CHRONIC HEPATITIS B VIRUS
Prospects for Cure

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Chronic HBV Infection

- 350 million people worldwide with CHB
- >600,000 deaths per year
- 80% of deaths in those infected at birth/early childhood
- 25% of those infected in childhood develop cirrhosis or HCC
Unmet challenges in HBV therapy

1. Strategies to achieve HBsAg loss and ‘cure’
2. Reducing the risk of HCC
3. Defining treatment endpoints
4. Finite therapy options
Chronic HBV Infection

Locarnini & Zoulim, Anitvir Ther 2010
Chronic HBV Infection

Locarnini & Zoulim, Anitvir Ther 2010
Chronic HBV Infection

Locarnini & Zoulim, Antivir Ther 2010
Natural history & disease phase
Natural History & Disease Phase

- **HBeAg**
- **Anti-HBe**

HBV DNA/HBsAg (log10 IU/ml)

ALT (IU/L)

**Natural History & Disease Phase**

- **Immune Tolerant**
- **Immune Clearance**
- **Immune Control**
- **Immune Escape**

adapted from Gill & Kennedy; Clin Med 2015

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Natural History & Disease Phase

HBeAg

Anti-HBe

ALT HBV DNA HBsAg

IMMUNE TOLERANT IMMUNE CLEARANCE IMMUNE CONTROL IMMUNE ESCAPE

adapted from Gill & Kennedy; Clin Med 2015
Is our current understanding of natural history & disease phase accurate?
Evidence of immune activity in the ‘immune tolerant’ disease phase

Kennedy/Bertoletti et al., Gastroenterology 2012

%PD-1+ CD8 T cells

% PD-1+ CD4 T cells

P<0.001

P<0.001

P<0.001
Evidence of immune activity in the ‘immune tolerant’ disease phase

Kennedy/Bertoletti et al., Gastroenterology 2012

$P = .006$

$P = .4383$
Evidence of liver damage in the ‘immune tolerant’ disease phase

Mason/Kennedy et al., Gastroenterology 2016
Nuclear core positive hepatocytes differentiate ‘immune tolerant’ disease

Mason/Kennedy et al., Gastroenterology 2016
Clonal hepatocyte expansion in ‘immune tolerant’ disease

Mason/Kennedy et al., Gastroenterology 2016
Redefining disease phase in CHB

Bertoletti & Kennedy, Cell & Mol. Immunol 2014

**Immune Tolerance**

**Immune Clearance**

**Non-Inflammatory**

**Inflammatory**

Conventional representation of the immuno-tolerance and immune clearance phases:
- HBV-specific T cells are present only in the second phase.

Proposed representation of non-inflammatory and inflammatory phases of CHB:
- HBV-specific T cells are present more in young patients but do not cause recruitment of inflammatory cells.
- Monocytes, granulocytes, T-cells.
- Pro-inflammatory events mainly present in adults.
Treatment & management strategies
Current Treatment Regimes

Peg-IFN

- Immunomodulatory agent
- HBsAg decline or loss
- Moderate rate of relapse
- Finite therapy
- Use of stopping rules

NUCs

- Excellent viral suppression
- Long term therapy
- High barrier to resistance
- Poor HBsAg reduction
- ? Treatment endpoints
HBV Treatment regimes

Nucleos(t)ide Analogue (NUCs)

**TENOFOVIR**

**ENTECAVIR**

Current therapies are non-curative

• Peg-IFN sustained immune control, but only in a minority of patients\(^1\)

• HBeAg-negative & positive disease:
  – limited decline in HBsAg during NUC monotherapy\(^2\)

• Long-term viral suppression is achieved, but sustained immune control following treatment cessation is limited\(^3\)

Assessment of Bone Mineral Density in Tenofovir-Treated Patients With Chronic Hepatitis B: Can the Fracture Risk Assessment Tool Identify Those at Greatest Risk?

Upkar S. Gill,1 Alexandra Zissimopoulos,2 Safa Al-Shamma,2 Katherine Burke,2 Mark J. W. McPhail,3 David A. Barr,4 Yiannis N. Kallis,2 Richard T. C. Marley,2 Paul Kooner,2 Graham R. Foster,1 and Patrick T. F. Kennedy1

1Hepatology Unit, Centre for Digestive Diseases, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, 2Department of Hepatology, Barts Health NHS Trust, 3Department of Hepatology, Faculty of Medicine, Imperial College London, St Mary’s Hospital, Paddington, and 4Department of Infectious Diseases, Brownlee Centre for Infectious and Communicable Diseases, NHS Greater Glasgow and Clyde, United Kingdom

Background. Tenofovir disoproxil fumarate (TDF) is an established nucleotide analogue in the treatment of chronic hepatitis B. Bone mineral density loss has been described in TDF-treated patients with human immunodeficiency virus infection, but limited data exist for patients with chronic hepatitis B. Dual X-ray absorptiometry (DEXA) was used to determine bone mineral density changes in TDF-exposed patients. We evaluated the accuracy
What are the available options.....
What are the available options.....

1. Sequential therapy strategies
Sequential NUC Therapy

Altered NK cell responsiveness to viral load suppression following PegIFNα priming

Sequential NUC Therapy

Greater HBsAg decline with NUC therapy following PegIFNα priming compared to de novo NUC therapy

Gill/Kennedy et al., PLoS Pathog. 2016, in press
What are the available options.....

1. Sequential therapy strategies

2. Combination therapies
Adding Pegylated Interferon to Entecavir for Hepatitis B e Antigen–Positive Chronic Hepatitis B: A Multicenter Randomized Trial (ARES Study)

Willem Pieter Brouwer,1 Qing Xie,2 Milan J. Sonneveld,1 Ningping Zhang,3 Qin Zhang,4 Fehmi Tabak,5 Adrian Streinu-Cercel,6 Ji-Yao Wang,3 Ramazan Idilman,7 Hendrik W. Reesink,8 Mircea Diculescu,9 Krzysztof Simon,10 Mihai Voiculescu,11 Meral Akdogan,12 Wlodzimierz Mazur,13 Jurrien G.P. Reijnders,1 Elke Verhey,1 Bettina E. Hansen,1,14 and Harry L.A. Janssen,1,15 for the ARES Study Group
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**Graphs:**
- **HBV DNA decline (log IU/mL)**: Treatment weeks 24, 36, 48, 60, 72.
- **qHBeAg decline (log IU/mL)**: Treatment weeks 24, 36, 48, 60, 72.
- **qHBsAg decline (log IU/mL)**: Treatment weeks 24, 36, 48, 60, 72.

- **Randomized**
- **Consolidation**

**Legend:**
- **ETV monotherapy**
- **PEG-IFN add-on**

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What are the available options.....

1. Sequential therapy strategies
2. Combination therapies
3. Discontinuation of NUCs
Can NUCs be discontinued after a period of consolidation therapy following HBeAg seroconversion?
HBeAg positive disease

Can NUCs be discontinued after a period of consolidation therapy following HBeAg seroconversion?
HBeAg negative disease
**HBeAg negative disease**

**Immune Profiling Study**

- **HBeAg Negative patients**
  - Virally suppressed >24 months
  - No evidence of cirrhosis

- **4 weekly collection:**
  - Routine laboratory tests
  - PBMC

- **Immunoprofiling** by CyTOF
- **Ag-specific T cell analysis**
  - *ex vivo* by CyTOF
  - by flow cytometry
- **mRNA expression**
  - By NanoString
  - by CyTOF
- **T cell phenotyping**
  - by flow cytometry
- **Ag-specific T cell analysis** after
  - *in vitro* expansion by Elispot

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Patient Profiles

controllers: n = 2
viral rebound: -
hepatic flare: -

partial controllers: n = 11
viral rebound: +
hepatic flare: -

flare: n = 6
viral rebound: +
hepatic flare: +

* equal contribution

Rivino*, Le Bert*, Gill*, et al., Manuscript in preparation
Increased frequency of HBV-specific T cell responses in ‘non-flare’ vs. flare patients prior to NUC discontinuation

* equal contribution

Rivino*, Le Bert*, Gill*, et al., Manuscript in preparation
Novel Strategies for HBsAg loss

Bertoletti & Rivino, Curr Opin Infect Dis., 2014
Selective oral TLR Agonists in CHB

**TLR agonists enhance:**

- Production of IFN-γ and inflammatory cytokines like IL-12
- Upregulation of costimulatory molecules such as CD80 and CD86
- Induction of interferon stimulated genes

GS-9620, an Oral Agonist of Toll-Like Receptor-7, Induces Prolonged Suppression of Hepatitis B Virus in Chronically Infected Chimpanzees. *Lanford et al Gastroenterology 2013*

Gs-9620, an oral TLR7 agonist in development for chronic viral hepatitis has demonstrated a potential for induction of an antiviral response with an acceptable adverse event profile

Phase 1b safety, pharmacokinetics and pharmacodynamics of GS-9620

*Gane et al, J Hepatol 2015*
Current Trials of Therapeutic vaccination in HBV

Phase II in HBV patients suppressed on antivirals
GS-4774 (Tarmogen)

GS-4774 Recombinant Antigen

GS-4774

Densigen™

• ~ 30-40 amino acids long peptides
• CD4+/CD8+ T cell epitopes
• Net positive charge/Hydrophobicity

APC

CD4+

CD8+

Reversal of T cell exhaustion

The goal of checkpoint inhibitors

CD8 T cells

- Granzyme
- Perforin

INF-γ
TNF-α
IL-2

Infected hepatocytes

- Effective T cells control virus
- Exhausted T cells loose control of virus

Checkpoint blockade
Lessons from cancer checkpoint inhibitor trials: PD-1

PD-1 and PD-L1 blockade

Exhausted T cell

Re-invigorated T cell

Cytotoxicity

Nivolumab in Previously Untreated Melanoma without BRAF Mutation

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer
Lessons from woodchuck hepadnaviral infection

Combining PD-1 blockade with therapeutic vaccination

Enhancing Virus-Specific Immunity *In Vivo* by Combining Therapeutic Vaccination and PD-L1 Blockade in Chronic Hepadnaviral Infection

Jia Liu¹, Ejuan Zhang¹, Zhiyong Ma¹, Weimin Wu¹, Anna Kosinska¹, Xiaoyong Zhang¹,², Inga Möller¹, Pia Seiz³, Dieter Glebe³, Baoju Wang⁴, Dongliang Yang⁴, Mengji Lu¹, Michael Roggendorf¹*

- Boosting of T and B cell immunity
- Sustained viral suppression and sAg seroconversion
# Summary of future drug targets for HBV therapies

<table>
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<th>MOA</th>
<th>Target</th>
<th>Compound</th>
<th>Sponsor</th>
<th>Phase</th>
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<td>GST340</td>
<td>Gilead</td>
<td>Phase 3</td>
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<td>CMX157</td>
<td>Chimerix</td>
<td>Phase 2</td>
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<td>Capsid</td>
<td>MVR 1221/3778</td>
<td>Novira Therapeutics</td>
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<td>GLS4</td>
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<td>Bay41-4109</td>
<td>AiCuris</td>
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<td>siRNA</td>
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<td>TKM-HBV</td>
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<td>Assembly/HBsAg</td>
<td>Rep 2139-Ca</td>
<td>Replicor</td>
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<td>Antisense</td>
<td>ISIS-HBV</td>
<td>Isis</td>
<td>Phase 1</td>
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<td>Host targets</td>
<td>Entry/NTCP</td>
<td>Myrcludex B</td>
<td>Myr-GmbH/ Hepatera</td>
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<td>Apoptosis</td>
<td>Birinapant</td>
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<td>Immune targets</td>
<td>TLR7 agonist</td>
<td>GS9620</td>
<td>Gilead</td>
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<td>PD1 blockade</td>
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<td>RIG1/NOD 2 activation</td>
<td>SB9200 HBV</td>
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<td>Therapeutic vaccine</td>
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<td>Nasvac</td>
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<td>Euvax + PegIFN</td>
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<td>Phase 4</td>
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<td>HBV vaccine + activated dendritic</td>
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<td>SunYat-Sen University</td>
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<td>HBV vaccine + IFN-α2b+IL2</td>
<td>Tongji Hospital</td>
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<td>HBIG+GM CSF+HBV vaccine</td>
<td>Beijing 302 Hospital</td>
<td>Phase 1/2</td>
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Summary

• Better understanding & re-definition of disease phase in CHB is central to better treatment outcomes

• Long term on-treatment viral suppression is standard of care – but suboptimal

• Strategies to target cccDNA & achieve global immune restoration will be critical to delivering cure in CHB
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