RP6557, a novel and selective PI3K δ/γ inhibitor, demonstrates efficacy in preclinical models of pulmonary fibrosis

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Introduction

Pulmonary fibrosis (PF) represents a debilitating disease of the lung that is often fatal without any known treatment. Although pirfenidone was approved for treatment of PF, patient response is limited and accompanied by severe adverse events. PI3K δ/γ are functionally expressed in human lung fibroblasts with the PI3Kγ shown to play a major role in TGF β induced fibroblast proliferation and differentiation (*Conte et al., 2011*). The objective of this study was to evaluate the therapeutic potential of RP6557, a novel, selective, and potent dual PI3Kδ/γ inhibitor in preclinical models of PF.

	IC_{50}/EC_{50} (nM)			
	PI3Kδ	**PI3Kα**	**PI3Kβ**	**PI3Kγ**
Enzyme	29.6	>10000	1141	28.9
Cell-based	38.1	>10000	4494	20.6

Table 1. Enzyme and cell-based activity of RP6557 for inhibition of PI3K isoforms. *Compound demonstrated >30-fold selectivity over a 451-kinase panel (KinomeScan)

Targeted Activity in Whole Blood

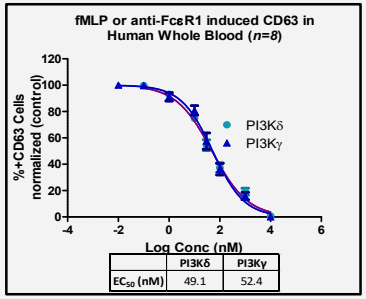


Fig. 1. *P110δ and γ mediate anti-FcεR1 or fMLP signaling in Human Whole Blood basophils manifested by an increase in CD63 expression and serve as ideal measures of target-specific activity. Expression was determined by flow cytometry.*

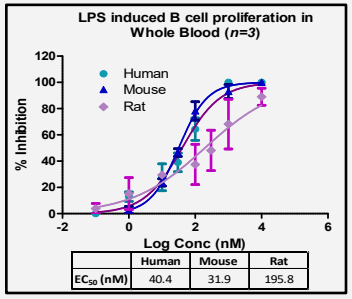


Fig. 2. *B-cell proliferation manifested by a change in expression of CD19+ (human) or **CD45R+** (mouse and rat) cells upon induction with LPS was determined by flow cytometry.*

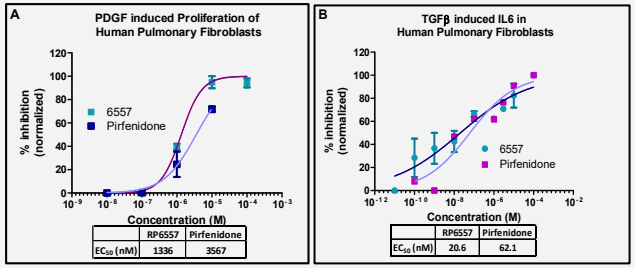


Fig. 3. A. *Isolated human pulmonary fibroblasts (HPF) were treated with 10 ng/ml Platelet Derived Growth Factor (PDGF) prior to incubation with desired concentrations of RP6557 or pirfenidone. Viability was assessed by a MTT assay after 48 h.* **B.** *TGFβ (50 ng/ml) induced IL-6 release from HPF. Cytokine release was measured by ELISA, 24 h after incubation with compounds.* ***RP6557 inhibited PDGF induced HPF proliferation as well as TGFβ mediated IL-6 release from HPF indicating a potential therapeutic role in PF.*** n=5

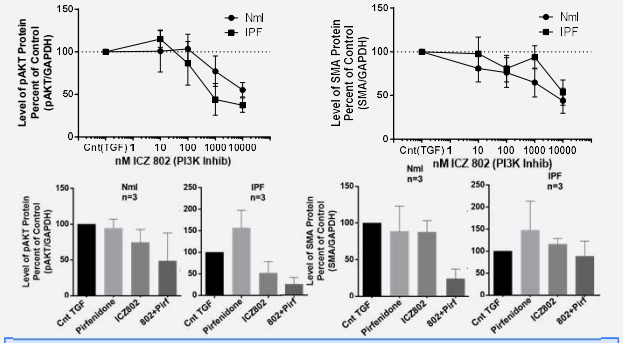
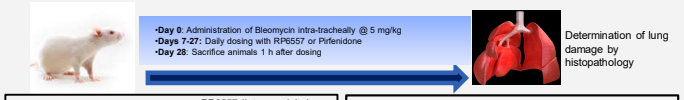


Fig. 4. *TGFβ induced expression of phospho-AKT (pAkt) and Smooth muscle alpha-actin (αSMA) in normal lung fibroblasts (Nml) from healthy volunteers and lung fibroblasts having fibrosis from Idiopathic pulmonary fibrosis (IPF) patients. Cells were stimulated with TGFβ and protein expression was analyzed by western-blot following incubation with ICZ802 (RP6557) or Pirfenidone (Pirf) or combination of both for 24 h.* ***Bottom panel:*** *ICZ802 (RP6557)=300 nM;; Pirf=1 µg/ml.* ***RP6557+ Pirf combination inhibited the expressionn of pAkt and αSMA in lung fibroblasts from IPF patients***



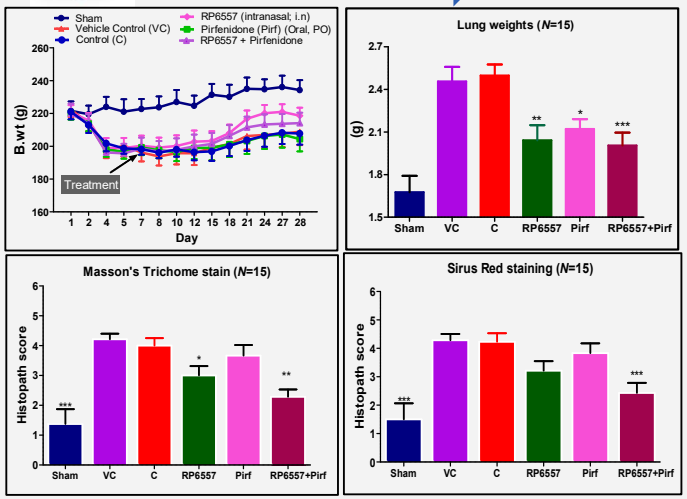


Fig. 5. ***Bleomycin induced pulmonary fibrosis in female Wistar Rats.*** *RP6557 (1 mg/kg/in/QD) or Pirfenidone (Pirf; 30 mg/kg/PO/QD) were administered from day 7 to day 28 following induction of fibrosis with Bleomycin. Upon termination, lung weights were measured and lung sections stained with Masson's Trichrome or Sirius Red for determination of fibrosis (*P<0.05; **P<0.01; ***P<0.001).* ***Combination of RP6557 with Pirf resulted in a significant reduction in lung weights compared to the individual agents. Reduced lung weights corroborated with a decrease in fibrosis evidenced upon histopathological examination.***

Summary

- *Dual inhibition of the delta and gamma isoforms of PI3K by RP6557 attenuated PDGF induced lung fibroblast proliferation and TGFβ-mediated IL-6 release*
- *Additionally, RP6557 in combination with Pirfenidone inhibited TGFβ-mediated p-Akt and α-SMA protein expression in lung fibroblasts from IPF patients*
- *Effective translation of activity in an animal model of pulmonary fibrosis with potent anti-inflammatory and anti-fibrotic activity especially in combination with pirfenidone*
- *Results provide a rationale for evaluating RP6557 as a single agent or in combination with pirfenidone in pulmonary fibrosis patients*

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