Inhibition of HSD17B13 by the small molecule inhibitor, INI-822, increases liver phosphatidylcholines in a diet-dependent manner

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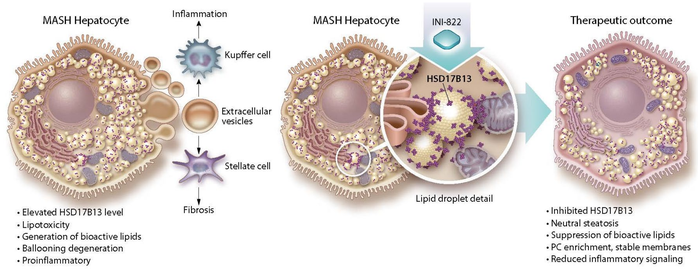
Introduction

Inactive alleles of HSD17B13 are associated with
- Decreased rates of NASH and cirrhosis[1]
- Decreased ballooning, inflammation and fibrosis[2]
- Increased hepatic phosphatidylcholine (PC) content[3,4]

HSD17B13 is a lipid droplet protein capable of oxidizing bioactive lipids[1]
HSD17B13 interacts with lipid metabolizing enzymes on the mitochondria and endoplasmic reticulum[5]
Suggesting a role for HSD17B13 in bioactive lipid flux mediating lipotoxicity



Background

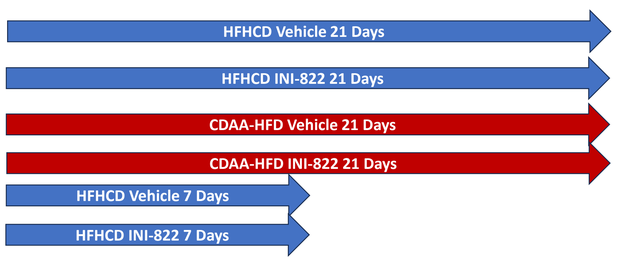
- INI-822 decreases fibrotic proteins in NASH-like Liver on a chip studies
- INI-822 has low clearance and good oral bioavailability in mice, rats and dogs.
- GLP-Toxicology and safety pharmacology complete and supportive of clinical development. Phase 1 studies with INI-822 are currently on-going (SAT-233)

INI-822 is potent and selective Well tolerated and stable	
B13 Ki 15-HETE (nM)	22.7
Selectivity of HSD17B2, B3, B11, B14 over HSD17B13	>100
Safety44/hERG	No significant off target
HepG2 and Hepatocyte cytotoxicity (µM)	>30
Rat clearance as % liver blood flow	<10%

Methods and Materials

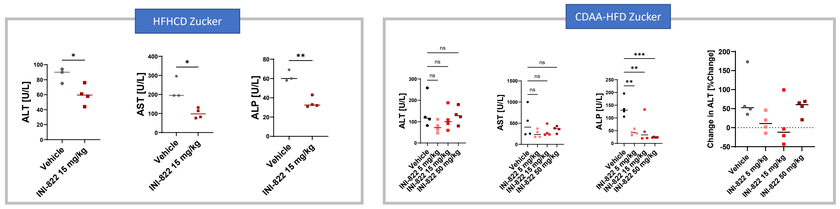
INI-822 was dosed orally once daily in obese Zucker rats on a normal chow (NC), high fat, high cholesterol atherogenic diet (HFHCD) and choline deficient, amino acid defined high fat diet (CDAA-HFD), n=4/group. Changes in liver transaminase levels, circulating and hepatic lipids (GC/MS, LC/MS) were measured. Statistical significance was evaluated by ANOVA followed by a Bonferroni multiple comparison test for liver transaminases, mean +/- SD. The lipidomics were evaluated by multiple unpaired t-tests with adjustment for a false discovery rate of <1%, significance reported for p<0.01.

Zucker Obese Rat Phenocopy



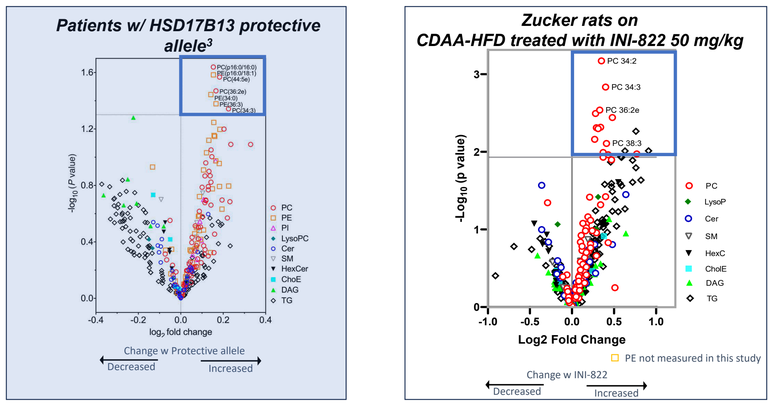
Results

Clinical Chemistry



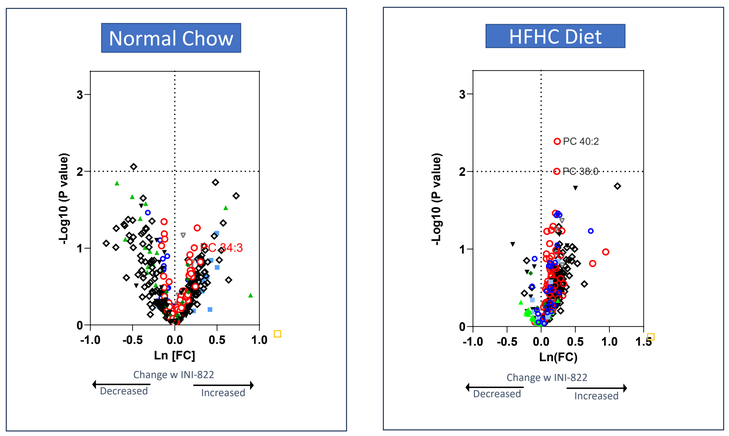
- INI-822 treatment is associated with lower ALT, AST and ALP in Zucker rats on the HFHCD
- INI-822 treatment is associated with lower ALP and a trend toward lower ALT, AST on the CDAA-HFD

Hepatic Lipids in Zucker Rats on CDAA-HFD



- INI-822 treatment in Zucker rats on CDAA-HFD leads to a shift in the hepatic lipids to increases in PCs
- Individual PCs that were previously observed to be elevated in Metabolic Syndrome patients who underwent bariatric surgery were observed to be elevated in the rats as well, including PC C34:3 and C36:2[3]

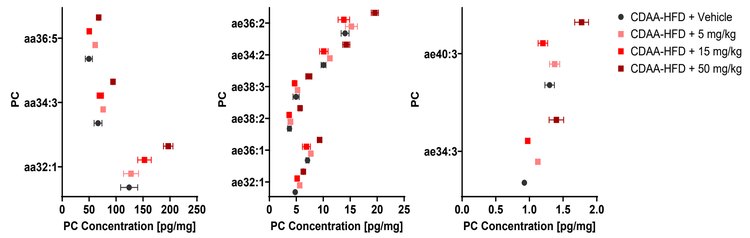
Hepatic Lipids in Zucker Rats on Different Diets



- INI-822 treatment in Zucker rats on a HFHCD show trends for increases in PCs
- Suggesting HSD17B13 inhibition compensates for the choline deficiency in the CDAA-HFD

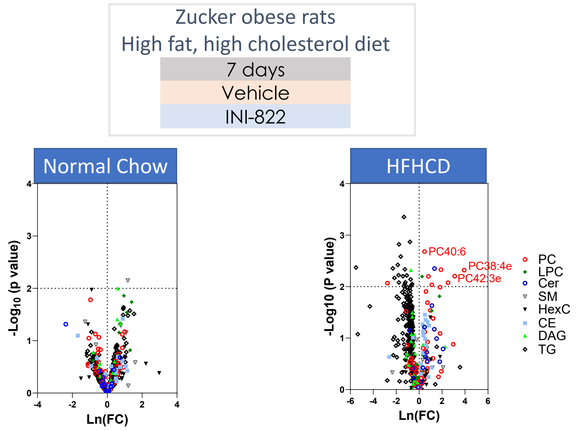
Results

Dose Dependent Increases in PCs



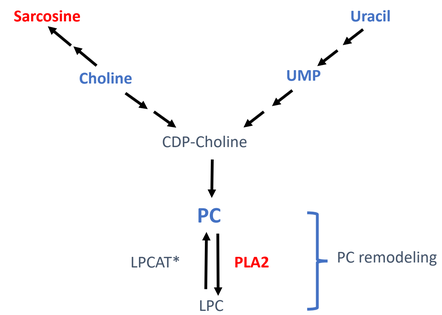
- INI-822 treatment leads to dose dependent increases in hepatic PCs

Plasma Lipidomics on Normal Chow or HFHCD with INI-822



- INI-822 treatment does not lead to changes in rats eating normal chow
- INI-822-treated rats eating a high fat, high cholesterol diet show decreases in plasma triglycerides and increase in PCs relative to vehicle

HSD17B13 Activity Impacts PCs



- Protective HSD17B13 increases hepatic and plasma PCs, specifically PUFA-PC[4]
- PCs are the building blocks of cell membranes and important for lipid droplet biogenesis[8]
- Hepatic PUFA-PCs are low in MASLD[4]
- Impaired PUFA-PC synthesis causes fatty liver in rodents[7]

Conclusion: HSD17B13 inhibition with INI-822 decreased liver transaminases and led to increased hepatic PC content in Zucker rats on metabolic diets. HSD17B13 inhibition led to lipidomic changes consistent with those found in patients with the loss-of-function protective allele.

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