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Oral treatment with a novel first-in-class anti-fibrotic compound PBI-4050 reduces hepatic steatosis and improves kidney function in the diabetic db/db mouse model

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BACKGROUND

Type 2 diabetes is strongly associated with nonalcoholic steatohepatitis (NASH). Also, severity of NASH histology (i.e., fibrosis stage) is associated with decreased kidney function. Obese and diabetic db/db mice develop hepatic steatosis, and exhibit a consistent and robust increase in albuminuria and mesangial matrix expansion in the kidney. PBI-4050, a potential first-in-class treatment for fibrotic diseases, possesses a pleiotropic mechanism of action with anti-inflammatory, anti-oxidant and anti-fibrotic properties. The aim of this study was to investigate the effect of PBI-4050 on hepatic steatosis and on inflammatory/fibrotic markers in liver and kidney of uninephrectomized (NX) diabetic (db/db) mice.

STUDY DESIGN

C57BL/6 mice and db/db mice male, 6-week old

RANDOMIZATION	ORAL TREATMENT PBI-4050 Day 1-130 1x/day 100 mg/kg

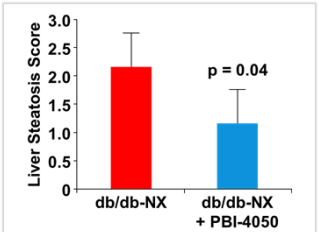
- DAY -1: Randomization based on starved blood glucose level
- DAY 0: Total nephrectomy right kidney (NX)
- DAY 97: GFR test (FITC-inulin)
- DAY 131: Sacrifice, histology

Six-week old db/db or C57BL/6 mice were subjected to uninephrectomy (NX) or sham operations. Sham operated mice underwent exposition of the kidney and removal of the perirenal fat. NX animals were treated by gastric gavage with vehicle or PBI-4050 administered once daily at 100 mg/kg. Animals were treated from day 1 to 130. Renal functions were evaluated by measurement of proteinuria, albuminuria and glomerular filtration rate (GFR). On day 131, animals were sacrificed. Kidney and liver were removed for histological lesion score.

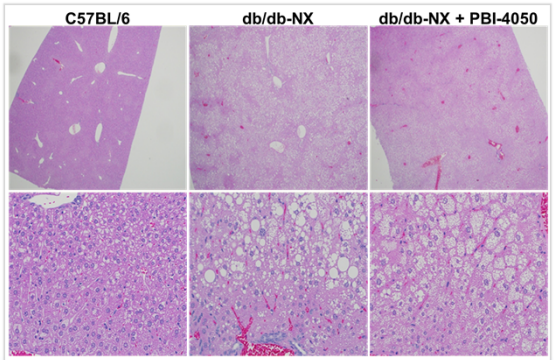
RESULTS

❖ PBI-4050 REDUCES HEPATIC STEATOSIS

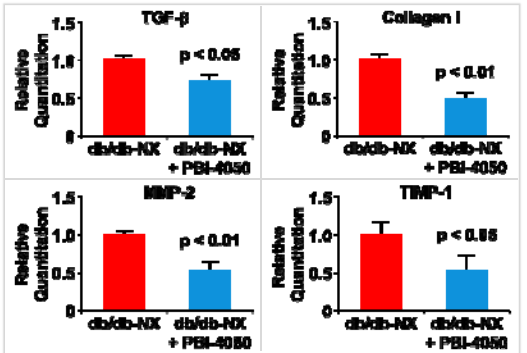
Treatment with PBI-4050 reduced lesions and liver steatosis (fat deposition, clear cells). Furthermore, qPCR analysis of NX-db/db mice indicated that PBI-4050 treatment resulted in a significant reduction of the expression of TGF-β1, collagen I, TIMP-1 and MMP-2 in liver tissue



PBI-4050 significantly decreases liver steatosis.



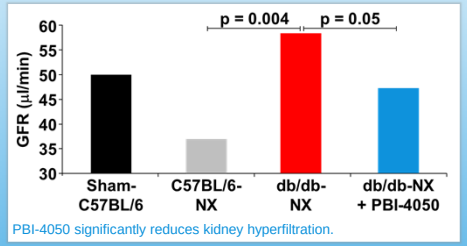
Photomicrographs of liver tissue: PBI-4050 significantly reduces liver steatosis.



Real-Time PCR using Mouse TaqMan® Gene Expression Assays.

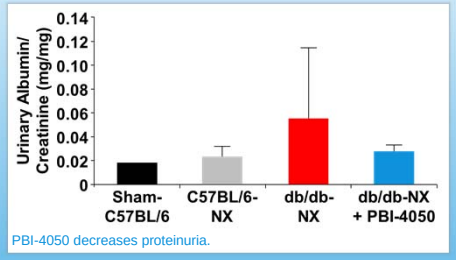
❖ PBI-4050 IMPROVES KIDNEY FUNCTION

GFR was measured by inulin clearance. Kidney GFR was significantly reduced in NX-C57BL/6 mice. NX-db/db mice demonstrated a significant increase in GFR (hyperfiltration), which was significantly reduced by treatment with PBI-4050.



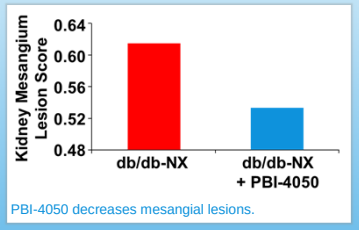
PBI-4050 significantly reduces kidney hyperfiltration.

Proteinuria was also increased by 3 fold in NX-db/db mice compared to sham C57BL/6 mice. Treatment with PBI-4050 reduced proteinuria to the sham C57BL/6 mice level.



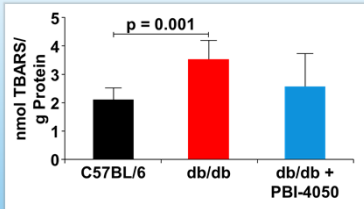
PBI-4050 decreases proteinuria.

db/db-NX mice had larger glomeruli with increased mesangial matrix as shown by periodic acid-Schiff (PAS) staining. Mesangium lesion scores were reduced in db/db mice treated with PBI-4050.



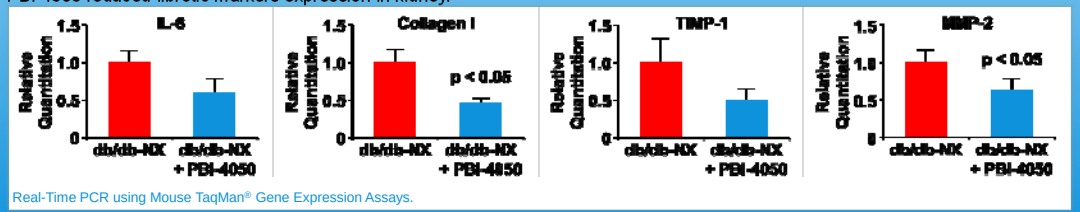
PBI-4050 decreases mesangial lesions.

PBI-4050 reduced lipid peroxidation in kidney.



Lipid peroxidation (TBARS) in kidney is increased in NX-db/db mice and is reverted to the control level by treatment with PBI-4050.

PBI-4050 reduced fibrotic markers expression in kidney.



Real-Time PCR using Mouse TaqMan® Gene Expression Assays.

CONCLUSION

These results suggest that PBI-4050 offers the potential as a novel therapy for the treatment of liver steatosis and diabetic nephropathy.

PBI-4050 effects in the uninephrectomized-db/db mouse model:

- ↓ Liver steatosis
- ↓ Expression of fibrosis markers in liver and kidney
- ↓ Kidney hyperfiltration
- ↓ Proteinuria
- ↓ Kidney and liver lesions