Oral Treatment with a Novel First-in-class Anti-fibrotic Compound PBI-Compound Delays Tubulo-interstitial Fibrosis in Unilateral Ureteral Obstruction Model

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#SA147

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Introduction and Aim

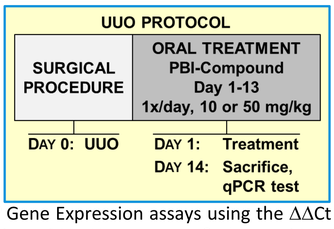
Tubulointerstitial fibrosis is the final common result of a variety of progressive injuries leading to chronic renal failure. Unilateral Ureteral Obstruction (UUO) is a well-established experimental model of renal injury leading to interstitial fibrosis.

Recently, we discovered a novel, first-in-class, orally active low molecular weight compound which displays anti-inflammatory and anti-fibrotic activities via a new mechanism of action.

The aim of this study was to investigate the effect of PBI-Compound on the UUO rat model of kidney interstitial fibrosis.

Methods

UUO rat model: Sprague-Dawley rats were used at 6-8 weeks of age and 200-250 g in body weight. On day 0, an incision was made in the left side of the back, and the left proximal ureter was exposed and triple-ligated (n=7-8 rats per group). Sham-operated rats (n=4) had their ureter exposed but not ligated.



qPCR: RNA was isolated from rat whole kidney using TRIzol® reagent and cDNA was prepared. qPCR analysis of relative gene expression was performed with TaqMan® Gene Expression assays using the ΔΔCt method. mRNA expression levels were normalized against GAPDH or mean β-glucoronidase (GUSB)/lactate dehydrogenase (LDHA) endogenous control levels in each sample and calculated relative to control UUO rats.

Results

Serum albumin loss was used as an indication of kidney injury. UUO induced a significant decrease of serum albumin which was prevented by oral administration of PBI-Compound.

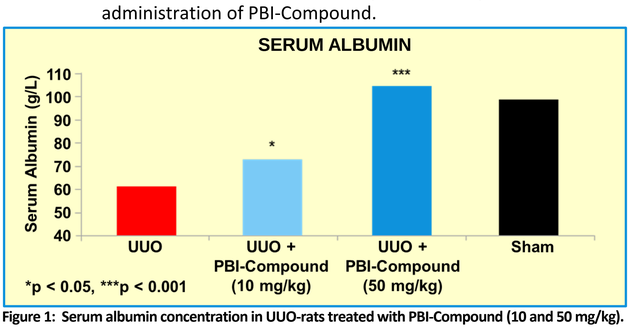


Figure 1: Serum albumin concentration in UUO-rats treated with PBI-Compound (10 and 50 mg/kg).

Kidney Monocyte Chemoattractant Protein 1 (MCP-1) protein level is markedly increased in the ligated kidney which is indicative of inflammation. Kidney MCP-1 is significantly reduced with 50 mg/kg treatment of PBI-Compound in UUO rats.

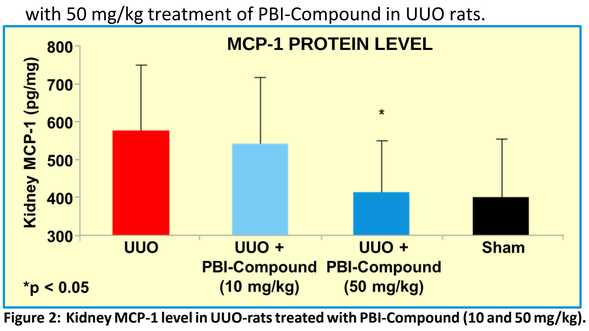


Figure 2: Kidney MCP-1 level in UUO-rats treated with PBI-Compound (10 and 50 mg/kg).

mRNA Expression

Further analysis of the renal tissue revealed that oral treatment of PBI-Compound reduced TGF-β1 expression in the kidney.

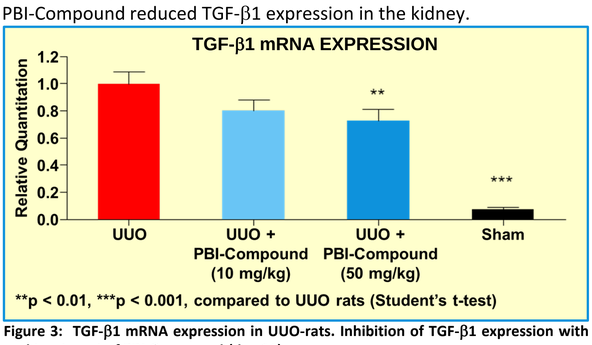


Figure 3: TGF-β1 mRNA expression in UUO-rats. Inhibition of TGF-β1 expression with oral treatment of PBI-Compound (day 14).

A significant dose-response inhibition of the expression of the major mediator of fibrosis Connective Tissue Growth Factor (CTGF) is also observed in the kidney of animals treated with PBI-Compound.

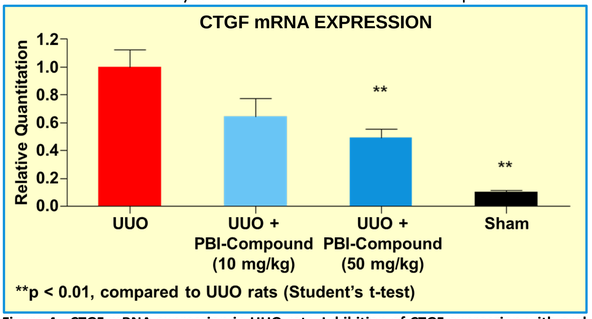


Figure 4: CTGF mRNA expression in UUO-rats. Inhibition of CTGF expression with oral treatment of PBI-Compound (day 14).

A significant dose-response inhibition of the expression of collagen I is also observed in animals treated with PBI-Compound.

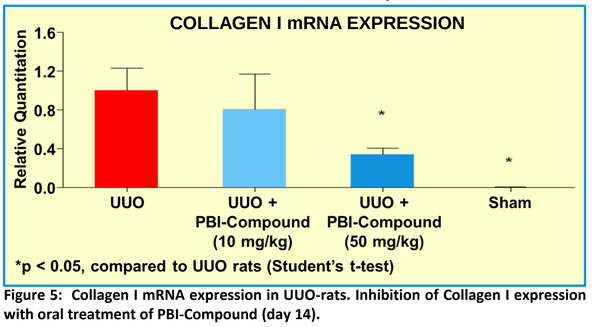


Figure 5: Collagen I mRNA expression in UUO-rats. Inhibition of Collagen I expression with oral treatment of PBI-Compound (day 14).

Other markers of fibrosis and extracellular matrix remodeling were assessed. The accumulation of extracellular matrix proteins (ECM) is a common feature of fibrotic kidney disease.

Secreted-protein acidic rich cysteine (SPARC) is a mediator of collagen deposition and promotes fibrosis. Matrix metalloproteinase 2 (MMP2) and Tenascin C (TNC) are ECM proteins which are implicated in extracellular matrix remodeling.

A significant reduction in SPARC, MMP2 and TNC expression in kidneys is observed in PBI-Compound-treated rat.

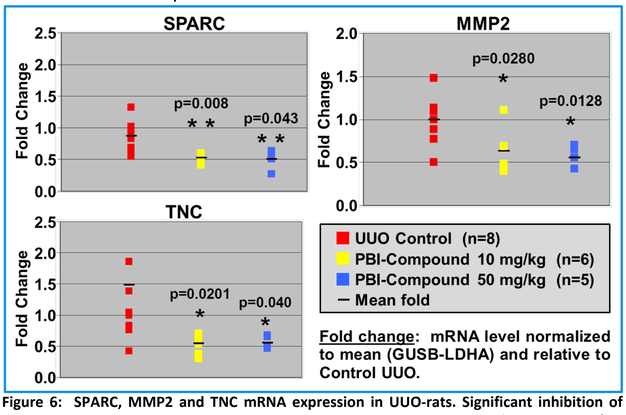


Figure 6: SPARC, MMP2 and TNC mRNA expression in UUO-rats. Significant inhibition of SPARC, MMP2 and TNC expression with oral treatment of PBI-Compound (10 and 50 mg/kg, day 14).

In UUO, the obstructed kidney displays fibronectin overexpression which is also observed in myofibroblastic transdifferentiation from tubular epithelial cells (EMT), *in vitro*. Fibronectin 1 (FN1) expression is significantly reduced in PBI-Compound-treated rats.

Bone morphogenetic protein 7 (BMP7) is a morphogen that is important for kidney development and which is also an integral part of the kidney's physiological response to repair acute kidney injury. Interestingly, BMP7 kidney expression is significantly increased in PBI-Compound-treated animals.

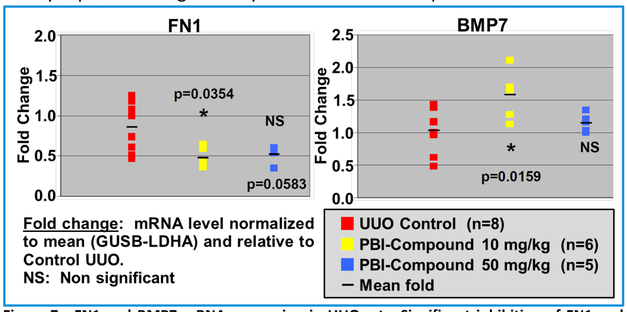


Figure 7: FN1 and BMP7 mRNA expression in UUO-rats. Significant inhibition of FN1 and restoration of BMP7 expression with oral treatment of PBI-Compound (10 mg/kg, day 14).

Conclusions

These results suggest that PBI-Compound offers the potential as a novel therapy for the prevention or reduction of fibrosis in acute kidney diseases.

Reduction of inflammation (↓MCP-1)

Reduction of fibrosis and remodelling (↓TGF-β, CTGF, collagen I, SPARC, TNC, MMP2, FN1 and ↑BMP7)