The HBV pipeline and what the SIG can offer

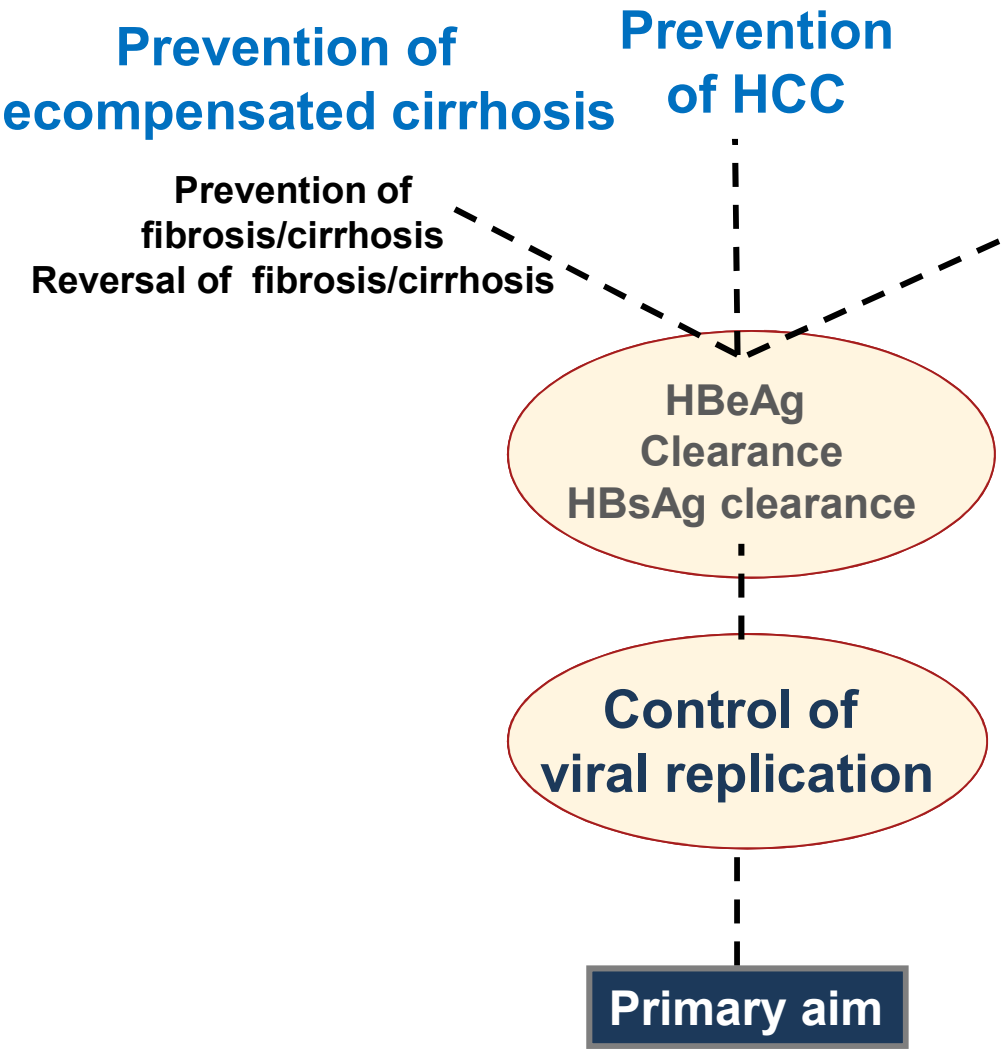
Current treatments and definition of cure

- Where can we get to with current therapies?
  - Special interest group possibilities
- Where are we headed with HBV “cure” and how is cure being defined?
  - Select therapeutic targets
  - Special interest group possibilities

Current treatments and definition of cure

- Where can we get to with current therapies?
- Where are we headed with HBV “cure” and how is cure being defined?

Therapeutic goals in hepatitis B



Risk of progression

- HBV DNA (HBeAg) HBsAg
- Fibrosis stage of disease
- HBV genotype
- Age, gender, family history
- Coinfection HDV, HCV and HIV
- Environmental (alcohol, smoking, aflatoxin)
- Diabetes mellitus

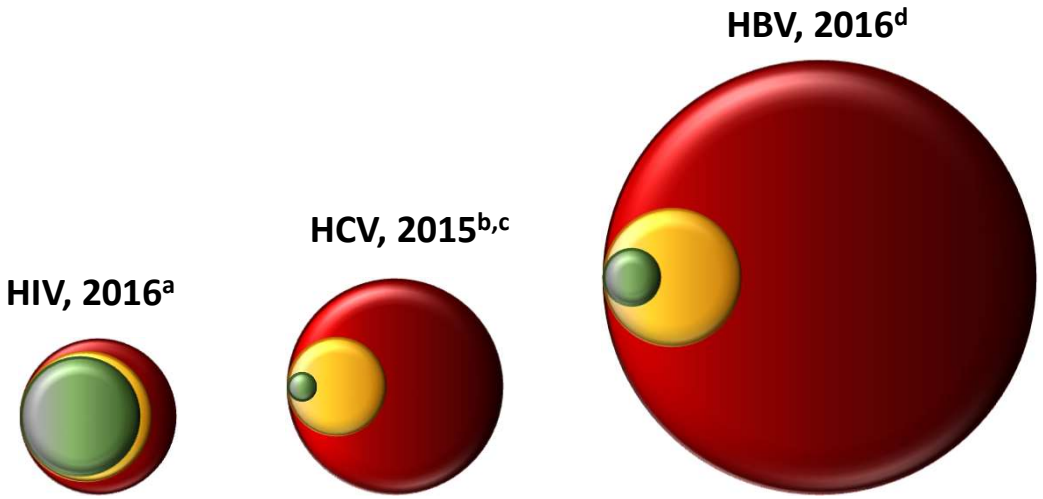
- 1. EASL Clinical Practice Guidelines. J Hepatol 2012;57:167–85;
  2. Liaw YF, et al. Hepatol Int 2012;6:809–10; Marcellin Lancet 2103: 381, 468
  3. Lok A, McMahon B. Hepatology 2009;50:661–2,1–36.; Wong G Hepatology 2013: 58:1537; Kim Hepatology 2017: 66:335

Current treatment strategies: HBV

HBeAg positive and negative				
PEG IFN	NUC	NUC + PEG IFN	Cessation NUC	Add on /switch NUC IFN
Finite duration	Long term	Finite duration	Finite duration	Finite duration
HBeAg loss HBV DNA UD HBsAg loss	HBV DNA suppression HBeAg UD	HBsAg loss	HBsAg loss	HBsAg loss
Poor tolerability	Oral; tolerability	Poor tolerability	Greater tolerability	Poorer tolerability
No resistance heterogenous response	Low resistance	Heterogeneous response	Heterogenous response	Heterogenous response
Excludes decompensated cirrhosis	Decompensated cirrhosis	Excludes decompensated cirrhosis	Compensated liver disease; HBeAg negative?	Excludes decompensated cirrhosis

NUC nucleoside analogue; PEG IFN pegylated interferon; UD undetectable

Gaps in prevalence, diagnosed and treated – HIV, HCV, HBV



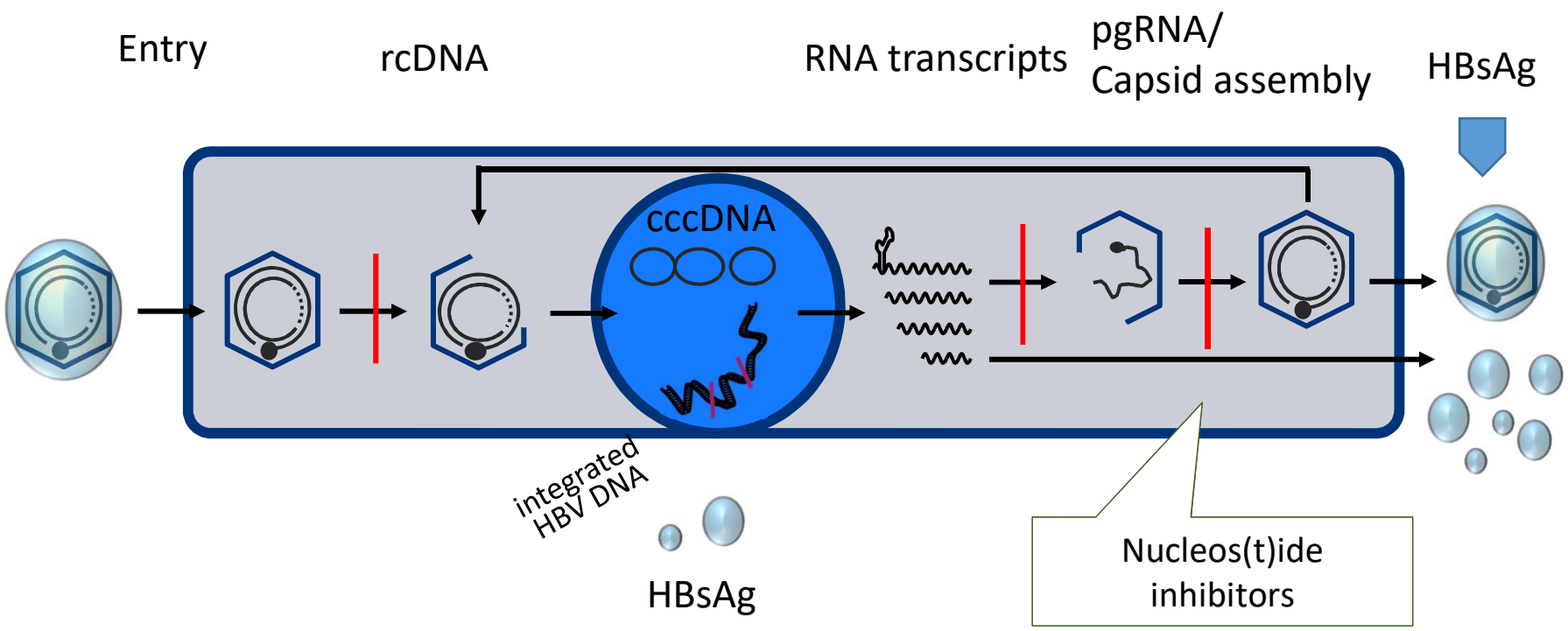
Global Estimates in Million of Patients			
Prevalence	36.7	71.1	292.0
Diagnosed	25.7	14.2	28.8
Treated	20.9e	1.1	4.8

a. UNAIDS Fact Sheet, World AIDS Day 2017. http://www.unaids.org/en/resources/fact-sheet; b. Blach et al., *Lancet Gastroenterol. Hepatol.*, 2017.
c. WHO Global Hepatitis Report, 2017. http://www.who.int/hepatitis/publications/global-hepatitis-report2017-executive-summary/en/;
d. Razavi et al., *Lancet Gastroenterol. Hepatol.*, 2018; e. 2017 data.

Courtesy John Martin

Nucleoside analogues: effect on HBV replication but little effect on cccDNA and HBsAg

Continued transcription from cccDNA and integrated viral genomes: relatively minor decrease serum HBsAg nucleoside analogue therapy despite undetectable serum HBV DNA



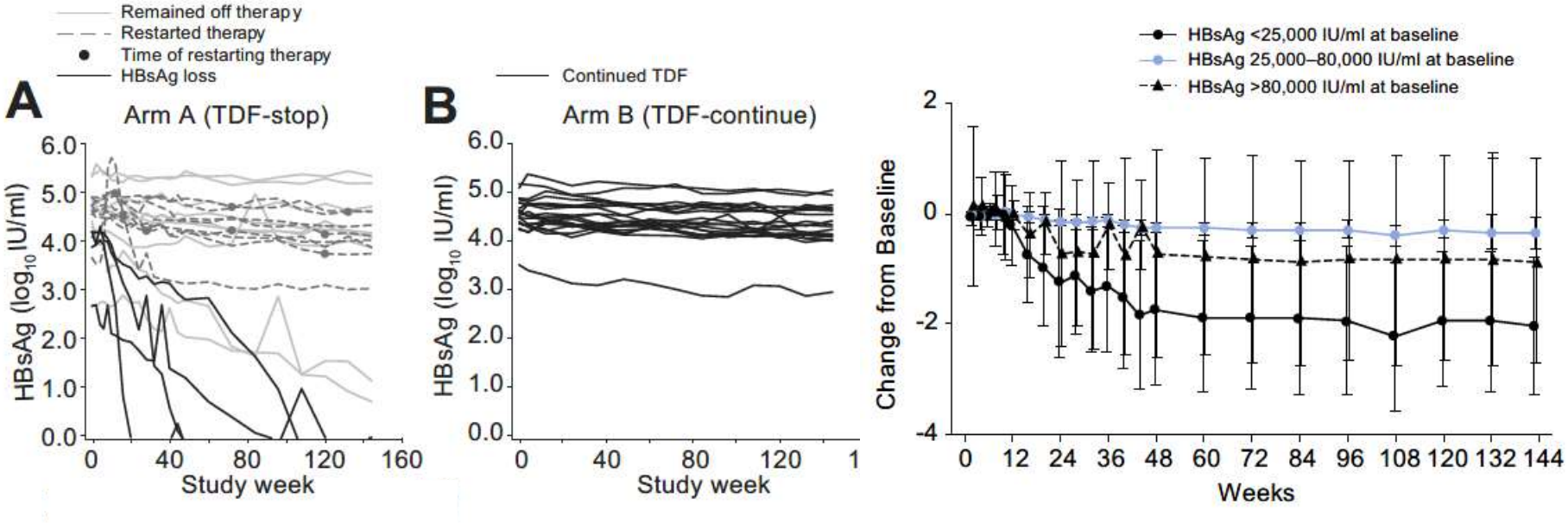
rcDNA – relaxed circular DNA; cccDNA –covalently closed DNA; pgRNA pre-genomic RNA

How many pills to control disease?

HIV	HBV	HCV
20.9 million patients on treatment	150 million patients need treatment	71 million patients need treatment
1 pill/day 365 pills/year for rest of life	1 pill/day 365 pills/year for rest of life	1 pill/day 84 pills for 12 weeks
7.6 billion pills in one year	54.7 billion pills in one year	6 billion pills

Therapeutic responses: HBsAg declines FINITE study

Median HBsAg change in this group was -0.59 log_{10} IU/ml (range -4.49 to 0.02 log_{10}IU/ml) vs. 0.21log10IU/ml in patients who continued TDF therapy. Four patients (19%) achieved HBsAg loss.



Berg, T., et al. (2017) Hepatol **67**(5): 918-924.

Some SIG possibilities?

- Immunological profiling nucleotide analogues (cessation)
- Elimination strategies: (control and treatment)
  - Big data access
- HCC development
- NIHR Research and Innovation for Global Health Transformation
- New biomarkers
- Point of care nucleic acid testing: microfluidic engineering and miniaturisation
- HCC treatment: T cell engineering
- HDV: natural history, pathogenesis, treatment

Current treatments and definition of cure

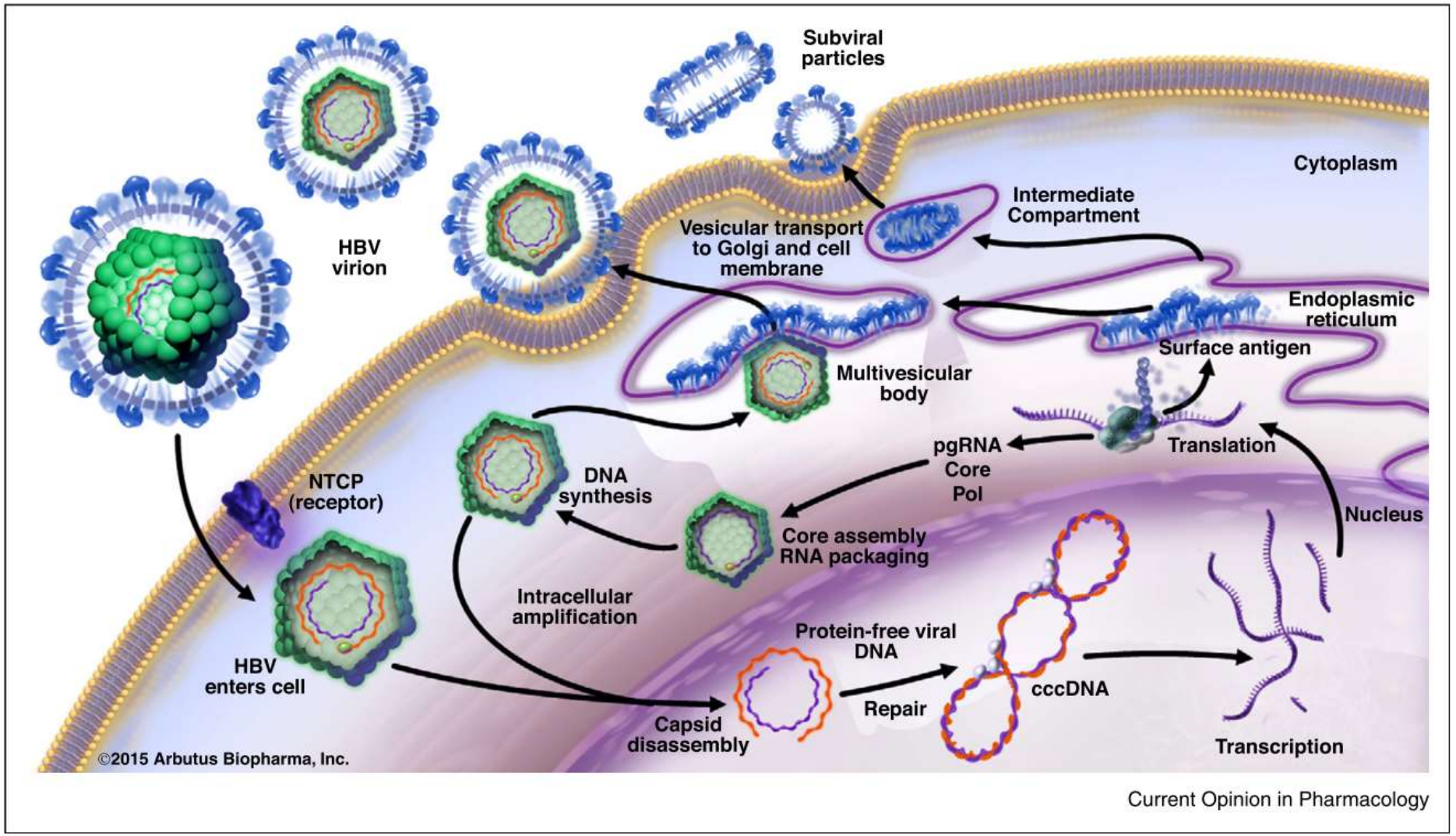
- Where can we get to with current therapies?
- Where are we headed with HBV “cure” and how is cure being defined?
  - Markers utilised – for therapy and prognosis

Three definitions of HBV cure
AASLD EASL consensus

- Complete sterilizing cure
  - Undetectable HBsAg in serum and eradication of HBV DNA including intrahepatic cccDNA and integrated HBV DNA.
- Functional cure
  - Sustained, undetectable HBsAg and HBV DNA in serum with or without seroconversion to anti-HBs after completion of a finite course of treatment
  - resolution of residual liver injury and a decrease in risk of HCC over time.
- Partial cure
  - Detectable HBsAg but persistently undetectable HBV DNA in serum after completion of a finite course of treatment.

Lok, Zoulim Dusheiko and Ghany Hepatology and Journal of Hepatology 2017

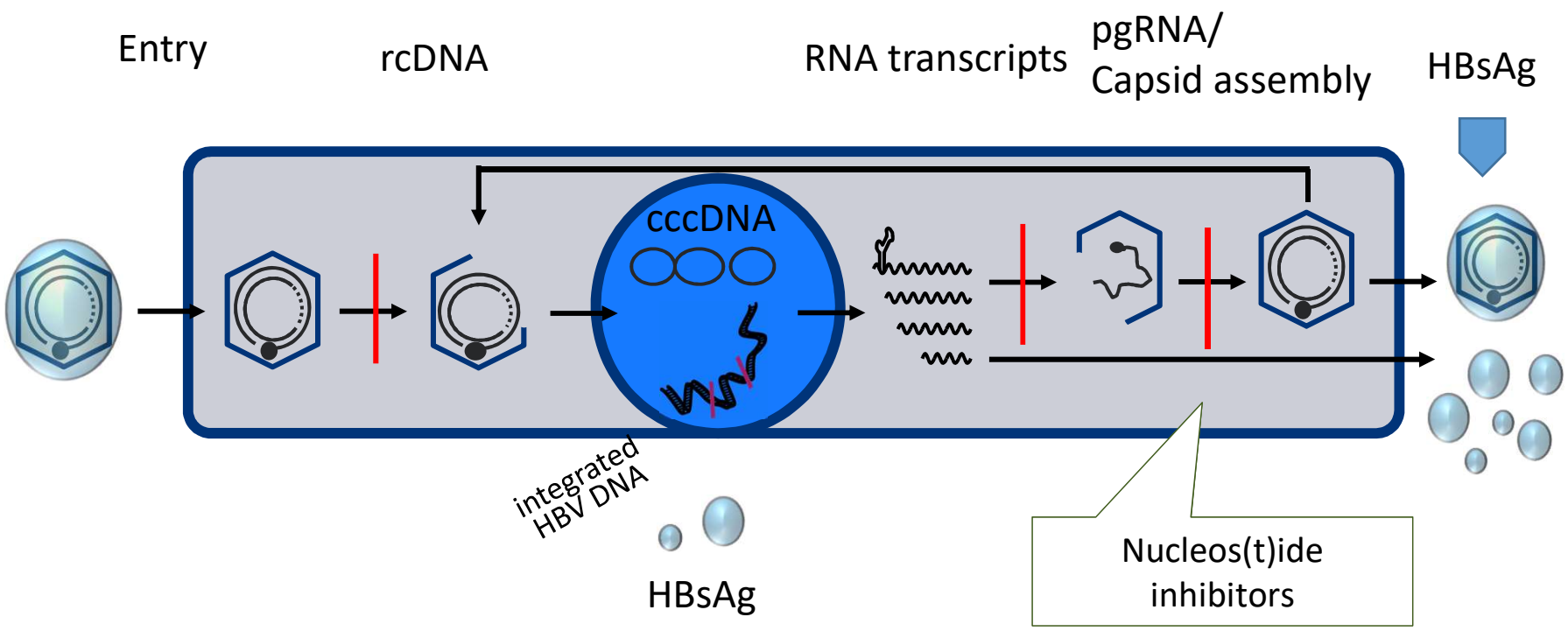
HBV life cycle and targets



Cole, A. G. (2016). Curr Opin Pharmacol **30**: 131-137.

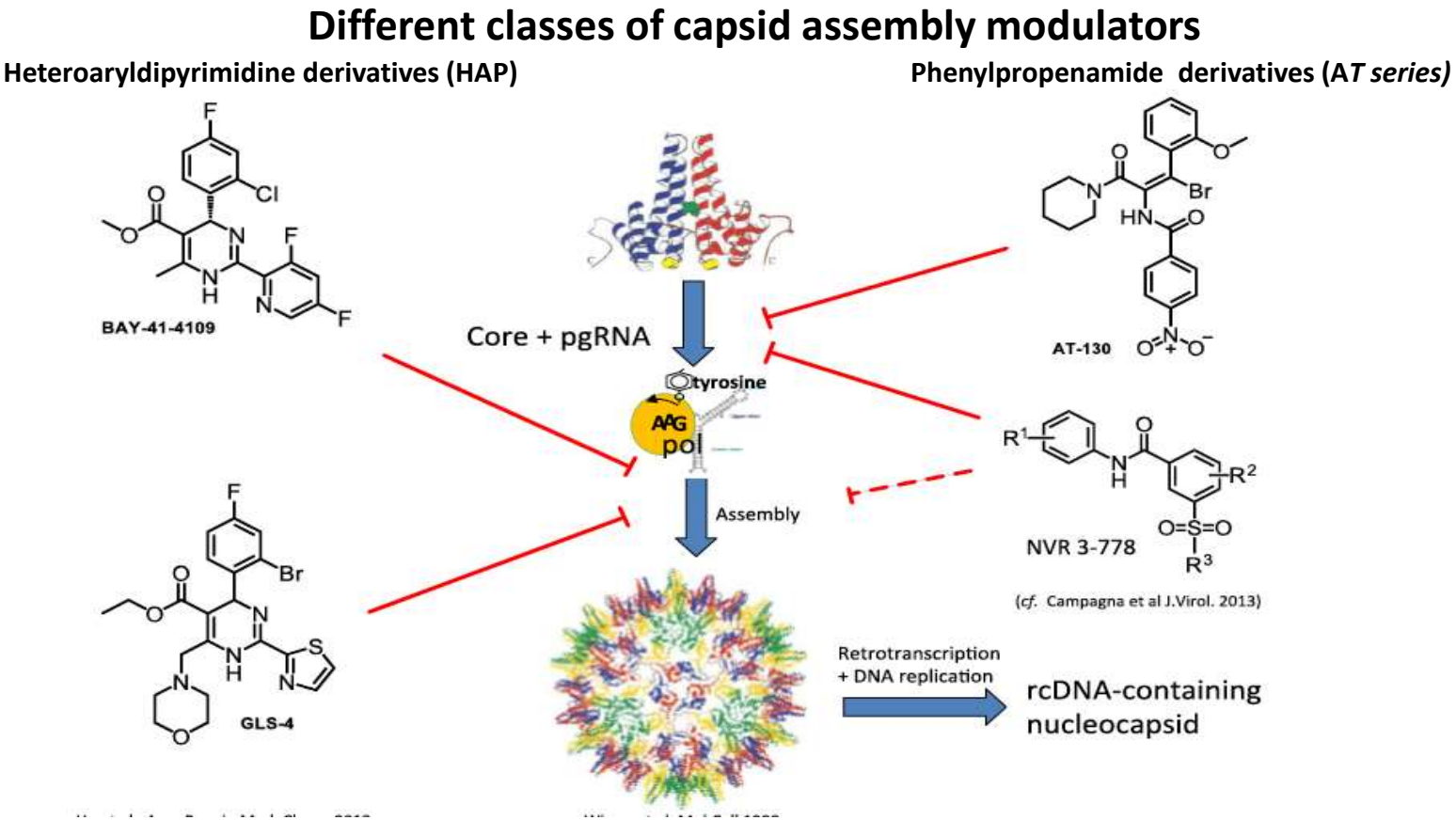
Nucleoside analogues: effect on HBV replication but little effect on cccDNA and HBsAg

Continued transcription from cccDNA and integrated viral genomes: relatively minor decrease serum HBsAg nucleoside analogue therapy despite undetectable serum HBV DNA



rcDNA – relaxed circular DNA; cccDNA –covalently closed DNA; pgRNA pre-genomic RNA

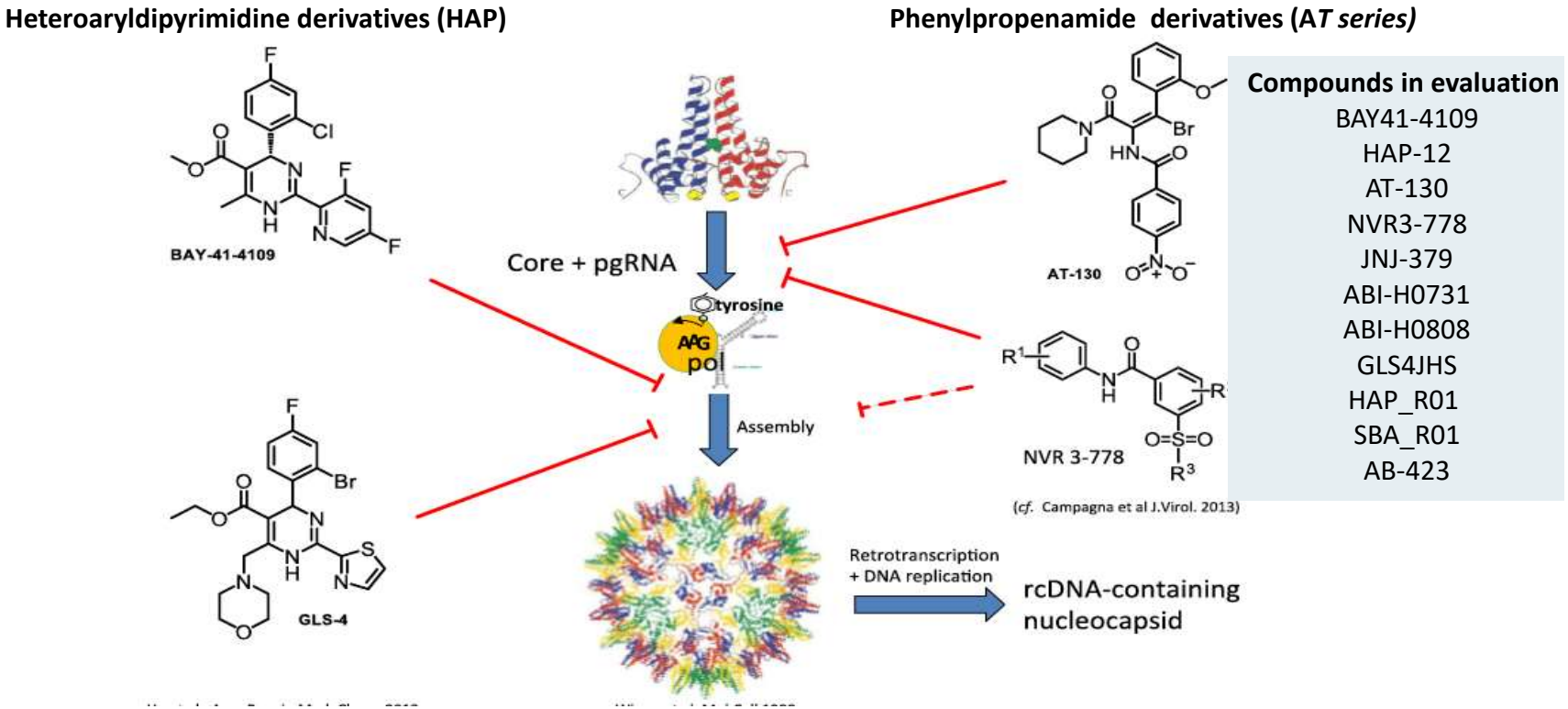
Heteroaryldihydropyrimidine compound GLS4 regulates both assembly and disassembly of HBV capsids to inhibit cccDNA formation



Wang J, et al. AASLD 2017, Washington DC. #937

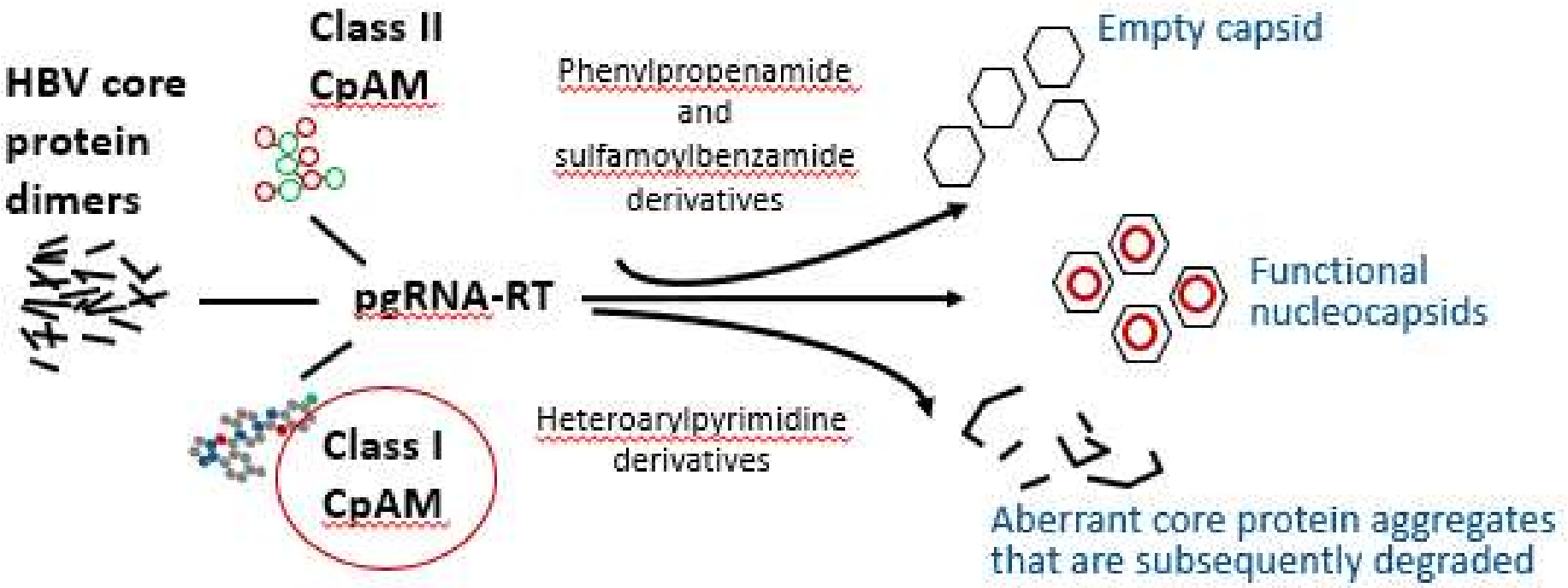
Different classes of capsid assembly modulators

Different classes of capsid assembly modulators



Wang J, et al. AASLD 2017, Washington DC. #937

HBV capsid as a potential therapeutic target: CpAM classes and actions



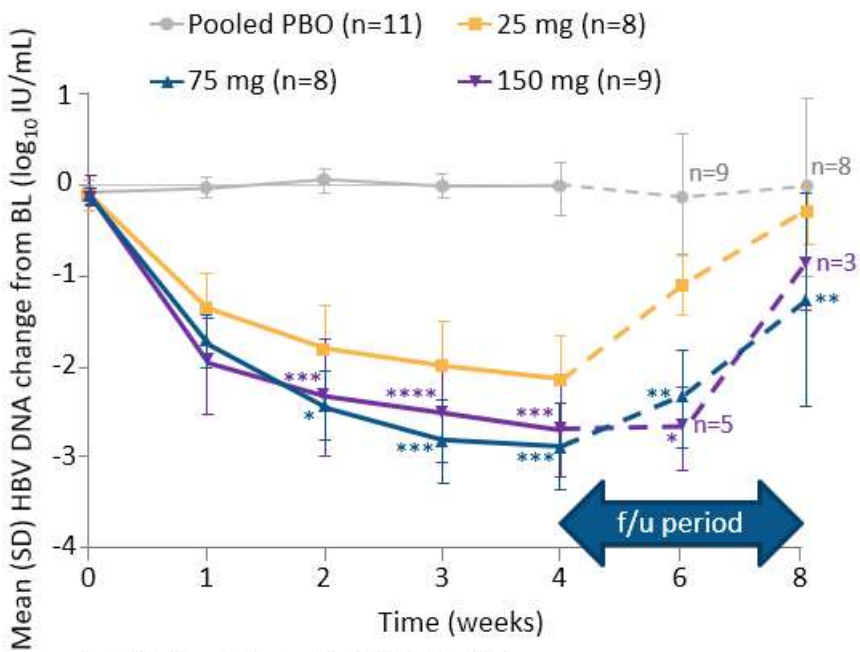
Safety, pharmacokinetics and antiviral activity of novel capsid assembly modulator (CAM) JNJ-56136379 (JNJ-6379) in treatment-naive CHB patients without cirrhosis

Baseline characteristics

ITT analysis	25 mg QD (n=12)*	75 mg QD (n=12)*	150 mg QD (n=12)**
Mean age, years (SD)	39.5 (11.6)	36.5 (10.2)	45.8 (9.9)
Sex – Male, n (%)	11 (92)	10 (83)	9 (75)
Race – White, n (%)	6 (50)	12 (100)	10 (83.3)
ALT Grade, n (%)			
Grade 0	9 (75)	9 (75)	9 (75)
Grade 1	3 (25)	3 (25)	3 (25)
Metavir fibrosis stage n, (%)			
F0	4 (33)	5 (42)	5 (42)
F1	6 (50)	4 (33)	7 (58)
F2	2 (17)	3 (25)	0
HBeAg positive, n (%)	6 (50)	3 (25)	0
Mean HBV DNA $\log_{10}$ IU/mL (SD)	6.41 (1.99)	5.36 (1.54)	4.84 (1.43)
Mean HBsAg $\log_{10}$ IU/mL (SD)	4.07 (0.96)	3.95 (0.55)	3.91 (0.70)
HBV genotype D, n (%)	5 (42)	10 (83)	8 (67)†

*Sessions 8 and 9: JNJ-6379 (n=8); PBO (n=4) **Session 10: JNJ-6379 (n=9); PBO (n=3)
†including one pt with recombinant genotype C/D

Mean HBV DNA change from BL up to 4 weeks f/u

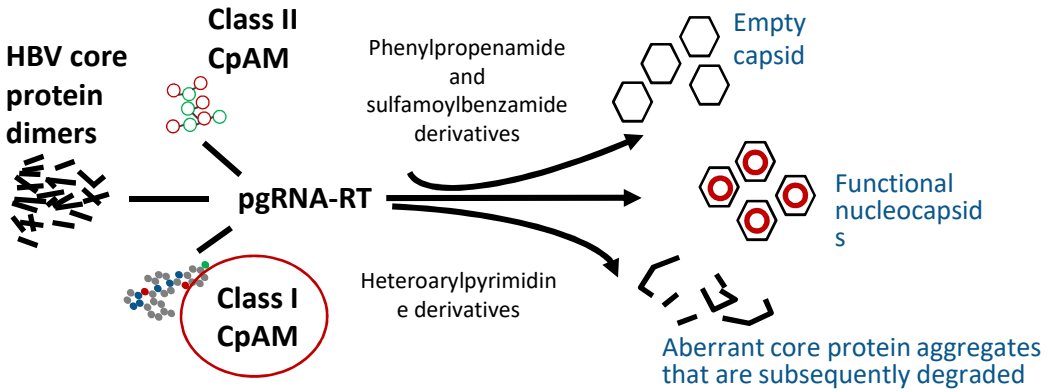


Each * refers to 1 pt with HBV DNA <LLQ

Zoulim F, et al. EASL 2018, Paris. #LBO-004

Acknowledgement: IHEP group

RO7049389, a core protein allosteric modulator, demonstrates robust anti-HBV activity in chronic hepatitis B patients and is safe and well tolerated: AAV mouse model

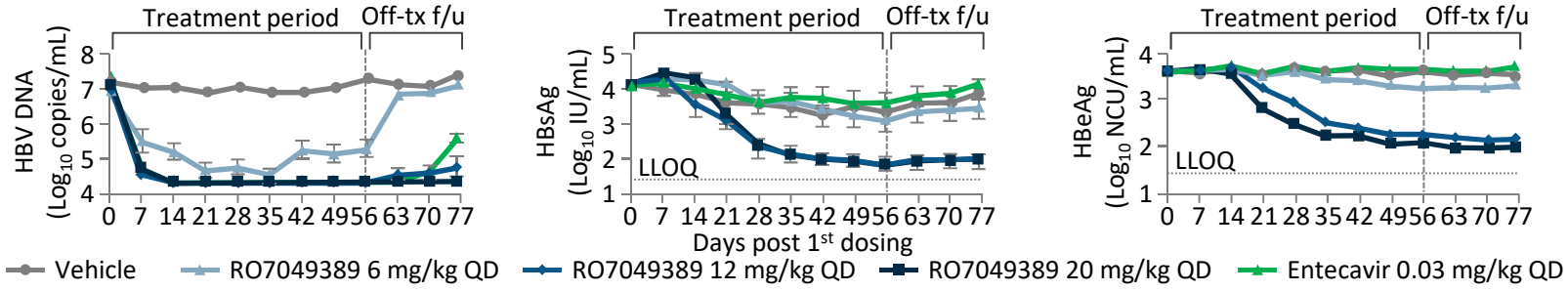


Antiviral activity and cytotoxicity HepG2.2.15 cells

RO7049389	
EC_{50} (HBV DNA, n=3)	6.1 ± 0.9 nM
CC_{50}	>100 μM
Selectivity index	>10,000

- Active against the most prevalent HBV genotypes (A–D)
- No cross resistance with nucleo(t)ide analog resistance variants
- substrate of human liver transporters, hepatocyte enrichment
- $T_{1/2}$ 5.5 hours

***In vivo* efficacy in AAV-HBV mouse model**



RO7049389 treatment not only suppresses serum HBV DNA but also HBsAg and HBeAg levels in AAV-HBV mice

Gane E, et al. EASL 2018, Paris. #LBO-003

Acknowledgement: IHEP group

RO7049389, a core protein allosteric modulator, demonstrates robust anti-HBV activity in chronic hepatitis B patients and is safe and well tolerated

(after SAD and 2 week MAD)

Part 2 – HBV patients

HBV patients Part 2: POM 4-week

Ongoing

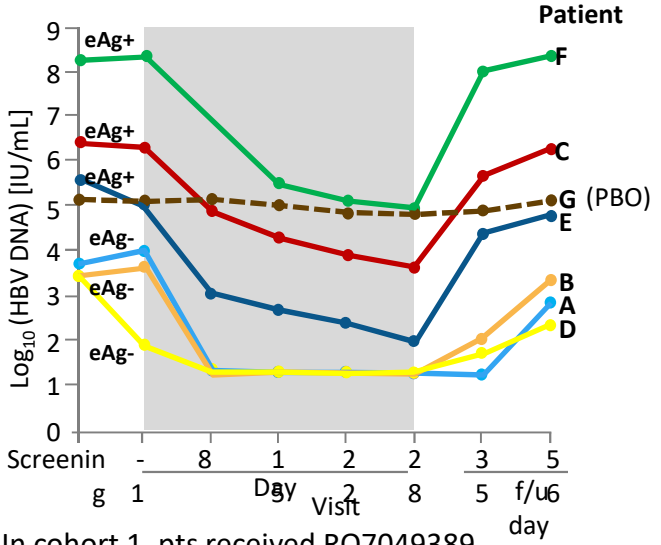
Cohort 4	n=6+1
Cohort 3	n=6+1
Cohort 2	n=6+1
200 mg BID for 28 days	n=6+1

Non-cirrhotic CHB pts, not currently on HBV therapy
HBV DNA at screening:
≥2 x 10^4 IU/mL for HBeAg +ve
≥2 x 10^3 IU/mL for HBeAg –ve
ALT at screening ≤5 x ULN

- Potent HBV DNA suppression, median –2.7 log, maximal –3.4 log, with return to pre-treatment levels after EOT
- Safe and well tolerated
- HBsAg levels, other markers, not reported
- Higher doses, daily dosing to be studied
- Further development warranted

Virologic responses in CHB patients

Absolute HBV-DNA change over time



- In cohort 1, pts received RO7049389 200 mg BID (n=6) or PBO BID (n=1) for 28 days
- Median (maximal) HBV DNA change at Day 28 was –2.7 (–3.4) $\log_{10}$ IU/mL
- In 3 pts who were HBeAg –ve, HBV DNA levels were <LLOQ
- No SAEs, no d/c for AEs

Gane E, et al. EASL 2018, Paris. #LBO-003

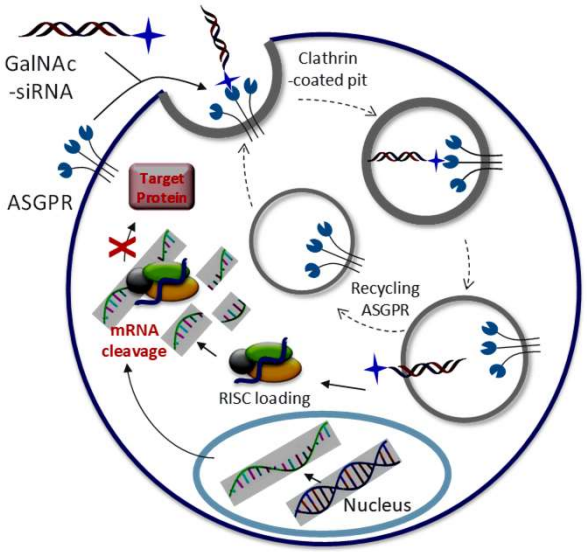
Acknowledgement: IHEP group

Next-generation RNA interference:
Small interfering RNA (siRNA) therapeutics targeted to hepatocytes

- Using a novel conjugated moieties

Durable inhibition of HBV replication and antigenemia using a subcutaneously administered siRNA agent in preclinical models

- ARB-1467: RNA interference product (IV) with a 3-trigger design inhibiting HBV replication, reducing HBV transcripts, and lowering HBV antigens, delivered via proprietary lipid nanoparticle (LNP) technology (P2)
- Here second generation preclinical:
  - AB-729: Novel RNA interference agent (SC), N-acetylgalactosamine (GalNAc) conjugate liver targeting technology, pan-genotypic activity, multi-month duration of surface antigen inhibition after a single SC dose, 10-fold larger dose for HBsAg reduction



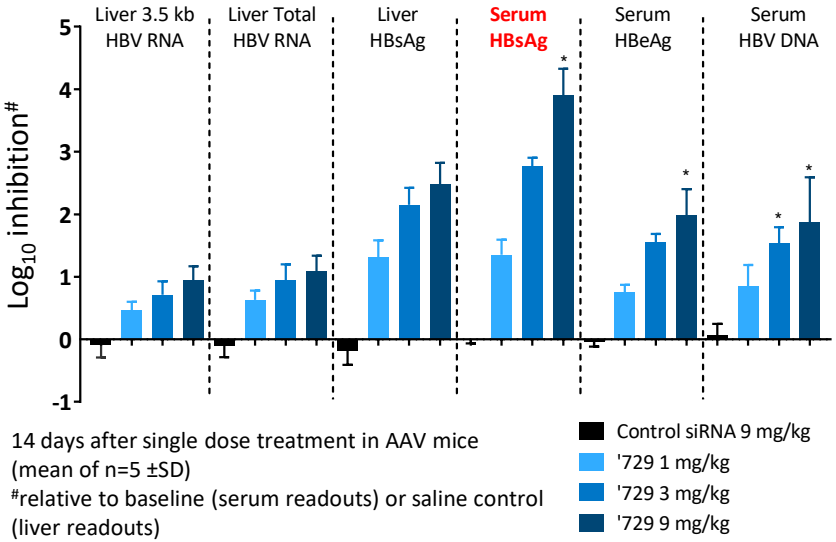
- siRNA delivery is mediated by a conjugated targeting ligand; GalNAc
  - **Cell uptake via GalNAc interaction with ASGPR**
  - Asialoglycoprotein Receptor
    - Highly expressed in/on hepatocytes
    - High rate of uptake
    - 15 min recycling time
    - Conserved across species

Lee A, et al. EASL 2018, Paris. #PS-029

Acknowledgement: IHEP group

AB-729 versus ARB 1467
Durable inhibition of HBV replication and antigenemia using a subcutaneously administered siRNA agent in preclinical models

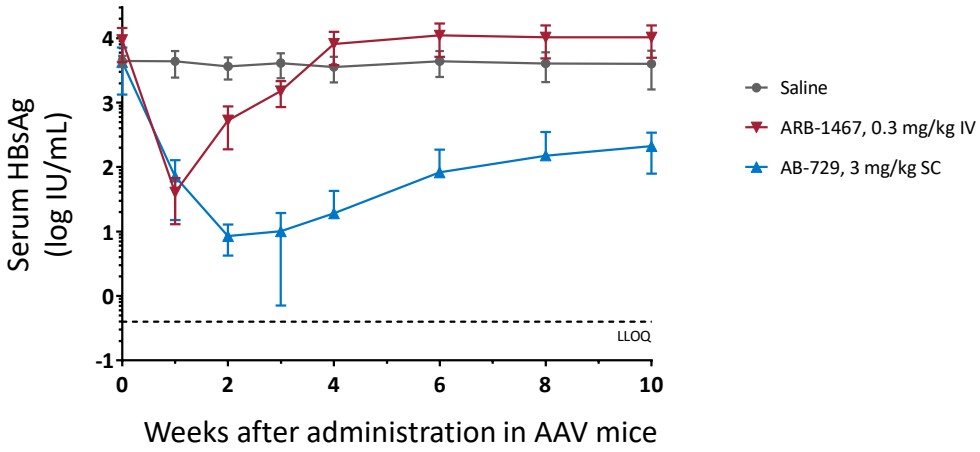
Inhibition of multiple HBV markers by '729



14 days after single dose treatment in AAV mice
(mean of n=5 ±SD)
#relative to baseline (serum readouts) or saline control (liver readouts)
*indicates signal for ≥1 animal below LLOQ

- Next generation siRNA agent with long half-life, SC route, demonstrating suppression of replication and reduction of antigenemia

AB-729 has longer duration of activity than ARB-1467



- Dose responsive effects on all measured HBV markers
- cccDNA not significantly present in this model; not expected to be directly impacted by RNAi
- Next step: Safety studies

Lee A, et al. EASL 2018, Paris. #PS-029

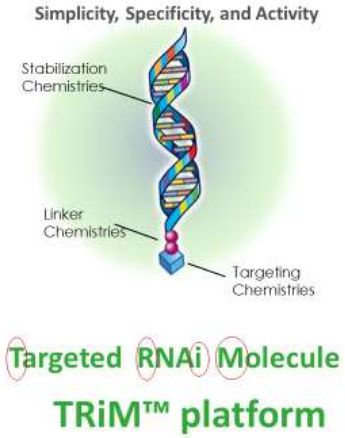
Acknowledgement: IHEP group

Development of subcutaneously administered RNAi therapeutic ARO-HBV for chronic hepatitis B virus infection

Key design elements for next generation of ARO-HBV

- Address full HBV transcriptome
  - cccDNA and integrated HBV-derived transcripts
- SC dosing, monthly or less frequent
- No need for active endosomal escape agent
- Multiple triggers to avoid developing resistance
- Expectation of wide therapeutic index
- Efficacy and safety in HBV patients

Arrowhead RNAi platform (TRiM™)



Importance of integrated HBV DNA as S mRNA source has changed RNA strategy

- Single siRNA can reduce all mRNA from cccDNA but can miss integrated HBV-derived mRNA
- Combination of X and S triggers → ARO-HBV
  - Greater genome coverage
  - Reduce change of resistance

HBV transcript map

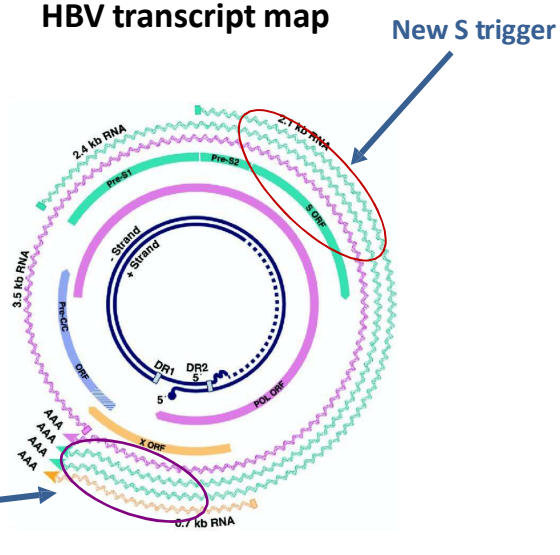


Figure adapted from Ghany & Liang (2007), Gastroenterology 132: 1574-1585

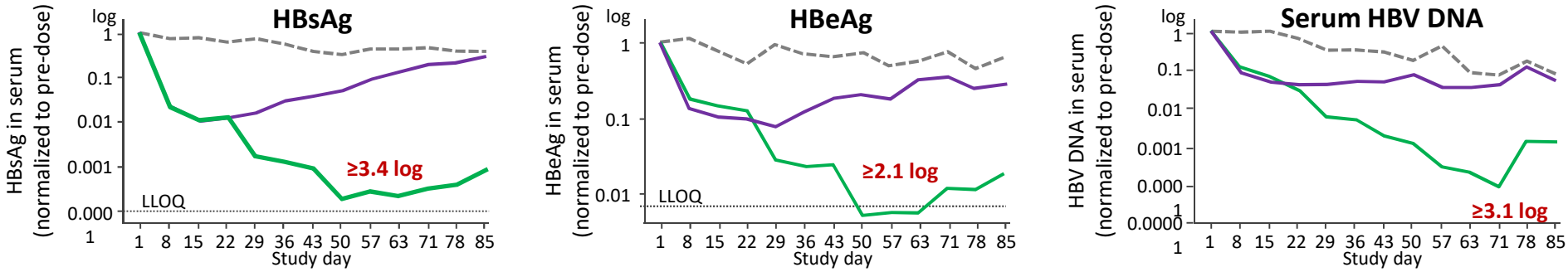
Study aim: To develop a subcutaneously administered RNAi therapeutic ARO-HBV for chronic hepatitis B virus infection

Wooddell C, et al. EASL 2018, Paris. #PS-030

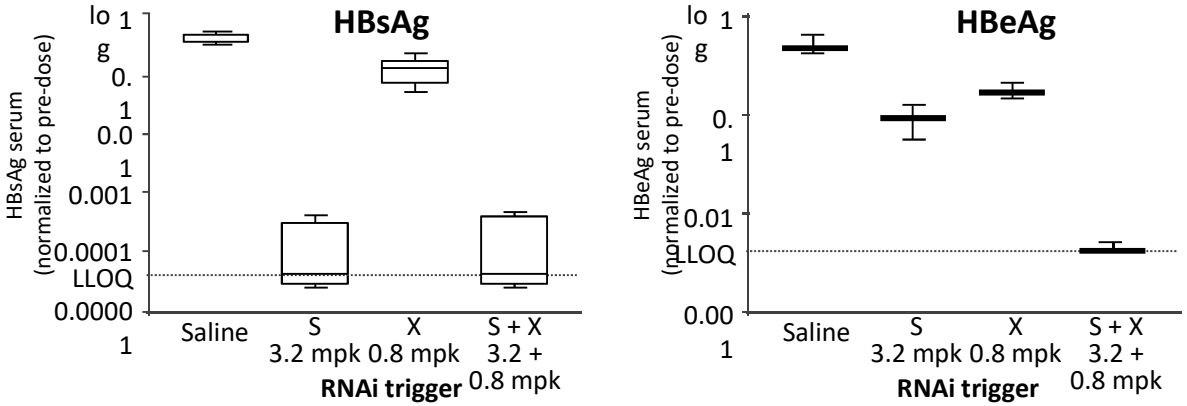
Acknowledgement: IHEP group

Development of subcutaneously administered RNAi therapeutic ARO-HBV for chronic hepatitis B virus infection

Durable reduction of HBsAg, HBeAg, and serum HBV DNA increasingly reduced with each injection



HDI minicircle HBV1.3 (n=6), 3 x Q3Q doses, Day 57 evaluation



- Saline control
- 4 mg/kg ARO-HBV (single dose)
- 4 mg/kg ARO-HBV (days 1, 22, 43)

- S trigger alone effectively reduced HBsAg but not as effective for HBeAg
- Addition of small amount X trigger resulted in significantly greater HBeAg reduction

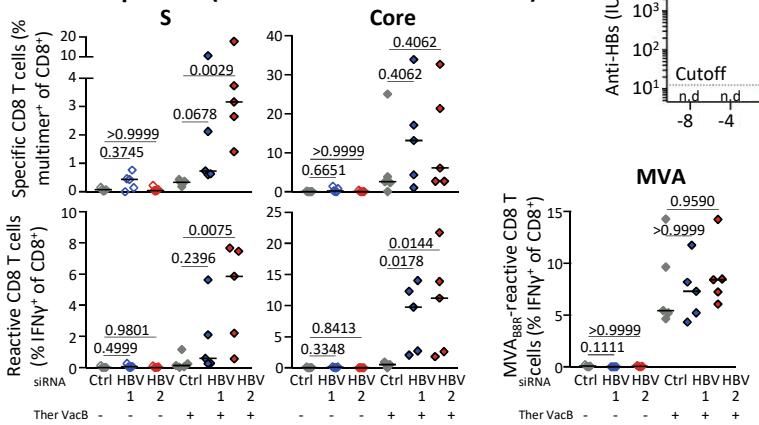
Wooddell C, et al. EASL 2018, Paris. #PS-030

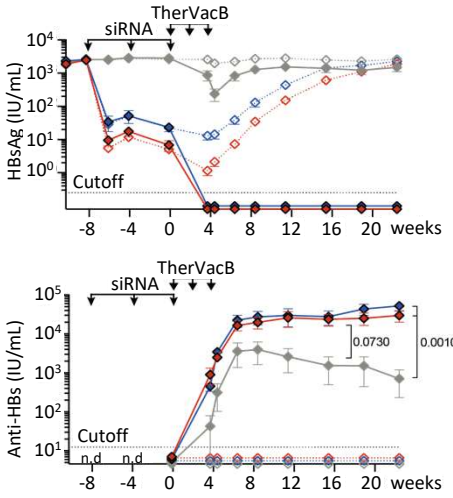
Acknowledgement: IHEP group

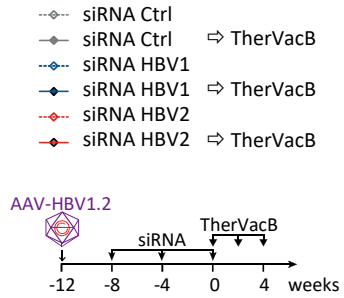
Combinatorial RNAi/vaccination therapy for chronic hepatitis B achieves long-term functional cure in preclinical mouse model

- Heterologous therapeutic hepatitis B vaccine (**TherVacB**) consisting of a protein prime / Modified Vaccinia Ankara Virus (MVA) boost vaccination
- N-acetylgalactosamine-coupled siRNA enables hepatocyte-specific delivery of siRNA targeting the common 3' end of HBV transcripts to suppress all viral transcripts and proteins

T cell responses (5 months after MVA-boost)







AAV-HBV1.2: $2x10^{10}$ geq i.v.
GalNAc-siRNAs: 3 mg/kg bw s.c.

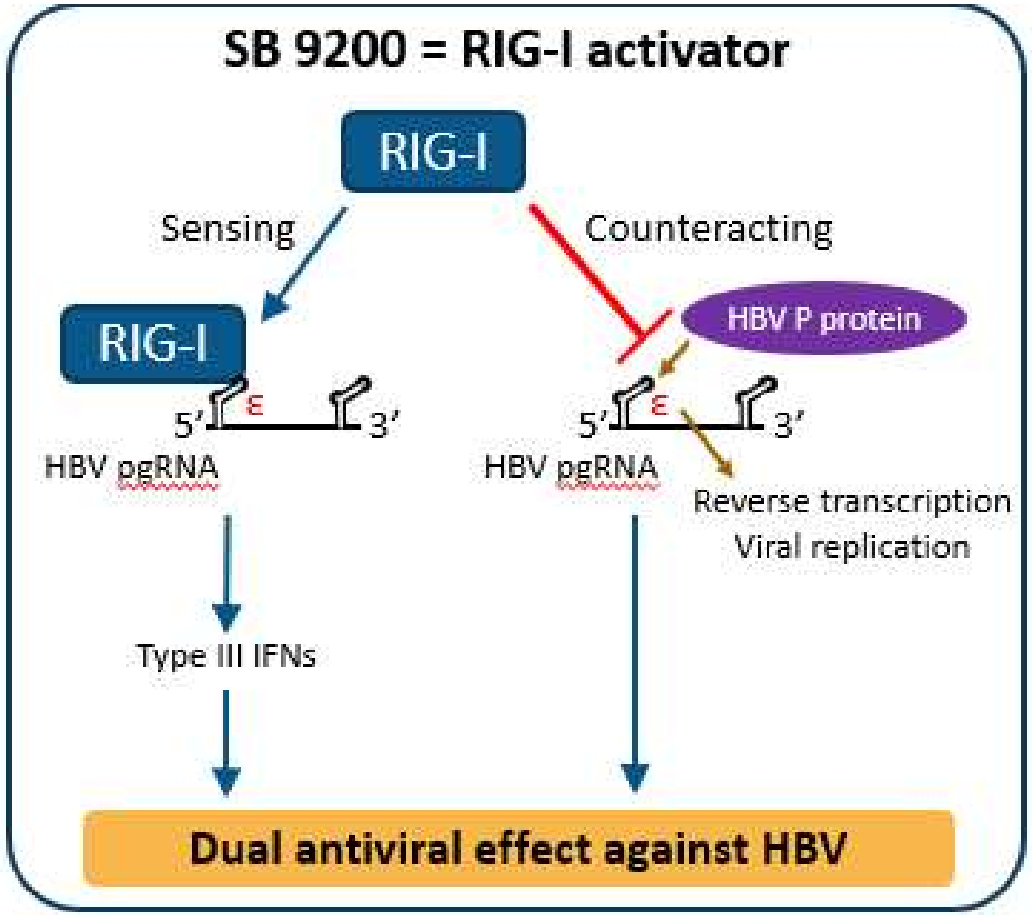
n.d. not determined

- Functional cure in all 12 mice treated with HBV siRNA ⇨ TherVacB
- 3/12 animals showed mild and transient HBeAg relapse 4 months after stop of treatment

- Combinational siRNA/vaccination therapy achieved functional cure through induction of virus-specific CD8+ T cell response
- Proof of concept on suppression of all viral antigens but not HBV DNA alone is needed for immune induction by therapeutic vaccine

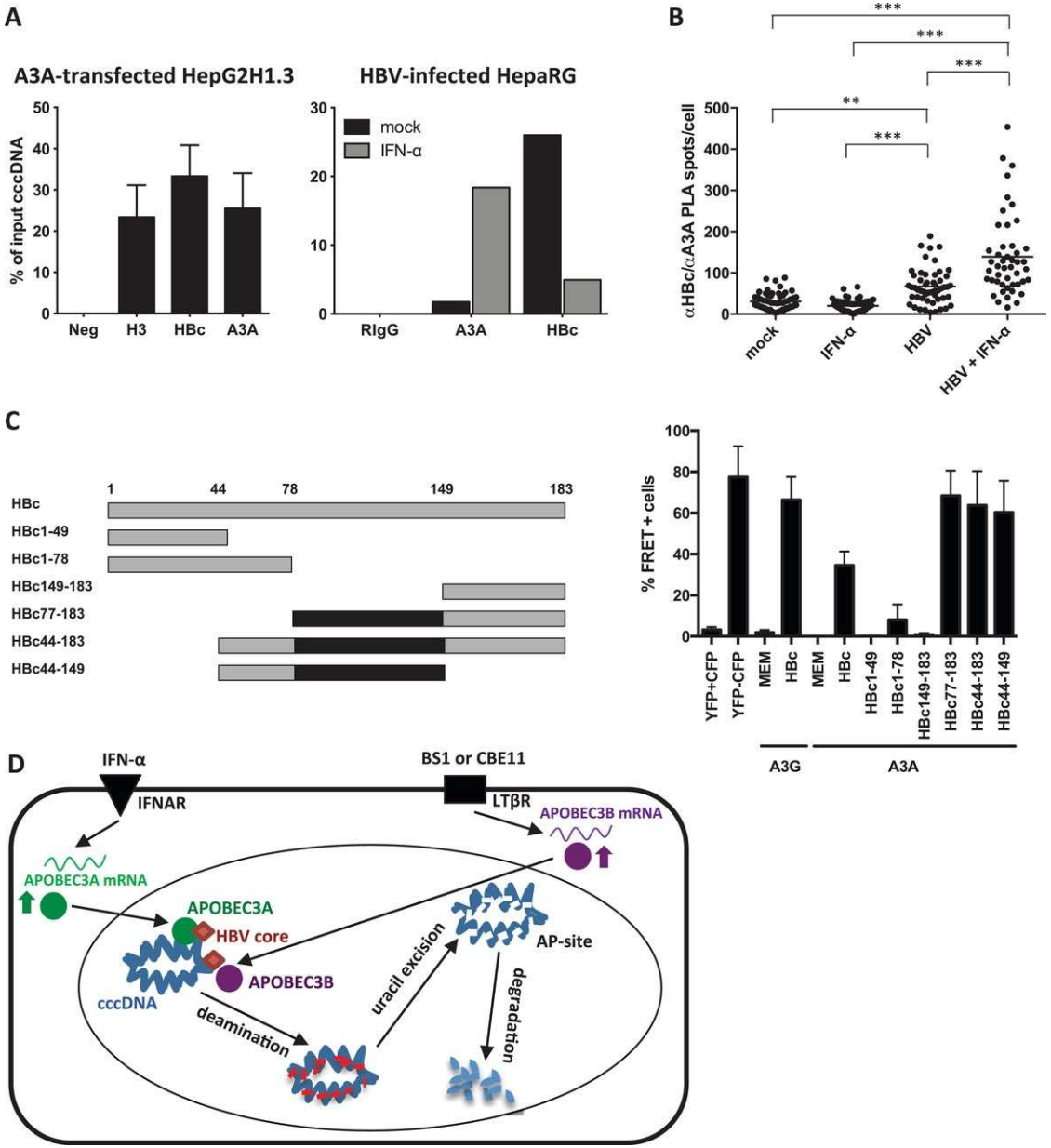
Michler T, et al. EASL 2018, Paris. #PS-025

Pathogen sensor agonists



Yuen M-F, et al. EASL 2018, Paris. #FRI-327

Model of cccDNA degradation induced by IFN-α treatment or LTβR activation.



Published by AAAS

Julie Lucifora et al. Science 2014;343:1221-1228

SIG possibilities: new molecules

- New molecules: Discovery-medicinal chemistry?
  - Screening libraries
  - Capsid chemistry
  - X gene modifications of transcription
- New molecules: molecular virology?
  - Effect of molecules on antiviral targets:
  - ccc DNA amplification
- New molecules: clinical trials:
  - Viral targets, host targets and immune modulation: Define effective therapeutic combinations
  - Capsid mutations and efficacy
- Immune phenotype associated with response to different “phenotypes” and “stages” of disease
  - Precision immunological profiing
  - Cellular immune responses
- Role of interferon
- Biomarkers
  - RNA containing viral particles (serum)
  - cccDNA quantification (liver)