Galectin-3 Targeting Drugs Inhibit Multiple Pathological Pathways Leading to Improvement of Non-Alcoholic Steatohepatitis (NASH)

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Introduction:

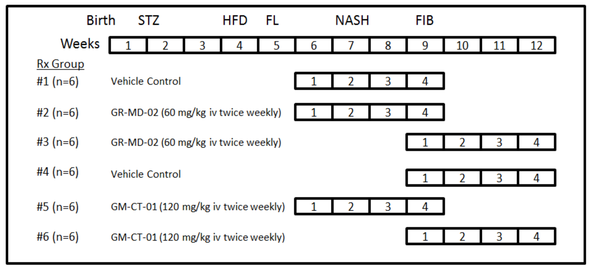
- Steatohepatitis, or NASH (non-alcoholic steatohepatitis), consists of fat accumulation, hepatocellular degeneration and necrosis, lobular inflammation, and fibrosis which can lead to cirrhosis.
- NASH affects up to 5% of the U.S. population and there is currently no accepted medical treatment for NASH or fibrosis.
- The galactose binding protein galectin-3 has been implicated in the pathogenesis of NASH.

Objective:

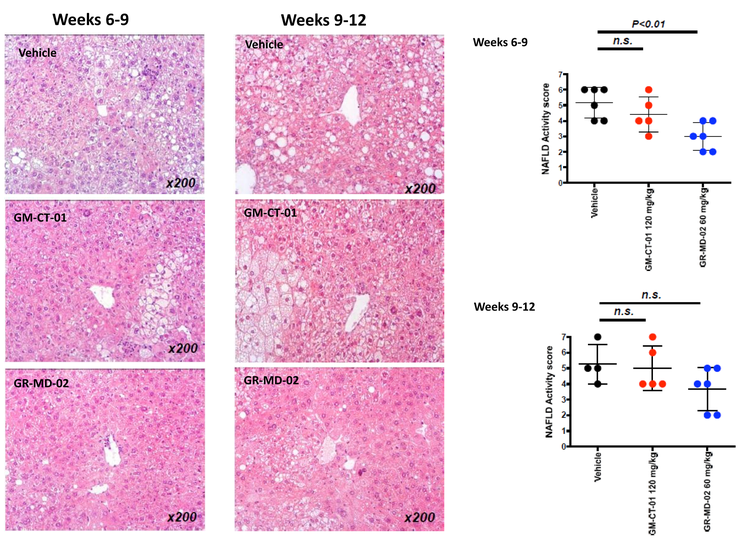
- To evaluate the efficacy and mechanism of novel complex carbohydrate drugs that inhibit galectin proteins in the treatment of NASH.

Methods:

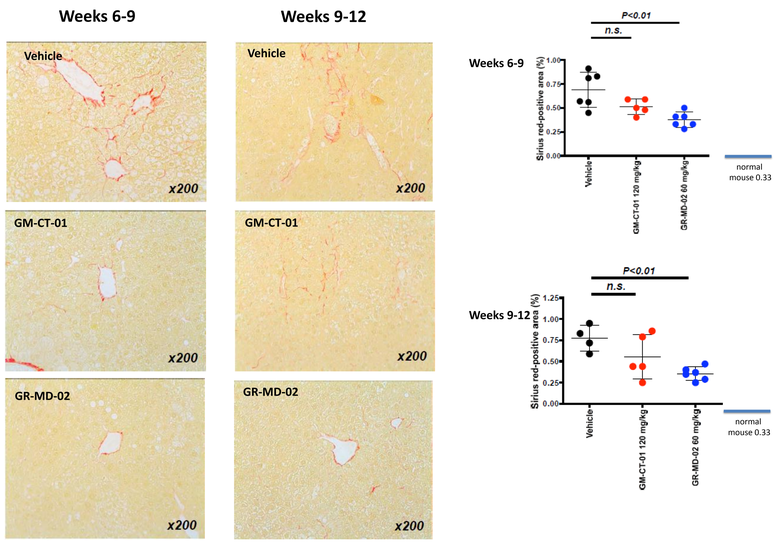
- NASH was induced in mice by making them diabetic and feed a high fat diet, which reproducibly caused steatohepatitis with fibrosis (Stelic Institute & Co., Tokyo, Japan).
- NASH mice were treated with either vehicle as a control or various concentrations of GM-CT-01 (galactomannan) or GR-MD-02 (arabinogalacto-rhamnogalacturonan), both of which bind galectin-3.

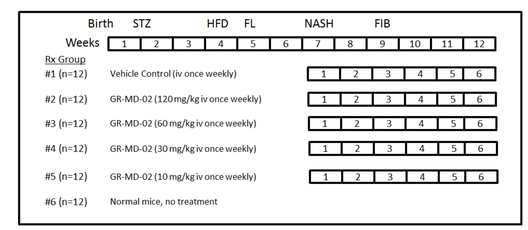


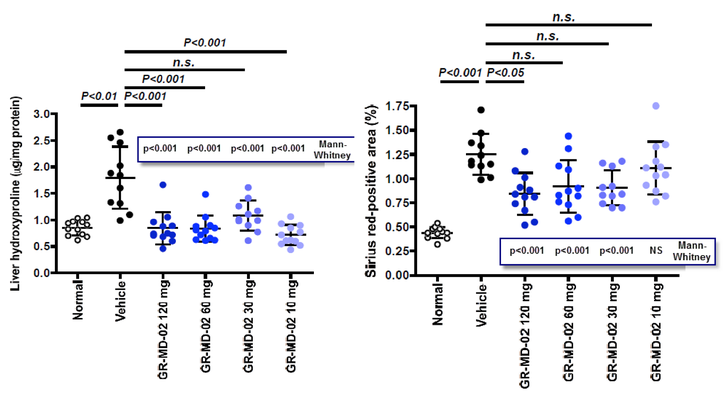
Treatment with GR-MD-02 markedly improved the NAFLD Activity Score (fat deposition, hepatocellular ballooning degeneration and necrosis, inflammatory infiltrate) in early and late treatment groups.



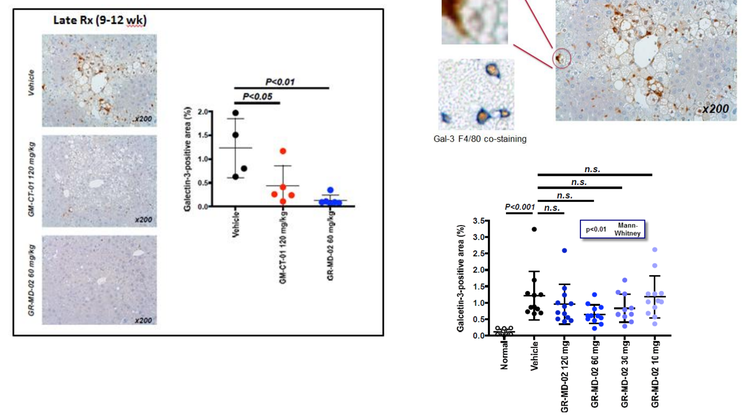
Collagen deposition was evaluated by digital morphometric analysis following Sirius Red staining. Treatment with GR-MD-02 reduced collagen deposition to normal levels whereas GM-CT-01 had a less marked effect.



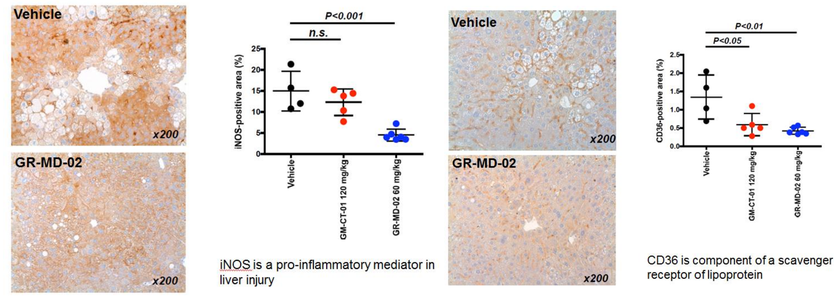




GR-MD-02 appears to reduce the number of galectin-3 expressing macrophages in NASH mice



GR-MD-02 markedly reduces expression of iNOS and CD36 in the livers of NASH mice



iNOS is a pro-inflammatory mediator in liver injury

CD36 is component of a scavenger receptor of lipoprotein

Conclusions:

- The model of NASH in mice developed robust histologic findings of NASH with fibrosis.
- Treatment with galectin inhibitors GM-CT-01 and GR-MD-02 had no effect on blood glucose levels, body weight, or general condition of the animals.
- Treatment with GR-MD-02 had approximately four fold greater effect on NASH pathology and fibrosis than GM-CT-01.
- GR-MD-02 ameliorated NASH pathology and reduced or eliminated fibrosis when administered as a single weekly dose in a relatively dose dependent fashion down to doses of 30 mg/kg.
- GR-MD-02 reduced the number of galectin-3 expressing macrophages in the liver while not reducing the absolute number of macrophages.
- GR-MD-02 markedly reduced hepatocellular expression of iNOS in NASH mice livers, a potent pro-inflammatory mediator.
- GR-MD-02 reduced the expression of CD36 which is a component of a scavenger receptor for lipoprotein.
- GR-MD-02 is an inhibitor of galectin-3 which is efficacious in a mouse model of NASH and appears to act through multiple pathways.