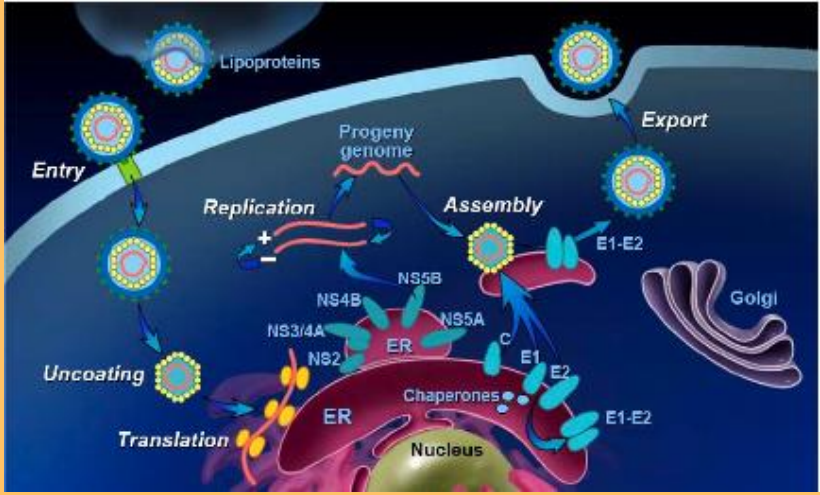
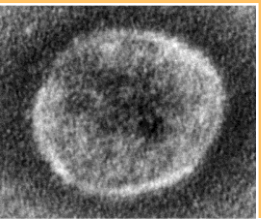


Discovery and Development of Novel Antiviral Agents to Eliminate HCV and HBV Infections



Raymond F. Schinazi, PhD, Hon DSc

Frances Winship Walters Professor

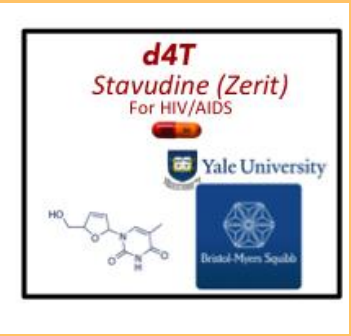
Director, Scientific Working Group on Viral Eradication, Emory University CFAR

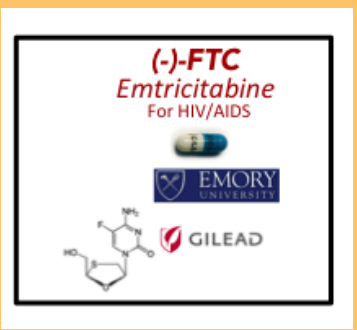
Center for Drug Discovery

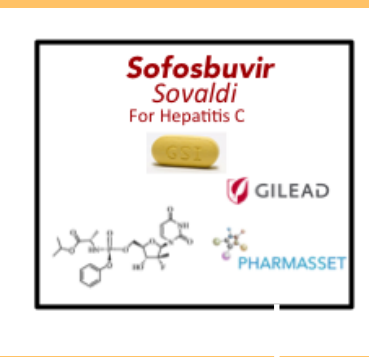
Magna Meeting - Rio, Brazil – May 9, 2017

rschina@emory.edu

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



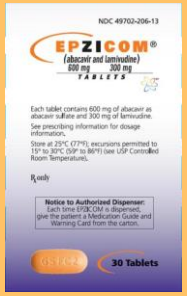




lamivudine + zidovudine

lamivudine + zidovudine + abacavir

lamivudine + abacavir



emtricitabine + efavirenz + tenofovir disoproxil fumarate

emtricitabine + elvitegravir + tenofovir disoproxil fumarate + cobicistat

emtricitabine + tenofovir disoproxil fumarate

emtricitabine + rilpivirine + tenofovir disoproxil fumarate

emtricitabine + tenofovir alafenamide

sofosbuvir + ledipasvir

sofosbuvir + velpatasvir

Discovery of Hepatitis C

TRANSFUSION-ASSOCIATED HEPATITIS NOT DUE TO VIRAL HEPATITIS TYPE A OR B

Stephen M. Feinstone, M.D., Albert Z. Kapikian, M.D., Robert H. Purcell, M.D., Harvey J. Alter, M.D., and Paul V. Holland, M.D.

Abstract Twenty-two patients who had an episode of transfusion-associated hepatitis not positive for hepatitis B antigen were examined for development of antibody to hepatitis A and B antigens, cytomegalovirus and Epstein-Barr virus. Antibody response to the 27-nm virus-like hepatitis A antigen was measured by immune electron microscopy. In none of the 22 patients studied did serologic evidence of infection with hepatitis A virus develop during the study period.

Nine of the 22 patients had antibody responses to cytomegalovirus, but it was difficult to relate these seroconversions to their hepatitis. In addition, all 22 patients had pre-existing antibody to the Epstein-Barr virus. It seems likely that at least a proportion of such antigen-negative transfusion-associated hepatitis is caused by other infectious agents, not yet identified. (N Engl J Med 292:767-770, 1975)

Discovery of the Hepatitis C Virus

64 -170 million persons globaly 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

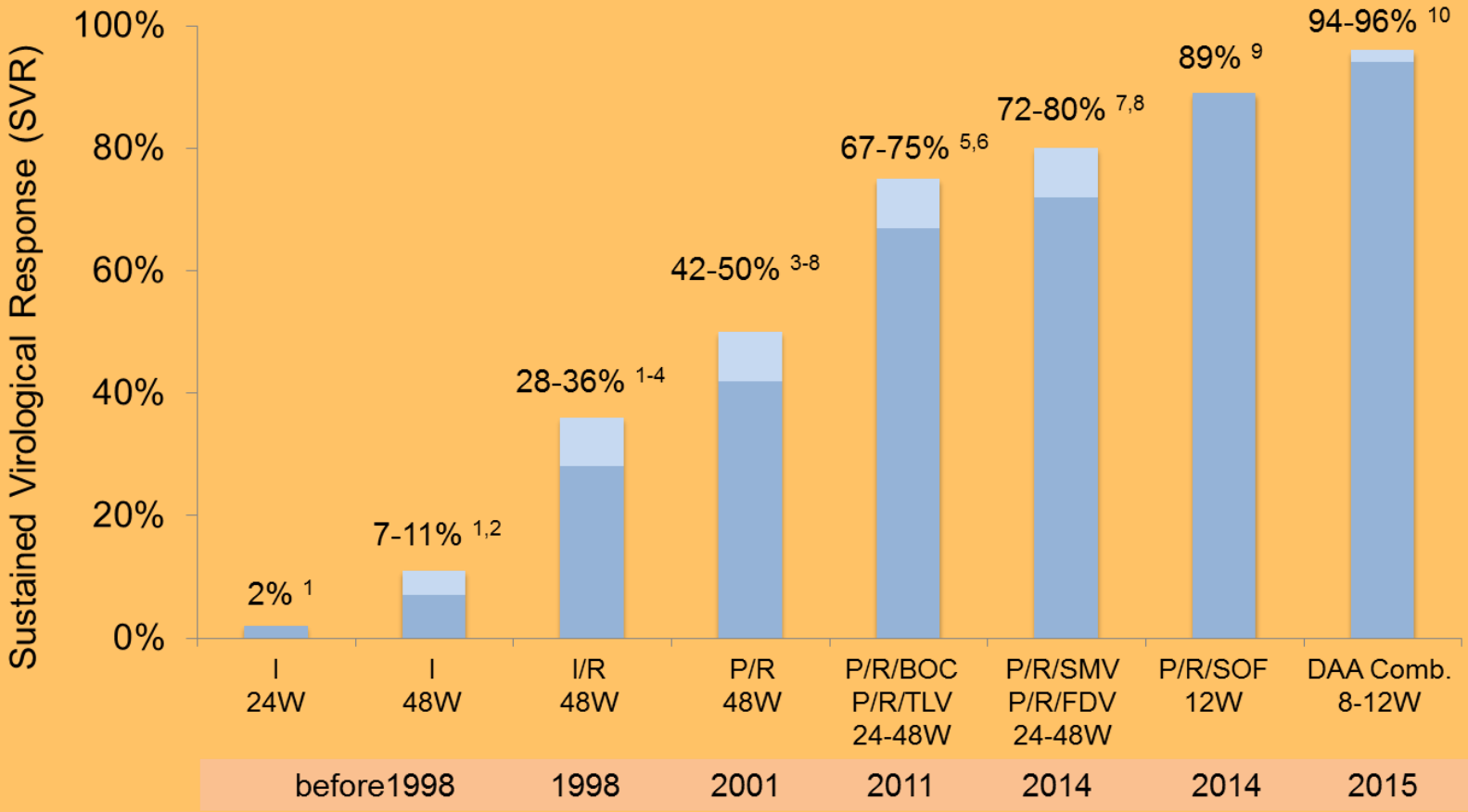
Source: Nature Medicine **6**:1082-1086, 2000

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.

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

Cornberg et al, Der Internist, 2014

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.**

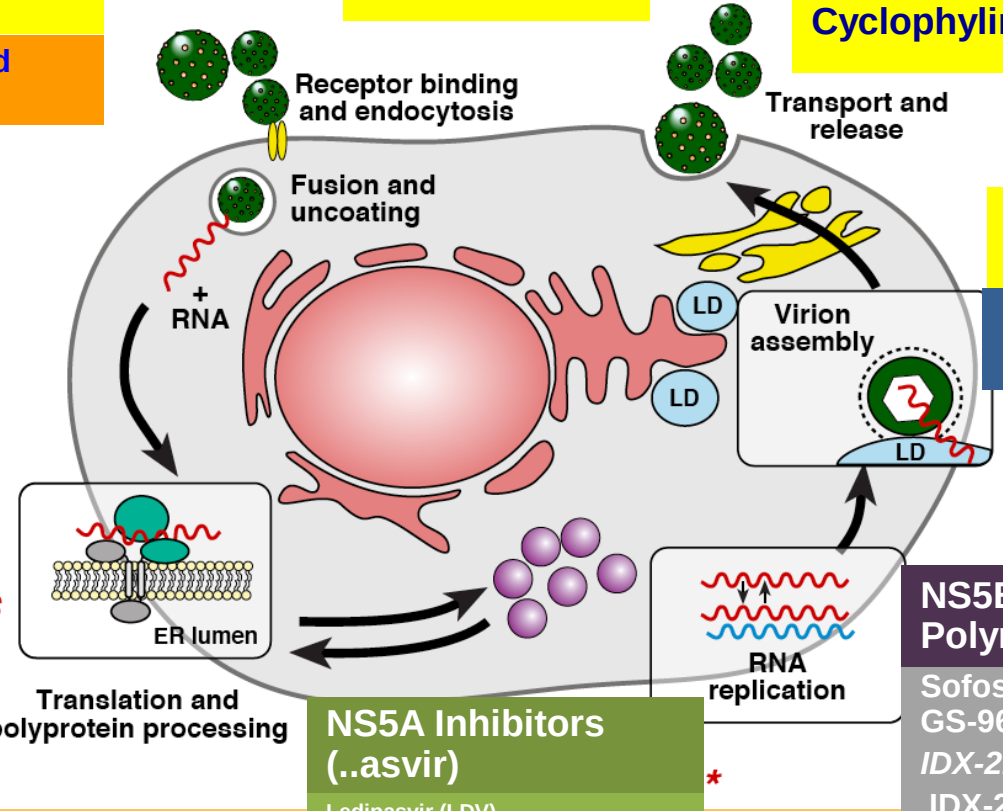
Multiple HCV targets & Drugs are available

DNA-directed RNA interference (ddRNAi)

TT-034 via Adeno-Associated Virus vector

Entry inhibitors

Cyclophylin Inhibitors



Antisense oligonucleotides

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

NS3/4 (..previr) Protease Inhibitors

Simeprevir (SIM)
Asunaprevir
ABT-450/ritonavir (r)
GS-9451
Faldaprevir (FDV)
Grazoprevir
Paritaprevir/r
Glecoprevir

NS5A Inhibitors (..asvir)

Ledipasvir (LDV)
Ombitasvir
Daclatasvir (DCV)
Ledipasvir (LDV)
MK-8742
TD6450
Velpatasvir (GS-5816)
Samatasvir (Merck)
ACH-3102
Pibrentasvir (ABT-530)
Elbasvir

NS5B (…buvir) Polymerase Inhibitors

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

2017: Hepatitis C Virus and Curative Tx

- **Oral, direct acting antiviral agents (DAA):**
  - NS5B, Entry, Protease, NS5A, Cyclophilins, microRNA, etc.
  - December 2013: Sofosbuvir and Simeprivir
  - September 2014: Daclatasvir (Europe, Japan)
  - October 2014 : SOF + Ledispavir (Harvoni).
  - December 2014: Viekira pak (FDC of 4-5 drugs)
  - July 2015: Harvoni (Japan) - April 2017 approved in Children
  - July 2015: Daclatasvir (US) for genotype 3
  - July 2015: Technivie (ombitasvir/paritaprevir/ritonavir)
  - Jan 2016: Grazoprevir + elbasvir (*Zepatier*)
  - 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

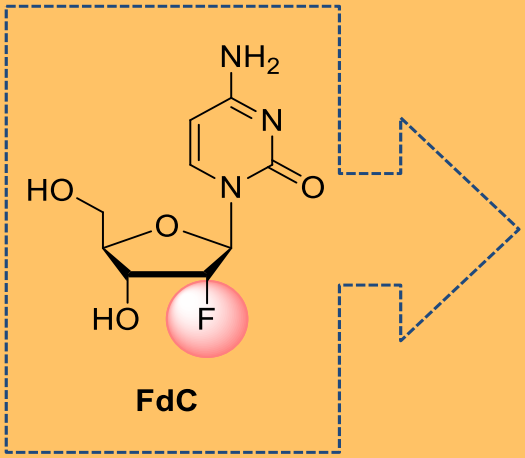
Goals Obtained by Achieving

Sustained Virological Response (SVR) ≈ Cure

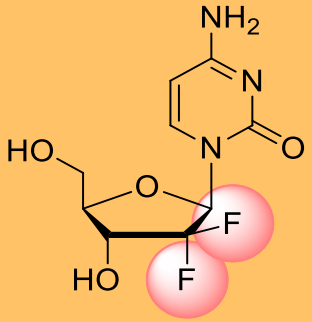
- Eradicate the virus (HCV clearance)
- Reduce necroinflammation
- Stop fibrosis progression
- Prevent cirrhosis & complications
- Prevent hepatocellular carcinoma
- Reduce extra-hepatic manifestations
- **Increase lifespan**

Schinazi, RF & Asselah, T, Liver Int. 2017 Jan;37 Suppl 1:73-80

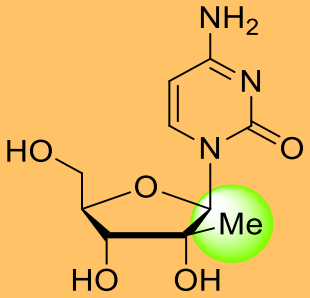
Evolution of thought leading to PSI-6130 and eventually PSI-7977 (GS-7977 or Sofosbuvir)



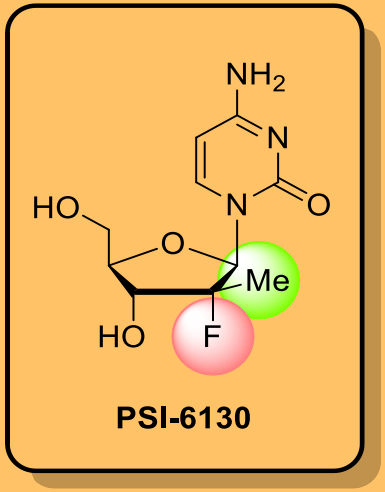
FdC



dFdC (Gemcitabine)



NM-107



PSI-6130

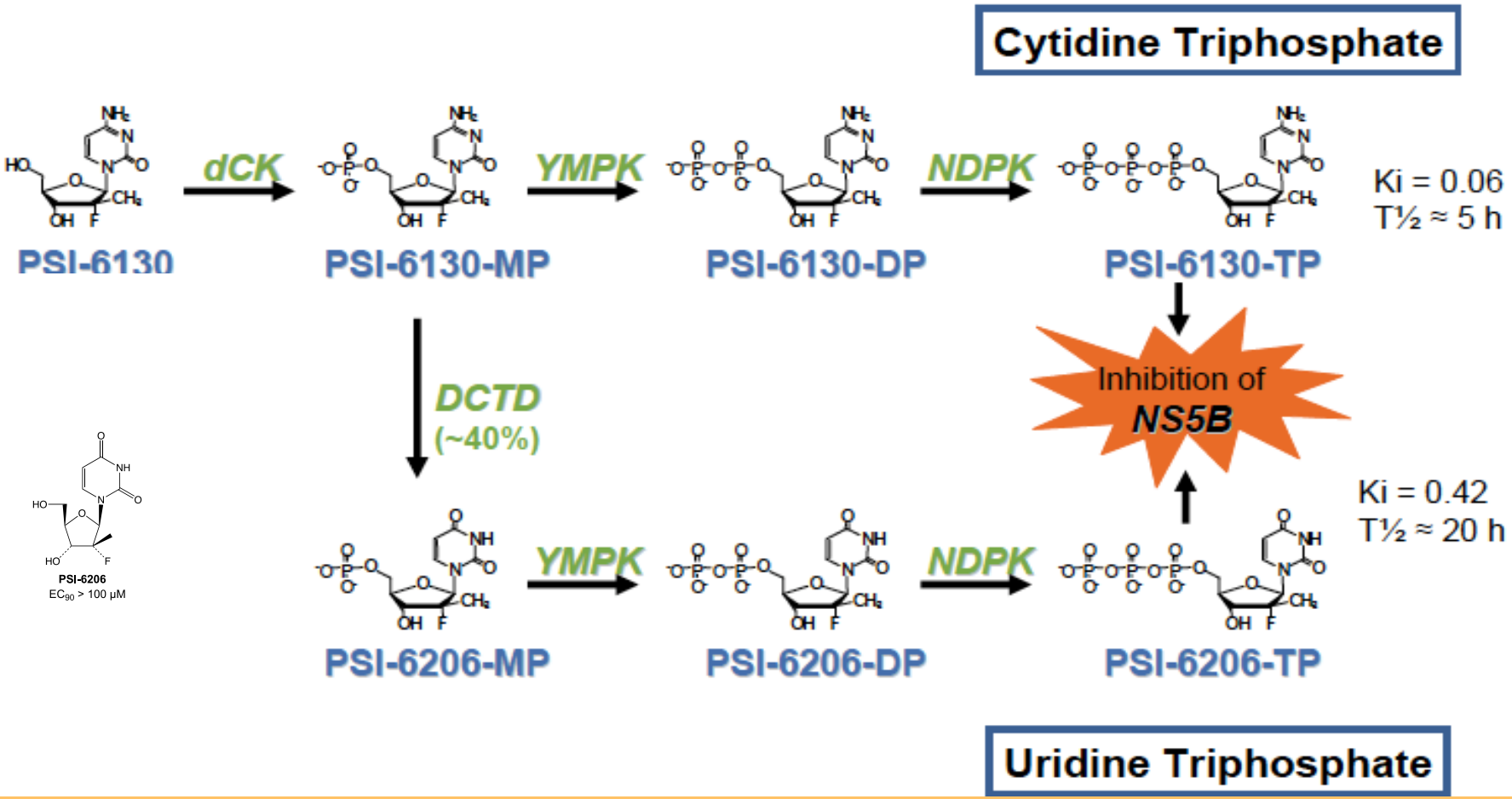
Difficult to select resistant HCV– S282T virus unfit

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

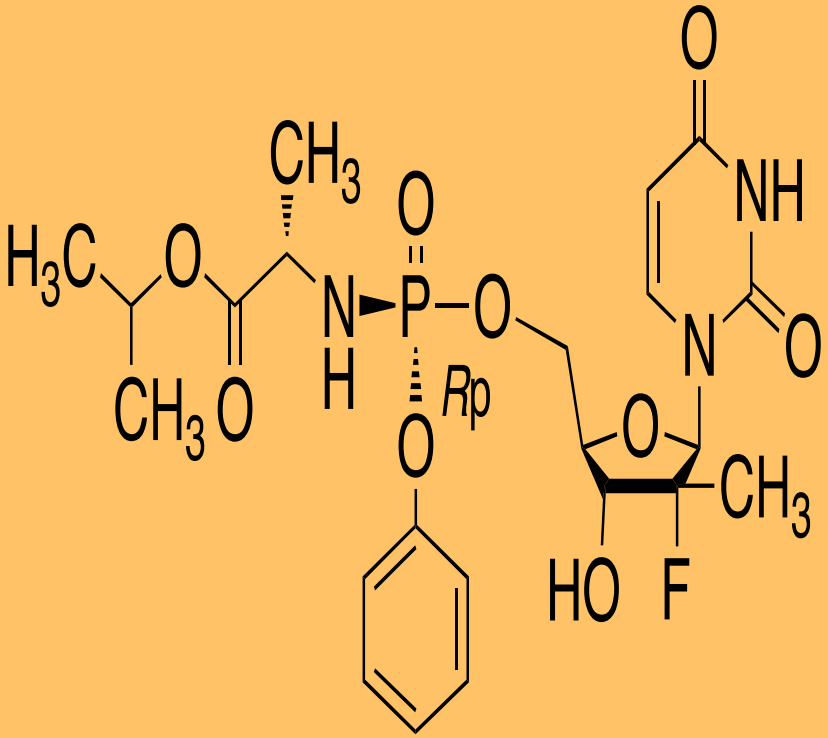
NM-107 : Sommadossi, J.-P.; La Colla, P. WO 2001092282 .

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



Clark, Schinazi et al, J Med Chem,, 48(17):5504-8, 2005; Asif, Schinazi et al, *AAC*: 51:2877-2882, 2007;
Murakami, Schinazi et al, AAC: 51, 503-9, 2007

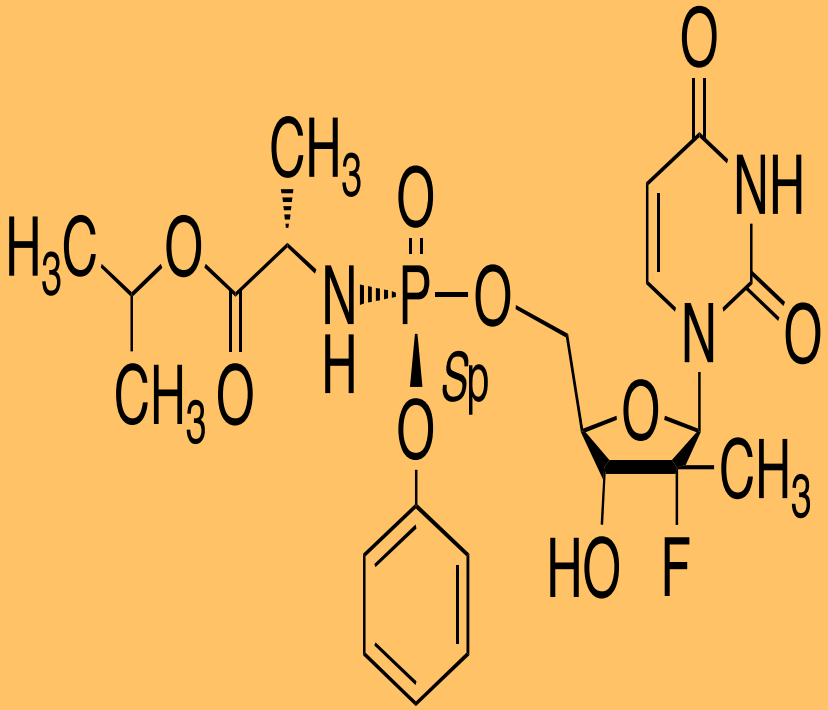
Activity of Diastereomericaly Pure Nucleotide Phosphoramidates



PSI-7976

HCV 1b replicon: EC_{90} = 7.5 µM (WT);

> 100 µM (S282T); 1.3 µM (S96T)



PSI-7977 (GS-7977, Sofosbuvir)

HCV 1b replicon: EC_{90} = 0.42 µM (WT);

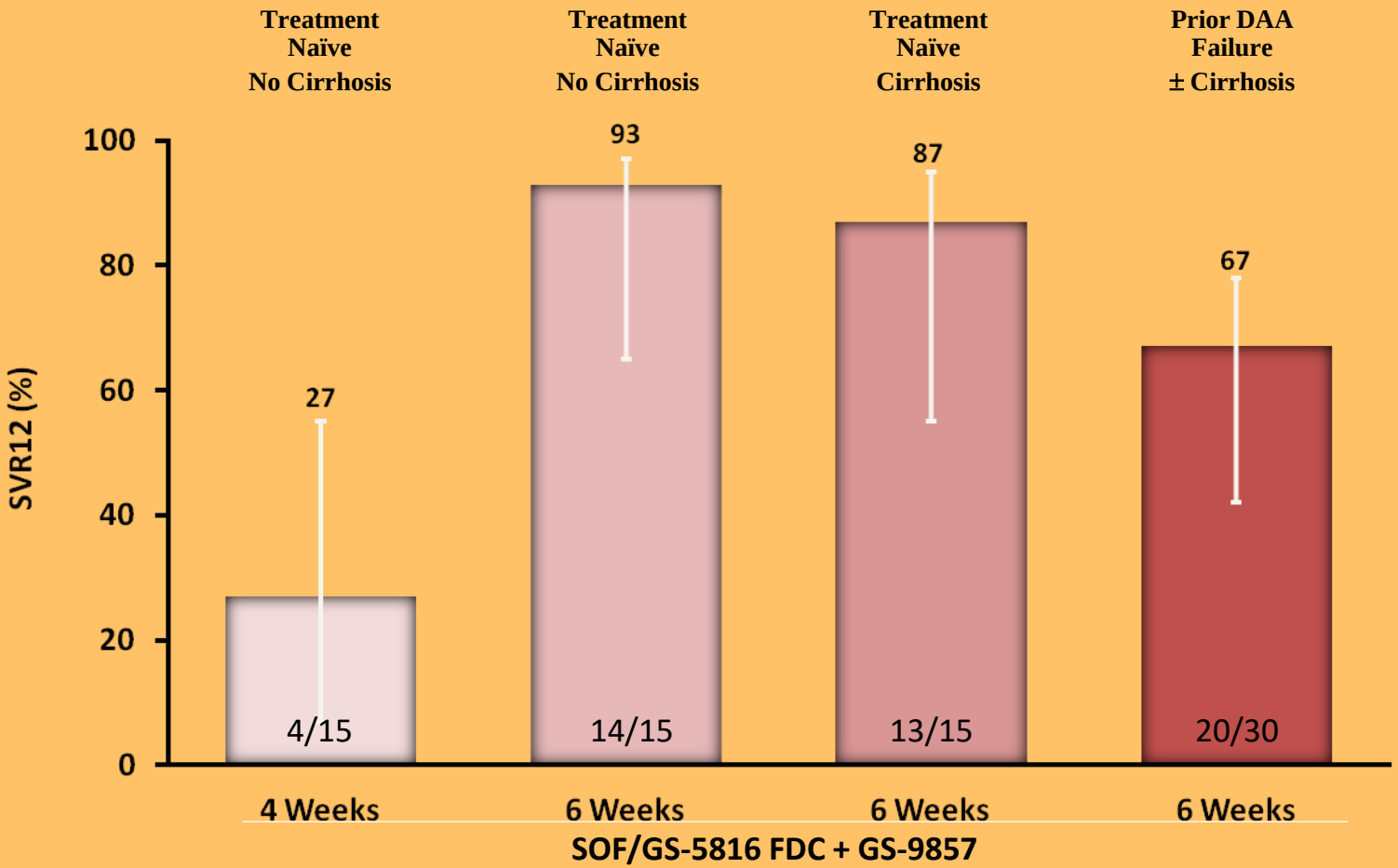
7.8 µM (S282T); 0.11 µM (S96T)

Truncation of therapy possible

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

- 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 subjectswho did not achieve SVR12
- For prior DAA failure, SVR12 in persons without cirrhosis was 68% (17/25) and with cirrhosis was 60% (3/5)

Gane et al. EASL 2015. Abstract LP03.

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

Lau, Schinazi et al., *Lancet Gastro Hepatol*, **1**(2):97-104, 2016.

SODAPI STUDY (3 x 3)

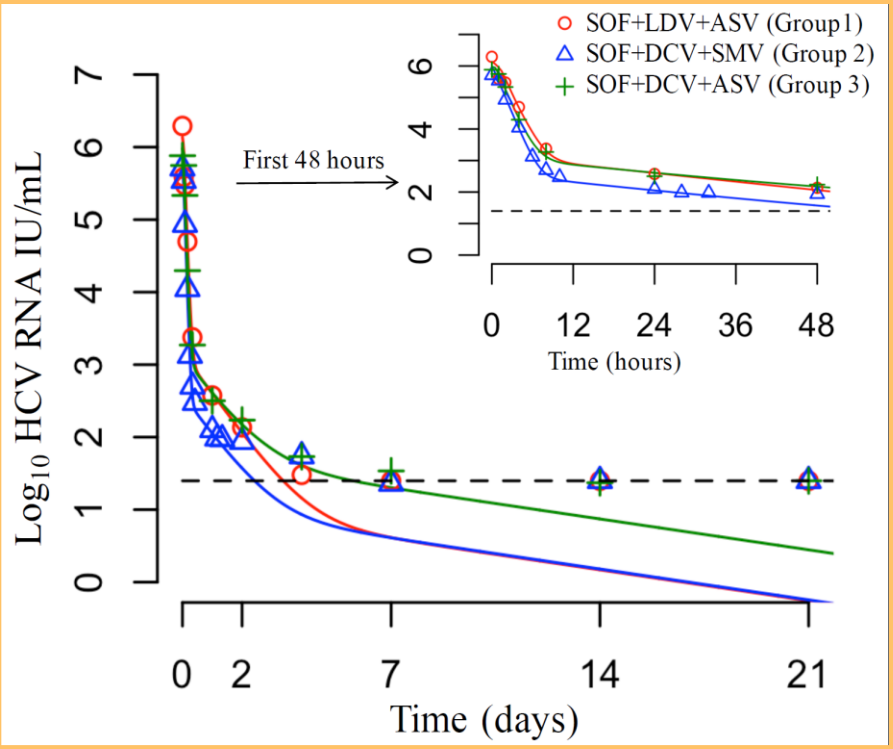
- Divided the **26** Chinese Naïve **genotype 1b** subjects into three groups. A “rapid virologic response” (RVR), defined as plasma viral RNA less than **500 IU/ml** by day two, was achieved in **18** persons (RGT; *Response Guided Therapy*).

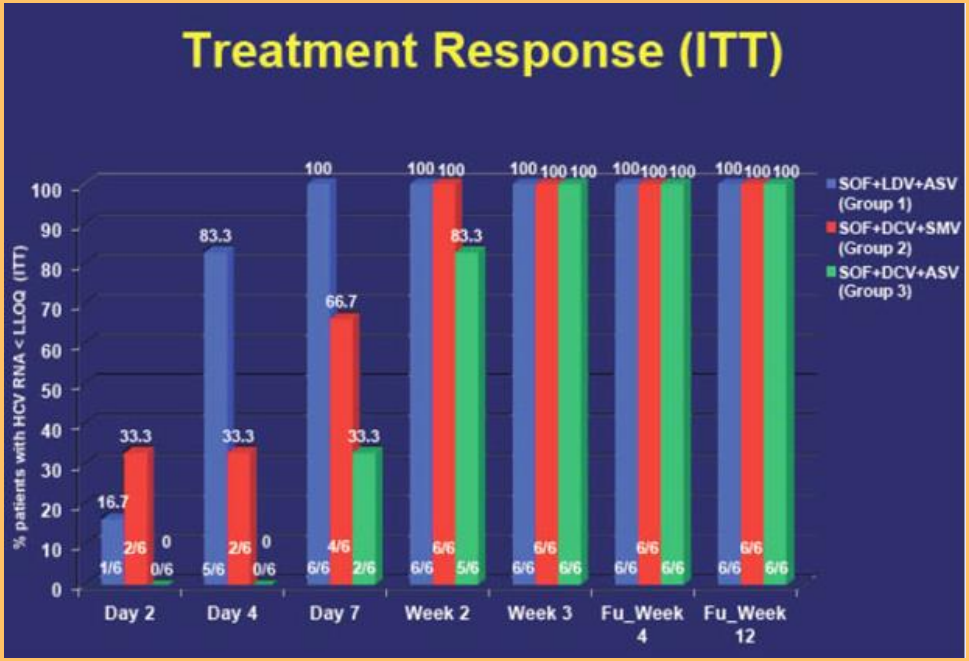
- Sofosbuvir, ledipasvir, asunaprevir (Harvoni, Sunvepra); RVR in 6/12
- sofosbuvir, daclatasvir, simeprevir (Sovaldi, Daklinza, Olysio); RVR in 6/6
- Sofosbuvir, daclatasvir, asunaprevir (Sovaldi, Daklinza, Sunvepra); RVR in 6/8

- 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





Lau, Schinazi et al., Lancet Gastro Hepatol, **1**(2):97-104, 2016. PMID: 27917405.

Ultra-short treatment duration in clinical trials with DAA regimens in HCV genotype 1 patients

DAA regimen	Duration (weeks)	Treatment-naïve	Cirrhotic Status	SVR %	Clinical Trial
Sofosbuvir and Odalasvir	6	Yes	No	100 (12/12)	PROXY (33)
Ledipasvir, Sofosbuvir, and GS-9669	6	Yes	No	95 (19/20)	SYNERGY (28)
Ledipasvir, Sofosbuvir, and GS-9451	6	Yes	No	95 (19/20)	SYNERGY(28)
Sofosbuvir, Ledipasvir, and Ribavirin	6	Yes	No	68 (17/25)	ELECTRON (32)
Sofosbuvir, Velpatasvir, Voxilaprevir (formerly, GS-9857)	6	Yes	No	93 (14/15)	LEPTON(30)
Grazoprevir, Elbasvir, Sofosbuvir	6	Yes	No	87 (26/30)	C-SWIFT(29)
Daclatasvir, Asunaprevir, Beclabuvir and Sofosbuvir	6	Yes	No	57 (8/14)	FOURward(31)
Grazoprevir, Elbasvir, Sofosbuvir	6	Yes	Yes	80 (16/20)	C-SWIFT(29)
Sofosbuvir, Velpatasvir, Voxilaprevir	6	Yes	Yes	87 (13/15)	LEPTON(30)
Ledipasvir, Sofosbuvir, GS-9451	6	Yes	Yes (40%)	72 (18/25)	SYNERGY(27)
Sofosbuvir, Velpatasvir, Voxilaprevir	6	No	Yes	67 (20/30)	LEPTON(30)
Ledipasvir, Sofosbuvir, GS-9451	6	No	Yes (48%)	80 (20/25)	SYNERGY(27)
Ledipasvir, Sofosbuvir, GS-9451	4	Yes	No	40 (10/25)	SYNERGY(26)
Ledipasvir, Sofosbuvir, GS-9451, GS-9669	4	Yes	No	20 (5/25)	SYNERGY(26)
Grazoprevir, Elbasvir, Sofosbuvir	4	Yes	No	32 (10/31)	C-SWIFT(29)
Sofosbuvir, Velpatasvir, Voxilaprevir	4	Yes	No	27 (4/15)	LEPTON(30)
Daclatasvir, Asunaprevir, Beclabuvir and Sofosbuvir	4	Yes	No	29 (4/14)	FOURward(31)

Emmanuel B…..Kottilil S. Lau G. (2017) Lancet G&H (in press)

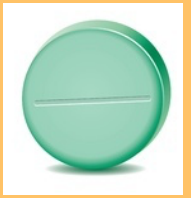
HCV approach: 3+ Direct-acting antiviral agents for ultra-short modalities

De-risked near-term approach creating multiple "shots on goal"

Pan-genotypic NS5B Nuc

Pan-genotypic NS5A Inhibitor

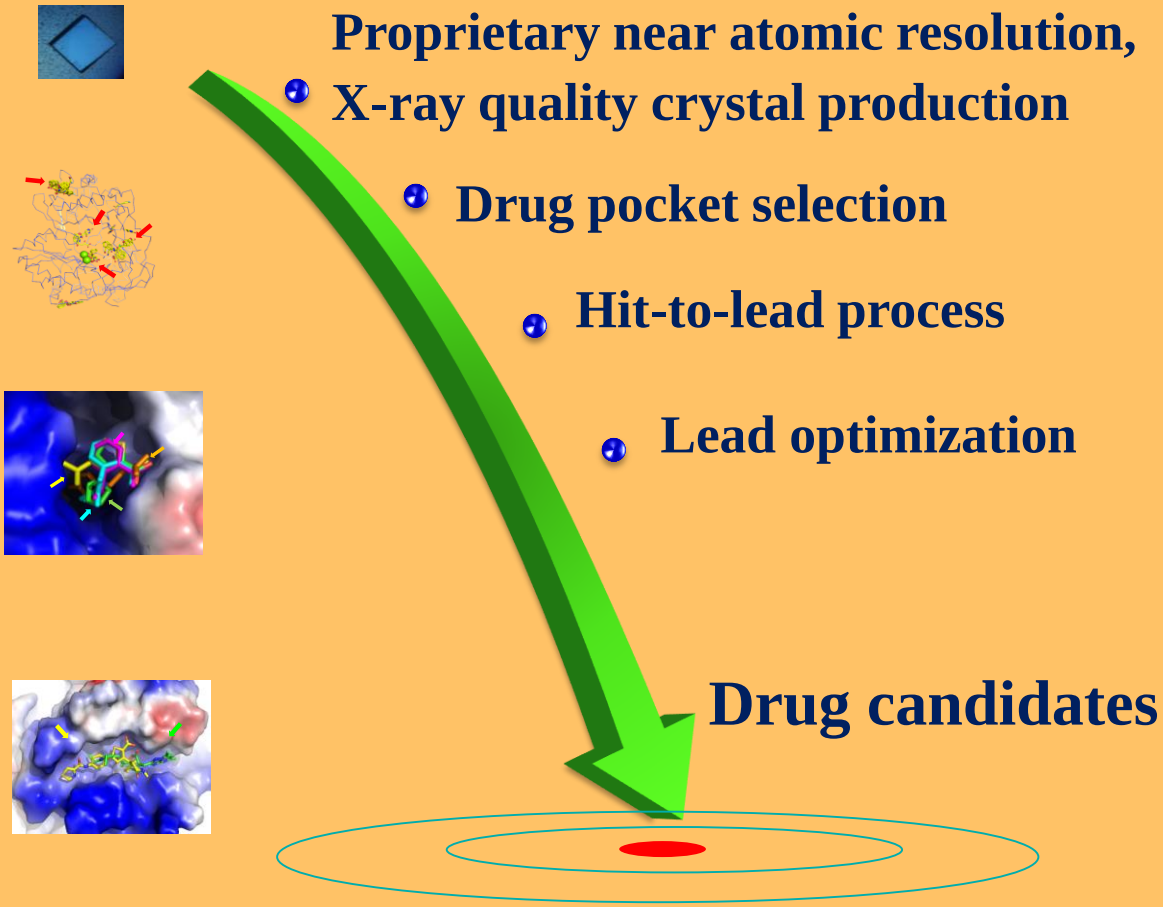
Pan-genotypic NS5B NNI



Pan-genotypic Helicase Inhibitor

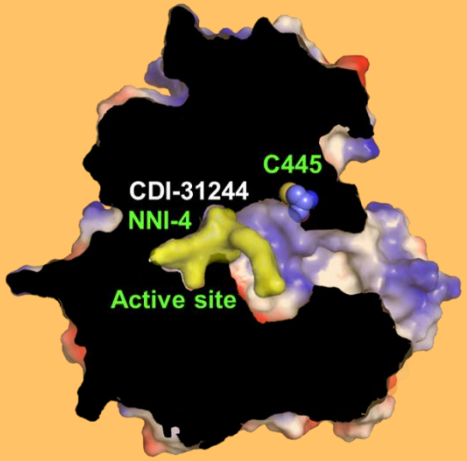
All oral pangenotypic HCV regimen

Structure-Based Drug Design & Discovery Process: Investing on Attractive Drug Binding Pockets



CC-31244 Developed By Cocrystal's Structure-based Drug Discovery Platform Technology

HCV GT1 – GT6 NS5B polymerase crystals



CC-31244: Pan-genotypic NS5B NNI

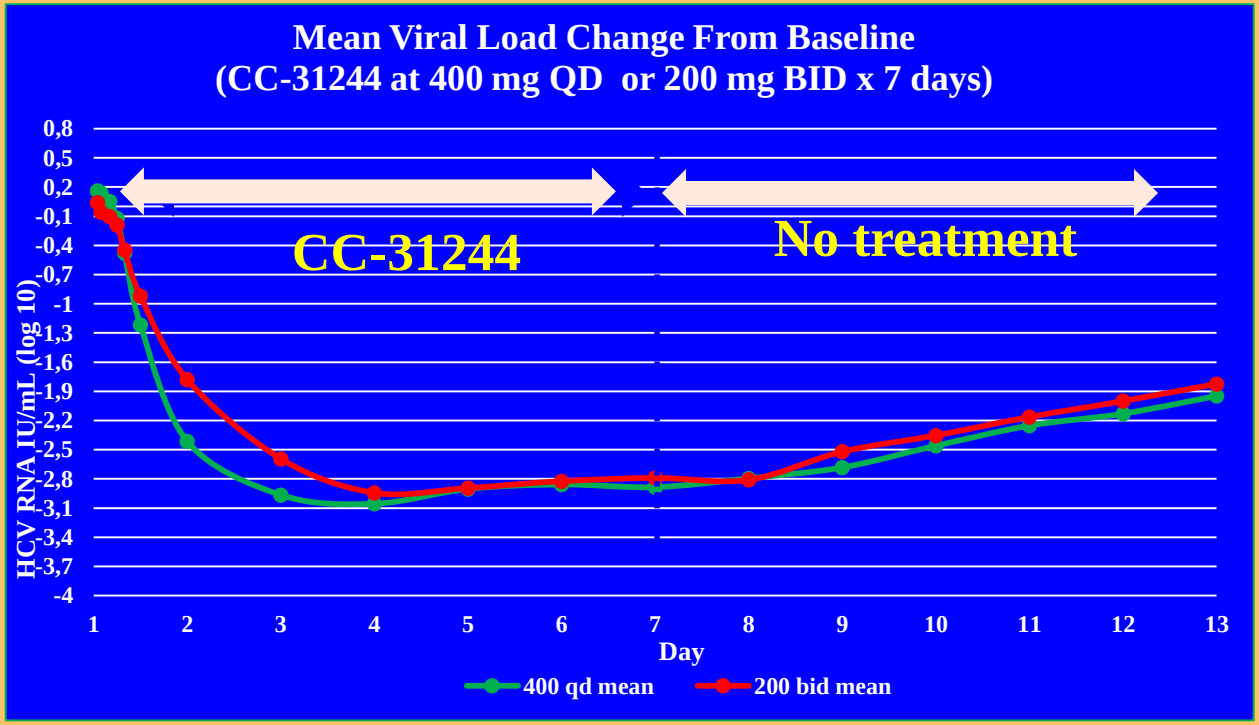
CC-31244 HCV replicon EC_{50} fold change, <6 fold

HCV replicon/chimeric replicon EC_{50} results

Genotype	CDI-31244 EC_{50}, μM	EC_{50} Fold change	Sofosbuvir EC_{50}, μM	EC_{50} fold change
1b	0.005	1.0	0.042	1.0
1a	0.009	1.8	0.034	0.8
2b	0.026	5.2	0.028	0.66
3a	0.011	2.2	0.14	3.2
4a	0.021	4.2	0.047	1.1
5a	0.002	0.4	0.075	1.7

Successful Viral Reduction in HCV GT1 Patients with HCV NNI, CC-31244

- HCV RNA viral load decline of **3 logs** by 48 hours
- After the NNI treatment, the viral load levels were slowly increased
- Drug resistance analysis ongoing



HCV NNIs: Viral Load Comparison: CC-31244 is Best in class NNI

Drug	Genotype	Dose (mg)	Treatment Duration (days)	Viral load reduction (Log_{10}IU/ml)
CC-31244 ←	Genotype 1-6 ←	400	7 (QD)	-3.0 ←
ABT-333* (Dasabuvir)	Genotype 1	400	3 (BID)	-1.08
		800	3 (BID)	-0.95
GS-9190 (Tegobuvir)	Genotype 1	40	3 (BID)	-1.0
		120	3 (BID)	-1.5

* FDA approved DAA

CC-31244 will be useful for ultrashort therapy and for salvage HCV therapy

As of April 2017, about 2 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 expectency**

Nanopatricles 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

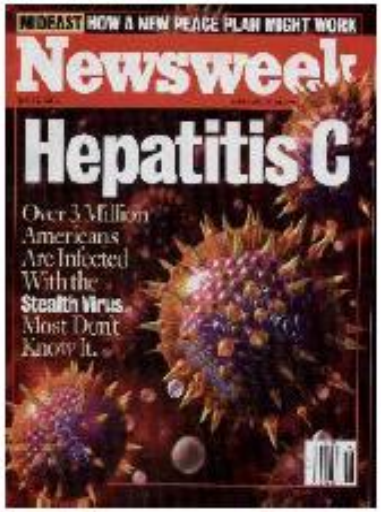
Think about Cure rather than Tx or band-aids

From Z-Pak to C-Pak?

C-PAK®

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

Global Threat of Infectious Diseases



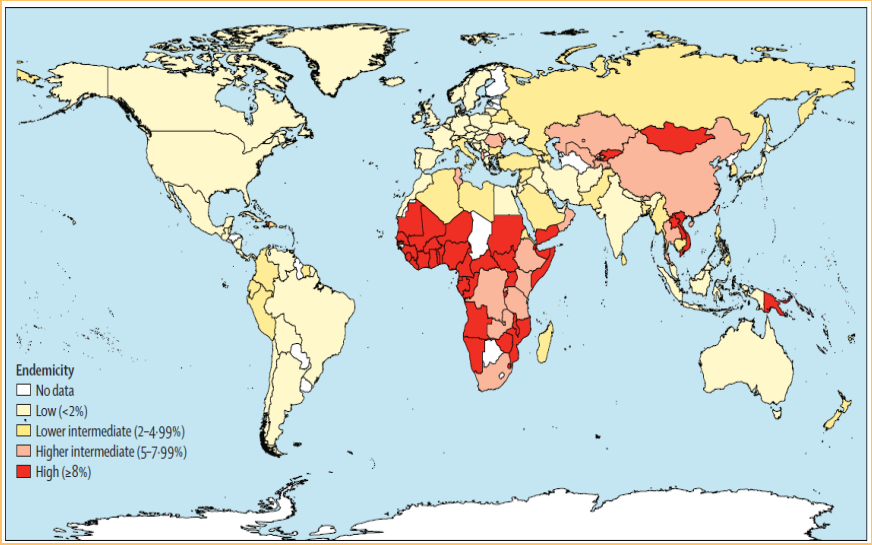
HIV **Hepatitis** **Zika Virus** **Ebola** **???**

- Viruses are one of the leading causes of morbidity and mortality worldwide.
- Emerging and reemerging virus strains constantly pose global health risks, including pandemics.

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**

- **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)***



•Schweitzer, a, *et al.*; *Lancet* (2015) 386: 1546-1555.

IS HBV ERADICATION POSSIBLE?

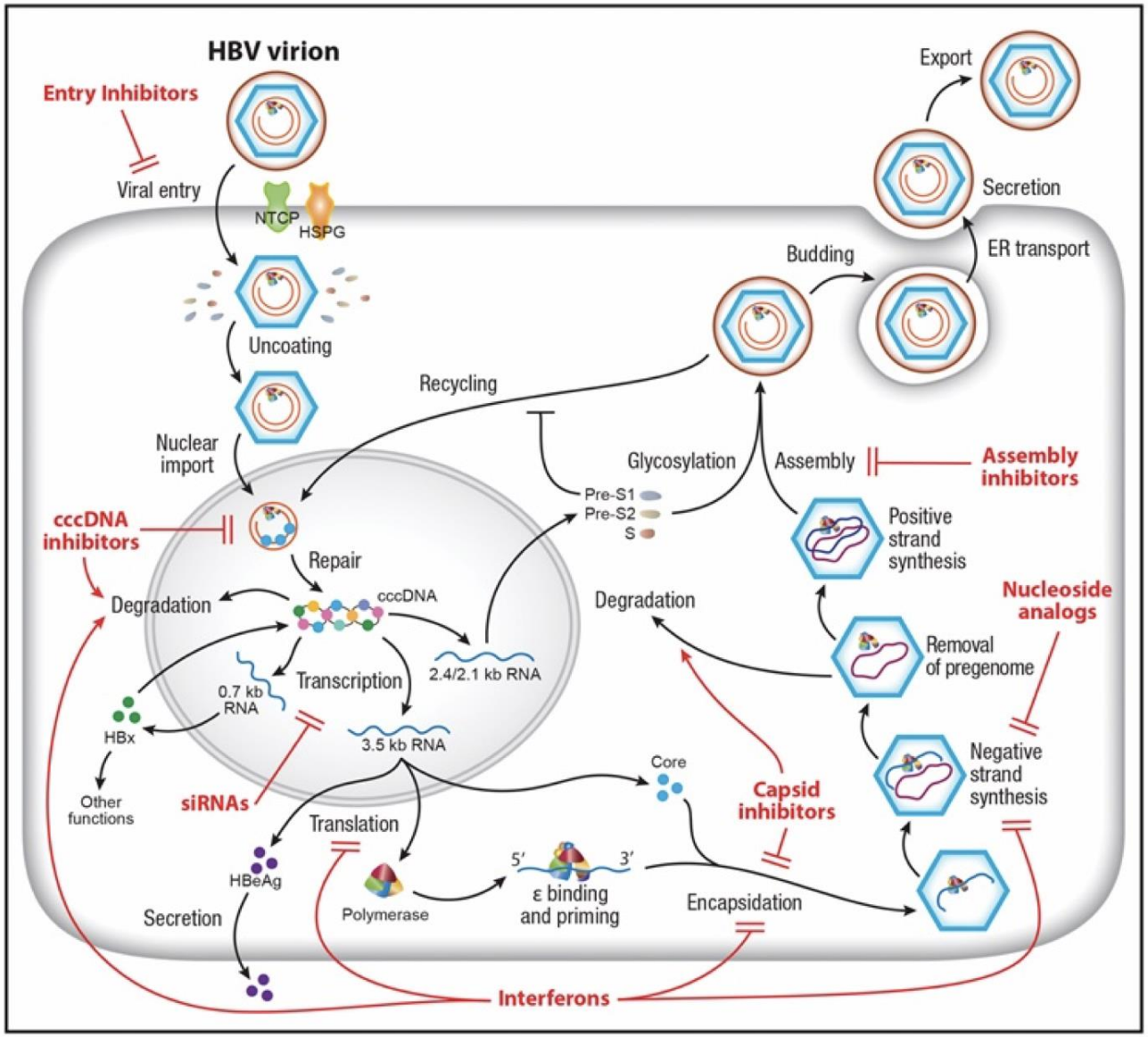
Impossible n'est pas Français

Everything is theoretically impossible until done

Robert Anson Heinlein,

American Science Fiction writer

Multiple Targets For Antiviral Therapies

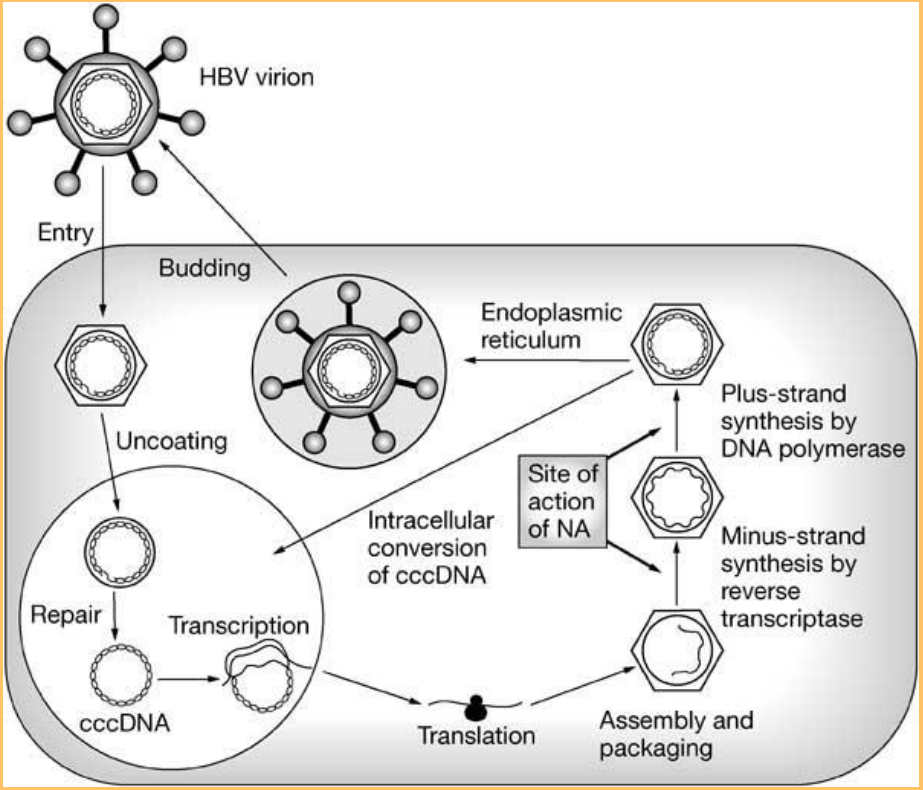


Barriers to Eradicating HBV

- ccc DNA
  - Long $t_{1/2}$
  - 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

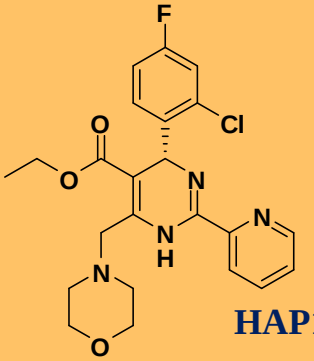
Role of Capsid in Viral Replication Cycle



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

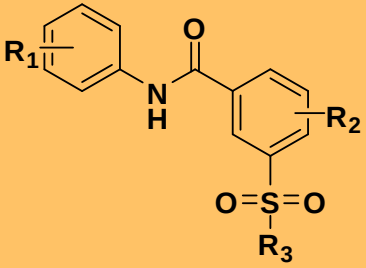
Capsid Effectors as HBV Antiviral Agents

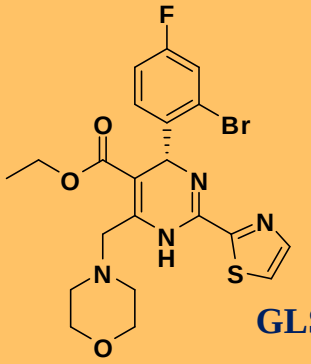
Phenylpropenamides **HeteroArylPyrimidines (HAP)**



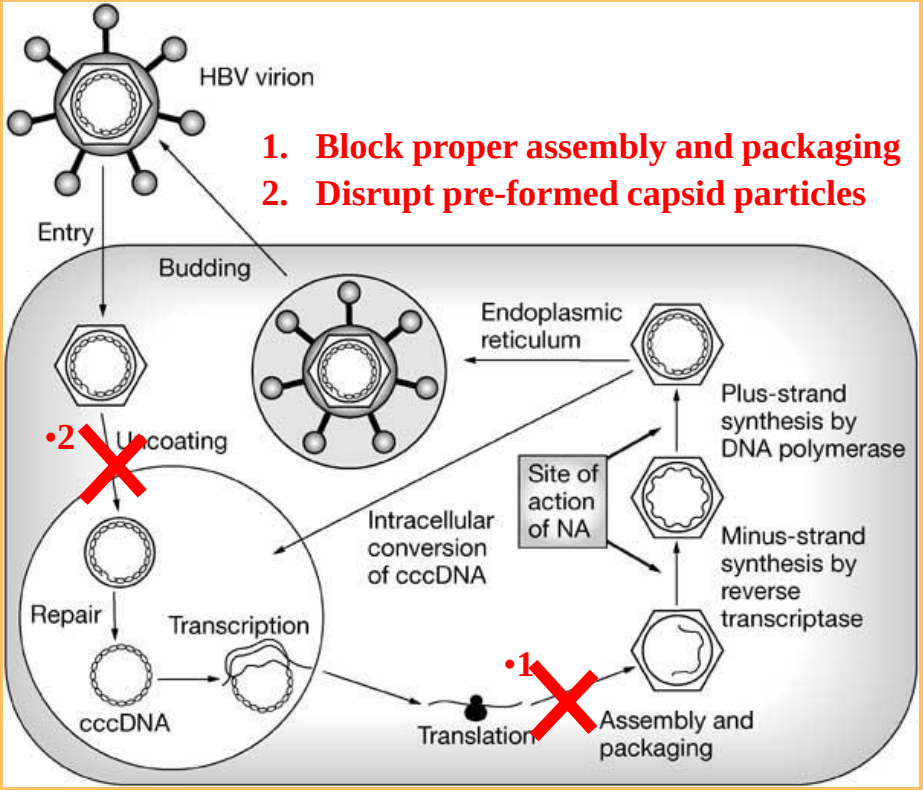
HAP12

Sulfamoyl Carboxamides





GLS4

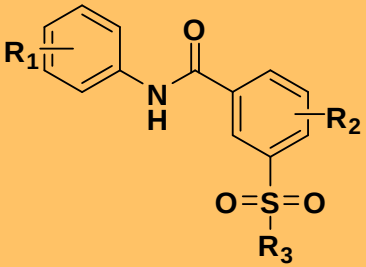


Boucle, S *et al.*; *Clinics in Liver Disease* (2016)

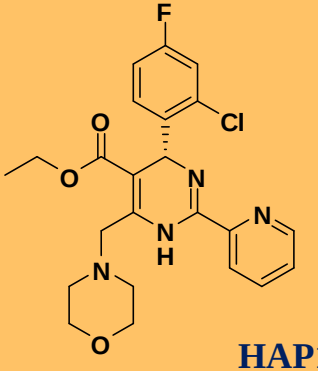
Capsid Effectors Deplete cccDNA

Phenylpropenamides

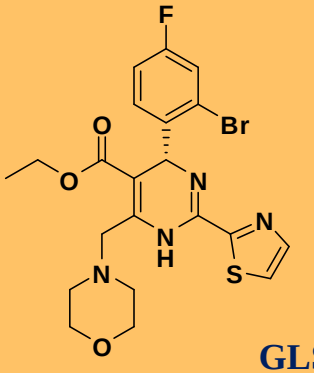
Sulfamoyl Carboxamides



HeteroArylPyrimidines (HAP)

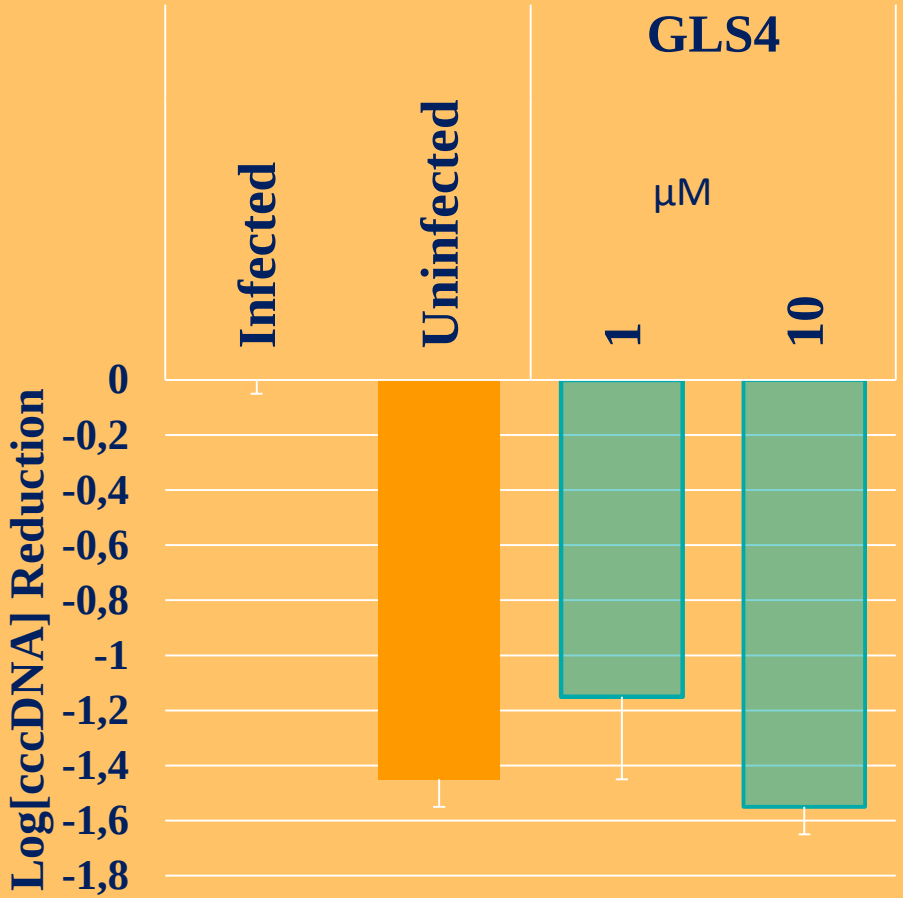


HAP12



GLS4

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



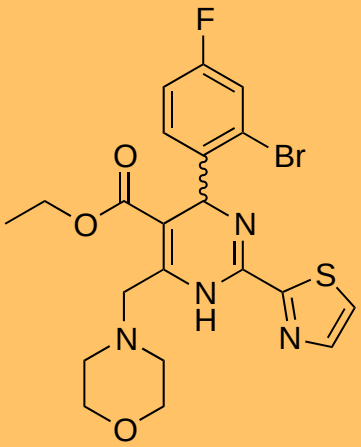
Discovery of a new class of non-nucleoside inhibitors

HepAD38 system

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

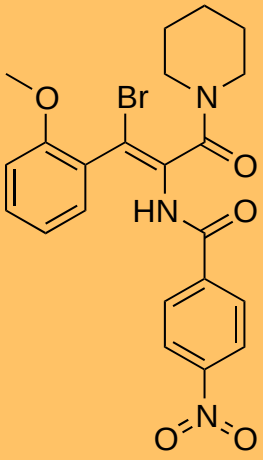
Capsid Assembly Effectors

Class 1
HAP analogs



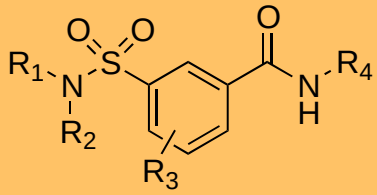
GLS4

Class 2
Phenylpropenamides



AT-130

Sulfamoylbenzamides



NVR 3-778

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

GLP

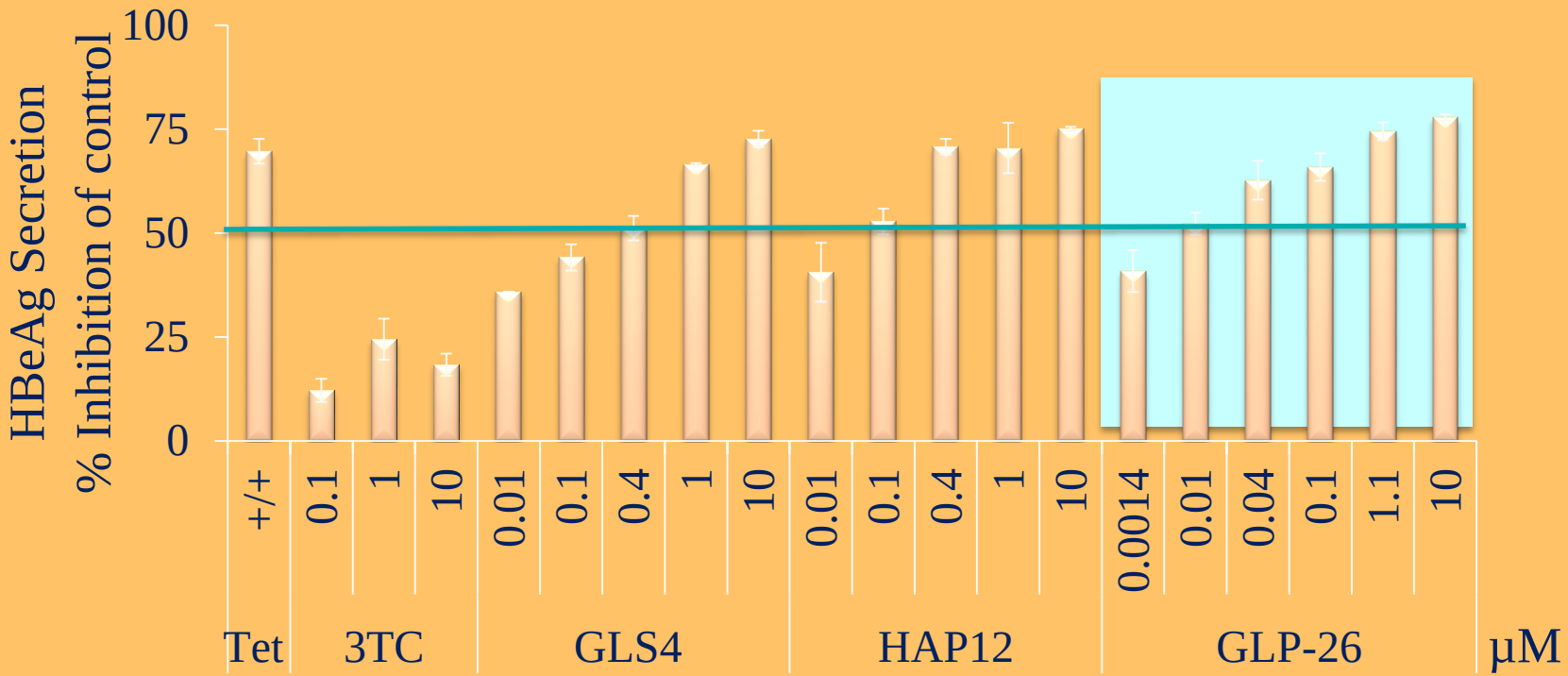
HAP, Heteroaryldihydropyrimidines

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

	Potency		Cytotoxicity HepG2
Drugs	Anti-HBV Activity		Therapeutic index
	EC_{50}, μM	EC_{90}, μM	IC_{50}/EC_{50}
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

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

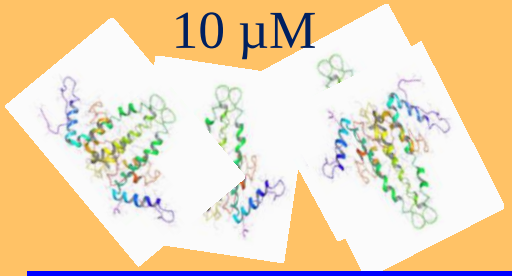


		3TC	GLS4	HAP12	GLP-26
HBeAg	EC_{50}, µM	> 10	0.16	0.03	**0.003**

Monitoring HBV Capsid Assembly using Electron Microscopy

Capsid Formation Assay

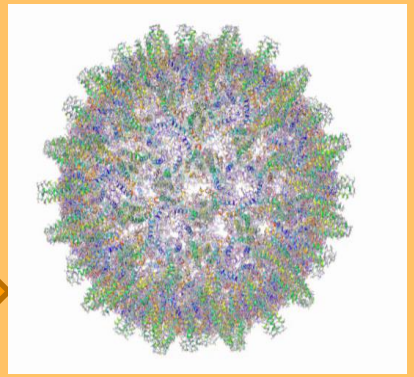
HBV Cp149
10 µM



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

Induce Assembly

+ 500 mM NaCl, 4°C overnight



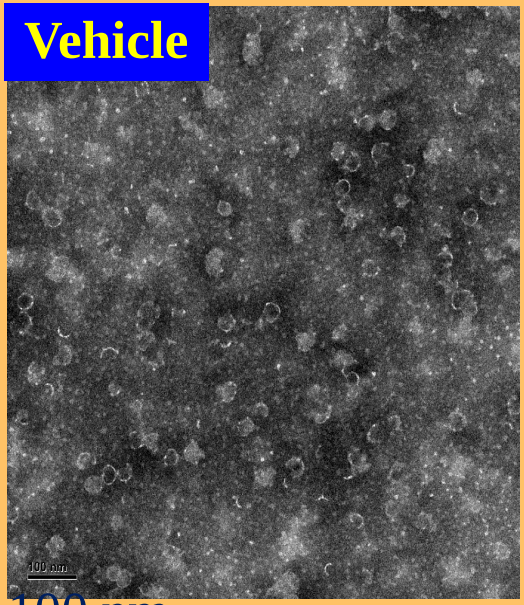
HBV Cp149 Capsid

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

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

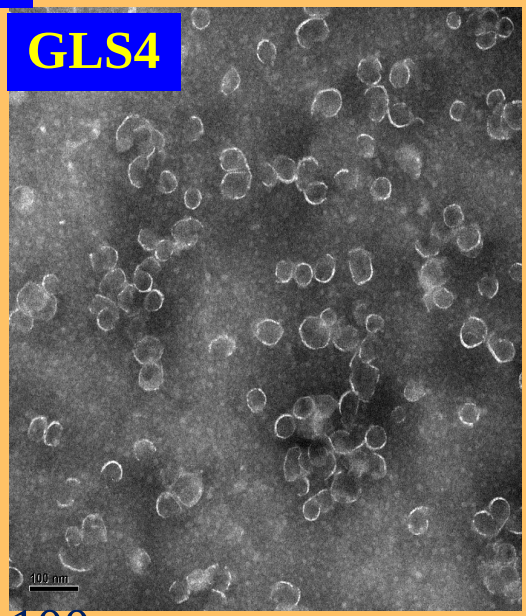
GLP-26 – Inhibition?
- **Incomplete hollow spheres**
- **Low abundance**
- **Diameter < 20 nm**

Vehicle



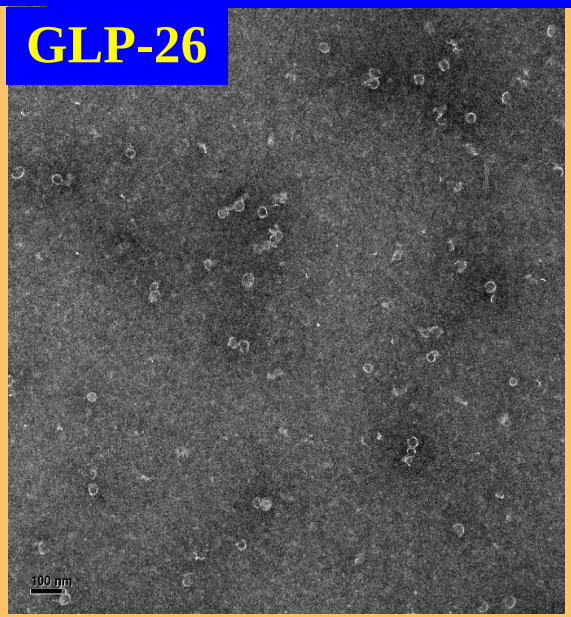
100 nm

GLS4



100 nm

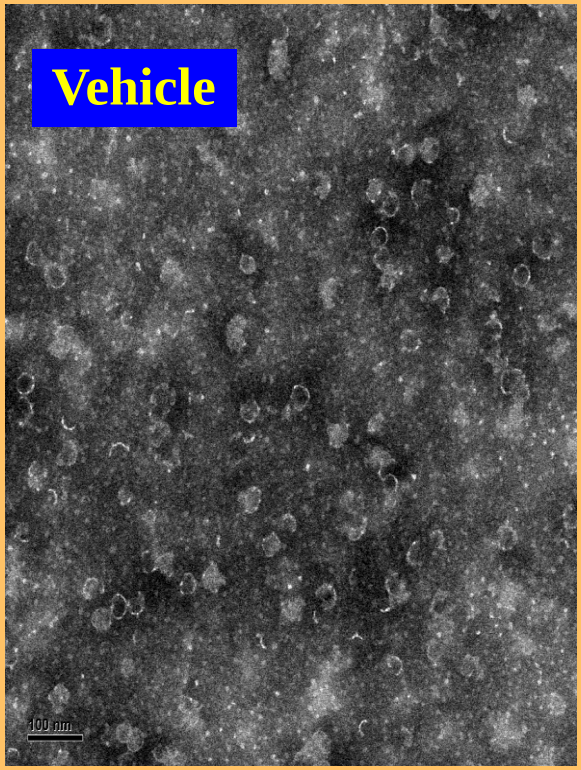
GLP-26



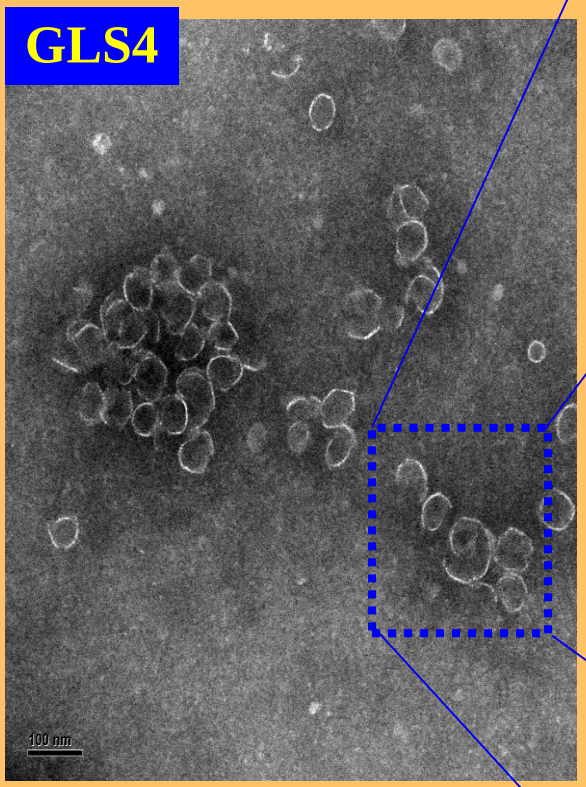
100 nm

Capsid Disruption Results – GLS4

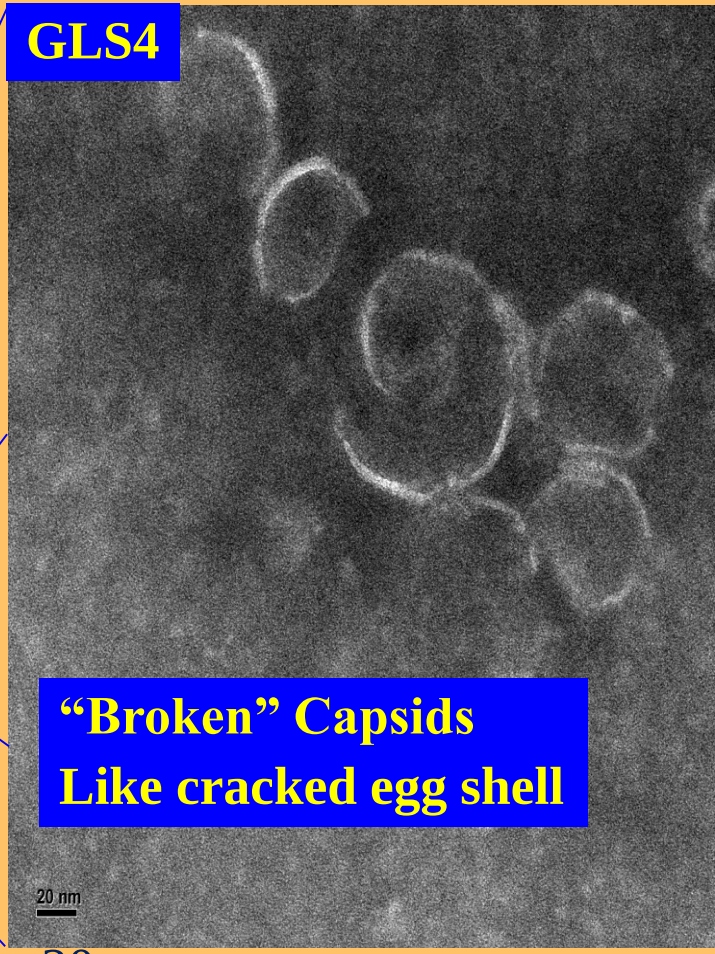
A picture is worth 1,000 words



100 nm

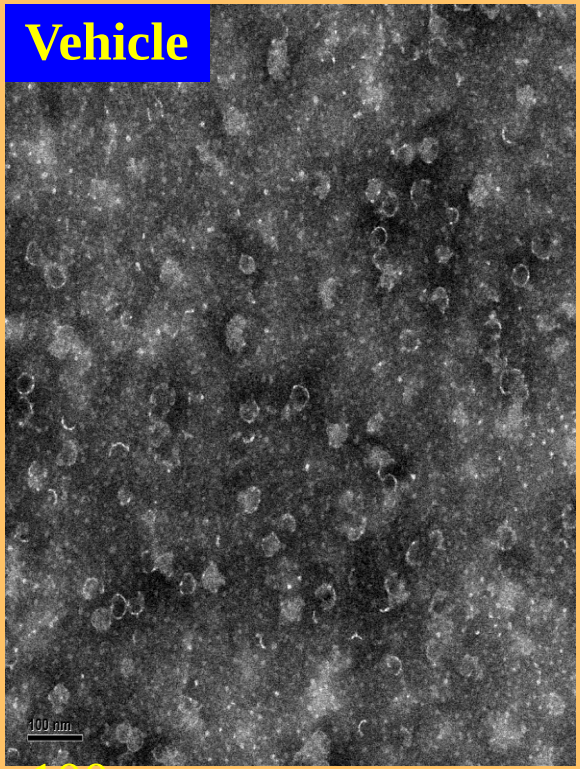


100 nm

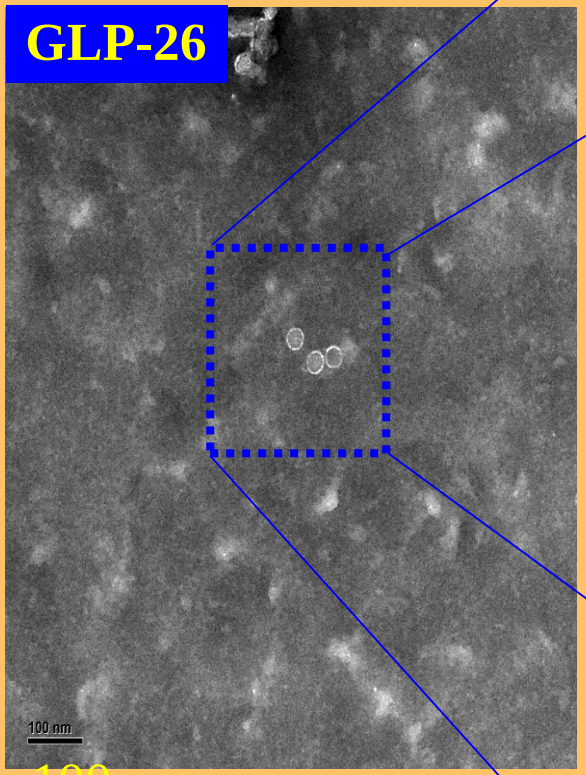


20 nm

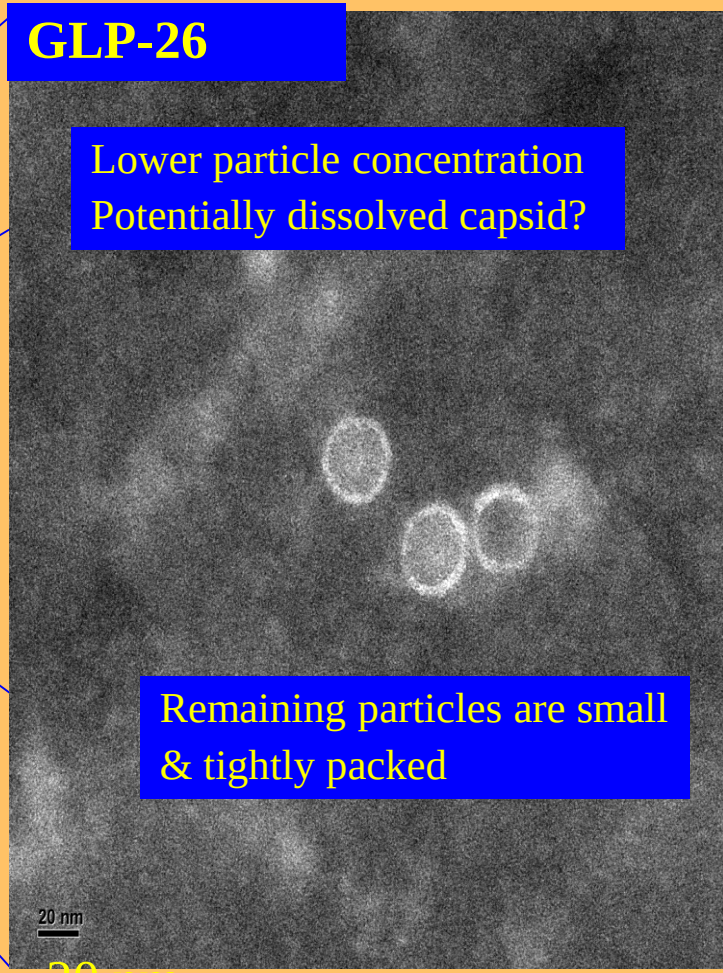
HBV Capsid Disruption Results – GLP-26



•100 nm



•100 nm



•20 nm

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 (up to 3.5 logs decline)**
- ✓ **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!

Thank You

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

Raymond F. Schinazi (PI), Sebastien Boucle, Fanck Amblard, Leda C. Bassit, and Team of 53 scientists and staff

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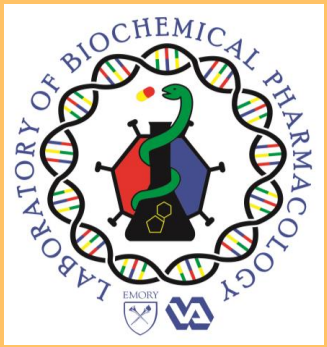
George Lau, Alan Perelson, and HK Team

Jaime Rabi (Microbiologica, Brazil)

Hélène Strick-Marchand (Pasteur)

CoCrystal Pharma, Inc (Nasdaq: COCP)



Supported by NIH, CFAR

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