



**Potent and durable RNAi mediated  
suppression of Hepatitis B Virus  
infection in a mouse model by a non-  
viral Closed Ended Linear DNA (CELID)  
vector**

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## Contributors



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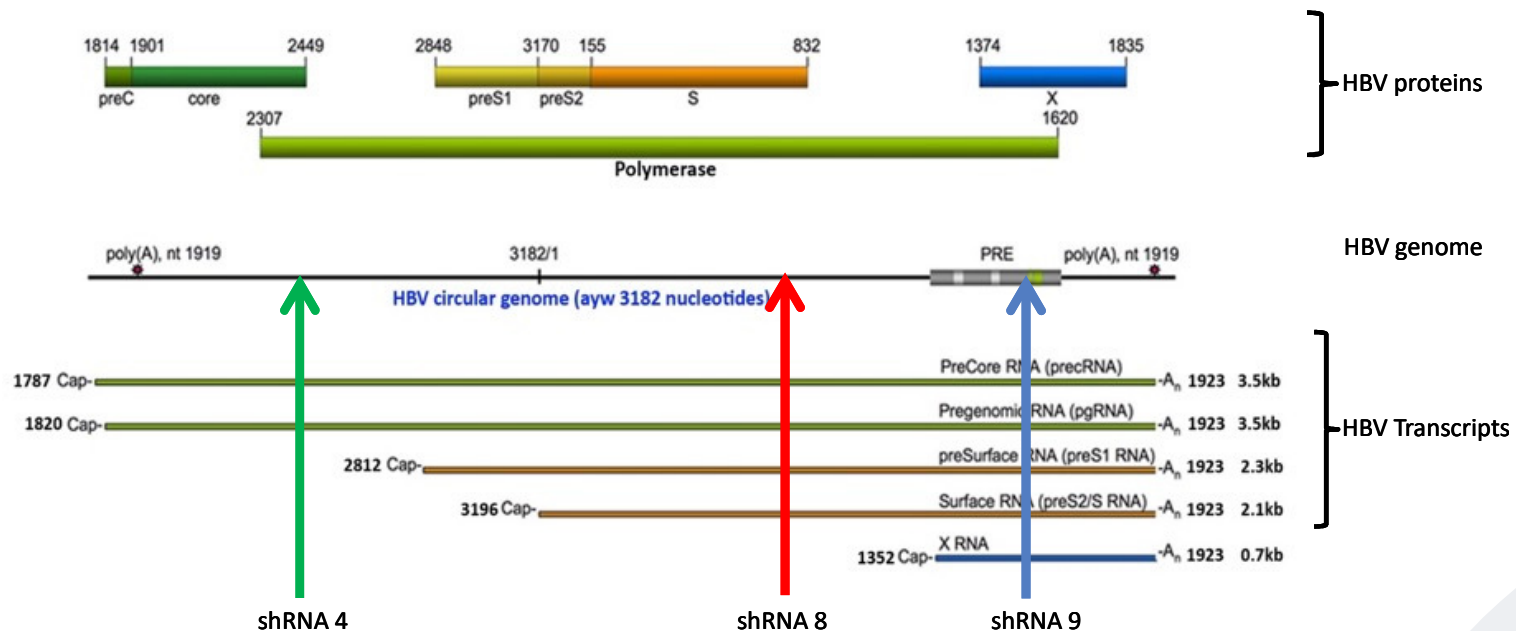
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**Peter Roelvink**

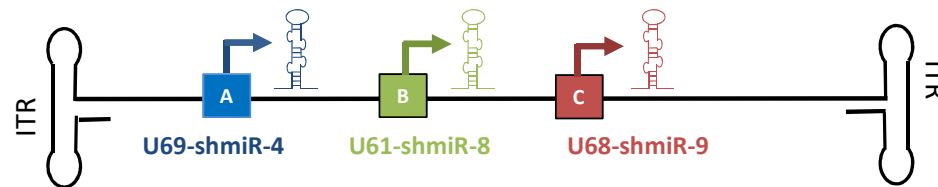
**David Suhy**

## 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

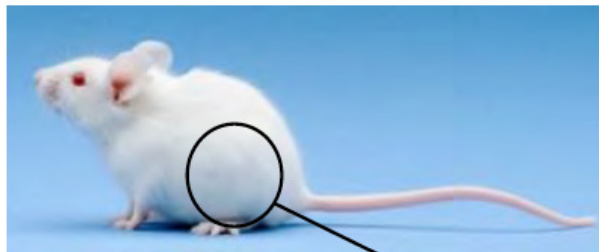
## BB-103: Triple shmiR anti HBV



- Single stranded recombinant DNA
- Wild type Pol III promoters for high expression
- Model shRNA into miRNA backbone for safety
- High fidelity: a few predominant, highly active species of siRNA
- May help reduce potential toxicity

## Overview of Phoenix Bio's PXB Human Liver Chimeric Mouse

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



1. Human hepatocytes proliferating under physiologically relevant conditions
2. Histologically normal liver constitution
3. Human specific metabolism and excretion pathways
4. Infectable with HBV and HCV



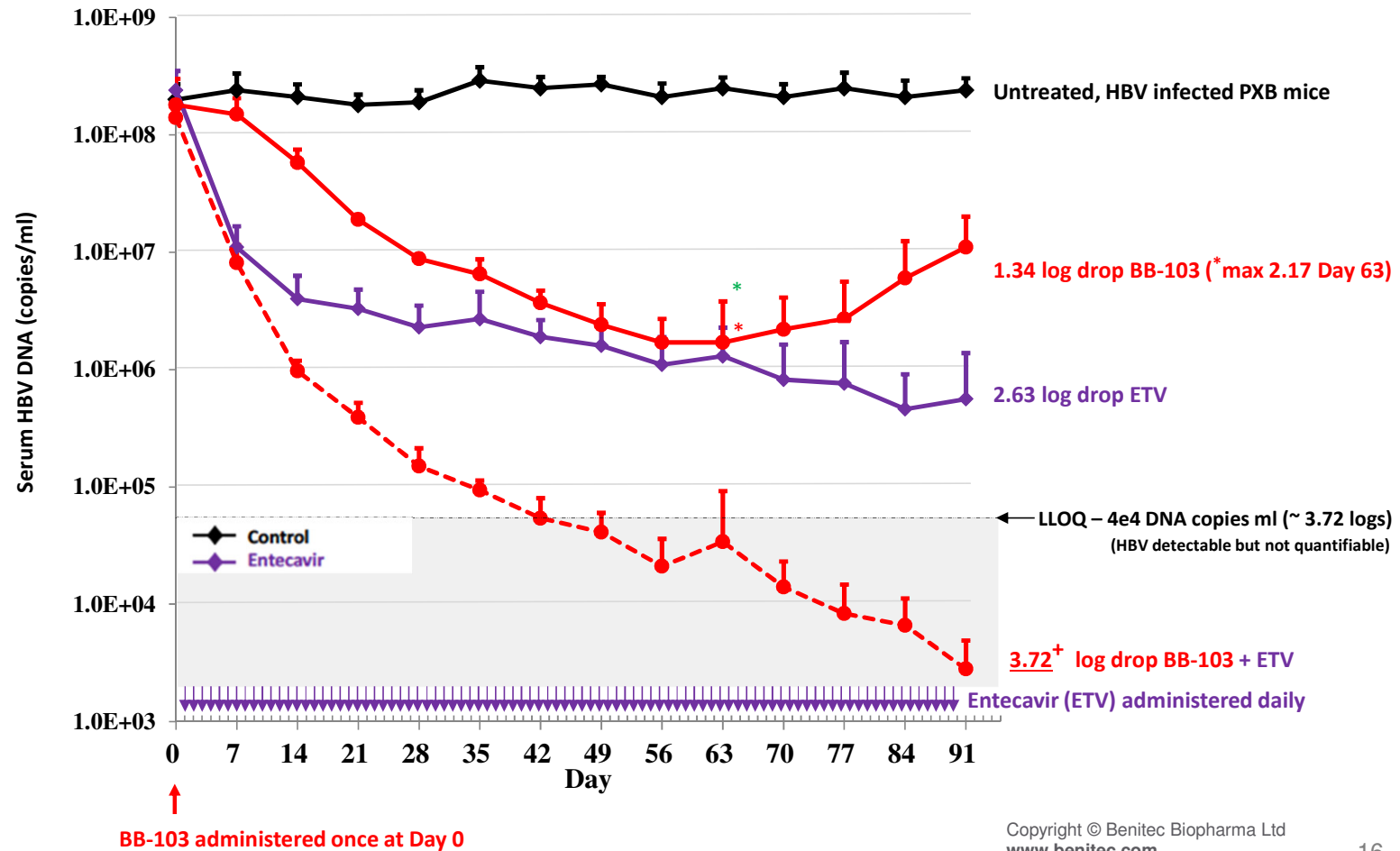
cDNA-uPA/SCID  
Liver weight: 0.7 – 1 g

**Transplantation**

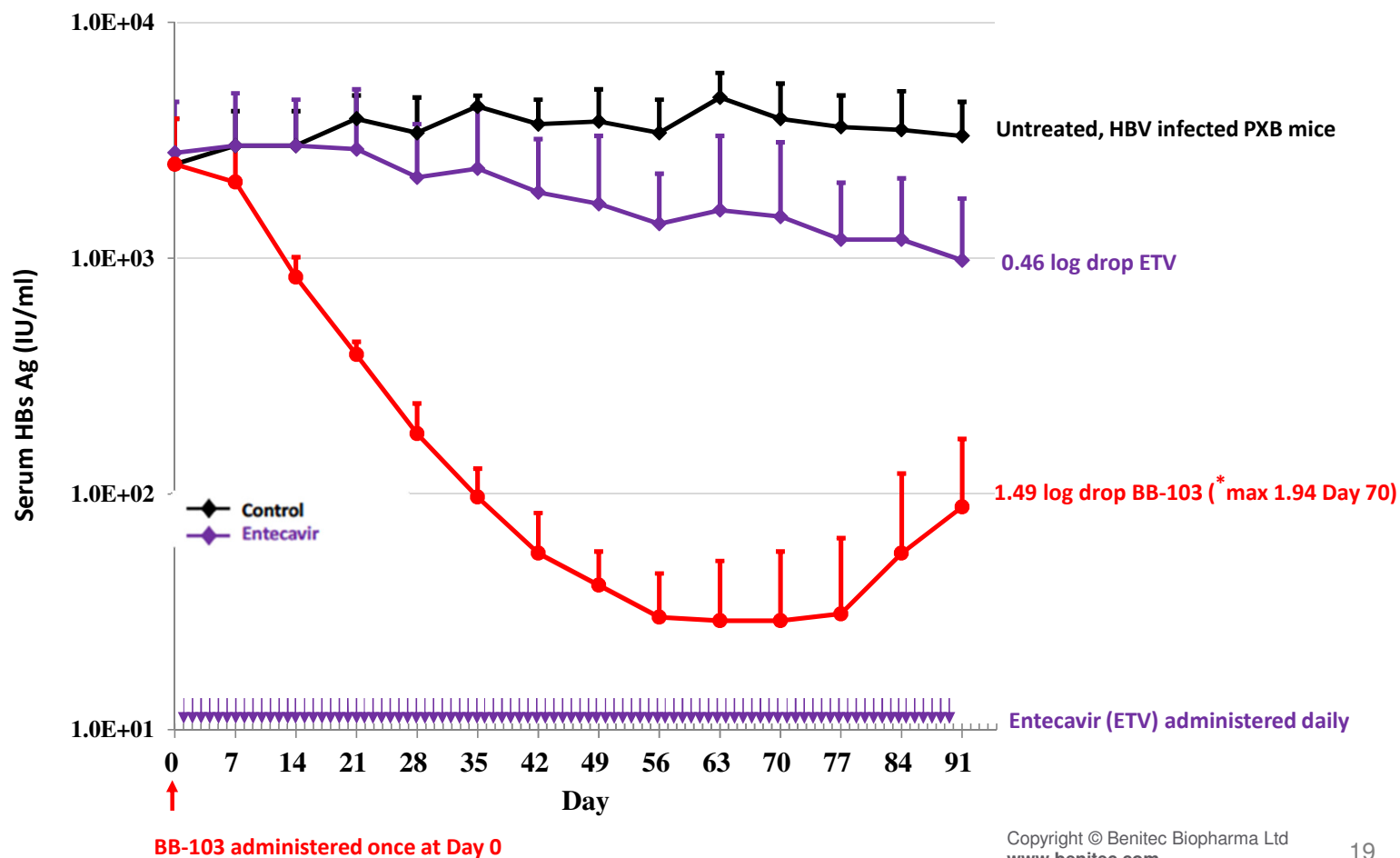


PXB-Mouse®  
Liver weight: 2 – 2.5 g  
(RI: 98 %)

## BB-103 Combo with Entecavir: Reduction of Serum HBV DNA Levels



# BB-103 and Entecavir as Monotherapy: Reduction of Serum HBsAg (S-Antigen) Levels



**Complex Manufacturing in mammalian or insect cells**

**Pre-existing antibodies in patients against AAV serotypes prevents administration of an AAV vector**

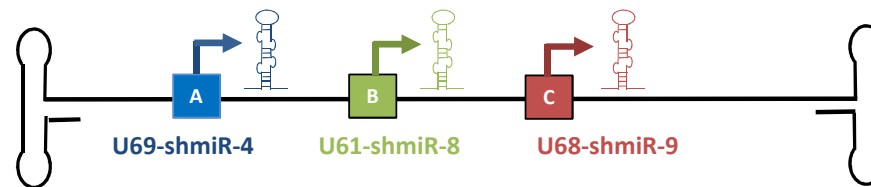
**Administration of an AAV vector prevents repeat dosing**

**Solution (perhaps): Celids**

## What is a Celid?

It's a Closed Ended Linear DNA and to be more precise:

It looks like the genome of an AAV minus the capsid, but is not size restricted and thus can be much shorter than 4.6 Kb

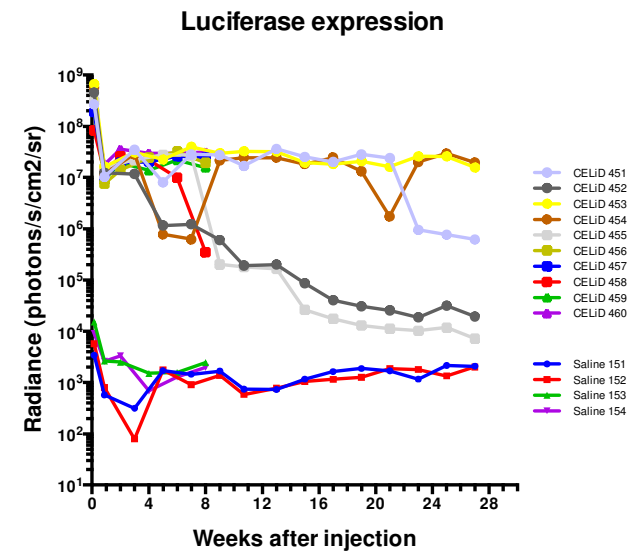
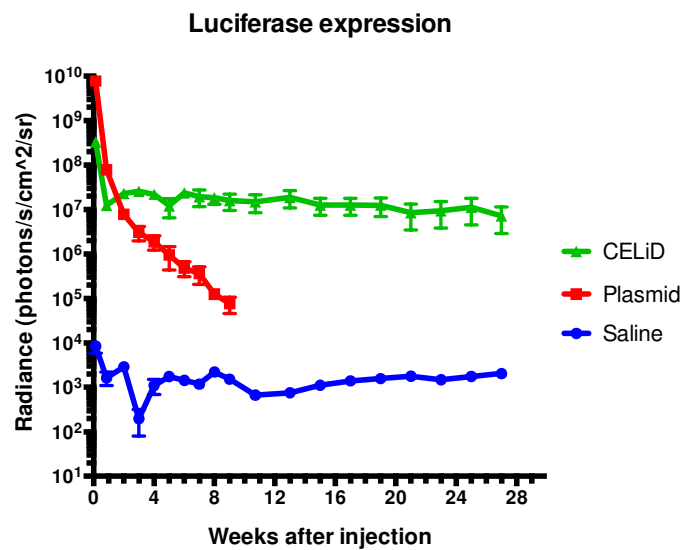


Celids are produced by infection of insect cells by two baculoviruses. One carries the Celid, the other carries the Replication genes of an AAV but NOT the capsid genes.

This results in production of Celids that can be purified from harvested insect cells using DNA purification kits followed by HPLC (size exclusion).

The first in vivo evaluation was with a Celid that expresses luciferase (female BALB/c by Hydrodynamic Injection)

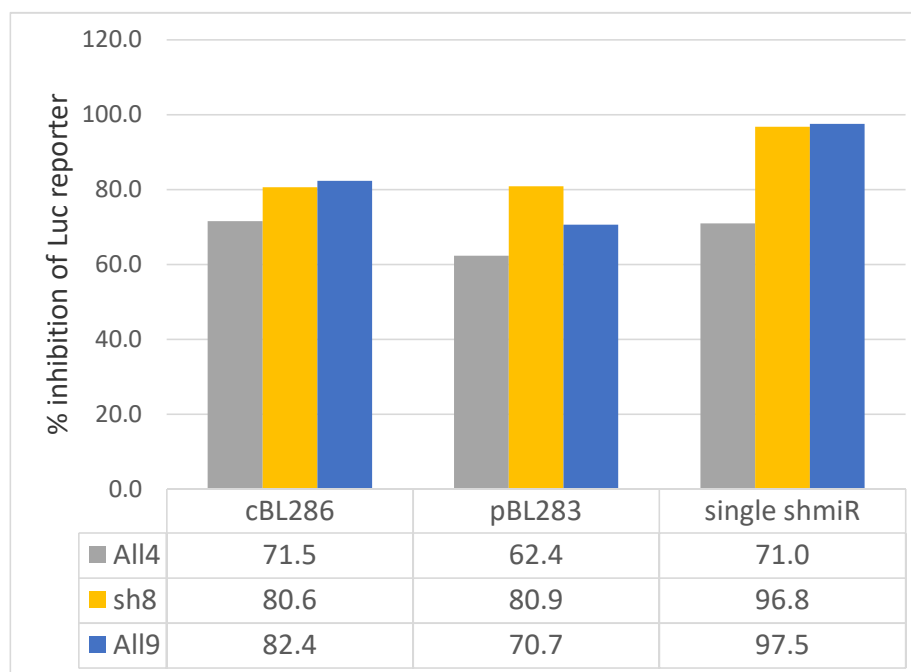
# Long term expression of luc-Celid in vivo



## Characterizing Celids

- Fully characterized CEliD 286 (HBV triple shmiR)

- Purified (glycerol gradients)
- Mapped
- Sequenced
- Activity



## **HBV Hydro Dynamic Injection study in NOD-SCID mice**

**WUXI study 20170123A**

**Test groups:**

**Saline + HepB plasmid (Group D)**

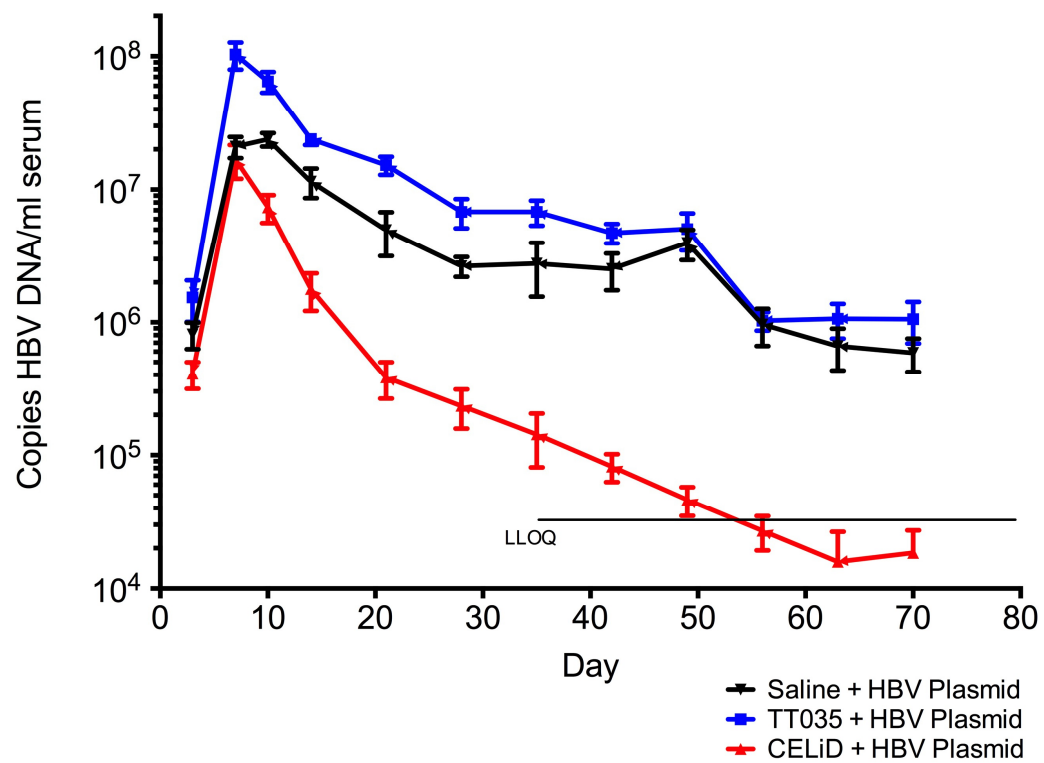
**TT035 + HepB plasmid (negative control that produces 3 anti-HepC shmiRs)**

**Celid (produces 3 anti-HBV shmiRs) + HepB plasmid**

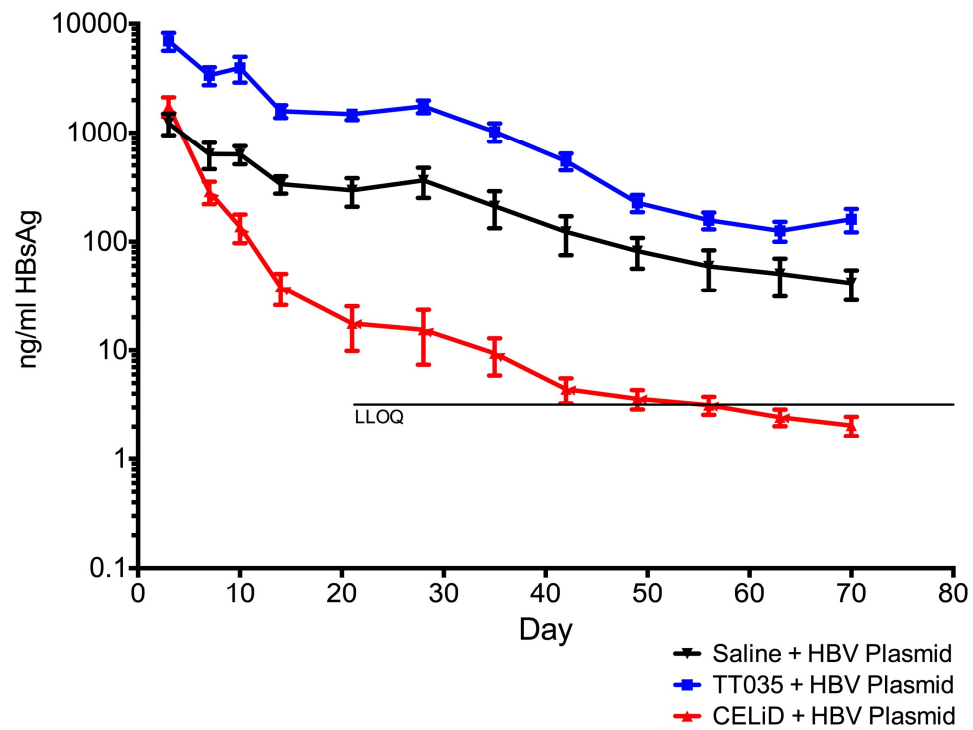
**HDI of 10 ug in volume of 8% of mouse bodyweight/5 seconds**

**HepB DNA levels determined in serum by Q-PCR, S and E antigens by ELISA**

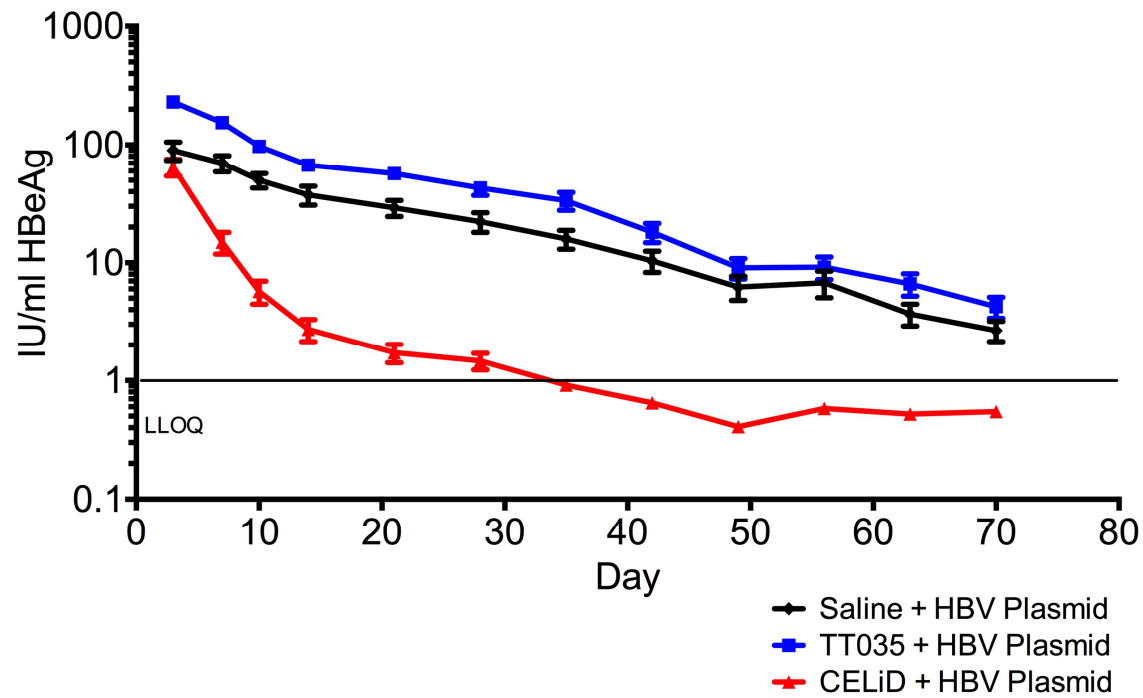
## Serum HBV DNA



## Serum HBsAg



## Serum HBeAg



## Conclusions

The NOD-SCID HDI mouse model appears suitable for quick evaluation/ranking of potential anti HepB therapeutics.

The model is not necessarily suitable for long term (i.e. over 30 days p.i.) evaluation.

Celids are molecular therapeutic tools that have utility in a preclinical setting.