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In vitro and ex-vivo evaluation of anti-inflammatory and anti-fibrotic effects of NXP002 in rat and human cells and lung tissue

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Introduction

These studies investigated anti-inflammatory (AI) and anti-fibrotic (AF) effects of NXP002, a new salt form of tranilast and potential novel inhaled treatment for Idiopathic Pulmonary Fibrosis (IPF), in rodent and human cells and lung tissue.

Methods

Freshly isolated rat splenocytes or human peripheral blood mononuclear cells (PBMCs) were incubated with NXP002 (1 to 3000 µM) prior to stimulation with LPS (100 ng/mL). Inflammatory and fibrotic mediators were measured by Luminex multiplex 4 and 24 hours after stimulation.

Precision-cut lung slices (PCLS) were prepared from Sprague Dawley rats. Inflammatory and fibrotic responses were induced with LPS (1µg/ml; 24hrs) or TGF-β1 + PDGF-ββ (3µg/mL and 50ng/mL; 72hrs). The effects of concomitant administration of NXP002 (75, 150 or 300µM) on inflammatory cytokines, measured by ELISA, and tissue fibrosis marker gene expression by qPCR was assessed.

Similar assessments were made in PCLS prepared post transplant from 6 end stage IPF patients.

Results

NXP002 concentration-dependently inhibited LPS-induced cytokine production (IL-6, IL-10, MCP-1) by rat splenocytes and human PBMCs.

In rat PCLS, NXP002 concentration-dependently attenuated LPS induced MCP-1 and dampened IL-6 secretion, and attenuated TGF-β1 + PDGF-ββ induced upregulation in collagen 1 and αSMA gene expression.

NXP002 demonstrated an AF effect in human IPF tissue, with reduced production of MCP-1, Col1a1 and fibronectin.

Conclusion

NXP002 consistently demonstrated AI and AF effects in rat and human cells and lung tissue. Reductions in key biomarkers of fibrosis in IPF tissue support further evaluation of NXP002 as an inhaled therapy in IPF.