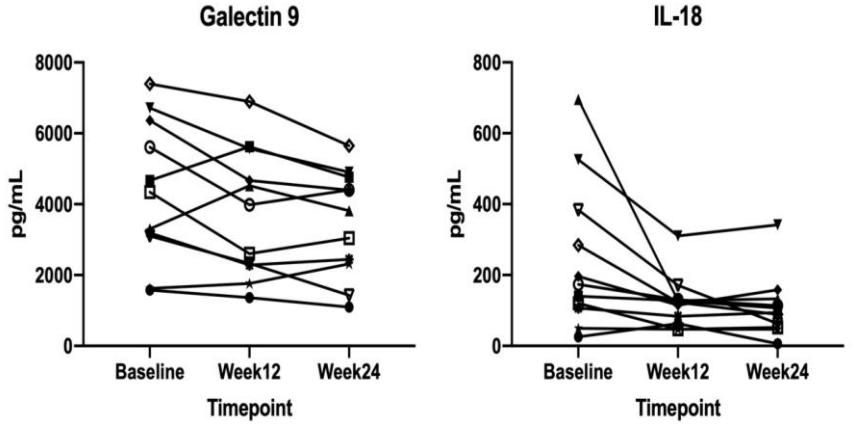


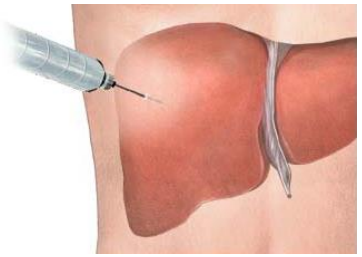


Capitalize on the Growing Use of Liver Fine-needle Aspirates

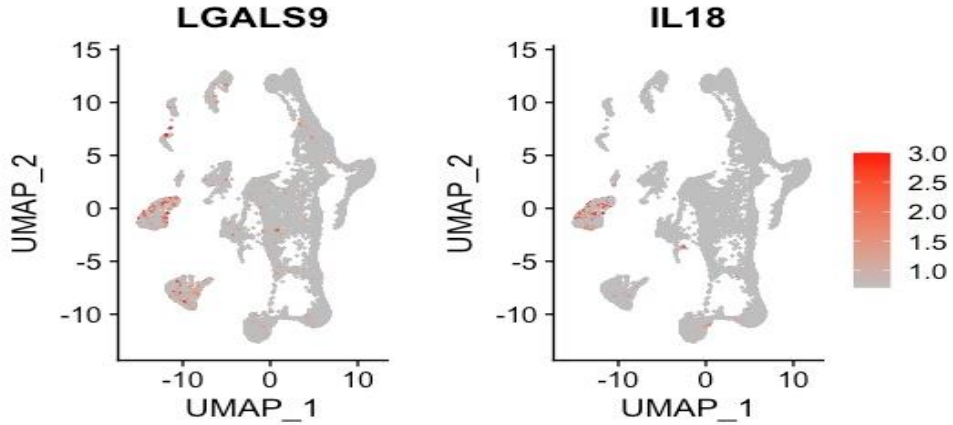
- **Link intrahepatic gene expression to peripheral biomarkers to identify cell types responsible for a response**

Plasma Proteomics (>1,000 markers)



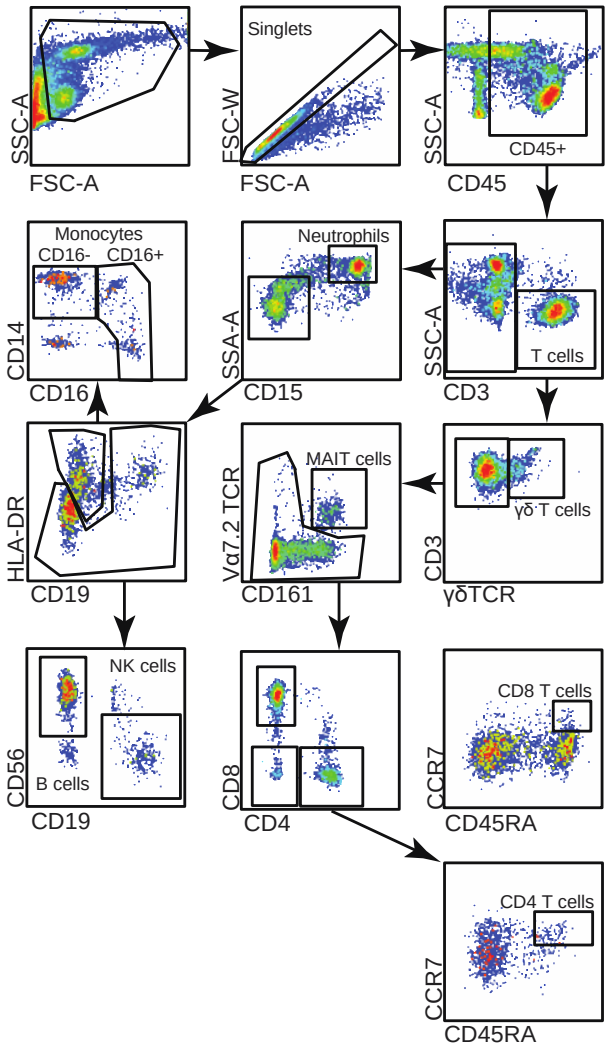


Transcripts in Liver

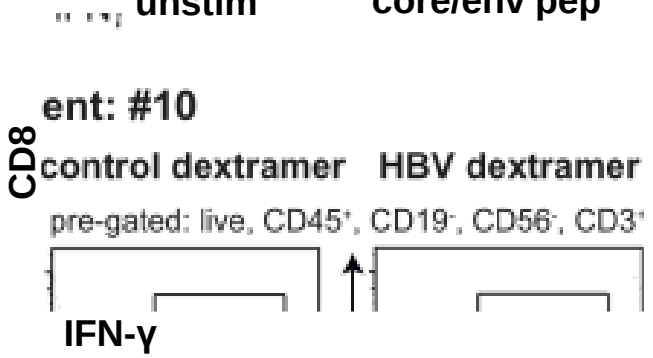


Capitalize on the Growing Use of Liver Fine-needle Aspirates

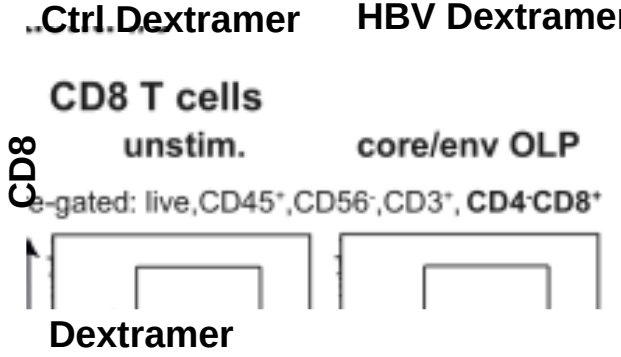
Immuno-phenotyping



HBV-specific functional analysis



HBV-specific dextramer analysis



Gehring et. al. unpublished

Gill, U. S. *et al*. *Gut* **68**, 1493–1503 (2018).

Summary

- **Increase investigation on chronic patients that have achieved functional cure over comparison to acute/resolved/vaccinated individuals**

- **Defining an immunological biomarker associated with viral control in CHB patient will refine immunotherapy development**

- **Early-stage clinical trials provide the best opportunity to define immunological biomarkers**
  - **focused substudies to investigate immune response to intervention and mechanism of action**
    - **clearly gaining traction with sponsors**
  - **Understanding the immune response is informative whether there is an antiviral effect or not.**
    - **drug targeting to specific cell types**
    - **inform combination strategies**
    - **provide ”no go” data to preserve resources**

- **Simultaneous blood and liver sampling should be considered a priority in sub-studies**
  - **Liver data provides information regarding the response at site of infection**
  - **Liver sampling is not feasible for large studies: Link peripheral biomarkers to liver responses.**