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.

WNT1-inducible 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 (HHSCs) were seeded in the top chamber of a transwell coated with rWISP1 +/- antibodies. 10% FBS was added to the lower chamber as chemoattractant. Images were captured by Incucyte. 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 MWSP10). Gene expression was determined by Taqman. Pathologist scoring (Ashcroft) of lung tissue was conducted at Inotiv.

Formalin-fixed Paraffin Embedded (FFPE) blocks of normal (n=5) or IPF (n=10) human lung tissues were obtained from a commercial vendor. 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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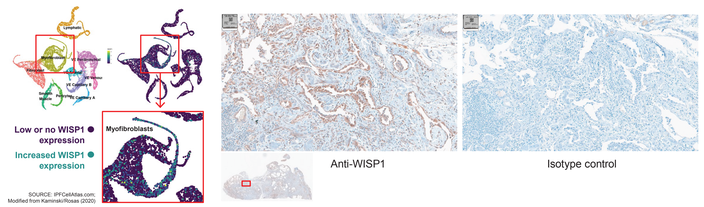
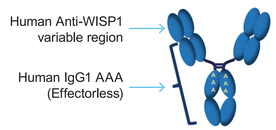
Results

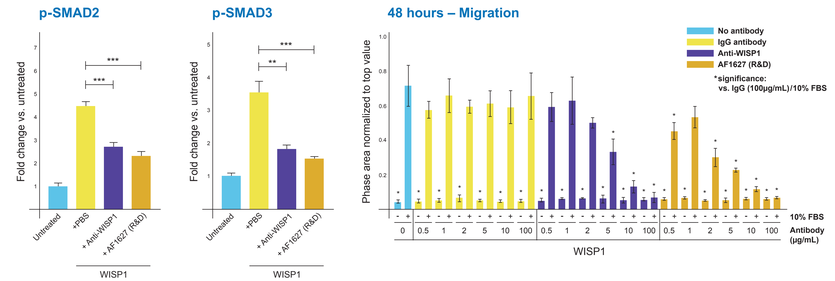
Significant WISP1 expression in fibrotic areas of IPF lungs



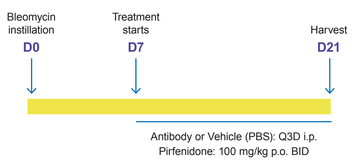
MTX-463: human IgG1 monoclonal antibody that binds CCN4/WISP1 with high specificity and high affinity

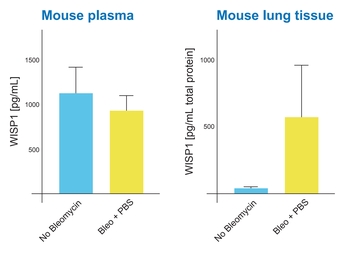


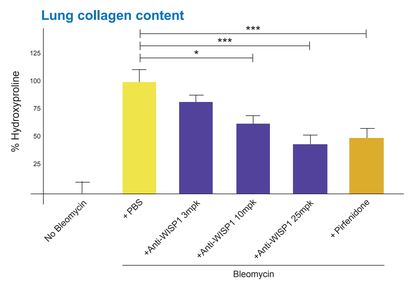
Anti-WISP1 reduces pSMAD2/3 and inhibits fibroblast migration

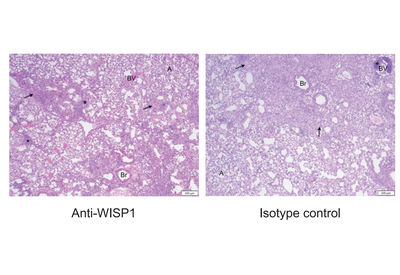


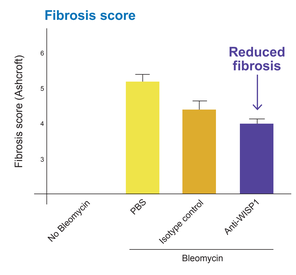
Anti-WISP1 neutralizing antibody suppresses lung fibrosis in a bleomycin mouse model

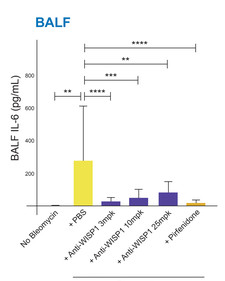


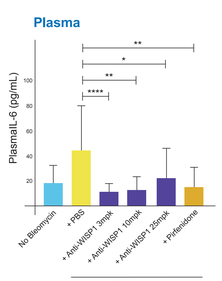


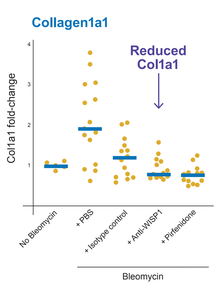


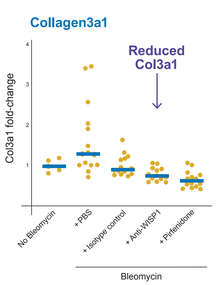


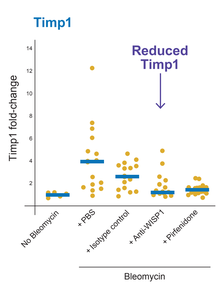


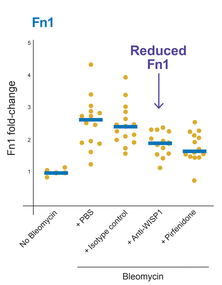


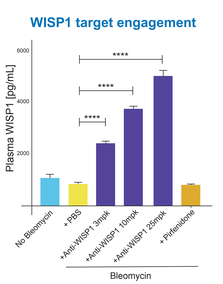


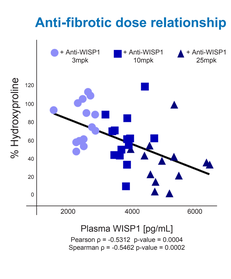












Disclosure: All authors are current or former employees and shareholders of Mediar Therapeutics.