AN ORALLY ADMINISTERED SMALL MOLECULE THAT INHIBITS HEPATIC SULFATASE-2 EXPRESSION IN VIVO: A NOVEL STRATEGY TO CORRECT DIABETIC DYSLIPOPROTEINEMIA WITH IMPLICATIONS FOR RESIDUAL ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) RISK

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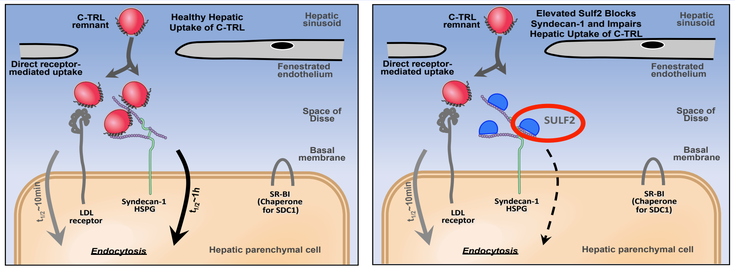
BACKGROUND



- Patients treated with optimal statin therapy and even PCSK9 inhibitors exhibit considerable residual risk for ASCVD events.[1, 2, 3]
- Residual ASCVD risk may occur, in part, because these medications only slightly lower plasma levels of cholesterol-(C) and triglyceride-(TG) rich remnant apoB-lipoproteins (C-TRLs).[4, 5, 6]
- The atherometabolic syndrome and type 2 diabetes (T2DM) increase plasma levels of C-TRLs, owing largely to a defect in hepatic clearance.[7]
- We identified syndecan-1 as a major receptor for uptake of C-TRLs by hepatocytes, [8, 9, 10] and syndecan-1 also functions in vivo.[11]
- We also showed that obesity and T2DM cause hepatic overexpression of sulfatase-2 (SULF2),[12, 13] and that SULF2 inhibits hepatic disposal of C-TRLs in *human* T2DM dyslipoproteinemia.[14]
- **Thus, SULF2 is a key target in ASCVD. Still, no small molecule has been identified that can normalize hepatic SULF2 expression in diabetes.**

HYPOTHESIS

- ***A novel small molecule, gemcabene, that lowers plasma apoB-lipoprotein concentrations in mice and in humans,*[15-22] *may regulate SULF2 in the liver.***

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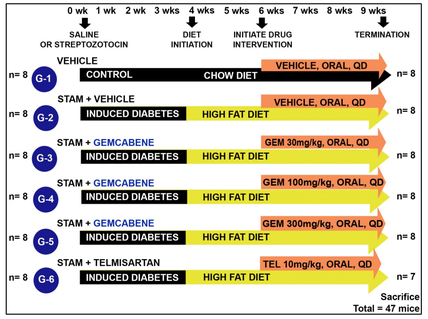
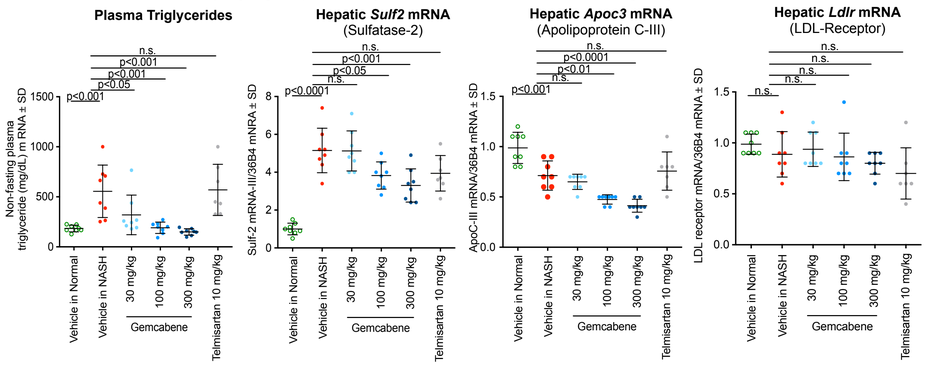
METHODS

STUDY DESIGN TO TEST GEMCABENE IN THE STAM™ MURINE MODEL OF DIABETES AND NASH

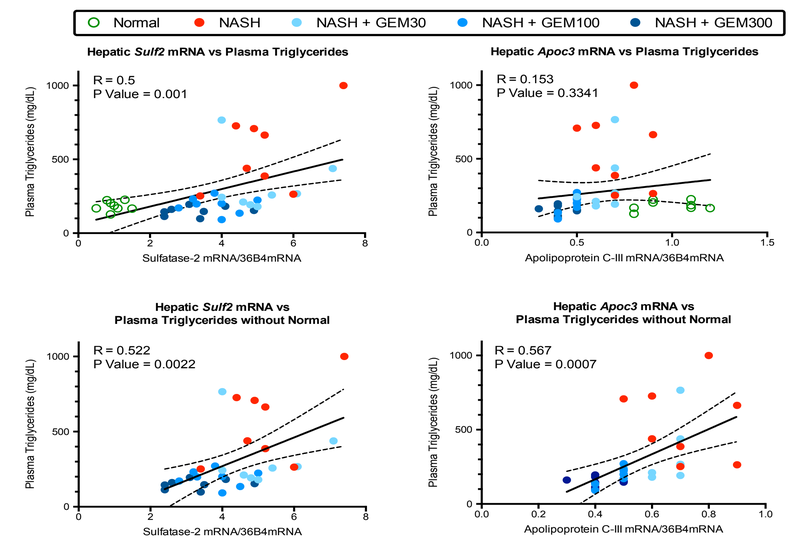


RESULTS

EFFECT OF GEMCABENE ON PLASMA AND LIVER MARKERS IN STAM™ MICE

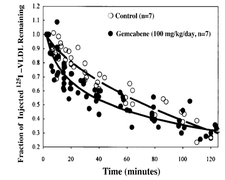


CORRELATIONS OF PLASMA TRIGLYCERIDES WITH HEPATIC *Sulf2* mRNA AND WITH HEPATIC APOLIPOPROTEIN C-III *(Apoc3)* mRNA IN A DIABETIC MOUSE MODEL TREATED WITH GEMCABENE

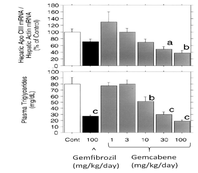


ADDITIONAL LDL RECEPTOR-INDEPENDENT EFFECTS OF GEMCABENE IN PRECLINICAL RODENT MODELS

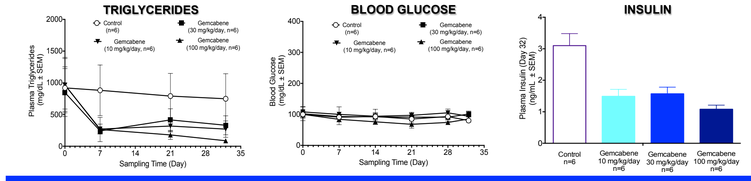
GEMCABENE ENHANCES VLDL CLEARANCE IN CHOW-FED MALE SPRAGUE-DAWLEY RATS



GEMCABENE CAUSES DOSE-DEPENDENT REDUCTIONS IN *Apoc3* mRNA AND PLASMA TG IN CHOW-FED MALE SPRAGUE-DAWLEY RATS

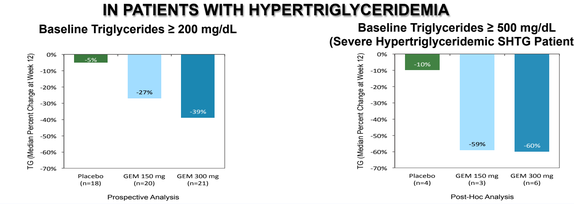


GEMCABENE LOWERS PLASMA TG AND IMPROVES INSULIN SENSITIVITY FOR HANDLING GLUCOSE IN FEMALE ZUCKER RATS



GEMCABENE LOWERS PLASMA TG LEVELS IN HUMANS

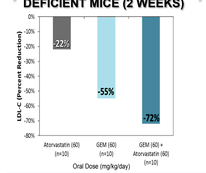
TRIGLYCERIDE MEDIAN PERCENT CHANGE FROM BASELINE AT WEEK 12 IN PATIENTS WITH HYPERTRIGLYCERIDEMIA



GEMCABENE IS EFFECTIVE IN HETEROZYGOUS AND HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

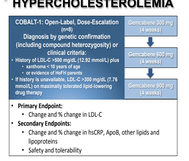
MICE

GEMCABENE REDUCES LDL-C IN LDL-RECEPTOR DEFICIENT MICE (2 WEEKS)

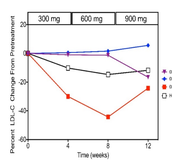


HUMANS

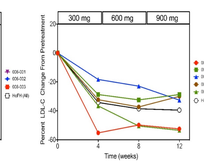
COBALT-1 TRIAL DESIGN: FAMILIAL HYPERCHOLESTEROLEMIA



COBALT-1 (HoFH PATIENTS) (LDL RECEPTOR DEFICIENT)



COBALT-1 (HeFH PATIENTS)



CONCLUSIONS

- **Induction of diabetes elevates hepatic *Sulf2* mRNA expression and plasma TGs.**
- **Treatment of diabetic mice with gemcabene lowers hepatic *Sulf2* and *Apoc3* mRNA levels.**
- **During gemcabene treatment, reductions in plasma TGs correlate with reduced hepatic *Sulf2* and *Apoc3* mRNA levels.**
- **Gemcabene may enhance clearance of C-TRLs in diabetic mice via suppression of hepatic SULF2, independent of *Ldlr* mRNA.**
- **These findings indicate unprecedented regulation of atherogenic remnant lipoproteins by a small molecule.**
- **Lowering plasma levels of C-TRLs may reduce residual risk for ASCVD events.**
- **Rescue of the remnant lipoprotein receptor by gemcabene, an inhibitor of *Sulf2* expression, is analogous to rescue of the LDL receptor by inhibition of PCSK9.**