Rationale for Modulating Innate Immunity

Mala Maini
Division of Infection and Immunity
UCL, UK

5th International Workshop on HBV Cure
Toronto 2018
Innate/Adaptive Identity Crisis: Cross-over and Cross-talk

adapted from: G. Dranoff Nat Rev Cancer (2014)
Rationale for innate immunomodulation in HBV cure

• Directly target hepatocyte cell intrinsic immunity

• Supplementing soluble mediators
  • To mediate direct antiviral effects
  • To modulate innate and adaptive immunity

• Harnessing innate cell types e.g. APC, NK cells, MAITs
  • To produce antiviral mediators e.g. IFN-γ
  • To modulate adaptive immune responses
Considerations for developing innate immunomodulators

• Can bypass need to rescue exhausted adaptive immunity?

• Innate mediators typically short-lived
  • Need repeated administration?
  • Or conjunctive adaptive boosting for long-lasting immunosurveillance?

• Effects often not exclusively directed against infected hepatocytes
  • Difficult efficacy/toxicity balance?

• Issues with model systems for testing efficacy
  • Differences between hepatoma and primary hepatocyte cell intrinsic immunity
  • Differences between murine and human innate cell phenotypes
  • Differences between peripheral and gut/liver innate immune composition –especially relevant for orally-acting agents
  • Differences between healthy and HBV-infected liver innate composition
Boosting cell intrinsic immunity

Limited induction of IFN-I & downstream cell-intrinsic immunity -but HBV susceptible to these mediators

HBV fails to induce/repress INFα – but partially responsive to it
e.g. Mutz Gastro 2018, Cheng Hepatol 2018, Suslov Gastro 2018

HBV fails to induce INFα in chimp and human acute HBV
e.g. Wieland PNAS, Fletcher Hepatol 2012, Stacey J Virol 2009, Dunn Gastro 2009
Boosting cell intrinsic immunity

Limited induction of IFN-I & downstream cell-intrinsic immunity - but HBV susceptible to these mediators

Solution: Direct activation cell-intrinsic immunity

e.g. Direct anti-HBV activity of TLR1/2/3 agonists; Lucifora, Sci Rep 2018
FXR agonists

Phase II ACHIEVE trial of oral RIG-I/Nod-2 agonist Inarigivir – DAA + IFN-λ induction
NK cells have defective IFN-γ production

Oliviero Gastro 2009
Bonorino J Hep 2009
Peppa PLoS Path 2010
Tjwa J Hep 2011
HBV-specific T cells upregulate TRAIL-R2 rendering them susceptible to NK cell-mediated deletion.
MAITs & γδ-T cells are enriched in liver - can their antiviral potential be harnessed by innate immunomodulators?

Jo et al PLoS Path 2014
Innate intrahepatic effectors to be targeted?

Degranulating arginase+ gMDSC accumulate in the liver - scavenge arginine

Arginine starvation of T cells:

Impairs T cell metabolism, proliferation, survival & antiviral function

Can B cells be targeted with TLR agonists?

HBsAg-specific B cells persist in blood and liver in CHB - respond to TLR agonists?

Entering the spotlight: hepatitis B surface antigen–specific B cells

Christoph Neumann-Haefelin and Robert Thimme

Circulating and intrahepatic antiviral B cells are defective in hepatitis B

Alice R. Burton, …, Nadege Pelletier, Mala K. Maini

PD-1 blockade partially recovers dysfunctional virus–specific B cells in chronic hepatitis B infection

Loghman Salimzadeh, …, Patrick T.F. Kennedy, Antonio Bertoletti
RNA sensor RIG-I: innate sensor & direct antiviral factor

**Inarigivir:**
- **immune modulation:** induction of endogenous host IFN via the activation of RIG-I and NOD2
- **antiviral activity:** counteracts the interaction of HBV pol with pgRNA

Phase II ACHIEVE trial: randomized, placebo controlled multiple dose trial

Harnessing innate and adaptive immunity: Oral Selective TLR agonists

Oral TLR agonists

GUT LUMEN

pDCs

PORTAL VEIN

SYSTEMIC CIRCULATION

Antiviral cytokines
Selective oral TLR Agonists can activate innate and adaptive immunity

Induce cytokines in gut acting predominantly in liver

Oral TLR-7 agonist GS-9620:
- showed efficacy in chimpanzees and woodchucks
- induced IFN-I & intrahepatic T/B cell aggregates, boosted peripheral HBV-specific T cells & NK cells in patients

BUT:
- no HBsAg reduction in virally suppressed patients with CHB
  Janssen J Hep 2018

Modification/use in combination based on better understanding of mechanism of action
?combination with antigen reduction

Combination treatment of a TLR7 agonist RO7020531 and a capsid assembly modulator RO7049389
Harnessing the innate/adaptive immune axis: TLR7

differentiation toward Ig-producing plasma cells: humoral immunity

cross-priming of CD8 T cells

cell intrinsic antiviral activity

cross-priming of CD8 T cells

adapted from: Boni Gastroenterology 2018
Niu C. et al J. Hepatology 2018
Li L. et al J. Hepatology 2018
Harnessing the innate/adaptive immune axis: TLR7

- TLR7 agonist
- differentiation toward Ig-producing plasma cells: humoral immunity
- cell intrinsic antiviral activity
- liver-resident
- NK + GS-9620
- Expansion
- Functional improvement
- No T cell inhibition
- during combo therapy
- HBV-specific
- T cells + GS-9620
- Expansion
- Functional improvement
**Harnessing the innate/adaptive immune axis: TLR8**

*Potent and selective small molecule agonist for TLR8 (GS-9688)*

- Production of antiviral cytokines e.g. IL-12, IL-18, IFNγ
- Prolonged suppression of serum WHV and WHsAg
  - **Minimal induction of IFNα**
  - Reduction in HBV DNA, HBsAg titre in vitro PHH studies
- TLR8-induced cytokine profile augments HBV-specific T cells responses, activates MAITS/NK cells, and suppress HBV via induction of cytokines
**TLR-8 agonists can harness additional components of innate and adaptive immunity?**

**TLR8 agonists induce IL-12:**
- Activates NK cells
- Promotes HBV-specific CD8 metabolism and functionality
IL-12 synergises PD-1 rescue and overcomes mitochondrial defects

The Third Signal Cytokine IL-12 Rescues the Anti-Viral Function of Exhausted HBV-Specific CD8 T Cells

Anna Schurich1, Laura J. Pallett1, Marcin Lubowiecki1, Harshimran D. Singh1,2, Upkar S. Gill3, Patrick T. Kennedy3, Eleni Nastouli4, Sudeep Tanwar2, William Rosenberg2, Mala K. Maini1

Cell Reports
Volume 16, Issue 5, 2 August 2016, Pages 1243–1252

Distinct Metabolic Requirements of Exhausted and Functional Virus-Specific CD8 T Cells in the Same Host

Anna Schurich1, Laura J. Pallett1, Danyal Jajbhay1, Jessica Wijngaarden1, Itziar Otano1, Upkar S. Gill2, Naviyot Hani2, Patrick T. Kennedy3, Eleni Nastouli4, Richard Gilson5, Christian Frezza6, Sian M. Henson7, Mala K. Maini1
Compartmentalised intrahepatic virology and immunology

For monitoring and optimising HBV functional cure strategies – liver sampling useful for detection of:

• **viral reservoirs: cccDNA & integrated DNA**

• **liver-resident NK cells - not in blood**

• **other immune cells enriched/altered in liver e.g. MAITs, γδ-T cells, gMDSC**

• **HBV-specific T cells & liver-resident T cells - mostly compartmentalised in liver**

Recent advances in basic science

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

Upkar S Gill¹, Laura J Pallet², Patrick T F Kennedy¹, Mala K Maini²

Can FNA sample intrahepatic immunity?
Fine needle aspirates for HBV functional cure trials

**Fine needle aspirates:**

- sufficient cells for 3 flow cytometry panels (16-30 parameters each)
- simultaneous analysis of viable leukocytes & hepatocytes
  e.g. PD1 T cells /PD-L1 hepatocytes; HBV-specific T cells/HBsAg+hepatocytes
- proportional representation of all intrahepatic lymphocytes
- sample tissue-resident T and NK cells
- enriched for HBV-specific T cells
- can be scored for liver vs blood composition – standardization
- well tolerated for repeated sampling

Gill, Pallett et al, Gut in press
Rationale for innate immunomodulation in HBV cure

• Directly target hepatocyte cell intrinsic immunity
  
• Supplementing soluble mediators
  • To mediate direct antiviral effects
  • To modulate innate and adaptive immunity

• Harnessing innate cell types e.g. APC, NK cells, MAITs
  • To produce antiviral mediators e.g. IFN-γ
  • To modulate adaptive immune responses

Inarigavir

GS-9688
R07020531
AIC649
Acknowledgements

Division of Infection and Immunity, UCL

Ross Lopes
Abhishek Das
Claire Dunn
Pooja Khanna
Lorenzo Micco
Gaia Nebbia
Wei-Chen Huang
Simran Singh
Itziar Otano
Kasha Singh
Dimitra Peppa
Emily Colbeck

UCL collaborators
Niclas Thomas
Nathan Davies
Victoria Male
Guiseppe Fusai
Eleni Nastouli
Richard Gilson
Amir Gander
Brian Davidson
Francis Robertson
William Rosenberg
Tu Vinh Luong

Laura Pallett
Kerstin Stegmann
Anna Schurich
Jessica Davies
Nicholas Easom
Alice Burton
Nathalie Schmidt
Leo Swadling
Mariana Diniz
Kornelija Suveizdyte
Oliver Amin

IDIBAPS
Xavier Forns

University of Dundee
Linda Sinclair
Doreen Cantrell

A*Star, Singapore
Antonio Bertoletti

Barts & the London Hospital
Upkar Gill
Jyoti Hansi
Patrick Kennedy

All healthy donors, patients and clinic staff

Wellcome Trust Investigator

Supported by the MRC