New HBV Treatment Options on the Horizon

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Key Considerations for Current Treatment Options

- All HBV nucleos(t)ides are generally well tolerated but with low rates of succesfull discontinuation
- The long-term safety of nucleos(t)ide-analogues remains to be determined
- PEG-IFN monotherapy is finite but only effective in subgroup of patients and its use is limited due to toxicity

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

New Strategies for Finite HBV Treatment

Strategies with Licensed Medication

Strategies with Unlicensed Medication

New Strategies for Finite HBV Treatment

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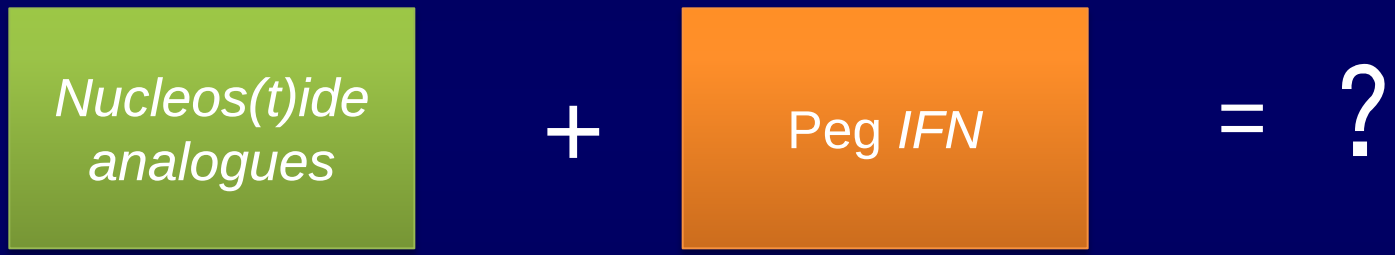
Strategies with Unlicensed Medication

How to enhance response rate through combination therapy? What's the best combination therapy?

- The discussion about the combination of IFN and nucleos(t)ide analogues has never ceased.



- The clinical trials on IFN and other nucleos(t)ide analogues combination thus far did not provide sufficient evidence, proving that combination therapy can bring more benefit

Current Initiatives PEG-IFN Treatment

- PEG IFN in immune tolerant patients (NIH)
- PEG-IFN in combination with TDF (NIH, Gilead)
- PEG-IFN add-on in virally suppressed patients on NA (PEGON, Fudan)
- PEG-IFN in combination with ETV (ARES)
- PEG-IFN RGT study (EXCEL)
- PEG-IFN alfa 2b registration study in Asia (Merck)

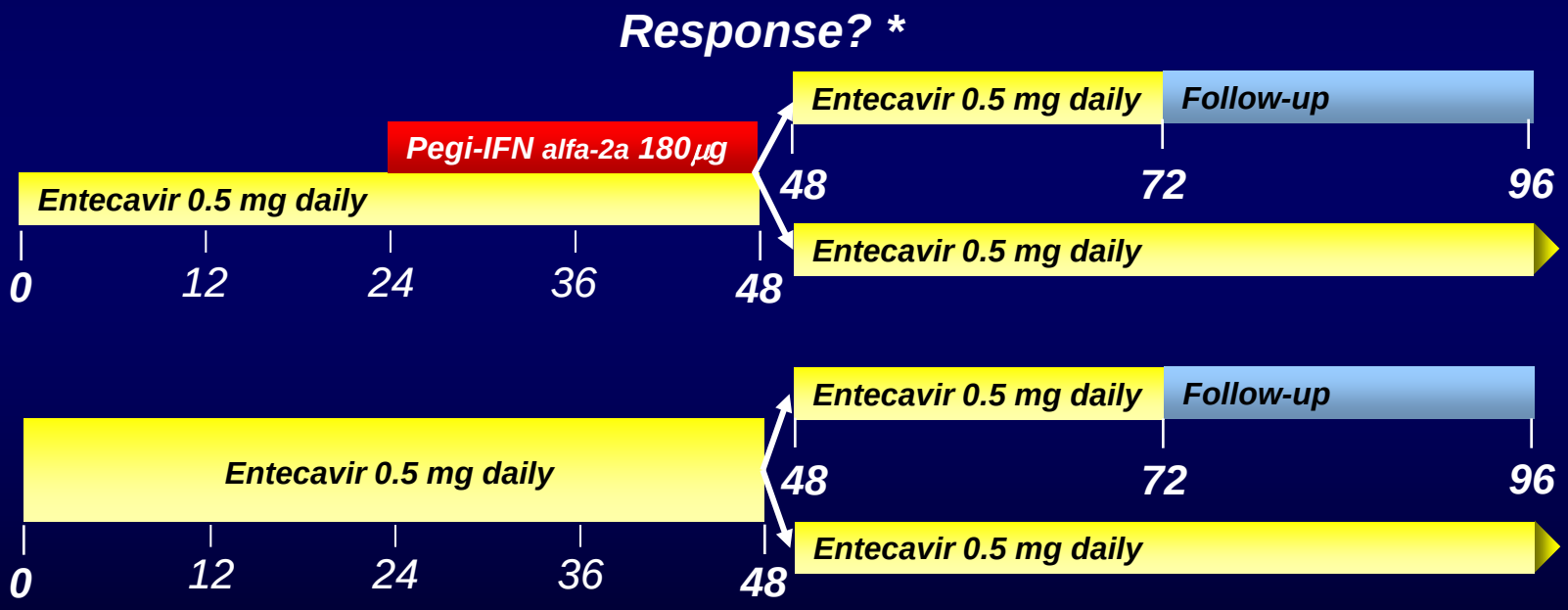
Pre-Treatment with Nucleos(t)ide Analogues?

- **Partial immune restoration (NK cells, dendritic cells and T cells) after viral load reduction with almost all NA's**
- **In clinical practice hardly sustained off-treatment immune control**
- **However could be used as priming therapy for PEG-IFN**

Boni et al. Hepatology 2001; vd Molen Hepatology 2006; Tjwa et al. J Hepatol 2011; Boni et al. Gastroenterology 2013

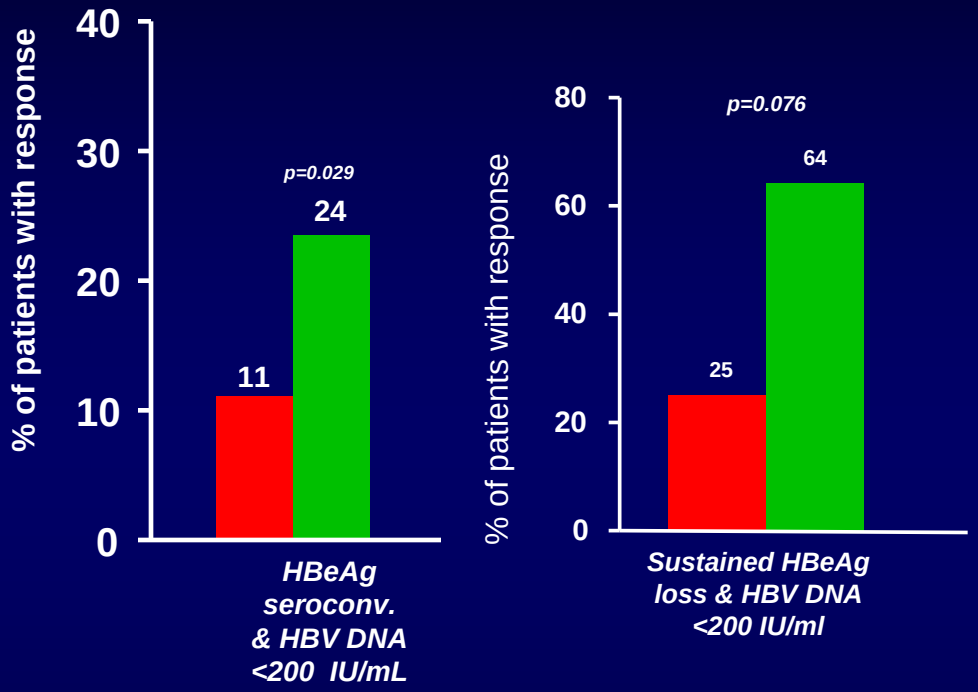
ETV and PEG-IFN (ARES Study)

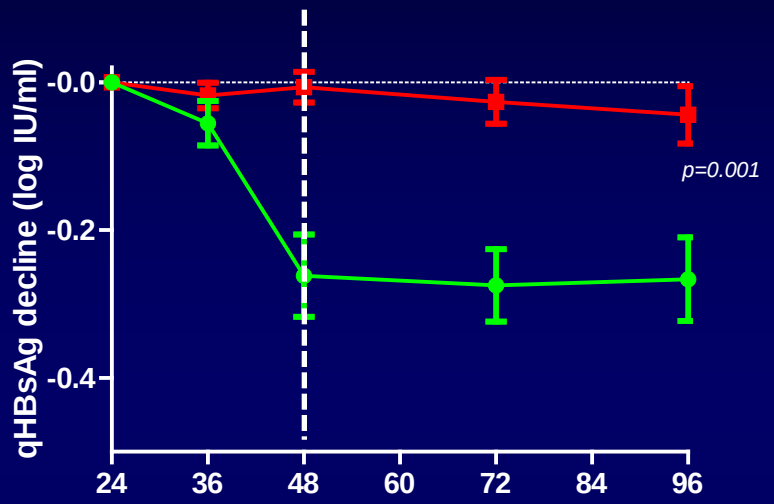
- HBeAg positive study
- Multicenter, open-label, randomized controlled trial



Response: combined presence of HBeAg loss and HBV DNA level < 200 IU/ml at week 48

Week 96 results: PEG-IFN addition leads to increased response rates (ARES Study)





PEG-IFN add-on therapy:

- *Significantly associated with response (OR 3.1, p=0.007)*
- *Significantly more decline in HBsAg, HBeAg and HBV DNA during treatment*
- *More sustained response after ETV discontinuation at wk72*

ETV ***N=90***

ETV+PEG ***N=85***

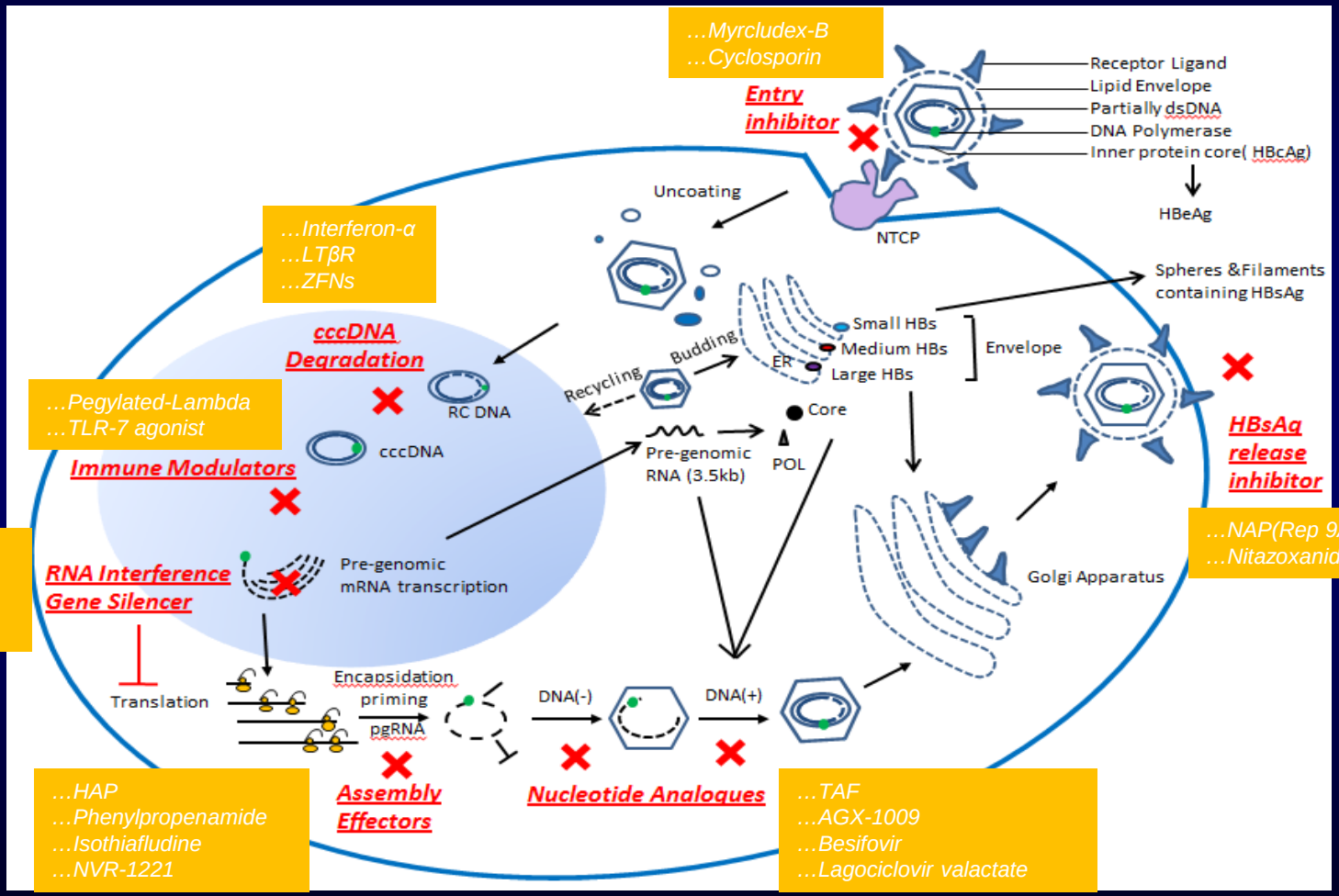
Brouwer et al. Hepatology 2014

New Strategies for Finite HBV Treatment

Strategies with Licensed Medication

Strategies with Unlicensed Medication

HBV Life cycle
Towards New HBV Treatment Targets



New HBV Treatments

Virology

- *New Nucleos(t)ide Analogues*
- *HBsAg release inhibitors*
- *Antisense oligonucleotides/si-RNA's*
- *Entry inhibitors*

Immunology

- *PEG-IFN Lambda*
- *TLR agonists*
- *Therapeutic vaccination*
- *PD-1, PDL-1 Blocking*

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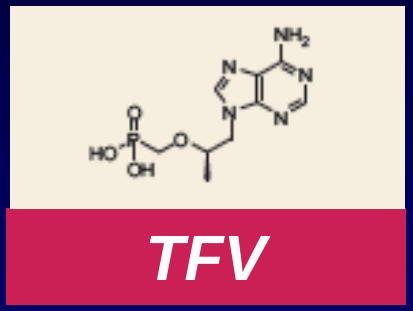
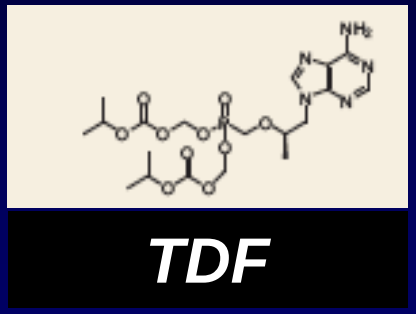
Tenofovir Alafenamide Fumarate (TAF)

Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI s)



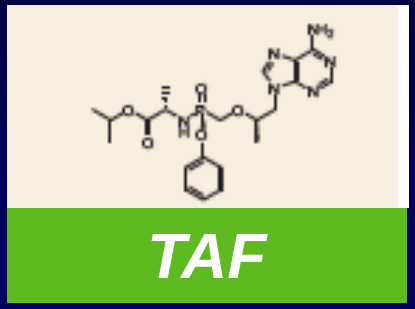
TFV

Tenofovir



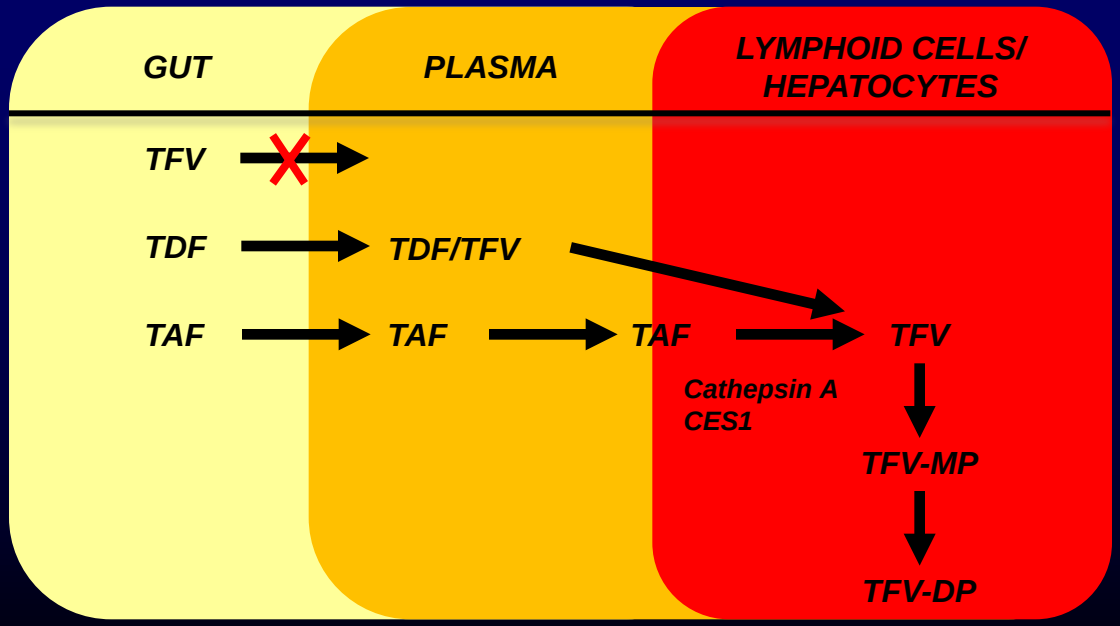
TDF

Tenofovir Disoproxil Fumarate



TAF

Tenofovir Alafenamide



- *Improved stability in plasma:*
  - *Enhanced delivery of active form (TFV-DP) to hepatocytes*
  - *Lower doses are used; systemic exposures of TFV reduced*

Agarwal K et al. AASLD 2013
Murakami E et al. HepDART 2013

CES1 = carboxylesterase 1; DP= di-phosphate; MP= mono-phosphate.

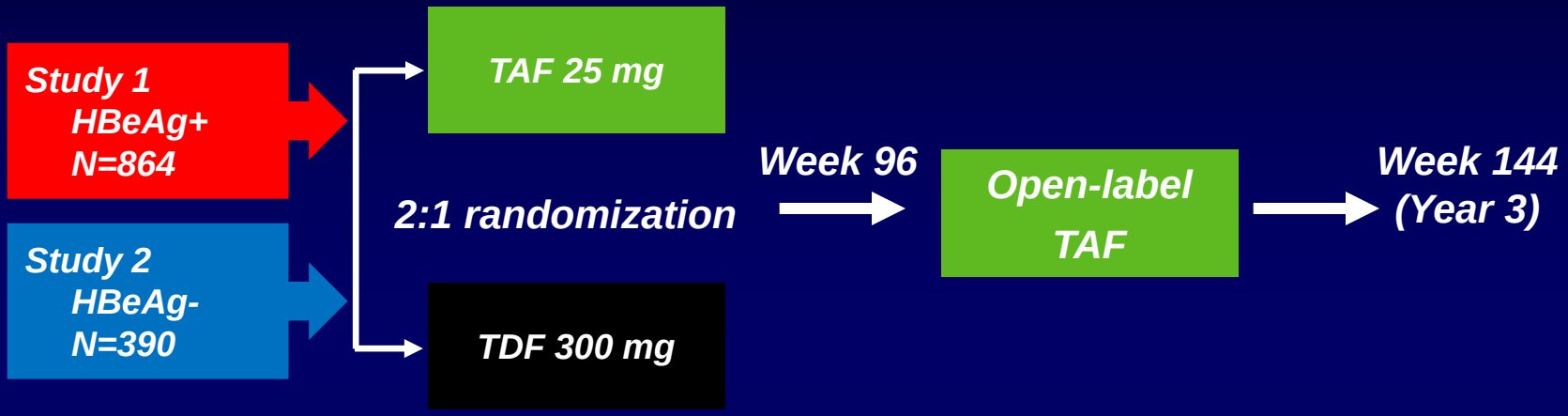
Tenofovir Alafenamide Fumarate (TAF)

Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI s)

- **“Super” Tenofovir**
- **Once daily oral single regimen use in HIV**
- **25 mg TAF similar antiviral activity but reduces systemic exposure to < 8% of exposures generated by 300 mg tenofovir**
- **Probably less nefrotoxic than tenofovir**
- **Also beneficial for HBV+HIV co-infected**

Agarwal et al. AASLD 2013

TAF Phase III Studies



- 2 phase 3, randomized, double-blind studies
- Primary endpoint (non inferiority margin of 10%)
  - HBV DNA <29 IU/mL at Week 48
- Secondary endpoints
  - Bone mineral density
  - Renal parameters

Besifovir (LB80380)

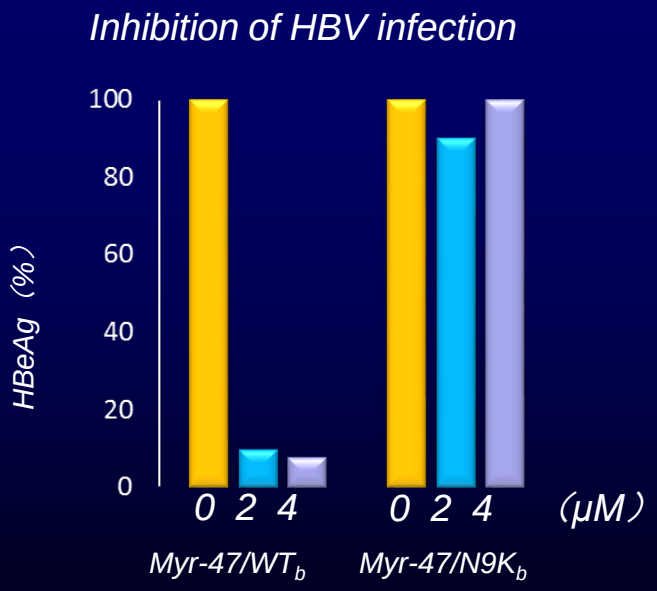
- Acyclic Nucleotide Phosphonate
- Effective for Naïve and LAM resistant
- Multicenter phase II trial in Asia: Besifovir 90mg,150 mg for 48 weeks was found to be non-inferior to 0.5 mg Entecavir
- No resistant mutations or renal toxicity
- Besifovir group needed oral L-carnitine supplementation

Lai CL et al. Gut 2013

Functional Receptor for HBV Discovered (NTCP)

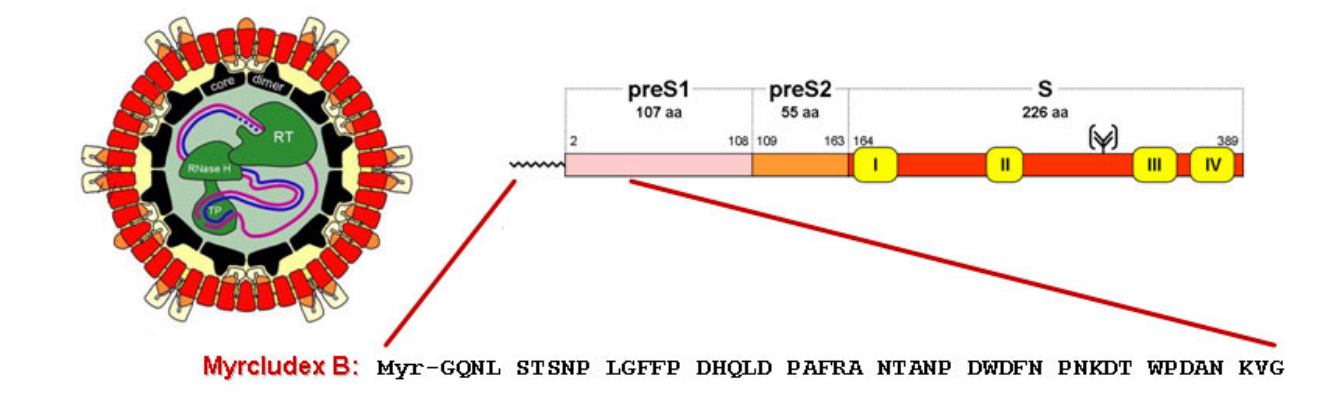
- Scientists from National Institute of Biological Sciences (NIBS), Beijing discovered a functional receptor for Hepatitis B virus (HBV) infection
  - It opens doors for future high throughput drug screen
  - as well as revealed an important new target for treating HBV infection and related diseases

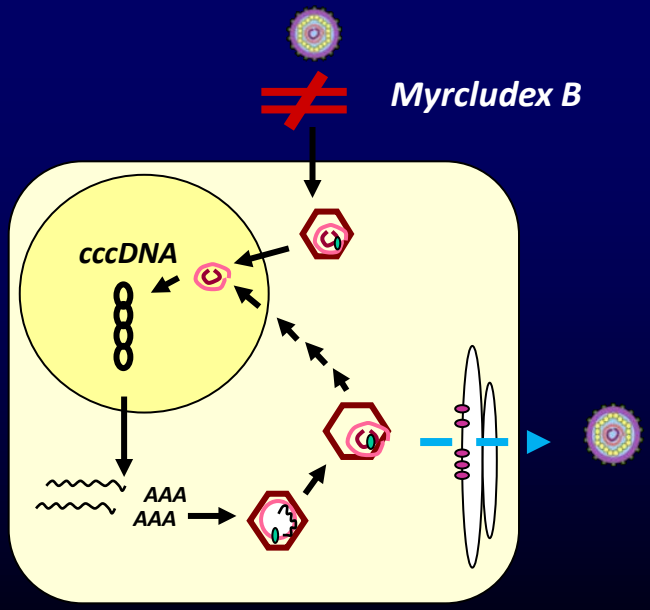
the receptor-binding region of pre-S1 specifically interacts with sodium taurocholate cotransporting polypeptide (NTCP), a multiple transmembrane transporter predominantly expressed in the liver.



Yan, Huan, et al. "Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus." eLife Sciences 1 (2012).

Myrcludex B: Acylated HBV preS1-derived peptides block HBV infection <u>in vitro</u> – 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

MyrB blocks NTCP-mediated Bile Salt Transport & Inhibits HBV infection

- *Normal function of NTCP is to import bile salts*
- *Whether HBV exploits this property for entry into hepatocytes?*

Myristolyted preS1peptide

⬇

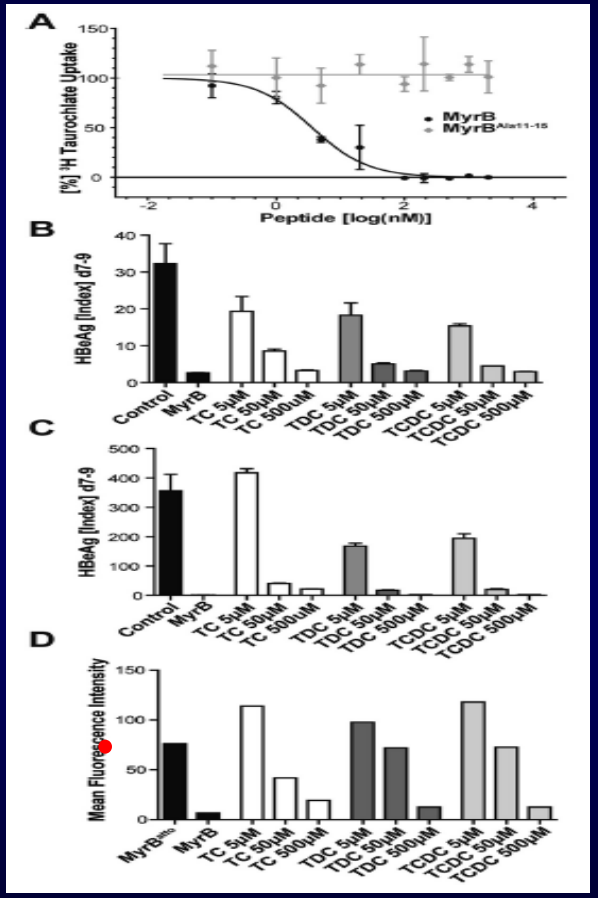
Inhibits transport of taurocholate into hNTCP transfected HepG2 cells

⬇

Several bile salts inhibit binding of the preS1 peptide

⬇

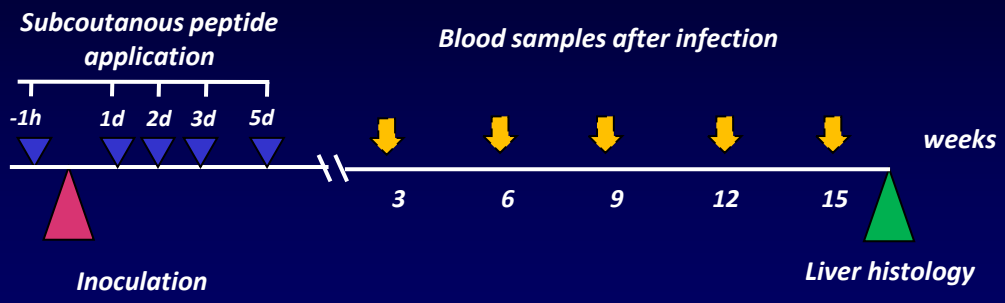
Inhibit HBV infection of hNTCP transfected Huh7 cells

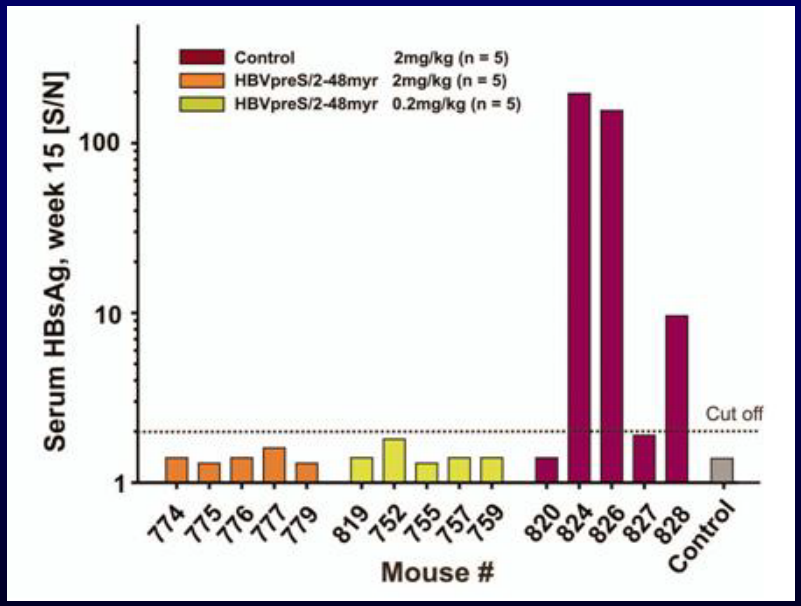


- *Taurocholate, taurodeoxycholate & taurochenodeoxy-cholate in the presence of MyrB ^{atto} (500 µm), all substrates profoundly interfered with preS- binding*

Ni Y et al. Gastroenterology 2014,Tong S et al. Gastroenterology 2014

Myrcludex B prevents the establishment of de novo HBV infection in vivo





- Strongly limited HBV dissemination and ccc DNA accumulation in mice
- Phase 2 study currently conducted for HBV and HDV in Russia (Heptera)
- Results expected late 2014

Petersen, Dandri et al. Nature Biotech. 2008; Volz et al. J Hep 2013

RNA Interference

- HBV is susceptible to RNAi because it replicates via an RNA intermediate
- Small interfering RNA (siRNA) therapeutics have the capacity to knockdown production of all hepatitis B genes and thereby significantly decrease the number of infectious viral particles and viral antigens
- This reduction in viral and antigen load is designed to permit the immune system to mount an effective response to CHB
- Phase II study of ARC 520 (Arrowhead) ongoing
- Delivery is possible through different platforms, Nanoparticles (Tekmira)

RNA Interference

Antisense Oligonucleotides

- Investigational drug designed to target viral mRNA -> reduce production of viral protein (HBsAg) associated with HBV infection and replication
- Dose dependent reduction in liver and serum viral DNA and proteins in animal models of HBV infection
- Phase I randomized, placebo-controlled dose escalation study in healthy volunteers (ISIS)
- Enhances viral + immune system activity against HBV virus

What are the new Strategies for Finite HBV Treatment?

Virus Targeting

Entry Inhibitors	*Targets NTCP receptor to inhibit viral infection*
Assembly Effectors	*Inhibits HBV replication by causing destabilization of viral nucleocapsid*
RNA Interference	*RNA molecules inhibiting gene expression and release of new virions*
New Nucleos(t)ide Analogues	*DNA polymerase inhibitor*
HBsAg Release Inhibitor	*Inhibits the release of HBsAg SVPs and boosts restoration of the immune response*
cccDNA Degradation	*Up-regulation of APOBEC3A and APOBEC3B causing cccDNA degradation*

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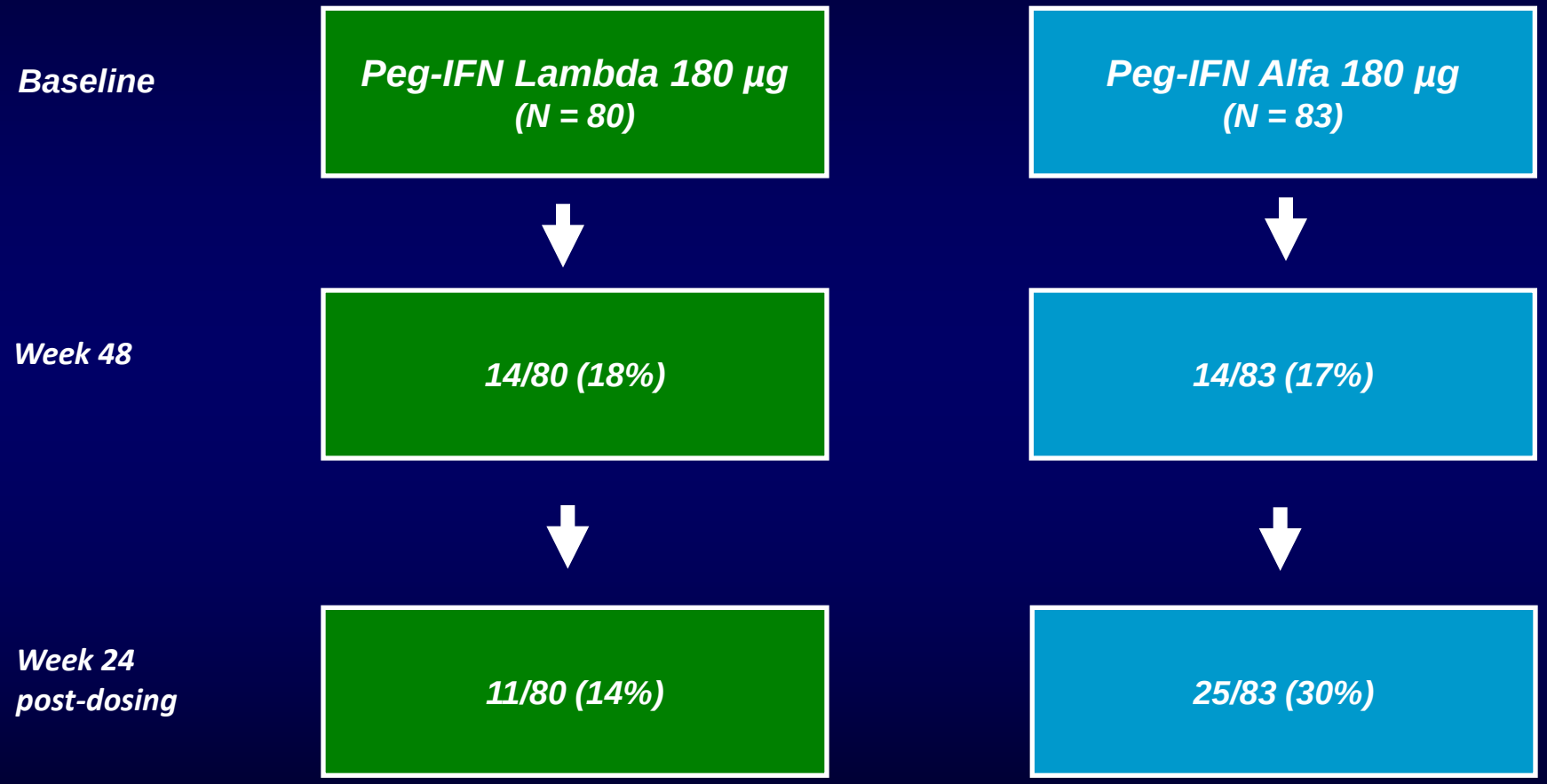
Peg-IFN Lambda vs Alfa One Year of Therapy
HBeAg Seroconversion

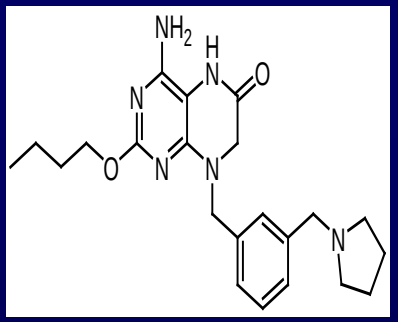


Chan HL, et al. EASL 2014

Toll Like Receptor (TLR) 7 Agonist

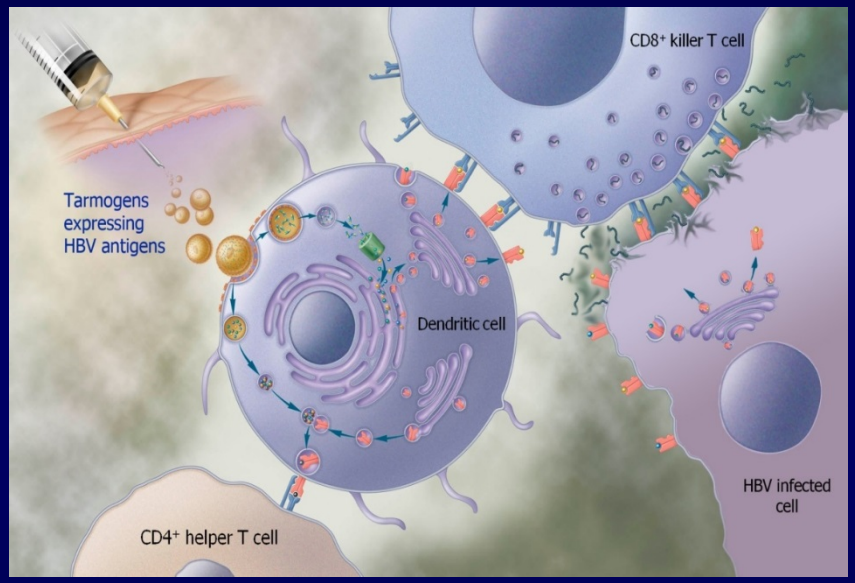
- TLR-7 is a pattern recognition receptor in endolysosomal compartment of plasmacytoid dendritic cells(pDC) and B cells
- Agonism induces anti-viral response via innate immune activation

- 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. AASLD 2013

Therapeutic Vaccination
Tarmogen/GS-4774

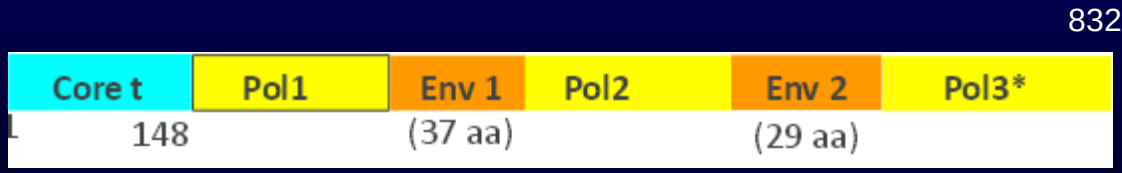


- Tarmogens are made from genetically modified yeast that express one or more disease-associated antigens
- Activate T cells to specifically target and eliminate diseased cells with the same target antigen
- Elicited an immune response to recombinant antigens and peptides in healthy volunteers (independent of host HLA alleles); well-tolerated
- Further evaluation of GS-4774 in virally suppressed chronic HBV patients is ongoing

Gaggar et al. AASLD 2013

Therapeutic Vaccination
TG1050

- Based on a non-replicative E1 and E3 deleted human adenovirus fusion protein serotype 5
- HBV Core (truncated) fused to a deleted and mutated HBV polymerase (full length) and 2 selected HBsAg domains (genotype D sequence)
- Capable of inducing a potent, multispecific, sustained and cross reactive T cell responses in mice
- First in human phase 1 trial in 2014



Dion et al 2013 J Virol

Therapeutic vaccines for CHB

GS-4774 [Gilead] USA	**Preclinical** Tarmogen product candidate expressing HBV antigens (HBV X, S and Core antigens) for the treatment of chronic HBV infection. Commercialisation strategy will be to combine GI-13020 with Viread to determine if the combination can reduce or eliminate HBV infection.	• Vaccine is not delivering a polymerase antigen. • Vaccine is delivering the surface antigen known to be subject to strong immune tolerance. • X antigen is poorly immunogenic • Likely issue related to anti-vector neutralising immunity • The technology demonstrated low levels of immunogenicity in chronic viral infection in a HCV vaccine trial.
TG-1050 Transgene, France	**Preclinical proof of concept** Recombinant non-replicative human adenovirus expressing multiple specific HBV antigens (Core, Envelope and Polymerase) from genotype D.	• Adenoviruses have a limited use due to pre-existing immunity • Viral vectors induce anti-vector immunity reducing vaccine immunogenicity upon repeat injection • Likely to be restricted in terms of genotype coverage

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

Interventions for HBV Cure

Therapeutic Targets	Example	Mechanism of Action	Phase of Clinical Trial
New Nucleos(t)ide Analogues	Tenofovir Alafenamide	DNA polymerase inhibitor	III
	AGX-1009		II
	Besifovir		III
	Lagociclovir valactate		II
Immune Modulators	Pegylated-Lambda	Cytokines with immunomodulating and antiviral effects	II
	TLR-7 agonist		III
Viral Entry Inhibitor	Myrcludex B	Targets NTCP receptor to inhibit viral infection	IIa
	Cyclosporins		Preclinical
	Oxysterols		Preclinical
Assembly Effectors	HAP	Inhibits HBV replication by causing destabilization of viral nucleocapsid	I
	Phenylpropenamide		Preclinical
	Isothiafludine		II
	NVR-1221		I
HBsAg Release Inhibitor	REP 9AC	Inhibits the release of HBsAg SVPs and boosts restoration of the immune response	II
RNA interference/ RNAi Gene silencer	ARC-520	RNA molecules inhibiting gene expression and release of new virions	I
	Antisense Oligonucleotide		II
	ISIS- HBVRX		****
	ALN-HBV		Preclinical
	TKM-HBV		Preclinical
	NUC B 1000		Preclinical
Therapeutic Vaccines	Tarmogen	Induce and stimulate CD4 + and CD8 + T-cell response	III
	Transgene		I
cccDNA Degradation/Silencing	Interferon-α	Up-regulation of APOBEC3A and APOBEC3B causing cccDNA degradation	I
	Lymphotoxin-β receptor		I
Inhibitory T lymphocytes	PD-L1 Blockade	Blockade of the inhibitory signal and/or activation of costimulatory signal	IIa

HBV Curative Regimen?

Antiviral	***Agent to prevent viral spread, cccDNA re-amplification***
+	
Immune activator	***Agents to activate antiviral immunity or relieve repression of the system***
+	
cccDNA inhibitor	***Selective agent to deplete or perturb cccDNA***
+	
HBV antigen inhibition	***Agents to inhibit other components in the HBV life cycle [entry or cell-spread, capsid, HBX, HBsAg]***

Conclusions

- Shift towards endpoint of true immune control and HBsAg seroconversion
- Combination of the most potent nucleos(t)ide:

  Peg-IFN add on therapy in different regimens
- HBV entry inhibitors, antisense therapy promising but early in development
- Direct ccc-DNA inhibition may be needed but is difficult to reach
- Peg-IFN lambda disappointing thus far
- Different immune modifying agents with hopefully limited systemic effects potentially to be combined with antiviral agents