Immunological Correlates of Functional Cure

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Boston, MA, USA

Disclosures : **GSK (Grant support, consulting), Janssen (Grant support)**

HBV cure Task Force

RB-RNA

ICE-HBV
International Coalition to Eliminate HBV

IP-cure-B

LYON HEPATOLOGY INSTITUTE
COMPREHENSIVE LIVER CENTER

HBV Functional Cure (FC)

Is clearly feasible

- Almost universal outcome in adults with primary HBV infection
- Can occur even after decades of chronic infection (with or without therapy)

Must be immune mediated

- cccDNA and integrated DNA persist
- Immune deficiency can lead to viral relapse (chemotherapy, rituximab, etc)
- Immune reconstitution after ART in HIV/HBV coinfection has high rate of FC

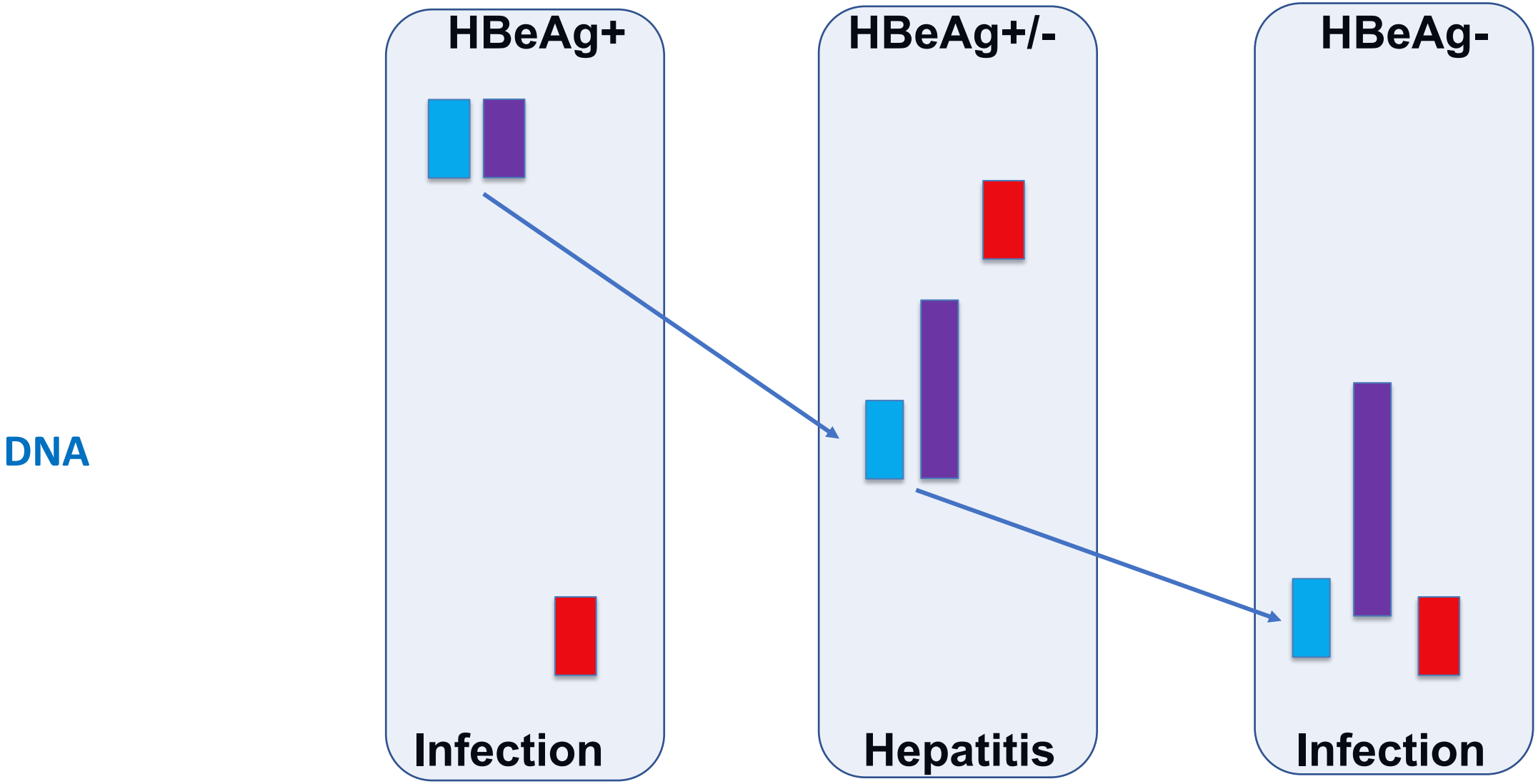
<u>But immune correlates of FC and the roadblocks to achieve it remain poorly defined</u>

Too many treatment strategies for HBV FC based on limited evidence

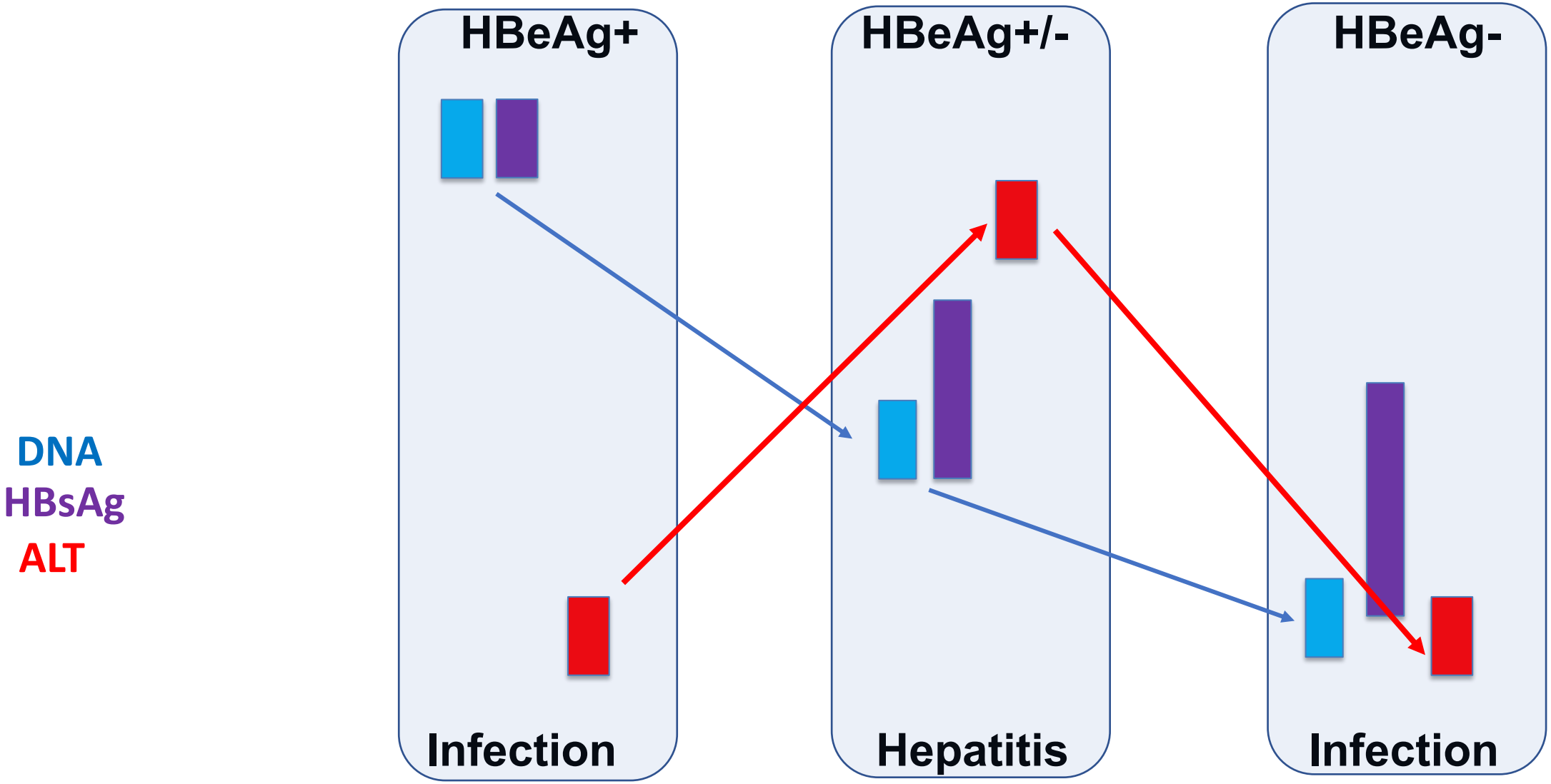
(HBsAg↓, PD-1?)

HBV: A chronic infection like no other

It continues to evolve for decades: Improving control of HBV replication



HBV: Not one, but several rather distinct chronic infections (with distinct immunity)



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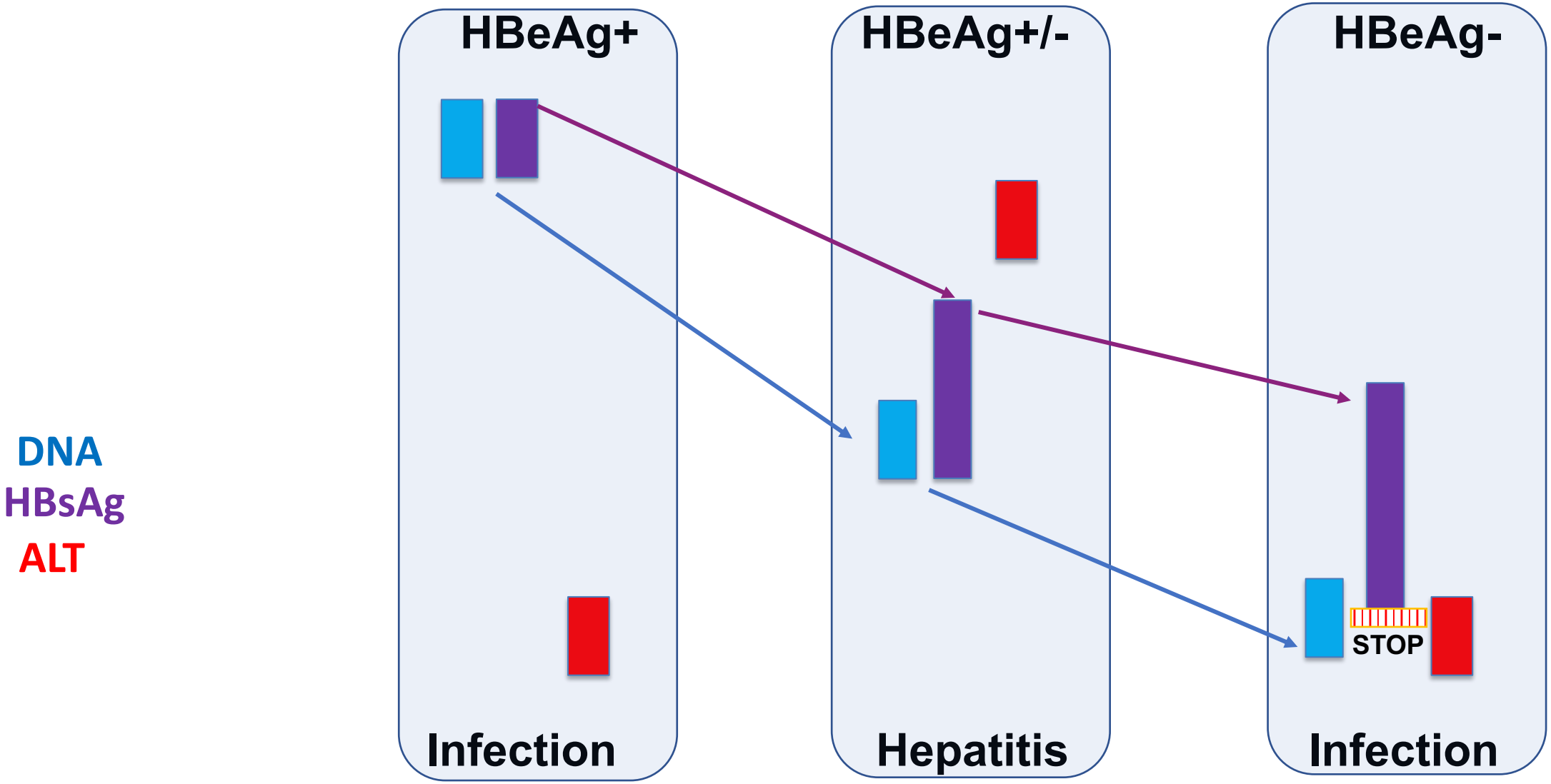

Lessons from HBV Natural History

Anti HBV Immunity is not static and increases in efficacy over time

Different (combinations of) immune effectors/mechanisms likely to drive control of replication, antigenemia, and liver damage

More rational treatment development requires:

- To identify the hurdles to HBV control in different stages of chronic HBV infection
- To define the immune correlates of functional cure

Janssen Liver Consortium

U Toronto
H. Janssen clinic
Jordan feld clinic
Gehring lab

MGH/Broad/MIT
Chung clinic
Shalek lab
Alatrakchi lab
Hacohen Lab
Lauer lab

Erasmus Rotterdam
Liver clinic
Boonstra lab

Janssen Pharma
Jacques Bollekens
Nadia Neto
Jeroen Aerssens

Additional acute HBV samples
Fiocruz
Lia Lewis-Ximenez

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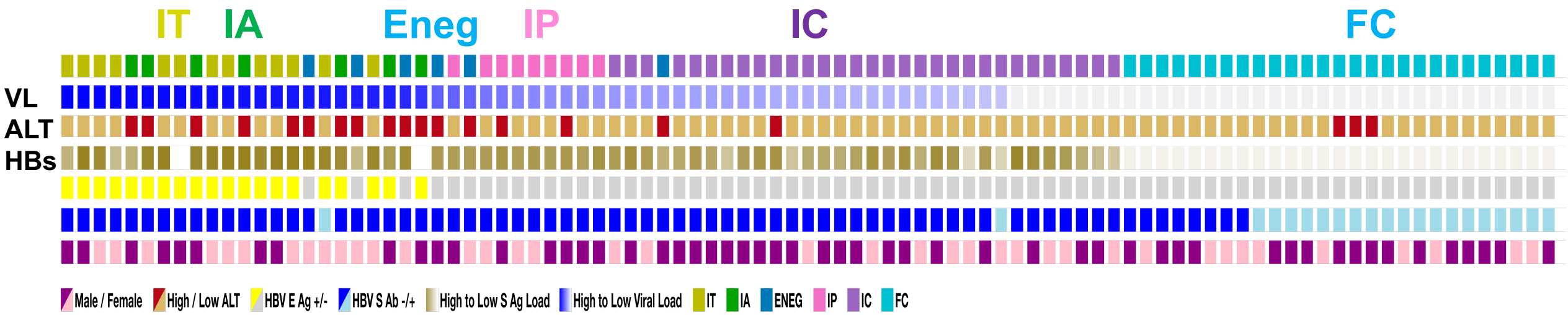
Cross-sectional analysis of all CHB stages, including FC

More than 100 individuals with both blood and liver (FNA) samples.
Seqwell analysis (intrahepatic immune landscape) and scRNAseq of HBV-specific CD8 T cells.



Genshaft et al., Hepatology 2023
Villanueva et al., unpublished

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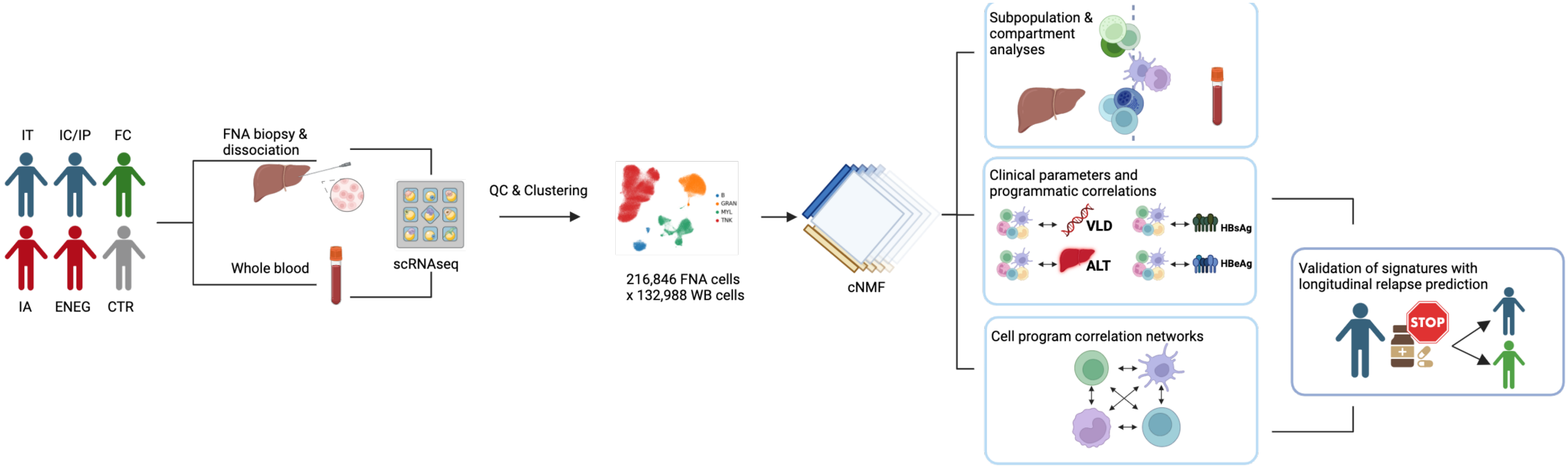
Seqwell Study



Liver sc transcriptomes: 352,161 cells
Blood sc transcriptomes: 142,731 cells

Genshaft et al., Hepatology 2023
Villanueva et al., unpublished

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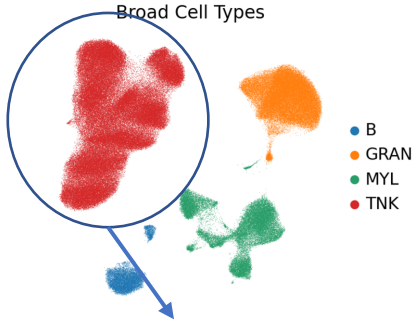
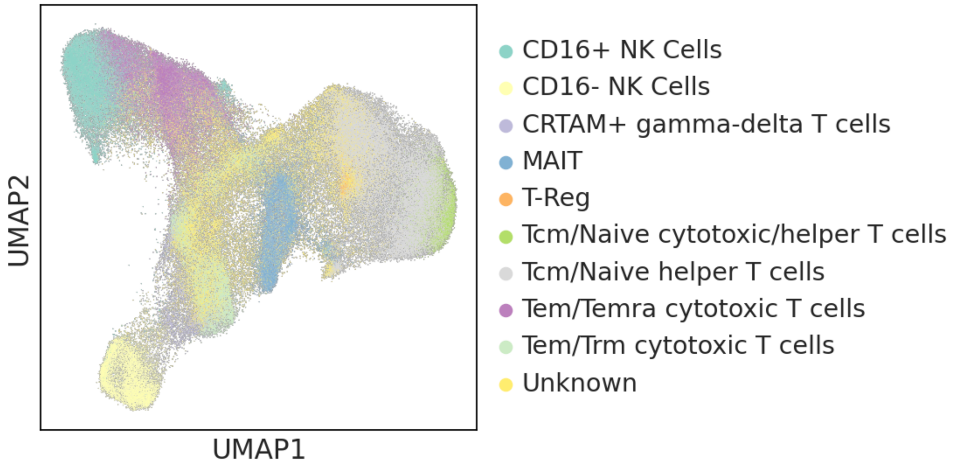
Seqwell Study



consensus Non-negative Matrix Factorization (cNMF) reveals both cell identity and cellular activities (e.g. life-cycle processes, responses to environmental cues)

T/NK cells

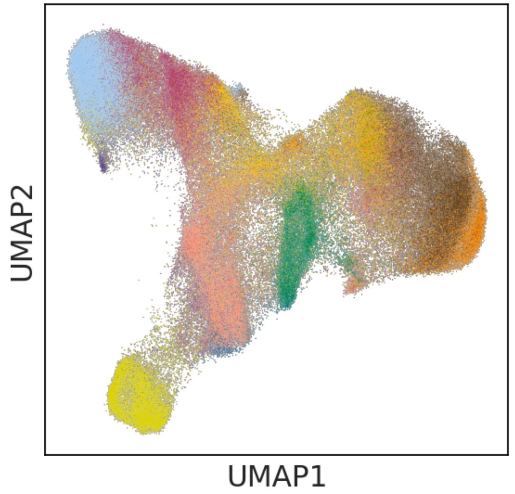
Usage Clusters
(Primary Identity)



Identities AND activities

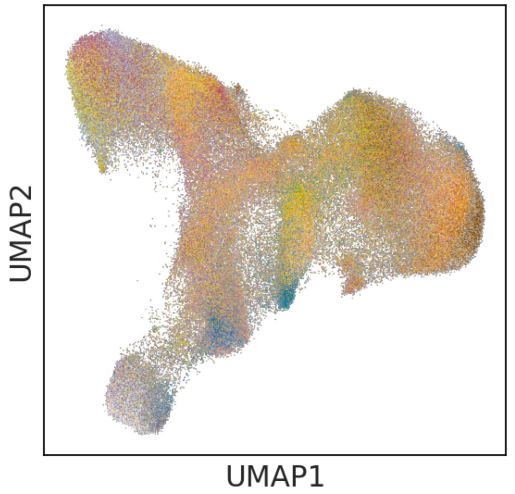
Primary usages

Primary Activity



Secondary usage

Secondary Activity



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Villanueva et al., unpublished

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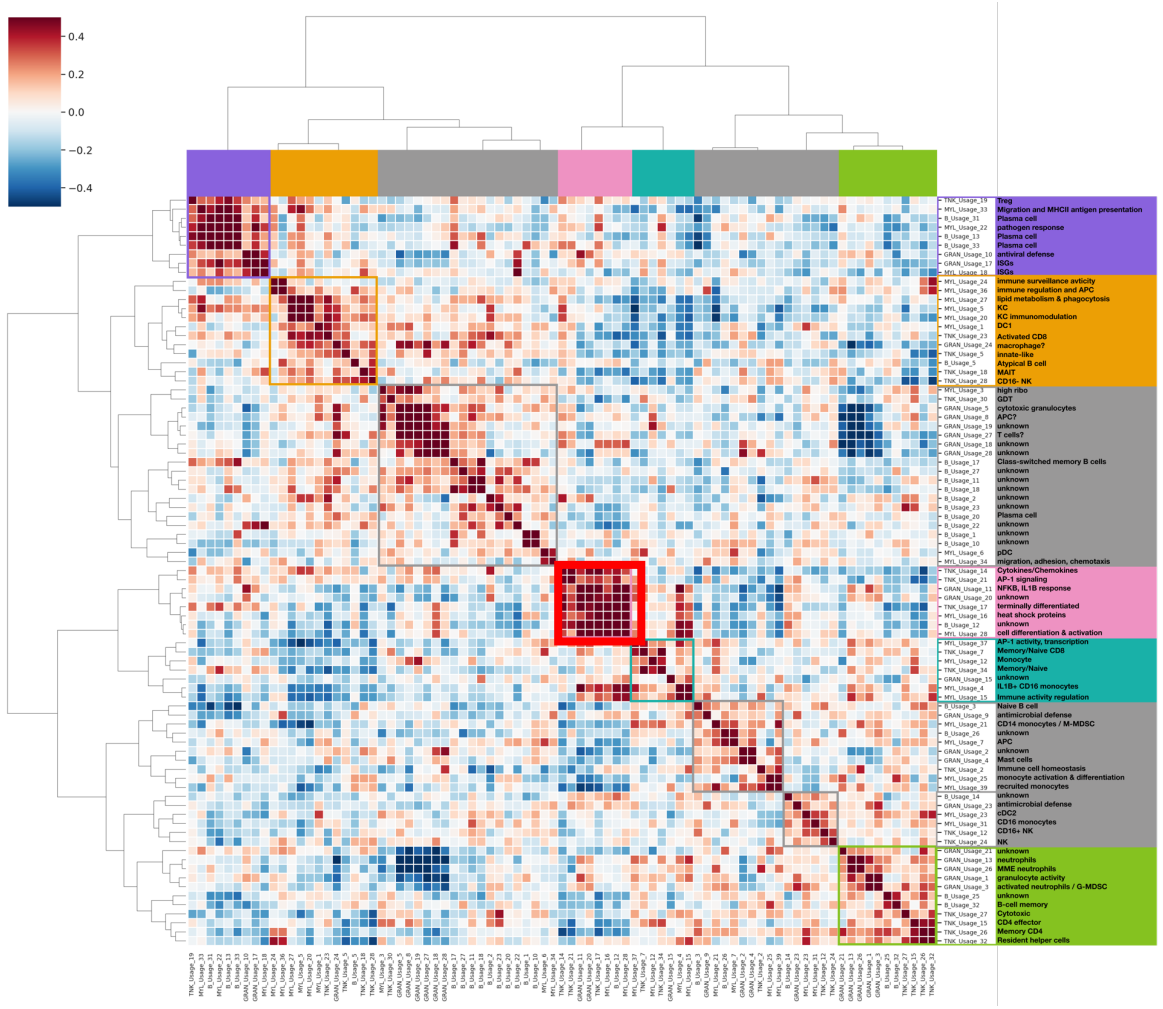
Seqwell Study: Potential immune cell interactions

Over whole object: 103 distinct usages (identities and activities) with correlation patterns across persons



Usages from Myeloid cells, neutrophils, T cells, B cells

Genshaft et al., Hepatology 2023
Villanueva et al., unpublished

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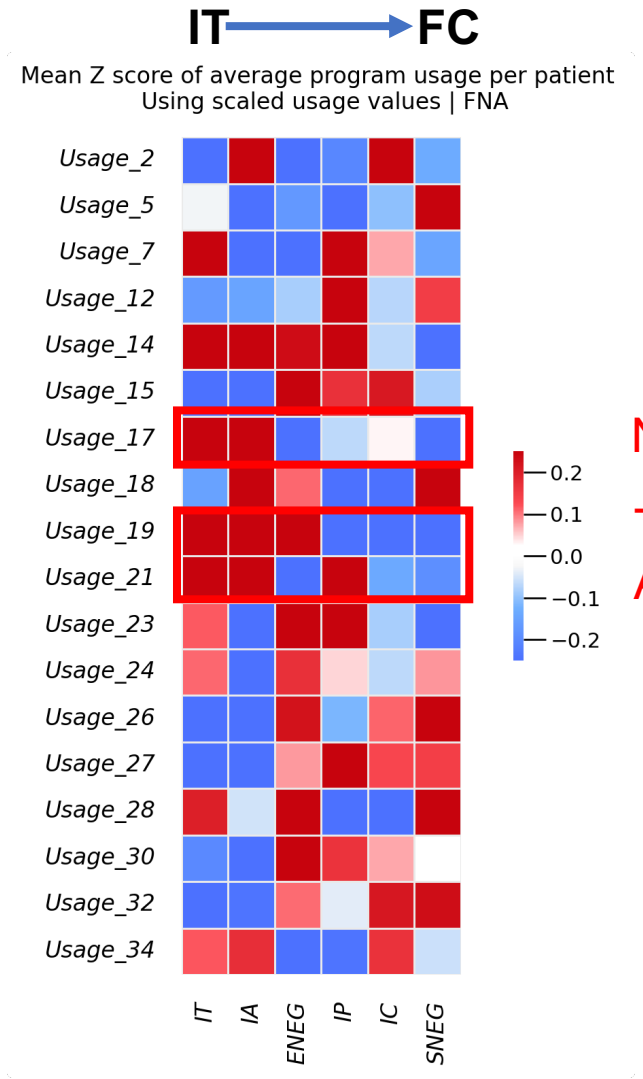
Seqwell Study: Usages associated with CHB stages/clinical parameters



NR4A2, CXCR4, CREM T cells

Treg

AP-1 signaling

Genshaft et al., Hepatology 2023

Villanueva et al., unpublished

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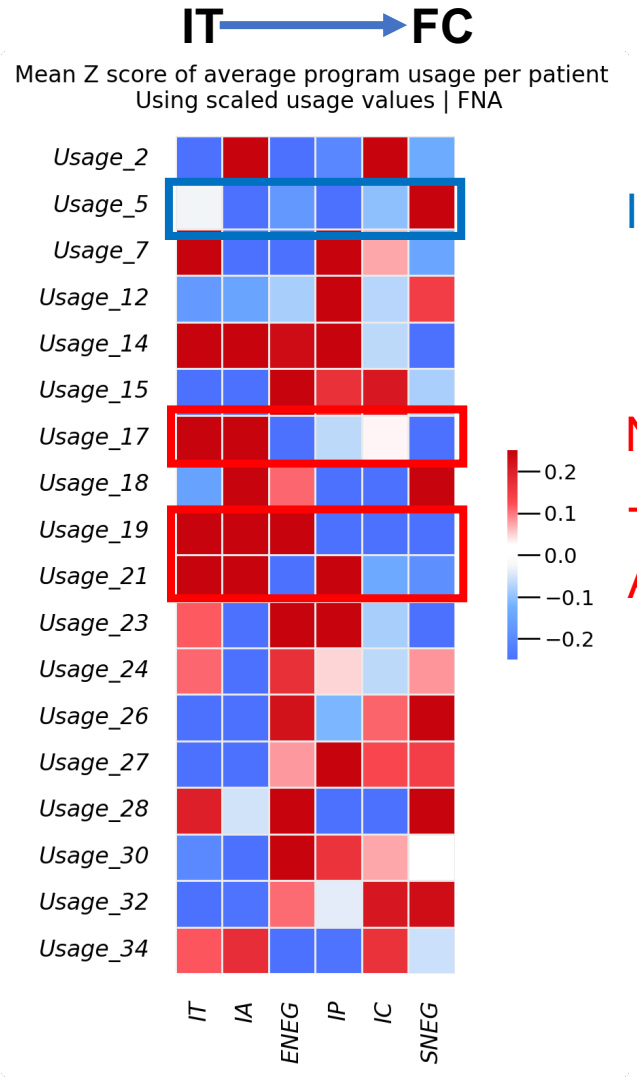

Innate-like T cells

NR4A2, CXCR4, CREM T cells

Treg

AP-1 signaling

Genshaft et al., Hepatology 2023

Villanueva et al., unpublished

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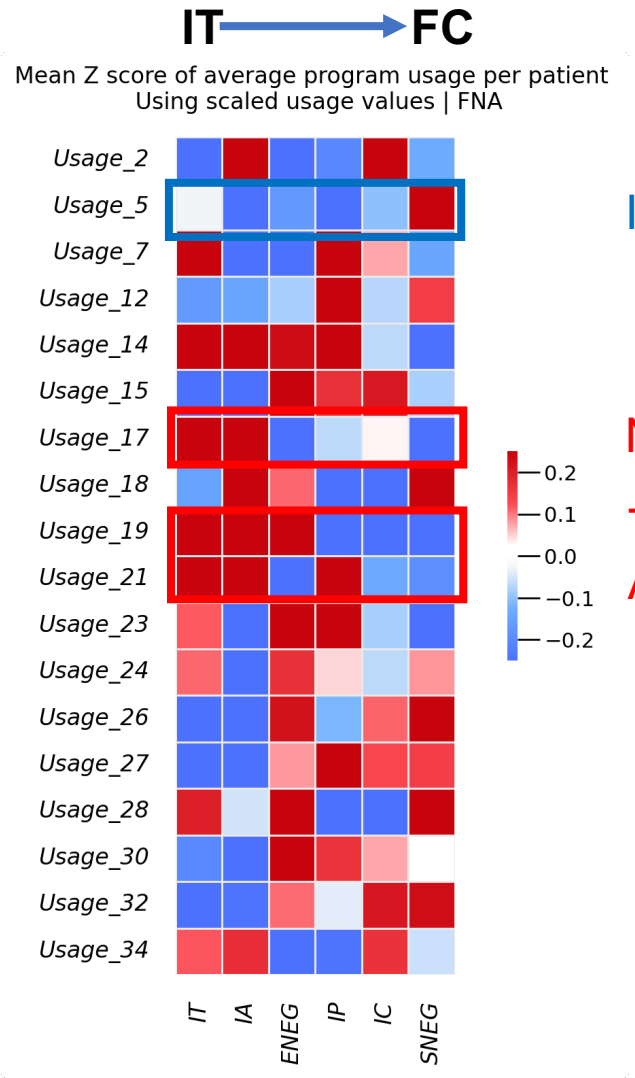
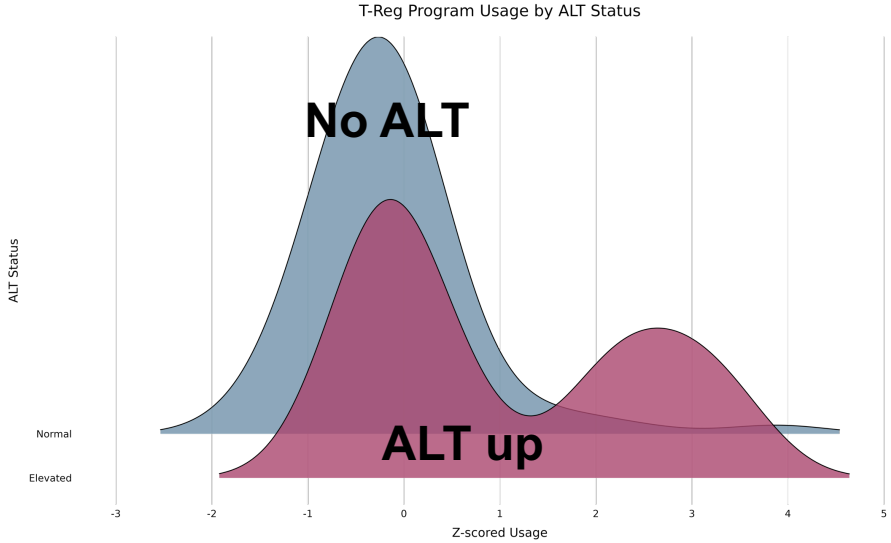


Innate-like T cells

NR4A2, CXCR4, CREM T cells

Treg
AP-1 signaling

Tregs: Only with ALT elevation



Genshaft et al., Hepatology 2023
Villanueva et al., unpublished

Preliminary Lessons from Liver Seqwell Study

Many significant differences in immune cell activities across CHB stages and FC

- HBV immunity changing throughout natural history

VL, HBsAg, and ALT partially correlated with specific immune cell activities

- Different immune cells key to HBV control and liver damage

Coordination between immune cells across lineages

- Cell networks might reveal multiple opportunities for intervention at different immune regulation levels

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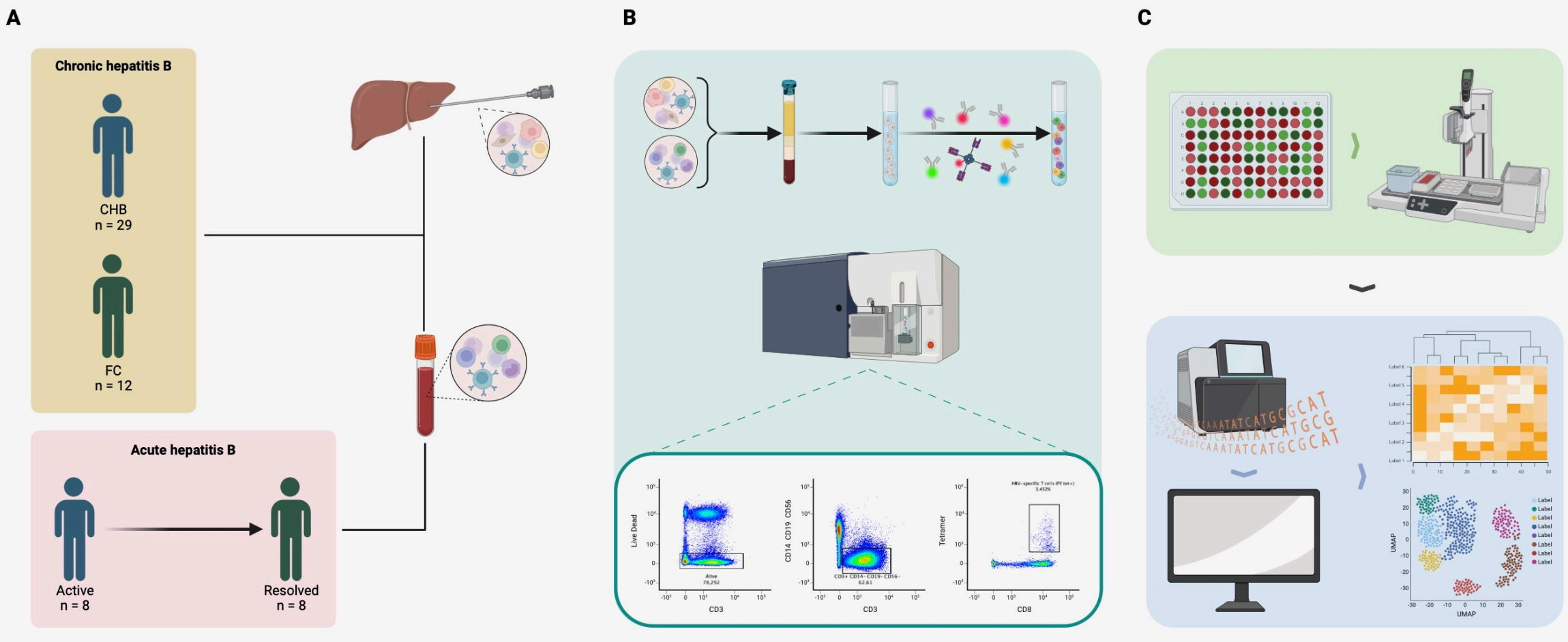
Analysis of HBV-specific CD8 T cells (SmartSeq2)

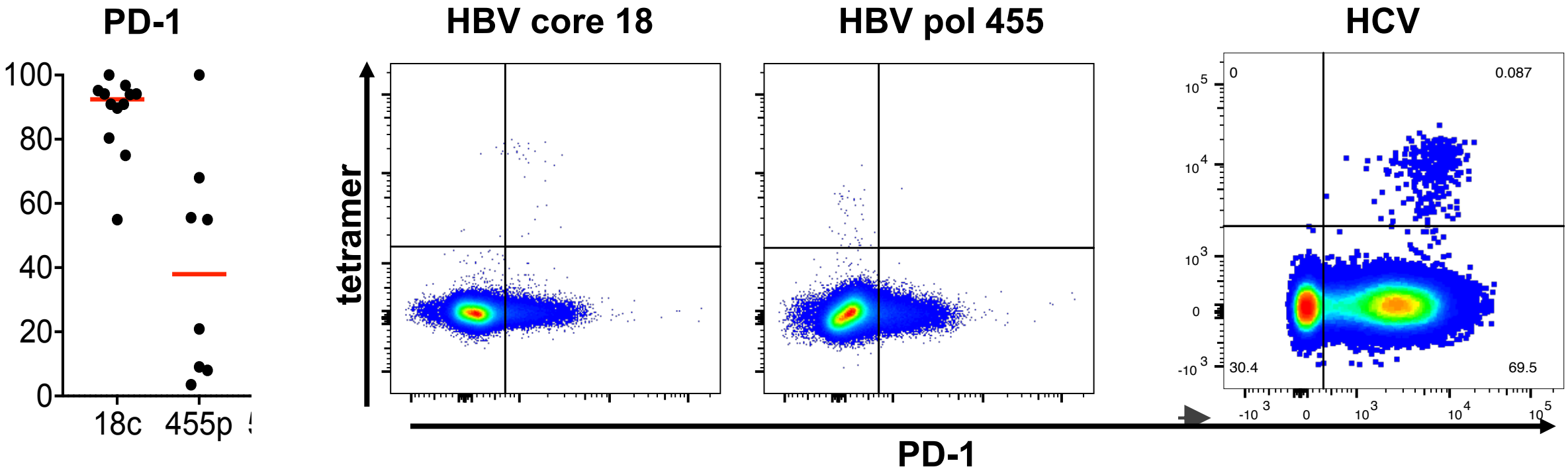


CHB Blood: 4155 cells **CHB Liver: 1087 cells** **Acute HBV: 2523 cells**

Is T Cell Exhaustion the Main Hurdle to HBV FC?

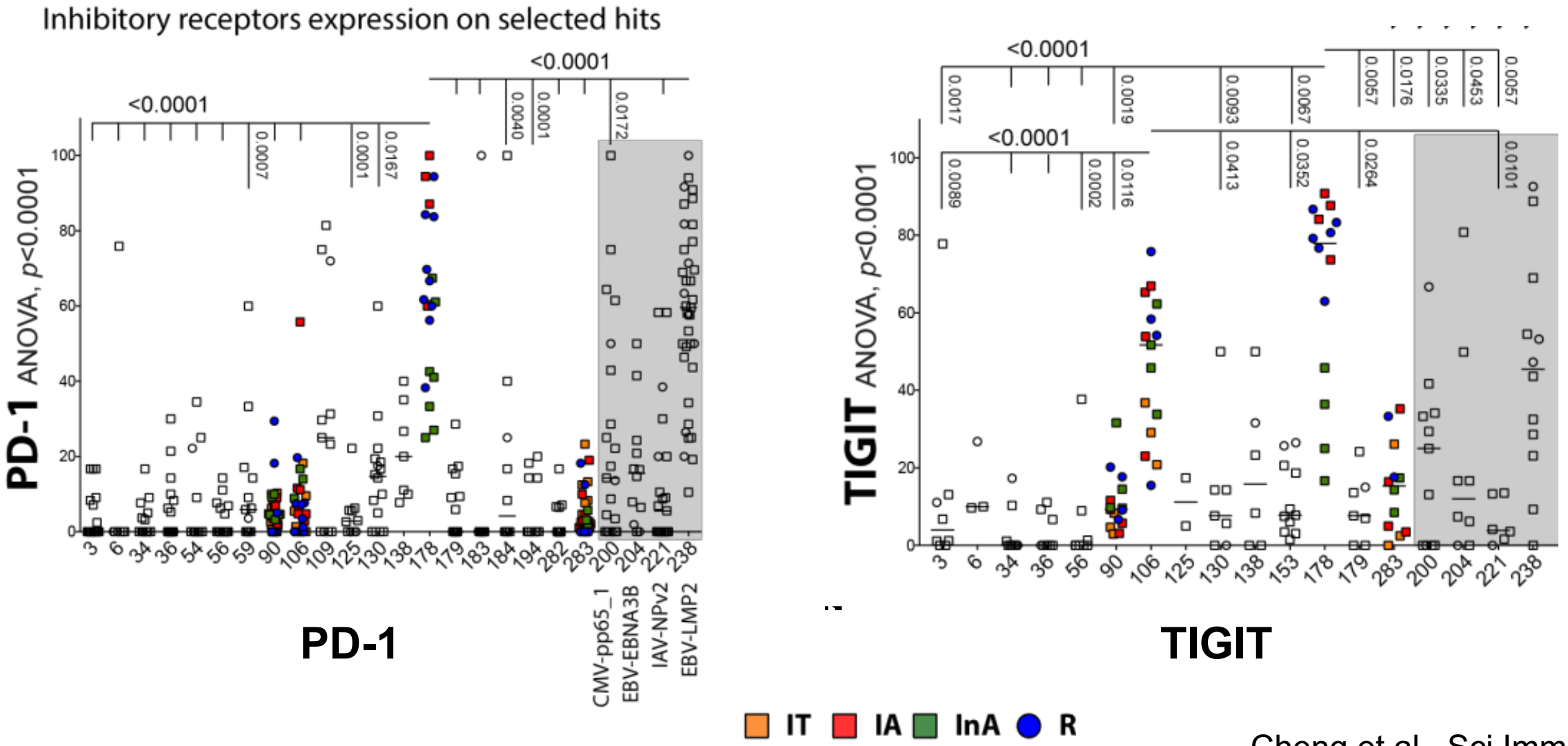
T Cell Exhaustion in CHB

PD-1 is (lowly)expressed on some HBV-specific CD8 T cells in CHB



Hoogeveen et al., GUT 2018

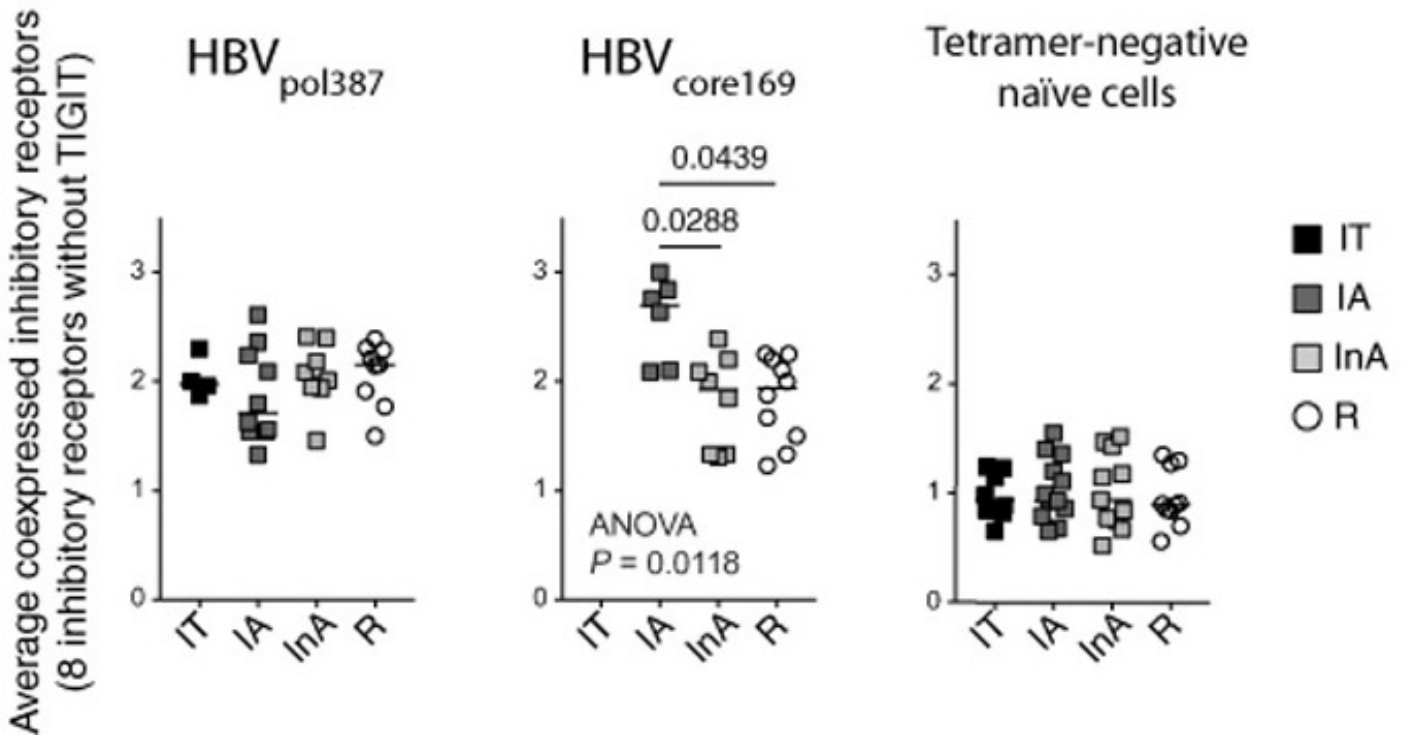
High PD-1 or TIGIT expression on few specificities



Cheng et al., Sci Immunol 2019

Limited co-expression of IRs in most HBV-specific CD8

Unlike classical T cell exhaustion



Cheng et al., Sci Immunol 2019

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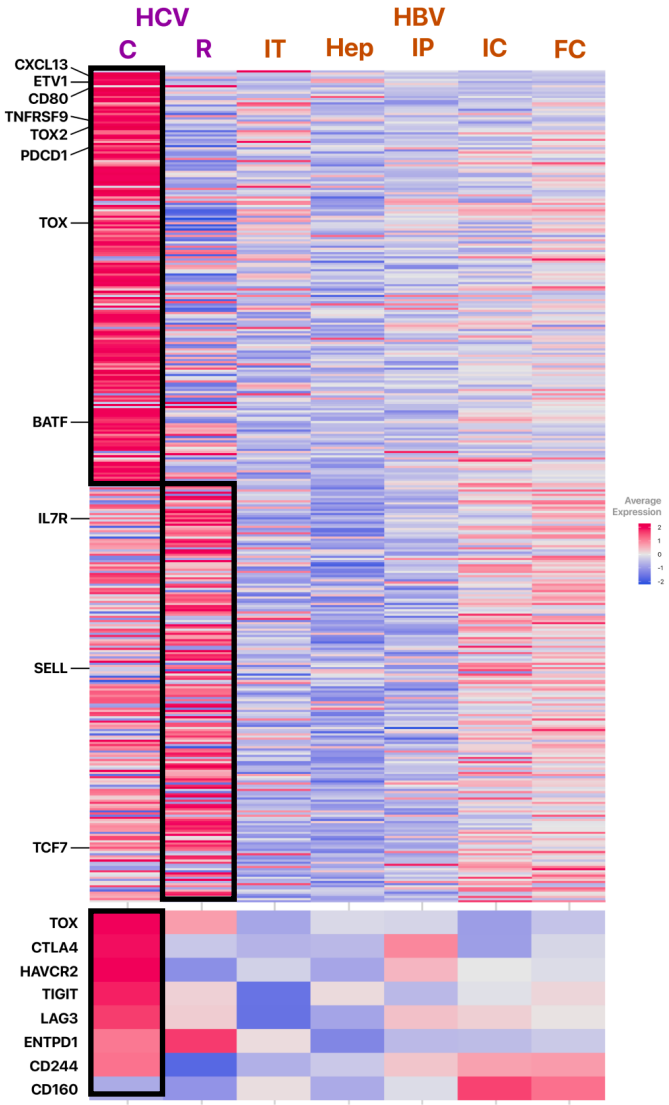
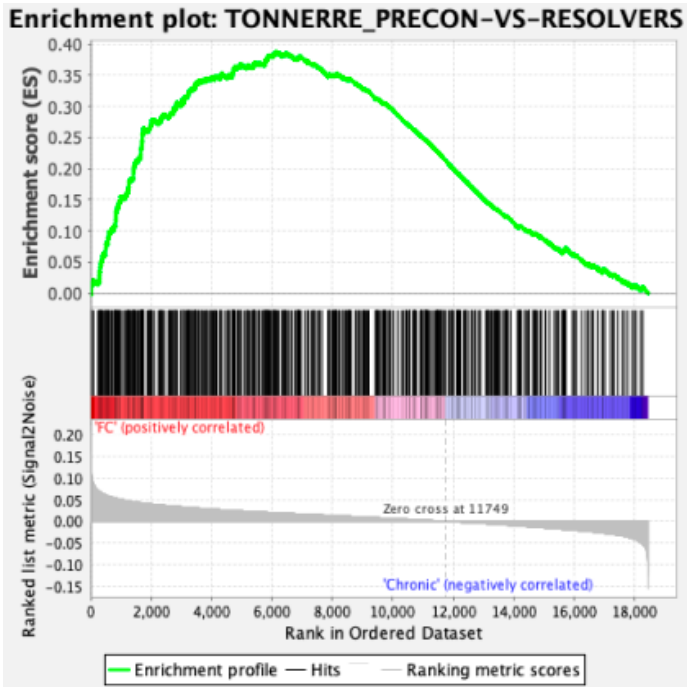
HBV-specific T cells lack the classic T cell exhaustion signature



FC **CHB**



Unpublished data with Janssen Liver Consortium

CHB and T Cell Exhaustion

HBV-specific CD8 T cells seem not as terminally exhausted in CHB compared to HCV

- PD-1 (and other IRs) expression diverse across specificities
- IR expression lower/less broad compared to cHCV
- Lack of deep T cell exhaustion signature across CHB

Does a less terminally exhausted T cell state allow more likely T cell recovery?
Or is anti-PD-1 treatment not targeting the main roadblock to CHB FC?

What drives HBV Functional Cure?

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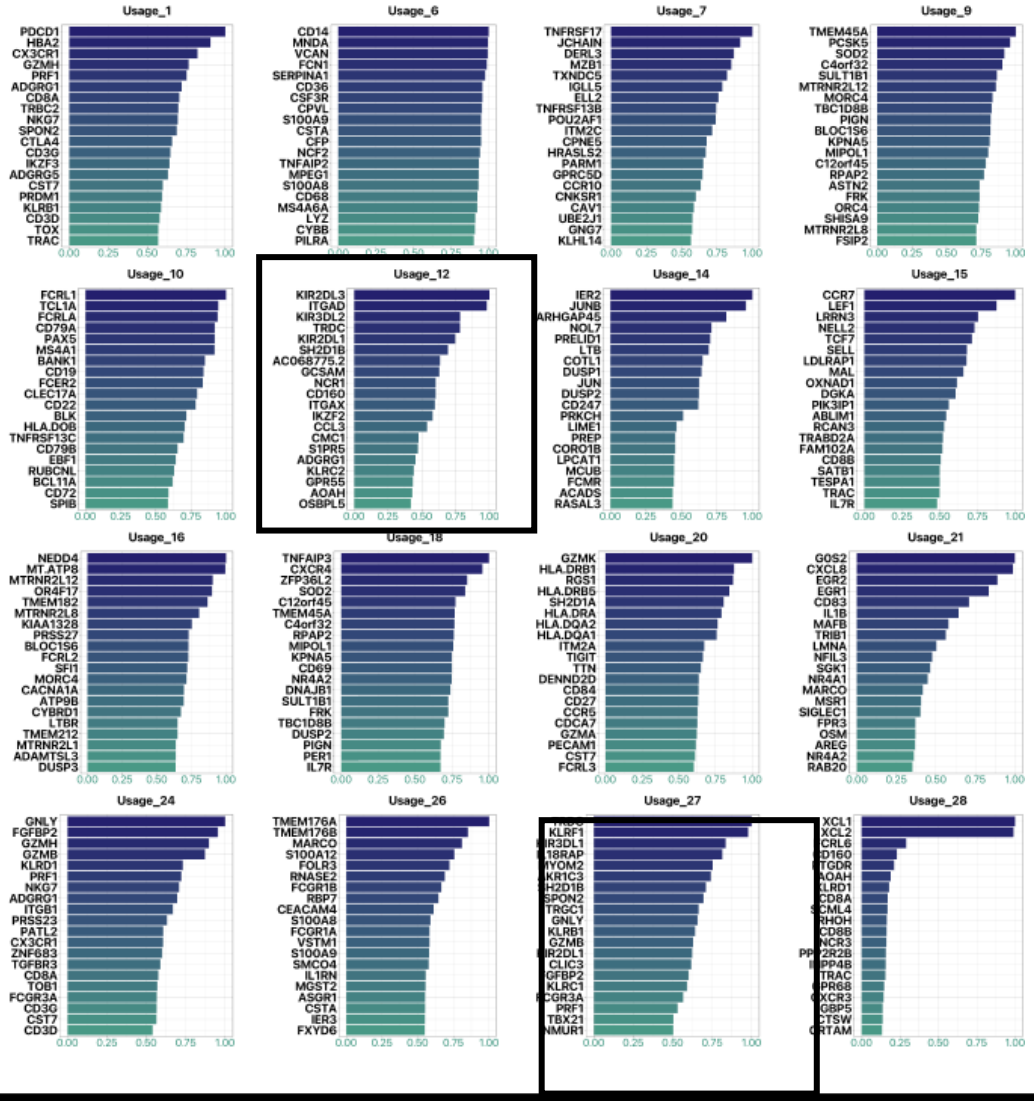
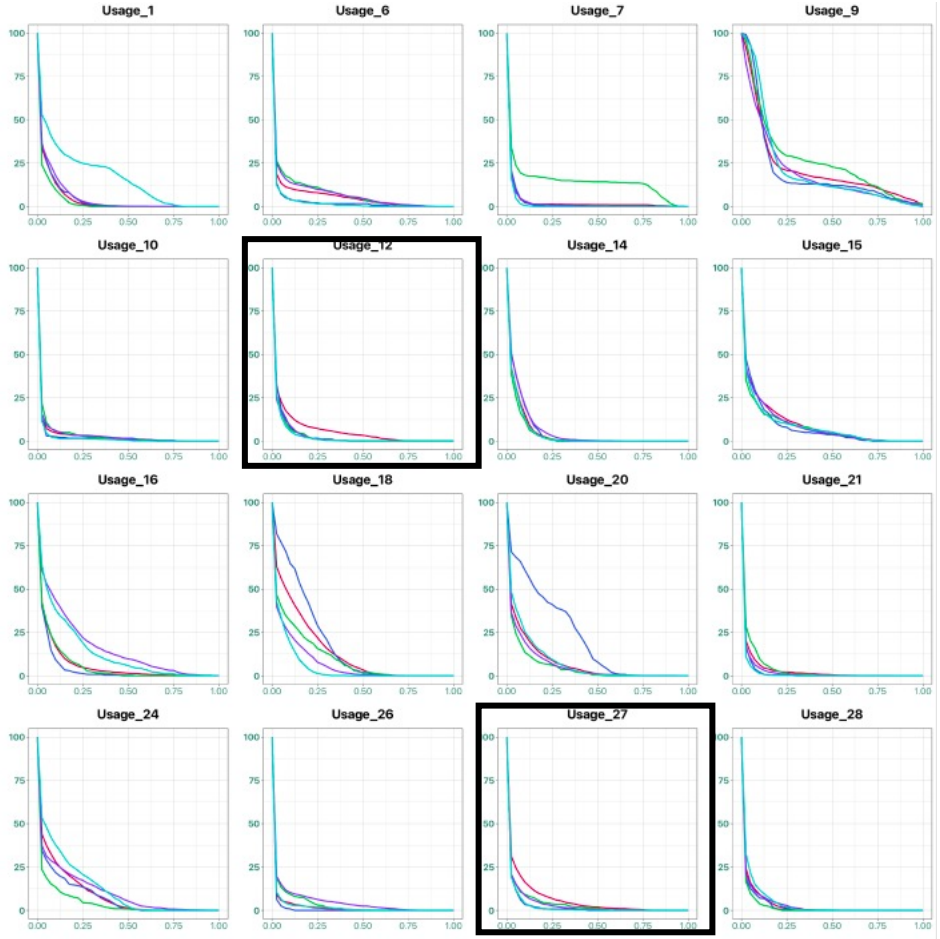
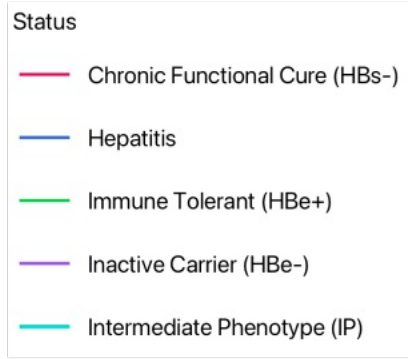
scRNAseq of HBV-specific CD8 T cells (Blood, SmartSeq2, cNMF)







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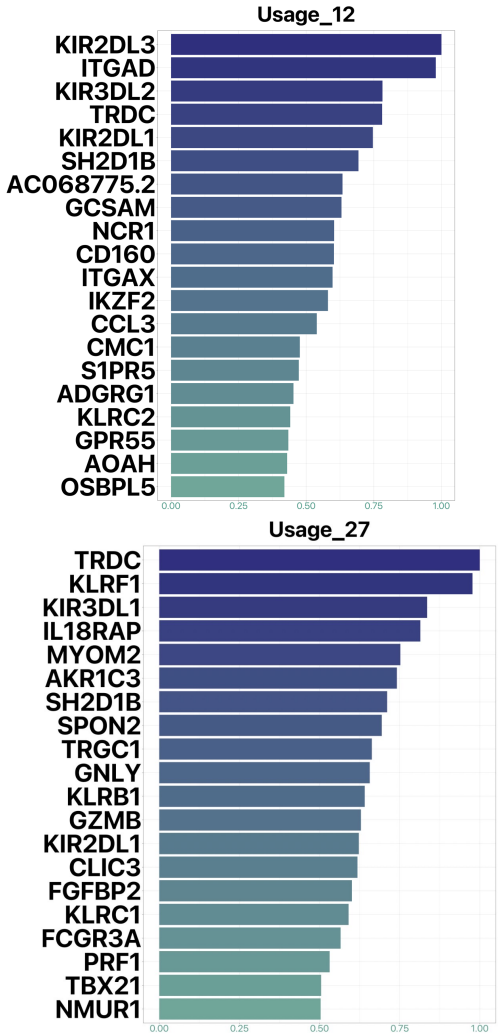
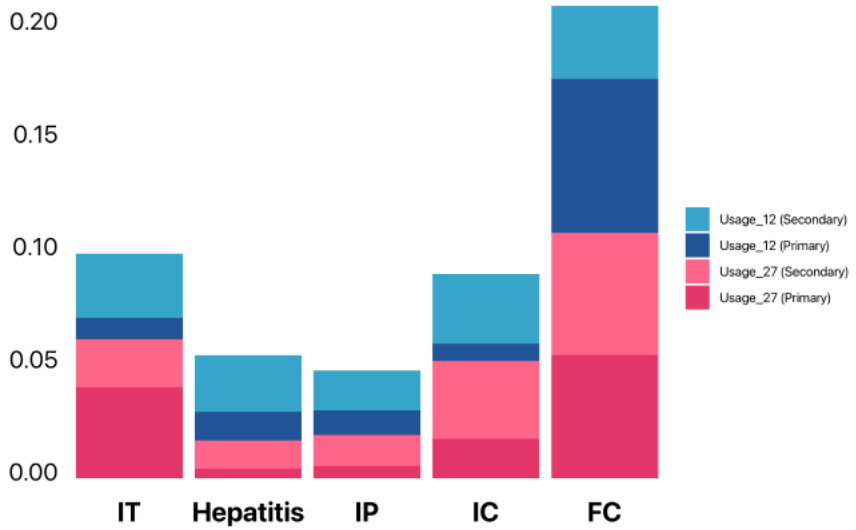
What drives HBV Functional Cure?

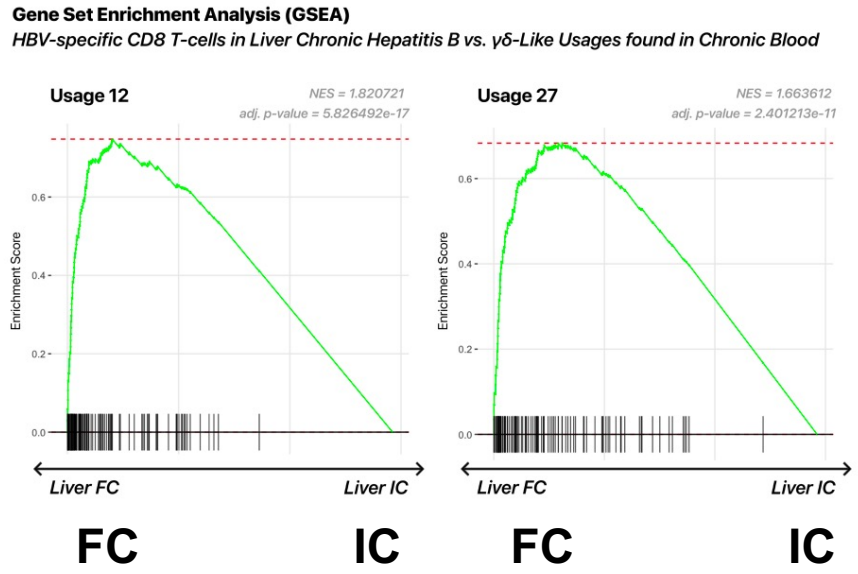
Innate-like/γδ-like cells are enriched in FC



Usages 12 and 27
HBV-spec. T cells Blood



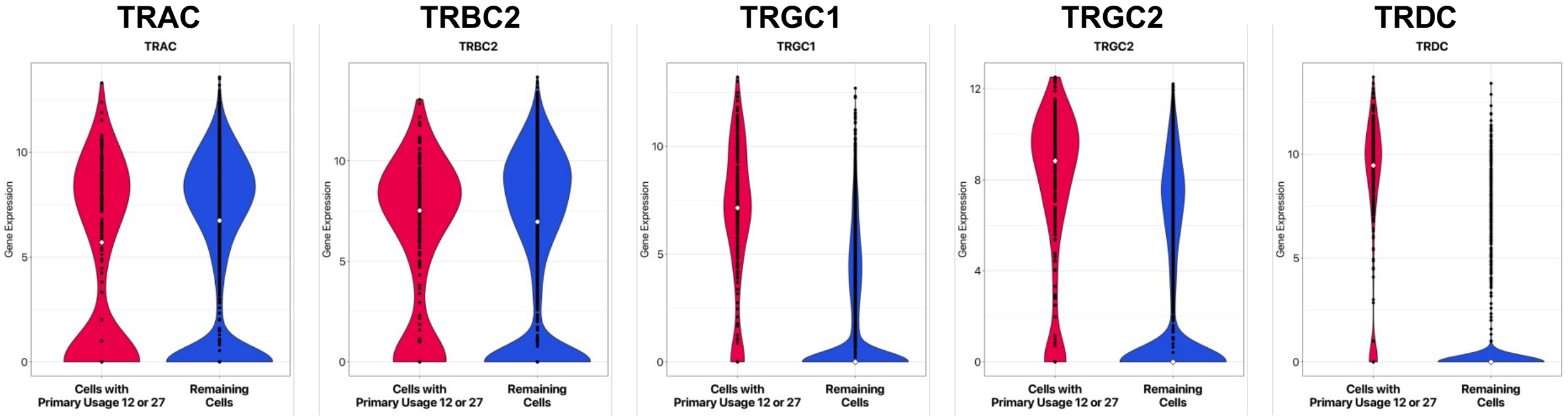
Enriched also in liver HBV-spec T cells



Unpublished data with Janssen Liver Consortium

What drives HBV Functional Cure?

HBV-specific CD8 T cells express both αβ and γδ TCR



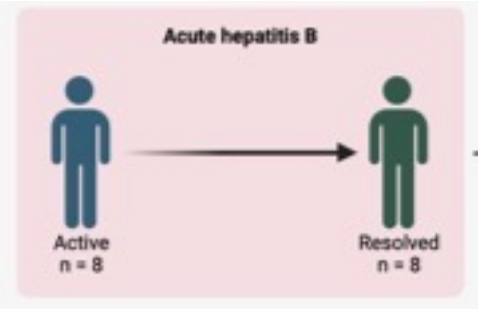
Cells <u>with</u> usage 12/27

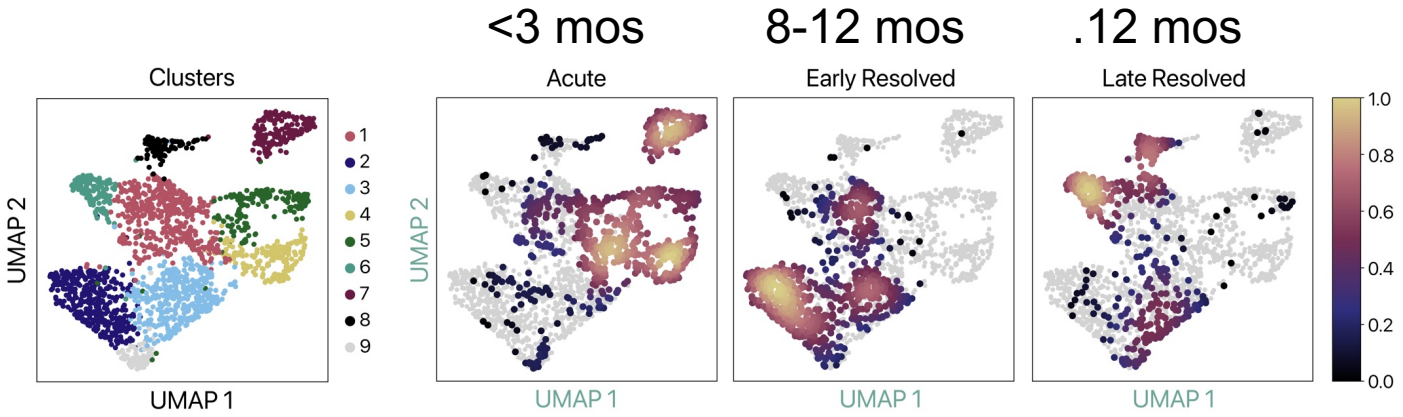
Cells <u>without</u> usage 12/27

Unpublished data with Janssen Liver Consortium

What drives HBV Functional Cure?

HBV-specific CD8 T cells during adult acute HBV infection with FC (PBMC)





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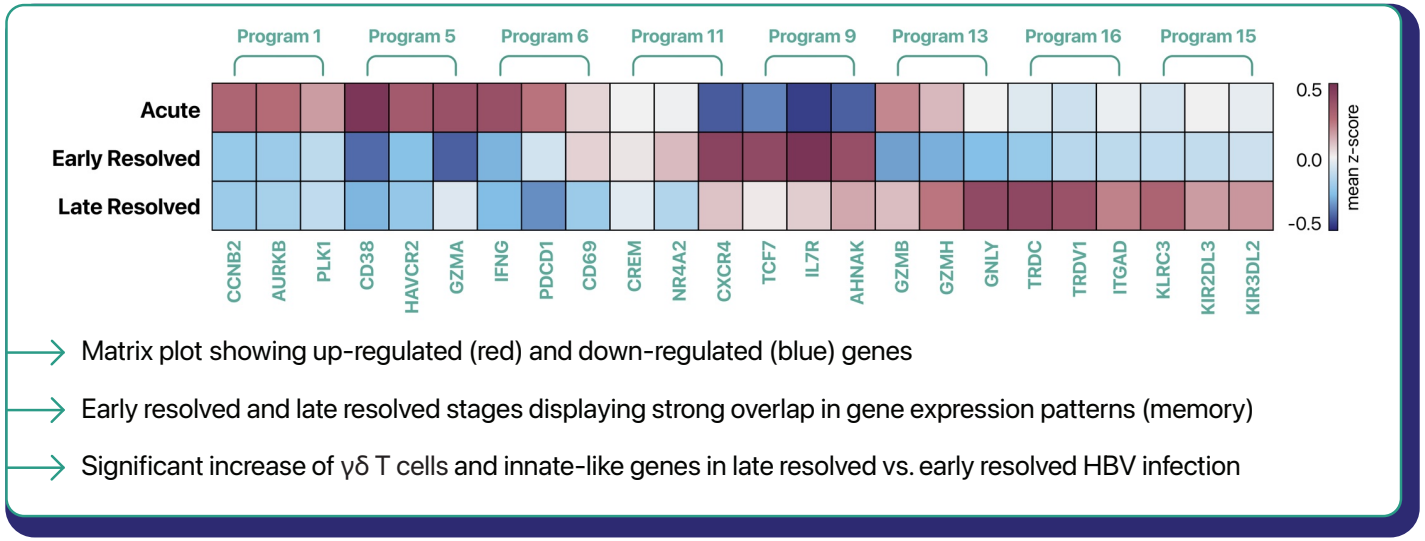
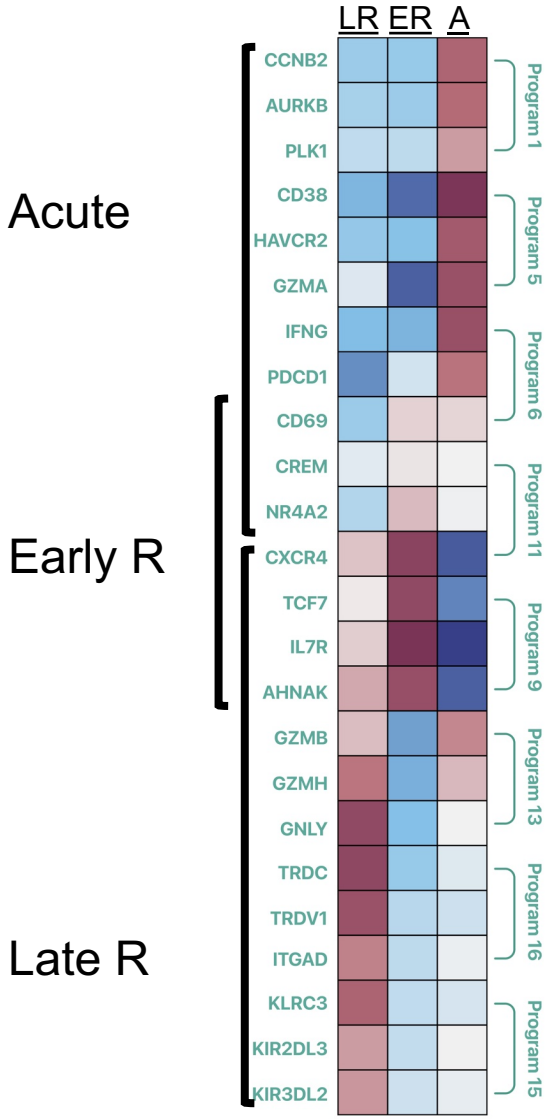


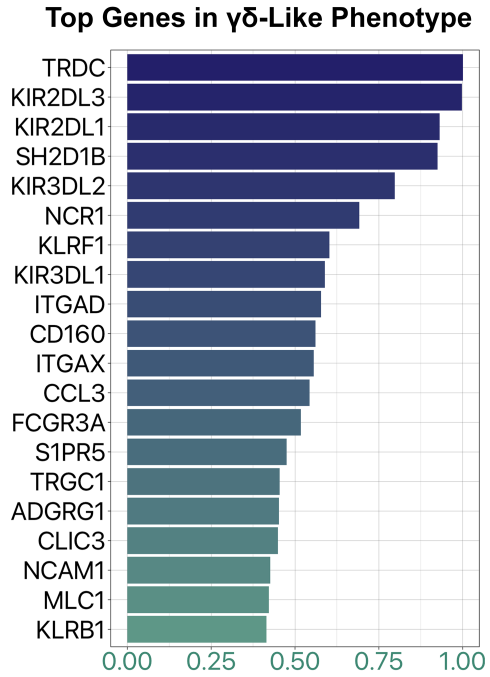
- Matrix plot showing up-regulated (red) and down-regulated (blue) genes
- Early resolved and late resolved stages displaying strong overlap in gene expression patterns (memory)
- Significant increase of γδ T cells and innate-like genes in late resolved vs. early resolved HBV infection

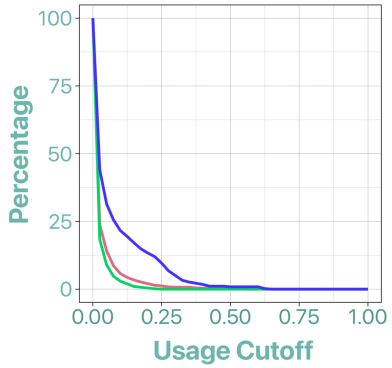
Unpublished data with Janssen Liver Consortium

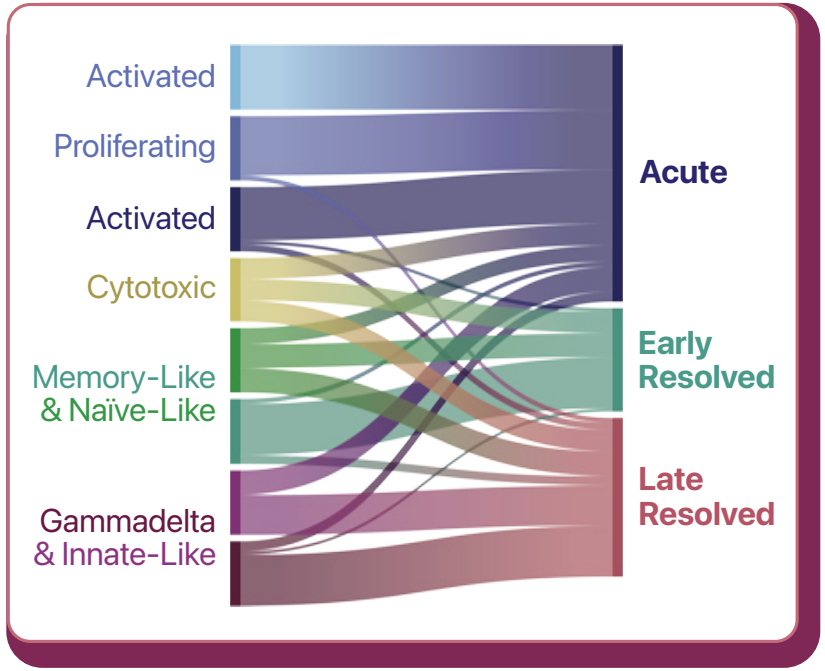
What drives HBV Functional Cure?

FC after adult acute infection also characterized by γδ-like/innate-like CD8 T cells









Acute
Early Resolved
Late Resolved

Unpublished data with Janssen Liver Consortium

HBV-specific CD8 T cell responses

HBV FC associated with the appearance of γδ-like/innate-like CD8 T cells expressing cytotoxic molecules.
Similar results after acute adult and after chronic HBV infection (in both blood and liver)

Innate qualities more appropriate than memory for controlled, not eliminated infection?

Summary and Outlook

HBV infection and immune response NOT static

- Immune control improves over decades, FC just final (and rare) step

Detailed *ex vivo* analyses allow new insights

- Needs to consider the complexity of CHB
- Questionable role of T cell exhaustion in CHB
- Role of CD4 T cells?
- FC associated with innate like HBV-specific CD8 T cells (surveillance?)

We need more and better immunology in HBV natural history and clinical trials

- Adequate sampling and planning of immunological assays needs to be included during cohort/trial design
- Human immunology needs to establish framework for animal models

<u>HBV FC is a realistic goal, but exploration of new treatments needs to be based on solid scientific evidence</u>

Acknowledgments

LAUER KIM Lab

Elias LATTOUF
Martin FEUERHERD
Lea BARTSCH
Suzan DIJKSTRA
Zhu ZHANG
Jasmin MISCHKE
Wei-Chen HUANG
Ruben HOOGEVEEN
Hannah DRESCHER
Jonathan EDDY
Oiza DIMOWO
Ava BROOKSHIER
Sonu SUBUDHU
Edoardo DIONISIO
Pierre TONNERRE

Arthur KIM
Jasneet ANEJA
Eliana EPSTEIN
Hai Yen CHIEN

Liver Consortium (HBV)

Adam GEHRING
André BOONSTRA
Harry JANSSEN
Jordan FELD
Alex SHALEK
Nir HACOHEN
Raymond CHUNG
Nadia ALATRAKCHI
Jacques BOLLEKENS
Jeroen AERSSENS

SHALEK Lab (MIT/Ragon/Broad)

Alex SHALEK
Alex GENSHAFT
Martin VILLANUEVA
Jasmin JOSEPH-CHAZAN

SEN Lab (MGH)

Debattama SEN

Other Collaborators

Lia LEWIS (FIOCRUZ)
Jörg TIMM (Düsseldorg)
John WHERRY (UPenn)
Paul KLENERMAN (Oxford)

Funding

NIH U19 AI082630 (CCHI)
NIH U19 AI066345
NIH R01 DA046277
NIH R37 AI179640
NIH R01 AI236 681
CZI Liver Cell Atlas
Janssen Pharma
GSK

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