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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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

Transplantation

cDNA-uPA/SCID
Liver weight: 0.7 – 1 g

PXB-Mouse®
Liver weight: 2 – 2.5 g
(RI: 98 %)
BB-103 Combo with Entecavir: Reduction of Serum HBV DNA Levels

Untreated, HBV infected PXB mice

- 1.34 log drop BB-103 (max 2.17 Day 63)
- 2.63 log drop ETV
- 3.72 log drop BB-103 + ETV

LLOQ – 4e4 DNA copies ml (~ 3.72 logs)
(HBV detectable but not quantifiable)

BB-103 administered once at Day 0
Entecavir (ETV) administered daily
BB-103 and Entecavir as Monotherapy: Reduction of Serum HBsAg (S-Antigen) Levels

- **Untreated, HBV infected PXB mice**
- **0.46 log drop ETV**
- **1.49 log drop BB-103 (max 1.94 Day 70)**

BB-103 administered once at Day 0
Entecavir (ETV) administered daily
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

Weeks after injection

Radiance (photons/s/cm²/sr)

Luciferase expression

Weeks after injection

Radiance (photons/s/cm²/sr)

CELID
Plasmid
Saline
Characterizing Celids

- Fully characterized CEliD 286 (HBV triple shmiR)
  - Purified (glycerol gradients)
  - Mapped
  - Sequenced
  - Activity

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HBV Hydro Dynamic Injection study in NOD-SCID mice

WUXI study 20170123A
In Vivo Evaluation of Celid Activity: set up

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 HBsAg

![Graph showing Serum HBsAg levels over time for different treatments. The x-axis represents days, and the y-axis represents ng/ml HBsAg. The graph compares Saline + HBV Plasmid, TT035 + HBV Plasmid, and CELiD + HBV Plasmid treatments. The lowest level of detection (LLOQ) is indicated.]
Serum HBeAg

- Saline + HBV Plasmid
- TT035 + HBV Plasmid
- CELiD + HBV Plasmid

IU/ml HBeAg vs Day graph with LLOQ (Lower Limit of Quantification)
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.