Viral Hepatitis: The Search for a Cure

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Arbutus Biopharma, Inc.

Forms of Viral Hepatitis

Five forms of viral hepatitis: Hepatitis A, B, C, D, E

- **Hepatitis A**
  - Acute self-limiting infection
  - Contracted by eating contaminated foods
  - Rarely leads to permanent liver damage

- **Hepatitis B**
  - Acute infection can lead to chronic infection
  - Contracted by vertical infection or from contaminated blood sources
  - Lead to liver damage and HCC

- **Hepatitis C**
  - Acute infection can lead to chronic infection
  - Contracted from contaminated blood sources
  - Lead to liver damage and HCC

- **Hepatitis D**
  - Occurs only in conjunction with HBV
  - Leads to a more severe form of HBV-related liver disease

- **Hepatitis E**
  - Typically only an acute self-limiting infection – problem in immune compromised individuals
  - Fecal to oral transmission route
Chronic Viral Hepatitis: HBV & HCV

- **Every third person** on the planet shows evidence of infection with viral hepatitis

- **500 million people** are chronically infected with hepatitis B or C

- 1 million die every year: **1 every 30 seconds**

- Globally **57% of cirrhosis** and **78% of primary liver cancer** are due to these 2 diseases

- **80-90% of liver transplants** associated with HBV & HCV infection

- The majority of those chronically infected are **undiagnosed** – hepatitis B and C are often asymptomatic for years

- **The sheer size of the problem is intimidating** - as many people are chronically infected with viral hepatitis in 2 African countries as there are people living with HIV/AIDS in the whole world

Summary of Epidemiology and Natural History of Chronic Viral Hepatitis

- **HCV**
  - 170-200 Million infected
  - 20% lifetime risk of cirrhosis
  - 4% lifetime risk of HCC
  - Leading cause of liver transplant in North America and Europe
  - No vaccine available

- **HBV**
  - 2 Billion ever infected
  - ~400 Million infected now
  - 1 Million die each year of HCC or cirrhosis
  - 25% lifetime risk for each HBsAg+ patient of HCC or cirrhosis
  - Second most common carcinogen (liver cancer) after cigarettes
  - Preventive vaccine available

- Linked to the co-existence of multiple co-morbidities
ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Which chronic viral disease has the highest worldwide prevalence rate?

- HIV
- HCV
- HBV
- None of the above

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>HCV</th>
<th>HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. Prevalence</td>
<td>1 million</td>
<td>3 million</td>
<td>1.3–3 million</td>
</tr>
<tr>
<td>Worldwide Prevalence</td>
<td>35 million</td>
<td>160 million</td>
<td>350 million</td>
</tr>
<tr>
<td>Percent Diagnosed in U.S.</td>
<td>80%</td>
<td>50%</td>
<td>30%</td>
</tr>
<tr>
<td>Percent Diagnosed Who Are Treated in U.S.</td>
<td>70%</td>
<td>33%</td>
<td>6-10%</td>
</tr>
<tr>
<td>Nature</td>
<td>RNA retrovirus</td>
<td>RNA virus</td>
<td>DNA virus</td>
</tr>
<tr>
<td>Virions Produced per Day</td>
<td>$10^{10}$</td>
<td>$10^{12}$</td>
<td>$10^{13}$</td>
</tr>
<tr>
<td>Enzyme Targets for Therapy</td>
<td>Multiple</td>
<td>Multiple</td>
<td>One</td>
</tr>
<tr>
<td>Curable?</td>
<td>Unclear; lifelong suppression with HAART therapy</td>
<td>Yes</td>
<td>Unclear; lifelong suppression with Nuc therapy</td>
</tr>
<tr>
<td>Why Easy / Difficult?</td>
<td>Proviral DNA integrated into host genome, difficult to eliminate</td>
<td>RNA virus existing in the host cytoplasm; can eradicate with cocktail of small molecules DAA</td>
<td>cccDNA inside the nucleus, also integrated into host genome, difficult to eliminate</td>
</tr>
<tr>
<td>Need Immune Component in Therapeutic Regimen for Cure?</td>
<td>Maybe</td>
<td>No</td>
<td>Maybe</td>
</tr>
<tr>
<td>Transmission</td>
<td>Infected blood/needles, sex</td>
<td>Infected blood/needles, sex</td>
<td>Infected blood/needles, sex</td>
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<tr>
<td>Vertical Transmission</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Vaccine</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2115 U.S. Sales</td>
<td>$9.3 billion</td>
<td>$13.3 billion</td>
<td>$700 million</td>
</tr>
</tbody>
</table>
HEPATITIS C

Can it become a disease of the past?

HCV: Prevalence, Total Infected, Genotype

Growing Burden of Mortality Associated with Viral Hepatitis in the US (1999-2007)


- 73% of HCV and 59% of HBV-related deaths in persons aged 45-64

- Co-morbidities associated with increased odds ratio of mortality
  - Chronic Liver Disease (32.1;HCV and 34.4;HBV)
  - Co-infection with other hepatitis virus (22.9;HCV and 31.5;HBV)
  - Alcohol related (4.6;HCV and 3.7;HBV)
  - HIV co-infection (1.8;HCV and 4.0;HBV)

- Mortality rates of HBV, HCV, and HIV; United States 1999-2007

SVR is Associated with Reduced All-Cause Mortality Among HCV-infected Persons

- 530 adults in Europe prospectively followed for median 8.4 years after HCV treatment
- 192 (36%) achieved SVR

Hepatitis C Virus: Morphology and Characteristics

- Nucleic Acid: 9.6 kb ssRNA(+)  
- Classification: Flaviviridae, Hepacivirus  
- Genotypes: 1 to 6  
- Enveloped  
- No known viral reservoir  
- Does not integrate into host genome

High Risk of Infection

- Clotting factor treatment prior to 1987  
- Injection drug use  
- Injection treatments prior to universal precautions  
- Long-term hemodialysis

CDC, MMWR 1998; 47:4

170 Million Infected Worldwide

- 83% Injecting illicit drug use  
- 10% Sexual activity  
- 7% Unknown  
- 3% Blood transfusion, hemodialysis  
- 2% Health care employment  

1 in 30 Baby Boomers Infected
The Hepatitis C Virus

HCV Lifecycle

HCV Genome

- Error-prone RNA-dependent, RNA polymerase
  - poor proofreading function
  - high replication rate in vivo
- ~9.6 kb genome: 0.1-1 error per RNA synthesized


Replication Rates

HCV: $10^{12}$
HIV: $10^{10}-10^{11}$

Key Target Areas of Drug Discovery Focus and Key Drugs

Adapted from: Liver International
pages 69-78, 23 DEC 2013 DOI: 10.1111/liv.12423
What was the first IFN-free HCV cure therapy to be approved by the US FDA?

- **Harvoni®** (sofosbuvir + ledipasvir)
- **Viekira Pak®** (ombitasvir + paritaprevir + dasabuvir + ritonavir)
- **Zepatier®** (grazoprevir + elbasvir)
- **Sovaldi®** (sofosbuvir) + RBV

**FDA Approved IFN-Free HCV Cure Drug Combinations**

<table>
<thead>
<tr>
<th>Year and Order of Approval</th>
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</thead>
<tbody>
<tr>
<td>2013</td>
</tr>
<tr>
<td>2014</td>
</tr>
<tr>
<td>2015</td>
</tr>
<tr>
<td>2016</td>
</tr>
<tr>
<td>2017</td>
</tr>
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</table>
The History of HCV Therapy Development

HCV Curative Therapy Today

- IFN-Free curative therapies are a reality
- Simple oral fixed-dose and short duration therapies
- >95% cure rates across multiple genotypes
- High cure rates in difficult to treat patient populations
- Patient access is the issue
- HCV can become a rare disease in the future
Is there a path to a cure?

Hepatitis B Virus (HBV)

- **Hepadnaviridae** member that primarily infects liver cells
- DNA virus
- 100 times more infective than HIV
- Found in blood and body fluids
  - Able to survive in dried blood for longer than 1 week
- Viral reservoir: cccDNA in nucleus of hepatocytes
- Small segments of viral DNA do integrate but do not code for viral proteins

Chronic Hepatitis B: By The Numbers

More than 350 million or 1 in 20 people worldwide have chronic hepatitis B infection. (Compared with the 33 million living with HIV).

1.46-2 million people in the United States are chronically infected.

14 million in Europe.

112 million in Asia-Pacific.

93 million people in China.

1 Million die each year of HCC or cirrhosis.

25% life time risk for each HBsAg patient of HCC or cirrhosis.

Second most common carcinogen (liver cancer) after cigarettes.

7 HBV Genotypes (based on complete HBV genome): A-G

A – World-wide

B & C – Asia

D – Southern Europe, Middle East

E – Africa

F – South America, Polynesia

G – USA and Europe

The Hepatitis B Virus

Intact Hepatitis B Virion (Dane Particle)

GBV

Source: Gerlich, W. 2013. Virology Journal, 10:239

5 mRNAs:

• Pregenomic/core/pol (3.5 kb)
• Precore (3.5 kb)
• PreS1 (2.4 kb)
• PreS2/S (2.1 kb)
• X (0.7 kb)

Genome Structure of HBV

Transmission of HBV

Horizontal Transmission
- Child-to-Child
- Contaminated Needles
- Sexual
- Health Care Worker
- Transfusion

6% infected after age 5 years become chronically infected

Vertical Transmission
- Mother
- Perinatal
- Infant

90% infected infants become chronically infected

No clear risk factors in 20-30% of patients


Three Phases of Chronic HBV Infection

- Immune tolerance: High infectivity
- Immune elimination: chronic hepatitis
- Low-viraemic: HBsAg carrier

Source: Gerlich, W. 2013. Virology Journal, 10:239
REVEAL-HBV: Clearance of HBV DNA Reduces Risk of HCC

- REVEAL-HBV study cohort (N = 2946; aged 30-65 yrs)

- HBV DNA suppression independently associated with significantly reduced risk of HCC
  - Pts with HBeAg suppression (n = 185) still had high HBV DNA levels and still at high risk of HCC
  - HBsAg suppression not associated with reduced incidence of HCC, but study not powered to detect difference

- Greatest reduction in HCC incidence observed among pts with high baseline HBV DNA (≥ 100,000 copies/mL) who cleared HBV DNA during follow-up
  - HCC incidence highest in pts HBeAg seropositive throughout follow-up

HBV Approved Therapies

<table>
<thead>
<tr>
<th>Nucleosides/Nucleotides</th>
<th></th>
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<tbody>
<tr>
<td>Tenofovir</td>
<td>VEMLIDY®</td>
<td>Gilead Sciences</td>
<td>2016</td>
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<tr>
<td>Alafenamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>VIREAD®</td>
<td>Gilead Sciences</td>
<td>2006</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>TYZEKA™</td>
<td>Idenix/Novartis</td>
<td>2006</td>
</tr>
<tr>
<td>Entecavir</td>
<td>BARACLUDE™</td>
<td>Bristol-Myers Squibb</td>
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<tr>
<td>Adefovir Dipivoxil</td>
<td>HEPRESA”</td>
<td>Gilead Sciences</td>
<td>2002</td>
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<tr>
<td>Lamivudine</td>
<td>EPIVIR-HBV®</td>
<td>GlaxoSmithKline</td>
<td>1998</td>
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<table>
<thead>
<tr>
<th>Interferons</th>
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<tbody>
<tr>
<td>Peginterferon alfa-2a</td>
<td>PEGASYS®</td>
<td>Roche Laboratories</td>
<td>2005</td>
</tr>
<tr>
<td>Interferon alfa-2b</td>
<td>INTRON® A</td>
<td>Schering/Merck</td>
<td>1992</td>
</tr>
<tr>
<td>recombinant</td>
<td></td>
<td></td>
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</tbody>
</table>

Preferred Therapies – AASLD Guidelines
## Relative Efficacy of Approved HBV Therapies

<table>
<thead>
<tr>
<th></th>
<th>Entecavir¹,²</th>
<th>Tenofovir³</th>
<th>PEG-IFN α-2a⁴,⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg positive</strong></td>
<td>n = 354</td>
<td>n = 176</td>
<td>n = 271</td>
</tr>
<tr>
<td>HBV DNA undetectable</td>
<td>67%</td>
<td>76%</td>
<td>25%</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>21%</td>
<td>21%</td>
<td>27%</td>
</tr>
<tr>
<td>ALT normalisation</td>
<td>68%</td>
<td>68%</td>
<td>39%</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>2%</td>
<td>3.2%</td>
<td>2.9%</td>
</tr>
<tr>
<td><strong>HBeAg negative</strong></td>
<td>n = 325</td>
<td>n = 250</td>
<td>n = 177</td>
</tr>
<tr>
<td>HBV DNA undetectable</td>
<td>90%</td>
<td>93%</td>
<td>63%</td>
</tr>
<tr>
<td>ALT normalisation</td>
<td>78%</td>
<td>76%</td>
<td>38%</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>0.3%</td>
<td>0%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Results at 48 weeks

* HBV DNA < 400 copies/mL; † At 72 weeks


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## Long-term Therapy is Required to Maintain Viral Suppression

![Graph showing the decline of HBV DNA change from baseline](image)

*Werle et al, Gastroenterology 2004*
What Does a Cure Look Like?

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Functional Cure</th>
<th>Absolute Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>As if recovery after acute HBV infection</td>
<td>As if never infected</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-HBsAg</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Serum HBV DNA</td>
<td>Not Detected</td>
<td>Not Detected</td>
</tr>
<tr>
<td>HBV cccDNA</td>
<td>Detected, but not transcriptionally active</td>
<td>Not Detected</td>
</tr>
<tr>
<td>Hepatic integrated HBV DNA</td>
<td>Detected</td>
<td>Not Detected</td>
</tr>
<tr>
<td>Current Status</td>
<td>Achievable in a few patients</td>
<td>Not yet achievable</td>
</tr>
</tbody>
</table>

Jiang, et al., DDW, 2016

HBV Chronic Infection

- $10^{13}$ virons produced per day
- Infection is not cytopathic
- Outcome of infection and severity of associated liver disease are determined by nature and magnitude of host immune response
HBV and the Host Immune Response

- Inhibition of innate immune signaling
- Inhibition of HBV specific T cell responses
- Inhibition of antibody responses to HBV
- Outcome: Immune tolerance, chronicity

How to Achieve a Cure?

- Control viral replication
  - Cripple the virus
- Reactivate the host immune response
  - Release immune tolerance
- Clear cccDNA

Functional Cure

Absolute Cure
**HBV Cure: Potential DAA Drug Targets**

**HBV Cure: Emerging Strategies**

**Viral Attachment Inhibition**

- Preclinical and Clinical POC
- Clinical results modest and variable
- Effects in HDV also
Entry Inhibition: Myrcludex B

1. Infection of PHH-transplanted uPA/SCID mice with HBV for 3 weeks
2. Treatment of infected mice with Myrcludex B for another 3 weeks blocks HBV spread

Myrcludex B monotherapy in chronically infected patients

Myrcludex reduces HBV DNA by 0.8log (w12)

2016 AASLD/EASL HBV Workshop Sept. 8th 2016

Nucleoside Prodrugs

Liver Targeted Tenofovir Prodrugs

Advantages
- Increase drug levels in liver
- Reduce renal and bone toxicity associated with Tenofovir
Hepatitis B virus replication is strictly dependent upon capsid assembly around pregenomic RNA (pgRNA) prior to rcDNA synthesis and subsequent cccDNA synthesis.

Assembly of HBV nucleocapsid is dependent on ordered folding of the viral capsid protein.

Interfering with HBV capsid assembly with small molecule inhibitors has been shown to translate into antiviral activity in vitro and in vivo and constitutes a novel mechanism that is distinct from the nucleos(t)ide analogues currently available for clinical use.

Inhibition of HBV Capsid Assembly and pgRNA Encapsidation

**First Clinical POC of Capsid Inhibitors (NVR-3-778)**

Mean 1.72 log10 (98.1%) HBV DNA reduction for cohort I

- Cohort I patient range: 1.06-3.71 log10 IU/mL (91.3-99.9%)
- Tripling of daily dose from 400mg QD (cohort H) to 600mg BD (cohort I) produced large efficacy increase

Mean 0.86 log10 (86%) serum HBV RNA reduction for cohort I

- Cohort I patient range: 0.16 – 1.5 log10 copies/mL
- Mean 0.001 log10 change for placebo patients across dose groups (n=8)

Higher dose currently under study, to explore maximal efficacy of NVR 3-778

Summary Table

<table>
<thead>
<tr>
<th>Treatment</th>
<th>d28 HBV DNA (log10 from BL)</th>
<th>d28 HBV RNA (log10 from BL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVR 3-778</td>
<td>-1.72</td>
<td>-0.82</td>
</tr>
<tr>
<td>PegIFNa-2a</td>
<td>-1</td>
<td>-0.73</td>
</tr>
<tr>
<td>NVR3-778 + PegIFN</td>
<td>1.87</td>
<td>-1.51</td>
</tr>
</tbody>
</table>

(NVR 3-778 @ 600 mg BID; Peg IFN 180 ug/wk)
Capsid Assembly Inhibitor AB-423

- In vitro AB-423 showed:
  - additive/synergistic activity in combination with Nuca and RNAi agents
  - potent activity against HBV NucR variants and pan-genotypic activity
  - no significant activity against unrelated viruses
  - AB-423 inhibited cccDNA synthesis during de novo HBV infection of C3A NPCP cells

Data suggests AB-423 has a dual mode of inhibition:
- Inhibits encapsidation of pgRNA during ongoing infection
- Inhibits cccDNA synthesis presumably via inhibition of the capsid uncoating step

Capsid (Core Protein) Assembly Inhibitors

**Class I**
Heteroaryldihydropyrimidine (HAP)

- BAY-41-4109

**Class II**
Propenamides

- AT-150

Sulfonylbenzamides

- DVR-23
Capsid Assembly Inhibitor Patent Landscape

Crystal Structure of Bound Capsid Assembly Inhibitor

HBV Cure: Emerging Strategies

Inhibit HBsAg Production or Secretion

RNAi Approach
- Clinical and preclinical POC
- Potency & safety
- LNP Delivery
- Triple Trigger
- Chol-siRNA
- GalNAc-siRNA

Nucleic Acid Polymers Sequestration
- Clinical POC?
- MOA?

Small Molecules
- Preclinical in vitro POC

Controlling S-Antigen Production via RNAi (ARC-520)
- Preclinical study in 9 HBV-infected chimpanzees (9-37y)
- NUC pretreatment 8-24w, repeated injections of ARC-520

- Dose escalation study (single dose i.v.):
  - 32 HBeAg-, 8 HBeAg+ CHB patients under ENT
  - Well tolerated up to 4 mg/kg under pretreatment with oral antihistamine
  - Reduction of serum HBsAg up to 0.5 log (HBeAg- patients)
  - 0.7 log (HBeAg+ patients)
  - Reduction of HBeAg up to 2 log

Program Terminated due to tox signal
Controlling S-Antigen Production via RNAi (ARB-1467)

- LNP Delivery Technology
- Triple trigger RNAi

**PXB Mouse Study**

![Graph showing serum HBsAg levels](image)

**Human Clinical Study**

- Single-dose results show significant reductions in serum HBsAg levels
- Multi-dose results show a step-wise, additive reduction in serum HBsAg
  - Reductions of ≥ 1.0 log_{10} in 3/5 patients (after 3 monthly doses at 0.4 mg/kg)

Streinu-Cercel, A., et al., EASL 2017, Abst # SAT-155

Controlling sAg via Nucleic Acid Polymers (NAPS)

**Mono therapy with REP 2139-Ca**

Reducing or Eliminating cccDNA

- Long term nuc treatment results in multi-log reduction of cccDNA pool
- IFN treatment inhibits transcription and capsid stability, reduces cccDNA pool

cccDNA Formation and Stability

What We Know and What We Don’t Know

- Chromatization --Complexed with H3 and H4 histones, acetylation regulates HBV replication
- Regulation of expression --HBX destabilizes SMC5/6 episomal silencing complex --HBX itself is likely transcribed very early, active at low levels
- Modulation of cccDNA copy number in non-dividing cells? --IFN/TNF/LTβ upregulation of APOBEC3A

- Capsid conformational shift
- rcDNA deproteinization --TDP2 implicated but unconfirmed
- Completion of (+) strand and removal of RNA primer ---PolK implicated
- DNA ligation of both strands over gap --Factors? DNA ligase 1+3 implicated
Regulating cccDNA Transcription

Epigenetic Control of cccDNA

LOW-REPLICATIVE STATE
- Histones acetylases, deacetylases, methyltransferases
- Transcription factors
- Binding of viral proteins: HBc & HBx

HIGH-REPLICATIVE STATE
Silencing
- Interferon alpha,
- Capsid inhibitors,
- Epigenome modifiers

Pollicino et al. Gastroenteroplogy 2006
Leverero et al. J Hepatol, 2009
Lucifora et al, J Hepatol 2012
Belloni et al, PNAS 2009
Belloni et al, J Clin Invest 2012

cccDNA: A Target for Gene Editing

Gene Editing

Targeted DNA Cleavage Endpoints
- Custom-designed Nucleases
- Double-strand break
- Disruption by NHEJ
- Insertion by HR
- Donor construct
- Gene Knockout
- Gene Replacement/Tagging/Correction

Engineered Endonucleases
- Meganucleases/Homing endonucleases (HEs)
- Zinc Finger Nucleases (ZFNs)
- Tal-effector nucleases (TALENs)
- CRISPR/Cas9

NHEJ – Non-Homologous End-Joining; results in short mutations, insertions and deletions (indels)
HR – Homologous Recombination; accompanied by donor DNA, capable to insert / replace sequence

Nishimasu et al, Cell 2014
Stone et al, Curr Opin HIV/AIDS 2013
cccDNA: A Target for Gene Editing

Gene Editing: Targeting HBV with CRISPR/Cas9

- Co-transfection of 1.3x WT HBV and sgRNA-Cas9-2A-mCherry plasmid by HDI in mice, followed by monitoring viral markers in mouse blood
- Total HBV DNA and cccDNA exhibit dramatic, increasing reductions over time

Immunmodulation: Challenges on the Path to a Cure

1. Heterogeneous host immunity among HBV patients.
   - what is a clinical biomarker for host immune re-awakening?

2. Lack of understanding of the immunological function of viral proteins.
   - all inhibitory? or stimulatory?
HBV Cure: Potential Immune Modulatory Drug Targets

Restoration of Antiviral Immunity

TLR7 Agonist GS-9620

**Woodchuck Study**

**HBV DNA Levels**

- 5 mg/kg QOD, 4-8 weeks
- Mean Max viral load decline of 6.1, 2.9, and 5.8 observed
- sAg levels reduced to undetectable in 100% of animals
- Reduced sAg levels were sustained after cessation of therapy

**Human Clinical Study**

- Discontinued due to lack of efficacy
- Dose limiting toxicity?

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**RIG-I Agonist: SB9200**

- Dinucleotide
- Reduction in serum HBV DNA
- Reduction in sAg levels
- Induction of ISGs
- Induction of type 1 IFN
STING Activation Controls HBV Replication and Induces Cytokine Production

- STING expressed in hepatocytes (low level), antigen presenting cells and T cells
- An innate immune adaptor that regulates responses to cytosolic/viral dsDNA

**Figure:**
- DMXAA: Mouse STING agonist
- 2’3’ cGAMP bisphosphorothioate: Human/multi-species active

**Graphs:**
- Dose response graphs for serum HBV DNA and IL-6 production.

**HBV Cure:**
The Drug Discovery Landscape

**Immune modulation**
- Toll-like receptors agonists, Gilead, Roche
- Anti-PD-1 mAb, BMS, Merck, Roche, Medimmune, others
- Vaccine therapy
  - Transgene, Gilead, Roche Innovio, others
  - STING: ABUS
  - Cyclophilin: Contavir
  - RIG-I: Springbank, Rigontec

**RNA interference**
- ABUS, ARVR, ALNY, GSK/Ionis, Arcturus/JNJ

**Targeting HBsAg**
- ABUS, Replicor, Roche

**Polymerase inhibitors**
- Nucleoside: Gilead, BMS, CoCrystal, Contavir

**Entry inhibitors**
- Lipopeptides, e.g. Myrcludex-B

**Targeting cccDNA**
- ABUS, JNJ, Chromis, Enyo, Intellia, Gilead, Precision Bio

**Inhibition of nucleocapsid assembly**
- JNJ, Assembly, Gilead, Janssen, Roche, ABUS, Enanta, Sunshine Lake

**References**
Current Pipeline of Investigational Agents

Phase I
- ARB-1740
- Acuvir AIC 549
- JNJ-379
- AB-423
- ALN-HBV
- JnJ/Arcturus RNAi
- Dicerna RNAi
- Assembly ABI-60731
- Ionis-HBVx
- RG-7834

Phase II
- Myrcludex B
- NVR3-778
- CMX157
- REP 9AC
- SB-9200
- GS-5901
- GS-9620

Phase III
- ARB-1467
- Aicuris
- AIC 649
- JNJ-379
- AB-423
- ALN-HBV
- JnJ/Arcturus RNAi
- Dicerna RNAi
- Assembly ABI-60731
- Ionis-HBVx
- RG-7834

Launch
- Tenofovir Alafenamide

Combination Therapy

- General belief that no single approach will be sufficient to deliver a cure
- As in HCV and HIV combinations of drugs with different MOA will be the solution
- Which combination will deliver the ultimate “cure” is yet to be determined
- How to assess combinations pre-clinically that may guide clinical studies is developing
Key Challenges in Finding an HBV Cure

- How to completely control viral replication?
- How to address the virus’ ability to control the host immune response?
- How to eradicate the viral reservoir, cccDNA?
- What is the best combination of MOA?
- Can significant reduction in the duration of therapy be achieved?
**HBV: Is There a Path to a Cure?**

- Increased focus by both academic and industry labs well beyond historic levels

- Many new targets and strategies under investigation

- Increased efforts to understand the virus and how the host immune system responds to the virus

- Combination of drugs with different MOA have the potential to deliver major therapeutic advances

**A Cure Yet To Be Realized: HBV**

**50 years without a cure**

*But light is at the end of the tunnel*