Differentiating Characteristics of Cudetaxestat (BLD-0409), a Non-Competitive Autotaxin Inhibitor Under Development for Idiopathic Pulmonary Fibrosis

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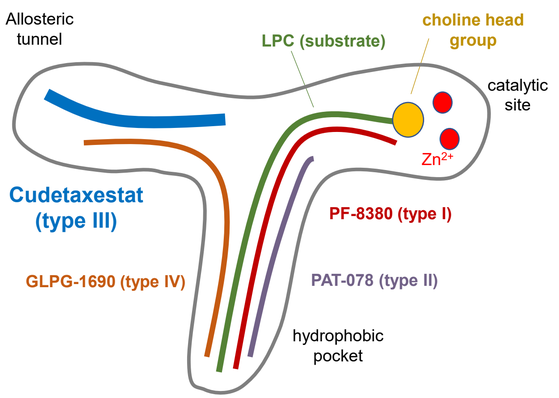
Abstract

RATIONALE: Autotaxin (ATX) is a secreted glycoprotein responsible for generating most of the bioactive lipid lysophosphatidic acid (LPA) from its substrate, lysophosphatidylcholine (LPC). LPA signaling occurs via six LPA receptors (LPARs) with overlapping specificity and tissue distribution. LPARs regulate numerous biological processes including inflammation, wound healing, fibrosis, and tumorigenesis. Tissue levels of ATX and LPA are elevated in fibrotic disease states including idiopathic pulmonary fibrosis (IPF), and cancer. Thus, inhibition of the ATX-LPA pathway represents a compelling therapeutic strategy. Cudetaxestat (BLD-0409) is an orally active, differentiated and phase 2-ready, non-competitive ATX inhibitor that is targeted to treat patients with fibrosis.

METHODS: *In vitro* ATX activity was assayed by measuring choline release under varying substrate (14:0 LPC) concentrations. Various ATX inhibitors (including cudetaxestat and GLPG-1690) were assayed and global mixed-model fitting of the data was used to classify their mode of inhibition. Efficacy of cudetaxestat was evaluated in a mouse model of bleomycin-induced lung fibrosis. Cudetaxestat and GLPG-1690 were dosed daily (3, 10 and 30 mg/kg) and therapeutically starting 7 days after bleomycin lung injury. Efficacy was assessed by Ashcroft score, picrosirius red (PSR) quantitation as well as *in situ* hybridization of actin alpha 2 smooth muscle (*ACTA2*) and collagen type 1 alpha 1 (*COL1A1*). Pharmacodynamics was assessed by measurement of C18:2 LPA levels in plasma. Transcriptomic (RNASeq) data from fibrotic lung tissue was collected and analyzed using Ingenuity Pathway Analysis (Qiagen, Inc.). Statistical analysis were performed using GraphPad Prism (San Diego, CA) ANOVA One-Way variance with Dunnett's multiple comparisons. Significant values indicates p-value of 0.05 or less

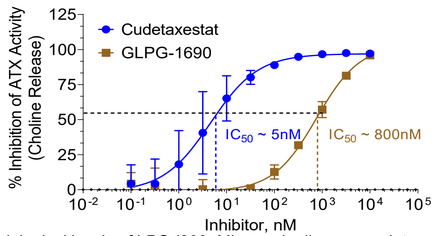
RESULTS: Cudetaxestat displays a reversible, non-competitive inhibitory profile *in vitro* that is distinct from competitive ATX inhibitors. Under elevated LPC substrate concentrations observed in fibrotic disease states, cudetaxestat maintained its low nanomolar biochemical potency which is ~160-fold stronger than that of GLPG-1690. In a bleomycin-induced lung fibrosis model, cudetaxestat significantly reduced Ashcroft score, assembled collagen (PSR) and mRNA levels of *ACTA2* and *COL1A1*, consistent with direct anti-fibrotic activity. Cudetaxestat treatment effects were dose-dependent while GLPG-1690 did not display dose-dependence at the same doses tested. Although both drugs showed similar reductions of plasma LPA levels, efficacy differences may be reflective of non-competitive vs. competitive inhibition as well as differences in tissue penetration and pathway modulation noted in the transcriptomic data.

Binding and Inhibition of ATX by Cudetaxestat



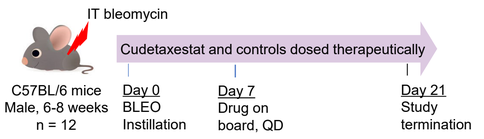
- Four types of ATX inhibitors have been described with distinct binding modes within the active site (*Salgado-Polo, et al., 2018, J. Biol. Chem. 293*).
- Cudetaxestat and GLPG-1690 bind differently within the ATX active site (*Zhai et al, 2018, Biomed J Sci & Tech Res 7*).
- Cudetaxestat (BLD-0409) exhibits non-competitive inhibition whereas GLPG-1690 exhibits competitive inhibition of ATX

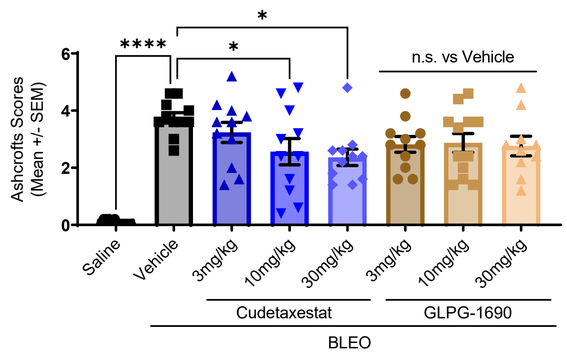
Potency of Cudetaxestat at Physiological Concentration of LPC

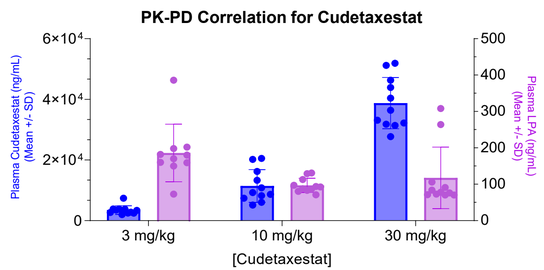


- At physiological levels of LPC (200μM) seen in disease, cudetaxestat displays ~160-fold potency advantage over GLPG-1690
- Non-competitive inhibition by cudetaxestat maintains potency under elevated substrate (LPC) concentrations (data not shown)

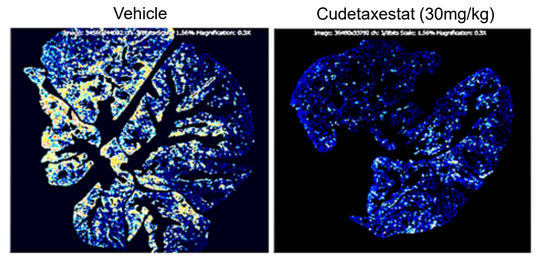
Cudetaxestat Reduces Lung Fibrosis in a Dose-Dependent Manner

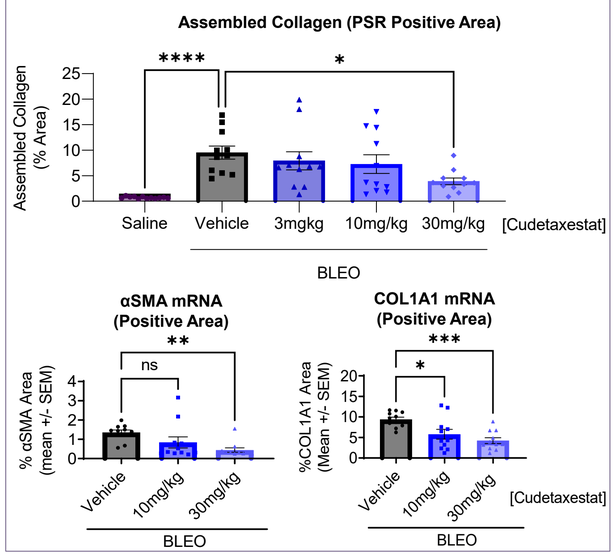




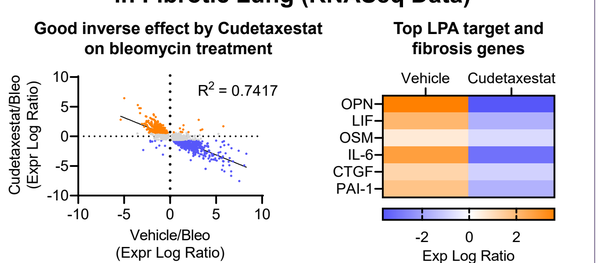


Cudetaxestat Displays Robust Activity on Various Markers of Lung Fibrosis



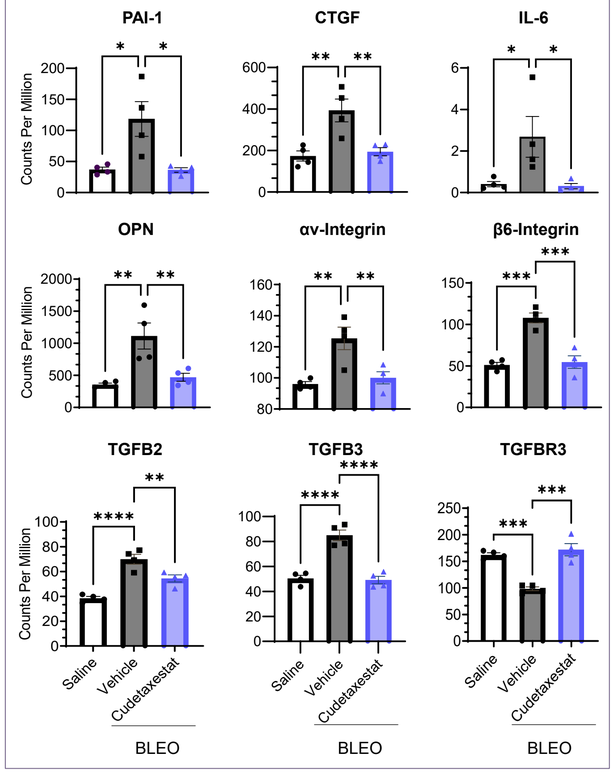


Cudetaxestat Reduces ATX/LPA Target Genes in Fibrotic Lung (RNASeq Data)



- Cudetaxestat dosed BID for RNAseq study

Cudetaxestat Regulates Expression of Key Drivers of Lung Fibrosis



Conclusions

- Non-competitive ATX inhibition by cudetaxestat provides a differentiated profile that maintains potency in the presence of elevated substrate (LPC) concentrations
- In a mouse model of lung fibrosis, cudetaxestat displays direct anti-fibrotic activity (reduced αSMA, Col1A1 expression, reduced fibrosis and assembled collagen)
- Inhibition of the ATX/LPA pathway by cudetaxestat significantly reduced activation (gene expression) of several key pro-fibrotic pathways
- These data support the potential for cudetaxestat as a differentiated therapeutic treatment for lung fibrosis

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