The path towards the cure of HBV infection

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Chronic Hepatitis B (CHB) - a global health problem
from viral suppression to cure

- 240 million CHB worldwide
- 1.7 million CHB treated worldwide
- Hepatocellular Carcinoma (HCC) : 2nd cause of cancer death worldwide

Elimination of HBV infection and HBV-related diseases

HBV susceptible

\[ \begin{align*}
\text{Vaccine} \\
\text{Universal precautions}
\end{align*} \]

\[ \begin{align*}
\text{Antiviral treatment}
\end{align*} \]

\[ \begin{align*}
\text{Acute HBV} \\
\text{Chronic HBV} \\
\text{Cirrhosis/HCC}
\end{align*} \]
Current treatments: virus suppression and sustained disease control

From viral suppression to cure

**UNTREATED**

Liver Blood
- ccc-DNA
- Rc-DNA
- HBV-DNA
- HBsAg

Liver Blood
- ccc-DNA
- Integrated HBV DNA
- HBsAg

Liver Blood
- ccc-DNA
- Integrated HBV DNA

Liver Blood
- ccc-DNA
- Integrated HBV DNA

**NUCs**

Normal Cirrhosis Hepatocellular carcinoma

Risk of HCC reduced (after 5 yrs) but not eliminated

**NMEs**

“Cure”

Direct Antiviral Agents

Immunomodulatory strategies

Normal Cirrhosis Hepatocellular carcinoma

Normal Cirrhosis Hepatocellular carcinoma
Definition of HBV cure: what do we want to achieve?

- **Therapy**
  - HBV DNA change from baseline (log₁₀ c/mL)
    - 0.0
    - 1.0
    - 2.0
    - 3.0
    - 4.0

- **Time**
  - HBsAg
  - Partial Cure
  - Functional Cure
  - +/- Anti-HBsAb

- **Serum**
  - Virus Suppression
  - HBV DNA

- **Liver**
  - cccDNA

**Complete Cure**
Lok et al, Hepatology / J Hepatol joint publication, in press; Testoni et al, Sem Liver Dis, in press.
Mechanisms of viral persistence

Mechanisms of HBV persistence

- cccDNA reservoir
- Antigenic load
- Liver tolerance

Defective immune responses

- Defective CD8+ response
- Defective B cell response
- Inefficient innate response

Vaccine therapy
Check-point inhibitors
Blockade of immune-suppressive cytokines
Chimeric antigen Receptors (CAR)
Antiviral cytokines
Entry inhibitors
Egress Inhibitors
Targeting HBx
Targeting cccDNA
RNA interference
Core modulators
Polymerase inhibitors
Core modulators
Testoni and Zoulim, Hepatology 2015
Persistence of intrahepatic viral DNA synthesis and cccDNA during Tenofovir therapy (HIV-HBV cohort)

New round of infection and/or replenishment of the cccDNA pool occur despite « viral suppression »

Boyd et al, J Hepatol 2016
Targeting cccDNA, the viral minichromosome

- cccDNA replenishment
- cccDNA formation
- cccDNA degradation
- cccDNA silencing

Lucifora et al, Science 2014
Belloni et al, JCI 2012
Koeniger et al, PNAS 2014
Durantel&Zoulim, J Hepatol 2016
Targeting the HBV capsid with capsid assembly modulators

Phase 1b clinical trial: CpAM NVR 3-778 reduces serum HBV DNA and RNA

Pre-clinical evaluation in hepatocyte culture and chimeric mouse models

Serum HBV DNA: mean 1.7 log reduction (600 mg BID)

Serum HBV RNA: mean 0.86 log reduction (600 mg BID)

Cohort I: 600 mg BID
Decrease of circulating HBV RNA contained in viral particles

Yuen M-F, et al. AASLD 2015, San Francisco. #LB-10

Combination trials with NUCs and/or PegIFN
HBsAg targeting strategies

- HBsAg clearance an **endpoint of therapy**
- Decline in HBsAg levels may **restore the antiviral activity of exhausted T cells**

**Several strategies** in evaluation

- RNA interference (SiRNA): « gene silencing »
- Nucleic acid polymers (NAPs): HBsAg release
- HBs antibodies
SiRNA ARC-520 produces deep and durable knockdown of viral antigens and DNA in a phase II study

Yuen M-F, et al. AASLD 2015, San Francisco. #LB-9

Impact of integrated sequences on siRNA efficacy

Will this result in restoration of immune responses?
Restoration of antiviral immunity

A Phase 1 study evaluating anti-PD-1 treatment with or without GS-4774 in HBeAg negative chronic hepatitis B patients
The main targets & drug discovery efforts

- Entry inhibitors
- Targeting cccDNA
- RNA interference
- NUCs (“Polymerase inhibitors”)
- CpAMs (“Capsid inhibitors”)
- Inhibitors of HBsAg release
- Immune modulation
  - Toll-like receptors agonists
  - Anti-PD-1 mAb
  - Vaccine therapy
  - Redirection of T cells

HBV cure - New treatment concepts – Will we need combination of DAA and immune therapy?

Testoni et al, Liver International 2017
HBV cure: An attainable goal within the next decade!

- Collaboration between Academia, Industry and Stakeholders
- International HBV cure programs
The International Coalition for the Eradication of HBV
ICE-HBV

• Created in September 2016 by ANRS, Doherty Institute, and The International HBV Conference.

• Aim#1: to support the discovery of a safe, affordable, scalable and effective cure, available to all persons living with CHB.

• Aim#2: to create an international, independent, research-based and patient-centered forum in order to coordinate, promote and foster collaborative partnerships working towards a cure for HBV.

www.ICE-HBV.org
Governing Board
Chairs: P Revill & F Zoulim

Stakeholders Consulting Group
Chairs: U Protzer, T Block, V Miller

Scientific Working Group

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M Dandri & H Guo

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Clinical Sciences
H Janssen, P Lampertico, SG Lim

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J Hu & F Lu

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What are we doing?

• Define research priorities to achieve a cure of HBV infection and produce a position paper on a research roadmap, similar to papers published in the HIV field (Deeks et al. Nat. Med. 2016)

• Foster international collaborations on specific projects:
  • cccDNA assay standardization with ANRS and DZIF
  • HBV cure mathematical modelling with Stanford

• Promote HBV cure initiatives to increase awareness and funding for HBV research worldwide.
  • Contacts with NIAID, NCI, EU, etc.
  • World Hepatitis Summit, Sao Paulo

www.ICE-HBV.org
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