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The novel galectin-3 inhibitor GB1211 reduces inflammation & fibrosis in a rabbit high fat diet model of NASH & fibrosis

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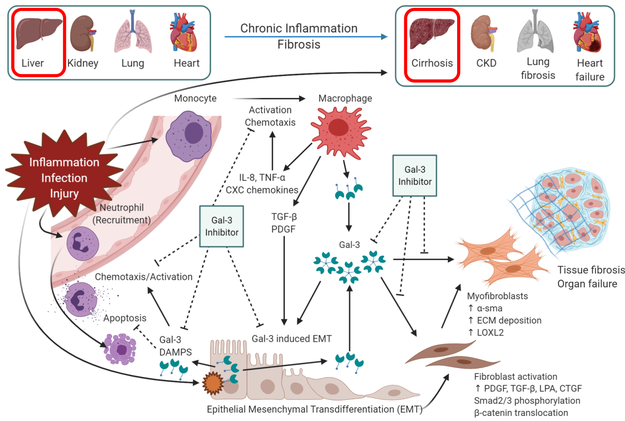
Background

- Galectin-3 (Gal-3) is a pro-fibrotic β-galactoside binding lectin highly expressed in fibrotic liver[1] & implicated in hepatic fibrosis[2] (see Diagram 1).
- GB1211 is a novel orally active Gal-3 small molecule inhibitor[3] that has high affinity for Gal-3 (human K_D = 25nM; rabbit K_D = 12nM) & high oral bioavailability in rabbits & man.
- In this study the efficacy of GB1211 was investigated in a high fat diet (HFD) rabbit model of non-alcoholic steatohepatitis (NASH)[4].

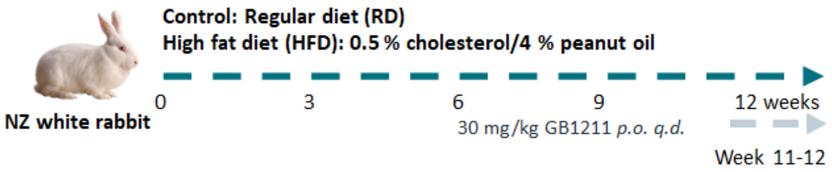
Diagram 1. The infection, inflammatory & injury pathways driven by galectin-3 that lead to organ fibrosis.



Methods

- Male New Zealand White rabbits were individually caged under standard conditions in a temperature & humidity-controlled room on a 12h light/darkness cycle.
- After 1 week of regular diet (RD), rabbits were randomly assigned to 4 different groups (n=3/group): RD/vehicle, RD/30mg/kg GB1211, HFD/vehicle & HFD/30 mg/kg GB1211 (vehicle/GB1211 *p.o.* dosed therapeutically *q.d.* 5 days from week 11) for 12 weeks.
- Liver inflammation, steatosis, ballooning, & fibrosis was measured via blood metabolic markers, histomorphological analysis (Masson's trichome, Giemsa, oil red O & picrosirius red (PSR)), second generation harmonics (SHG collagen content) & fibrotic gene signature.
- Plasma concentrations of GB1211 were determined by LC-MS.

Figure 1. Study design for GB1211 in a rabbit HFD model



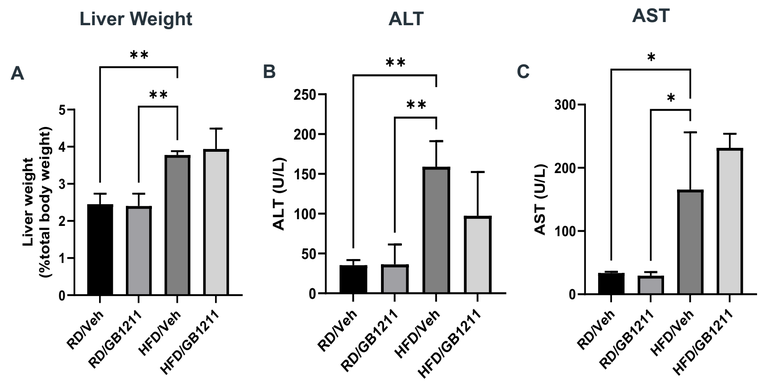
Summary

- GB1211 normalized inflammation & fibrosis in a HFD rabbit model of NASH & liver fibrosis following less than a week of dosing.
- Further studies to investigate a full dose response for GB1211 & further understand the concentration/response relationship is on-going to investigate 0.3 mg/kg, 1 mg/kg, 5 mg/kg & 30 mg/kg dose levels.
- The rabbit HFD model has the potential to support clinical dose selection & rationale for GB1211 with further studies to understand rabbit ADME & PK parameters on-going to complete the translational data package.
- This data supports the current ongoing phase 2b study investigating GB1211 in liver cirrhosis patients **(NCT05009680 presented at AASLD in 2022 poster abstract 3627 & oral abstract 5014)**.

Results

Demonstration of HFD-induced disease phenotype

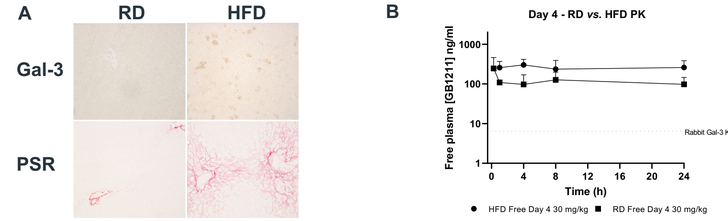
Figure 2. Liver weight (A), ALT (B) and AST (C) are increased from RD to HFD rabbits.



- Liver weight, ALT and AST VAT were all significantly increased from RD to HFD vehicle groups.

Results

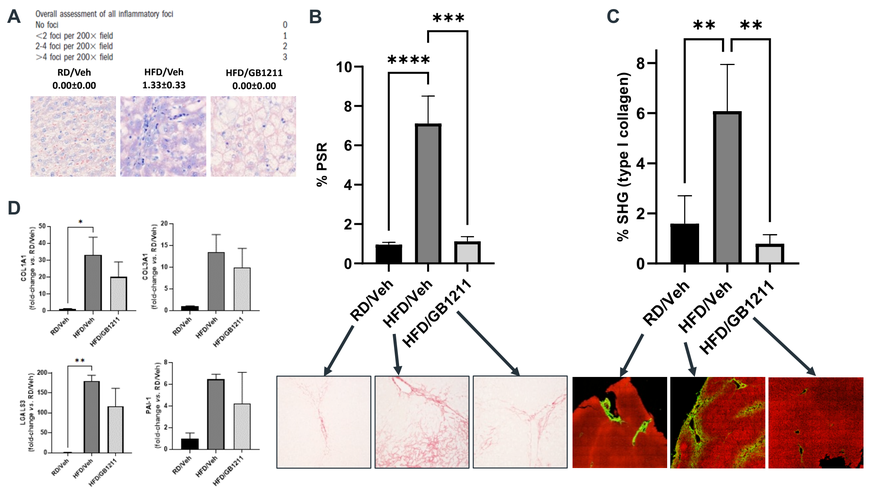
Figure 3. Galectin-3 & collagen deposition is increased from RD to HFD rabbits (A) with GB1211 demonstrates high exposure of free drug at 30 mg/kg in RD & HFD rabbits at steady state (B).



PK data

- Marginal increase in exposure following dosing in HFD compared with RD rabbits.
- GB1211 reached steady state free plasma concentrations at C_{min} of 40 x K_D when dosed once daily for 4 days.

Figure 4. GB1211 reduced inflammation (Giemsa inflammatory foci score[5]) (A) & fibrosis (B (PSR), C (SHG)) in HFD rabbits to levels observed in RD rabbits with trends for reduction in mRNA levels of pro-fibrotic mediators (D).



Efficacy data

- Inflammation score, steatosis (binomial score & % area oil red O), ballooning score & fibrosis (% PSR, SHG) were all significantly increased from RD to HFD vehicle groups.
- GB1211 significantly reduced all measures of inflammation & fibrosis compared with the HFD/vehicle group. There were also trends for reduction in fibrotic & Gal-3 mechanistic genes (COL1A1, COL3A1, SNAI2, LGALS3, PAI-1).
- The neoepitope collagen biomarker pro-C3 was detectable in rabbit plasma & elevated between RD & HFD, though no reduction in levels was observed with GB1211 over 5 days.

References

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