Synergy of SOAT2-inhibitor PRD001 and resmetirom in reducing MASH and fibrosis in obese Ldlr-/-.Leiden mice

Eveline Gart[1], Kanji Hosoda[2], Martine C. Morrison[1], Anita M. van den Hoek[1], Hans M.G. Princen[1], Hiroshi Tomoda[2]

[1]Department of Biomedical Research, TNO, Leiden, the Netherlands; [2] PRD Therapeutics, Inc., Tokyo, Japan

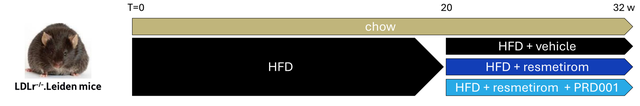
1. Introduction

MASH is characterized by hepatic lipid accumulation and inflammation. Sterol O-acyltransferase 2 (SOAT2), formerly known as ACAT2, plays a key role in intestinal absorption and hepatic secretion of cholesterol. PRD001 is a SOAT2 selective inhibitor under development by PRD Therapeutics, Inc., and is currently undergoing Phase 1 clinical trials targeting homozygous familial hypercholesterolemia. Inhibition of SOAT2 reduces cholesterol uptake, thereby limiting hepatic lipid accumulation and secretion. In this study, we investigated the combination of a SOAT2 inhibitor with resmetirom, an approved therapy for MASH, to assess not only effects on circulating lipids, but also potential complementary benefits on fatty liver disease through SOAT2 inhibition.

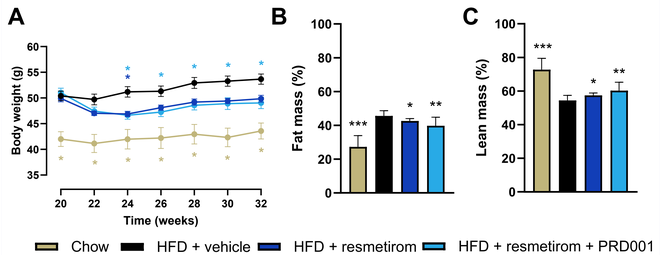
2. Study aim and design

This study aimed to assess the effects of the SOAT2 inhibitor PRD001 combined with resmetirom on obesity-associated dyslipidemia, MASH and liver fibrosis.

Ldlr-/-.Leiden mice were fed a high-fat diet (HFD) without added cholesterol for 20 weeks to induce obesity, dyslipidemia and early MASH. Subsequently they were treated with vehicle, resmetirom 3mg/kg, or resmetirom 3 mg/kg+ PRD001 30mg/kg for 12 weeks.

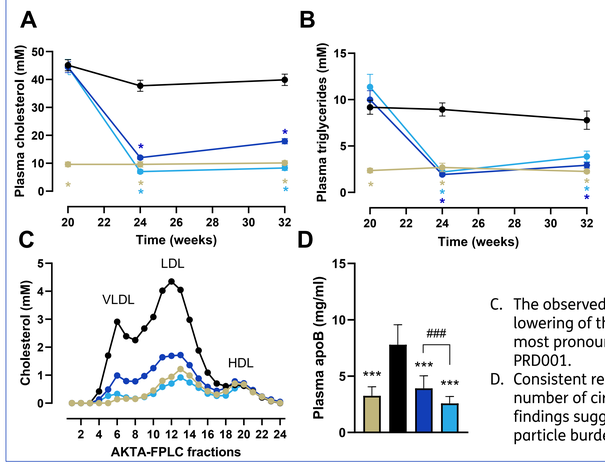


3. Resmetirom and PRD001 reduced body weight and fat mass while preserving lean mass



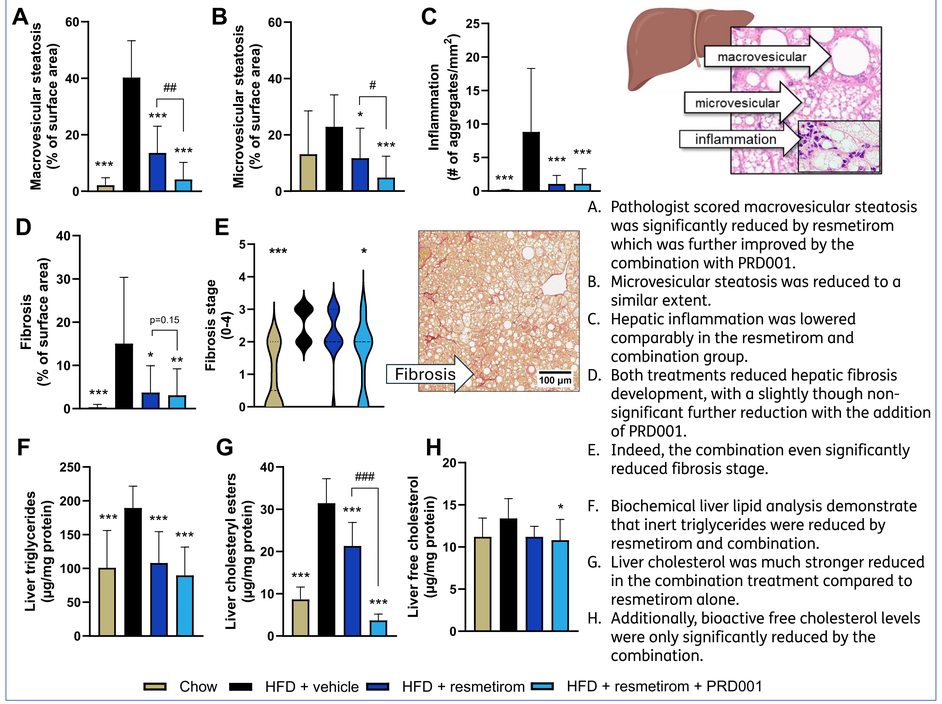
A. Resmetirom and combination of resmetirom+PRD001 lowered HFD-induced body weight to a comparable extent.
B. HFD-induced fat mass % was lowered with resmetirom and even more pronounced in the combination.
C. Interestingly, obesity associated lean mass % loss was attenuated by both treatments compared to HFD+vehicle, suggesting maintaince of lean mass.

4. Resmetirom lowered plasma lipids and apoB with a significant further reduction when combined with PRD001



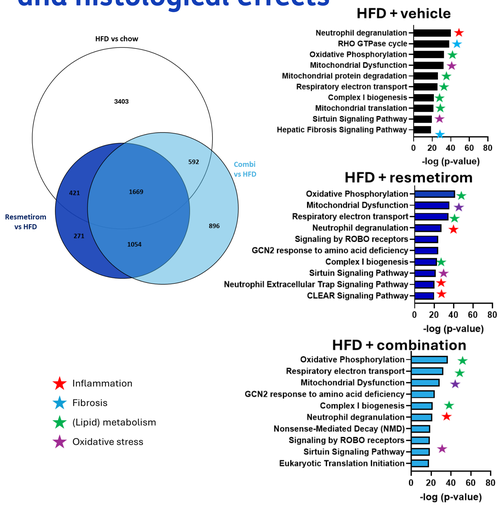
A. Resmetirom and the combination reduced HFD-induced dyslipidemia with significant reductions in plasma cholesterol.
B. Plasma triglycerides were reduced to a similar extent.
C. The observed reduction in cholesterol was attributable to lowering of the atherogenic (V)LDL particles, which was most pronounced when resmetirom was combined with PRD001.
D. Consistent reductions in ApoB100 indicate a lower number of circulating atherogenic (V)LDL particles, these findings suggest a meaningful reduction in atherogenic particle burden.

5. Complementary benefits of combining Resmetirom with PRD001 to reduce MASH and liver fibrosis



A. Pathologist scored macrovesicular steatosis was significantly reduced by resmetirom which was further improved by the combination with PRD001.
B. Microvesicular steatosis was reduced to a similar extent.
C. Hepatic inflammation was lowered comparably in the resmetirom and combination group.
D. Both treatments reduced hepatic fibrosis development, with a slightly though non-significant further reduction with the addition of PRD001.
E. Indeed, the combination even significantly reduced fibrosis stage.
F. Biochemical liver lipid analysis demonstrate that inert triglycerides were reduced by resmetirom and combination.
G. Liver cholesterol was much stronger reduced in the combination treatment compared to resmetirom alone.
H. Additionally, bioactive free cholesterol levels were only significantly reduced by the combination.

6. Hepatic gene expression analysis confirmed biochemical and histological effects



Inflammation

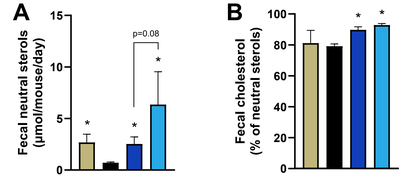
	HFD + vehicle vs chow		HFD+resmetirom vs HFD		HFD+resmetirom+PRD001 vs HFD	
Upstream regulator	Z-score	-logP	Z-score	-logP	Z-score	-logP
IL1B	7,2	35,6	-3,3	12,4	-1,4	10,3
TNF	10,2	56,5	-4,1	27,9	-0,8	21,3
IL6	4,7	29,2	-3,5	11,0	-2,0	9,2
IL13	3,9	24,4	-3,0	12,0	-3,2	7,9
IL15	3,7	20,6	-0,1	5,4	1,1	3,0
IL17A	4,3	8,8	-1,7	3,9	-0,8	2,0
IL33	5,9	32,1	-3,5	15,9	-0,6	6,5
IFNG	8,3	61,9	-5,7	30,9	-2,5	21,8
MIF	2,5	4,4	-0,5	1,4	N/A	0,0
OSM	5,2	14,3	-4,8	6,7	-3,2	6,5
NFKB1	5,3	10,1	-2,0	4,4	-1,7	2,0

Lipid metabolism

	HFD + vehicle vs chow		HFD+resmetirom vs HFD		HFD+resmetirom+PRD001 vs HFD	
Upstream regulator	Z-score	-logP	Z-score	-logP	Z-score	-logP
SOAT1	0,7	4,6	2,2	10,8	1,5	9,5
AMPK	-2,4	3,6	2,3	3,4	2,3	3,0
PPARGC1A	-7,1	32,8	5,4	15,5	4,5	16,8
ACOX1	-6,6	24,3	2,4	15,0	2,7	26,9
UCP1	-3,5	16,7	4,0	6,0	2,6	7,6
FGF21	-2,3	3,6	3,0	1,9	3,2	2,2
NRF1	-2,9	16,6	3,8	11,3	2,5	11,0
KEAP1	-0,6	2,6	1,5	1,6	1,9	2,2
SOD1	-2,9	14,2	1,4	4,1	0,0	3,2
SOD3	-2,8	2,4	2,0	0,3	2,2	0,4
CAT	-2,7	3,1	N/A	0,0	0,9	1,5
GPX1	0,0	4,3	2,2	1,7	2,0	0,9
HMGCR	0,0	2,1	N/A	0,0	N/A	0,0
ABCA1	0,0	1,7	-0,2	4,1	-1,5	3,1
CYP7A1	0,0	0,0	0,9	4,4	0,9	3,6

The Venn diagram demonstrates that more significant differentially expressed genes are observed when resmetirom was combined with PRD001. Subsequent pathways analysis confirmed involvement of (lipid)metabolism, inflammation pathways and mitochondrial pathways for the observed beneficial effects on MASH and liver fibrosis. A selection of upstream regulators are shown in the table in the inflammation and lipid metabolism pathways.

7. Fecal neutral sterol excretion is increased by resmetirom and this effect tended to be further enhanced with PRD001



A. Fecal neutral sterol excretion was increased by resmetirom and tended to be further increased in combination with PRD001.
B. The observed increase in fecal neutral sterol excretion was largely attributable to increased excretion of cholesterol in both groups.

8. Conclusion

Using a translational obesity-associated MASH model, we demonstrate resmetirom improves MASH and hepatic fibrosis. Adding PRD001 provides further benefits, including enhanced cholesterol excretion, reductions in plasma lipids and lipoproteins, and additional improvements in steatosis and fibrosis stage, highlighting the complementary mechanisms of PRD001 and resmetirom. These findings indicate that patients with more advanced MASH may still benefit from combination therapy aimed at augmenting anti-fibrotic efficacy. Together, the combined effects of resmetirom and PRD001 provide added therapeutic benefit and support further clinical evaluation of this combination for the treatment of MASH and liver fibrosis.

Contact | eveline.gart@tno.nl | hosodak@prdtherapeutics.com