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Development of HSD17B13 Targeting siRNA-GalNAc as a Potential Therapy for Fibrosis in NASH

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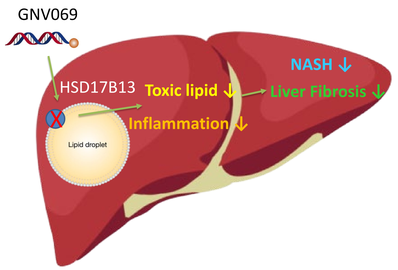
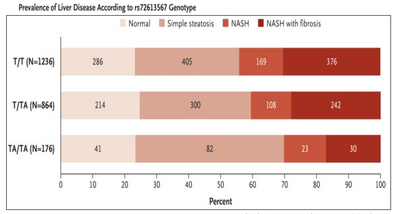
ABSTRACT

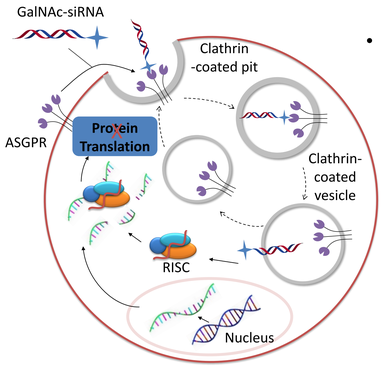
- Nonalcoholic steatohepatitis (NASH) is one of the most common chronic liver diseases.
- Increased risk of liver fibrosis is a key pathogenic factor for morbidity and mortality in NASH, yet no approved therapy is available.
- HSD17B13 is a genetically validated target for treating liver fibrosis in NASH. It is overexpressed in NASH patients and hypothesized to be related to generation of cytotoxic lipids. Deficiency is associated with reduced fibrosis.
- GNV069 is a HSD17B13-targeting siRNA-GalNAc conjugate that demonstrated potency in reducing hepatic HSD17B13 levels and favorable tolerability in nonclinical studies, providing promise as a treatment for fibrosis in NASH.





Abul-Hsun, et al. NEJM. 2018

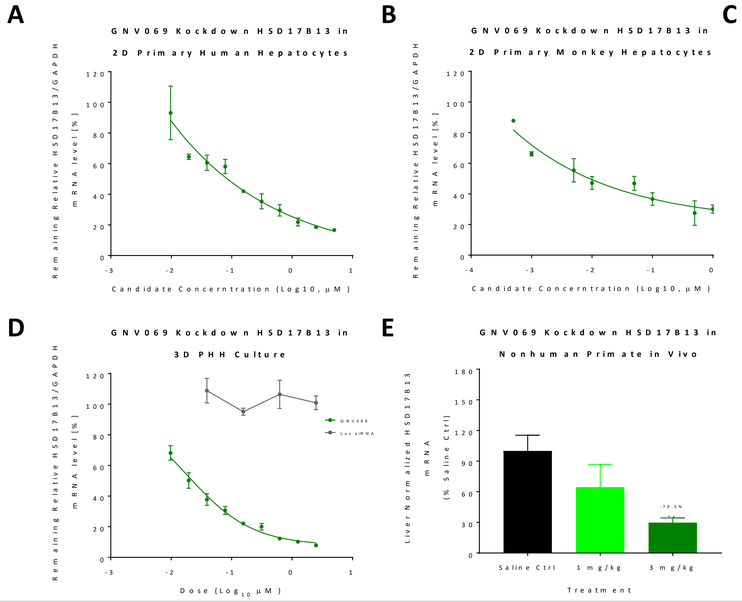
INTRODUCTION



- Delivery of GalNAc-siRNA is mediated by the Asialoglycoprotein Receptor (ASGPR). This receptor is:
  - Highly expressed in hepatocytes
  - Recycled every 15 min, allowing rapid uptake.
  - Well conserved across species, affording high translatability

RESULTS

GNV069 Reduced HSD17B13 *in Vitro* & *in Vivo*



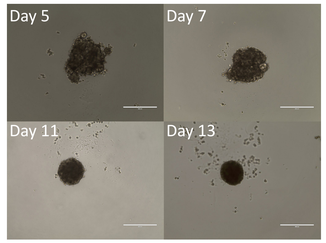


Figure 1. GNV069 Reduces HSD17B13 *in Vitro* & *in Vivo*. *In vitro* potency of GNV069 inhibiting HSD17B13 is demonstrated in 2-dimensional (2D) culture of primary human **(A)** or monkey **(B)** hepatocytes and in spheroid cultures established with primary human hepatocytes **(C, D)**. A single subcutaneous dose of GNV069 at 3 mg/kg in NHP achieved 70% inhibition on liver HSD17B13 levels analyzed by qPCR at Day 14 post dosing (n=4) **(E)**.

GNV069 was Well Tolerated in Rats

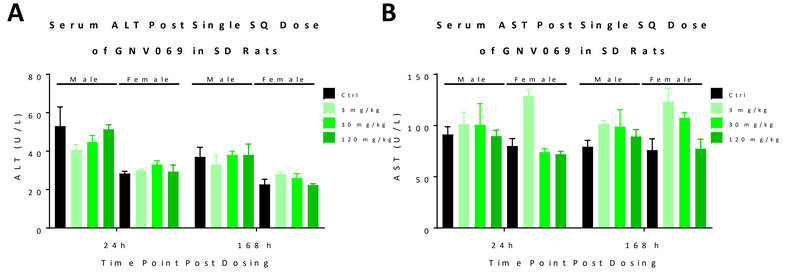


Figure 2. GNV069 is well tolerated in rats. SD rats were dosed with 3-120 mg/kg GNV069 subcutaneously. Liver enzyme ALT **(A)** and AST **(B)** levels in GNV069 treated animals were comparable to the control animals, suggesting no liver damage (n=3).

GNV069 was Well Tolerated in NHP

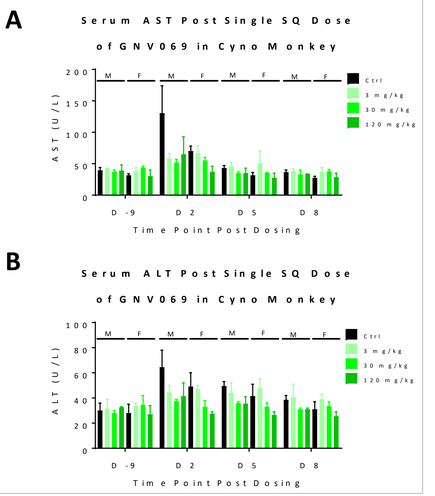


Figure 3. GNV069 is well tolerated in NHP. Cyno monkeys were dosed with a single subcutaneous dose of GNV069 at 3-120 mg/kg. Liver enzyme ALT **(A)** and AST **(B)** levels in GNV069 treated animals were comparable to control animals. (n=2)

CONCLUSIONS

- GNV069 demonstrated knockdown of HSD17B13 expression in both human and NHP hepatocytes *in vitro*.
- *In vivo* studies demonstrated potent reductions of hepatic HSD17B13 levels in nonhuman primates treated with GNV069.
- A single subcutaneous dose of GNV069 was well tolerated in rats and NHP, exhibiting no liver enzyme elevations.
- GNV069 is a promising candidate for further development.

CONTACT INFORMATION

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