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Laboratory Director (retired),
City of Bristol Connecticut

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*Session 7 of the 2017 Industrial Science Series*

Dan Sutherlin, Principal Scientist and Director, Discovery Chemistry, Genentech

Mark Jones, Executive External Strategy and Communications Fellow, Dow Chemical

Thursday, August 10, 2017

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Sam Kean, *New York Times* bestselling author

Celia Arnaud, Senior Editor, *Chemical & Engineering News*

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Kevin Hodgetts of Harvard Medical School
Inaugural Pharma Leaders Symposium
ACS National Meeting in DC
Aug. 21, 2017 - 1 to 4 PM
Walter E. Washington Convention Center - Room 146C

“ACS Pharma Leaders: Working together to make a difference”

- neglected diseases
- chemistry collaborations
- predictive science

Speakers:
Richard Connell of Pfizer
Lisa Shewchuk of GlaxoSmithKline
Bradley Sherborne of Merck
Anil Vasudevan and Dale Kempf of AbbVie
Peter Warner of The Gates Foundation

Organizers: Philip Kym of AbbVie, Catherine Peishoff (formerly of GSK), and Wendy Young of Genentech

For more information, Contact: Susan Ainsworth at s_ainsworth@acs.org

ACS Webinars

2017 Drug Design and Delivery Symposium
“Viral Hepatitis: The Search for a Cure”

Slides available now! Recordings are an exclusive ACS member benefit.
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The 2017 DDDS is co-produced with ACS Division of Medicinal Chemistry and the AAPS
Viral Hepatitis: The Search for a Cure

Michael J. Sofia, Chief Scientific Officer
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% life time 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
Challenge Question

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 DAAs</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>
</tr>
<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>
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
The Hepatitis C Virus

### HCV Lifecycle

- Error-prone RNA-dependent, RNA polymerase
  - poor proofreading function
  - high replication rate \textit{in vivo}

\textasciitilde 9.6 kb genome: 0.1-1 error per RNA synthesized


### HCV Genome

![HCV Genome Diagram](image)

#### Replication Rates

<table>
<thead>
<tr>
<th></th>
<th>HCV</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(10^{12})</td>
<td>(10^{10}-10^{11})</td>
</tr>
</tbody>
</table>

Key Target Areas of Drug Discovery Focus and Key Drugs

#### Protease Inhibitors

- Telaprevir
- Boceprevir
- Asunaprevir
- Grazoprevir
- Simeprevir
- Paritaprevir

#### NSSA Inhibitors

- Daclatasvir
- Ledipasvir
- Velpatasvir
- Ombitasvir
- Elbasvir

#### Polymerase Inhibitors

- **Nucleosid(t)e**
  - Sofosbuvir

- **Non-nucleoside**
  - Dasabuvir
  - Beclabuvir

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**

Year and Order of Approval:

2013 | 2014 | 2015 | 2016 | 2017
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
HEPATITIS B

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\(^1\) (Compared with the 33 million living with HIV\(^2\))

- 1.46-2 million people in the United States are chronically infected\(^6\)
- 14 million in Europe\(^3,4\)
- 112 million in Asia-Pacific
- 93 million people in China\(^1,2\)

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)

- View of Outer Surface Diameter = 42 nm
- Transparent View of Core Diameter = 28 nm
- Exposed View of Core
- Internal Cross-Sectional View

The intact hepatitis B virion, also known as the Dane Particle, is a sphere that is approximately 42 nm in diameter. The intact HBV virion consists of an outer envelope and an inner 28 nm icosahedral core, also known as the nucleocapsid. The HBV core contains a single molecule of partially double stranded HBV DNA and viral DNA polymerase.

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

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

---

1 WHO. Available at: [www.who.int/topics/hepatitis](http://www.who.int/topics/hepatitis)
3 Records of the thematic press conference of the Ministry of Health of the PRC at April 21, 2008, from the website of the Ministry of Health of the People’s Republic of China;
4 Ulmer, T et al. (2007). European orientation towards the better management of hepatitis B in Europe; 5 CDC. Hepatitis B FAQs for Health Professionals. Available at [http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#overview](http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#overview)
Transmission of HBV

**Horizontal Transmission**

- Host → Recipient

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

6% infected after age 5 years become chronically infected

**Vertical Transmission**

- Mother → 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

<table>
<thead>
<tr>
<th>HBV DNA</th>
<th>HBSAg</th>
<th>HBeAg</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10^7 IU/ml</td>
<td>&gt;30,000 IU/ml</td>
<td>highly positive</td>
</tr>
</tbody>
</table>

ALT: Normal

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>Product Name</th>
<th>Company</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>VEMLIDY®</td>
<td>Gilead Sciences</td>
<td>2016</td>
</tr>
<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>BARACLADE™</td>
<td>Bristol-Myers Squibb</td>
<td>2005</td>
</tr>
<tr>
<td>Adefovir Dipivoxil</td>
<td>HEPSENRA™</td>
<td>Gilead Sciences</td>
<td>2002</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>EPIVIR-HBV®</td>
<td>GlaxoSmithKline</td>
<td>1998</td>
</tr>
</tbody>
</table>

Interferons

<table>
<thead>
<tr>
<th>Interferon</th>
<th>Product Name</th>
<th>Company</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon alfa-2a</td>
<td>PEGASYS®</td>
<td>Roche Laboratories</td>
<td>2005</td>
</tr>
<tr>
<td>Interferon alfa-2b recombinant</td>
<td>INTRON® A</td>
<td>Schering/Merck</td>
<td>1992</td>
</tr>
</tbody>
</table>

Preferred Therapies – AASLD Guidelines
Relative Efficacy of Approved HBV Therapies

<table>
<thead>
<tr>
<th></th>
<th>Entecavir 1,2</th>
<th>Tenofovir 3</th>
<th>PEG-IFN α-2a 4,5</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg positive</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%³</td>
</tr>
<tr>
<td>HBeAg negative</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%³</td>
</tr>
</tbody>
</table>

Results at 48 weeks

‡ HBV DNA < 400 copies/mL; ³ At 72 weeks


Long-term Therapy is Required to Maintain Viral Suppression

![Graph showing HBV DNA change from baseline (log10 c/mL) vs Time (years) with Therapy effect on HBsAg and HBV DNA.](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>As if recovery after acute HBV infection</td>
<td>As if never infected</td>
<td></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 Viral Life Cycle
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
HBV Cure: Potential DAA Drug Targets

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

Nucleoside Prodrugs

Liver Targeted Tenofovir Prodrugs

Launched as Vemlidy®

Phase II Clinical Development

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 Encapsulation

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 µg/wk)
Capsid Assembly Inhibitor AB-423

- In vitro AB-423 showed:
  - additive/synergistic activity in combination with Nuc inhibitors
  - potent activity against HBV Nuc inhibitors and pan-genotypic activity
  - no significant activity against unrelated viruses
- AB-423 inhibited cccDNA synthesis during de novo HBV infection of C3A 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-41-109

**Class II**

Propenamides

- AT-150

Sulfonylbenzamides

- DVR-23
Capsid Assembly Inhibitor Patent Landscape

Bayer

![Bayer molecule structure](image)

Janssen

![Janssen molecule structure](image)

Novira

![Novira molecule structure](image)

Roche

![Roche molecule structure](image)

Sunshine Lake Pharm

![Sunshine Lake Pharm molecule structure](image)

Assembly

![Assembly molecule structure](image)

Crystal Structure of Bound Capsid Assembly Inhibitor

![Crystal structure image](image)

HAP (Class I)

**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?
- ~40 mer

**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

- Serum HBsAg as % Baseline
- **Treatments**
  - Untreated
  - TKM-HBV 0.3 mg/kg

### 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 nucleotide treatment results in multi-log reduction of cccDNA pool
- IFN treatment inhibits transcription and capsid stability, reduces cccDNA pool

pgRNA to rcDNA conversion

- Can inhibition contribute to reduction of 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/LTB upregulation of APOBEC3A

Cytoplasm

- 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

Nucleus

- cccDNA decay?
Regulating cccDNA Transcription

Epigenetic Control of cccDNA

- **Epigenetic regulation:**
  - Histones acetylases, deacetylases, methyltransferases
  - Transcription factors
  - Binding of viral proteins: HBc & HBx

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

**End Joining (NHEJ):**
- Non-Homologous End Joining; results in short mutations, insertions and deletions (indels)

**Homologous Recombination (HR):**
- Homologous Recombination; accompanied by donor DNA, capable to insert / replace sequence

References:

- 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

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

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**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

- Duration of therapy: 4 weeks for Group 3 and 8 weeks for Groups 4 and 5.
- 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.

HBsAg Levels

- 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?

Menne, S, et al., J. Hepatology, 2015, 62, 1237-1245

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

**Insight:**

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

**Graphs:**

- Serum HBV DNA Log10 (Copies/mL)
- IL-6 (pg/mL)
- IP-10 (pg/mL)

**Legend:**

- Untreated
- IFN-α
- DMXAA - 12.5 mg/kg
- cGAMP - 12.5 mg/kg
- cGAMP - 25 mg/kg

**Schematic:**

- Immune modulation
- RNA interference, ABUS, ARWR, 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:**

- Thi, E. et al. ICAR, 2017 Abs # 135
Current Pipeline of Investigational Agents

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
Combination Therapy

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
2017 Drug Design and Delivery Symposium
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*Session 7 of the 2017 Industrial Science Series*
Dan Sutherlin, Principal Scientist and Director, Discovery Chemistry, Genentech
Mark Jones, Executive External Strategy and Communications Fellow, Dow Chemical

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Sam Kean, *New York Times* bestselling author
Celia Arnaud, Senior Editor, *Chemical & Engineering News*

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Stephen Mason
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Friday August 4, 2017 (8:00 a.m. – 5:00 p.m.)
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- Early Phase Drug Development and Population PK
- Transforming skillsets in early development to meet the changing NCE/NBE landscape in discovery space
- Academic collaboration and preparing for the discovery support role in industry

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- Discovery Biology
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- Pharmacokinetics
- Toxicology

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- Capt. Edward D. Baslaw, PharmD (Director, U.S. Food and Drug Administration)
- Justin Pennington, PhD (Director, Merck & Co.)

Featured Speakers:
- Vladimir Popov, PhD (Bayer Schering Pharma)
- Jonathan Philips, PhD (Toxicology Fellow, Vertex Pharmaceuticals)
- David Rodrigues, PhD (Research Fellow, Pfizer Inc.)
- Joseph Fortunak, PhD (Associate Professor, Howard University)
- Steven Fletcher, PhD (Associate Professor, University of Maryland School of Pharmacy)

Contact: Sunny Bhardwaj
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