# WHAT'S HOT AT THE LIVER MEETING

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# Disclosures for Ed Gane

- Member of the following Sc
  Boards: **AbbVie, ALIOS, ALIG**
  **Assembly, Arrowhead, Avali**
  **Dicerna, Enanta, Gilead Scie**
  **Kline, IMMUNOCORE, Inovic**
  **Novira, Roche and VIR Bio**
- The opinions expressed t

# What's Hot at the Liver Meeting

1. Basic immunology & virology of HBV

2. Natural history studies
   - Benefit of HBsAg loss

3. Current HBV treatments
   - Is risk for HCC lower with TDF than ETV?
   - NUC Stop studies

4. New HBV therapies
   - Clinical studies
   - Early development

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699 PRECLINICAL ASSESSMENT OF A NOVEL CAPSID ASSEMBLY MODULATOR, ALG-001075, DEMONSTRATES BEST-IN-CLASS IN VITRO POTENCY AND IN VIVO ANTIVIRAL EFFICACY

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704 LIVER-TARGETED INHIBITION OF PAPD5 AND PAPD7 LEADS TO SUSTAINABLE HBsAg REDUCTION IN THE AAV-HBV MOUSE MODEL.

705 ONGOING ANALYSIS OF FUNCTIONAL CONTROL / CURE OF HBV AND HDV INFECTION FOLLOWING REP 2139-CA AND PEGYLATED INTERFERON ALPHA-2a THERAPY IN PATIENTS WITH CHRONIC HBV / HDV CO-INFECTION: 3-YEAR FOLLOW-UP RESULTS FROM THE REP 301-LTF STUDY

706 PERIPHERAL IMMUNE RESPONSES TO TOLL-LIKE RECEPTOR 8 AGONIST GS-9688 IN PATIENTS WITH CHRONIC HEPATITIS B

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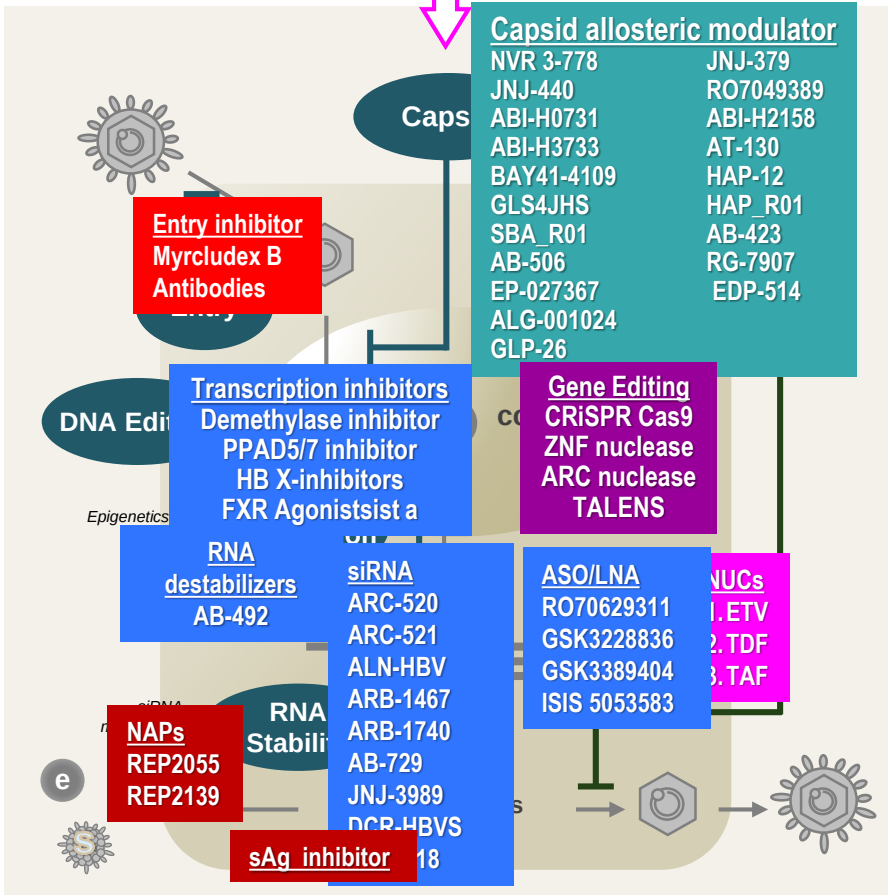
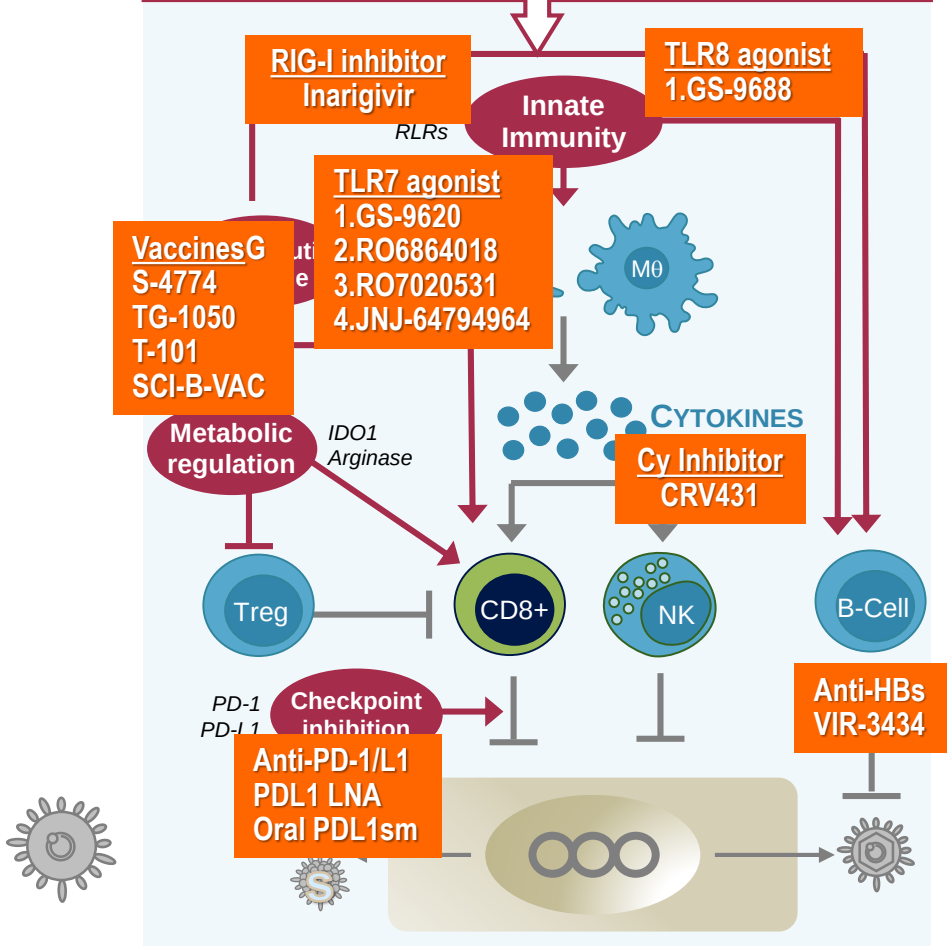
# HBV CURE Targets

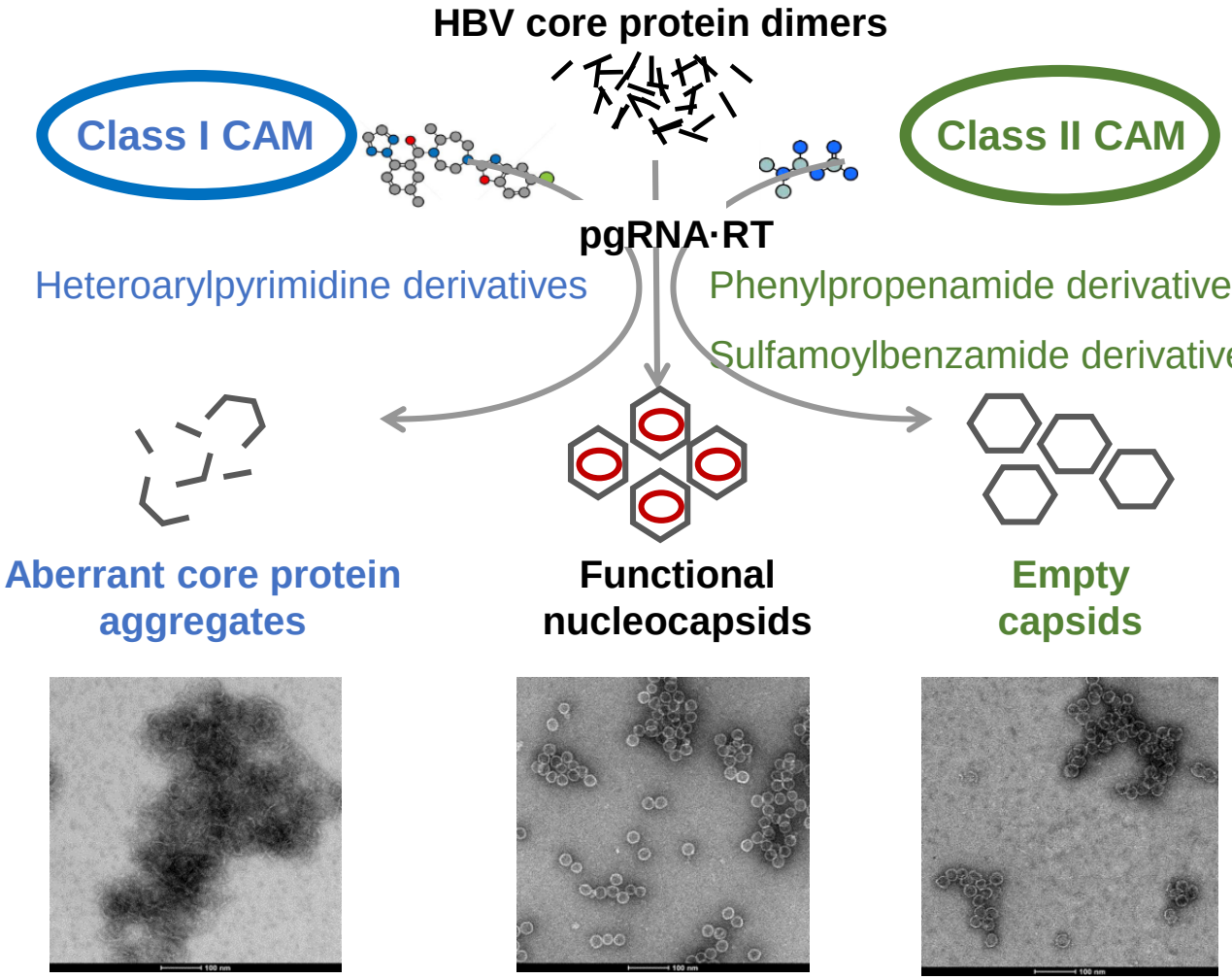
## Reduce Viral Burden




## Activate Host Immunity



# Capsid Allosteric Modulators (CAMs)




Capsid assembly *in vitro* (electron microscopy)

**CAM-I or A Class**

- RO7049389
- BAY41-4109[1]
- HAP-12
- GLS4JHS
- HAP_R01
- SBA_R01
- RG-7907

**CAM-II or N Class**

- NVR 3-778
- JNJ-379[2]
- JNJ-440[3]
- AT130
- AB-506[4]
- GLP-26
- ABI-H0731[5]
- ABI-H2158[6]
- ABI-H3733
- ALG-001024[7]
- ALG-001075[8]
- TBA #701[9]

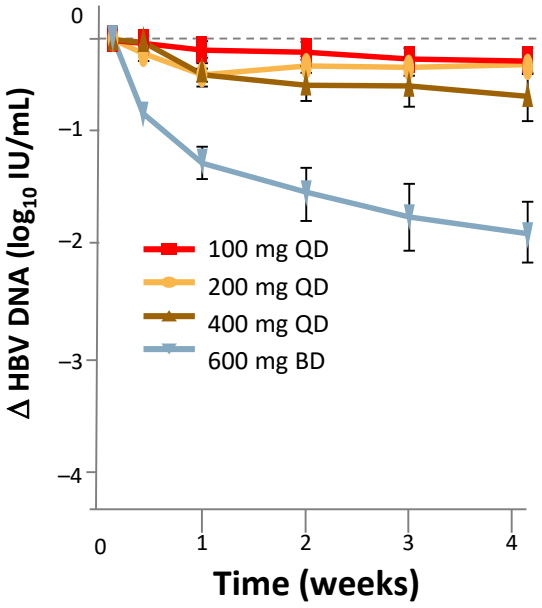
1.Fukutomi K, et al. Oral #90

2.Yuen M-F, et al. Poster #LP4
3.Gane E , et al. Oral #89
4.Yuen M-F, et al. Poster #LP7
5.Sulkowski M , et al. Poster #LP1
6.Yuen M-F, et al. Poster #LP14
7.Debing Y, et al. Poster #699
8.Jeckle A, et al. Poster #703
9.Mani N, et al. Poster #701

# Oral HBV capsid assembly modulator (CAMs)

- **Antiviral effect during 28 days dosing**

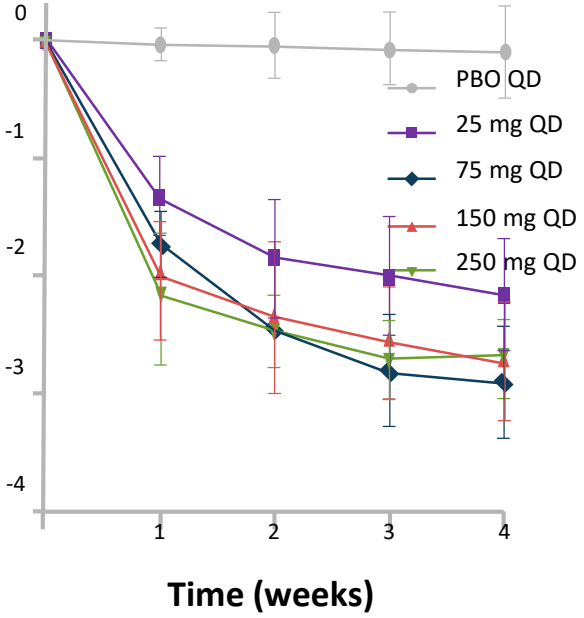
## 1. NVR3-778




Yuen M-F, et al. EASL 2016, Barcelona. LBO6

- 1200mg⇨2log reduction
- No effect on HBsAg
- Skin rash

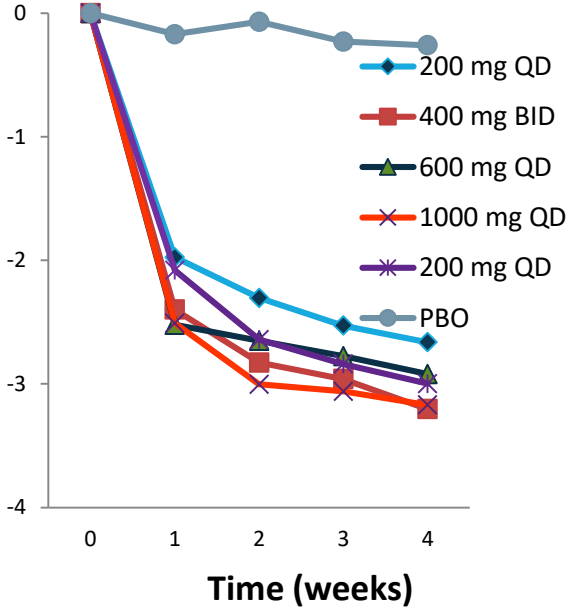
## 2. JNJ-379




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

- 250mg⇨2.9 log reduction
- No effect on HBsAg
- Occ ALT elevation

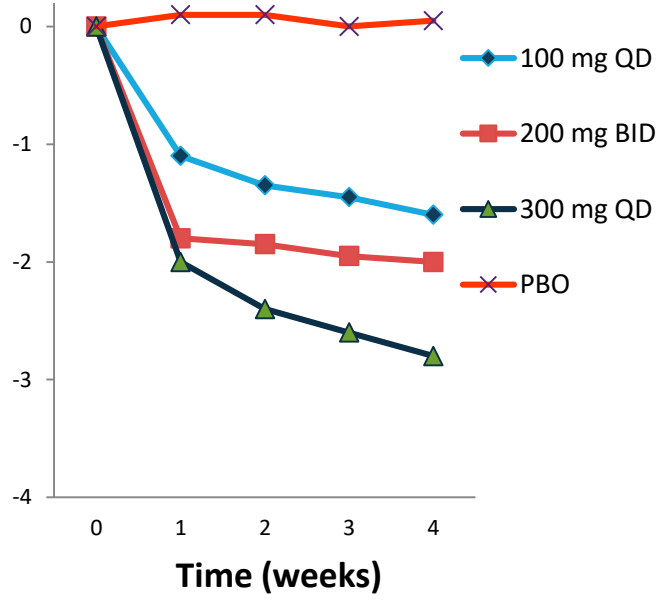
## 3. RO7049389




Gane E, et al. EASL 2018, Paris. #LBO-003
Yuen M-F.EASL 2019, Vienna., **#FRI-219**

- 200mg⇨3.2 log reduction
- No effect on HBsAg
- ALT elevation in 20%

## 4. ABI-H0731



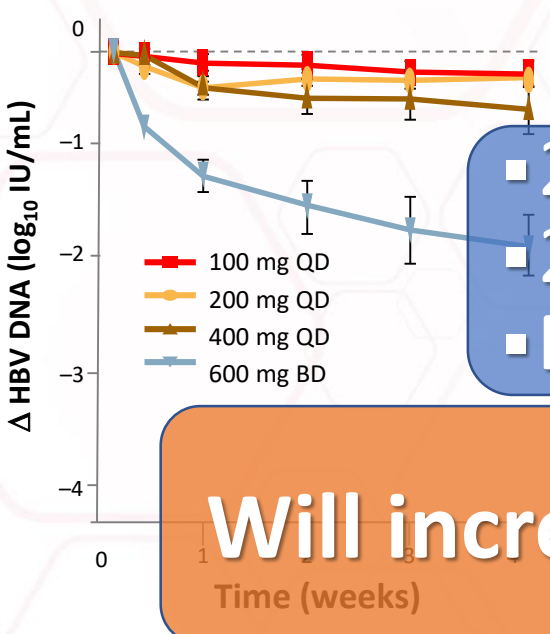

Yuen M-F, et al. AASL D2016, San Francisco

- 400mg⇨3.9 log reduction
- No effect on HBsAg
- Skin rash

# Oral HBV capsid assembly modulator (CAMs)

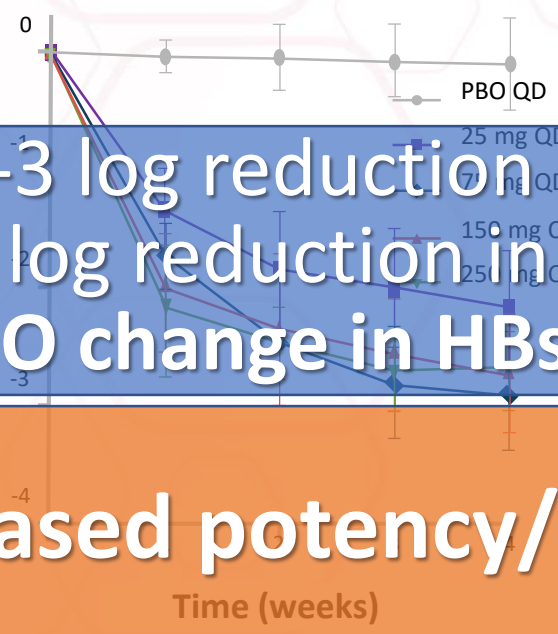
- **Antiviral effect during 28 days dosing**

**1. NVR3-778**



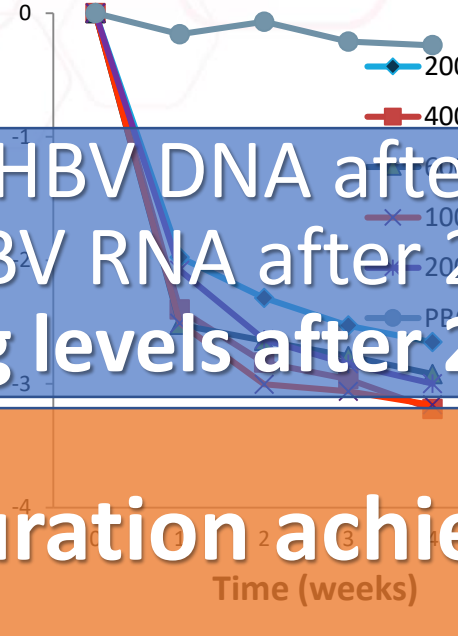

Yuen M-F, et al. EASL 2016, Barcelona. LBO6

**2. JNJ-379**



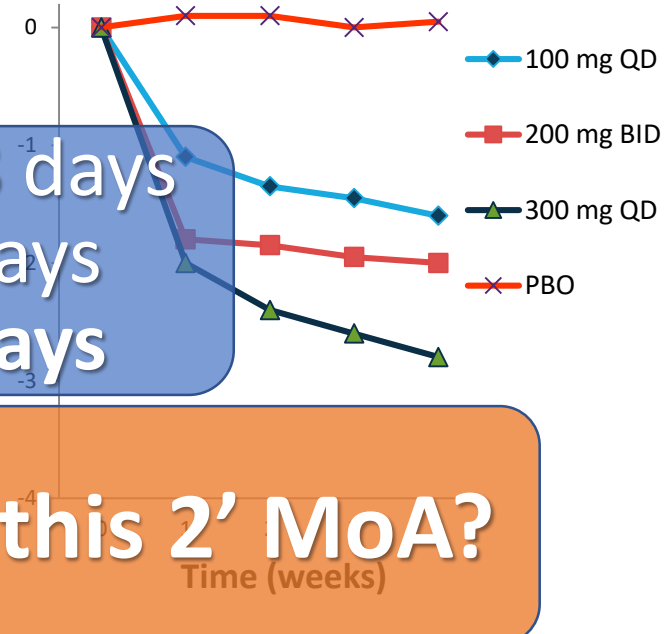

Zoulim F, et al. EASL 2018, Paris. #LBO-004

**3. RO7049389**




Gane E, et al. EASL 2018, Paris. #LBO-003
Yuen M-F.EASL 2019, Vienna., **#FRI-219**

**4. ABI-H0731**




Yuen M-F, et al. AASL D2016, San Francisco

- 2-3 log reduction in HBV DNA after 28 days
- 2 log reduction in HBV RNA after 28 days
- **NO change in HBsAg levels after 28 days**

**Will increased potency/duration achieve this 2' MoA?**

- 1200mg⇨2log reduction
- No effect on HBsAg
- Skin rash

- 250mg⇨2.9 log reduction
- No effect on HBsAg
- Occ ALT elevation

- 200mg⇨3.2 log reduction
- No effect on HBsAg
- ALT elevation in 20%

- 400mg⇨3.9 log reduction
- No effect on HBsAg
- Skin rash

# Oral HBV capsid assembly inhibitor (CpAMs)

## AASLD 2019, Abstract #LP14: Increased potency of 2nd Gen CAMs

- ABI-H2158 >10-fold in vitro potency for inhibition of capsid assembly and cccDNA synthesis compared to 1st Gen CAMs Colonno R, et al. EASL 2019
- ABI-H2158 100mg OD for 14 days in Rx-naïve HBeAg-positive CHB
  - Safe and well tolerated, with no Grade ≥2 ALT elevations
  - Mean HBV DNA decline 2.3 log10 IU/mL [range 1.7 – 3.0]
  - Mean HBV RNA decline 2.0 log10 IU/mL [range 1.5 - 2.6]
- Next cohort of ABI-H2158 300mg OD for 14 days in progress

Yuen M-F, et al. AASLD 2019,. #LP14

# Oral HBV capsid assembly inhibitor (CpAMs)

## AASLD 2019, Abstract #LP1: Longer Duration of 1st Gen CAMs

- Study #211: Open label ETV+ ABI-H0731 for 52 weeks in patients who have completed Studies #201 and #202 (24 weeks ETV + ABI-H0731/Plac)
  - Interim results for HBeAg+ completed ≥ 32 wks ETV + ABI-H0731

1. 27 patients from Study #201 (DNA suppressed on NUCs at Baseline)
   ⇨ 11 (41%) are HBV DNA TND, RNA <35 iu/mL and HBeAg <1 IU/mL
2. 22 patients from Study #202 (Rx-naïve, DNA> 5 log iu/mL at Baseline)
   ⇨ **Mean HBV DNA decline 6.1 $\log_{10}$**
   ⇨ Mean HBV RNA decline 3.0 $\log_{10}$
   ⇨ Mean HBcrAg decline 0.8 $\log_{10}$ (7 pts ≥1.0)
   ⇨ Mean HBeAg decline 0.6 $\log_{10}$ (4 pts ≥1.0)

Sulkowski M , et al. AASLD 2019,. #LP1

# Oral HBV capsid assembly inhibitor (CpAMs)

## AASLD 2019, Abstract #LP1: Longer Duration of 1st Gen CAMs

- Study #211: Open label ETV+ ABI-H0731 for 52 weeks in patients who have completed Studies #201 and #202 (24 weeks ETV + ABI-H0731/Plac)
  - Interim results for HBeAg+ completed ≥ 32 wks ETV + ABI-H0731

1. 27 patients from Study #201 (DNA suppressed on NUCs at Baseline)
   - ⇨ 11 (41%) are HBV DNA TND, RNA <35 iu/mL and HBeAg <1 IU/mL
2. 22 patients from Study #202 (DNA >2000 IU/mL at Baseline)
   - ⇨ Mean HBV DNA decline 6.1 log
   - ⇨ Mean HBV RNA decline 3.0 $log_{10}$
   - ⇨ Mean HBcrAg decline 0.8 $log_{10}$ (7 pts ≥1.0)
   - ⇨ Mean HBeAg decline 0.6 $log_{10}$ (4 pts ≥1.0)

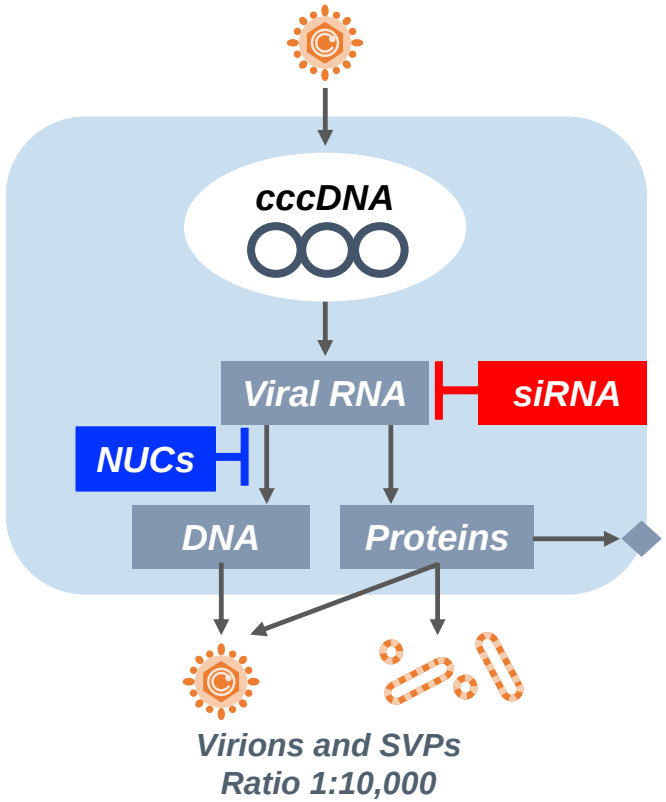
**First evidence of cccDNA pool depletion**
**Will CAM-NUC achieve Functional Cure?**

➡ **Mean HBsAg decline 0.4 $log_{10}$ (7 pts ≥0.5, 3 pts ≥1.0)**

assemblybio

Sulkowski M , et al. AASLD 2019,. #LP1

# Mechanism of Translation Inhibitors




- Inhibition of virion and SVP production
  - Inhibition of HBV antigen expression could stimulate endogenous immune responses AND increase effectiveness of immunotherapies

**ASO/LNAs**

- RO7062931[1]
- GSK3228836
- GSK3389404[2]
- ISIS 505358[3]

1.Gane E, et al. Poster #698
2.Yuen M-F, et al. Poster #695
3. Yuen-M-F, et al. Poster #700

**siRNAs**

- ARC-520
- ARC-521
- ALN-HBV
- ARB-1467
- ARB-1740
- AB-729
- ARO-B/JNJ-3989[4,5]
- GalXC-HBVS/DCR-HBVS
- ALN HBV02/VIR-2218

4.Gane E, et al. Poster #696
5.Yuen M-F, et al. Poster #LP4

# Challenges of Translation Inhibitors in CHB

## 1. What HBV targets are most effective

- First gen siRNA (ARC-520) had little effect in HBeAg negative patients
  - ➡ target sequences downstream from DR1-DR2 region to silence intergrated S

Wooddell C, et al. Sci Transl Med 2017; eaan0241

- Are multiple targets needed to prevent resistance?
- Should "X" be targeted as well as "S"?

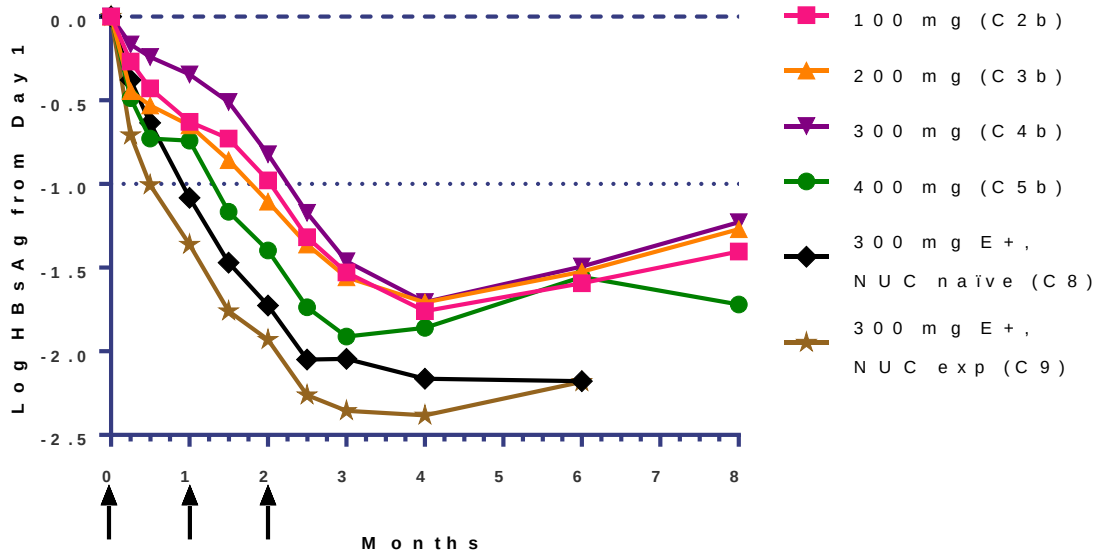
## 2. What is best delivery system to hepatocytes

- 1st Gen NAG-MLP siRNAs (ARC-520/521); LNP siRNAs (ARB-1467/1740) required weekly intravenous dosing, infusion reactions and premeds

➡Gal-NAC conjugated: subcutaneous , monthly dosing, no premeds

# JNJ-3989 (ARO-HBV) in eAg pos and eAg neg CHB

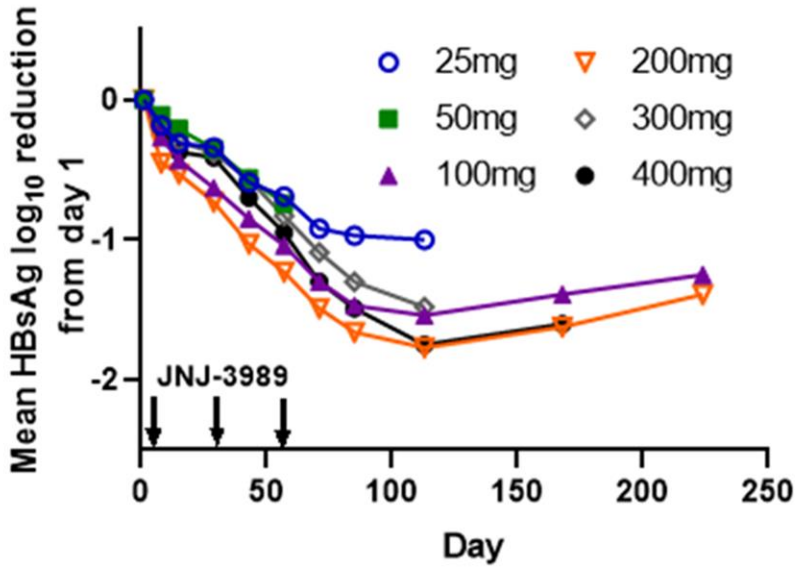
- MAD Ph1b (AASLD 2018; EASL 2019)
  - Cohorts 1-6:  3 doses Q4W
  - Cohorts 7-8: 3 doses QW or Q2W




- HBsAg declined by 1 log in all patients
- No dose-response from 100-400mg
- 1 Gr 2 ALT elevation, 3 months post-Rx,

Yuen M-F, et al. EASL 2019, Vienna, Austria. #PS-080

- Phase 1b (AASLD 2019 #PS-080)
  - Expanded 100–400 mg cohorts
  - Added low-dose 25, 50mg cohorts
  - Longer follow-up



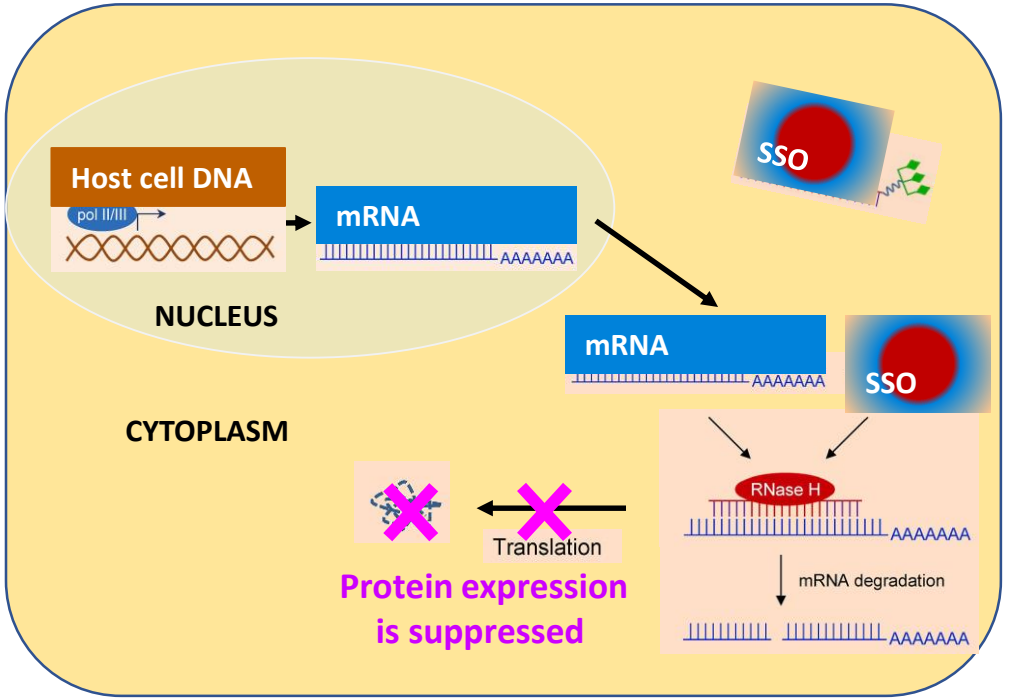

- Doses < 100mg less effective
- No more ALT elevations

Gane E, et al. AASLD 2019,; #696

# Translation Inhibition: other approaches at AASLD

## 1. Antisense oligonucleotides

- ASOs silence HBV gene expression by hybridising to HBV mRNA and activating host RNAse H mediated degradation (not RISC)
- Gal-Nac-conjugation should reduce ASO toxicities of renal dysfunction, low platelets




1. RO7062931: Phase 1a in HVs (Gane #704)
   - Safe, no toxicity
2. GSK3389404: Phase 1b in NUC-suppressed CHB patients (Yuen #695)
   - 12 week dosing 120mg ⇨ HBsAg decline 0.75 log
3. ISIS505358: Phase 1b in treatment naïve-CHB patients (Yuen #700)
   - 3 week dosing 300mg⇨ HBsAg decline 1.6 log ; HBV DNA decline 1.7 log
   - **HBsAg and HBV DNA <LLOQ** in 2 pts maintained for 1-4 months post-treatment

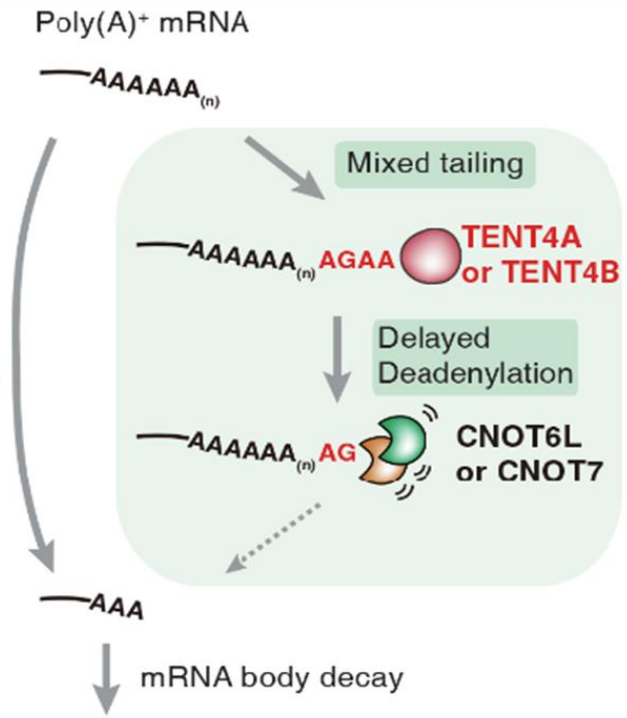
# Translation Inhibition: other approaches at AASLD

## 2. mRNA destabilisers

- Small molecules target host poly-A polymerases PAPD5/7 (TENT4A/4B) which destabilise HBV transcripts from both integrated and cccDNA Mueller Hepatol 2019; 69: 1398
  - Initial compounds associated with preclinical toxicity
- Gal-NAC LNA ASOs targeting host PAPD5/7
  - POC study in AAV-HBV mouse model (Poster #704)
  - Subcut injection Q2 weekly x3
  - ➡ decrease HBsAg in all animals - mean 2.3 $log_{10}$
  - ➡ **4/8 mice had sustained HBsAg** loss with anti-HBs, i.e. achieved functional cure

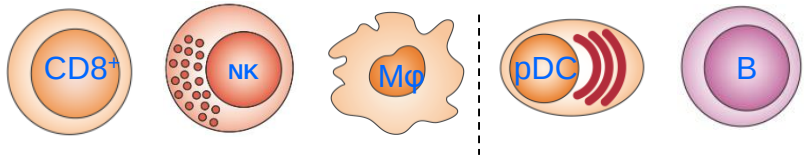
Mueller H, et al. AASLD 2019; #704

**Mixed tailing by PPAD5/PPAD7 shields mRNA from rapid deadenylation and decay[1]**



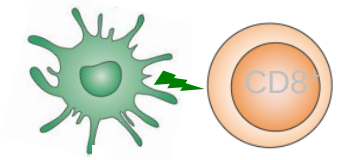
# Ways to activate Antiviral Immunity against HBV

## 1. Stimulate Antiviral Effector Cells



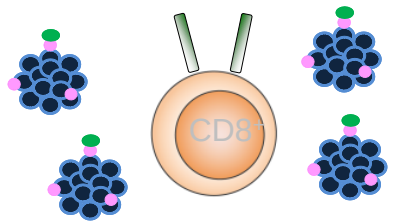

- TLR-7, TLR-8, RLRs, CLRs, NLRs
- DNA sensors

## 2. Generate New T cells




- Therapeutic vaccines

## 3. "Rescue" Exhausted T cells

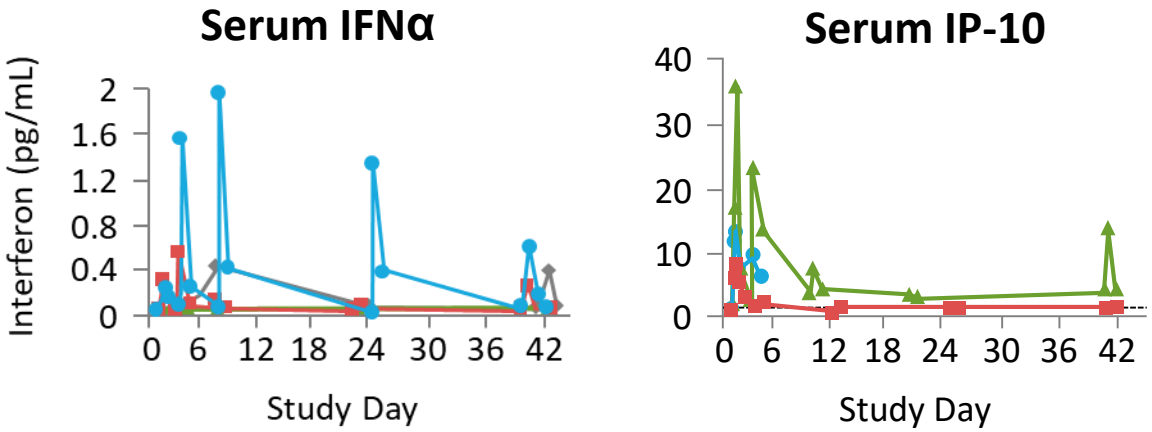



- Reduce viral antigens
- Modulate immune receptors (PD-1)
- Relieve suppression of T cells
- Inhibit T regs

# TLR-7 agonist RO7020531

- Liver targeting specific TLR-7
  - 150 mg QOD dosing for 6 weeks in NUC-suppressed CHB patients at AASLD 2018

**PD activity in patients with flu-like symptoms**




**Relationship between exposure and PD activity (maximum fold of change in individual patients)**

| | Fraction responding | Geometric mean fold change (range) |
|---|---|---|
| **Neopterin** | 6/8 | 3.13 (1.86–6.08) |
| **IP-10** | 7/8 | 3.55 (1.37–36.43) |
| **ISG15** | 8/8 | 11.21 (2.31–270.26) |
| **OAS-1** | 8/8 | 4.85 (1.71–41.45) |
| **MX1** | 8/8 | 6.78 (2.16–87.43) |
| **TLR7** | 7/8 | 3.46 (2.04–6.84) |

- At AASLD this year, additional 150 and 170 mg cohorts (Yuen #692)
  - full virologic results including HBsAg to be presented
  - Next year planned Phase II platform studies with other agents

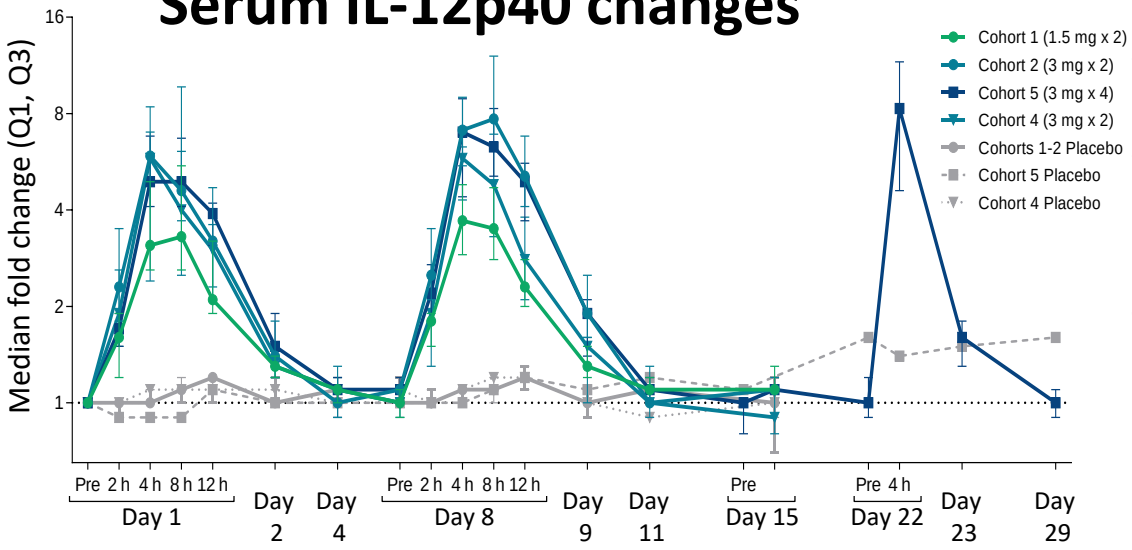

Gane E, et al. AASLD 2018, San Francisco, USA. #LB-33

Yuen M-F, et al. AASLD 2019, Boston, USA. #692

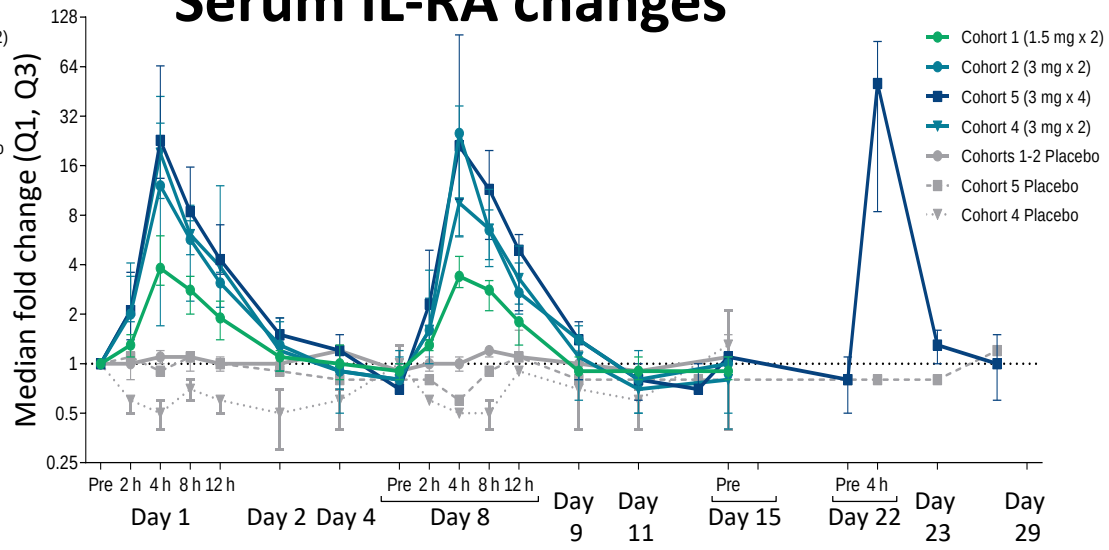
# TLR-8 agonist GS-9688

- EASL 2019: Phase 1b: 4 weekly doses in NUC suppressed CHB

**Serum IL-12p40 changes**




**Serum IL-RA changes**

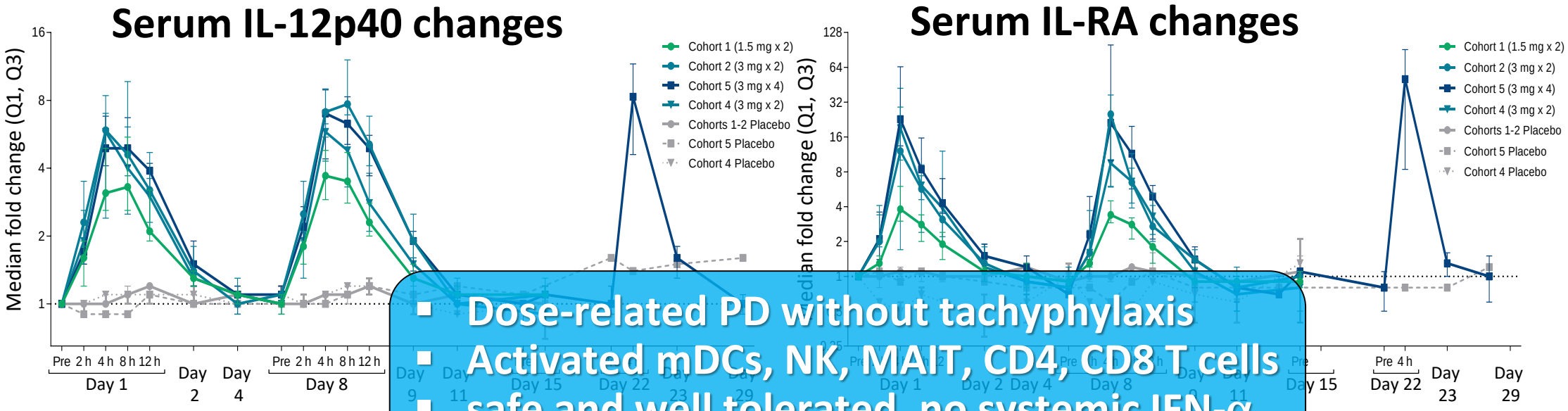



Reyes M, et al. AASLD 2018, San Francisco, USA. #390
Khanam A, et al. AASLD 2018, San Francisco, USA. #550
Amin AE, et al. EASL 2019, Vienna, Austria. #FRI-132

- At this meeting, results of Phase II study in NUC suppressed CHB (Gane #697)
  - 24 HBeAg pos and 24 HBeAg neg CHB patients on NUCs
  - Safe and well tolerated
  - HBsAg loss (Week 24)

# TLR-8 agonist GS-9688

- EASL 2019: Phase 1b: 4 weekly doses in NUC suppressed CHB



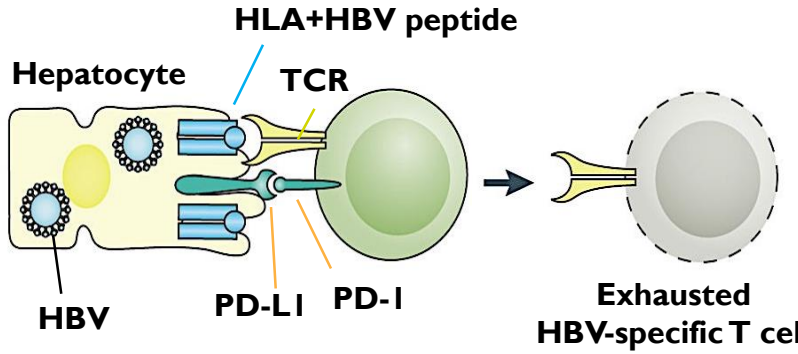

- Dose-related PD without tachyphylaxis
- Activated mDCs, NK, MAIT, CD4, CD8 T cells
- safe and well tolerated, no systemic IFN-α
- NO change in HBsAg after 4 weeks

Reyes M, et al. AASLD 2018, San Francisco, USA. #390
Khanam A, et al. AASLD 2018, San Francisco, USA. #550
Janssen AE, et al. EASL 2019, Vienna, Austria. #FRI-132

- At this meeting, results of Phase II study in NUC suppressed CHB (Gane #697)
  - 24 HBeAg pos and 24 HBeAg neg CHB patients on NUCs
  - Safe and well tolerated
  - HBsAg loss (Week 24)

# PD1/L1 blockade

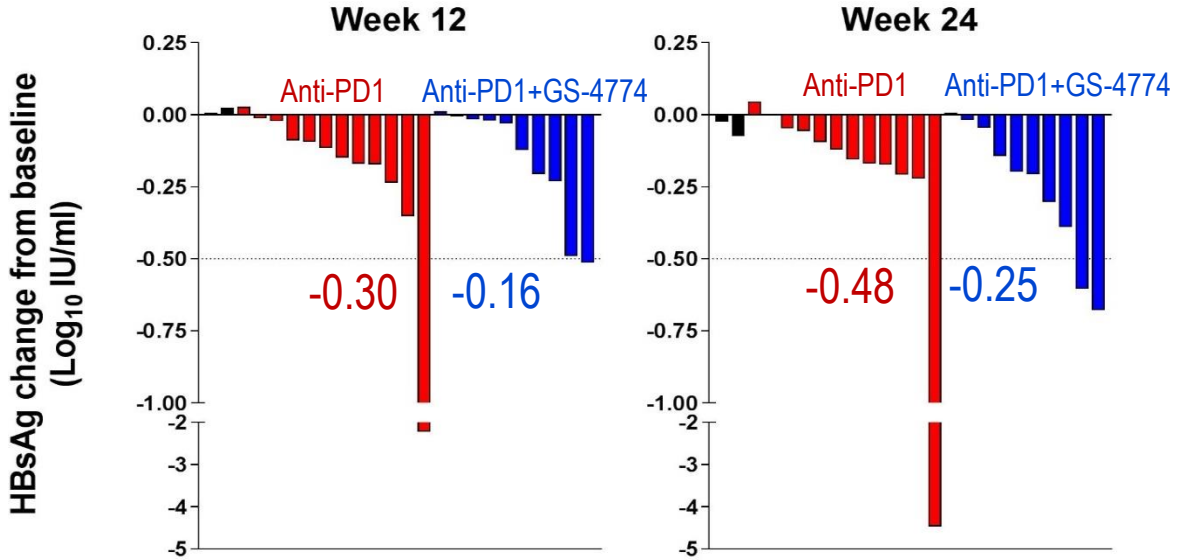
- CHB characterised by immune exhaustion
- PDL1 blockade should restore effective intra-hepatic HBV-specific T-cell responses




- Single dose IV nivolumab 0.3mg/kg in CHB
  - 20/22 had reduction in HBsAg
  - One functional cure
  - Overall effect was small

Gane E, et al. J Hepatol 2019; 71: 900–7

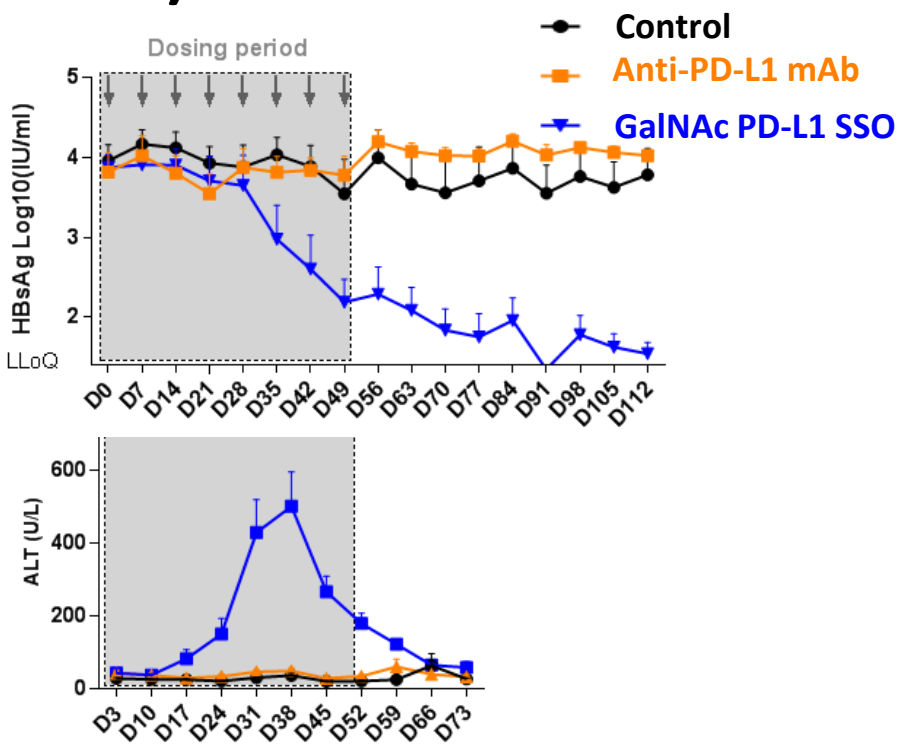
- Dose will be limited by IR-AEs which can be prolonged and life-threatening
  - ACTG study exploring repeated doses
  - Need new approaches to PD1/L1 blockade



# PD1/L1 blockade: new approaches at AALSD 2019

- **Inhibition of PD-L1 synthesis by LNA (Abstract #691)**
  - GalNAc-conjugated LNA ASO directed against PD-L1
    - Mice received 5 weekly subcut doses 5 mg/kg
      - 50% reduction in PD-L1 maintained for 8 weeks
      - 40-fold increase in liver HBV specific IFN-γ cells
      - 2.4 log reduction in HBsAg which was sustained

Luangsay S et al. #691




- **Inactivation of PD-L1 by small molecule inhibitors**
  - Several small molecules can bind to and dimerise PD-L1 and inactivate the receptor
    - short lived PD effect improving safety if IR-AEs develop

Ganesan A, et al. Nature (Scientific Reports). 2019; 9:12392,

# HBV CURE Combination Studies

**Replication inhibition** ± **Antigen reduction** ± **Immune stimulation**

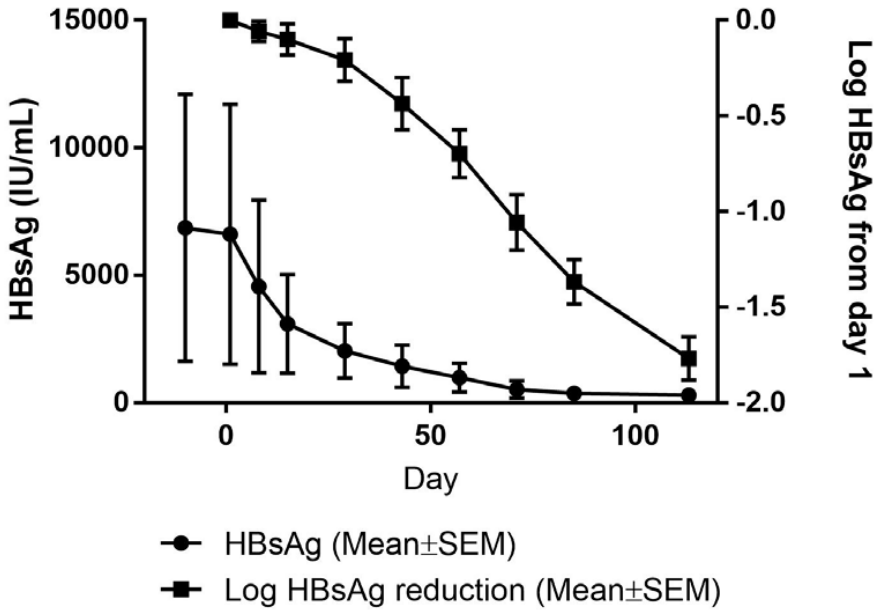
| RNAi | CAM |
|---|---|
| RNA destabiliser | CAM |
| RNAi | Th. vaccine |
| RNAi | TLR Agonist |
| RNAi | PD1/L1 inhibitor |
| RNA destabiliser | PD1/L1 inhibitor |
| RNA destabiliser | TLR Agonist |

| NUC | CAM |
|---|---|
| TLR agonist | CAM |
| Th Vaccine | CAM |
| TLR agonist | New DNA inhibitor |
| PD1/L1 inhibitor | New DNA inhibitor |
| Th. vaccine | PD1/L1 inhibitor |
| TLR agonist | PD1/L1 inhibitor |

# HBV CURE Combination Studies

RNAi | CAM

- **Triple therapy: siRNA plus CAM plus NUC (Yuen #LP4)**
  - –12 eAg+/eAg- CHB patients in open label POC study
    1. JNJ-3989 200 mg subcut on Days 1, 28 and 56
    2. JNJ-6379 250mg OD for 12 weeks
    3. ETV/TDV OD
  - Well tolerated, few Gr1 ALT increases
  - Robust antiviral activity
    - –HBsAg decline 1.8 log by Day 111
    - –Robust declines in other viral parameters




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

# AASLD 2019 Conclusions

- Several promising candidates already in Phase II
  1. Will CAMs + NUC be enough to clear HBsAg?
  2. Will siRNAs achieve off-treatment HBsAg loss?
  3. Will reports of ALT elevations with some CAMs and siRNAs be deemed agent specific or become a class dose-limiting effect
  4. How should the immunomodulators be used?
  5. Will PD1 blockade be safe at the dose needed to clear HBsAg?
  6. Which combinations should be prioritised in Platform studies and in which patient populations?

# Class of 2019:

who d?

# Special thanks to


- Dr Anuj Gaggar, Audrey Lau, Gilead Sciences
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