ICE-HBV

International Coalition to Eliminate HBV

PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

HBV Cure Science 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

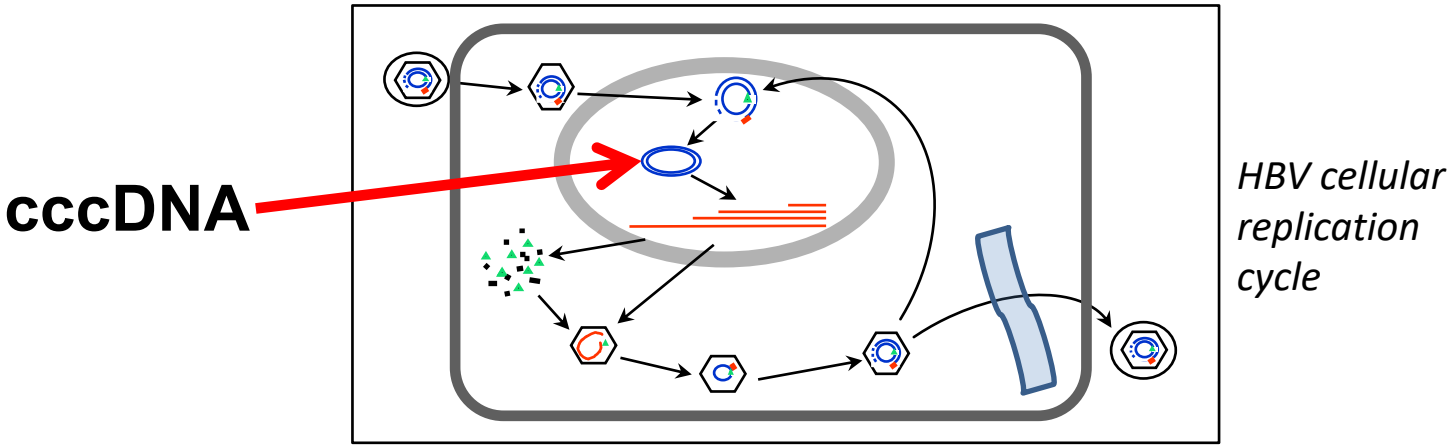
Big problem #1 to curing HBV infections

- 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

Sincere apologies to Clint Eastwood

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

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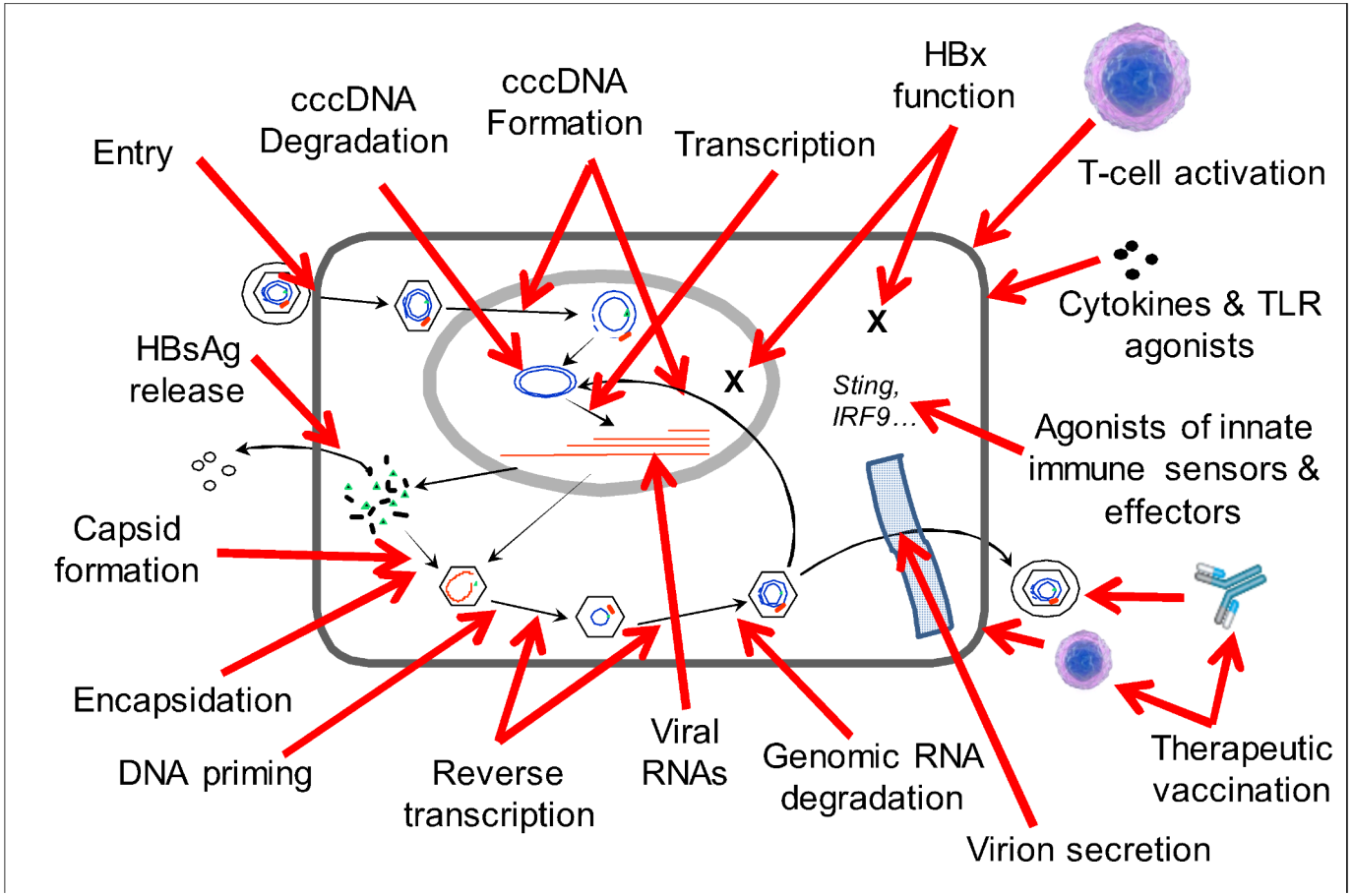
HBV cure research targets



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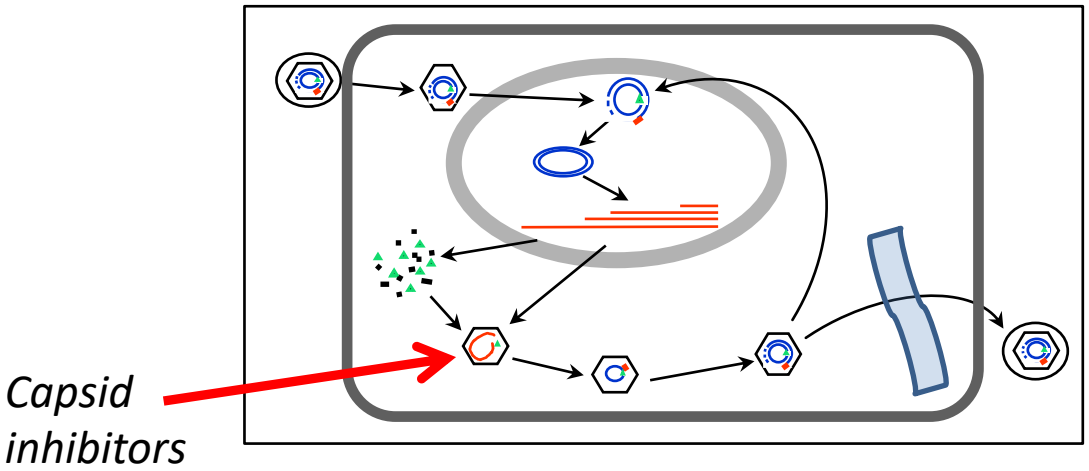
Reference site: www.hepb.org/treatment-and-management/drug-watch/

What types of HBV drug discovery are ongoing?

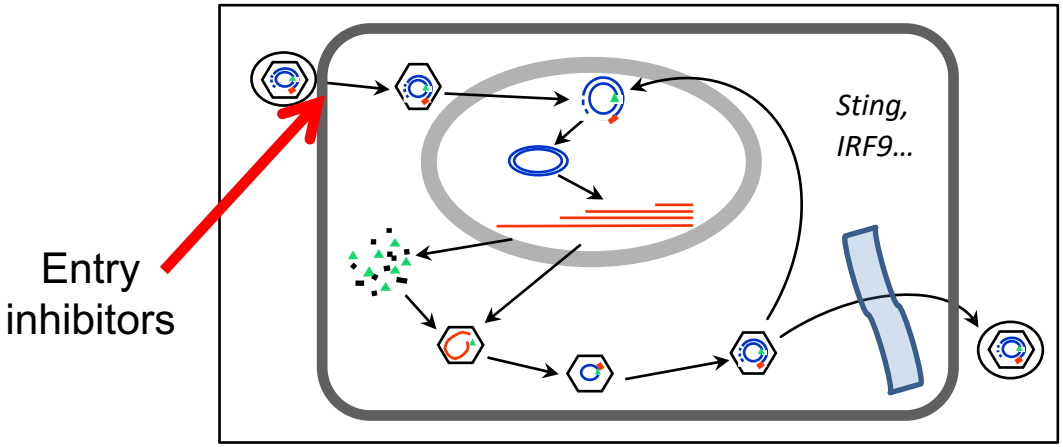
- Cure discovery research falls into 3 categories
  - Direct-acting drugs that target HBV itself
  - Host-targeted drugs that cause a patient's cells to block HBV
  - Immune-stimulating drugs that train the patient's immune system to attack HBV
- The work is being done in universities, biotech companies, and big pharma

Example direct-acting drug



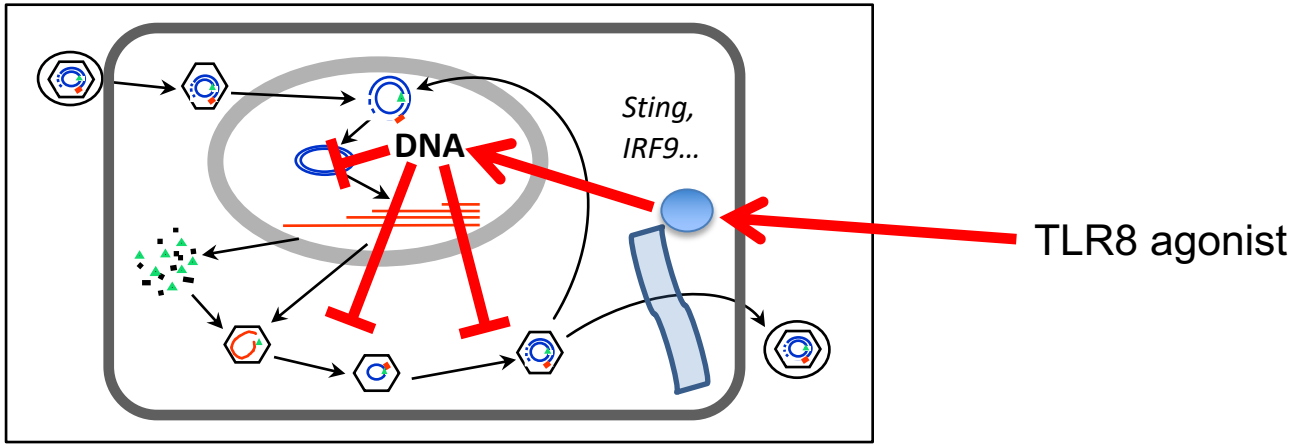
- Capsid inhibitors stop HBV from making the protein shell holding the viral DNA
- Promising in pre-clinical and phase II clinical studies

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 NFκB 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