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Development of a Novel Seven-Day Dosing Mouse Efficacy Model to Evaluate Thyroid Hormone Receptor Agonists for the Treatment of NASH

ALIGOS THERAPEUTICS

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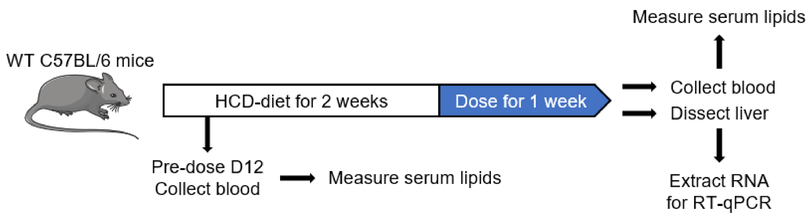
1. Background

Nonalcoholic steatohepatitis (NASH) is an emerging major public health issue, with no approved treatment. Thyroid hormone receptor β (THR-β) agonists have demonstrated the potential to reduce liver fat, restore liver function, and possibly reverse fibrosis in NASH patients. Standard animal efficacy models, specifically the diet-induced obesity (DIO) mouse, are time-consuming and limit early-stage preclinical profiling of novel THR-β agonists. The goal of this study was to develop a short duration mouse model adapted towards thyromimetic testing that is predictive of patient response at clinically relevant exposures.

2. Methods

C57BL/6 mice were fed a high cholesterol diet (HCD) for two weeks. The clinically validated THRβ agonist MGL-3196 (resmetirom) was used as a reference molecule and dosed at 0.3, 1.0, and 3.0 mg/kg once-daily for seven days to investigate modulation of serum lipid levels, liver gene expression, transaminases (ALT/AST), and the thyroid hormone levels.



Study design included high cholesterol diet (HCD) pre-feeding of mice for 2 weeks prior to dosing with thyromimetic agents for 1 week

3. Results

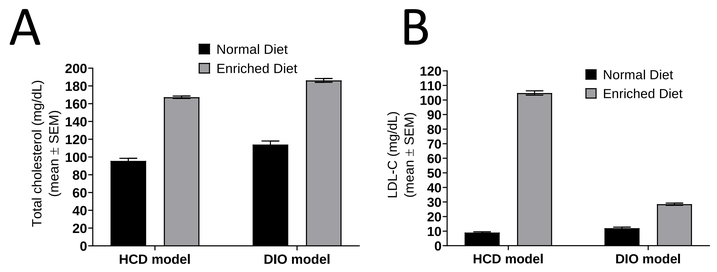


Figure 1: Baseline serum lipid levels

- A and B: Effects on total and LDL cholesterol (LDL-c) levels after feeding mice with HCD for 2 weeks, and comparison with levels obtained with standard DIO mouse model after 3 months.

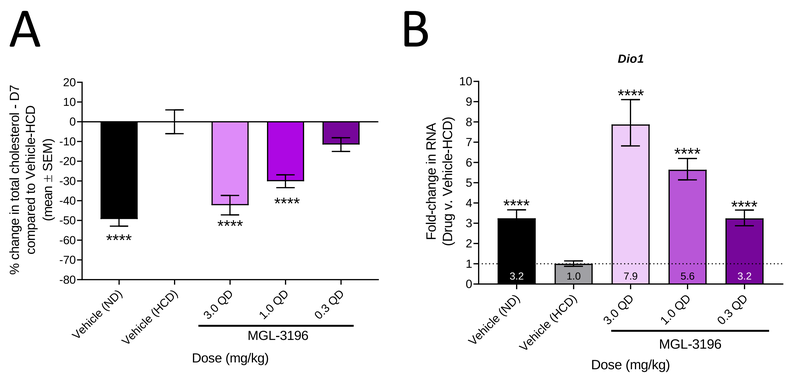


Figure 2: Changes in total cholesterol (A) and Dio1 gene expression (B)

- A and B: MGL-3196 dosed for 7 days in the HCD model lowered total cholesterol levels and increased Dio1 mRNA liver levels in a concentration-dependent manner. The minimum efficacious dose of MGL-3196 required to decrease total cholesterol in the 7-day dosing model was between 0.3 and 1.0 mg/kg. Increases in Dio1 expression, an early gene biomarker of target engagement in the liver, was observed at 0.3 mg/kg. Plasma AUC and C_{min} levels at these doses were comparable (data not shown) with those obtained in humans[1].

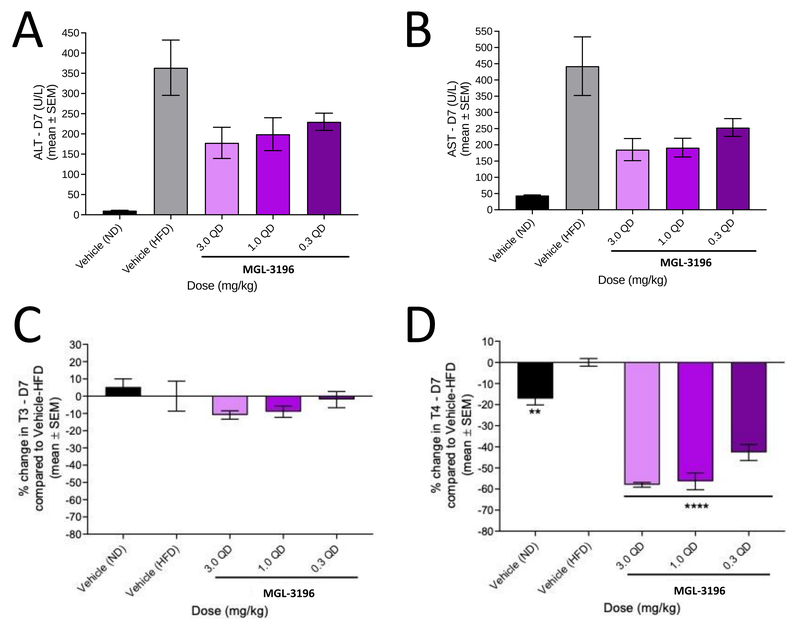


Figure 3: Changes in ALT/AST and T3/T4 levels

- A and B: MGL-3196 dosed for 7 days in the HCD model lowered ALT and AST levels at all three doses.
- C and D: MGL-3196 dosed for 7 days in the HCD model had no effect on endogenous T3 but lowered T4 levels at all three doses.

4. Conclusions

Pharmacokinetic/pharmacodynamic profiling of MGL-3196 in the 7-day dosing mouse model was predictive of NASH patient responses at clinically relevant exposures. This newly developed HCD mouse model provides a rapid and clinically relevant alternative to standard efficacy models for the efficient in vivo screening of THR-β agonists as potential NASH therapeutic agents.

References:
1: Taub *et al.*, Atherosclerosis (2013)

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