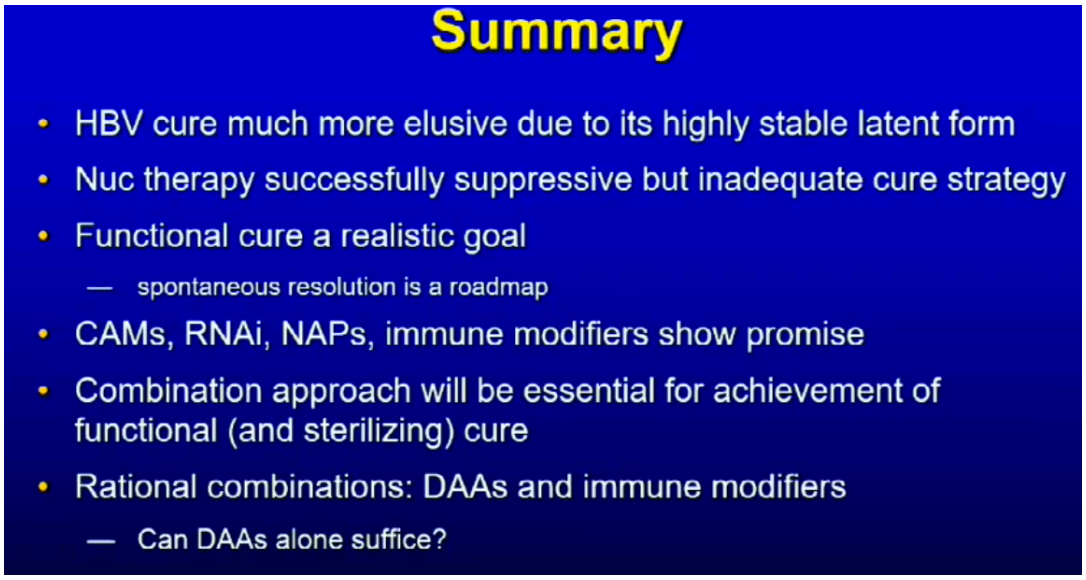
HBV New Agents

Ray Chung MD

http://www.croiwebcasts.org/console/player/44766?mediaType=slideVideo&

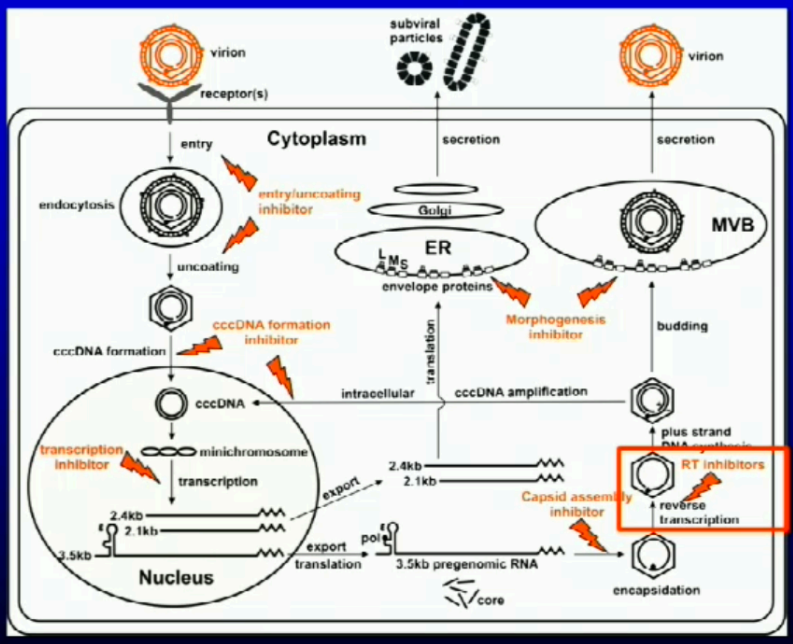
HBV at NATAP, including AASLD 2019
More Hep B Articles...



How do we define HBV cure?

- HBV largely a lifelong infection – high latency
- Unlike HCV, cure is elusive
- Functional cure
  - Maintain undetectable HBV DNA off therapy
  - Loss of HBsAg, +/- anti-HBs+
  - Clinically relevant
  - Naturally achieved
- Complete (sterilizing) cure
  - Eliminate cccDNA

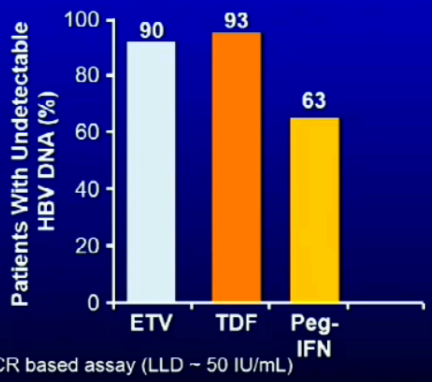
The HBV replication cycle



Block et al, *Antiviral Res* 2013 98:27

Virologic Response to Nucs in HBeAg- CHB (undetectable HBV DNA at Wk 48-52)

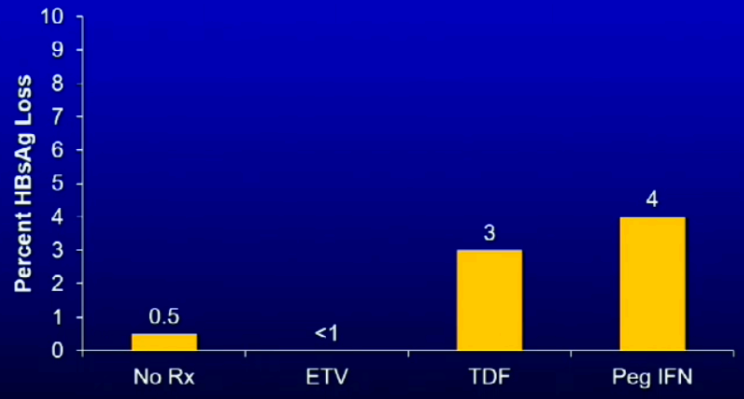
Not head-to-head trials



*By PCR based assay (LLD ~ 50 IU/mL)

Lai et al New Engl J Med 2007;357:2576; Marcellin P et al N Engl J Med. 2004;351:1206-17; Marcellin P et al N Engl J Med. 2008;359(23):2442-55.

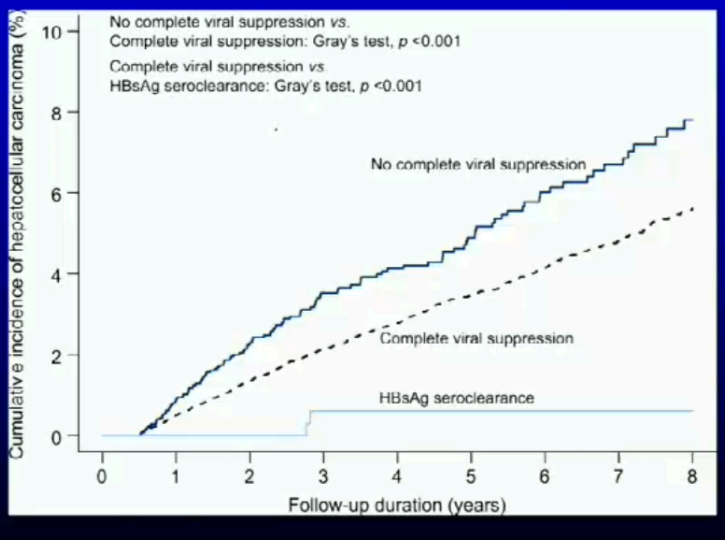
Cure is elusive: HBsAg loss During Therapy HBeAg Negative CHB at 1 Year



Lai et al New Engl J Med 2007;357:2576; Marcellin P et al N Engl J Med. 2004;351:1206-17; Marcellin P et al N Engl J Med. 2008;359(23):2442 55.

Benefits of functional cure compared to suppression: less HCC

- 20,263 NUC-suppressed pts between 2005-16, median f/u 5 yrs

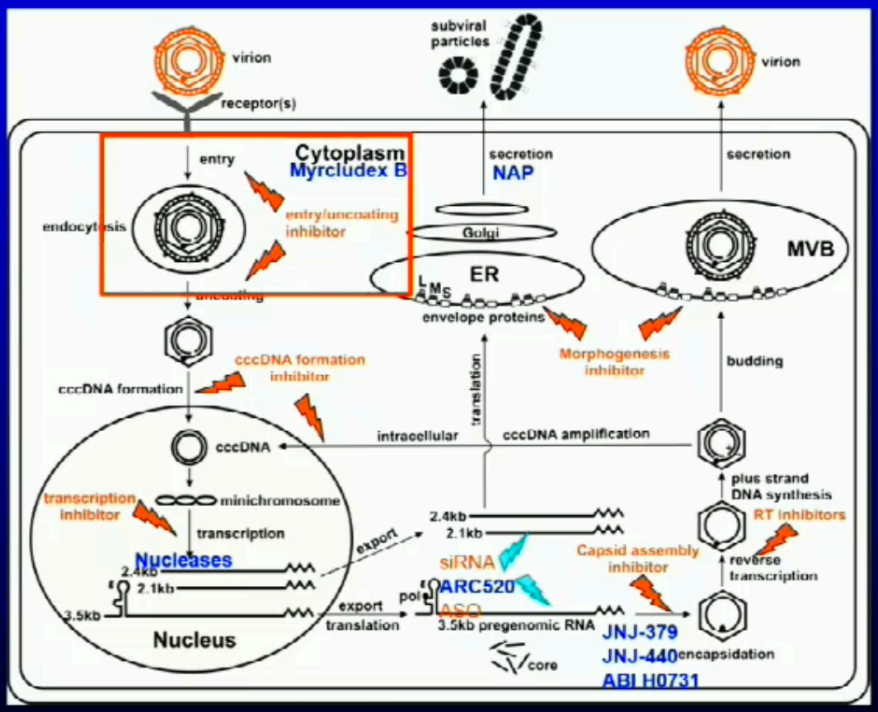


Yip TCK J Hepatol 2019; 70:361

Virological approaches (DAAs)

- Polymerase inhibitors (NUCs)
- Entry blockers
- Nucleases to edit, degrade cccDNA
- siRNA/ASO targeted to viral mRNA
- HBV capsid assembly modifiers
- HBsAg release inhibitors

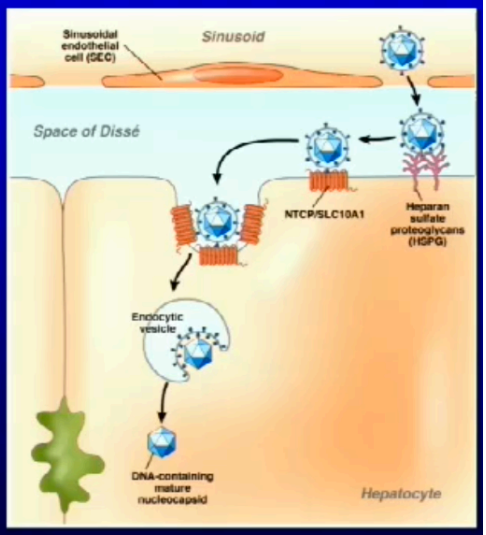
Drug targets in HBV replication cycle



Block et al, *Antiviral Res* 2013 98:27

Entry inhibitors

- HBV/HDV enters through NTCP receptor
- Decrease new cccDNA production
- Myrcludex B
- Potential utility in antiviral prophylaxis
- Limitations: inhibits bile salt transport
- Effects on HBV thus far modest

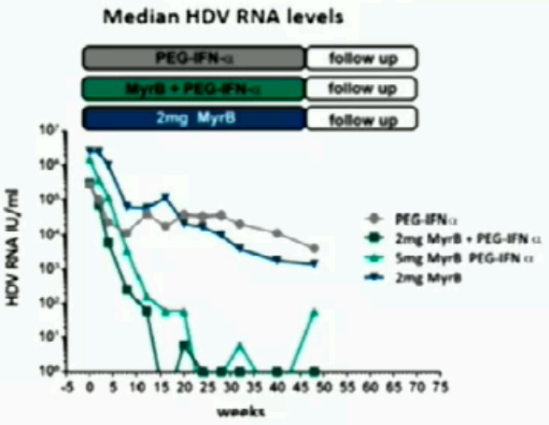


Urban S, Gastro 2014

Myrcludex B and anti-HDV effects
n=60

Virological Response (HDV RNA)

Median HDV RNA levels



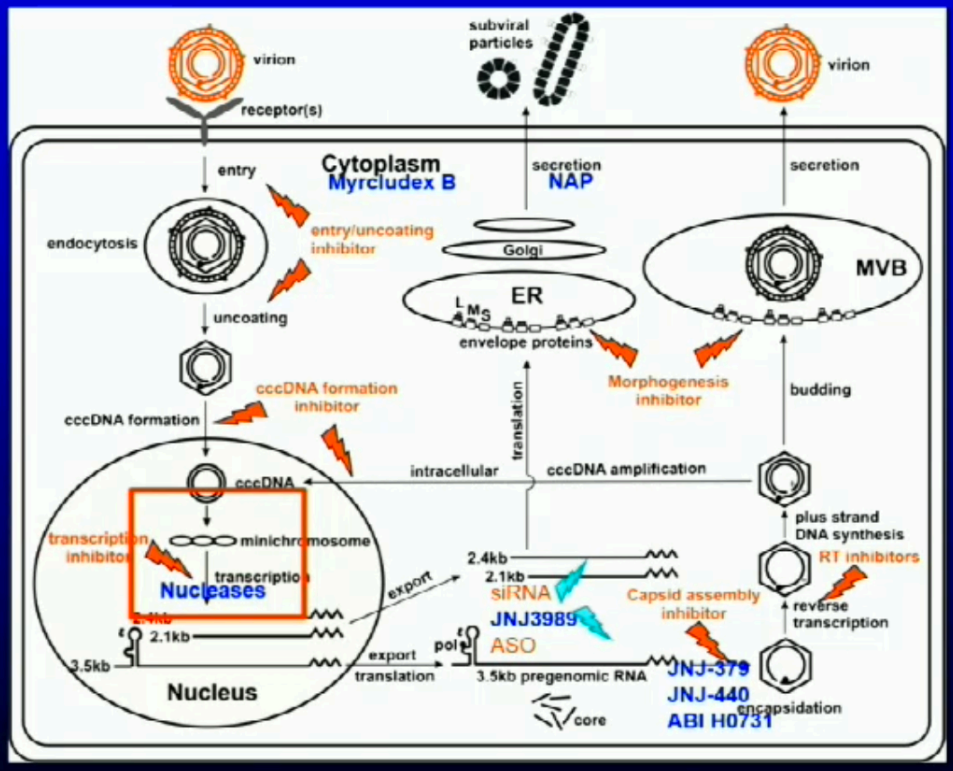
Median RNA log_{10} change to BL at week 48:

2mg MyrB/PEG-IFNα:	-3.62
5mg MyrB/PEG-IFNα:	-4.48
2mg MyrB:	-2.84
PEG-IFNα:	-1.14

- No AEs necessitating D/C
- Asymptomatic elevation in bile salts

Wedemeyer H, AASLD 2018

Drug targets in HBV replication cycle

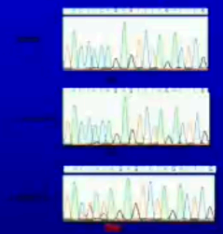


Block et al, *Antiviral Res* 2013 98:27

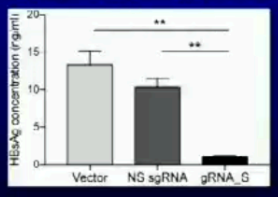
Efficient silencing of hepatitis B virus S gene through CRISPR-mediated base editing

- CRISPR-mediated base editing to induce stop codons (CRISPR-STOP)
- Cell line transduced with lentivectors producing a base editor and a single guide RNA (sgRNA) targeting HBV S
- CRISPR editing silences HBV S gene *in vitro*, suggesting potential for clinical use
- Main barrier: *in vivo* delivery, off-target effects

CRISPR-based base editing induced a premature stop codon in the integrated HBV S gene of PLC/PRF/5 cells

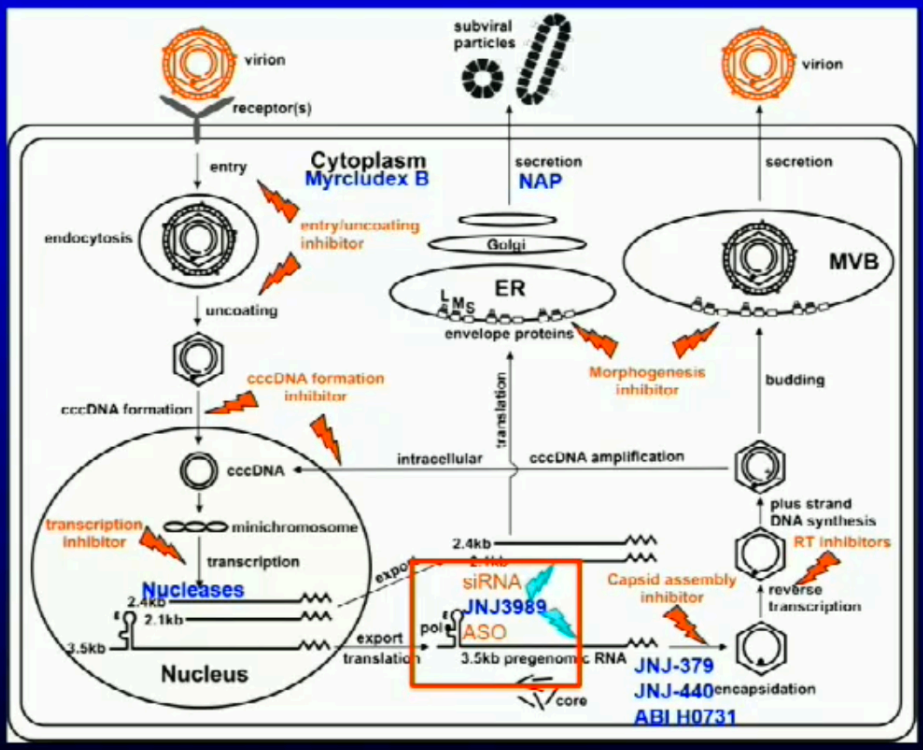


CRISPR-STOP suppressed HBsAg production *in vitro*



Zhou H, et al., Abstract 86

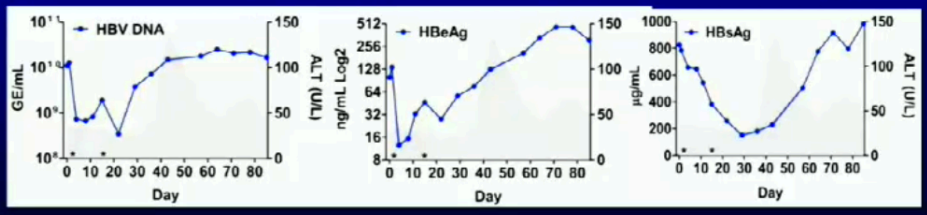
Drug targets in HBV replication cycle



Block et al, *Antiviral Res* 2013 98:27

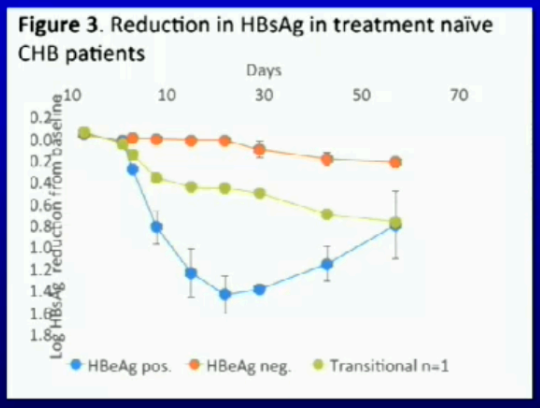
siRNA: ARC520

- siRNAs directed against conserved HBV RNA sequences induce degradation, knocking down HBV RNA, protein and DNA levels
- LNPs conjugated to hepatocyte-targeted ligands (GalNac)
- taken up by endosomes then released into cytoplasm after lysis of endosomal membrane
- in chimps, suppressed both DNA and HBsAg → ?restore IR



Lanford RE et al, AASLD 2013; Woodell C, Sci Transl Med 2017

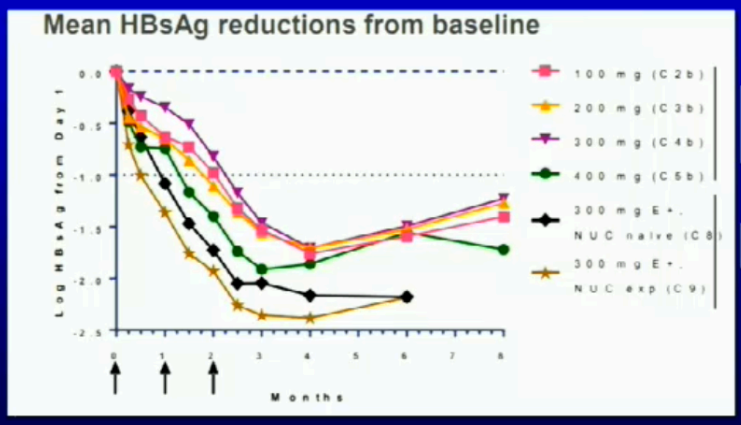
ARC-520: phase 2 data (n=58)



Challenge: differential effect in eAg+, eAg- due to integrant DNA in eAg- CHB

Yuen MF AASLD 2015
Woodell C, Sci Transl Med 2017

JNJ3989 (ARO-HBV) targeting both cccDNA and integrant HBV results in uniform sAg decline



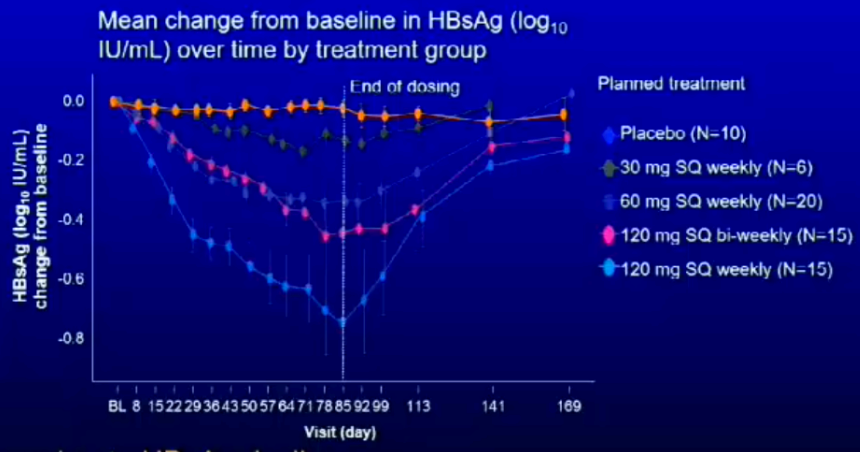
13/16 eAg-

8/8 eAg+

Woodell C et al, Sci Transl Med 2017
Yuen MF et al ILC 2019 PS-080

GSK404 (liver-targeted antisense oligonucleotide) in Nuc-Suppressed Patients

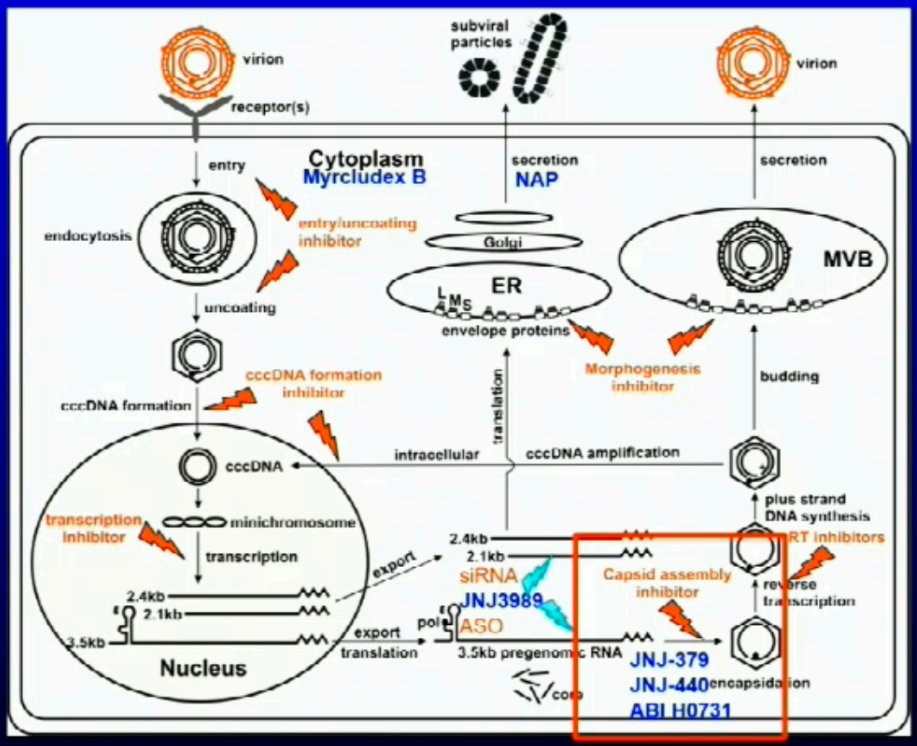
Phase 2a, multicenter, randomized, double-blind, placebo-controlled study in HBeAg+/-, n=66



- Well tolerated, moderate HBsAg declines
- Proof of principle that ASOs can decrease HBsAg levels

Yuen et al TLM 2019 Abstract 0695

Drug targets in HBV replication cycle



Block et al, *Antiviral Res* 2013 98:27

HBV core protein as a multifunctional target

- Essential for
  - HBV genome packaging and assembly
  - HBV DNA replication
  - maintenance of cccDNA
  - recycling of nucleocapsids to the nucleus
- Core assembly modulators (CAM)
  - allosterically modify core structure and alter assembly (aberrant or empty)
  - modulate synthesis of cccDNA
  - could contribute to greater functional cure rates through multiple pathways
  - phase 2 trials
- Attractive for combination with nucs, DAAs, RNAi, IFN

Zeisel Gut 2015

The CAM JNJ-440 is potent and safe

Two cohorts of 10 treatment-naïve HBeAg +/- patients randomized to JNJ-0440 or placebo x 28 days

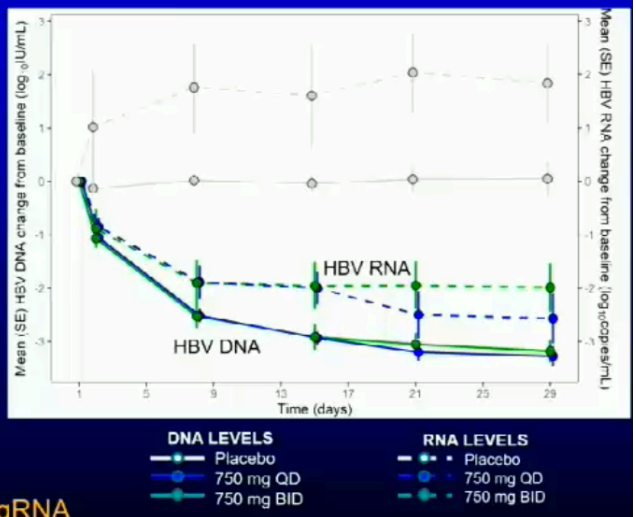
Efficacy

	750 mg QD	750 mg BID
Mean change in HBV DNA vs. BL log_{10} IU/mL	-3.2	-3.3
Mean change in HBV RNA vs. BL log_{10} copies/mL	-2.0	-2.6

- Mean change in HBeAg vs. BL log_{10} IU/mL -0.2
- No relevant changes in HBsAg levels

Safety

No treatment discontinuations/serious AEs



Potent inhibition of viral replication and reduced pgRNA

Gane et al TLM 2019 Abstract 89

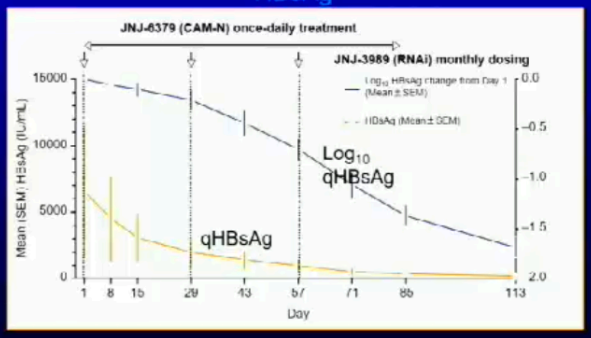
M. Ghany

Triple Therapy: RNAi + CAM + NA

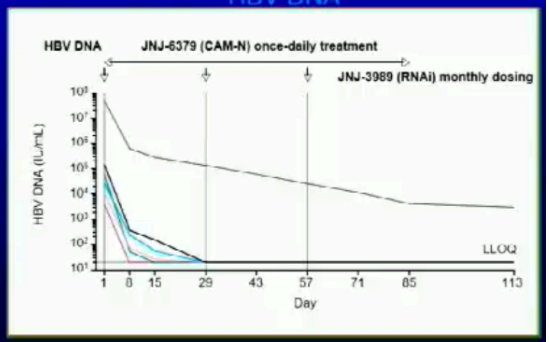
HBeAg+ n=4 / HBeAg- n=8, NA-naïve n=5 / experienced n= 7, all 12 Asian

- Three 200 mg JNJ-3989 subcutaneous doses on Days 1, 29 and 57
- Oral JNJ-6379 250 mg once daily for 12 weeks (until Day 85)
- Started or already on ETV or TDF treatment on Day 1 to beyond end of JNJ-6379 dosing
- Response rates similar between HBeAg+ and HBeAg-

HBsAg



HBV DNA

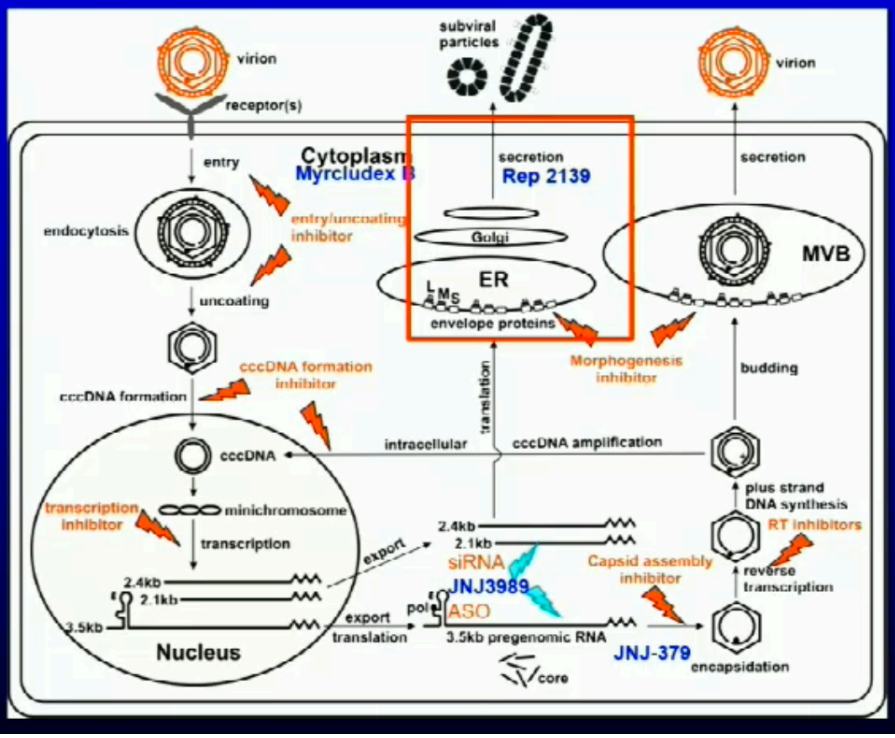


- Triple therapy resulted in marked decline in HBsAg levels, HBV DNA
- Target engagement or functional cure? Need extended off-treatment data

Yuen et al TLM 2019 Abstract LP4

M. Ghany

Drug targets in HBV replication cycle



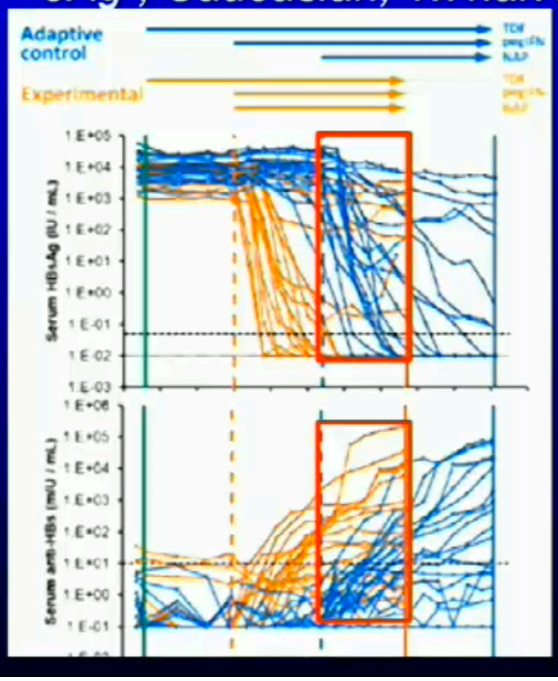
HBsAg release inhibitor: REP 2139

- Nucleic acid polymer interferes with release of subviral particles
- Leads to decreased HBsAg secretion
  - — May lead to enhanced immune response (sAg as tolerogen)
  - — Does not directly decrease HBV DNA

Bazinet M et al. EASL 2018

Rep2139 + PEG + TDF results in 4+ log HBsAg reductions (n=60)

eAg-, Caucasian, Tx naive

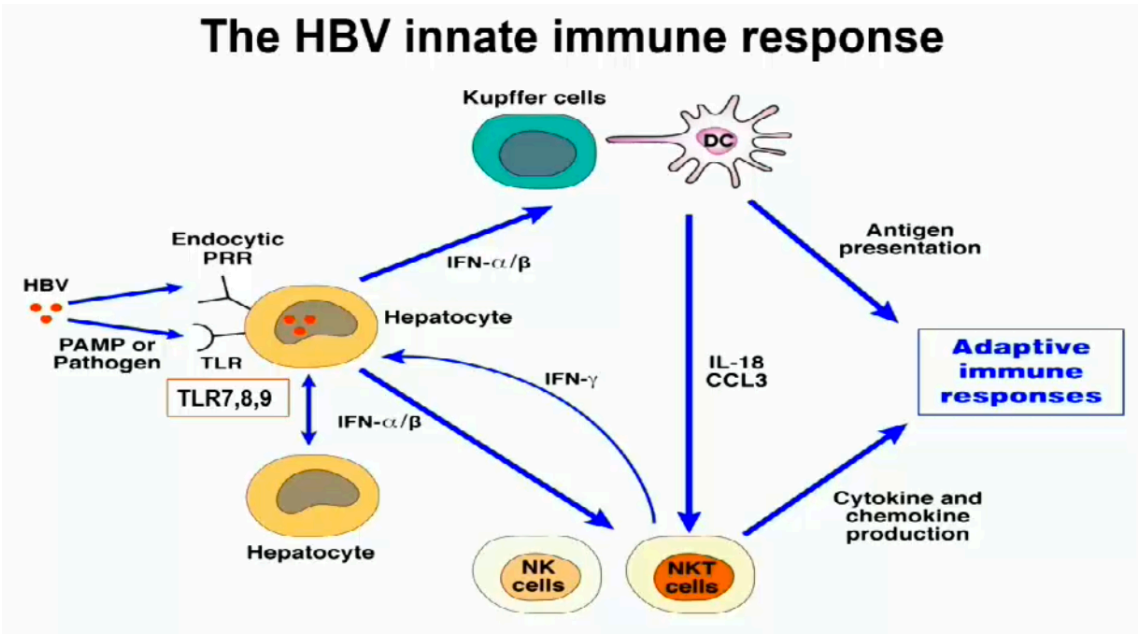


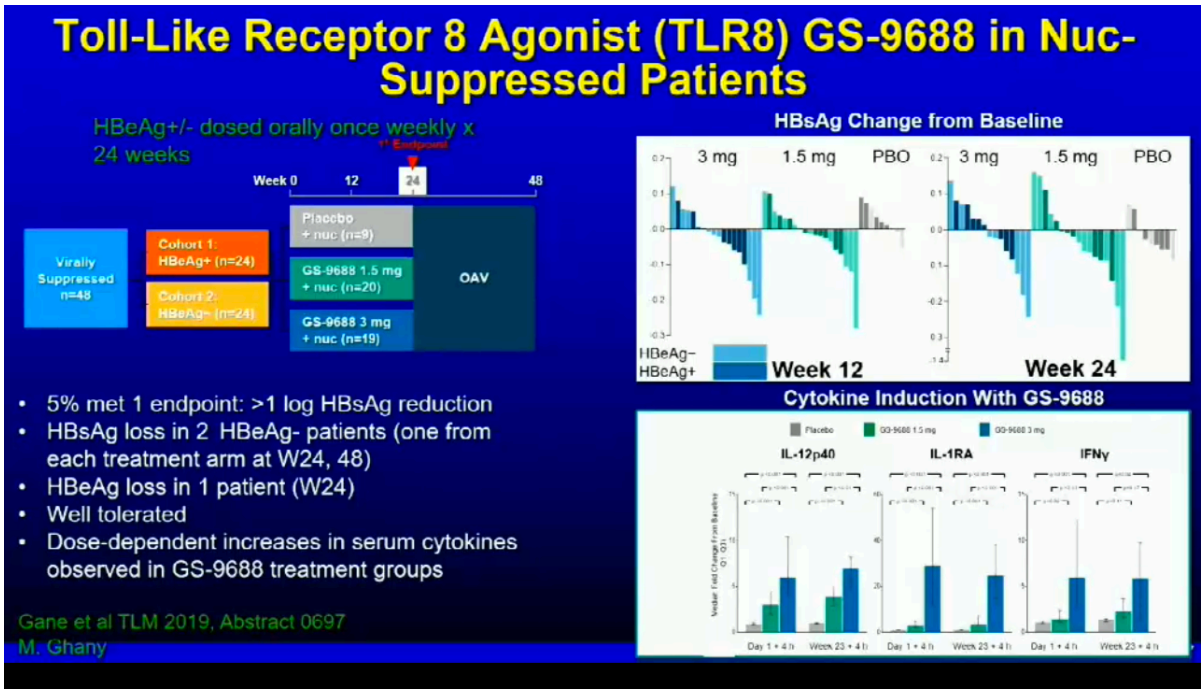
- Intriguing data
- High frequency of ALT elevations ?flares
- Monotherapy arm warranted
- ?durability of effects
- ?intracellular HBsAg effects

Bazinet M et al, AASLD 2016 LB-7

Immunological approaches

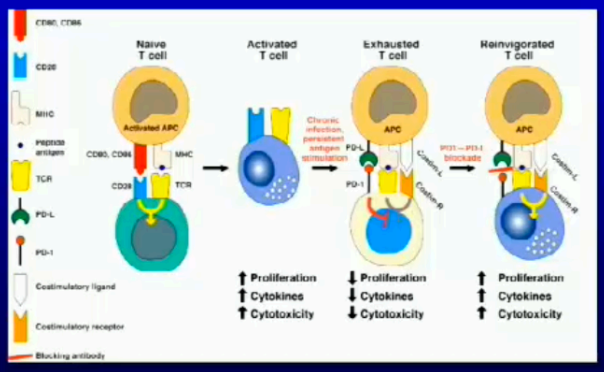
- DAA strategies may be insufficient for functional cure – clearance of latent reservoirs
- Natural resolved infection → roadmap for functional cure
- Vigorous and multispecific T cell responses hallmark of successful spontaneous resolution
- Can we reinvigorate these responses in chronic infection?
- Innate, adaptive approaches


The HBV innate immune response
Kupffer cells
DC
Antigen presentation
Endocytic PRR
HBV
PAMP or Pathogen
TLR
Hepatocyte
IFN-α/β
IFN-γ
IL-18
CCL3
Adaptive immune responses
TLR7,8,9
IFN-α/β
Hepatocyte
Cytokine and chemokine production
NK cells
NKT cells


Toll-Like Receptor 8 Agonist (TLR8) GS-9688 in Nuc-Suppressed Patients
HBeAg+/- dosed orally once weekly x 24 weeks
1° Endpoint
Week 0
12
24
48
Virally Suppressed n=48
Cohort 1: HBeAg+ (n=24)
Cohort 2: HBeAg- (n=24)
Placebo + nuc (n=9)
GS-9688 1.5 mg + nuc (n=20)
GS-9688 3 mg + nuc (n=19)
OAV
HBsAg Change from Baseline
3 mg
1.5 mg
PBO
3 mg
1.5 mg
PBO
HBeAg−
HBeAg+
Week 12
Week 24
Cytokine Induction With GS-9688
Placebo
GS-9688 1.5 mg
GS-9688 3 mg
IL-12p40
IL-1RA
IFNγ
Day 1 + 4 h
Week 23 + 4 h
Day 1 + 4 h
Week 23 + 4 h
Day 1 + 4 h
Week 23 + 4 h
• 5% met 1 endpoint: >1 log HBsAg reduction
• HBsAg loss in 2 HBeAg- patients (one from each treatment arm at W24, 48)
• HBeAg loss in 1 patient (W24)
• Well tolerated
• Dose-dependent increases in serum cytokines observed in GS-9688 treatment groups
Gane et al TLM 2019, Abstract 0697
M. Ghany

Targeting the T cell response for reinvigoration

- CD8 T cell response central to control of HBV infection
- Therapeutic vaccine approaches disappointing to date
- CHB associated with high PD-1/hepatocyte PD-L1
- POC in cancer
- POC in HCV: 45 pts received anti-PD-1
  - well tolerated, 1 pt with SVR, 1 grade 4 ALT flare
- HBV as an appealing target
  - Caution: autoimmunity, flares



Topalian S et al NEJM 2012; Brahmer JR et al NEJM 2012
Gardiner D et al. PLoS One. 2013 May 22;8(5):e63818

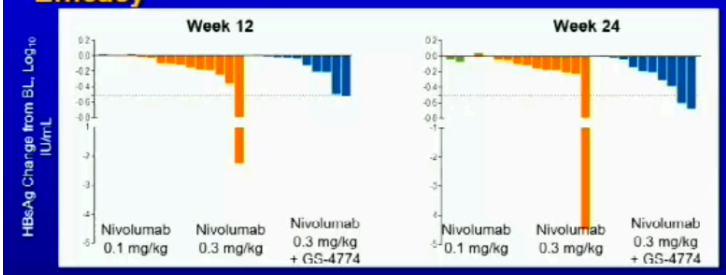
A checkpoint inhibitor can be administered safely in HCC pts with HBV

- Nivolumab administered to 47 pts with advanced HCC
- **HBV (n=11),** HCV (n=12), no infection (n=24)
- CTP 5-6
- Dose escalation 0.1-10 mg/kg IV q2 wks for up to 2 yrs
- No safety concerns in HBV (suppressed), HCV groups
  - No significant clinical flares or D/C
  - 9% grade 3 ALT
- Minimal-modest anti-HBV effect
  - 3 pts with >1 log HBsAg drop

El Khoueiry AB et al. Lancet 2017

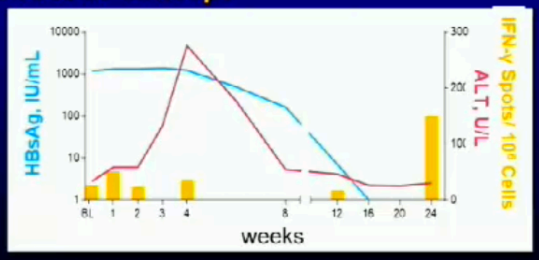
Study of single low dose of Nivolumab +/- Tx vaccine in HBV-infected participants

Efficacy



- Additional trials planned (ACTG A5368)
- ?reprogrammed T cell therapy (CAR-T)

Proof of concept



- Cleared HBsAg, stopped TDF 4 weeks after dosing
- 8 months later – remains HBsAg-negative and anti-HBs positive
- Important POC – very low dose
- Minimal toxicity reported (1 grade 3 ALT in 24 pts)

Gane E, et al. J Hepatol 2019

Summary

- HBV cure much more elusive due to its highly stable latent form
- Nuc therapy successfully suppressive but inadequate cure strategy
- Functional cure a realistic goal
  - spontaneous resolution is a roadmap
- CAMs, RNAi, NAPs, immune modifiers show promise
- Combination approach will be essential for achievement of functional (and sterilizing) cure
- Rational combinations: DAAs and immune modifiers
  - Can DAAs alone suffice?