
# Characterisation of the novel galectin-3 inhibitor GB1107 in the $CCl_4$-induced liver fibrosis model in mice


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## 1 Introduction

Galectin-3 (Gal-3) is a pro-fibrotic β-galactoside binding lectin highly expressed in fibrotic liver (1) and implicated in hepatic fibrosis (2). GB1107 is a novel orally active anti-Gal-3 small molecule inhibitor that has high affinity for galectin-3 (27 nM) and >1000 fold selectively over other galectins and high oral bioavailability in mice (3).

## 2 Aim

The aim of this study was to evaluate the effect of GB1107 on $CCl_4$-induced liver fibrosis in mice.

## 3 Method

- Liver fibrosis was induced by administration of $CCl_4$ (1:3 $CCl_4$:olive oil) at 1μL per g or olive oil control twice weekly by intraperitoneal injection in male C57Bl/6 mice for 8 weeks.
- GB1107 or vehicle control (n=8) was administered once daily orally (10mg/kg) for the last 4 weeks of $CCl_4$ treatment.
- Fibrosis assessed by Sirius red staining of FFPE sections, second harmonic generation (2HG) and gene sequencing.
- Paired-end sequencing was performed on the NextSeq 2000 platform.
- Pathway enrichment analysis was performed to determine enrichment of differentially expressed genes (DEGs) within Reactome pathways and Gene Ontology (GO) terms.

## 4 Results

GB1107 significantly reduced plasma ALT and AST. There was a reduction in plasma galectin-3 and YKL-40. GB1107 reduced $CCl_4$-induced liver fibrosis as assessed by Sirius red ($CCl_4$-vehicle 2.70+0.24%; $CCl_4$-GB1107 1.99+0.10% (P=0.09)). In addition, stain-free SHG/TPEF microscopy (Genesis®200, HistoIndex, Singapore) showed a reduction in septal collagen in GB1107 treated $CCl_4$ mice (Figure 1).

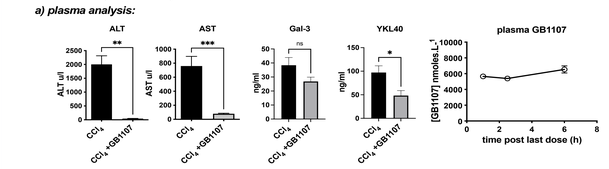
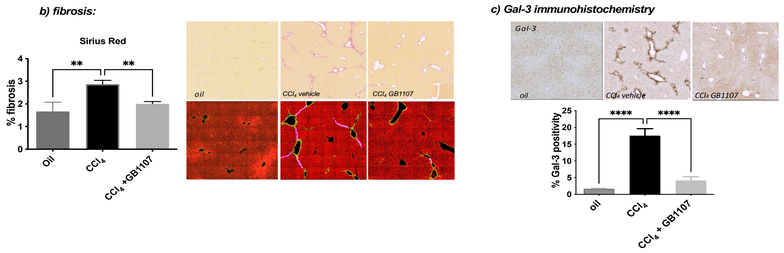



Figure 1. a) Plasma transaminases ALT and AST and galectin-3 and YKL-40 from $CCl_4$ mice treated for 4 weeks with GB1107 10mg/Kg *P.O.* QD. Data represented as mean ± SEM. Analysed via 1-way ANOVA (n = 8 , **P < .01). Images taken at x 200 magnification. c) Quantitation of Sirius red stained sections of liver tissue and images from unstained section analysed by SHG/TPEF microscopy (SHG in green, TPEF in red and detected septa in pink).




RNAseq analysis showed that 1,659 DEGs were identified with $CCl_4$ treatment compared to control. Comparing GB1107 treatment with $CCl_4$ vehicle mice 1147 DEGs were identified. Pathways strongly enriched in up-regulated genes in the $CCl_4$ group included those related to the extracellular matrix, and collagen biosynthesis and assembly, cell cycle and the immune system whilst pathways related to fatty acid or lipid metabolism were enriched in the down regulated genes. PCA analysis revealed that GB1107 overlapped significantly with the control group and effectively reversed the $CCl_4$ induced gene changes.

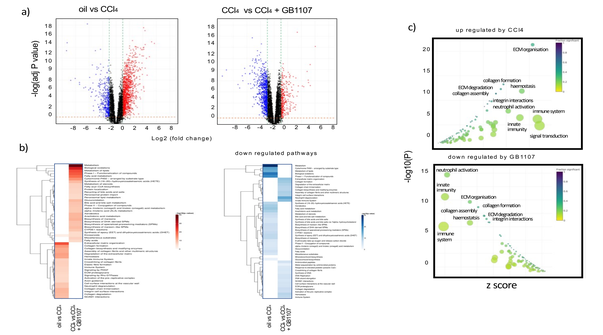



*Figure 2. a) Volcano plots for all comparisons, showing significance (as -log10 transformed p-values) against magnitude (log2(fold change)). Genes identified as significantly differentially expressed are represented as red (up-regulated) or blue (down-regulated). b) Heatmaps of significantly enriched Reactome pathways: Comparisons are shown on the X axis with Reactome pathways on the Y axis. Only Reactome pathways with an enrichment p-value less than 0.05, were included. Data represented as heat maps comparing up and down regulated genes. c) Pathway analysis represented by z stack showing pathways upregulated by $CCl_4$ and consequently down regulated by GB1107 treatment.*

## 5 Conclusions

- GB1107 inhibited $CCl_4$-induced fibrosis and reversed $CCl_4$-induced gene changes.
- Small molecular weight and orally active inhibitors of galectin-3 show promise as potential new oral anti-fibrotic agents for the treatment of liver fibrosis.
- A first-in-human study with the analogue GB1211 shows that it is both safe and well tolerated in man with PK that supports twice daily dosing. A phase IIb study is underway in liver cirrhosis patients (NCT05009680).

## 6 Acknowledgements


Sequencing analysis was by Fios. 2HG was carried out by Histoindex


## 7 References


1) Gudowska, M., et al., (2015). Ann. Clin. Lab. Sci., 45, 669-673.
2) Henderson, N. C., et al., (2006) Proc Natl Acad Sci U S A103, 5060-5065
3) Zetterberg et al., (2018) ChemMedChem 13, 133-137.


## 8 Contact information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**Inhibition of galectin-3 with the orally active-small molecular weight inhibitor GB1107 reduces liver fibrosis in mice, giving proof of concept for the development of this series of compounds for the treatment of liver fibrosis.**

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