Expanding Immune Monitoring in HBV Trials, Part II

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HBV Forum 4
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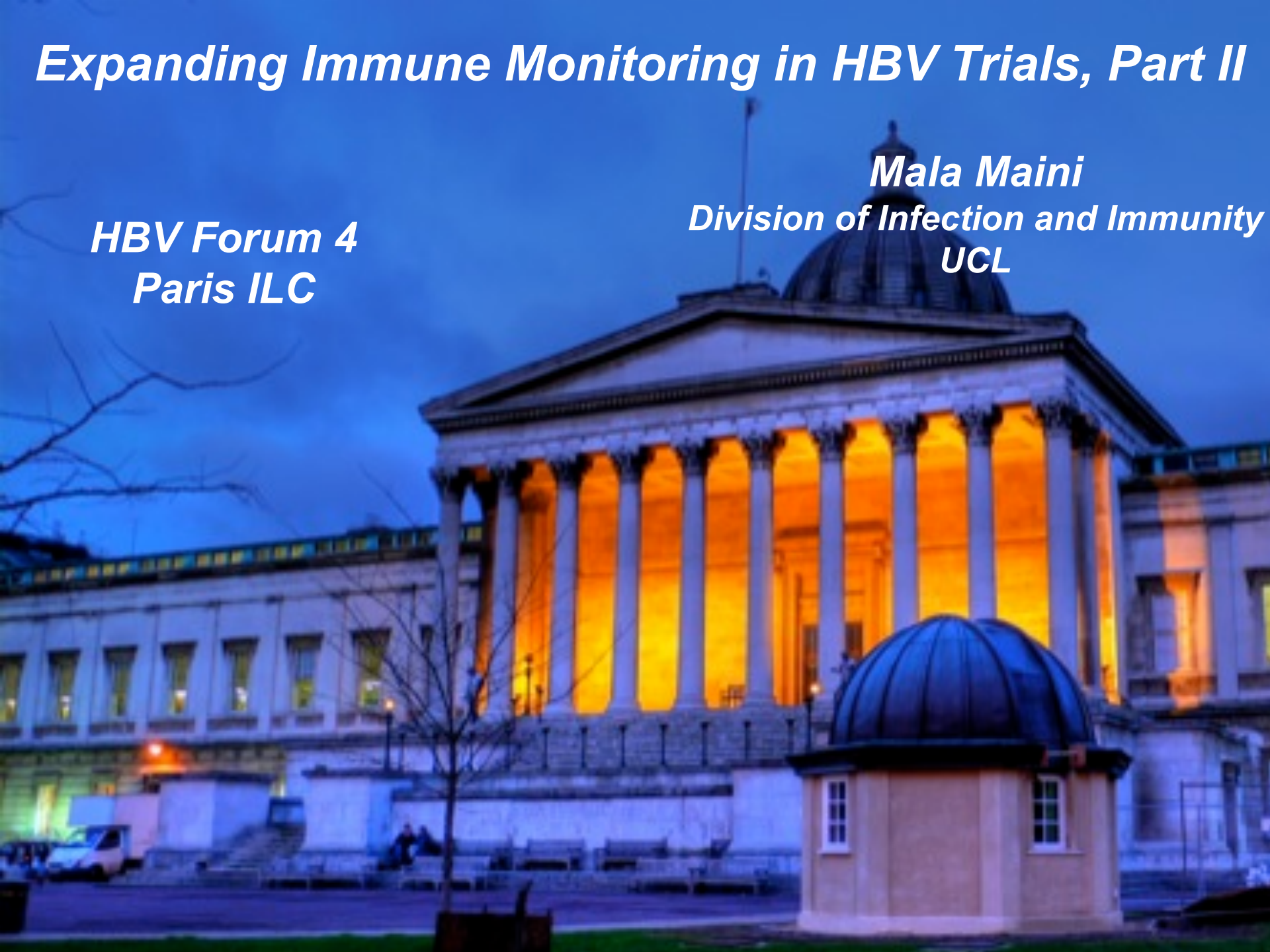


Disclosures

Mala K Maini FMedSci MD PhD

- *receives collaborative research funding from Gilead Sciences, Roche and Immunocore*

- *sits on advisory boards and /or acts as a consultant for Gilead Sciences, Roche, Immunocore, Arbutus Biopharma, Janessen*

Immune monitoring for which drug trials?

Immune-based therapies

e.g. checkpoint inhibitors, therapeutic vaccines

Therapies with antiviral and immunomodulatory potential

e.g. TLR agonists, combined therapies

Antiviral therapies

–indirect immunomodulation secondary to reduction in viral antigen load etc, e.g. siRNA, capsid inhibitors

Immune monitoring for which drug trials?

Especially important for:

Early phase trials

Failed / suboptimal /toxic therapies

Understanding immune mechanism of action can:

- **inform future drug development by:**
- driving further tailoring of therapy
- allowing selection of optimal combinations
- uncovering mechanism of toxicity
- **Provide immune biomarkers for:**
- selecting responders
- timing therapy withdrawal

How to focus immune monitoring?

Involve immunology colleagues early,

Select trial centres with immunology unit attached

Which immune mediators are likely drug targets?

Comprehensive, unbiased or hypothesis-driven, focused?

Global or HBV-specific responses?

Ex vivo or after in vitro expansion?

Phenotyping +/- functional?

Peripheral +/- intrahepatic?

Drug target tissue? e.g oral - gut, iv – liver

What is the goal of immune monitoring?

Tailor according to primary goals:

Evaluating antiviral potential

Detection of induction of:

- robust immune responses able to reduce infected hepatocytes
- long-lasting immune surveillance for residual cccDNA

Evaluating mechanism of action

Evaluating immunomodulatory effects

Evaluating toxicity through induction of immunopathology

Is Drug X inducing immune responses capable of HBV control?

Evaluating antiviral potential by induction of:

- robust immune responses able to reduce infected hepatocytes
- long-lasting immune surveillance for residual cccDNA

Direct:

- HBV-specific T cells
- HBV-specific B cells

Indirect:

- Antiviral cytokines (IFN-g, TNF) produced by NK cells, MAITs etc

Is Drug X inducing immune responses capable of HBV control?

Quantitation of HBV-specific T cells:

Elispot/Intracellular cytokine staining

–overnight / 10-day, allows assessment of function,

–cytolytic and non-cytolytic control

Overlapping peptides spanning core/pol/env/whole HBV proteome?

Genotype-specific / pan-genotypic?

Can simplify cf Quantiferon in TB?

HLA-peptide multimers

–require pre-defined epitopes (mostly HLA-A2),

-allow ex vivo phenotyping

Is Drug X inducing immune responses capable of HBV control?

Quantitation & characterization of HBV-specific B cells:

Also have defects that could reflect prognosis +/- be targeted therapeutically

e.g. IL-10-producing regulatory B cells Das et al JI 2012

Exhaustion of virus-specific and total B cell populations by HBV infection
Salimzadeh et al, EASL ILC Paris 2018

Dysfunctional surface antigen-specific memory B cells accumulate in CHB
Burton et al, EASL ILC Paris 2018

Is Drug X driving immunomodulatory responses?

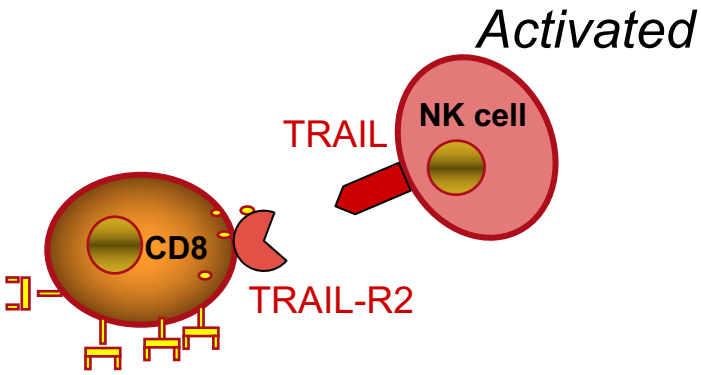
Immunosuppressive effects

- Induction of Tregs, IL-10, MDSC, regulatory NK cells

e.g. TRAIL-expressing NK cells can delete HBV-specific T cells,

Peppa et al, J Exp Med 2013

Activated TRAIL+ NK cells correlate inversely with HBV-specific T cells on NUCs, *Boni et al, Hepatol 2015*



Immunostimulatory effects

-e.g. Induction of IL-12, IFN-γ

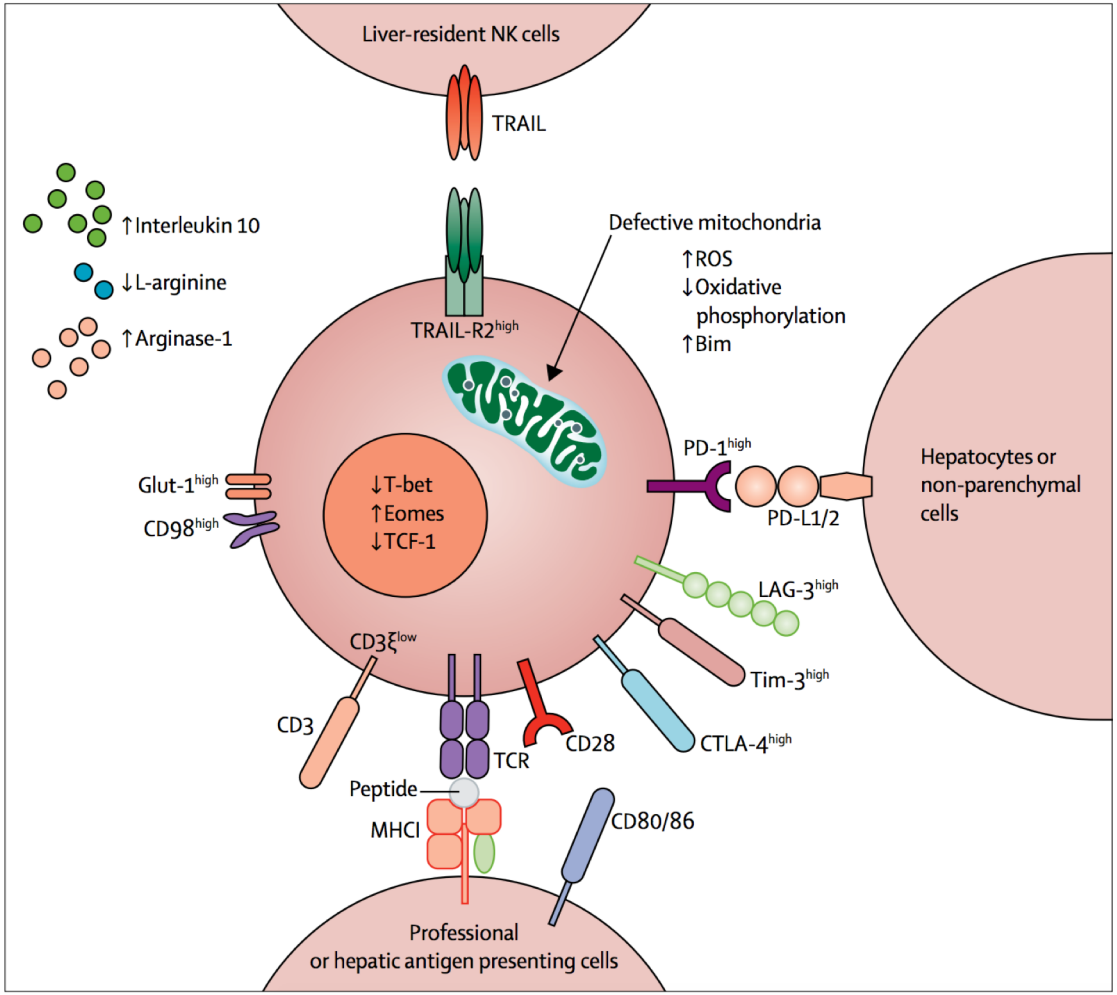
IL-12 enhances functionality of HBV-specific T cells,

Schurich et al PLoS Path 2013

What is the mechanism of action and limitations of Drug X?

Induction of immunsuppressive populations **e.g. activated NK cells, MDSC, Tregs**

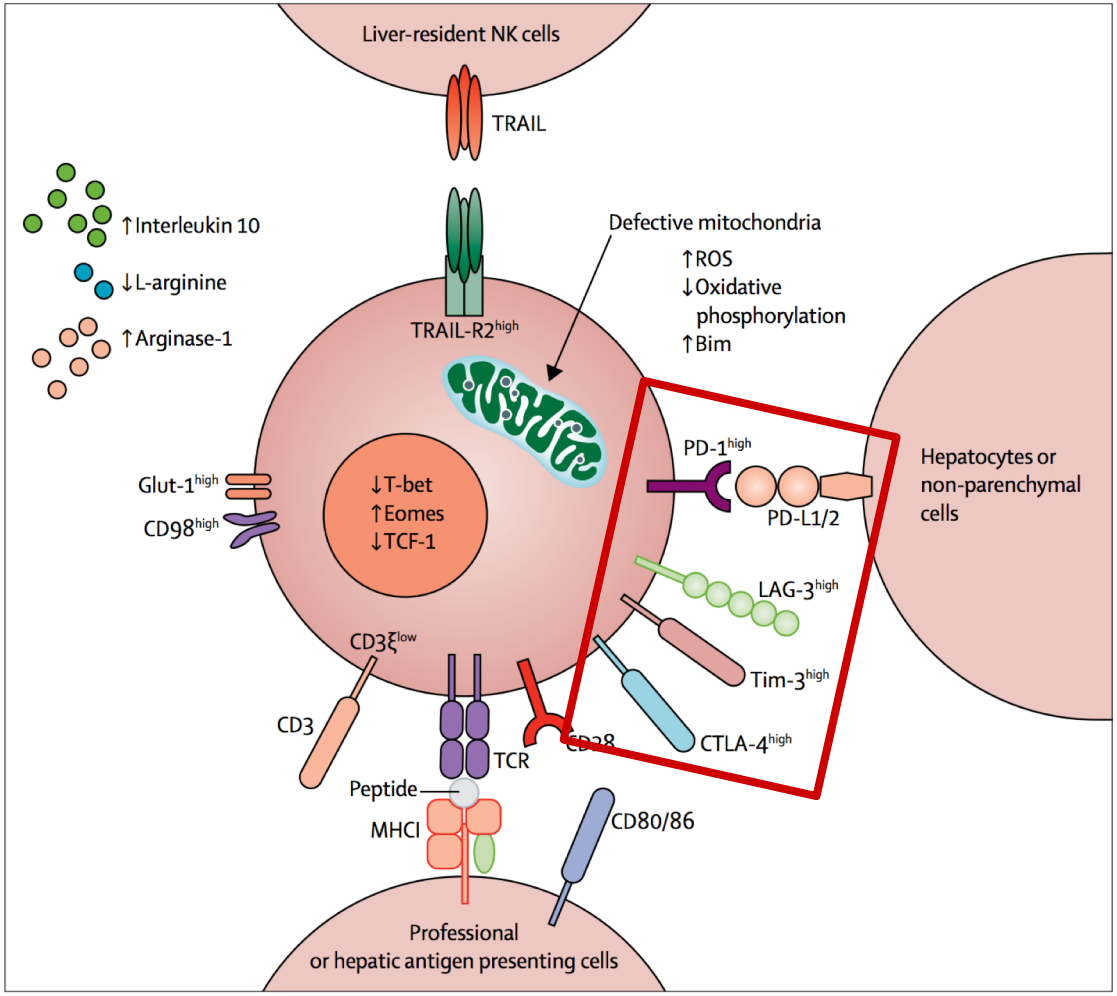
Remaining intrinsic constraints on HBV-specific T cells



What is the mechanism of action and limitations of Drug X?

Remaining intrinsic constraints on HBV-specific T cells:

e.g. compensatory upregulation of alternative co-receptors upon PD-1 blockade



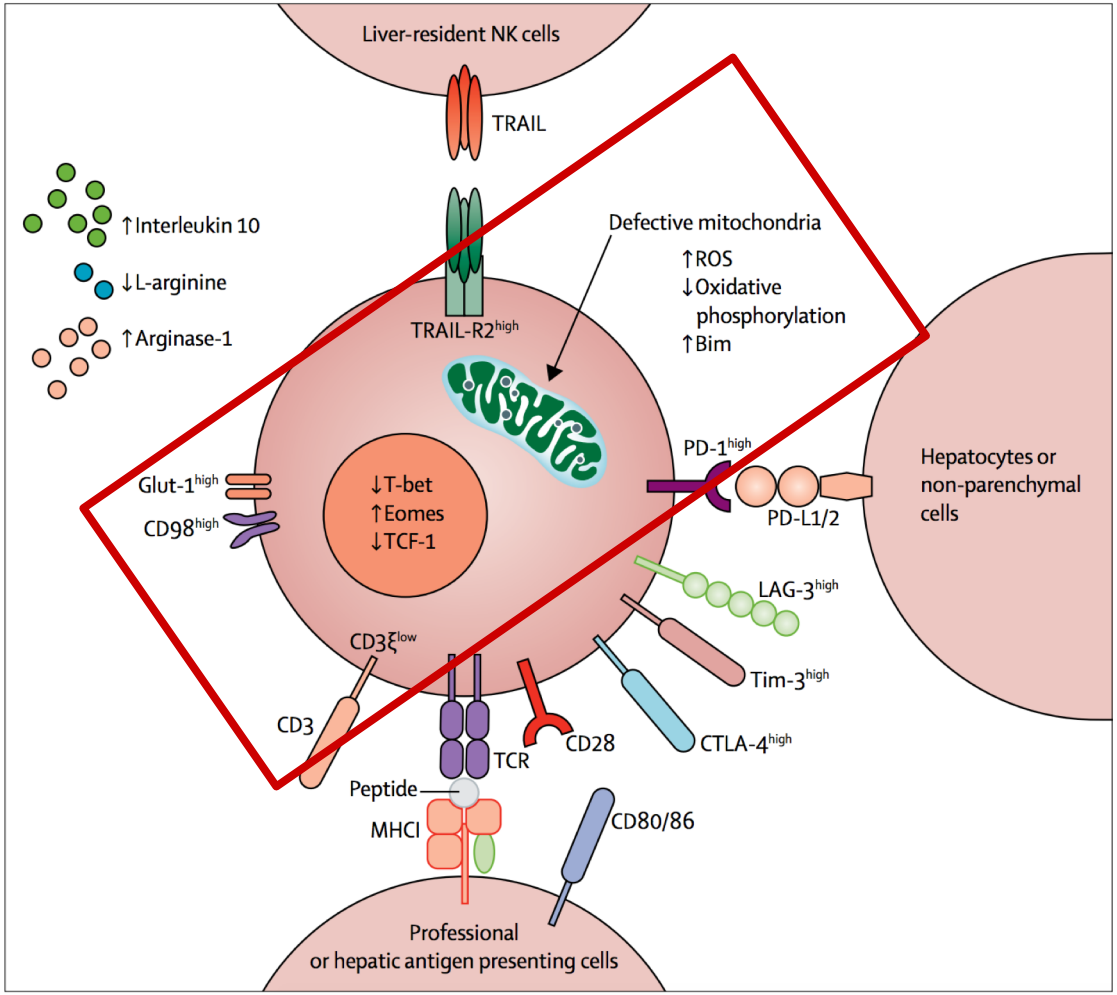
What is the mechanism of action and limitations of Drug X?

Induction of immunsuppressive populations **e.g. activated NK cells, MDSC, Tregs**

Remaining intrinsic constraints on HBV-specific T cells:

e.g. compensatory upregulation of alternative co-receptors upon PD-1 blockade

e.g. underlying metabolic & epigenetic defects



Schurich et al Cell Rep 2015, Fisicaro et al Nat Med 2015

Is Drug X inducing immune-driven pathology /side effects

HBV is a non-cytopathic virus

Resultant liver disease is immune-mediated

The same immune responses that need to be boosted to mediate protection will also usually induce liver injury

e.g. increased HBV-specific T cells can kill hepatocytes (cytotoxic) or initiate inflammatory infiltrate (IFN-γ).

Limit toxicity by reducing bystander inflammation which amplifies liver damage

e.g. gMDSC can inhibit non-antigen-specific T cells

Pallett et al, Nat Med 2015

The trade-off between immunity and immunopathology

Hepatic flares an inevitable result of effective immune boosting?

- Minimise antigen load –need studies on extent of infected hepatocytes
- Select patients with good liver reserve
- Focus boosting on HBV-specific components
- Develop adjunctive approaches to limit collateral damage

The need for liver sampling for HBV functional cure trials

- **Diagnostic liver biopsies being replaced by non-invasive fibrosis tests**

- **BUT liver sampling vital for:**

- Detection of viral reservoirs: cccDNA & intergrated DNA

- Detection of liver-resident NK cells
  -not in blood

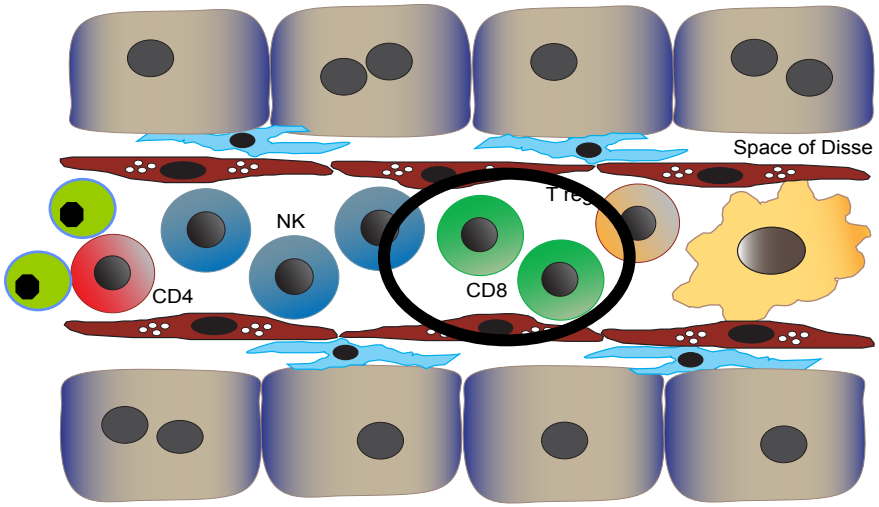
  e.g. Marquardt et al, JI 2015
  Stegmann et al, Sci Rep 2016

- Detection of HBV-specific T cells –mostly compartmentalised in liver

- Detection of liver resident T cells –vital frontline immunosurveillance
  -not in blood

  Pallett et al JEM 2017

Tissue-resident T cells in the human liver: Poised for frontline defence



Define signature of tissue-resident CD8 T cells in human liver

-CD69+CD103+ T-bet^{lo}Eomes^{lo}Blimp-1^{hi}

-cannot be sampled in periphery

-expand in HBV especially in those with good viral control

-features that instruct their retention, survival, rapid non-cytolytic antiviral function

-signals capable of recapitulating their induction

Aim for induction of tissue-resident memory cells for functional cure

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