Viral Hepatitis:
The Search for a Cure

Michael J. Sofia, Chief Scientific Officer
Arbutus Biopharma, Inc.

Arbutus BIOPHARMA

17

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 sever 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

18

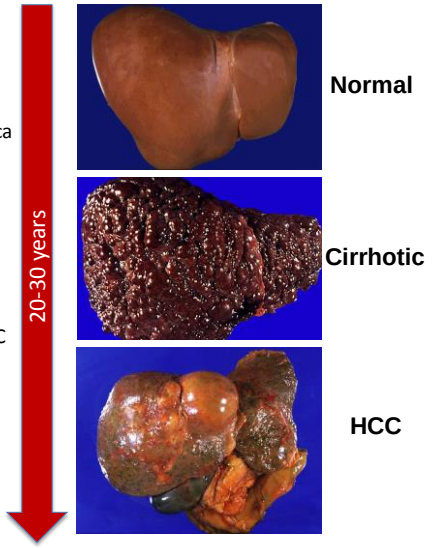
Chronic Viral Hepatitis: HBV & HCV

- **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

19

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



20

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

21

HBV vs HIV vs HCV

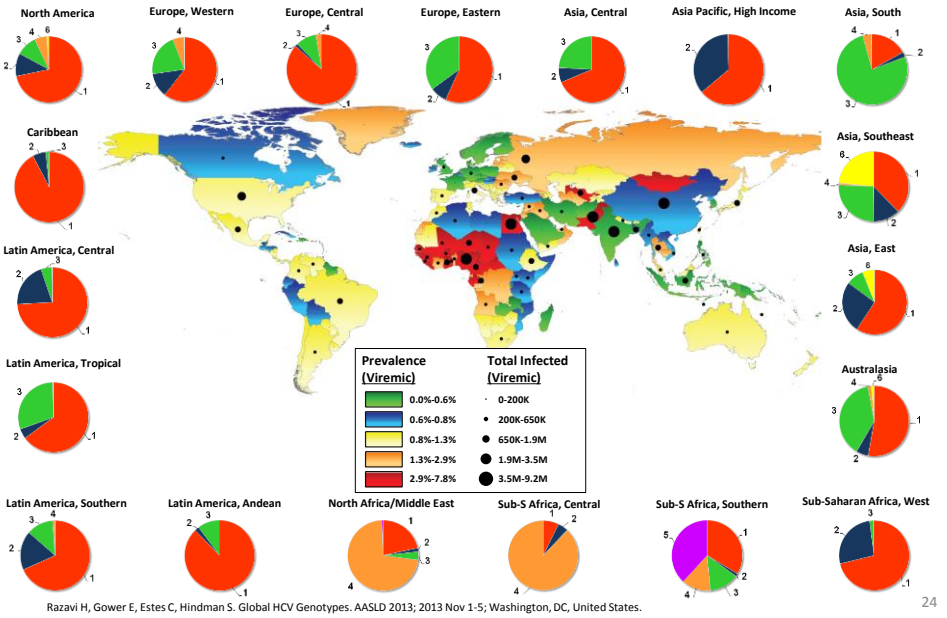
	HIV	HCV	HBV
U.S. Prevalence	1 million	3 million	1.3– 3 million
Worldwide Prevalence	35 million	160 million	350 million
Percent Diagnosed in U.S.	80%	50%	30%
Percent Diagnosed Who Are Treated in U.S.	70%	33%	6-10%
Nature	RNA retrovirus	RNA virus	DNA virus
Virions Produced per Day	10^{10}	10^{12}	10^{13}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

22

HEPATITIS C

Can it become a disease of the past?

HCV: Prevalence, Total Infected, Genotype

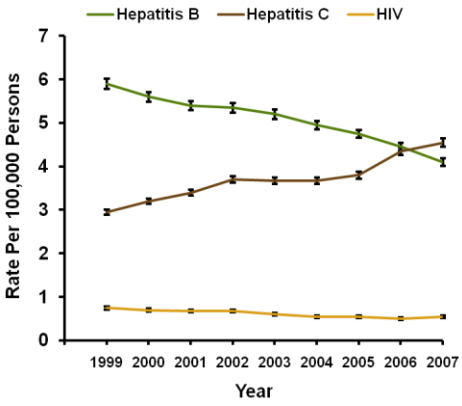


Razavi H, Gower E, Estes C, Hindman S. Global HCV Genotypes. AASLD 2013; 2013 Nov 1-5; Washington, DC, United States.

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

- National multiple-cause mortality data 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 (29.9;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

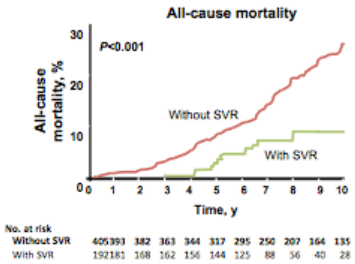


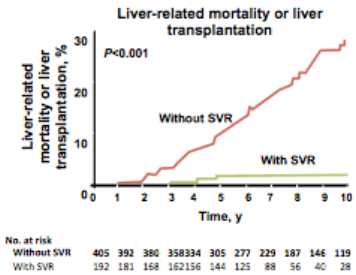
Holmberg SD , et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 243

25

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

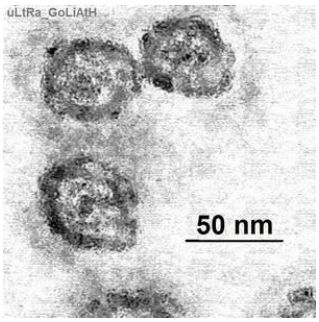
- 530 adults in Europe prospectively followed for median 8.4 years after HCV treatment
- 192 (36%) achieved SVR





Van der Meer, et al. *JAMA* 2012:308:2584-2593.

Hepatitis C Virus:
Morphology and Characteristics



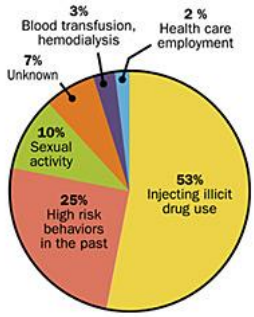
- **Nucleic Acid: 9.6 kb ssRNA(+)**
- **Classification*: Flaviviridae, Hepacivirus***
- **Genotypes: 1 to 6**
- **Enveloped**
- **No known viral reservoir**
- **Does not integrate into host genome**

27

High Risk of Infection

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

170 Million Infected Worldwide



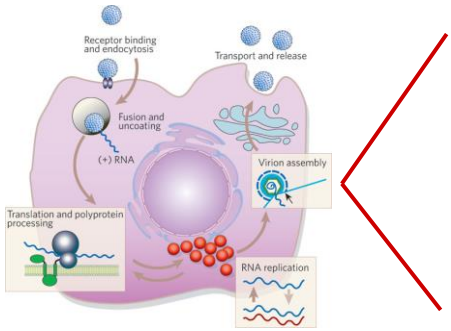
1 in 30 Baby Boomers Infected

CDC, MMWR 1998; 47:4

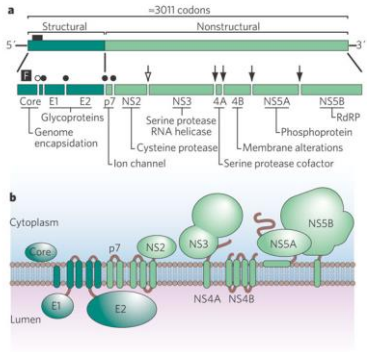
28

The Hepatitis C Virus

HCV Lifecycle



HCV Genome



- Error-prone RNA-dependent, RNA polymerase
  - poor proofreading function
  - high replication rate *in vivo*

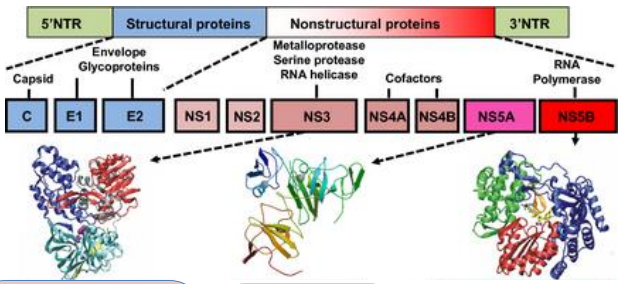
  ~9.6 kb genome: 0.1-1 error per RNA synthesized

Replication Rates	
HCV	HIV
10^{12}	10^{10}-10^{11}

Lindenbach, B and Rice, C., *Nature*, 2005, 436,933

29

Key Target Areas of Drug Discovery Focus and Key Drugs



Protease Inhibitors
Telaprevir
Boceprevir
Asunaprevir
Grazoprevir
Simeprevir
Paritaprevir

NS5A 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
http://onlinelibrary.wiley.com/doi/10.1111/liv.12423/full#liv12423-fig-0001

30

Challenge Question

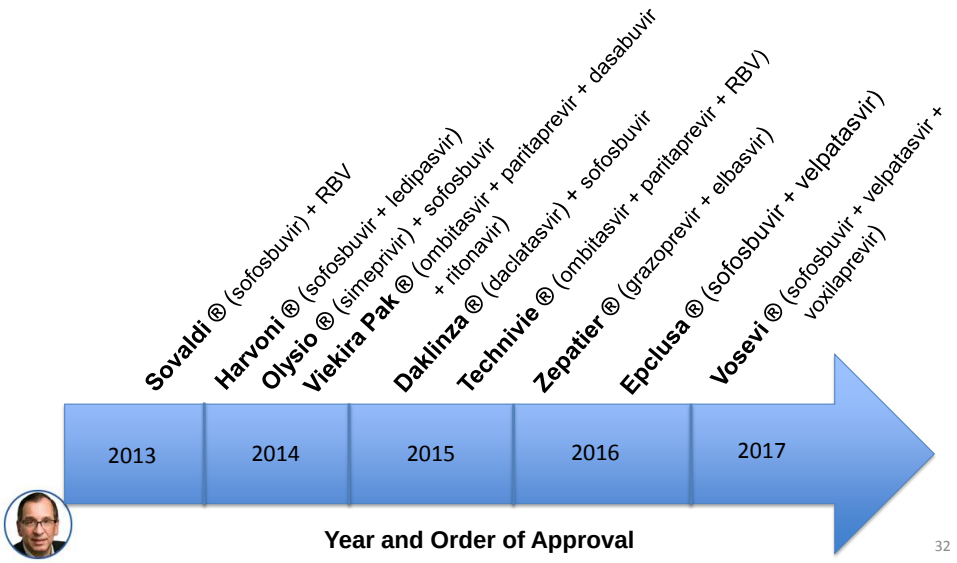
ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

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

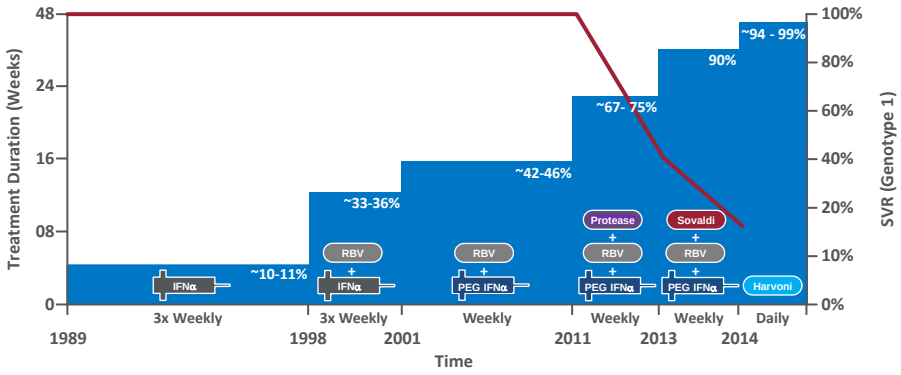
31

FDA Approved IFN-Free HCV Cure Drug Combinations



32

The History of HCV Therapy Development



33

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

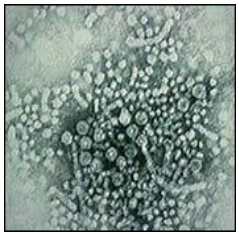
34

34

HEPATITIS B

Is there a path to a cure?

Hepatitis B Virus (HBV)

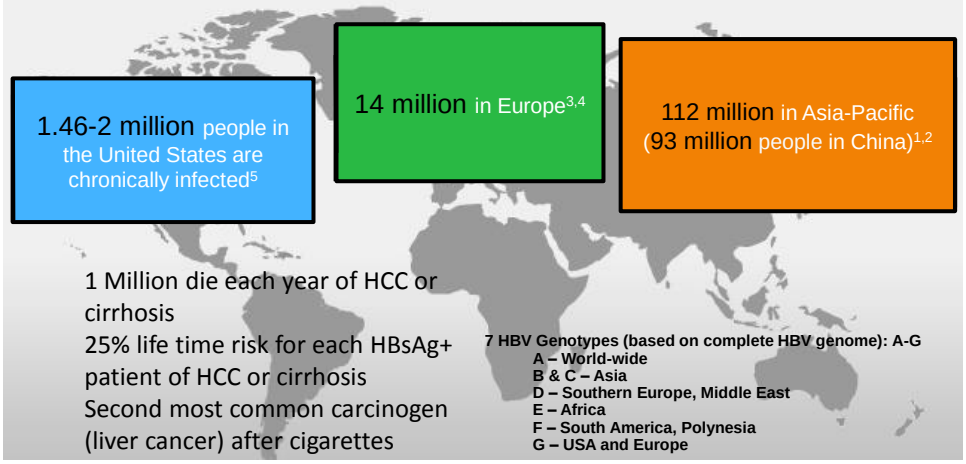


- *Hepadnaviridae* member that primarily infects liver cells
- DNA virus
- 100 times more infective than HIV
- Found in blood and body fluids
  - Able to survive in dried blood for longer than 1 week
- Viral reservoir: cccDNA in nucleus of hepatocytes
- Small segments of viral DNA do integrate but do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

Ott et al. *J Pediatr Health Care.* 1999;13(5):211-216.
Ribeiro, et al. *Microbes and Infection.* 2002;4:829-835.
MMWR. 2003;52:1-33.

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])

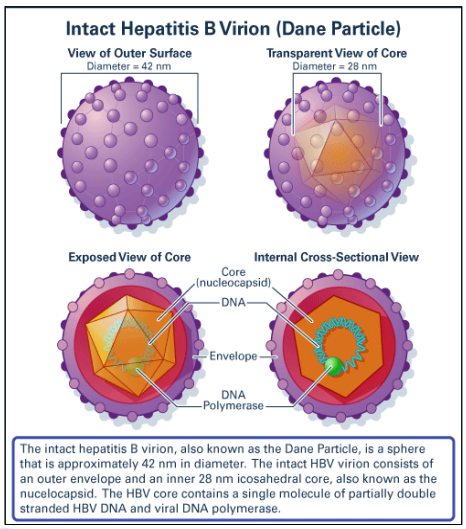


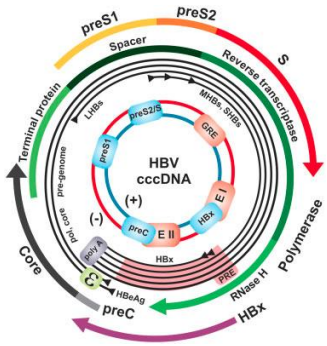
1 Million die each year of HCC or cirrhosis
25% life time risk for each HBsAg+ patient of HCC or cirrhosis
Second most common carcinogen (liver cancer) after cigarettes

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

1 WHO. Available at: www.who.int/csr/disease/hepatitis/en/. 2 Ferlay et al. Globocan 2002, Cancer incidence, mortality and prevalence worldwide, IARC Press, Lyon 2004. 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.

The Hepatitis B Virus





- **4 Promoter elements**
- **2 enhancer elements**
- **10 start sites**

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)**

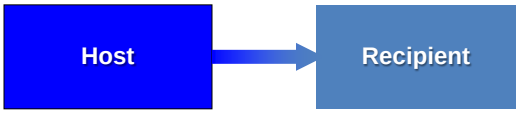
Genome Structure of HBV

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

Glebe, D., et al, Sem. Liver Dis, 33, 2013, 103

Transmission of HBV

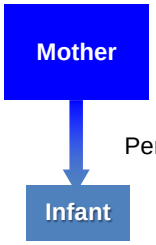
Horizontal Transmission



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

6% infected after age 5 years become chronically infected

Vertical Transmission

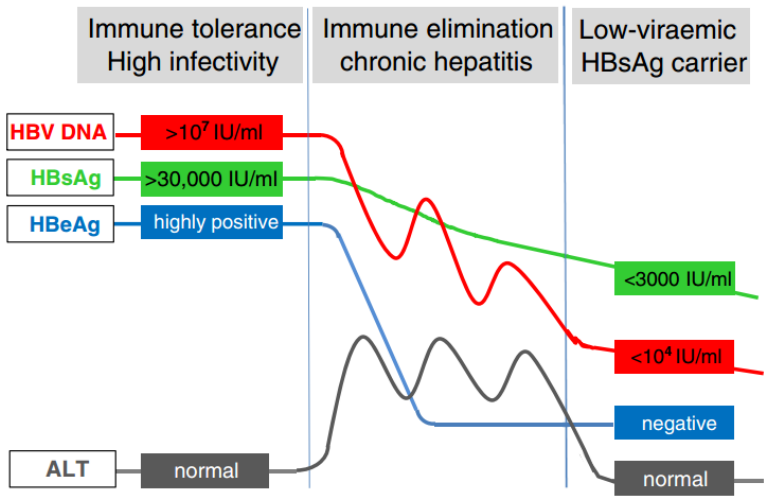


90% infected infants become chronically infected

No clear risk factors in 20-30% of patients

CDC Fact Sheet. http://www.cdc.gov/ncidod/diseases/hepatitis/b/. Accessed: October 2, 2004.
Lee. *N Engl J Med.* 1997;337(24):1733-1745.
Lavanchy. *J Viral Hepat.* 2004;11(2):97-107.

Three Phases of Chronic HBV Infection



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)
  - Pts recruited 1991-1992, serum markers evaluated every 6-12 mos until June 30, 2004; HCC rates followed until December 31, 2008
- 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

41

HBV Approved Therapies

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

Preferred Therapies – AASLD Guidelines

42

Relative Efficacy of Approved HBV Therapies

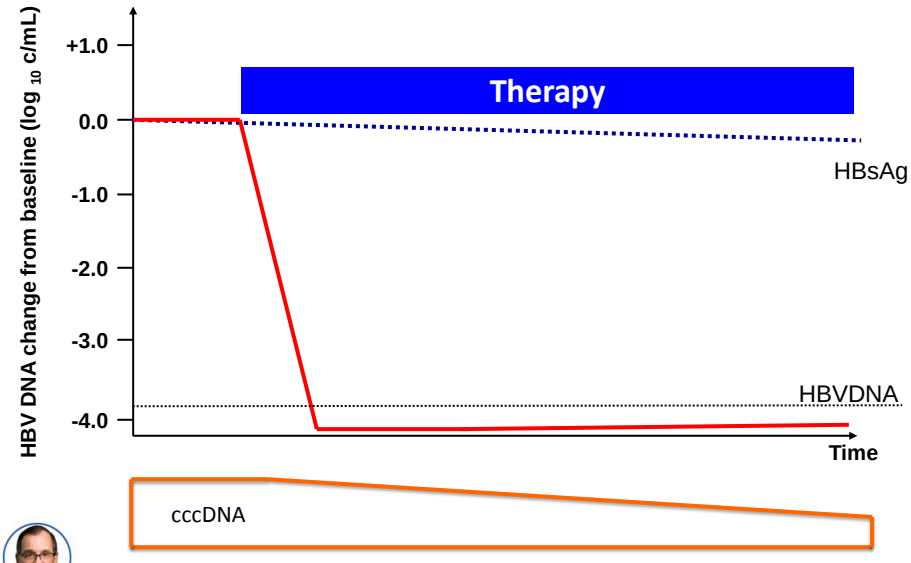
	Entecavir[1,2]	Tenofovir[3]	PEG-IFN α-2a[4,5]
HBeAg positive	n = 354	n = 176	n = 271
HBV DNA undetectable	67%	76%	25%[a]
HBeAg seroconversion	21%	21%	27%
ALT normalisation	68%	68%	39%
HBsAg loss	2%	3.2%	2.9%[b]
HBeAg negative	n = 325	n = 250	n = 177
HBV DNA undetectable	90%	93%	63%[a]
ALT normalisation	78%	76%	38%
HBsAg loss	0.3%	0%	0.6%[b]

Results at 48 weeks
[a] HBV DNA < 400 copies/mL; [b] At 72 weeks

1. Chang T-T, et al. N Engl J Med 2006;354:1001–10.
2. Lai C-L, et al. N Engl J Med 2006;354:1011–20.
3. Marcellin P, et al. N Engl J Med 2008;359:2442–55.
4. Lau GKK, et al. N Engl J Med 2005;352:2682–95.
5. Marcellin P, et al. N Engl J Med 2004;351:1206–17.

43

Long-term Therapy is Required to Maintain Viral Suppression



Werle et al, Gastroenterology 2004

44

What Does a Cure Look Like?

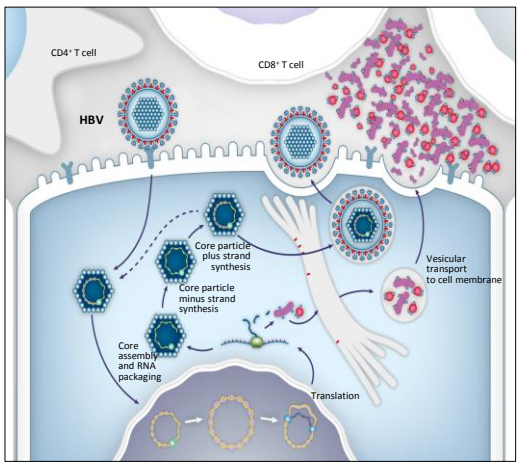
	Functional Cure	Absolute Cure
Clinical Scenario	As if recovery after acute HBV infection	As if never infected
HBsAg	Negative	Negative
Anti-HBsAg	Positive	Positive
Serum HBV DNA	Not Detected	Not Detected
HBV cccDNA	Detected, but not transcriptionally active	Not Detected
Hepatic integrated HBV DNA	Detected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

Jiang, et al., DDW, 2016

45

HBV Chronic Infection

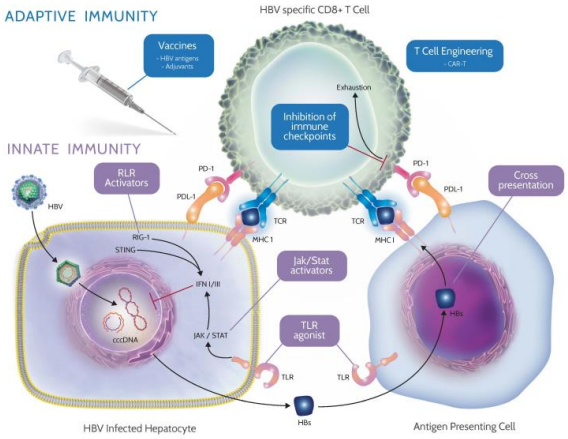
- 10^{13} virons produced per day
- Infection is not cytopathic
- Outcome of infection and severity of associated liver disease are determined by nature and magnitude of host immune response



HBV Viral Life Cycle

46

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

47

How to Achieve a Cure?

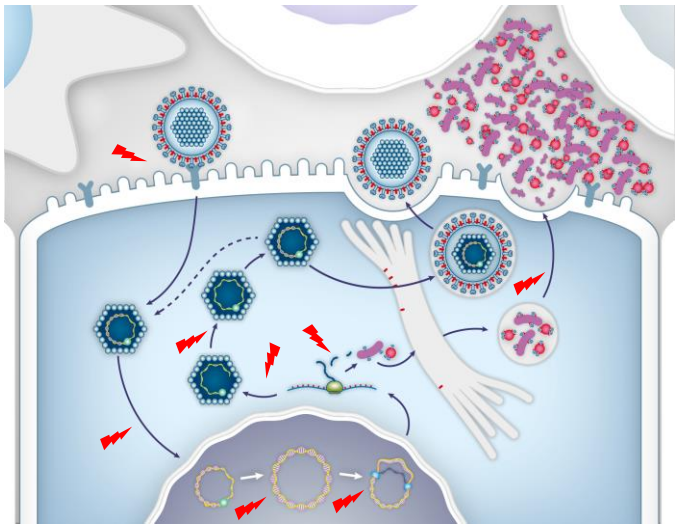
Functional Cure

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

Absolute Cure

48

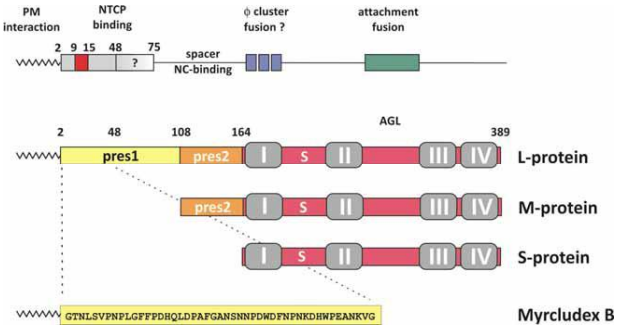
HBV Cure: Potential DAA Drug Targets



49

HBV Cure: Emerging Strategies

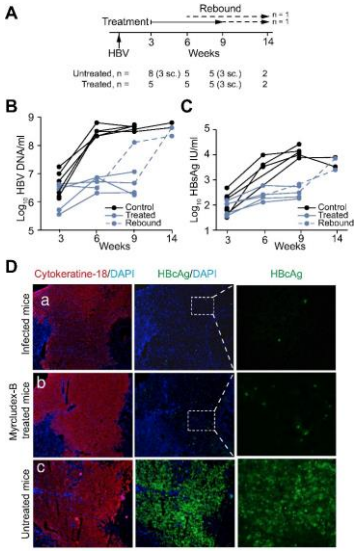
Viral Attachment Inhibition



- Preclinical and Clinical POC
- Clinical results modest and variable
- Effects in HDV also

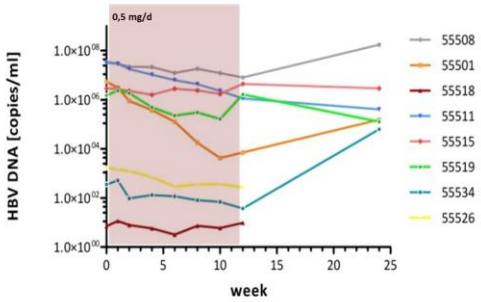
50

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

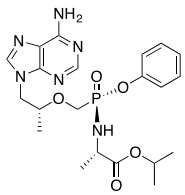


Myrcludex reduces HBV DNA by 0.8log (w12)

2016 AASLD/EASL HBV Workshop Sept. 8th 2016

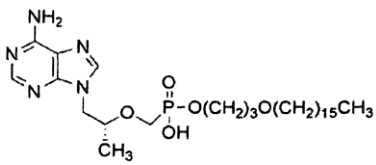
Nucleoside Prodrugs

Liver Targeted Tenofovir Prodrugs



(Tenofovir Alafenamide, TAF)

Launched as Vemlidy®



CMX157

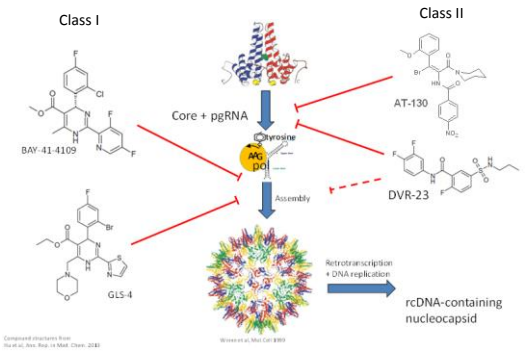
Phase II Clinical Development

Advantages

- Increase drug levels in liver
- Reduce renal and bone toxicity associated with Tenofovir

Inhibition of HBV Capsid Assembly and pgRNA Encapsidation

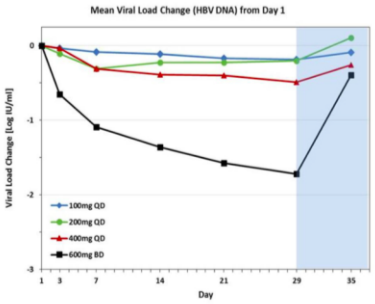
- Hepatitis B virus replication is strictly dependent upon capsid assembly around pregenomic RNA (pgRNA) prior to rcDNA synthesis and subsequent cccDNA synthesis.
- Assembly of HBV nucleocapsid is dependent on ordered folding of the viral capsid protein.
- Interfering with HBV capsid assembly with small 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.

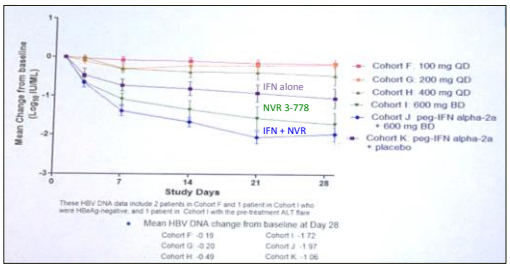


HBV capsid assembly pathway and examples of inhibitors [core protein allosteric modulators (CpAM)]

53

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



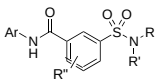


Yuen et al EASL 2016 Oral Presentation

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

Treatment	d28 HBV DNA (log10 from BL)	d28 HBV RNA (log10 from BL)
NVR 3-778	-1.72	-0.82
PegIFNa-2a	-1	-0.73
NVR3 -778 + PegIFN	-1.97	-1.51

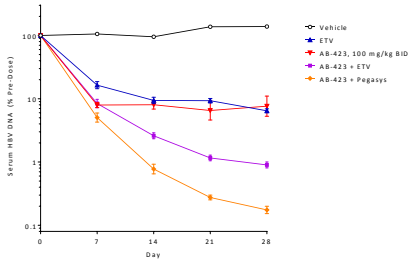
(NVR 3-778 @ 600 mg BID; Peg-IFN 180 ug/wk)

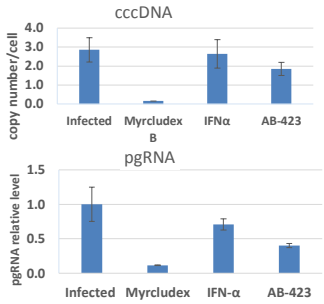
54

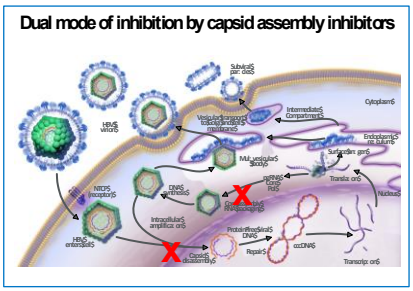
Capsid Assembly Inhibitor AB-423

- ***In vitro* AB-423 showed:**
  - *additive/synergistic activity in combination with Nucs and RNAi agents*
  - *potent activity against HBV Nuc^{R} variants and pan-genotypic activity*
  - *no significant activity against unrelated viruses*
- **AB-423 inhibited cccDNA synthesis during *de novo* HBV infection of C3A^{hNTCP} 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





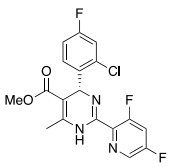


55

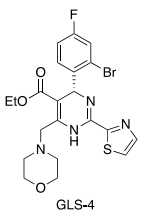
Capsid (Core Protein) Assembly Inhibitors

Class I

Heteroaryldihydropyrimidine (HAP)



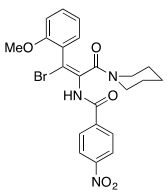
BAY-41-4109



GLS-4

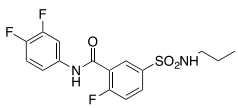
Class II

Propenamides



AT-130

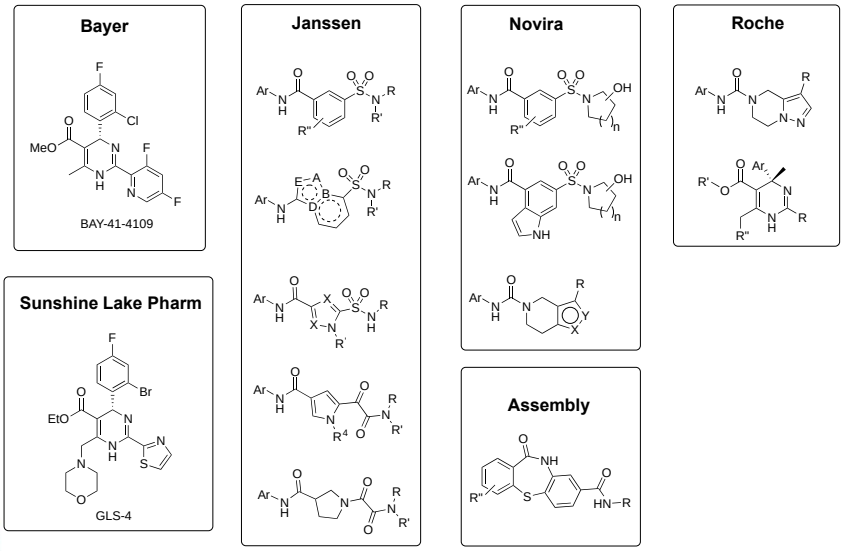
Sulfonylbenzamides



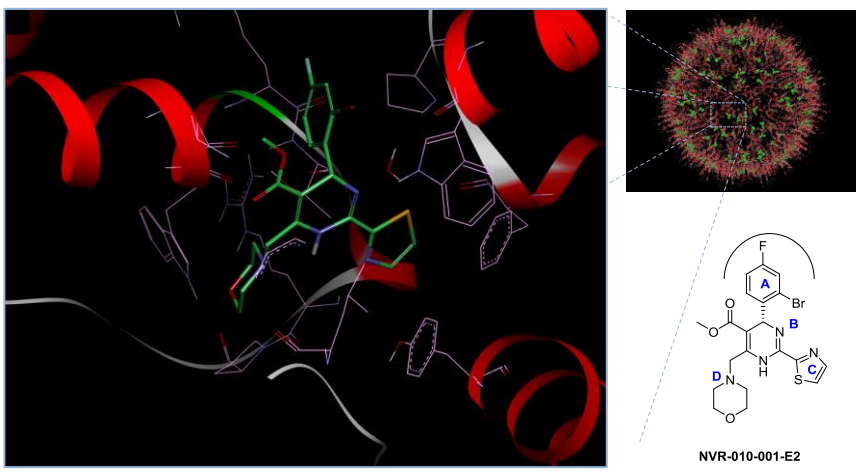
DVR-23

56

Capsid Assembly Inhibitor Patent Landscape



Crystal Structure of Bound Capsid Assembly Inhibitor



HAP (Class I)

- *Proc. Natl. Acad. Sci.* 2015, *112*, 15196.

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?

CACACACACACACACACACACACACACAcacacacaca

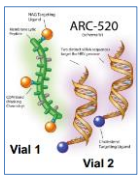
~40 mer

Small Molecules

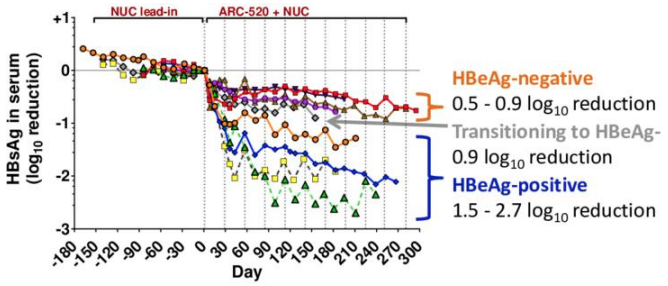
- Preclinical in vitro POC

?

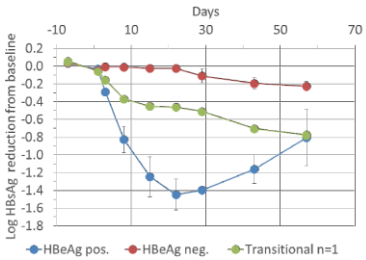
Controlling S-Antigen Production via RNAi (ARC-520)



- 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

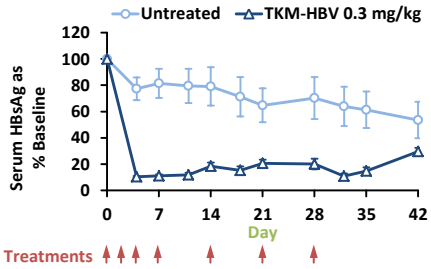


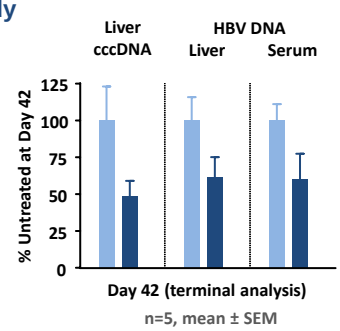
Program Terminated do to tox signal

Controlling S-Antigen Production via RNAi (ARB-1467)

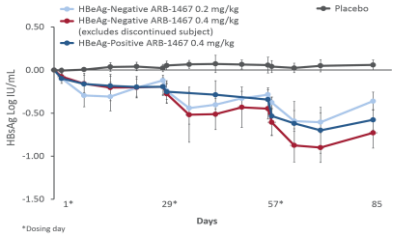
- LNP Delivery Technology
- Triple trigger RNAi

PXB Mouse Study





Human Clinical Study

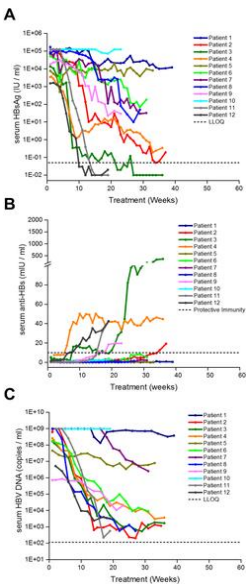


- Single-dose results show significant reductions in serum HBsAg levels
- Multi-dose results show a step-wise, additive reduction in serum HBsAg
  - **Reductions of ≥ 1.0 log_{10} in 3/5 patients** (after 3 monthly doses at 0.4 mg/kg)

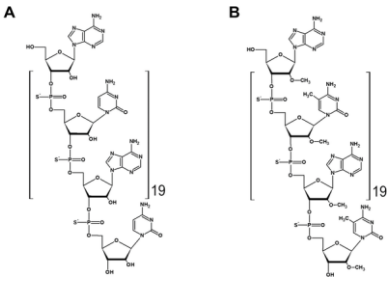
Streinu-Cercel, A., et al., EASL 2017, Abst # SAT-155

61

Controlling sAg via Nucleic Acid Polymers (NAPS)



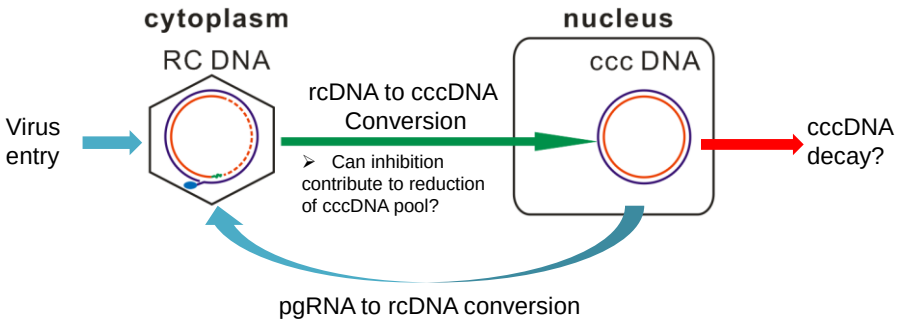
Mono therapy with REP 2139-Ca



Al-Mahtab M, Bazinet M, Vaillant A (2016) Safety and Efficacy of Nucleic Acid Polymers in Monotherapy and Combined with Immunotherapy in Treatment-Naive Bangladeshi Patients with HBeAg+ Chronic Hepatitis B Infection. PLoS ONE 11(6): e0156667. doi:10.1371/

62

Reducing or Eliminating cccDNA

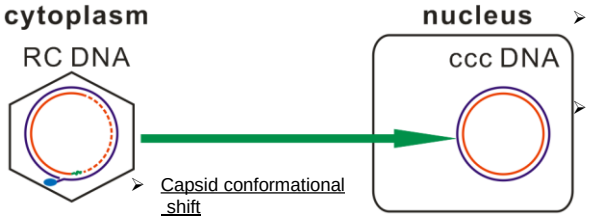


- Long term nuc treatment results in multi-log reduction of cccDNA pool
- IFN treatment inhibits transcription and capsid stability, reduces cccDNA pool

63

cccDNA Formation and Stability

What We Know and What We Don't Know



- 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

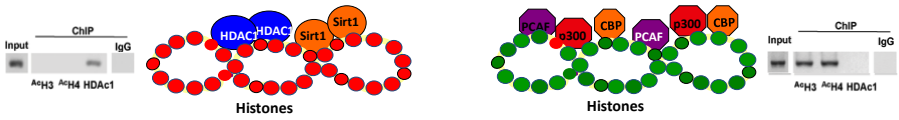
- Chromatization
  --Complexed with H3 and H4 histones, acetylation regulates HBV replication
- Regulation of expression
  --HBX destabilizes SMC5/6 episomal silencing complex

  --HBX itself is likely transcribed very early, active at low levels
- Modulation of cccDNA copy number in non-dividing cells?
  --IFN/TNF/LTß upregulation of APOBEC3A

64

Regulating cccDNA Transcription

Epigenetic Control of cccDNA



LOW-REPLICATIVE STATE ⟺ **HIGH-REPLICATIVE STATE**

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

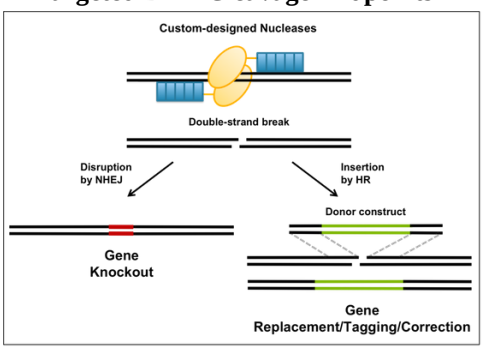
Silencing
Interferon alpha,
Capsid inhibitors,
Epigenome modifyers

Pollicino et al. Gastroenteroplogy 2006
Levrero et al. J Hepatol, 2009
Lucifora et al, J Hepatol 2012
Belloni et al, PNAS 20O9
Belloni et al, J Clin Invest 2012

cccDNA: A Target for Gene Editing

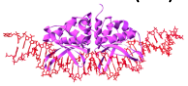
Gene Editing

Targeted DNA Cleavage Endpoints

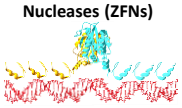


Engineered Endonucleases

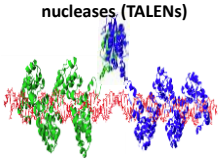
Meganucleases/Homing endonucleases (HEs)



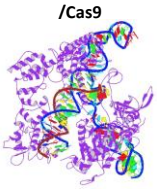
Zinc Finger Nucleases (ZFNs)



Tal-effector nucleases (TALENs)



CRISPR /Cas9



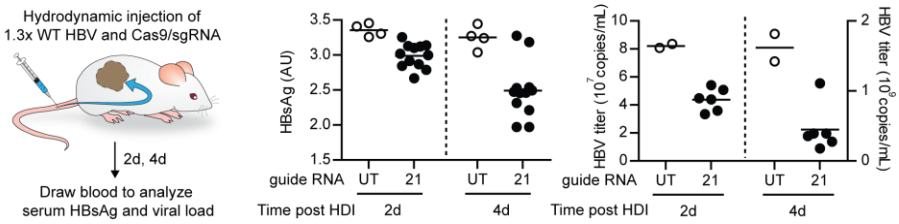
NHEJ – Non-Homologous End-Joining; results in short mutations, insertions and deletions (indels)

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



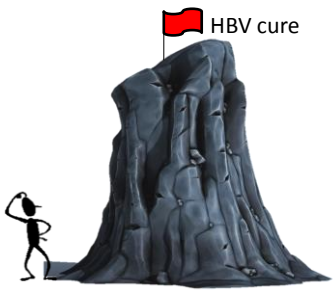
- Co-transfection of 1.3x WT HBV and sgRNA-Cas9-2A-mCherry plasmid by HDI in mice, followed by monitoring viral markers in mouse blood
- Total HBV DNA and cccDNA exhibit dramatic, increasing reductions over time

67

Immunmodulation:
Challenges on the Path to a Cure

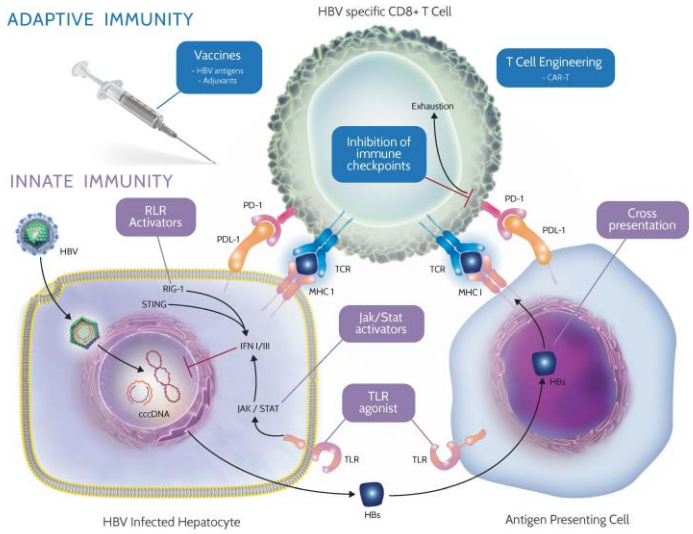
1. Heterogeneous host immunity among HBV patients.
   -what is a clinical biomarker for host immune re-awakening?

2. Lack of understanding of the immunological function of viral proteins.
   -all inhibitory? or stimulatory?



68

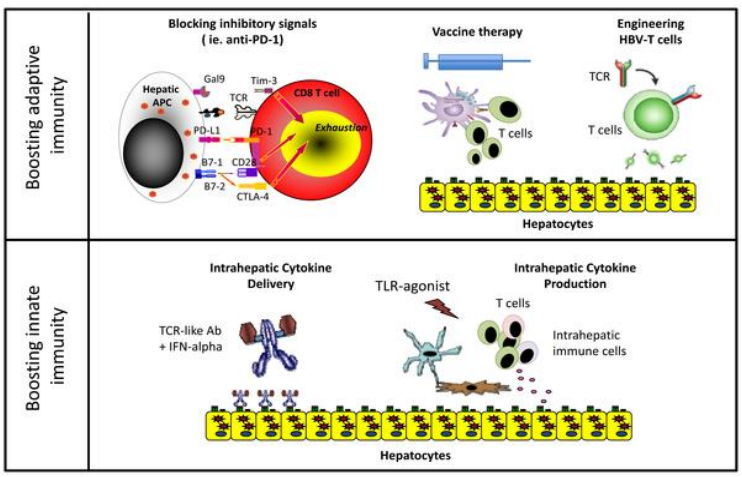
HBV Cure: Potential Immune Modulatory Drug Targets



69

HBV Cure: Emerging Strategies

Restoration of Antiviral Immunity



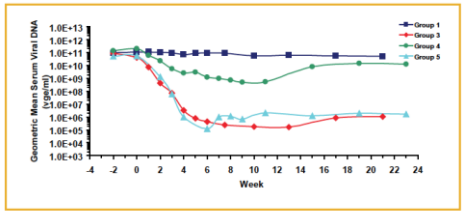
Bertoletti A, Gehring AJ (2013) Immune Therapeutic Strategies in Chronic Hepatitis B Virus Infection: Virus or Inflammation Control?. PLoS Pathog 9(12): e1003784. doi:10.1371/journal.ppat.1003784

70

TLR7 Agonist GS-9620

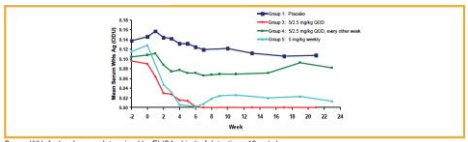
Woodchuck Study

HBV DNA Levels



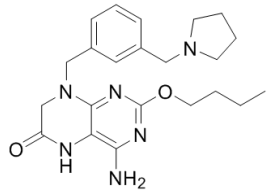
Duration of dosing was approximately 4 weeks for Group 3 and 8 weeks for Groups 4 and 5. The limit of detection for serum viral DNA levels 1 x 10^3 vge/ml.

HBsAg Levels



Serum WHsAg levels were determined by ELISA. Limit of detection ~16 ng/mL.

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



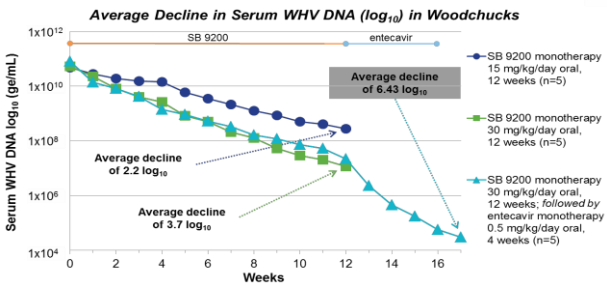
GS-9620

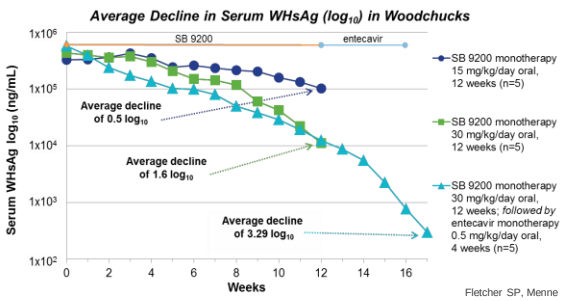
- 5 mg/kg QOD, 4-8 weeks
- Mean Max viral load decline of 6.1 2.9, and 5.8 observed
- sAg levels reduced to undetectable in 100% of animals
- Reduced sAg levels were sustained after cessation of therapy

Human Clinical Study

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

RIG-I Agonist: SB9200



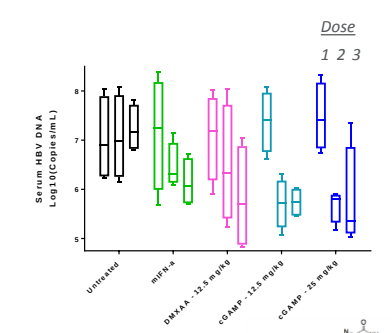


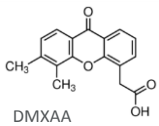
Fletcher SP, Menne S (2015) PLOS Pathogens (Sept. 2015).

- Dinucleotide
- Reduction in serum HBV DNA
- Reduction in sAg levels
- Induction of ISGs
- Induction of type 1 IFN

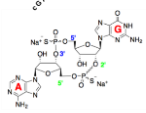
STING Activation Controls HBV Replication and Induces Cytokine Production

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

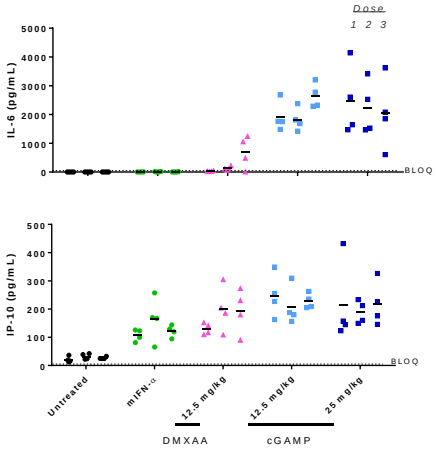




DMXAA
Mouse STING agonist

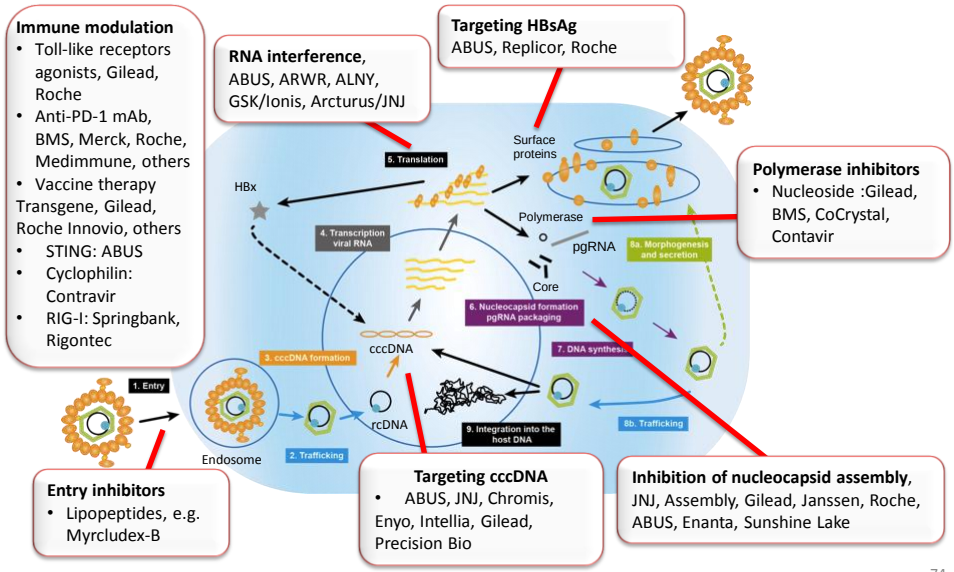


2'3' cGAMP bisphosphorothioate
Human/multi-species active



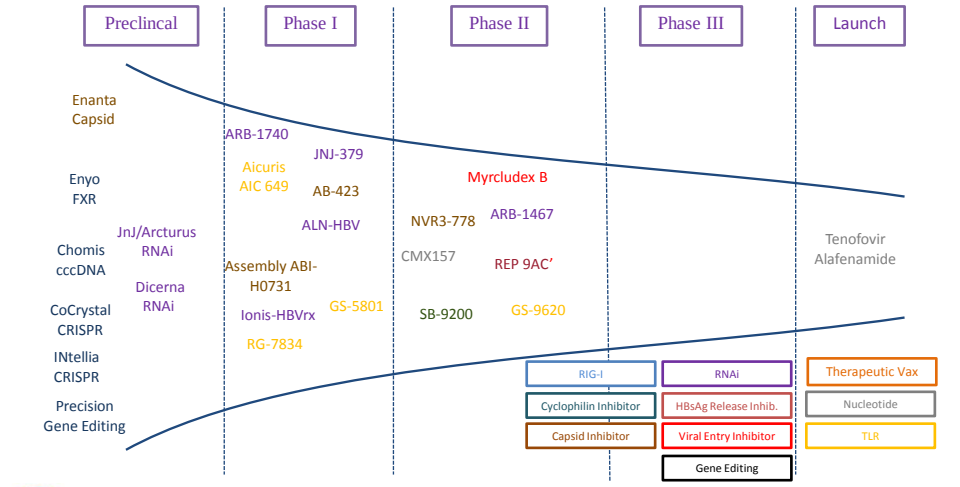
Thi, E. et al., ICAR, 2017 Abs # 135

HBV Cure: The Drug Discovery Landscape



Zoulim F, et al. Antiviral Res 2012;96(2):256–9; HBF Drug Watch, Available at: http://www.hepb.org/professionals/hbf_drug_watch.htm.

Current Pipeline of Investigational Agents



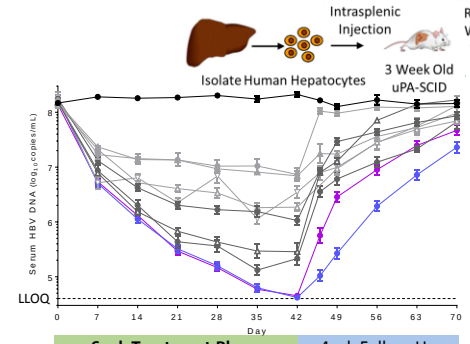
75

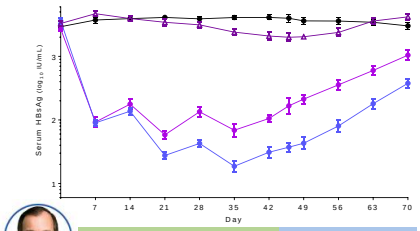
Combination Therapy

- 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

76

Combination Therapy





	Dosage	Route	Frequency
AB-423 (Capsid Assembly inhibitor)	100 mg/kg	PO	BID
ETV (Nuc)	1.2 µg/kg	PO	QD
PegIFN (Immune Stimulator)	30 µg/kg	SQ	2×/wk
ARB-1740 (RNAi)	3 mg/kg	IV	biweekly

Lee, A., et al., AASLD 2016, Abs # 232

77

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?

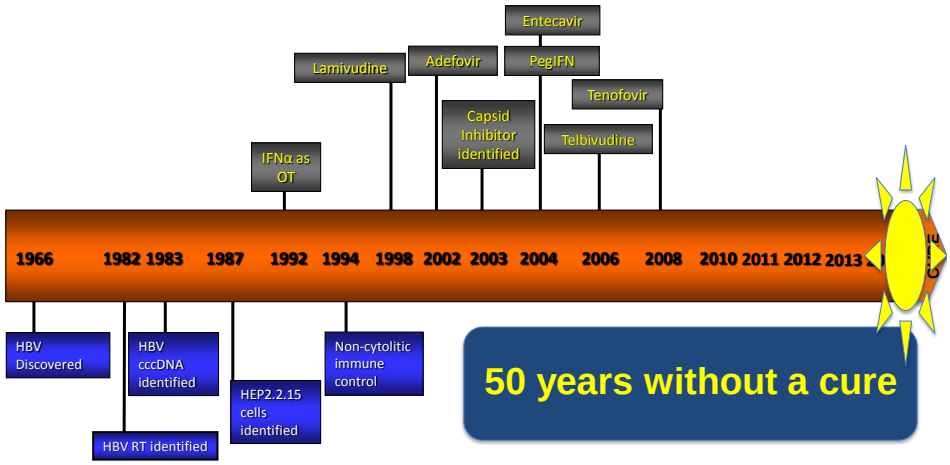
78

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

79

A Cure Yet To Be Realized: HBV



But light is at the end of the tunnel

80