Abstract 260:

BB-HB-331, a DNA-Directed RNA Interference (ddRNAi) Agent Targeting Hepatitis B Virus (HBV), Can Effectively Suppress HBV *In Vitro* and *In Vivo*

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Disclosure:

David Suhy is employed by Benitec Biopharma as Chief Scientific Officer and receives a salary as well as stock options as part of a compensation package

Scientific Advisory Board of Regen Biopharma

Forward Looking Statements

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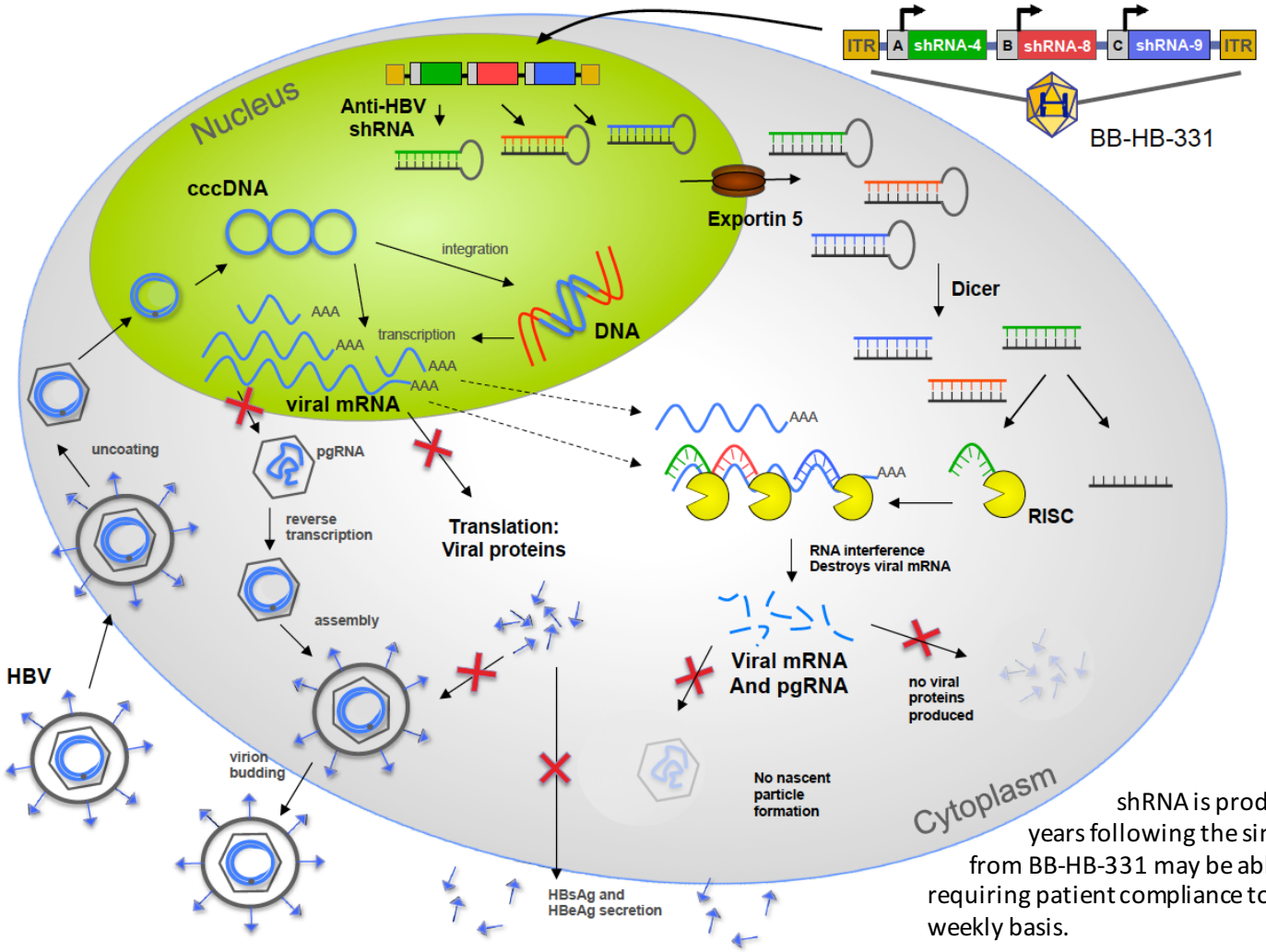
HBV Overview

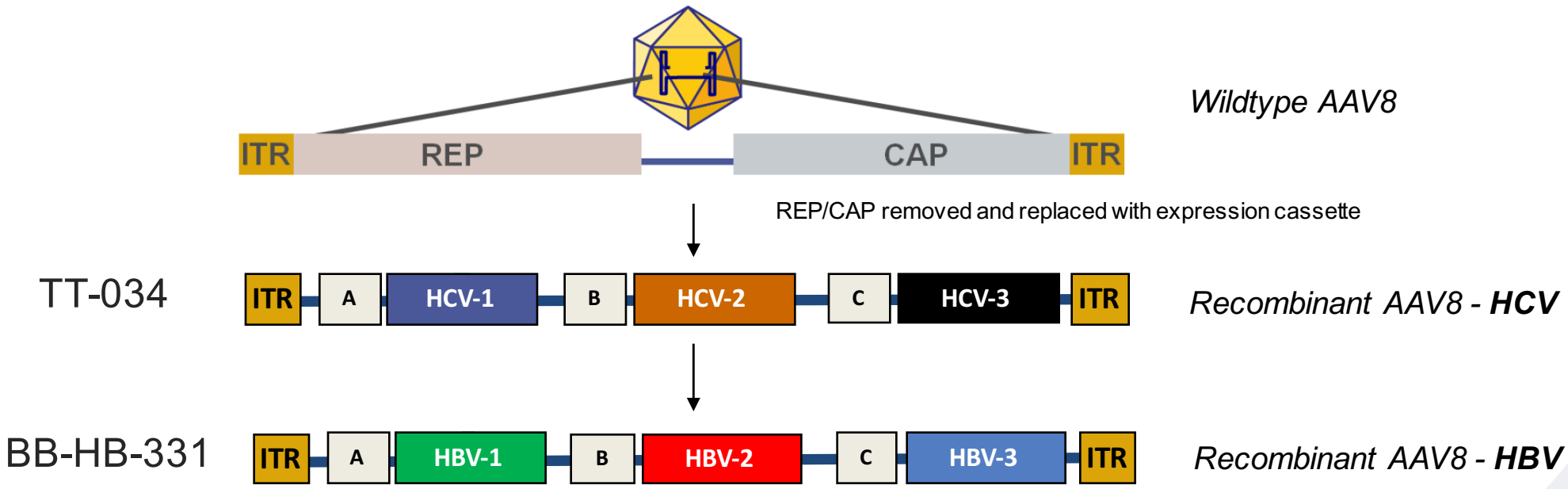
- DNA virus that infects 240 million infected worldwide, resulting in up to 780,000 deaths per year
- HBV only infects human hepatocytes and replicates inside of those cells
- Infection occurs in phases ranging from a silent, acute phase that can be resolved by the immune system to a persistent chronic infection requiring life-long therapy
- In chronic HBV, the presence of viral proteins, especially the s-antigen, causes hepatic inflammation leading to liver dysfunction, acute hepatic failure, cirrhosis, or hepatocellular carcinoma (HCC)
- Hepatitis B virus or co-infection cause 60-80% of the world's primary liver cancers
- Cure rates of existing drugs (defined as HBsAg seroconversion) are exceptionally low

Mechanism of Action of BB-HB-331



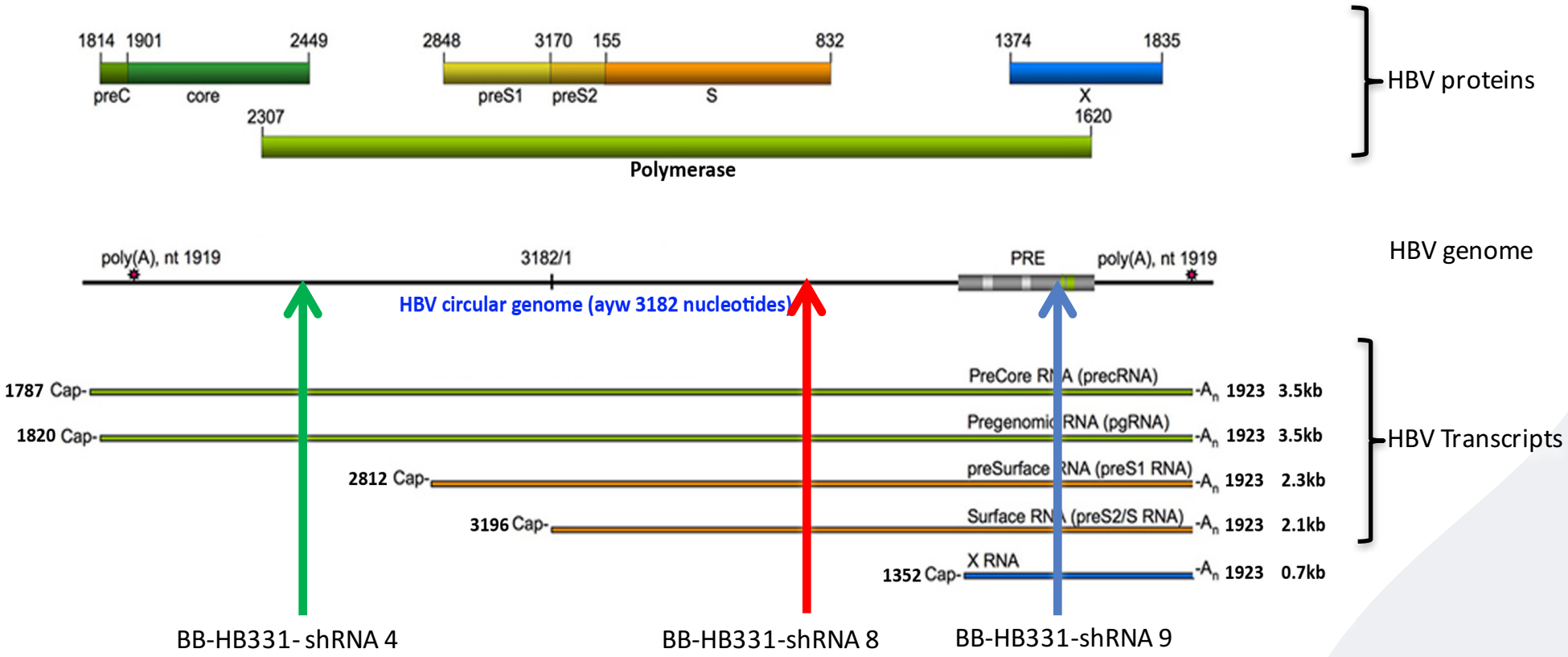
shRNA is produced continuously for months or even years following the single administration, thus anti-HBV shRNA from BB-HB-331 may be able to exert anti-viral activity without requiring patient compliance to take small molecule drugs on a daily or weekly basis.

BB-HB-331: Learnings from TT-034 Provides a Springboard for Development of the HBV Program



- Swap of three anti-HBV shRNA into anti-HCV shRNA position
- Keeps the same AAV8 capsid – identical biodistribution as TT-034
- Mimics some aspects of the expression cassette
- TT-034 clinical data guides HBV Protocol development and provides simpler regulatory path

Positioning of shRNA Used in Clinical Construct Ensure Cleavage of Multiple HBV Transcripts



* Sequences selected for shRNA are well conserved across HBV genotypes A-H

Overview of Phoenix Bio's PXB Human Liver Chimeric Mouse

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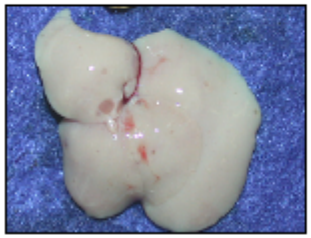
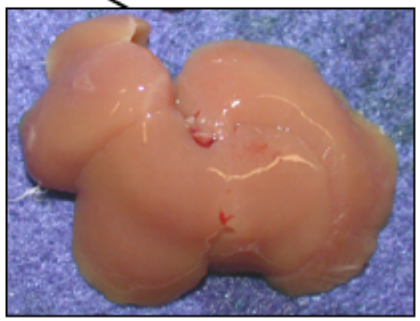
A chimeric mouse with a liver highly replaced by human hepatocytes.



uPA/SCID
Liver weight: 0.7 – 1 g

Transplantation



PXB-mice
Liver weight: 2 – 2.5 g
(RI: 98 %)

Human hepatocytes proliferate in mouse liver.

Histologically normal liver constitution

Gene expression and activities of human metabolic enzymes and transporters

Infectable with HCV and HBV

TT-034 transduction and shRNA expression in human liver biopsy samples versus a chimeric mouse model with humanized liver

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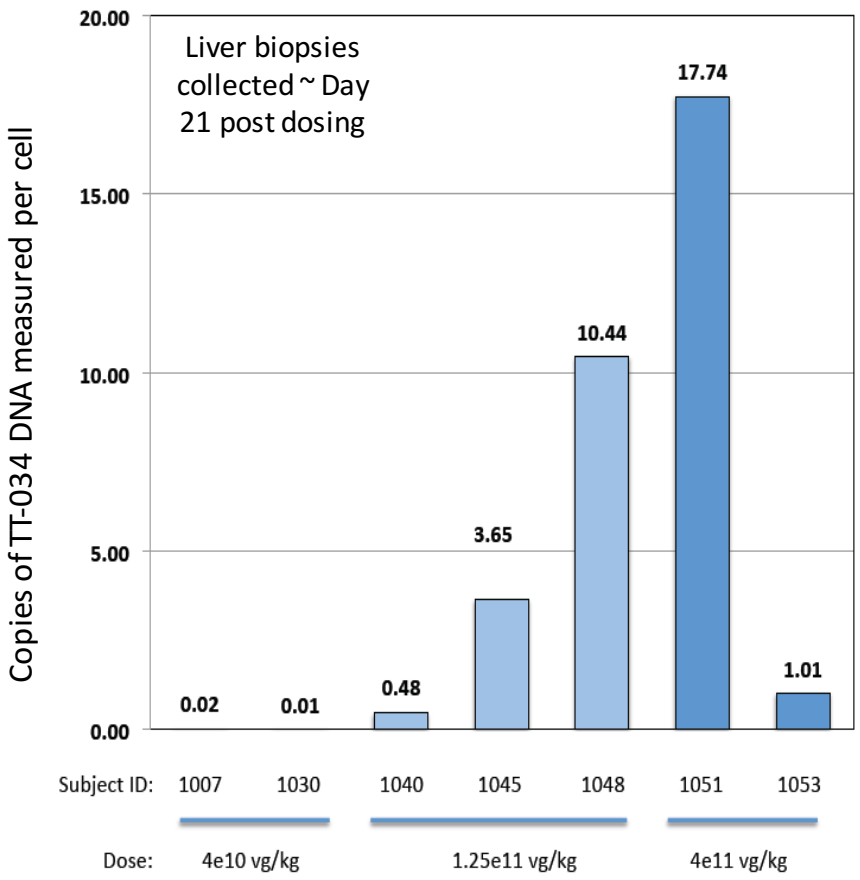
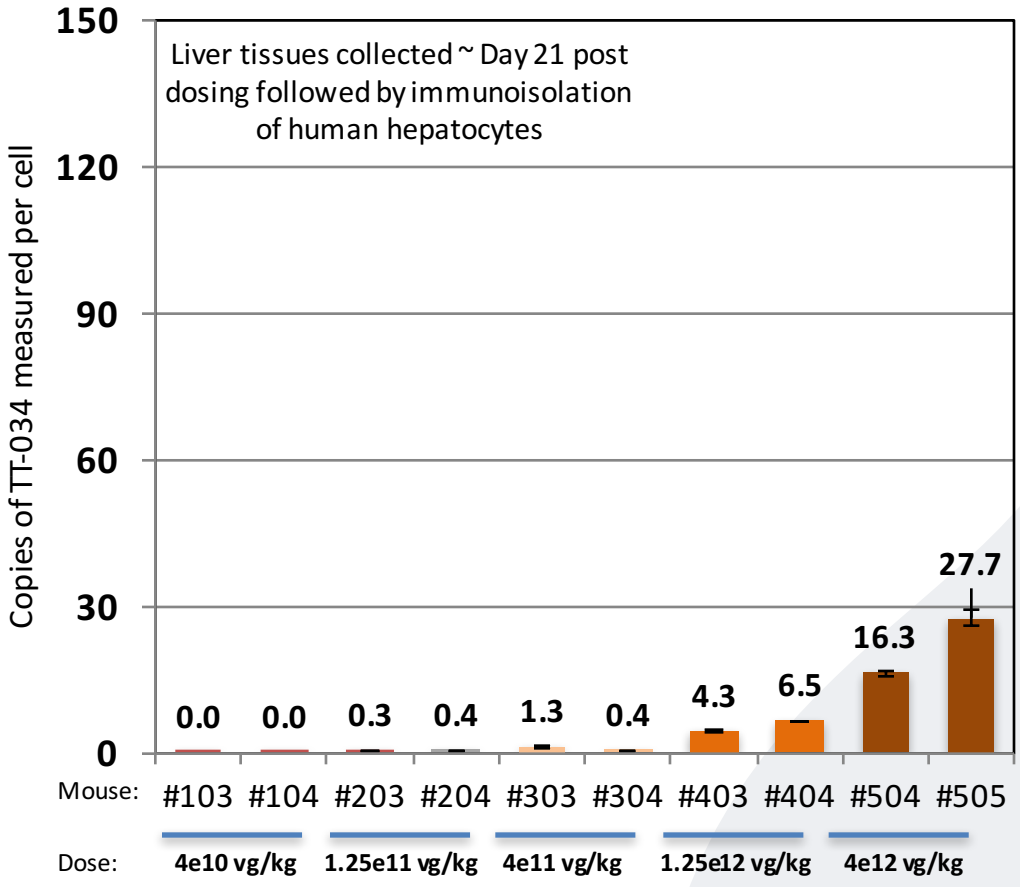
Human Liver Biopsies from TT-034 Clinical Study



Hepatic Tissues from Chimeric Mouse dosed with TT-034

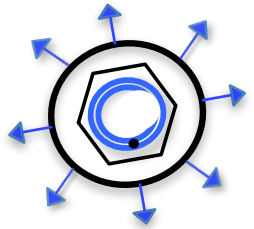


In Vitro Infectious HBV Studies Using Primary Hepatocytes Isolated from PXB mice

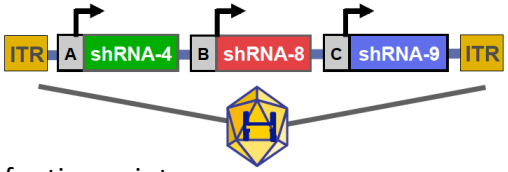
Chimeric mouse with humanized liver

1. Isolate human hepatocytes and plate

2. Infect plated cells with HBV genotype C and Incubate 12 days



3. Transduce infected cells with Ad-BB-HB-331 or Ad-TT-034



4. Harvest parallel wells for timepoints (4, 7, 10, 13 and 16 days post Ad-BB-HB-331 treatment)

RNA:

HBV viral transcripts
Production of anti-HBV shRNA

Supernatant:

Extracellular HBsAg
Extracellular HBeAg
Extracellular HBcrAg
Extracellular HBV DNA
Human Albumin

DNA:

Total Intracellular DNA (control)
Intracellular HBV DNA
HBV cccDNA

In vitro Reduction of HBV Parameters following a Single Treatment with BB-HB-331

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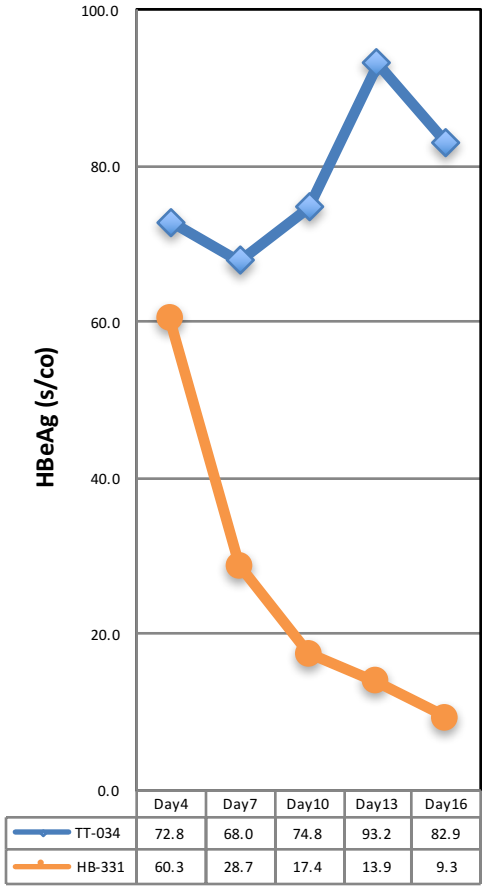
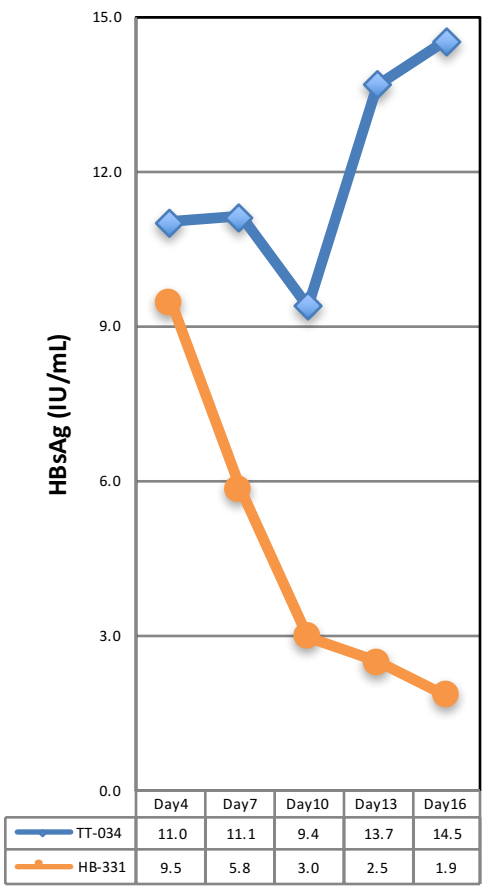
89% drop extracellular HBeAg at day 16



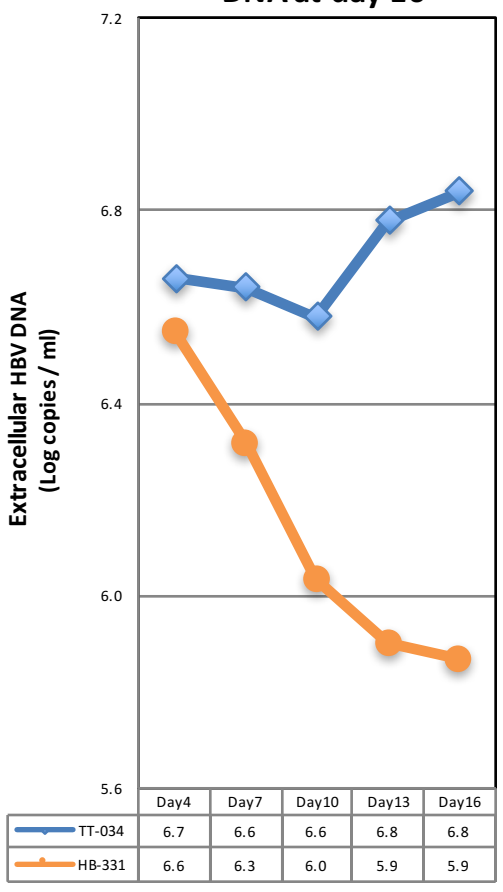
	Day4	Day7	Day10	Day13	Day16
TT-034	72.8	68.0	74.8	93.2	82.9
HB-331	60.3	28.7	17.4	13.9	9.3

87% drop extracellular HBsAg at day 16



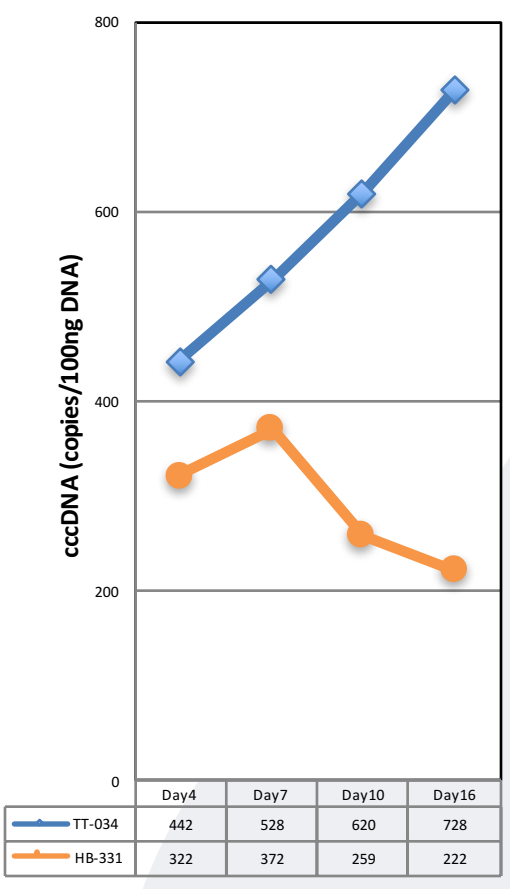
	Day4	Day7	Day10	Day13	Day16
TT-034	11.0	11.1	9.4	13.7	14.5
HB-331	9.5	5.8	3.0	2.5	1.9

1 log drop extracellular HBV DNA at day 16



	Day4	Day7	Day10	Day13	Day16
TT-034	6.7	6.6	6.6	6.8	6.8
HB-331	6.6	6.3	6.0	5.9	5.9

70% drop in cccDNA at day 16

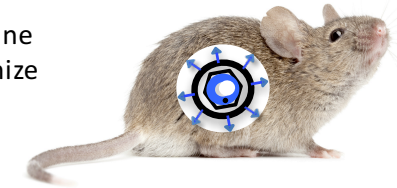


	Day4	Day7	Day10	Day16
TT-034	442	528	620	728
HB-331	322	372	259	222

In Vivo Infectious HBV Studies Using PXB Mice

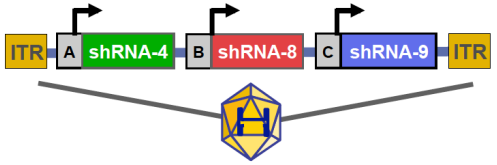
Chimeric mouse with humanized liver

2. Incubate mice for 4 weeks, establish baseline HBV infection, randomize



HBV infected Chimeric mouse

3. Transduce mice with BB-HB-331 at 2e12 or 2e13 vg/kg



1. Infect chimeric PXB mice with HBV genotype C

4. Follow the BB-HB-331 transduced, HBV infected mice for an additional 56 days

RNA (terminal):

HBV viral transcripts
Production of anti-HBV shRNA

Serum (weekly):

Extracellular HBsAg
Extracellular HBeAg
Extracellular HBV DNA
Human Albumin

DNA (terminal):

Total Intracellular DNA (control)
Intracellular HBV DNA
HBV cccDNA

A Single Dose of BB-HB-331 Durably Reduces Serum HBV Levels in PXB Chimeric Mice Infected with HBV

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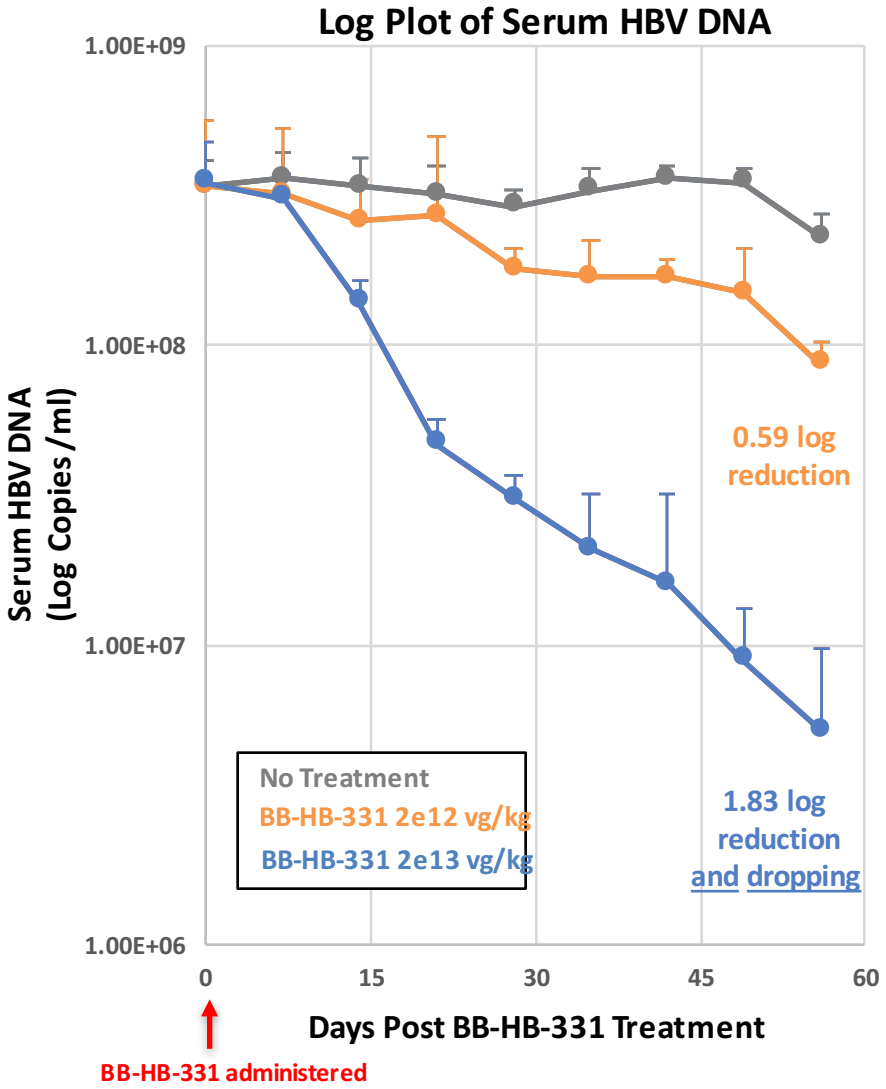
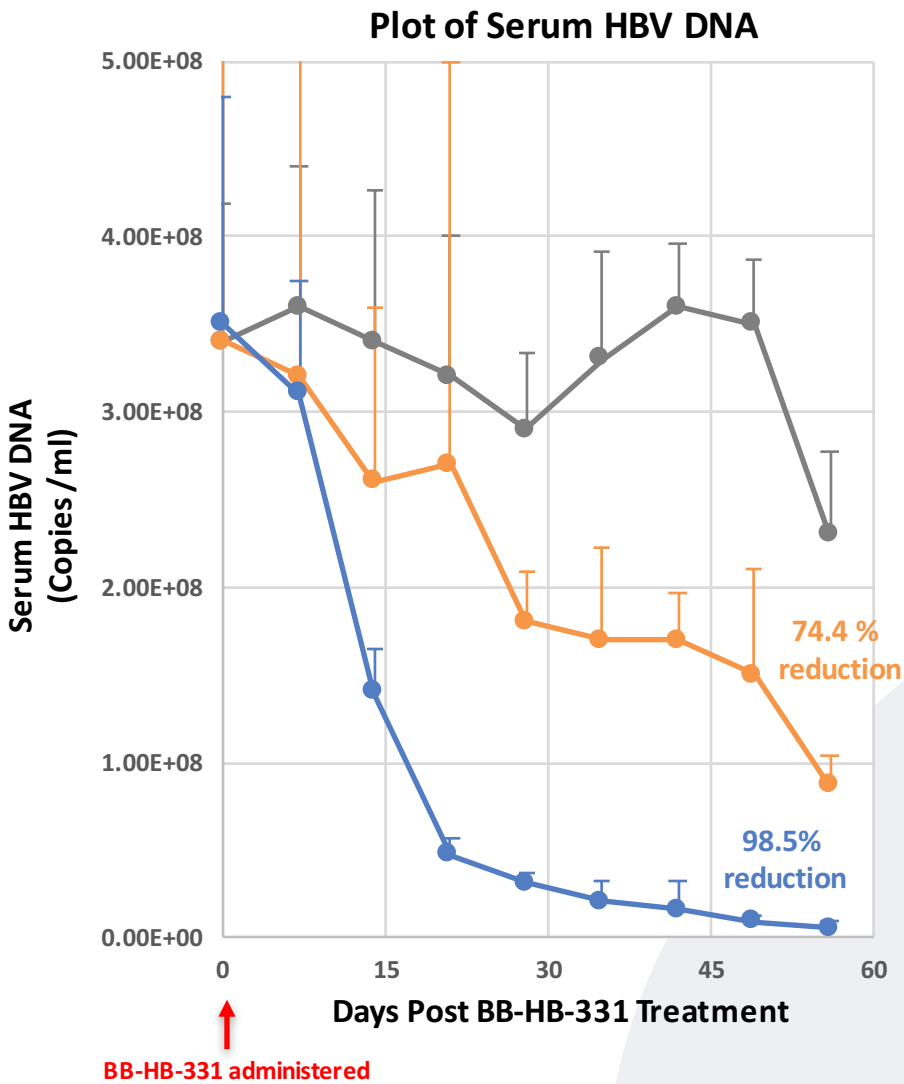
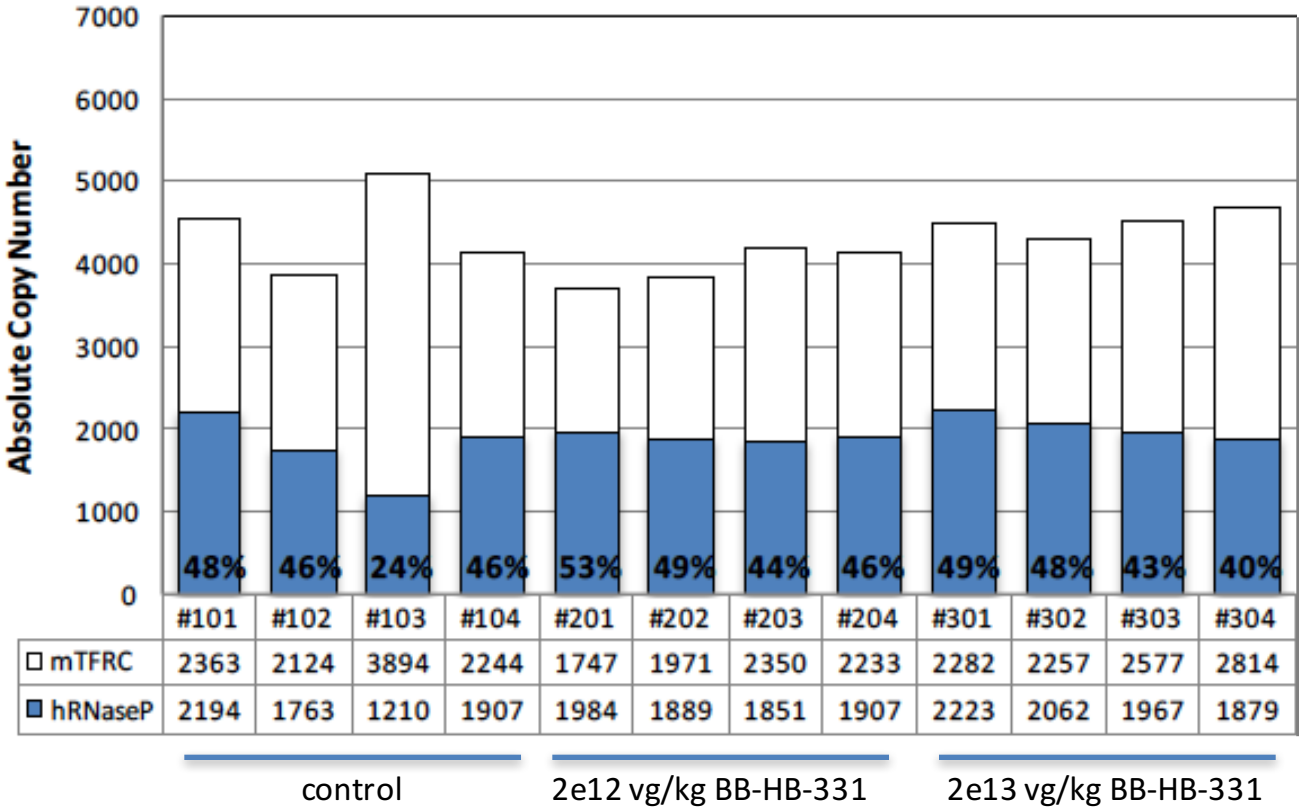




Constant Human:Mouse Genomic Index Demonstrates that Reduction of HBV was not Due to Liver Toxicity

- Liver tissue DNA was qPCR for human RNaseP and mouse TFRC (Transferrin Receptor)
- Both are present at 1 copy per haploid genome
- Standard Curve Method used to determine absolute copy number in 20ng DNA input.



	#101	#102	#103	#104	#201	#202	#203	#204	#301	#302	#303	#304
mTFRC	2363	2124	3894	2244	1747	1971	2350	2233	2282	2257	2577	2814
hRNaseP	2194	1763	1210	1907	1984	1889	1851	1907	2223	2062	1967	1879

A Single Dose of BB-HB-331 Durably Reduces HBsAg and HBeAg in PXB Chimeric mice Infected with HBV

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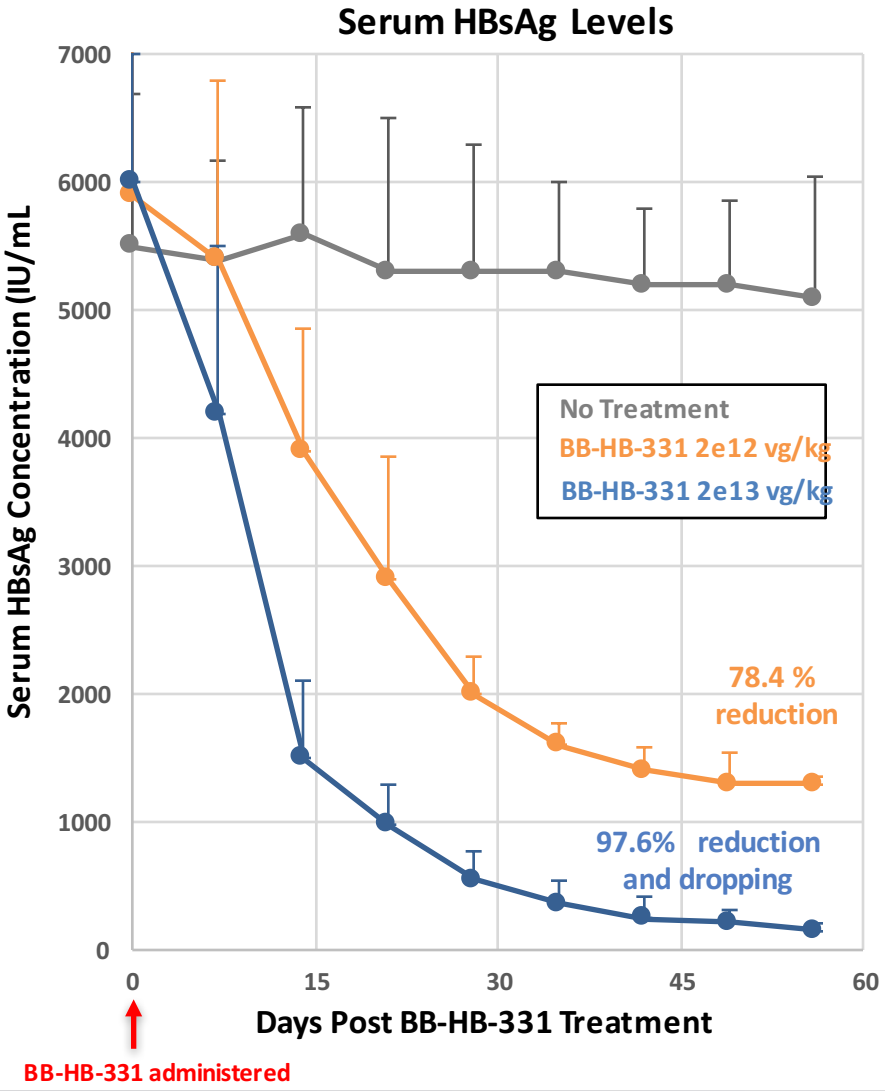

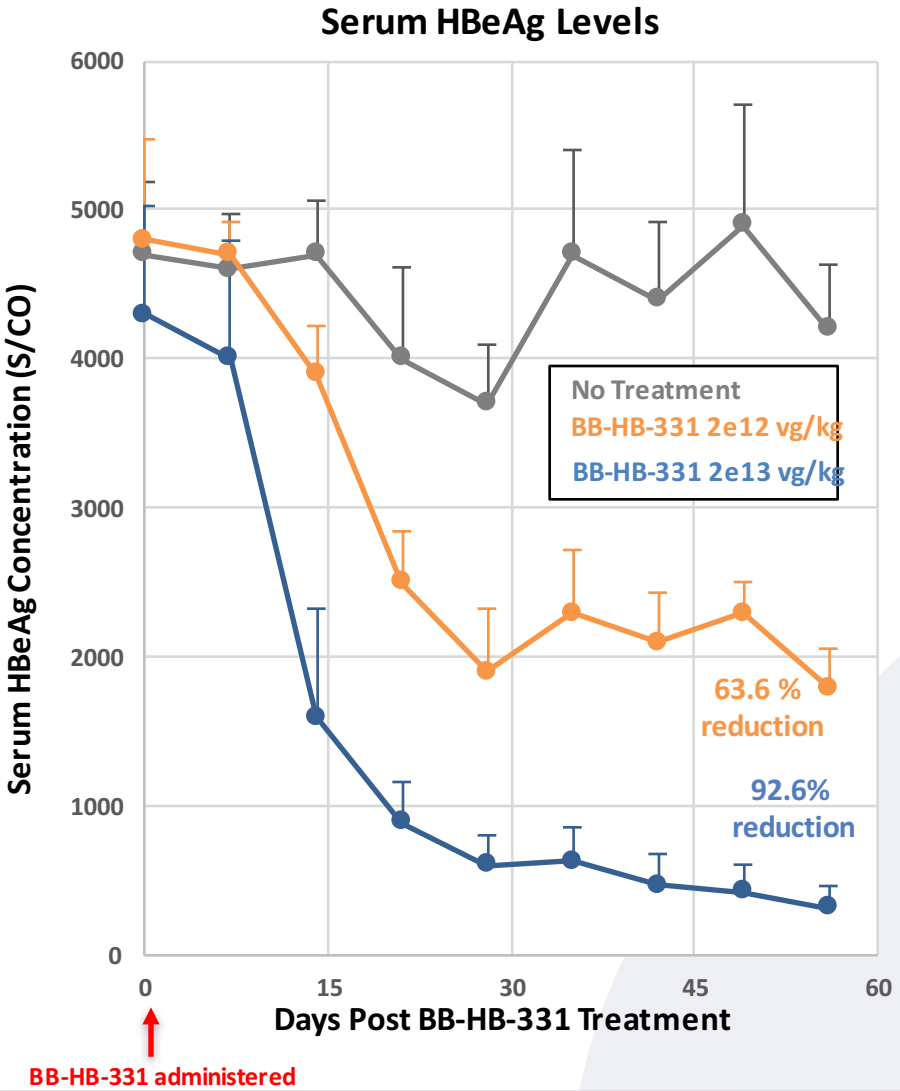

Terminal Intracellular HBV DNA and cccDNA Levels in Response to a Single BB-HB-331 Treatment in PXB Mice

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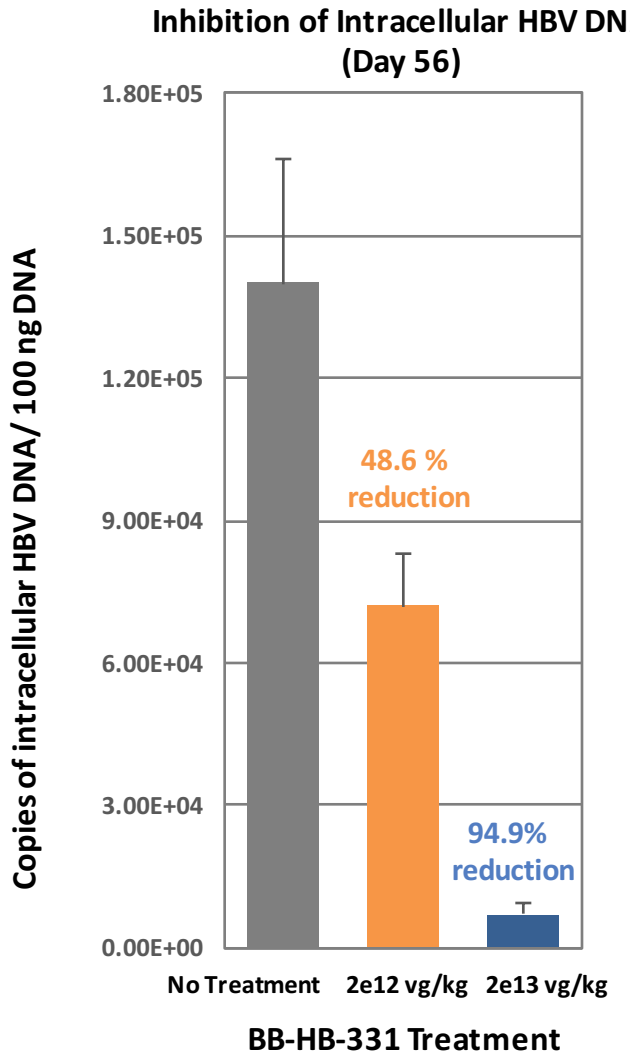

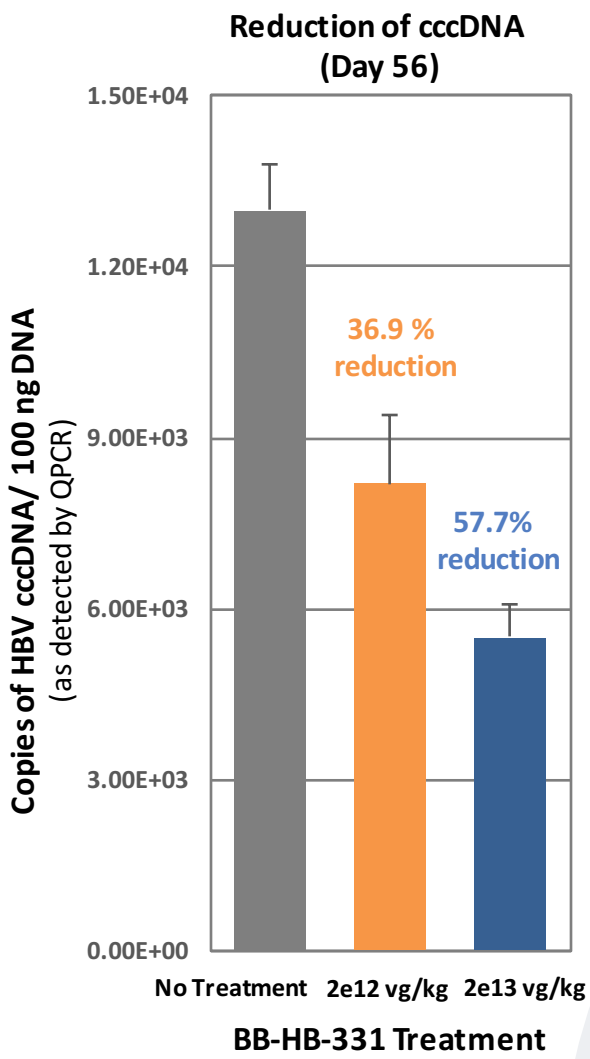

BB-HB-331: Target Product Profile

Design:

- Applies learnings of TT-034; a validated ddRNAi vector in use in a phase I/IIa clinical study
- shRNA target 3 separate, well conserved regions of HBV with many cleaving more than one of the five major transcripts and associated splice variants.
- Long term suppression of viral proteins from single intravenous infusion (years)
- Coverage of whole liver using AAV viral vectors

Results:

- A single IV administration reduced HBV serum DNA by 1.83 logs.
- HBsAg and HBeAg dropped by nearly 98% and 93% respectively.
- All extracellular HBV parameter continued to drop throughout the 56 day experiment suggestive that levels may continue to decline at longer time periods
- Intracellular DNA and cccDNA dropped by 94.5% and 57.7% respectively at the highest dose