#SA153

PBI-Compound, a Novel Orally Active Anti-Inflammatory/Anti-Fibrotic Agent, Reduces Fibrosis in Acute and Chronic Kidney Disease Models

Lyne Gagnon, François Sarra-Bournet, Brigitte Grouix, Kathy Hince, André Doucet, Liette Gervais, Martin Leduc, Alexandra Felton, Jean-Simon Duceppe, Shaun Abbott, Boulos Zacharie, Christopher Penney and Pierre Laurin

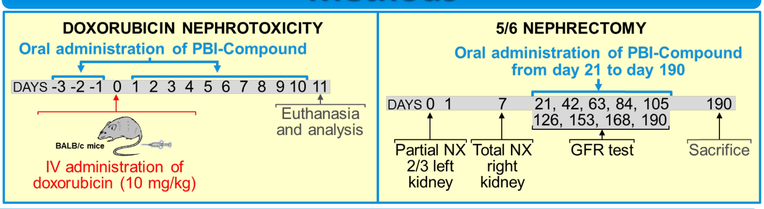
ProMetic BioSciences Inc., Laval, Québec, Canada

ProMetic

Introduction and Aim

PBI-Compound is a novel first-in-class, orally active low molecular weight compound which displays anti-inflammatory/anti-fibrotic activities via a novel mechanism of action. The aim of this study is to investigate the effect of PBI-Compound on an acute doxorubicin-induced nephrotoxicity mouse model, and a chronic kidney disease 5/6-nephrectomized rat model.

Methods

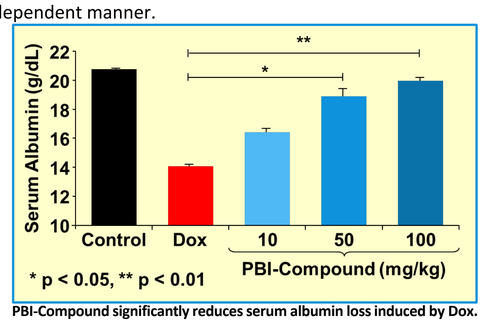


Results

A. Doxorubicin-Induced Nephrotoxicity: AKI Model

PBI-Compound reduces serum albumin loss induced by doxorubicin

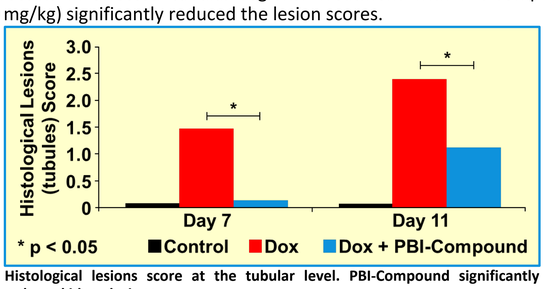
Serum albumin loss has been used as an indication of kidney injury. Doxorubicin (Dox) administration induced a significant decrease in serum albumin, while oral administration of PBI-Compound prevented this loss in a dose dependent manner.



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

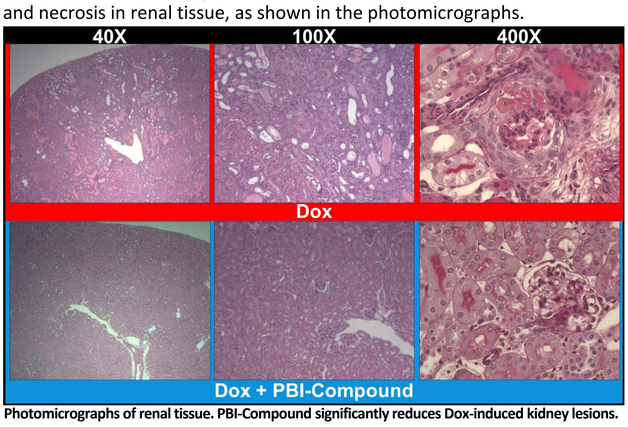
PBI-Compound reduces kidney lesions induced by doxorubicin

Histological examination of the kidneys on day 11 revealed that Dox induced severe lesions. Lesions consist of fibrosis, necrosis, sclerosis and accumulation of proteins in affected tubular regions. Treatment with PBI-Compound (100 mg/kg) significantly reduced the lesion scores.



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

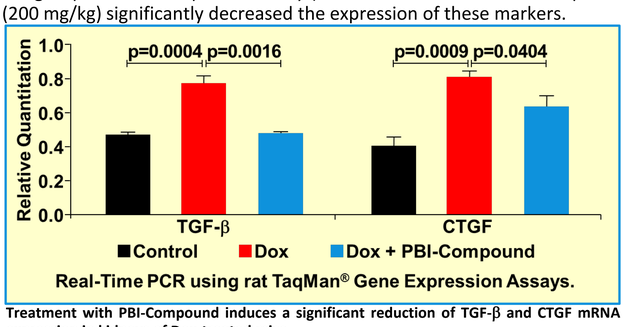
Treatment with PBI-Compound reduced tubule distention, fluid accumulation and necrosis in renal tissue, as shown in the photomicrographs.



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

PBI-Compound downregulates TGF-β and CTGF mRNA expression

Dox induces mRNA expression of the profibrotic cytokines transforming growth factor-β (TGF-β) and CTGF (quantified by real-time PCR in renal tissue using TaqMan® Gene Expression assays). Oral administration of PBI-Compound (200 mg/kg) significantly decreased the expression of these markers.

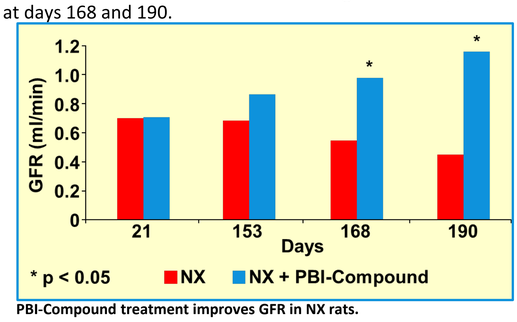


Treatment with PBI-Compound induces a significant reduction of TGF-β and CTGF mRNA expression in kidneys of Dox-treated mice.

B. 5/6-Nephrectomized Rat: CKD Model

PBI-Compound improves glomerular filtration rate (GFR)

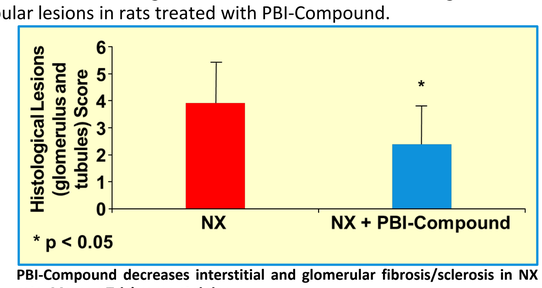
GFR is measured by creatinine clearance. While 5/6-NX rats showed a constant and gradual decrease of GFR from day 153 to day 190, PBI-Compound-treated animals exhibited significant improvement of GFR at days 168 and 190.



PBI-Compound treatment improves GFR in NX rats.

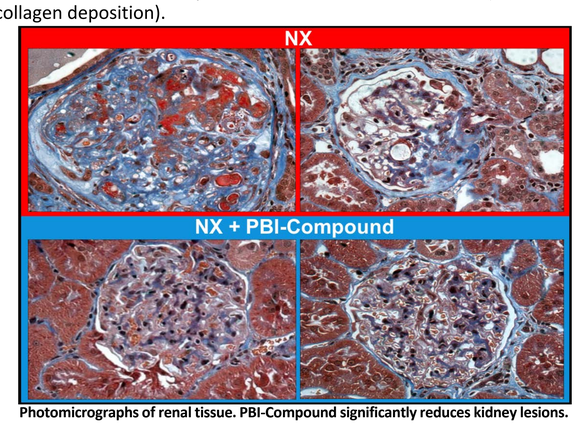
PBI-Compound reduces interstitial and glomerular fibrosis/sclerosis in remnant kidney

Histological examination of the remaining renal tissue from these animals revealed a significant reduction in the score of glomerular and tubular lesions in rats treated with PBI-Compound.



PBI-Compound decreases interstitial and glomerular fibrosis/sclerosis in NX rats. Masson Trichrome staining.

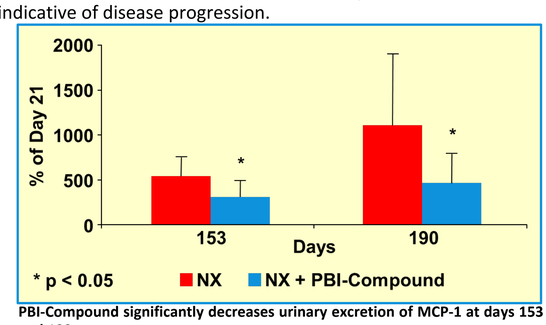
Treatment with PBI-Compound reduced lesions and fibrosis (blue-colored collagen deposition).



Photomicrographs of renal tissue. PBI-Compound significantly reduces kidney lesions.

PBI-Compound reduces urinary monocyte chemoattractant protein-1 (MCP-1)

Excretion of urinary MCP-1 is significantly reduced in PBI-Compound-treated 5/6-NX rats. This reduction correlates with GFR improvement and inhibition of fibrosis observed in PBI-Compound-treated rats. MCP-1 is indicative of disease progression.



PBI-Compound significantly decreases urinary excretion of MCP-1 at days 153 and 190.

Conclusions

PBI-Compound has a significant anti-fibrotic activity in both acute doxorubicin-induced nephrotoxicity and chronic 5/6-nephrectomy kidney disease models.

PBI-Compound Effects

Doxorubicin-induced (AKI)	5/6-nephrectomized (CKD)	
↓Serum albumin loss	↑ GFR	↓ Histological lesions
↓ Histological lesions	↓ Proteinuria	↓ Urinary MCP-1
↓TGF-β and CTGF mRNA expression		