Therapeutic Impact of an ALK5 Inhibitor Across Multiple Preclinical Fibrosis Models

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Background & Objective

Fibrosis is a progressive disease which affects multiple organs. Several signaling pathways impact progression of fibrosis including transforming growth factor-beta (TGF-β) which plays a critical role in multi-organ fibrosis by activating fibroblasts and promoting excessive extracellular matrix deposition, leading to tissue scarring and organ dysfunction. SB 525334 is a selective inhibitor of ALK5 (activin receptor-like kinase 5), a key receptor in the TGF-β signaling pathway implicated in fibrosis, inflammation, and cancer. By targeting ALK5, SB 525334 effectively blocks the profibrotic effects of TGF-β, presenting therapeutic potential in diseases driven by fibrosis. Aragen's preclinical studies using an ALK5 inhibitor demonstrate varying levels of improvement across various mouse models of fibrosis.

Summary & Conclusions

Therapeutic Effect of ALK5 Inhibitor in Multiple Fibrosis Models

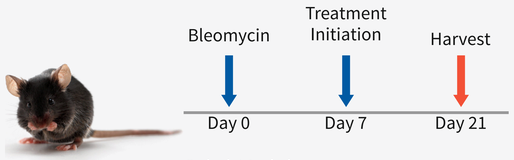
The ALK5 inhibitor demonstrates improvement in various parameters across multiple preclinical fibrosis models. In this presentation we have shown a snapshot of some of the potential readouts evaluated in these multi-organ fibrosis mouse models.

- **Lung Fibrosis:** Improved lung function, histology parameters including Ashcroft scores, and hydroxyproline levels.
- **Systemic Sclerosis:** Improved histological findings, reduced lung weights and lowered hydroxyproline levels in skin and lung tissue.
- **Renal Fibrosis:** Improved histological findings, including collogen deposition, tubular degeneration and hydronephrosis.
- **Liver Fibrosis:** Improved histological findings, decreased liver weights, lowered hydroxyproline levels and lowered liver enzyme levels.

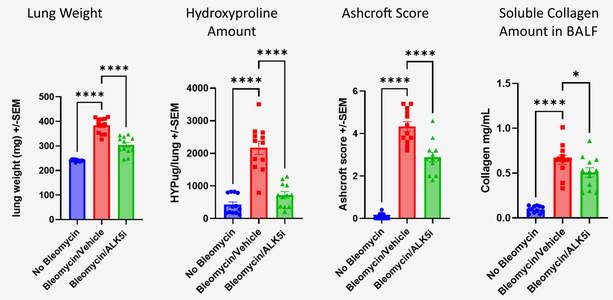
These consistent improvements highlight the ALK5inhibitor as a potential modelcontrol in fibrosis research.

At Aragen, our expert and experienced staff provide scientific input and support for all project stages. Visit our website at www.aragenbio.com and have Aragen become your partner for characterization and development of new drugs for fibrosis indications.

A. Acute Lung Fibrosis: Bleomycin Induced IPF

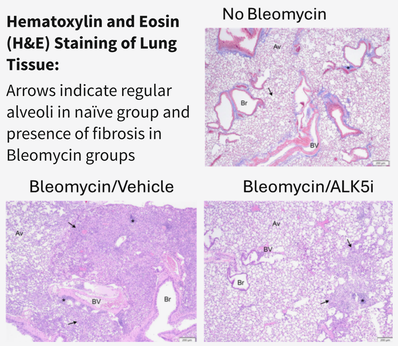


Endpoint Analysis:
Lung function, BAL leukocyte counts, cytokine analysis, Sircol assay, Hydroxyproline, gene expression, and histology

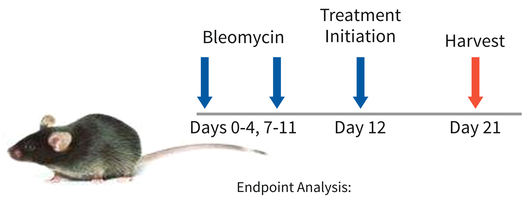


Hematoxylin and Eosin (H&E) Staining of Lung Tissue:

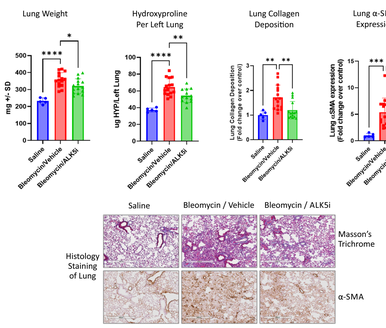
Arrows indicate regular alveoli in naïve group and presence of fibrosis in Bleomycin groups

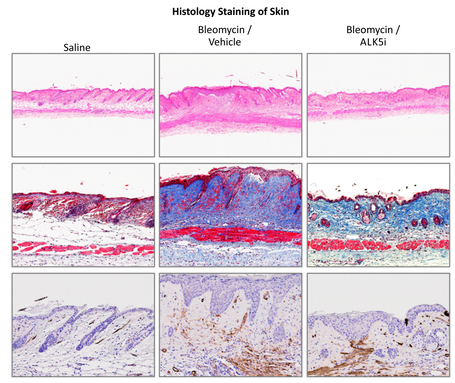


B. Systemic Sclerosis

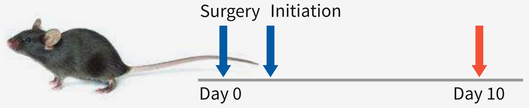


Endpoint Analysis:
Lung weights, cytokine analysis, Sircol assay, Hydroxyproline, dermal thickness, and histology

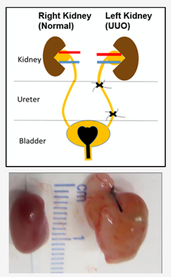


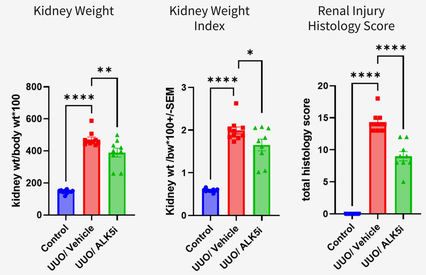


C. Renal Fibrosis: Unilateral Ureteral Obstruction (UUO)



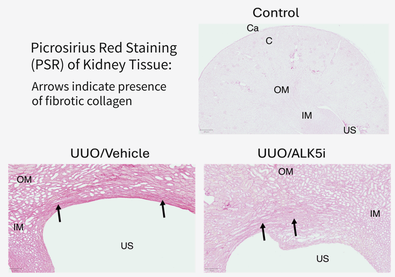
Endpoint Analysis:
Kidney enzymes, CBC analysis, kidney weight, and histology



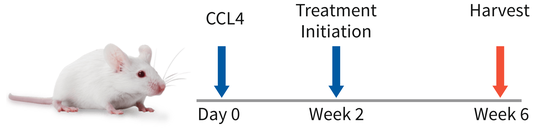


Picrosirius Red Staining (PSR) of Kidney Tissue:

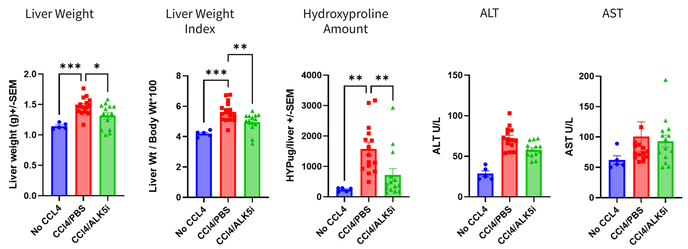
Arrows indicate presence of fibrotic collagen



D. Liver Fibrosis: CCl4 Induced



Endpoint Analysis:
Liver enzymes, CBC analysis, cytokine analysis, Hydroxyproline, gene expression, and histology



Picrosirius Red Staining (PSR) of Liver Tissue:

ALK5 inhibitor reduced mineralization and lowered collagen stained area

Histology done by Dallas Tissue Research