Anti-WISP1 (MTX-463) as a Novel Potential Therapy for Idiopathic Pulmonary Fibrosis

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Rationale
Myofibroblasts play a central role in the pathogenesis of fibrosis across various organs. Myofibroblast activation is characterized by persistent aberrant extracellular matrix (ECM) deposition and remodeling, leading to the accumulation of scar tissue and ultimately loss of organ function.

WNT7-induced signaling pathway protein-1 (WISP1), also known as cellular communication network factor 4 (CCN4) is a secreted matricellular protein elevated in idiopathic pulmonary fibrosis (IPF) patients and has been identified as a potential pro-fibrotic target.

We generated neutralizing antibodies to WISP1 and investigated whether its inhibition is anti-fibrotic both in vitro and in a preclinical mouse model of lung fibrosis.

Methods

In-vitro assays: Normal rat kidney fibroblasts (NRKF) were stimulated with recombinant WISP1 +/- antibodies for various time-points. pSMAD2/3 levels were determined by Luminex on cell lysates. Human Hepatic Stellate Cells (HSCs) were seeded in the top chamber of a transwell coated with WISP1 +/- antibodies. 10% FBS was added to the lower chamber as chemoattractant. Images were captured by Inouye. R&D anti-WISP1 goat polyclonal (AF1627) used as reference.

In vivo: Bleomycin mouse model of lung fibrosis was conducted at Aragen under IACUC approved protocols. Study design as shown in the Results. IL-6 levels were determined by MSD, WISP1 by ELISA (R&D Systems MHSIP10). Gene expression was determined by Tqman. Pathologist scoring (Ashcroft) of lung tissue was conducted at Inovio.

Formalin-fixed Paraffin Embedded (FFPE) blocks of normal (n=5) or IPF (n=10) human lung tissues were obtained from a commercialvendor. Slides were stained with WISP1 antibody (Abcam) and evaluated by a board-certified pathologist.

Conclusions

• **MTX-463**, an anti-WISP1 monoclonal antibody, significantly reduced fibrosis in vitro and in a preclinical mouse model of lung fibrosis.
• Based on these data, MTX-463 warrants assessment in clinical trials in patients with IPF.

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Significant WISP1 expression in fibrotic areas of IPF lungs

MTX-463: human IgG1 monoclonal antibody that binds CCN4/WISP1 with high specificity and high affinity

Anti-WISP1 reduces pSMAD2/3 and inhibits fibroblast migration

Anti-WISP1 neutralizing antibody suppresses lung fibrosis in a bleomycin mouse model

Results

**Anti-WISP1 target engagement**

**Anti-fibrotic dose relationship**

**Increased WISP1 expression**

**Reduced fibrosis**

**Fibrosis score (Ashcroft)**

**WISP1 target engagement**

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