Targets and new drugs for HBV

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Disclosures

Speaker/consultant:
AbbVie
Gilead Sciences
Janssen
Merck Sharp & Dohme
Roche
Targets and new drugs for HBV

1. Is an HBV cure a priority?
2. What are the objectives (endpoints)?
3. HBV virology, viral cycle and targets
4. Direct-acting antivirals
5. Host antivirals
6. Conclusion
HBV infection is a major medical need

- ~ One third of individuals exposed to HBV infection.
- ~ 257 million people are living with HBV infection.
- Main cause of Cirrhosis, Hepatocellular carcinoma (HCC), Transplantation
- HCC, one of leading cancer worldwide, ~ 1 million deaths / year

HBV drug development

- ADV
- ETV
- TDF
- TAF


- LAM
- Peg-IFN
- LdT

Schinazi RF, Ehteshami M, Bassit L, Asselah T. Liver Int. 2018;38 S1:102-114.
Do we need an HBV cure?

- A major public health problem, **257 million people** are living with HBV infection.
Do we need an HBV cure?

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- 30 millions of new HBV infection per year
Do we need an HBV cure?

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  - 30 millions of new HBV infection per year
- Vaccine with excellent efficacy
Do we need an HBV cure?

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  30 millions of new HBV infection per year

• Vaccine with excellent efficacy

  Problems of implementation for vaccination campaigns
Do we need an HBV cure?

- A major public health problem, **257 million people** are living with HBV infection.
  - 30 millions of new HBV infection per year

- **Vaccine** with excellent efficacy
  - Problems of implementation for vaccination campaigns

- **Nucleos(t)ides analogues** have high efficacy and favorable tolerability
Do we need an HBV cure?

- A major public health problem, **257 million people** are living with HBV infection.
  - 30 millions of new HBV infection per year

- **Vaccine** with excellent efficacy

- **Nucleos(t)ides analogues** have high efficacy and favorable tolerability
  - Nucs does not affect cccDNA and HBs seroconversion is rare;
  - HCC risk is reduced but remains
  - Long-life duration, costs, compliance, discrimination.
HBV: Limited access to treatment

- 257 million HBsAg +
- 22 million Diagnosed (9%)
- 1.7 million Treated (8%)

91% undiagnosed
HBsAg loss

Schinazi RF, Ehteshami M, Bassit L, Asselah T. Liver Int. 2018;38 S1:102-114.
Targets and new drugs for HBV

1. HBV cure is a priority

2. What are the objectives (endpoints) ?

3. HBV virology, viral cycle and targets

4. Direct-acting antivirals

5. Host antivirals

6. Conclusion
Clinical endpoints of therapy (Goals)
Sustained (after a finite course of treatment)

ALT normalisation

Biochemical response

ALT: alanine aminotransferase; CHB: chronic hepatitis B; anti-Hbe: anti-hepatitis B e antibody; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen
Clinical endpoints of therapy (Goals)

- HBV DNA suppression
- ALT normalisation
- Partial virological cure
- Biochemical response

ALT: alanine aminotransferase; CHB: chronic hepatitis B; anti-Hbe: anti-hepatitis B e antibody; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen

Asselah PHC 6
Clinical endpoints of therapy (Goals)

- ALT normalisation
- HBV DNA suppression
- HBeAg loss in HBeAg+
- Partial virological cure

ALT: alanine aminotransferase; CHB: chronic hepatitis B; anti-Hbe: anti-hepatitis B e antibody; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen

Asselah PHC 6
Clinical endpoints of therapy (Goals)

- ALT normalisation
- HBV DNA suppression
- HBeAg loss in HBeAg+
- HBsAg loss

Functional cure
Partial virological cure
Biochemical response

ALT: alanine aminotransferase; CHB: chronic hepatitis B; anti-Hbe: anti-hepatitis B e antibody; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen
Clinical endpoints of therapy (Goals)

- **ALT normalisation**
- **HBV DNA suppression**
- **HBeAg loss in HBeAg+**
- **HBsAg loss**
- **cccDNA**

**Sterilizing cure**

**Functional cure**

**Partial virological cure**

**Biochemical response**

ALT: alanine aminotransferase; CHB: chronic hepatitis B; anti-Hbe: anti-hepatitis B e antibody; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen
Clinical endpoints of therapy (Goals)

HCC decrease, Fibrosis regression, Increased Survival & Quality of life

- cccDNA
- HBsAg loss
- HBeAg loss in HBeAg+
- HBV DNA suppression
- ALT normalisation

Sterilizing cure (surrogate markers)
Functional cure
Partial virological cure
Biochemical response

ALT: alanine aminotransferase; CHB: chronic hepatitis B; anti-Hbe: anti-hepatitis B e antibody; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen

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HBV virion

Nucleocapsid

Viral envelope proteins

relaxed circular DNA (rcDNA)

Polymerase

Filamentous

Spherical

42-47nm

22nm

Asselah PHC 7
HBV: Genome

- Compact genomic structure (~ 3.2 kb).
- 4 overlapping open reading frames
- Reverse transcriptase/DNA polymerase domain overlaps with surface gene
- Encodes 4 sets of viral proteins – HBsAg, HB core Ag, viral polymerase and HBx protein.
Hepatitis B virus (HBV) cycle

Entry into hepatocyte

NTCP

Nucleus

Asselah PHC 9

HBV cycle

1. Entry
2. Transport to nucleus

Hepatitis B virus
NTCP
rcDNA
nucleus
hepatocyte
Asselah PHC 9
HBV cycle

1. Entry
2. Transport to nucleus
3. cccDNA formation

Hepatitis B virus
NTCP
rcDNA
cccDNA
nucleus
hepatocyte

cccDNA: covalently closed circular DNA

Asselah PHC 9
HBV cycle

1. Entry

2. Transport to nucleus

3. cccDNA formation

4. cccDNA transcription

Hepatitis B virus

NTCP

rcDNA

cccDNA

pgRNA

mRNAs

nucleus

hepatocyte

Asselah PHC 9
HBV cycle

1. Entry
2. Transport to nucleus
3. cccDNA formation
4. cccDNA transcription
5. Translation

Hepatitis B virus

Hepatocyte

hbDNA, pgRNA, mRNAs...
HBV cycle

1. Entry
2. Transport to nucleus
3. cccDNA formation
4. cccDNA transcription
5. Translation
6. Encapsidation

Hepatitis B virus

NTCP

rcDNA

cccDNA

pgRNA

mRNAs

nucleus

HBx, HBc, HBe, HBs...

HBc, HBx, HBe, HBs...

 HBc

HBx

pgRNA

Pol

hepatocyte

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Hepatitis B virus

1. **Entry**
   - NTCP

2. **Transport to nucleus**
   - HBx
   - HBe

3. **cccDNA formation**
   - rcDNA
   - cccDNA
   - pgRNA
   - mRNAs
   - nucleus

4. **cccDNA transcription**
   - HBe, HBx, HBs...
   - Pol
   - pgRNA

5. **Translation**
   - HBc, HBx, HBe, HBs...
   - HBC
   - Hepatocyte

6. **Encapsidation**
   - DNA(-) synthesis

7. **DNA(-) synthesis**
   - Hepatocyte

Asselah PHC 9
HBV cycle

Hepatitis B virus

1. Entry

2. Transport to nucleus

3. cccDNA formation

4. cccDNA transcription

5. Translation

6. Encapsidation

7. DNA(-) synthesis

8. DNA(+) synthesis

rcDNA

pgRNA

mRNAs

nucleus

Hepatocyte

HBx

Hbc

HBc, HBx, HBe, HBs...

Pol

DNA(+) synthesis

DNA(-) synthesis

Asselah PHC 9
Hepatitis B virus (HBV) cycle

1. **Entry**
   - NTCP

2. **Transport to nucleus**
   - cccDNA formation
   - rcDNA

3. **cccDNA transcription**
   - pgRNA
   - mRNAs

4. **Translation**
   - Pol
   - HBC, HBx, HBe, HBs...

5. **Encapsidation**
   - Hepatocyte

6. **cccDNA amplification**

7. **DNA(-) synthesis**

8. **DNA(+) synthesis**

9. **Morphogenesis and secretion**

   - HBsAg secretion
   - HBeAg secretion
   - HBx, HBc

Asselah PHC 9
Therapeutic targets: points of inhibition

1. Entry
2. Transport to nucleus
3. cccDNA formation
4. cccDNA transcription
5. Translation
6. Encapsidation
7. DNA(-) synthesis
8. DNA(+) synthesis
9. Morphogenesis and secretion

Hepatitis B virus

- NTCP
- rcDNA
- cccDNA
- pgRNA
- mRNAs
- nucleus
- HBe
- HBsAg
- HBx
- HBeAg
- HBeAg secretion
- HBsAg secretion
- DNA synthesis
- Morphogenesis and secretion
- Encapsidation
- Hepatocyte

Asselah PHC 9
Therapeutic targets: points of inhibition

1. Entry
2. Transport to nucleus
3. cccDNA formation
4. cccDNA transcription
5. Translation
6. Encapsidation
7. DNA(-) synthesis
8. DNA(+) synthesis
9. Morphogenesis and secretion

- Hepatitis B virus
- NTCP
- Hepatocyte
- HBe
- HBsAg secretion
- HBeAg secretion
- HBx
- Hbc
- pgRNA
- mRNAs
- rcDNA
- cccDNA
- cccDNA amplification
- Hepatocyte

Therapeutic targets: points of inhibition

Asselah PHC 9
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HBV receptor:
Sodium taurocholate cotransporting polypeptide (NTCP)


Asselah PHC 10
**Entry inhibitor: Myrcludex B (Bulevirtide) + PEG-IFN: HDV chronic infection (MyrPharma)**

**Phase II, Myrcludex B (NTCP inhibitor) + PEG-IFN for 48 weeks**

**HDV RNA**

- 2 mg Myr B
- Suivi

**Undetectable HDV RNA at W48**

- **PEG-IFNα**
- 2 mg Myr B + PEG-IFNα
- 5 mg Myr B + PEG-IFNα
- 2 mg Myr B

* p < 0.01

**Asselah PHC 11**

*Wedemeyer et al. A16; AASLD 2018,*
Capsid as an attractive target (interaction with cccDNA synthesis)

= Interaction Sites

Interraction between capside and cccDNA precursors

Direct Interraction with cccDNA

Guo et al. 2007
Y-H Guo et al. 2011

Asselah PHC 12
Capsid assembly modulator (CAM) : JNJ-6379
HBV DNA decrease after 4 weeks on treatment (Janssen)

Phase II, JNJ-6379 (Capsid inhibitor) for 4 weeks, Janssen

- 3 of 8 patients (38%) had values <LLOQ
- 5 of 9 patients (56%) had values <LLOQ

LLOQ = Lower limit of quantification (20 IU/mL) of the HBV DNA assay
Zoulim et al, AASLD 2018, A74
Core protein allosteric modifier (CpAM) : ABI-HO731 : HBV DNA decrease after 28 days on treatment (Assembly Biosciences)

Phase Ib, ABI-HO731, 12 patients for 28 days, Assembly Biosciences

Log$_{10}$ Declines from Baseline

*Max decline $\geq 3.8$ Log$_{10}$

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg Pos</td>
<td>-1.3 (0.3)</td>
<td>-1.9 (0.7)</td>
<td>-2.9 (0.8)</td>
<td>N/A</td>
</tr>
<tr>
<td>HBeAg Neg</td>
<td>-2.2 (1.3)</td>
<td>-2.4 (0.9)</td>
<td>-2.5 (1.7)</td>
<td>-3.9 (0.1)</td>
</tr>
<tr>
<td>Overall</td>
<td>-1.7 (0.9)</td>
<td>-2.1 (0.8)</td>
<td>-2.8 (1.1)</td>
<td>-3.9 (0.1)</td>
</tr>
</tbody>
</table>

Asselah PHC 14

Yuen et al. AASLD 2018, Abstract 73
GalNAc-conjugated siRNA

- siRNA delivery is mediated by a conjugated targeting ligand; GalNAc
- **Cell uptake via GalNAc interaction with ASGPR**
  - Asialoglycoprotein Receptor
    - Highly expressed in/on hepatocytes
    - High rate of uptake
    - 15 min recycling time
    - Conserved across species

SC GalNAc-conjugated siRNA agent AB-729 in preclinical models: HBV DNA and HBs decline (Arbutus)

Day 14 inhibition of multiple HBV markers by AB-729

<table>
<thead>
<tr>
<th>Marker</th>
<th>Control siRNA 9 mg/kg</th>
<th>'729 1 mg/kg</th>
<th>'729 3 mg/kg</th>
<th>'729 9 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver 3.5 kb HBV RNA</td>
<td>LLOQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver total HBV RNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver HBsAg</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Serum HBsAg</td>
<td></td>
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</tr>
<tr>
<td>Serum HBeAg</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Serum HBV DNA</td>
<td></td>
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</tr>
</tbody>
</table>

Mean (n=5) ± SD

Weeks after 1 SC dose in AAV mouse

Weeks after admin in AAV mouse

Lee ACH, et al. ILC 2018, #PS-029
RNA interference (RNAi) therapeutic ARO-HBV: HBs decline (Arrowhead)

*Includes samples <LLOQ. Combination index study in the pHBV mouse model demonstrated synergy between ARO-HBV and entecavir. ARO-HBV is a promising new candidate for progression to clinical trials of chronic HBV and is expected to synergize with other antiviral compounds.

Asselah PHC 17
cccDNA as an important target
HBV Persistence

**cccDNA persistence** is thought to be the cause of **chronic** HBV disease

- cccDNA exists as a minichromosome in the nucleus
- cccDNA persists in the absence of active viral replication
- cccDNA levels reduced, but not eliminated with treatment/ liver regeneration

**HBV Cure:**

Elimination, suppression or control of cccDNA

Importance to develop “surrogate markers” of cccDNA

Asselah PHC 18
cccDNA: Target

cccDNA formation

Transcription

Translation

HBV transcription/replication

Asselah PHC 19
Inhibition of cccDNA formation

Anti-host DNA repair factors

No cccDNA formation, inhibition of HBV transcription/replication

Asselah PHC 19
RNA Pol (+) (-) RNA rcDNA P-free rcDNA HBx cccDNA silencing HBx/HBc inhibitors RNAi Inhibition of HBV transcription/replication Epigenetic modifications

Asselah PHC 19
cccDNA elimination

Translation of non-functional HBV proteins, inhibition of HBV replication

Immune mediated degradation
Genome editing nuclease

Asselah PHC 19
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HBV and Toll Like Receptors (TLR)

[Diagram showing the interaction between HBV infected hepatocytes, non-parenchymal liver cells, and TLR agonists leading to activation of TRIF/MyD88, JAK/STAT, and production of antiviral ISGs and IFNs and inflammatory cytokines.]
TLR7 agonist RO7020531 + CpAM RO7049389:
HBV DNA decrease and HBsAg loss in an AAV-HBV mouse model (Roche)

Combination of RO7049389 and RO7020531 reduced HBsAg level to below LLOQ at the end of treatment in 5 of 7 animals, reduced HBV DNA level to below LLOQ in all animals, which sustained in 4 of 7 during 6-week off-treatment follow-up.

Note: Serum samples were collected at indicated time points to measure HBsAg, HBV DNA, HBeAg, and anti-HBs levels after compound treatment and during the off-treatment period.

Results are presented as mean ± SEM (n=7)

Dai L, et al. ILC 2018, #PS-028
HBV and RIG-I pathway
RIG-I agonist: Inarigivir

HBV DNA decrease after 28 days on treatment (Spring Bank)

Inarigivir (oral RIG-1 agonist), for 12 weeks

Inarigivir demonstrates a continuing positive
dose response in HBeAg-ve patients at week 12

Inarigivir demonstrates a continuing positive
dose response in HBeAg+ve patients at week 12

Asselah PHC 23

Yuen et al. AASLD 2018, Abstract 75
HBV interactions with Mitochondrial Immune Response

Mansouri, Gattolliat and Asselah. Gastroenterology 2018
HBV Cure

HOST

HBV DAAs

2019 2022 2025

HBV DAAs
« Failure is the foundation of success »

Lao Tseu, 6th-century BC
« A pessimist sees the difficulty in every opportunity, 
An optimist sees the opportunity in each difficulty »

Winston Churchill