New Drug Research for Chronic Hepatitis B

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Emerging Drugs against HBV
- Direct-acting antiviral agents (DAAs)
- Host-targeting antiviral agents (HTAs)

Conclusions and Future perspectives
Emerging Drugs Against HBV
Hepatitis B virus (HBV) life cycle

Direct-acting antivirals (DAAs)

Host-targeting antivirals (HTAs)

Zeisel MB et al. Gut 2015;64:1314-25
Emerging Drugs Against HBV

- Direct-acting antiviral agents (DAAs)
- Host-targeting antiviral agents (HTAs)
Hepatitis B virus (HBV) life cycle

- **Entry inhibitors**
  - hNTCP

- **Entry**
  - Virion
  - Polymerase
  - cccDNA formation
  - cccDNA destruction
  - cccDNA silencing

- **HBV DNA integration**
  - Transcription
  - pgRNA
  - mRNA
  - RNA interference

- **Nucleus**
  - cccDNA formation
  - rcDNA
  - cccDNA

- **Translation**
  - DNA+ + strand synthesis
  - Encapsulation
  - Reverse transcription
  - pgRNA

- **Immune modulation**
  - Toll-like receptors agonists
  - AntiPD-1 mAb
  - Therapeutic vaccine

- **ER**
  - Inhibitors of nucleocapsid assembly
  - Viral proteins secretion
  - HBsAg
  - HBeAg

- **Inhibitors of HBs release**

Zeisel MB et al. Gut 2015;64:1314-25
## Direct-acting antiviral agents

### Entry inhibitors

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Mechanism</th>
<th>Compound</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myrcludex-B</td>
<td>Competitive inhibition of viral entry via NTCP</td>
<td>HBV preS1-derived lipopeptide</td>
<td>Phase II</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>Competitive inhibition of viral entry via NTCP</td>
<td>Cyclic nonribosomal peptide</td>
<td>FDA approved, but not tested for HBV</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Competitive inhibition of viral entry via NTCP</td>
<td>Ezetimibe</td>
<td>FDA approved, but not tested for HBV</td>
</tr>
</tbody>
</table>

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. 2015;64:1314-25
Entry inhibitor: Myrcludex-B

- Synthetic lipopeptide derived from pre-S1 domain of HBV envelope protein
- Specifically targets NTCP, the functional receptor for HBV

Yuen et al. Nat Rev Gastroenterol Hepatol 2015;12:70-72
Entry inhibitor: Myrcludex-B

Pre-clinical results

Lutgehetmann M et al. Hepatology 2012
Entry inhibitor: Myrcludex-B

- Phase IIa clinical trial
  - Safety, tolerability and efficacy of multiple doses of Myrcludex B (0.5mg, 1mg, 2mg, 5mg and 10mg Myrcludex-B SC QD) in comparison with the control group receiving standard therapy with NAs is recently completed

- Results:
  - Very well tolerated; injection site dermatitis in 3/40 patients
  - HBV DNA decline > 1 log\textsubscript{10} at Wk 12: 6/8 (75%) patients receiving 10 mg Myrcludex-B
  - ALT normalization: 22/40 (55%) patients
  - HBsAg levels: no significant changes

Urban S et al. AASLD 2014 (LB-20)
Hepatitis B virus (HBV) life cycle

Zeisel MB et al. Gut 2015;64:1314-26
## Direct-acting antiviral agents

### Inhibitors of cccDNA

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</thead>
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<tr>
<td>BSBI-25</td>
<td>cccDNA inhibitor</td>
<td>N/A</td>
<td>Preclinical</td>
</tr>
<tr>
<td>CCC-0975</td>
<td>Inhibition of rcDNA-cccDNA conversion</td>
<td>Disubstituted sulfonamide (DSS)</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Zinc-finger nucleases</td>
<td>cccDNA-targeted endonuclease</td>
<td>Zinc-finger nucleases</td>
<td>Preclinical</td>
</tr>
<tr>
<td>TALENs</td>
<td>cccDNA-targeted endonuclease</td>
<td>Transcription activator-like effector nucleases</td>
<td>Preclinical</td>
</tr>
<tr>
<td>CRISPR/Cas9</td>
<td>cccDNA-targeted endonuclease</td>
<td>CRISPR/Cas9 system</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015;64:1314-26
cccDNA targeted endonucleases

- cccDNA-targeting TALENs

Bloom K et al. Molecular Therapy 2013; Weber ND et al. Molecular Therapy 2013; Chen J et al. Molecular Therapy 2014; Seeger C et al. Molecular Therapy Nucleic Acids 2014
Hepatitis B virus (HBV) life cycle

Zeisel MB et al. Gut 2015;64:1314-26
## Direct-acting antiviral agents

### RNA interference

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Target</th>
<th>Compound</th>
<th>Stage of Development</th>
</tr>
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<tr>
<td>ARC-520</td>
<td>HBV mRNA</td>
<td>siRNA</td>
<td>Phase II / III</td>
</tr>
<tr>
<td>TKM-HBV</td>
<td>HBV mRNA</td>
<td>siRNA</td>
<td>Phase I</td>
</tr>
<tr>
<td>ISIS-HBVRx</td>
<td>HBV mRNA</td>
<td>Anti-sense RNA</td>
<td>Phase I</td>
</tr>
<tr>
<td>dd-RNAi compound</td>
<td>HBV mRNA (Pol)</td>
<td>shRNA</td>
<td>Preclinical</td>
</tr>
<tr>
<td>ALN-HBV</td>
<td>HBV mRNA</td>
<td>siRNA - LNP</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015;64:1314-26
HBV mRNA-targeting siRNA: ARC-520

- siRNAs in ARC-520 intervene at the mRNA level.

![Diagram showing the mechanism of action of HBV mRNA-targeting siRNA ARC-520](image)
HBV mRNA-targeting siRNA: ARC-520

- Pre-clinical results: mouse model of HBV infection
  - Decreased HBsAg
    - 3-4 log reduction with the most potent chol-siHBVs
    - > 2 log_{10} reduction for 1 month
  - Decreased HBV DNA
    - approximately 3 log_{10} reduction for 1 month

Wooddell CI et al. Molecular Therapy 2013
**HBV mRNA-targeting siRNA: ARC-520**

- Pre-clinical results: HBV-infected chimpanzee
  - Decreased HBV DNA, HBeAg and HBsAg

Lanford R et al. AASLD 2013
HBV mRNA-targeting siRNA: ARC-520

- Phase IIa clinical trial (Heparc-2001)
  - A multicenter, randomized, double-blind, placebo-controlled, multi-dose study of ARC-520 (1-4 mg/kg) administered intravenously to patients with chronic immune active HBV infection maintained on entecavir or tenofovir therapy

- Results:
  - When given as a single, IV administration, ARC-520 was well tolerated up to and including a dose of 3 mg/kg in CHB patients, who were also receiving entecavir, and up to 4 mg/kg in normal volunteers
  - A single injection of ARC-520 resulted in significant reduction in HBsAg for up to 43 days

Yuen MF et al. AASLD 2014
HBV mRNA-targeting siRNA: ARC-520

Figure 1. Log reduction in HBsAg and HBV core related antigen (HbcAg) in cohorts 1-4.

Figure 2. Reduction in HBsAg, HBeAg and HBcrAg in cohort 5.
# Direct-acting antiviral agents

## Inhibitors of nucleocapsid assembly

<table>
<thead>
<tr>
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<th>Target</th>
<th>Compound</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS4</td>
<td>Interfere with capsid formation/ stability</td>
<td>Heteroaryldihydropyrimidine</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(HAPs)</td>
<td></td>
</tr>
<tr>
<td>Bay 41-4109</td>
<td>Viral nucleocapsid inhibitor</td>
<td>HAPs</td>
<td>Phase I</td>
</tr>
<tr>
<td>AT-130</td>
<td>Inhibition of HBV capsid assembly</td>
<td>Phenylpropenamide derivatives</td>
<td>Preclinical and early clinical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>phase</td>
</tr>
<tr>
<td>NVR-3-778 (NVR1221)</td>
<td>Inhibition of HBV capsid assembly</td>
<td>Small molecule</td>
<td>Phase Ib</td>
</tr>
</tbody>
</table>
HBV nucleocapsid inhibitor

Yuen MF et al. AASLD 2015
## Polymerase inhibitors

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Target</th>
<th>Compound</th>
<th>State of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir alafenamide (TAF)</td>
<td>HBV polymerase</td>
<td>Prodrug of Tenofovir</td>
<td>Phase III</td>
</tr>
<tr>
<td>CMX157</td>
<td>HBV polymerase</td>
<td>Prodrug of Tenofovir</td>
<td>Phase II</td>
</tr>
<tr>
<td>AGX-1009</td>
<td>HBV polymerase</td>
<td>Prodrug of Tenofovir</td>
<td>Phase I, China</td>
</tr>
<tr>
<td>Besifovir</td>
<td>HBV polymerase</td>
<td>Acyclic nucleotide phosphonate</td>
<td>Phase III, Korea</td>
</tr>
</tbody>
</table>

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015;64:1314-26
Tenofovir alafenamide (TAF)

- ↑ stability in plasma
- ↑ delivery to hepatocytes
- ↓ doses with TAF
- ↓ systemic exposures of TFV

CES1 = Carboxylesterase 1

Argarwal K et al. AASLD 2013
Emerging Drugs Against HBV

- Direct-acting antiviral agents (DAAs)
- Host-targeting antiviral agents (HTAs)
## Host-targeting agents

### Inhibitors of HBsAg release

<table>
<thead>
<tr>
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<th>Target</th>
<th>Compound</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>REP-2139 (REP 9AC)</td>
<td>Subviral particle formation</td>
<td>Phosphorothioated oligonucleotides</td>
<td>Phase II</td>
</tr>
<tr>
<td>BM601</td>
<td>Inhibits HBsAg secretion</td>
<td>Benzimidazole derivative</td>
<td>Preclinical</td>
</tr>
<tr>
<td>NVPO18</td>
<td>Inhibits HBsAg secretion</td>
<td>Cyclophilin inhibitor</td>
<td>Preclinical</td>
</tr>
<tr>
<td>CPI-431-32</td>
<td>Inhibits HBsAg secretion</td>
<td>Cyclophilin inhibitor</td>
<td>Preclinical</td>
</tr>
<tr>
<td>PBHBV-001</td>
<td>Inhibits HBsAg secretion</td>
<td>Triazolo-pyrimidine derivatives</td>
<td>Preclinical</td>
</tr>
<tr>
<td>PBHBV-2-15</td>
<td>Inhibits HBsAg secretion</td>
<td>Triazolo-pyrimidine derivatives</td>
<td>Preclinical</td>
</tr>
<tr>
<td>DNJ</td>
<td>Inhibits HBsAg secretion</td>
<td>α-glucosidase inhibitors / Iminosugar derivatives of butyldeoxynojirimycin</td>
<td>Preclinical</td>
</tr>
<tr>
<td>GC1102</td>
<td>Neutralizing HBsAg</td>
<td>Recombinant Hepatitis B Human Immunoglobulin</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015;64:1314-26
REP-2139 (REP 9AC, Replicor), i.v qw

- REP-2139 prevents subviral particle (SVP) formation in HBV-infected hepatocytes and inhibits HBsAg release

* NAPs: nucleic acid polymers
### REP-2139-Ca, significantly reduces HBV RNA levels in CHB

- **Phase 2 study in 12 HBeAg-positive patients**
  - REP-2139-Ca for 20–38 weeks
  - Patients with HBsAg decline subsequently treated with PEG-IFN and/or thymosin alpha-1

<table>
<thead>
<tr>
<th>HBV RNA decline at Weeks 20–24</th>
<th>-2.54 log copies/mL (P&lt;0.001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA decline at Weeks 20–24</td>
<td>-3.34 log copies/mL (P&lt;0.001)</td>
</tr>
<tr>
<td>HBsAg decline at Weeks 20–24</td>
<td>-3.12 IU/mL (P&lt;0.001)</td>
</tr>
<tr>
<td>Undetectable HBV RNA</td>
<td></td>
</tr>
<tr>
<td>At Weeks 20–24</td>
<td>67% (8/12)</td>
</tr>
<tr>
<td>Treatment-free follow-up</td>
<td>88% (7/8)</td>
</tr>
<tr>
<td>HBsAg loss/seroconversion during treatment-free follow-up</td>
<td>50% (4/8)</td>
</tr>
</tbody>
</table>

This slide includes investigational agents that are not approved for use in CHB by the EMA; additional data presented at ILC 2015 as a late breaker.
## Host-targeting agents

### Immune modulation

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Targets</th>
<th>Compounds</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>INO-1800</td>
<td>Therapeutic vaccine</td>
<td>DNA plasmids encoding HBsAg and HBcAg</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>Induction of host immune responses via activation of RIG-I and NOD2</td>
<td>Small molecule nucleic acid hybrids (SMNH)</td>
<td>Phase II</td>
</tr>
<tr>
<td>SB-9200</td>
<td>Cellular inhibitor of apoptosis proteins (cIAPs)</td>
<td>SMAC inhibitor</td>
<td>Phase I / IIa</td>
</tr>
<tr>
<td>Birinapant (TL32711)</td>
<td>Activation of Protein kinase R (PKR)</td>
<td>Nitazoxanide</td>
<td>Preclinical</td>
</tr>
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</table>

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015;64:1314-26
## Host-targeting agents

### Immune modulation

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<tbody>
<tr>
<td>ABX-203</td>
<td>Therapeutic vaccine</td>
<td>Recombinant antigen containing HBsAg and HBcAg</td>
<td>Phase IIb / III</td>
</tr>
<tr>
<td>GS-4774</td>
<td>Therapeutic vaccine</td>
<td>Recombinant antigen containing X, Env, Core epitopes</td>
<td>Phase II</td>
</tr>
<tr>
<td>GS-9620</td>
<td>TLR7 agonist</td>
<td>Oral TLR7 agonist</td>
<td>Phase II</td>
</tr>
<tr>
<td>CYT107</td>
<td>Immune-modulator</td>
<td>Recombinant human IL-7</td>
<td>Phase I / Ila</td>
</tr>
<tr>
<td>TG-1050</td>
<td>Immunotherapeutic</td>
<td>Non-replicative adenovirus serotype 5 encoding a large fusion protein</td>
<td>Phase I</td>
</tr>
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</table>
Therapeutic vaccine: GS-4774

- Recombinant antigen containing X, Large S (env) and Core epitopes
- GS-4774 activates dendritic cells after phagocytosis
- Recombinant antigen epitopes are displayed via MHC class I and II and stimulate CD4\(^+\) and CD8\(^+\) T cells

Therapeutic vaccine: GS-4774

Phase II clinical trial: in progress

- CHB patients without cirrhosis on oral antiviral treatment for >1 year
- Randomization stratified by HBeAg status and HBsAg level
- GS-4774 administered SC every 4 weeks x 6 doses

Primary endpoint: HBsAg decline at Week 24
Host-targeting agents

## Immune modulation

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TLR7 agonist: GS-9620

- Potent and selective oral TLR7 agonist
- Activates plasmacytoid DCs and induce antiviral cytokines
TLR7 agonist: GS-9620

- Pre-clinical results: Male Cynomolgus Monkeys
  - Low oral doses induced serum IFN-α, immunomodulatory cytokines, chemokines and ISGs in blood cells

- IFN-α induction with GS-9620

- ISG induction with GS-9620

Tumas D et al. EASL 2011
**TLR7 agonist: GS-9620**

- **Phase II clinical trial: in progress**

- CHB patients without cirrhosis on oral antiviral treatment for >1 year

- 50 patients per cohort, stratified by HBeAg status and HBsAg level

- Placebo (n=5); 1 / 2 / 4 mg GS-9620 PO QOW (n=15, respectively)
Conclusions

- Current treatments can only control disease and cannot lead to substantial HBsAg seroclearance, the benchmark of successful therapy

- Two types of new drugs are developed
  - Direct-acting antiviral agents (DAAs)
  - Host-targeting antiviral agents (HTAs)

- Clinical trial results of new therapeutic agents are awaited
Future perspectives: Future HBV curative regimen?

- **Potent NA**
  - Agent to prevent viral spread and cccDNA re-amplification

- **Immune modulator**
  - Agents to activate specific antiviral immunity or relieve repression/exhaustion of the system

- **cccDNA inhibitor**
  - Safe and selective agent to reduce or silence cccDNA

- **HBV antigen inhibition**
  - Agents to inhibit other components in the HBV life cycle (i.e. entry, cell-spread, capsid assembly, HBx, HBeAg, HBsAg)
Thank you