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.

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

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.