

From HCV to HBV Cure
Raymond F. Schinazi, PhD, Hon DSc

Frances Winship Walters Professor

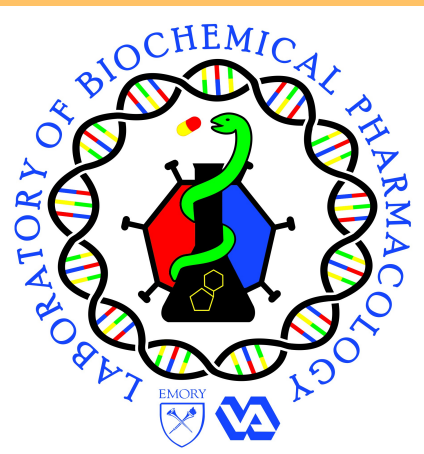
Director, Scientific Working Group on Viral Eradication, Emory University CFAR

Center for Drug Discovery

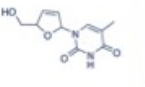
Paris – Jan 30, 2017

rschina@emory.edu

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

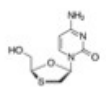


d4T
Stavudine (Zerit)
For HIV/AIDS



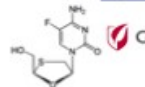
Yale University
British-Meyers Squibb

3TC
Lamivudine
For HIV/AIDS and Hepatitis B



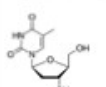
EMORY UNIVERSITY
ViiV Healthcare

(-)-FTC
Emtricitabine
For HIV/AIDS



EMORY UNIVERSITY
GILEAD

LdT
Telbivudine
For Hepatitis B



EMORY UNIVERSITY
THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
LVS
Idenix
NOVARTIS

Sofosbuvir
Sofaldi
For Hepatitis C



GILEAD
PHARMASSET

lamivudine + zidovudine



lamivudine + zidovudine + abacavir



lamivudine + abacavir



emtricitabine + efavirenz +
tenofovir disoproxil fumarate



emtricitabine + elvitegravir
+ tenofovir disoproxil fumarate
+ cobicistat



emtricitabine + tenofovir alafenamide



emtricitabine +

tenofovir disoproxil fumarate



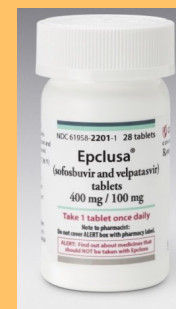
emtricitabine + rilpivirine +
tenofovir disoproxil fumarate



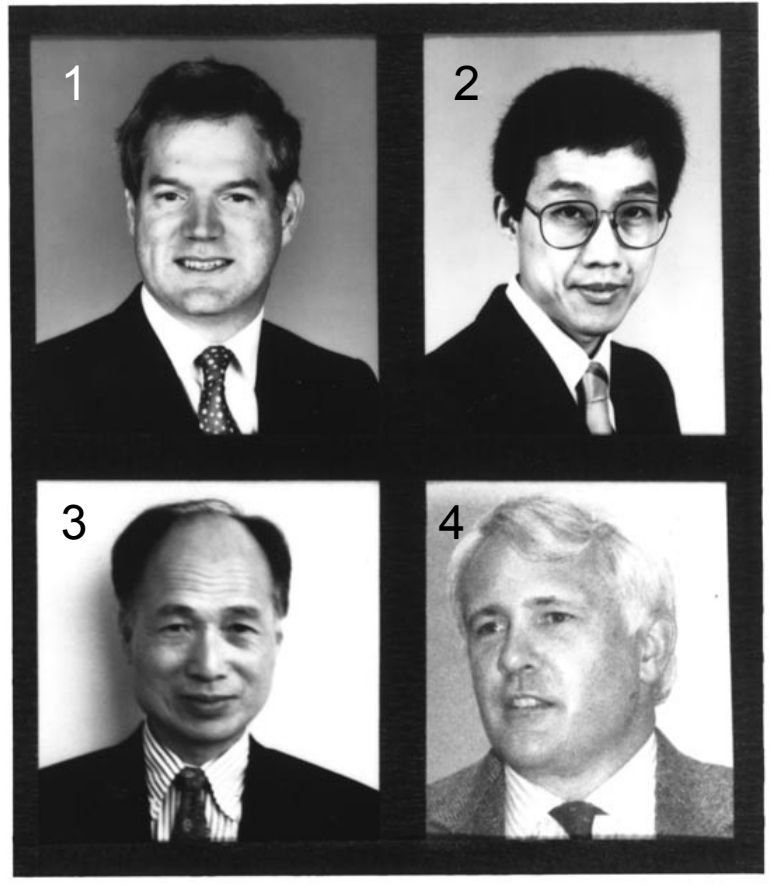
sofosbuvir +
ledipasvir



sofosbuvir +
velpatasvir



Discovery of the Hepatitis C Virus



64 -170 million persons globally with chronic hepatitis C

Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome.

1. M. Houghton
2. Q-L Choo
3. G. Kuo
4. D. Bradley

Source: *Nature Medicine* 6:1082-1086, 2000

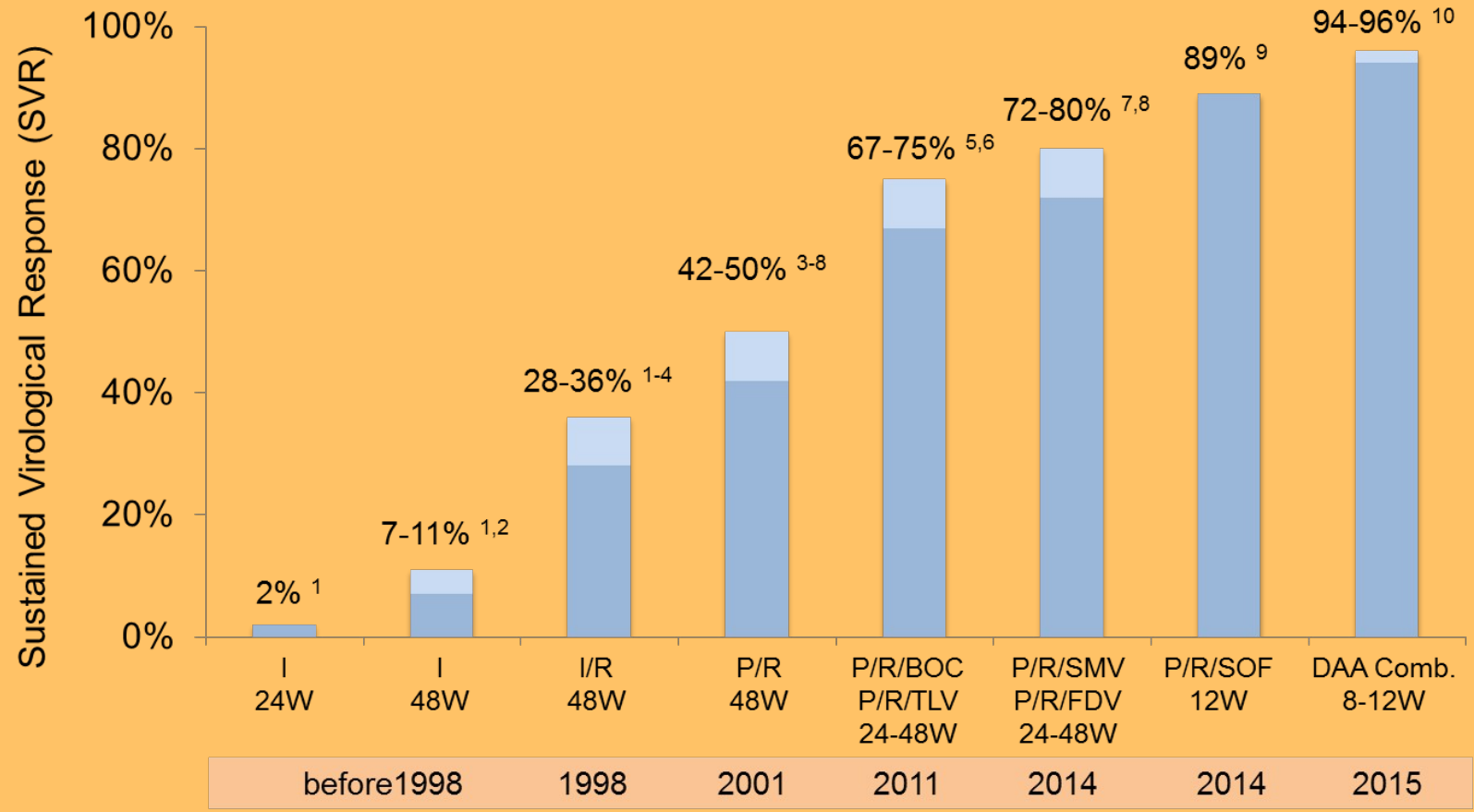
**Science 1989 – 2013 = 24 years
to an efficient cure**

The advent of the HCV replicon systems in the early 1990 transformed HCV drug discovery in academia and industry.

Charles Rice and Ralf Bartenschlager



25 years of HCV GT 1 Therapy: from 0 to ≥ 95 %



IFN trials 1998

1 USA trial: McHutchison et al., NEJM 1998
 2 Int. Trial: Poynard et al., Lancet 1998

PEG-IFN trials since 2001

3 PEG-IFN2b: Manns et al., Lancet 2001
 4 PEG-IFN2a: Fried et al., NEJM 2002

DAA trials since 2011

5 BOC: Poordad et al., NEJM 2011
 6 TLV: Jacobson et al., NEJM 2001
 7 SMV: Jacobson et al., AASLD 2013
 8 FDV: Jensen et al., AASLD 2013
 9 SOF: Lawitz et al., NEJM 2013
 10 Press release Gilead / Abbvie 2013

Success and Challenges to HCV cure

Interferon alfa and Ribavirin is **no longer** part of the first line regimens for the treatment of HCV infection

- Minimal on-treatment monitoring is required

Contraindications to treatment are relatively rare, but remaining challenges include:

- Cirrhosis F4

- Re-infection following HCV cure

Short duration may be highly advantageous in the real world

- Increase adherence; lower toxicity, decrease cost and possibly drug resistance

- Compromise in efficacy is acceptable *since re-treatment options are effective and readily available*

In the absence of generics, global access to low cost HCV treatment is currently the primary unmet challenge.

Ultrashort treatments would improve adherence, reduce cost, simplify Tx, reduce exposure to drugs and more affordable and increase access for all towards global eradication of HCV infections.

Multiple HCV targets & Drugs are available

DNA-directed RNA interference (ddRNAi)

TT-034 via Adeno-Associated Virus vector

NS3/4 Protease Inhibitors

Simeprevir (SIM)
Asunaprevir
ABT-450/ritonavir (r)
GS-9451

Entry inhibitors

Cyclophylin Inhibitors

Antisense oligonucleotides

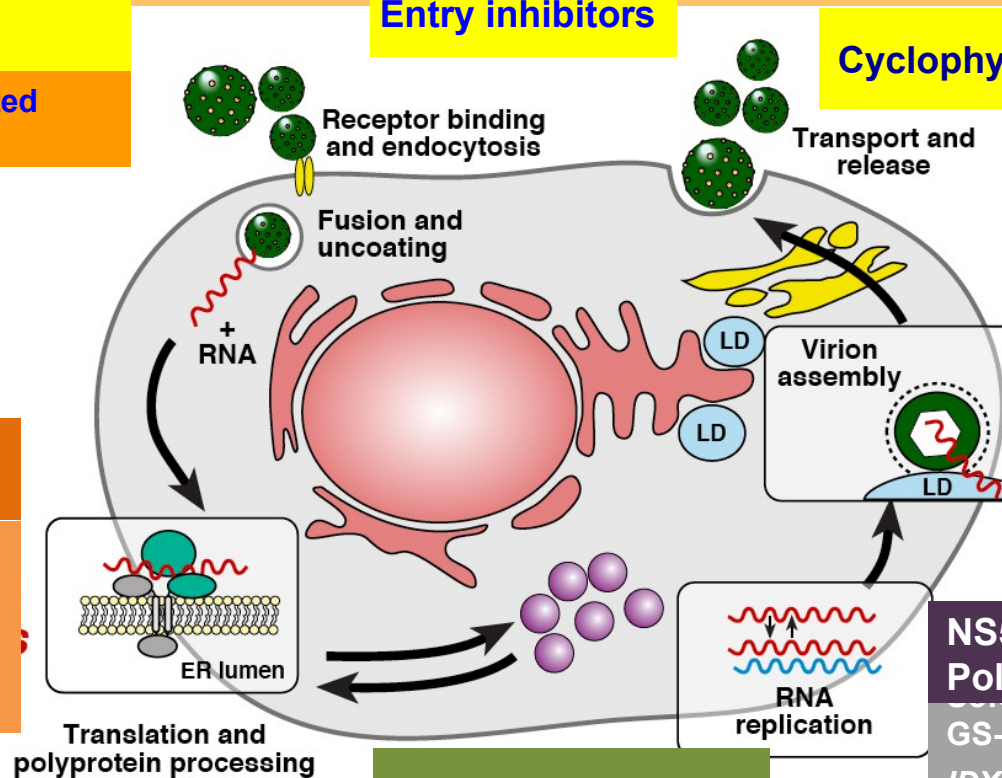
Miravirsen (miR-122)
Regulus (RG-101)

NS5B Polymerase Inhibitors

GS-9669
IDX-21437 (nuc)
IDX-21459 (nuc)
ACH-3422 (Nuc)
BMS-325
Dasabuvir
CC-1845 (nuc)
CC-31326 (NNI)

NS5A Inhibitors































Ledipasvir (LDV)
Ombitasvir
Daclatasvir (DCV)
Ledipasvir (LDV)
MK-8742
GS-5816 (velpatasvir)
Samatasvir (Merck)
ACH-3102



2017: Hepatitis C Virus and Curative Tx

- **Oral, direct acting antiviral agents (DAA):**
 - NS5B, Entry, Protease, NS5A, Cyclophilins, microRNA, etc.
 - December 2013: Sofosbuvir and Simeprvir
 - September 2014: Daclatasvir (Europe, Japan)
 - October 2014: SOF + Ledispavir (Harvoni)
 - December 2014: Viekira pak (FDC of 4-5 drugs)
 - July 2015: Harvoni (Japan)
 - July 2015: Daclatasvir (US) for genotype 3
 - July 2015: Technivie (ombitasvir/paritaprevir/ritonavir)
 - Jan 2016: Grazoprevir and elbasvir
 - June 2016: Epclusa (Velpatasvir + Sofosbuvir, US/Europe)
- **Nucleoside Analog Inhibitors (NAI) are Best in Class:**
 - High potency – no drug-drug interactions
 - Pan-genotypic
 - High barrier to resistance
 - Low pill burden and orally bioavailable

General Characteristics of Direct-Acting Antiviral Agents

| | PI, 1st Generation | PI, 2nd Generation | NS5A Inhibitors 1st Generation | NS5A Inhibitors 2nd Generation | NS5B Nucleoside Inhibitors | NS5B Non- Nucleoside Inhibitors |
|------------------------|---|---|--|---|---|---|
| Efficacy |  |  |  |  |  |  |
| Resistance Profile |  |  |  |  |  |  |
| Pangenotypic Efficacy |  |  |  |  |  |  |
| Adverse events |  |  |  |  |  |  |
| Drug-drug interactions |  |  |  |  |  |  |

 Good profile

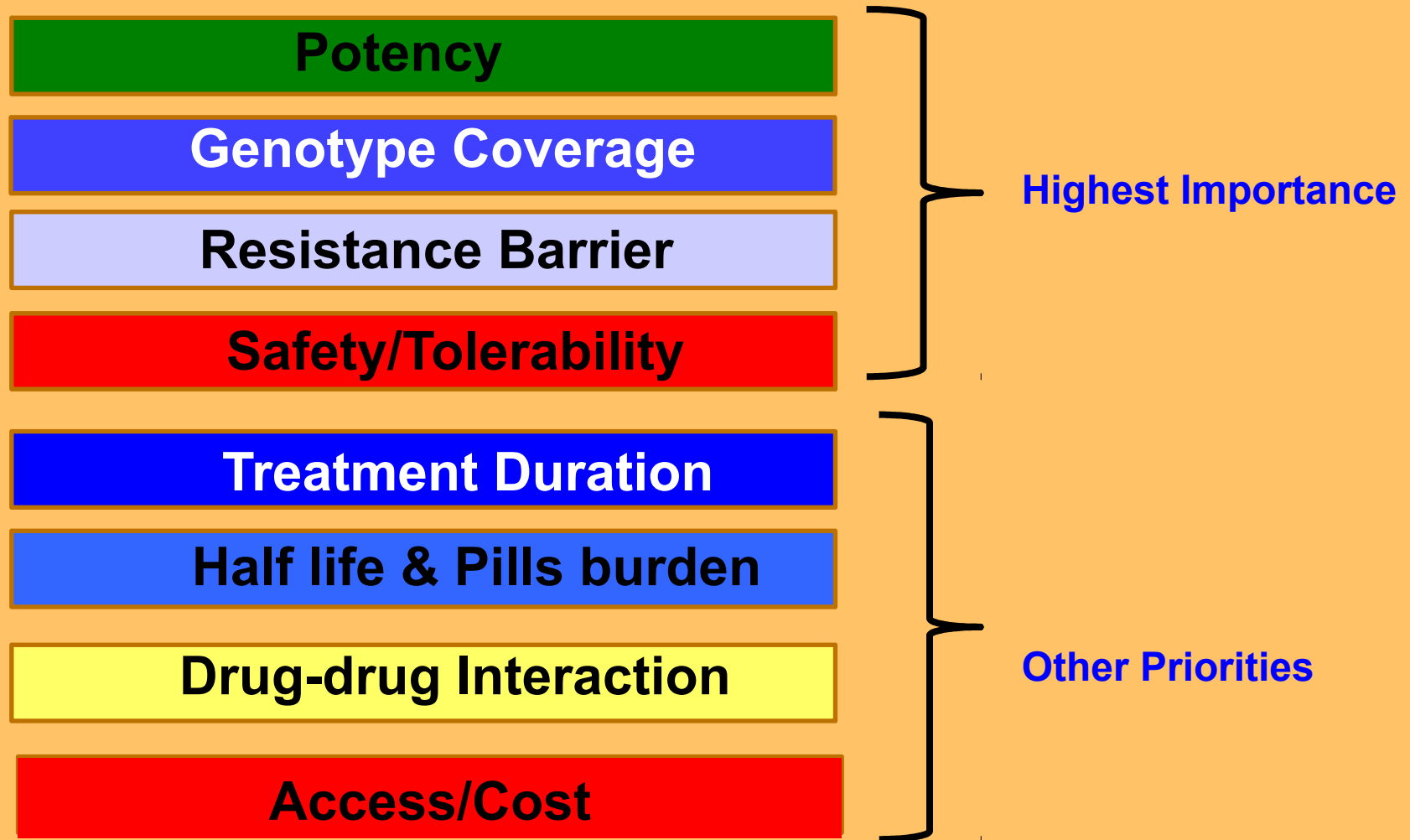
 Average profile

 Least favorable profile

Schinazi, R.F., Halfon, P., Marcellin, P., and Asselah, T.

HCV direct-acting antiviral agents: the best interferon-free combinations. *Liver Int.*, **34 Suppl 1**:69-78, 2014

Priorities for Direct-Acting Antiviral Agents



Goals obtained by achieving Sustained Virological Response (SVR) \approx cure

- Eradicate the virus (HCV clearance)
- Reduce Necroinflammation
- Stop Fibrosis progression
- Prevent Cirrhosis & complications
- Prevent Hepatocellular carcinoma
- Reduce extra-hepatic manifestations
- **Increase Lifespan**

Evolution of thought leading to PSI-6130 and eventually PSI-7977 (GS-7977 or Sofosbuvir)



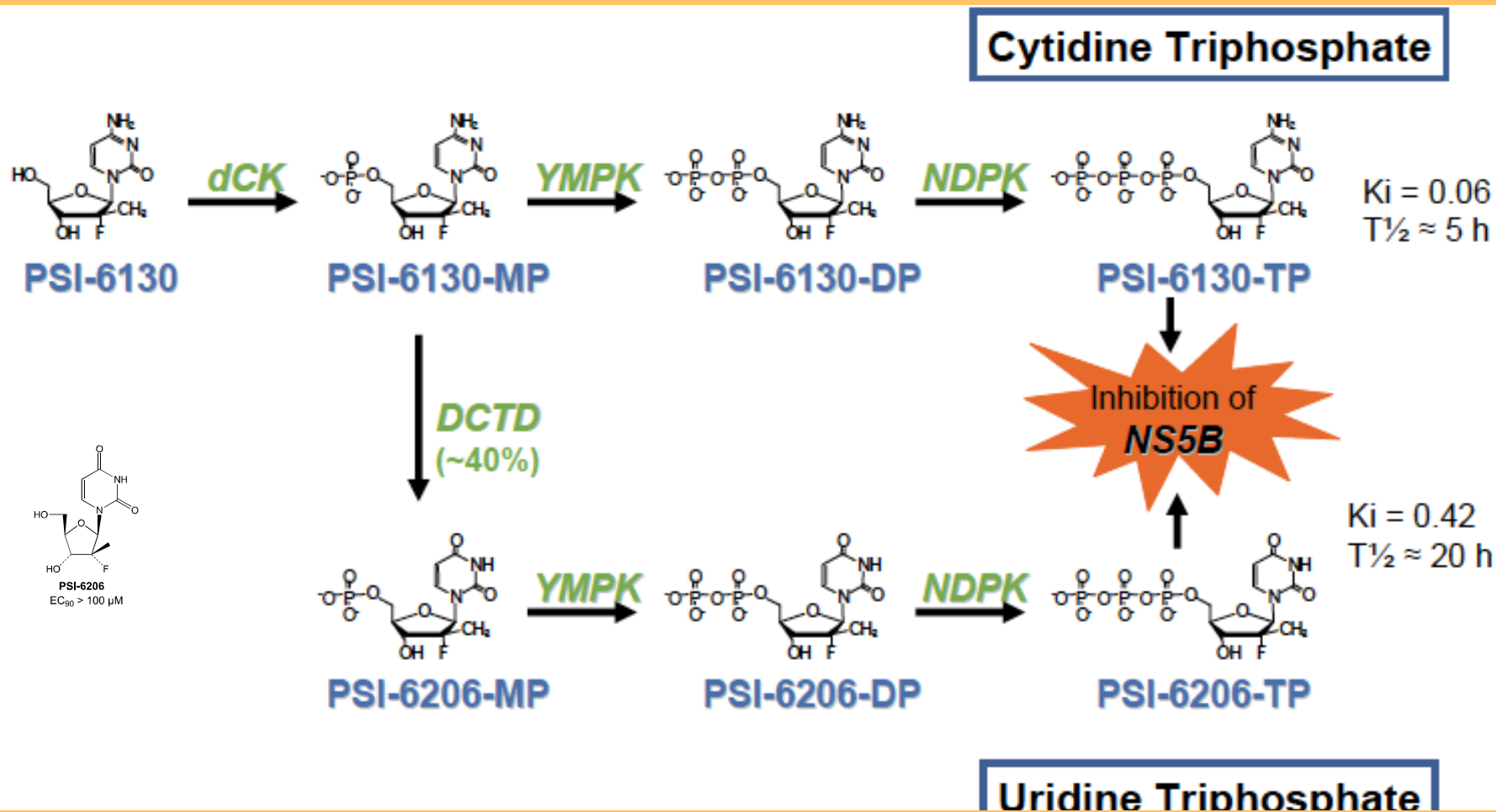
Difficult to select resistant
HCV– S282T virus unfit

FdC : Stuyver, Lieven J.; McBrayer, Tamara R.; Whitaker, Tony; Tharnish, Phillip M.; Ramesh, Mangala; Lostia, Stefania; Cartee, Leanne; Shi, Junxing; Hobbs, Ann; Schinazi, Raymond F.; *Antimicrob. Agents Chemother.*, **2004**, 48(2), 651-654

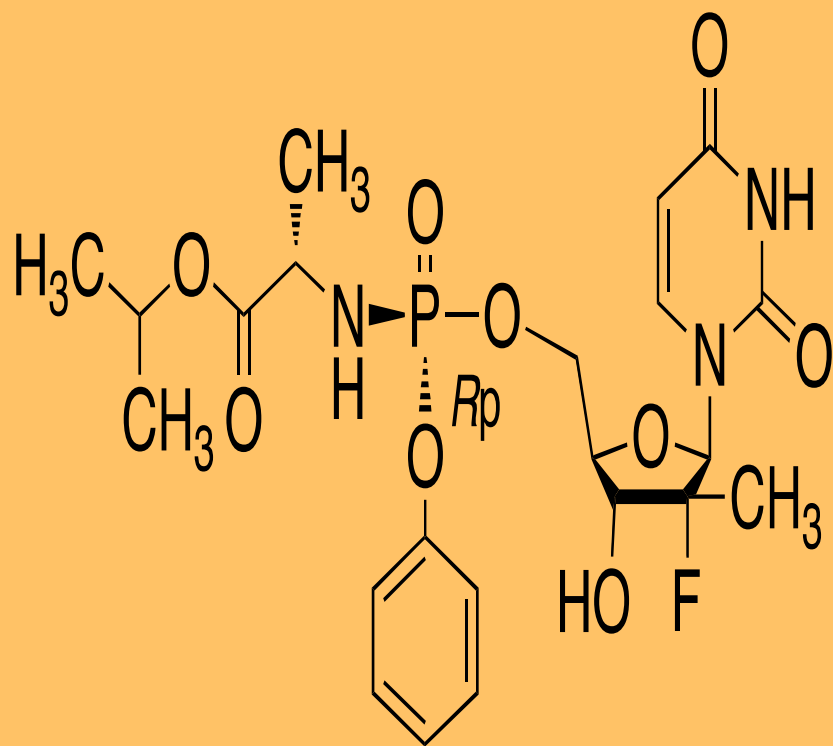
dFdC : Stuyver, Lieven J.; McBrayer, Tamara R.; Tharnish, Phillip M.; Hassan, Abdalla E. A.; Chu, Chung K.; Pankiewicz, Krzysztof W.; Watanabe, Kyochi A.; Schinazi, Raymond F.; Otto, Michael J. *J. Virol.*, **2003**, 77(19), 10689-10694

NM-107 : Sommadossi, J.-P.; La Colla, P. WO 2001092282 .

PSI-6130 is metabolized to two active NTP of HCV Polymerase



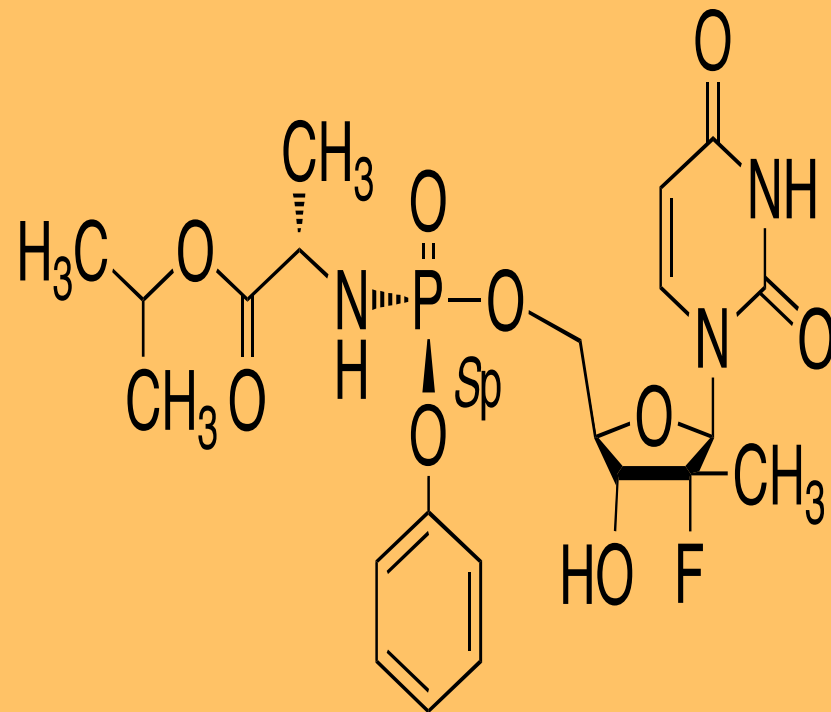
Activity of Diastereomerically Pure Nucleotide Phosphoramidates



PSI-7976

HCV 1b replicon: EC₉₀ = 7.5 μM (WT);

> 100 μM (S282T); 1.3 μM (S96T)



PSI-7977 (GS-7977, Sofosbuvir)

HCV 1b replicon: EC₉₀ = 0.42 μM (WT);

7.8 μM (S282T); 0.11 μM (S96T)

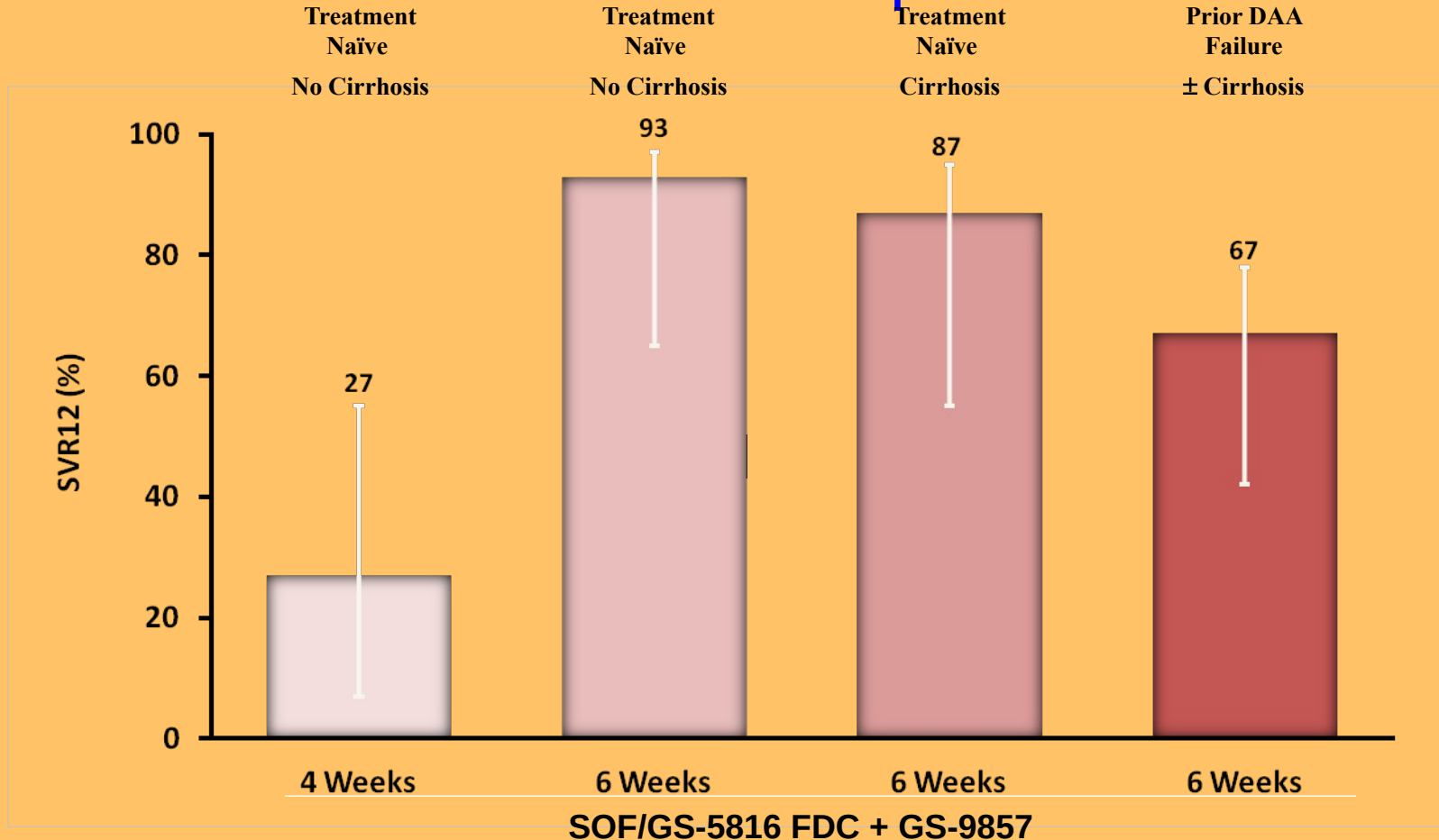
Truncation of therapy possible

Short duration may be highly advantageous in the real world –simplify Tx, reduce exposure to drugs and reduce cost

- Increase adherence; decrease cost; less tox and resistance (dead viruses don't mutate)
- Use the most potent and safest DAA together
- Plan scenario in case of failure like we do for HIV (*need markers for success or failure and when to stop therapy*) – *treat shorter based on Response-Guided Therapy (RGT)*

Triple Therapy PI, NS5A-Inh + NUC: 6 weeks possible?

GS-9857+SOF/Velpatasvir



- Relapse accounted for all subjects who did not achieve SVR12
- For prior DAA failure, SVR12 in persons without cirrhosis was 68% (17/25) and with cirrhosis was 60% (3/5)

Background to SODAPI Study

GT1b

Major disease burden for CHC in Chinese

~5.7 M – Most prevalent genotype in Asia

Current recommendation

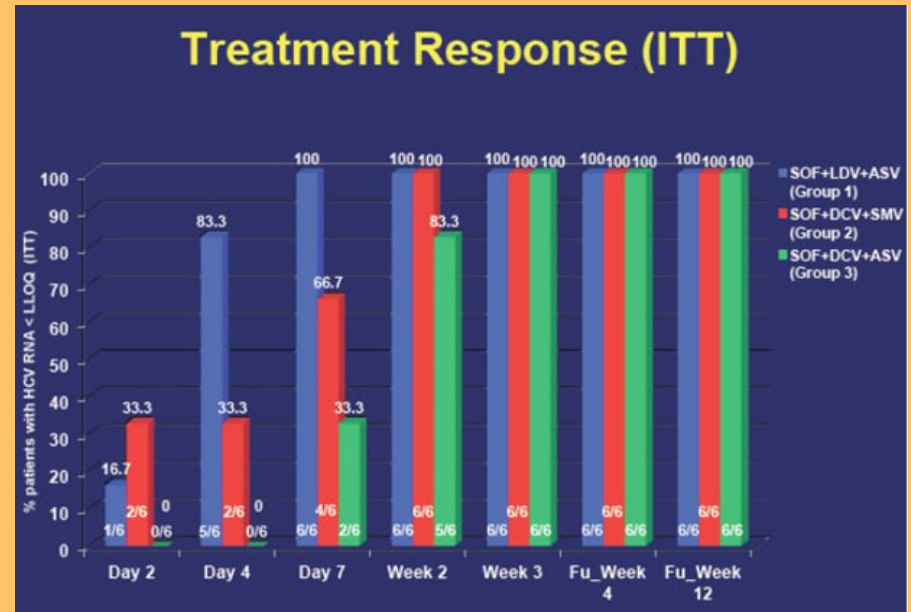
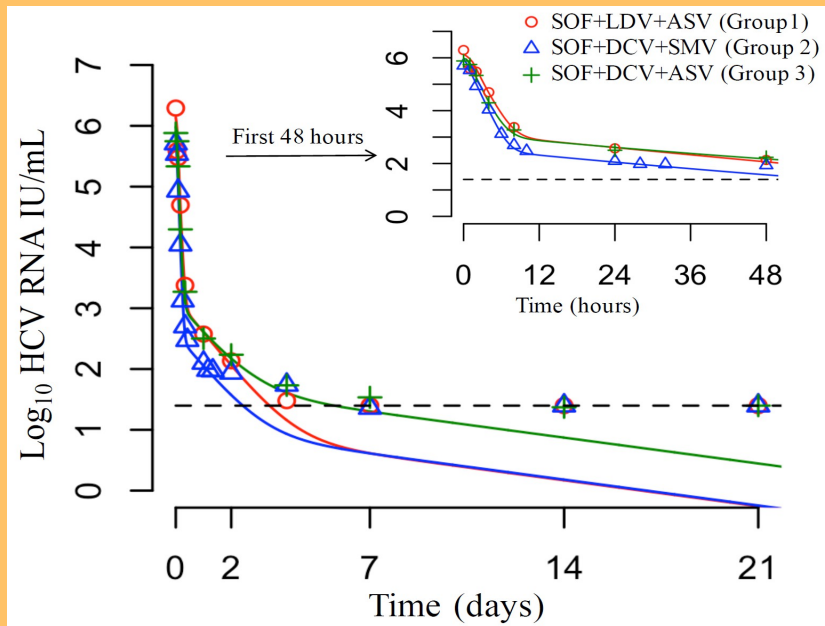
Pan-oral DAAs for 12 weeks

Cost is onerous

SODAPI STUDY (3 x 3)

- Divided the **26** Chinese Naïve **genotype 1b** subjects into three groups. A “rapid virologic response” (RVR), defined as plasma viral RNA less than **500 IU/ml** by day two, was achieved in **18** persons (RGT; *Response Guided Therapy*).
- Sofosbuvir, ledipasvir, asunaprevir (Harvoni, Sunvepra); RVR in 6/12
- sofosbuvir, daclatasvir, simeprevir (Sovaldi, Daklinza, Olysio); RVR in 6/6
- Sofosbuvir, daclatasvir, asunaprevir (Sovaldi, Daklinza, Sunvepra); RVR in 6/8
- All subjects (100%) followed achieved SVR12, including those that took drugs only for 3 weeks
- Lau, Schinazi et al., Lancet Gastro Hepatol, 1(2):97-104, 2016. PMID: 27917405– Not funded by pharma

100% SVR with 3 weeks DAA triplet (previr/asvir/buvir) combination, if HCV-RNA <500 IU/ml after 48 hours



HCV approach: 3+ Direct-acting antiviral agents for ultra-short modalities

De-risked
near-term
approach
creating
multiple
“shots on
goal”

**Pan-genotypic
NS5B Nuc**



**Pan-genotypic
NS5A Inhibitor**



**Pan-genotypic
NS5B NNI**



**Pan-genotypic
Helicase
Inhibitor**



**All oral HCV
regimen**



*As of July 2016, about 1.5 MM
individuals have been cured of HCV
worldwide with DAAs*

*Problem in the US will persist until
2036*

*Lots of populations to treat including
people in prisons and newly infected*

Hep C solution is one of the greatest success story in human medical history

The products are getting better and better with each generation of product. Sovaldi --> combo --> pan-genotype combo -->

Shorter Tx --> nanoparticles --> **increase life expectancy**

Nanoparticles and ***shorter treatments*** will offer an efficient convenient way to reduce cost and increase adherence

“Treatment as prevention” will be a powerful tool towards global elimination and eventual eradication

Think about Cure rather than Tx or band-aids

From Z-Pak to C-Pak?



Ultimate goal – “One pill one cure” for Global HCV eradication and huge cost saving

IS HBV ERADICATION POSSIBLE?



*Impossible n'est pas
Français*

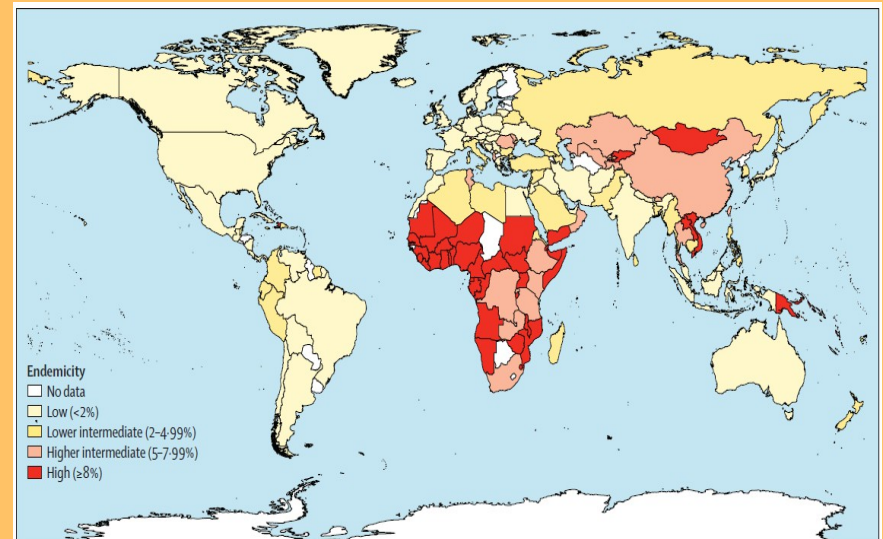
**Everything is theoretically
impossible until done**

Robert Anson Heinlein,

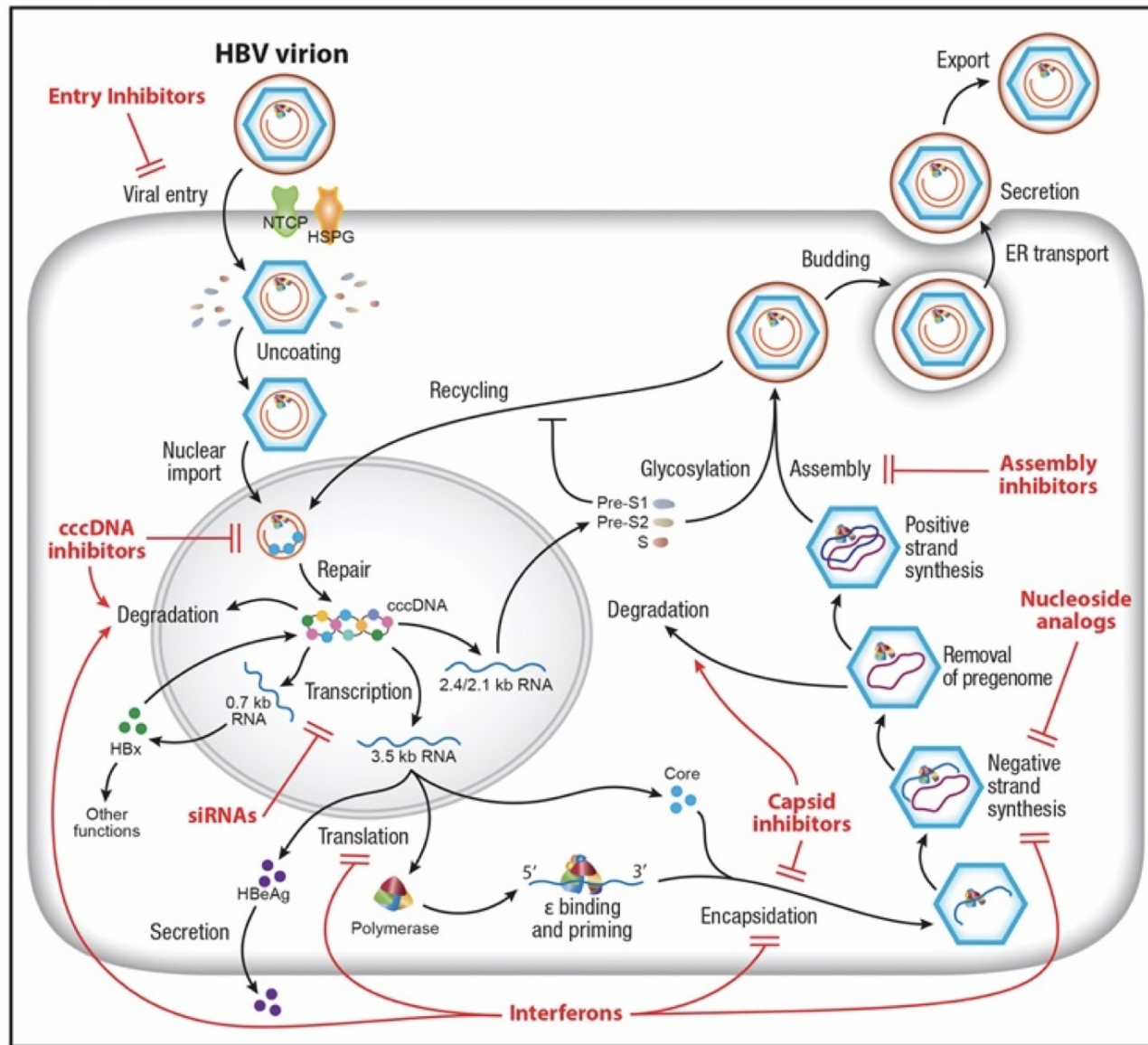
American Science Fiction writer

Hepatitis B Virus (HBV) Epidemic

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



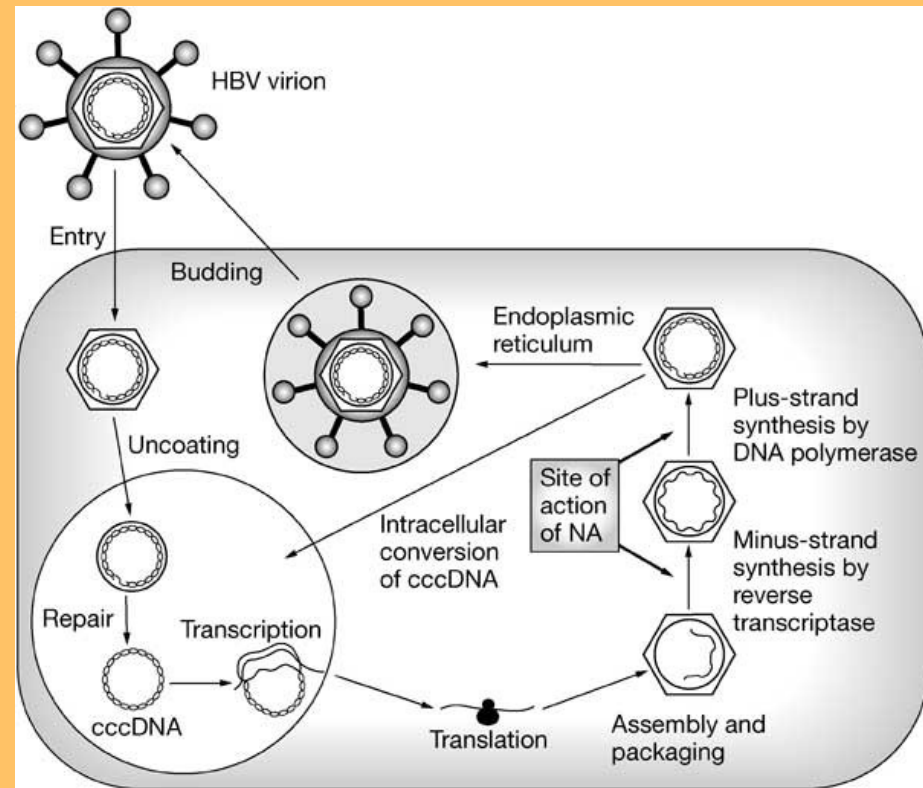
Multiple Targets For Antiviral Therapies



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

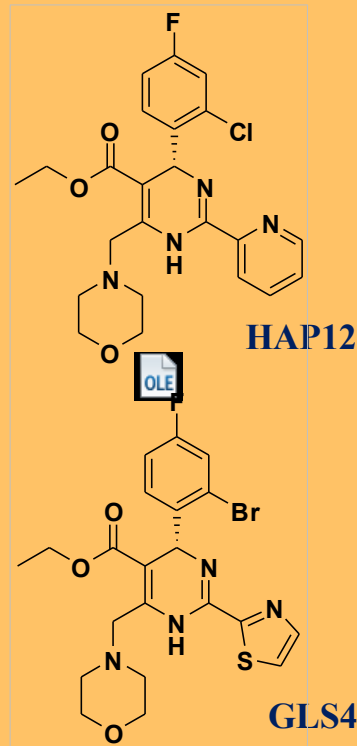
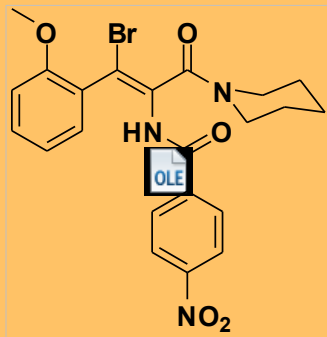
Role of Capsid in Viral Replication Cycle



Fung SK and Lok ASF; *Nat Clin Pract Gastroenterol Hepatol* (2004) 1: 90-97.

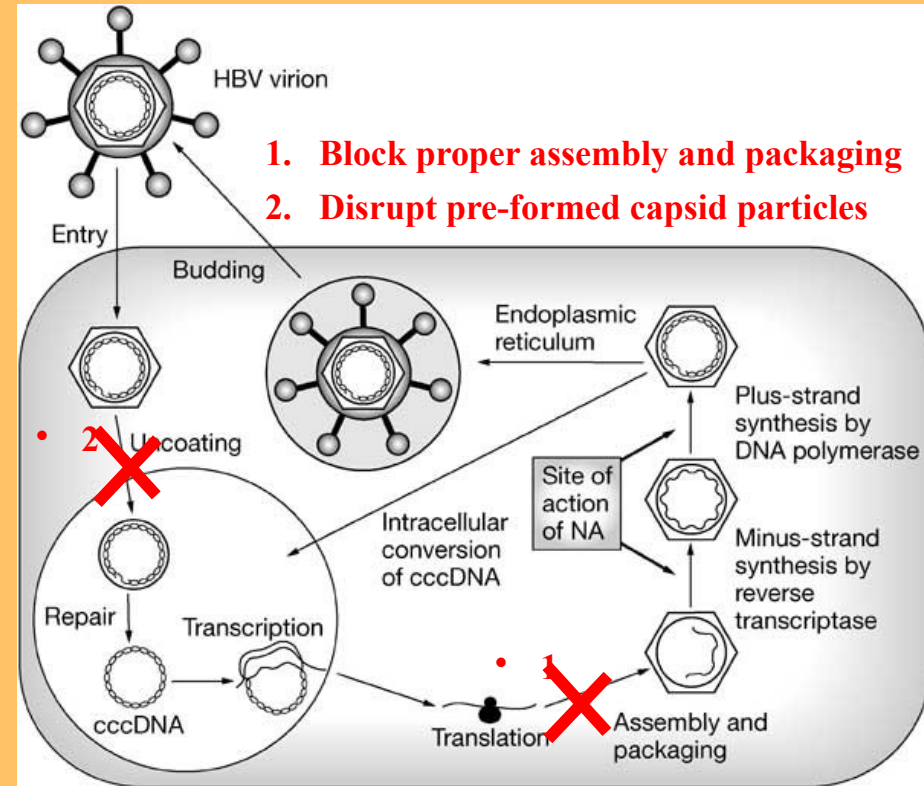
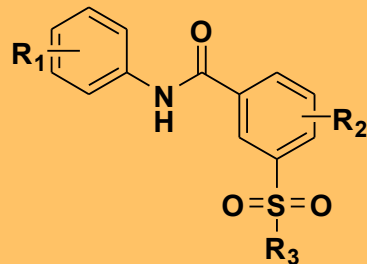
Capsid Effectors as HBV Antiviral Agents

Phenylpropenamides HeteroArylPyrimidines (HAP)



Sulfamoyl

Carboxamides



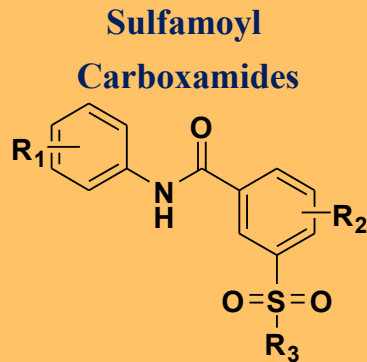
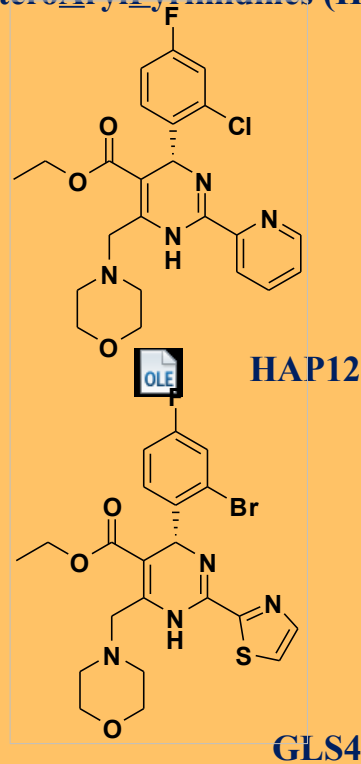
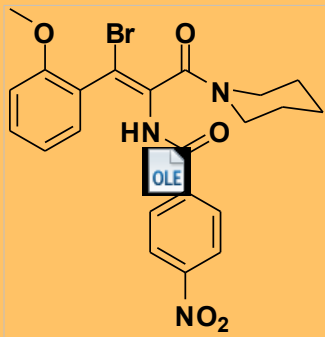
Boucle, S et al.; Clinics in Liver Disease (2016)

Capsid Effectors Deplete cccDNA

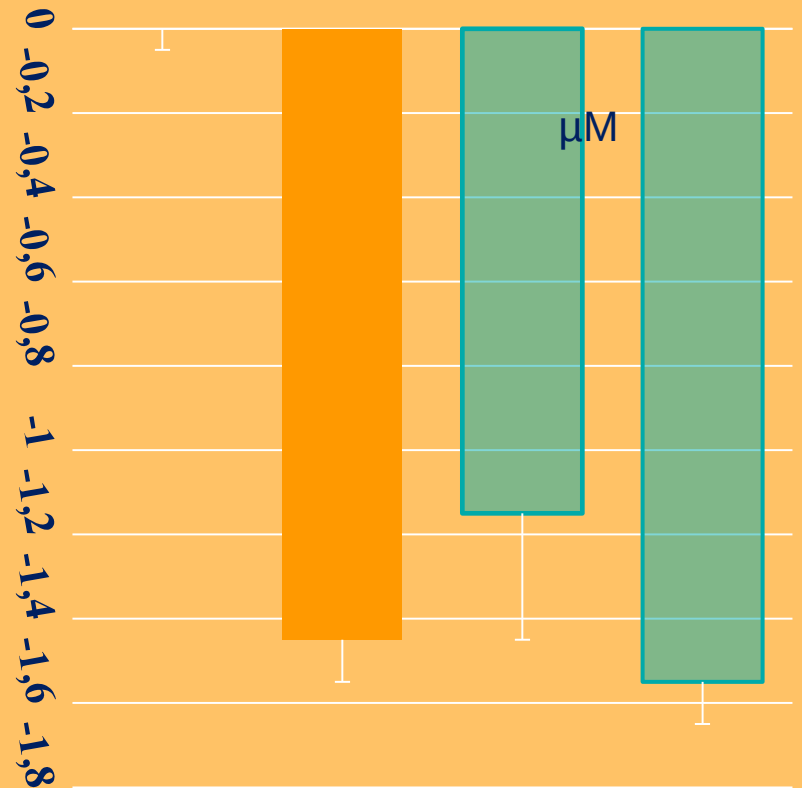
HBV cccDNA Levels in HEP-AD38 System

Determined by RT-PCR

Phenylpropenamides HeteroArylPyrimidines (HAP)



Log[cccDNA] Reduction



Discovery of a new class of non-nucleoside inhibitors

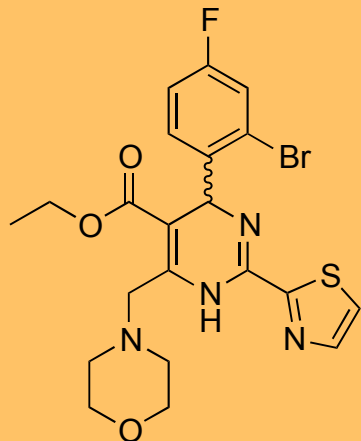
HepAD38 system

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

Capsid Assembly Effectors

Class 1

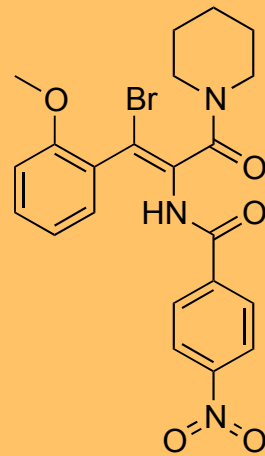
HAP analogs



GLS4

Class 2

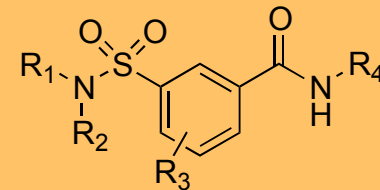
Phenylpropenamides



AT-130

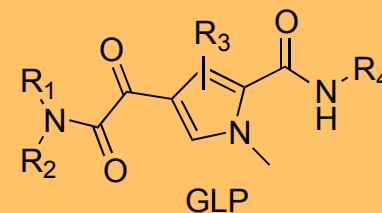
HAP, Heteroaryldihydropyrimidines

Sulfamoylbenzamides



NVR 3-778

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



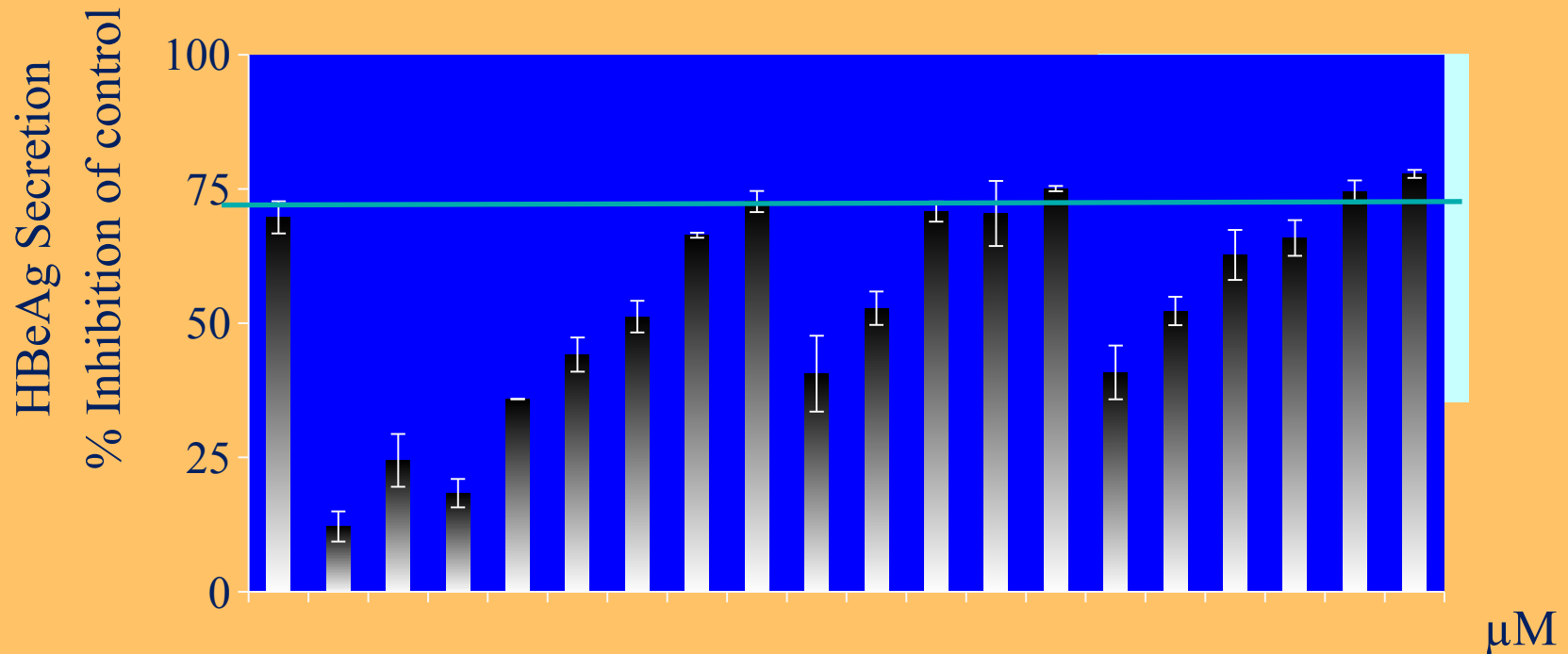
GLP

GLP-26 has sub-micromolar potency against HBV with no relevant cytotoxicity in several cell lines

| Drugs | Potency | | Cytotoxicity HepG2 |
|--------|---------------------|---------------------|-----------------------|
| | Anti-HBV Activity | | Therapeutic index |
| | EC50, μM | EC90, μM | IC50/EC50 |
| GLP-26 | 0.003 | 0.03 | > 10,000 |
| GLS4 | 0.08 | 0.28 | \geq 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

Novel GLP-26 inhibits HBeAg secretion at sub-micromolar concentration



| HBeAg | EC50, μM | 3TC | GLS4 | HAP12 | GLP-26 |
|-------|----------|------|------|-------|--------------|
| | | > 10 | 0.16 | 0.03 | 0.003 |

Monitoring HBV Capsid Assembly using Electron Microscopy

Capsid Formation Assay

HBV Cp149

10 μ M

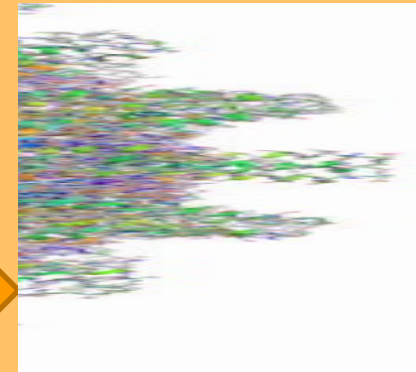


Incubate with 25 μ M
Compound for 1 h, 4°C



Induce Assembly

+ 500 mM NaCl, 4°C
overnight



HBV
Cp149
Capsid

Vehicle

- Fully-formed hollow sphere
- Diameter ~30-40 nm

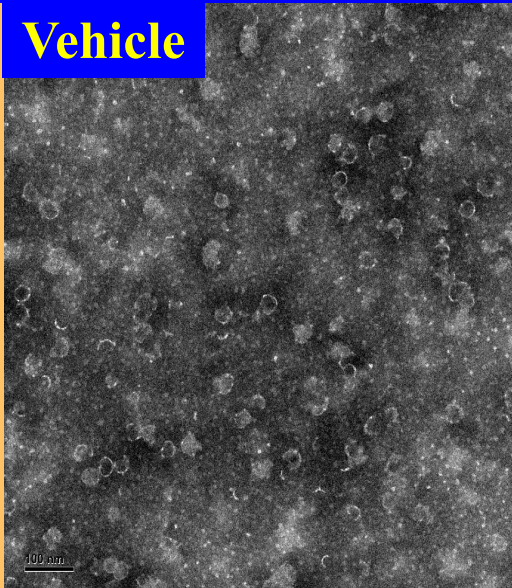
GLS4 - Misassemble

- Misassembled hollow sphere
- Diameter ~80-100 nm

GLP-26 - Inhibition?

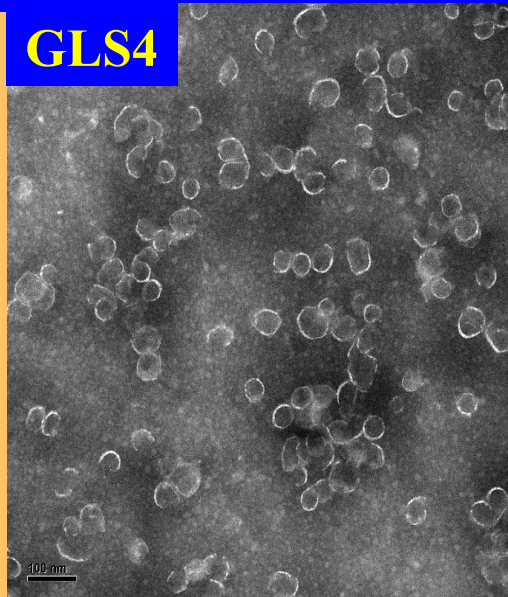
- Incomplete hollow spheres
- Low abundance
- Diameter < 20 nm

Vehicle



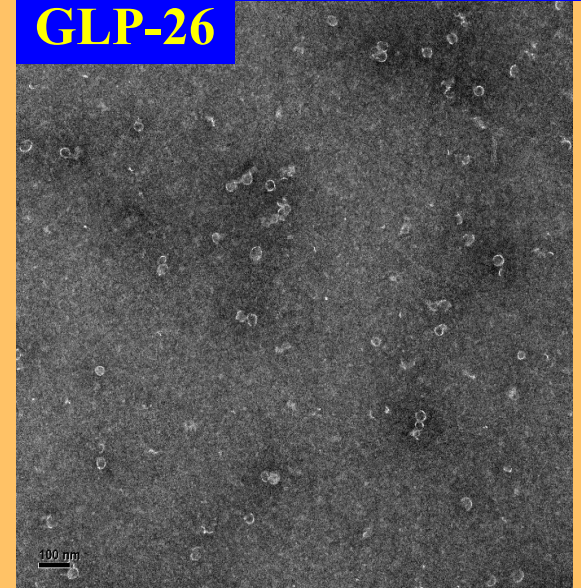
100 nm

GLS4



100 nm

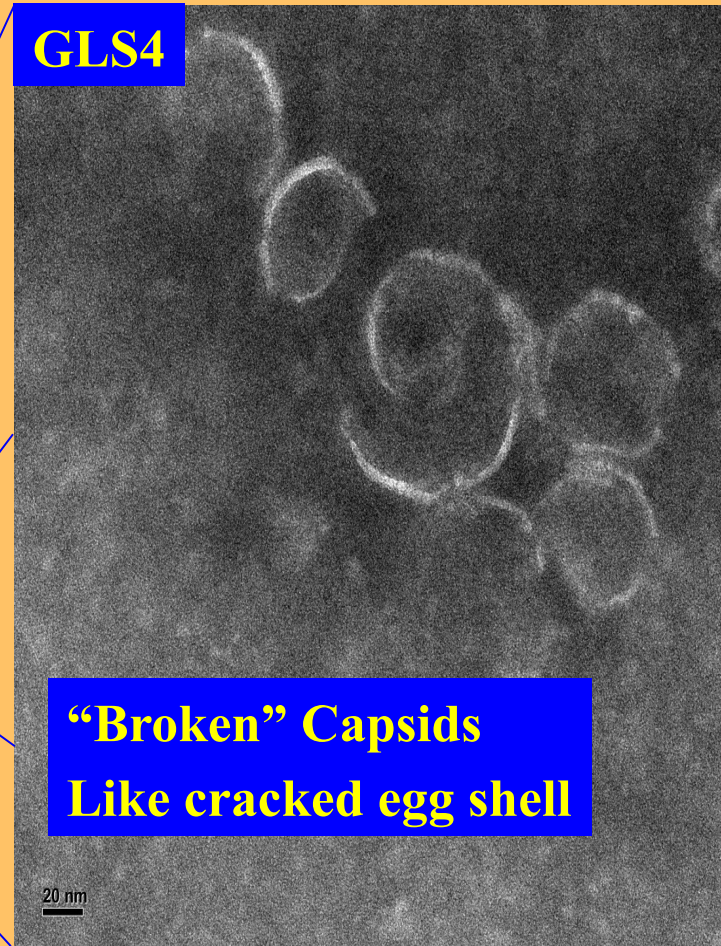
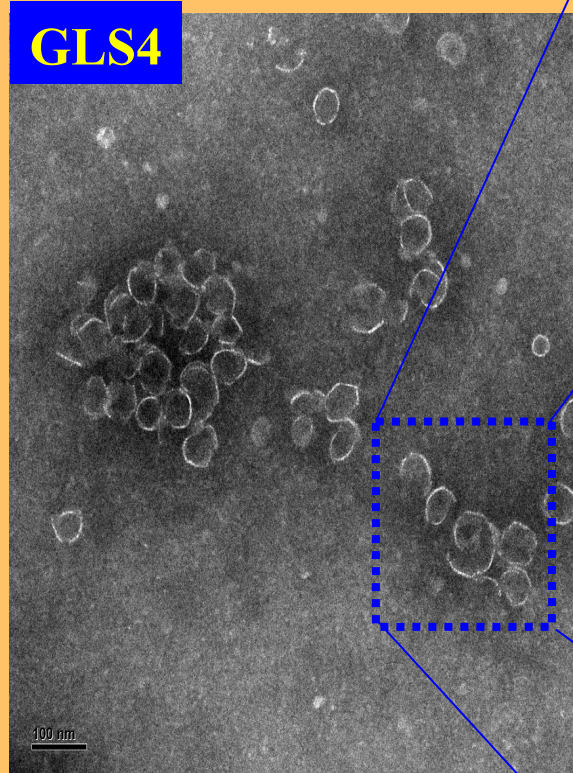
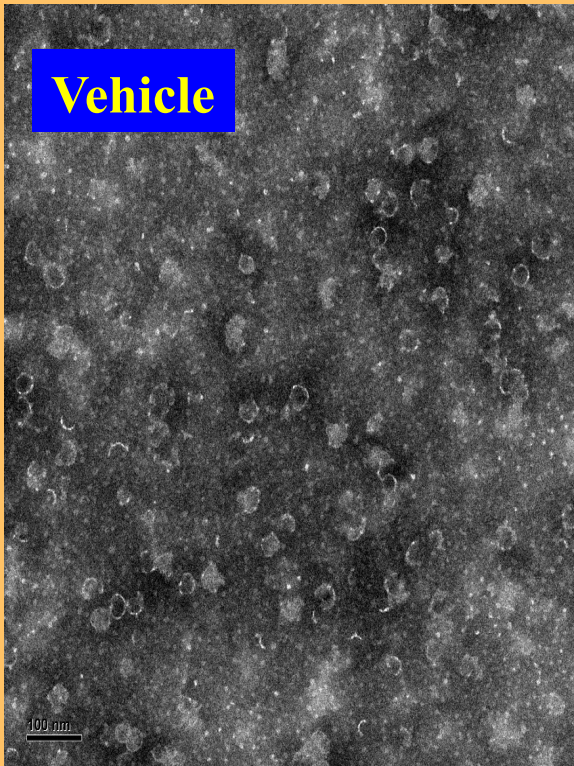
GLP-26



100 nm

Capsid Disruption Results – GLS4

A picture is worth 1,000 words



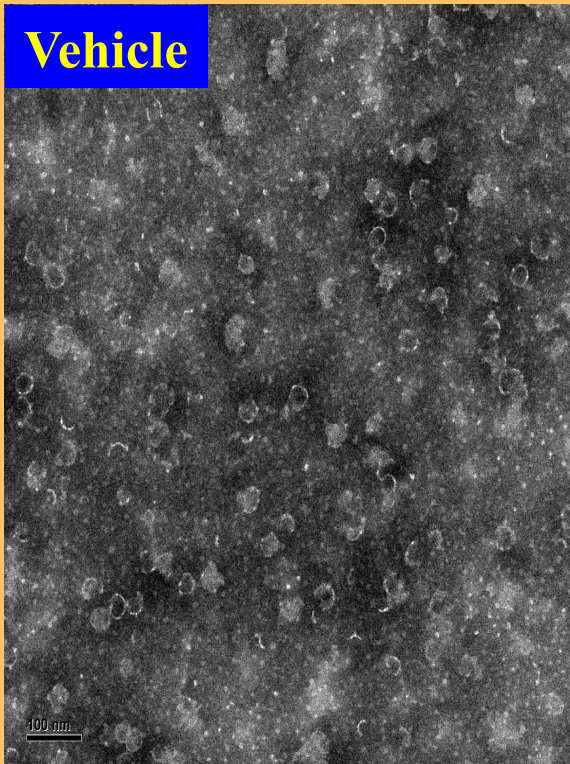
100 nm

100 nm

20 nm

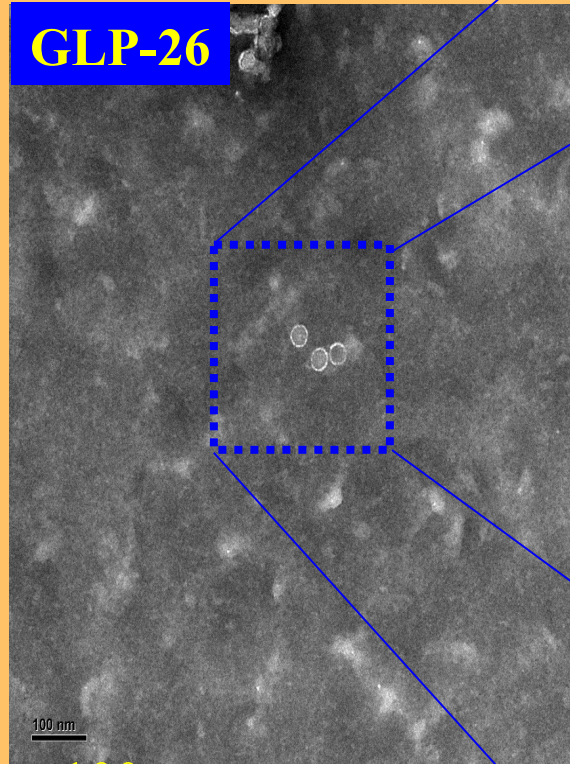
HBV Capsid Disruption Results – GLP-26

Vehicle



• 100 nm

GLP-26



• 100 nm

GLP-26

Lower particle concentration
Potentially dissolved capsid?

Remaining particles are small
& tightly packed

20 nm

• 20 nm • 35

Conclusions

HBV inhibitor GLP-26

- ✓ **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**
 - **Most potent and selective HBV inhibitor of this class**

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

The game is NOT over!

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

Thank You

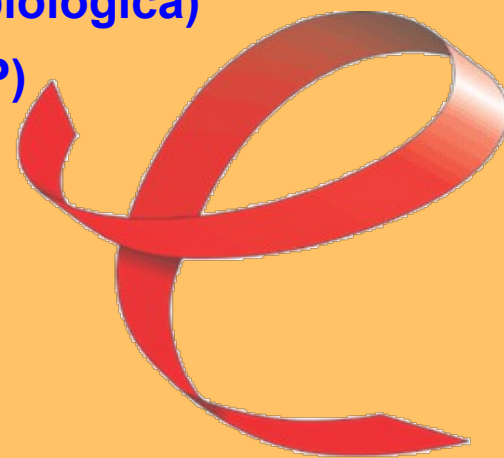
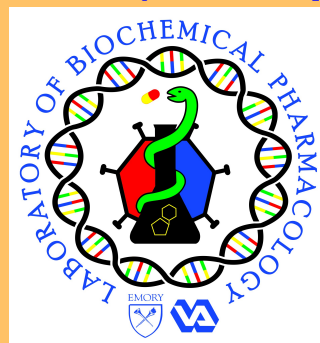
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COI: I am the Founder, Chairman & major shareholder of CoCrystal Pharma Inc.