HBV Cure Research 101
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HBV Cure – Why do we need it?

• Current drugs have big limitations
  – Rarely cure patients and don’t stop disease in everyone
  – Nucleos(t)ide analogs need to be taken for life

• We really have only 2 flavors of drugs for HBV
  – All nucleos(t)ide analogs work the same way on the same viral target
  – All interferon α derivatives stimulate the same set of cellular immune responses
Current Treatments

Reduce HBV DNA
Infection and HBsAg are still present

Liver

Hep B virus (HBV DNA)
ccccDNA
Hep B surface antigen (HBsAg)

PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH
A key obstacle to curing HBV

- The central molecule in HBV replication is the viral “cccDNA”
  - It is the master copy of the viral genome in cells
- cccDNA appears to be long-lived in liver cells
- Considered as a viral minichromosome and an archive of the virus responsible viral persistence

ICE-HBV

International Coalition to Eliminate HBV

Promoting Global Collaboration in HBV Cure Research
So how do we get rid of the cccDNA?

• Nobody knows!

• But…..
  – Clearance of an acute infection gets rid of the vast majority of the cccDNA safely, so the immune system can do it!
  – The cccDNA is not always completely eliminated during resolution of an acute infection
  – The immune system can keep any residual cccDNA under control in almost all patients who resolved the infection
What is “HBV Cure”?

• The current goal is a Functional Cure
  – A complete cure eliminates cccDNA, a functional cure does not

• The clinical definition of a functional cure is undetectable HBV DNA and HBsAg in serum 6 months post-treatment
  – No disease progression
  – Decreased cccDNA in cells to very low levels (similar to resolution of acute infection)
  – Immune control of any residual cccDNA in the body
What will cure therapies look like?

• **Combination therapy will be needed** because:
  – HBV’s many genotypes and variable disease course mean no one drug will cure everyone
  – cccDNA’s durability means we will have to hit it from multiple angles at the same time

• Cure therapy is likely to be long (a year?) and need exceptionally **safe drugs**
What types of HBV drug discovery are ongoing?

- Cure discovery research falls into 3 categories
  - Direct-acting drugs that target HBV itself
  - Host-targeted drugs that cause a patient’s cells to block HBV replication
  - Immune-stimulating drugs that train the patient’s immune system to attack HBV and control infected cells

- The work is being done in universities, biotech companies, and big pharma

Reference site: www.hepb.org/treatment-and-management/drug-watch/
A translational approach for innovation in HBV & HDV therapies

Viral persistence

Experimental studies

Molecular pathogenesis

Biomarkers

Clinical studies

Target identification & MoA

Improved cure rate

Prevention of HCC

F Zoulim, ICAR 2020, Seattle Webinar
How can we cure the infection?

1) Remove the underlying virus multiplication
2) Suppress the virus protein production
3) Activate the immune response

Hep B virus (HBV DNA)
cccDNA
Hep B surface antigen (HBsAg)
New concepts of Combination Therapy to Cure HBV
Consideration for clinical trial design

- Replication inhibition
  - hNTCP
    - Entry inhibitors: bulevirtide
  - HBV polymerase
  - NUC: ETV, TDF, TAF, novel NUCs and RNaseH inhibitors
  - Nucleocapsids
    - CAM: ABI-H0731, JNJ-56136379, RO7049389

- Antigen reduction
  - Transcription
    - FXR agonist: EYP001
    - Viral RNAs
      - siRNA: JNJ-3989 VIR-2218
      - ASO: GSK3228836
      - LNA: RO7062931
    - HBsAg release
      - NAPs: REP 2139 or REP 2165
      - STOPS
      - RNA destabilizers
      - FXR agonists

- Immune stimulation
  - Invigorate immune responses
    - Innate immunity
      - TLR7: GS9620, RO6864018, RO7020531, JNJ6479464
      - TLR8: GS9688
    - Immune check points
      - Anti-PD1: nivolumab
      - Anti-PDL1
      - PDL1 LNA
      - Oral PDL1 sm
  - Stimulate HBV specific B/T cells
    - Therapeutic Vaccines
      - GS4774
      - TG1050
      - T101
      - SCI-B-VAC

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New Clinical Trial Design
Combination of direct acting antivirals and immune stimulation

- Therapy
- Replication inhibition
- Antigen reduction
- Immune stimulation

Serum
LIVER

HBV DNA change from baseline (log_{10} c/mL)
-0.0
-1.0
-2.0
-3.0
-4.0
0.0
+1.0

HBV DNA
HBsAg
Anti-HBsAb
cccDNA

Adapted from Testoni et al. Semin Liver Dis. 2017, Roca et al, Liver International 2021
Take-home messages

• The goal is a **Functional Cure**
• Combinations of drugs that work different ways are needed
• Understanding of how HBV persists has been improved
• Many promising drug candidates are being developed
• Functional cure rates up to ~30-40% have been seen in a Phase 2 study

• There is HOPE!
HBV cure: An attainable goal within the next decade!