HBV Cure
Overview of Viral and Immune Targets

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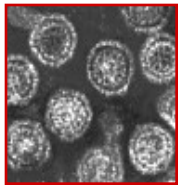
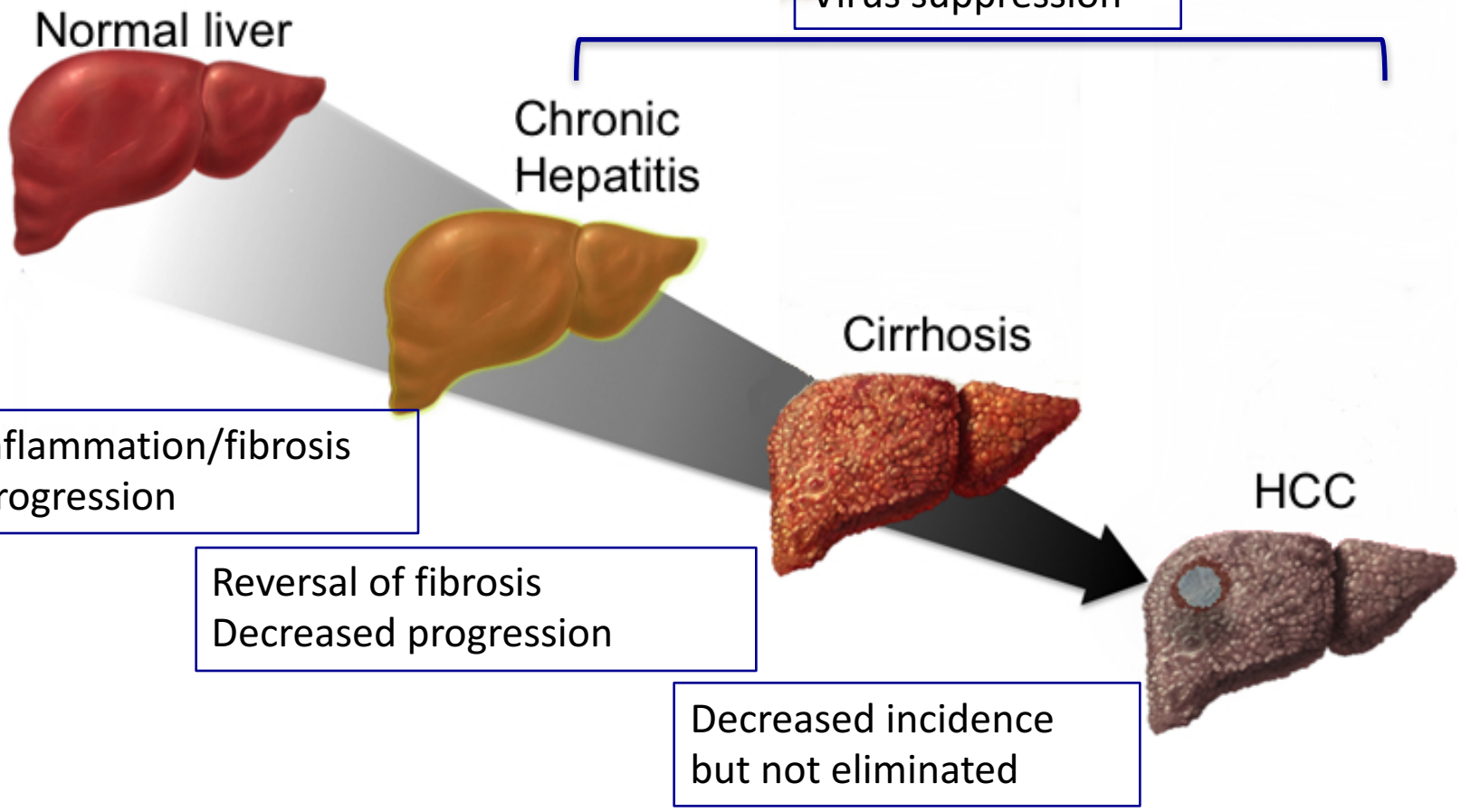
Washington

Current treatments: virus suppression and sustained disease control





Liaw YF et al, N Engl J Med. 2004; Chang et al, Hepatology 2010; Marcellin et al, Lancet 2013; Hosaka et al, Hepatology 2013; Kim et al, Cancer 2015; Papatheodoridis et al, J Hepatol 2015; Zoulim EASL ILC 2016

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Key Considerations for Current Treatment Options

- HBV nucleos(t)ides are highly effective and generally well tolerated, but with low rates of successful discontinuation
- Long-term nucleos(t)ide-analogues reduce cirrhosis, liver failure and HCC; safety remains to be determined but appears very good
- PEG-IFN monotherapy is finite but only effective in subgroup of patients and its use is limited due to toxicity
- Thus, unlike in HCV drug development there is effective and safe therapy available which suppresses HBV

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Why is Finite Therapy a Goal for HBV Treatment?

Younger patients may find lifelong treatment hard to accept

Women who want to become pregnant

Patients reluctant to start treatment

Working days lost to hospital visits

Cost savings to healthcare system

Long-term adherence issues

Is HBV Treatment Paradigm Changing?

Current PARADIGM

- *Indefinite Treatment*
- *Poor off-Rx response*
- *Reduces overall mortality*
- *Reduce but does not eliminate the risk of HCC*
- *Potent NAs :suppresses viral replication but cannot cure the disease*

New PARADIGM

- *Finite treatment duration*
- *Sustained off-Rx response shift towards endpoint of true immune control &HBsAg seroconversion*
- *No increased risk of mortality and HCC*
- *New HBV treatments with increased chance of curing disease*

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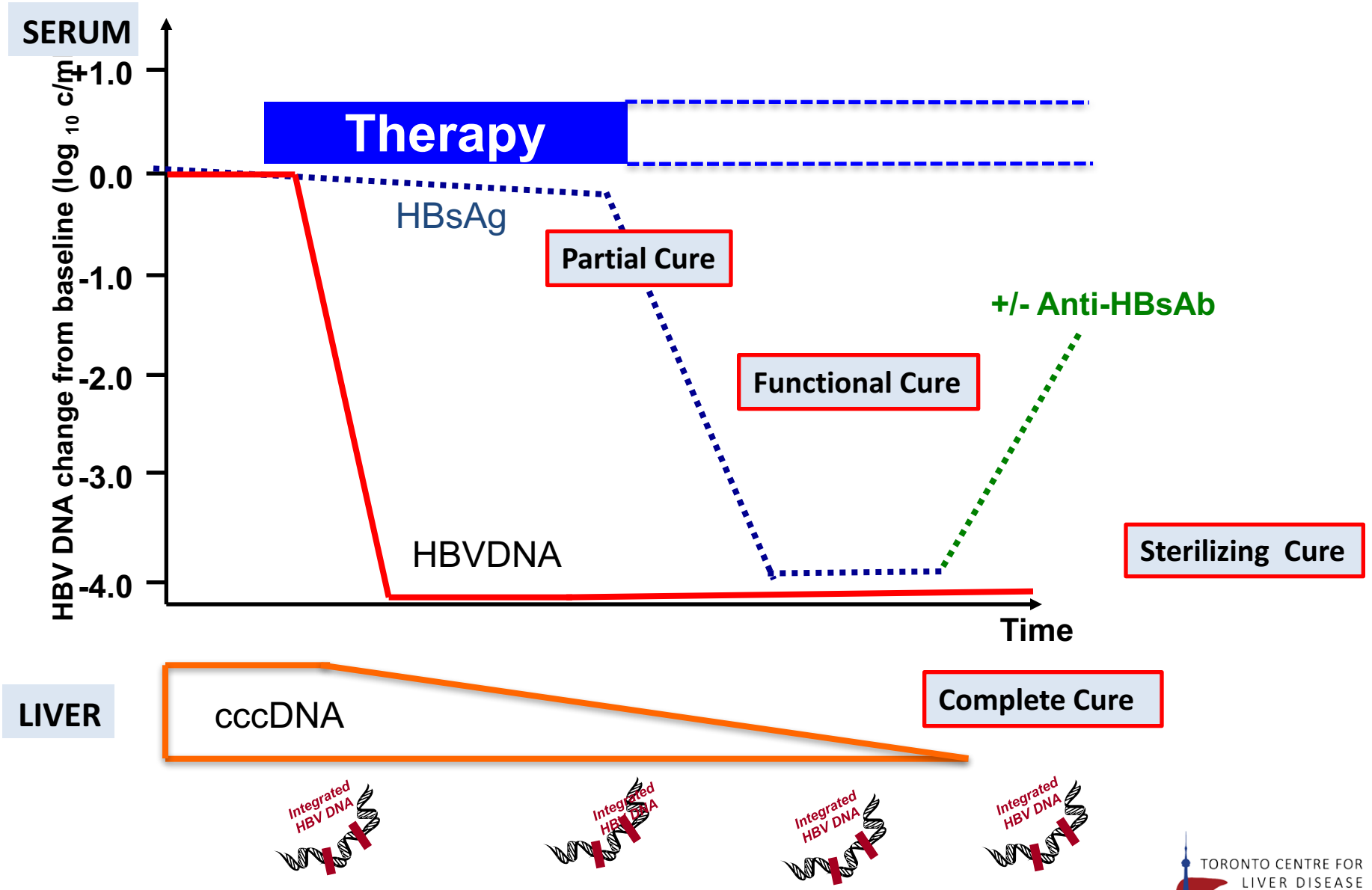
Definition of HBV Cure



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Lok et al, Hepatitis B Cure: From Discovery to Regulatory Approval; Hepatology 2017

Defining HBV Cure

Functional cure

Associated with clinical benefit (disease progression and HCC)

Off-therapy sustained HBV suppression and disease remission

HBsAg serocnversion and cccDNA inactivation/reduction

Risk under immunosuppression

Feasible

Complete cure

Associated with clinical benefit (disease progression and HCC)

HBsAg seroconversion and cccDNA eradication

Feasibility very uncertain

Zeisel, Lucifora et al, Gut 2015; Revill et al, Nature Reviews Gastroenterol Hepatol 2016

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Experimental HBV treatment in naive vs virally suppressed patients

Treatment Naive

Younger

Active Disease

HBVDNA can be used as a biomarker

No resistance

May be more likely to accept finite therapy

Suppressed

Have safe and effective therapy with reduction of HCC and improved survival

Partial immune restoration may benefit immune modifying therapy

Potentially better protection against flares

May have more objections to accept experimental therapy

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Virology vs Immunology

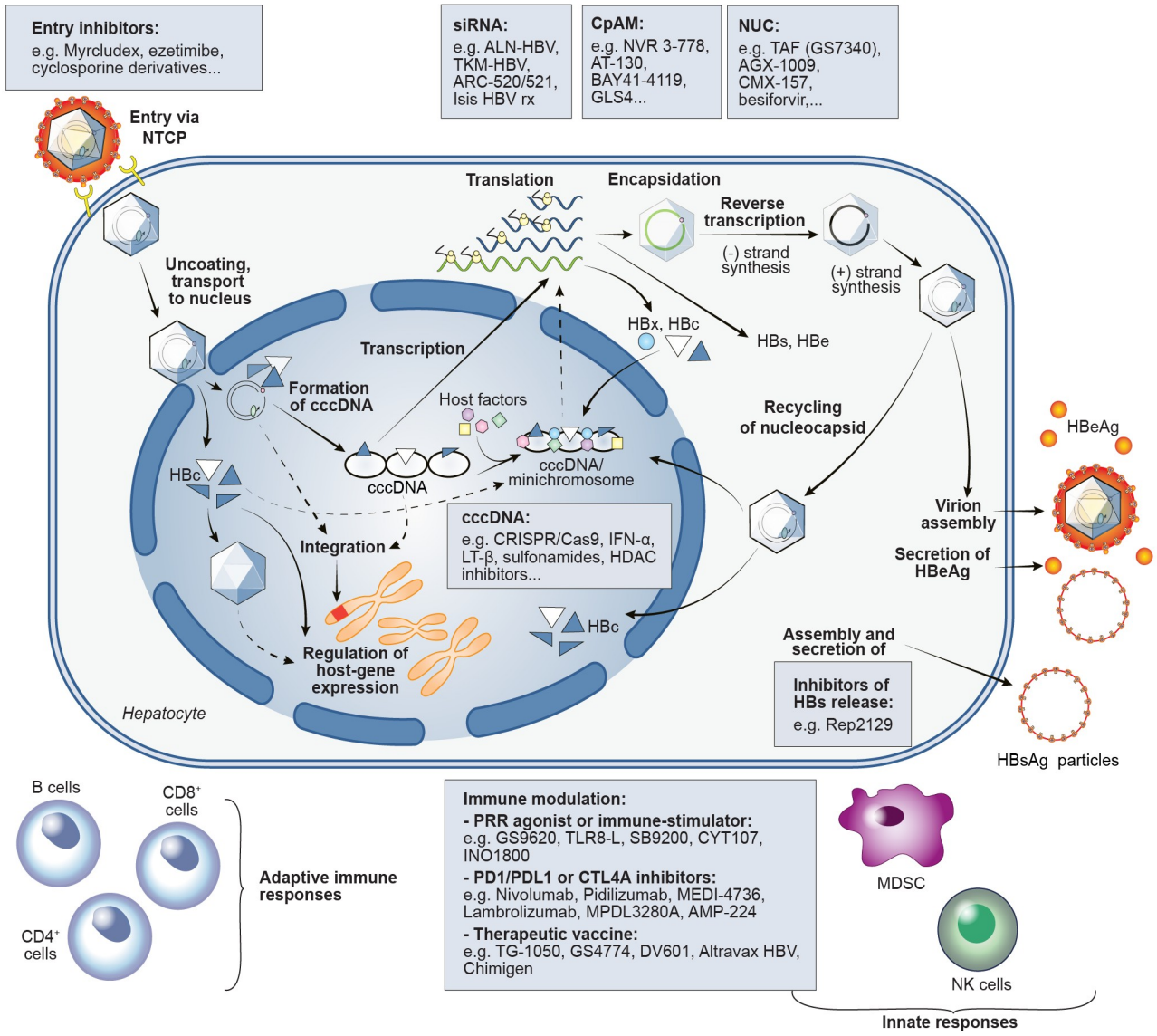
Virology

- Blocking viral replication at multiple steps and elimination of ccc DNA will eventually cure HBV infection: no infected hepatocytes left
- Need assays to detect low level replication below current LOD to determine efficacy
- Intense inhibition of protein and virus production may by itself mount an effective immune response

Immunology

- Virus integrates in host genome and will always remain present in the hepatocytes (or elsewhere?)
- Proof is the HBV relapse (even HBsAg sero-reversion) during immune suppression
- Effective immune control is most likely delivered by immune modulation agents: example efficacy PEG-IFN

HBV cure – Compounds in Development



Testoni & Zoulim, Hepatology 2015; Durantel & Zoulim, J Hepatol 2016

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New HBV Treatments

Virology

Entry inhibitors
cccDNA Degradation/Silencing/Elimination
RNA interference (RNAi)/Gene silencing
Assembly (Nucleocapsid) inhibitors

Immunology

TLR, RIG-I agonists
Therapeutic vaccination
PD-1, PDL-1 Blocking

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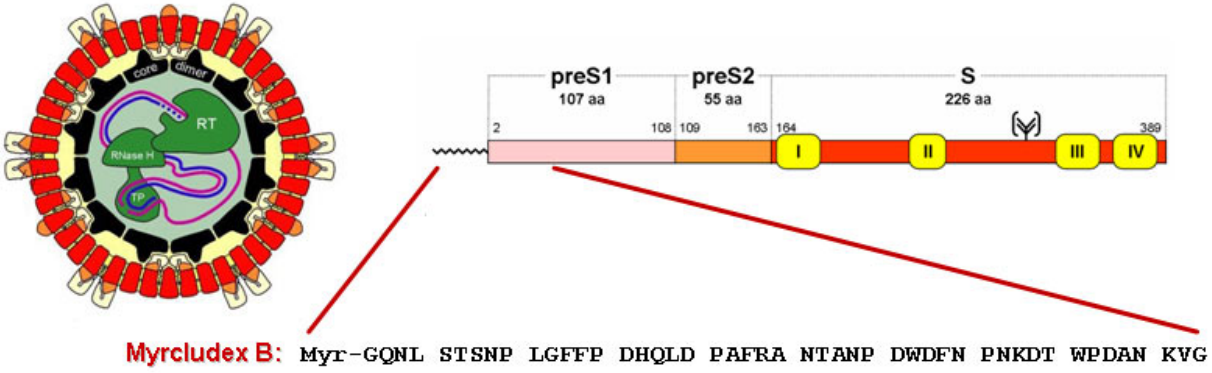
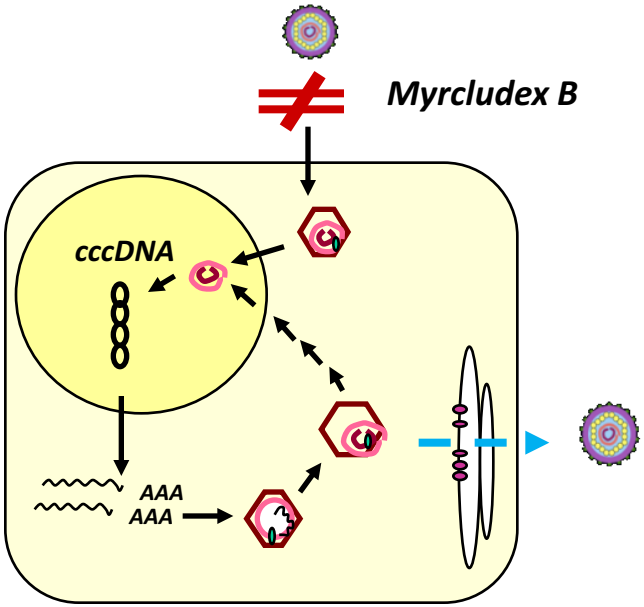
Myrcludex B: Acylated HBV preS1-derived peptides block HBV infection in vitro – entry inhibitor





Chemically synthesized lipopeptides derived from the envelope of HBV block virus infection in cell culture (HepaRG & PTH, PHH)

Gripon et al., PNAS, 99 (24) 2002
Urban et al., J. Virol, 79 (3), 2005
Glebe et al., Gastroenterology, 129, 2005
Engelke et al., Hepatology, 43, 2006
Schulze et al., Hepatology, 46, 2007

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Phase 2a clinical trial with the HBV/HDV entry inhibitor Myrcludex B

Patient Population	Treatment Arms	End points
-CHB HBeAg negative -HBV DNA>2000IU/ML -No cirrhosis -N=40	-Myr B daily S.C (0.5, 1, 2, 5, 10 mg) for 12 w (10mg for 24w) -12 weeks follow-up	-Safety and tolerability -Efficacy (HBV DNA, ALT, HBsAg) -PK -Immunogenicity -Bile acids levels

At 24w, HBV DNA declined in all treatment groups

>1log reduction in HBV DNA in 6/8 (75%) of the10mg (24w) group

7/40 patients >1log reduction HBV DNA in lower dose groups

ALT normalization in 55%

No significant effect on HBsAg at 24 weeks

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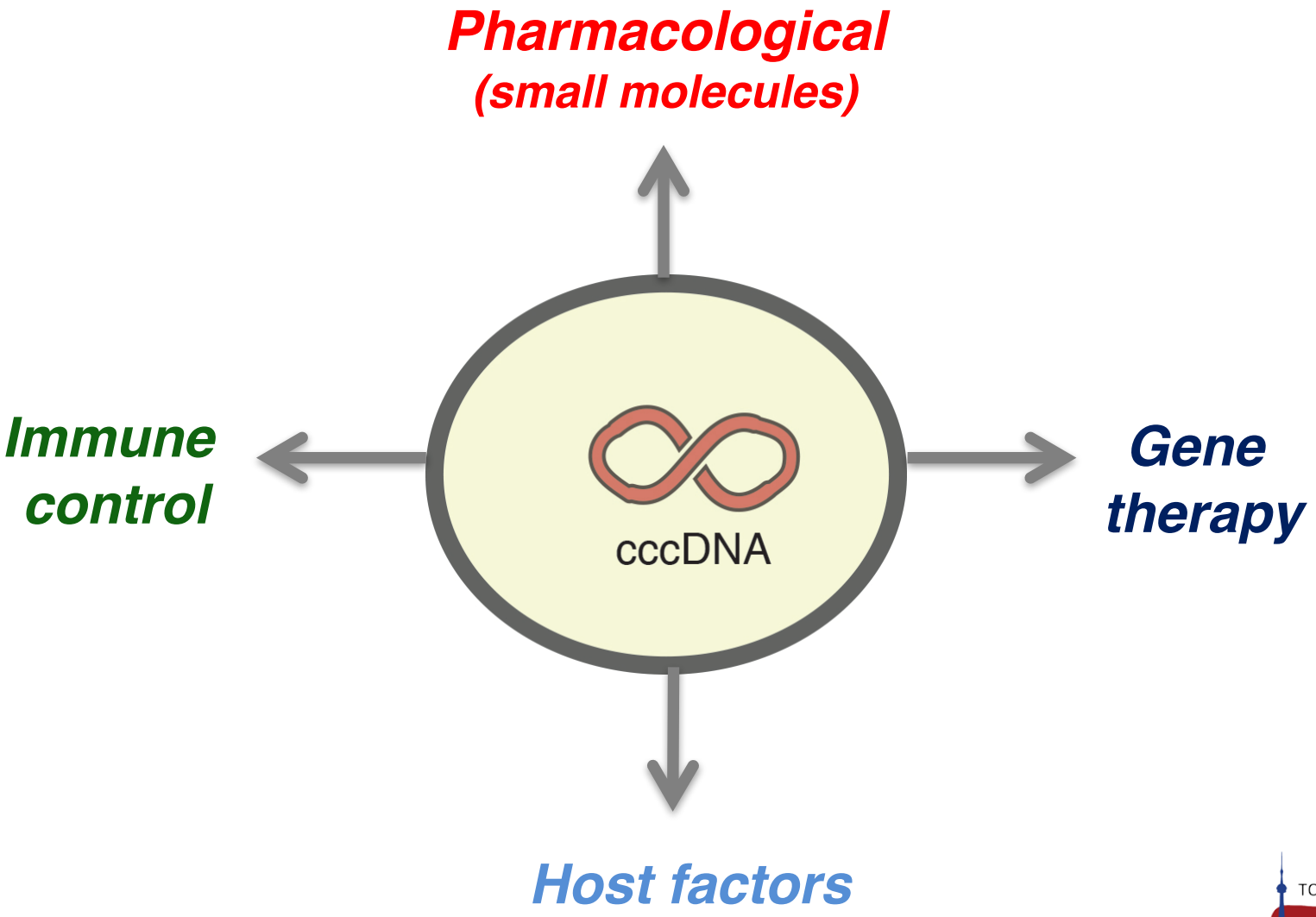
Urban S et al, AASLD 2014

Strategies to control/eliminate cccDNA



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cccDNA Degradation/Silencing/Elimination

Zinc finger nucleases and Sulfonamide compounds: direct destruction of cccDNA, inhibiting rcDNA conversion to cccDNA and by targeting the epigenetic control of cccDNA

Early development: cell culture/primary duck hepatocytes

CRISPR/CAS 9: use target RNA with sequence specificity for conserved regions of DNA to guide nuclease to cleave the DNA at that site

- Suppression of cccDNA in HBV transgenic mice
- CRISPR strategy holds promise for human gene editing and may be useful targeting a stable viral genome like HBV

Difficult to achieve. High risk off-target effect.

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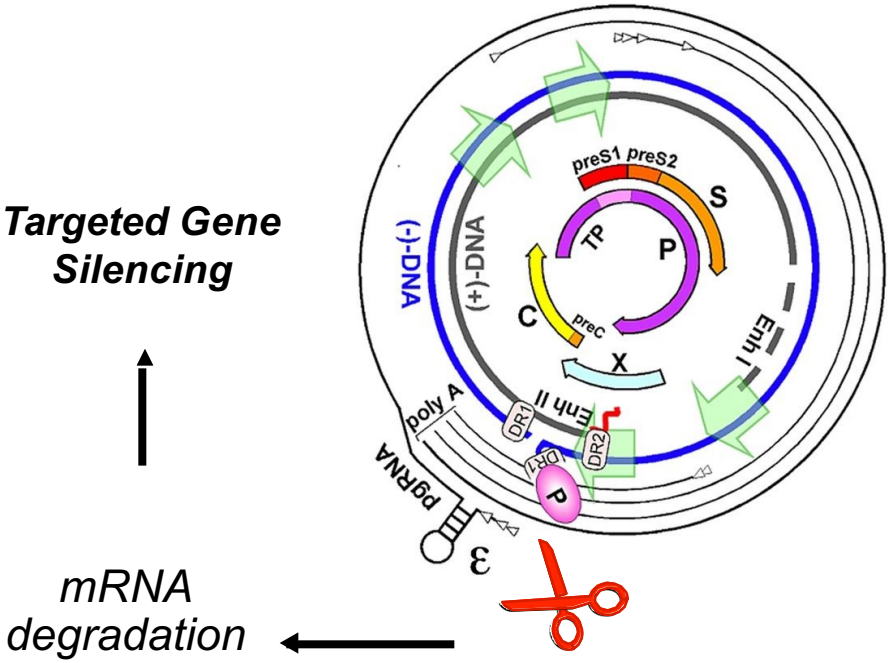
Kennedy et al. Virology 2015

Targeting HBsAg by RNA interference



Moore, J Gen Med 2005; Ebert et al, Gastroenterology 2011; Wooddell CI et al, AASLD 2015
Lorenzino et al, AASLD 2015

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RNA Interference/ Gene Silencing

- HBV susceptible to RNAi because it replicates via an RNA intermediate
- Delivery is now possible through different platforms (LNA,nano particles). However needs to be given IV and risk of allergic reactions
- SI RNA can knockdown production of all HBV genes and thereby significantly decrease the number of infectious viral particles and Ag's
- May lead to "artificial" HBsAg or HBeAg loss
- This reduction in viral and antigen load is designed to permit the immune system to mount an effective response to CHB
- Could well be used as priming therapy for immune modulators

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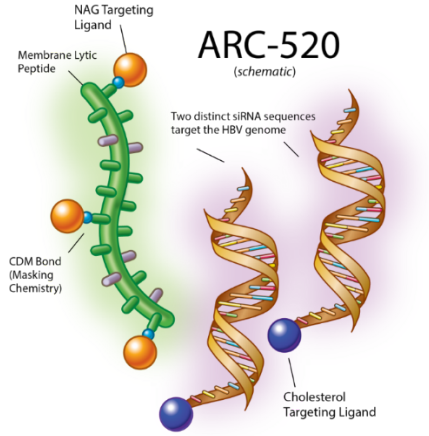
Billioud et al. EASL 2014, Janssen et al. NEJM 2013, Yuen er al. AASLD 2015

RNAi therapy with ARC-520 in treatment-naive, HBeAg + and – CHB patients

HBV RNAi therapeutics
- NUCs target HBV DNA only
- Aim to silence entire HBV genome by also targeting HBV mRNA with siRNA



ARC-520 is designed to reduce all mRNA transcripts from HBV cccDNA

- ARC-520 resulted in reductions in all HBV markers
- Reduction in HBeAg+ patients (-2.2 Log) greater than in HBeAg– patients (-0.7 Log)
- Difference reflects reductions in HBsAg from cccDNA in HBeAg+ patients vs. integrated DNA in HBeAg- patients
- Currently on hold because of toxicity in animal models

Yuen MF, et al. EASL 2017

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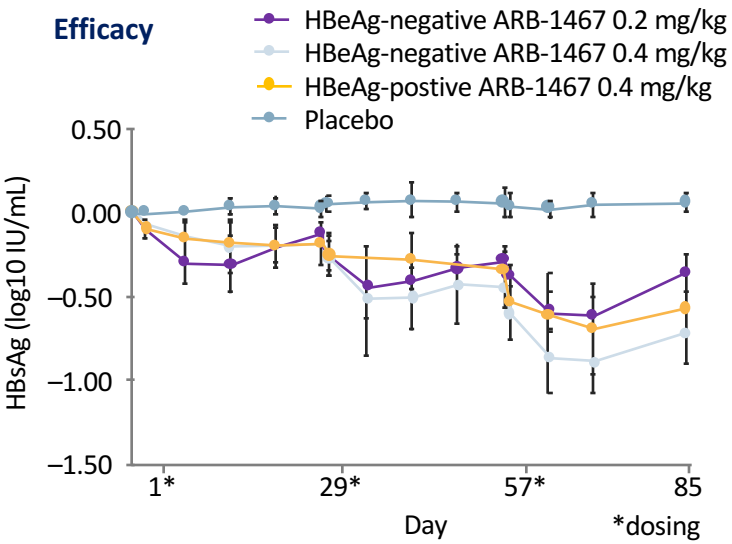
RNAi Therapy: phase 2a study on multi-dose activity of ARB-1467 in HBeAg+/- virally suppressed CHB



Safety, n (%)	HBeAg– 0.2 mg/kg (n=6)	HBeAg– 0.4 mg/kg (n=6)	HBeAg+ 0.4 mg/kg (n=6)	Placebo (n=6)
Any AE	5 (83)	5 (83)	2 (33)	5 (83)
Grade 3–4 AE	1 (17)	0	0	0
Serious AE	1 (17)	0	0	0
D/C due to AE	0	1 (17)	0	0
Grade 3 or 4 lab abnormalities	4 (67)	5 (83)	4 (67)	4 (67)

- Isolated elevated glucose, decreased lymphocytes, and low phosphate seen across all groups, included placebo

- Significant reductions in HBsAg with single doses of ARB-1467
- Stepwise, additive reductions with multiple doses (>1 log10 IU/mL in 5/11 with 0.4 mg/kg)
- No significant differences in serum HBsAg between HBeAg + and - CHB
- Well tolerated

Streinu-Cercel A, et al. EASL 2017

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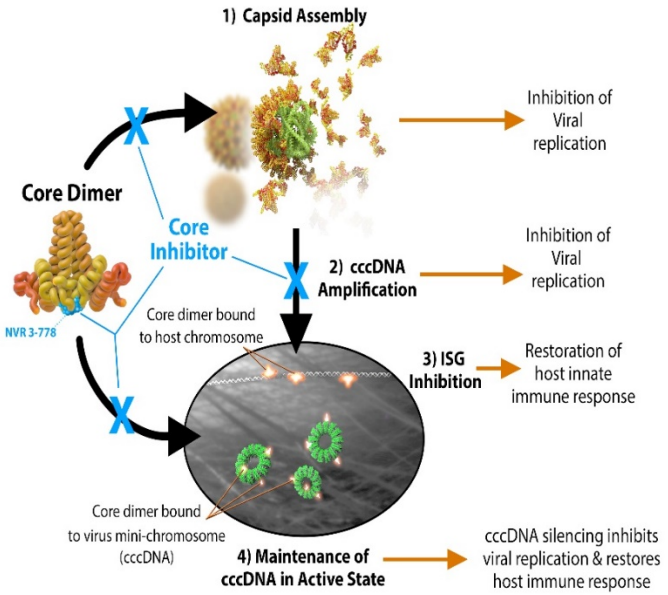
Capsid Inhibitors

Capsid inhibitors disrupt the HBV lifecycle by destabilizing the nucleocapsid and/or by blocking RNA packaging thus producing empty capsids lacking genetic information



Potentially inhibit viral assembly, HBV genome replication, cccDNA replenishment and hepatic reinfection cycles

NVR 3-778

- No adverse events in volunteers
- Phase 1b: 100 to 600 mg BD
- Mean HBVDNA decline 1.72 log in highest dose group after 28 days
- One patient serious rash hand and feet
- Studies with higher doses and combination with PEG-IFN

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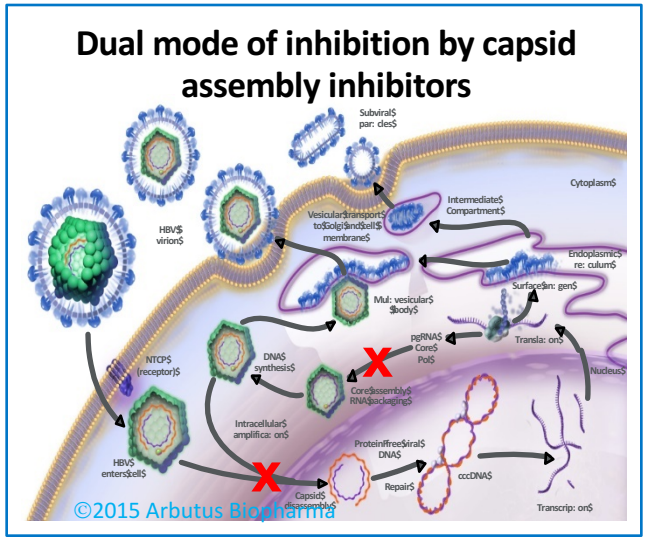
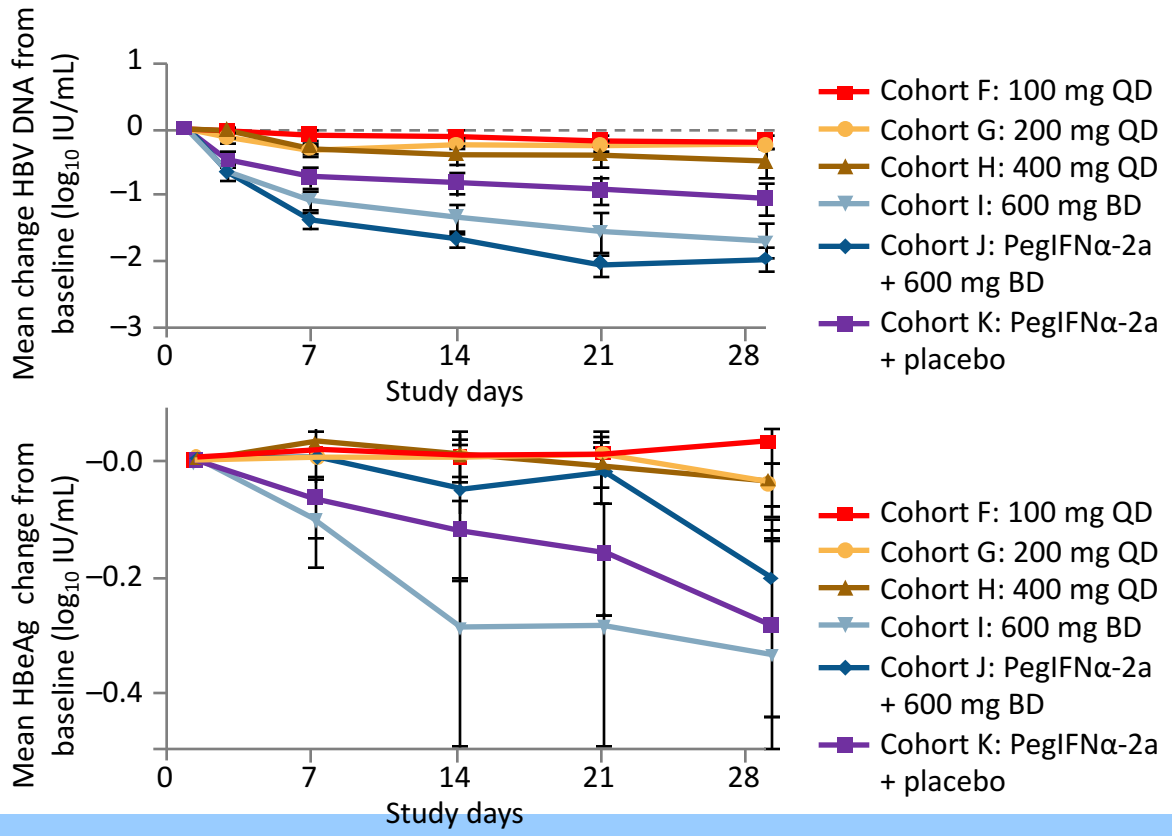
Stray PNAS 2005, Feld Antiviral Res 2007, Wu J Chemother 2008, Wang 2014 Antiviral Therapy, Yuen AASLD 2015

HBV capsid modulator: Phase 1B study NVR 3-778 alone and in combination with PegIFN, in naive HBeAg+ CHB



Treatment duration 28 days



- Additive antiviral effect of NVR 3-778 with PegIFN on HBVDNA and HBeAg
- Negligible effect on HBsAg
- Need data on combination of NVR 3-778 and NUC
- Longer-term outcomes including HBeAg seroconversion and HBsAg loss needed

Yuen M-F, et al. EASL 2016

New HBV Treatments

Virology

- *Entry inhibitors*
- *cccDNA Degradation/Silencing/Elimination*
- *RNA interference (RNAi)/Gene silencing*
- *Assembly (Nucleocapsid) inhibitors*

Immunology

- ***TLR, RIG-I agonists***
- ***Therapeutic vaccination***
- ***PD-1, PDL-1 Blocking***

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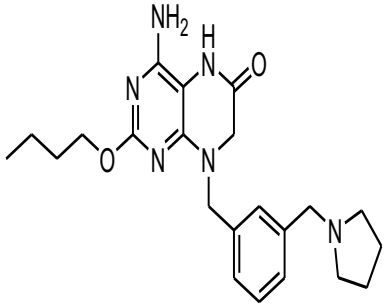
Toll Like Receptor (TLR) 7 Agonist

- TLR-7 is a pattern recognition receptor in endolysosomal compartment of plasmacytoid dendritic cells(pDC) and B cells
- Agonism induces anti-viral response via innate immune activation

- GS-9620
  - Potent oral TLR-7 agonist tested in several animal models
  - Decline in HBVDNA and HBsAg during GS-9620 therapy in HBV-infected chimpanzees
  - Safe and well tolerated in 84 patients, significant dose dependant ISG-15 m RNA induction was observed in peripheral blood



Lanford R et al. Gastroenterology 2013; Gane E et al. J Hep 2015

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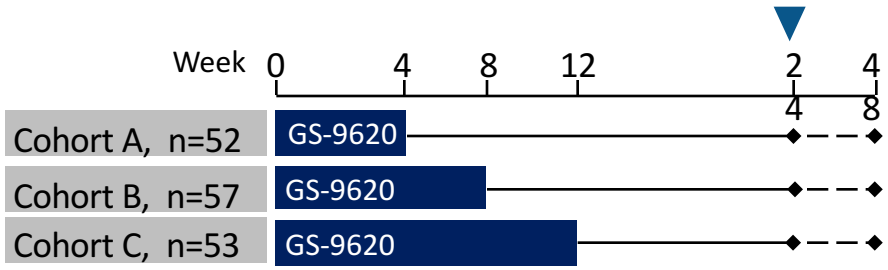
TLR 7 Agonist: Efficacy of GS-9620 in virally suppressed patients with CHB

- **GS-9620**: oral, small-molecule, TLR7 agonist
  - Toll-like receptor 7 (TLR7) is a pattern-recognition receptor located in the endolysosomal compartment of plasmacytoid dendritic cells (pDC) and B cells
  - TLR7 activation results in innate and adaptive immune stimulation

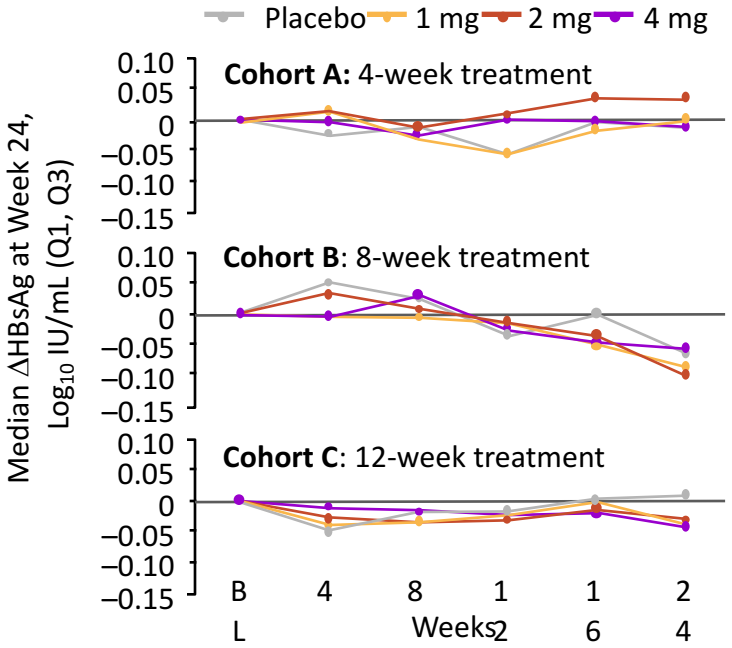
Phase 2 study

- 1:3:3:3 randomization (placebo; GS-9620 1, 2, and 4 mg)

1° Endpoint: HBsAg Decline



Median changes in HBsAg up to Week 24

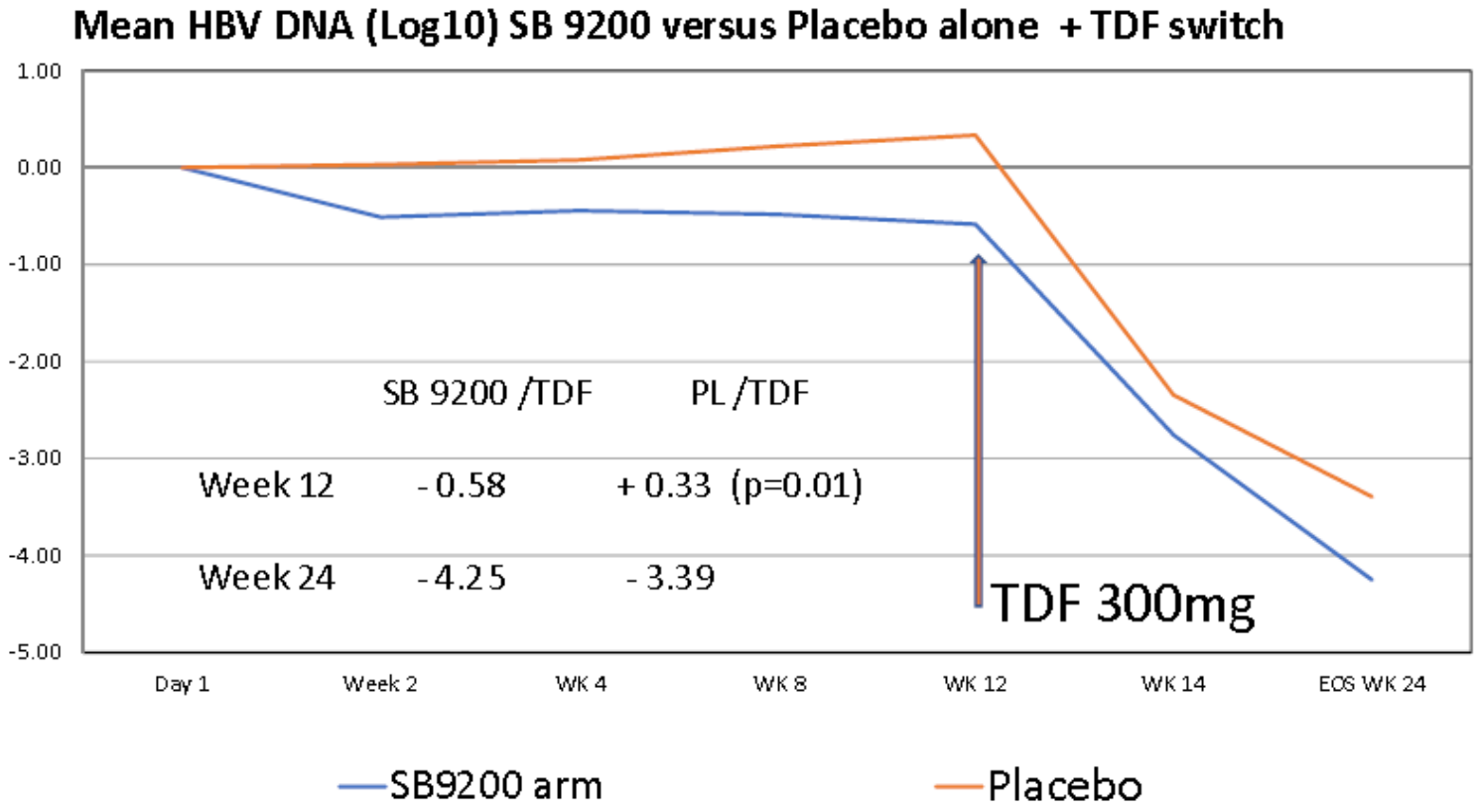


- HBsAg changes were minimal in all cohorts, with no patients having >0.5 Log_{10} declines in HBsAg at Week 24 in any GS-9620 arm
- No patients had HBsAg loss; 2 patients had HBeAg loss

- GS-9620 is safe and well-tolerated
- Dose-dependent induction of ISGs, but no significant HBsAg decline

Janssen HL, et al. AASLD 2016

RIG-I stimulator: SB 9200 25 mg
12 week HBVDNA reduction

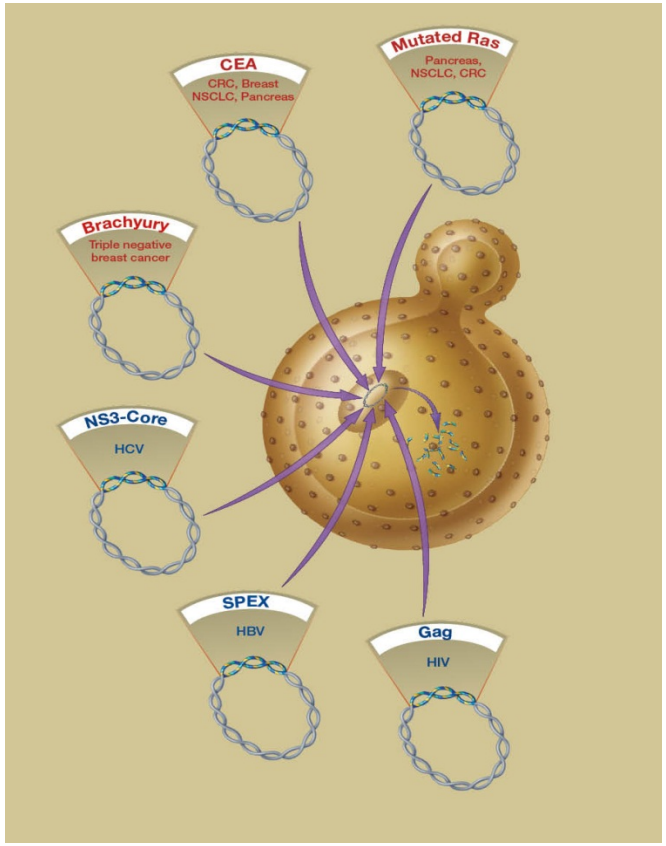


3 of 16 patients > 0.5 log10 sustained reduction in HBsAg at week 12 on monotherapy – all HBeAg –ve
6 of 16 patients > 0.5 log10 sustained reduction in HBsAg at week 24 after TDF including HBeAg +ve

Yuen MF et al. HBV Meeting Washington 2017

RIG-I stimulates production of type III interferons

Therapeutic Vaccination Tarmogen/GS-4774



GS-4774 Recombinant Antigen

- Tarmogens are made from genetically modified yeast that express one or more disease-associated antigens
- Activate T cells to specifically target and eliminate diseased cells with the same target antigen
- Elicited an immune response to recombinant antigens and peptides in healthy volunteers (independent of host HLA alleles); well-tolerated

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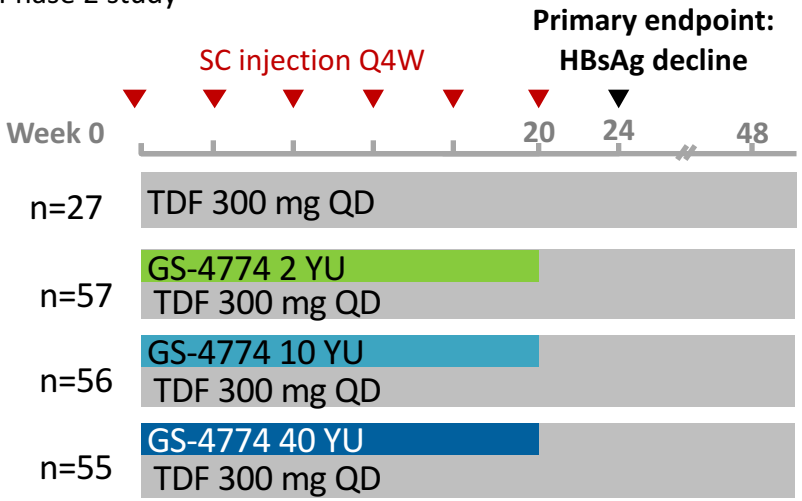
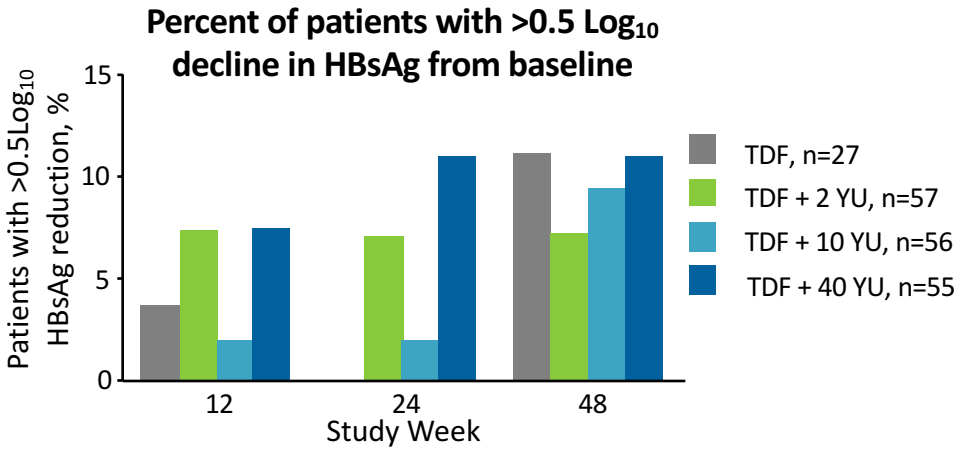
Therapeutic Vaccine: GS-4774 in combination with TDF in patients with chronic hepatitis B not on antivirals

- GS-4774 is a heat-inactivated, yeast-based T-cell vaccine
  - Recombinant protein containing HBV core, surface, and X proteins
- Immunogenic in mouse models and healthy volunteers[1,2]
  - In virally suppressed CHB patients, GS-4774 showed modest effect on HBsAg decline[3]
- Phase 2 study





- GS-4774 + TDF safe and well tolerated
- At Week 24, more patients receiving GS-4774 had >0.5 Log_{10} IU/mL decline in HBsAg
- By Week 48, all cohorts had similar proportion of patients with >0.5 Log_{10} decline in HBsAg
- No indication for this vaccine as monotherapy or in combination with NA currently

1 YU, 107 yeast cells

Janssen HL, et al. AASLD 2016

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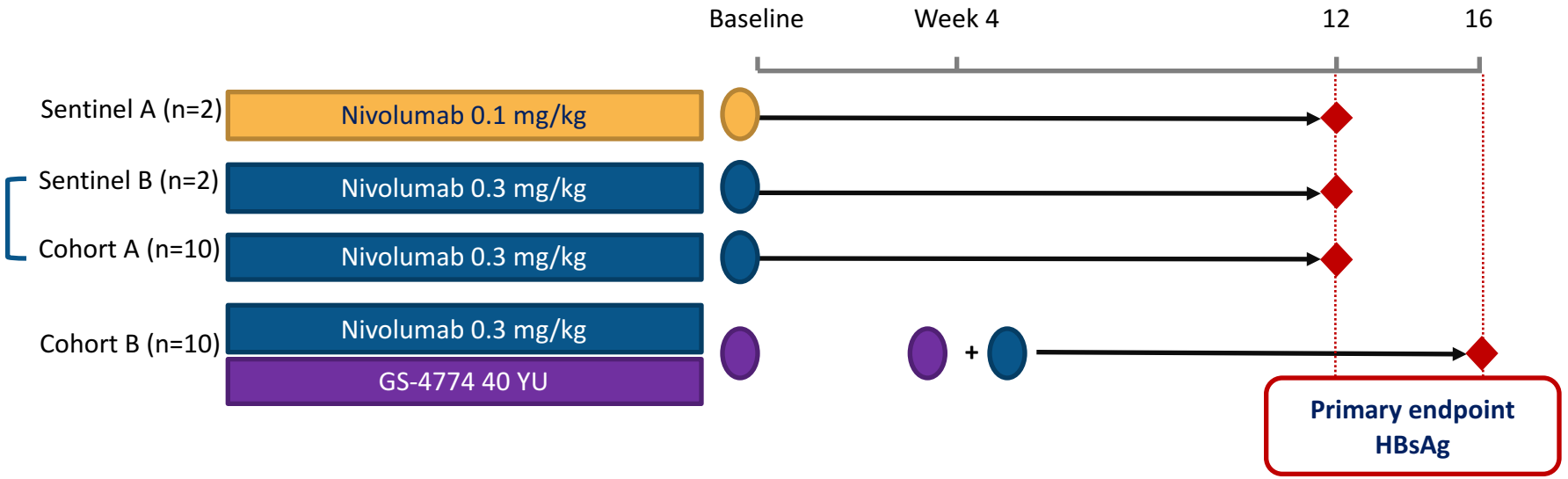
Reversing the exhausted Phenotype of HBV-specific T cells

- Inability to eliminate virus in CHB has been attributed to high levels of expression of programmed death 1 (PD-1) and its ligand (PD-L1/B7-H1) on viral antigen-specific T-cells and APC's
- Blocking the PD-1/PD-L1 interaction in vitro reversed exhausted cytokine production and proliferation of these HBV specific T cells
- Side effects: autoimmune disease

NA and anti-PD-1 treatment with or without Therapeutic Vaccine in HBeAg-negative CHB

Strategies to mitigate T-cell exhaustion	Blockade of programmed cell death protein (PD-1) or its ligand (PD-L1) to rescue HBV-specific T-cell responses

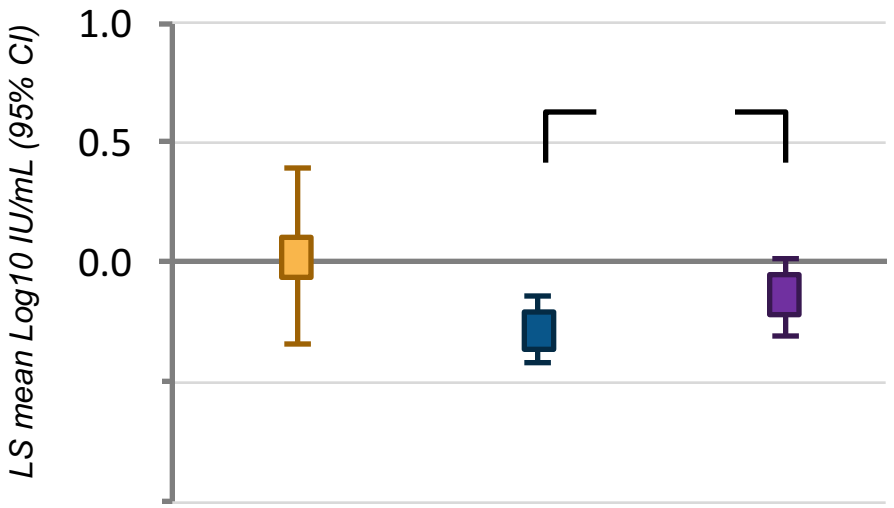
STUDY DESIGN: Anti-PD-1 antibody nivolumab 0.1 mg/kg (receptor occupancy) to 3 mg/kg plus GS-4774 in HBeAg-negative, virally suppressed (NUC) patients



Gane E, et al. EASL 2017

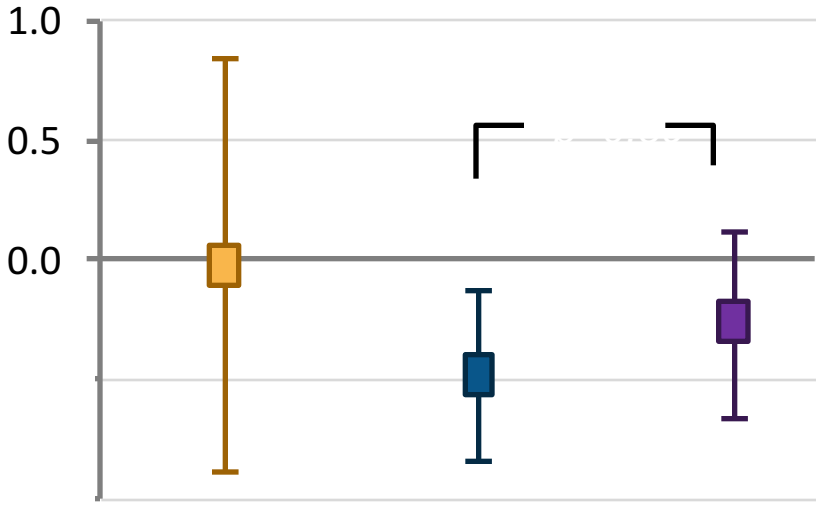
NA and anti-PD-1 treatment with or without Therapeutic Vaccine in HBeAg-negative CHB

Week 12 HBsAg change from baseline



	Nivolumab 0.1 mg/kg (n=2)	Nivolumab 0.3 mg/kg (n=12)	Nivolumab 0.3 mg/kg + GS-4774 (n=10)
Mean (SD)	0.016 (0.011)	–0.30 (0.61)	–0.16 (0.20)
Median (IQR)	0.016 (0.008, 0.024)	–0.13 (–0.20, 0.06)	–0.08 (–0.21, –0.02)

Week 24 HBsAg change from baseline

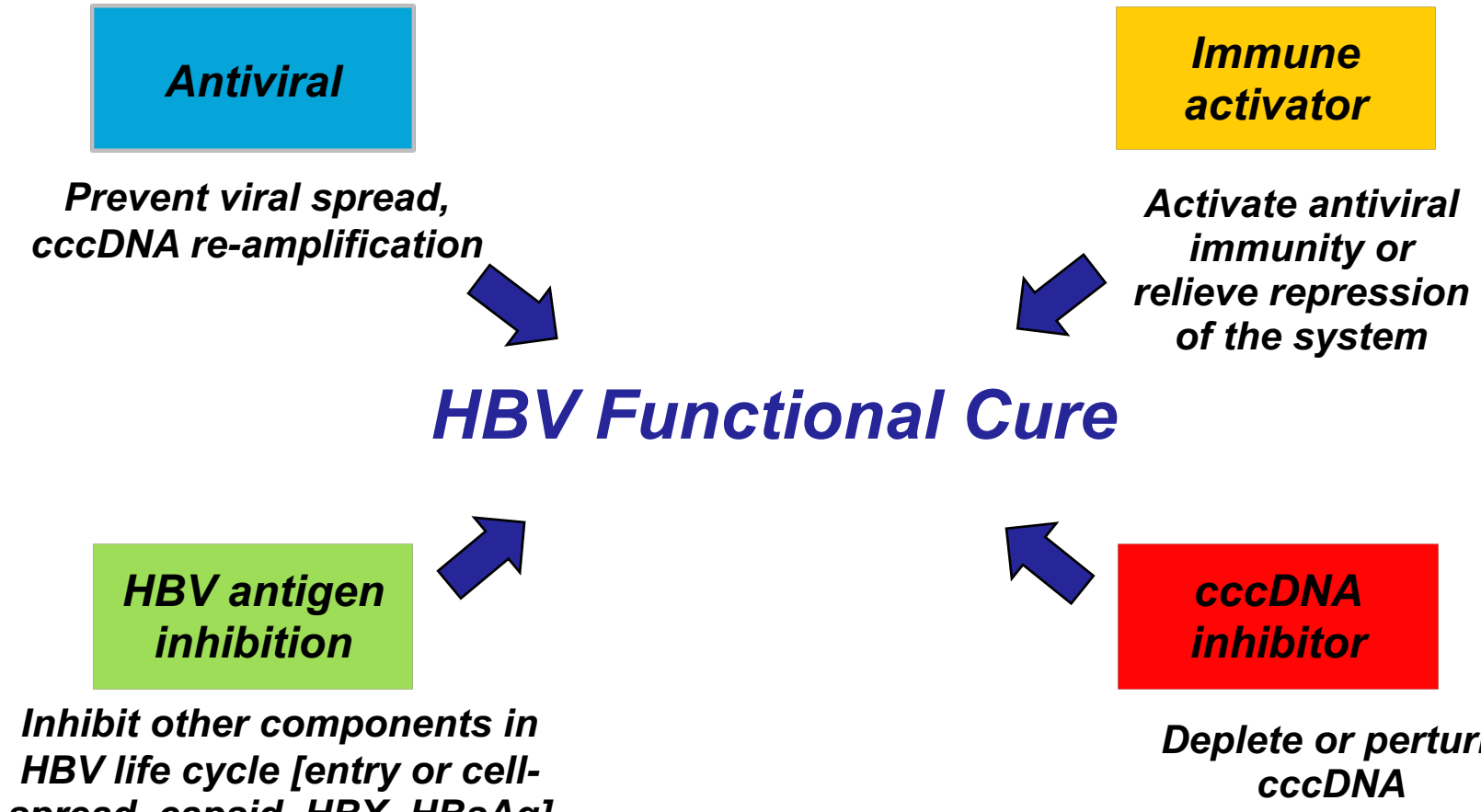


Nivolumab 0.1 mg/kg (n=2)	Nivolumab 0.3 mg/kg (n=12)	Nivolumab 0.3 mg/kg + GS-4774 (n=10)
–0.049 (0.035)	–0.47 (1.26)	–0.26 (0.24)
–0.049 (0.074, 0.024)	–0.14 (–0.19, 0.05)	–0.20 (–0.39, –0.05)

- Single dose anti–PD-1 mAb ± GS-4774 well tolerated
- Modest reduction of HBsAg in all treatment arms

Gane E, et al. EASL 2017

HBV Curative Regimen?



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Viral + Immune Target

- Remains an attractive option: agents complementary to each other
- HBV impairs innate and adaptive immune function
  - Viral replication
  - Viral protein production
- Viral inhibition → improve immune function and responsiveness
- Immunotherapy: - Eventual push to tip the balance?
  - Smaller therapeutic window (side effects)
  - Heterogeneous response

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Potential Combinations

HBV DNA suppression	+	***Viral protein depletion (s, x, core)***	+	***Immuno-therapy***
Nuc		*RNAi*		*TLR/RIG-I agonist*
+/- cccDNAi *+/- entry inhibitor* *+/- RNAi* *+/- Capsid inhibitor*		*Nucleic Acid Polymers?* *cccDNAi*		*αPD1/PDL1* *Therapeutic vaccine*

May not need all 3 'classes'…mix and match

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Conclusions

- NA are effective, safe and not so easy to replace
- Shift towards endpoint of true immune control, functional cure and HBsAg seroconversion
- New Viral agents: HBV entry inhibitors, small interfering RNA, capsid inhibitors promising but early in development
- Direct ccc-DNA inhibition may be needed but difficult to reach
- Immune modification: TLR/RIG-I agonist, therapeutic vaccination, PD1-PDL1 blocking in development: first results negative or modest, but too early to tell
- Combination therapy most likely needed!
- Science is the 'easy part'…getting these agents into people, doing the right trials and getting them approved is a whole other story…

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GLOBAL HEPATITIS SUMMIT 2018 TORONTO CANADA

THE 16TH INTERNATIONAL SYMPOSIUM ON VIRAL HEPATITIS AND LIVER DISEASE, ISVHLD

JUNE 14-17, 2018

Registration Opening: October 3, 2017
Abstract Submission Opening: October 3, 2017
Abstract Submission Closing: February 12, 2018

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