BBT-877, a potent ATX inhibitor in development to treat idiopathic pulmonary fibrosis

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ABSTRACT

Idiopathic Pulmonary Fibrosis (IPF) is a progressive, irreversible and fatal lung disease. A number of investigational drugs have been tested in clinical trials. However, to date, two drugs, Pirfenidone and Nintedanib, were approved for the treatment of IPF. The ATX-LPA-LPAR axis has been suggested to play a pivotal role in the pathogenesis and the progression of IPF. Genetic deletion of ATX, LPAR1 and LPAR2 significantly improved the severity of bleomycin-induced pulmonary fibrosis in mouse. Pharmacological inhibition of ATX and LPAR1 reduced lung fibrosis parameters resulted from the bleomycin treatment in mouse. Positive efficacy data were obtained from clinical trials with drugs targeting the ATX-LPAR pathway. BBT-877 is a small molecule inhibitor to ATX. *In vitro* and *ex vivo* IC_{50} of BBT-877 were determined to be 2.4 nM and 6.89 nM (LPA 18:2), respectively. LPA-induced cell migration was effectively inhibited by BBT-877. *In vivo* anti-fibrotic efficacy of BBT-877 was shown in the mouse model of bleomycin-induced pulmonary fibrosis. BBT-877 did not significantly impair the viability of various cell types even when treated at higher concentration (CC_{50}: >100 uM). Currently, GLP toxicity study is ongoing. Taken together, BBT-877 is an orally available ATX inhibitor with high potency and low toxicity for the treatment of IPF.

RESULTS

Table 1. Inhibitory potency of BBT-877 to inhibit ATX enzyme activity *in vitro*

Compound	IC_{50} (nM)
BBT-877	2.4
GLPG1690	4.99
PAT-505	>100

Table 2. *Ex vivo* LysoPLD activity assay using mouse plasma

Compound	IC_{50} (nM)				
	LPA 16:0	LPA 18:0	LPA 18:1	LPA 18:2	LPA 20:4
BBT-877	3.33	16.9	8.28	5.31	5.36
GLPG1690	-	-	36.4	-	-

Table 3. *Ex vivo* LysoPLD activity assay using human plasma

Compound	IC_{50} (nM)				
	LPA 16:0	LPA 18:0	LPA 18:1	LPA 18:2	LPA 20:4
BBT-877	6.19	8.35	7.66	6.89	8.76
GLPG1690	102	149	133	132	150
PAT-505	36.9	92.6	70.5	66.4	56.9

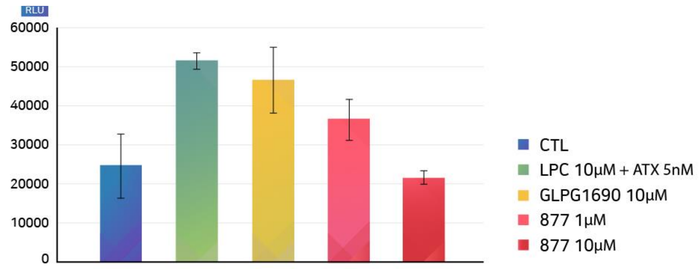

Figure 1. *In vitro* chemotaxis assay

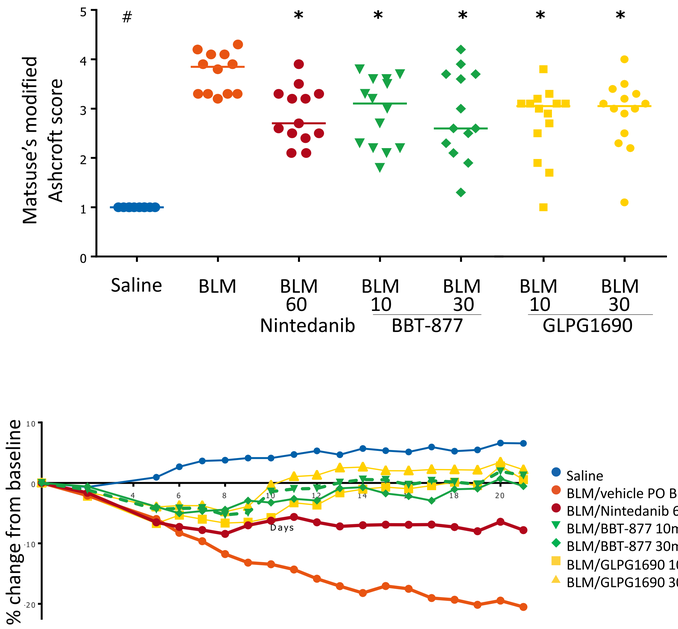

Figure 2. BLM-induced IPF mouse model

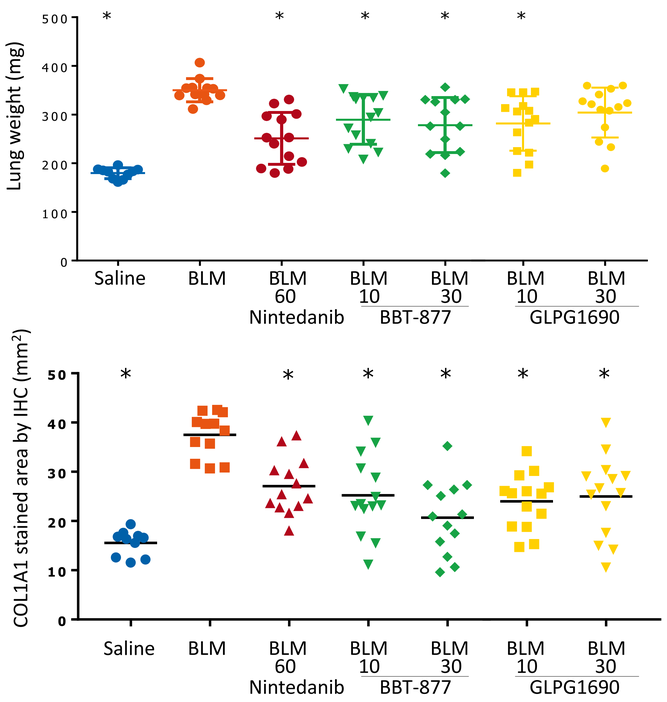

Table 4. PK data of BBT-877 in various animal species

Compound	Mice	Rats	Dogs	Monkeys
IV Dose (mg/kg)	**10**	**10**	**10**	**10**
App $t_{1/2}$ (hr)	3.73	3.88	5.51	6.35
CL (mL/min/kg)	29.7	21.0	7.01	9.68
$V_{d,ss}$ (mL/kg)	1130	776	691	885
PO Dose (mg/kg)	**10, 30**	**10, 30**	**10, 30**	**10, 30**
AUC range (μg.hr/mL)	1.9, 8.8	4.4, 9.3	7.9, 10.4	9.0, 34.6
C_{max} range (μg/mL)	2.3, 4.1	3.5, 3.4	3.0, 3.9	3.3, 13.6
BA range (%)	35, 53	56, 39	36, 16	49, 63

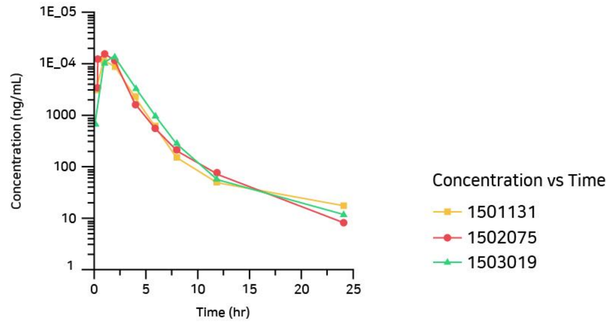

Figure 3. Plasma concentration profiles of BBT-877 in monkeys at 30 mg/kg

Table 5. *In vitro* cytotoxicity assay

Compound	Cell types and CC_{50} (uM)			
	HepG2 (hepatocellular carcinoma cell)	CHO-K1 (Chinese hamster ovary cell)	CCD-8Lu (normal lung fibroblast)	FA2N4 (immortalized human hepatocyte)
Pirfenidone	> 100	> 100		
Nintedanib	2.65	8.02	9.009	5.804
GLPG1690	9.39	36.9	5.794	36.457
PAT-505	> 100	94.965	> 100	5.411
BBT-877	> 100	> 100	> 100	> 100

CONCLUSION

1. BBT-877 is an orally available drug candidate for IPF treatment.
2. BBT-877 is targeting ATX. ATX is a preclinically and clinically validated IPF target.
3. BBT-877 is a potent inhibitor than competing drugs.
   ex vivo IC_{50} (LPA 18:2): 6.89 nM
4. BBT-877 is a safe compound. Less cytotoxic to various cell types compared to GLPG1690. GLP toxicity study is ongoing.