Future therapies for HBV Cure

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Disclosures

Massimo Levrero

Advisory Committees or Review Panels:
- BMS
- Jansen
- Gilead
- Arbutus
- Galapagos
- Assembly Pharma
- Sanofi/Aventis

Speaking and Teaching:
- MSD
- Roche
- BMS
- Jansen
- Gilead
Licensed drugs

- Peg IFN
- Nucleos(t)ide analogues

Off-label use of licensed drugs

- PEG-IFN + NAs
- PEG-IFN “add-on” on NAs

New approaches

- early clinical development
- pre-clinical studies
- target discovery
Dysfunctional T-cell response
Insufficient B-cell response

1. cccDNA reservoir

2. Dysfunctional T-cell response
   - PD-1
   - CD8+ T cell

3. Insufficient B-cell response
   - B cell

HBV: concepts about « persistence »

High Replication
- Histones
- PCAF
- p300

Low Replication
- Histones
- HDAC1
- Elk2
- Sirt1

Bock, T. et al. 1994
Newbold, J. et al. 1995
Bock, T. et al. 2001
Pollicino, T. et al. 2006
Eradication
- Equates to driving the virus to extinction from the earth [e.g. small pox (vaccination)]

versus

Cure
- Equates to eliminating the virus from the infected host [e.g. HCV (treatment)]

HEPATITIS B can theoretically be eradicated (vaccine) AND “maybe cured”
**HBV: concepts about « cure »**

- **Sustained suppression of viral replication**
  undetectable viremia with sensitive HBV-DNA assays

- **Functional cure**
  “off therapy” persistent HBV suppression [*make all patients true "inactive carriers"]
  immune control / silencing of cccDNA
  HBsAg loss as preferred endpoint

- **Complete / sterilizing cure**
  elimination of cccDNA
  elimination of infected hepatocytes, including cells with integrated HBV DNA
  HBsAg loss and anti-HBs seroconversion: surrogate endpoint
Adapted from Liang et al, Hepatology 2015
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Adapted from Liang et al, Hepatology 2015
Towards HBV cure

- Complete inhibition of HBV replication and [including entry inhibitors and capsid inhibitor] - to avoid new hepatocytes infection and low level core particles recycling
  - Restoration of host innate/adaptive antiviral immunity against HBV
    - reduce HBs load [si/shRNA approaches; NAPs]
    - checkpoint inhibitors [anti-PD1/PDL1; others]
    - TCR engineering
    - TLRs agonists [TLR7 and others]
  - Direct targeting of cccDNA
    - inhibit cccDNA formation
    - target cccDNA with endonucleases
    - transcriptional silencing of cccDNA [FUNCTIONAL CURE]
    - cccDNA bound viral proteins: HBc and HBx
HBV cure landscape

Entry inhibitors
- Lipopeptides, e.g. Myrcludex-B
- Cyclosporin derivatives

Targeting cccDNA

RNA interference, Arrowhead, Tekmira, Alnylam, GSK

Polymerase inhibitors
- Nucleoside analogues, e.g. Gilead, BMS
- Non-nucleoside, e.g. LB80380

Entry inhibitors
- Lipopeptides, e.g. Myrcludex-B
- Cyclosporin derivatives

Immune modulation
- Toll-like receptors agonists, Gilead, Roche
- Anti-PD-1 mAb, BMS, Merck
- Vaccine therapy: Transgene, Gilead, Roche Innovio, Medimmune, ITS

Inhibitors of HBsAg release
- Replicor

Inhibition of nucleocapsid assembly
- Novira, AssemblyPHARMA, Gilead, Janssen
Core inhibitors drugs

- HBC binds the cccDNA and modifies cccDNA nucleosome spacing
- HBC binds to cellular promoters and regulates gene expression
- HBC binds to (and represses) the IFN-b, IL-29 and OAS1 cellular promoters


Core inhibitors are the first “viral specific” compounds capable to target the cccDNA

Several compounds are being developed (different spectrum of activities ??)

Core inhibitors potentially target both cytoplamic (capsid) and nucler HBC:
- block new cccDNA accumulation (Rc-DNA delivery and/or core particles recycling [1])
  • inhibit cccDNA transcription [2]
  • inhibit HBC recruitment on the cccDNA [3]
  • modulate HBC cellular target genes [4]

Core inhibitors drugs

Core inhibitors are the first “viral specific” compounds capable to target the cccDNA

Preclinical and Early Clinical Profile of NVR 3-778, a Potential First-In-Class HBV Core Inhibitor
Gane, AASLD 2014

[NVR3-778-101 Protocol, Clinicaltrials.org # NCT02112799]

Phase 1b clinical trial [4 dosing cohorts]
[100, 200, 400 mg QD and 600 mg BD]
Yuen, AASLD 2015

Core inhibitors are the first “viral specific” compounds capable to target the cccDNA

- block new cccDNA accumulation (Rc-DNA delivery and/or core particles recycling [1])


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HBc binds the cccDNA and modifies cccDNA nucleosome spacing
HBc binds to cellular promoters and regulates gene expression
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Core inhibitors are the first “viral specific” compounds capable to target the cccDNA

Several compounds are being developed (different spectrum of activities ??)

Core inhibitors potentially target both cytoplasmic (capsid) and nuclear HBc:

- block new cccDNA accumulation (Rc-DNA delivery and/or core particles recycling [1])
- inhibit cccDNA transcription [2]
- inhibit HBc recruitment on the cccDNA [3]
- modulate HBc cellular target genes [4]
What Might HBV Cure Will Look Like?

*let’s keep an open mind*

**Potent NA**
- to prevent viral spread and cccDNA re-amplification
  - [new anti-Pol; anti-RNaseH][anti-capsid]

**cccDNA inhibitor**
- inhibit cccDNA formation [CCC-0975, *entry inhibitors* ...]
- deplete cccDNA [LTb, *anti-capsid* ...]
- silence cccDNA pool [epigenetic drugs, IFNa ...][anti-HBx]

**Entry inhibitors**
- Entry inhibitors [Mircludex and others]

**Immune Activator**
- activate or restore antiviral immunity
  - [target HBs: siRNA, HBs secretion blockers]
  - [innate immunity stimulators, *anti caspsid*]
  - [anti-PD1/anti-PDL1]

*Modified from S. Locarnini 6.2014*
What Might HBV Cure Will Look Like?

*let’s keep an open mind*

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  - activate or restore antiviral immunity
  - [target HBs: siRNA, HBs secretion blockers]
  - [innate immunity stimulators, **anti caspsid**] [anti-PD1/anti-PDL1]

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Discover biomarkers (back to biopsy ??)

Define endpoints

Reshape the regulatory landscape

*Modified from S. Locarnini 6.2014*
TOWARDS HBV CURE:
RESTORING T CELL FUNCTION / DIFFERENTIATION

Naïve CD8 cell
Effector CD8 cell

Chronic HBV infection
Inefficient T cell function/differentiation

Acute Self-limited Infection
Efficient T cell function/differentiation

Rapid Proliferation / Differentiation

High viral / antigen load (HBsAg, HBeAg)

siRNAs
HBsAg

Reduction of HBsAg (and HBeAg) should translate in a revival of adaptive immune response and functional cure

Nucleic Acid Polymers (NAPs)

Dynamic polyconjugates

Tekmira
Arbutus
Arrowhead

TOWARDS HBV CURE: RESTORING T CELL FUNCTION / DIFFERENTIATION

Naïve CD8 cell

Effector CD8 cell

Chronic HBV infection

In efficient T cell function/differentiation

Acute Self-limited Infection

Efficient T cell function/differentiation

Ineff cient T cell function/differentiation

Nucleic Acid Polymers (NAPs)

NAPs Replicor: phase 2 at AASLD 2015

ARC-520: phase 2; efficacy vs toxicity signals

Tekmira/Oncor/Arbutus: clinical developmet from Q1 2015

siRNAs

HBsAg

Reduction of HBsAg (and HBeAg) should translate in a revival of adaptive immune response and functional cure
Blocking inhibitory receptors on T cells

RESTORATION OF THE T CELL FUNCTION BY COMBINED MANIPULATION OF PD-1/PD-L1 AND CD137/CD137L PATHWAYS

Fisicaro P et al. Gastroenterology 2012

PD-1 PATHWAY BLOCKADE
Proof of concept of α-PD-1 in Chronic HCV


Oral TLR7 Agonist

- **TLR7**
- **MyD88**
- **IRF7**
- **NF-κB**

IFN-α and other IFNs → Proinflammatory cytokines

2 double-blind phase 1b trials
[49 treatment-naïve; 51 virologically suppressed]

Persistent HBV viremia suppression and increased HBsAg in chimps (Menne et al., J Hepatol 2015) and woodchucks (Landorf et al., Gastroenterology 2013)

GS-9620

**Fig. 1. ISG15 (mRNA) fold change.** The figure shows the ISG15 mRNA mean fold change over time in the SAD and MAD cohorts in each patient population. *Induction at these time points driven by a single patient.
Oral TLR7 Agonist

GS-9620

Persistent HBV viremia suppression and increased HBsAg in chimps (Menne et al., J Hepatol 2015) and woodchucks (Landorf et al., Gastroenterology 2013)

Oral GS-9620 was safe, well tolerated; absence of significant systemic IFN-alpha levels or related symptoms

Fig. 1. ISG15 (mRNA) fold change. The figure shows the ISG15 mRNA mean fold change over time in the SAD and MAD cohorts in each patient population. *Induction at these time points driven by a single patient.
Engineering anti-HBV immunity

Case Report

A


CHBV HBeAg neg Liver cirrhosis

Good health

Treatment: IqG anti HBs Lam + Actel Tacrolimus

Radiation therapy

Surgery April 2001

Immuo-therapy July 2012

Liver transplant July 2001

Detection of lesions: lung, right HLA, 6-7 ribs

Pre-therapy characterization

B

Adopted (2014, June)

HBeAg’

CK18

HLA-A*EBV

HLA-A03/HBe’

183-91

Fig. 1. Clinical history and expression of HBV antigens in HCC metastatic. (A) Schematic representation of the clinical history of the treated patient. (B) Sections (40x) of
HBV cure landscape

Entry inhibitors
- Lipopeptides, e.g. Myrcludex-B
- Cyclosporin derivatives

Inhibitors of HBsAg release
Replicor

Targeting cccDNA

RNA interference,
Arrowhead, Tekmira, Alnylam, GSK

Polymerase inhibitors
- Nucleoside analogues, e.g. Gilead, BMS
- Non-nucleoside, e.g. LB80380

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Cell proliferation combined with antiviral treatment to block re-infection (Myrcludex B) promoted cccDNA clearance in the majority of the human hepatocytes.

Allweiss, Petersen, Dandri et al, EASL 2014, O101
Cell proliferation combined with antiviral treatment to block re-infection (Myrcludex B) promoted cccDNA clearance in the majority of the human hepatocytes.

Allweiss, Petersen, Dandri et al, EASL 2014, O101
Mycludex B: Targeting Entry of HBV into Hepatocytes

**HBV Phase 2a Results**

- 0.5mg, 1mg, 2mg, 5mg
- 30 evaluable patients
- 7 patients >1log HBV DNA
  - 23%
- 6 patients → 2

- 10mg
- 8 evaluable patients
- 7 patients >1log HBV DNA
  - 87%

**HDV Pilot Study**

- Myr 2mg
- 7 evaluable patients
- 6 patients >1log HDV RNA
  - 85%
- Myr 2mg + PEG int 180 µg
- 7 evaluable patients
  - 100%
Myrcludex B: Targeting Entry of HBV into Hepatocytes

HBV Phase 2a Results

- Well tolerated (increase bile acids)

Efficacy vs treatment schedule

HDV Pilot Study

- 0.5mg, 1mg, 2mg, 5mg
  - 30 evaluable patients
  - 23%
  - week 12
  - 7 patients >1log HBV DNA
  - 20.6%
  - week 24

- 10mg
  - 8 evaluable patients
  - 87%
  - week 10-11

- Myr 2mg
  - 7 evaluable patients
  - 85%
  - week 24
  - 6 patients >1log HDV RNA

- Myr 2mg + PEG int 180 µg
  - 7 evaluable patients
  - 100%
  - week 24
  - 7 patients: >1log HDV RNA
Epigenetic silencing
Pre-clinical proof of concept stage

Make active carriers „true” inactive and, eventually, over time „occult” carriers by „locking” the cccDNA
Palumbo EASL 2014

Hepatocyte turn-over

Böttler et al, J Hepatol 2014
- Interferon-α and lymphotoxin-β-receptor activation up-regulated APOBEC3A and 3B cytidine-deaminases, respectively, in HBV-infected cells, primary hepatocytes and human liver-needle biopsies.
- HBV-core protein mediates the interaction with nuclear cccDNA resulting in cytidine-deamination, apurinic/apyrimidinic site formation and finally cccDNA degradation.