

Nephroprotection: PBI-4050, a Novel Orally Active, Anti-inflammatory/Antifibrotic Agent, Reduces Doxorubicin-induced Nephrotoxicity in Mice

Abstract
#24739

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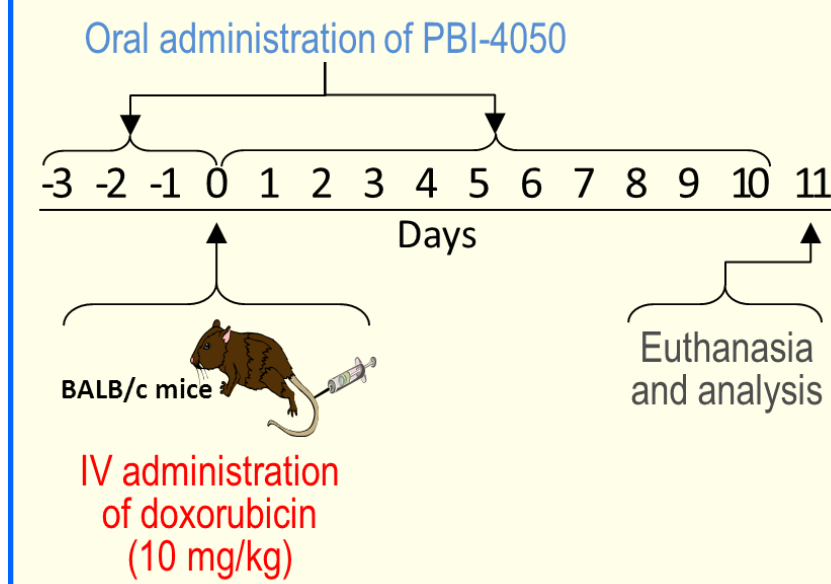
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Rationale

PBI-4050 is a novel, first-in-class, orally active low molecular weight compound which displays antifibrotic activity via inhibition of connective tissue growth factor (CTGF) expression and production. The clinical use of doxorubicin (Dox), a potent anticancer agent, is associated with marked nephrotoxicity characterized by tubulointerstitial lesions. Dox-induced nephrotoxicity is a model of acute kidney injury. The aim of this study is to investigate antifibrotic activity of PBI-4050 on Dox-induced nephrotoxicity in mice.

Study Design

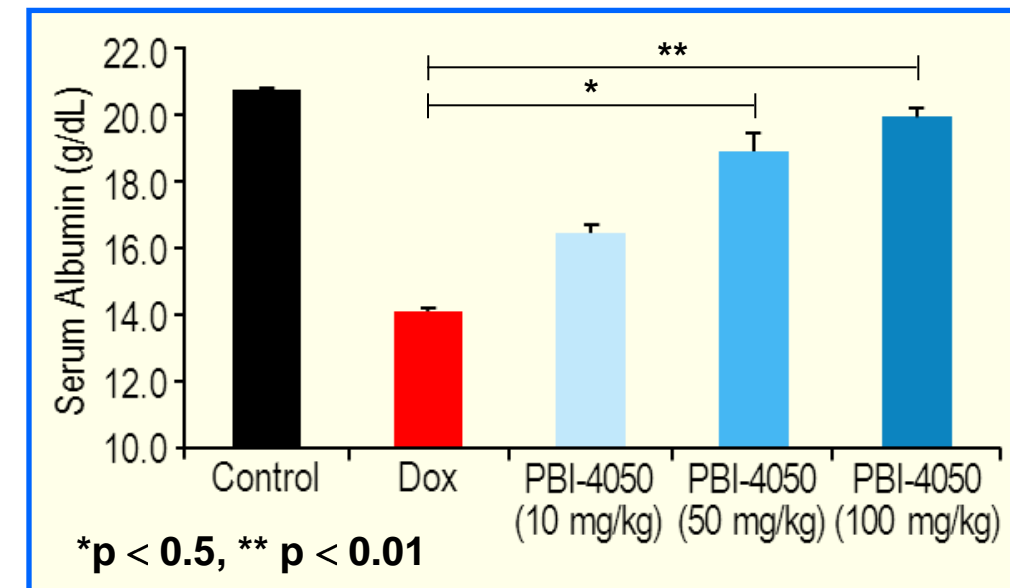
Study Design: (n=5 per group)



Nephrotoxicity was induced in BALB/c mice by an intravenous injection of 10 mg/kg of Dox on day 0. Mice were treated with PBI-4050 (10-200 mg/kg, oral, once daily) from day -3 to -1 and day 1 to 10. On day 11, animals were sacrificed. Albumin and CTGF levels were quantified in serum of the animals, and kidneys were removed for histological examination and profibrotic cytokines gene expression quantitation.

A. PBI-4050 reduces serum albumin loss induced by doxorubicin

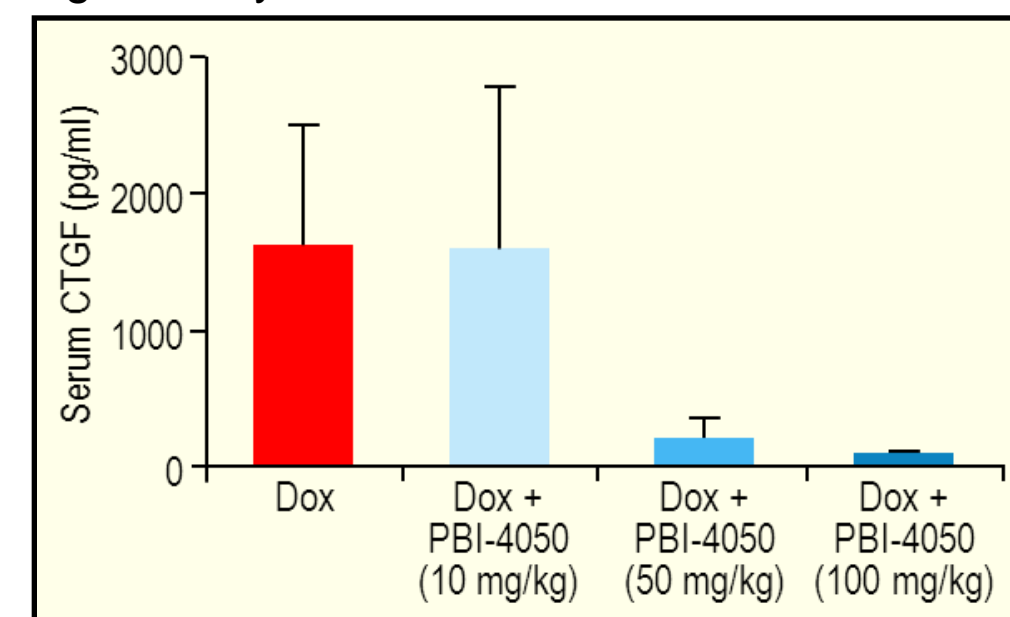
Serum albumin loss has been used as an indication of kidney injury. Doxorubicin (Dox) administration induced a significant decrease in serum albumin, while oral administration of PBI-4050 prevented this loss in a dose dependent manner.



PBI-4050 significantly reduces serum albumin loss induced by Dox.

B. PBI-4050 significantly reduces serum CTGF induced by doxorubicin

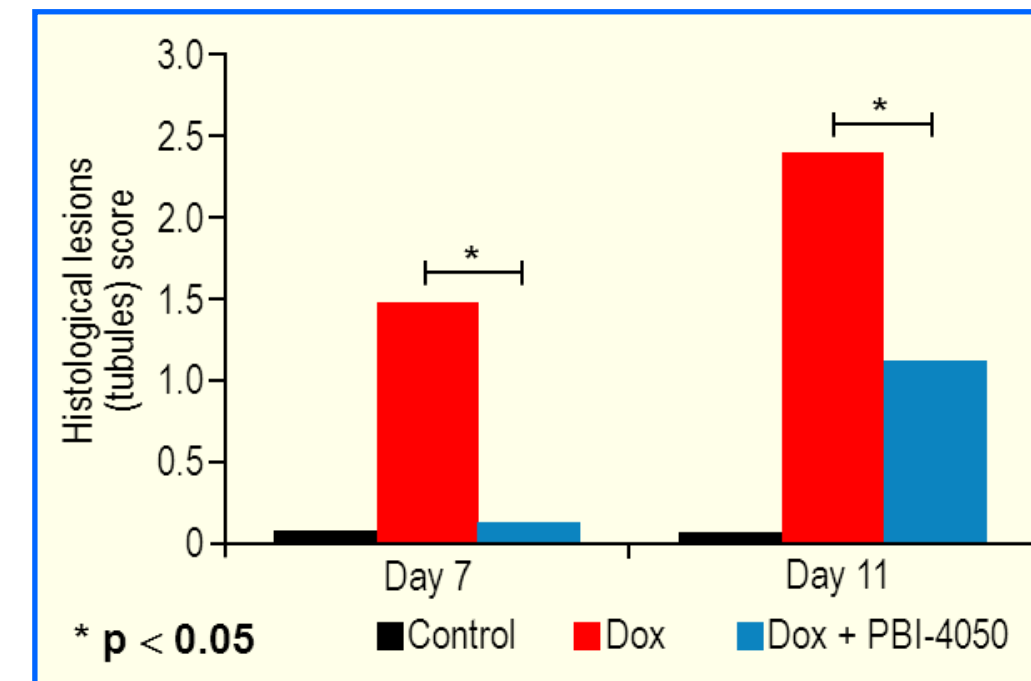
Connective tissue growth factor (CTGF), a profibrotic cytokine, has been used to assess the development of fibrosis in a number of diseases. Dox administration enhanced serum CTGF while oral administration of PBI-4050 significantly reduced serum CTGF.



PBI-4050 significantly reduces serum CTGF induced by Dox.

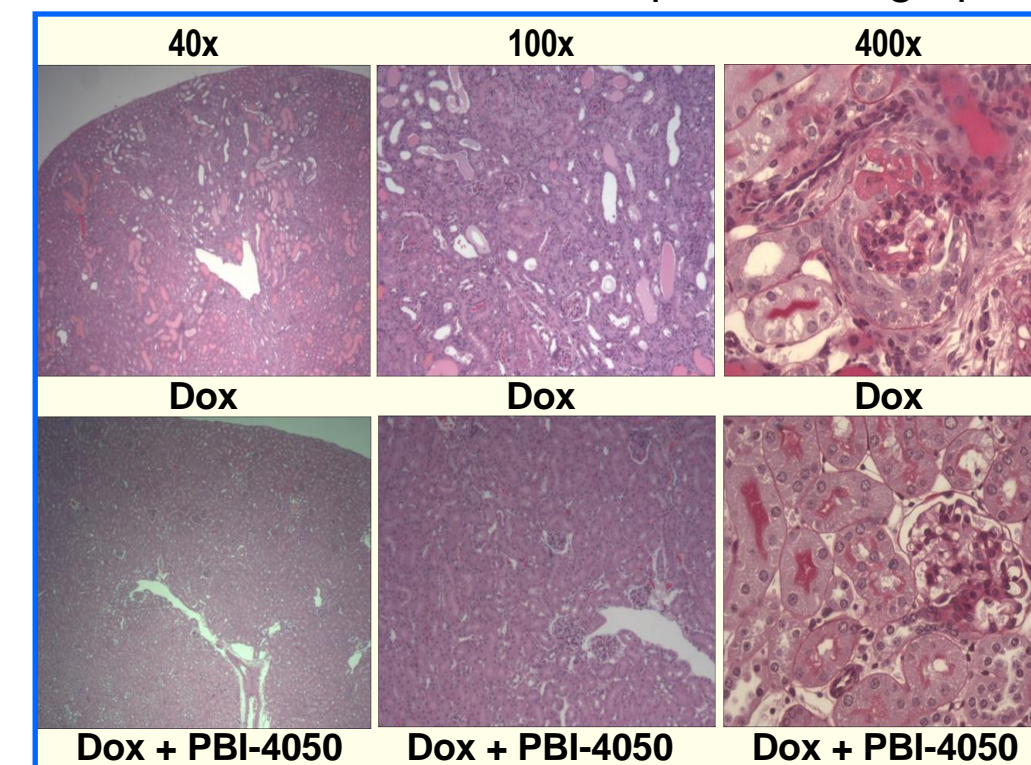
C. PBI-4050 reduces kidney lesions induced by doxorubicin

Histological examination of the kidneys revealed that Dox induced severe lesions on day 11. Lesions consist of fibrosis, necrosis, sclerosis and accumulation of proteins in affected tubular regions. Treatment with PBI-4050 (200 mg/kg) significantly reduced the lesion scores.



Histological lesions score at the tubular level. PBI-4050 significantly reduces kidney lesions.

Treatment with PBI-4050 reduced tubule distention, fluid accumulation and necrosis in renal tissue, as shown in the photomicrographs.

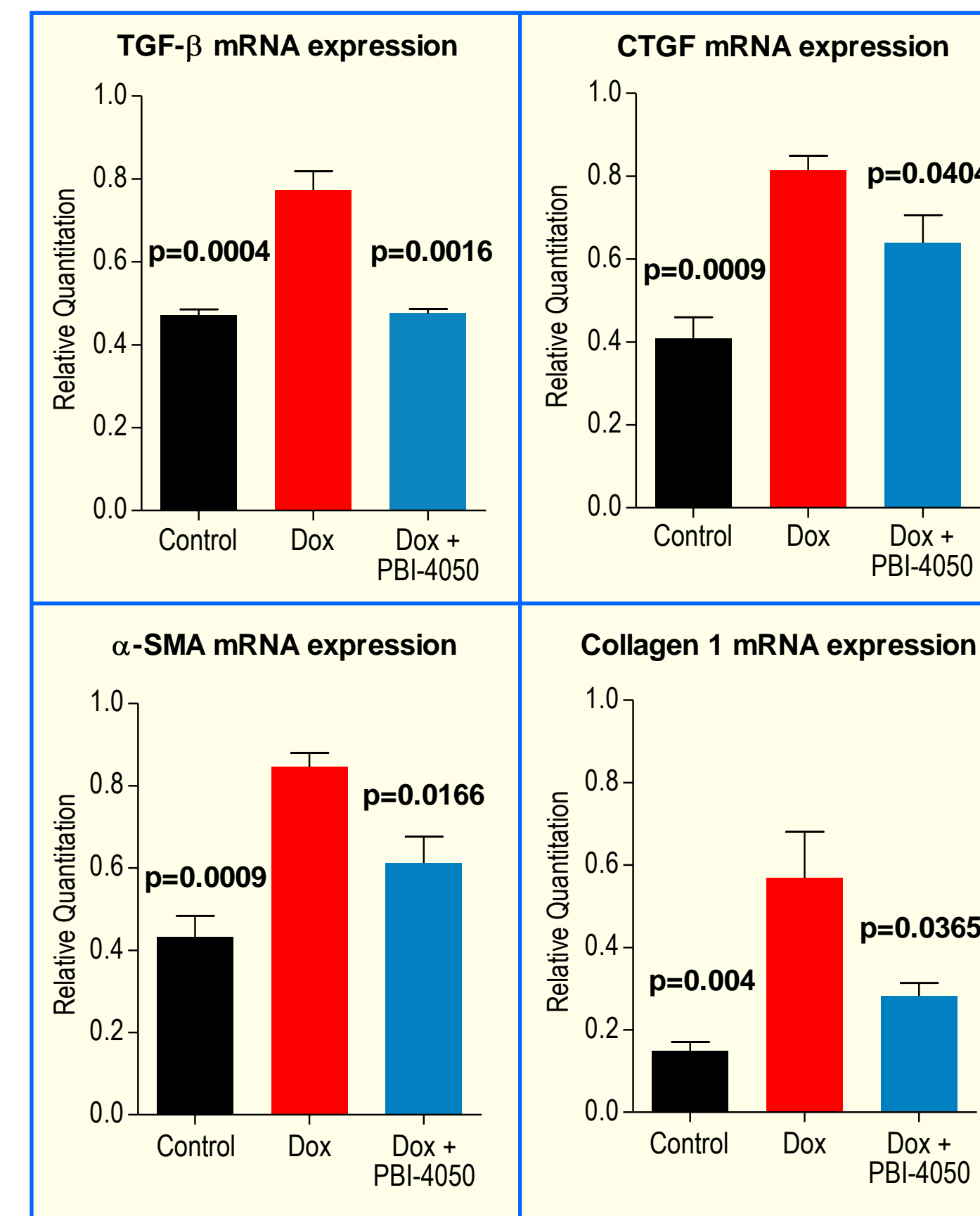


Photomicrographs of renal tissue. PBI-4050 significantly reduces Dox-induced kidney lesions.

Results

D. PBI-4050 downregulates, TGF-β, CTGF, α-SMA and collagen 1 mRNA expression

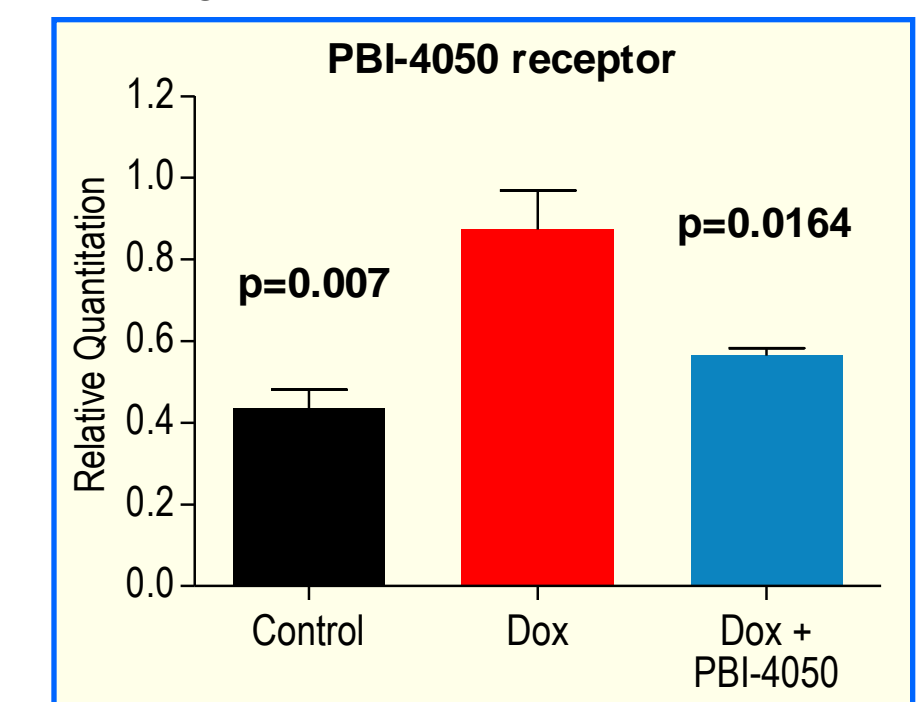
Dox induces mRNA expression of the profibrotic cytokines transforming growth factor-β (TGF-β) and CTGF as well as the myofibroblast marker α-smooth muscle actin (α-SMA), and collagen 1 (quantified by real-time PCR in renal tissue using TaqMan® Gene Expression assays). Oral administration of PBI-4050 (200 mg/kg) significantly decreased the expression of these markers.



Treatment with PBI-4050 induces a significant reduction of TGF-β, CTGF, α-SMA and collagen 1 mRNA expression in kidneys of Dox-treated mice.

E. PBI-4050 receptor is upregulated under inflammatory conditions

Administration of Dox results in a significant increase of the mRNA expression of the PBI-4050 receptor in the kidney. Receptor expression was reduced with PBI-4050 treatment (200 mg/kg). This indicates that the PBI-4050 receptor is highly expressed during inflammation and corroborates our *in vitro* data obtained under inflammatory conditions in macrophage, fibroblast, and mesangial cells (data not shown).



PBI-4050 receptor expression is upregulated under inflammatory conditions.

Conclusion

Our results show that:

- ❖ PBI-4050 has a protective effect against Dox-induced kidney damage.
- ❖ PBI-4050 nephroprotective effect relies in part on its ability to reduce CTGF and TGF-β and hence fibrosis.
- ❖ PBI-4050 appears to inhibit fibrocyte differentiation into myofibroblasts as shown by a reduction in the myofibroblast marker α-SMA.