ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

HBV Cure Science 101
John Tavis, Ph.D.
Professor, Saint Louis University School of Medicine
Co-Director, SLU Institute for Drug and Biotherapeutic Innovation
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
Big problem #1 to curing HBV infections

• HBV replicates in the liver
  – The liver is “immunosuppressive”, handicapping the ability of the body’s immune system to kill HBV
  – HBV “exhausts” immune responses, promoting chronic infection

• Training the immune system to clear HBV with vaccines or cytokine drugs will be very hard
Big problem #2 to curing HBV infections

• The central molecule in HBV replication is the viral “cccDNA”
  – The cccDNA is the template for all of the viral RNAs
  – It is the master copy of the viral genome in cells
• cccDNA is long-lived in liver cells
• cccDNA is not replicated in cells
  – Cellular DNA maintenance molecules largely ignore it
Public Enemy #1

- Eliminating a long-lived, metabolically inert DNA molecule is really hard!
- Even a single copy of functional cccDNA in one cell could restart HBV replication if immunity has not been restored
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
Why all the excitement about HBV cure?

• The successes in developing drugs that cure HCV infections have motivated the pharmaceutical industry to attack HBV

• Advances in basic HBV science have made drug discovery more feasible
  – Discovery of NTCP as the protein that lets HBV get into cells has greatly expanded the types of studies that can be done
  – Advances in pre-clinical animal models are improving sophistication of drug development studies
So what is “HBV Cure”? 

• The goal is a **Functional Cure**

• Achieving a stable state after therapy with:
  – No detectable cccDNA in cells or HBV DNA in the blood
  – **No disease progression**
  – Immune control of any residual cccDNA in the body

• The clinical definition of a functional cure is still being debated
HBV drug discovery: The Wild West

- This is a crowded, dynamic, and competitive field
- *We are throwing everything we can at the virus!*
HBV cure research targets

Reference site: www.hepb.org/treatment-and-management/drug-watch/
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
  – Immune-stimulating drugs that train the patient’s immune system to attack HBV

• The work is being done in universities, biotech companies, and big pharma
Example direct-acting drug

Capsid inhibitors stop HBV from making the protein shell holding the viral DNA

Promising in pre-clinical and phase II clinical studies
Example host-targeting drug

- Entry inhibitors stop HBV from getting into liver cells
- The drug furthest along is Myrcludex B
- Myrcludex B is likely to be approved in Europe for HBV and HDV in 2019
Example immune-stimulating drug

- TLR8 detects viruses inside people’s cells and turns on the cells’ defenses such as NFkB and IRF5/7 that block HBV
- The leading compound working through TLR8, GS9688, is entering phase II trials
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
My view of a cure therapy

• **Step 1:**
  – Multi-drug treatment with direct-acting and host-targeting drugs to push HBV far below the limit of detection

• **Step 2:**
  – Add immune modulators (cytokines? therapeutic vaccination? adjuvants?) to induce immune-mediated cccDNA elimination/control

• **Step 3 (needed?):**
  – Therapeutic vaccination to produce long-term immune control of HBV