# TKM-HBV, a Novel RNA Interference Treatment for Chronic Hepatitis B, has a Complementary Mode of Action to Current Standard of Care Nucleos(t)ide Analogs

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## INTRODUCTION & AIMS

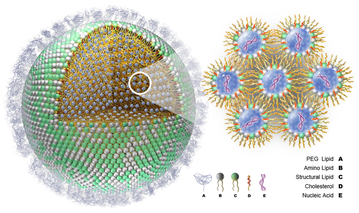
TKM-HBV is a novel RNA interference (RNAi) therapeutic for chronic HBV and currently in Phase 1 clinical development. It is designed to reduce the viral antigen load in chronically infected patients and allow the body to escape the state of immune repression imposed by the virus.

Comprised of 3 oligonucleotide triggers encapsulated within a lipid nanoparticle (LNP) delivery system, TKM-HBV cleaves all forms of HBV RNAs thus suppressing synthesis of viral proteins.

Current approved nucleos(t)ide analog (NA) drugs for HBV are highly effective at inhibiting viral replication but are largely ineffective in preventing viral protein production.

**AIM:** Show that TKM-HBV and NA modes of action are complementary, and that combination therapy allows effective disease targeting at multiple critical nodes of the viral life cycle.

## RNAi DRUG TECHNOLOGY



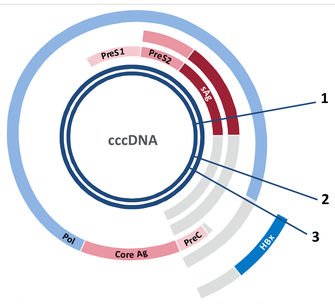

LNPs are composed of various lipids formulated in specific ratios in order to confer desired PKBD and PD properties.

LNPs protect nucleic acid drugs against nuclease degradation in the blood, and enable effective delivery of these macro-molecules to the target hepatocytes. To date, 9 LNP products have entered clinical trials with hundreds of patients treated, some with >1 year repeat-dosing duration. LNP enabled RNAi drugs have strong clinical validation.

## RNAi TRIGGER DESIGN

Inclusion of 3 RNAi triggers allows for broad reductions of all viral antigens and pan-genotypic activity. Viral inhibition at multiple target sites reduces the risk of escape mutations.

Trigger 1 cleaves within the HBsAg coding region, thus TKM-HBV silences HBsAg even when it is expressed from Integrated DNA.




Each target site is ≥ 94% conserved. TKM-HBV has ≥ 1 match to 99.8% of >4,000 surveyed genomes (gt A-H).

## RESULTS

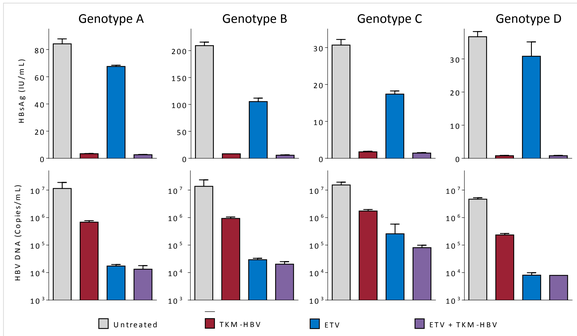



**Figure 1.** Antigen Reduction Across Multiple Genotypes. Primary human hepatocytes (PHH) were infected with one of HBV genotypes A through D then treated with entecavir (ETV) and TKM-HBV. TKM-HBV treatment resulted in HBV surface antigen reduction that is not seen with ETV treatment alone. Data are means± SD of technical triplicates from one biological replicate. Supernatant HBV DNA was measured by QPCR and HBsAg by Abbott Architect CLIA.

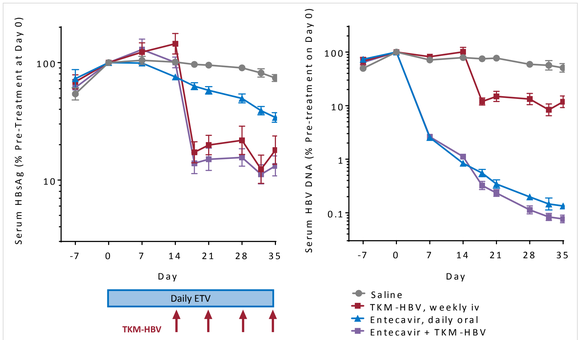



**Figure 3.** Control of Antigenemia and Viral Load with Combination Treatment in Infected Chimeric Mice. To mimic a potential clinical study setting, TKM-HBV was administered after onset of NA treatment in hepatohumanized chimeric mice chronically infected with HBV Gt C. Means ± SD of n=5 or 6 animals. HBV DNA measured by QPCR and HBsAg by Abbott Architect CLIA.

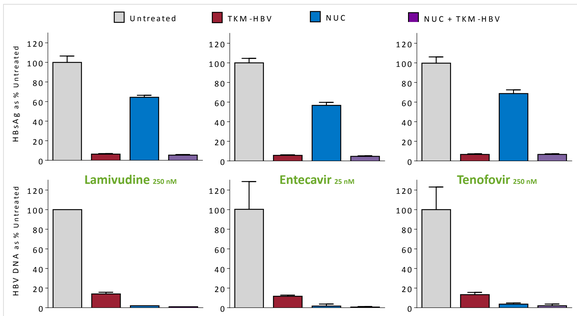



**Figure 2.** TKM-HBV Complements Standard-of-Care NA Antiviral Activity. PHH were infected with HBV gt C and then treated with either lamivudine, entecavir or tenofovir disoproxil fumarate in combination with TKM-HBV. Data are means ± SD of technical triplicates from one biological replicate. Supernatant HBV DNA assessed by QPCR and HBsAg by Abbott Architect CLIA.

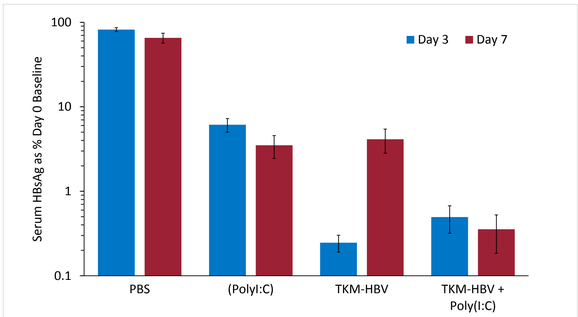
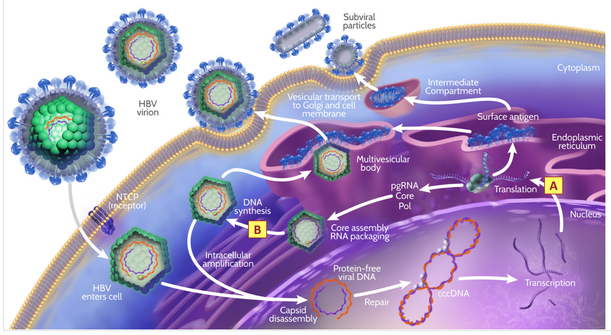


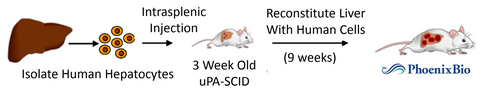

**Figure 4.** TKM-HBV and Immune-stimulant Combined Result in Stronger & More Sustained HBsAg Reduction than Either Alone. TKM-HBV and/or poly(I:C) (20 µg HDI, [4]) was administered at Day 0 in immunocompetent HDI mice. Mean (n=4-5) ± SEM. Quantitation using BioRad GS 3.0 EIA.

### Targeting Different Nodes Of the Viral Life Cycle

- TKM-HBV blocks at point A, NAs block at point B




### Hepato-Humanized PXB Chimeric Mouse Model of CHB




- > 70% human hepatocyte replacement index [1]
- 8 week stabilized chronic infection of HBV genotype C
- Human-like viral titres and serum HBsAg levels
- Human cells can be infected and accumulate cccDNA whereas mouse cells cannot

### Immunocompetent HDI Mouse Model of HBV

- Immunocompetent C3H/H3N mice injected with pAAV/HBV1.2 plasmid encoding HBV genes
- Large volume hydrodynamic injection (HDI) forces plasmid into mouse liver cells
- Expression of viral RNAs, DNA & proteins from plasmid
- Infectious particles are formed & secreted into blood
- HBV genotype A
- No cccDNA
- 90% animals shown to be HBsAg-positive long term [2]

## CONCLUSION

HBV proteins are understood to play a variety of roles in contributing to suppression of host immune responses and viral persistence. Quantitative changes in serum HBsAg in particular have been correlated with differences in clinical outcomes [3].

- Fig 1: TKM-HBV reduced HBsAg in gt A, B, C & D infected PHH

TKM-HBV acts on a separate viral target (mRNAs, pgRNA) and in a different compartment than NAs (Pol in capsid). Indeed, no drug:drug interference was seen in co-treatment settings:

- Fig 1: When combined with ETV in gt A, B, C, D infected PHH
- Fig 2: When combined with TDF, ETV or 3TC in infected PHH
- Fig 3: When combined with ETV in infected chimeric mice

Combination of TKM-HBV with ETV resulted in simultaneous control of viral titre and HBsAg in HBV-infected PXB mice.

Combination of TKM-HBV with the immunostimulant poly(I:C) resulted in greater and more sustained serum HBsAg reduction than either alone in an immunocompetent mouse model of HBV (Fig 4).

## REFERENCES

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2. Peng et al., World J Gastroenterol. 2015 Mar 28; 21(12): 3527–3536.
3. Sonneveld et al., Hepatology. 2013 Sep;58(3):872-80.
4. Wu et al., J Virol. 2014 Sep; 88(18): 10421–10431.

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