Hepatitis B
Future Therapies Towards a Cure

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DISCLOSURES
Activity Within 12 Months

• Research Support (to institution)
  – AbbVie
  – BMS
  – Gilead
  – Innovio
  – Intercept
  – Merck
  – Medimmune

• Advisory Board/Consultant
  – Medimmune
  – Merck
  – Viiv

• DSMB
  – MedPace
  – SynteractHCR
Overview

• Significance
• HBV Replication Schema
• HBV Antiviral Agents
• Cure
Prevalence of Hepatitis B Virus

- Globally 2 billion people have been exposed
- 350 million people with chronic HBV infection
HBV/HIV Disease Burden

Worldwide Prevalence of Chronic Hepatitis B and HIV

- HIV: 50 million
- HBV: 350 million
- 4-8 million HBV/HIV coinfected
Hepatitis B Virus

- Hepadnavirus family of DNA viruses
- Narrow host range
  - Woodchucks
  - Ducks
  - Ground squirrels
  - Humans
HBV Genome

- 3.2 kb of circular, partially double stranded DNA
- DNA polymerase for production of DNA
- Four open reading frames (ORFs)
  1. P (polymerase)
  2. PreS/S (surface)
  3. PreC/C (core)
  4. X
Binding and entry

Uncoating

RC-DNA to nucleus

Translation of HBx protein

cccDNA formed

Transcription of mRNAs

pgRNA

HBeAg, polymerase and core proteins translated

HBeAg secreted

Core is enveloped in HBsAgs

Secretion of subviral particles

Virion budding

Reverse Transcription of pgRNA into RC-DNA

HBsAgs synthesized in ER

Translation of HBx protein

X

PS1 PS2/S

pgRNA and polymerase packaged in forming capsid

cccDNA = covalently closed circular DNA
NATURAL HISTORY

Kwon and Lok, NATURE REVIEWS GASTROENTEROL HEPATOL, 2011
HBV Agents

**FDA APPROVED**
- Lamivudine
- Adefovir
- Entecavir
- Telbivudine
- Tenofovir
- Interferon alfa
- Pegylated Interferon alfa

**NOT FDA APPROVED**
- Tenofovir/Emtricitabine
- Emtricitabine
- TAF (Tenofovir alafenamide)
  - Rilpivirene/Emtricitibine/TAF
  - Elvitegravir/Cobicistat/Emtricitibine/TAF
TREATMENT OUTCOMES
Definitions

• Suppression
• Seroconversion
  – HBeAg negative
  – HBeAg negative, HBeAb positive
  – Durable Seroconversion
• Functional Cure- HBsAg Undetectable
• Cure
RESPONSE DEFINITIONS

Today

- **Primary non-response** (<1 log decline at 12 weeks)
- **Partial response** (detectable HBV DNA)
- **Nadir**
- **1 log** (>1 log HBV DNA vs nadir)

EASL 2012 HBV Guidelines (Ref. 7)
## TREATMENT OUTCOMES

### Table 1 | Response rates (%) to approved therapies for HBeAg-positive and HBeAg-negative chronic hepatitis B

<table>
<thead>
<tr>
<th>Treatment response parameters</th>
<th>Lamivudine</th>
<th>Adefovir dipivoxil</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir disoproxil</th>
<th>PEG-IFN*</th>
<th>PEG-IFN plus lamivudine*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg-positive patients at week 48 or 52</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Histologic improvement †</td>
<td>49–62</td>
<td>53–68</td>
<td>72</td>
<td>65</td>
<td>74</td>
<td>38</td>
<td>41</td>
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<tr>
<td>Undetectable HBV DNA</td>
<td>40–44</td>
<td>21</td>
<td>67</td>
<td>60</td>
<td>76</td>
<td>25</td>
<td>69</td>
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<tr>
<td>HBeAg seroconversion</td>
<td>16–21</td>
<td>12</td>
<td>21</td>
<td>22</td>
<td>21</td>
<td>27</td>
<td>24</td>
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<tr>
<td>HBsAg loss</td>
<td>&lt;1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>3</td>
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<tr>
<td><strong>HBeAg-positive patients during extended treatment ‡</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable HBV DNA</td>
<td>NA</td>
<td>39 (5.0)</td>
<td>94 (5.0)</td>
<td>79 (4.0)</td>
<td>77 (4.0)</td>
<td>13 † (4.5)</td>
<td>26 † (4.5)</td>
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<tr>
<td>HBeAg seroconversion</td>
<td>47 (3.0)</td>
<td>48 (5.0)</td>
<td>41 (5.0)</td>
<td>42 (4.0)</td>
<td>31 (3.0)</td>
<td>37 † (4.5)</td>
<td>36 † (4.5)</td>
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<tr>
<td>HBsAg loss</td>
<td>0–3 (2.0–3.0)</td>
<td>2 (5.0)</td>
<td>5 (2.0)</td>
<td>1 (2.0)</td>
<td>10 (4.0)</td>
<td>8 † (4.5)</td>
<td>15 † (4.5)</td>
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<tr>
<td><strong>HBeAg-negative patients at week 48 or 52</strong></td>
<td></td>
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<tr>
<td>Histologic improvement †</td>
<td>60–66</td>
<td>64–69</td>
<td>70</td>
<td>67</td>
<td>72</td>
<td>48</td>
<td>38</td>
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<tr>
<td>Undetectable HBV DNA</td>
<td>60–73</td>
<td>51</td>
<td>90</td>
<td>88</td>
<td>93</td>
<td>63</td>
<td>87</td>
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<tr>
<td>HBsAg loss</td>
<td>&lt;1</td>
<td>NA</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>0</td>
<td>4</td>
<td>3</td>
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<tr>
<td><strong>HBeAg-negative patients during extended treatment ‡</strong></td>
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<td></td>
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<tr>
<td>Undetectable HBV DNA</td>
<td>6 (4.0)</td>
<td>67 (5.0)</td>
<td>NA</td>
<td>84 (4.0)</td>
<td>86 (3.0)</td>
<td>18 † (4.0)</td>
<td>13 † (4.0)</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>&lt;1 (4.0)</td>
<td>5 (5.0)</td>
<td>NA</td>
<td>&lt;1 (2.0)</td>
<td>0 (4.0)</td>
<td>8 † (4.0)</td>
<td>8 † (4.0)</td>
</tr>
</tbody>
</table>

Data obtained from several sources: 15, 21, 22, 24, 40, 42, 44, 46, 47, 50. *Liver biopsy performed 24 weeks after stopping treatment. †Histologic improvement defined as a >2-point decrease in the necroinflammatory score and no worsening of the fibrosis score. ‡The time point at which response was assessed in years is shown in brackets. ††Assessment performed off treatment. Abbreviations: HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; NA, not available.
Entry of HBV into cell

HBV Targets

Transcription

Translation

Core assembly and RNA packaging

Recycling

Core particle minus strand synthesis

Core particle plus strand synthesis

Vesicular transport to cell membrane

cccDNA

HBsAg

HBeAg
THERAPEUTIC APPROACHES

VIROLOGIC

ENTRY/UNCOATING INHIBITION
DNA PROCESSING INHIBITION

IMMUNOLOGIC

VIRION ASSEMBLY INHIBITION
THERAPEUTIC VACCINE
REVERSE TRANSCRIPTION INHIBITION
IMMUNE STIMULATION
cccDNA INHIBITION OR CLEAVAGE
BIOMARKERS OF RESPONSE Beyond HBV DNA and Serology

- Quantitative HBsAg
- HBV RNA in SERUM
- cccDNA
- Elimination of Integrated HBV DNA
EFFECT OF TENOFOVIR ON HBsAg DECLINE

HBeAg +

HBeAg -

Zoutendijk R et al, JID, 2012
TENOFOVIR MEDIATED HBsAG DECLINE IN FUNCTIONAL CURE

Zoutendijk R et al, JID, 2012
ENTRY INHIBITORS
Myrcludex-B

- Myrcludex B is a synthetic N-acylated preS1 lipopeptide that binds NTCP (Sodium taurocholate co-transporting peptide)
- NTCP is receptor for hepadnaviruses
- Myrcludex B inhibited virus spread to uninfected hepatocytes in humanized mice and stabilized cccDNA levels during acute infection
- Human Phase 1 trial showed good safety/tolerability to 20 mg IV dosing

Volz et al, J HEPATOL 2013
Blank A, J HEPATOL 2016

- Quantitative measurements of (A) intrahepatic cccDNA levels and (B) rcDNA copies per human hepatocyte, as well as of (C) rcDNA copies/cccDNA molecule and (D) total HBV RNAs relative to amounts of human-specific GAPDH house-keeping gene
GENE SILENCING
ARC-520

• Chimp Study
  – First nucs given
  – Then ARC-520
• ARC-520 (siRNA)
  – Reduces transcripts from HBV cccDNA

RESULTS
• Nuc reduced HBV DNA
• ARC-520 cccDNA and total HBV DNA declined

Woodell CI et al, AASLD, 2015
ARC-520 Human Trial

• 7 Cohort Trial
• $N= 58$
• Treatment Naïve, non-cirrhotic
• Started on oral entecavir + IV ARC-520 (single dose)

RESULTS
  – No AEs

Yuen et al, AASLD, 2015
HBV GENE FUNCTION INHIBITORS

• Sirtinol - Inhibitor of SIRT-1
  – SIRT1 is Class III histone deactylase that is part of HBV cccDNA minichromosome

• Erythrocentaurin
  – Derivative of *Swertia* (Gentian Violet family)
  – Mechanism unclear - Inhibits HBV gene expression/replication possibly through PGC-1 alpha
ENDONUCLEASES
cccDNA Targeting

Schiffer et al, J VIROL 2012
CRISPR-Cas9
HBV cccDNA Targeting

Kennedy EM et al, ANTIVIRAL RES, 2015
HBV DNA KINETICS
Tenofovir Alefenamide (TAF)

Agarwal K et al, J HEPATOLOGY, 2015
Cyclophilin Inhibition

• Cyclophilins
  – Cellular Proteins That Facilitate Protein Folding
• Cyclophilin Inhibitors
  – Alisporivir
  – NIM-811
• Tested in 4 hepatocyte cell lines
• Reductions in replication of 40-60% observed
• HBsAg levels reduced less than HBV DNA
• Effect appeared to be synergistic with telbivudine

Phillips S et al, GASTRO 2015
HAPs

• Heteroaryldihydropyrimidines
  – Inhibit HBV Capsid Assembly
HAPS

• BAY 41-4109 and GLS4
• Part of HAP family
  – Triggers aberrant HBV core particle assembly
  – Some hepatotoxicity seen in cell culture with some analogs

Wu G et al, ANTIMICROB AGENTS CHEMOTHER 2013
BAY 41-4109 and GLS4 in HBV-infected HepAD38 Cells

Lamivudine Δ
BAY 41-4109 Diamond
GLS4 □

Wu et al, ANTIMICROB AGENTS CHEMOTHER, 2013
### HBsAg Blockade

<table>
<thead>
<tr>
<th>Agent</th>
<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 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>Humabs</td>
<td>Inhibits HBsAg secretion</td>
<td>High affinity oligoclonal aby prep</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>
HBV THERAPEUTIC VACCINE TYPES

Kutscher et al, MICRO BIOTECHNOL, 2012
Targeted Molecular Immunogen

- Yeast-based immunotherapy platform
- Expressed X, S and Core Antigens of HBV
- GlobeImmune 0101 Phase II trial showed minimal activity at highest tested dose (press release 2015)

King TH et al., PLOS1, 2014
IMMUNE CHECKPOINT MOLECULES

- PD-L1
- PD-1
- CTLA-4
- TIM3
- B7H3
- LAG3
- OX40
Effect of PD-1/L1 on Antiviral Immunity

- Naive T cell
  - Activated APC
  - Peptide antigen
  - TCR
  - CD80, CD86
  - MHC
  - CD28

- Activated T cell
  - Chronic infection, persistent antigen stimulation
  - PD-L
  - PD-1
  - Costim-L blockade
  - Proliferation
  - Cytokines
  - Cytotoxicity

- Exhausted T cell
  - APC
  - Proliferation
  - Cytokines
  - Cytotoxicity

- Reinvigorated T cell
  - APC
  - Proliferation
  - Cytokines
  - Cytotoxicity

Slide Courtesy of S. Kottilil, MD, PhD
Expansion of HBV-specific CD8 T Cell Response by Blocking PD-1/L1/2 Interaction *In Vitro*

Sherman AC et al. AIDS Res Hum Retr 2012
TLR AGONIST GS-9620

- 3 Chimps with Chronic HBV
- Dosed 3x week for 4 weeks
- With GS-9620 1mg/kg day 1-25, then 4 weeks 2 mg/kg
- HBV DNA in serum and liver declined

Lanford RE et al, GASTRO, 2013
GS-9620
Woodchuck Hepatitis cccDNA

Menne et al, J HEPATOL, 2014
GS-9620 Human Trials

- Two Phase 1b Trials
  - Multiple doses
  - Treatment Naïve and Virological Suppressed Subjects (1:1)
- Well Tolerated
- No effect on HBV DNA or HBsAg
- ISG15 Stimulation noted

Gane EJ et al, J HEPATOL, 2015
Conclusions

• Current treatment goal is complete suppression of HBV viral replication

• Long term suppression will rarely lead to functional cure (HBsAg negative state) with current agents

• Other modalities are needed- Combination therapies may be Essential

• Experimental options appear promising, but remain to be tested in meaningful clinical trials