PBI-4050, a novel first-in-class anti-inflammatory/fibrotic compound, reduces bleomycin-induced pulmonary fibrosis by inhibition of multiple pro-inflammatory/fibrotic key mediators

Brigitte Grouix, Mikaël Tremblay, François Sarra-Bournet, Alexandra Felton, André Doucet, Pierre Laurin and Lyne Gagnon

ProMetic BioSciences Inc.

ProMetic

BACKGROUND

The pathobiological mechanisms underlying the development of idiopathic pulmonary fibrosis (IPF) are highly complex. PBI-4050, a novel first-in-class, orally active low molecular weight compound, plays a key role in inflammation/fibrosis regulation by reducing pro-fibrotic cytokines, fibrocyte differentiation, myofibroblast activation and EMT, resulting in improvement of organ function.

The aim of this study was to determine the effect of PBI-4050 on the expression of pro-inflammatory/fibrotic key mediators involved in IPF using the bleomycin-induced mouse model of pulmonary fibrosis.

STUDY DESIGN

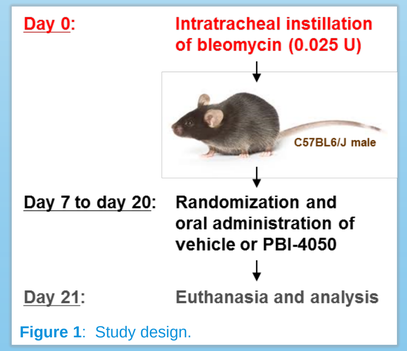

Figure 1: Study design.

Mice were randomized according to their bleomycin-induced body weight loss, and treatments with PBI-4050 started on day 7. Only animals that recovered their body weight loss by day 20 were used for data analysis.

RESULTS

A. Effect of oral treatment with PBI-4050 on fibrotic markers mRNA expression in lung

IPF is characterized by exaggerated fibroblast proliferation and accumulation of collagens and fibronectin. Bleomycin induced a significant increase in mRNA expression of fibrotic/remodeling markers in lung tissue. Oral treatment with PBI-4050 resulted in a significant reduction of collagen I and fibronectin 1 expression to the control level (no bleomycin).

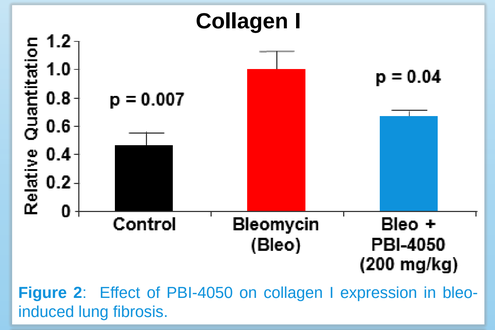

Figure 2: Effect of PBI-4050 on collagen I expression in bleo-induced lung fibrosis.

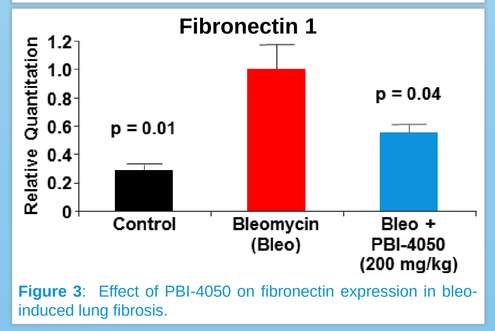

Figure 3: Effect of PBI-4050 on fibronectin expression in bleo-induced lung fibrosis.

B. Effect of oral treatment with PBI-4050 on pro-inflammatory/fibrotic mediators

TGF-β1, CTGF, IL-23p19, and IL-6 mRNA expression was quantified by real-time PCR. Our results show that oral administration of PBI-4050 significantly decreased the expression of these inflammatory and fibrotic markers in lung tissue.

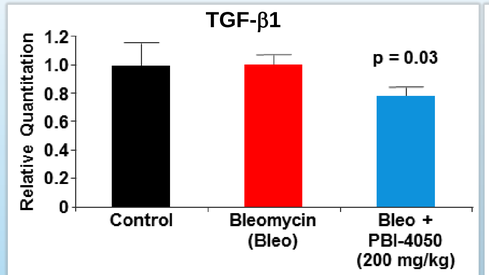

Figure 4: Effect of PBI-4050 on TGF-β1 expression in bleo-induced lung fibrosis.

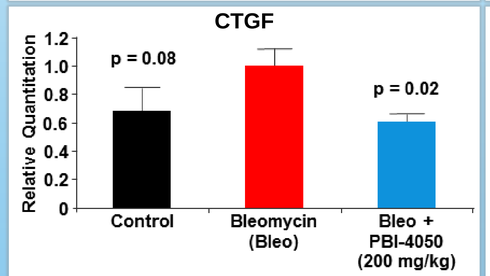

Figure 5: Effect of PBI-4050 on CTGF expression in bleo-induced lung fibrosis.

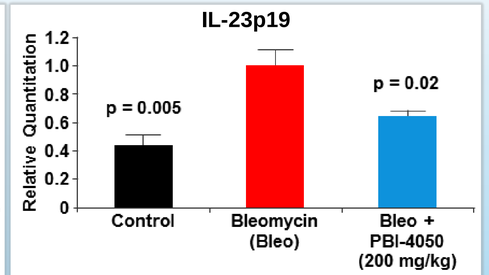

Figure 6: Effect of PBI-4050 on IL-23p19 expression in bleo-induced lung fibrosis.

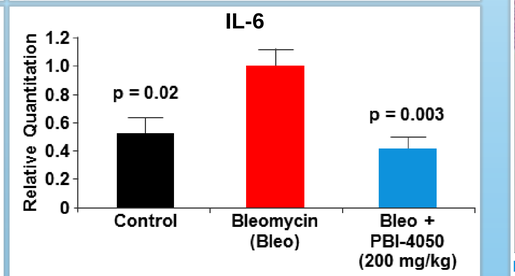

Figure 7: Effect of PBI-4050 on IL-6 expression in bleo-induced lung fibrosis.

C. Effect of PBI-4050 treatment on lung fibrosis

Masson's Trichrome staining showed that alveolar spaces were widened and filled with collagen fibers, indicating proliferative fibroblastic lesions in bleomycin-induced lung fibrosis that were reduced with oral treatment with PBI-4050.

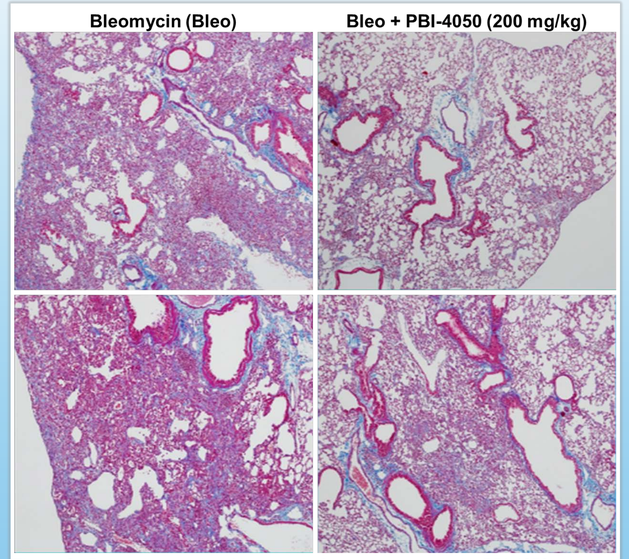

Figure 8: Photomicrographs of lung tissue from mice treated with PBI-4050 showing significant reduction of fibrosis (Masson's Trichrome staining, 40X) by PBI-4050.

CONCLUSION

Our results show that oral treatment with PBI-4050:

- ❖ Reduces fibrotic markers (collagen I and fibronectin 1) mRNA expression
- ❖ Reduces pro-inflammatory/pro-fibrotic cytokines (TGF-β1, CTGF, IL-23p19 and IL-6) mRNA expression
- ❖ Reduces histological lesions

PBI-4050 may be an efficacious treatment in IPF