PhD, Hon DSc

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COI: Founder, Chairman & major shareholder of CoCrystal Pharma Inc.

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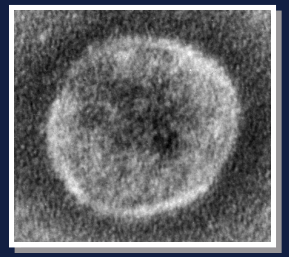

NEW HBV THERAPIES

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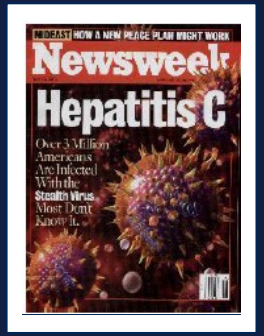
NEXT

11th PHC
Paris, Jan 16, 2018

Global threat of infectious diseases

HIV



Hepatitis

Zika Virus

Ebola

???

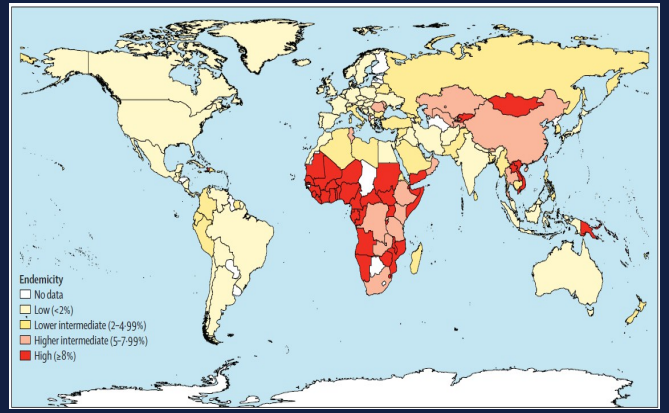
- Viruses are one of the leading causes of morbidity and mortality worldwide
- Emerging and reemerging virus strains constantly pose global health risks, including pandemics
- HBV is still one of the most infectious and prevalent virus globally

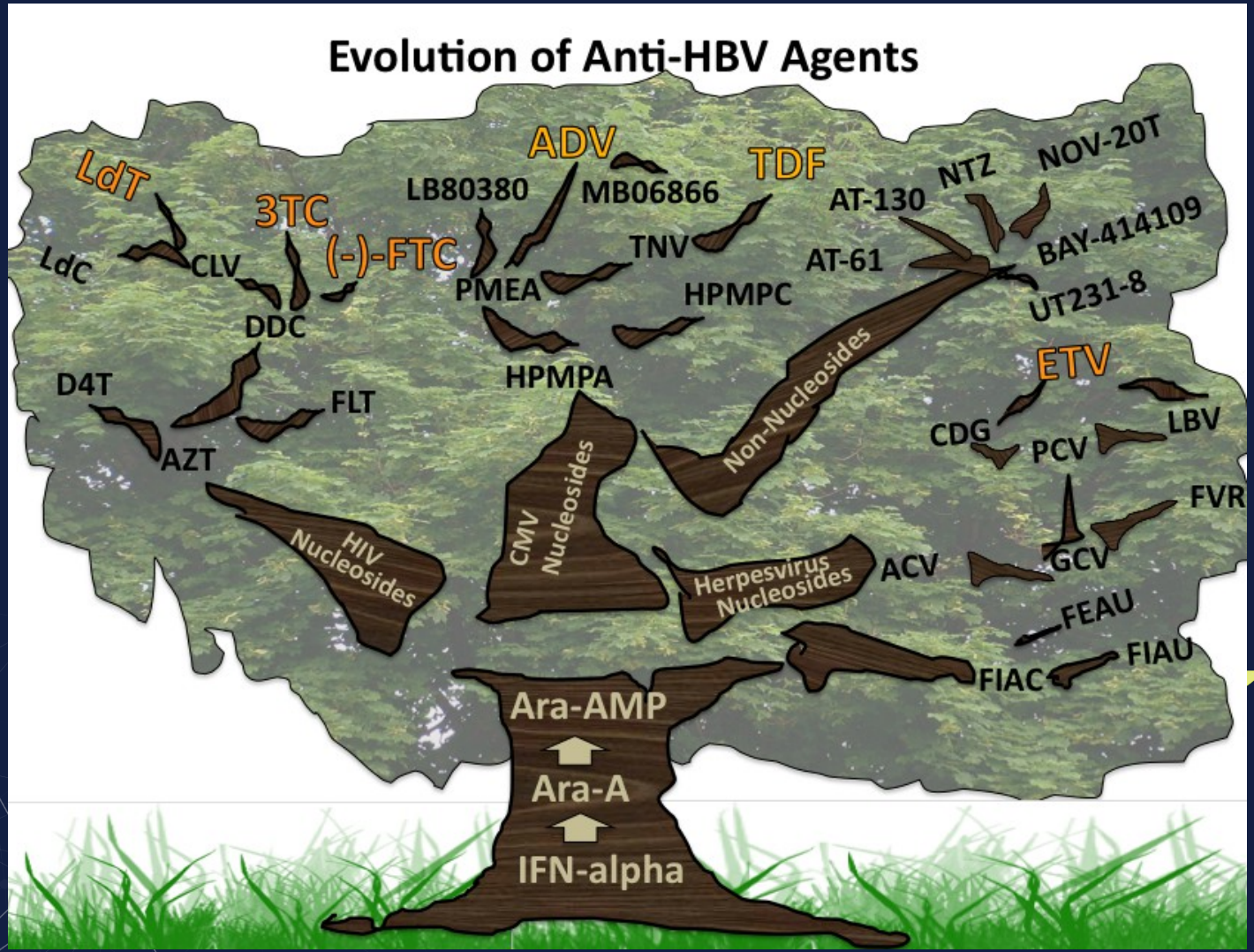
Hepatitis B Virus (HBV) Epidemic

- HBV Vaccine available since 1981
- Therapeutic nucleoside analogs are current treatment options – given for life
  - PEG-INFα, tenofovir disoproxil fumarate (TDF), entecavir (ETV), and tenofovir alafenamide (TAF)
  - Lamivudine, telbivudine, and adefovir dipivoxil

~686,000 deaths worldwide per year due to chronic HBV

- 400 million estimated to be chronically infected worldwide
  - *2/3rd of cases in poor and developing countries*
- Even on existing therapy, infected individuals can develop:
  - *Chronic liver disease*
  - *Liver cirrhosis*
  - *Hepatocellular carcinoma (HCC)*




Evolution of Anti-HBV Agents
LdT
3TC
ADV
TDF
LB80380
MB06866
AT-130
NTZ
NOV-20T
BAY-414109
UT231-8
AT-61
TNV
(-)-FTC
LdC
CLV
PMEA
HPMPC
DDC
HPMPA
Non-Nucleosides
ETV
D4T
FLT
CDG
LBV
PCV
AZT
CMV Nucleosides
FVR
HIV Nucleosides
Herpesvirus Nucleosides
ACV
GCV
FEAU
FIAU
FIAC
Ara-AMP
Ara-A
IFN-alpha

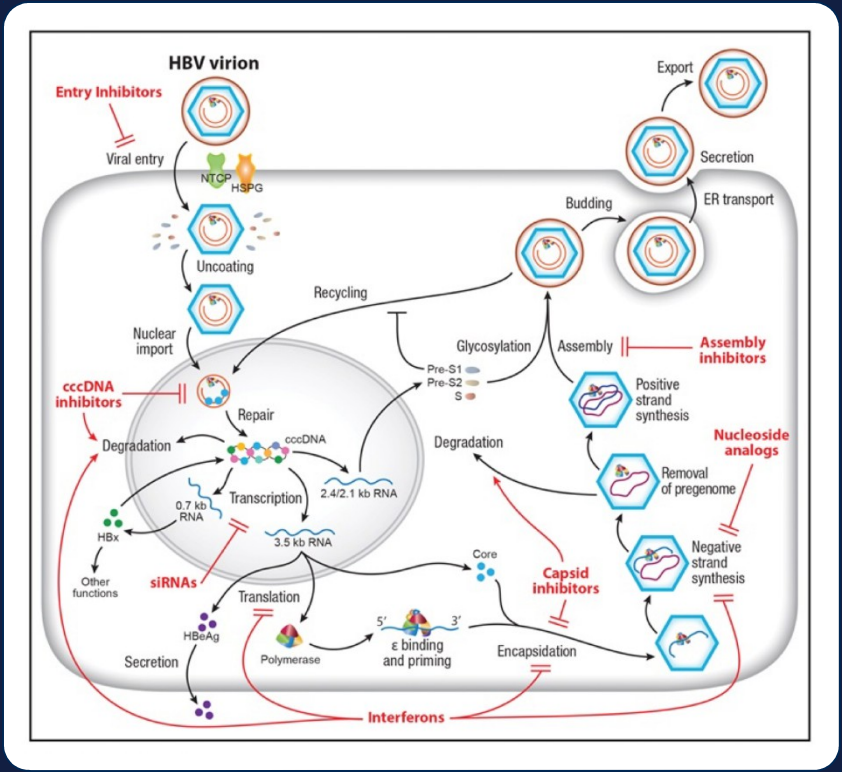
Is HBV eradication possible?

Impossible n'est pas Français

Everything is theoretically impossible until done

Robert Anson Heinlein,
American Science Fiction writer

Multiple Challenges and Targets For Anti-HBV Therapies



Barriers to Eradicating HBV

- ccc DNA
  - Long t1/2
  - Not affected by nucs
  - Partially impacted by IFN
  - Replenished from cytoplasmic core
- Integrated HBV DNA
- Impaired immune response
- Existing therapies act only on a few steps in HBV replication cycle

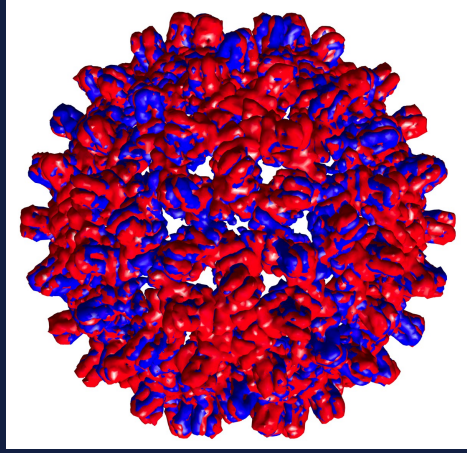
Adapted from: Liang TJ, Hepatology 62: 1893, 2015

Preclinical and clinical approaches

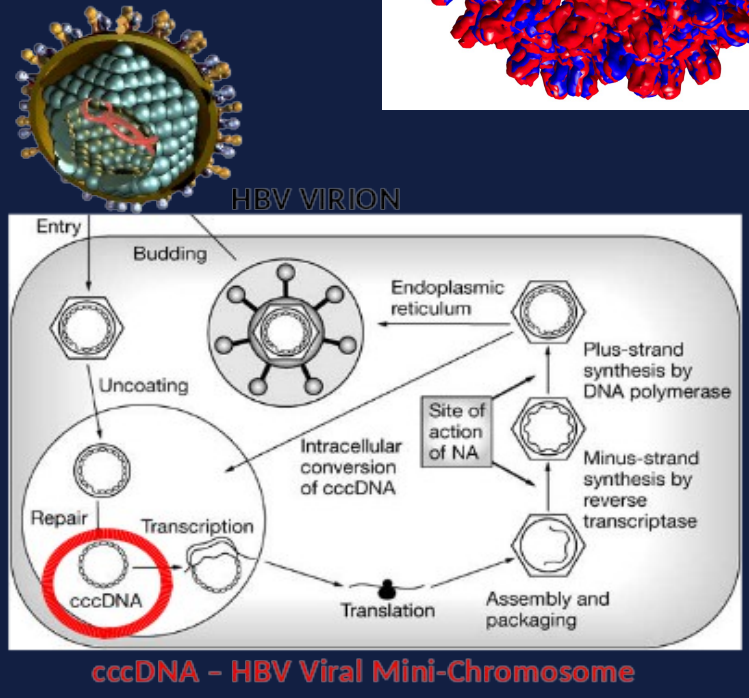
- Various approaches are being developed including the development of capsid effectors, CRISPR/Cas9, TALENS, siRNA, entry inhibitors (NCTP receptor), HBsAg secretion inhibitors, inhibitors of cccDNA formation, silencing cccDNA, inhibitors of viral mRNA, as well as immunological approaches, including therapeutic vaccines & TLR agonists.

- RF Schinazi et al. Towards HBV curative therapies, Liver Intl. in press 2018
- Boucle S, et al. Toward elimination of hepatitis B virus using novel drugs, approaches, and combined modalities.
- Clin Liver Dis. 20:737 - 749, 2016.
- Lok AS, Zoulim F, Dusheiko G, et al. Hepatitis B cure: from discovery to regulatory approval. J Hepatol. 67:847 - 861, 2017.

Central role of HBV Capsid Protein in Viral Replication Cycle



- **HBV capsid is essential for viral replication**
  - Viral entry and nuclear trafficking
  - Uncoating and release of rcDNA
  - Packaging and assembly of pgRNA
  - Scaffold for viral genomic processing
  - Budding and release of viral particles
  - Establishing and maintaining cccDNA
- **HBV capsid assembly effectors inhibit replication**
  - Capsid is conserved across HBV serotypes
  - Effective against nucleoside-resistant strains
  - Potential synergy with existing therapies
  - ***Suppress cccDNA levels***



- Cole AG, *Curr Opinion Pharm* (2016) 30:131-127.
- Fung SK and Lok ASF, *Nat Clin Pract Gastroenterol Hepatol* (2004) 1:90-97.

Discovery of a new class of non-nucleoside inhibitors

HepAD38 system

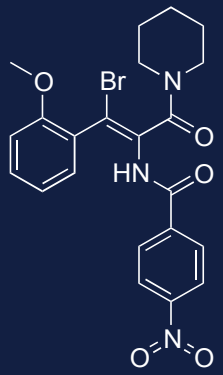
Ladner SK et al., Antimicrob. Agents Chemother 41 (1997) 1715.

Capsid Assembly Effectors

Class 1
HAP analogs

GLS4

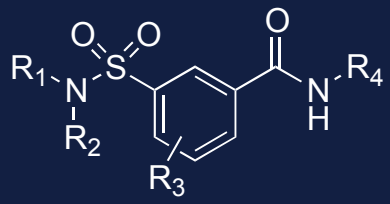
Class 2
Phenylpropenamides



AT-130

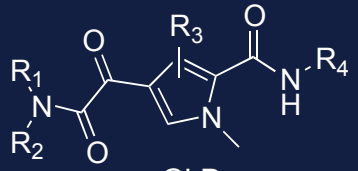
HAP, Heteroaryldihydropyrimidines

Sulfamoylbenzamides



NVR 3-778

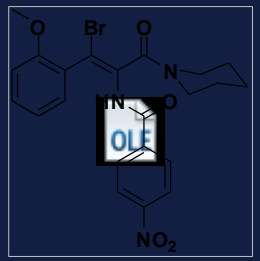
New class of non nucleoside inhibitors glyoxamide-pyrrolamides (GLP)



GLP

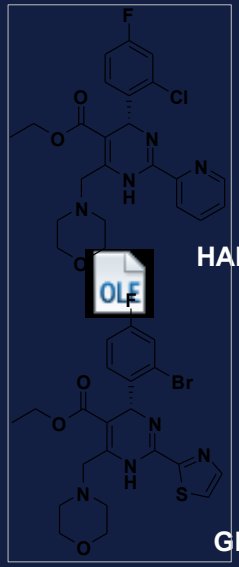
Capsid Effectors Deplete cccDNA

Phenylpropenamides



Sulfamoyl Carboxamides

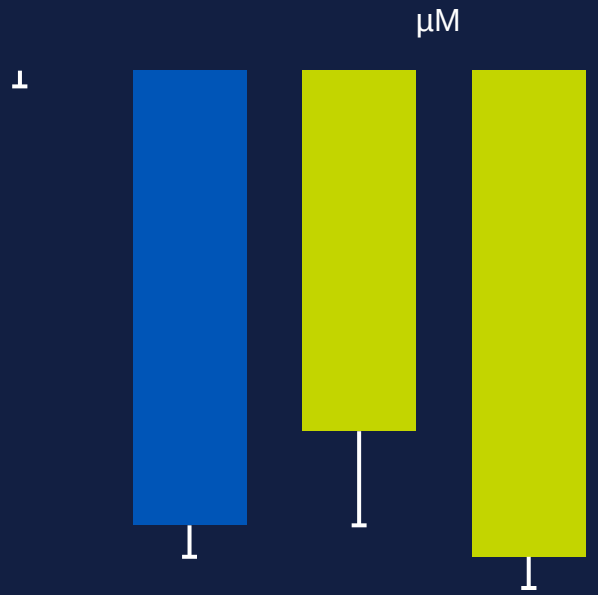
HeteroArylPyrimidines (HAP)



HAP12

GLS4

HBV cccDNA Levels in HEP-AD38 System Determined by RT-PCR



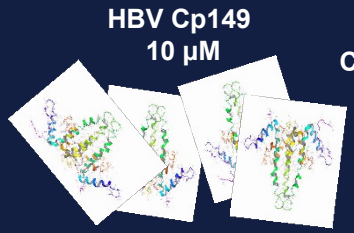
GLP-26 has pico-molar potency against HBV with no relevant cytotoxicity in several cell lines

	Potency		Cytotoxicity HepG2
Drugs	Anti-HBV Activity		Therapeutic index
	EC50, μM	EC90, μM	IC50/EC50
GLP-26	0.003	0.03	> 10,000
GLS4	0.08	0.28	≥ 1,000
HAP12	0.18	1.74	> 10,000
3TC	0.14	0.30	> 10,000

Therapeutic index (TI) of GLP-26: > 5,000 in PBM, CEM or Vero cells. *Not toxic (> 25 μM) for mitochondrial or nuclear DNA

Monitoring HBV Capsid Assembly using Electron Microscopy

Capsid Formation Assay

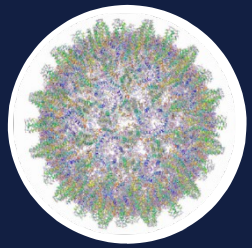


HBV Cp149
10 µM

Incubate with 25 µM
Compound for 1 h, 4°C

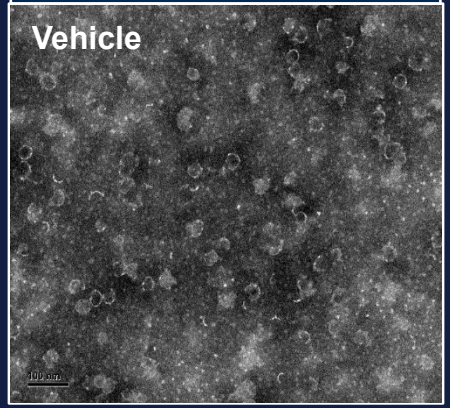
Induce Assembly

+ 500 mM NaCl, 4°C
overnight



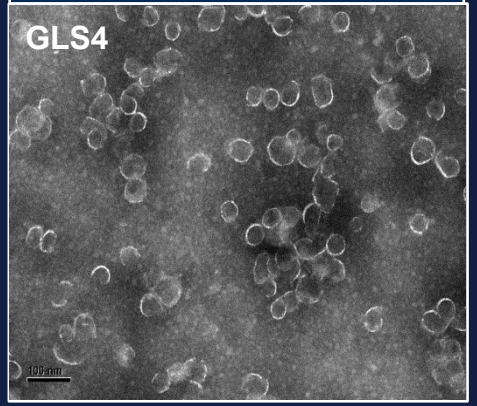
HBV Cp149
Capsid

Vehicle
- Fully-formed hollow spheres
- Diameter ~30-40 nm



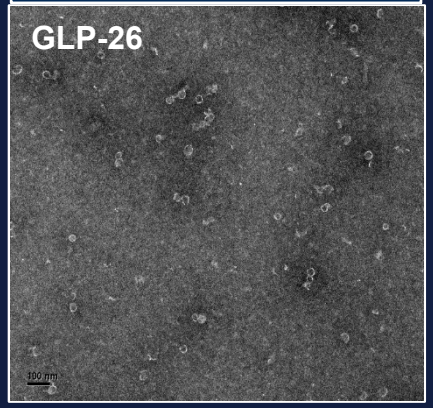
100 nm

GLS4 - Misassemble
- Misassembled hollow spheres
- Diameter ~80-100 nm



100 nm

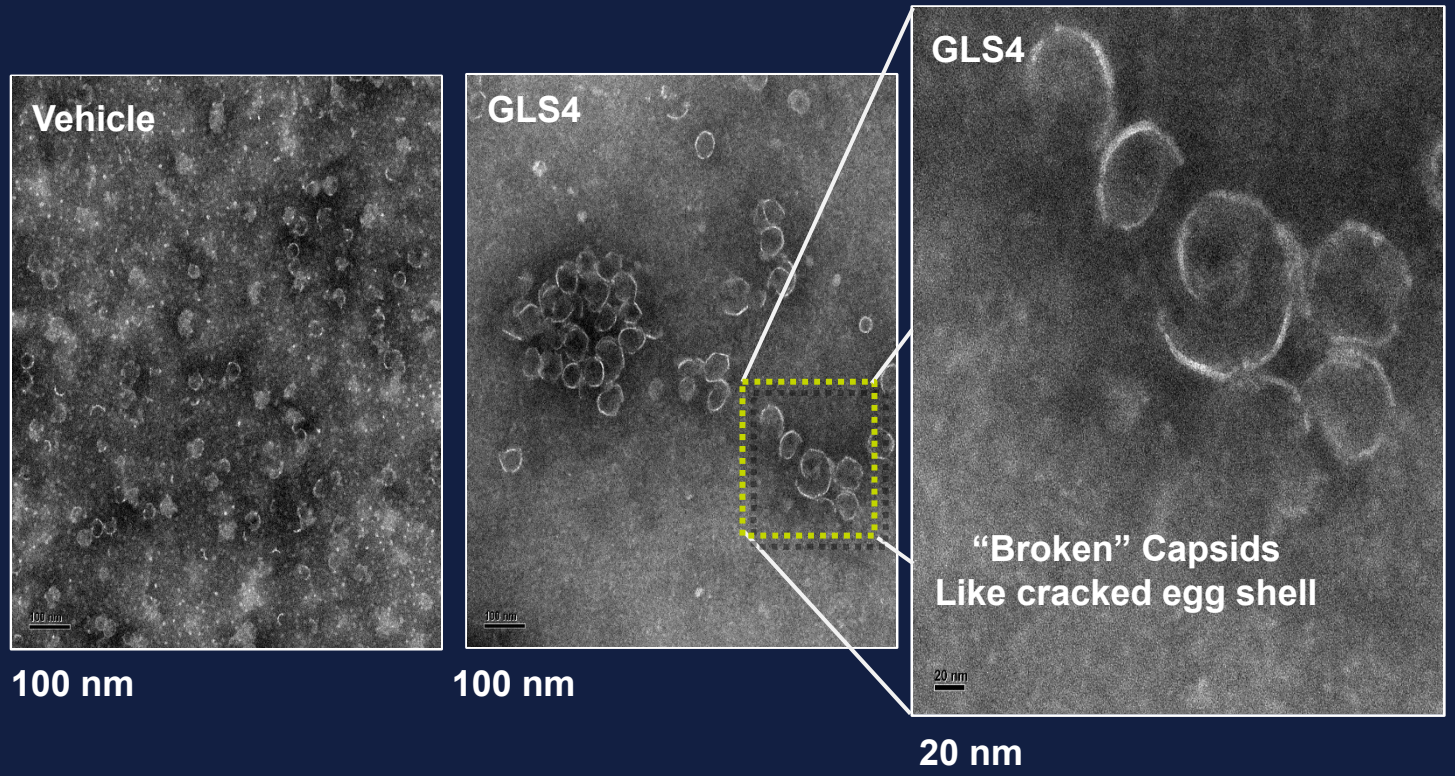
GLP-26 – Inhibition?
- Incomplete hollow spheres
- Low abundance
- Diameter < 20 nm



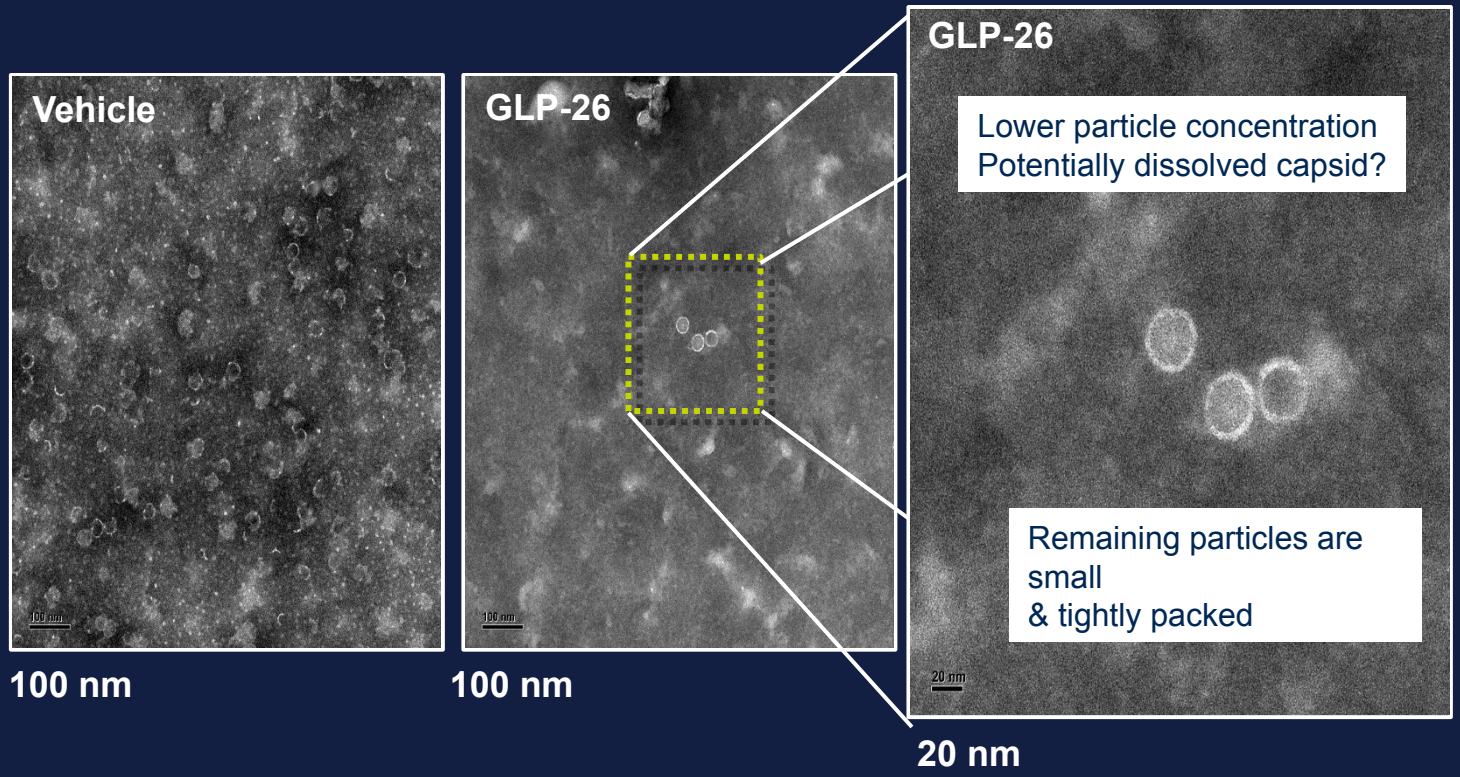
100 nm

Capsid Disruption Results – GLS4

A picture is worth 1,000 words



HBV Capsid Disruption Results – GLP-26

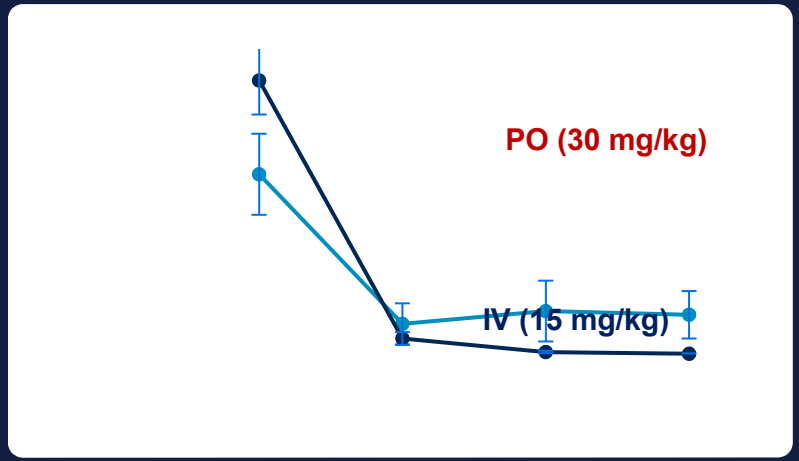


Favorable Pharmacokinetic Properties of GLP-26

GLP-26 Stability in Plasma T1/2 (hr) at 10μM			
Mouse	**Rat**	**Dog**	**Human**
24.5	8.5	>>24	>>24

GLP-26 Stability in Liver Microsomes T1/2 (hr) at 10μM		
Mouse	**Human**	**Fold Change**
1.2	7.6	6.4x

Pharmacokinetics in Mice



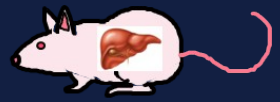
Route	AUC(0-7 hr) (hr.ng/ml)	T1/2 (hr)
PO (30 mg/kg)	1,306.5	> 6
IV (15 mg/kg)	1,587.8	1.5

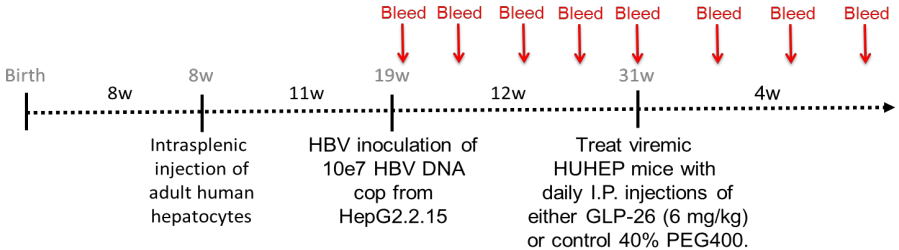
GLP-26 Inhibits HBV in Mouse Models

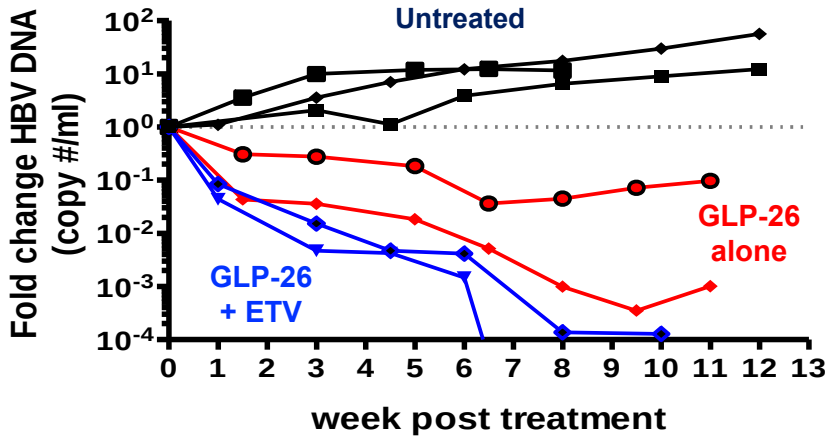
Chimeric Human Liver Mouse Model of HBV Infection

Intrasplenic Injection of Human Hepatocytes

HBV Inoculation From HepG2.2.15

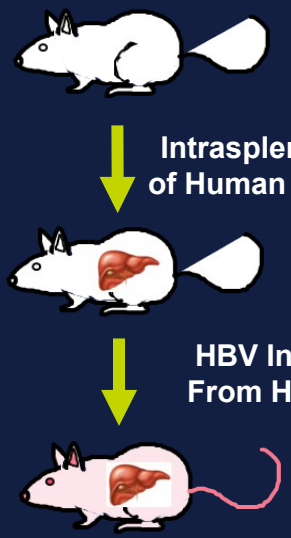


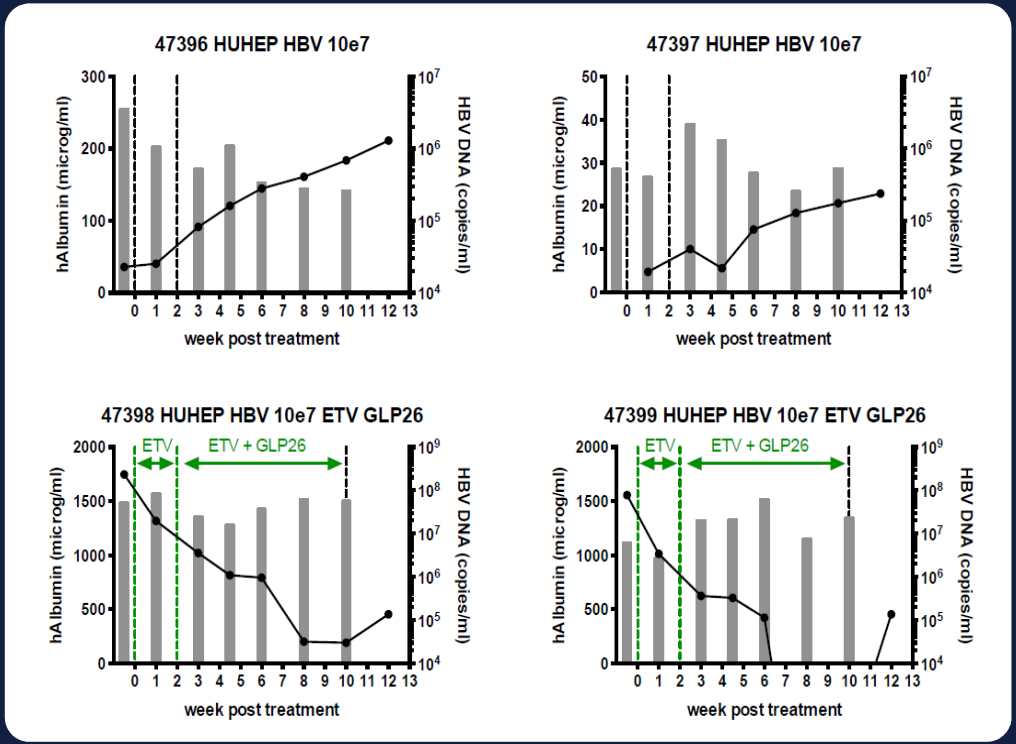




Low Viral Rebound after GLP-26/ETV Treatment

Chimeric Human Liver Mouse Model of HBV Infection





Conclusions
HBV inhibitor GLP-26

- **Hepatitis B Virus is a persistent global problem**
  - Chronic infection due to viral mini-chromosome (cccDNA)
- **HBV capsid is an attractive, drugable target**
  - Prevents formation and reduces levels of cccDNA
- **Discovered potent and novel HBV capsid effector that possesses attractive pre-clinical profile**

- ✓ **Inhibits HBV DNA replication and HBeAg secretion/cccDNA amplification at nM levels, with no apparent cytotoxicity**
- ✓ **Interferes with capsid formation by promoting formation of smaller capsid particles:**
  - **Incubation leads to capsid misassembly & disruption of pre-formed capsid particles**
  - **Long stability (> 24 h) in dog and human plasma**
  - **Good human liver microsomal stability**
  - **Synergistic antiviral activity in culture with ETV**
  - **Excellent oral bioavailability in mice**
  - **Activity demonstrated in chimeric humanized liver mice (up to 3.5 logs decline)**
  - **Most potent and selective HBV inhibitor of this class**

Unknowns and Priorities in Eliminating Latent HBV

- **Specificity**: how to **only** kill cells that contain latent HBV and eliminate cccDNA. Target new formation of cccDNA, silencing, degradation, and/or dilution.
- **Delivery**: how to deliver the “deadly punch”, or drug(s) to initiate cell apoptosis. Role of siRNA? Mircludex-B? TLR7 agonist? HAP? Crisper/Cas9?
- Better ***in vitro*** and **animal models** to evaluate new strategies, alone and in combination. Ideal models to tackle cccDNA and integrated DNA?
- **Drug development** to increase specificity for latently infected cells and/or enhanced tissue delivery. Nanoparticles?
- Improve understanding of relationship between **capsid effectors** and **cccDNA** decline.
- Better understanding of the **immune system** in controlling latency and activation. Role of **IFN**?
- How do we best measure latent and active viral **replication *in vivo*** in **different compartment**? What other cells have the HBV receptor (NTCP) other than liver cells? How do we identify **extra-hepatic HBV** reservoirs? Why liver **tropism**?

Elimination of HBV is Possible

Academia + public health + industry + regulatory agency + government

We have the tools, we need to have the will power to make this a priority

The best is yet to come!

Thank You

Schinazi's Laboratory of Biochemical Pharmacology – CFAR, Emory University

Raymond F. Schinazi (PI), Sebastien Boucle, Fanck Amblard, Leda C. Bassit,

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Elizabeth Wright, PhD (Emory)

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COI: I am the Founder, Chairman & major shareholder of CoCrystal Pharma Inc.